This is a non-final version of an article published in final form in Jayo-Montoya, Jon Ander MS; Jurio-Iriarte, Borja PhD; Aispuru, G. Rodrigo MD; Villar-Zabala, Beatriz LPN; Blanco-Guzman, Sonia MD; Maldonado-Martín, Sara PhD. Chronotropic Responses to Exercise and Recovery in Myocardial Infarction Patients Taking β-Blockers Following Aerobic High-Intensity Interval Training: AN INTERFARCT STUDY. *Journal of Cardiopulmonary Rehabilitation and Prevention* 42(1):p 22-27, January 2022. | DOI: 10.1097/HCR.0000000000000607 .

Type of submission: Brief Report

Title: **Chronotropic Responses to Exercise and Recovery in Myocardial Infarction Patients Taking Beta-Blockers following Aerobic High-Intensity Interval Training: INTERFARCT Study**

Short title: Chronotropic Responses in Myocardial Infarction

The authors of this manuscript are:

Jon Ander JAYO-MONTOYA, MS[1], Borja JURIO-IRIARTE, PhD [1], G. Rodrigo AISPURU, MD[2], Beatriz VILLAR-ZABALA, LPN[2], Sonia BLANCO-GUZMAN, MD[3], Sara MALDONADO-MARTÍN, PhD [1,4]

[1] GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Physical Exercise Research Group. Department of Physical Education and Sport. Physical Activity and Sport Sciences Section of the Faculty of Education and Sport. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain.

[2] Primary Care Administration of Burgos. Health Service of the Castile & Leon Community (Sacyl), Spain

[3] Internal Medicine Department. Santiago Apóstol Hospital, Miranda de Ebro, Burgos

[4] BIOARABA-GIKAFIT. Vitoria-Gasteiz. The Basque Country, Spain

Corresponding author: Sara Maldonado-Martín. Department of Physical Education and Sport. Physical Activity and Sport Science Section of the Faculty of Education and Sport. University of the Basque Country (UPV/EHU). Portal de Lasarte, 71. 01007 Vitoria-Gasteiz (Araba/Alava)-Basque Country, Spain. Phone: +34 945013534

Fax: +34 945013501. E-mail: sara.maldonado@ehu.eus

Keywords: Exercise design; Heart rate; Low-volume training; High-intensity interval training; Myocardial infarction

Funding sources: The trial was supported by the Santiago Apostol Hospital (Miranda de Ebro, Burgos, Spain) and the Department of Physical Education and Sport (University of the Basque Country, UPV/EHU).

All authors declare no conflicts of interest.

All authors have read and approved the manuscript

Word count: 2114

Number of tables: 2

Number of Figures: 0 (two figures are presented as supplemental digital content)

Number of references: 19

Introduction

After an acute event such as a myocardial infarction (MI), patient assessment including symptom-limited exercise testing, along with exercise training and nutritional counselling are considered some of the core components of any cardiac rehabilitation program.[1] Heart rate (HR) response during and after the exercise test provides both independent and complementary information to estimate risk and prognosis, because of the significant indicator of myocardial oxygen demand.[2] Thus, it is very well known that HR reflects the dynamic balance between the sympathetic and parasympathetic divisions of the autonomic nervous system (*i.e.,* sympathovagal balance).[3,4] Therefore, both an attenuated HR response to exercise (*i.e.,* chronotropic incompetence) and slowed HR recovery (HRR) are associated with all-cause mortality and cardiac events,[2,3,5] even in patients taking β-blockers.[6]

Along with pharmacological treatment, supervised exercise training enhances sympathovagal balance based on both moderate-intensity continuous aerobic exercise training as well as high-intensity interval training (HIIT) programs,[7] independently of medication or diet[8]. Low-volume HIIT (*i.e.,* less than 10 min of exercise work at high intensity in one session) has been promoted to improve different cardiorespiratory and metabolic markers after MI,[9] despite lower time commitment and reduced total exercise volume. However, little is known regarding the effects of different HIIT volumes (*i.e.,* low- *vs.* high-volume,) in post-MI patients taking regular pharmacotherapy on the chronotropic responses to exercise and recovery.

Further, several commonly used cardiovascular medications, including β-blockers and others, may induce chronotropic incompetence and affect autonomic function.[10] Nevertheless, chronic pharmacological treatment with β-blockers may paradoxically improve chronotropic response by decreasing sympathetic tone or increasing β-receptor activity.[3,11]

Therefore, the objectives of this study were: 1) to compare the effects of two different HIIT programs (low-volume *vs.* high-volume) on chronotropic responses during exercise and recovery, and 2) to contrast the results of the HIIT groups together to the group receiving only physical activity recommendations, in post-MI patients taking β-blockers.

