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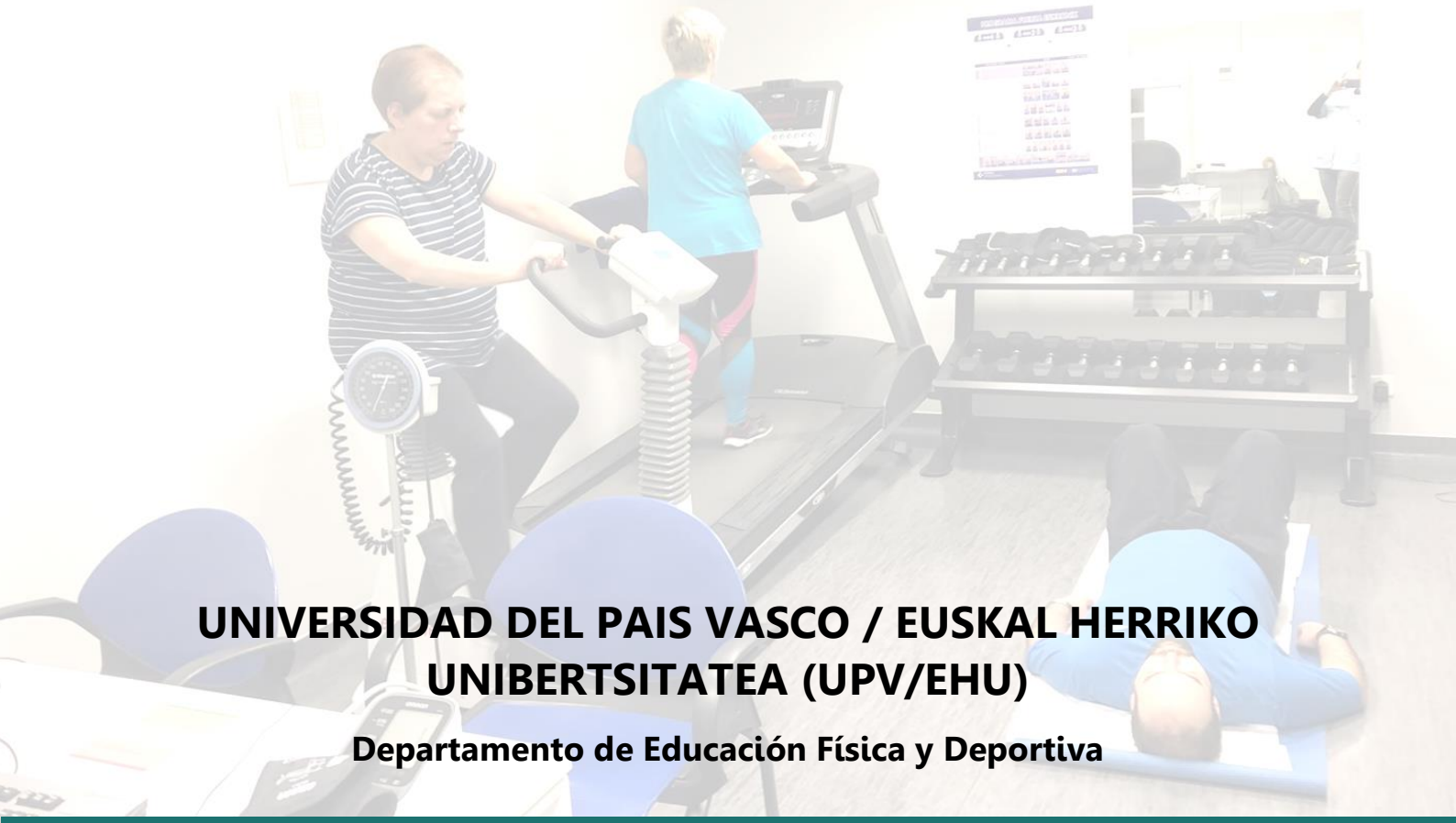

UNIVERSIDAD DEL PAIS VASCO / EUSKAL HERRIKO UNIBERTSITATEA (UPV/EHU)

Departamento de Educación Física y Deportiva

TESIS DOCTORAL • VITORIA-GASTEIZ, 2019

Measurement of Relative Physical Activity and Exercise Intensity through Metabolic Thresholds in Healthy Women and Cancer Patients

Medición de la Actividad Física Relativa y de la Intensidad del Ejercicio Físico mediante Umbrales Metabólicos en Mujeres Sanas y Pacientes con Cáncer

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Departamento de Educación Física y Deportiva
Gorputz eta Kirol Hezkuntzako Saila

PROGRAMA DE DOCTORADO • PhD PROGRAM

Ciencias de la Actividad Física y del Deporte

Physical Activity and Sport Sciences

TESIS DOCTORAL • DOCTORAL THESIS

Medición de la Actividad Física Relativa y de la Intensidad del Ejercicio Físico mediante Umbrales Metabólicos en Mujeres Sanas y Pacientes con Cáncer

Measurement of Relative Physical Activity and Exercise Intensity through Metabolic Thresholds in Healthy Women and Cancer Patients

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"If we had a pill that conferred all the confirmed health benefits of exercise, would we not do everything humanly possible to see to it that everyone had access to this wonder drug? Would it not be the most prescribed pill in the history of mankind?" (Sallis, 2009).

Declaración

Yo, Erreka Gil-Rey declaro que las investigaciones llevadas a cabo en esta tesis doctoral se han desarrollado en dos centros de Investigación y Medicina del Deporte (Gabinete de Medicina Deportiva de Miranda del Ayuntamiento de Miranda de Ebro y el Centro de Estudios, Investigación y Medicina del Deporte del Gobierno de Navarra, CEIMD, en Pamplona) bajo la continua supervisión y apoyo de la Universidad del País Vasco (UPV/EHU), que han generado cuatro artículos científicos publicados o aceptados para su publicación en revistas científicas internacionales revisadas por pares, y que se presentan con el mismo formato en los capítulos 4, 5, 6, y 7. La contribución de cada uno de los autores que participaron en dichos estudios es la siguiente.

- Gil-Rey E, Quevedo-Jerez K, Maldonado-Martin S, Herrero-Román, F. Exercise Intensity Guidelines for Cancer Survivors: A Comparison with Reference Values. *International Journal of Sports Medicine*. 2014;35(14):e1-e9. DOI: 10.1055/s-0034-1389972.

  La Fundación GIAFyS-Cáncer contribuyó en la captación y aportación de fondos para la publicación del estudio. FHR y KQJ diseñaron el estudio y registraron datos de las pruebas de esfuerzo realizadas en supervivientes de cáncer durante 10 años. EGR contribuyó a la recopilación de datos, análisis estadístico y redacción del manuscrito. FHR y SMM contribuyeron a la discusión de los resultados y a la revisión del manuscrito.

- Gil-Rey, E, Maldonado-Martín S, Gorostiaga EM. Individualized Accelerometer Activity Cut-Points for the Measurement of Relative Physical Activity Intensity Levels. *Research Quarterly for Exercise and Sport.* 2019;6:1-9. DOI: 10.1080/02701367.2019.1599801.

  EGR y EGA concibieron la idea del estudio. EGR y EGA realizaron todas las pruebas de esfuerzo y la recogida de datos. EGR analizó los datos y redactó el primer draft del manuscrito junto a EGA y SMM, que conjuntamente revisaron críticamente el manuscrito y dieron su consentimiento final.

- Gil-Rey, E, Maldonado-Martín S, Palacios-Samper N, Gorostiaga EM. Objectively Measured Absolute and Relative Physical Activity Intensity Levels in Postmenopausal

Women. *European Journal of Sports Science*. 2019;19(4):539-548. DOI: 10.1080/17461391.2018.1539528.

EGR y EGA concibieron la idea del estudio y junto a la ayuda del equipo del CEIMD (NPS, J Ibañez, JC Lizarazu, M Ruesta y L Sánchez Medina) y SMM diseñaron el estudio. EGR y EGA realizaron todas las pruebas de esfuerzo y recogieron los datos. EGR analizó los datos y redactó el primer draft del manuscrito junto a EGA. EGR, EGA, SMM, y NPS revisaron críticamente el manuscrito y dieron su consentimiento final.

- Gil-Rey, E, Maldonado-Martín S, Palacios-Samper N, Gorostiaga EM. Estimation of the Maximal Lactate Steady State in Postmenopausal Women. *Journal of Sports Sciences.* 2019;5:1-9. DOI: 10.1080/02640414.2019.1586814.

  EGR y EGA concibieron la idea del estudio y junto a la ayuda del equipo del CEIMD (NPS, J Ibañez, JC Lizarazu, M Ruesta y L Sánchez Medina) y SMM diseñaron el estudio. EGR y EGA realizaron todas las pruebas de esfuerzo y la recogida de datos. EGR analizó los datos y redactó el primer draft del manuscrito junto a EGA. EGR, EGA, SMM, y NPS revisaron críticamente el manuscrito y dieron su consentimiento final.

Consentimiento Ético: El estudio desarrollado en el capítulo 4 fue aprobado por el Comité Ético de Investigación Clínica de Burgos y Soria. El Comité Ético de Investigación Clínica del Complejo Hospitalario de Navarra aprobó el estudio que se desarrolla en los capítulos 5, 6 y 7 (Pyto2011/71). Se obtuvo el consentimiento informado de cada una de las participantes del estudio. Los procedimientos de estos estudios de investigación van acorde a la Declaración de Helsinki. El estudio realizado en el CEIMD se registró y puede consultarse en *ClinicalTrials.gov PRS* (NCT02984553).

Conflictos de interés: Ningún autor ha mantenido o mantiene relación profesional con las compañias que pudieran beneficiarse de los resultados de la presente tesis doctoral. Los autores declaran no tener conflicto de interés alguno.

Ayuda financiera, estancias de investigación y contribuciones científicas

Universidad del País Vasco Euskal Herriko Unibertsitatea
HEZKUNTZA ETA KIROL FAKULTATEA
FACULTAD DE EDUCACIÓN Y DEPORTE

CEiMD

University of BRISTOL

UNIVERSITY OF BATH

Exercise Medicine Research Institute
vario health clinic
AUSTRALIA ECU EDITH COWAN UNIVERSITY

Osakidetza
IKERKETA UNITATEA
LEHEN MAILAKO ARRETA
UNIDAD DE INVESTIGACIÓN ATENCIÓN PRIMARIA DE BIZKAIA

GIAFyS CÁNCER FundaciÓN

Ayuda financiera y becas

La Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU) ha sido el principal órgano financiero durante la presente tesis doctoral, por medio de las siguientes becas predoctorales:

- Contrato de Investigador Predoctoral en formación (desde el 01/02/2015 hasta el 15/10/2018). Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU).
- Erasmus+ Academic Year 2017/2018 (01/10/2017-31/12/2017). Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU).
- Convocatoria de Ayudas para la movilidad y divulgación de resultados de investigación en la Universidad del País Vasco 2018 (01/09/2018-15/10/2018). Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU).

Tanto el Gabinete de Medicina Deportiva de Miranda de Ebro, como el Centro de Estudios, Investigación y Medicina del Deporte del Gobierno de Navarra, han contribuido en mi formación profesional e investigadora, facilitando el espacio físico y los recursos materiales y de personal necesarios para desarrollar las tareas de ingestigación.

Estancias de Investigación

- 07/2012 - 06/2013. Grupo de Investigación en Actividad Física y Salud (GIAFyS). Miranda de Ebro, Burgos.
- 03/2015 – 07/2017. Centro de Estudios, Investigación y Medicina del Deporte (CEIMD). Instituto Navarro de Deporte y Juventud. Gobierno de Navarra. Pamplona, Navarra.
- 07/2016 – 08/2016. University of Bristol. School of Clinical Sciences. Musculoskeletal Research Unit. Bristol, UK.
- 08/2017 – 12/2017. University of Bath. Department for Health. Sport, Health & Exercise Science. Active Lifespan research group: Chronic disease, obesity & ageing. Bath, UK.
- 12/2017 - actual. Unidad de Investigación en Atención Primaria de Osakidetza. Bilbao, Bizkaia.
- 09/2018 – 10/2018. Exercise Medicine Research Institute. Edith Cowan University. Perth, Western Australia.

Publicaciones científicas

- Gil-Rey E, Quevedo-Jerez K, Maldonado-Martin S, Herrero-Román F. Exercise Intensity Guidelines for Cancer Survivors: A Comparison with Reference Values. *International Journal of Sports Medicine*. 2014;35(14):e1-e9. DOI: 10.1055/s-0034-1389972.

- Gil-Rey E, Maldonado-Martín S, Palacios-Samper N, Gorostiaga EM. Objectively Measured Absolute and Relative Physical Activity Intensity Levels in Postmenopausal Women. *European Journal of Sports Science*. 2019;19(4):539-548. DOI: 10.1080/17461391.2018.1539528.

- Gil-Rey E, Maldonado-Martín S, Palacios-Samper N, Gorostiaga EM. Estimation of the Maximal Lactate Steady State in Postmenopausal Women. *Journal of Sports Sciences.* 2019;5:1-9. DOI: 10.1080/02640414.2019.1586814.

- Gil-Rey E, Maldonado-Martín S, Gorostiaga EM. Individualized Accelerometer Activity Cut-Points for the Measurement of Relative Physical Activity Intensity Levels. *Research Quarterly for Exercise and Sport.* 2019;6:1-9. DOI: 10.1080/02701367.2019.1599801.

- Quevedo-Jerez K, Gil-Rey E, Maldonado-Martin S, Herrero-Román F. Exercise-Intensity Adherence During Aerobic Training and Cardiovascular Response During Resistance Training in Cancer Survivors. *Journal of Strength and Conditioning Research*. 2019. DOI: 10.1519/JSC.0000000000003144. [Epub ahead of print]

Contribución docente

- Ponencia en la FCAFD de la UPV/EHU (Vitoria-Gasteiz) dentro del marco de la asignatura de "Actividad Física para la Salud de las Personas con Patologías" en el curso 2014-2015. "*Diseño del ejercicio físico en supervivientes de cáncer*" (2h).

- Ponencia en la FCAFD de la UPV/EHU (Vitoria-Gasteiz) dentro del marco de la asignatura de "Actividad y Nutrición para la Salud" en el curso 2014-2015. "*Nutrición y cáncer*" (2h).

- Ponencia en la FCAFD de la UPV/EHU (Vitoria-Gasteiz) dentro del marco de la asignatura de "Actividad Física para la Salud de las Personas con Patologías" en el curso 2015-2016. "*¿caminar o correr? ¿Cuál es la dosis terapéutica de actividad física para el*

tratamiento del cáncer? Uso de acelerómetros triaxiales para medir la actividad física y la intensidad de los impactos" (3h).

- Ponencia en la FCAFD de la UPV/EHU (Vitoria-Gasteiz) dentro del marco de la asignatura de "Diseño de la Actividad física en Personas con Patologías" en el curso 2016-2017. "*¿Caminar o correr? ¿Individualización de la Dosis de Actividad Física para Reducir la Inflamación, el Tumor y los Efectos Secundarios Asociados en Supervivientes de Cáncer de Mama*" (3h).
- Ponencia en la FCAFD de la UPV/EHU (Vitoria-Gasteiz) dentro del marco de la asignatura de "Diseño de la Actividad física en Personas con Patologías" en el curso 2017-2018. "*Implementación de un Programa de Ejercicio Físico Terapéutico para Personas con Cáncer en el Sistema Sanitario Público*" (3h).
- Profesor laboral Interino a tiempo parcial en el Departamento de Educación Física y Deportiva de la Facultad de Educación y Deporte (UPV/EHU). Curso académico 2018-2019. Desde el 3 de Abril de 2019. Asignatura de Biomecánica.
- Ponencia en la Diputación de Bizkaia dentro del marco de las jornadas de "Ejercicio Físico para la Salud, de la Teoría a la Práctica" en el curso 2017-2018. "*Ejercicio físico y Osteoporosis*" (6h).
- Ponencia en la Diputación de Bizkaia dentro del marco de las jornadas de "Ejercicio Físico para la Salud, de la Teoría a la Práctica" en el curso 2016-2017. "*Dosis de Actividad Física para la Prevención y el Tratamiento de Enfermedades Crónicas*" (3h).
- Ponencia organizada por Lanbide y Kirolene dentro del marco de las jornadas de "*Actividad Física para Patologías Crónicas" en el curso* 2016-2017. "*Actividad Física para la Prevención y el Tratamiento de la Osteoporosis*" (3h).
- Ponencia organizada por Lanbide y Kirolene dentro del marco de las jornadas de "*Actividad Física para Patologías Crónicas" en el curso* 2016-2017. "*Dosis de Actividad Física para la Prevención y Tratamiento de Enfermedades Crónicas*" (3h).
- Ponencia organizada por Lanbide y Kirolene dentro del marco de las jornadas de "*Actividad Física para Patologías Crónicas" en el curso* 2016-2017. "*Fisiología del Ejercicio*" (6h).

Contribución en congresos científicos

- Maldonado-Martin S, Gil-Rey E., Quevedo-Jerez K, Herrero-Román F. Exercise Intensity Guidelines for Cancer Survivors: Are we Heading in the Right Direction? *EuroPrevent. European Association of Preventive Cardiology*.
  Presentación de poster a cargo de Sara Maldonado-Martín.
  Mayo 2014, Amsterdam, Holanda.

- Gil-Rey E, Palacios N, Ibañez J, Maldonado-Martín S, Gorostiaga EM. Individualization of Metabolic Accelerometer Cut-Points to Objectively Assess Physical Activity Levels in Post-Menopausal Women. The Importance of Fitness Level. *Simposio Exernet. Investigación en Ejercicio Físico, Salud y Bienestar: "Exercise is Medicine".*
  Presentación de poster moderado a cargo de Erreka Gil-Rey.
  Oct 2016, Cádiz, España.

- Gil-Rey E, Palacios N, Ibañez J, Maldonado-Martín S, Gorostiaga EM. Individualization of Metabolic Accelerometer Cut-Points to Objectively Assess Physical Activity Levels in Breast Cancer and Healthy Post-Menopausal Women. "Are we Sure of Doing Enough Physical Activity? *EuroPrevent. European Association of Preventive Cardiology*.
  Presentación de poster moderado a cargo de Erreka Gil-Rey.
  Abril 2017, Málaga, España.

- Gil-Rey E, Maldonado-Martín S, Gorostiaga EM. Defining Exercise Intensity Levels in Accelerometers. Fixed or Individually Tailored Cut-Points? *Sports Medicine Australia conference.*
  Presentación de poster a cargo de Erreka Gil-Rey.
  Oct 2018, Perth, Western Australia.

- Gil-Rey E, Maldonado-Martín S, Gorostiaga EM. Assessment of Absolute and Relative Intensity Physical Activity in Postmenopausal Women. *Sports Medicine Australia conference.*
  Presentación de poster a cargo de Erreka Gil-Rey.
  Oct 2018, Perth, Western Australia.

- Pablo S, Arietaleanizbeaskoa MS, Mendizabal N, et al. Linkages between Health and Community Organizations for Increasing Long-Term Adherence to Physical Exercise:

Experiences of Patients Involved in the EfiKroniK Program. *19th International Conference for Integrated Care 2019.*
Poster presentation by Susana Pablo.
Abril 2019, San-Sebastian, España.

Formación continua durante el programa de doctorado

- Curso en estadística SPSS Avanzado, R y Rcmdr. UPV/EHU. 32h. Vitoria-Gasteiz, Mayo 2013.
- Curso de Actualización en Bases del Entrenamiento. Centro de Estudios, Investigación y Medicina del Deporte. Gobierno de Navarra. 40h. Pamplona, curso 2015-2016.
- Certificado en Nutrición en Enfermedades Crónicas Asociadas al Envejecimiento. Universidad de Navarra. Facultad de Nutrición y Farmacia. 13cr. Pamplona, curso 2015-2016.
- Curso en estadística SPSS: Procedimientos Estadísticos Inferenciales de Comparación de Medias y Regresión Lineal Múltiple. UPV/EHU. 12h. Vitoria-Gasteiz, Mayo 2018.
- Curso estadística: Magnitude Based Inference: ¿Ángel o Demonio?. UPV/EHU Escuela de Máster y Doctorado. 10h. Vitoria-Gasteiz, Mayo 2018.
- AGUDEZIA 2018. Taller de emprendizaje del campus de Álava. UPV/EHU y BIC Araba. 36h. Vitoria-Gasteiz, Marzo-Junio 2018.
- Exercise for the Management of Cancer: Exercise Oncology Course. *Exercise Medicine Research Institute. Edith Cowan University*. 13 CPD points. Perth, WA, Oct 2018.

Prefacio y agradecimientos

Ya ha llovido desde que comenzó esta aventura gracias al entusiasmo trasmitido por Sara Maldonado-Martín en sus clases de Fisiología y Ejercicio Físico para la Salud durante los cinco fabulosos años vividos en la Facultad de Ciencias de la Actividad Física y del Deporte en Vitoria-Gasteiz. Esos, los del chándal, que andan correteando y saltando en las clases de vóleibol bajo los ánimos de Rafa Sagastume ("leña al mono hasta que aprenda catecismo"), han conseguido trasladar el conocimiento generado en el ámbito del entrenamiento deportivo, al ámbito sanitario, investigando los mecanismos moleculares a través de los cuáles el ejercicio físico ofrece un papel protector frente a un abanico de enfermedades crónicas causadas principalmente por la inactividad, malos hábitos dietéticos y el tabaquismo.

Con la mira puesta en el ámbito del ejercicio físico terapéutico, antes de comenzar el Máster en Investigación en Ciencias de la Actividad Física y del Deporte, surgió la oportunidad de embarcarme en el grupo GIAFyS bajo la tutela de Fernando Herrero y Koro Quevedo en Miranda de Ebro, pioneros en el Ejercicio Físico Oncológico a nivel estatal. El primer estudio de esta tesis doctoral es fruto del trabajo realizado en Miranda de Ebro, con el que quisimos guiar la práctica diaria de los clínicos y profesionales del ejercicio físico que trabajaban en los gimnasios supervisando las sesiones de ejercicio físico programadas. Tras analizar más de 150 pruebas de esfuerzo realizadas en el Gabinete de Medicina Deportiva por pacientes diagnosticados de diversos tipos y estadíos de cáncer, publicamos una guía estándar de intensidad de ejercicio adaptada a esta población para hacer ejercicio físico de una forma eficaz y segura, que fue presentada en el congreso "Europrevent" en Amsterdam (2014). Por otro lado, en otro estudio recién publicado en el *J Strength Cond Res*, analizamos la respuesta cardiovascular de 50 pacientes durante sus sesiones de ejercicio físico aeróbico y de fuerza con el fin de entender las dificultades de los propios pacientes para adherirse a las intensidades programadas. De Fernando y de Koro me quedo con la perseverancia, empatía, compasión y cercanía que transmiten en su trabajo diario, involucrando a todo el pueblo por un fin común y solidario.

"El sol, que ilumina y da calor"
"Paciencia, vas a conseguir todo lo que te propongas"

Tras recibir la tan esperada beca predoctoral y debido a ciertos contratiempos, con los conocimientos y la experiencia adquirida en Miranda de Ebro en la mochila, cambiamos de rumbo, esta vez a mi tierra natal, a Pamplona. En el Centro de Estudios, Investigación y Medicina del Deporte (CEIMD) del Gobierno de Navarra fue donde pude desarrollar mi actividad investigadora principal durante esta tesis doctoral. La gran formación como fisiólogo del ejercicio se la debo en especial a Esteban Gorostiaga, doctor en Medicina Deportiva y director del CEIMD, un apasionado e incansable Investigador que me ha trasmitido su pasión por la evaluación de la capacidad aeróbica mediante umbrales de lactato, me ha hecho reflexionar, desmontar ideas, incluso leer artículos de principios del siglo pasado para comprender el origen, la trayectoria y la interpretación de conceptos de fisiología del ejercicio y del entrenamiento. Sin duda alguna, un gran impulso de seguridad y confianza. Con la ayuda de todos los integrantes del CEIMD, y tras tropezar y aprender de las adversidades del camino, conseguimos fusionar mis inquietudes en el área de la medición de la actividad física generadas por la experiencia de Miranda de Ebro y tras la lectura en profundidad sobre el tema, con los conocimientos, experiencia y los intereses de investigación del CEIMD. Del mismo modo que se utilizaba la intensidad relativa medida a través de umbrales metabólicos o en base a la máxima capacidad cardiorrespiratoria en atletas y pacientes como referencia para guiar la programación y las sesiones de entrenamiento/ejercicio, ¿por qué a la hora de medir los niveles de actividad física mediante cuestionarios o monitores de actividad no se aplicaba este principio? Con el fin de dar una solución a este problema que abarca todo el ámbito de la epidemiología, investigación clínica, incluso el ámbito comercial y del fitness donde el uso de monitores de actividad está en auge, comenzábamos un nuevo proyecto.

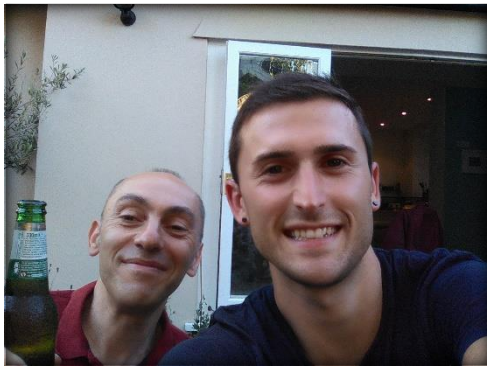
Tras año y medio de recogida de datos, perdí la cuenta del número de orejas perforadas, pero sigo recordando la felicidad de las más de 100 mujeres que participaron en este estudio y que continúan correteando por la Vuelta del Castillo tras los consejos recibidos.

Este estudio da un paso más en la medición objetiva de la actividad física mediante monitores de actividad, aplicando conceptos de fisiología del ejercicio para individualizar las diferentes categorías de intensidad en las que se desglosa la actividad registrada por el acelerómetro. Es a partir de estos valores por los cuales los estudios epidemiológicos evalúan la proporción de personas inactivas en la población de estudio, por lo que una evaluación precisa resulta trascendental para la interpretación de los resultados.

"Vísteme despacio que tengo prisa"
"To be effective, exercise has to be daily and moderate in intensity and never excessive or to exceed the half-maximum limit for exhaustion, because disease or even death can ensue" Sushruta, India (600 B.C)

Y qué decir de la experiencia de los congresos… el equipo LAKET de Sara Maldonado-Martín al completo por tierras andaluzas, con gente acogedora que desprende alegría. Mi primera exposición en inglés que se vería mejorada tras las tres estancias de investigación posteriores realizadas en el extranjero. La primera de ellas fue en la Unidad de Investigación Musculo Esquelética de la Universidad de Bristol, Reino Unido. Intrigado por su experiencia clínica e investigadora sobre el impacto de la actividad física medida a través de acelerómetros en el hueso, contactamos con el Profesor Jon Tobias, y tras un par de conversaciones por Skype, en un abrir y cerrar de ojos me encontraba en Bristol, con Jon, su mujer Isabelle y su hijo Zak con los que compartí muy buenos momentos. En ese mes y medio profundicé en la medición de la actividad física mediante acelerometría y su relación osteogénica en el proyecto VIBE.

"Exercise to be osteogenic have to exceed a minimum stress threshold, which can vary among individuals and across the lifespan. Individually tailored impact-training can be an effective strategy to prevent osteoporosis"



Recomendado por Jon Tobias, y tras finalizar la parte experimental del Proyecto del CEIMD, me mude de nuevo al Reino Unido, a Bath, una localidad encantadora a tan solo 40 minutos de Bristol por el "cycle path". De nuevo, el grupo del estudio de investigación multicéntrico REACT (REtirement in ACTion) liderado por la Doctora Afroditi Stathi me acogió con los brazos abiertos. El objetivo del ensayo clínico aleatorizado REACT era evaluar la efectividad clínica y el coste-efectividad de una intervención de ejercicio físico comunitario para reducir las limitaciones funcionales a causa de problemas de movilidad de personas mayores con alto riesgo de dependencia. Aún recuerdo esos desplazamientos en bici a Bristol con Max Western, más vale que salíamos con tiempo de Bath, ya que el compañero pinchó la rueda dos días en el mismo sitio. Aquellas sesiones de ejercicio físico a cargo de Jolanthe De Koning, donde los ancianos tomaban su cafecito entre un ejercicio y otro, o las sesiones de medición de la batería SPPB y los interminables cuestionarios que agotaban la memoria de los encantadores ancianos, que tenían que echar mano a las pastas y los racimos de uvas para poder seguir concentrados.

Durante ese tiempo aproveché también para avanzar en el análisis de datos y redacción de artículos del estudio principal del CEIMD. No podían faltar los monitores de actividad en la Universidad de Bath, por lo que indagamos en el análisis de los acelerómetros Geneactive mediante procedimientos en el programa estadístico "R". Conocí, aprendí y ayudé en diferentes proyectos de investigación en Cáncer, Ejercicio e Inmunología, en la estimación del gasto energético con diferentes marcas comerciales de monitores de actividad utilizando las famosas "Douglas Bags", e incluso me presté voluntario para un estudio de biopsias musculares, tejido graso y muestras sanguíneas, aunque después de ver el procedimiento con dos participantes se me quitaron las ganas de prestar mi muslo. Gracias al grupo de postdoc en Química, al equipo de triatlón de "Bath Amphibians" y las largas tiradas en bici de los domingos con Adrián y el club ciclista de Bath, los cinco meses trascurridos dejaron un poso de felicidad a pesar de las noches oscuras y lluviosas.

"Just coming to the session and having a nice chat with their peers, makes the exercise enjoyable"

Pero ahí no terminaba la historia, incluso antes de marchar a Bath, en uno de los cursos impartidos en la Diputación de Bizkaia sobre el ejercicio físico terapéutico en enfermedades crónicas conocí a Marisol Arietaleanizbeaskoa y a Gontzal Grandes, jefes de la Unidad de Investigación en Atención Primaria de Osakidetza. Ahí comenzó una nueva amistad y una nueva etapa investigadora ambiciosa en el ámbito sanitario. Con sus más de 10 años de experiencia en investigación en implementación en atención primaria y con diversas enfermedades crónicas y mi granito de arena como fisiólogo del ejercicio, aplicamos las técnicas y protocolos de medición de la capacidad aeróbica mediante umbrales de lactato y la actividad física con acelerómetros en el proyecto EFIKRONIK, financiado por el Ministerio de Investigación y Cultura, y el Instituto de salud Carlos III. EFIKRONIK es un estudio de investigación híbrido, un ensayo clínico aleatorizado de dos grupos paralelos en una primera fase, donde se compara el efecto común que tiene un programa de ejercicio físico de tres meses de duración, individualizado y supervisado por enfermería en una red de centros de salud de Bilbao, en la capacidad funcional, sintomatología, calidad de vida y en biomarcadores de inflamación específica en pacientes con diversas enfermedades crónicas, desde cánceres sólidos metastásicos o hematológicos, hasta pacientes con esquizofrenia. En una segunda fase, EFIKRONIK evalúa la dosis-respuesta entre la actividad realizada a los 3, 6 y 12 meses y las principales medidas de resultado, además de investigar cualitativamente el proceso de implementación, describir la percepción de los pacientes sobre el programa e identificar barreras y facilitadores para que EFIKRONIK se implemente de manera generalizada, sostenible y continuada.

No me pude resistir ante un proyecto tan tentador, así que cogí las maletas y me marché a Bilbao, donde continúo aprendiendo cada día de la piel de los pacientes y rodeado de un equipo multidisciplinar que abarca los retos que supone la implementación real de este tipo de proyectos de investigación. Todos y cada uno de los pacientes sois los que dan color y sentido a ese trayecto diario en bicicleta por la ría desde Algorta a Deusto. Ayudaros en esa lucha ante ese contratiempo, es sin duda lo más gratificante.

"Cambiar los hábitos de vida de los pacientes comienza por investigar el proceso de implementación, identificar barreras y facilitadores para una práctica sostenida y desarrollar múltiples estrategias que involucran a diferentes agestes del ámbito sanitario y comunitario"

Y para ponerle la guinda al pastel, recomendado por Marisol y Gontzal, y con el inmensurable apoyo de la UPV/EHU, cogí un largo vuelo que me llevaría a uno de los centros de investigación más conocidos a nivel mundial en cáncer y ejercicio físico, el "Exercise Medicine Research Institute, EMRI", en Perth, Australia Occidental. Entre canguros y koalas y largas playas se encontraba este centro, liderado por Robert Newton y Daniel Galvao, dos de las personas que redactan las guías de ejercicio físico para pacientes con cáncer a nivel mundial, junto a otros expertos que se reúnen en el ACSM. A través de la Investigación han conseguido implementar programas de ejercicio físico comunitarios para pacientes con cáncer con el apoyo del "Cancer Council Western Australia". Tan solo en la clínica de ejercicio físico del EMRI, reciben más de 30.000 visitas de pacientes anuales bajo la supervisión continua de un grupo compacto de fisiólogos del ejercicio físico con formación en oncología, investigadores y estudiantes universitarios. En el congreso "Sports Medicine Australia" celebrado en Perth, tuve la oportunidad de compartir ideas y presentar dos de los trabajos de la presente tesis doctoral, despidiéndome de esta etapa predoctoral.



"To promote exercise you should persuade clinicians and patients to feel what you say with the heart" Nigel Spry, Oncologist.

Este largo recorrido no hubiera sido posible sin el constante apoyo, comprensión, consejos y la educación recibida por parte de mi aita Ioxeba, mi ama Lurdes, y mi hermano Lur, así como de toda la cuadrilla de amigos de la Txantrea, compañeros y compañeras de Licenciatura, Máster y Doctorado, y como no, de personas maravillosas que han pintado de colores mi vida, Iraia y Maialen.

ABREVIACIONES

AF: Actividad Física

AFMV: Actividad Física Moderada y/o Vigorosa

CCR: Capacidad Cardiorrespiratoria

CEIMD: Centro de Estudios, Investigación y Medicina del Deporte

CO_2: Dióxido de Carbono

FC_{max}: Frecuencia Cardíaca Máxima

FC_{res}: Frecuencia Cardíaca de Reserva ($FC_{max} - FC_{reposo}$)

O_2: Oxígeno

SC: Superviviente de Cáncer

TA: Tensión Arterial

UCR: Umbral de Compensación Respiratoria

UPV/EHU: Universidad del País Vasco/Euskal Herriko Unibertsitatea

$\dot{V}CO_2$: Producción de Dióxido de Carbono

$\dot{V}O_2$: Consumo de Oxígeno

$\dot{V}O_{2pico}$: Consumo de Oxígeno Pico

$\dot{V}O_{2max}$: Consumo de Oxígeno Máximo

ABBREVIATIONS

ACSM: American College of Sports Medicine

ANOVA: Analysis of Variance

AnT: Anaerobic Threshold

BLC: Blood Lactate Concentration ($mmol \cdot L^{-1}$)

BL_RTs: Blood Lactate-Related Thresholds

BMI: Body Mass Index

CHD: Coronary Heart Disease

CI: Confidence Interval

CO_2: Carbon Dioxide

CPET: Cardiopulmonary Exercise Test

CRF: Cardiorespiratory Fitness

CRP: C-Reactive Protein

CS: Cancer Survivor

$ct \cdot min^{-1}$: Activity Counts per minute

CVT: Constant Velocity Test

CVD: Cardiovascular Disease

ECOG: Eastern Cooperative Oncology Group

EE: Energy Expenditure

ES: Effect Size (Cohen´s d)

ESSA: Exercise and Sport Science Australia

g: Gravitational Force (9.81 m/s^2 = 1g)

HR: Heart Rate

HR_{max}: Maximum Heart Rate

HR_{peak}: Peak Heart Rate

HR_{res}: Heart Rate Reserve ($HR_{max} - HR_{rest}$)

HIIT: High Intensity Interval Training

IST: Incremental Shuttle Test

ICC: Intraclass Correlation Coeficient

LE_{min}: Minimum Lactate Equivalent

LT: Lactate Threshold

LoA: Limits of Agreement

MET: rates of energy expenditure (1 MET is equivalent to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$)

MLSS: Maximal Lactate Steady State

MVPA: Moderate-to-Vigorous Physical Activity

O_2: Oxygen

RCP: Respiratory Compensation Point

RER: Respiratory Exchange Ratio = $\dot{V}CO_2/\dot{V}O_2$)

RM: Maximal Repetition (kg)

RPE: Rating of Perceived Effort

PA: Physical Activity

SEE: Standard Error of the Estimate

V: Velocity

$\dot{V}CO_2$: Carbon Dioxide Production

V_E: Ventilation

$\dot{V}O_2$: Oxigen Uptake

$\dot{V}O_{2max}$: Maximum Oxygen Uptake

$\dot{V}O_{2peak}$: Peak Oxygen Uptake

$\dot{V}O_{2res}$: Reserve Oxygen Uptake ($\dot{V}O_{2max} - \dot{V}O_{2rest}$)

VT: ventilatory Threshold

W: Power Output in Watts

WHO: World Health Organization

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Resumen

Antecedentes: La capacidad cardiorrespiratoria (CCR) y el nivel de actividad física (AF) son dos robustos predictores de la mortalidad. Las recomendaciones actuales, basadas en evidencia científica, abogan por acumular un mínimo de 150 min·sem^{-1} en actividades de intensidad moderada y/o vigorosa (AFMV), debido a la estrecha relación existente entre la dosis de AF medida a través de cuestionarios y la reducción en las tasas de mortalidad. Sin embargo, el término de "intensidad del ejercicio físico" (EF) es ambiguo. Con el fin de simplificar y agrupar las actividades físicas en relación a su intensidad, las autoridades internacionales han establecido unas categorías genéricas, basadas en equivalentes metabólicos de gasto energético (METs). No obstante, la intensidad del EF expresada en términos relativos es la que presenta una mayor asociación con el riesgo de mortalidad y proporciona beneficios en diferentes marcadores de salud.

Esta tesis doctoral Internacional que tiene entre manos se ha realizado en forma de compendio de 4 artículos científicos que abordan la temática de la intensidad del EF en dos poblaciones diferentes. El primer estudio evalúa la factibilidad de prescribir/diseñar un programa de EF en pacientes diagnosticados de diferentes tipos de cánceres en base a las guías genéricas disponibles, y ofrece una guía de prescripción de la intensidad del EF adaptada a la respuesta cardiopulmonar de pacientes y supervivientes de cáncer (SC). Los dos siguientes estudios tratan de dar solución a la utilización de categorías de intensidad de EF en términos absolutos mediante la medición de la AF con acelerómetros en un grupo de mujeres postmenopáusicas, comparándola frente a categorías de intensidades relativas, individualizadas en función de sus umbrales de lactato. El último estudio, utilizando la misma muestra que en los dos estudios anteriores, ofrece un método sencillo y preciso para estimar el máximo estadio estable de lactato, comúnmente conocido como "umbral anaeróbico", y diseñar un programa de EF individualizado, a través de un único test de ejercicio incremental y submáximo, con el fin de evitar el largo proceso necesario para una correcta determinación del máximo estado estable de lactato o para evitar las desventajas derivadas de realizar una prueba de esfuerzo cardiopulmonar hasta el agotamiento.

Capítulo 4: La diversidad de tipos de cáncer, tratamientos y los efectos adversos asociados dificultan el establecimiento de unas guías de EF apropiadas para todos los SC. La Asociación Americana en Cáncer y el Colegio Americano de Medicina del Deporte (ACSM) recomiendan

evitar la inactividad y progresar hacia la dosis de AF recomendada para la población general. Sin embargo, la reducción significativa en la CCR, en la masa y fuerza muscular, sumado a los efectos adversos de los tratamientos como fatiga, dolor o afectaciones cardiovasculares que presentan los SC, hacen de estas recomendaciones de AF todo un reto para esta población. El objetivo principal de este estudio fue adaptar las intensidades recomendadas para la población adulta a la capacidad cardiopulmonar de SC. Para ello, se recolectaron y analizaron datos de las pruebas de esfuerzo cardiopulmonares realizadas a 152 SC durante 10 años. El primer umbral ventilatorio (VT1) y el umbral de compensación respiratoria (UCR) de cada participante sirvieron de referencia para categorizar tres zonas de intensidad relativa de ejercicio; suave (< VT1), moderada (VT1-UCR), y vigorosa (>UCR), que se compararon con la clasificación de intensidad basada en términos absolutos y relativos recomendada para la población general. Tanto el consumo de oxígeno pico ($\dot{V}O_{2pico}$) (5.3 ± 1.3 METs), como la frecuencia cardíaca máxima (FC_{max}) (145 ±18 ppm) de los SC se situaron muy por debajo de los valores estimados en función de su edad. La zona de intensidad moderada se situó por debajo de las intensidades recomendadas para la población general. El rango de intensidad moderada se situó entre 2.4-4 METs en términos absolutos, y en términos relativos entre 8-14 puntos en la escala de percepción del esfuerzo de Borg (6-20), el 41-64%$\dot{V}O_{2max}$ y el 55-70%FC_{max} sobre los valores máximos estimados. Este estudio demuestra que **las recomendaciones de intensidad de EF actuales para programar una intervención de EF a la población general, pueden generar un sobreesfuerzo a personas diagnosticadas de un cáncer, debido a su reducida CCR** en relación a la estimada por las ecuaciones disponibles. Por lo tanto, se recomienda utilizar la guía de intensidad de EF propuesta y adaptada a la CCR de los SC con objeto de garantizar seguridad y proporcionar el éstimulo adecuado que provoque adaptaciones cardiopulmonares y metabólicas, aspecto de gran relevancia debido a la baja CCR de los SC, y a su estrecha asociación con la mortalidad.

Capítulos 5 & 6: Los acelerómetros proporcionan información objetiva acerca del movimiento humano y, como consecuencia, reducen el riesgo derivado de la interpretación y de la AF medida a través de cuestionarios. Sin embargo, este resultado final depende en gran medida de los puntos de corte seleccionados para demarcar las diferentes categorías de intensidad de la AF (actividad sedentaria, suave, moderada y vigorosa). Por ello, los dos siguientes estudios investigan en qué medida la selección de estos puntos de corte afecta al resultado final. Para ello, se comparó el método tradicional que utiliza puntos de corte de conteos de actividad por minuto ($ct \cdot min^{-1}$) fijos que representan la categoría de intensidad moderada en términos absolutos (3-6 METs) establecida en el Compendio Internacional de Actividades Físicas, y utilizada en estudios epidemiológicos para analizar la relación entre la

dosis de AF y la mortalidad, así como por las grandes Instituciones Internacionales como el ACSM para ofrecer unas recomendaciones basadas en evidencia científica a la población, con un método basado en intensidades relativas, a través de la medición de umbrales de lactato para determinar los ct·min^{-1} que delimitan las diferentes zonas de intensidad. Para ello, 75 mujeres postmenopáusicas se sometieron en días diferentes a un test de marcha-correr incremental y a sucesivos test a velocidad constante mientras portaban un acelerómetro triaxial en la cadera, para identificar los ct·min^{-1} asociados a los umbrales de lactato (LT1 y LT2). Por medio de regresiones lineales se establecieron las siguientes categorías de actividad: 1) sedentaria (<200 ct·min^{-1}), 2) suave (desde 200 ct·min^{-1} hasta ct·min^{-1}al LT1), 3) moderada (ct·min^{-1} entre LT1 y LT2), y 4) vigorosa (ct·min^{-1} >LT2). Posteriormente, se registró su AF semanal mediante acelerometría para comparar el tiempo trascurrido en cada categoría de intensidad en términos absolutos y relativos. Un sub-grupo de 30 participantes realizó dos pruebas de esfuerzo adicionales con medición de intercambio de gases y así comparar los ct·min^{-1} producidos en los límites asignados a la intensidad moderada tanto en términos absolutos (3-6 METs) como relativos (46-63%$\dot{V}O_{2max}$) y en relación a los umbrales de lactato submáximos (LT1-LT2). Los conteos de actividad producidos al umbral de 3 METs, (2026 ± 808 ct·min^{-1}), fueron significativamente menores que los conteos de actividad producidos a intensidades relativas, tanto al 46%$\dot{V}O_{2max}$ (p <0.01, ES: 1.95), como al LT1 (p <0.01, ES: 2.27), que se situaron a una intensidad de 4.6 ± 0.7 METs en mujeres postmenopáusicas con una CCR de 10.0 ± 4.2 METs. Los ct·min^{-1} medidos a la intensidad del LT2 (7249 ± 2499 ct·min^{-1}) (situado al 73%$\dot{V}O_{2max}$) fueron significativamente mayores que los registrados al límite superior de intensidades moderadas absolutas de 6 METs (p <0.01, ES: 0.72) y al límite de intensidades relativas de 63%$\dot{V}O_{2max}$ (p <0.01, ES: 0.55). La CCR explicó en un ~50% la amplia variabilidad en los ct·min^{-1} (CV = 30-34%) producidos en los límites de intensidad relativa. Como consecuencia, y conforme a lo esperado, al seleccionar los ct·min^{-1} individualizados, el tiempo promedio trascurrido en AFMV se redujo a la mitad (p <0.01) en comparación a los puntos de corte estándares basados en intensidades absolutas (3-6 METs). Sorprendentemente, a pesar de que las mujeres con mayor CCR estuvieron ~1 h·día^{-1} menos en actividades sedentarias (p <0.01), registraron ~3000 pasos diarios más (p <0.01) y estuvieron el doble de tiempo en AFMV en términos absolutos (p <0.01) en comparación al grupo de menor CCR, estas diferencias desaparecieron (p = 0.62) al utilizar unos puntos de corte individualizados, ya que ambos grupos estuvieron ~20 min·día^{-1} en AFMV en términos relativos. En conclusión, en este estudio se demuestra que **individualizar los puntos de corte acorde a los umbrales de lactato es una manera más precisa y significativa de medir la AF con acelerómetros, reduciendo el**

riesgo de subestimar o sobreestimar los niveles de AF y el porcentaje de personas inactivas, en comparación al método de intensidad absoluta ampliamente aceptado y utilizado.

Capítulo 7: La programación de la intensidad del EF en base a los umbrales de lactato proporciona un estímulo cardiometabólico más homogéneo entre individuos sujetos a una intervención de EF, en comparación a ejercitarse a un determinado nivel de intensidad tanto en términos absolutos (e.j. 6 METs), como en términos relativos (e.j. 70%$\dot{V}O_{2max}$). El primer incremento en la concentración de lactato durante un ejercicio incremental, denominado como "Lactate Threshold" o LT1, ha sido postulado como la mínima intensidad requerida para provocar mejoras en la CCR y en marcadores de salud en personas sedentarias. En el otro extremo, la máxima carga sostenible en el tiempo sin incrementos continuos de lactato durante un ejercicio a carga constante, conocido como máximo estado-estable de lactato, también denominado MLSS o LT2, es el indicador gold-estándar del rendimiento deportivo en deportes de resistencia, y podría reflejar el límite superior de intensidad del ejercicio en términos de seguridad cardiovascular en la población general. En la práctica diaria, estos dos umbrales de lactato (LT1 y MLSS) se utilizan para individualizar la intensidad de intervenciones de EF/entrenamiento y evaluar su efectividad. Sin embargo, la determinación del MLSS es costosa debido a que requiere realizar entre 2-5 pruebas de al menos 20min de duración a una intensidad constante en días diferentes. Para evitar dicho proceso, en este estudio tratamos de estimar el MLSS en el mismo grupo de mujeres que en los capítulos 5 y 6 a través de la determinación de variables relacionadas con la acumulación del ácido láctico y otras variables no-invasivas (frecuencia cardíaca y percepción del esfuerzo) durante un único test incremental submáximo. Los resultados de este estudio muestran que la velocidad correspondiente al MLSS puede estimarse con precisión (R^2 = 0.85, p <0.001; SEE = 0.38 km·h^{-1}) a través de una combinación de variables relacionadas con la acumulación de ácido láctico y marcadores no-invasivos durante una sola prueba incremental submáxima. Si además se realiza una prueba adicional a velocidad constante durante 20min, se puede explicar en un 90% la variación del MLSS con un error estándar de estimación estrecho (0.32 km·h^{-1}). En definitiva, **se recomienda incluir el test incremental submáximo dentro de la práctica clínica/deportiva diaria como una alternativa segura, fácil de administrar y altamente eficiente a la clásica determinación del MLSS o a pruebas de esfuerzo máximas**, al menos para el tipo de población estudiado.

Conclusiones: En la presente tesis doctoral se demuestra que, cuando realizar una prueba de esfuerzo no es factible y la programación del EF se basa en intensidades relativas respecto a los valores de $\dot{V}O_{2max}$ or FC_{max} estimados, las guías de intensidad del EF recomendadas para

la población adulta pueden provocar sobreesfuerzos en SC que presentan una CCR y una respuesta cardíaca reducida con respecto a la población sana de la misma edad. Este inconveniente se puede solventar midiendo la CCR a través de umbrales metabólicos submáximos, que también pueden ser utilizados para prescribir o diseñar una intervención EF individualizada. Este procedimiento garantiza la seguridad y la idoneidad de la dosis de EF administrada a cada paciente, maximizando los beneficios terapéuticos. En ausencia del equipamiento adecuado para ello, se ofrece una guía de intensidad de EF adaptada a SC como herramienta útil y sencilla para clínicos, profesionales del EF y para los propios pacientes, con la que monitorizar la intensidad de las sesiones de ejercicio.

Los estudios epidemiológicos deberían, al menos, ajustar la relación entre la AF y la mortalidad por la CCR de los individuos, ya que, tal y como se demuestra, es más fácil realizar mayores niveles de AF en términos absolutos para los individuos con mayor CCR, aunque no necesariamente significa que esa actividad la estén realizando a mayor intensidad relativa. Por esta razón, la reducción en el riesgo de mortalidad asociada a mayores niveles de AF probablemente esté sobreestimada debido a la mayor influencia de la CCR en la mortalidad.

En esta tesis doctoral se presenta una manera más precisa de cuantificar la AF en términos relativos, la cual podría aplicarse en futuros ensayos clínicos o incluso en consultas clínicas individuales. Su aplicación reduciría el riesgo de subestimar o sobreestimar los niveles de AF en comparación a la utilización de categorías de AF basadas en intensidades absolutas.

La medición de los umbrales de lactato a través de una prueba incremental y submáxima caminando y/o corriendo es una manera eficaz de; 1) evaluar la CCR y la efectividad de una intervención de EF, 2) Diseñar una intervención de EF por medio de categorías de intensidad relativa apropiadas, y 3) medir con mayor precisión los niveles de AF habitual a través de acelerómetros, para comprobar su adherencia a las recomendaciones actuales, modificar hábitos de vida y/o evaluar la efectividad de una intervención en el cambio en los niveles de AF, sin tener que someter a las personas a pruebas de esfuerzo hasta el agotamiento.

Palabras clave: Actividad física, intensidad relativa, umbrales de lactato, acelerómetro, supervivientes de cáncer, mujeres postmenopáusicas.

Summary

Background: Cardiorespiratory fitness (CRF) and physical activity (PA) levels are strong predictors of all-cause mortality. Current PA guidelines recommend to engage in a minimum of 150 min·wk^{-1} of moderate to vigorous physical activity (MVPA) based on the accumulated evidence from questionnaire-based reported PA levels and its association with chronic disease and mortality. However, the "exercise intensity" concept is ambiguous. While, most of epidemiological studies have categorized reported physical activities according to their energy cost in absolute rates of energy expenditure (METs), it is widely recognized that relative exercise intensity plays a major role in the association with CRF and health benefits, and avoids the underestimation or overestimation of PA levels in people differing in age or CRF, compared to absolute exercise intensity.

The present International doctoral thesis is composed of four scientific articles that address the issue of exercise intensity in two different populations. The first study of this doctoral thesis looks at whether current guidelines for exercise intensity prescription for healthy adults could be safely applied in cancer patients and survivors (CS). The next two studies try to overcome the drawbacks of using absolute exercise intensity categories to objectively measure PA with accelerometers. The last study, using the same sample as the last two studies, offers an easy-to-administer and accurate method to estimate the maximal lactate steady-state or the so-called "anaerobic threshold", and therefore, to design a tailored exercise program, using blood lactate-related thresholds (BL_RTs) from a single, submaximal incremental exercise test, as opposed to the widely used maximal cardiopulmonary testing.

Chapter 4: The large number of cancer types, treatments and related toxicities make difficult to state general guidelines that fit all CS. Whenever possible CS should avoid inactivity and progressively build the amounts and intensities of PA recommended for healthy population. However, the significant reductions in CRF, muscle mass and strength, as well as common side effects related to treatments, such as, fatigue, pain and cardiovascular impairments, could hinder the adherence to recommended PA guidelines, as well as the compliance of prescribed exercise intensities. Therefore, the purpose of this study was to adapt the general guidelines for exercise intensity prescription to the CRF of CS. Data from 152 CS who performed a maximal cardiopulmonary test (CPET) was collected during a ten-years period, and analysed thereafter. The exercise intensities corresponding to the first and second ventilatory thresholds (VT and

RCP, respectively) of each participant defined the "moderate" intensity category, which was compared to that recommended by current guidelines. Peak oxygen uptake ($\dot{V}O_{2peak}$) (5.3 ± 1.3 METs) and maximum heart rate (HR_{max}) (145 ±18 bpm) of CS were well below from the age and maximum workload-adjusted estimated values ($p < 0.01$). Thus, the "moderate intensity" category was placed at 2.4-4 METs in absolute intensity, 8-14 points of perceived effort (6-20 Borg´s scale) and at 41-64%$\dot{V}O_{2max}$ or 55-70%HR_{max} from the maximum estimated values in relative intensity. When CPET is not feasible, it is accepted to prescribe exercise intensity according to maximum estimated values. However, **due to the lower peak values of CS compared to those estimated by validated equations, CS could be overstressed when exercise is programmed according to generic guidelines**. Therefore, it is recommended using the proposed exercise intensity guideline for CS to guarantee the safety during exercise, and to induce training adaptations through adequate exercise intensity programming, which is of paramount importance due to the low CRF values of CS and its strong association with mortality.

Chapter 5 & 6: Accelerometers can objectively measure human movement and reduce the shortcomings of subjective questionnaires to report the number of individuals meeting the current recommended target of 150 min·wk^{-1} of MVPA. However, the final outcome largely depends on the selection of accelerometer activity cut-points to demarcate different PA intensity categories (i.e., sedentary, light, moderate and vigorous). Therefore, we aimed to investigate how objectively measured PA levels (i.e., time spent in each PA intensity category) using standard absolute intensity cut-points based on recommended moderate intensity targets (3-6 METs) for adults by international agencies, such as, the American College of Sports Medicine (ACSM), differed from an individualized relative intensity cut-points approach, using the gold-standard lactate thresholds to categorize PA intensity. Seventy-five postmenopausal women performed an incremental exercise test and several constant-velocity tests wearing an accelerometer to identify the activity counts (ct·min^{-1}) corresponding to the lactate thresholds (LT1 and LT2). Individual linear regression determined activity counts cut-points for each intensity: 1) sedentary (<200 ct·min^{-1}), 2) light (from 200 ct·min^{-1} to ct·min^{-1}at LT1), 3) moderate (ct·min^{-1} between LT1 and LT2) and 4) vigorous (ct·min^{-1} >LT2). Participants then wore an accelerometer during a week to measure the time spent at each PA intensity level, which was compared to previously validated cut-points from recommended moderate absolute intensity target (3-6 METs). A sub-group of 30 postmenopausal women conducted two additional submaximal and maximal CPETs to compare the activity counts cut-points for moderate intensity category in absolute rates of energy expenditure (3-6 METs), with relative intensity cut-points according to CRF (46-63% $\dot{V}O_{2max}$) and to individual lactate thresholds (LT1-LT2). The

activity counts measured at the widely used 3 METs threshold (2026 ± 808 ct·min^{-1}) were well below than its relative intensity counterparts either at 46%$\dot{V}O_{2max}$ intensity threshold (p <0.01, ES: 1.95) or at LT1 (p <0.01, ES: 2.27), which corresponded to 4.6 ± 0.7 METs in these women with CRF values of 10.0 ± 4.2 METs. The activity counts measured at LT2 (7249 ± 2499 ct·min^{-1}) were higher compared to the absolute 6-METs threshold (p <0.01, ES: 0.72) and to the relative 63% $\dot{V}O_{2max}$ intensity threshold (p <0.01, ES: 0.55). There was a large interindividual variability in the activity counts measured at relative intensity cut-points (CV = 30-34%), which was largely explained by CRF level (R^2 = ~50%). Therefore, as expected, when individualized activity cut-points were selected, recorded MVPA was reduced by half (p <0.01) in comparison to the widely used cut-points derived from absolute intensities (3-6 METs). The high-fit women were ~1 h·day^{-1} less sedentary (p <0.01), recorded ~3000 more daily steps (p <0.01), and they engaged in twice as much time (p <0.01) at absolute MVPA compared to low-fit women. However, these differences disappeared (p = 0.62) when appropriate relative intensity cut-points (LT1 and LT2) were applied to each participant, with the two groups recording ~20 min·day^{-1} of MVPA on average. In this study it was demonstrated that **individually-tailored accelerometer cut-points demarcated through lactate thresholds could reduce the risk of under- or over estimating PA levels and may provide a more representative PA profile of individuals differing in CRF, in comparison to the widely-used and accepted method of fixed absolute intensity.**

Chapter 7: Programming exercise intensity through lactate thresholds can provide a more homogenous cardiometabolic stimulus to individuals undergoing an exercise intervention, rather than exercising at a certain absolute or even relative intensity level (expressed as a %$\dot{V}O_{2max}$). The first increase in lactate concentrations during an incremental test (i.e., LT1) has been suggested as the lower boundary of moderate exercise intensity and the minimum exercise intensity to improve CRF and health. On the other hand, the highest workload that can be sustained over-time without continual blood lactate accumulation (i.e., maximal lactate steady-state or MLSS) is nowadays considered the gold-standard marker of endurance performance in athletes, and can be used as the upper boundary of moderate exercise intensity (LT2), or the highest point from a safety perspective in non-athlete population. These two lactate thresholds are used in practice to individualize the intensity of exercise interventions/training and to assess its efficacy. To avoid the extensive procedure needed to accurately measure the MLSS, we aimed to elucidate whether it could be accurately estimated from blood lactate-related thresholds (BL_RTs) and or bloodless variables (heart rate and perceived effort) measured during a single, incremental submaximal exercise test in the same group of postmenopausal women. The results of this study showed that a combination of BL_RTs

and bloodless variables from a single incremental and submaximal exercise test can accurately estimate MLSS velocity (R^2 = 0.85, p <0.001; SEE = 0.38 km·h^{-1}). The addition of a constant velocity test of 20 min carried out a few days later can still improve the estimation of the velocity associated with MLSS, explaining up to a 90% of its variation, with a lower standard error of the estimate (0.32 km·h^{-1}). **It is, therefore, recommended to include the incremental submaximal shuttle test as a simple non-exhaustive and time-efficient alternative to the classical determination of MLSS or maximal exercise tests for non-athletic population**.

Conclusions: This doctoral thesis shows that when exercise testing is not feasible and intensity prescription is based on estimated $\dot{V}O_{2max}$ or HR_{max} values, applying currently recommended absolute and relative exercise intensity targets for adults by the ACSM, could overstress CS, who present a much lower CRF and maximum cardiac response compared to healthy adults. This drawback could be solved by prescribing exercise intensity or designing/delivering exercise interventions according to submaximal physiologic breakpoints such as, ventilatory or lactate thresholds from submaximal exercise tests. This procedure guarantees the safety and the adequacy of the exercise dose administered to each patient and might maximize the therapeutic benefits. In the absence of exercise testing equipment, we offer an adapted exercise intensity guideline for CS that can guide clinicians, exercise physiologists and the patients themselves during exercise training.

Epidemiology studies should at least consider adjusting the association between PA and mortality risk by CRF, because as it has been demonstrated, it is easier for high-fit individuals engaging in higher levels of PA, but it does not necessarily mean that they are having higher relative intensities. Thus, the aforementioned association might have been inflated by the higher CRF in those reporting higher PA dose. Another, more accurate way of quantifying PA levels that suits better to small clinical trials or to one-on-one consultations, that overcomes with the risk of under-or overestimating PA when using fixed absolute intensity cut-points to define the PA intensity categories, is, to individualize this intensity cut-points according to relative intensities. Measuring the lactate thresholds through an incremental and submaximal walking exercise test is a feasible way of; 1) evaluating the CRF and assessing the efficacy of an exercise intervention, 2) Designing a tailored exercise intervention, and 3) measuring PA levels with accelerometers to provide behaviour change feedback and evaluate its efficacy, without the need to expose the individual to exhaustion.

Key words: Physical activity, relative intensity, lactate thresholds, accelerometer, cancer survivors, postmenopausal women.

1 Theoretical Framework

1.1. Dose-response relationship between physical activity, cardiorespiratory fitness and mortality

Every steps counts

Physical activity (PA) (a behavior) and cardiorespiratory fitness (CRF) (an attribute) are inversely associated with all-cause mortality rates, as well as with lower incidence and mortality from several chronic diseases, such as cardiovascular diseases (CVD) and cancers [1,2]. The findings are consistent for men and women and hold after adjustment for age, serum cholesterol level, blood pressure, smoking habit, fasting blood glucose level, family history of coronary heart disease (CHD), and length of follow-up [2]. The apparently protective effect of a more active life was first seen for occupational activity and death from CVD by the mid '50s by Morris and colleagues [3]. They demonstrated that men in physically active jobs had a lower incidence of CHD. Bus conductors (double-decker vehicles) were found to have less incidence and severity of CHD than bus drivers, and postmen less than telephonists, executive officers and clerks. In another experiment conducted by the same group, they examined the role of the physical work involved in different jobs by social classes and they concluded with that statement: "In brief, the coronary mortality of the groups doing physically heavy work is rather less than half that of light groups. More important, the disease is not so severe in physically active workers, tending to present first in them as angina pectoris and other relatively benign forms and to have a smaller early case-fatality and a lower early-mortality rate" [3].

Since then, it has been an enormous interest in quantifying the physical demand (energy expenditure by indirect calorimetry) of different tasks and jobs [4]. Brown and Crowden [5] obtained metabolic data from 381 factory and industrial workers to establish an objective

classification of work grades according to energy expenditure (EE) and nutritional requirements. The intensity of occupational work can be summarized in the following ranges; Sedentary (<1.9 metabolic equivalents of EE or METs), Light (1.9-3.3 METs), Moderate (3.4-4.7 METs), Heavy (4.8-7.1 METs), and Very Heavy (>7.1 METs) [6].

A few years later, British and German researchers started to develop and validate PA questionnaires against personal interviews to record the whole daily activity, which essentially consisted of follow-up questions relative to the intensity of effort and frequency of participation in the physical activities which the respondent had indicated in the self-administered form [7]. A decision classifying each individual into one of four PA groups (very active, active, moderate, light) on each component (occupation, leisure, and home) was made by consideration of the questionnaire and interview responses by three judges. Next, each activity was weighted relative to EE (light; 0.5-1 Kcal·min^{-1}, moderately active; 1-1.5 Kcal·min^{-1}, active; 1.5-2 Kcal·min^{-1}, and very active; 2-5 Kcal·min^{-1}) using previously reported tables [4] and was checked against previous decision, resulting in a high discrepancy between the two methods.

The study conducted on 10.269 Harvard Alumni by Paffenbarger and colleagues [8] is another classic work assessing changes in personal and lifestyle characteristics recorded in questionnaires from 1977 through 1985 and their relationship with all-cause mortality. Those individuals with an EE <2000 kcal·week^{-1}, walked less than 14 km·week^{-1} or men who did not engage in moderate-to-vigorous intensity sports activity had a 25, 16 and 44% higher risk of all-cause mortality than more active individuals, respectively. Overweighed, smokers and hypertensive people had also a 31, 87 and 69% higher risk of all-cause mortality after controlling for other factors. They also showed that favorable changes in lifestyle, such as taking up moderate-to-vigorous sports activities had a substantial reduction in mortality for all causes (23%) and from CHD (41%) compared to the most sedentary classmates, resulting in 0.72 years of life gained. This association was higher than the change to higher total EE per week. The women´s health study [9] also showed a strong inverse association between PA and CHD in a large sample of women aged 45 years or older with little activity. Women who spent 600 to 1500 Kcal·wk^{-1} were at significantly lower risk (45%) of developing CHD after adjustment for smoking status, diet, and other confounders. Particularly the energy spent in vigorous-intensity activities contributed to such benefits. However, among women who did not perform vigorous intensity activities, walking at least 1 hour per week resulted in about half the CHD risk of women who did not walk regularly. All these findings are evidence that among people with little activity, engaging in even light-to-moderate activity is associated with health

benefits. Among people who are more active and fit, however, vigorous activity is required to obtain such benefits [8,9].

Overall, large prospective cohort studies show that EE in the range of 500-1000 Kcal·wk^{-1} of moderate-intensity PA (an equivalent minimum of 150 min·wk^{-1}) is associated with ~30% lower rates of CVD and premature mortality. Compared to inactive individuals, at age 30 years, life expectancy for individuals achieving this target is 4.21 years longer for men and 3.67 years longer for women, and significant all-cause mortality reductions are evident with only 15 minutes per day of moderate intensity activities [10]. As shown in ¡Error! No se encuentra el origen de la referencia., the mortality risk appears to continue to decrease (up to 40%) with increased exposure up to five times the recommended amount of PA [8,9,11,12].

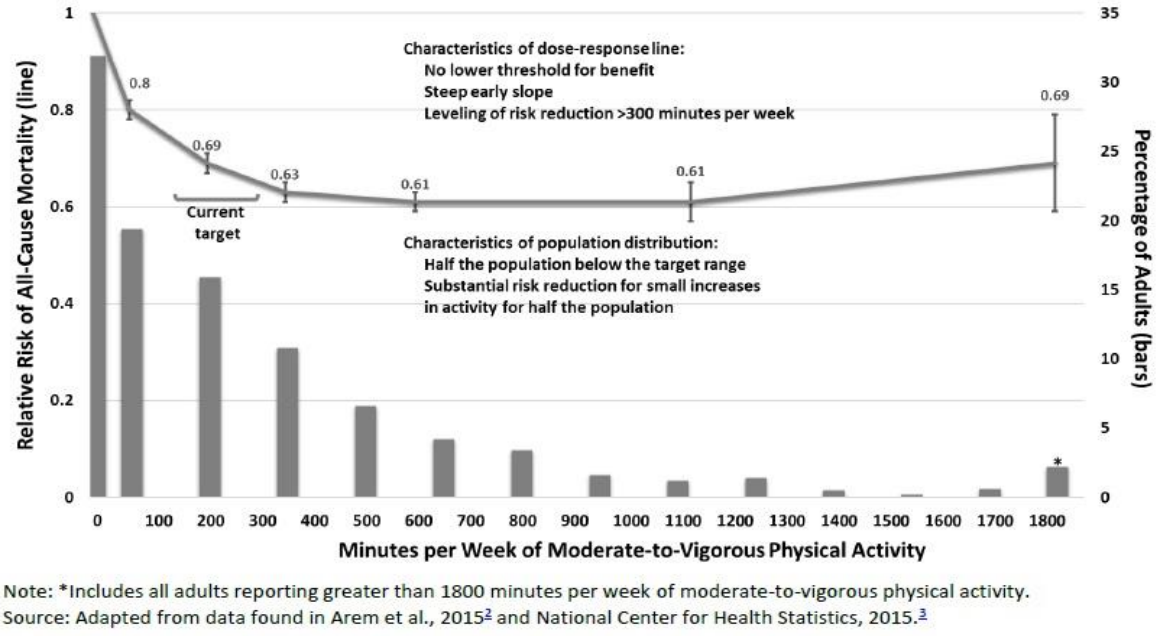

Figure 1. Risk of all-cause mortality and self-reported physical activity, by minutes of moderate-to-vigorous physical activity per week [12].

Determining the amount of PA that is adequate for maintenance of health and that is in accordance with our biological makeup is possible by analyzing the habits of traditional populations that still follow a preindustrial lifestyle. To standardize PA levels, researchers have used the so-called PA ratio (PAR), calculated as the daily total EE of an individual divided by the daily basal metabolic rate. A PAR value of 1.40–1.69 represents the inactive to lightly active lifestyle that is characteristic of Western societies, whereas values of 1.70–1.99 and ≥2.00 represent moderately active and vigorously active lifestyles, respectively. Among hunter-gatherers, the Hadza people of Tanzania, who show an absence of CVD risk factors, have an average PAR of 1.78 in women and 2.26 in men. Moreover, Hadza people spend on average

950min each week performing moderate-to-vigorous physical activity (MVPA), which is approximately sixfold greater than the minimum 150min per week recommended for adults by the World Health Organization (WHO). A high PAR is also characteristic of forager–horticulturalist, pastoralist, and traditional farming populations. The Tsimané people of Bolivia, who still follow a forager–horticulturalist lifestyle and have a low incidence of coronary atherosclerosis and a near-absence of CVD risk factors, have a PAR of 2.02–2.15 in men and 1.73–1.85 in women. Moreover, the estimated PAR is 1.70 in non-Westernized horticulturalists from Kitava, Papua New Guinea, who reportedly have a very low incidence of stroke, ischaemic heart disease, diabetes mellitus, and metabolic syndrome. These examples illustrate that a very active lifestyle that is well above the minimum WHO recommendations has been a normal characteristic throughout human evolution. Nonetheless, technological improvements over the past ~350 generations (that is, during the agricultural, industrial, and, most recently, digital revolutions) have led to substantial decreases in human PA levels. Indeed, physical inactivity is now the fourth leading cause of death worldwide. Approximately one-third of adults worldwide (~50% of adults in the United States) do not meet the minimum WHO recommendations for MVPA; the trend towards inactivity starts in adolescence (age 13–15 years), leading to a suboptimal cardiovascular phenotype and an increased risk of cardiometabolic disorders [13]. Inactivity has been estimated to be comparable to smoking one packet of cigarettes a day, it is responsible for 12% of the deaths in the United States, and it is estimated to be the main cause for approximately 21-25% of breast and colon cancers, 27% of diabetes and approximately 30% of ischemic heart disease worldwide [14].

In contrast, higher levels of PA, and regular moderate-to-vigorous exercise induces myriad physiological adaptations that benefit human health either directly or indirectly. Many of these benefits seem to be independent of traditional CVD risk factors, blood lipid and glucose levels, obesity, and high blood pressure and cholesterol levels. Skeletal muscle is an endocrine organ that can produce and release myokines into the bloodstream (particularly during muscle contraction in a dose-dependent manner), where they function locally and/or systematically to elicit myriad beneficial effects, including decreased inflammation and insulin resistance [13,15] Of particular relevance to older adults and postmenopausal women, exercise preserves bone mass and reduces the risk of falling [16,17]. Prevention of and improvement in mild to moderate depressive disorders and anxiety can occur with exercise [18]. A physically active lifestyle enhances feelings of ''energy'', well-being, quality of life, and cognitive function and is associated with a lower risk of cognitive decline and dementia [19]. Vigorous-intensity exercise is associated with even greater reductions of CVD and all-cause mortality, as well as with greater adaptations in CRF, blood pressure, lipid profile, oxidative stress and inflammation,

insulin sensitivity and cardiac function compared with moderate-intensity activity of similar energy expended [15,19,20].

A higher level of cardiorespiratory fitness protects against death

The most widely accepted index of CRF is maximum oxygen uptake ($\dot{V}O_{2max}$), expressed in ml $O_2 \cdot kg^{-1} \cdot min^{-1}$or in metabolic equivalents of EE (1 MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) [2]. The minimum level of CRF that is associated with significantly lower event rates for men and women is approximately 9 and 7 METs (at 40 years old), 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively (corresponding to the ability of continuous walking speed of 6.4 $km \cdot h^{-1}$ and 4.8 $km \cdot h^{-1}$ for men and women around 50 years of age, respectively) [1]. Epidemiology studies show that 1 MET higher level of CRF (corresponding to 1 $km \cdot h^{-1}$ higher running/jogging speed) is associated with 13% and 15% decrements in all-cause mortality and cardiovascular disease risk, and is comparable to the risk reduction associated to a 7 cm, 5 mmHg, 1 $mmol \cdot l^{-1}$ and 1 $mmol \cdot l^{-1}$ decrement in waist circumference, systolic blood pressure, triglyceride level and fasting plasma glucose, respectively [1,21,22]. A meta-analysis conducted by Williams [23] reported higher potential to reduce the risk of developing CVD in favour of CRF compared to the amount of PA. Although PA increases CRF and may be an appropriate therapy mostly for the unfit, only 35% of the variance in CRF is explained by PA, probably because of the low correlation of CRF with the amounts of light or moderate intensity activity. The reductions in relative risk are nearly twice as great for CRF than PA. Individuals below the 25th percentile of the fitness distribution are at substantially higher risk than those at higher percentiles.

Although $\dot{V}O_{2max}$ testing has become the gold standard method for measuring CRF in healthy adults and in people with chronic diseases, it requires to perform a maximal stress test, which is very often not posible nor advisable in middle-aged people due to motivational, safety or financial reasons [22]. Failure of participants to reach maximal exertion would result in $\dot{V}O_{2max}$ or maximum heart rate (HR_{max}) being underestimated. It is common to apply certain checks to evaluate wheter the measurement was trully maximal. For example criteria such as respiratory exchange ratio (RER) >1.1 or 1.15, a "plateau" in $\dot{V}O_{2max}$ with an increased workload, an absolute heart rate >85% of the predicted HR_{max}, and blood lactate concentration (BLC) >8 $mmol \cdot L^{-1}$ are often used to verify a true $\dot{V}O_{2max}$ [24]. CRF is usually determined by a maximal incremental treadmill or cycling test with slow increments in work-rate and/or grade (in treadmill) until individual's volitional fatigue. The test protocol should be individualized according to the characteristics and experience of the individual to achieve exercise durations of 8 to 12 minutes. For a non-athlete population, the use of smaller, more frequent increments in work-rate is preferable to larger, less frequent increases, both physiologically and

psychologically. For cycle ergometry, the initial power output is usually 10 or 25W, followed by increases of 25W every 2 or 3 minutes until end points are reached. Ramp protocols that increase in small steps have many advantages, including a more accurate estimate of submaximal MET level and $\dot{V}O_{2max}$, in contrast to the more widely used stepwise Bruce protocol, which requires more gait changes that can hinder a true $\dot{V}O_{2max}$ achievement as a consequence of a premature neuromuscular fatigue or discomfort, or inability to tolerate the high workload increments [22]. However, in the types of protocols that the work-rate increase continuously or in short increments, complete steady states are not reached [22,24]. Hence, the exercise training prescription based on an incremental protocol by setting workload or HR targets should be taken with caution when exercising for longer periods at constant work-rates. A given $\dot{V}O_{2max}$ or $\%HR_{max}$ value would thus be reached at a lower workload during constant work-rate exercise due to an increased oxygen uptake ($\dot{V}O_2$) slow component above the first ventilatory (VT1) or lactate threshold (LT1), where the abrupt accumulation of metabolites occurs, leading to an accelerated fatigue.

Key points

- An EE of 500-1000 Kcal·wk^{-1} of moderate-intensity PA (an equivalent minimum of 150 min·wk^{-1}) is associated with ~30% lower risk of all-cause mortality and is even lower in more active individuals (up to 5 times recommended levels).
- Vigorous intensity PA is associated with even greater reductions in health biomarkers, CVD and all-cause mortality.
- 1 MET higher level of CRF is associated with 13% and 15% decrements in all-cause mortality and cardiovascular disease risk. The minimum CRF level associated with lower event rates for middle age (~50 years) men is ~8METs and ~6METs for women.

Research Gaps

- The associations established between the dose of PA and all-cause mortality is derived from questionnaires. Accurate measurement of PA is, therefore, essential to evaluate its effects with health biomarkers and all-cause mortality.
- Performing a "true" maximal exercise test to measure and prescribe exercise based on $\dot{V}O_{2max}$ or HR_{max} values is problematic, not free of risks, costly and within the reach of very few people. Alternatively, the measurement of submaximal lactate thresholds is a single, cost-effective and accurate method to evaluate CRF and to design individually tailored exercise programs.

1.2. Physical activity guidelines for adults. Is exercise intensity the key?

In the past, exercise recommendations were based on scientific studies that investigated dose-response improvements in performance capacity after exercise training and they usually involved 20 to 60 min of moderate-to-high intensity endurance exercise (60-90%HR_{max}) performed three or more times per week [25]. The classification of exercise intensity and its standardization for exercise prescription based on a 20- to-60-min training session has been confusing, misinterpreted, and often taken out of context. The origin of these exercise classification systems [6,25] was based on EE values of industrial tasks for an 8-h workday. The classification of industrial and leisure-time tasks by using absolute values of EE has been valuable for use in the occupational and nutritional setting, but it has no meaning to extrapolate these values for preventive and rehabilitation exercise training programs unless adapted for age and regimens lasting up to 60 min. In 1993 and in the following updates Ainsworth et al. [26] collected EE data of multiple daily occupational, recreational, transportation and home activities for use in epidemiologic studies to standardize the assignment of MET intensities in PA questionnaires.

Given the low prevalence of adults performing the above-mentioned target and the high prevalence of sedentary behaviour, the following recommendations of the Centers for Disease Control and Prevention and the American College of Sports Medicine (ACSM) [27] by the 90ties extended the traditional exercise-fitness model to a broader PA-health paradigm and claimed that every adult should accumulate about 30 minutes (enough to expend approximately 200 Kcal·day^{-1}) of moderate intensity activities (definition of light, moderate and vigorous activities is displayed on **Table 1**) on most, preferably all days of the week. This is equivalent of activities of absolute EE of 3-6 METs (for people weighting ~68-91 kg) and ~7.5-10 MET·h·wk^{-1} [19].

Table 1. Examples of common physical activities for healthy US adults by intensity off effort required in MET scores and Kilocalories per minute.

Light (<3 METs or < 4 kcal·min^{-1})	**Moderate** (3-6 METs or 4-7 kcal·min^{-1})	**Hard/Vigorous** (>6 METs or < 7 kcal·min^{-1})
Walking, slowly (strolling) (1.6-3.2 km·h^{-1})	Walking, briskly (strolling) (4.8-6.4 km·h^{-1})	Walking, briskly uphill or with a load
Cycling, stationary (<50W)	Cycling for pleasure or transportation (≤16 km·h^{-1})	Cycling, fast or racing (≥16 km·h^{-1})
Swimming, slow treading	Swimming, moderate effort	Swimming, fast treading or crawl
Conditioning exercise, light stretching	Conditioning exercise, general calisthenics	Conditioning exercise, stair ergometer, ski machine
…	Racket sports, table tennis	Racket sports, singles tennis, racketball
Golf, power cart	Golf, pulling cart or carrying clubs	…
Bowling	…	…
Fishing, sitting	Fishing, standing/casting	Fishing in stream
Boating, power	Canoeing, leisurely (3.2-6.4 km·h^{-1})	Canoeing, rapidly (≥6.4 km·h^{-1})
Home care, carpet sweeping	Home care, general cleaning	Moving furniture
Mowing lawn, riding mower	Mowing lawn, power mower	Mowing lawn, hand mower
Home repair, carpentry	Home repair, painting	…

*Adapted from [27]. The METs (work metabolic rate/resting metabolic rate) are multiples of the resting rate of oxygen consumption during physical activity. One MET represents the approximate rate of oxygen consumption of a seated adult at rest, or about 3.5 ml·kg^{-1}·min^{-1}. The equivalent energy cost of 1 MET in kilocalories·min^{-1} is about 1.2 for a 70-kg person, or approximately 1 kcal·kg^{-1}·hr^{-1}.

However, the energy cost of PA from compendium-derived values do not account for individual differences in body mass, age, sex, adiposity, the efficiency of movement, or geographic and environmental conditions in which the activities are performed. Besides, people differing in CRF respond in markedly different ways to an exercise challenge (i.e., relative intensity). For example, **Figure 2** shows why one must use caution when interpreting an absolute intensity of exercise being "moderate" when it is applied to individuals differing in CRF. On average, $\dot{V}O_{2max}$ decreases with age, and is lower in women, compared to men, across age. Therefore, the 3.8 MET activity identified in **Figure 2** represents a range of relative intensities of 32-76%$\dot{V}O_{2max}$ for different fitness groups.

Therefore, for individual exercise prescription, a relative measure of intensity (i.e., relative to the individual's maximal capacity) is more appropriate, especially for older and deconditioned persons. The minimum training intensity threshold for improvement of $\dot{V}O_{2max}$ and the lactate threshold is aproximately 40-50%$\dot{V}O_2$ reserve (i.e., the difference between the $\dot{V}O_{2max}$ and the $\dot{V}O_2$ at rest, also known as $\dot{V}O_2R$) or an equivalent of 55-65% of the maximum heart rate (HR_{max}), although it is greatly influenced by initial CRF level. The person who has a

very low level of fitness can achieve a significant effect with a training heart rate (HR) as low as ~55%HR_{max}, whereas people with higher fitness levels require a higher training stimulus [25]. Exercising at the appropriate intensity is especially important for the improvement of CRF and plays a significant role to control the altered lipidic and hormonal profile, insuline sensitivity and inflamatory biomarkers, as well as for the prevention of sarcopenia and osteoporosis associated with ageing, particularly in post-menopausal women [28-31].

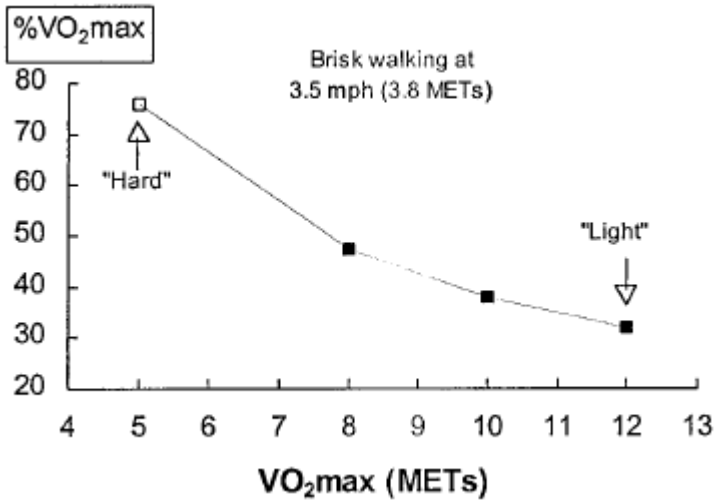

Figure 2. Changes in the relative intensity of exercise (%VO_{2max}) when the same absolute intensity of exercise is performed by groups differing in VO_{2max} [34].

In fact, a large-scale surveillance study showed that relative intensity (the level of exertion perceived when individuals exercise on their usual fashion) presented a stronger association with CHD rates in healthy men compared to the energy expended on all physical activities or to the absolute intensity of sports and recreational activities. Compared to men rating their exercise as "weak" or less intense (0 to 2 on the Borg scale), those rating their relative intensity as "moderate" (3 on the Borg scale), "somewhat strong" (4 on the Borg scale), and "strong" or more intense (≥5 on the Borg scale) had 19%, 38%, and 40% lower CHD rates, respectively. Of note, the inverse association between relative intensity of exercise and CHD risk persisted among men who did not satisfy current recommendations for PA [32]. This study goes hand in hand with the results obtained in another large British study [33], where walking at self-rated average or brisk/fast pace was associated with a 24% reduction in all-cause mortality after adjusting for total duration of MVPA and light-intensity PA. The authors suggest that this association may be explained by the increased relative exercise intensity elicited by a faster pace providing a greater stimulus for physiologic adaptations in functions known to influence CVD mortality. Walking is a cornerstone of PA promotion for public health, but volume of

walking (steps per day) has often been emphasized. Given the perceived time barrier cited by those who fail to meet current PA guidelines, a pace change may be more feasible than the increased volume of walking [33].

As a reference international agency in the science behind PA, the ACSM develops evidence-based position stands and guidelines in the use of physical exercise for the development of cardiorespiratory, musculoskeletal and neuromotor fitness in healthy adults [19]. These exercise intensity classifications are based in $\%\dot{V}O_2R$ and %HRR as a reference for the other expressions of exercise intensity ($\%HR_{max}$ is based on $\dot{V}O_{2max}$ values of the 10-MET fitness group), and absolute MET values for groups differning in $\dot{V}O_{2max}$. Direct measurements of HR and $\dot{V}O_2$ are recommended for individualized exercise prescription for greater accuracy, but when it is not feasible, estimation of exercise intensity is acceptable. In brief, "moderate" intensity is defined as 40-59%$\dot{V}O_2R$ or HRR, 46-63%$\dot{V}O_{2max}$, 64-76%HR_{max}, 3-6 METs, or an equivalent walking pace of 4.8-6.4 $km \cdot h^{-1}$ (brisk walking). Recommended PA target by public guidelines [19,35] is to engage in MVPA for ≥30 $min \cdot day^{-1}$ on ≥5 $d \cdot wk^{-1}$ for a total of ≥150 $min \cdot wk^{-1}$. On 2-3 $d \cdot wk^{-1}$ adults should also perform muscle strengthening exercises.

However, PA recommendations and exercise intensity classifications from position stands of the ACSM [19,25,35], the American Heart Association [22,36] or the European Heart Association [24], as well as reports of the U.S. Department of Health and Human Services [12] have been continuously updating, leading to confusion among exercise professionals to prescribe exercise intensity in healthy adults and people with chronic diseases. **Figure 3** shows how the usual intensity target for adults, ie., moderate intensity, can range from 50% to 65% HR_{max} at the lower boundary and from 70 to 80% at the upper boundary depending on the reference used.

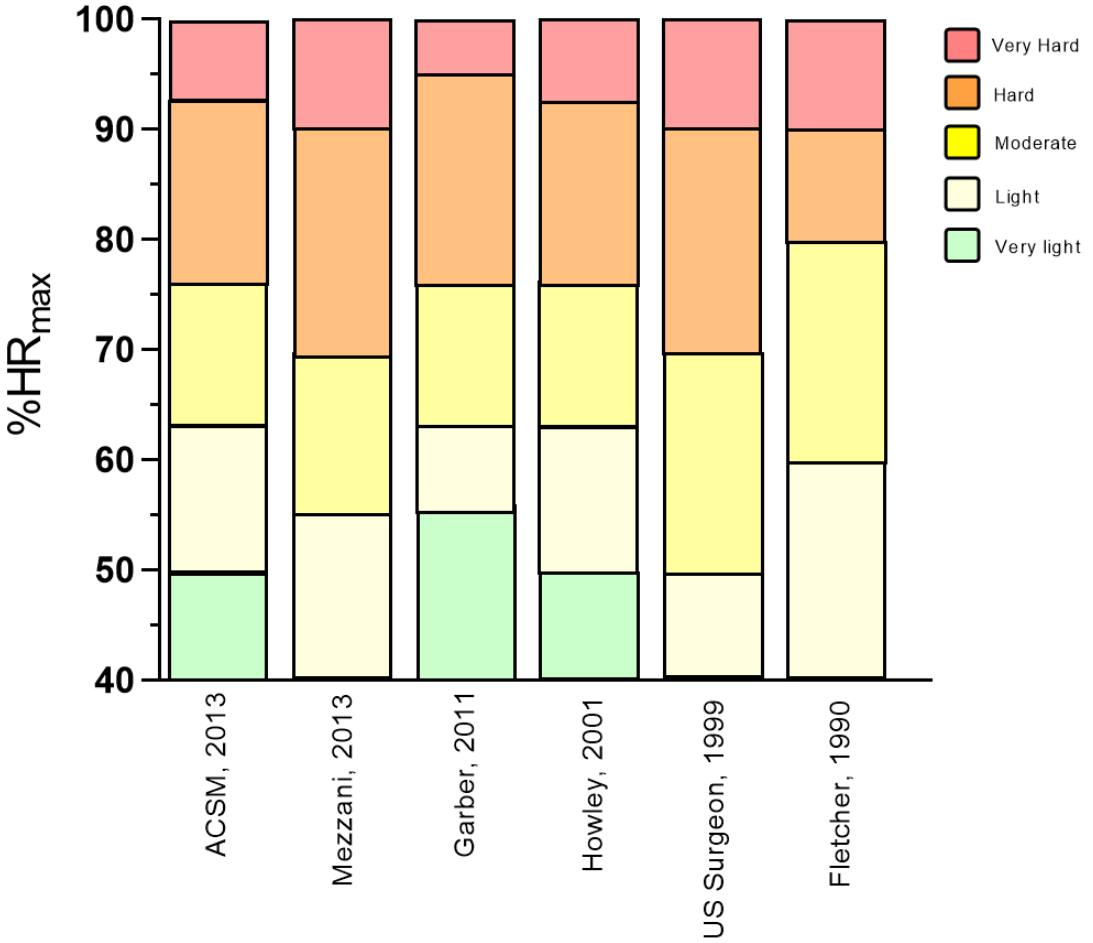

Figure 3. A representative summary of exercise intensity categories defined by different position stands.

More than half of the population has at least 1 chronic condition. What are the physical activity guidelines for people with chronic diseases?

Reports from the WHO manifest that CVD and cancers are the leading causes of death worldwide, accounting for 17.7 and 8.8 million deaths in 2014, respectively [37]. Unfortunately the incidence of chronic diseases increases with advancing age and unhealthy lifestyles. Accordingly, more than 80% of older adults (>65 years) in the Basque Country suffer from a minimum of one chronic disease, and more than 65% suffers from two or more chronic conditions, generating up to 70% of public health costs [38].

Evidence for prescribing exercise as a therapy in chronic diseases is gaining. It is acknowledged that exercise has a role as medicine in at least 26 diseases, from psychiatric diseases to cancers or CVD [39]. The secretion of muscle-derived peptides and myokines through muscle contraction during exercise favors muscle hypertrophy, adipose tissue oxidation, insulin sensitivity, osteogenesis, anti-inflammation, antitumor defense, improves pancreas and endothelial function and revascularization of ischemic vessels [28]. The evidence suggests that in selected cases exercise therapy is just as effective as medical treatment and in special situations more effective or adds to its effect. The accumulative knowledge is now so extensive that it has to be implemented.

While extensive research has postulated exercise to be safe and effective in cardiac patients, leading to specific guidelines for exercise prescription [24] and cardiac rehabilitation programs as part of the standard care of cardiac patients, little has been advanced in terms of exercise implementation in oncology. Early post-hospitalization exercise training in cardiac patients usually involves a minimum of 20-30 minutes per session, three to four days per week [24]. Aerobic exercise training intensities as low as 40% $\dot{V}O_{2peak}$ have proven to be effective in cardiac patients with reduced exercise capacity and thus, light to moderate intensity training (up to the first ventilatory or lactate threshold) is possibly the most indicated for hemodynamically decompensated patients, those at high exercise-related risk, and those in need for weight loss. During the last years, high-intensity interval training (HIIT) (85-95%HR_{peak}) has gained popularity, since its significantly greater cardiovascular effects when compared with isocaloric moderate to high-intensity continuous training, both in coronary artery disease and CHD patients. High-intensity interval training also favors the improvement of endothelial function, reduction in atherosclerosis, better calcium regulation and left ventricular systolic and diastolic properties, and greater $\dot{V}O_{2peak}$ improvements [24].

Cancer is one of the diseases that causes major public health problems in Spain. The probability of developing any type of cancer in Spain during the lifetime is of 50% in men and 30% in women [40]. The Basque Country is the autonomous community that records the highest incidence rates in men (550 per 100.000 European age-adjusted rates) and the second in women (287 per 100.000) [40]. Currently increasing incidence rates and decreasing mortality rates due to advances in earlier detection and treatments have translated to a higher number of people living with cancer (i.e., cancer survivors or CS). This leads to increased costs of cancer care and a growing burden on health care systems in terms of medical management, cancer surveillance and supportive care.

Both, the disease itself and the treatments lead to an increase in psychosocial distress, depression and to an impaired cognitive function, increased levels of pain and fatigue. Consequently, CS experience a decrease in their quality of life (QoL) and a greater risk of developing comorbidities. Cancer patients have lower CRF and strength levels [41] as a consequence of several factors; 1) direct results of cancer such as anaemia, resulting in a decreased oxygen carrying capacity of the blood, 2) cardiac and pulmonary limitations caused by systematic therapy, 3) a reduction of PA after cancer diagnosis, 4) loss of muscle and bone mass as a consequence of accelerated thermogenesis and catabolic state [42]. The oxygen uptake at the first lactate/ventilatory threshold in CS and people diagnosed with many other similar chronic diseases is really low, indicating that any light stimulus could induce a relatively high metabolic effort. Therefore, the first lactate/ventilatory threshold can be considered a valid indicator of the functional capacity of CS. Besides, it is closely associated with the intensities of daily activities (walking, gardening, climbing stairs, household activities…) which are closely associated with QoL [43].

It has been estimated that approximately one-third of cancer deaths are related to obesity, lack of PA and poor nutrition, and therefore may have been prevented [44]. A growing body of evidence has demonstrated that CS who achieve a minimum of 150 min·wk^{-1} of MVPA recommended by the ACSM [45] and the Australian Association for Exercise and Sport Science [46] have ~27-50% lower cancer deaths and recurrences [47-51]. Unfortunately, only ~4-20% of CS meet international PA guidelines according to objectively measured PA with accelerometers and they show a high sedentary behavior (~7-9.5 h·day^{-1}) [52-55].

Current evidence from experimental studies indicates that exercise reduces tumour growth and cancer-specific mortality, in a dose-dependent manner. Moderate to high-intensity endurance exercise (at intensities associated with increases in catecholamine levels) is superior to light exercise when aiming to target tumour intrinsic factors [56]. During exercise, the release of several systemic factors (i.e., catecholamines, myokines, etc.), sympathetic activation, increased blood flow, shear stress, and increased temperature exert immediate stress on tumour metabolism and homeostasis. Following long-term training, these acute effects lead to a reduction of a systemic inflammation and oxidative stress, hormone-receptor and circulating factors modulation adaptations (i.e., insulin, growth factors, sex-steroid hormones etc.), intratumoral adaptations of improved blood perfusion, enhanced immunogenicity, and gene expression, and metabolism adjustments, which contribute to slower tumour progression and can reduce the ability of cancer cells to form tumours in distant tissues [56-59]. Thus, cancer patients should not just exercise because it improves their overall health, but exercise training

should be implemented in standard healthcare systems as a targeted approach in order to regulate cancer progression and formation, ameliorate cancer-associated adverse events and improve anti-cancer treatment efficacy [56].

The ACSM [45] generally recommends to avoid inactivity, returning to normal daily activities as quickly as possible after surgery, and to continue normal daily activities and exercise as much as possible during and after non-surgical treatments. Recommendations for aerobic and resistance/strength exercise training are the same as PA guidelines for the general population [19], with several alterations for patients with and at risk of lymphedema, and care about fracture risk among some cancer populations (e.g., those treated with hormone therapies, diagnosed osteoporosis or bony metastases) and infection risk among those who are immune-compromised because of treatment (e.g., care is needed to avoid the spread of infection through the use of equipment at public gyms). Exercise tolerance of patients currently undergoing treatment and immediately after treatment may vary from exercise session-to-session. Patients who have received hematopoietic stem cell transplantation should exercise at the lighter intensity and lower progression to avoid overtraining given the immune effects of vigorous exercise. Resistance training might be more important than aerobic exercise in bone marrow transplant patients. If peripheral neuropathy is present, a stationary bike might be preferable over weight bearing exercise. Morbidly obese patients would require additional supervision and altered programming. In addition, several contraindications for exercise are identified, including arm and shoulder problems secondary to breast cancer treatment, having an ostomy after colon cancer, or swelling or inflammation in the abdomen, groin, or lower extremity following gynecologic cancer.

The Exercise and Sport Science Australia (ESSA) published a position statement in 2009 [46] indicating that the optimal exercise prescription for CS remains unknown, and may depend on the type of cancer, treatments, and characteristics of the patient. It was recommended to avoid certain types of aerobic or strength exercises (e.g., high impact activities) during periods of increased risk of infection, ataxia, dizziness, peripheral sensory neuropathy, low platelet counts, bone pain, or in patients with primary or metastatic bone cancer. The ESSA highlights that exercise programs need to be flexible, particularly during periods of cancer treatment. Programs need to be adjusted according to changes in treatment, the presence of side effects, functional and physical status of the patient, and presence of contraindications and clinical concerns. At least 3-5 times per week of 20-30 minutes of moderate intensity aerobic exercise is recommended (50-75%$\dot{V}O_{2max}$ or 60-80%HR_{max}, or an RPE of 11-14). Daily exercise at a shorter duration and lower intensity may be preferable for deconditioned patients. Guidance

for strength training is to perform dynamic resistance exercises (6-10 involving the largest muscle groups), 1-3 times/week at intensities ranging from 50 to 80%1RM, along with exercises that replicate daily tasks causing problems for patients (e.g., getting up from a chair, breast cancer patients finding hanging clothes on the line troublesome). Resistance exercise is particularly important for CS experiencing loss of muscle mass (sarcopenia or cachexia) during and following treatment [48,60]. This type of training is associated with a 33% lower risk of all-cause mortality after adjusting for potential confounders, including PA [61].

Definitely, exercise prescription in this population should be considered a vital adjuvant therapy aimed at maintaining or improving structure and function, alleviating symptoms, and assisting the recovery of survivors or slowing the decline of palliative patients. Current PA guidelines for CS are generic and more research is needed to develop specific exercise prescription guidelines (e.g., mode, frequency, intensity, duration), for a given cancer site at a particular phase of cancer trajectory, disease impact and treatment side effects [48].

Key points

- Current PA guidelines for adults recommend to engage in MVPA for ≥30 min·day^{-1} on ≥5 d·wk^{-1} for a total of ≥150 min·wk^{-1}, and 2-3 d·wk^{-1} of muscle strengthening exercises.
- There are high discrepancies in the classification of exercise intensity categories by different expert panels and position stands, leading to confusion with regards to exercise intensity terminology.
- Cancer is one of the chronic diseases that causes major public burden is Spain. Exercise training has a therapeutic role in the disease, improves physical function and QoL of patients, reduces the secondary effects associated with cancer treatments and extends their survival. However, most CS are inactive.

Research Gaps

- There is a high prevalence of CS worldwide, who could decrease their cancer progression and improve their physical function, QoL and survival engaging in recommended amounts of PA. However, unlike with cardiac patients, there is not uniformity in the optimal exercise type, frequency, duration and intensity to be prescribed, and this exercise dose should be likely adapted to each type of cancer, stage, treatments and adverse effects, and participant's characteristics.
- An exercise intensity classification based on individual metabolic thresholds could overcome with the over- or underestimation of exercise intensity prescribed to each patient, and thus; 1) ensure that a sufficient therapeutic dose is provided, and 2) avoid an overdose of exercise given the immune effects of vigorous exercise.

1.3. Individualization of exercise intensity categories through lactate thresholds

A criticism to the use of $\%\dot{V}O_{2max}$ or $\%HR_{max}$ for exercise intensity prescription is that this methods fail to account for differences in metabolic stress between individuals [24,62,63]. Authors highlighting this discrepancy have advocated the use of metabolic thresholds as preferable "anchors" for relative exercise intensity prescription. For example, Katch and colleagues showed that at an intensity corresponding to $80\%HR_{max}$ (~$62\%\dot{V}O_{2max}$) half of the athletes were training below their anaerobic threshold (AnT), but the other half were training at higher intensities than their AnT [62] (**Figure 4**). Dwyer and Bybee observed that for an intensity between 58 and $75\%\dot{V}O_{2max}$, some of their participants were below, and others above their AnT. Conversely, Meyer and colleagues [63] showed that the workload associated with $75\%\dot{V}O_{2max}$ corresponded to 86-118% of the individual AnT and blood lactate concentrations (BLC) of 1.4-4.6 $mmol \cdot l^{-1}$ in different individuals following an incremental exercise test. In contrast, exercise intensity prescribed relative to metabolic thresholds would be expected to produce less individual variation in metabolic responses and less individual variation in time to exhaustion at constant exercise intensity, providing a more homogenous training stimulus than training prescribed as a given $\%\dot{V}O_{2max}$ or $\%HR_{max}$ [64].

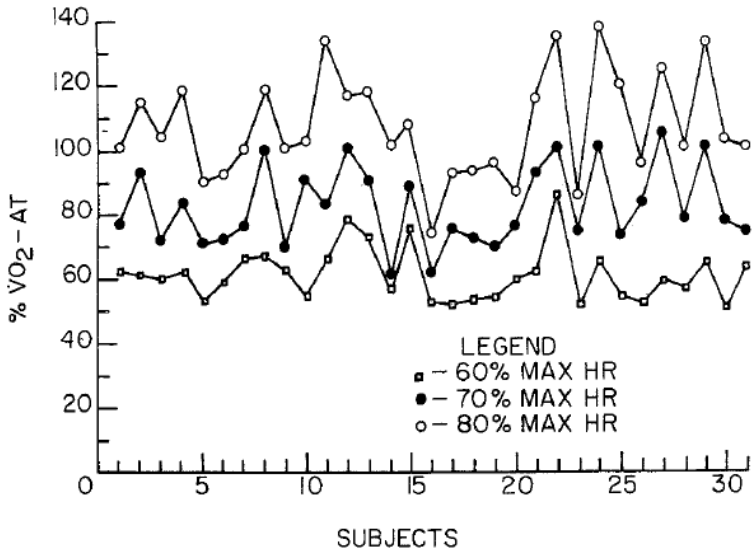

Figure 4. Plot of individual subject´s percent of anaerobic threshold (AT) at the different percent HR_{max}. On the left axis is labeled the corresponding oxygen uptake for the respective percent AT [62].

Besides, the European Heart association [24] acknowledges that beyond the first lactate/ventilatory threshold, a given relative exercise intensity expressed either as $\%\dot{V}O_{2max}$ or as $\%HR_{max}$ measured during an incremental exercise protocol would result in an EE higher than expected when performing a constant-work-rate exercise. In other words, for a given $\dot{V}O_2$ value, the workloads are not the same when performing incremental versus constant work-rate exercise. Consequently, when prescribing constant workload training (i.e, 10 min cycing at 100W) based on incremental exercise data, it is necessary to reduce the work-rate prescription.

An easier, safer, non-dependent on motivation and widely accepted approach to evaluate CRF is, therefore, the analysis of variables related to the accumulation of blood lactate concentration (BLC) plotted against exercise intensity or duration during submaximal exercise. It has been recognized since early independent experiments published in the 1920s that lactate increases in blood from resting values only above a certain exercise level or threshold [65,66]. When the oxygen supply is inadequate to meet the oxygen requirement of the contracting muscles, it increases anaerobic glycolysis for energy generation, converting pyruvate to lactate. This mechanism helps to sustain the total energy needed when O_2 transport to the metabolically active muscles becomes inadequate to meet the total oxidative requirement for energy generation [67].

The physiologic breakpoint representing the first abrupt rise in BLC above resting levels during incremental exercise (**Figure 5**) was proposed by Hollmann and thereafter by Wasserman and Mcllroy by the 1960ties as an exercise intensity that provided a substantial, yet safe, amount of physical stress for patients suffering from CVD, and was considered a valid indicator of exercise capacity in cardiac patients [68,69]. In these patients, this first lactate threshold (LT1) might be evident at less than twice the resting metabolic rate, whereas in sedentary healthy subjects this threshold might be surpassed at about four times the resting metabolic rate. In trained individuals, the LT1 may not be observed until the subject exercises to a level that is 10 to 20 times the resting metabolic rate (see differences between participant A, B, and C on **Figure 5**). The first exponential increase in BLC (i.e., LT1) has been suggested as the minimum exercise intensity required by inactive individuals to improve CRF [70-72], and presents a high association with $\dot{V}O_{2max}$ and sport performance [72-75].

Due to the time-consuming and invasive procedures related to blood lactate measurements in the mid 50ties, non-invasive methods that relied on respiratory gas exchange measurements were introduced for physiological detection of this threshold [76]. These methods are supported by the concomitant increase in H^+ above the intensity of LT1, which is buffered by bicarbonate (HCO_3^-) resulting in increased production in CO_2 and to a steeper increase in

ventilation (V_E), whereas the increase of $\dot{V}O_2$ remains linear with increasing workload. Although there is a high correlation between gas-measurements and blood lactate methods for the detection of this threshold, they do not always occur together [68]. The beginning of arterial or venous lactate increase is the standard against which indirect methods must be evaluated [77].

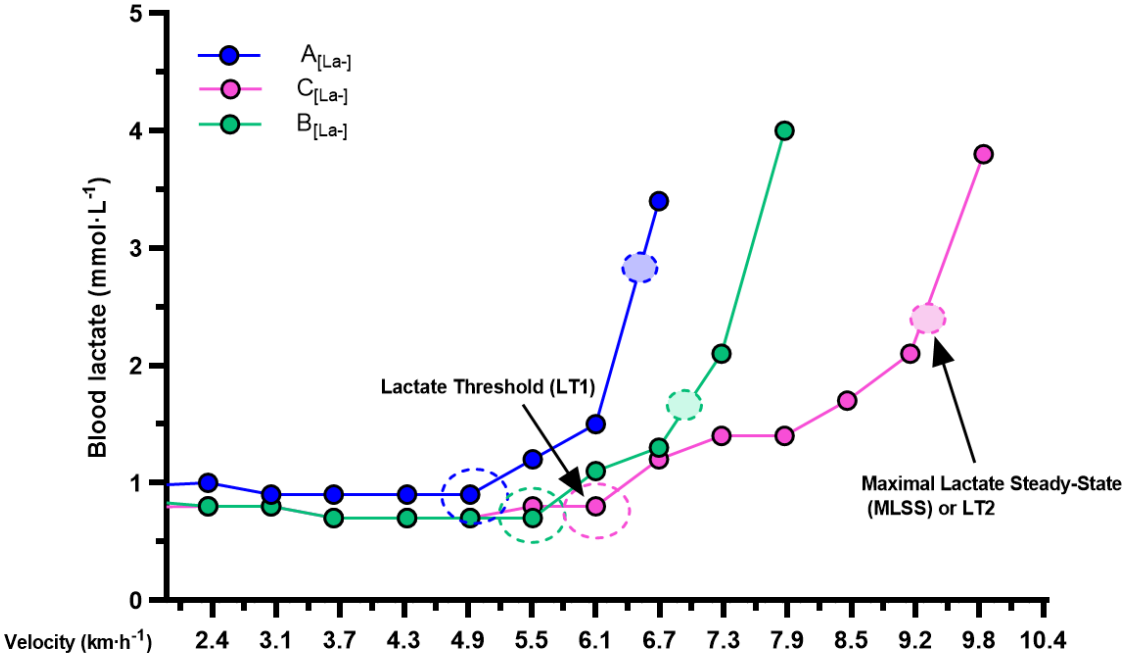

Figure 5. Lactate-workload plot during incremental exercise in three different representative participants of the current study.

With increasing exercise intensity above LT1 during constant workload exercise, the lactate production rate is higher than the metabolizing capacity of the cell, and intensities only slightly above LT1 result in elevated but constant BLC (an equilibrium between BLC appearance and elimination) during steady-state exercise that can be maintained for prolonged periods of time. The highest constant workload which can be maintained over time without a systematic increase in BLC is called the "maximal lactate steady-state" (MLSS) and reflects the gold standard for the determination of the second (i.e., LT2) or the so-called "anaerobic threshold" [68,74,78,79]. With further increase in the workload above the MLSS, the muscular lactate production rate exceeds the systemic elimination rate. This leads to an exponential increase in BLC and catecholamine levels [80] during incremental exercise and to non-steady increase (>0.05 $mmol \cdot l^{-1} \cdot min^{-1}$) of BLC during constant work-rate exercise [74] (**Figure 6**). A further nonlinear increase in $\dot{V}CO_2$, and more pronounced in V_E, is observed.

These blood markers are closely related to metabolic activity in the muscle through significant correlations with muscle capillarization (r = 0.59-0.77), percentage of slow twitch fibers (r = 0.74-0.77), oxidative capacity (r = 0.94), and muscle enzyme activity (r = 0.54-0.68) and it is not surprising that blood lactate markers have been shown to explain more variation in sport performance than $\dot{V}O_{2max}$ (r = 0.51-0.83 vs 0.61-0.91) [75].

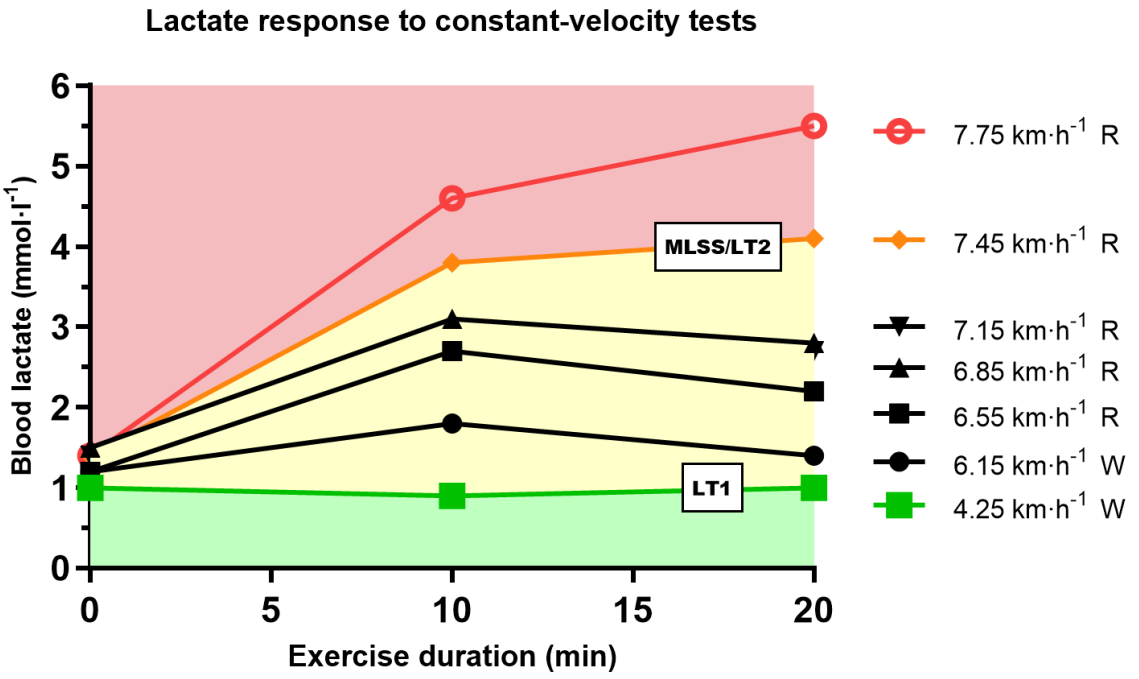

Figure 6. Blood lactate response to several constant walking (W) and running (R) velocities in one representative participant included in this study. The highest velocity with steady-state blood lactate concentration as a function of time (an increase <0.5mmol·l^{-1} during the last 10min of the trial) is defined as the maximal lactate steady-state (MLSS) [74,75].

In the 1960s, the enzymatic method for measuring BLC from capillary blood samples was developed. This led to the increasing popularity of using blood lactate as a parameter to assess endurance capacity as well as for exercise intensity prescription. In the following years, numerous blood lactate-related thresholds (BL_RTs) concepts were developed, leading to considerable confusion and misinterpretation [64,75], but the aforementioned two physiologic breakpoints of energy supply are considered the gold standard lactate thresholds. The intensity range between LT1 and LT2 is called the aerobic-anaerobic transition and clearly demarcates three intensity levels according to energy supply: light (<LT1), moderate (LT1-LT2) and vigorous (>LT2) [68,75], allowing an accurate prescription of exercise intensity for endurance training, as well as an objective evaluation of training adaptations [81-83].

While LT1 can be determined in a single graded submaximal test, the assessment of MLSS is, however, cumbersome since it requires several (3-6) constant workload tests on separate days, lengthening aerobic conditioning evaluation to a minimum of 1-3 week period [84]. To avoid such an extensive procedure, simpler methods have been proposed to estimate MLSS intensity from a single incremental test, involving the use of either blood lactate [71,74,75,85-88] respiratory [67,89] or the maximum workload achieved during an exercise test to exhaustion [72,90], showing a wide range of correlations (r = 0.63-0.95) with MLSS. However, all existing single session MLSS-estimating tests are variably handicapped by compromised validity, accuracy, resolution and reliability due to methodological differences and a suboptimal statistical approach (i.e. correlation analysis) leading to incomparable and inconclusive results [75,77,85,91]. Most of these studies have been conducted in small groups of athletes using exercise tests to volitional fatigue, but little is known about the prediction of MLSS from BL_RTs using submaximal tests in adults. This might reduce the premature fatigue, dyspnea and symptoms of discomfort associated with maximal exercise testing in sedentary adults, as well as the economic cost associated with it [22]. From a practical and statistical point of view, it would be of interest to know the variability of individual differences between respective BL_RTs and the MLSS, which is rarely reported [75]. Low individual differences between BL_RTs and MLSS in large heterogeneous samples would guarantee an accurate estimation of MLSS intensity from a single exercise test and its usefulness for individualized exercise intensity prescription [78].

Key points

- Exercising at the same relative intensity (i.e., $\%\dot{V}O_{2max}$ or $\%HR_{max}$) produces a large variability in the metabolic stress among individuals.
- The first exponential increase in BLC during an incremental exercise (ie., lactate threshold or LT1), and the highest work-load sustained over time with steady-state BLC during continuous exercise (i.e, MLSS or LT2) are the two gold-standard physiologic thresholds to demarcate individualized exercise intensity categories.
- The determination of MLSS is handicapped due to the extensive exercise testing required. Simpler single-session MLSS-estimating exercise protocols have been proposed, involving either, the use of blood lactate, ventilatory thresholds, or the maximum workload or time attained at exhaustion.

Research Gaps

- Most studies aiming to estimate MLSS intensity from single exercise tests have been conducted in small groups of athletes. Besides, they do not reflect accurately the individual responses on this association. More research in the non-athlete population is needed to implement simple and accurate exercise tests for a proper exercise intensity prescription.
- Compared to relative intensity categories defined by PA authorities (e.g., ACSM), exercise intensities corresponding to the gold-standard lactate thresholds are not well studied.

1.4. Measurement of Physical Activity. From questionnaires to activity monitors.

How do activity monitors work? Principles and data processing

Physical activity has been studied for the purposes of understating the basic characteristics of human movement and its association with chronic diseases and mortality. The accurate and detailed measurement is, therefore, a crucial prerequisite. In an attempt to overcome the shortcomings of subjective reports and questionnaires, portable PA monitors gained popularity since their initial designs by the 1970s as modified wristwatches that showed an accumulated count of movements [92]. In the following years, different kind of activity monitors were developed with integrated circuitry and memory to provide internal control and timing as well as off-line data retrieval. In the beginning, these activity monitors were used to study rest/activity cycles and other behavioral variables of soldiers involved in sustained operations and other conditions that adversely affect sleep and performance, as well as to evaluate hyperactivity and related disorders in children [93]. These devices use one or multiple piezoelectric accelerometers that measure body movements in terms of acceleration (both amplitude and frequency), which can then be used to estimate the intensity of PA over time. A piezoelectric acceleration sensor consists of a piezoelectric element and a seismic mass, housed in an enclosure (**Figure 7**).

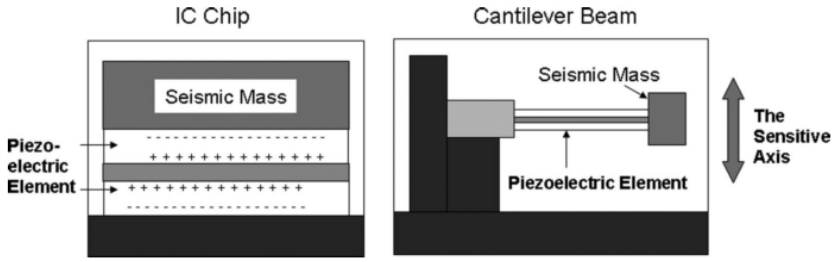

Figure 7. Schematic of the two common piezoelectric accelerometer configurations.

When the sensor undergoes acceleration (change in speed with respect to time; 1 g = gravitational acceleration or 9.8 $m \cdot s^{-1}$), the seismic mass causes the piezoelectric element to experience deformation in the form of bending or direct tension or compression. These conformational changes cause displaced charge to build up on one side of the sensor, which can generate a variable output voltage signal that is proportional to the applied acceleration. This signal which is recorded in different frequencies is filtered to overcome with non-human

movement. Most of human PA is below the frequency of 5 Hz, although the accelerations during certain vigorous movements such as running (< 8 Hz) or specific movements of the arms can be as high as 25 Hz [93,94]. The limits of the band pass filter are also determined by the type of movement the device is intending to capture and is generally in the range of 0.1-10g. This voltage signal, after being filtered and amplified, is then sampled at a prefixed frequency by the device to convert the analog voltage signal to a digital series of numbers (raw accelerations). These accelerations can then be simplified applying different analytical approaches to report the final output for a selected time window (epoch) (**Figure 8**). The most commonly applied method is to use the area under the curve algorithm (integration or average) above a certain acceleration threshold, which favours movements in low frequencies in contrast to peak counting that favours the higher frequency component (counting the number of times per epoch that the signal level exceeds and then recedes below the reference threshold. The final output can be further incremented in proportion to the magnitude of displacement from baseline reference). This final output is known as "activity counts" which are summed for each given time window or epoch (**Figure 8**). The advantages of using integrated signals include the simplicity for general understanding, the ease of processing for both hardware and software needs, and statistical robustness (integrated algorithm). However, the use of such processing techniques to extract PA measurements has significant limitations. First, the integration process diminishes the details of the signals within each time window. The common duration for such time windows, at least in adults, is 1 min. However, it should be recognized that the time period over which accelerometer counts are averaged (termed an epoch) can affect the interpretation of data. Choosing a short epoch yields a higher resolution of bout durations, which may be important if PA is accumulated in multiple short bouts. On the other hand, a disadvantage of short epochs is that the EE associated with 10- to 30-s epochs has little physiological value. Choosing a longer epoch has the normal data-smoothing advantage of time averaging. The main drawback is that if a long epoch contains a mixture of two activities of different intensity, then the data will be averaged to reflect an intermediate intensity. If the bout of a higher intensity PA within a particular epoch is shorter than the width of the epoch, the averaged PA count for the epoch will be lower than the actual PA intensity. This can lead to misclassifying higher intensity PA, which is usually intermittent, into moderate or light categories [94].

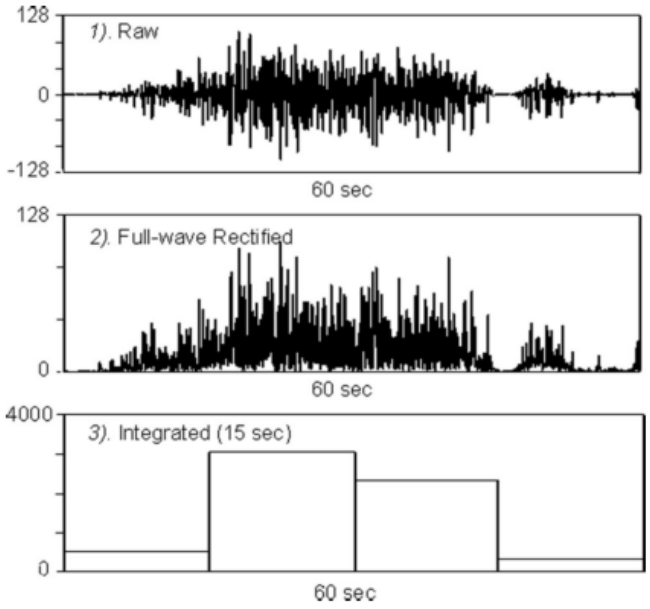

Figure 8. Analytical processing of the acceleration data. 1. Raw: a 60-s window of a digitized raw signal collected at 32Hz and using a 8-bit A/D conversion. 2. Rectification: all negative signal from (1) was tuned into positive. 3. Integration in 15-s epochs [94].

From early steps to the present

Since the early works of Montoye and colleagues validating uniaxial accelerometers against movement counters to measure daily EE [95], its use rapidly spread in behavioural and epidemiology studies replacing PA questionnaires to objectively measure PA behaviour and adherence to recommended PA targets [96]. Montoye and colleagues [95] used one of the first portable accelerometers to measure human movement integrating and summing the absolute values of acceleration-deceleration curves during different daily activities and found that the two activity monitors (i.e., the accelerometer and the mercury switch activity monitor) underestimated EE of either graded walking or running activities and static exercise, or when the body mass is partially supported, as in cycling or rowing. In the following years numerous accelerometers with higher storage capacity and advanced software features (e.g., Caltrac, Actical, CSA, Actigraph, Geneactive…), worn either, on the hip or on the wrist, were developed. Melanson and Freedson [97] tested the accuracy of both the Caltrac and the Computer Sceince and Applications (CSA) with estimates (r) of EE ranging from 0.66 to 0.82 from single-location accelerometers. The best model included body mass and a combination of activity counts from different locations (hip, wrist, and ankle) and explained 92% of the variance in EE, and predicted mean EE to within 1%, but had relatively large standard error of the estimate (SEE) of 0.85

kcal·min^{-1} (11.4%). A few years later Freedson, Melanson and Sirard [98] using the same uniaxial accelerometer model on the hip were the first authors defining activity counts cut-points for adults that corresponded to different activity intensity levels operationally defined as light (<3METs), moderate (3-6 METs), hard/vigorous (6-9 METs) and very hard/vigorous (>9 METs) categories. Fifty young adults (25 males and 25 females) performed 6 min on different exercise conditions on a motorized treadmill wearing the accelerometer on the right hip (slow walking at 4.8 km·h^{-1}, fast walking at 6.4 km·h^{-1} and jogging at 9.7 km·h^{-1} ranging from 3.7 to 9.7 METs) while oxygen consumption was recorded. They used linear regression analysis (R^2 = 0.82, SEE = 1.12 METs) to establish count ranges corresponding to previously mentioned MET-level categories (e.g. 1952-5724 ct·min^{-1} for moderate intensity) and to estimate EE.

Crouter, Churilla and Basset Jr [99] compared one of the most widely used accelerometers that was being utilized in the US National Health and Examination Survey, the Actigraph model 7164 (formerly known as CSA), to the Actical counterpart to estimate EE from previously validated equations. In general, they showed that EE estimating equations through activity counts work quite well for walking and running activities, but underestimated lifestyle activities from not accounting for the additional EE of arm activity, uphill walking, stair climbing, lifting and carrying objects. Regarding the classification accuracy in light, moderate and vigorous intensity activities, several equations gave close estimates of time spent in moderate PA, but failed to give close estimates of light and vigorous PA [99].

Accurate measurement of PA is essential in evaluating the efficacy of interventions and understanding the relationship between PA and health. During the last years, accelerometers have replaced PA questionnaires to capture objective human activity, and different techniques have developed to summarize population-level PA patterns and the prevalence of individuals meeting PA guidelines [100]. Currently, on the one hand, novel machine-learned algorithms are applied to the raw acceleration data to predict specific behaviors (PA type) and EE estimation models from acceleration and HR data (e.g., sitting, standing, walking, running and lifestyle activities), rather than measuring intensity levels [101]. On the other hand, epidemiology studies interested in the adherence of certain populations to recommended amounts of MVPA use standard or population-specific intensity cut-points.

Categorization of physical activity intensity levels with accelerometers

Both, the traditional count-based Actigraph approach [98,102,103] and the new method analysing data in "R software" called "GGIR" [104] use raw vector magnitude (a combination of three axis or VM_3) accelerations to quantify the time spent in different PA intensity levels applying accelerometer cut-points derived from the traditional absolute intensity recommendations for moderate intensity (3–6 METs) activities. The use of a wide range of activity types (treadmill walking, running and overground activities) and intensities in these studies has produced a great deal of variation in the resulting prediction equations and cut points (**Table 2**), even when using the same monitor [99,105,106]. For example, Gorman and colleagues [107] identified eight Actigraph uniaxial accelerometer cut-points used for classifying MVPA in adults. This wide range of cut-points resulted in a correspondingly large range in minutes of MVPA (4 to 80 min·day^{-1}). Ideally, individualized cut-points would allow the most accurate assessment of an individual´s activity level and reduce the risk of overestimating or underestimating PA.

Table 2. Description of existing Actigraph prediction equations and cut points [106].

	Source Activities				Prediction Equation					Cut Points		
Reference	Sit Rest	Walk	Run	Mixed Dynamic-Static	Units	Intercept	Slope	R^2	SEE	Inactive/ Light	Moderate	Vigorous
Freedson (11) N = 50; men/women (avg ~24 yr)		2	1		METs	1.439	0.000795	0.82	1.12	0–1951	1952	5725
Nichols (28) N = 30; men/women (18–35 yr)		2	1		METs[a]	1.731	0.0007271	0.89	1.06	0–1576[b]	3285[b]	5677[b]
Yngve (42)		2	1		METs	0.751	0.0008198	0.86	1.10	0–2742	2743	6403
N = 28; men/women (avg ~23 yr) (see equation code below)[c]					METs	1.136	0.0008249	0.85	1.14	0–2259	2260	5896
					METs	1.004	0.0007587	0.89	0.96	0–2630	2631	6585
					METs	1.762	0.0007371	0.86	1.09	0–1679	1680	5750
Brage (7)		2	2		METs[a,d]	2.886	0.0007429	0.89	0.91	0–1809	1810	5850
N = 12; men (23–30 yr)							−0.02 ($\dot{V}O_2$)					
Hendelman (14)		4			METs	1.602	0.000638	0.59	0.87	0–2190	2191	6893
N = 25; men/women (30–50 yr)		4		6	METs	2.922	0.000409	0.35	0.96	0–190	191	7526
Swartz (34)		4		24	METs	2.606	0.0006863	0.32	1.16	0–573	574	4945
N ~10/activity; men/ women (19–74 yr)												
Leenders (18)		5			METs	2.240	0.0006	0.74	0.53	0–1266	1267	6252
N = 28, men/women (avg ~24 yr)												

Inactive/light (1.0–2.9 METs); moderate (3.0–6.0 METs); vigorous (≥ 6.1 METs).
[a] METs calculated from original units by dividing by 3.5 mL·kg^{-1}·min^{-1}.
[b] Intensity definitions employed by Nichols; light (2.0–3.9 METs); moderate (4.0–6.9 METs); vigorous (≥ 7.0 METs); cut points are from field-based study.
[c] Yngve equation code: a. Hip – track; b. Hip – treadmill; c. Back – track; d. Back – treadmill.
[d] Brage cut points estimated using this equation and the mean fitness level of participants in study (61.6 mL·kg^{-1}·min^{-1}).

As such, with increasing age or decreasing CRF, an activity at a given absolute intensity (MET) requires a greater percentage of relative intensity [19,108] and thus, using the absolute

intensity approach may not be the most accurate option for assessing PA outcomes in samples varying in age or CRF [109,110]. If the cut-points are too high when evaluating accelerometry data, then participants will not be credited for engaging in MVPA even when being adherent to their prescriptions; conversely, using cut-points that are too low would falsely elevate levels of MVPA [111]. In an attempt to individualize intensity cut-points relative to $\dot{V}O_{2max}$ (45-60%), both Miller et al. [109] and Ozemek et al. [110] reported large interindividual variability in the activity counts at these cut-points. CRF level ($\dot{V}O_{2max)}$ explained 26% and 32% of the variability in activity counts at these thresholds. However, less than 1% of the variability in activity counts was explained by individuals´ age and BMI [110]. These results indicated that younger and most fit individuals had higher activity counts at relative intensity cut-points (4573-6786 cpm in the vertical axis) compared to older individuals (2847-5376cpm in the vertical axis). This suggest that the standard 3-6 METs absolute intensity approach will underestimate PA intensity particularly for older and less fit groups, while overestimating PA intensity in younger and most fit groups.

Large epidemiology studies using self-reported PA questionnaires [11] have commonly grouped recreational PA into three intensity categories according to their energy requirements, supported by evidence-informed guideline recommendations [12,19,26,27,35,112]: light (<3 metabolic equivalents [MET]), moderate (3-6 METs, or an equivalent of brisk walking at 4.8-6.4 $km \cdot h^{-1}$) and vigorous (>6 METs). Contrary to self-reported estimates, results of accelerometer-based objective assessments of PA report much lower volumes of MVPA [11,113] indicating that only a small proportion of adults (7-15%) meet current PA recommendations [113-116]. Reported objective weekly volumes of MVPA are significantly lower in women and vary from as low as seven $min \cdot day^{-1}$ to 57 $min \cdot day^{-1}$ [113-116]. However, interestingly, Kujala and colleagues (2017) using HR-based PA assessment reported that although the time spent at MVPA applying fixed absolute intensity cut-points was higher in men compared to women, and decreased with age, when intensity levels were calculated relative to individual´s CRF, these differences disappeared.