Methods

The design, selection criteria, and procedures for the INTERFARCT study have been detailed previously.[12]. The protocol and informed consent procedures were approved by two different ethics committees (UPV/EHU, CEISH, 2016; CEIC 1462).

Seventy non-Hispanic white patients (11 women, 59 men) with diagnosed MI type 1, called "Spontaneous MI"[13] with and without ST elevation and left ventricular ejection fraction >50% were enrolled in the study (see Figure, Supplemental Digital Content 1).

The measurements were taken before the intervention period (T1) and after (T2), at 16-weeks. Participants performed a peak, gradual cardiopulmonary symptom-limited exercise test in the upright position on a cycle ergometer (Lode Excalibur Sport Cycle, Groningen, The Netherlands). Heart rate was measured continuously before, during, and after the exercise test by twelve-lead electrocardiogram monitoring (Ergocard Medisoft, Belgium, Ref. USM001 V1.0). Resting HR (HR_{rest}) was evaluated after five minutes of supine rest prior to the exercise test. To calculate HRR, the peak HR (HR_{peak}) during the exercise test was recorded. After completion of the test, participants remained passively on the bike for the following five minutes and their post-exercise minute HR (HR_{rec})

was registered in the first (HR_{rec1}), second (HR_{rec2}), and fifth (HR_{rec5}) minute. The difference between HR_{peak} and these three recovery period measurements were considered HRR_1, HRR_2, and HRR_5, respectively. Heart rate reserve was calculated as the difference between HR_{peak} during exercise and HR_{rest}. Assessment of chronotropic incompetence was carried out using Wilkoff *et al.* criteria:[14] *i.e.,* failure to reach 85% of the age-predicted maximum HR on a peak effort cardiopulmonary exercise test, or failure to reach 80% of the $HR_{reserve}$ to the metabolic reserve ratio during submaximal exercise. The cardiopulmonary exercise test was carried out in the afternoon, and patients were advised not to exercise that same day or the day before, not smoke or consume caffeine, and take their regular medications.

After baseline measurements, the participants were randomly assigned to one of the three intervention groups. The attention control (AC) group was advised to practice regular unsupervised physical activity to keep ethical procedures regarding health.[12] The exercise groups (low- and high-volume HIIT) trained two non-consecutive days per week for 16 weeks under the supervision of an exercise specialist. Procedures and design have already been published.[12]

Descriptive statistics were calculated for all independent variables and data are expressed as the mean ± standard deviation (SD), or frequency and percentage. One-way analysis of variance was used to determine if there were significant pre-intervention differences among groups. The comparison of frequencies in categorical variables among groups was performed using the *Chi*^{2} test.

Data were analyzed according to the intention-to-treat principle. The paired-sample *t*-test was used to compare the baseline and follow-up values of all the independent variables. Analysis of covariance was used to examine training effects across intervention groups; post-intervention outcomes were selected as dependent variables, and analysis was adjusted for age, sex, β-blocker treatment, and pre-intervention outcome of each dependent variable. Bonferroni post hoc comparisons and Helmert contrasts were performed to analyze the differences between all groups or the two exercise training groups pooled together *vs.* AC group, respectively. Statistical significance (*P*-value) was set at 95% ($\alpha<0.05$). As the sample size was too small to achieve statistical significance, the current report takes the effect size for each outcome variable into special consideration. Hedges'*g* (*g*) was used as the index of effect size for comparisons within and between the two groups (*i.e.*, T1 *vs.* T2; after-intervention change in AC *vs.* HIIT). A *g* index of 0.2 was considered a small effect, 0.5 medium, and 0.8 large.[15] Cohen's *f* (*f*) was used to assess training effects across the different intervention groups (AC, low-volume HIIT, and high-volume HIIT). An *f* index of 0.1 was considered a small effect, 0.25 medium, and 0.4 large.[16]

Results

At baseline (T1), 100% of participants showed one or more cardiovascular risk factors after suffering MI. As such, all participants were under pharmacological treatment. There were no significant between-group differences (*P*>0.05) in anthropometrics, physiological, and pharmacological treatment (Table 1), except for resting systolic blood pressure between the AC and high-volume HIIT groups (*P*=0.003). Of the 70 participants considered eligible for this study, the presence of chronotropic incompetence was identified in 36% (5/14) from AC, 43% (12/28) from low-volume HIIT, and 50% (14/28) from high-volume HIIT (Table 1).