The inactivity, along with the lower CRF observed in women [6] and the increased risk of CVD [117] and osteoporosis [16,118] after menopause and with advancing age requiere well-designed and adequately powered PA programs.

Key points

- Accelerometer-based PA quantification shows that a small proportion of adults (7-15%) meet current PA recommendations, and women are less physically active.
- All existing accelerometer activity cut-points used to classify PA in different intensity categories are derived from the widely used absolute intensity (METs) ranges (i.e., 3-6 METs for moderate intensity activities).
- Activity counts measured at moderate relative intensity recommendations (relative to $\dot{V}O_{2max}$) show high variability among participants. CRF is the strongest predictor of activity counts at these relative intensity thresholds. Thus, individualizing accelerometer activity counts relative to CRF might overcome with the under or overestimation of the time spent in different PA categories in people varying in CRF.

Research Gaps

- It is unknown whether accelerometer activity cut-points based on relative intensities differ from the widely used fixed absolute intensity cut-points on the time spent in different PA intensity categories.
- Although absolute intensity MVPA is higher in men and decreases with advancing age, does still follow the same tendency when activity counts cut-points are individualized relative to CRF values?

2 Objectives and Hypothesis

ESTUDIO 1

Exercise intensity guidelines for cancer survivors: a comparison with reference values

Objetivos

1. Evaluar los parámetros cardiorespiratorios (pico y umbrales submáximos) de pacientes diagnosticados de un cáncer para establecer una guía de prescripción de intensidad del ejercicio físico adaptada a esta población, que permita la comparación con las guías estándares actuales.

Hipótesis

1. Se espera que los pacientes con cáncer presenten una capacidad cardiorrespiratoria un ~30% menor que la población sana, y por lo tanto las guías de clasificación de intensidad para la población sana no se ajustarán a las características fisiológicas de estos pacientes.

ESTUDIO 2

Individualized accelerometer activity cut-points for the measurement of relative physical activity intensity levels

Objetivos

1. Comparar los conteos de actividad de acelerometría derivados de los 3 y 6 METs que delimitan la categoría de intensidad moderada en términos absolutos, recomendados de forma habitual, con los conteos de actividad medidos en base a la capacidad cardiorrespiratoria en términos relativos (46-63%$\dot{V}O_{2max}$) y en los umbrales de lactato individuales (LT1 y LT2).

Hipótesis

1. Se espera que los conteos de actividad medidos en el límite inferior de la categoría de intensidad moderada (3 METs) establecida por las guías de actividad física de referencia sean un ~45% menores que los medidos al límite inferior de intensidades relativas o LT1.

ESTUDIO 3

Objectively measured absolute and relative physical activity intensity levels in postmenopausal women

Objetivos

1. Comparar los niveles de actividad física medidos con acelerómetros entre el método existente basado en umbrales de conteos de actividad fijos a intensidades absolutas (3-6 METs), y un método que individualiza los umbrales de conteos de actividad en base a los umbrales de lactato (LT1 y LT2).
2. Verificar si mujeres postmenopáusicas con mayor capacidad cardiorrespiratoria presentan mayores niveles de actividad física tanto en términos absolutos (3-6 METs) como en relativos (LT1-LT2) que aquellas con una capacidad cardiorrespiratoria menor.

Hipótesis

1. Se prevé que las mujeres con mayor capacidad cardiorrespiratoria presenten un nivel de conteos de actividad en torno a un 25% mayor al LT1 y se incremente al LT2.
2. Las mujeres con mayor capacidad cardiorrespiratoria presentarán mayores niveles de actividad física tanto en términos absolutos como en términos relativos.

ESTUDIO 4

Estimation of the maximal lactate steady state in postmenopausal women

Objetivos

1. Estimar la velocidad del máximo estado estable de lactato (LT2) desde variables no invasivas y/o umbrales de lactato a través de un solo test incremental submáximo, y verificar si hacer una prueba submáxima adicional a velocidad constante puede mejorar la estimación del máximo estado estable de lactato.

Hipótesis

1. Los umbrales de lactato extraídos de las curvas individuales (lactato-velocidad) de un solo test progresivo incremental serán las variables individuales que estimen el máximo estado estable de lactato con mayor precisión. El añadir una prueba adicional a velocidad constante mejorará la estimación.

3 Methods

3.1. Design of the doctoral dissertation

La presente tesis doctoral engloba cuatro estudios observacionales llevados a cabo entre los años 2013 y 2017 en dos centros de medicina deportiva de dos localidades diferentes. El primero de ellos se llevó a cabo en el Gabinete de Medicina Deportiva del Ayuntamiento de Miranda de Ebro (Burgos) en 2013, bajo la tutela del Dr. Fernando Herrero Román. Los tres restantes se realizaron en Pamplona, en el Centro de Estudios, Investigación y Medicina del Deporte (CEIMD) del Gobierno de Navarra desde el 2015 hasta el 2017, bajo la tutela del Dr. Esteban Gorostiaga Ayestarán. Todo ello coordinado y supervisado por la Dra. Sara Maldonado Martín, profesora agregada de la Facultad de Educación y Deporte-Sección Ciencias de la Actividad Física y del Deporte (Vitoria-Gasteiz) de la Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU).

- **1st STUDY: Exercise intensity guidelines for cancer survivors: a comparison with reference values**

Este estudio recoge la información de las pruebas de esfuerzo iniciales de 152 pacientes/supervivientes (78% mujeres y 34% hombres) con diversos tipos de cáncer (SC) (57% cáncer de mama), asintomáticos para realizar sus actividades habituales de la vida diaria (escala ECOG 0) y con bajos niveles de actividad física (AF) (≤90 minutos de AF moderada a la semana) que acudieron por primera vez al Gabinete de Medicina del Deporte del Ayuntamiento de Miranda de Ebro (Burgos) tras recibir el consentimiento de su oncólogo del hospital Santiago Apóstol de Miranda de Ebro (32.7 ± 42.7 meses post-diagnóstico). El protocolo del estudio ha sido aprobado por el Comité Ético de Investigación Clínica de Burgos y Soria.

Esta prueba de esfuerzo inicial se realizó con el objetivo de evaluar la capacidad cardiorespiratoria (CCR) inicial del paciente y su evolución, así como de diseñar un programa

de ejercicio físico (EF) individualizado a partir de los datos obtenidos en dicha prueba. La **Figure 9** representa esquemáticamente el proceso metodológico del estudio.

- **2nd, 3rd, and 4th STUDIES:**
  - **(2) Individualized accelerometer activity cut-points for the measurement of relative physical activity intensity levels**
  - **(3) Objectively measured absolute and relative physical activity intensity levels in postmenopausal women**
  - **(4) Estimation of the maximal lactate steady state in postmenopausal women**

Estos estudios responden a diferentes preguntas dentro del mismo proyecto de investigación que aborda la problemática de la prescripción-diseño de la intensidad del EF y la medición de la AF mediante acelerómetros desde un enfoque individualizado (**Figure 10**).

Las participantes del estudio fueron reclutadas a través de anuncios y gracias a la colaboración de enfermeras y médicos de atención primaria de tres centros de salud situados en los alrededores del CEIMD. Para poder participar en el estudio debían cumplir los siguientes criterios de inclusión; 1) edad entre 50 y 75 años, 2) encontrarse en periodo post-menopausia (al menos 12 meses sin periodo menstrual). Aquellas con limitaciones funcionales, cardiovasculares y/o músculo esqueléticas que pudieran ser agravadas durante la evaluación por medio de un test de ejercicio incremental, o no fueran capaces de caminar durante 20 minutos seguidos (duración de la prueba a velocidad constante) fueron excluidas del estudio.

Un total de 104 mujeres expresaron su interés en participar en el estudio, de las cuales 12 no cumplían los criterios de elegibilidad y dos no aceptaron participar. De las 88 participantes elegibles, 13 quedaron excluidas del análisis de datos debido a inhabilidad, dolor musculoesquelético o molestias al correr (n = 6), detección imprecisa del segundo umbral de lactato (LT2) (n = 3), registro de AF semanal con acelerómetro inválido (n = 1), enfermedad cardiovascular o pulmonar (n = 2), e incapacidad de seguir asistiendo a las mediciones (n = 1). Setenta y cinco participantes completaron con éxito todas las mediciones y fueron incluidas en el análisis de datos final.

Una vez revisados los criterios de elegibilidad y la historia clínica de cada participante, se procedió a realizar una prueba incremental progresiva submáxima con medición de frecuencia cardiaca (FC), lactato y percepción del esfuerzo (RPE), caminando en una pista de 20 metros (ida y vuelta girando alrededor de un cono) con un acelerómetro situado a la altura de la cadera derecha, para determinar la velocidad, FC y conteos de actividad al primer umbral de lactato (LT1). Una vez terminada la prueba, se suministró un acelerómetro triaxial a cada

participante junto a un diario de actividad, para registrar su AF habitual durante una semana. A la vuelta, una vez recogido el acelerómetro y revisado su diario de actividad, se realizaron dos test de fuerza máxima (press banca y press de piernas) con medición de la velocidad de ejecución en cada repetición. Tras 10 minutos de descanso, la participante realizó un test a velocidad constante durante dos bloques de 10 minutos, separados por dos minutos de descanso para tomar una muestra de sangre para la determinación de su concentración de lactato, con el objetivo de determinar la velocidad, FC y conteos de actividad al máximo estado estable de lactato (MLSS) o LT2. Esta misma prueba se repitió semanalmente aumentando o reduciendo la velocidad de la prueba hasta determinar el MLSS con una precisión de ≤0.30 $km \cdot h^{-1}$. Al finalizar las mediciones y una vez analizados los datos, cada participante recibió un informe sobre su nivel de capacidad aeróbica, fuerza y sus niveles de AF, junto a recomendaciones y un programa de EF adaptado.

Un sub-grupo de 30 participantes del estudio, realizaron dos pruebas adicionales en tapiz rodante (una submáxima replicando la prueba incremental realizada en pista y otra máxima aumentando progresivamente la pendiente) con medición de oxígeno, dióxido de carbono y flujo de inspiración, para; 1) determinar el consumo máximo de oxígeno ($\dot{V}O_{2max}$), y 2) para conocer el consumo de oxígeno ($\dot{V}O_2$) correspondiente al LT1 y LT2 y compararlo con los puntos de corte utilizados en estudios epidemiológicos que miden la AF con acelerómetros basados en intensidades absolutas de 3 y 6 METs que limitan la categoría de intensidad moderada definida por las autoridades científicas que crean las guías de AF reconocidas a nivel internacional.

3.2. Overview and main characteristics of the studies

La **Table 3** resume las características metodológicas principales de los cuatro estudios incluidos en esta tesis doctoral, siguiendo las guías STROBE para estudios observacionales. No es objeto del presente apartado dar detalles concretos acerca de cada uno de los estudios, sino ofrecer una visión global sobre cada uno de los proyectos de investigación que permita compararlos entre ellos. En los siguientes capítulos se profundiza sobre los procedimientos metodológicos, protocolos de los test de ejercicio, las principales variables medidas en cada uno de los estudios, así como una detallada discusión acerca de los resultados obtenidos y su implicación.

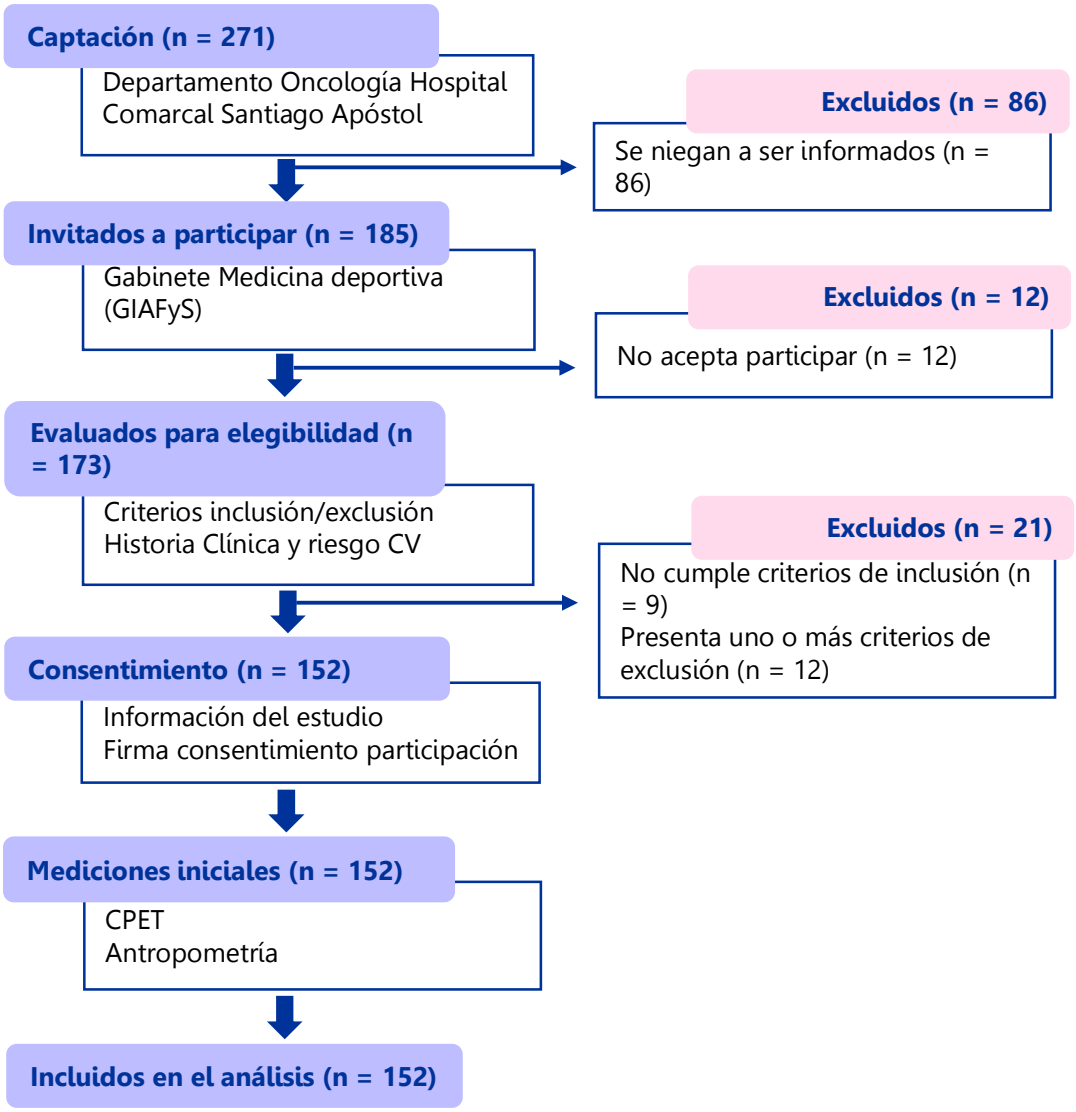

Figure 9. Diagrama de flujo del estudio 1: Exercise intensity guidelines for cancer survivors: a comparison with reference values.

Figure 10. Diagrama de flujo de los estudios 2, 3 y 4 llevados a cabo en el centro de Estudios, Investigación y Medicina del Deporte con mujeres postmenopáusicas.

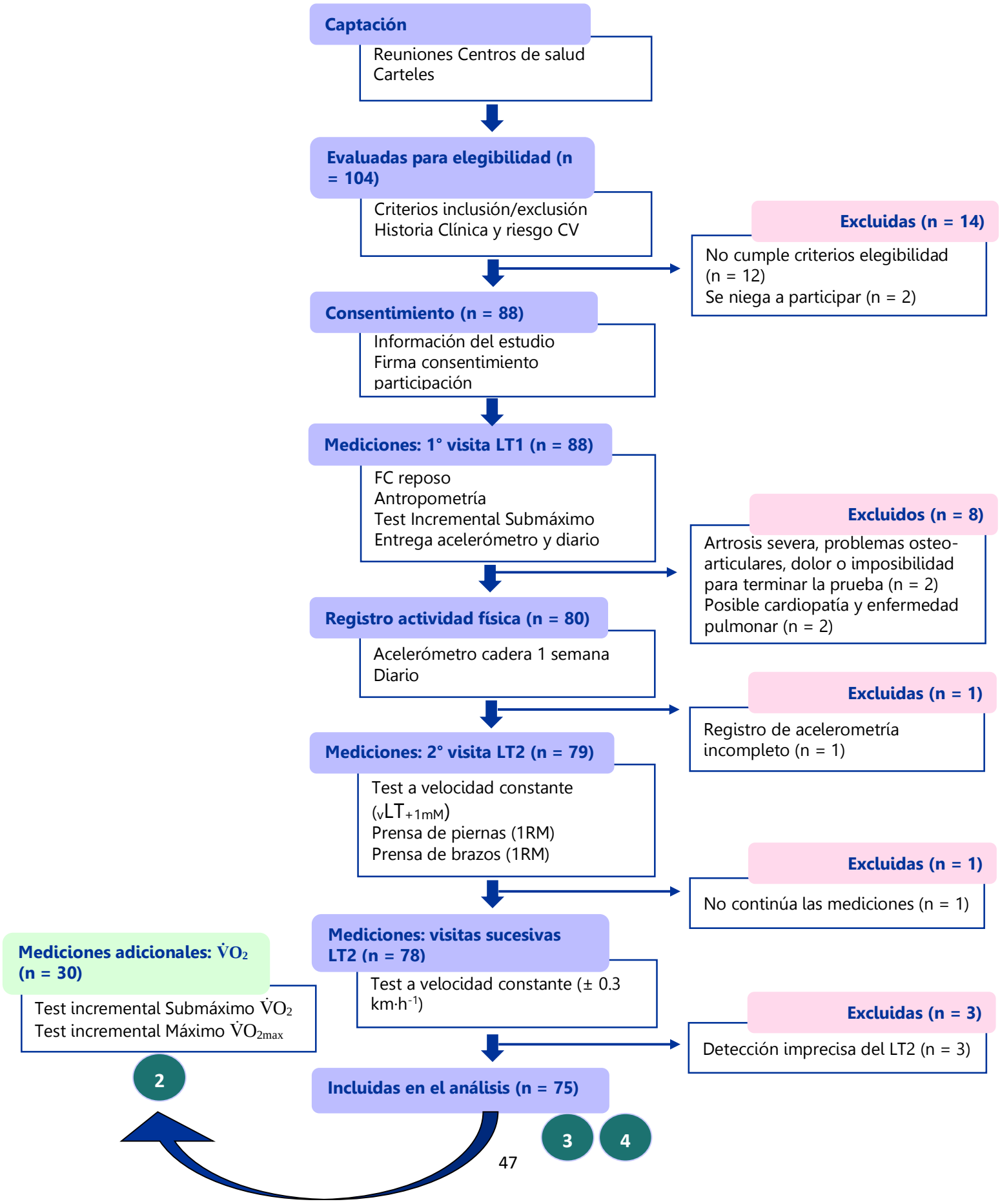

Table 3. Características metodológicas de los estudios incluidos en la tesis doctoral.

Estudio	(1) Exercise intensity guidelines for cancer survivors: a comparison with reference values	(2) Individualized accelerometer activity cut-points for the measurement of relative physical activity intensity levels	(3) Objectively measured absolute and relative physical activity intensity levels in postmenopausal women	(4) Estimation of the maximal lactate steady state in postmenopausal women
Diseño del estudio	Observacional retrospectivo	Observacional cross-sectional	Observacional cross-sectional	Observacional cross-sectional
Comité ético	Comité Ético de Investigación Clínica Burgos y Soria	Comité Ético de Investigación Clínica de Navarra	Comité Ético de Investigación Clínica de Navarra	Comité Ético de Investigación Clínica de Navarra
Entorno del estudio	Miranda de Ebro	Pamplona	Pamplona	Pamplona
Captación	Hospital Santiago Apostol	Centros de salud	Centros de salud	Centros de salud
Ubicación	Gabinete Medicina Deportiva	CEIMD	CEIMD	CEIMD
Fechas	2004 – 2013	03/17 – 06/17	11/15 – 06/17	11/15 – 06/17
Participantes analizados y características	N =152 Edad = 55.1 ± 12.3 años IMC = 26.5 ± 4.1 $kg \cdot m^{-2}$ MET_{pico} = 5.3 ± 1.3 MET VT1 = 2.5 ± 0.6 MET VT2 = 4.0 ± 1.1	N = 30 Edad = 57.2 ± 5.0 años IMC = 26.5 ± 4.1 $kg \cdot m^{-2}$ MET_{max} = 10.0 ± 2.0 LT1 = 4.6 ± 0.7 METs o 5.5 ± 0.6 $km \cdot h^{-1}$ LT2 = 7.3 ± 1.9 METs o 7.3 ± 1.1 $km \cdot h^{-1}$	N = 75 Edad = 59.0 ± 5.5 años IMC = 26.0 ± 3.9 $kg \cdot m^{-2}$ LT1 = 5.1 ± 0.7 $km \cdot h^{-1}$ LT2 = 7.1 ± 1.0 $km \cdot h^{-1}$	N = 75 Edad = 59.0 ± 5.5 años IMC = 26.0 ± 3.9 $kg \cdot m^{-2}$ LT1 = 5.1 ± 0.7 $km \cdot h^{-1}$ LT2 = 7.1 ± 1.0 $km \cdot h^{-1}$
Criterios de Inclusión	Diagnóstico de cáncer ECOG = 0 AF<90min/sem	Mujer postmenopáusica (>12 meses) <75 años	Mujer postmenopáusica (>12 meses) <75 años	Mujer postmenopáusica (>12 meses) <75 años
Criterios de exclusión	Enfermedad CV TA no controlada Dolor no controlado Contraindicaciones específicas al ejercicio (anemia severa, plaquetas, riesgo fracturas)	Artrosis severa, o fracturas Limitación funcional para caminar 20min Enfermedad crónica con alto riesgo CV	Artrosis severa, o fracturas Limitación funcional para caminar 20min Enfermedad crónica con alto riesgo CV	Artrosis severa, o fracturas Limitación funcional para caminar 20min Enfermedad crónica con alto riesgo CV

Protocolo del test de ejercicio	Cardiopulmonar máximo	(1) Cardiopulmonar submáximo [a] (2) Cardiopulmonar máximo [b]	(1) Incremental submáximo [a] (2) Velocidad constante [b]	(1) Incremental submáximo [a] (2) Velocidad constante [b]
Modo	Cicloergómetro	Tapiz rodante	Pista	Pista
Carga Inicial	20W	2.4 $km \cdot h^{-1}$ [a] 4.9 $km \cdot h^{-1}$ [b]	2.4 $km \cdot h^{-1}$ [a] 5.5 – 10.0 $km \cdot h^{-1}$ [b]	2.4 $km \cdot h^{-1}$ [a] 5.5 – 10.0 $km \cdot h^{-1}$ [b]
Duración (nº estadíos)	8-12 min	24 – 42 min [a] (8-14) 9 – 20 min [b]	21 – 42 min [a] (7-14) 22 min [b] (2)	21 – 42 min (7-14) 22 min [b] (2)
Duración del estadio	1 min	2 min [a] 1 min [b]	2 min [a] 10 min [b]	2 min [a] 10 min [b]
Intervalos de descanso	-	1 min [a] Sin Descanso [b]	1 min [a] 2 min [b]	1 min [a] 2 min [b]
Incrementos de carga	8-10W	0.6 $km \cdot h^{-1}$ [a] – 0.6 $km \cdot h^{-1}$ + 0.5% 2º estadío y + 1.3% restantes [b]	0.6 $km \cdot h^{-1}$ [a] Velocidad constante [b]	0.6 $km \cdot h^{-1}$ [a] Velocidad constante [b]
Criterios finalización	No incremento de $\dot{V}O_2$ y/o FC con aumento de carga FC >85%FC_{max} RER ≥ 1.10 RPE = 20 (20)	≥3 $mmol \cdot l^{-1}$ [a] Agotamiento [a, b] Incapacidad de seguir con el ritmo marcado [a, b] No incremento de $\dot{V}O_2$ y/o FC con aumento de carga [b] RPE ≥ 8 (10) [b] FC >85%FC_{max} [b] RER ≥ 1.10 [b] BLC_{max} >8 $mmol \cdot L^{-1}$ [b]	≥3 $mmol \cdot l^{-1}$ [a] Agotamiento [a, b] Incapacidad de seguir con el ritmo marcado [a, b]	≥3 $mmol \cdot l^{-1}$ [a] Agotamiento [a, b] Incapacidad de seguir con el ritmo marcado [a, b]
Mediciones	$\dot{V}O_2$ - $\dot{V}CO_2$ y variables ventilatorias FC RPE TA	$\dot{V}O_2$ - $\dot{V}CO_2$ y variables ventilatorias Conteos de actividad FC Lactato RPE	Conteos de actividad FC Lactato RPE Actividad física seminal (acelerómetro triaxial)	Conteos de actividad FC Lactato RPE

Principales medidas de resultado	$\dot{V}O_{2pico}$ Umbrales ventilatorios (VT y RCP)	Conteos de actividad en los límites de la categoría de intensidad moderada (absolutos a 3-6 METs, relativos a 46-63%VO_{2max} y en los umbrales de lactato LT1-LT2)	Tiempo (promedio diario) transcurrido en cada una de las categorías de intensidad en términos absolutos y relativos MVPA Pasos Tiempo sedentario	Predicción de $_{v}$MLSS (R^2, SEE y 95%LoA)
Variables independientes	Edad $\dot{V}O_{2pico}$	$\dot{V}O_{2max}$ IMC Edad	Capacidad aeróbica (LT2) Conteos de actividad Velocidad	BL_RTs Edad Variables antropométricas FC, RPE Cambio en el lactato del min10 al 20 en la prueba a velocidad constante
Variables confusoras	Tiempo post-diagnóstico Tipo de cáncer		IMC Edad	
Subgrupos	METs Tiempo post-diagnóstico Edad	Tipo de intensidad (absoluta, relativa, umbrales de lactato)	Capacidad aeróbica (LT2) Tipo de intensidad (absoluta, umbrales de lactato)	
Análisis de datos principal	Comparación de medias por subgrupo (ANOVA de un factor)	Regresiones individuales polinómicas ANOVA de medidas repetidas	Comparación por pares (variables intra grupo y entre grupos)	Regresión lineal múltiple y validez individual de las ecuaciones predictivas de cada modelo

CEIMD, Centro de Estudios, Investigación y Medicina del Deporte; IMC, índice de masa corporal; MET, equivalente metabólico del gasto energético de las actividades, VT1; primer umbral ventilatorio durante una prueba incremental; VT2, segundo umbral ventilatorio durante una prueba incremental, conocido como umbral de compensación respiratoria o RCP; LT1, primer umbral de lactato durante una prueba incremental; LT2, segundo umbral de lactato o máximo estado estable de lactato durante una prueba a carga constante; ECOG, Eastern Cooperative Oncology Gorup; AF, actividad física; CV, cardiovascular; W, vatios; $\dot{V}O_2$, consumo de oxígeno; $\dot{V}O_{2max}$, consumo de oxígeno máximo; FC, frecuencia cardíaca; RER, coeficiente respiratorio; RPE, percepción del esfuerzo; $\dot{V}CO_2$, producción de dióxido de carbono; BLC, concentración de ácido láctico; TA, tensión arterial; BL_RTs, umbrales relacionados con la concentración de ácido láctico en sangre; MVPA, actividad física moderada y vigorosa; MLSS, máximo estado estable de lactato.

4 Results
1st Study

Exercise intensity guidelines for cancer survivors: a comparison with reference values

Reference:

Gil-Rey E, Quevedo-Jerez K, Maldonado-Martin S, Herrero-Román F. Exercise Intensity Guidelines for Cancer Survivors: A Comparison with Reference Values. *International Journal of Sports Medicine*. 2014;35(14):e1-e9. DOI: 10.1055/s-0034-1389972.

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Abstract

The optimal dose of PA in CS is unknown due to the large variety of types of cancer, illness stages and treatments, low C, and physical inactivity. It is recommended that CS follow current PA guidelines for healthy population. There are no specific exercise prescription guidelines for CS. ***Purpose:*** To know the cardiorespiratory parameters of CS in order to create exercise prescription guidelines for this population, 152 inactive CS were recruited to perform a cardiopulmonary exercise test. ***Methods:*** Peak oxygen uptake ($\dot{V}O_{2peak}$), ventilatory threshold (VT) and respiratory compensation point (RCP), determined three exercise intensity zones to create exercise intensity classification guidelines for CS. ***Results:*** $\dot{V}O_{2peak}$ (18.7 ± 4.6 $mL \cdot kg^{-1} \cdot min^{-1}$) and peak heart rate ($HR_{peak}$) (145.1±17.9 bpm) were lower than the estimated values ($p < 0.001$). Moderate intensity zone for CS was different from the current PA guidelines for healthy population: 41-64% $\dot{V}O_{2max}$, 55-70% HR_{max}, 23-48% HR_{res}, 2.5-4 METs and 8-14 points in RPE scale. ***Conclusion:*** Intensities in PA guidelines for healthy population are not adapted to the characteristics of CS. For individual exercise prescription in CS specific PA guidelines should be used in order to maximize the benefits obtained by the use of aerobic exercise training.

Key words: Exercise prescription; Survivorship; Physical activity; Quality of life.

Introduction

There were around 12.7 million cancer cases all over the world in 2008. This number is expected to increase, reaching 21 million by 2030. One out of three people will develop cancer before the age of 75 years [119]. Currently increasing incidence rates and decreasing mortality rates due to the advances in earlier detection and in therapeutic modalities have translated to a higher number of CS [120].

Both the disease itself, the treatments and the lack of PA lead to an increase of pain and fatigue thresholds, a significant reduction of the muscle mass and strength, a higher level of adipose tissue, and decreased CRF. All of the factors mentioned negatively impact daily activities and reduce the QoL of CS [120-123]. Related to this topic, PA offers important psychological and physiologic benefits in CS [122,124,125], and plays an important role on preventing or delaying other chronic diseases (e.g. cardiovascular diseases, hypertension, diabetes, osteoporosis, obesity, depression), thereby contributing positively to their survival [120,126].

However, there are no specific guidelines for exercise prescription for CS. Current PA guidelines for CS are generic. Whenever possible, CS should avoid inactivity and maintain an active and healthy lifestyle [35,45]. PA guidelines for CS are based on guidelines for healthy population; i.e., for aerobic activity 150 minutes per week of moderate PA (30 min 5 days a week) or 75 min per week of vigorous PA (20 min 3 days a week) or any combination thereof. Furthermore, strength training guidelines recommend 2-3 weekly sessions that include exercises for major muscle groups [35,45,127]. In this regard, it has been shown that CS meet international recommendations for moderate PA, but very few complete those for vigorous PA [128]. The optimal dose of PA in this population is unknown [129], possibly affecting each CS differently due to the large variety of types of cancer, illness stages and treatments, low CRF, physical inactivity and co-morbidities. Thus, it is crucial to create individualized exercise programs, starting from specific PA guidelines for CS.

Compared to healthy individuals of the same sex and age, CS usually exhibit ~30% lower $\dot{V}O_{2peak}$ [35]. It has recently shown that many of the CS present poor CRF [130]. In addition to $\dot{V}O_{2peak}$, gas exchange thresholds (i.e., ventilatory threshold, VT, and respiratory compensation point, RCP) are currently the gold standard references for the evaluation of aerobic metabolism function and, consequently, for aerobic exercise intensity assessment and prescription [24,131]. VT could be considered as a valid indicator of functional capacity of CS and it is closely associated with the intensities of daily activities (e.g., walking, gardening, climbing stairs, household activities) [132]. It has been previously observed that the $\dot{V}O_2$ at VT in CS is very low [132], indicating

that any light stimulation could induce moderate intensities in this population [131]. It was investigated whether submaximal indices of CRF such as VT and RCP were related to QoL in women survivors of breast cancer and they concluded that the improvement of these indices could have a beneficial effect on QoL [132]. Therefore, exercising at those intensities to improve submaximal thresholds (i.e., VT and RCP) could be an effective strategy [132]. In practice, these submaximal thresholds are used to define individualized intensity zones and prescribe exercise. Generally, 3 intensity zones are defined: intensity below VT, intensity between VT and RCP and intensity above RCP. This exercise-prescribing method has been used with athletes [133], healthy sedentary individuals [134] and with chronic heart failure patients or chronic obstructive pulmonary disease patients [131]. Regarding the optimum PA level, CS should exercise at a higher level than the minimum recommended whenever possible to achieve more benefits [45,128]. Nevertheless, exercise intensity is more complicated to prescribe, measure and control. Whereas with high intensity activities there is still high controversy, moderate intensity has proven to be safe and provide health benefits [128].

But what is considered to be light, moderate and high intensity? Where are the limits of each? Light intensity is defined as 6–11 points on the RPE scale, <63%HR_{max}, and 20–39%HR_{res}. Moderate intensity is defined as 12–13 points on the RPE scale, 3–6 METs, 64–76%HR_{max} and 40–59%HR_{res}. High intensity is defined as 14–19 points on the RPE scale, 77–93%HR_{max} and 60–84%HR_{res} [19,35,123]. There are slight differences in exercise intensity reference guidelines. Absolute intensities like METs, cannot be generalized due to the high variability in CRF among subjects. What is considered to be a light walk for some people could be considered to be moderate or vigorous for others. For this reason, relative intensity was introduced [135]. However, the same relative intensity for 2 subjects could result in different metabolic responses (above or below anaerobic threshold) [136]. It seems that an individualized prescription based on ventilatory thresholds (VT and RCP), could be less variable among individuals. Those thresholds show the metabolic adaptations and the evolution induced by exercise training [64,137].

The main purpose of this study was to assess the cardiorespiratory parameters of CS (peak and submaximal thresholds) for the purpose of creating an adapted exercise intensity prescription guideline for this population that allows the comparison with current standard guidelines. The secondary purposes were: 1) to analyse the CRF of CS, classifying them by age ranges; to compare it to that of the healthy population; and 2) to evaluate the association between the HR_{max} and $\dot{V}O_{2max}$ estimated by equations to prescribe exercise and the real peak values obtained in the cardiopulmonary exercise test (CPET).

Methods

Participants

One hundred and fifty-two CS were recruited from the oncology department of the "Santiago Apóstol" Hospital of Miranda de Ebro, Burgos, Spain. Inclusion criteria: 1) cancer survivor, 2) Eastern Cooperative Oncology Group (ECOG) scale = 0, 3) physical activity ≤ 90 min/week. Exclusion criteria: 1) heart disease (≥New York Heart Association II), 2) uncontrolled hypertension (blood pressure >160/90 mmHg), 3) uncontrolled pain or 4) any other contraindication for participation in a physical exercise program such as high risk of bone fractures, severe anemia (<8g/dL), or $<50{\cdot}10^9$/μL of platelet count [138]. Participants were informed about the study. Each participant obtained the consent of the oncologist and gave their written informed consent before participating in the study. The study received ethical approval from The Clinical Research Ethics Board of Burgos and Soria and meets the ethical standards in sport and exercise sciences research [139]. After obtaining peak and submaximal cardiorespiratory variables in the CPET, participants were offered an individualized exercise program (3 sessions per week of 90 min each combining aerobic and resistance exercise). With the data obtained in the CPET, the exercise intensity classification guideline was created.

Measurements

Each participant performed a CPET in the same center of sport medicine (Gabinete Médico Deportivo, Miranda de Ebro, Burgos, Spain) at the same time (10 a.m. – 2 p.m.) and in similar environmental conditions (temperature, ~20ºC; relative humidity, 45-55%; barometric pressure, ~720 mmHg). The test was performed on an electric braking cycle-ergometer (Variobike 600, Marquette Hellige, Freiburg, Germany). Participants were not involved in any exercise during the previous 24h before the test. After an unloaded 5-min warm-up, the load was increased 8-10W per minute starting with an initial load of 20W. Participants were informed to maintain cadence between 60-70 rpm, cadence being displayed on a monitor placed in front of them. Gas exchange data were measured breath by breath using an open spirometer circuit (MasterScreen CPX, Jaeger, Viasys Healthcare, Hoechberg, Germany). The test was performed until volitional fatigue or when the cadence could not be maintained above 60 rpm. Confirmation of a maximal effort was determined by meeting three out of four of the following criteria: 1) no increases in $\dot{V}O_2$ with increased workload, 2) HR values ≥85% estimated maximum HR (HR_{maxT}), 3) RER ≥1.10, and 4) RPE = 20 (Borg 6-20) [35]. Regardless of achieving maximal criteria, the maximal values achieved during the CPET are referenced as "peak" [124,127].

$\dot{V}O_{2peak}$ was defined as the highest 20-s value of $\dot{V}O_2$ elicited during the CPET. Peak $\dot{V}O_2$ is expressed in terms relative to body mass (mL·kg^{-1}·min^{-1}).

Ratings of perceived exertion (RPE) and blood pressure were evaluated at the end of each stage (1 min). HR was monitored during the test using a 12-lead ECG. $\dot{V}O_2$, ventilation, ventilatory equivalents (for oxygen and carbon dioxide) and respiratory quotient for peak and submaximal values (VT and RCP) were also measured. To detect the VT the first exponential increase in the O_2 ventilatory equivalent (V_E/ $\dot{V}O_2$) without a concomitant increase in the CO_2 ventilatory equivalent was considered. The RCP was determined using the ventilatory equivalent method (the first exponential increase in CO_2 ventilator equivalent alongside an increase in the ventilatory equivalent for O_2) [123]. Two experienced researchers detected those points individually and in case of disagreement, a third researcher´s opinon was obtained. CS were classified by age to compare their CRF against the age and sex-matched ACSM 50th percentile [35].

To estimate HR_{max} the equation (206.9 – (0.67 * age)) was used given its higher accuracy compared to other equations [140]. To estimate the maximum $\dot{V}O_2$ ($\dot{V}O_{2maxT}$), we used the ACSM´s metabolic equation for bike ergometer (1.8 * (W * 6.1183) / (body mass + 7)) [35]. Absolute and relative values below VT determined the light intensity zone (zone 1). Values between VT and RCP were considered as moderate intensity (zone 2) and values above the RCP determined the high intensity zone (zone 3) [131,133].

Cancer survivors were categorized into 3 groups according to their CRF. The first group corresponded to the most deconditioned individuals and was considered <4.5 METs (<15.75 mL·kg^{-1}·min^{-1} of $\dot{V}O_{2peak}$). In the second group CS were between 4.5 and 6 METs (15.75-21 mL·kg^{-1}·min^{-1} of $\dot{V}O_{2peak}$. The third group corresponded to CS with >6 METs (>21 mL·kg^{-1}·min^{-1} of $\dot{V}O_{2peak}$.

Statistical analysis

Descriptive statistics were calculated for continuous variables (mean, standard deviations or SD) and for non-continuous variables (frequencies). To determine the statistical analysis type, normality criteria was verified for each variable (Kolmogorov-Smirnov test) and for the groups which they would be compared with different variables (Kolmogorov-Smirnov or Shapiro-Wilk). To verify the variance homogeneity, Levene´s test of homogeneity of variances was performed. To examine the validity of the equations estimating HR_{maxT} and $\dot{V}O_{2maxT}$ a linear regression was used, while to examine the differences between the real and estimated values, a paired samples t-test was performed. Pearson´s correlation coefficient was used to examine the association between the estimated and real values, as well as to determine whether there

was any relationship between post-diagnosis time and cardiorespiratory variables. Correlations were categorized as follows: 0.26 to 0.49 is a low correlation, 0.50 to 0.69 is a moderate correlation, 0.70-0.89 is high correlation, and 0.90 to 1.00 is very high correlation. One-way ANOVA for parametric samples and Kruskal Wallis H test for non-parametric samples, were used to compare the cardiorespiratory values in submaximal point among CRF groups (<4.5 METs, 4.5-6 METs and >6 METs), post-diagnosis time (<6 months, 7-12 months, 13-24 months, 25-60 months and >60 months) and $\dot{V}O_{2peak}$ among age ranges (30-39, 40-49, 50-59, 60-69, >70). Bonferroni post-hoc test was applied to define the groups with statistical differences. Data are presented as mean ± SD. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS statistical software (version 20.0, IBM SPSS Statistics, Chicago, IL).

Results

The flow diagram in **Figure 11** shows how the CS participants were recruited and the final numbers of individuals. Participant characteristics are displayed in **Table 4**. Physiologic values of CS obtained in the CPET and estimated by equations, are listed in **Table 5**. CS showed a mean $\dot{V}O_2$ significantly ($p < 0.001$) lower than the estimated $\dot{V}O_2$. The relationship between estimated $\dot{V}O_{2max}$ and the obtained $\dot{V}O_{2peak}$ was significant and high ($r = 0.82$, $p < 0.001$) (Figure 2).

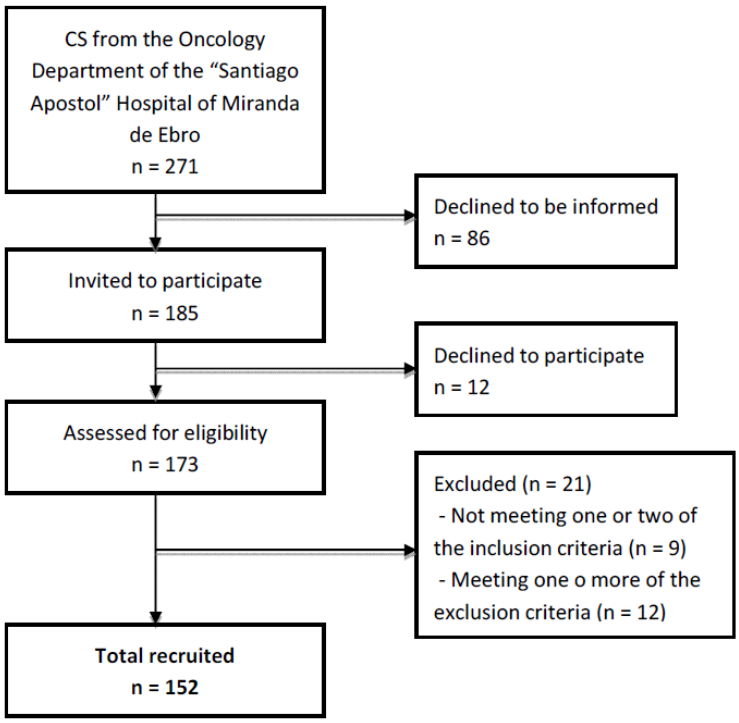


Figure 11. Recruitment of CS participants.

The HR_{peak} obtained in the CPET was 25bpm less than the estimated HR ($p < 0.001$). The relationship between the estimated HR_{max} and the obtained HR_{peak} was statistically significant ($r = 0.56$, $p < 0.001$) (**Figure 12**). The VT was located at 48.0 ± 11.6% of the $\dot{V}O_{2peak}$, whereas the RCP corresponded to 75.3 ± 9.7% of the $\dot{V}O_{2peak}$. The moderate intensity range (VT-RCP) in METs was between 2.5 ± 0.6 and 4.0 ± 1.1. The perceived effort (Borg 6-20 scale) for moderate intensity was between 8.0 ± 1.3 and 14.4 ± 1.5 points. The mean HR in the VT was 93.9 ± 14.0 bpm, while the mean HR for the RCP was 118.5 ± 16.5 bpm. These values corresponded to 65.1 ± 8.8% and 81.9 ± 7.6% of the HR_{peak}, respectively. The HR_{res} was 74.2 ± 18 bpm and the ventilatory thresholds were located at 31.3 ± 12.9% (VT) and 64.3 ± 13.7% (RCP) of the HR_{res}.

Table 4. Participant´s characteristics.

Age (years)	55.1 ± 12.3
Sex	
Male	34 (22.4)
Female	118 (77.6)
BMI ($kg \cdot m^{-2}$)	26.5 ± 4.1
Cancer type	
Colon	16 (10.5)
Uteri cervix	3 (2.0)
Endometrium	4 (2.6)
Gastric	5 (3.3)
Breast	87 (57.2)
Melanoma	2 (1.3)
Ovarian	5 (3.3)
Pancreatic	4 (2.6)
Prostate	7 (4.6)
Lung	3 (2.0)
Thyroid	2 (1.3)
Bladder	4 (2.6)
Others	10 (6.6)
Total	152 (100)
Treatment type	
S	22 (14.5)
S+Q	59 (38.8)
S+R	12 (7.9)
S+Q+R	42 (27.6)
Other	17 (11.2)
Post-Diagnosis time (months)	32.7 ± 42.7

Data are presented as mean ± DS for continuous variables and as frequency (%) for categorical variables.

DS, standard deviation; BMI, body mass index; S, surgery; Chemotherapy; R, radiotherapy.

Comparisons to published age and sex-matched CRF [35] are presented in **Figure 13**. Participants of this study presented a significantly lower CRF than healthy population in all age ranges. CS ages 30-39 years showed a mean $\dot{V}O_{2peak}$ of 17.1 ± 5.5 $mL \cdot kg^{-1} \cdot min^{-1}$, representing a difference of greater than 50% (i.e., lower values) compared to the $\dot{V}O_{2peak}$ of the healthy

population (36.8 mL·kg^{-1}·min^{-1}). CS ages 40-49 years showed the highest CRF (20.0 ± 4.5 mL·kg^{-1}·min^{-1}), but the difference with the ACSM healthy population continued to be high (-43%). Among the individuals ages 50-59 years, the $\dot{V}O_{2peak}$ showed greater similarity than that of the group ages 0-49 years (19.5 ± 5.0 mL·kg^{-1}·min^{-1}). CS of this study showed a decreasing trend in the CRF without large differences among age groups.

Table 6 shows the intensity ranges defined after obtaining submaximal (VT and RCP) and peak parameters in the CPET. The peak values obtained during the CPET placed the moderate intensity zone (VT-RCP) at 48-75% of $\dot{V}O_{2peak}$, 65-82% of the HR_{peak}, 31-64% of HR_{res}, 2.5-4 METs and 8-14 points in the RPE scale. There were differences when CS were classified into CRF groups. Less than 6 METs group showed the VT in a lower % of $\dot{V}O_{2peak}$ than the others ($p < 0.001$). Less than 4.5 METs group showed the $\%HR_{peak}$ at VT higher than the others, exhibiting a reduced moderate intensity zone compared with the other two groups. There were statistically significant differences among all groups in moderate intensity zone thresholds for absolute values in METs. While for the moderate intensity zone was 2-3 METs for the most deconditioned group, the same intensity zone corresponded to 2.9-5.3 METs for the fittest group. There were no differences when using HR reserve as the exercise prescription method.

Table 7 shows an exercise intensity classification guide for CS based on the absolute and relative submaximal values obtained in the CPET, for the purpose of creating intensity ranges relative to the estimated maximal values. The intensity zone values obtained relative to the estimated HR_{max} and $\dot{V}O_{2max}$ were lower than those obtained through the peak values. In this case, moderate intensity zone corresponded to 41-64% of $\dot{V}O_{2max}$, 55-70% of HR_{max} or 23-48% of the HR_{res}.

No association was found between post-diagnosis time (from diagnosis to CPET) and cardiorespiratory variables ($\dot{V}O_{2peak}$, $\dot{V}O_2$ at VT and RCP, HR_{peak}, HR at VT and RCP, HR_{res}, HR_{rest}), without following a physical exercise program. No significant differences were either found in any variable when the patients were separated by post-diagnosis time (<6 months, 7-12 months, 13-24 months, 25-60 months and >60 months).

Table 5. Absolute and relative physiologic values of the participants determined in CPET and Estimated.

CPET		Estimated	
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	18.7 ± 4.6	$\dot{V}O_{2maxT}$ (mL·kg^{-1}·min^{-1})	22.0 ± 4.9
$\dot{V}O_2$ VT (mL·kg^{-1}·min^{-1})	8.7 ± 2.2		
$\dot{V}O_2$ RCP (mL·kg^{-1}·min^{-1})	14.0 ± 3.7		
%$\dot{V}O_{2peak}$ VT	48.0 ± 11.6	%$\dot{V}O_{2maxT}$ VT	40.7 ± 10.7
%$\dot{V}O_{2peak}$ RCP	75.3 ± 9.7	%$\dot{V}O_{2maxT}$ RCP	64.0 ± 11.4
MET_{peak}	5.3 ± 1.3	MET_{maxT}	6.3 ± 1.4
MET VT	2.5 ± 0.6		
MET RCP	4.0 ± 1.1		
RPE VT	8.0 ± 1.3		
RPE RCP	14.4 ± 1.5		
W_{peak}	94.0 ± 33.7		
RER_{peak}	1.19 ± 0.11		
HR_{peak} (bpm)	145.1 ± 17.9	HR_{maxT} (bpm)	170.0 ± 8.2
HR VT (bpm)	93.9 ± 14.0		
HR RCP (lpm)	118.5 ± 16.5		
% HR_{peak} VT	65.1 ± 8.8	% HR_{maxT} VT	55.2 ± 7.7
% HR_{peak} RCP	81.9 ± 7.6	% HR_{maxT} RCP	69.7 ± 8.6
HR_{rest} (bpm)	70.8 ± 11.0		
HR_{res} (bpm)	74.2 ± 18.0	HR_{resT} (bpm)	99.1 ± 12.5
% HR_{res} VT	31.3 ± 12.9	% HR_{resT} VT	23.2 ± 10.3
% HR_{res} RCP	64.3 ± 13.7	% HR_{resT} RCP	48.0 ± 13.8

Data are presented as mean ± DS. DS, standard deviation; HR, heart rate; MET, metabolic equivalent (1 MET = 3,5 mlO_2·kg^{-1}·min^{-1} or 1 kcal·kg^{-1}·h^{-1}); RCP, respiratory compensation point; RER, respiratory exchange ratio; RPE, rating of perceived effort (Borg, 6-20); $\dot{V}O_2$, oxygen uptake; VT, ventilatory threshold; W,watt; HR_{maxT}, estimated maximum heart rate by ACSM (2013) equation (206.9 – (0.67 * age); HR_{res}, (HR_{maxT}– HR_{rest}); RCP, respiratory compensation point; $\dot{V}O_{2maxT}$, estimated maximum oxygen uptake by ACSM (2013) equation ($\dot{V}O_2$= 1.8 (W·6.1183) / body mass + 7).

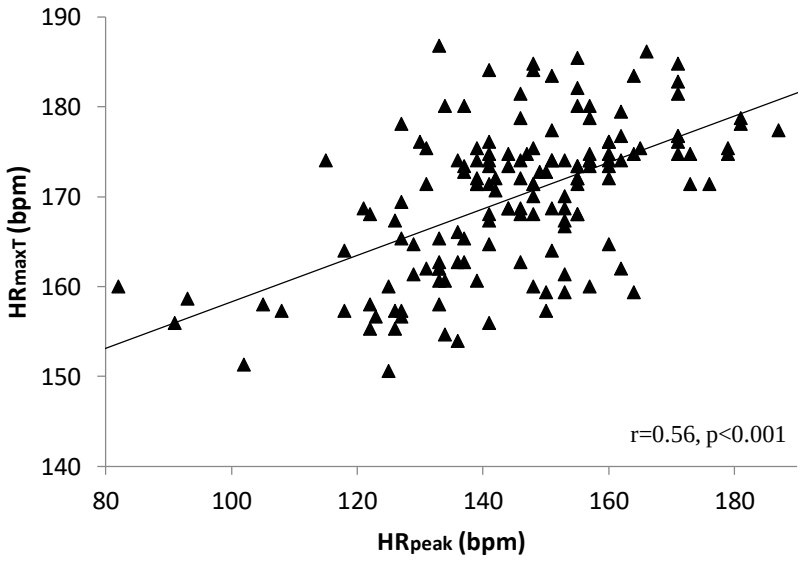
Discussion

The main purpose of this study, was to assess the cardiorespiratory parameters of CS (peak and submaximal thresholds), for the purpose of creating an adapted exercise intensity prescription guideline for this population, which facilitates comparison with current standard guidelines. The mean $\dot{V}O_{2peak}$ of the 152 CS of this study was 18.7 ± 4.6 mL·kg^{-1}·min^{-1}. This value is within the normal range of CRF of CS [127], and is lower than that of the healthy population [35]. It is also worth mentioning that in the present study CS did not meet the threshold of 8 METs that indicates an increased risk for mortality and cardiac events [1]. This deconditioning could

be attributed to several factors, such as the low PA level (<90 min/week) adopted following cancer diagnosis, the disease itself, treatment and side effects such as chronic fatigue, pain or cardiopulmonary dysfunction and the high BMI level (65.1% of participants presented overweight or obesity) [120,132]

In fact, a recent study in another Spanish cohort also showed that the prevalence in obesity in CS leads to a low cardiometabolic profile [130]. Relative intensity (%$\dot{V}O_{2peak}$) at VT and RCP (48.0 ± 11.6% and 75.3 ± 9.7%, respectively) was similar to that of the sedentary adults. It seems that for CS any increase of PA could lead to a disproportionately rapid rise of VCO_2 and minute ventilation as related to $\dot{V}O_2$ [131]. The %$\dot{V}O_{2peak}$ at RCP was similar to that found by others [141] in CS (75%$\dot{V}O_{2peak}$).

The difference between the estimated and peak HR was 25 bpm. Other studies have reported a wide range of HR_{peak} in CS, varying from 124 to 169 bpm [132,142-144]. For this reason, it is recommended that heart rate be measured in an incremental exercise test whenever possible [35]. The ventilatory thresholds corresponded to 65.1 ± 8.8% (VT) and 81.9 ± 7.6% (RCP) of HR_{peak} or 31.3 ± 12.9% (VT) and 64.3 ± 13.7% (RCP) of $HR_{reserve}$. In a recent study with breast CS, higher values of HR_{peak} (169 ± 12 bpm) were obtained, and the RCP was placed at a higher percentage of HR_{peak} (87.6%) [145]. Another study placed the VT at 73 ± 10% of HR_{peak} and the RCP at 88 ± 5% of HR_{peak} in breast cancer survivors with a $\dot{V}O_{2peak}$ of 24.6 ± 5.8 mL·kg^{-1}·min^{-1} [132].



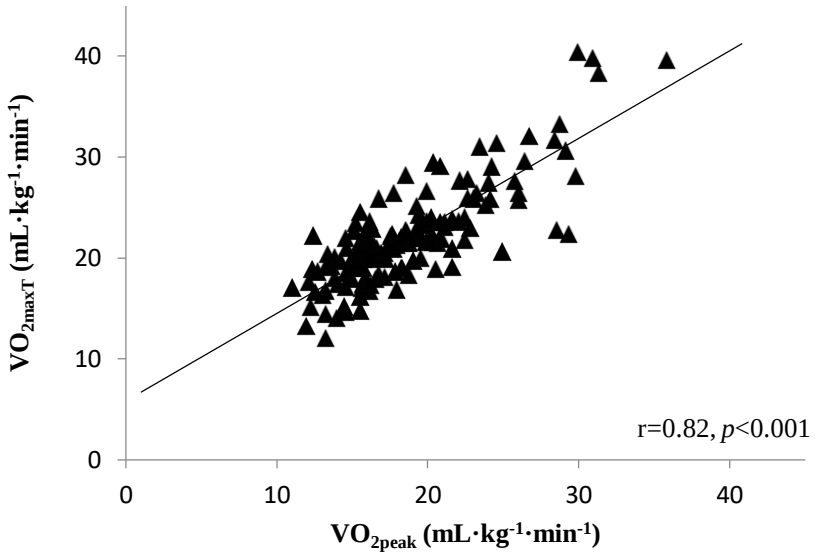


Figure 12. Association between HR_{peak}-HR_{maxT} and $\dot{V}O_{2peak}$- $\dot{V}O_{2maxT}$

ACSM suggests determining the HR_{peak} of the individual in an incremental exercise test in order to prescribe an exercise program. When it is not feasible, the estimation is accepted. In our study, the equation of Gellish [140] (206.9 – (0.67 * age) was used as it is the formula that is best adapted to this population [35,146]. The correlation obtained between the estimated HR and the HR_{peak} was only moderate (r = 0.56, p <0.001). Whereas the estimated maximum HR was 170 ± 8.2 bpm, the peak HR obtained in the CPET was 25 bpm lower (145 ± 17.9 bpm). The type of test (cycle-ergometer), the physical deconditioning (caused by the illness itself, treatments and inactivity) and the lack of familiarization with these type of tests, could contribute to the low $HR_{peak.}$ However, all CS satisfied 3 of 4 criteria of maximal effort. It may be necessary to create a new equation for this population in the future. These differences between the estimated and the real values could cause large differences in determining the intensity in CS if the equations to estimate the peak values were used. What the international PA guidelines classify as moderate intensity (40-59%HR_{res} or 64-76%HR_{max}) could cause varied responses when the prescription is based on the peak HR (145 bpm in CS of the study) or the estimated maximum HR (170 bpm in CS of the study). Basing exercise intensity on the estimated maximum values, i.e., 64-76%HR_{max} of 170 bpm (109-129 bpm), would actually result in a vigorous intensity (75-89%HR_{peak}) for a CS with 145 bpm of HR_{peak}. The correlation between the $\dot{V}O_{2peak}$ and the estimated $\dot{V}O_{2max}$ was higher than that obtained for the HR (r = 0.82, p <0.001, **Figure 12**).

CS showed considerably lower CRF than that of the healthy population [35] in every age group, with $\dot{V}O_{2peak}$ decreasing with age (**Figure 13**). The greatest differences were found in

the youngest groups (~53.5% of $\dot{V}O_{2peak}$ lower in CS of 30-39 years and ~43% of $\dot{V}O_{2peak}$ lower in CS of 40-49 years). Starting with these age groups, the difference appears to decrease (~38.5% of $\dot{V}O_{2peak}$ lower in CS of 50-59 years and ~37% of $\dot{V}O_{2peak}$ lower in CS >60 years). The scientific literature has reported differences between ~38-50% of $\dot{V}O_{2peak}$ in favour of the healthy population [124,147]. In contrast to the healthy population, which exhibits clearly decreasing $\dot{V}O_{2peak}$ with age, CS does not present such differences among age groups, and the CRF is very low and similar in all age groups (**Figure 13**). A systematic review about cardiorespiratory exercise in the rehabilitation of CS, shows that most patients present a $\dot{V}O_{2peak}$ of 16-25 mL·kg^{-1}·min^{-1} [127]. CS of our study had low $\dot{V}O_{2peak}$ values in all age groups (lower than a mean of 20.0 ± 4.5 mL·kg^{-1}·min^{-1}). These results thus emphasize the need for monitoring CRF and creating adapted exercise programs to improve those $\dot{V}O_{2peak}$ values as early as possible.

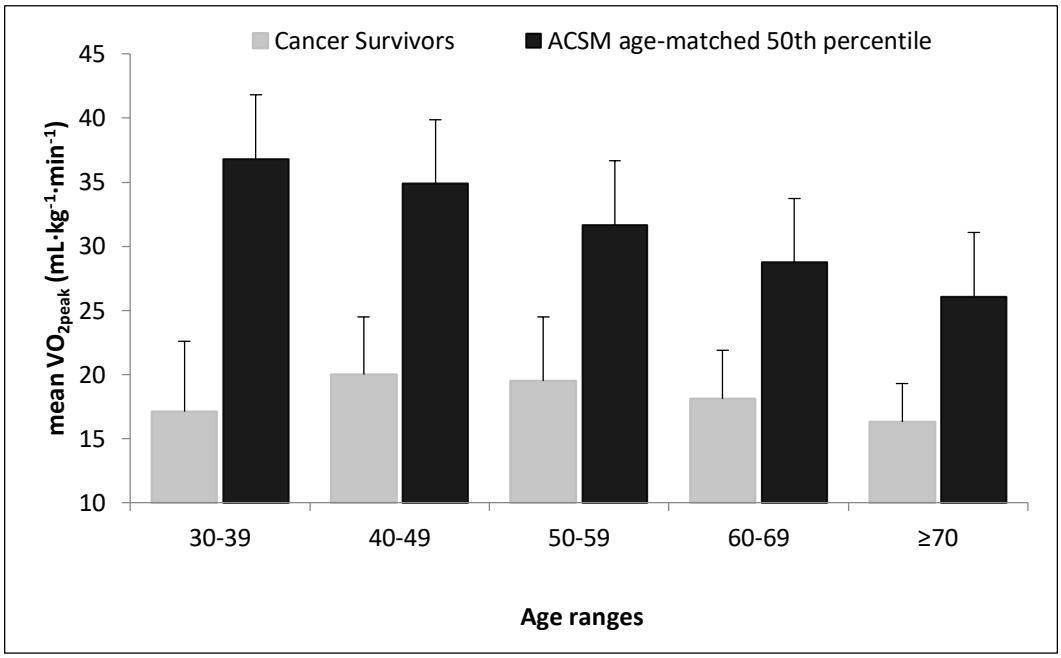


Figure 13. Comparison of $\dot{V}O_{2peak}$ between ACSM (2013) age-matched 50th percentile of healthy population and cancer survivors of the study.

VO_2, oxygen uptake; ACSM, American College of Sport Medicine.
****** p <0.01 vs ≥ 70
***** p <0.05 vs ≥ 70

Despite $\dot{V}O_{2peak}$ decreasing with age, the absolute $\dot{V}O_2$ values of VT and RCP were not affected. Thus, the relative values (%$\dot{V}O_{2peak}$) of VT and RCP relative to $\dot{V}O_{2peak}$ increased. Older people have tend to have ventilatory thresholds relatively closer to the nearest to $\dot{V}O_{2peak}$ than younger people [131]. Previous studies conducted among CS pointed to the importance of improving the $\dot{V}O_{2peak}$ and even more the VT and RCP, because the increases are positively associated with QoL and they imply intensities near those of daily activities [144].

As a result of $\dot{V}O_{2peak}$ decreasing with age and the lower CRF of individuals with chronic diseases, the general PA guidelines for healthy individuals may not be the most appropriate for CS. Furthermore, this population has cardiorespiratory limitations and low cardiorespiratory values when exercise intensity is based on absolute intensity, i.e., the MET method [35,131]. The relative intensity approach tries to eliminate the differences in the absolute values in people of different CRF levels [135]. Nevertheless, relative intensity approach has been criticized by some authors because, at the same relative intensity, the metabolic response of two people could be different (i.e., moderate intensity for one but high intensity for the other). It is expected that a prescription based on the individual ventilatory thresholds (VT and RCP) produces less variability in the metabolic response of patients and offers more homogenous training stimulus than the use of other relative prescription methods such as $\%\dot{V}O_{2peak}$, $\%HR_{peak}$ or $\%HR_{reserve}$. Additionally, ventilatory thresholds better reflect progress or training adaptations [123,137].

Table 6. Exercise intensity classification of the participants. Data are presented as relative to the peak values obtained in the CPET.

						Intensity relative to maximal exercise capacity in METs		
Intensity	**$\%\dot{V}O_{2peak}$**	**$\%HR_{peak}$**	**$\%HR_{res}$**	**METs**	**RPE**		**<4.5 METs** n = 39	**4.5-6 METs** n = 79	**>6 METs** n = 34
Light	<48	<65	<31	<2.5	<8	**$\%\dot{V}O_{2peak}$** **$\%HR_{peak}$** **$\%HR_{res}$** **METs**	<51 <70 <34 <2	<50 <64 <31 <2.5	<41 <62 <29 <2.9
Moderate	48-75	65-82	31-64	2.5-4	8-14	**$\%\dot{V}O_{2peak}$** **$\%HR_{peak}$** **$\%HR_{res}$** **METs**	51-76 †70-84 34-64 ‡2-3†	50-76 64-81 31-63 ‡2.5-3.9‖	*41-72 62-82 29-67 2.9-5.3
Vigorous	>75	>82	>64	>4	>14	**$\%\dot{V}O_{2peak}$** **$\%HR_{peak}$** **$\%HR_{res}$** **METs**	>76 >84 >64 >3	>76 >81 >63 >3.9	>72 >82 >67 >5.3

$\dot{V}O_{2peak}$, peak oxygen uptake; HR_{peak}, peak heart rate; HR_{res}, reserve heart rate (HR_{max}– HR_{rest}); MET, metabolic equivalent; RPE, rating of perceived effort (Borg, 6-20).
*p <0.001 vs <4.5 METs & 4.5-6 METs
†p <0.001 vs 4.5-6 METs & >6 METs
‡p <0.001 vs 4.5-6 METs & >6 METs
ǂp <0.01 vs 6 METs
ᵗp <0.001 vs 4.5-6 METs & >6 METs
‖p <0.001 vs >6 METs

There is a wide range of exercise intensity classifications which define intensity categories according to relative intensities ($\%\dot{V}O_{2peak}$, $\%HR_{peak}$ or $\%HR_{reserve}$) or absolute intensities (MET´s, RPE) [35]. The determination of these intensity categories is based on

regressions of $\dot{V}O_{2max}$ or % $\dot{V}O_{2max}$ for conversion into %HR_{max} or %HR_{res} and modifications of previous exercise intensity classifications [35,135], since $\dot{V}O_{2res}$ and HR_{res} have been closely associated [148] . In the ACSM´s position stand moderate intensity corresponds to 46-63% of $\dot{V}O_{2max}$ (52-67% for individuals with a CRF lower than 5 METs), 64-76% of HR_{max} or 40-59% of HR_{res}. The results of our study for moderate intensity (VT-RCP) corresponded to 41-64% of $\dot{V}O_{2max}$, 55-70% of HR_{max} or 23-48% of HR_{res} (**Table 7**). The consequence of that it could be to overstress the patients when exercise design is performed using the intensity classification of international guidelines recommended for healthy population and for CS [19]; e.g., from 70% of HR_{max} or 48% of HR_{res} CS would be training at high intensity and not in moderate intensity as the international guidelines establish. The position statement of the Exercise and Sport Science Australia [46] also places moderate intensity at 50-75% of $\dot{V}O_{2max}$/HR_{res} and 60-80% of HR_{max}. Once again, these intensities are overestimating what CS can perform at moderate intensity. Previous study classified moderate intensity at 40-60% of $\dot{V}O_{2max}$/HR_{res} or 55-70 of HR_{max} [149]. In that case, the relative intensity of $\dot{V}O_{2max}$ and HR_{max} is similar to the ones found in the present study, but prescribing with HR_{res} individuals could be overstressed.

The perceived effort of moderate intensity was between 8 and 14 points in RPE 20 points scale, signalling that CS overtake VT early after starting the exercise and in low subjective appreciation of the effort. If exercise is designed based on this method, activities which are considered as light in international guidelines, such as 9-11 points in RPE, actually are moderate intensities for CS. On the other hand, when exercise intensity is based on absolute MET values following the typical classification of moderate intensity (3-6 METs) established by current guidelines [19,35,46], actually CS would be exercising at maximal intensities and some of them would not be able to perform at 6 METs, since the mean peak CRF of CS of this study in METs is 5.3 ± 1.3. In this study, moderate intensity corresponded to 2.5-4 METs. The classification of 3.1-4 METs for individuals with a CRF lower than 6 METs as suggested by ACSM [35], appears to be better adapted to the characteristics of CS. Daily activities such as moving light loads and boxes from one place to another, or climbing stairs, which are considered to induce 4-6 METs, actually represents high-intensity physical activity for CS. The present study categorized CS into different groups based on their CRF to further specify exercise prescription (**Table 6**). Relative exercise intensity should be modified according to the CRF of CS. For the most fit CS group (>6 METs) the moderate-intensity zone relative to %$\dot{V}O_{2peak}$ was more intense (41-72%$\dot{V}O_{2peak}$) due to the lower relative value of VT, showing significant differences with the other two groups ($p < 0.001$). The most deconditioned group (<4.5 METs) showed the moderate-intensity zone relative to %HR_{peak} (70-84%HR_{peak}) to be significantly higher than the other two groups due to the higher level of VT at relative intensities ($p < 0.001$).

Due to low cardiorespiratory values of patients of certain diseases, the $\%\dot{V}O_2$ corresponding to the ventilatory thresholds is quite high and it could increase with the severity of the disease [131]. This paradoxical phenomenon could be due to the attenuated increase of $\dot{V}O_2$ over the VT and/or the low exercise tolerance. In this population, any increase over the resting values (~3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ of $\dot{V}O_2$) represents a high proportion of $\dot{V}O_{2peak}$. In this study, the more deconditioned the CS was, the higher relative his or her values at VT without any difference in RCP.

Table 7. Exercise intensity classification guidelines for cancer survivors. Data are presented as relative to estimated HR_{max} and $\dot{V}O_{2max}$.

						Intensity relative to maximal exercise capacity in METs		
Intensity	**$\%\dot{V}O_{2max}$**	**$\%HR_{max}$**	**$\%HR_{res}$**	**METs**	**RPE**		**<4.5 METs** n = 39	**4.5-6 METs** n = 79	**>6 METs** n = 34
Light	<41	<55	<23	<2.5	<8	**$\%\dot{V}O_{2peak}$**	<40	<42	<38
						$\%HR_{peak}$	<56	<55	<55
						$\%HR_{res}$	<22	<23	<24
						METs	<2	<2.5	<2.9
Moderate	41-64	55-70	23-48	2.5-4	8-14	**$\%\dot{V}O_{2peak}$**	40-60	42-65	38-67
						$\%HR_{peak}$	56-68	55-70	55-73
						$\%HR_{res}$	22-43	23-47	24-56
						METs	2-3	2.5-3.9	2.9-5.3
Vigorous	>64	>70	>48	>4	>14	**$\%\dot{V}O_{2peak}$**	>60	>65	>67
						$\%HR_{peak}$	>68	>70	>73
						$\%HR_{res}$	>43	>47	>56
						METs	>3	>3.9	>5.3

HR_{max}, estimated maximum heart rate by ACSM (2013) equation (206.9 – (0.67 * age); HR_{res}, reserve heart rate (HR_{max}– HR_{rest}); $\dot{V}O_{2max}$, estimated maximum oxygen uptake by ACSM (2013) equation (($\dot{V}O_2$= 1.8 (W·6.1183) / body mass + 7)); MET, metabolic equivalent; RPE, rating of perceived effort (Borg, 6-20).

While the perceived effort does not vary with respect to the CRF, the absolute $\dot{V}O_2$ values in METs showed statistically significant differences among groups, suggesting that the prescription should be modified according to the $\dot{V}O_{2peak}$ of the CS. Moderate PA for <4.5 METs group was 2-3 METs, showing significant differences with the other two groups. For the 4.5-6 METs group the same intensity was 2.5-3.9 METs, whereas for the >6 METs group moderate intensity was defined as 2.5-5.3 METs, closer to those of the healthy population [19,35].

Finally, the outcomes of this study suggest that without following an exercise program, the post-diagnosis time does not have any effect on cardiorespiratory variables and the $\dot{V}O_{2peak}$ does not change. Furthermore, when CS were divided into post-diagnosis time groups (<6 months, 6-12 months, 13-24 months, 25-60 months and >60 months) there were no significant differences.

Given the strong association between $\dot{V}O_{2peak}$ and mortality in populations with low CRF [124], CS must start exercise programs as early as possible. Following exercise programs, the improvement of $\dot{V}O_{2peak}$ has been reported to be 2.90 mL·kg^{-1}·min^{-1} and there have been decreases of 1.02 mL·kg^{-1}·min^{-1} of $\dot{V}O_{2peak}$ in CS who did not participate in exercise programs [124]. An oncologist should advise his or her patient as early as possible to increase their PA levels doing light activities such as walking, cycling or swimming. This would improve the adherence [148].

Compared to CS of low CRF (<13 mL·kg^{-1}·min^{-1}), those of a moderate CRF (13.1-16.9 mL·kg^{-1}·min^{-1}) and high CRF (≥17 mL·kg^{-1}·min^{-1}) exhibit a 21% and 24% decrease in mortality of any cause. In contrast, a decrease of 1 mL·kg^{-1}·min^{-1} (the decrease of inactive CS) has been associated with a 4% increase in mortality of any cause [146].

The limitations of the study should be mentioned. There is a risk of population stratification due to the diagnosis data (i.e., differences of cancer categories and comorbid conditions). On the other hand, the sample is very homogeneous with regard to types of CS, most being breast CS, and very little data being present for the remaining cancer types. Despite this, the investigation poses the question, "Are we heading in the right direction?".

In summary, the intensities defined by current international PA guidelines recommended for healthy population and additionally suggested for CS are not adjusted to the physiological characteristics of CS, and those individuals could be overstressed following the prescription of the exercise intensity of those guidelines. Furthermore, absolute and relative intensities should be modified taking into consideration the CRF of the CS. When the individualization of exercise intensity in CS is not possible, an exercise intensity design guideline specific for CS must be employed to provide adapted stimulation and achieve the required outcomes. For this reason, a more adapted set of exercise intensity prescription guidelines is presented.

Exercise programs should be considered as an important part of cancer recovery therapies as early as possible after diagnosis, because CS do not improve their CRF independently of the post-diagnosis time unless they follow an exercise program.

5 Results 2nd Study

Individualized accelerometer activity cut-points for the measurement of relative physical activity intensity levels

Reference:

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Abstract

Purpose: The aim of this study was to compare the widely used accelerometer activity cut-points derived from the absolute moderate intensity recommendation (3–6 METs), with relative intensity cut-points according to maximum CRF (46–63%$\dot{V}O_{2max}$) and to individual lactate thresholds (LT1 and LT2) in postmenopausal women. ***Method:*** Thirty postmenopausal women performed several exercise tests with measures of heart rate, blood lactate, accelerometer activity counts and oxygen consumption. Individual regressions were developed to derive the accelerometer activity counts at absolute and relative moderate intensity recommendations and at individual LTs. ***Results:*** The activity counts calculated at the lower moderate intensity boundary were lower for the absolute 3 METs threshold (2026 ± 808 ct·min^{-1}) compared to relative 46%$\dot{V}O_{2max}$ intensity threshold ($p < 0.01$, ES: 1.95) and LT1 ($p < 0.01$, ES: 2.27), which corresponded to 4.6 ± 0.7 METs. The activity counts at the upper moderate intensity boundary were higher for LT2 (7249 ± 2499 ct·min^{-1}) compared to the absolute 6-METs threshold ($p < 0.01$, ES: 0.72) and relative 63%$\dot{V}O_{2max}$ intensity threshold ($p < 0.01$, ES: 0.55). The interindividual variability in activity counts at relative intensity thresholds was high (CV = 30-34%), and was largely explained by CRF level (R^2 = ~50%). ***Conclusion:*** Individually-tailored (relative to $\dot{V}O_{2max}$ or submaximal LTs), rather than fixed accelerometer intensity cut-points derived from the classic absolute moderate PA intensity (3-6 METs) would result in a more accurate measurement of an individual´s activity levels and reduce the risk of overestimating or underestimating PA.

Keywords: Activity counts; cardiorespiratory fitness; lactate thresholds; exercise intensity

Introduction

Compelling scientific evidence indicates that both, PA and CRF provide important health benefits [12,150]. Physical activity intensity and CRF are often expressed in METs. Each 1-MET increment in CRF is associated with 13 and 15% decrements in all-cause mortality and cardiovascular disease, respectively [1]. Epidemiologic studies suggest that a minimal CRF of 8 METs may be important for significant prevention of all-cause and cardiovascular disease mortality [1]. It is well documented that increases in the amounts and intensities of PA typically produce increases in CRF, particularly in those who are less physically active or present poor CRF [12]. Epidemiological studies using self-reported questionnaires suggest that meeting current PA recommendations of a minimum of 150 min·wk^{-1} of MVPA reduces all-cause mortality risk by 26-31% [11,12].

Since the early works of Montoye and colleagues validating uniaxial accelerometers against movement counters to measure daily EE [95], its use spread rapidly in behavioural and epidemiologic studies replacing PA questionnaires to objectively measure PA behaviour and adherence to recommended PA targets [96]. Contrary to self-reported estimates, results of accelerometer-based objective assessments of PA report much lower volumes of MVPA [11,113], indicating that only a small proportion of adults (7-15%) meet current PA recommendations [113,114,116]. Reported objective weekly volumes of MVPA are significantly lower in women and vary from as low as seven min·day^{-1} to 57 min·day^{-1} [113,114,116]. The inactivity, along with the lower CRF observed in women [6] and the increased risk of cardiovascular disease [117] and osteoporosis [118] after menopause and with advancing age underline the necessity of a well-designed and adequately powered PA program (i.e., intensity).

Both, the traditional count-based Actigraph approach [98,102,103]and other newer methods processing accelerometer data in "R" software [104] use raw accelerations (either vertical axis only, or a combination of three axes, also known as Vector Magnitude or VM_3) accelerations to quantify the time spent in different PA intensity levels applying accelerometer cut-points derived from the traditional absolute intensity recommendations for moderate intensity (3-6 METs) activities [19]. These studies have generated widely divergent regression models for converting counts to EE, yielding different cut-points for PA intensity categories [105]. As such, with increasing age or decreasing CRF, an activity at a given absolute intensity (MET) requires a greater percentage of the $\dot{V}O_{2max}$ (i.e., relative intensity) [19,111]. Therefore, using the absolute intensity approach may not be the most accurate option for assessing PA outcomes in samples varying in age or CRF [109,110]. Alternatively, when activity counts cut-points representing

moderate intensity activities have been calculated relative to $\dot{V}O_{2max}$ (i.e., 46-63%) [19], the results show substantial differences between less fit and most fit groups, even if no differences are evident when activity counts are determined according to the absolute intensity criteria [109,110].

The validity of this "relative intensity" approach has also been substantially criticized because exercising at the same relative intensity could elicit a wide range of metabolic stress across individuals [63]. In contrast, exercise intensity designed relative to lactate thresholds (LT) would be expected to produce less individual variation in metabolic responses and in time to exhaustion at a constant exercise intensity, providing a more homogenous training stimulus [64,74]. Although more than 20 lactate-related thresholds have been defined until now leading to considerable confusion and misinterpretation [75], there are two of these thresolds that have emerged as the preferred endurance perfomance markers among the vast majority of sport and exercise physiologists: 1) The more frequently called "Lactate Threshold" (LT1) defined as the critical exercise intensity level above which BLC first begin to increase above resting values during a graded incremental submaximal exercise [151]. LT1 has been suggested as the minimum exercise intensity required by inactive individuals to improve CRF [70], and is a valid indicator of CRF in athletes and inactive people due to its high association with $\dot{V}O_{2max,}$ sport performance [74,75] and functional capacity in patients [69], and 2) the so-called "Maximal Lactate Steady State" (MLSS or LT2), defined as the highest intensity that can be sustained over time without continual blood lactate accumulation during a constant intensity exercise [74]. Lactate thresholds are more sensitive than $\dot{V}O_{2max}$ to predict endurance performance and to evaluate training adaptations [83], allowing the definition of three individual intensity domains to guide exercise training: light (<LT1), moderate (LT1-LT2) and vigorous (>LT2) [75].

As far as we know, there are no studies addressing individually-tailored activity counts cut-points through LT, that would allow a more accurate design of exercise intensity and a proper quantification of the time spent in different PA intensity levels. We hypothesized that accelerometer intensity cut-points derived from 3 METs as a representative of the lower boundary of moderate intensity were below LT1, and could lead to an overestimation of MVPA and the number of postmenopausal women meeting current PA targets. Thus, the aim of this study was to compare the widely used accelerometer activity cut-points derived from the absolute moderate intensity recommendation (3-6 METs), with relative intensity cut-points according to maximal CRF (46-63% $\dot{V}O_{2max}$) and to individual lactate thresholds (LT1 and LT2) in postmenopausal women.

Methods

Study design

Participants performed on different days (with a minimum of one week in between) a submaximal incremental exercise test with gas exchange measurement wearing an accelerometer to determine the first LT (LT1), several constant velocity tests (CVT) to determine the second LT (LT2), and a maximal cardiopulmonary exercise test to determine the CRF level ($\dot{V}O_{2max}$).

Study participants

Thirty post-menopausal women (57.6 ± 5.3 yr) from Pamplona (Spain) participated in several exercise tests from March to June 2017. Inclusion criteria were: (1) surgical or natural menopause (no menstrual periods during previous 12 months); (2) age <75 years old. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: (1) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees or feet; (2) functional limitation to walk for 20 minutes; (3) presence of any chronic disease that would impair the cardiorespiratory system during testing. The local hospital´s ethical committee approved the study (Pyto2011/71) and written informed consent was obtained from all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in *ClinicalTrials.gov PRS* (NCT02984553).

Exercise tests protocols

Submaximal incremental cardiopulmonary test

Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least four hours and strenuous activity for ≥24 h before testing. During the first visit, and prior to the first testing session, participants were familiarized with the exercise testing protocol and the treadmill ergometer. The metabolimeter was warmed up for at least 2 h prior to every exercise test to minimize any possible electrical drift. Calibration of the oxygen (O_2) and carbon dioxide (CO_2) analysers was performed immediately prior to every test using two-point calibration with two precision-analysed gas mixtures. Turbine flow calibration was determined using a high-precision 3-L calibration syringe (Vacu-Med, Calibringe 1092, Ventura, CA, USA). Participants' height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest 0.1kg (Seca, Germany). Each participant wore a triaxial accelerometer (Actigraph wGT3X-BT Pensacola, FL, USA) over the

right iliac crest in the mid-axillary line throughout the test. Testing was performed in a laboratory setting in controlled conditions (temperature: ~20°, humidity: ~27%, barometric pressure: ~960mmHg) over a treadmill ergometer (Kuntaväline, Hyper Treadmill 2040, Finland).

The exercise protocol started with three minutes rest in a standing position. Capillary blood samples (0.3 µL) were taken from a hyperemic earlobe for the measurement of BLC (Lactate Pro2, Arkray, Japan). Heart rate (Polar V800, Polar Electro Oy, Kempele, Finland) and metabolic data were continuously collected using a Vista Mini-CPX computer-integrated metabolic system (Vacu-Med, Silver Edition 17670, Ventura, CA, USA). Gas exchange and ventilatory variables were measured continuously while participants breathed into a two-way breathing mask (Series 7930, Hans Rudolph, Kansas City, MO, USA) and were reported as 30-s averages. Participants then started to walk at 2.4 $km \cdot h^{-1}$. The intensity was progressively increased by 0.61 $km \cdot h^{-1}$ [152] at each 2-min stage with 1-min rest in between. At the end of each stage a capillary blood sample was taken for BLC analysis. Each participant was free to start running from the 7th stage onwards (6.1 $km \cdot h^{-1}$), or the operator suggested to do so when the participant was not able to match the required speed. The test was stopped when: (1) BLC was ≥3.0 $mmol \cdot l^{-1}$ to avoid excessive fatigue; and/or (2) participant was exhausted. First LT was defined as the highest velocity above which BLC increased by an amount of ≥0.1 $mmol \cdot l^{-1}$ in the following stage and ≥0.2 $mmol \cdot l^{-1}$ in the subsequent stage.

Constant velocity tests (CVT)

On the following visits, participants completed two to seven 20 min CVT. Testing was performed in a laboratory setting in a controlled temperature environment (~20°) over a 20 m indoor track. Five cones were positioned at 0.5–5–10–15 and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start. The speed at which the participant walked was dictated by an audio signal pre-recorded in MP3 audio format. Each participant performed the corresponding tests on separate testing days (one week in between). Each CVT consisted of two stages of 10 min at a constant pace with a 2-min break for blood sampling. Heart rate was continuously recorded, and capillary blood samples were obtained at rest, at the 10th min and the end of the test (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which BLC increased by 1 $mmol \cdot l^{-1}$ above the blood lactate value at LT1 during the incremental exercise test. In the following tests, the velocity was increased or decreased by ~0.30 $km \cdot h^{-1}$ until the maximum lactate steady state velocity (i.e., LT2) could be determined [153]. An increase in BLC ≤0.4 $mmol \cdot l^{-1}$ during the final 10 min of exercise was defined as steady state [74].

Maximum cardiopulmonary exercise test

On the last visit, a maximum CPET was performed over a treadmill ergometer (Kuntaväline, Hyper Treadmill 2040, Finland) using a graded protocol. Gas exchange and ventilatory variables were measured continuously while the participants breathed into a two-way breathing mask (Series 7930, Hans Rudolph, Kansas City, MO, USA). After 3-min rest, participants walked at 4.9 $km \cdot h^{-1}$ for a minute. Then, the speed was increased and maintained in 5.5 $km \cdot h^{-1}$ and the inclination of the treadmill was increased by 0.5% and by 1.3% in the first and next 1-min stages, respectively, to induce a ~0.6METs increment per stage until volitional fatigue. The perceived exertion was rated by Borg´s scale [154]. A capillary blood sample was taken for lactate analysis at the termination of exercise, and at 1, 3 and 5 minutes of recovery if the BLC continued increasing (Lactate Pro; KDK Corporation or ABL 800; Radiometer Medical AS). All metabolic data were averaged over 30-second periods with the highest 1-min $\dot{V}O_2$ recorded as $\dot{V}O_{2max}$. Achievement of $\dot{V}O_{2max}$ was assumed in the presence of a minimum of three of the following criteria: (1) failure of $\dot{V}O_2$ and/or heart rate to increase with further increases in workload, (2) individual´s volitional fatigue, rating a perceived effort of a minimum of 8 points out of 10 [154], (3) elicited an exercise maximum heart rate (HR_{max}) that exceeded 85% of the individuals age-predicted maximum based on the HR_{max} estimated by 208-0.66·age [155], (4) RER ≥1.10, and (5) BLC_{max} >8 $mmol \cdot L^{-1}$ [24].

Determination of accelerometer activity cut-points and Data Analyses

Accelerometer activity counts during the submaximal incremental test were calculated by averaging the VM_3 activity counts in 1-sec epochs during the central 90-sec of each stage to avoid the accelerations/decelerations produced during the start or the end of each stage (first or last 15 sec). These activity counts were then averaged in 1-min epochs ($ct \cdot min^{-1}$). We used individual centered third order polynomial regression equations between rates of energy expenditure (METs) and VM_3 activity counts measured at each speed (R^2 = 0.98) to derive the activity counts at selected moderate intensity thresholds (i.e., at lower and upper boundaries of absolute 3-6 METs, relative 46-63%$\dot{V}O_{2max}$ and at individual LTs) [102]. Data were analyzed using parametric statistics following confirmation of normality (Shapiro-Wilk test), homoscedasticity (Levene´s test), and when appropriate sphericity (Mauchly's test). Repeated measures ANOVA with Bonferroni adjusted post hoc test was used to compare the activity counts of the three moderate intensity cut-points. The Greenhouse-Geisser correction factor to reduce the risk of type I error was applied where sphericity assumptions were violated. Data are presented as mean ± standard deviation and 95% confidence interval (CI). Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS statistical

software (version 22.0, IBM SPSS Statistics, Chicago, IL) and GraphPad Prism 7 was used for figures.

Results

One of the study participants was excluded from data analysis due to not-meeting maximum exercise criteria. Study participants had a $\dot{V}O_{2max}$ of 10.0 ± 4.2 METs (**Table 8**). **Figure 14** shows measured METs and activity counts during the submaximal incremental exercise test. The average velocity at the classic lower moderate intensity boundary in absolute rates of energy expenditure (3 METs) was 3.2 km·h^{-1}, corresponding to a 30%$\dot{V}O_{2max}$ and a 49%HR_{max}. Average velocities at LT1 and LT2 were 5.5 ± 0.6 km·h^{-1} and 7.3 ± 1.1 km·h^{-1}, respectively, which corresponded to 4.6 ± 0.7 METs (47 ± 8%$\dot{V}O_{2max}$ and 59 ± 6%HR_{max}) and 7.3 ± 1.9 METs (73 ± 11%$\dot{V}O_{2max}$ and 85 ± 10%HR_{max}) during the incremental exercise test.

Table 8. Descriptive characteristics of study participants (n = 29).

Characteristics	
Age (years)	57.2 ± 5.0
Height (cm)	158.3 ± 5.5
Body mass (kg)	65.4 ± 12.2
BMI (kg/m^2)	26.0 ± 4.2
$\dot{V}O_{2max}$ (METs)	10.0 ± 4.2
BLC_{max}	7.8 ± 3.2
RER_{max}	1.22 ± 0.07
RPE_{max}	8.8 ± 1.9
HR_{max}	172.7 ± 11.3
LT1 (km·h^{-1})	5.5 ± 0.6
LT1 (METs)	4.6 ± 0.7
LT2 (km·h^{-1})	7.3 ± 1.1
LT2 (METs)	7.3 ± 1.9

BMI = body mass index, $\dot{V}O_{2max}$ = oxygen consumption, MET = rates of energy expenditure (1 MET is equivalent to 3.5 ml·kg^{-1}·min^{-1}), BLC = blood lactate concentration, RER = respiratory exchange ratio RER = $\dot{V}CO_2/\dot{V}O_2$), RPE = rating of perceived effort, HR_{max} = maximum heart rate, LT1 =first lactate threshold, LT2 = second lactate threshold.

The activity counts calculated at the lower boundary of moderate intensity were 2026 ± 808 ct·min^{-1} (95%CI; 1719-2334) at 3 METs, 4306 ± 1447 ct·min^{-1} (95%CI; 3756-4857) at 46%$\dot{V}O_{2max}$ and 4247 ± 1122 ct·min^{-1} (95%CI; 3820-4674) at LT1. There was a significant difference between the three intensity indicators ($F_{2,56}$ = 79,2, p <0.01) with Bonferroni adjusted post hoc tests revealing that the activity counts at 3 METs threshold were significantly lower (p <0.01) than activity counts at 46% $\dot{V}O_{2max}$ (p <0.01; 95%CI: -2774 to -1786; ES: 1.95) or at LT1 (p <0.01; 95%CI: -2559 to -1882; ES: 2.27). No differences were observed in the average activity counts between the lower threshold of 46%$\dot{V}O_{2max}$ assigned to relative moderate intensities and LT1 (p = 0.72; 95%CI: -363 to 482; ES: 0.05) (**Figure 15**). The data revealed large interindividual variability in activity counts at the three lower boundaries of moderate intensity (coefficient of variation, CV = 40, 34, 26%, respectively).

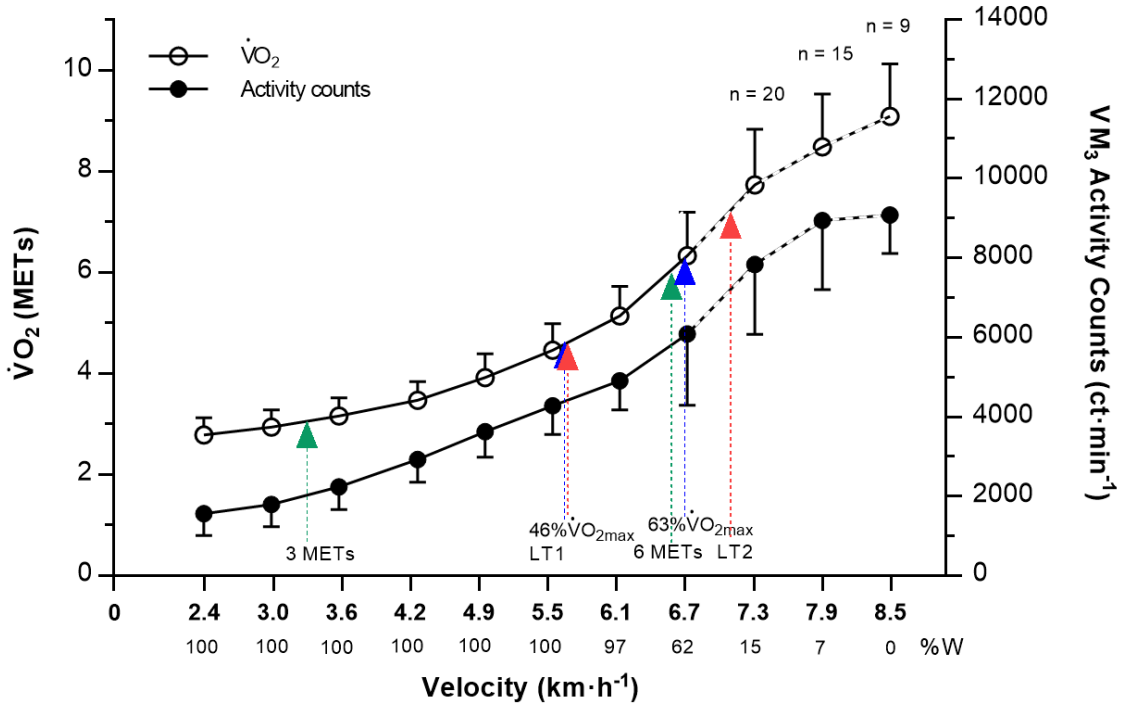

Figure 14. Measured rates of energy expenditure (METs) and activity counts across the velocities of the submaximal incremental test (n = 29). Dashed arrows indicate the lower and upper boundaries of moderate absolute (green), relative (blue), and individual (red) intensity.

The activity counts measured at the upper boundary of moderate intensity were 5820 ± 1297 ct·min^{-1} (95% CI; 5326-6313) at 6 METs, 6068 ± 1765 ct·min^{-1} (95% CI; 5397-6740) at 63%$\dot{V}O_{2max}$ and 7249 ± 2499 ct·min^{-1} (95% CI; 6298-8199) at LT2. The activity counts at LT2 were significantly higher than those at 63%$\dot{V}O_{2max}$ (p <0.01; 95%CI: 637 to 2221; ES: 0.55) and at 6 METs thresholds (p <0.01; 95%CI: 569 to 1792; ES: 0.72) which did not differ between

them (p = 0.38; 95%CI: -327 to 824; ES: 0.16) (**Figure 15**). The data revealed large interindividual variability at the three upper boundaries of moderate intensity (CV = 22, 29, 34%, respectively). The large variation in activity counts at the lower and upper relative moderate intensity boundaries was largely explained by $\dot{V}O_{2max}$ (R^2 = 54% and 48%, respectively), whereas less than 2% of the variability was explained by individuals age and BMI.

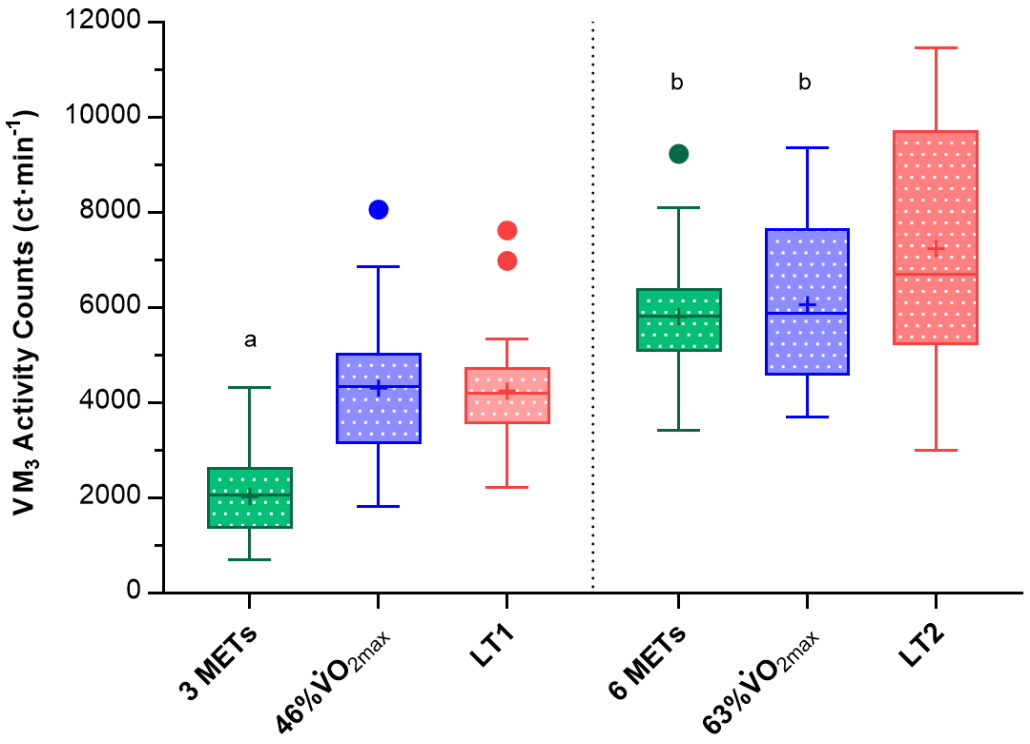

Figure 15. Measured-activity counts at the lower and upper boundaries of moderate absolute (3-6 METs), relative (46-63% $\dot{V}O_{2max}$) and individual (LT1-LT2) intensity. The data are derived from individual regressions between rates of energy expenditure (METs) and VM_3 activity counts measured at each speed during the submaximal incremental test in 29 participants. VM = vector magnitude activity counts per minute, MET = metabolic equivalent of energy expenditure, LT1 = first lactate threshold, LT2 = second lactate threshold. Dashed line separates lower and upper boundaries of moderate intensity.

Dashed line separates lower and upper boundaries of moderate intensity.
[a] significantly different from 46% $\dot{V}O_{2max}$ and LT1 ($p < 0.01$).
[b] significantly different from LT2 ($p < 0.01$).

Discussion

The selection of appropriate accelerometer cut-points to demarcate PA intensity levels is the cornerstone to obtain reliable PA outcomes and their association with health markers and mortality [111]. If the cut-points are too high when evaluating accelerometry data, then

participants will not be credited for engaging in MVPA even when being adherent to their prescriptions. Conversely, using cut-points that are too low would falsely elevate levels of MVPA [111]. A possible solution to this problem could be to individualize the activity cut-points according to relative intensities, rather than using fixed cut-points for all individuals [109,110].

An important finding of this study was that the energy cost at the lower moderate intensity boundary expressed either, relative to $\dot{V}O_{2max}$ (46%$\dot{V}O_{2max}$, corresponding to 4.6 ± 0.9 METs) or to LT1 (5.5 ± 0.6 km·h^{-1}, corresponding to 4.6 ± 0.7 METs) was higher than the classic 3 METs threshold assigned to the lower boundary of moderate intensity activities, which has been widely utilized by expert panels to create PA guidelines [12,19,150] as well as to establish the health benefits of engaging in MVPA [11]. A possible explanation could be the higher CRF of our study participants (10.0 ± 2.0 METs) compared to the 8-8.5 METs reported for women of the same age in other studies [155]. Interestingly, the energy cost of the LT1 agrees with the relative intensity value assigned to the lower moderate intensity boundary of individuals with a CRF of 10 METs [6,19].

Consequently, measured activity counts at 3 METs fell well below the relative intensity and individual cut-points derived from LT ($p < 0.01$). This finding is in agreement with the results of Miller and colleagues [109] who showed that the activity counts at 3 METs were much lower than those obtained at relative intensity cut-points, even in the oldest individuals, and this difference increased in individuals with higher CRF [110]. Epidemiological studies measuring PA with accelerometers [113,114] have commonly used activity counts cut-points derived at 3 METs intensity as the lower boundary of moderate intensity [98,102,103]. Hence, the finding of the present study has important consequences, as it could falsely elevate the time spent at MVPA and the percentage of people meeting current PA guidelines. In this investigation, measured activity counts at 3 METs intensity were 25-37% lower compared to previous actigraph triaxial accelerometer validation studies [102,103]. However, these two studies obtained ~4000 ct·min^{-1} at 4.8 km·h^{-1}, which is close to the value of 3616 ct·min^{-1} found in our study when participants walked at the same speed. These two studies used an incremental treadmill protocol with activity counts obtained at only 2-4 velocity stages to derive the activity counts at 3 and 6 METs using linear regression analysis [102] and artificial neural networks [103]. In contrast, our incremental exercise test provided a minimum of seven data points from all participants, with smaller velocity increments between stages (0.6 km·h^{-1}). Besides, we used individual, rather than whole-group regression equations to determine the activity counts at moderate intensity thresholds. Another possible explanation to the low activity counts observed at 3 METs intensity could be related to the slightly higher METs measured in our study participants

(i.e., 3.9 METs at 4.9 km·h^{-1}) compared to the estimated values of 3.6 METs from the equation of Weyand et al. [156] or the 3.5 METs assigned in the compendium of physical activities [26] to walking at 4.8 km·h^{-1}. Both, Miller and colleagues [109] and Santos-Lozano et al. [103] reported a large variation in measured METs for that speed (from 3 to 4 METs) between young and older adults. In our study, age was not a significant predictor of measured METs at a certain velocity, but resting METs (standing) contributed in a range of 15-42% of its variance, mainly at slow velocities ($p < 0.001$).

On the other hand, the activity counts measured at the upper boundary of moderate intensity were similar between absolute and relative intensities ($p = 0.384$) and go hand in hand with the cut-point derived at 6 METs by Sasaki and colleagues [102]. However, LT2 corresponded to a higher intensity (7.3 ± 1.9 METs or 73%$\dot{V}O_{2max}$) than either, absolute (6 METs) or relative (63%$\dot{V}O_{2max}$) upper boundaries of moderate intensity established by exercise intensity guidelines [12,19,150]. Consequently, the activity counts measured at LT2 were higher ($p < 0.01$) than absolute and relative cut-points. The second LT (i.e., the so-called maximum lactate steady-state or MLSS) represents the highest constant-rate velocity or power output that can be sustained over time without a continual blood lactate accumulation [74] and is the upper limit of exercise beyond which there is an abrupt rise in plasma catecholamine levels and fatigue [80]. There is a lack of normative values of LTs in adults, but our results demonstrate that both moderate and vigorous intensities defined by current PA guidelines [12,19,24,150] are included in the relative intensity range between LT1 and LT2 (46-73%$\dot{V}O_{2max}$ or 58-85%HR_{max}). These exercise intensity categories were initially defined according to %$\dot{V}O_2$ reserve as a standard for conversion to other expressions of exercise intensity (e.g., METs, %$\dot{V}O_{2max}$ or %HR_{max}) based on a 10 MET fitness group [6,19]. In less fit individuals, health/fitness benefits have been reported with a minimum exercise intensity of ~40-50%$\dot{V}O_2$ reserve or 55-65%HR_{max}. Owing to the high proportion of physically inactive and unfit adults, and people with increased risk of cardiovascular disease, PA authorities reduced the recommended amount and intensity of PA from the original recommendations, which were based on athletic population [25]. It is acknowledged that individuals with higher fitness levels require higher training stimulus to improve health/fitness [25]. Therefore, and in line with the 1998 ACSM´s position stand, vigorous exercise or exercise intensities close to LT2 (i.e., 70-90%HR_{max}) should be recommended for larger health/fitness benefits in postmenopausal women with maximum CRF values ~10 METs.

The large interindividual variability in activity counts at absolute, relative and individual LT intensities is evidence that individually-tailored rather than fixed accelerometer intensity cut-points might better represent meaningful volumes of light, moderate and vigorous intensities

during daily activities. Our results go hand-in-hand with the findings of Ozemek and colleagues [110] showing that CRF, rather than age or BMI influenced individual´s activity count cut-points at relative intensities, explaining half of their variance. As we showed in a previous study, it was easier for high-fit individuals engaging in higher levels of PA when using the same fixed accelerometer intensity cut-points for everyone, but it does not necessarily mean that they are having higher relative intensities. In fact, there was no difference in the time spent at MVPA when the accelerometer activity cut-points were individualized according to their lactate thresholds [157]. Therefore, epidemiology studies should at least consider adjusting the association between PA and mortality risk by CRF. Besides, a meta-analysis conducted by Williams [23] reported higher potential to reduce the risk of developing CVD in favour of CRF compared to the amount of PA. Although PA increases CRF and may be an appropriate therapy mostly for the unfit, only 35% of the variance in CRF is explained by PA, probably because of the low correlation of CRF with the amounts of light or moderate intensity activity. Thus, the aforementioned association might have been inflated by the higher CRF in those reporting higher physical activity dose.

This study used a novel approach to set individualized accelerometer activity cut-points through LTs. Despite the methodological shortcomings of accelerometers-based measures in PA surveillance [158], the proposed method in this study avoids the misinterpretation of intensity-specific PA levels when using fixed activity cut-points in individuals or groups varying in CRF. The current study is not without limitations. First, the applicability of this individualized approach is not feasible for large epidemiological studies, although they could benefit from population-specific relative intensity cut-points to obtain more reliable PA outcomes. Second, the generalizability of these findings are limited to postmenopausal women with such $\dot{V}O_{2max}$ values (range: 6-14 METs), who are worthy of distinct attention due to the increased risk of cardiovascular disease [117] and osteoporosis [118]. Third, our study was a cross-sectional study. Although higher relative intensity of daily activities has been associated with reduced CHD mortality [32], randomized controlled trials are needed to confirm whether PA recommended by guidelines applying relative intensity thresholds brings greater long-term health benefits compared to absolute intensity. Finally, we did not directly measure the $\dot{V}O_2$ during the CVTs for the determination of the LT2. The gold standard method for the determination of LT2 requires at least two or three CVT; consequently, increasing the time and cost related to cardiopulmonary exercise testing. Instead, we accurately determined LT2 velocity from CVTs to derive the activity counts from individual regression equations with measured $\dot{V}O_2$ values from the incremental test.

Conclusions

In conclusion, the widely utilized 3 METs threshold to derive accelerometer activity counts cut-points that represent the lower boundary of moderate intensity physical activities was well below from both, the relative intensity threshold (46%$\dot{V}O_{2max}$) and LT1. Further, the large interindividual variability in activity counts at relative moderate intensities is evidence that individually-tailored activity counts cut-points expressed either, relative to CRF level or to LT velocities may better represent meaningful PA intensity levels compared to fixed cut-points derived from the recommended absolute intensities of 3 and 6 METs in postmenopausal women.

What does this article add?

The article provides valuable information regarding the use and interpretation of objectively measured PA levels using accelerometers. The study highlights the important role of CRF in the selection of appropriate accelerometer intensity cut-points. Besides, it provides the procedures for the individualization of accelerometer intensity cut-points through an easy-to-administer submaximal walking test that could overcome the under- or overestimation of PA levels using fixed cut-points derived from the absolute moderate intensity recommendations.

6 Results 3rd Study

Objectively measured absolute and relative physical activity intensity levels in postmenopausal women

Reference:

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Abstract

Purpose. To investigate how objectively measured PA levels differ according to absolute moderate intensity recommendation (3-6 METs) and relative to individual lactate thresholds (LT1 and LT2), and to verify if high-fit women record higher PA levels compared to women with lower aerobic fitness. ***Methods.*** Seventy-five postmenopausal women performed an incremental exercise test and several constant-velocity tests wearing an accelerometer to identify the activity counts ($ct \cdot min^{-1}$) corresponding to LT1 and LT2. Individual linear regression determined activity counts cut-points for each intensity: 1) sedentary (<200 $ct \cdot min^{-1}$), 2) light (from 200 $ct \cdot min^{-1}$ to $ct \cdot min^{-1}$at LT1), 3) moderate ($ct \cdot min^{-1}$ between LT1 and LT2) and 4) vigorous ($ct \cdot min^{-1}$ >LT2). Participants then wore an accelerometer during a week to measure the time spent at each PA intensity level. ***Results.*** According to absolute intensity categorization, high-fit postmenopausal women recorded twice as much time at MVPA ($p < 0.01$) than low-fit women. However, when PA intensity was calculated relative to individual lactate thresholds, MVPA was significantly reduced by half ($p < 0.01$) and the data revealed no differences ($p = 0.62$) between groups (~20 $min \cdot day^{-1}$ at MVPA). ***Conclusions.*** Accelerometer cut-points derived from absolute moderate-intensity recommendations overestimated MVPA. Similar time at MVPA was recorded by high- and low-fit postmenopausal women when the cut-points were tailored to individual lactate thresholds. A more accurate estimation of PA behavior could be provided with the use of individually tailored accelerometer cut-points.

Keywords: Accelerometry; cardiorespiratory fitness; individually tailored cut-points; moderate-to-vigorous physical activity.

Introduction

Physical activity level and CRF are two of the most powerful predictive factors of premature death and chronic disease [1,11]. Observational prospective cohort studies using self-reported questionnaires suggest that meeting current PA guidelines [12,19,35] of 150 min·wk^{-1} of MVPA reduces all-cause mortality risk by 26-31% [9-11]. Several studies have reported that MVPA, rather than total EE or light intensity PA is determinant to reduce the levels of cardiometabolic risk factors [11,15,20] and osteoporosis [159].

Large epidemiology studies using self-reported PA questionnaires [10,11] have commonly grouped recreational PA into three intensity categories according to their energy requirements, supported by evidence-informed guideline recommendations [12,19,26,27,35]: light (<3 METs), moderate (3-6 METs) and vigorous (>6 METs). Interestingly, Lee and colleagues [32] showed that it is the relative intensity of exercise, rather than total EE or absolute intensity of activities what causes greater reduction in CHD mortality risk. During the last years, accelerometers have replaced PA questionnaires to objectively capture human activity, applying activity cut-points derived from the traditional absolute 3-6 MET intensities to obtain representative volumes of MVPA [98,102,103]. These studies have generated widely divergent regression models for converting activity counts to EE, yielding different cut-points for PA intensity categories [105]. Contrary to self-reported estimates, results of accelerometer-based objective assessments of PA report much lower volumes of MVPA [11,113] indicating that only a small proportion of adults (7-15%) meet current PA recommendations [113-116]. Reported objective weekly volumes of MVPA are significantly lower in women and vary from as low as seven min·day^{-1} to 57 min·day^{-1} [113-116]. Previous studies have demonstrated that the use of fixed cut-points may under or overestimate MVPA due to the lack of consideration of an individual´s CRF [109-111]. When moderate intensity activity counts cut-points have been calculated based on relative intensities (i.e., 45-60%$\dot{V}O_{2max}$) the results show substantial differences in measured activity counts between less fit and most fit individuals [109,110]. Furthermore, Kujala and colleagues [116] using heart-rate based PA assessment reported that although the time spent at MVPA applying fixed absolute intensity cut-points was higher in men compared to women, and decreased with age, when intensity levels were calculated relative to individual´s CRF, these differences disappeared.

The validity of this "relative intensity" approach has also been substantially criticized because exercising at the same relative intensity could elicit a wide range of metabolic stress across individuals [63]. The determination of individual physiological break points of energy

supply, as the lactate thresholds (LT), is the gold standard method for accurate exercise intensity prescription [72,74,78]. Besides, the achieved workload at LT is an accurate indicator of CRF [75]. In this study, we were interested in accurately quantifying PA volumes in postmenopausal women because they usually report lower MVPA compared to men [113,116], and because they have an increased risk of osteoporosis and cardio-metabolic diseases related to menopause, lower fitness and inactivity [117,118]. It is unknown how well individually-tailored accelerometer cut-points derived from LT reflect PA levels during routine activities of daily living, and whether differences exist between less fit and most fit women.

This study aimed to investigate how objectively measured PA levels differ according to absolute moderate intensity recommendation (3-6 METs) and relative to individual lactate thresholds (LT1 and LT2), and to verify if high-fit women record higher PA levels, especially MVPA, compared to women with lower fitness level.

Methods

Study design

This cross-sectional study investigated the volumes of absolutely and relatively (*i.e.*, relative to participant´s LT) determined PA at different intensity levels (sedentary, light, moderate, vigorous, and moderate-to-vigorous combined) during one week in postmenopausal women. Participant´s aerobic fitness and PA data were collected from November 2015 to June 2017. Participants performed on different days an incremental submaximal shuttle test (IST) and several CVT wearing an accelerometer to identify the activity counts corresponding to LT1 and LT2 velocities. Participants then wore an accelerometer for seven complete days to assess their PA patterns.

Study participants

Participants were recruited through advertisements placed on healthcare centers. One hundred and four participants were screened by telephone, 88 were deemed eligible and were invited to participate in the study. Inclusion criteria were: 1) surgical or natural menopause (no menstrual periods during previous 12 months), 2) age <75 years. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: 1) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees or feet, 2) functional limitation to walk for 20 minutes, 3) presence of any chronic disease that would impair the cardiorespiratory system during testing. The local hospital´s ethical committee approved the study (Pyto2011/71) and written informed consent was obtained from

all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in *ClinicalTrials.gov PRS* (NCT02984553).

Exercise tests

Incremental shuttle test (IST)

Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least four hours and strenuous activity for ≥24 h before testing. Height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest 0.1kg (Seca, Germany). Before starting the test each participant´s resting HR (Polar V800, Polar Electro Oy, Kempele, Finland) and BLC (Lactate Pro2, Arkray, Japan) were measured on a standing position. Capillary blood samples (0.3 µL) were taken from a hyperemic earlobe. Testing was performed in a laboratory setting in a controlled temperature environment (~20º) over a 20 m indoor track. The distance of the course was extended to 20 m from the original test [152] to keep the pace constant avoiding excessive turns that might increase the energy cost and musculoskeletal demand, potentially leading to premature fatigue, discomfort or even injury. Five cones were positioned at 0.5–5–10–15 and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start (**Figure 16a**). The speed was dictated by an audio signal. A double beep indicated the start of each stage. After that, participants were instructed to be at the next cone with each beep while keeping the pace as constant as possible. The IST started at 2.4 $km \cdot h^{-1}$ (~2.1 METs). The intensity was progressively increased by 0.61 $km \cdot h^{-1}$ [152] at each 2-min stage with 1-min rest in between. At the end of each stage, HR and BLC were recorded. Each participant wore a triaxial accelerometer (Actigraph wGT3X-BT Pensacola, FL, USA) over the right iliac crest in the mid-axillary line throughout the test.

Each participant was free to start running from the 7th stage onwards (6.1 $km \cdot h^{-1}$), or the operator suggested to do so when the participant was not able to match the required speed. The test was stopped when: 1) BLC values were ≥3.0 $mmol \cdot l^{-1}$ to avoid excessive fatigue, and/or 2) participant repeatedly failed to match the pace programmed, and/or 3) participant was exhausted. LT1 was defined as the highest velocity above which BLC increased by an amount of ≥0.1 $mmol \cdot l^{-1}$ in the following stage and ≥0.2 $mmol \cdot l^{-1}$ in the subsequent stage (**Figure 16b**).

Constant-velocity tests (CVT)

Participants completed two to seven 20 min CVT on the same 20 m track used for the IST. Each participant performed the corresponding tests on separate testing days (one week in between).

Each CVT consisted of two stages of 10 min at a constant pace with a two minutes interruption for blood sampling. Heart rate was continuously recorded, and capillary blood samples were obtained before at rest, at the 10th min and the end of exercise (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which blood lactate increased by 1 mmol·l^{-1} above the blood lactate value at LT1 during the IST. In the following tests, the velocity was increased or decreased by ~0.30 km·h^{-1} until the maximal lactate steady state velocity (i.e., LT2) could be determined [153]. An increase in BLC ≤0.4 mmol·l^{-1} during the final 10 min of exercise was defined as steady state [74] (**Figure 16c**).

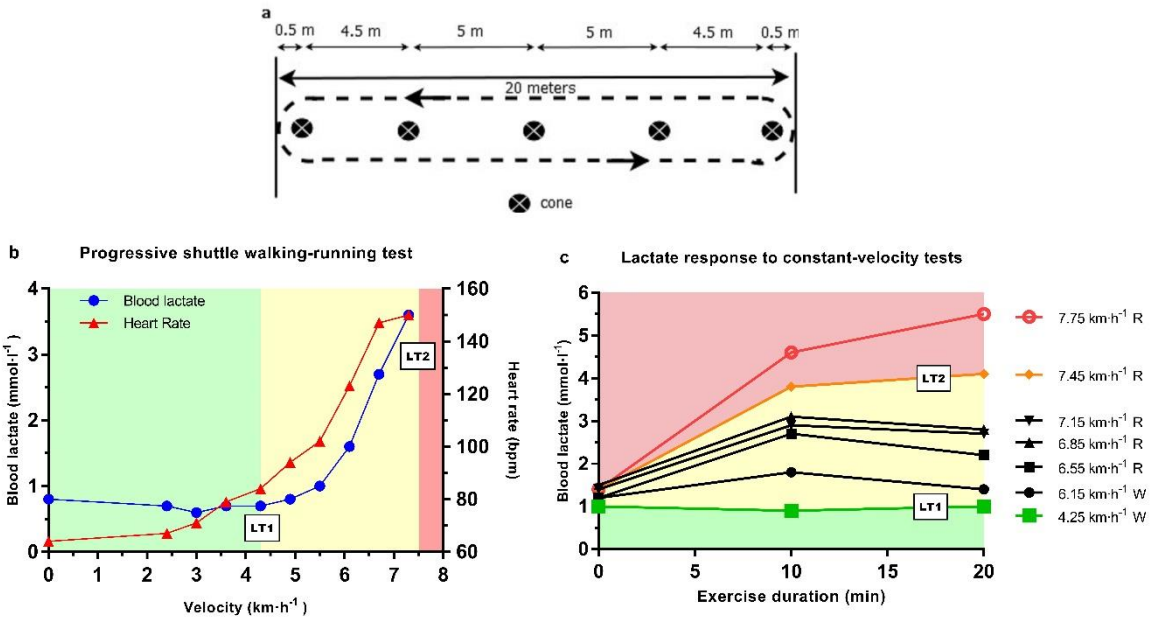

Figure 16. a) Schematic representation of the 20 m track used in the IST and CVT. **b)** Blood lactate and heart rate response during the IST for the individual determination of the LT1 in a representative participant. The participant started running at 6.7 km·h^{-1} **c)** Lactate response during several CVT for the determination of the LT2 in the same representative participant. Three metabolic intensity zones: light (<4.25 km·h^{-1}), moderate (4.25-7.45 km·h^{-1}) and vigorous (>7.45 km·h^{-1}) are indicated by different background colours (green, yellow and red, respectively). LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, W: walk, R: run.

Physical activity assessment

Each participant was instructed to wear an Actigraph wGT3X-BT accelerometer over the right iliac crest at the mid-axillary line on an elasticized belt for eight consecutive days (24h) alongside a daily log.

Each monitor was previously initialized at a 50Hz frequency and downloaded after the 8-day period in VM_3 activity counts in 1-min epochs (ct·min^{-1}). Data were analyzed with Actilife 6® full software (Actigraph, Pensacola, FL, USA). The first recording day was not used for the

analysis. Sleep periods were selected from participant's daily logs. For the present analysis, only data over the day were used. Participants were included in the analysis if they had a minimum of five days of monitoring, including two weekend days and daily wear time was ≥12 hours [105]. Periods of continuous zeros lasting more than 60 min with allowance for 2 min interruptions of activity counts between 0 and 200 [96] were checked in participant´s daily logs and assigned as non-wear time if corresponded [105]. High activity levels (>10.000 ct·min^{-1}) or high step counts (>20.000 steps·day^{-1}) were verified against participant's daily logs.

Accelerometer activity counts measured during the IST at the velocities corresponding to each participant´s LT1 and LT2 were used to determine three individual intensity zones: light (<LT1 ct·min^{-1}), moderate (LT1 ct·min^{-1} - LT2 ct·min^{-1}) and vigorous (>LT2 ct·min^{-1}). Both, the light-intensity and the moderate-intensity zones were subdivided into other identical two zones (low and high) (**Figure 17**). The time (min·day^{-1}) spent in each of these intensity zones for every valid day and the number of daily steps were averaged. Both, sedentary time and MVPA were reported in one (+1) and ten (+10) minute bouts (the minimum time required to be between the specified intensity cut-points). The time spent at each relative intensity category was compared to absolute accelerometer activity counts cut-points, which have been previously validated against direct measurement of oxygen uptake during treadmill walking and running activities designated as movements that represent moderate intensity recommendations (3-6 METs) (i.e., light = 200-2689 ct·min^{-1}, moderate = 2690-6166 ct·min^{-1}, vigorous ≥6167 ct·min^{-1} [102].

Statistical analysis

Accelerometer activity counts during IST were calculated by averaging the VM_3 activity counts in one-second epochs during the central 90sec of each stage. These activity counts were then averaged in 1-min epochs (ct·min^{-1}). The corresponding ct·min^{-1} at LT2 were selected from the individual regression equations obtained in the IST. For women who walked at the LT2 during the CVT, the data of running stages were removed. For women who ran at LT2 during the CVT and for whom this velocity was between the last walking stage and the first running stage of the IST, linear interpolation was performed.

For the whole sample, repeated measures ANOVA was used to determine differences in both, [La$^-$] and activity counts throughout the IST. Bonferroni Post Hoc analysis was applied when significant effects were observed for velocity stages.

Participants were categorized into two groups according to their LT2 velocity (Low-fitness group; as ≤6.8 km·h^{-1} [n = 37], and high-fitness group; as >6.8 km·h^{-1} [n = 38]), which

represented the median speed of LT2 and corresponded to the minimum level of CRF (6-7 METs) associated with lower event rates in 40 to 60 years old women [1]. The differences in the activity count cut-points at LT1 and LT2 between groups were presented using Tukey Box Plots and Mann Whitney U-test was used for comparison between groups.

The primary outcome of the study was the volume of objectively measured PA (particularly $MVPA_{+10}$) expressed as mean ± SD, using both, relative and absolute cut-points. Intra-group PA levels ($min \cdot day^{-1}$) were compared using a paired *t*-test or Wilcoxon test (for non-parametric data), and Independent samples test or Mann Whitney U test were used for inter-group analysis.

We conducted a post hoc power analysis using the G*Power software [160]. The level of statistical power reached in this study was 0.99 for the following variables; alpha level (α = 0.05), sample size (n = 75), and effect size (ES = 0.80 relative *vs.* absolute $MVPA_{+10}$). Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS statistical software (version 22.0, IBM SPSS Statistics, Chicago, IL).

Results

Population selection and characteristics

Among 104 interested participants who were screened for eligibility, 14 were excluded. Reasons for exclusion were; 1) not meeting eligibility criteria (n = 12), and 2) declined to participate (n = 2). Among 88 participants who were invited to participate, 75 completed all the assessments and were included in the study for data analysis. Reasons for exclusion in data analysis were inability, musculoskeletal pain or discomfort when running (n = 6), failure to get the LT2 with accuracy (n = 3), invalid 7-day accelerometry recording (n = 1), cardiovascular or pulmonary disease (n = 2), and failure to keep testing appointment (n = 1). All participants had a minimum of 5-valid days (2 weekend days included), and 78% had 7-valid days.

Determination of PA intensity levels through lactate thresholds

The average velocity *vs.* BLC curve during the IST in the whole group of participants is presented in **Figure 17**. During the first five stages BLC did not change noticeably. From the fifth stage onwards, BLC significantly increased ($F_{8,568}$ = 137.5, $p < 0.001$) in each subsequent exercise stage. Accelerometer activity counts increased linearly and significantly ($F_{7,497}$ = 892, $P < 0.001$) over the duration of the IST. Average LT1 was 5.1 ± 0.7 $km \cdot h^{-1}$, and the corresponding activity counts, BLC, and HR values were 4133 ± 1152 $ct \cdot min^{-1}$, 0.8 ± 0.2 $mmol \cdot l^{-1}$ and 98 ± 12 $beats \cdot min^{-1}$ (bpm), respectively. Mean LT2 was 7.1 ± 1.0 $km \cdot h^{-1}$, and the corresponding activity

counts, BLC, and HR values in the IST were 6783 ± 2077 ct·min^{-1}, 2.4 ± 0.7 mmol·l^{-1}, and 141 ± 17 bpm.

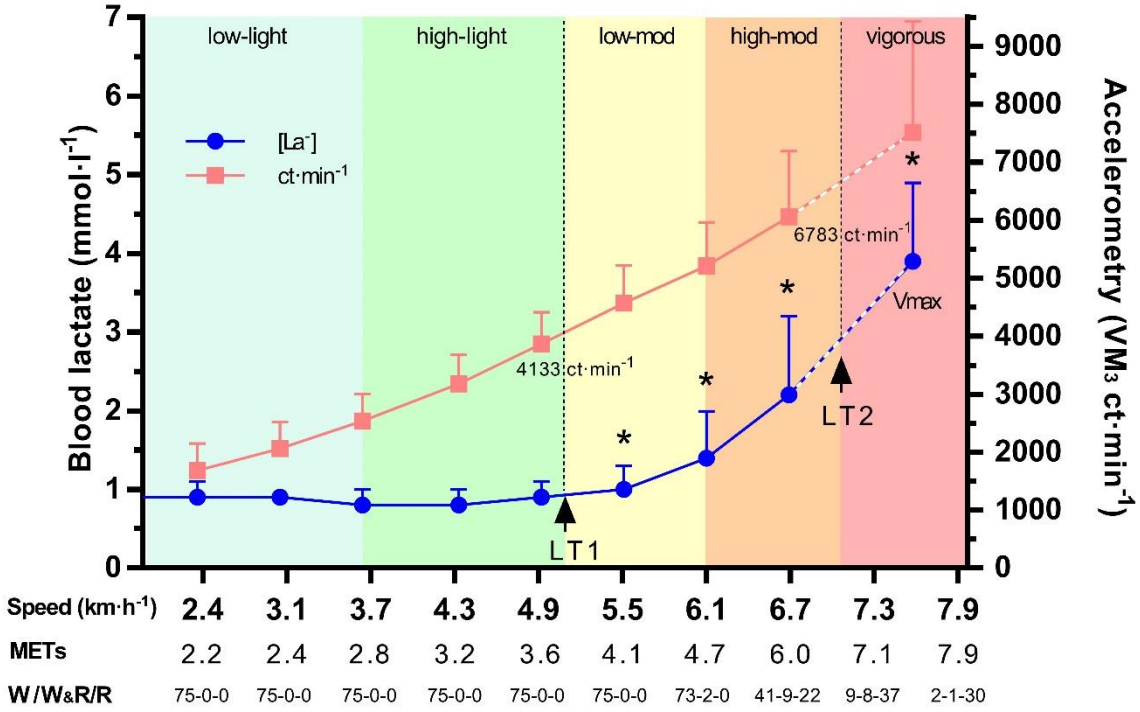

Figure 17. Blood lactate concentration and accelerometer activity counts during the IST. Data are mean values for the whole sample (n = 75). Five metabolic intensity zones: low-light and high light (<LT1), mod-low and high-low (between LT1 and LT2) and vigorous (>LT2) are indicated by different background colours (blue-green, yellow-orange and red, respectively). [La^{-}] = blood lactate, ct·min^{-1} = activity counts per minute, LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, V_{max} = maximal velocity obtained during the test, VM_3 = vector magnitude activity counts, MET = estimated metabolic equivalents [156], W, W&R, R = number of subjects walking, a combination of walking and running or running, respectively, at each stage. ***** Significantly (p <0.01) different from the previous stage.

Individually tailored activity counts cut-points by fitness group

High-fit women were five years younger (p <0.01) and their body mass was eight kg lower (p <0.01) compared to the low-fit group. LT1 and LT2 were 17% and 24% higher in high-fit compared to low-fit women (p <0.01), respectively. Accordingly, measured activity counts were greater in the high fit group (p <0.01) at both, LT1 (4659 ± 1250 *vs.* 3592 ± 729 ct·min^{-1}) and LT2 (7989 ± 2035 *vs.* 5543 ± 1223 ct·min^{-1}) (**Figure 18**).

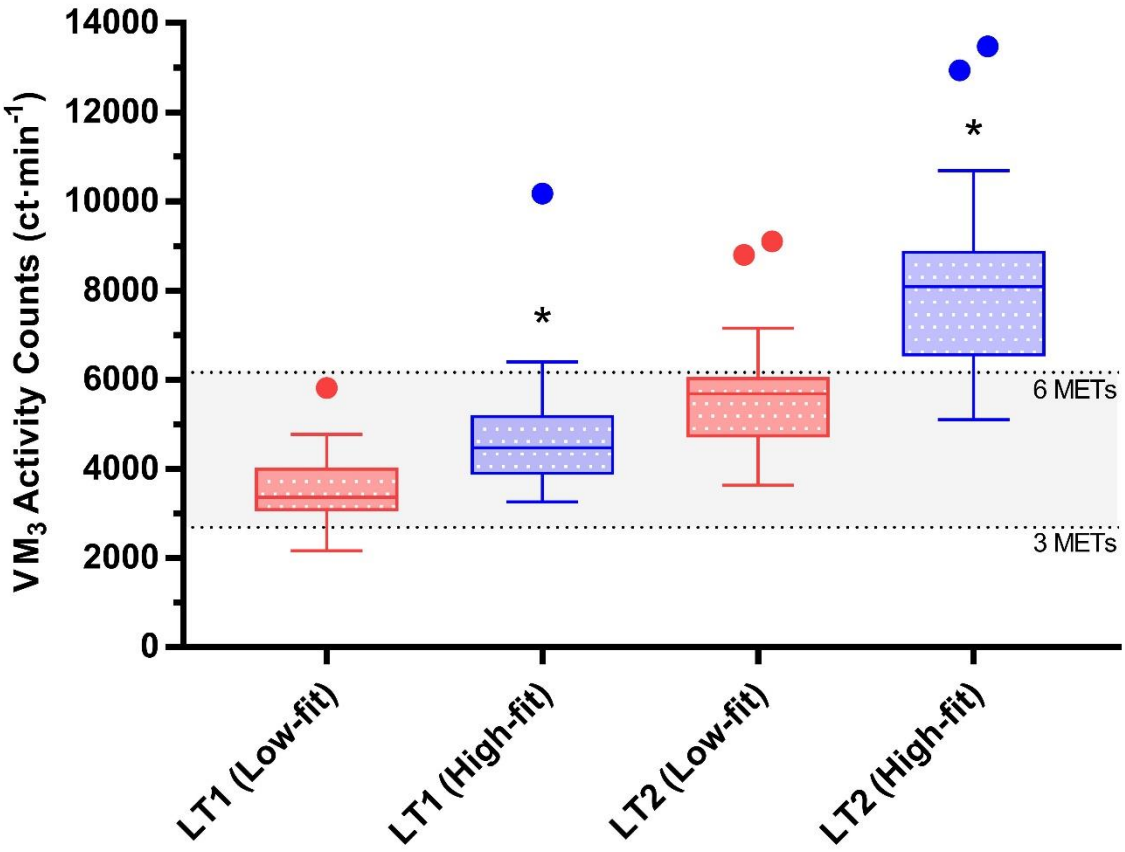

Figure 18. Tukey Box Plot showing the median and the 25-75 percentiles of the VM_3 activity counts at LT1 and LT2 velocities in Low-fit (red coloured) and High-fit (blue coloured) groups. The grey coloured area shows the VM_3 activity counts cut-points derived from walking and running activities that represent an intensity of 3 and 6 METs [102]. VM_3 = vector magnitude, MET = metabolic equivalent, LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, Low-fit = low aerobic fitness group (≤6.8 km·h^{-1}), High-fit = High aerobic fitness group (>6.8 km·h^{-1}). ***** Significantly different between groups ($p < 0.01$).

Physical activity levels

Table 9 shows the results of the minutes spent per day at each intensity level for each group, using both, absolute intensity cut-points [102] and individually-tailored LT cut-points. The two groups exceeded the target of 10.000 daily steps recommended by PA guidelines [19]. Recorded $MVPA_{+10}$ using the absolute intensity cut-points (31.1 ± 24.2 min·day^{-1} or ~218 min·week^{-1} in low-fit and 51.8 ± 31.4 min·day^{-1} or ~363 min·week^{-1} in high-fit) approached the recommended target of 150 min·week^{-1} [19]. High-fit women were ~1 h·day^{-1} less sedentary ($p < 0.01$), they recorded on average 3156 more daily steps ($p < 0.01$), and they engaged in twice as much time ($p < 0.01$) at absolute MVPA compared to low-fit women. However, when PA intensity boundaries were individually tailored, daily time spent at $MVPA_{+10}$ was significantly reduced ($p < 0.01$) by ~40% in low-fit and by ~60% in high-fit groups. These data revealed no differences

(p = 0.62) between groups (~20 min·day^{-1} in 10-min). Accordingly, the number of participants meeting PA guidelines dropped from 62% to 32% in low-fit and from 82% to 40% in high-fit (p <0.01). The only difference between groups using relative intensity cut-points was in low-light PA. The high-fit group spent ~1 h·day^{-1} more at the lowest intensity activities (p <0.01).

Table 9. Comparison of daily physical activity levels (min·day^{-1}) according to relative or absolute intensity activity cut-points in high and low cardiorespiratory fitness groups.

	Low-fit (n=37)		**High-fit (n=38)**	
Age (years)	61.4 ± 5.8		56.6 ± 4.0**	
Height (cm)	157.8 ± 5.0		159.3 ± 5.8	
Body mass (kg)	69.7 ± 12.7		61.4 ± 6.0**	
BMI (kg/m^2)	27.9 ± 4.3		24.2 ± 2.5**	
LT1 (km·h^{-1})	4.7 ± 0.5		5.5 ± 0.6**	
LT2 (km·h^{-1})	6.3 ± 0.4		7.8 ± 0.9**	
Steps	10682.1 ± 3402.0		13837.7 ± 4074.3**	
Sedentary $_{+1}$ *(min·day^{-1})*	503.2 ± 103.7		449.9 ± 96.7*	
Sedentary $_{+10}$ *(min·day^{-1})*	426.0 ± 121.7		363.4 ± 104.7*	
Activity intensity level (min·day^{-1})	*Relative*	*Absolute*	*Relative*	*Absolute*
Low-light	342.6 ± 86.2	297.6 ± 69.5††	402.9 ± 78.8≠	311.5 ± 65.9††
High-light	75.8 ± 34.0	99.1 ± 39.5††	73.9 ± 27.6	112.7 ± 32.5††
Low-mod	20.6 ± 16.5	41.8 ± 19.5††	25.2 ± 26.7	47.9 ± 18.9††
High-mod	7.5 ± 11.4	13.2 ± 18.5†	6.2 ± 8.3	31.1 ± 24.2*††
Vigorous	3.3 ± 7.8	0.7 ± 1.5††	2.3 ± 5.2	6.0 ± 8.9*††
MVPA$_{+1}$	31.4 ± 24.7	55.6 ± 28.0††	33.7 ± 28.5	85.0 ± 32.9*††
MVPA$_{+10}$	18.8 ± 21.2	31.1 ± 24.2††	21.6 ± 25.9	51.8 ± 31.4*††
Meeting PA guidelines (%)	32.4	62.2††	39.5	81.6†

Data presented as mean ± standard deviation or percentages. Low-fit = Low LT2 velocity group, High-fit = High LT2 velocity group, relative = relative intensity method based on lactate thresholds, Absolute = absolute intensity method based on measured activity counts at 3-6 METs [102], MVPA = Moderate-to-vigorous physical activity. Physical activity (PA) guidelines = ≥150 min·wk^{-1} of MVPA in 10-min bouts [19]. Sedentary time and MVPA are reported in 1 and 10 minute bouts (+1, +10, respectively).
†Significant intra-group differences between relative and absolute cut-points (p <0.05).
††Significant intra-group differences between relative and absolute cut-points (p <0.01).
* Significant inter-group differences at absolute cut-points (p <0.05).
** Significant inter-group differences at absolute cut-points (p <0.01).
≠ Significant inter-group differences at relative cut-points (p <0.05).

Discussion

In this study, we tested whether individually-tailored cut-points based on lactate thresholds differed in the time spent at different PA intensity levels to fixed cut-points obtained at absolute moderate intensity (i.e., 3-6 METs) [102] in postmenopausal women differing in CRF. Our findings demonstrated that high-fit women were 1h less sedentary, recorded ~3000 more daily steps and twice as much time at MVPA compared to low-fit individuals using absolute intensity cut-points. However, when PA intensity cut-points were individually tailored according to LT,

the time spent at MVPA was significantly reduced by 60% in high-fit and by 40% in low-fit groups, showing no difference in the time spent at MVPA between groups.

Fixed or individually tailored cut-points. The role of cardiorespiratory fitness

The selection of appropriate accelerometer cut-points to demarcate PA intensity levels is the cornerstone to obtain reliable PA outcomes and their association with health markers and mortality [111]. LT represent individual physiologic adaptations in the use of energy pathways, and they are accurate indicators of relative exercise intensity [78]. The average activity counts at LT1 were 4133 ± 1152 ct·min^{-1}, showing a substantial interindividual variability (~2000–10000 ct·min^{-1}) due to the large range in LT1 (3.6-7.3 km·h^{-1}). This value is 54% and 29% higher than previously reported values of 2690 [102] and 3208 ct·min^{-1} [103]for the lower boundary of moderate intensity (3 METs), respectively. These differences could be related to the higher energy expenditure value estimated at LT1 (3.7 ± 0.7 METs) [156] compared to the classic 3 METs threshold. Besides, the above mentioned studies [102,103] obtained ~4000 ct·min^{-1} at 4.8 km·h^{-1}, which is closer to the value of 3869 ct·min^{-1} found in our study at the same speed, suggesting that the 3 METs classic boundary falls below the LT1, and thus is not representative of the lower relative moderate intensity boundary in our group of postmenopausal women.

The activity counts measured at LT2 (6783 ± 2077 ct·min^{-1}) were 9% higher and 21% lower than those reported by Sasaki et al. (2011) and by Santos Lozano et al. (2013), respectively, at the upper classic boundary of moderate intensity (6 METs). These two studies used an incremental treadmill protocol with only 2-4 stages to derive activity counts cut-points at 3 and 6 METs. In contrast, our IST provided a minimum of seven data points from all participants, with small speed increments (0.6 km·h^{-1}). Besides, we directly determined the activity counts at LT1 and we used individual, rather than whole-group regression equations to determine the activity counts at LT2. Our results go hand-in-hand with the findings of Ozemek and colleagues (2013) showing that CRF (i.e., LT2 velocity) (R^2 = 0.35–0.56), rather than age or body mass index (R^2 <0.03) influenced individual´s activity count cut-points at relative intensities (**Figure 18**). These findings are evidence that individually tailored cut-points may better represent intensity-specific PA levels.

Implications in the measurement of physical activity

Large variations exist in the volume of objectively monitored MVPA across different countries and studies, and, therefore, in the percentage of adults meeting current PA recommendations [113-116]. These differences could be explained in part by the non-harmonized data collection, and the use of different activity monitors and intensity cut-points between studies [105]. In our study,

using the absolute intensity approach, daily time spent at $MVPA_{+10}$ was 42 min·day^{-1} or 294 min·week$^{-1,}$ and 72% of the study participants met the MVPA target. These values are higher than the 8 min·day^{-1} [113] or the 21 min·day^{-1} [115] reported by US and Canadian women, corresponding to 7% and 15% of American and Canadian women meeting PA guidelines, respectively. The high number of daily steps (~12300) also confirms that our sample was more active than the vast majority of women in previous studies [113,113,115]. This finding is supported by the results of the IPEN study [114], where, among the 17 city-regions, the participants from Pamplona (Spain) recorded the highest levels of MVPA (51 min·day^{-1} in 1-min bouts). Our findings strongly suggest that CRF, rather that BMI has a stronger relationship with both, MVPA and daily steps ($p < 0.01$, $r = 0.49$ and 0.53 *vs.* $r = -0.24$ and -0.28, respectively), without being affected after adjusting for BMI or age. An important finding of our study was that MVPA was significantly reduced ($p < 0.01$) by half (40% in low-fit and 60% in high-fit) when the cut-points were individually-tailored. Thus, the data confirmed that the use of fixed absolute intensity cut-points derived from 3 and 6 MET intensities overestimated MVPA.

Another important finding of this study was that although the high-fit group was ~1h less sedentary, recorded ~3000 more daily steps and twice as much time at absolute MVPA compared to the low-fit group, these differences disappeared when PA levels were analysed according to their relative intensity cut-points, and both groups recorded similar time at MVPA (~20 min·day^{-1} in 10-min bouts). Our results are in line with a large-scale Finish study [116] who found that using HR-based absolute intensity thresholds men recorded twice as much MVPA than women (~45 vs ~22 min·day^{-1} in 1-min bouts). However, using relative intensity thresholds, MVPA was reduced by half (~17 min·day^{-1}) without differences between them. Overall, this information is evidence that using fixed accelerometer activity cut-points derived from the recommended 3-6 METs moderate PA intensity approach may not be the most accurate option when examining PA behavior in samples varying in CRF.

Strengths and limitations of the study

This is the first study measuring accelerometer-based PA using individually tailored cut-points corresponding to LT. Despite the methodological shortcomings of accelerometers-based measures in PA surveillance [158], the proposed method in this study avoids the misinterpretation of intensity-specific PA levels when using fixed activity cut-points in individuals or groups varying in CRF. However, the current study is not without limitations. First, the applicability of this individualized approach is not feasible for large epidemiological studies, although they could benefit from population-specific relative intensity cut-points to obtain more reliable PA outcomes. Second, the generalizability of these findings is limited to postmenopausal women,

who are worthy of distinct attention due to the increased risk of cardiovascular disease [117] and osteoporosis [159]. Third, our study was a cross-sectional study. Although higher relative intensity of daily activities has been associated with reduced CHD mortality [32], randomized controlled trials are needed to confirm whether PA recommended by guidelines applying relative intensity thresholds brings greater long-term health benefits compared to absolute intensity. Fourth, accelerometers do not capture accurate energy expenditure of certain activities (*e.g.*, cycling, swimming, weight training, and some complex low-intensity activities) [106]. Besides, habitual PA could be much more variable than constant velocity exercise tests used to demarcate PA intensity categories, in a way that makes the same ct·min^{-1} more intense (e.g., uphill, involving arm movement or resistance). Nonetheless, LT are the gold standard markers of relative exercise intensity, and the present focus on walking exercise tests is appropriate, because it is the most common type of activity among adults [11].

Conclusions

This study demonstrated that applying recommended absolute moderate intensity criteria of 3-6 METs to accelerometer activity counts cut-points overestimated the time spent at MVPA. Compared to low-fit individuals, it was easier for high-fit individuals to reach MVPA target according to absolute criteria. However, no differences were observed in the time spent at MVPA between high- and low-fit postmenopausal women when the intensity cut-points were individually tailored to their lactate thresholds velocities. Our findings suggest that individually-tailored accelerometer cut-points may provide a more representative PA profile of individuals differing in CRF, compared to the widely used absolute intensity cut-points.

7 Results 4th Study

Estimation of the maximal lactate steady state in postmenopausal women

Reference:

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Abstract

Purpose: This study aimed to estimate the maximal lactate steady-state velocity ($_{v}$MLSS) from non-invasive bloodless variables and/or BL_RTs measured during an IST, and to determine whether the addition of a CVT could improve the estimation. ***Methods:*** Seventy-five postmenopausal women conducted the IST to determine several BL_RTs and bloodless variables, and two to seven CVTs to determine $_{v}$MLSS. Determined BL_RTs were conventionally used LT measured either visually ($_{v}LT_{+0.1mM}$) or mathematically ($_{v}LE_{min}$), and 0.5, 1 and 1.5 mmol·L^{-1} above LT, along with fixed BL_RTs. ***Results:*** The best single predictor of $_{v}$MLSS (7.1 ± 1.0 km·h^{-1}) was $_{v}LE_{min+1.5mM}$ (R^2 = 0.80, p <0.001; SEE = 0.46 km·h^{-1}). The combination of BL_RTs and bloodless variables improved the estimation of $_{v}$MLSS (R^2 = 0.85, p <0.001; SEE = 0.38 km·h^{-1}). The addition of a CVT still improved the prediction of $_{v}$MLSS up to 89.2%, with lower SEE (0.32 km·h^{-1}). ***Conclusion:*** This study suggests that $_{v}LE_{min}$-related thresholds obtained from a single submaximal IST are accurate estimates of $_{v}$MLSS in postmenopausal women, and thus the time-consuming procedure of $_{v}$MLSS testing could be avoided. Performing an additional CVT is encouraged because it improves the prediction of $_{v}$MLSS.

Keywords: Cardiorespiratory fitness, blood lactate-related thresholds; exercise testing; intensity prescription.

Introduction

Epidemiological studies have shown an inverse association between CRF and the incidence of CHD or all-cause mortality in healthy or asymptomatic men and women [1]. The most widely accepted index of CRF is $\dot{V}O_{2max}$ expressed in mL $O_2 \cdot kg^{-1} \cdot min^{-1}$or in METs [2]. It is acknowledged that the minimum level associated with significantly lower event rates for men and women is approximately 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively [1,2]. However, the measurement of $\dot{V}O_{2max}$ requires maximal exercise testing, which is very often not accesible nor possible in middle-aged people due to motivational or financial reasons [22]. An easier, non-dependent on motivation and widely accepted approach to evaluate CRF is the analysis of BLC plotted against exercise intensity or duration during submaximal exercise.

More than 20 BL_RTs have been defined so far, leading to considerable confusion and misinterpretation [75]. However, two of these thresholds have emerged as the preferred endurance performance markers among the vast majority of sport and exercise physiologists: 1) The so-called "Lactate Threshold" (LT) defined as the critical exercise intensity level above which BLC first begin to increase above resting values during incremental exercise [151]. The LT has been suggested as the minimum exercise intensity required by inactive individuals to improve CRF [70-72] and is a valid indicator of CRF in athletes and inactive people due to its high association with $\dot{V}O_{2max}$, sports performance [72,74,75,153] and functional capacity in patients [69], and 2) the so-called "Maximal Lactate Steady State" (MLSS), defined as the highest constant workload that can be sustained over time without continual blood lactate accumulation [74]. Both LT and MLSS are more sensitive than $\dot{V}O_{2max}$ to predict endurance performance and to evaluate training adaptations [83], allowing the definition of three individual intensity categories to guide exercise training: light (<LT), moderate (LT-MLSS) and vigorous (>MLSS) [75]. While LT can be determined in a single graded submaximal test, the assessment of MLSS is, however, cumbersome, since it requires several (3-6) constant workload tests on separate days, lengthening the aerobic conditioning evaluation to a minimum of 1-3 weeks [74]. For this reason, simpler methods have been proposed to estimate MLSS intensity from a single incremental test, involving the use of either blood lactate [74,75,85-87], respiratory [67,89], or the maximum workload achieved during an exercise test to exhaustion [72,90], resulting in a wide range of correlations (r = 0.63-0.95) with MLSS. However, all existing single session MLSS-estimating tests are variably handicapped by compromised validity, accuracy, resolution, and reliability due to methodological differences and a suboptimal statistical approach (i.e., correlation analysis) leading to incomparable and inconclusive results [75,85,91]. Most of these studies have been conducted in small groups of athletes using exercise tests to volitional fatigue, but little

is known about the prediction of MLSS from BL_RTs using submaximal tests in adults. The inactivity, along with the lower CRF observed in women [155], and the increased risk of cardiovascular disease [117] and osteoporosis [16] after menopause and with advancing age, underline the necessity of well-designed and adequately powered (i.e., intensity) PA programs for postmenopausal women.

To avoid the extensive procedure needed to assess MLSS velocity ($_v$MLSS), we aimed to elucidate whether $_v$MLSS could be accurately predicted from lactate-related and/or bloodless variables measured during an IST in 50-75 years old postmenopausal women. A secondary purpose of the study was to determine the extent to which a single CVT, performed several days after the IST, could improve the prediction of $_v$MLSS. Based on a previous study performed with endurance-trained athletes [161], we hypothesized that BL_RTs that rely on the individual lactate curve would be accurate predictors of $_v$MLSS, showing stronger agreement compared to bloodless variables. We expected that an additional CVT performed on subsequent days would improve the estimation of $_v$MLSS.

Methods

Study participants

Participants were recruited through advertisements placed on healthcare centres. One hundred and four participants were screened by telephone, 88 were deemed eligible and were invited to participate in the study. Inclusion criteria were: 1) surgical or natural menopause (no menstrual periods during the previous 12 months), 2) age <75 years. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: 1) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees or feet, 2) functional limitation to walk for 20 minutes, 3) presence of any known chronic disease that would impair the cardiorespiratory system during testing. The local hospital´s ethical committee for human studies approved the study (Pyto2011/71) and written informed consent was obtained from all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in *ClinicalTrials.gov PRS* (NCT02984553).

Incremental shuttle test (IST)

Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least four hours and strenuous activity for ≥24 h before testing. Height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest

0.1kg (Seca, Germany). Testing was performed in a laboratory setting in a controlled temperature environment (~20º) over a 20 m indoor track [152]. The distance of the course was extended to 20 m from the original test to keep the pace constant avoiding excessive turns that might increase the energy cost and musculoskeletal demand, potentially leading to premature fatigue, pain, discomfort or even injury. Five cones were positioned at 0.5–5–10–15 and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start. The speed at which the participant walked was dictated by an audio signal pre-recorded in MP3 audio format. The IST started at 2.4 $km \cdot h^{-1}$. The velocity was increased by 0.61 $km \cdot h^{-1}$ every 2-min [152], with 1-min intervals between stages. Each participant was free to start running from the 7th stage onwards (6.1 $km \cdot h^{-1}$), or the operator suggested to do so when the participant was not able to match the required speed. Immediately after each stage, heart rate (HR) (Polar V800, Polar Electro Oy, Kempele, Finland), a rating of perceived effort in Borg´s 0-10 scale [154] and capillary blood samples for blood lactate measurements were obtained from a hyperemic earlobe. The test was stopped when: 1) BLC values were ≥3.0 $mmol \cdot L^{-1}$ to avoid excessive fatigue, and/or 2) participant repeatedly failed to match the pace programmed, and/or 3) participant was exhausted.

Constant-velocity tests (CVT)

On subsequent laboratory visits, participants completed two to seven 20 min CVTs on the same 20 m track used for the IST. Each participant performed the corresponding tests on separate testing days (one week in between). Each CVT consisted of two stages of 10 min at a constant pace with 2 min interruption for blood sampling (i.e., 22 min duration). Heart rate was continuously recorded, and capillary blood samples were obtained at rest, at the 10th min and the end of exercise (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which blood lactate increased by one $mmol \cdot L^{-1}$ above LT during the IST. Depending on the BLC stability of the first CVT, the velocity was increased or decreased by ~0.30 $km \cdot h^{-1}$ in the following CVTs. If during the first CVT a steady state or a decrease in BLC was found, the velocity for the next CVT was increased by 0.3 $km \cdot h^{-1}$. Conversely, if an increase in BLC superior to the stability criterion was observed, the speed of the following CVT was decreased by 0.3 $km \cdot h^{-1}$ until the $_{v}$MLSS was determined. The highest constant velocity with an increase in BLC ≤0.4 $mmol \cdot L^{-1}$ during the final 10 min of exercise was defined as the $_{v}$MLSS [74,153,153] (**Figure 20**).

Blood Sampling and Blood Lactate Concentration (BLC) determination

A hyperaemic earlobe was cleaned and dried before puncturing by a lancet device to aspirate a 0,3 μL whole blood sample into an enzyme-coated electrode test strip. Blood lactate concentration was determined via amperometric measurement using a portable analyzer (Arkray KDK Corporation, Lactate Pro2 LT-1710, Shiga, Japan) calibrated before each test. The instrument has shown a good accuracy (R^2 = 0.97; standard error of the estimates, SEE = 0.69 mmol·L^{-1}) and intra-assay reliability (coefficient of variation, CV = 2.9%; intraclass correlation coefficient, ICC = 0.999) at a wide range of BLC [162].

Determination of Blood Lactate-related Thresholds (BL_RT)

Nine different BL_RTs were determined (**Figure 19A**). The velocity at the LT ($_vLT_{+0.1mM}$) was defined as the highest stage-velocity above which BLC increased by ≥0.1 mmol·L^{-1} in the following stage and ≥0.2 mmol·L^{-1} in the subsequent stage. The velocities at 0.5 mmol·L^{-1}, 1 mmol·L^{-1}, or 1.5 mmol·L^{-1} above $_vLT_{+0.1mM}$, were called $_vLT_{+0,5mM}$, $_vLT_{+1mM}$, and $_vLT_{+1.5mM}$, respectively. The velocity corresponding to the Minimum Lactate Equivalent ($_vLE_{min}$) [34]was considered the minimum value of the quotient BLC/velocity in the individual BLC/velocity *vs*. velocity second-order polynomial curves (**Figure 19B**). The velocities at 1.0 and 1.5 mmol·L^{-1} above the $_vLE_{min}$ in the individual BLC *vs*. velocity second-order polynomial curves where called $_vLE_{min+1mM}$ and $_vLE_{min+1.5mM}$, respectively. The velocity at a fixed blood lactate concentration of 2.5 mmol·L^{-1} [163] ($_vFBLC_{2.5mM}$) was determined from the individual BLC *vs*. velocity second-order polynomial curves. The lowest velocity at which BLC was ≥3 mmol·L^{-1} was defined as $V_{≥3mM}$. Besides, the average magnitude of the differences in BLC between successive velocities [[(BLC 4.9-4.3) + (BLC 5.5-4.9) + (BLC 6.1-5.5) + (BLC 6.7-6.1)] / 4] during the IST was tested as an independent predictor (ΔBLC)**.**

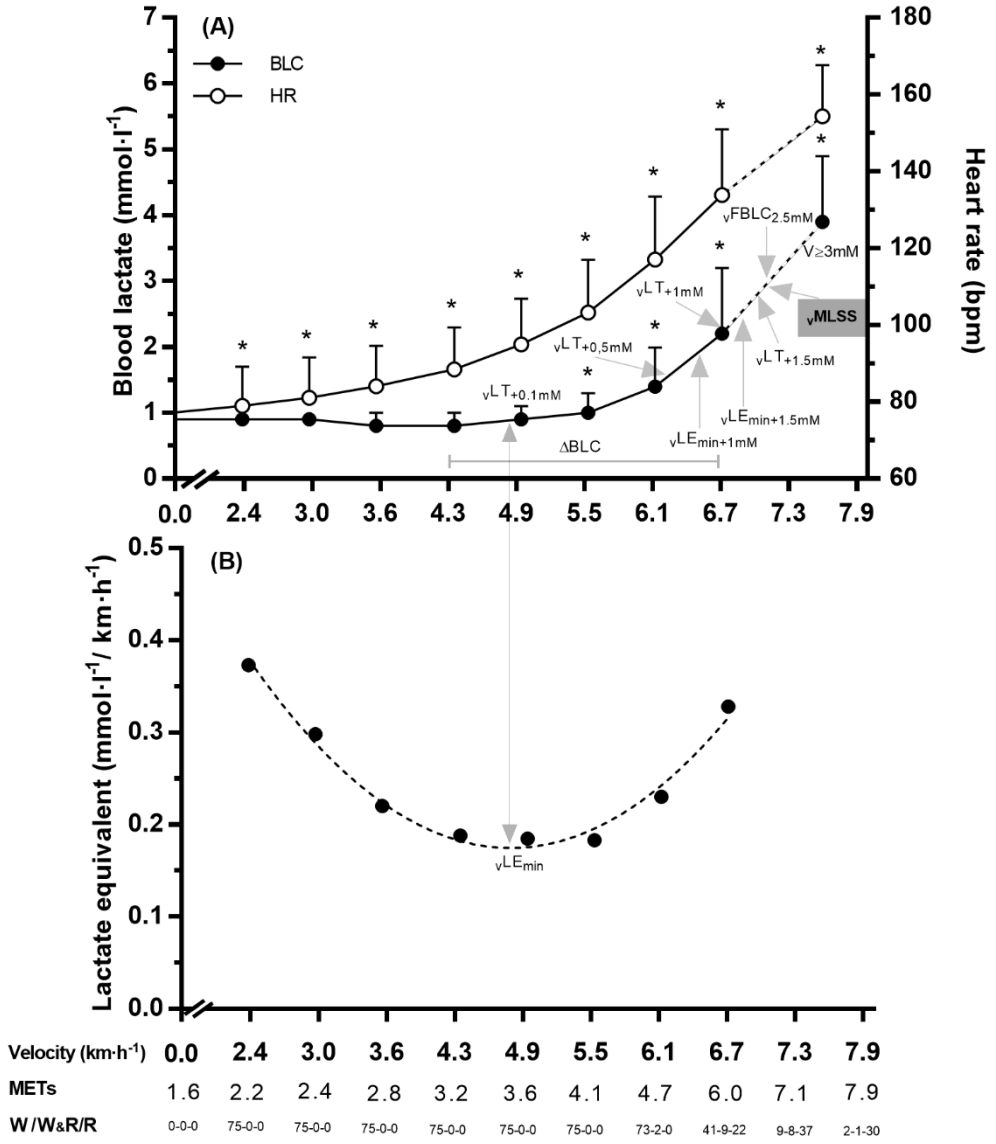


Figure 19. Mean velocity vs. blood lactate/heart rate curve during the submaximal Incremental Shuttle Test (IST) in the whole group of participants and selected BL_RTs (n = 75). Schematic representation of **A)** average BL_RTs values and **B)** determination of $_vLE_{min}$ by modeling the quotient BLC/velocity in the individual BLC/velocity vs. velocity second-order polynomial curve. $_vLE_{min}$ = velocity at the minimum lactate equivalent (km·h-1), $_vLT_{+0.1mM}$ = highest stage-velocity above which BLC increased by ≥0.1 mmol·L^{-1} in the following stage and ≥0.2 mmol·L^{-1} in the subsequent stage, $_vLT_{+0.5mM}$, $_vLT_{+1mM}$, $_vLE_{min+1.5mM}$ = velocity at the lactate threshold + 0.5, 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_vLE_{min+1mM}$, $_vLE_{min+1.5mM}$ = velocity at the minimum lactate equivalent + 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_vFBLC_{2.5mM}$ = velocity at the fixed blood lactate concentration at 2.5 mmol·L^{-1} (km·h^{-1}), $_vMLSS$ = velocity at the maximal lactate steady-state (km·h^{-1}), $V_{≥3mM}$ = the lowest velocity of the IST where the blood lactate value was ≥ 3 mmol·L^{-1}, ΔBLC = mean differences in blood lactate between successive stages (from 4.3 to 6.7 km·h^{-1}), ΔHR = mean differences in heart rate between successive stages (from 4.3 to 6.7 km·h^{-1}). * significantly different ($p < 0.01$) from the previous stage.

Velocities at BL_RTs were determined using MATLAB R2015a (The MathWorks Inc., Natick, MA, USA). Coefficients of determination (R^2) of the individual second-order BLC *vs*. velocity, and second-order quotient BLC/velocity *vs*. velocity polynomial curves were all >0.90. Velocities at BL_RTs [72], as well as $_vMLSS$ [64] frequently show test-retest intra-class correlation coefficients >0.94, and coefficients of variation ≤3%. Heart rate values at BL_RTs were computed from the individual HR *vs.* velocity second order polynomial equations (r >0.98; p <0.001) obtained during the IST.

Bloodless variables

Participant´s age, anthropometric characteristics [body mass, height, and body mass index, (BMI)] and the following HR and perceived exertion [154] related variables were obtained from the IST: minimum resting HR (HR_{rest}) in a supine position for 10min, average magnitude of the differences in HR (ΔHR) between successive velocities during the IST [[(HR 4.9-4.3) + (HR 5.5-4.9) + (HR 6.1-5.5) + (HR 6.7-6.1)], the velocity associated with the minimum value of the quotient HR/velocity obtained from the HR/velocity *vs*. velocity second-order polynomial curve (HR_{min}), and the velocity corresponding to a value of 4 (i.e., "something hard") on Borg´s scale of perceived exertion (0-10) [154] obtained from the second-order polynomial curve between perceived exertion values and velocity (RPE_4).

Statistical analysis

Standard statistical methods were used for the calculation of means, SD, SEE and CI. Data were analyzed using parametric statistics following confirmation of normality (Shapiro-Wilk test), homoscedasticity (Levene´s test), and when appropriate sphericity (Mauchly's test). Repeated ANOVA measures with Bonferroni post-hoc test was used to compare BLC and HR at different velocities during the IST and at different time-points during the CVT.

Student´s paired t-test was used to evaluate differences between each BL_RT with $_vMLSS$. The magnitudes of the differences were assessed with 95% CI and Cohen´s effect sizes (ES). Two-factorial ANOVA with Tukey´s post-hoc test was used to identify differences in BLC between CVTs. We studied the strength of the individual relationships between independent variables and $_vMLSS$ before fitting the models using *Pearson* product-moment correlation coefficients (r). Using $_vMLSS$ determination as the reference method, three different multiple regression models were assessed against it. After checking normality and homoscedasticity by paired plots, all significant variables were entered in a block to each model with the main independent variables of each model defined as: 1) Bloodless variables from a single IST, 2) BL_RTs along with bloodless variables from a single IST and 3) Change in BLC from the 20th to the 10th minute (ΔBLC_{20-10}) during an additional CVT at $_vLT_{+1mM}$, in addition to BL_RTs and

bloodless variables from the IST. Non-significant variables and those producing collinearity were excluded from the final model. Adjusted R^2 was used to assess the proportion of the variance explained by the model. The validity of each predictive equation was investigated with the SEE and the 95% limits of agreement method (LoA, mean difference ± 1.96 SD) [164]. A regression analysis between mean $_{v}$MLSS and the difference in $_{v}$MLSS between the estimated and the measured value was applied to explore whether the degree of systematic error is uniform over the range of values. The level of significance was set at $p < 0.05$. Statistical analyses were performed using SPSS statistical software (version 22.0, IBM SPSS Statistics, Chicago, IL) and GraphPad Prism 7 was used for figures.

Results

Population selection and characteristics

Among 104 interested participants who were screened for eligibility, 14 were excluded. Reasons for exclusion were; 1) not meeting eligibility criteria (n = 12), and 2) declined to participate (n = 2). Among the 88 participants who were invited to participate, 75 completed all assessments and had valid data for analysis (age = 59.0 ± 5.5 years old, BMI = 26.0 ± 3.9 kg/m^2).

Submaximal Incremental Shuttle test

Mean velocity *vs.* BLC curve during the IST in the whole group of participants (n = 75) is presented in **Figure 19A**. Blood lactate concentration started to increase from the fifth stage onwards ($F_{8,568}$ = 137.5, $p < 0.001$). Velocity at LE_{min} (4.8 ± 0.6 km·h^{-1}) was 5.9% lower than $_{v}LT_{+0.1mM}$ ($p < 0.001$; 95%CI: 0.14 to 0.32; ES: 0.38) and both of them were 32% ($p < 0.001$) and 28% ($p > 0.001$) lower than $_{v}$MLSS, respectively (**Table 10**). Average $_{v}FBLC_{2.5mM}$ ($p = 0.984$; 95%CI: -0.10 to 0.11; ES: 0.00) and $_{v}LT_{+1.5mM}$ ($p = 0.742$; 95%CI: -0.13 to 0.09; ES: 0.02) did not differ from $_{v}$MLSS whereas $_{v}LE_{min+1.5mM}$ was only 2.8% lower ($p < 0.01$; 95%CI: -0.26 to -0.05; ES: 0.16) than $_{v}$MLSS. Heart rate increased significantly ($F_{9,639}$ = 1095.5, $p < 0.001$) throughout the test. The HR values at $_{v}LE_{min}$ and $_{v}LT_{+0.1mM}$ were 95 ± 11 bpm and 98 ± 12 bpm, respectively. When $_{v}$MLSS determined from the CVT was set in the velocity *vs.* BLC or the velocity *vs.* HR curves obtained during the IST, the corresponding BLC and HR values were 2.4 ± 0.7 mmol·L^{-1} and 141 ± 17 bpm, respectively.

Table 10. Descriptive features of BL_RTs and their association with $_vMLSS$ (n = 75).

	km·h^{-1}		%$_v$MLSS		*Association with vMLSS*
Variables	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	***r***
$_vLE_{min}$	4.8 ± 0.6 [b]	3.8 – 7.0	68.8 ± 5.5	57.3 – 80.7	0.833 [b]
$_vLT_{+0.1mM}$	5.1 ± 0.7 [b]	3.6 – 7.3	72.1 ± 7.2	56.1 – 91.2	0.722 [b]
$_vLT_{+0.5mM}$	6.2 ± 0.7 [b]	4.6 – 9.2	88.2 ± 8.0	68.6 – 101.7	0.746 [b]
$_vLE_{min+1mM}$	6.5 ± 0.8 [b]	5.0 – 9.5	91.7 ± 6.0	79.2 – 104.5	0.895 [b]
$_vLT_{+1mM}$	6.7 ± 0.8 [b]	5.2 – 9.5	95.5 ± 7.3	77.4 – 110.8	0.839 [b]
$_vLE_{min+1.5mM}$	6.9 ± 0.9 [a]	5.3 – 10.4	98.2 ± 6.4	85.1 – 112.4	0.897 [b]
$_vLT_{+1.5mM}$	7.0 ± 0.9	5.4 – 9.9	100.1 ± 6.5	83.4 – 114.6	0.890 [b]
$_vFBLC_{2.5mM}$	7.1 ± 0.9	5.3 – 9.8	100.4 ± 6.5	87.6 – 114.5	0.896 [b]
$_vMLSS$	7.1 ± 1.0	5.4 – 10.0	100.0 ± N/A	N/A	N/A
$V_{≥3mM}$	7.6 ± 1.0 [b]	6.1 – 10.4	108.5 ± 6.5	89.9 – 125.2	0.869 [b]

BL_RTs = blood lactate-related thresholds, $_vLE_{min}$ = velocity at minimum lactate equivalent (km·h^{-1}), $_vLT_{+0.1mM}$ = highest stage-velocity above which blood lactate concentration increased by ≥ 0.1 mmol·L^{-1} in the following stage and ≥ 0.2 mmol·L^{-1} in the subsequent stage, $_vLT_{+0.5mM}$, $_vLT_{+1mM}$, $_vLT_{+1.5mM}$ = velocity at lactate threshold + 0.5, 1 and 1.5 mmol·L^{-1} above $_vLT_{+0.1mM}$ (km·h^{-1}), $_vLE_{min+1mM}$, $_vLE_{min+1.5mM}$ = velocity at the minimum lactate equivalent + 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_vFBLC_{2.5mM}$ = velocity at the fixed blood lactate at 2.5 mmol·L^{-1} (km·h^{-1}), vMLSS = velocity at maximal lactate steady-state (km·h^{-1}). $V_{≥3mM}$ = the lowest velocity of the IST where the blood lactate value was ≥ 3 mmol·L^{-1}, N/A = not applicable.
[a] p <0.01 vs $_vMLSS$.
[b] p <0.001 vs $_vMLSS$.

Constant Velocity Tests (CVTs)

Figure 20 shows the BLC during 3 CVTs at $_vLT_{+1mM}$, at $_vMLSS$, and at 0.3 km·h^{-1} faster velocity than $_vMLSS$ ($_vMLSS_{+≤0.3}$). At $_vLT_{+1mM}$ (6.7 ± 0.8 km·h^{-1}), BLC increased from rest (1.2 ± 0.3 mmol·L^{-1}) to the 10th minute of exercise (2.8 ± 1.1 mmol·L^{-1}) and remained constant (2.7 ± 1.1 mmol·l^{-1}) throughout exercise (p = 0.17; 95% CI: -0.3 to 0.0; ES: 0.10). However, at this velocity, 25% of the participants showed a blood lactate accumulation during exercise (increase in BLC ≥0.4 km·h^{-1} during the last 10 min of exercise). Slightly higher (p <0.01; 95% CI: 0.3 to 1.0; ES: 0.58) BLC values were obtained at $_vMLSS$ (7.1 ± 1.0 km·h^{-1}; range: 5.4-10.0 km·h^{-1}), increasing from

1.2 ± 0.3 mmol·L^{-1} at rest to 3.3 ± 1.1 mmol·L^{-1} at the 10th minute of exercise, and remained constant throughout exercise. Average HR values during the CVT at $_{v}$MLSS slightly increased from the 10th min (146 ± 13 bpm) to the end of exercise (151 ± 13 bpm) (p <0.01; 95% CI: 3.9 to 5.6; ES: 0.03). At $_{v}$MLSS$_{+\leq 0.3}$, nine participants failed to finish the CVT, and in the remaining participants BLC increased as a function of time from 4.5 ± 1.8 mmol·L^{-1} at the 10th minute of exercise to 5.5 ± 2.0 mmol·L^{-1} at the end of exercise (p <0.01; 95% CI: 1.0 to 1.4; ES: 0.65).

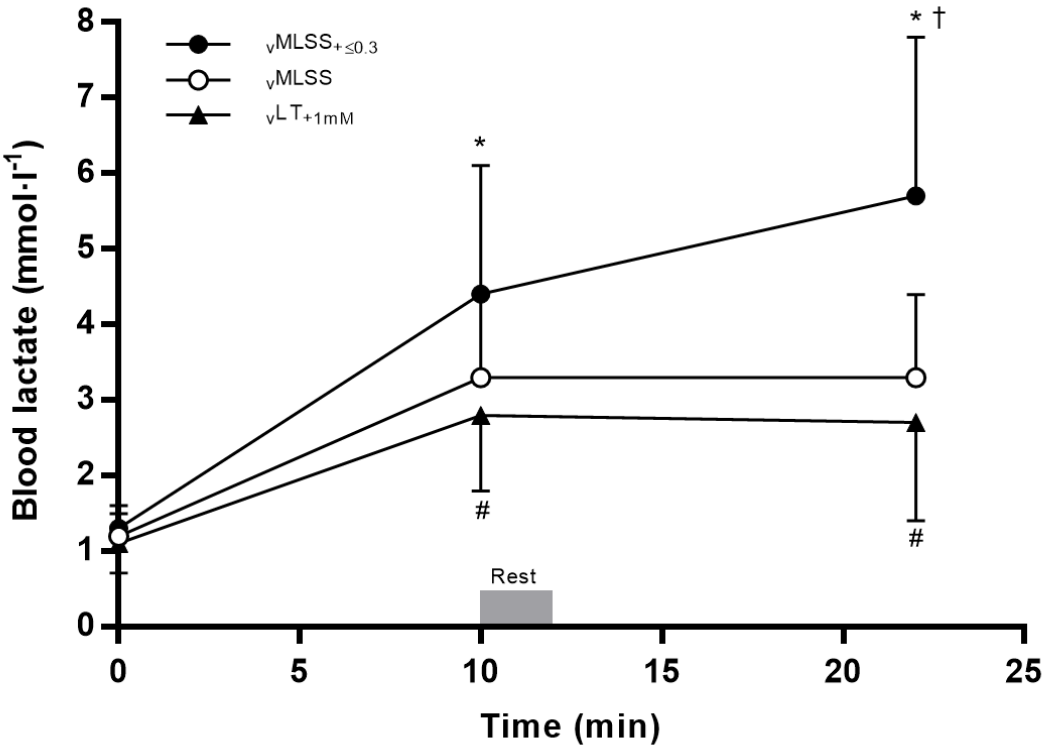


Figure 20. Evolution of blood lactate concentration during the constant velocity tests for the determination of $_{v}$MLSS at $_{v}$LT$_{+1mM}$, $_{v}$MLSS, and at 0.3 km·h^{-1} faster velocity than $_{v}$MLSS ($_{v}$MLSS$_{+\leq 0.3}$). $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}), $_{v}$LT$_{+1mM}$ = velocity at the lactate threshold + 1 mmol·L^{-1} (km·h^{-1}), $_{v}$MLSS$_{+\leq 0.3}$ = constant velocity test performed ≤0.3 km·h^{-1} faster velocity than $_{v}$MLSS. * significantly different (p <0.01) from $_{v}$MLSS and $_{v}$LT$_{+1mM.}$, # significantly different from $_{v}$MLSS, † significant effect for time on BLC (min 10 vs min 22).

Prediction of $_{v}$MLSS

Every BL$_{R}$T correlated significantly with $_{v}$MLSS (p <0.001, r = 0.72-0.90) (**Table 10**). Velocity at LE$_{min+1.5mM}$ was the best single predictor of $_{v}$MLSS (R^2 = 0.801, p <0.001; SEE = 0.456; 95% LoA = -0.90 to 0.89) (**Figure 21**), closely followed by $_{v}$FBLC$_{2.5mM}$ and $_{v}$LE$_{min+1mM}$ (R^2 = 0.799, p <0.001; SEE = 0.461; 95% LoA = -0.90 to 0.90), and $_{v}$LT$_{+1.5mM}$ (R^2 = 0.789, p <0.001; SEE = 0.467; 95%

LoA = -0.91 to 0.92), indicating that the prediction of $_{v}$MLSS from these four single BL_RTs could be biased up to ~13% above or below the actual $_{v}$MLSS.

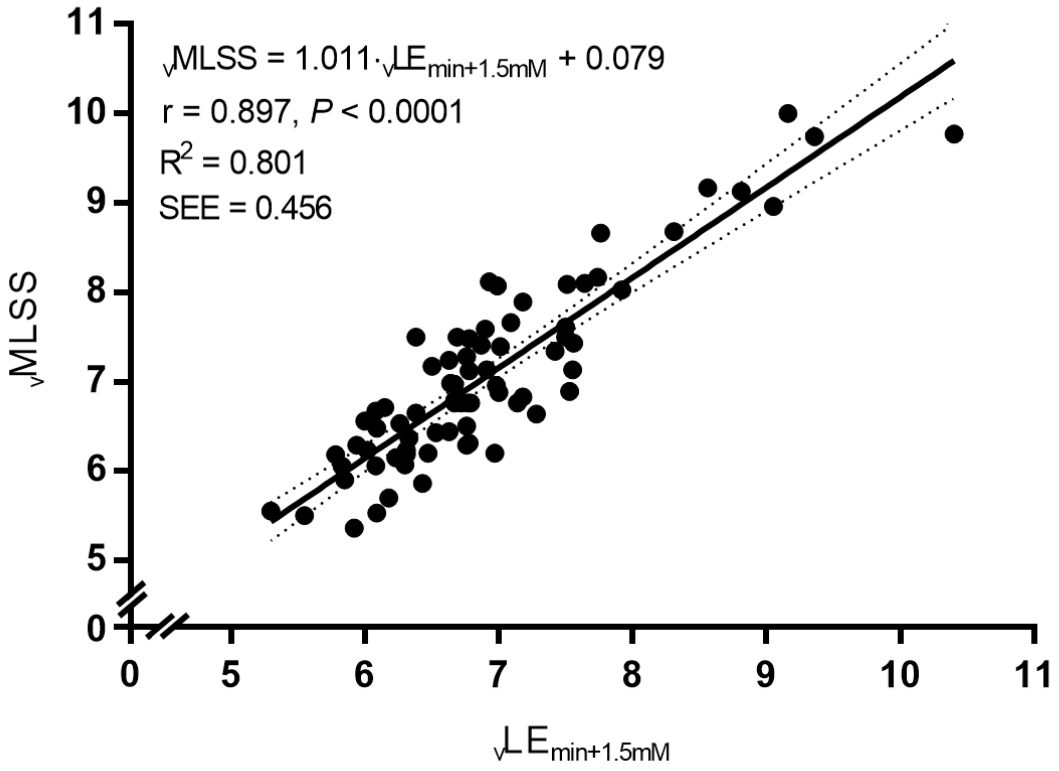


Figure 21. Linear regression between the best single predictor of $_{v}$MLSS ($_{v}LE_{min+1.5mM}$) and $_{v}$MLSS. $_{v}LE_{min+1.5mM}$ = minimum lactate equivalent + 1.5 mmol·l^{-1} (km·h^{-1}), $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}). Solid line: linear regression. Dashed lines: 95% confidence intervals.

After checking individual associations between BL_RTs, bloodless and anthropometric variables, we created three multiple regression models to predict $_{v}$MLSS. In the first model, we tested the accuracy of bloodless variables obtained during the IST for predicting $_{v}$MLSS (**Table 11, model 1**). The key determinants identified for the prediction of $_{v}$MLSS were; ΔFC, age, resting HR in supine position (HR_{rest}), and body mass (kg), accounting for 59% of the the variance, with a large SEE (0.64 km·h^{-1}; 9% of the mean $_{v}$MLSS). The regression equation for the sample (n = 70) was:

$_{v}$MLSS´ = 16.574 – (0.078 · ΔFC) – (0.075 · age) – (0.036 · HR_{rest}) – (0.027 · Body mass)

(eq. 1)

Table 11. Prediction of $_{v}$MLSS from BL_RTs and bloodless models from a single IST and an additional CVT (n = 75)

Model	Predictors	B	SE(B)	β	t	Adjusted R^2	Sig. (p)
1	ΔHR	-0.078	0.016	-0.374	-4.723	**0.588**	<0.001
Bloodless	Age	-0.075	0.015	-0.398	-4.959		
	HR_{rest}	-0.036	0.009	-0.318	-3.963		
	Body mass	-0.027	0.008	-0.285	-3.563		
2	$_{v}LE_{min+1mM}$	1.085	0.072	0.837	15.001	**0.853**	<0.001
BL_RT & Bloodless	Age	-0.040	0.009	-0.211	-4.338		
	$_{HR}LE_{min+1mM}$	-0.012	0.004	-0.137	-2.703		
	Body mass	-0.012	0.005	-0.125	-2.593		
3	$_{v}LE_{min+1mM}$	1.120	0.063	0.864	17.757	**0.892**	<0.001
BL_RT & Blodless + CVT	ΔBLC_{20-10}	-0.304	0.083	-0.162	-3.652		
	Age	-0.021	0.009	-0.114	-2.460		
	Body mass	-0.012	0.004	-0.120	-2.775		
	$_{HR}LT_{+1mM\ 16-20}$	-0.010	0.003	-0.154	-3.555		

vMLSS = velocity at maximal lactate steady-state, BL_RT = Blood lactate-related thresholds, IST = incremental submaximal shuttle test, CVT = constant velocity test, ΔHR = average magnitude of the differences heart rate between successive velocities during IST, HR_{rest} = resting HR supine position, $_{v}LE_{min+1mM}$ = velocity at the minimum lactate equivalent + 1 mmol·L^{-1} (km·h^{-1}), $_{HR}LE_{min+1mM}$ = HR at $_{v}LE_{min+1mM}$, ΔBLC_{20-10} = Change in blood lactate from the 20th to the 10th of the CVT at Lactate Threshold$_{+1mM}$ velocity, $_{HR}LT_{+1.5mM\ 16-20}$ = average HR of the last 5min (min16-20) of the CVT at LT_{+1mM} velocity.

The Bland-Altman method between predicted and the actual $_{v}$MLSS against their mean for eq.1 showed small bias but wide LoA [-0.00 (1.24) km·h^{-1}] (**Figure 22A**). The gradient of the regression line was significantly different from zero (p <0.01) indicating a higher bias in fitter individuals.

In the second model, a combination of single BL_RTs and bloodless variables from the IST were entered to a multiple regression (**Table 11, model 2**). The best model revealed that the velocity and HR at $LE_{min+1mM}$, age, and body mass accounted for 85.3% of the variation in $_{v}$MLSS, with a lower SEE (0.38 km·h^{-1}; 5.4% of mean $_{v}$MLSS). The regression equation for the sample (n = 75) was as follows:

$$_{v}\mathbf{MLSS´ = 4.630 + (1.085 \cdot {}_{v}LE_{min+1mM}) - (0.04 \cdot age) - (0.012 \cdot Body\ mass) - (0.012 \cdot {}_{HR}LE_{min+1mM})\ (eq.\ 2)}$$

The Bland-Altman method between the predicted and the actual $_{v}$MLSS against their mean for eq. 2 showed strong agreement and narrow individual LoA [Bias (95% CI)] [0.08 (0.76) km·h^{-1}] (**Figure 22B**). The deviation of the regression line was not significantly different from zero (p = 0.087).

The prediction of $_{v}$MLSS still improved with an additional CVT performed one week after the IST at a velocity corresponding to 1 mmol·L^{-1} above the $_{v}LT_{+0.1mM}$, accounting for 89.2% of the variation in $_{v}$MLSS (p <0.001), with a low SEE (0.32 km·h^{-1}; 4.5% of mean $_{v}$MLSS). The determinants identified for the prediction of $_{v}$MLSS were $_{v}LE_{min+1mM}$, the difference in BLC

measured between the 20th and 10th minute of exercise during the CVT at $_{v}LT_{+1mM}$ (ΔBLC_{20-10}), age, body mass (kg), and the average absolute HR during the last 5 min of the CVT at $_{v}LT_{+1mM}$ ($_{HR}LT_{+1.5mM\ 16-20}$) (**Table 11, model 3**). The regression equation for the sample (n = 69) was:

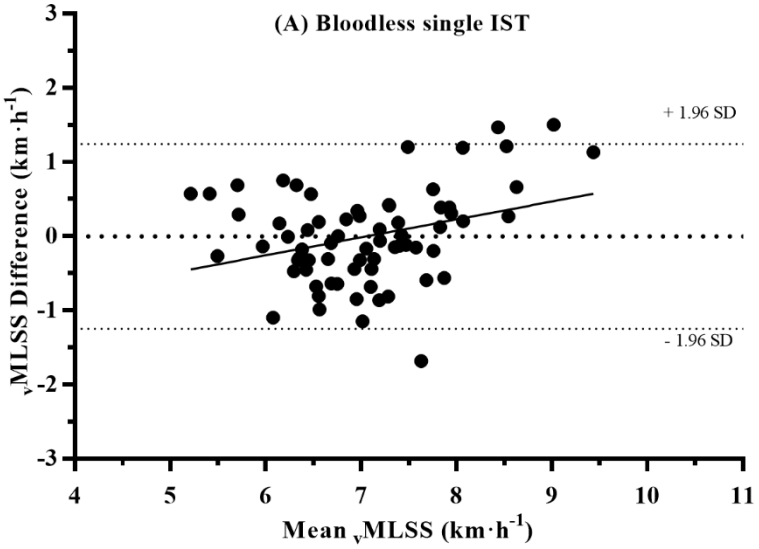
$$_{v}MLSS´ = 3.262 + (1.120 \cdot {}_{v}LE_{min+1mM}) - (0.304 \cdot \Delta BLC_{20-10}) - (0.021 \cdot age) - (0.012 \cdot body\ mass) - (0.010 \cdot {}_{HR}LT_{+1mM\ 16-20}) \quad \text{(eq. 3)}$$

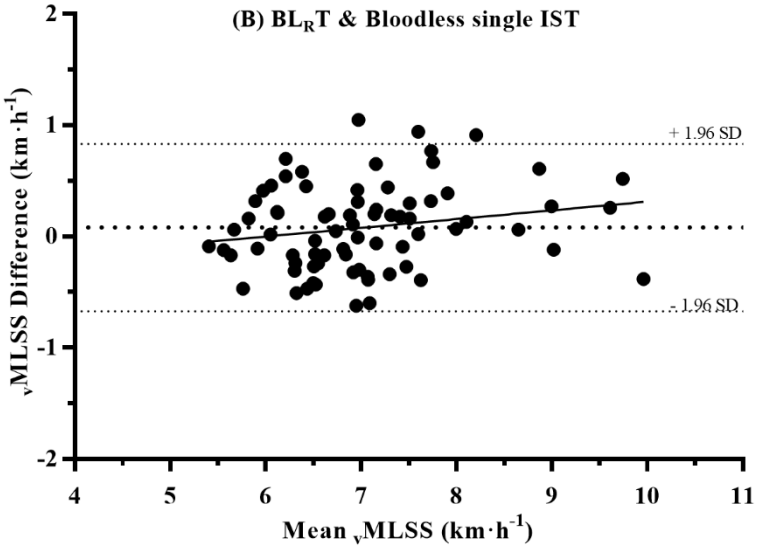
The Bland-Altman method between the predicted and the actual $_{v}$MLSS against their mean for eq. 3 showed a small bias, and the narrower LoA [0.06 (0.63) km·h^{-1}] (**Figure 22C**). The gradient of the regression line did not deviate from zero (p = 0.30).

Discussion

The main finding of this study was that $_{v}LE_{min+1.5mM}$ determined from a single IST was the strongest single predictor of $_{v}$MLSS, closely followed by $_{v}FBLC_{2.5mM}$, $_{v}LE_{min+1mM}$, and $_{v}LT_{+1.5mM}$ and the rest of the predictor variables (**Table 10**) in a large sample of postmenopausal women. The prediction of $_{v}$MLSS was improved when the velocity and HR at $_{v}LE_{min+1mM}$ along with age and body mass were entered in a multiple regression model. The addition of a CVT performed one week after the initial IST still improved the explained variance of $_{v}$MLSS.

The first exponential increase in BLC during incremental exercise (i.e., $_{v}$LT) and the highest constant workload where the participant is still able to maintain steady blood lactate concentrations (i.e., $_{v}$MLSS) during prolonged exercise are particularly relevant $BL_{R}Ts$, due to its practicability to transfer these lower and upper limits of effective but still safe exercise intensities into guidelines for individualized training [78]. On average, $_{v}$LT ($_{v}LT_{+0.1mM}$) and $_{v}$MLSS of our study participants were 5.1 km·h^{-}1 and 7.1 km·h^{-1}, respectively. This $_{v}$LT value is 11% higher than that reported in diabetic 50-years old women [165] and 21% lower than untrained younger women (~32 years old) using a similar protocol [72]. These two physiologic breakpoints may serve as a basis for exercise intensity prescription as well as to evaluate the effects of exercise training without the need to expose individuals to volitional fatigue [75]. However, it is not feasible, because of the number of trials necessary to directly determine the $_{v}$MLSS. Consequently, numerous authors have sought easier and less time-consuming exercise tests to identify lactate-related or ventilatory thresholds as a surrogate of $_{v}$MLSS [75,90,166-168]. Nevertheless, most of these studies have focused on athletic population, and little is known about the prediction of $_{v}$MLSS in adults, and even less in postmenopausal women.


(A) Bloodless single IST
+ 1.96 SD
- 1.96 SD
vMLSS Difference (km·h-1)
Mean vMLSS (km·h-1)


(B) BLRT & Bloodless single IST
+ 1.96 SD
- 1.96 SD
vMLSS Difference (km·h-1)
Mean vMLSS (km·h-1)

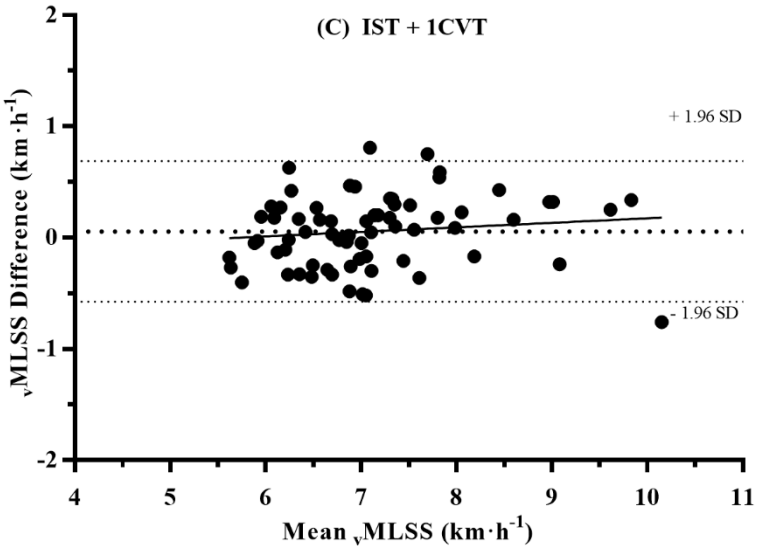

(C) IST + 1CVT
+ 1.96 SD
- 1.96 SD
vMLSS Difference (km·h-1)
Mean vMLSS (km·h-1)

Figure 22. Bland-Altman plots of agreement between measured and predicted $_{v}$MLSS from **A)** bloodless variables obtained in the IST, **B)** Bloodless and BL_RTs obtained in the IST, **C)** the addition of variables obtained in the CVT at $_{v}LT_{+1mM}$. $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}), IST = Incremental Shuttle test, BL_RT = Blood Lactate-related thresholds, CVT = Constant Velocity Test. Dotted bold line represent mean Bias and upper and lower dotted lines represent the 95% limits of agreement. The thick black line represents the slope of the association.

The magnitudes of the association between $_{v}$LT (measured either visually as $_{v}LT_{+0.1mM}$ or using a polynomic equation as $_{v}LE_{min}$) and $_{v}$MLSS in our sample (r = 0.72 and r = 0.83, respectively) are similar to those reported between LT and MLSS in cyclists (r = 0.71-0.76) [166,167], and lower to those reported in college students (r = 0.95) [71] and in a previous study conducted in our laboratory with endurance runners (r = 0.86) [161]. Exercise intensities above $_{v}$LT that rely on the individual lactate curve presented higher associations with $_{v}$MLSS. The $_{v}LE_{min+1.5mM}$ was the best single predictor of $_{v}$MLSS accounting for 80% of its variance (SEE = 6.5% and LoA = 12.6% of mean $_{v}$MLSS), closely followed by $_{v}FBLC_{2.5mM}$, $_{v}LE_{min+1mM}$, and $_{v}LT_{+1.5mM}$. These findings agree with previous research performed in young recreational or endurance-trained athletes showing that BL_RTs, such as $_{v}LE_{min}$ and $_{v}LE_{min+1.5mM}$ [161], OBLA [84,169], IAT [84], D_{max} [169], LT [83], or other BL_RTs [170] obtained during a single incremental exercise test are significant determinants of $_{v}$MLSS.

Non-invasive low cost and easy-to-administer exercise test protocols have traditionally been of general interest to the sport and fitness community. However, our results suggest that the prediction of $_{v}$MLSS by submaximal bloodless variables in postmenopausal women lacks of accuracy and is, therefore, not recommended because the explained variance was low (R^2 = 59%) (**Table 11**), and it could be biased up to 17% above or below actual $_{v}$MLSS in some individual cases (**Figure 22A**). In the absence of blood lactate, García-Tabar and colleagues [163] found that the velocity corresponding to the 90% of HR_{max} (V90) is a more accurate bloodless predictor of $_{v}$MLSS (R^2 = 64%; 90% LoA: 9.5% of $_{v}$MLSS). However, the maximal effort required to assess V90 is not practical for non-clinicians in sedentary and diseased people.

The prediction of $_{v}$MLSS improved when several bloodless variables (age and body mass) along with the velocity and HR at $LE_{min+1mM}$ were entered into the same model, explaining up to 85.3% of its variance (**Table 11**). This value is among the highest reported in the literature (55-88%) [75,90,161,166-168]. Differences such as homogeneity of the sample, number of participants involved, test protocol characteristics and specificity, precision and stability criterion in the $_{v}$MLSS determination, determination of BL_RTs and other variables, as well as age and training

status of the participants of each study might explain these discrepancies. For instance, the sample size of this study was larger and showed similar heterogeneity in $_{v}$MLSS (CV = 15%) compared to the studies mentioned above (CV = 7-17%). Probably, the higher accuracy in $_{v}$MLSS determination (± 0.3 km·h^{-1}; ± 4.5% of mean $_{v}$MLSS) compared to most of previous research in the field (3-10% of the mean), and the low-velocity increments of the IST for blood sampling (0.61 km·h^{-1} or 8.5% of $_{v}$MLSS) could have positively contributed to the estimation of $_{v}$MLSS. The prediction of $_{v}$MLSS resulted in a low SEE (0.38 km·h^{-1}), which corresponds to 5.4 % of the mean $_{v}$MLSS. (**Equation 2**). The 95% LoA (± 0.76 km·h^{-1}; i.e., ± 10.7 % mean $_{v}$MLSS) are similar or lower to the values reported in the literature from maximal exercise trials (≈6% of the mean $_{v}$MLSS) [86,86,90], BL_RTs (5.9-23.5% of the mean $_{v}$MLSS) [75,161,167,170], or ventilatory thresholds (9-22 % of the mean) [89,168] in cyclists [75,167,170], runners [75,86,89], and soccer players [90].

The reason why LE_{min}-related variables would offer significant prediction advantages over other BL_RTs to estimate $_{v}$MLSS can be related to: 1) the resolution of $_{v}LE_{min}$ determination that is finer than other BL_RTs (e.g., $_{v}LT_{+0.1mM}$) because all the data points before and after the transition are used to project the LE_{min} value (**Figure 19B**); 2) the $_{v}LE_{min}$ could essentially take on an infinite number of values, whereas $_{v}LT_{+0.1mM}$ and $_{v}LT_{+0,5mM}$ determination, for example, could only be based on the discrete values of the specific velocity-rate stages; 3) the troublesome identification of the first BLC elevation above baseline values due to initial BLC fluctuations associated with the error of the analyzer [72]; and 4) as opposed to FBLC, $_{v}LE_{min}$-related variables (e.g., $_{v}LE_{min+1.5mM}$) do not seem to be influenced by pre-test intramuscular glycogen stores and BLC values [85] or by exercise patterns [171]. This fluctuation is solved by the "U"-shape BLC curve, for the identification of $_{v}LE_{min}$.

The second purpose of this study was to investigate whether the prediction accuracy of $_{v}$MLSS could still improve by the addition of a CVT at $_{v}LT_{+1mM}$, one week after the IST. The results showed that BLC and HR values observed between the 10th and 20th min of the CVT, along with age, body mass and $_{v}LE_{min+1mM}$ obtained during the IST, improved the explained variance up to 89.2%, with narrower SEE (0.32 km·h^{-1} or 4.5% of the mean $_{v}$MLSS) and 95% LoA (0.63 km·h^{-1}; 8.9% of the mean $_{v}$MLSS). These results are in agreement with previous studies performed with soccer players [90] and endurance-trained runners [172] in our laboratory. It is, therefore, suggested to perform an additional CVT whenever possible.

This study presents some important strengths such as the large sample size, the accurate estimation of $_{v}$MLSS, and the utilization of a single test of submaximal nature, or the addition of a CVT to improve the accuracy of the estimation. However, the present investigation is not without limitations. First, the generalizability of the results is limited to 50-

75 years old women with $_{v}$MLSS values ranging from 5.4 to 10 km·h^{-1}. Second, the reported prediction equations are only recommended to be used with the specific testing procedures described in this study. Third, a test-retest analysis of $_{v}LE_{min}$ was beyond the scope of this study, and therefore, whether $_{v}LE_{min}$ is reliable was not verified. Dickhuth et al. [173], however, found a good test-retest reproducibility (r = 0.90) of $_{v}LE_{min}$ in young males. Finally, this study is a cross-sectional study. Further longitudinal studies are required to examine whether longitudinal training-induced changes in $_{v}$MLSS could be predicted and monitored by $_{v}LE_{min}$-related variables.

Conclusions

The results of the present study indicate that when BLC assessment is available but only one testing session is feasible, $_{v}LE_{min}$-related variables obtained from an incremental submaximal test are accurate estimates of $_{v}$MLSS. The use of only bloodless variables to estimate $_{v}$MLSS is not recommended, due to its low accuracy. Performing an additional CVT one week after the incremental test is encouraged because it improves the prediction of $_{v}$MLSS. We, therefore, recommended the IST as a simple non-exhaustive and time-efficient alternative to the classical determination of $_{v}$MLSS or maximal exercise tests for non-athletic population.

8 Conclusions & Perspectives

Measuring CRF and reliable PA levels is the cornerstone; 1) to evaluate whether an individual is within the evidence-based minimum scores associated with health benefits and reductions in the risk of chronic disease and all-cause mortality, and 2) to design an individualized PA or exercise intervention.

In this doctoral thesis we showed that when exercise testing is not feasible and intensity prescription is based on estimated $\dot{V}O_{2max}$ or HR_{max} values, applying currently recommended absolute and relative exercise intensity targets for adults by the ACSM could overstress CS, who present a much lower CRF and maximum cardiac response compared to healthy adults. This drawback can be solved by prescribing exercise intensity or designing/delivering exercise interventions according to submaximal physiologic breakpoints such as, ventilatory or lactate thresholds from submaximal exercise tests. This procedure guarantees the safety and the adequacy of the exercise dose administered to each patient and might maximize the therapeutic benefits. In the absence of exercise testing equipment, we offer an adapted exercise intensity guideline for CS that can guide clinicians, exercise physiologists and the patients themselves during exercise training.

The determination of the first increase in blood lactate during an incremental exercise (i.e., the lactate threshold) and the highest sustainable intensity with steady-state BLC during prolonged exercise at constant work-rate (the so-called MLSS) is the gold standard method for exercise intensity prescription and for the assessment of CRF/endurance, without the need to expose individuals to volitional fatigue. However, the determination of MLSS is time consuming since it requires several (3-6) constant workload tests performed on separate days. The results of this study indicate that this extensive procedure can be avoided with a single, easy-to-administer, submaximal incremental exercise test with measurement of blood lactate. The prediction equations reported in this study can be used for the assessment of CRF and for exercise intensity prescription in postmenopausal women, and very likely, by other adults showing similar fitness levels. When it is feasible, performing an additional constant workload

test several days after, is highly encouraged because it improves MLSS estimation and adds information about the metabolic, cardiac and perceived effort responses during a more real exercise-training environment, where exercise is performed during prolonged time, instead of been gradually incremented like in standard testing conditions.

Interestingly, both, the VT1 in CS during an incremental cycling test, and the LT1 in postmenopausal women during an incremental walking test agreed in average with the lower boundary of relative moderate intensity activities recommended by PA guidelines and position stands for adults (i.e., ~45%$\dot{V}O_{2max}$ or ~60%HR_{max}), which can be considered the minimum exercise intensity that can provide health and fitness benefits in sedentary adults, supported by evidence-based studies. However, the large variability observed in the absolute (e.g., METs, speed or Watts) and relative exercise intensities associated with this first physiological threshold (from as low as 1 MET in CS to 7 METs in healthy postmenopausal women or from ~30% to ~70%$\dot{V}O_{2peak}$) is evidence that a threshold-based approach is preferred to provide a tailored cardiopulmonary and metabolic stress to each individual. Further, our results show that both, moderate and vigorous intensities defined by current PA guidelines are included in the relative intensity range between thresholds (~45-75%$\dot{V}O_{2max}$ or 60-85%HR_{max}) both in CS, and in postmenopausal women.

Finally, while most of research studies using accelerometer-based objective measurement of PA levels have simply chosen previously validated accelerometer cut-points estimated from walking or running at 3 and 6 MET absolute intensities (current target of moderate intensity activities, which has been extensively used in epidemiology studies to establish the relationship between the time spent in questionnaire-based MVPA and mortality), our data support the use of individually tailored cut-points for a meaningful and a more accurate quantification of PA levels. Hence, these findings have important implications for the use and interpretations of accelerometer data and for the design/delivery of PA interventions for adults. Epidemiology studies should at least consider adjusting the association between PA and mortality risk by CRF, because as we demonstrated, it is easier for high-fit individuals engaging in higher levels of PA, but it does not necessarily mean that they are having higher relative intensities. Thus, the aforementioned association might have been inflated by the higher CRF in those reporting higher PA dose. Another, more accurate way of quantifying PA levels that suits better to small clinical trials or to one-on-one consultations, that overcomes with the risk of under-or overestimating PA when using fixed absolute intensity cut-points to define the PA intensity categories, is, to individualize this intensity cut-points according to relative intensities. Setting individualized relative intensity categories from submaximal

ventilatory or lactate thresholds accounts for differences in CRF between individuals, and thus, reduces the risk of underestimating or overestimating individual PA levels, and provides the appropriate exercise intensity stimulus for an individual. Measuring LTs through an incremental and submaximal walking exercise test is a feasible way of; 1) evaluating aerobic fitness and assessing the efficacy of an exercise intervention, 2) individualizing exercise intensity categories to design a tailored exercise intervention, and 3) measuring reliable PA levels with accelerometers to provide behaviour change feedback and evaluate its efficacy, without the need to expose the individual to exhaustion.

Take home messages

- Recommended exercise intensity guidelines for the general population can overstress CS who have a lower CRF and cardiac response. Accordingly, using the proposed exercise intensity guideline adapted to CS´s cardiopulmonary responses is highly recommended.
- The individualization of accelerometer intensity cut-points through LTs may better represent the time spent in different PA intensity levels during daily activities, and reduce the risk of underestimating or overestimating PA levels, compared to the classic absolute moderate intensity (3-6 METs) fixed cut-points approach.
- Even that high-fit postmenopausal women recorded more daily steps and reached the MVPA target more easily than less fit individuals according to absolute intensity criteria, when accelerometer intensity cut-points were individually-tailored according to relative intensity criteria, these differences disappeared.
- Maximal lactate steady-state can be accurately estimated from BL_RTs obtained during a single, non-exhaustive exercise test in postmenopausal women.

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10 Supplementary Material

10.1 Practical Applications

Bridging the gap between research and practice

Exercise programming in a cancer patient from physical activity and fitness measurements

Medical history
Age: 55
Body mass, height and BMI: 48kg · 1.54m · 20.3 BMI
BP: 130/75 Resting HR: 53
Sociodemographic status: married, retired, lives in Bilbao, no economic problems
Primary reason for attendance
GP´s referral. Cancer rehabilitation and reduction of side-effects
Cancer specific
05-02-2018 Metastatic Lung cancer Stage IV (metastasised to the liver)
Thoracoscopic surgery (pain and stiffness on the area)
Undergoing chemotherapy (3 out of 6 cycles every 3 weeks)

Cancer related fatigue (7 out of 10 average)

Neutropenia

Decreased pulmonary function

Gastro-intestinal discomfort (nausea)

Impaired immune function

Cardiac/metabolic

Early menopause

Shortness of breath walking

Slightly high sugar levels (not taking medication)

Reflux

Diarrea

Musculoskeletal

Osteopenia

Peripheral neuropathy

Low back pain

Other

Depression

Former smoker (1 pack of cigarettes a day)

Medications

Platinol + taxotere (chemo)

Erlotinib (targeted therapy)

Calcium+Vit D

Omeoprazol

Family history

Father with prostate cancer

Reported past and current Physical activity levels: enjoyment barriers, facilitators

Past: Walking, hiking (enjoys nature sports)

Sedentary work (administrative)

Current: walking 3-4 times per week 15-30min

CV risk (SCORE)

3-4% (low)

Physical fitness

Cardiopulmonary exercise test with gas exchange measures

To obtain reliable cardiorespiratory fitness values, a maximal incremental exercise test can be performed. An initial workload of 20W and 8-10W increment per minute until volitional exhaustion is suitable for cancer survivors.

$\dot{V}O_{2peak}$: 5.3 METs

HR_{peak}: 155

W_{peak}: 94

VT1: 2.5 METs (45W, 94bpm)

VT2: 4.0 METs (70W, 120bpm)

* The VT2 obtained during an incremental test does not guarantee that during prolonged exercise at 70W the energy expenditure is going to be 4 METs (It will probably be higher) nor that training at 120bpm is the highest sustainable intensity over time without continual blood lactate accumulation.

Measurement of lactate thresholds

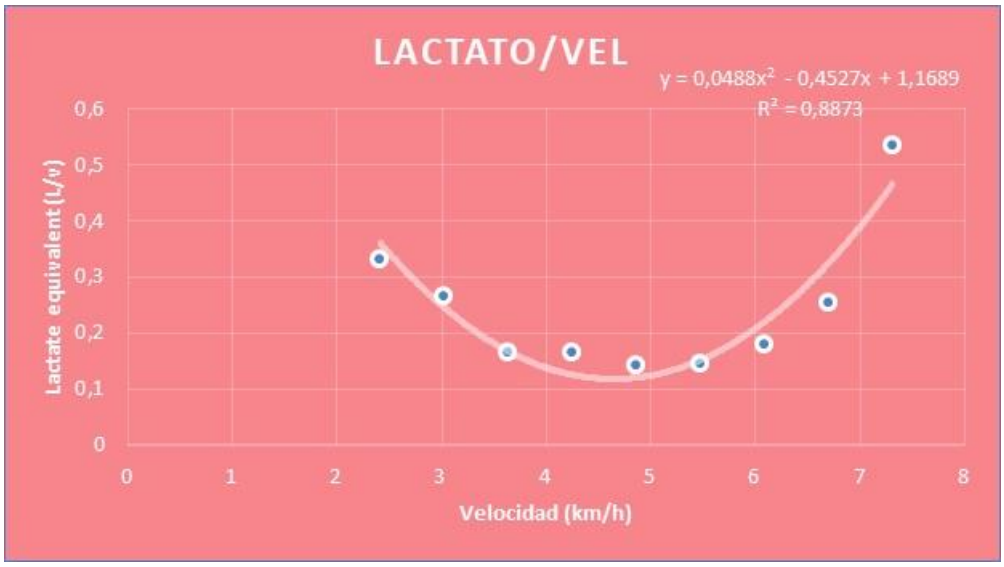
This is the preferred method since it does not require a maximal effort and provides valuable information to design an exercise program according to lactate thresholds, guarantying the safety and the adequacy of the prescribed exercise.

1) **Incremental walking exercise test with blood lactate measurement wearing an accelerometer**

Estadio	Duración	V (km/h)	MET	FC	[L]	RPE	Counts
Reposo	0 - 3	0	1	61	0,8	0	0
1	3 - 5	**2,4**	2,2	62	0,8	0	1994
2	6 - 8	**3,0**	2,4	67	0,8	0,3	2570
3	9 - 11	**3,6**	2,8	67	0,6	0,5	3115
4	12 - 14	**4,3**	3,1	73	0,7	1	3919
5	15 - 17	**4,9**	3,6	77	**0,7**	2,5	4780
6	18 - 20	**5,5**	4,1	81	0,8	4	5568
7	21 - 23	**6,1**	4,6	93	1,1	4,5	6246
8	24 - 26	**6,7**	7,2	111	1,7	5	6130
9	27 - 29	**7,3**	7,6	138	3,9	7	7088
Post 1' rec				116			

From this data, LT1 can be visually determined at 4.9 $km \cdot h^{-1}$ and corresponding activity counts are 4780 $ct \cdot min^{-1}$. As shown in the 7th chapter, LT1 can be mathematically determined (LE_{min}) for a higher resolution as shown in the next graph, resulting in 4.6 $km \cdot h^{-1}$.

Using the Equation 2 of the 7th chapter we could estimate the maximal lactate steady-state (LT2). This estimation results in 5.5 $km \cdot h^{-1}$. However, it is highly encouraged to confirm this estimation by a constant velocity test. We have two choices to select the speed for the next test: 1) As shown in Chapter 7, we can choose the speed associated with 1 $mmol \cdot L^{-1}$ above LT1, which is usually a tolerable exercise with steady-state lactate values. Then, we only need to use the equation 3 provided in this text to estimate the MLSS with a higher accuracy. 2) We could directly try with the estimated speed from the equation 2. In this specific case, we suspect that the MLSS is at higher velocity than 5.5 $km \cdot h^{-1}$ due to the low HR and BLC at this speed during the incremental exercise test. Therefore, we chose the first alternative.



2) Constant velocity test for the confirmation of MLSS.

Estadío	Duración	V (km/h)	FC	[L]	RPE
Rep	0 - 3	-	70	**1,2**	-
1	3 - 13	6,7	122	**3,9**	3
Rec.	13 - 15	-		-	-
2	15 - 25	6,7	135	**4,8**	5
Rec 1´	25 - 26	-	122	-	-
Rec 3´	25 - 28	-	111	-	-

Min by min	FC
1	67
2	70
3	70
4	101
5	117
6	121
7	125
8	127
9	129
10	129
11	131
12	130
13	132
14	111
15	104
16	118
17	131
18	135
19	137
20	139
21	138
22	142
23	143
24	145
25	142
26	122
27	117
28	111

There is a 0.9 $mmol \cdot L^{-1}$ increment in BLC between the 10^{th} and the 20^{th} minute of exercise, so we can conclude that this speed is above LT2. In order to avoid more constant velocity

tests for the determination of the MLSS, we can apply the equation 3 of the Chapter 7. This results in 6.4 km·h^{-1}, which is just 0.1 km·h^{-1} above the actual $_{v}$MLSS. Performing this additional exercise test gives us important information about the cardiac response and the perceived effort during prolonged exercise, which is very useful to design an exercise program because it reflects the effort in real conditions. We might expect that exercising above ~140 bpm would elevate the lactate levels over time, accelerating fatigue and compromising the immune system in patients suffering from anaemia or neutropenia as a consequence of chemotherapy treatments.

Exercise testing without cardiopulmonary or metabolic equipment

If cardiopulmonary or metabolic exercise testing is not feasible other simpler exercise tests are available to estimate $\dot{V}O_{2peak}$. In this doctoral dissertation we used the ACSM´s (2013) equation with peak power output obtained during an incremental (8-10W per minute with an initial load of 20W) maximal cycling exercise protocol (1.8 (W·6.1183)/BM + 7).

As we showed in the 4th study, MLSS can be estimated through basic information such as heart rate and anthropometric data, using the 1st equation provided in that study.
Continuing with the previous example, MLSS would be as follows:

$_{v}$MLSS´ = 16.574 – (0.078 · ΔFC 9.5) – (0.075 · age 55) – (0.036 · HR$_{rest}$ 53) – (0.027 · Body mass 48) = 8.5 km·h^{-1}

This estimation is far from the actual MLSS value (6.3 km·h^{-1}). Taking into account that 40% of the variation of $_{v}$MLSS is not explained by these variables, it does not seem reasonable to use it.

Another easier exercise test to evaluate cardiorespiratory fitness is the 400m walk test [174,175,175,176,176], widely used with cancer patients by one of the top exercise oncology institutes in the world (Exercise Medicine Research Institute, Edith Cowan University. Western Australia). Maximum HR can be estimated using the equation of Gellish (2007) (206.9 – (0.67*age)).

Estimated VO_{2max}: 6.3 METs

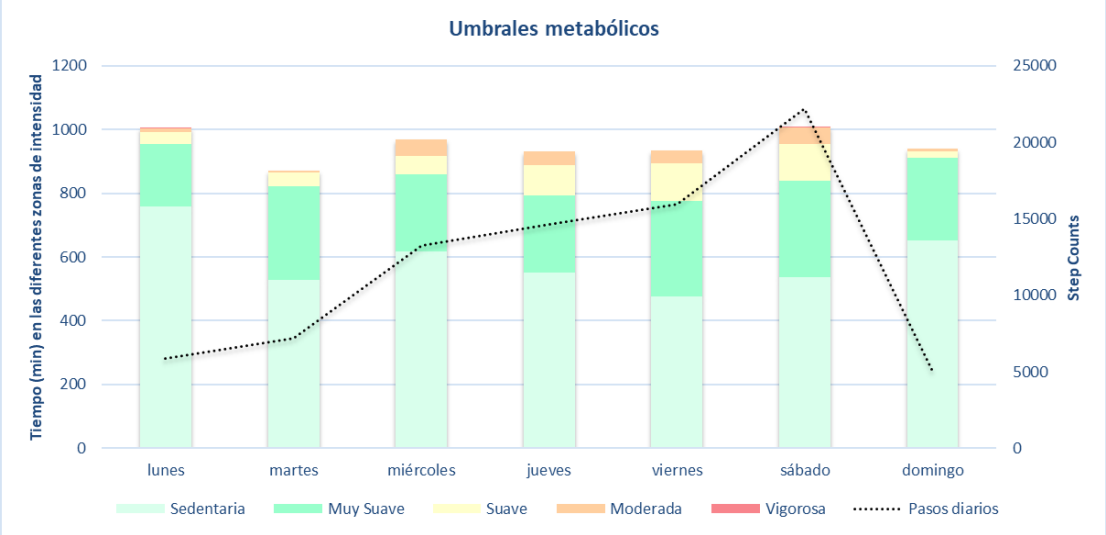
Estimated HR$_{max}$: 170 bpm

Physical activity assessment

7-day accelerometry recording on the right-hip.

First, we have to individualize the activity counts cut-points according to the patient's lactate thresholds (LT1 = 4.9 km·h^{-1} and 4780 ct·min^{-1}, and LT2 = 6.4 km·h^{-1} and 6318 obtained from the regression equation between speed and activity counts.

The results of the weekly physical activity analysis show that the patient meets the 10.000 daily steps target. Using the absolute intensity cut-points criteria she engages in ~50 min·day^{-1} at moderate intensity activities (in 10-min bouts), exceeding current recommended minimum target of 150 min·wk^{-1} of MVPA. However, as her LT1 (4.1 METs) is at a higher intensity than the 3 MET-s threshold, we can see that when individually-tailored cut-points are selected, the patient only spend ~10 min·day^{-1} at moderate intensity activities (over LT1), which is more meaningful for her health/fitness. Finally, we can observe that she spends too much time in sedentary activities (~10 h·day^{-1}). Therefore, a possible realistic goal for this patient could be to engage in a structured exercise program at moderate intensities two days per week and to reduce the sedentary time, mostly on Sundays and Mondays.



Promedio actividad física diaria (min/día)

	Relative	Absolute
Zona de intensidad (min/día)		
Sedentaria	559	559
Muy Suave	262,1	196,4
Suave	70,1	73,3
MVPA (mod + vig)	**11,6**	**52,6**
Vigorosa	**0**	**0**
Pasos diarios		12020

¿Suficiente AF MVPA?	**No**
¿Tiempo sedentario <8h?	**9,8h (no)**

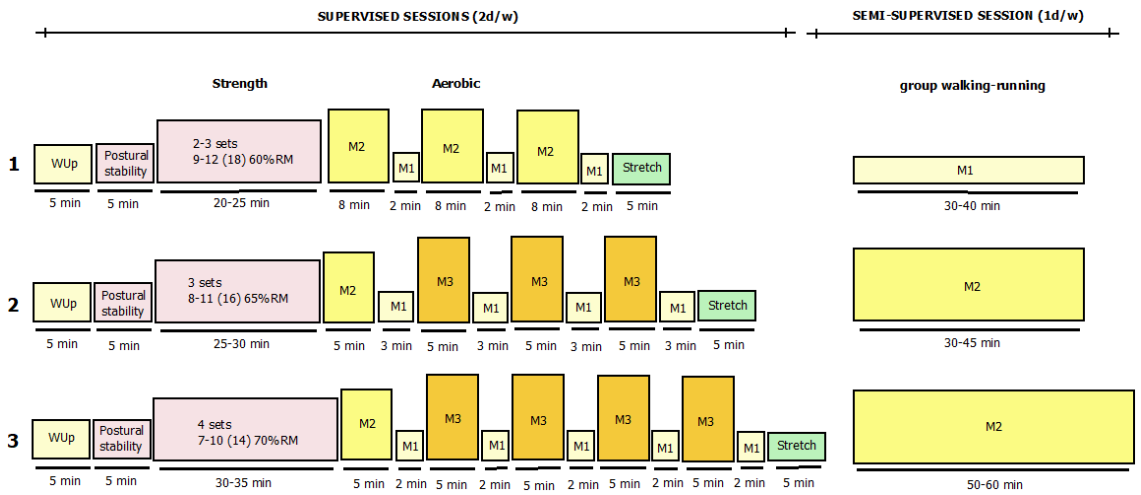
Individualized exercise programming

From the results of the incremental and the constant velocity tests, individualized exercise intensity zones can be designed. In the absence of exercise testing, we can use the Table 4 provided in the Chapter 4 as a start point.

These exercise intensity zones are used to guide the exercise training as seen in the next figure, starting with 8min bouts at M2 intensities during the first month, and progressing to 5min intervals at M3 intensities during the third month.

Zone	V	HR	RPE	Training type
HIT	>6,4	>140	>4,5	High-intensity training where blood lactate rises exponentially, and is no longer sustained at steady-state
M3	5,8-**6,4**	119-**140**	4,0-**4,5**	Intensive moderate-intensity training with steady-state lactate values. The patient has difficulties to talk and sweating increases
M2	5,1-5,7	98-118	3,0-3,5	Moderate-intensity training. The patient feels an increased breathing frequency
M1	**4,6**-5,0	**76**-97	**2,0**-3,0	Low-moderate intensity training. There is almost no elevation of blood lactate
LIT	<4,6	<76	<2,0	Low intensity. Daily activities requiring low levels of effort. No elevation of lactate

The intensity zones are based on the values obtained during incremental and constant velocity tests. The lower end of M1 and the upper end of M3 zones ("moderate intensity" are anchored on LT1 and LT2 (MLSS), respectively. V = velocity, HR = heart rate, RPE = rating of perceived effort.



Interpretation of exercise sessions

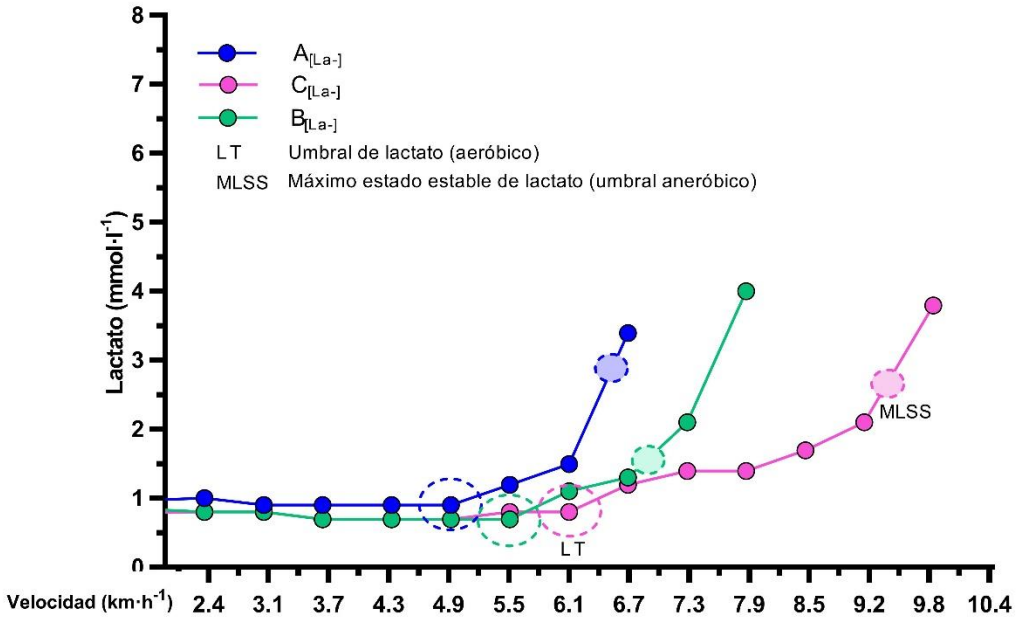
This is an important and often forgotten part of the exercise interventions. The exercise benefits are associated with the cardiovascular and metabolic responses during the sessions, and not with the exercise program designed on the paper. Therefore, exercise intensity monitoring during the sessions is crucial. Below, we can see an example of the quantification of the training "dose" and the adherence to the prescribed exercise. This is very useful to adapt the training session to the patient´s current physical and emotional state, due to common side effects of the treatments.

Nombre: Altura Sillín:

MES 1	Pre-sesión						Durante		Post-sesión				Tiempo en zona de intensidad (min)					
Sesión	Fecha	Peso	Fatiga	TA	FC	Sat	RPE	W/V(%)	TA	RPE A	RPE F	FCm	LIT	M1	M2	M3	HIT	Carga
1	04/07/2018	48,2	5	120/65	76	95	4	5,5	125/70	5	3	105	10,4	20,3	18	5,4	2,1	104
2	07/07/2018	48,3	2	115/65	74	97	3	5,5	123/68	4	3	103	6,7	25,3	21	3,6	3	120
3	11/07/2018	48,6	8	110/60	78	93	4	5	112/65	4	-	97	26,8	2,1	1	0	0	78
Sesión caminar. Se encuentra cansada. Ayer sesión de quimio																		
4	13/07/2018	48,5	7	118/63	77	94	6	5,5	126/72	6	4	107	10,3	15	22	5,3	3,4	132
Sigue cansada, con mucha fatiga y náuseas																		

Follow-ups: continuous feedback and re-programing

It is well known that continuous feedback is an important for the long-term adherence to the exercise program. Here, we show an example of the evaluation of the aerobic fitness through the incremental submaximal exercise test at three different time-points. The next figure shows how both LT1 and LT2 (MLSS) have been displaced rightwards to higher velocities. As the aerobic fitness improves, the patient would need to work at higher loads to have the same cardiovascular response.



10.2 Quality Measures and Original Papers

The quality measures of the published articles are provided from the Journal of Citation Reports (JCR).

Paper	DOI and Date of publication	Journal	ISSN	Country	Category	JCR IF	JCR Rank, Quartile and JIF Percentile
Exercise intensity guidelines for Cancer Survivors: A Comparison with reference values	10.1055/s-0034-1389972 2014	International Journal of Sports Medicine	0172 - 4622	Stuttgart - Germany	Sport Sciences	2.065	24/81 Q2 70.988
Objectively measured absolute and relative physical activity intensity levels in postmenopausal women	10.1080/17461391.2018.1539528 2019	European Journal of Sport Science	1746-1391	London – England	Sport Sciences	2.567	22/81 Q2 73.457
Estimation of the Maximal Lactate Steady State in Postmenopausal Women	10.1080/02640414.2019.1586814 2019	Journal of Sports Sciences	0264-0414	London – England	Sport Sciences	2.733	19/81 Q1 77.160
Individualized accelerometer activity cut-points for the measurement of relative physical activity intensity levels	10.1080/02701367.2019.1599801 2019	Research Quarterly for Exercise and Sport	0270-1367	London – England	Sports Sciences Physiology	2.268	32/81 Q2 61.111 38/78 Q2 51.923

Exercise Intensity Guidelines for Cancer Survivors: a Comparison with Reference Values

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Key words
- exercise prescription
- survivorship
- physical activity
- quality of life

Abstract

The optimal dose of physical activity (PA) in cancer survivors (CS) is unknown due to the large variety of types of cancer, illness stages and treatments, low cardiorespiratory fitness, and physical inactivity. It is recommended that CS follow current PA guidelines for healthy population. There are no specific exercise prescription guidelines for CS. To know the cardiorespiratory parameters of CS in order to create exercise prescription guidelines for this population, 152 inactive CS were recruited to perform a cardiopulmonary exercise test. Peak oxygen uptake (VO_{2peak}), ventilatory threshold (VT) and respiratory compensation point (RCP) determined 3 exercise intensity zones to create exercise intensity classification guidelines for CS. VO_{2peak} (18.7 ±4.6 mL·kg^{-1}·min^{-1}) and peak heart rate (HR_{peak}) (145.1 ± 17.9 bpm) were lower than the estimated values ($p < 0.001$). Moderate intensity zone for CS was different from the current PA guidelines for healthy population: 41–64% VO_{2max}, 55–70% HR_{max}, 23–48% HR_{res}, 2.5–4 METs and 8–14 points on RPE scale. Intensities in PA guidelines for healthy population are not adapted to the characteristics of CS. For individual exercise prescription in CS specific PA guidelines should be used in order to maximize the benefits obtained by the use of aerobic exercise training.

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Bibliography
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Introduction

There were around 12.7 million cancer cases worldwide in 2008. This number is expected to increase, reaching 21 million by 2030. One out of 3 people will develop cancer before the age of 75 years [19]. Currently increasing incidence rates and decreasing mortality rates due to the advances in earlier detection and in therapeutic modalities have translated to a higher number of cancer survivors (CS) (person who suffers from cancer, measured from the moment of the diagnosis until the end of his or her life) [18].

Both the disease itself, the treatments and the lack of physical activity (PA) lead to an increase of pain and fatigue thresholds, a significant reduction of the muscle mass and strength, a higher level of adipose tissue and decreased cardiorespiratory fitness. All of the factors mentioned negatively impact daily activities and reduce the quality of life (QoL) of CS [5,9,18,29]. Related to this topic, PA offers important psychological and physiologic benefits in CS [9,21,34] and plays an important role in preventing or delaying other chronic diseases (e.g., cardiovascular diseases, hypertension, diabetes, osteoporosis, obesity, depression), thereby contributing positively to their survival [16,18].

However, there are no specific guidelines for exercise prescription for CS. Current PA guidelines for CS are generic. Whenever possible, CS should avoid inactivity and maintain an active and healthy lifestyle [1,33]. PA guidelines for CS are based on guidelines for healthy population; i.e., for aerobic activity 150 min per week of moderate PA (30 min 5 days a week) or 75 min per week of vigorous PA (20 min 3 days a week) or any combination thereof. Furthermore, strength training guidelines recommend 2–3 weekly sessions that include exercises for major muscle groups [1,33,35]. In this regard, it has been shown that CS meet international recommendations for moderate PA, but very few complete those for vigorous PA [31]. The optimal dose of PA in this population is unknown [17], possibly affecting each CS differently due to the large variety of types of cancer, illness stages and treatments, low cardiorespiratory fitness, physical inactivity and co-morbidities. Thus, it is crucial to create individualized exercise programs, starting from specific PA guidelines for CS.

Compared to healthy individuals of the same sex and age, CS usually exhibit ~30% lower cardiorespiratory fitness (VO_{2peak}) [1]. It has recently shown that many of the CS present poor cardiorespiratory fitness [32]. In addition to VO_{2peak}, gas exchange thresholds (i.e., ventilatory threshold, VT, and respiratory compensation point, RCP) are currently the gold standard references for the evaluation of aerobic metabolism function and, consequently, for aerobic exercise intensity assessment and prescription [27,28]. VT could be considered as a valid indicator of functional capacity of CS and it is closely associated with the intensities of daily activities (e.g., walking, gardening, climbing stairs, household activities) [15]. It has been previously observed that the oxygen uptake at VT in cancer patients is very low [15], indicating that any light stimulation could induce moderate intensities in this population [27]. It was investigated whether submaximal indices of cardiorespiratory fitness such as VT and RCP were related to QOL in women survivors of breast cancer and they concluded that the improvement of these indices could have a beneficial effect on QOL [15]. Therefore, exercising at those intensities to improve submaximal thresholds (i.e., VT and RCP) could be an effective strategy [15]. In practice, these submaximal thresholds are used to define individualized intensity zones and prescribe exercise. Generally 3 intensity zones are defined: intensity below VT, intensity between VT and RCP and intensity above RCP. This exercise-prescribing method has been used with athletes [8], healthy sedentary individuals [22] and with chronic heart failure patients or chronic obstructive pulmonary disease patients [27]. Regarding the optimum PA level, CS should exercise at a higher level than the minimum recommended whenever possible to achieve more benefits [31,33]. Nevertheless, exercise intensity is more complicated to prescribe, measure and control. Whereas with high intensity activities there is still high controversy, moderate intensity has proven to be safe and provide health benefits [31].

But what is considered to be light, moderate and high intensity? Where are the limits of each? Light intensity is defined as 6–11 points on the RPE scale, <63%HR_{max}, and 20–39%HR_{res}. Moderate intensity is defined as 12–13 points on the RPE scale, 3–6 METs, 64–76%HR_{max} and 40–59%HR_{res}. High intensity is defined as 14–19 points on the RPE scale, 77–93%HR_{max} and 60–84%HR_{res} [1,10,29]. There are slight differences in exercise intensity reference guidelines. Absolute intensities like METs, cannot be generalized due to the high variability in cardiorespiratory fitness among subjects. What is considered to be a light walk for some people could be considered to be moderate or vigorous for others. For this reason, relative intensity was introduced [36]. However, the same relative intensity for 2 subjects could result in different metabolic responses (above or below anaerobic threshold) [26]. It seems that an individualized prescription based on ventilatory thresholds (VT and RCP), could be less variable among individuals. Those thresholds show the metabolic adaptations and the evolution induced by exercise training [3,26].

The main purpose of this study was to assess the cardiorespiratory parameters of CS (peak and submaximal thresholds) for the purpose of creating an adapted exercise intensity prescription guideline for this population that allows the comparison with current standard guidelines. The secondary purposes were: 1) to analyze the cardiorespiratory capacity of CS, classifying them by age ranges; to compare it to that of the healthy population; and 2) to evaluate the association between the HR_{max} and VO_{2max} estimated by equations to prescribe exercise and the real peak values obtained in the cardiopulmonary exercise test (CPET).

Methods

Participants

152 CS were recruited from the oncology department of the "Santiago Apóstol" Hospital of Miranda de Ebro, Burgos, Spain. Inclusion criteria: 1) cancer survivor, 2) Eastern Cooperative Oncology Group (ECOG) scale = 0, 3) physical activity ≤ 90 min/week. Exclusion criteria: 1) heart disease (≥ New York Heart Association II), 2) uncontrolled hypertension (blood pressure > 160/90 mmHg), 3) uncontrolled pain or 4) any other contraindication for participation in a physical exercise program such as high risk of bone fractures, severe anemia (< 8 g/dL), or $< 50 \cdot 10^9$/µL of platelet count [25]. Participants were informed about the study. Each participant obtained the consent of the oncologist and gave their written informed consent before participating in the study. The study received ethical approval from The Clinical Research Ethics Board of Burgos and Soria and meets the ethical standards in sport and exercise sciences research [12]. After obtaining peak and submaximal cardiorespiratory variables in the CPET, participants were offered an individualized exercise program (3 sessions per week of 90 min each combining aerobic and resistance exercise). With the data obtained in the CPET, the exercise intensity classification guideline was created.

Measurements

Each participant performed a CPET in the same center of sport medicine (Gabinete Médico Deportivo, Miranda de Ebro, Burgos, Spain) at the same time (10 a.m. – 2 p.m.) and in similar environmental conditions (temperature, ~20 °C; relative humidity, 45–55%; barometric pressure, ~720 mmHg). The test was performed on an electric braking cycle-ergometer (Variobike 600, Marquette Hellige, Freiburg, Germany). Participants were not involved in any exercise during the previous 24 h before the test. Following an unloaded 5-min warm-up, the load was increased 8–10 W per minute starting from an initial load of 20 W. Participants were instructed to maintain cadence between 60–70 rpm, cadence being displayed on a monitor placed in front of them. Gas exchange data were measured breath by breath using an open spirometer circuit (MasterScreen CPX, Jaeger, Viasys Healthcare, Hoechberg, Germany). The test was performed until volitional fatigue or when the cadence could not be maintained above 60 rpm. Confirmation of a maximal effort was determined by meeting 3 out of 4 of the following criteria: 1) no increases in VO_2 with increased workload, 2) HR values ≥ 85% estimated maximum HR (HR_{maxT}), 3) RER ≥ 1.10, and 4) RPE = 20 (Borg 6–20) [1]. Regardless of achieving maximal criteria, the maximal values achieved during the CPET are referenced as "peak" [20,35]. Peak oxygen consumption (VO_{2peak}) was defined as the highest 20-s value of oxygen consumption elicited during the CPET. Peak VO_2 is expressed in terms relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$).

Ratings of perceived exertion (RPE) and blood pressure were evaluated at the end of each stage (1 min). HR was monitored during the test using a 12-lead ECG. VO_2, ventilation, ventilatory equivalents (for oxygen and carbon dioxide) and respiratory quotient for peak and submaximal values (VT and RCP) were also measured. To detect the VT the first exponential increase in the O_2 ventilatory equivalent (V_E/VO_2) without a concomitant increase in the CO_2 ventilatory equivalent was considered. The RCP was determined using the ventilatory equivalent method (the first exponential increase in CO_2 ventilator equivalent alongside an increase in the ventilator equivalent for O_2) [29]. 2

experienced researchers detected those points individually and in case of disagreement, a third researcher's opinon was obtained. CS were classified by age to compare their cardiorespiratory fitness against the age and sex-matched ACSM 50th percentile [1].

To estimate maximum HR (HR_{maxT}) the equation (206.9 – (0.67*age)) was used given its higher accuracy compared to other equations [11]. To estimate the maximal VO_2 (VO_{2maxT}), we used the ACSM's metabolic equation for bike ergometer (1.8*(W*6.1183)/(body mass+7)) [1]. Absolute and relative values below VT determined the light-intensity zone (zone 1). Values between VT and RCP were considered as moderate intensity (zone 2) and values above the RCP determined the high-intensity zone (zone 3) [8,27].

CS were categorized into 3 groups according to their cardiorespiratory fitness. The first group corresponded to the most deconditioned individuals and was considered <4.5 METs (<15.75 mL·kg^{-1}·min^{-1} of VO_{2peak}). In the second group CS were between 4.5 and 6 METs (15.75–21 mL·kg^{-1}·min^{-1} of VO_{2peak}). The third group corresponded to CS with >6 METs (>21 mL·kg^{-1}·min^{-1} of VO_{2peak}).

Statistical analysis

Descriptive statistics were calculated for continuous variables (mean, standard deviations) and for non-continuous variables (frequencies). To determine the statistical analysis type, normality criteria was verified for each variable (Kolmogorov-Smirnov test) and for the groups to which they would be compared according to different variables (Kolmogorov-Smirnov or Shapiro-Wilk). To verify the variance homogeneity, the Levene's test of homogeneity of variances was performed. To examine the validity of the equations estimating HR_{maxT} and VO_{2maxT}, a linear regression was used, while to examine the differences between the real and estimated values, a paired samples t-test was performed. Pearson's correlation coefficient was used to examine the association between the estimated and real values, as well as to determine whether there was any relationship between post-diagnosis time and cardiorespiratory variables. Correlations were categorized as follows: 0.26–0.49 is a low correlation, 0.50–0.69 is a moderate correlation, 0.70–0.89 is high correlation, and 0.90–1.00 is very high correlation. One-way ANOVA for parametric samples and Kruskal Wallis H test for non-parametric samples, were used to compare the cardiorespiratory values in submaximal point among cardiorespiratory fitness groups (<4.5 METs, 4.5–6 METs and >6 METs), post-diagnosis time (<6 months, 7–12 months, 13–24 months, 25–60 months and >60 months) and VO_{2peak} among age ranges (30–39, 40–49, 50–59, 60–69, >70). Bonferroni post-hoc test was applied to define the groups with statistical differences. Data are presented as mean±SD. Statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS statistical software (version 20.0, IBM SPSS Statistics, Chicago, IL).

Results

The flow diagram in **Fig. 1** shows how the CS participants were recruited and the final numbers of individuals. Participant characteristics are displayed in **Table 1**. Physiologic values of CS obtained in the CPET and estimated by equations are listed in **Table 2**. CS showed a mean VO_2 significantly ($p<0.001$) lower than the estimated VO_2. The relationship between estimated VO_{2max} and the obtained VO_{2peak} was significant and high ($r=0.82$, $p<0.001$) (**Fig. 2**).

The HR_{peak} obtained in the CPET was 25 bpm less than the estimated HR ($p<0.001$). The relationship between the estimated HR_{max} and the obtained HR_{peak} was statistically significant ($r=0.56$, $p<0.001$) (**Fig. 2**). The VT was located at 48.0±11.6%

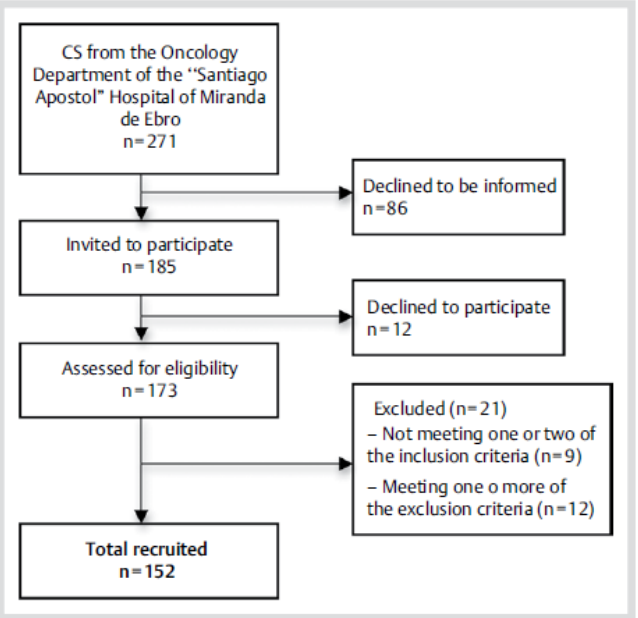

Fig. 1 Recruitment of CS participants.

Table 1 Participants' characteristics.

Age (years)	55.1±12.3
sex	
male	34 (22.4)
female	118 (77.6)
BMI (kg·m^{-2})	26.5±4.1
cancer type	
colon	16 (10.5)
cervical	3 (2.0)
endometrial	4 (2.6)
gastric	5 (3.3)
breast	87 (57.2)
melanoma	2 (1.3)
ovarian	5 (3.3)
pancreatic	4 (2.6)
prostate	7 (4.6)
lung	3 (2.0)
thyroid	2 (1.3)
bladder	4 (2.6)
others	10 (6.6)
total	152 (100)
treatment type	
S	22 (14.5)
S+C	59 (38.8)
S+R	12 (7.9)
S+C+R	42 (27.6)
other	17 (11.2)
post-diagnosis time (months)	32.7±42.7

Data are presented as mean±SD for continuous variables and as frequency (%) for categorical variables

SD, standard deviation; BMI, body mass index; S, surgery; C, chemotherapy; R, radiotherapy

CPET		Estimated	
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	18.7 ± 4.6	VO_{2maxT}	22.0 ± 4.9
VO_2 VT ($mL \cdot kg^{-1} \cdot min^{-1}$)	8.7 ± 2.2		
VO_2 RCP ($mL \cdot kg^{-1} \cdot min^{-1}$)	14.0 ± 3.7		
% VO_{2peak} VT	48.0 ± 11.6	% VO_{2maxT} VT	40.7 ± 10.7
% VO_{2peak} RCP	75.3 ± 9.7	% VO_{2maxT} RCP	64.0 ± 11.4
MET_{peak}	5.3 ± 1.3	MET_{maxT}	6.3 ± 1.4
MET VT	2.5 ± 0.6		
MET RCP	4.0 ± 1.1		
RPE VT	8.0 ± 1.3		
RPE RCP	14.4 ± 1.5		
W_{peak}	94.0 ± 33.7		
RER_{peak}	1.19 ± 0.11		
HR_{peak} (bpm)	145.1 ± 17.9	HR_{maxT} (bpm)	170.0 ± 8.2
HR VT (bpm)	93.9 ± 14.0		
HR RCP (lpm)	118.5 ± 16.5		
% HR_{peak} VT	65.1 ± 8.8	%HR_{maxT} VT	55.2 ± 7.7
% HR_{peak} RCP	81.9 ± 7.6	%HR_{maxT} RCP	69.7 ± 8.6
HR_{rest} (bpm)	70.8 ± 11.0		
$HR_{reserve}$ (bpm)	74.2 ± 18.0	$HR_{reserve}$ (bpm)	99.1 ± 12.5
% $HR_{reserve}$ VT	31.3 ± 12.9	%$HR_{reserve}$ VT	23.2 ± 10.3
% $HR_{reserve}$ RCP	64.3 ± 13.7	%$HR_{reserve}$ RCP	48.0 ± 13.8

Data are presented as mean ± SD. DS, standard deviation; HR, heart rate; MET, metabolic equivalent (1 MET = 3,5 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ or 1 $kcal \cdot kg^{-1} \cdot h^{-1}$); RCP, respiratory compensation point; RER, respiratory exchange ratio; RPE, rating of perceived effort (Borg, 6–20); VO_2, oxygen uptake; VT, ventilatory threshold; W,watt. HR_{maxT}, estimated maximum heart rate by equation (206.9 – (0.67 * age); $HR_{reserve}$, (HR_{maxT} – HR_{rest}); RCP, respiratory compensation point; VO_{2maxT}, estimated maximum oxygen uptake by ACSM (2013) equation (1.8 (W · 6.1183)/body mass + 7)

Table 2 Absolute and relative physiologic values of the participants determined in CPET and Estimated.

of the VO_{2peak}, whereas the RCP corresponded to 75.3 ± 9.7% of the VO_{2peak}. The moderate intensity range (VT-RCP) in METs was between 2.5 ± 0.6 and 4.0 ± 1.1. The perceived effort (Borg 6–20 scale) for moderate intensity was between 8.0 ± 1.3 and 14.4 ± 1.5 points. The mean HR in the VT was 93.9 ± 14.0 bpm, while the mean HR for the RCP was 118.5 ± 16.5 bpm. These values corresponded to 65.1 ± 8.8% and 81.9 ± 7.6% of the HR_{peak}, respectively. The HR_{res} was 74.2 ± 18 bpm and the ventilatory thresholds were located at 31.3 ± 12.9% (VT) and 64.3 ± 13.7% (RCP) of the HR_{res}.

Comparisons to published age and sex-matched cardiorespiratory fitness [1] are presented in **Fig. 3**. Participants of this study presented a significantly lower cardiorespiratory fitness than healthy population in all age ranges. CS ages 30–39 years showed a mean VO_{2peak} of 17.1 ± 5.5 $mL \cdot kg^{-1} \cdot min^{-1}$, representing a difference of greater than 50% (i.e., lower values) compared to the VO_{2peak} of the healthy population (36.8 $mL \cdot kg^{-1} \cdot min^{-1}$). CS ages 40–49 years showed the highest cardiorespiratory fitness (20.0 ± 4.5 $mL \cdot kg^{-1} \cdot min^{-1}$), but the difference with the ACSM healthy population continued to be high (−43%). Among the individuals ages 50–59 years, the VO_{2peak} showed greater similarity than that of the group ages 40–49 years (19.5 ± 5.0 $mL \cdot kg^{-1} \cdot min^{-1}$). CS of this study showed a decreasing trend in the cardiorespiratory fitness without large differences among age groups.

Table 3 shows the intensity ranges defined after obtaining submaximal (VT and RCP) and peak parameters in the CPET. The peak values obtained during the CPET placed the moderate-intensity zone (VT-RCP) at 48–75% of VO_{2peak}, 65–82% of the HR_{peak}, 31–64% of HR_{res}, 2.5–4 METs and 8–14 points on the RPE scale. There were differences when CS were classified into cardiorespiratory capacity groups. Less than 6 METs group showed the VT in a lower % of VO_{2peak} than the others ($p < 0.001$). Less than 4.5 METs group showed the %HR_{peak} at VT higher than the others, exhibiting a reduced moderate intensity zone compared with the other 2 groups. There were statistically significant differences among all groups in moderate intensity zone thresholds for absolute values in METs. While the moderate-intensity zone was 2–3 METs for the most deconditioned group, the same intensity zone corresponded to 2.9–5.3 METs for the fittest group. There were no differences when using HR reserve as the exercise prescription method.

Table 4 shows an exercise intensity classification guide for CS based on the absolute and relative submaximal values obtained in the CPET for the purpose of creating intensity ranges relative to the estimated maximal values. The intensity zone values obtained relative to the estimated HR_{max} and VO_{2max} were lower than those obtained through the peak values. In this case, moderate-intensity zone corresponded to 41–64% of VO_{2max}, 55–70% of HR_{max} or 23–48% of the HR_{res}.

No association was found between post-diagnosis time (from diagnosis to CPET) and cardiorespiratory variables (VO_{2peak}, VO_2 at VT and RCP, HR_{peak}, HR at VT and RCP, $HR_{reserve}$, HR_{rest}) without following a physical exercise program. No significant differences were either found in any variable when the patients were separated by post-diagnosis time (< 6 months, 7–12 months, 13–24 months, 25–60 months and > 60 months).

Discussion

The main purpose of this study was to assess the cardiorespiratory parameters of CS (peak and submaximal thresholds) for the purpose of creating an adapted exercise intensity prescription guideline for this population, which facilitates comparison with current standard guidelines. The mean VO_{2peak} of the 152 CS of this study was 18.7 ± 4.6 $mL \cdot kg^{-1} \cdot min^{-1}$. This value is within the normal range of cardiorespiratory fitness of CS [35], and is lower than that of the healthy population [1]. It is also worth mentioning that in the present study CS did not meet the threshold of 8 METs that indicates an increased risk for mortality and cardiac

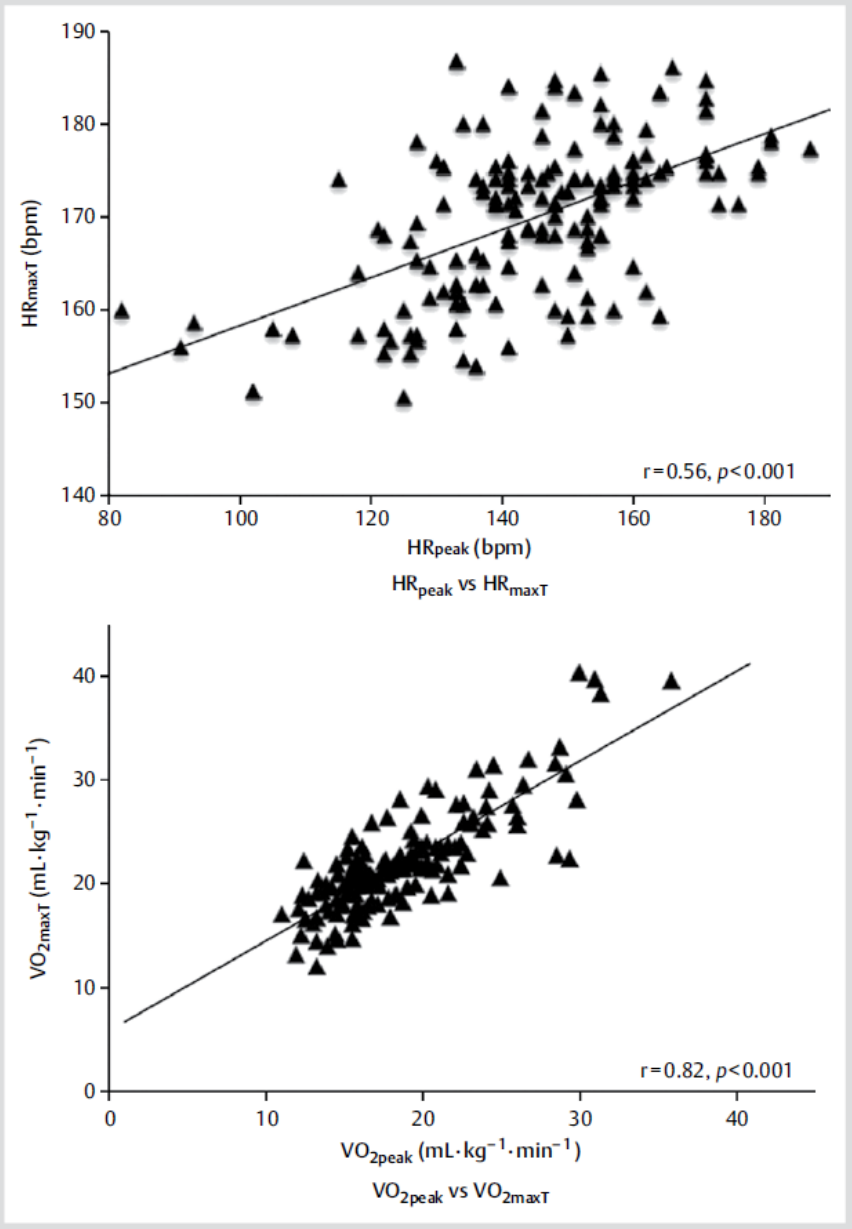

Fig. 2 Association HR_{peak} – HR_{maxT} and VO_{2peak} – VO_{2maxT}.

events [24]. This deconditioning could be attributed to several factors, such as the low PA level (< 90 min/week) adopted following cancer diagnosis, the disease itself, treatment and side effects such as chronic fatigue, pain or cardiopulmonary dysfunction and the high BMI level (65.1% of participants presented overweight or obesity) [15, 18].

In fact, a recent study among another Spanish cohort also showed that the prevalence of obesity in CS leads to a low cardiometabolic profile [32]. Relative intensity ($\%VO_{2peak}$) at VT and RCP (48.0 ± 11.6% and 75.3 ± 9.7%, respectively) was similar to that of the sedentary adults. It seems that for CS any increase of physical activity could lead to a disproportionately rapid rise of carbon dioxide output and minute ventilation as related to VO_2 [27]. The $\%VO_{2peak}$ at RCP was similar to that found by others [20] in CS ($75\%VO_{2peak}$).

The difference between the estimated and peak HR was 25 bpm. Other studies have reported a wide range of HR_{peak} in CS, varying from 124 to 169 bpm [4, 7, 14, 15]. For this reason, it is recommended that heart rate be measured in an incremental exercise test whenever possible [1]. The ventilatory thresholds corresponded to 65.1 ± 8.8% (VT) and 81.9 ± 7.6% (RCP) of HR_{peak} or 31.3 ± 12.9% (VT) and 64.3 ± 13.7% (RCP) of $HR_{reserve}$. In a recent study with breast CS, higher values of HR_{peak} (169 ± 12 bpm) were obtained, and the RCP was placed at a higher percentage of HR_{peak} (87.6%) [2]. Another study placed the VT at 73 ± 10% of HR_{peak} and the RCP at 88 ± 5% of HR_{peak} in breast cancer survivors with a VO_{2peak} of 24.6 ± 5.8 $mL \cdot kg^{-1} \cdot min^{-1}$ [15].

ACSM suggests determining the HR_{peak} of the individual in an incremental exercise test in order to prescribe an exercise program. When it is not feasible, the estimation is accepted. In our study, the equation of Gellish [11] (206.9 – (0.67 * age) was used as it is the formula that is best adapted to this population [1, 23]. The correlation obtained between the estimated HR and the HR_{peak} was only moderate ($r = 0.56$, $p < 0.001$). Whereas the estimated maximum HR was 170 ± 8.2 bpm, the peak HR obtained in the CPET was 25 bpm lower (145 ± 17.9 bpm). The type of test (cycle-ergometer), the physical deconditioning (caused by the illness itself, treatments and inactivity) and the lack of familiari-

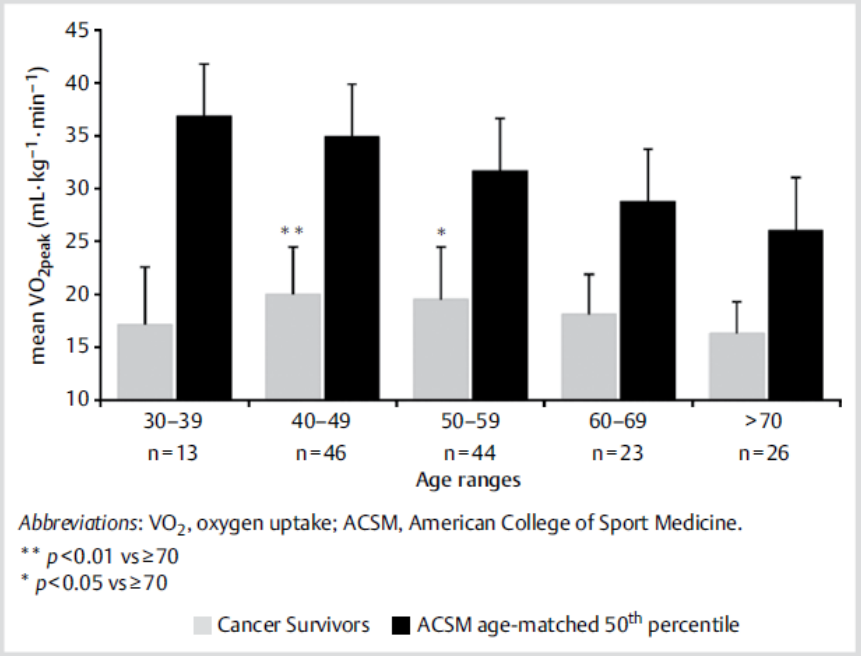

Fig. 3 Comparison of VO_{2peak} between ACSM (2013) age-matched 50th percentile of healthy population and cancer survivors of the study.

Table 3 Exercise intensity classification of the participants. Data are presented as relative to the peak values obtained in the CPET.

							Intensity relative to maximal exercise capacity in METs		
Intensity	**%VO_{2peak}**	**%HR_{peak}**	**%HR_{res}**	**METs**	**RPE**		**<4.5 METs n=39**	**4.5–6 METs n=79**	**>6 METs n=34**
Light	<48	<65	<31	<2.5	<8	***%VO_{2peak}***	<51	<50	<41
						%HR_{peak}	<70	<64	<62
						%HR_{res}	<34	<31	<29
						METs	<2	<2.5	<2.9
Moderate	48–75	65–82	31–64	2.5–4	8–14	***%VO_{2peak}***	51–76	50–76	*41–72
						%HR_{peak}	†70–84	64–81	62–82
						%HR_{res}	34–64	31–63	29–67
						METs	‡2–3†	‡2.5–3.9‖	2.9–5.3
Vigorous	>75	>82	>64	>4	>14	***%VO_{2peak}***	>76	>76	>72
						%HR_{peak}	>84	>81	>82
						%HR_{res}	>64	>63	>67
						METs	>3	>3.9	>5.3

Abbreviations: HR, heart rate; MET, metabolic equivalent; VO_2, oxygen uptake; RPE, rating of perceived effort (Borg, 6–20)
*$p<0.001$ vs. <4.5 METs & 4.5–6 METs
†$p<0.001$ vs. 4.5–6 METs & >6 METs
‡$p<0.001$ vs. 4.5–6 METs & >6 METs
‡$p<0.01$ vs. 6 METs
†$p<0.001$ vs. 4.5–6 METs & >6 METs
‖ $p<0.001$ vs. >6 METs

zation with these type of tests could contribute to the low HR_{peak}. However, all CS satisfied 3 of 4 criteria of maximal effort. It may be necessary to create a new equation for this population in the future. These differences between the estimated and the real values could cause large differences in determining the intensity in CS if the equations for estimating the peak values were used. What the international PA guidelines classify as moderate intensity (40–59%HR_{res} or 64–76%HR_{max}) could cause varied responses when the prescription is based on the peak HR (145 bpm in CS of the study) or the estimated maximum HR (170 bpm in CS of the study). Basing exercise intensity on the estimated maximum values, i.e., 64–76%HR_{max} of 170 bpm (109–129 bpm), would actually result in a vigorous intensity (75–89%HR_{peak}) for a CS with 145 bpm of HR_{peak}. The correlation between the VO_{2peak} and the estimated VO_{2max} was higher than that obtained for the HR ($r=0.82$, $p<0.001$, ◉ **Fig. 2**).

CS showed considerably lower cardiorespiratory fitness than that of the healthy population [1] in every age group, with VO_{2peak} decreasing with age (◉ **Fig. 3**). The greatest differences were found in the youngest groups (~53.5% of VO_{2peak} lower in CS of 30–39 years and ~43% of VO_{2peak} lower in CS of 40–49 years). Starting with these age groups the difference appears to decrease (~38.5% of VO_{2peak} lower in CS of 50–59 years and ~37% of VO_{2peak} lower in CS>60 years). The scientific literature has reported differences between ~38–50% of VO_{2peak} in favor of the healthy population [6,20]. In contrast to the healthy population, which exhibits clearly decreasing VO_{2peak} with age, CS does not present such differences among age groups, and the cardiorespiratory fitness is very low and similar in all age groups (◉ **Fig. 3**). A systematic review about cardiorespiratory exercise in the rehabilitation of CS shows that most patients present a VO_{2peak} of 16–25 mL·kg^{-1}·min^{-1} [35]. CS of our study had low VO_{2peak} val-

Table 4 Exercise intensity classification guidelines for cancer survivors. Data are presented as relative to estimated HR_{max} and VO_{2max}.

						Intensity relative to maximal exercise capacity in METs		
Intensity	**%VO_{2max}**	**%HR_{max}**	**%HR_{res}**	**METs**	**RPE**		**<4.5 METs n=39**	**4.5–6 METs n=79**	**>6 METs n=34**
Light	<41	<55	<23	<2.5	<8	***%VO_{2max}***	<40	<42	<38
						%HR_{max}	<56	<55	<55
						%HR_{res}	<22	<23	<24
						METs	<2	<2.5	<2.9
Moderate	41–64	55–70	23–48	2.5–4	8–14	***%VO_{2max}***	40–60	42–65	38–67
						%HR_{max}	56–68	55–70	55–73
						%HR_{res}	22–43	23–47	24–56
						METs	2–3	2.5–3.9	2.9–5.3
Vigorous	>64	>70	>48	>4	>14	***%VO_{2max}***	>60	>65	>67
						%HR_{max}	>68	>70	>73
						%HR_{res}	>43	>47	>56
						METs	>3	>3.9	>5.3

HR_{max}, estimated by equation (206.9 – (0.67 * age)): HR_{res}, reserve heart rate (HR_{max}– HR_{rest}): VO_{2max}, estimated by equation (1.8 (W · 6.1183)/body mass + 7): MET, metabolic equivalent; RPE, rating of perceived effort (Borg, 6–20)

ues in all age groups (lower than a mean of 20.0 ± 4.5 mL · kg^{-1} · min^{-1}). These results thus emphasize the need for monitoring cardiorespiratory fitness and creating adapted exercise programs to improve those VO_{2peak} values as early as possible.

Despite VO_{2peak} decreasing with age, the absolute VO_2 values of VT and RCP were not affected. Thus, the relative values (%VO_{2peak}) of VT and RCP relative to VO_{2peak} increased. Older people have tend to have ventilatory thresholds relatively closer to the nearest to VO_{2peak} than younger people [27]. Previous studies conducted among CS pointed to the importance of improving the VO_{2peak} and even more the VT and RCP, because the increases are positively associated with QoL and they imply intensities near those of daily activities [14].

As a result of VO_{2peak} decreasing with age and the lower cardiorespiratory fitness of individuals with chronic diseases, the general PA guidelines for healthy individuals may not be the most appropriate for CS. Furthermore, this population has cardiorespiratory limitations and low cardiorespiratory values when exercise intensity is based on absolute intensity, i.e., the MET method [1,27]. The relative intensity approach tries to eliminate the differences in the absolute values in people of different cardiorespiratory fitness levels [36]. Nevertheless, relative intensity approach has been criticized by some authors because, at the same relative intensity, the metabolic response of 2 people could be different (i.e., moderate intensity for one but high intensity for the other). It is expected that a prescription based on the individual ventilatory thresholds (VT and RCP) produces less variability in the metabolic response of patients and offers more homogenous training stimulus than the use of other relative prescription methods such as %VO_{2peak}, %HR_{peak} or %$HR_{reserve}$. Additionally, ventilatory thresholds better reflect progress or training adaptations [3,29].

There is a wide range of exercise intensity classifications which define intensity categories according to relative intensities (%VO_{2peak}, %HR_{peak} or %$HR_{reserve}$) or absolute intensities (MET's, RPE) [1]. The determination of these intensity categories is based on regressions of VO_{2max} or %VO_{2max} for conversion into %HR_{max} or %HR_{res} and modifications of previous exercise intensity classifications [1,36], since VO_{2res} and HR_{res} have been closely associated [37]. In the ACSM's position stand moderate intensity corresponds to 46–63% of VO_{2max} (52–67% for individuals with a cardiorespiratory fitness lower than 5 METs), 64–76% of HR_{max} or 40–59% of HR_{res}. The results of our study for moderate intensity (VT-RCP) corresponded to 41–64% of VO_{2max}, 55–70% of HR_{max} or 23–48% of HR_{res} (**Table 4**). The consequence of that it could be to overstress the patients when exercise design is perform using the intensity classification of international guidelines recommended for healthy population and for CS [10]; e.g., from 70% of HR_{max} or 48% of HR_{res} CS would be training at high intensity and not in moderate intensity as the international guidelines establish. The position statement of the Exercise and Sport Science Australia [13] also places moderate intensity at 50–75% of VO_{2max}/HR_{res} and 60–80% of HR_{max}. Once again, these intensities are overestimating what CS can perform at moderate intensity. Previous study classified moderate intensity at 40–60% of VO_{2max}/HR_{res} or 55–70 of HR_{max} [30]. In that case, the relative intensity of VO_{2max} and HR_{max} is similar to the ones found in the present study, but prescribing with HR_{res} individuals could be overstressed.

The perceived effort of moderate intensity was between 8 and 14 points in RPE 20 points scale, signaling that CS overtake VT early after starting the exercise and in low subjective appreciation of the effort. If exercise is designed based on this method, activities which are considered as light in international guidelines, such as 9–11 points in RPE, actually are moderate intensities for CS. On the other hand, when exercise intensity is based on absolute MET values following the typical classification of moderate intensity (3–6 METs) established by current guidelines [1,10,13], actually CS would be exercising at maximal intensities and some of them would not be able to perform at 6 METs, since the mean peak cardiorespiratory fitness of CS of this study in METs is 5.3 ± 1.3. In this study, moderate intensity corresponded to 2.5–4 METs. The classification of 3.1–4 METs for individuals with a cardiorespiratory fitness lower than 6 METs as suggested by ACSM [1] appears to be better adapted to the characteristics of CS. Daily activities such as moving light loads and boxes from one place to another, or climbing stairs, which are considered to induce 4–6 METs, actually represent high-intensity physical activity for CS. The present study categorized CS into different groups based on their cardiorespiratory fitness to further specify exercise prescription (**Table 3**). Relative exercise intensity should be modified according to the cardiorespiratory fitness of CS. For the most fit CS group (>6 METs) the moderate-intensity zone relative to %VO_{2peak} was more intense (41–72 %VO_{2peak}) due to the lower relative value of VT, showing significant differences with the other 2 groups ($p < 0.001$). The most deconditioned group (<4.5 METs) showed the moderate-intensity zone relative to %HR_{peak} (70–84% HR_{peak}) to be signifi-

cantly higher than the other 2 groups due to the higher level of VT at relative intensities ($p < 0.001$). Due to low cardiorespiratory values of patients of certain diseases, the $\%VO_2$ corresponding to the ventilatory thresholds is quite high and it could increase with the severity of the disease [27]. This paradoxical phenomenon could be due to the attenuated increase of VO_2 over the VT and/or the low exercise tolerance. In this population, any increase over the resting values (~3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ of VO_2) represents a high proportion of VO_{2peak}. In this study, the more deconditioned the CS was, the higher relative his or her values at VT without any difference in RCP.

While the perceived effort does not vary with respect to the cardiorespiratory fitness, the absolute VO_2 values in METs showed statistically significant differences among groups, suggesting that the prescription should be modified according to the VO_{2peak} of the CS. Moderate PA for <4.5 METs group was 2–3 METs, showing significant differences with the other 2 groups. For the 4.5–6 METs group the same intensity was 2.5–3.9 METs, whereas for the >6 METs group moderate intensity was defined as 2.5–5.3 METs, closer to those of the healthy population [1, 10].

Finally, the outcomes of this study suggest that without following an exercise program the post-diagnosis time does not have any effect on cardiorespiratory variables and the VO_{2peak} does not change. Furthermore, when CS were divided into post-diagnosis time groups (<6 months, 6–12 months, 13–24 months, 25–60 months and >60 months) there were no significant differences.

Given the strong association between VO_{2peak} and mortality in populations with low cardiorespiratory capacity [21], CS must start exercise programs as early as possible. Following exercise programs, the improvement in VO_{2peak} has been reported to be 2.90 $mL \cdot kg^{-1} \cdot min^{-1}$, and there have been decreases of 1.02 $mL \cdot kg^{-1} \cdot min^{-1}$ of VO_{2peak} in CS who did not participate in exercise programs [21]. An oncologist should advise his or her patients as early as possible to increase their PA levels by doing light activities such as walking, cycling or swimming. This would improve the adherence [37].

Compared to CS of low cardiorespiratory fitness (< 13 $mL \cdot kg^{-1} \cdot min^{-1}$), those of a moderate cardiorespiratory fitness (13.1–16.9 $mL \cdot kg^{-1} \cdot min^{-1}$) and high cardiorespiratory fitness (≥ 17 $mL \cdot kg^{-1} \cdot min^{-1}$) exhibit a 21% and 24% decrease in mortality of any cause. In contrast, a decrease of 1 $mL \cdot kg^{-1} \cdot min^{-1}$ (the decrease of inactive CS) has been associated with a 4% increase in mortality of any cause [23].

The limitations of the study should be mentioned. There is a risk of population stratification due to the diagnosis data (i. e., differences of cancer categories and comorbid conditions). On the other hand, the sample is very homogenous with regard to types of CS, most being breast CS, and very little data being present for the remaining cancer types. Despite this the investigation poses the question, "Are we heading in the right direction?".

In summary, the intensities defined by current international PA guidelines recommended for healthy population and additionally suggested for CS are not adjusted to the physiological characteristics of CS, and those individuals could be overstressed following the prescription of the exercise intensity of those guidelines. Furthermore, absolute and relative intensities should be modified taking into consideration the cardiorespiratory fitness of the CS. When the individualization of exercise intensity in CS is not possible, an exercise intensity design guideline specific for CS must be employed to provide adapted stimulation and achieve the required outcomes. For this reason, a more adapted set of exercise intensity prescription guidelines is presented.

Exercise programs should be considered as an important part of cancer recovery therapies as early as possible after diagnosis, because CS do not improve their cardiorespiratory fitness independently of the post-diagnosis time unless they follow an exercise program.

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Individualized Accelerometer Activity Cut-Points for the Measurement of Relative Physical Activity Intensity Levels

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ABSTRACT

Purpose: The aim of this study was to compare the widely used accelerometer activity cut-points derived from the absolute moderate intensity recommendation (3–6 METs), with relative intensity cut-points according to maximal cardiorespiratory fitness (46%–63% $\dot{V}O_{2max}$) and to individual lactate thresholds (LT1 and LT2) in postmenopausal women. **Method**: Thirty postmenopausal women performed several exercise tests with measures of heart rate, blood lactate, accelerometer activity counts and oxygen consumption. Individual regressions were developed to derive the accelerometer activity counts at absolute and relative moderate intensity recommendations and at individual LTs. **Results**: The activity counts calculated at the lower moderate intensity boundary were lower for the absolute 3 METs threshold (2026 ± 808 ct·min^{-1}) compared to relative 46 % $\dot{V}O_{2max}$ intensity threshold ($p < .01$, ES: 1.95) and LT1 ($p < .01$, ES: 2.27), which corresponded to 4.6 ± 0.7 METs. The activity counts at the upper moderate intensity boundary were higher for LT2 (7249 ± 2499 ct·min^{-1}) compared to the absolute 6 METs threshold ($p < .01$, ES: 0.72) and relative 63% $\dot{V}O_{2max}$ intensity threshold ($p < .01$, ES: 0.55). The interindividual variability in activity counts at relative intensity thresholds was high (CV = 30–34%), and was largely explained by cardiorespiratory fitness level (R^2 = ~ 50%). **Conclusion**: Individually tailored (relative to $\dot{V}O_{2max}$ or submaximal LTs) rather than fixed accelerometer intensity cut-points derived from the classic absolute moderate physical activity intensity (3–6 METs) would result in a more accurate measurement of an individual´s activity levels and reduce the risk of overestimating or underestimating physical activity.

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Compelling scientific evidence indicates that both physical activity (PA) and cardiorespiratory fitness (CRF) provide important health benefits (Physical Activity Guidelines Advisory Committee, 2018; Riebe, Ehrman, Liguori, & Magal, 2017). Physical activity intensity and CRF are often expressed in absolute rates of energy expenditure (METs). Each 1-MET increment in CRF is associated with 13 and 15% decrements in all-cause mortality and cardiovascular disease, respectively (Kodama et al., 2009). Epidemiologic studies suggest that a minimal CRF of 8 METs may be important for significant prevention of all-cause and cardiovascular disease mortality (Kodama et al., 2009). It is well documented that increases in the amounts and intensities of PA typically produce increases in CRF, particularly in those who are less physically active or present poor CRF (Physical Activity Guidelines Advisory Committee, 2018). Epidemiological studies using self-reported questionnaires suggest that meeting current PA recommendations of a minimum of 150 min·week^{-1} of moderate-to-vigorous physical activity (MVPA) reduces all-cause mortality risk by 26%–31% (Arem et al., 2015; Physical Activity Guidelines Advisory Committee, 2018).

Since the early works of Montoye and colleagues validating uniaxial accelerometers against movement counters to measure daily energy expenditure (Montoye et al., 1983), its use spread rapidly in behavioral and epidemiologic studies replacing PA questionnaires to objectively measure PA behavior and adherence to recommended PA targets (Troiano et al., 2008). Contrary to self-reported estimates, results of accelerometer-based objective assessments of PA report much lower volumes of MVPA (Arem et al., 2015; Tucker, Welk, & Beyler, 2011), indicating that only a small proportion of adults (7%–15%) meet current PA recommendations (Cerin et al., 2014; Kujala et al., 2017; Tucker et al., 2011). Reported objective weekly volumes of MVPA are significantly lower in women and vary from as low as seven min·day^{-1} to 57 min·day^{-1} (Cerin et al., 2014; Kujala et al., 2017; Tucker et al., 2011). The inactivity, along with the lower CRF observed in women (Howley, 2001) and the increased risk of

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cardiovascular disease (Kannel, Hjortland, McNamara, & Gordon, 1976) and osteoporosis (Kanis et al., 2012) after menopause and with advancing age underline the necessity of a well-designed and adequately powered PA program (i.e., intensity).

Both, the traditional count-based Actigraph approach (Freedson, Melanson, & Sirard, 1998; Santos-Lozano et al., 2013; Sasaki, John, & Freedson, 2011) and other newer methods processing accelerometer data in "R" software (Hildebrand, van Hees, Hansen, & Ekelund, 2014) use raw accelerations (either vertical axis only, or a combination of three axes, also known as vector magnitude or VM_3) accelerations to quantify the time spent in different PA intensity levels applying accelerometer cut-points derived from the traditional absolute intensity recommendations for moderate intensity (3-6 METs) activities (Garber et al., 2011). These studies have generated widely divergent regression models for converting counts to energy expenditure, yielding different cut-points for PA intensity categories (Migueles et al., 2017). As such, with increasing age or decreasing CRF, an activity at a given absolute intensity (MET) requires a greater percentage of the $\dot{V}O_{2max}$ (i.e., relative intensity) (Garber et al., 2011; Rejeski et al., 2015). Therefore, using the absolute intensity approach may not be the most accurate option for assessing PA outcomes in samples varying in age or CRF (Miller, Strath, Swartz, & Cashin, 2010; Ozemek, Cochran, Kaminsky, Strath, & Byun, 2013). Alternatively, when activity counts cut-points representing moderate intensity activities have been calculated relative to $\dot{V}O_{2max}$ (i.e., 46%-63%) (Garber et al., 2011), the results show substantial differences between less fit and most fit groups, even if no differences are evident when activity counts are determined according to the absolute intensity criteria (Miller et al., 2010; Ozemek et al., 2013).

The validity of this "relative intensity" approach has also been substantially criticized because exercising at the same relative intensity could elicit a wide range of metabolic stress across individuals (Meyer, Gabriel, & Kindermann, 1999). In contrast, exercise intensity designed relative to lactate thresholds (LT) would be expected to produce less individual variation in metabolic responses and in time to exhaustion at a constant exercise intensity, providing a more homogenous training stimulus (Beneke, 2003; Mann, Lamberts, & Lambert, 2013). Although more than 20 lactate-related thresholds have been defined until now leading to considerable confusion and misinterpretation (Faude, Kindermann, & Meyer, 2009), there are two of these thresholds that have emerged as the preferred endurance performance markers among the vast majority of sport and exercise physiologists: (a) the more frequently called "lactate threshold" (LT1) defined as the critical exercise intensity level above which BLC first begin to increase above resting values during a graded incremental submaximal exercise (Jones & Ehrsam, 1982). LT1 has been suggested as the minimum exercise intensity required by inactive individuals to improve CRF (Londeree, 1997) and is a valid indicator of CRF in athletes and inactive people due to its high association with $\dot{V}O_{2max}$ sport performance (Beneke, 2003; Faude et al., 2009) and functional capacity in patients (Weber, Kinasewitz, Janicki, & Fishman, 1982), and, p. 2) the so-called "maximal lactate steady state" (MLSS or LT2), defined as the highest intensity that can be sustained over time without continual blood lactate accumulation during a constant intensity exercise (Beneke, 2003). Lactate thresholds are more sensitive than $\dot{V}O_{2max}$ to predict endurance performance and to evaluate training adaptations (Philp, Macdonald, Carter, Watt, & Pringle, 2008), allowing the definition of three individual intensity domains to guide exercise training: light (< LT1), moderate (LT1-LT2), and vigorous (> LT2) (Faude et al., 2009).

As far as we know, there are no studies addressing individually tailored activity counts cut-points through LT, which would allow a more accurate design of exercise intensity and a proper quantification of the time spent in different PA intensity levels. We hypothesized that accelerometer intensity cut-points derived from 3 METs as a representative of the lower boundary of moderate intensity were below LT1 and could lead to an overestimation of MVPA and the number of postmenopausal women meeting current PA targets. Thus, the aim of this study was to compare the widely used accelerometer activity cut-points derived from the absolute moderate intensity recommendation (3-6 METs) with relative intensity cut-points according to maximal cardiorespiratory fitness (46%-63% $\dot{V}O_{2max}$) and to individual lactate thresholds (LT1 and LT2) in postmenopausal women.

Method

Study design

Participants performed on different days (with a minimum of one week in between) a submaximal incremental exercise test with gas exchange measurement wearing an accelerometer to determine the first LT (LT1), several constant velocity tests (CVT) to determine the second LT (LT2), and a maximal cardiopulmonary exercise test to determine the CRF level ($\dot{V}O_{2max}$).

Study participants

Thirty post-menopausal women (57.6 ± 5.3 yr) from Pamplona (Spain) participated in several exercise tests from March to June 2017. Inclusion criteria were: (a) surgical or natural menopause (no menstrual periods during previous 12 months) and (b) age <75 years old. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: (a) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees, or feet; (b) functional limitation to walk for 20 min; (c) presence of any chronic disease that would impair the cardiorespiratory system during testing. The local hospital´s ethical committee approved the study (Pyto2011/71) and written informed consent was obtained from all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in ClinicalTrials.gov PRS (NCT02984553).

Exercise tests protocols

Submaximal incremental cardiopulmonary test

Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least 4 h and strenuous activity for ≥ 24 h before testing. During the first visit and prior to the first testing session, participants were familiarized with the exercise testing protocol and the treadmill ergometer. The metabolimeter was warmed up for at least 2 h prior to every exercise test to minimize any possible electrical drift. Calibration of the oxygen (O_2) and carbon dioxide (CO_2) analyzers was performed immediately prior to every test using two-point calibration with two precision-analyzed gas mixtures. Turbine flow calibration was determined using a high-precision 3-L calibration syringe (Vacu-Med, Calibringe 1092, Ventura, CA, USA). Participants' height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest 0.1 kg (Seca, Germany). Each participant wore a triaxial accelerometer (Actigraph wGT3X-BT Pensacola, FL, USA) over the right iliac crest in the mid-axillary line throughout the test. Testing was performed in a laboratory setting in controlled conditions (temperature: ~20°, humidity: ~27%, barometric pressure: ~960 mmHg) over a treadmill ergometer (Kuntaväline, Hyper Treadmill 2040, Finland).

The exercise protocol started with 3 min rest in a standing position. Capillary blood samples (0.3 µL) were taken from a hyperemic earlobe for the measurement of blood lactate concentration (BLC) (Lactate Pro2, Arkray, Japan). Heart rate (Polar V800, Polar Electro Oy, Kempele, Finland) and metabolic data were continuously collected using a Vista Mini-CPX computer-integrated metabolic system (Vacu-Med, Silver Edition 17,670, Ventura, CA, USA). Gas exchange and ventilatory variables were measured continuously while participants breathed into a two-way breathing mask (Series 7930, Hans Rudolph, Kansas City, MO, USA) and were reported as 30-s averages. Participants then started to walk at 2.4 km·h^{-1}. The intensity was progressively increased by 0.61 km·h^{-1} (Singh, Morgan, Scott, Walters, & Hardman, 1992) at each 2-min stage with a 1-min rest in between. At the end of each stage a capillary blood sample was taken for BLC analysis. Each participant was free to start running from the seventh stage onward (6.1 km·h^{-1}) or the operator suggested doing so when the participant was not able to match the required speed. The test was stopped when: (a) BLC was ≥ 3.0 mmol·l^{-1} to avoid excessive fatigue and/or (b) the participant was exhausted. First LT was defined as the highest velocity above which BLC increased by an amount of ≥ 0.1 mmol·l^{-1} in the following stage and ≥ 0.2 mmol·l^{-1} in the subsequent stage.

Constant velocity tests

On the following visits, participants completed two to seven 20-min constant velocity tests (CVT). Testing was performed in a laboratory setting in a controlled temperature environment (~20 °C) over a 20-m indoor track. Five cones were positioned at 0.5 m, 5 m, 10 m, 15 m, and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start. The speed at which the participant walked was dictated by an audio signal prerecorded in MP3 audio format. Each participant performed the corresponding tests on separate testing days (one week in between). Each CVT consisted of two stages of 10 min at a constant pace with a 2-min break for blood sampling. Heart rate was continuously recorded, and capillary blood samples were obtained at rest, at the 10th min and the end of the test (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which BLC increased by 1 mmol·l^{-1} above the blood lactate value at LT1 during the incremental exercise test. In the following tests, the velocity was increased or decreased by ~0.30 km·h^{-1} until the maximum lactate steady state velocity (i.e., LT2) could be determined (Billat, Dalmay, Antonini, & Chassain, 1994). An increase in BLC ≤0.4 mmol·l^{-1} during the final 10 min of exercise was defined as steady state (Beneke, 2003).

Maximum cardiopulmonary exercise test

On the last visit, a maximum cardiopulmonary exercise test was performed over a treadmill ergometer (Kuntaväline, Hyper Treadmill 2040, Finland) using a

graded protocol. Gas exchange and ventilatory variables were measured continuously while the participants breathed into a two-way breathing mask (Series 7930, Hans Rudolph, Kansas City, MO, USA). After 3-min rest, participants walked at 4.9 km·h^{-1} for a minute. Then, the speed was increased and maintained in 5.5 km·h^{-1} and the inclination of the treadmill was increased by 0.5% and by 1.3% in the first and next 1-min stages, respectively, to induce a ~ 0.6 METs increment per stage until volitional fatigue. The perceived exertion was rated by Borg´s scale (Borg, Ljunggren, & Ceci, 1985). A capillary blood sample was taken for lactate analysis at the termination of exercise, and at 1, 3, and 5 min of recovery if the BLC continued increasing (Lactate Pro; KDK Corporation or ABL 800; Radiometer Medical AS). All metabolic data were averaged over 30-second periods with the highest 1-min oxygen uptake ($\dot{V}O_2$) recorded as $\dot{V}O_{2max}$. Achievement of $\dot{V}O_{2max}$ was assumed in the presence of a minimum of three of the following criteria: (a) failure of $\dot{V}O_2$ and/or heart rate to increase with further increases in workload, (b) individual´s volitional fatigue, rating a perceived effort of a minimum of 8 points out of 10 (Borg et al., 1985), (c) elicited an exercise maximum heart rate (HR_{max}) that exceeded 85% of the individuals age-predicted maximum based on the HR_{max} estimated by 208–0.66·age (Edvardsen, Hansen, Holme, Dyrstad, & Anderssen, 2013), (d) RER ≥1.10, and (e) BLC_{max} >8 mmol·L^{-1} (Mezzani et al., 2013).

Determination of accelerometer activity cut-points and data analyses

Accelerometer activity counts during the submaximal incremental test were calculated by averaging the VM_3 activity counts in 1-sec epochs during the central 90 s of each stage to avoid the accelerations/decelerations produced during the start or the end of each stage (first or last 15 s). These activity counts were then averaged in 1-min epochs (ct·min^{-1}). We used individual centered third order polynomial regression equations between rates of energy expenditure (METs) and VM_3 activity counts measured at each speed (R^2 = 0.98) to derive the activity counts at selected moderate intensity thresholds (i.e., at lower and upper boundaries of absolute 3–6 METs, relative 46%-63% $\dot{V}O_{2max}$, and at individual LTs) (Sasaki et al., 2011). Data were analyzed using parametric statistics following confirmation of normality (Shapiro-Wilks's test), homoscedasticity (Levene´s test), and when appropriate sphericity (Mauchly's test). Repeated measures ANOVA with Bonferroni-adjusted post hoc testing was used to compare the activity counts of the three moderate intensity cut-points. The Greenhouse-Geisser correction factor to reduce the risk of Type I error was applied where sphericity assumptions were violated. Data are presented as mean ± standard deviation and 95% confidence interval (CI). Statistical significance was set at $p < .05$. Statistical analyses were performed using SPSS statistical software (version 22.0, IBM SPSS Statistics, Chicago, IL, USA) and GraphPad Prism 7 was used for figures.

Results

One of the study participants was excluded from data analysis due to not meeting maximum exercise criteria. Study participants had a $\dot{V}O_{2max}$ of 10.0 ± 4.2 METs (Table 1). Figure 1 shows measured METs and activity counts during the submaximal incremental exercise test. The average velocity at the classic lower moderate intensity boundary in absolute rates of energy expenditure (3 METs) was 3.2 km·h^{-1}, corresponding to a 30% $\dot{V}O_{2max}$ and a 49% HR_{max}. Average velocities at LT1 and LT2 were 5.5 ± 0.6 km·h^{-1} and 7.3 ± 1.1 km·h^{-1}, respectively, which corresponded to 4.6 ± 0.7 METs (47 ± 8% $\dot{V}O_{2max}$ and 59 ± 6% HR_{max}) and 7.3 ± 1.9 METs (73 ± 11% $\dot{V}O_{2max}$ and 85 ± 10% HR_{max}) during the incremental exercise test.

The activity counts calculated at the lower boundary of moderate intensity were 2026 ± 808 ct·min^{-1} (95% CI; 1719–2334) at 3 METs, 4306 ± 1447 ct·min^{-1} (95% CI; 3756–4857) at 46% $\dot{V}O_{2max}$ and 4247 ± 1122 ct·min^{-1} (95% CI; 3820–4674) at LT1. There was a significant difference between the three intensity indicators ($F_{2,56}$ = 79,2, $p < .01$) with Bonferroni-adjusted post hoc tests revealing that the activity counts at 3 METs threshold were significantly lower ($p < .01$) than activity counts at 46% $\dot{V}O_{2max}$ ($p < .01$; 95% CI: −2774 to −1786; ES: 1.95) or at LT1 ($p < .01$; 95% CI: −2559 to

Table 1. Descriptive characteristics of study participants (n = 29).

Characteristics			
Age (yr)	57.2	±	5.0
Height (cm)	158.3	±	5.5
Body mass (kg)	65.4	±	12.2
BMI (kg/m^2)	26.0	±	4.2
$\dot{V}O_{2max}$ (METs)	10.0	±	4.2
BLC_{max}	7.8	±	3.2
RER_{max}	1.22	±	0.07
RPE_{max}	8.8	±	1.9
HR_{max}	172.7	±	11.3
LT1 (km·h^{-1})	5.5	±	0.6
LT1 (METs)	4.6	±	0.7
LT2 (km·h^{-1})	7.3	±	1.1
LT2 (METs)	7.3	±	1.9

Note. BMI = body mass index, $\dot{V}O_{2max}$ = oxygen consumption, MET = rates of energy expenditure (1 MET is equivalent to 3.5 ml·kg^{-1}·min^{-1}), BLC = blood lactate concentration, RER = respiratory exchange ratio RER = $\dot{V}CO_2/\dot{V}O_2$), RPE = rating of perceived effort, HR_{max} = maximum heart rate, LT1 = first lactate threshold, LT2 = second lactate threshold.

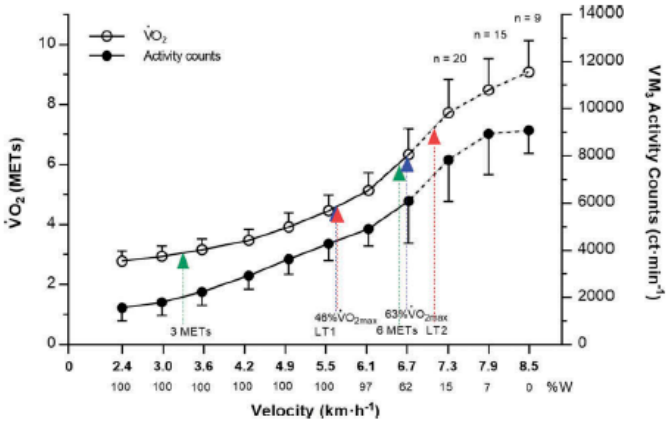

Figure 1. Measured rates of energy expenditure (METs) and activity counts across the velocities of the submaximal incremental test (n = 29). Dashed arrows indicate the lower and upper boundaries of moderate absolute (green), relative (blue), and individual (red) intensity.

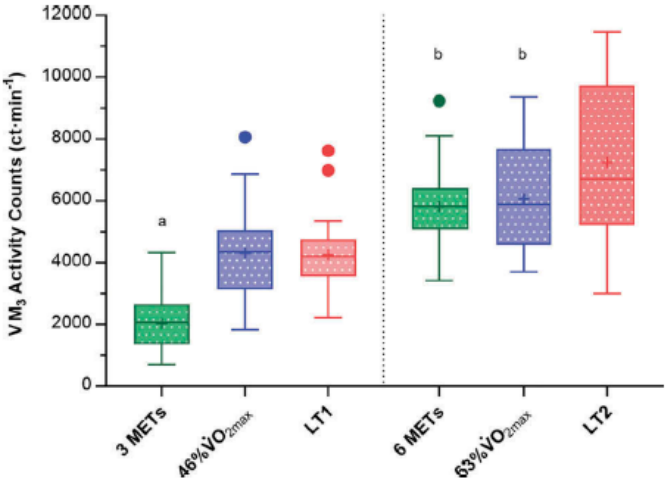

Figure 2. Measured-activity counts at the lower and upper boundaries of moderate absolute (3–6 METs), relative (46%–63% $\dot{V}O_{2max}$) and individual (LT1-LT2) intensity. The data are derived from individual regressions between rates of energy expenditure (METs) and VM_3 activity counts measured at each speed during the submaximal incremental test in 29 participants.

Note. VM = vector magnitude activity counts per minute, MET = metabolic equivalent of energy expenditure, LT1 = first lactate threshold, LT2 = second lactate threshold. The dashed line separates lower and upper boundaries of moderate intensity.

[a]Significantly different from 46% $\dot{V}O_{2max}$ and LT1 ($p < .01$).

[b]Significantly different from LT2 ($p < .01$).

–1882; ES: 2.27). No differences were observed in the average activity counts between the lower threshold of 46% $\dot{V}O_{2max}$ assigned to relative moderate intensities and LT1 (p = .72; 95% CI: −363 to 482; ES: 0.05) (Figure 2). The data revealed large interindividual variability in activity counts at the three lower boundaries of moderate intensity (coefficient of variation, CV = 40, 34, 26%, respectively).

The activity counts measured at the upper boundary of moderate intensity were 5820 ± 1297 ct·min^{-1} (95% CI; 5326–6313) at 6 METs, 6068 ± 1765 ct·min^{-1} (95% CI; 5397–6740) at 63% $\dot{V}O_{2max}$, and 7249 ± 2499 ct·min^{-1} (95% CI; 6298–8199) at LT2. The activity counts at LT2 were significantly higher than those at 63% $\dot{V}O_{2max}$ ($p < .01$; 95% CI: 637 to 2221; ES: 0.55) and at 6 METs thresholds ($p < .01$; 95% CI: 569 to 1792; ES: 0.72), which did not differ between them (p = .38; 95% CI: −327 to 824; ES: 0.16) (Figure 2). The data revealed large interindividual variability at the three upper boundaries of moderate intensity (CV = 22, 29, 34%, respectively). The large variation in activity counts at the lower and upper relative moderate intensity boundaries was largely explained by $\dot{V}O_{2max}$ (R^2 = 54% and 48%, respectively); whereas, less than 2% of the variability was explained by individuals' age and BMI.

Discussion

The selection of appropriate accelerometer cut-points to demarcate PA intensity levels is the cornerstone to obtaining reliable PA outcomes and their association with health markers and mortality (Rejeski et al., 2015). If the cut-points are too high when evaluating accelerometry data, then participants will not be credited for engaging in MVPA even when being adherent to their prescriptions. Conversely, using cut-points that are too low would falsely elevate levels of MVPA (Rejeski et al., 2015). A possible solution to this problem could be to individualize the activity cut-points according to relative intensities, rather than using fixed cut-points for all individuals (Miller et al., 2010; Ozemek et al., 2013).

An important finding of this study was that the energy cost at the lower moderate intensity boundary expressed either relative to $\dot{V}O_{2max}$ (46% $\dot{V}O_{2max}$, corresponding to 4.6 ± 0.9 METs) or to LT1 (5.5 ± 0.6 km·h^{-1}, corresponding to 4.6 ± 0.7 METs) was higher than the classic 3 METs threshold assigned to the lower boundary of moderate intensity activities, which has been widely utilized by expert panels to create PA guidelines (Garber et al., 2011; Physical Activity Guidelines Advisory Committee, 2018; Riebe et al., 2017) and to establish the health benefits of engaging in MVPA (Arem et al., 2015). A possible explanation could be the higher CRF of our study participants (10.0 ± 2.0 METs) compared to the 8–8.5 METs reported for women of the same age in other studies (Edvardsen et al., 2013). Interestingly, the energy cost of the LT1 agrees with the relative intensity value assigned to the lower moderate intensity boundary of individuals with a CRF of 10 METs (Garber et al., 2011; Howley, 2001).

Consequently, measured activity counts at 3 METs fell well below the relative intensity and individual cut-points derived from LT ($p < .01$). This finding is in agreement with the results of Miller and colleagues (Miller et al., 2010), who showed that the activity counts at 3 METs were much lower than those obtained at relative intensity cut-points, even in the oldest individuals, and this difference increased in individuals with higher CRF (Ozemek et al., 2013). Epidemiological studies measuring PA with accelerometers (Cerin et al., 2014; Tucker et al., 2011) have commonly used activity counts cut-points derived at 3 METs intensity as the lower boundary of moderate intensity (Freedson et al., 1998; Santos-Lozano et al., 2013; Sasaki et al., 2011). Hence, the finding of the present study has important consequences, as it could falsely elevate the time spent at MVPA and the percentage of people meeting current PA guidelines. In this investigation, measured activity counts at 3 METs intensity were 25%–37% lower compared to previous actigraph triaxial accelerometer validation studies (Santos-Lozano et al., 2013; Sasaki et al., 2011). However, these two studies obtained ~4000 ct·min^{-1} at 4.8 km·h^{-1}, which is close to the value of 3616 ct·min^{-1} found in our study when participants walked at the same speed. These two studies used an incremental treadmill protocol with activity counts obtained at only 2–4 velocity stages to derive the activity counts at 3 and 6 METs using linear regression analysis (Sasaki et al., 2011) and artificial neural networks (Santos-Lozano et al., 2013). In contrast, our incremental exercise test provided a minimum of seven data points from all participants, with smaller velocity increments between stages (0.6 km·h^{-1}). Besides, we used individual rather than whole-group regression equations to determine the activity counts at moderate intensity thresholds. Another possible explanation to the low activity counts observed at 3 METs intensity could be related to the slightly higher METs measured in our study participants (i.e., 3.9 METs at 4.9 km·h^{-1}) compared to the estimated values of 3.6 METs from the equation of Weyand et al. (Weyand et al., 2013) or the 3.5 METs assigned in the compendium of physical activities (Ainsworth et al., 2011) to walking at 4.8 km·h^{-1}. Both Miller and colleagues (Miller et al., 2010) and Santos-Lozano et al. (Santos-Lozano et al., 2013) reported a large variation in measured METs for that speed (from 3 to 4 METs) between young and older adults. In our study, age was not a significant predictor of measured METs at a certain velocity, but resting METs (standing) contributed in a range of 15%–42% of its variance, mainly at slow velocities ($p < .001$).

On the other hand, the activity counts measured at the upper boundary of moderate intensity were similar between absolute and relative intensities ($p = .384$) and go hand in hand with the cut-point derived at 6 METs by Sasaki and colleagues (Sasaki et al., 2011). However, LT2 corresponded to a higher intensity (7.3 ± 1.9 METs or 73% $\dot{V}O_{2max}$) than either absolute (6 METs) or relative (63% $\dot{V}O_{2max}$) upper boundaries of moderate intensity established by exercise intensity guidelines (Garber et al., 2011; Physical Activity Guidelines Advisory Committee, 2018; Riebe et al., 2017). Consequently, the activity counts measured at LT2 were higher ($p < .01$) than absolute and relative cut-points. The second LT (i.e., the so-called maximum lactate steady-state or MLSS) represents the highest constant-rate velocity or power output that can be sustained over time without a continual blood lactate accumulation (Beneke, 2003) and is the upper limit of exercise beyond which there is an abrupt rise in plasma catecholamine levels and fatigue (Urhausen, Weiler, Coen, & Kindermann, 1994). There is a lack of normative values of LTs in adults, but our results demonstrate that both moderate and vigorous intensities defined by current PA guidelines (Garber et al., 2011; Mezzani et al., 2013; Physical Activity Guidelines Advisory Committee, 2018; Riebe et al., 2017) are included in the relative intensity range between LT1 and LT2 (46%–73% $\dot{V}O_{2max}$ or 58%–85% HR_{max}). These exercise intensity categories were initially defined according to percentage of $\dot{V}O_2$ reserve as a standard for conversion to other expressions of exercise intensity (e.g., METs, % $\dot{V}O_{2max}$ or % HR_{max}) based on a 10 MET fitness group (Garber et al., 2011; Howley, 2001). In less fit individuals, health/fitness benefits have been reported with a minimum exercise intensity of ~40%–50% $\dot{V}O_2$ reserve or 55%–65% HR_{max}. Owing to the high proportion of physically inactive and unfit adults and people with increased risk of cardiovascular disease, PA authorities reduced the recommended amount and intensity of PA from the original recommendations, which were based on athletic population (Pollock et al., 1998). It is acknowledged that individuals with higher fitness levels require higher training stimulus to improve health/fitness (Pollock et al., 1998). Therefore and in line with the 1998 ACSM´s position, vigorous exercise or exercise intensities close to LT2 (i.e., 70%–90% HR_{max}) should be recommended for larger health/fitness benefits in postmenopausal women with maximum CRF values ~10 METs.

The large interindividual variability in activity counts at absolute, relative, and individual LT intensities is evidence that individually tailored rather than fixed accelerometer intensity cut-points might better represent meaningful volumes of light, moderate, and vigorous intensities during daily activities. Our results go hand in hand with the findings of Ozemek and colleagues (Ozemek et al., 2013) showing that CRF,

rather than age or BMI, influenced individual´s activity count cut-points at relative intensities, explaining half of their variance. As we showed in a previous study, it was easier for high-fit individuals engaging in higher levels of PA when using the same fixed accelerometer intensity cut-points for everyone, but it does not necessarily mean that they are having higher relative intensities. In fact, there was no difference in the time spent at MVPA when the accelerometer activity cut-points were individualized according to their lactate thresholds (Gil-Rey, Maldonado-Martín, Palacios-Samper, & Gorostiaga, 2018). Therefore, epidemiology studies should at least consider adjusting the association between PA and mortality risk by CRF. Besides, a meta-analysis conducted by Williams (Williams, 2001) reported higher potential to reduce the risk of developing CVD in favor of CRF compared to the amount of PA. Although PA increases CRF and may be an appropriate therapy mostly for the unfit, only 35% of the variance in CRF is explained by PA, probably because of the low correlation of CRF with the amounts of light or moderate intensity activity. Thus, the aforementioned association might have been inflated by the higher CRF in those reporting higher physical activity dose.

This study used a novel approach to set individualized accelerometer activity cut-points through LTs. Despite the methodological shortcomings of accelerometer-based measures in PA surveillance (Pedisic & Bauman, 2015), the proposed method in this study avoids the misinterpretation of intensity-specific PA levels when using fixed activity cut-points in individuals or groups varying in CRF. The current study is not without limitations. First, the applicability of this individualized approach is not feasible for large epidemiological studies, although they could benefit from population-specific relative intensity cut-points to obtain more-reliable PA outcomes. Second, the generalizability of these findings is limited to postmenopausal women with such $\dot{V}O_{2max}$ values (range: 6–14 METs), who are worthy of distinct attention due to the increased risk of cardiovascular disease (Kannel et al., 1976) and osteoporosis (Kanis et al., 2012). Third, our study was a cross-sectional study. Although higher relative intensity of daily activities has been associated with reduced CHD mortality (Lee, Sesso, Oguma, & Paffenbarger, 2003), randomized controlled trials are needed to confirm whether PA recommended by guidelines applying relative intensity thresholds brings greater long-term health benefits compared to absolute intensity. Finally, we did not directly measure the $\dot{V}O_2$ during the CVTs for the determination of the LT2. The gold standard method for the determination of LT2 requires at least two or three CVTs; consequently, increasing the time and cost related to cardiopulmonary exercise testing. Instead, we accurately determined LT2 velocity from CVTs to derive the activity counts from individual regression equations with measured $\dot{V}O_2$ values from the incremental test.

Conclusions

In conclusion, the widely utilized 3 METs threshold to derive accelerometer activity counts cut-points that represent the lower boundary of moderate intensity physical activities was well below from both, the relative intensity threshold (46% $\dot{V}O_{2max}$), and LT1. Further, the large interindividual variability in activity counts at relative moderate intensities is evidence that individually tailored activity counts cut-points expressed either, relative to CRF level or to LT velocities may better represent meaningful PA intensity levels compared to fixed cut-points derived from the recommended absolute intensities of 3 and 6 METs in postmenopausal women.

What does this article add?

The article provides valuable information regarding the use and interpretation of objectively measured physical activity levels using accelerometers. The study highlights the important role of cardiorespiratory fitness in the selection of appropriate accelerometer intensity cut-points. Besides, it provides the procedures for the individualization of accelerometer intensity cut-points through an easy-to-administer submaximal walking test that could overcome the under- or overestimation of PA levels using fixed cut-points derived from the absolute moderate intensity recommendations.

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ORIGINAL ARTICLE

Objectively measured absolute and relative physical activity intensity levels in postmenopausal women

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Abstract

Objectives: To investigate how objectively measured physical activity (PA) levels differ according to absolute moderate intensity recommendation (3–6 METs) and relative to individual lactate thresholds (LT1 and LT2), and to verify if high-fit women record higher PA levels compared to women with lower aerobic fitness.

Methods: Seventy-five postmenopausal women performed an incremental exercise test and several constant-velocity tests wearing an accelerometer to identify the activity counts (ct min^{-1}) corresponding to LT1 and LT2. Individual linear regression determined activity counts cut-points for each intensity: (1) sedentary (<200 ct min^{-1}), (2) light (from 200 ct min^{-1} to ct min^{-1} at LT1), (3) moderate (ct min^{-1} between LT1 and LT2) and (4) vigorous (ct min^{-1} > LT2). Participants then wore an accelerometer during a week to measure the time spent at each PA intensity level.

Results: According to absolute intensity categorisation, high-fit postmenopausal women recorded twice as much time at moderate-to-vigorous PA (MVPA) ($P < 0.01$) than low-fit women. However, when PA intensity was calculated relative to individual lactate thresholds, MVPA was significantly reduced by half ($P < 0.01$) and the data revealed no differences ($P = 0.62$) between groups (~20 min day^{-1} at MVPA).

Conclusions: Accelerometer cut-points derived from absolute moderate-intensity recommendations overestimated MVPA. Similar time at MVPA was recorded by high- and low-fit postmenopausal women when the cut-points were tailored to individual lactate thresholds. A more accurate estimation of PA behaviour could be provided with the use of individually tailored accelerometer cut-points.

Keywords: *Accelerometry, cardiorespiratory fitness, individually tailored cut-points, moderate-to-vigorous physical activity*

Highlights

- Fixed accelerometer intensity cut-points derived from the standard absolute moderate intensity thresholds of 3 and 6 METs overestimated MVPA in a sample of postmenopausal women.
- Individually-tailored cut-points revealed no differences in MVPA between High-fit and Low-fit women, despite attaining current PA target was easier fot High-Fit women when the same intensity cut-points were used for everyone.
- Accelerometer intensity cut-points should be individualized according to cardiorespiratory fitness. Wearing an accelerometer during a quick, simple and incremental submaximal walking test is a feasible way of obtaining appropiate intensity cut-points.

Introduction

Physical activity (PA) level and cardiorespiratory fitness (CRF) are two of the most powerful predictive factors of premature death and chronic disease (Arem et al., 2015; Kodama et al., 2009). Observational prospective cohort studies using self-reported questionnaires suggest that meeting current PA guidelines (American College of Sports Medicine, 2013; Garber et al., 2011; Physical Activity Guidelines Advisory Committee, 2018) of 150 min wk^{-1} of moderate-to-vigorous physical activity (MVPA) reduces all-cause mortality risk by 26–31% (Arem et al., 2015; Lee, Rexrode, Cook, Manson, &

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Buring, 2001; Wen et al., 2011). Several studies have reported that MVPA, rather than total energy expenditure or light intensity PA is determinant to reduce the levels of cardiometabolic risk factors (Arem et al., 2015; Swain & Franklin, 2006; Weston, Wisloff, & Coombes, 2014) and osteoporosis (Whitfield, Kohrt, Pettee Gabriel, Rahbar, & Kohl, 2015).

Large epidemiology studies using self-reported PA questionnaires (Arem et al., 2015; Wen et al., 2011) have commonly grouped recreational PA into three intensity categories according to their energy requirements, supported by evidence-informed guideline recommendations (Ainsworth et al., 2011; American College of Sports Medicine, 2013; Garber et al., 2011; Pate et al., 1995; Physical Activity Guidelines Advisory Committee, 2018): light (<3 metabolic equivalents [MET]), moderate (3–6 METs) and vigorous (>6 METs). Interestingly, Lee and colleagues (Lee, Sesso, Oguma, & Paffenbarger, 2003) showed that it is the relative intensity of exercise, rather than total energy expended or absolute intensity of activities what causes greater reduction in coronary heart disease (CHD) mortality risk. During the last years, accelerometers have replaced PA questionnaires to objectively capture human activity, applying activity cut-points derived from the traditional absolute 3–6 MET intensities to obtain representative volumes of MVPA (Freedson, Melanson, & Sirard, 1998; Santos-Lozano et al., 2013; Sasaki, John, & Freedson, 2011). These studies have generated widely divergent regression models for converting activity counts to energy expenditure, yielding different cut-points for PA intensity categories (Migueles et al., 2017). Contrary to self-reported estimates, results of accelerometer-based objective assessments of PA report much lower volumes of MVPA (Arem et al., 2015; Tucker, Welk, & Beyler, 2011) indicating that only a small proportion of adults (7–15%) meet current PA recommendations (Cerin et al., 2014; Colley et al., 2011; Kujala et al., 2017; Tucker et al., 2011). Reported objective weekly volumes of MVPA are significantly lower in women and vary from as low as seven $min \cdot day^{-1}$ to 57 $min\ day^{-1}$ (Cerin et al., 2014; Colley et al., 2011; Kujala et al., 2017; Tucker et al., 2011). Previous studies have demonstrated that the use of fixed cut-points may under or overestimate MVPA due to the lack of consideration of an individuaĺs CRF (Miller, Strath, Swartz, & Cashin, 2010; Ozemek, Cochran, Kaminsky, Strath, & Byun, 2013; Rejeski et al., 2016). When moderate intensity activity counts cut-points have been calculated based on relative intensities (*i.e.* 45–60% $\dot{V}O_{2max}$) the results show substantial differences in measured activity counts between less fit and most fit individuals (Miller et al., 2010; Ozemek et al., 2013). Furthermore, Kujala et al. (2017) using heart-rate based PA assessment reported that although the time spent at MVPA applying fixed absolute intensity cut-points was higher in men compared to women, and decreased with age, when intensity levels were calculated relative to individuaĺs CRF, these differences disappeared.

The validity of this "relative intensity" approach has also been substantially criticised because exercising at the same relative intensity could elicit a wide range of metabolic stress across individuals (Meyer, Gabriel, & Kindermann, 1999). The determination of individual physiological break points of energy supply, as the lactate thresholds (LT), is the gold standard method for accurate exercise intensity prescription (Beneke, 2003; Binder et al., 2008; Weltman et al., 1990). Besides, the achieved workload at LT is an accurate indicator of CRF (Faude, Kindermann, & Meyer, 2009). In this study, we were interested in accurately quantifying PA volumes in postmenopausal women because they usually report lower MVPA compared to men (Kujala et al., 2017; Tucker et al., 2011), and because they have an increased risk of osteoporosis and cardio-metabolic diseases related to menopause, lower fitness and inactivity (Kanis et al., 2012; Kannel, Hjortland, McNamara, & Gordon, 1976). It is unknown how well individually-tailored accelerometer cut-points derived from LT reflect PA levels during routine activities of daily living, and whether differences exist between less fit and most fit women.

This study aimed to investigate how objectively measured PA levels differ according to absolute moderate intensity recommendation (3–6 METs) and relative to individual lactate thresholds (LT1 and LT2), and to verify if high-fit women record higher PA levels, especially MVPA, compared to women with lower fitness level.

Materials and methods

Study design

This cross-sectional study investigated the volumes of absolutely and relatively (*i.e.* relative to participant´s LT) determined PA at different intensity levels (sedentary, light, moderate, vigorous, and moderate-to-vigorous combined) during one week in postmenopausal women. Participant´s aerobic fitness and PA data were collected from November 2015 to June 2017. Participants performed on different days an incremental submaximal shuttle test (IST) and several constant-velocity tests (CVT) wearing an accelerometer to identify the activity counts ($ct \cdot min^{-1}$) corresponding to LT1 and LT2 velocities.

Participants then wore an accelerometer for seven complete days to assess their PA patterns.

Study participants

Participants were recruited through advertisements placed on healthcare centres. One hundred and four participants were screened by telephone, 88 were deemed eligible and were invited to participate in the study. Inclusion criteria were: (1) surgical or natural menopause (no menstrual periods during previous 12 months), (2) age <75 years. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: (1) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees or feet, (2) functional limitation to walk for 20 min, (3) presence of any chronic disease that would impair the cardiorespiratory system during testing. The local hospitals ethical committee approved the study (Pyto2011/71) and written informed consent was obtained from all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in *ClinicalTrials.gov PRS* (NCT02984553).

Exercise tests

Incremental shuttle test (IST). Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least four hours and strenuous activity for ≥24 h before testing. Height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest 0.1 kg (Seca, Germany). Before starting the test each participant´s resting heart rate (HR) (Polar V800, Polar Electro Oy, Kempele, Finland) and blood lactate concentration ([La^-]) (Lactate Pro2, Arkray, Japan) were measured on a standing position. Capillary blood samples (0.3 µL) were taken from a hyperemic earlobe. Testing was performed in a laboratory setting in a controlled temperature environment (~20°) over a 20 m indoor track. The distance of the course was extended to 20 m from the original test (Singh, Morgan, Scott, Walters, & Hardman, 1992) to keep the pace constant avoiding excessive turns that might increase the energy cost and musculoskeletal demand, potentially leading to premature fatigue, discomfort or even injury. Five cones were positioned at 0.5–5–10–15 and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start (Figure 1(a)). The speed was dictated by an audio signal. A double beep indicated the start of each stage. After that, participants were instructed to be at the next cone with each beep while keeping the pace as constant as possible. The IST started at 2.4 km h^{-1} (~2.1 METs). The intensity was progressively increased by 0.61 km h^{-1} (Singh et al., 1992) at each 2-min stage with 1-min rest in between. At the end of each stage, HR and [La^-] were recorded. Each participant wore a triaxial accelerometer (Actigraph wGT3X-BT Pensacola, FL, USA) over the right iliac crest in the mid-axillary line throughout the test.

Each participant was free to start running from the 7th stage onwards (6.1 km h^{-1}), or the operator suggested to do so when the participant was not able to match the required speed. The test was stopped when: (1) [La^-] values were ≥3.0 mmol l^{-1} to avoid excessive fatigue, and/or (2) participant repeatedly failed to match the pace programmed, and/or (3) participant was exhausted. LT1 was defined as the highest velocity above which [La^-] increased by an amount of ≥0.1 mmol l^{-1} in the following stage and ≥0.2 mmol l^{-1} in the subsequent stage (Figure 1(b)).

Constant-velocity tests (CVT). Participants completed two to seven 20 min CVT on the same 20 m track used for the IST. Each participant performed the corresponding tests on separate testing days (one week in between). Each CVT consisted of two stages of 10 min at a constant pace with a two minutes interruption for blood sampling. Heart rate was continuously recorded, and capillary blood samples were obtained before at rest, at the 10th min and the end of exercise (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which blood lactate increased by 1 mmol l^{-1} above the blood lactate value at LT1 during the IST. In the following tests, the velocity was increased or decreased by ~0.30 km h^{-1} until the maximal lactate steady state velocity (*i.e.* LT2) could be determined (Billat, Dalmay, Antonini, & Chassain, 1994). An increase in [La^-] ≤0.4 mmol l^{-1} during the final 10 min of exercise was defined as steady state (Beneke, 2003) (Figure 1(c)).

Physical activity assessment

Each participant was instructed to wear an Actigraph wGT3X-BT accelerometer over the right iliac crest at the mid-axillary line on an elasticised belt for eight consecutive days (24 h) alongside a daily log.

Each monitor was previously initialised at a 50 Hz frequency and downloaded after the 8-day period in vector magnitude (VM_3) activity counts in 1-min epochs (ct min^{-1}). Data were analysed with Actilife 6® full software (Actigraph, Pensacola, FL, USA).

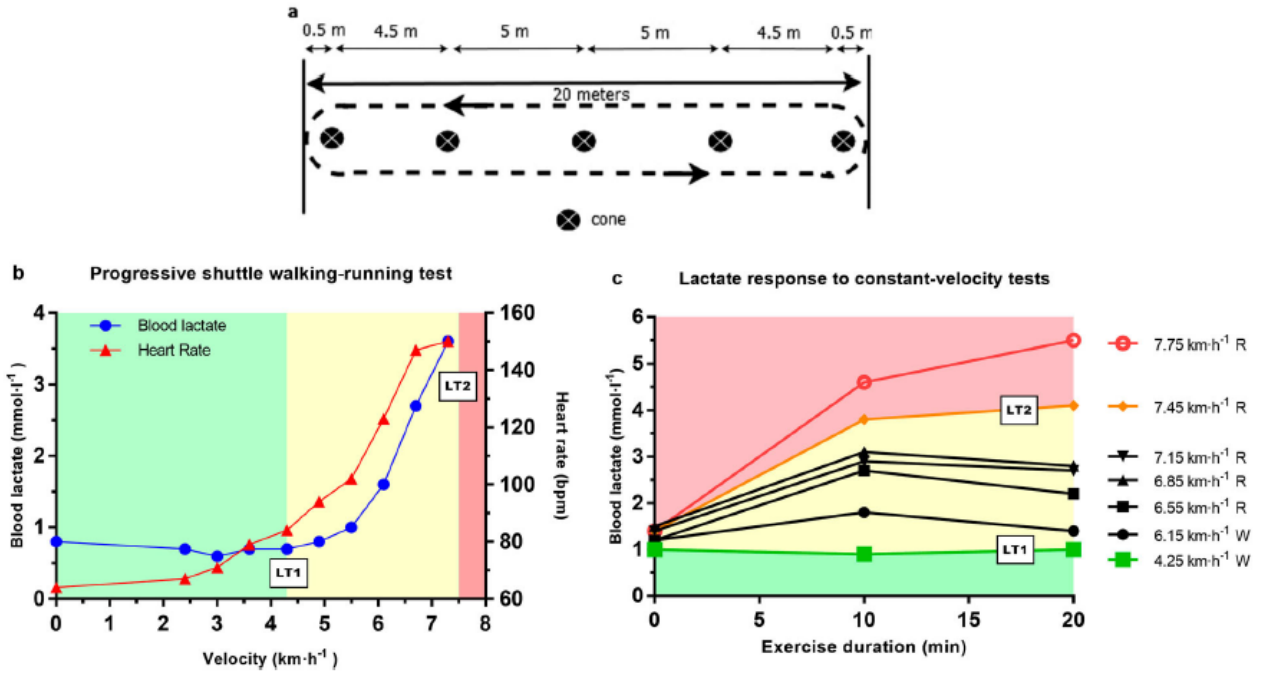

Figure 1. (a) Schematic representation of the 20 m track used in the IST and CVT; (b) Blood lactate and heart rate response during the IST for the individual determination of the LT1 in a representative participant. The participant started running at 6.7 km h^{-1}; (c) Lactate response during several CVT for the determination of the LT2 in the same representative participant. Three metabolic intensity zones: light (<4.25 km h^{-1}), moderate (4.25–7.45 km h^{-1}) and vigorous (>7.45 km h^{-1}) are indicated by different background colours (green, yellow and red, respectively). LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, W: walk, R: run.

The first recording day was not used for the analysis. Sleep periods were selected from participant's daily logs. For the present analysis, only data over the day were used. Participants were included in the analysis if they had a minimum of five days of monitoring, including two weekend days and daily wear time was ≥12 h (Migueles et al., 2017). Periods of continuous zeros lasting more than 60 min with

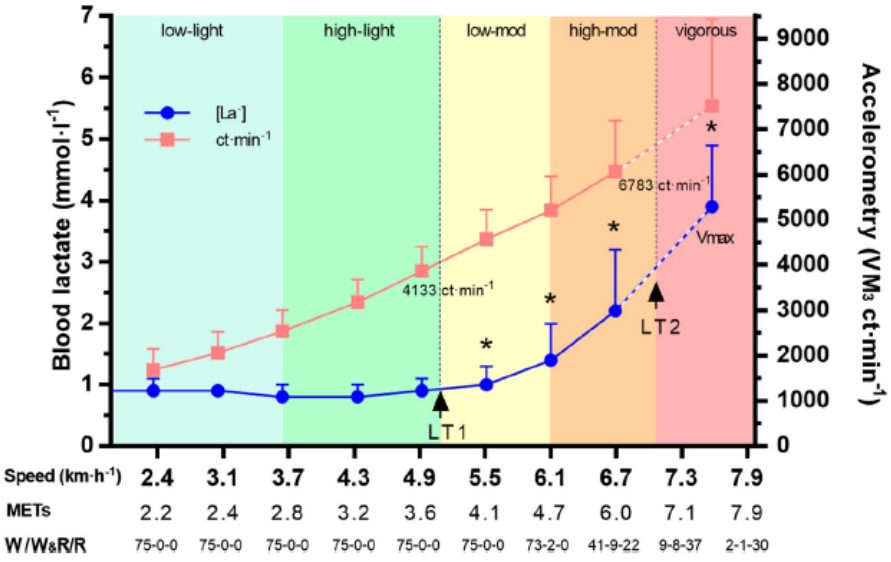

Figure 2. Blood lactate concentration and accelerometer activity counts during the IST. Data are mean values for the whole sample ($n = 75$). Five metabolic intensity zones: low-light and high light (<LT1), mod-low and high-low (between LT1 and LT2) and vigorous (>LT2) are indicated by different background colours (blue-green, yellow-orange and red, respectively). [La^-] = blood lactate, ct min^{-1} = activity counts per minute, LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, V_{max} = maximal velocity obtained during the test, VM_3 = vector magnitude activity counts, MET = estimated metabolic equivalents (Weyand et al., 2013), W, W&R, R = number of subjects walking, a combination of walking and running or running, respectively, at each stage. *Significantly ($P < 0.01$) different from the previous stage.

allowance for 2 min interruptions of activity counts between 0 and 200 (Troiano et al., 2008) were checked in participant´s daily logs and assigned as non-wear time if corresponded (Migueles et al., 2017). High activity levels (>10.000 ct min^{-1}) or high step counts (>20.000 steps day^{-1}) were verified against participant's daily logs.

Accelerometer activity counts measured during the IST at the velocities corresponding to each participant´s LT1 and LT2 were used to determine three individual intensity zones: light (<LT1 ct min^{-1}), moderate (LT1 ct min^{-1} – LT2 ct min^{-1}) and vigorous (>LT2 ct min^{-1}). Both, the light-intensity and the moderate-intensity zones were subdivided into other identical two zones (low and high) (Figure 2). The time (min·day^{-1}) spent in each of these intensity zones for every valid day and the number of daily steps were averaged. Both, sedentary time and MVPA were reported in one (+1) and ten (+10) minute bouts (the minimum time required to be between the specified intensity cut-points). The time spent at each relative intensity category was compared to absolute accelerometer activity counts cut-points, which have been previously validated against direct measurement of oxygen uptake during treadmill walking and running activities designated as movements that represent moderate intensity recommendations (3–6 METs) (*i.e.* light = 200–2689 ct min^{-1}, moderate = 2690–6166 ct min^{-1}, vigorous ≥6167 ct min^{-1} (Sasaki et al., 2011).

Statistical analysis

Accelerometer activity counts during IST were calculated by averaging the VM_3 activity counts in one-second epochs during the central 90sec of each stage. These activity counts were then averaged in 1-min epochs (ct·min^{-1}). The corresponding ct·min^{-1} at LT2 were selected from the individual regression equations obtained in the IST. For women who walked at the LT2 during the CVT, the data of running stages were removed. For women who ran at LT2 during the CVT and for whom this velocity was between the last walking stage and the first running stage of the IST, linear interpolation was performed.

For the whole sample, repeated measures ANOVA was used to determine differences in both, [La^-] and activity counts throughout the IST. Bonferroni Post Hoc analysis was applied when significant effects were observed for velocity stages.

Participants were categorised into two groups according to their LT2 velocity (Low-fitness group; as ≤6.8 km h^{-1} [$n = 37$], and high-fitness group; as >6.8 km h^{-1} [$n = 38$]), which represented the median speed of LT2 and corresponded to the minimum level of CRF (6–7 METs) associated with lower event rates in 40–60 years old women (Kodama et al., 2009). The differences in the activity count cut-points at LT1 and LT2 between groups were presented using Tukey Box Plots and Mann Whitney U-test was used for comparison between groups.

The primary outcome of the study was the volume of objectively measured PA (particularly $MVPA_{+10}$) expressed as mean ± SD, using both, relative and absolute cut-points. Intra-group PA levels (min·day^{-1}) were compared using a paired *t*-test or Wilcoxon test (for non-parametric data), and Independent samples test or Mann Whitney U test were used for inter-group analysis.

We conducted a post hoc power analysis using the G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007). The level of statistical power reached in this study was 0.99 for the following variables; alpha level ($\alpha = 0.05$), sample size ($n = 75$), and effect size (ES = 0.80 relative *vs.* absolute $MVPA_{+10}$). Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS statistical software (version 22.0, IBM SPSS Statistics, Chicago, IL).

Results

Population selection and characteristics

Among 104 interested participants who were screened for eligibility, 14 were excluded. Reasons for exclusion were; 1) not meeting eligibility criteria ($n = 12$), and 2) declined to participate ($n = 2$). Among 88 participants who were invited to participate, 75 completed all the assessments and were included in the study for data analysis. Reasons for exclusion in data analysis were inability, musculoskeletal pain or discomfort when running ($n = 6$), failure to get the LT2 with accuracy ($n = 3$), invalid 7-day accelerometry recording ($n = 1$), cardiovascular or pulmonary disease ($n = 2$), and failure to keep testing appointment ($n = 1$). All participants had a minimum of 5-valid days (2 weekend days included), and 78% had 7-valid days.

Determination of PA intensity levels through lactate thresholds

The average velocity *vs.* [La^-] curve during the IST in the whole group of participants is presented in Figure 2. During the first five stages [La^-] did not change noticeably. From the fifth stage onwards, [La^-] significantly increased ($F_{8,568} = 137.5$, $P < 0.001$) in each subsequent exercise stage. Accelerometer activity counts increased linearly and

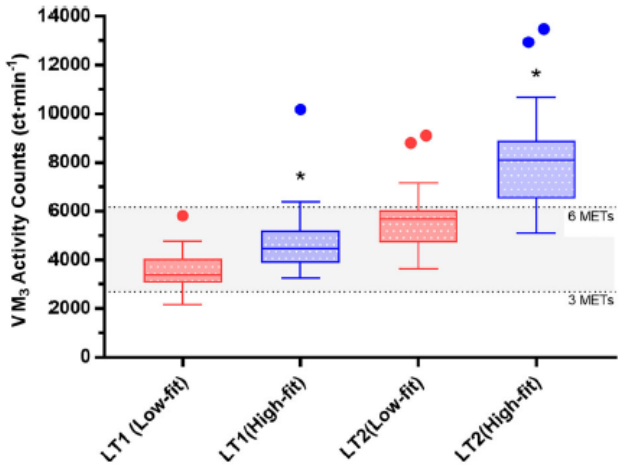

Figure 3. Tukey Box Plot showing the median and the 25–75 percentiles of the VM_3 activity counts at LT1 and LT2 velocities in Low-fit (red coloured) and High-fit (blue coloured) groups. The grey coloured area shows the VM_3 activity counts cut-points derived from walking and running activities that represent an intensity of 3 and 6 METs (Sasaki et al., 2011). VM_3 = vector magnitude, MET = metabolic equivalent, LT1 = first or aerobic threshold, LT2 = second or anaerobic threshold, Low-fit = low aerobic fitness group (≤6.8 km h^{-1}), High-fit = High aerobic fitness group (>6.8 km h^{-1}). *Significantly different between groups ($P < 0.01$).

significantly ($F_{7,497} = 892$, $P < 0.001$) over the duration of the IST. Average LT1 was 5.1 ± 0.7 km h^{-1}, and the corresponding activity counts, [La^-], and HR values were 4133 ± 1152 ct min^{-1}, 0.8 ± 0.2 mmol l^{-1} and 98 ± 12 beats min^{-1} (bpm), respectively. Mean LT2 was 7.1 ± 1.0 km h^{-1}, and the corresponding activity counts, [La^-], and HR values in the IST were 6783 ± 2077 ct min^{-1}, 2.4 ± 0.7 mmol l^{-1}, and 141 ± 17 bpm, respectively.

Individually tailored activity counts cut-points by fitness group

High-fit women were five years younger ($P < 0.01$) and their body mass was eight kg lower ($P < 0.01$) compared to the low-fit group. LT1 and LT2 were 17% and 24% higher in high-fit compared to low-fit women ($P < 0.01$), respectively. Accordingly, measured activity counts were greater in the high fit group ($P < 0.01$) at both, LT1 (4659 ± 1250 *vs.* 3592 ± 729 ct min^{-1}) and LT2 (7989 ± 2035 *vs.* 5543 ± 1223 ct min^{-1}) (Figure 3).

Physical activity levels

Table I shows the results of the minutes spent per day at each intensity level for each group, using both, absolute intensity cut-points (Sasaki et al., 2011) and individually-tailored LT cut-points. The two groups exceeded the target of 10.000 daily steps recommended by PA guidelines (Garber et al., 2011). Recorded $MVPA_{+10}$ using the absolute intensity cut-points (31.1 ± 24.2 min day^{-1} or ~218 min $week^{-1}$ in low-fit and 51.8 ± 31.4 min day^{-1} or ~363 min $week^{-1}$ in high-fit) approached the recommended target of 150 min $week^{-1}$ (Garber et al., 2011). High-fit women were ~1 h day^{-1} less sedentary ($P < 0.01$), they recorded on average 3156 more daily steps ($P < 0.01$), and they engaged in twice as much time ($P < 0.01$) at absolute MVPA compared to low-fit women. However, when PA intensity boundaries were individually tailored, daily time spent at $MVPA_{+10}$ was significantly reduced ($P < 0.01$) by ~40% in low-fit and by ~60% in high-fit groups. These data revealed no differences ($P = 0.62$) between groups (~20 min day^{-1} in 10-min). Accordingly, the number of participants meeting PA guidelines dropped from 62% to 32% in low-fit and from 82% to 40% in high-fit ($P < 0.01$). The only difference between groups using relative intensity cut-points was in low-light PA. The high-fit group spent ~1 h day^{-1} more at the lowest intensity activities ($P < 0.01$).

Discussion

In this study, we tested whether individually-tailored cut-points based on lactate thresholds differed in the time spent at different PA intensity levels to fixed cut-points obtained at absolute moderate intensity (*i.e.* 3–6 METs) (Sasaki et al., 2011) in postmenopausal women differing in CRF. Our findings demonstrated that high-fit women were 1 h less sedentary, recorded ~3000 more daily steps and twice as much time at MVPA compared to low-fit individuals using absolute intensity cut-points. However, when PA intensity cut-points were individually tailored according to LT, the time spent at MVPA was significantly reduced by 60% in high-fit and by 40% in low-fit groups, showing no difference in the time spent at MVPA between groups.

Fixed or individually tailored cut-points. The role of cardiorespiratory fitness

The selection of appropriate accelerometer cut-points to demarcate PA intensity levels is the cornerstone to obtain reliable PA outcomes and their association with health markers and mortality (Rejeski et al., 2016). LT represent individual physiologic adaptations in the use of energy pathways, and they are accurate indicators of relative exercise intensity (Binder et al., 2008). The average activity counts at LT1 were 4133 ± 1152 ct min^{-1}, showing a substantial interindividual variability (~2000–10000 ct min^{-1}) due to the large range in LT1 (3.6–7.3 km h^{-1}). This value is 54%

Table I. Comparison of daily physical activity levels (min·day^{-1}) according to relative or absolute intensity activity cut-points in high and low cardiorespiratory fitness groups.

	Low-fit (n = 37)		High-fit (n = 38)	
Age (years)	61.4 ± 5.8		56.6 ± 4.0**	
Height (cm)	57.8 ± 5.0		159.3 ± 5.8	
Body mass (kg)	69.7 ± 12.7		61.4 ± 6.0**	
BMI (kg/m^2)	27.9 ± 4.3		24.2 ± 2.5**	
LT1 (km·h^{-1})	4.7 ± 0.5		5.5 ± 0.6**	
LT2 (km·h^{-1})	6.3 ± 0.4		7.8 ± 0.9**	
Steps	10682.1 ± 3402.0		13837.7 ± 4074.3**	
Sedentary $_{+1}$ (min·day^{-1})	503.2 ± 103.7		449.9 ± 96.7*	
Sedentary $_{+10}$ (min·day^{-1})	426.0 ± 121.7		363.4 ± 104.7*	
Activity intensity level (min·day^{-1})	Relative	Absolute	Relative	Absolute
Low-light	342.6 ± 86.2	297.6 ± 69.5††	402.9 ± 78.8≠	311.5 ± 65.9††
High-light	75.8 ± 34.0	99.1 ± 39.5††	73.9 ± 27.6	112.7 ± 32.5††
Low-mod	20.6 ± 16.5	41.8 ± 19.5††	25.2 ± 26.7	47.9 ± 18.9††
High-mod	7.5 ± 11.4	13.2 ± 18.5†	6.2 ± 8.3	31.1 ± 24.2*††
Vigorous	3.3 ± 7.8	0.7 ± 1.5††	2.3 ± 5.2	6.0 ± 8.9*††
MVPA$_{+1}$	31.4 ± 24.7	55.6 ± 28.0††	33.7 ± 28.5	85.0 ± 32.9*††
MVPA$_{+10}$	18.8 ± 21.2	31.1 ± 24.2††	21.6 ± 25.9	51.8 ± 31.4*††
Meeting PA guidelines (%)	32.4	62.2††	39.5	81.6†

Data presented as mean ± standard deviation or percentages. Low-fit = Low LT2 velocity group, High-fit = High LT2 velocity group, relative = relative intensity method based on lactate thresholds, Absolute = absolute intensity method based on measured activity counts at 3–6 METs (Sasaki et al., 2011), MVPA = Moderate-to-vigorous physical activity. Physical activity (PA) guidelines = ≥150 min wk^{-1} of MVPA in 10-min bouts (Garber et al., 2011). Sedentary time and MVPA are reported in 1 and 10 min bouts (+1, +10, respectively).
†Significant intra-group differences between relative and absolute cut-points ($P < 0.05$).
††Significant intra-group differences between relative and absolute cut-points ($P < 0.01$).
*Significant inter-group differences at absolute cut-points ($P < 0.05$).
**Significant inter-group differences at absolute cut-points ($P < 0.01$).
≠Significant inter-group differences at relative cut-points ($P < 0.05$).

and 29% higher than previously reported values of 2690 (Sasaki et al., 2011) and 3208 ct min^{-1} (Santos-Lozano et al., 2013) for the lower boundary of moderate intensity (3 METs), respectively. These differences could be related to the higher energy expenditure value estimated at LT1 (3.7 ± 0.7 METs) (Weyand et al., 2013) compared to the classic 3 METs threshold. Besides, the above mentioned studies (Santos-Lozano et al., 2013; Sasaki et al., 2011) obtained ~4000 ct min^{-1} at 4.8 km h^{-1}, which is closer to the value of 3869 ct min^{-1} found in our study at the same speed, suggesting that the 3 METs classic boundary falls below the LT1, and thus is not representative of the lower relative moderate intensity boundary in our group of postmenopausal women.

The activity counts measured at LT2 (6783 ± 2077 ct min^{-1}) were 9% higher and 21% lower than those reported by Sasaki et al. (2011) and by Santos-Lozano et al. (2013), respectively, at the upper classic boundary of moderate intensity (6 METs). These two studies used an incremental treadmill protocol with only 2–4 stages to derive activity counts cut-points at 3 and 6 METs. In contrast, our IST provided a minimum of seven data points from all participants, with small speed increments (0.6 km h^{-1}). Besides, we directly determined the activity counts at LT1 and we used individual, rather than whole-group regression equations to determine the activity counts at LT2. Our results go hand-in-hand with the findings of Ozemek et al. (2013) showing that CRF (*i.e.* LT2 velocity) (R^2 = 0.35–0.56), rather than age or body mass index (R^2 < 0.03) influenced individuals activity count cut-points at relative intensities (Figure 3). These findings are evidence that individually tailored cut-points may better represent intensity-specific PA levels.

Implications in the measurement of physical activity

Large variations exist in the volume of objectively monitored MVPA across different countries and studies, and, therefore, in the percentage of adults meeting current PA recommendations (Cerin et al., 2014; Colley et al., 2011; Kujala et al., 2017; Tucker et al., 2011). These differences could be explained in part by the non-harmonized data collection, and the use of different activity monitors and intensity cut-points between studies (Migueles et al., 2017). In our study, using the absolute intensity approach, daily time spent at MVPA$_{+10}$ was 42 min day^{-1} or 294 min week^{-1}, and 72% of the study participants met the MVPA target. These values are higher than the 8 min day^{-1} (Tucker

et al., 2011) or the 21 min day^{-1} (Colley et al., 2011) reported by US and Canadian women, corresponding to 7% and 15% of American and Canadian women meeting PA guidelines, respectively. The high number of daily steps (~12300) also confirms that our sample was more active than the vast majority of women in previous studies (Colley et al., 2011; Tucker et al., 2011). This finding is supported by the results of the IPEN study (Cerin et al., 2014), where, among the 17 city-regions, the participants from Pamplona (Spain) recorded the highest levels of MVPA (51 min day^{-1} in 1-min bouts). Our findings strongly suggest that CRF, rather that BMI has a stronger relationship with both, MVPA and daily steps ($P < 0.01$, $r = 0.49$ and 0.53 *vs.* $r = -0.24$ and -0.28, respectively), without being affected after adjusting for BMI or age. An important finding of our study was that MVPA was significantly reduced ($P < 0.01$) by half (40% in low-fit and 60% in high-fit) when the cut-points were individually-tailored. Thus, the data confirmed that the use of fixed absolute intensity cut-points derived from 3 to 6 MET intensities overestimated MVPA.

Another important finding of this study was that although the high-fit group was ~1 h less sedentary, recorded ~3000 more daily steps and twice as much time at absolute MVPA compared to the low-fit group, these differences disappeared when PA levels were analysed according to their relative intensity cut-points, and both groups recorded similar time at MVPA (~20 min day^{-1} in 10-min bouts). Our results are in line with a large-scale Finish study (Kujala et al., 2017) who found that using HR-based absolute intensity thresholds men recorded twice as much MVPA than women (~45 vs ~22 min day^{-1} in 1-min bouts). However, using relative intensity thresholds, MVPA was reduced by half (~17 min day^{-1}) without differences between them. Overall, this information is evidence that using fixed accelerometer activity cut-points derived from the recommended 3–6 METs moderate PA intensity approach may not be the most accurate option when examining PA behaviour in samples varying in CRF.

Strengths and limitations of the study

This is the first study measuring accelerometer-based PA using individually tailored cut-points corresponding to LT. Despite the methodological shortcomings of accelerometers-based measures in PA surveillance (Pedisic & Bauman, 2015), the proposed method in this study avoids the misinterpretation of intensity-specific PA levels when using fixed activity cut-points in individuals or groups varying in CRF. However, the current study is not without limitations. First, the applicability of this individualised approach is not feasible for large epidemiological studies, although they could benefit from population-specific relative intensity cut-points to obtain more reliable PA outcomes. Second, the generalizability of these findings is limited to postmenopausal women, who are worthy of distinct attention due to the increased risk of cardiovascular disease (Kannel et al., 1976) and osteoporosis (Whitfield et al., 2015). Third, our study was a cross-sectional study. Although higher relative intensity of daily activities has been associated with reduced CHD mortality (Lee et al., 2003), randomised controlled trials are needed to confirm whether PA recommended by guidelines applying relative intensity thresholds brings greater long-term health benefits compared to absolute intensity. Fourth, accelerometers do not capture accurate energy expenditure of certain activities (*e.g.* cycling, swimming, weight training, and some complex low-intensity activities) (Matthew, 2005). Besides, habitual PA could be much more variable than constant velocity exercise tests used to demarcate PA intensity categories, in a way that makes the same ct·min^{-1} more intense (*e.g.* uphill, involving arm movement or resistance). Nonetheless, LT are the gold standard markers of relative exercise intensity, and the present focus on walking exercise tests is appropriate, because it is the most common type of activity among adults (Arem et al., 2015).

Conclusion

This study demonstrated that applying recommended absolute moderate intensity criteria of 3–6 METs to accelerometer activity counts cut-points overestimated the time spent at MVPA. Compared to low-fit individuals, it was easier for high-fit individuals to reach MVPA target according to absolute criteria. However, no differences were observed in the time spent at MVPA between high- and low-fit postmenopausal women when the intensity cut-points were individually tailored to their lactate thresholds velocities. Our findings suggest that individually-tailored accelerometer cut-points may provide a more representative PA profile of individuals differing in CRF, compared to the widely used absolute intensity cut-points.

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results of the present study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Estimation of the maximal lactate steady state in postmenopausal women

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ABSTRACT

This study aimed to estimate the maximal lactate steady-state velocity ($_{v}$MLSS) from non-invasive bloodless variables and/or blood lactate-related thresholds (BL_RTs) measured during an Incremental submaximal Shuttle Test (IST), and to determine whether the addition of a Constant Velocity Test (CVT) could improve the estimation. Seventy-five postmenopausal women conducted an IST to determine several BL_RTs and bloodless variables, and two to seven CVTs to determine $_{v}$MLSS. Determined BL_RTs were conventionally used lactate threshold (LT) measured either visually ($_{v}LT_{+0.1mM}$) or mathematically ($_{v}LE_{min}$), and 0.5, 1 and 1.5 mmol·L^{-1} above LT, along with fixed BL_RTs. The best single predictor of $_{v}$MLSS (7.1 ± 1.0 km·h^{-1}) was $_{v}LE_{min+1.5mM}$ (R^2 = 0.80, P < 0.001; SEE = 0.46 km·h^{-1}). The combination of BL_RTs and bloodless variables improved the estimation of $_{v}$MLSS (R^2 = 0.85, P < 0.001; SEE = 0.38 km·h^{-1}). The addition of a CVT still improved the prediction of $_{v}$MLSS up to 89.2%, with lower SEE (0.32 km·h^{-1}). This study suggests that $_{v}LE_{min}$-related thresholds obtained from a single submaximal IST are accurate estimates of $_{v}$MLSS in postmenopausal women, and thus the time-consuming procedure of $_{v}$MLSS testing could be avoided. Performing an additional CVT is encouraged because it improves the prediction of $_{v}$MLSS.

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KEYWORDS
Cardiorespiratory fitness; blood lactate-related thresholds; exercise testing; intensity prescription

Introduction

Epidemiological studies have shown an inverse association between cardiorespiratory fitness (CRF) and the incidence of coronary heart disease or all-cause mortality in healthy or asymptomatic men and women (Kodama et al., 2009). The most widely accepted index of CRF is maximal oxygen uptake ($\dot{V}O_{2max}$) expressed in mL O_2·kg^{-1}·min^{-1}or in metabolic equivalents (1 MET = 3.5 mL·kg^{-1}·min^{-1}) (Blair et al., 1989). It is acknowledged that the minimum level associated with significantly lower event rates for men and women is approximately 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively (Blair et al., 1989; Kodama et al., 2009). However, the measurement of $\dot{V}O_{2max}$ requires maximal exercise testing, which is very often not accesible nor possible in middle-aged people due to motivational or financial reasons (Fletcher et al., 2013). An easier, safer, non-dependent on motivation and widely accepted approach to evaluate CRF is the analysis of blood lactate concentration (BLC) plotted against exercise intensity or duration during submaximal exercise.

More than 20 blood lactate-related thresholds (BL_RTs) have been defined so far, leading to considerable confusion and misinterpretation (Faude, Kindermann, & Meyer, 2009). However, two of these thresholds have emerged as the preferred endurance performance markers among the vast majority of sport and exercise physiologists: 1) The so-called "Lactate Threshold" (LT) defined as the critical exercise intensity level above which BLC first begin to increase above resting values during incremental exercise (Jones & Ehrsam, 1982). The LT has been suggested as the minimum exercise intensity required by inactive individuals to improve CRF (Carter, Jones, & Doust, 1999; Londeree, 1997; Weltman et al., 1990) and is a valid indicator of CRF in athletes and inactive people due to its high association with $\dot{V}O_{2max}$, sports performance (Beneke, 2003; Billat, Dalmay, Antonini, & Chassain, 1994; Faude et al., 2009; Weltman et al., 1990) and functional capacity in patients (Weber, Kinasewitz, Janicki, & Fishman, 1982), and 2) the so-called "Maximal Lactate Steady State" (MLSS), defined as the highest constant workload that can be sustained over time without continual blood lactate accumulation (Beneke, 2003). Both LT and MLSS are more sensitive than $\dot{V}O_{2max}$ to predict endurance performance and to evaluate training adaptations (Philp, Macdonald, Carter, Watt, & Pringle, 2008), allowing the definition of three individual intensity categories to guide exercise training: light (<LT), moderate (LT-MLSS) and vigorous (>MLSS) (Faude et al., 2009). While LT can be determined in a single graded submaximal test, the assessment of MLSS is, however, cumbersome, since it requires several (3–6) constant workload tests on separate days, lengthening the aerobic conditioning evaluation to a minimum of 1–3 weeks (Ralph Beneke, 2003). For this reason, simpler methods have been proposed to estimate MLSS intensity from a single incremental test, involving the use of either blood lactate (Beneke, 2003; Carter, Jones, & Doust, 1999; Faude et al., 2009; Sjödin, Jacobs, & Svedenhag, 1982; Tegtbur, Busse, & Braumann, 1993), respiratory (Leti, Mendelson, Laplaud, & Flore, 2012; Wasserman, 1987), or the maximum workload achieved during an exercise test to exhaustion (Llodio, Garcia-Tabar, Sánchez-

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Medina, Ibáñez, & Gorostiaga, 2015; Weltman et al., 1990), resulting in a wide range of correlations (r = 0.63–0.95) with MLSS. However, all existing single session MLSS-estimating tests are variably handicapped by compromised validity, accuracy, resolution, and reliability due to methodological differences and a suboptimal statistical approach (*i.e.*, correlation analysis) leading to incomparable and inconclusive results (Baldari & Guidetti, 2000; Faude et al., 2009; Tegtbur et al., 1993). Most of these studies have been conducted in small groups of athletes using exercise tests to volitional fatigue, but little is known about the prediction of MLSS from BL_RTs using submaximal tests in adults. The inactivity, along with the lower CRF observed in women (Edvardsen, Hansen, Holme, Dyrstad, & Anderssen, 2013), and the increased risk of cardiovascular disease (Kannel, Hjortland, McNamara, & Gordon, 1976) and osteoporosis (Borer, 2005) after menopause and with advancing age, underline the necessity of well-designed and adequately powered (*i.e.*, intensity) PA programs for postmenopausal women.

To avoid the extensive procedure needed to assess MLSS velocity ($_v$MLSS), we aimed to elucidate whether $_v$MLSS could be accurately predicted from lactate-related and/or bloodless variables measured during an Incremental submaximal Shuttle Test (IST) in 50–75 years old postmenopausal women. A secondary purpose of the study was to determine the extent to which a single Constant Velocity Test (CVT), performed several days after the IST, could improve the prediction of $_v$MLSS. Based on a previous study performed with endurance-trained athletes (Garcia-Tabar & Gorostiaga, 2018), we hypothesized that BL_RTs that rely on the individual lactate curve would be accurate predictors of $_v$MLSS, showing stronger agreement compared to bloodless variables. We expected that an additional CVT performed on subsequent days would improve the estimation of $_v$MLSS.

Methods

Study participants

Participants were recruited through advertisements placed on healthcare centres. One hundred and four participants were screened by telephone, 88 were deemed eligible and were invited to participate in the study. Inclusion criteria were: 1) surgical or natural menopause (no menstrual periods during the previous 12 months), 2) age <75 years. Participants were excluded from the study if they had any of the following conditions that might interfere with exercise testing: 1) presence of spine or low-trauma fractures or severe arthrosis at the hip, knees or feet, 2) functional limitation to walk for 20 minutes, 3) presence of any known chronic disease that would impair the cardiorespiratory system during testing. The local hospital´s ethical committee for human studies approved the study (Pyto2011/71) and written informed consent was obtained from all participants before any study procedures were undertaken. The procedure of the study was in accordance with the Declaration of Helsinki and was registered in *ClinicalTrials.gov PRS* (NCT02984553).

Incremental shuttle test (IST)

Prior to the first visit, participants were instructed to abstain from caffeine and stimulants for at least four hours and strenuous activity for ≥24 h before testing. Height was measured using a wall stadiometer (Seca, Germany) and body mass was measured using a scale to the nearest 0.1kg (Seca, Germany). Testing was performed in a laboratory setting in a controlled temperature environment (~20º) over a 20 m indoor track (Singh, Morgan, Scott, Walters, & Hardman, 1992). The distance of the course was extended to 20 m from the original test to keep the pace constant avoiding excessive turns that might increase the energy cost and musculoskeletal demand, potentially leading to premature fatigue, pain, discomfort or even injury. Five cones were positioned at 0.5–5–10–15 and 19.5 m and participants had to walk in a straight line until the last cone, then turn around and return to the start. The speed at which the participant walked was dictated by an audio signal pre-recorded in MP3 audio format. The IST started at 2.4 km·h^{-1}. The velocity was increased by 0.61 km·h^{-1} every 2-min (Singh et al., 1992), with 1-min intervals between stages. Each participant was free to start running from the 7th stage onwards (6.1 km·h^{-1}), or the operator suggested to do so when the participant was not able to match the required speed. Immediately after each stage, heart rate (HR) (Polar V800, Polar Electro Oy, Kempele, Finland), a rating of perceived effort in Borg´s 0–10 scale (Borg, Ljunggren, & Ceci, 1985) and capillary blood samples for blood lactate measurements were obtained from a hyperemic earlobe. The test was stopped when: 1) BLC values were ≥3.0 mmol·L^{-1} to avoid excessive fatigue, and/or 2) participant repeatedly failed to match the pace programmed, and/or 3) participant was exhausted.

Constant-velocity tests (CVT)

On subsequent laboratory visits, participants completed two to seven 20 min CVTs on the same 20 m track used for the IST. Each participant performed the corresponding tests on separate testing days (one week in between). Each CVT consisted of two stages of 10 min at a constant pace with 2 min interruption for blood sampling (*i.e.*, 22 min duration). Heart rate was continuously recorded, and capillary blood samples were obtained at rest, at the 10th min and the end of exercise (22nd min). Walking or running velocity of the first CVT was programmed as the velocity at which blood lactate increased by one mmol·L^{-1} above LT during the IST. Depending on the BLC stability of the first CVT, the velocity was increased or decreased by ~0.30 km·h^{-1} in the following CVTs. If during the first CVT a steady state or a decrease in BLC was found, the velocity for the next CVT was increased by 0.3 km·h^{-1}. Conversely, if an increase in BLC superior to the stability criterion was observed, the speed of the following CVT was decreased by 0.3 km·h^{-1} until the $_v$MLSS was determined. The highest constant velocity with an increase in BLC ≤ 0.4 mmol·L^{-1} during the final 10 min of exercise was defined as the $_v$MLSS (Beneke, 2003; Billat et al., 1994) (Figure 2).

Blood sampling and blood lactate concentration (BLC) determination

A hyperaemic earlobe was cleaned and dried before puncturing by a lancet device to aspirate a 0,3 μL whole blood sample into an enzyme-coated electrode test strip. Blood lactate concentration was determined via amperometric measurement using a portable analyzer (Arkray KDK Corporation, Lactate Pro2 LT-1710, Shiga, Japan) calibrated before each test. The instrument has shown a good accuracy (R^2 = 0.97; standard error of the estimates, SEE = 0.69 mmol·L^{-1}) and intra-assay reliability (coefficient of variation, CV = 2.9%; intraclass correlation coefficient, ICC = 0.999) at a wide range of BLC (Baldari et al., 2009).

Determination of blood lactate-related thresholds (BL_RT)

Nine different BL_RTs were determined (Figure 1(a)). The velocity at the LT ($_vLT_{+0.1mM}$) was defined as the highest stage-velocity above which BLC increased by ≥ 0.1 mmol·L^{-1} in the following stage and ≥ 0.2 mmol·L^{-1} in the subsequent stage. The velocities at 0.5 mmol·L^{-1}, 1 mmol·L^{-1}, or 1.5 mmol·L^{-1} above $_vLT_{+0.1mM}$, were called $_vLT_{+0,5mM}$, $_vLT_{+1mM}$, and $_vLT_{+1.5mM}$, respectively. The velocity corresponding to the Minimum Lactate Equivalent ($_vLE_{min}$) (Berg et al., 1990) was considered the minimum value of the quotient BLC/velocity in the individual BLC/velocity *vs.* velocity second-order polynomial curves (Figure 1(b)). The velocities at 1.0 and 1.5 mmol·L^{-1} above the $_vLE_{min}$ in the individual

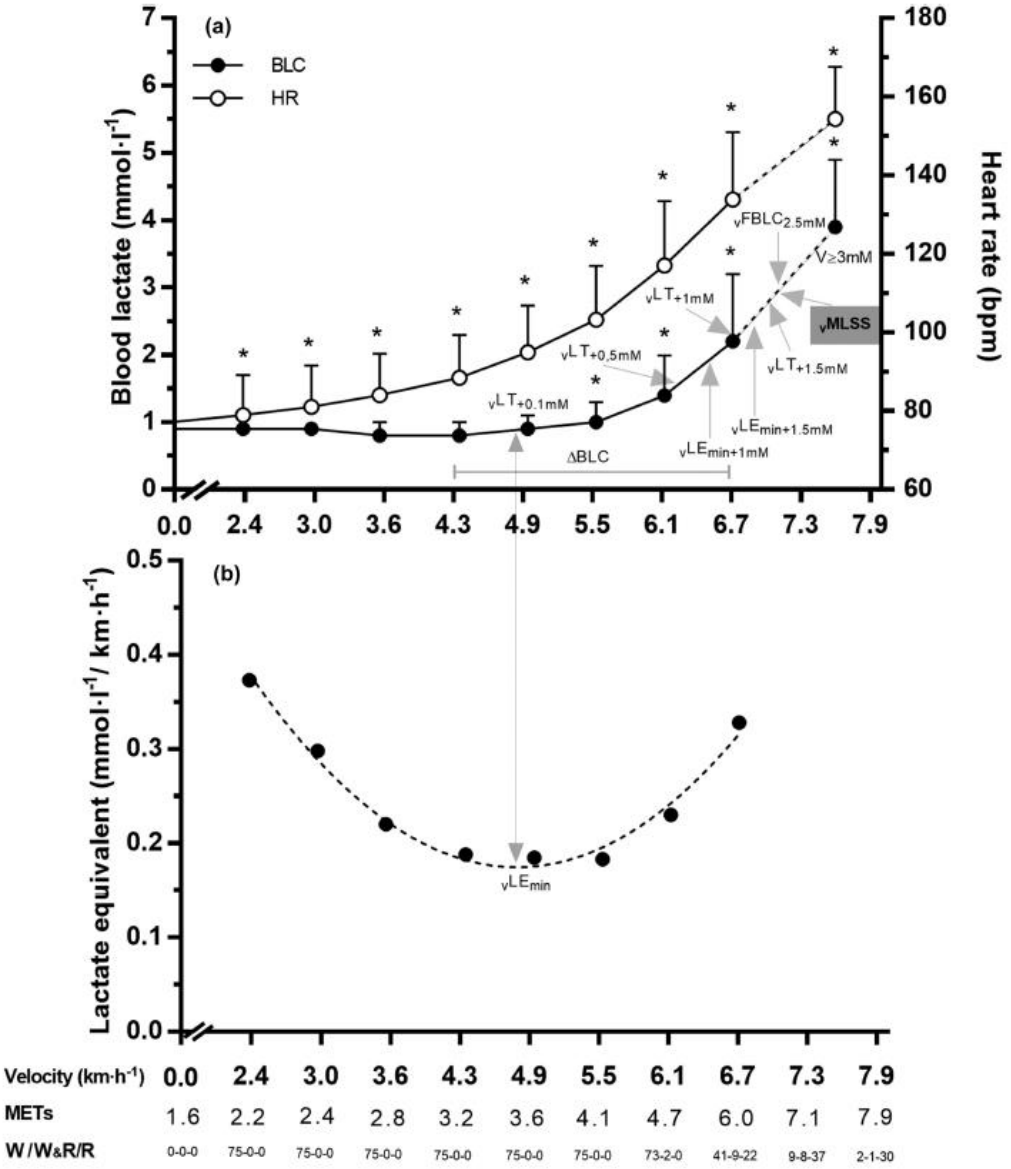

Figure 1. Mean velocity *vs.* blood lactate/heart rate curve during the submaximal Incremental Shuttle Test (IST) in the whole group of participants and selected BL_RTs (n = 75). Schematic representation of (a) average BL_RTs values and (b) determination of $_vLE_{min}$ by modeling the quotient BLC/velocity in the individual BLC/velocity *vs.* velocity second-order polynomial curve. $_vLE_{min}$ = velocity at the minimum lactate equivalent (km·h^{-}1), $_vLT_{+0.1mM}$ = highest stage-velocity above which BLC increased by ≥ 0.1 mmol·L^{-1} in the following stage and ≥ 0.2 mmol·L^{-1} in the subsequent stage, $_vLT_{+0.5mM}$, $_vLT_{+1mM}$, $_vLE_{min+1.5mM}$ = velocity at the lactate threshold + 0.5, 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_vLE_{min+1mM}$, $_vLE_{min+1.5mM}$ = velocity at the minimum lactate equivalent + 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_vFBLC_{2.5mM}$ = velocity at the fixed blood lactate concentration at 2.5 mmol·L^{-1} (km·h^{-1}), $_v$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}), $V_{≥3mM}$ = the lowest velocity of the IST where the blood lactate value was ≥ 3 mmol·L^{-1}, ΔBLC = mean differences in blood lactate between successive stages (from 4.3 to 6.7 km·h^{-1}), ΔHR = mean differences in heart rate between successive stages (from 4.3 to 6.7 km·h^{-1}). * significantly different (P < 0.01) from the previous stage.

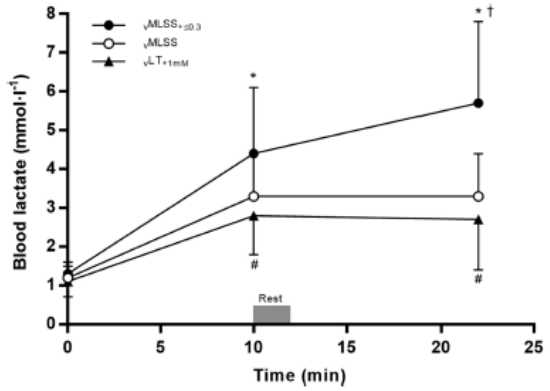

Figure 2. Evolution of blood lactate concentration during the constant velocity tests for the determination of $_{v}$MLSS at $_{v}LT_{+1mM}$, $_{v}$MLSS, and at 0.3 km·h^{-1} faster velocity than $_{v}$MLSS ($_{v}MLSS_{+\leq0.3}$). $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}), $_{v}LT_{+1mM}$ = velocity at the lactate threshold + 1 mmol·L^{-1} (km·h^{-1}), $_{v}MLSS_{+\leq0.3}$ = constant velocity test performed ≤ 0.3 km·h^{-1} faster velocity than $_{v}$MLSS. * significantly different ($P < 0.01$) from $_{v}$MLSS and $_{v}LT_{+1mM}$, # significantly different from $_{v}$MLSS, † significant effect for time on BLC (min 10 vs min 22).

BLC *vs*. velocity second-order polynomial curves where called $_{v}LE_{min+1mM}$ and $_{v}LE_{min+1.5mM}$, respectively. The velocity at a fixed blood lactate concentration of 2.5 mmol·L^{-1} (Garcia-Tabar, Izquierdo, & Gorostiaga, 2017) ($_{v}FBLC_{2.5mM}$) was determined from the individual BLC *vs*. velocity second-order polynomial curves. The lowest velocity at which BLC was ≥ 3 mmol·L^{-1} was defined as $V_{\geq3mM}$. Besides, the average magnitude of the differences in BLC between successive velocities [[(BLC 4.9–4.3) + (BLC 5.5–4.9) + (BLC 6.1–5.5) + (BLC 6.7–6.1)]/4] during the IST was tested as an independent predictor (ΔBLC).

Velocities at $BL_{R}Ts$ were determined using MATLAB R2015a (The MathWorks Inc., Natick, MA, USA). Coefficients of determination (R^2) of the individual second-order BLC *vs*. velocity, and second-order quotient BLC/velocity *vs*. velocity polynomial curves were all > 0.90. Velocities at $BL_{R}Ts$ (Weltman et al., 1990), as well as $_{v}$MLSS (Mann, Lamberts, & Lambert, 2013) frequently show test-retest intra-class correlation coefficients >0.94, and coefficients of variation ≤3%. Heart rate values at $BL_{R}Ts$ were computed from the individual HR *vs*. velocity second order polynomial equations ($r > 0.98$; $P < 0.001$) obtained during the IST.

Bloodless variables

Participant´s age, anthropometric characteristics [body mass, height, and body mass index, (BMI)] and the following HR and perceived exertion (Borg et al., 1985) related variables were obtained from the IST: minimum resting HR (HR_{rest}) in a supine position for 10min, average magnitude of the differences in HR (ΔHR) between successive velocities during the IST [[(HR 4.9–4.3) + (HR 5.5–4.9) + (HR 6.1–5.5) + (HR 6.7–6.1)], the velocity associated with the minimum value of the quotient HR/velocity obtained from the HR/velocity *vs*. velocity second-order polynomial curve (HR_{min}), and the velocity corresponding to a value of 4 (*i.e.*, "something hard") on Borg´s scale of perceived exertion (0–10) (Borg et al., 1985) obtained from the second-order polynomial curve between perceived exertion values and velocity (RPE_4).

Statistical analysis

Standard statistical methods were used for the calculation of means, standard deviations (SD), SEE and confidence intervals (CI). Data were analyzed using parametric statistics following confirmation of normality (Shapiro-Wilk test), homoscedasticity (Levene´s test), and when appropriate sphericity (Mauchly's test). Repeated ANOVA measures with Bonferroni post-hoc test was used to compare BLC and HR at different velocities during the IST and at different time-points during the CVT.

Student´s paired t-tests was used to evaluate differences between each $BL_{R}T$ with $_{v}$MLSS. The magnitudes of the differences were assessed with 95% CI and Cohen´s effect sizes (ES). Two-factorial ANOVA with Tukey´s post-hoc test was used to identify differences in BLC between CVTs. We studied the strength of the individual relationships between independent variables and $_{v}$MLSS before fitting the models using *Pearson* product-moment correlation coefficients (r). Using $_{v}$MLSS determination as the reference method, three different multiple regression models were assessed against it. After checking normality and homoscedasticity by paired plots, all significant variables were entered in a block to each model with the main independent variables of each model defined as: 1) Bloodless variables from a single IST, 2) $BL_{R}Ts$ along with bloodless variables from a single IST and 3) Change in BLC from the 20th to the 10th minute ($\Delta BLC_{20\text{-}10}$) during an additional CVT at $_{v}LT_{+1mM}$, in addition to $BL_{R}Ts$ and bloodless variables from the IST. Non-significant variables and those producing collinearity were excluded from the final model. Adjusted R^2 was used to assess the proportion of the variance explained by the model. The validity of each predictive equation was investigated with the SEE and the 95% limits of agreement method (LoA, mean difference ± 1.96 SD) (Bland & Altman, 2010). A regression analysis between mean $_{v}$MLSS and the difference in $_{v}$MLSS between the estimated and the measured value was applied to explore whether the degree of systematic error is uniform over the range of values. The level of significance was set at $P < 0.05$. Statistical analyses were performed using SPSS statistical software (version 22.0, IBM SPSS Statistics, Chicago, IL) and GraphPad Prism 7 was used for figures.

Results

Population selection and characteristics

Among 104 interested participants who were screened for eligibility, 14 were excluded. Reasons for exclusion were; 1) not meeting eligibility criteria (n = 12), and 2) declined to participate (n = 2). Among the 88 participants who were invited to participate, 75 completed all assessments and had valid data for analysis (age = 59.0 ± 5.5 years old, BMI = 26.0 ± 3.9 kg/m^2).

Submaximal incremental shuttle test

Mean velocity *vs*. BLC curve during the IST in the whole group of participants (n = 75) is presented in Figure 1(a). Blood lactate concentration started to increase from the fifth stage onwards ($F_{8,568} = 137.5$, $P < 0.001$). Velocity at LE_{min} (4.8 ± 0.6 km·h^{-1}) was

5.9% lower than $_{v}LT_{+0.1mM}$ ($P < 0.001$; 95%CI: 0.14 to 0.32; ES: 0.38) and both of them were 32% ($P < 0.001$) and 28% ($P > 0.001$) lower than $_{v}MLSS$, respectively (Table 1). Average $_{v}FBLC_{2.5mM}$ ($P = 0.984$; 95%CI: −0.10 to 0.11; ES: 0.00) and $_{v}LT_{+1.5mM}$ ($P = 0.742$; 95%CI: −0.13 to 0.09; ES: 0.02) did not differ from $_{v}MLSS$ whereas $_{v}LE_{min+1.5mM}$ was only 2.8% lower ($P < 0.01$; 95% CI: −0.26 to −0.05; ES: 0.16) than $_{v}MLSS$. Heart rate increased significantly ($F_{9,639} = 1095.5$, $P < 0.001$) throughout the test. The HR values at $_{v}LE_{min}$ and $_{v}LT_{+0.1mM}$ were 95 ± 11 bpm and 98 ± 12 bpm, respectively. When $_{v}MLSS$ determined from the CVT was set in the velocity *vs.* BLC or the velocity *vs.* HR curves obtained during the IST, the corresponding BLC and HR values were 2.4 ± 0.7 mmol·L^{-1} and 141 ± 17 bpm, respectively.

Constant velocity tests (CVTs)

Figure 2 shows the BLC during 3 CVTs at $_{v}LT_{+1mM}$, at $_{v}MLSS$, and at 0.3 km·h^{-1} faster velocity than $_{v}MLSS$ ($_{v}MLSS_{+\leq 0.3}$). At $_{v}LT_{+1mM}$ (6.7 ± 0.8 km·h^{-1}), BLC increased from rest (1.2 ± 0.3 mmol·L^{-1}) to the 10th minute of exercise (2.8 ± 1.1 mmol·L^{-1}) and remained constant (2.7 ± 1.1 mmol·l^{-1}) throughout exercise ($P = 0.17$; 95% CI: −0.3 to 0.0; ES: 0.10). However, at this velocity, 25% of the participants showed a blood lactate accumulation during exercise (increase in BLC ≥0.4 km·h^{-1} during the last 10 min of exercise). Slightly higher ($P < 0.01$; 95% CI: 0.3 to 1.0; ES: 0.58) BLC values were obtained at $_{v}MLSS$ (7.1 ± 1.0 km·h^{-1}; range: 5.4–10.0 km·h^{-1}), increasing from 1.2 ± 0.3 mmol·L^{-1} at rest to 3.3 ± 1.1 mmol·L^{-1} at the 10th minute of exercise, and remained constant throughout exercise. Average HR values during the CVT at $_{v}MLSS$ slightly increased from the 10th min (146 ± 13 bpm) to the end of exercise (151 ± 13 bpm) ($P < 0.01$; 95% CI: 3.9 to 5.6; ES: 0.03). At $_{v}MLSS_{+\leq 0.3}$, nine participants failed to finish the CVT, and in the remaining participants BLC increased as a function of time from 4.5 ± 1.8 mmol·L^{-1} at the 10th minute of exercise to 5.5 ± 2.0 mmol·L^{-1} at the end of exercise ($P < 0.01$; 95% CI: 1.0 to 1.4; ES: 0.65).

Prediction of $_{v}MLSS$

Every BL_RT correlated significantly with $_{v}MLSS$ ($P < 0.001$, $r = 0.72$–0.90) (Table 1). Velocity at $LE_{min+1.5mM}$ was the best single predictor of $_{v}MLSS$ ($R^2 = 0.801$, $P < 0.001$; SEE = 0.456; 95% LoA = −0.90 to 0.89) (Figure 3), closely followed by $_{v}FBLC_{2.5mM}$ and $_{v}LE_{min+1mM}$ ($R^2 = 0.799$, $P < 0.001$; SEE = 0.461; 95% LoA = −0.90 to 0.90), and $_{v}LT_{+1.5mM}$ ($R^2 = 0.789$, $P < 0.001$; SEE = 0.467; 95% LoA = −0.91 to 0.92), indicating that the prediction of $_{v}MLSS$ from these four single BL_RTs could be biased up to ~13% above or below the actual $_{v}MLSS$.

After checking individual associations between BL_RTs, bloodless and anthropometric variables, we created three multiple regression models to predict $_{v}MLSS$. In the first model, we tested the accuracy of bloodless variables obtained during the IST for predicting $_{v}MLSS$ (Table 2, model 1). The key determinants identified for the prediction of $_{v}MLSS$ were; ΔFC, age, resting HR in supine position (HR_{rest}), and body mass (kg), accounting for 59% of the variance, with a large SEE (0.64 km·h^{-1}; 9% of the mean $_{v}MLSS$). The regression equation for the sample (n = 70) was:

$$_{v}MLSS = 16.574 - (0.078 \cdot \Delta FC) - (0.075 \cdot age) - (0.036 \cdot HR_{rest}) - (0.027 \cdot Body\ mass) \quad (1)$$

The Bland-Altman method between predicted and the actual $_{v}MLSS$ against their mean for Equation (1) showed small bias but wide LoA [−0.00 (1.24) km·h^{-1}] (Figure 4(a)). The gradient of the regression line was significantly different from zero ($P < 0.01$) indicating a higher bias in fitter individuals.

In the second model, a combination of single BL_RTs and bloodless variables from the IST were entered to a multiple regression (Table 2, model 2). The best model revealed that the velocity and HR at $LE_{min+1mM}$, age, and body mass accounted for 85.3% of the variation in $_{v}MLSS$, with a lower SEE (0.38 km·h^{-1}; 5.4% of mean $_{v}MLSS$). The regression equation for the sample (n = 75) was as follows:

$$_{v}MLSS = 4.630 + (1.085 \cdot {}_{v}LE_{min+1mM}) - (0.04 \cdot age) - (0.012 \cdot Body\ mass) - (0.012 \cdot {}_{HR}LE_{min+1mM}) \quad (2)$$

The Bland-Altman method between the predicted and the actual $_{v}MLSS$ against their mean for Equation (2) showed strong agreement and narrow individual LoA [Bias (95% CI)]

Table 1. Descriptive features of BL_RTs and their association with $_{v}MLSS$ (n = 75).

	km·h^{-1}		%$_{v}MLSS$		*Association with vMLSS*
Variables	Mean ± SD	Range	Mean ± SD	Range	*r*
$_{v}LE_{min}$	4.8 ± 0.6[b]	3.8–7.0	68.8 ± 5.5	57.3–80.7	0.833[b]
$_{v}LT_{+0.1mM}$	5.1 ± 0.7[b]	3.6–7.3	72.1 ± 7.2	56.1–91.2	0.722[b]
$_{v}LT_{+0.5mM}$	6.2 ± 0.7[b]	4.6–9.2	88.2 ± 8.0	68.6–101.7	0.746[b]
$_{v}LE_{min+1mM}$	6.5 ± 0.8[b]	5.0–9.5	91.7 ± 6.0	79.2–104.5	0.895[b]
$_{v}LT_{+1mM}$	6.7 ± 0.8[b]	5.2–9.5	95.5 ± 7.3	77.4–110.8	0.839[b]
$_{v}LE_{min+1.5mM}$	6.9 ± 0.9[a]	5.3–10.4	98.2 ± 6.4	85.1–112.4	0.897[b]
$_{v}LT_{+1.5mM}$	7.0 ± 0.9	5.4–9.9	100.1 ± 6.5	83.4–114.6	0.890[b]
$_{v}FBLC_{2.5mM}$	7.1 ± 0.9	5.3–9.8	100.4 ± 6.5	87.6–114.5	0.896[b]
$_{v}MLSS$	7.1 ± 1.0	5.4–10.0	100.0 ± N/A	N/A	N/A
$V_{\geq 3mM}$	7.6 ± 1.0[b]	6.1–10.4	108.5 ± 6.5	89.9–125.2	0.869[b]

BL_RTs = blood lactate-related thresholds, $_{v}LE_{min}$ = velocity at minimum lactate equivalent (km·h^{-1}), $_{v}LT_{+0.1mM}$ = highest stage-velocity above which blood lactate concentration increased by ≥ 0.1 mmol·L^{-1} in the following stage and ≥ 0.2 mmol·L^{-1} in the subsequent stage, $_{v}LT_{+0.5mM}$, $_{v}LT_{+1mM}$, $_{v}LT_{+1.5mM}$ = velocity at lactate threshold + 0.5, 1 and 1.5 mmol·L^{-1} above $_{v}LT_{+0.1mM}$ (km·h^{-1}), $_{v}LE_{min+1mM}$, $_{v}LE_{min+1.5mM}$ = velocity at the minimum lactate equivalent + 1 and 1.5 mmol·L^{-1} (km·h^{-1}), $_{v}FBLC_{2.5mM}$ = velocity at the fixed blood lactate at 2.5 mmol·L^{-1} (km·h^{-1}), vMLSS = velocity at maximal lactate steady-state (km·h^{-1}). $V_{\geq 3mM}$ = the lowest velocity of the IST where the blood lactate value was ≥ 3 mmol·L^{-1}, N/A = not applicable.

[a] $P < 0.01$ vs $_{v}MLSS$.

[b] $P < 0.001$ vs $_{v}MLSS$.

[0.08 (0.76) km·h^{-1}] (Figure 4(b)). The deviation of the regression line was not significantly different from zero (P = 0.087).

The prediction of $_{v}$MLSS still improved with an additional CVT performed one week after the IST at a velocity corresponding to 1 mmol·L^{-1} above the $_{v}LT_{+0.1mM}$, accounting for 89.2% of the variation in $_{v}$MLSS (P < 0.001), with a low SEE (0.32 km·h^{-1}; 4.5% of mean $_{v}$MLSS). The determinants identified for the prediction of $_{v}$MLSS were $_{v}LE_{min+1mM}$, the difference in BLC measured between the 20th and 10th minute of exercise during the CVT at $_{v}LT_{+1mM}$ (ΔBLC_{20-10}), age, body mass (kg), and the average absolute HR during the last 5 min of the CVT at $_{v}LT_{+1mM}$ ($_{HR}LT_{+1.5mM\ 16-20}$) (Table 2, model 3). The regression equation for the sample (n = 69) was:

$$_{v}MLSS = 3.262 + (1.120 \cdot {}_{v}LE_{min+1mM}) - (0.304C_{20-10}) - (0.021 \cdot age) - (0.012 \cdot body\ mass) - (0.010 \cdot {}_{HR}LT_{+1mM\ 16-20}) \quad (3)$$

The Bland-Altman method between the predicted and the actual $_{v}$MLSS against their mean for Equation (2) showed a small bias, and the narrower LoA [0.06 (0.63) km·h^{-1}] (Figure 4(c)). The gradient of the regression line did not deviate from zero (P = 0.30).

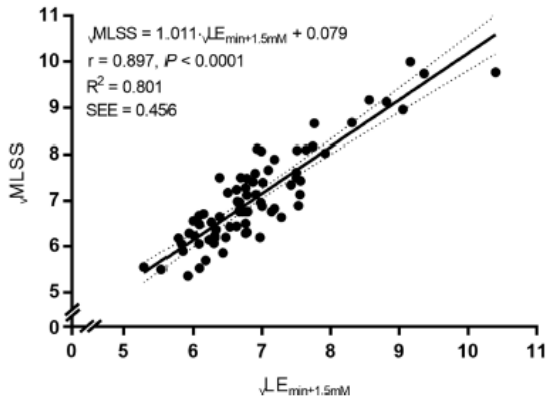

Figure 3. Linear regression between the best single predictor of $_{v}$MLSS ($_{v}LE_{min+1.5mM}$) and $_{v}$MLSS. $_{v}LE_{min+1.5mM}$ = minimum lactate equivalent + 1.5 mmol·l^{-1} (km·h^{-1}), $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}). Solid line: linear regression. Dashed lines: 95% confidence intervals.

Discussion

The main finding of this study was that $_{v}LE_{min+1.5mM}$ determined from a single IST was the strongest single predictor of $_{v}$MLSS, closely followed by $_{v}FBLC_{2.5mM}$, $_{v}LE_{min+1mM}$, and $_{v}LT_{+1.5mM}$ and the rest of the predictor variables (Table 1) in a large sample of postmenopausal women. The prediction of $_{v}$MLSS was improved when the velocity and HR at $_{v}LE_{min+1mM}$ along with age and body were entered in a multiple regression model. The addition of a CVT performed one week after the initial IST still improved the explained variance of $_{v}$MLSS.

The first exponential increase in BLC during incremental exercise (*i.e.*, $_{v}$LT) and the highest constant workload where the participant is still able to maintain steady blood lactate concentrations (*i.e.*, $_{v}$MLSS) during prolonged exercise are particularly relevant BL$_R$Ts, due to its practicability to transfer these lower and upper limits of effective but still safe exercise intensities into guidelines for individualized training (Binder et al., 2008). On average, $_{v}$LT ($_{v}LT_{+0.1mM}$) and $_{v}$MLSS of our study participants were 5.1 km·h^{-}1 and 7.1 km·h^{-1}, respectively. This $_{v}$LT value is 11% higher than that reported in diabetic 50-years old women (Belli et al., 2007) and 21% lower than untrained younger women (~32 years old) using a similar protocol (Weltman et al., 1990). These two physiologic breakpoints may serve as a basis for exercise intensity prescription as well as to evaluate the effects of exercise training without the need to expose individuals to volitional fatigue (Faude et al., 2009). However, it is not feasible, because of the number of trials necessary to directly determine the $_{v}$MLSS. Consequently, numerous authors have sought easier and less time-consuming exercise tests to identify lactate-related or ventilatory thresholds as a surrogate of $_{v}$MLSS (Bellotti, Calabria, Capelli, & Pogliaghi, 2013; Faude et al., 2009; Llodio et al., 2015; Pallarés, Morán-Navarro, Ortega, Fernández-Elías, & Mora-Rodriguez, 2016; Pardono et al., 2008). Nevertheless, most of these studies have focused on athletic population, and little is known about the prediction of $_{v}$MLSS in adults, and even less in postmenopausal women.

The magnitudes of the association between $_{v}$LT (measured either visually as $_{v}LT_{+0.1mM}$ or using a polynomic equation as $_{v}LE_{min}$) and $_{v}$MLSS in our sample (r = 0.72 and r = 0.83, respectively) are similar to those reported between LT and

Table 2. Prediction of $_{v}$MLSS from BL$_R$Ts and bloodless models from a single IST and an additional CVT (n = 75).

Model	Predictors	B	SE(B)	β	t	Adjusted R^2	Sig. (P)
1 *Bloodless*	ΔHR	−0.078	0.016	−0.374	−4.723	0.588	< 0.001
	Age	−0.075	0.015	−0.398	−4.959		
	HR_{rest}	−0.036	0.009	−0.318	−3.963		
	Body mass	−0.027	0.008	−0.285	−3.563		
2 *BL$_R$T & Bloodless*	$_{v}LE_{min+1mM}$	1.085	0.072	0.837	15.001	0.853	< 0.001
	Age	−0.040	0.009	−0.211	−4.338		
	$_{HR}LE_{min+1mM}$	−0.012	0.004	−0.137	−2.703		
	Body mass	−0.012	0.005	−0.125	−2.593		
3 *BL$_R$T & Blodless + CVT*	$_{v}LE_{min+1mM}$	1.120	0.063	0.864	17.757	0.892	< 0.001
	ΔBLC_{20-10}	−0.304	0.083	−0.162	−3.652		
	Age	−0.021	0.009	−0.114	−2.460		
	Body mass	−0.012	0.004	−0.120	−2.775		
	$_{HR}LT_{+1mM\ 16-20}$	−0.010	0.003	−0.154	−3.555		

vMLSS = velocity at maximal lactate steady-state, BL$_R$T = Blood lactate-related thresholds, IST = incremental submaximal shuttle test, CVT = constant velocity test, ΔHR = average magnitude of the differences heart rate between successive velocities during IST, HR_{rest} = resting HR supine position, $_{v}LE_{min+1mM}$ = velocity at the minimum lactate equivalent + 1 mmol·L^{-1} (km·h^{-1}), $_{HR}LE_{min+1mM}$ = HR at $_{v}LE_{min+1mM}$, ΔBLC_{20-10} = Change in blood lactate from the 20th to the 10th of the CVT at Lactate Threshold$_{+1mM}$ velocity, $_{HR}LT_{+1.5mM\ 16-20}$ = average HR of the last 5min (min16-20) of the CVT at LT_{+1mM} velocity.

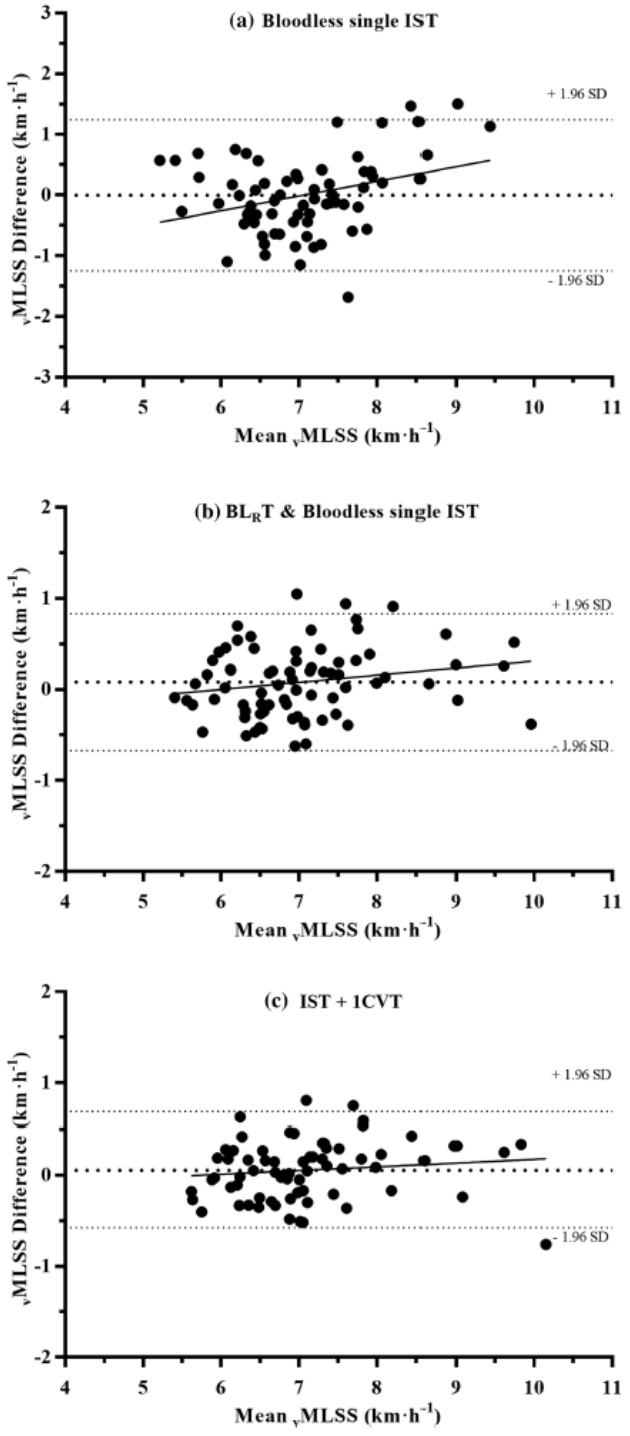

Figure 4. Bland-Altman plots of agreement between measured and predicted $_{v}$MLSS from (a) bloodless variables obtained in the IST, (b) Bloodless and BL_RTs obtained in the IST, (c) the addition of variables obtained in the CVT at $_{v}LT_{+1mM}$. $_{v}$MLSS = velocity at the maximal lactate steady-state (km·h^{-1}), IST = Incremental Shuttle test, BL_RT = Blood Lactate-related thresholds, CVT = Constant Velocity Test. Dotted bold line represent mean Bias and upper and lower dotted lines represent the 95% limits of agreement. The thick black line represents the slope of the association.

MLSS in cyclists (r = 0.71–0.76) (Pallarés et al., 2016; Pardono et al., 2008), and lower to those reported in college students (r = 0.95) (Carter et al., 1999) and in a previous study conducted in our laboratory with endurance runners (r = 0.86) (Garcia-Tabar & Gorostiaga, 2018). Exercise intensities above $_{v}$LT that rely on the individual lactate curve presented higher associations with $_{v}$MLSS. The $_{v}LE_{min+1.5mM}$ was the best single predictor of $_{v}$MLSS accounting for 80% of its variance (SEE = 6.5% and LoA = 12.6% of mean $_{v}$MLSS), closely followed by $_{v}FBLC_{2.5mM}$, $_{v}LE_{min+1mM}$, and $_{v}LT_{+1.5mM}$. These findings agree with previous research performed in young recreational or endurance-trained athletes showing that BL_RTs, such as $_{v}LE_{min}$ and $_{v}LE_{min+1.5mM}$ (Garcia-Tabar & Gorostiaga, 2018), OBLA (R. Beneke, 1995; Van Schuylenbergh, Eynde, & Hespel, 2004), IAT (Beneke, 1995), D_{max} (Van Schuylenbergh et al., 2004), LT (Philp et al., 2008), or other BL_RTs (Grossl, De Lucas, De Souza, & Antonacci Guglielmo, 2012) obtained during a single incremental exercise test are significant determinants of $_{v}$MLSS.

Non-invasive low cost and easy-to-administer exercise test protocols have traditionally been of general interest to the sport and fitness community. However, our results suggest that the prediction of $_{v}$MLSS by submaximal bloodless variables in postmenopausal women lacks of accuracy and is, therefore, not recommended because the explained variance was low (R^2 = 59%) (Table 2), and it could be biased up to 17% above or below actual $_{v}$MLSS in some individual cases (Figure 4(a)). In the absence of blood lactate, Garcia-Tabar et al. (2017) found that the velocity corresponding to the 90% of HR_{max} (V90) is a more accurate bloodless predictor of $_{v}$MLSS (R^2 = 64%; 90% LoA: 9.5% of $_{v}$MLSS). However, the maximal effort required to assess V90 is not practical for non-clinicians in sedentary and diseased people.

The prediction of $_{v}$MLSS improved when several bloodless variables (age and body mass) along with the velocity and HR at $LE_{min+1mM}$ were entered into the same model, explaining up to 85.3% of its variance (Table 2). This value is among the highest reported in the literature (55–88%) (Bellotti et al., 2013; Faude et al., 2009; Garcia-Tabar & Gorostiaga, 2018; Llodio et al., 2015; Pallarés et al., 2016; Pardono et al., 2008). Differences such as homogeneity of the sample, number of participants involved, test protocol characteristics and specificity, precision and stability criterion in the $_{v}$MLSS determination, determination of BL_RTs and other variables, as well as age and training status of the participants of each study might explain these discrepancies. For instance, the sample size of this study was larger and showed similar heterogeneity in $_{v}$MLSS (CV = 15%) compared to the studies mentioned above (CV = 7–17%). Probably, the higher accuracy in $_{v}$MLSS determination (± 0.3 km·h^{-1}; ± 4.5% of mean $_{v}$MLSS) compared to most of previous research in the field (3–10% of the mean), and the low-velocity increments of the IST for blood sampling (0.61 km·h^{-1} or 8.5% of $_{v}$MLSS) could have positively contributed to the estimation of $_{v}$MLSS. The prediction of $_{v}$MLSS resulted in a low SEE (0.38 km·h^{-1}), which corresponds to 5.4% of the mean $_{v}$MLSS. (Equation 2). The 95% LoA (± 0.76 km·h^{-1}; *i.e.*, ± 10.7% mean $_{v}$MLSS) are similar or lower to the values reported in the literature from maximal exercise trials (≈6% of the mean $_{v}$MLSS) (Llodio et al., 2015; Sjödin et al., 1982), BL_RTs (5.9–23.5% of the mean $_{v}$MLSS) (Faude et al., 2009; Garcia-Tabar & Gorostiaga, 2018; Grossl et al., 2012; Pallarés et al., 2016), or ventilatory thresholds (9–22% of the mean) (Bellotti et al., 2013; Leti et al., 2012) in cyclists (Faude et al., 2009; Grossl et al., 2012; Pallarés et al., 2016), runners (Faude et al., 2009; Leti et al., 2012; Sjödin et al., 1982), and soccer players (Llodio et al., 2015).

The reason why LE_{min}-related variables would offer significant prediction advantages over other BL_RTs to estimate $_vMLSS$ can be related to: 1) the resolution of $_vLE_{min}$ determination that is finer than other BL_RTs (*e.g.*, $_vLT_{+0.1mM}$) because all the data points before and after the transition are used to project the LE_{min} value (Figure 1(b)); 2) the $_vLE_{min}$ could essentially take on an infinite number of values, whereas $_vLT_{+0.1mM}$ and $_vLT_{+0,5mM}$ determination, for example, could only be based on the discrete values of the specific velocity-rate stages; 3) the troublesome identification of the first BLC elevation above baseline values due to initial BLC fluctuations associated with the error of the analyzer (Weltman et al., 1990); and 4) as opposed to FBLC, $_vLE_{min}$-related variables (*e.g.*, $_vLE_{min+1.5mM}$) do not seem to be influenced by pre-test intramuscular glycogen stores and BLC values (Tegtbur et al., 1993) or by exercise patterns (Beneke, Leithauser, & Hutler, 2001). This fluctuation is solved by the "U"-shape BLC curve, for the identification of $_vLE_{min}$.

The second purpose of this study was to investigate whether the prediction accuracy of $_vMLSS$ could still improve by the addition of a CVT at $_vLT_{+1mM}$, one week after the IST. The results showed that BLC and HR values observed between the 10^{th} and 20^{th} min of the CVT, along with age, body mass and $_vLE_{min+1mM}$ obtained during the IST, improved the explained variance up to 89.2%, with narrower SEE (0.32 $km{\cdot}h^{-1}$ or 4.5% of the mean $_vMLSS$) and 95% LoA (0.63 $km{\cdot}h^{-1}$; 8.9% of the mean $_vMLSS$). These results are in agreement with previous studies performed with soccer players (Llodio et al., 2015) and endurance-trained runners (Llodio, Gorostiaga, Garcia-Tabar, Granados, & Sánchez-Medina, 2016) in our laboratory. It is, therefore, suggested to perform an additional CVT whenever possible.

This study presents some important strengths such as the large sample size, the accurate estimation of $_vMLSS$, and the utilization of a single test of submaximal nature, or the addition of a CVT to improve the accuracy of the estimation. However, the present investigation is not without limitations. First, the generalizability of the results is limited to 50–75 years old women with $_vMLSS$ values ranging from 5.4 to 10 $km{\cdot}h^{-1}$. Second, the reported prediction equations are only recommended to be used with the specific testing procedures described in this study. Third, a test-retest analysis of $_vLE_{min}$ was beyond the scope of this study, and therefore, whether $_vLE_{min}$ is reliable was not verified. Dickhuth et al. (1999), however, found a good test-retest reproducibility (r = 0.90) of $_vLE_{min}$ in young males. Finally, this study is a cross-sectional study. Further longitudinal studies are required to examine whether longitudinal training-induced changes in $_vMLSS$ could be predicted and monitored by $_vLE_{min}$-related variables.

Conclusions

The results of the present study indicate that when BLC assessment is available but only one testing session is feasible, $_vLE_{min}$-related variables obtained from an incremental submaximal test are accurate estimates of $_vMLSS$. The use of only bloodless variables to estimate $_vMLSS$ is not recommended, due to its low accuracy. Performing an additional CVT one week after the incremental test is encouraged because it improves the prediction of $_vMLSS$. We, therefore, recommended the IST as a simple non-exhaustive and time-efficient alternative to the classical determination of $_vMLSS$ or maximal exercise tests for non-athletic population.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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