At follow-up (T2), fifteen participants (n=3 AC, n=7 low-volume HIIT, n=5 high-volume HIIT) did not complete the 16-week intervention due to causes unrelated to the study, or for not completing at least 80% attendance for exercise sessions (see Figure, Supplemental Digital Content 1). Table 2 shows the chronotropic responses during the cardiopulmonary exercise test and recovery, both pre- and post-intervention. There were no significant between-HIIT group differences observed in any of the studied variables at T2 (P>0.05). When comparing AC *vs.* HIIT groups, HR_{rest} showed large significant differences (P=0.02) with lower values in the AC group (Table 2). Regarding HR_{peak}, the HIIT groups had a significant small-sized increasing effect (Δ=8±18%, P=0.04 in low-volume HIIT and Δ=6±9%, P=0.01 in high-volume HIIT), in contrast with the minimal decreasing effect of AC (Δ=-2±12%, P=0.4) (Table 2), resulting in large significant differences (P=0.03). Accordingly, $HR_{reserve}$ increased significantly after high-volume HIIT intervention (P=0.02).

Post-intervention HRR_1 was barely altered in any of the three study groups. The same effect was observed in the subsequent recovery minutes of AC. However, HIIT had a medium-sized effect in HRR_2 due to the significant increase in high-volume HIIT (Δ=15±29%, P=0.02), and also a large-sized effect in HRR_5, due to the rise in the recovery of low-volume HIIT (Δ=19±31%, P=0.02) and high-volume HIIT (Δ=19±28%, P=0.005) (Table 2). Taking into consideration the relative change of HRR *vs.* $HR_{reserve}$, no within/between-group significant differences were found (P>0.05). While the aforementioned changes were medium-sized, differences were larger between the AC and HIIT groups in HRR_5 (Table 2). After the intervention, chronotropic incompetence was diagnosed in 36% (4/11), 38% (8/21), and 43% (10/23) of participants in AC, low-volume HIIT, and high-volume HIIT, respectively.

Angiotensin-converting enzyme inhibitors/angiotensin receptor antagonist dose was reduced in five participants during the intervention period (3 in low-volume and 2 in high-volume HIIT). β-blocker dose was not changed in any of the participants. During the intervention and training sessions, there were no adverse events reported.

Discussion

The lack of difference between the two HIIT protocols, with regards to the resulting positive adaptations in both cases, suggests that low-volume HIIT is a time-efficient and very attractive strategy for clinical practice after MI. Thus, the applicability of this strategy in cardiac rehabilitation sessions would allow for the design of training programs that simultaneously include resistance exercise as well as low-volume HIIT, as is currently recommended.[17] Furthermore, the positive effects that both of the HIIT protocols had on the autonomic nervous system are supported by the higher HR_{peak} and faster HRR observed after the intervention, with no change in the AC group (Table 2 and see Figure, Supplemental Digital Content 2). The contribution of HR to exercise performance and the ability to perform physical work is very well known through the Fick principle.[3] Therefore, it is clear that increases in HR_{peak} will improve the metabolic demands during exertion, leading to better cardiorespiratory fitness. Accordingly, in the current study, the significant increments in HR_{peak} in both the HIIT groups (Table 2), were parallel to the improvements in peak oxygen uptake by the participants.[9] In accordance with a previous study,[18] these results confirm that HIIT is a potent stimulus to induce both central and peripheral physiological improvements in healthy and unwell individuals.

The favorable effect of exercise training on the autonomic nervous system is also supported by the increased HRR in the HIIT groups (Table 2). It has been stated that HRR is a strong prognostic factor for cardiovascular events at 1, 2, and 5 minutes after an exercise test, with different cut-off values related to each minute (HRR_1<12-21 bpm, HRR_2<42 bpm, HRR_5<50 bpm).[3-5] In the present study, all participants showed a good baseline profile with intact autonomic function, given their normal HRR_1 (*i.e.,* more than 21 bpm drop in HR, Table 2). However, significant changes were observed in HRR_2 and HRR_5 only in the HIIT groups. With regards to this, it is well known that parasympathetic activation plays a substantial role early in HRR after HIIT.[4] Therefore, a higher stimulus through HIIT could be necessary for inducing larger increases in cardiac vagal activity,[19] underscoring the importance of individual exercise-intensity design.

Pharmacological treatment with β-blockers could induce an attenuated HR response to exercise and consequently chronotropic incompetence, or in some cases could increase HR responsiveness through β-1 receptor upregulation.[3] In the current study, the main consequence of the increase in HR_{peak} at follow-up was that the proportion of chronotropic incompetence was reduced, from 43% to 38% in the low-volume and from 50% to 43% in the high-volume HIIT. Even so, it has been shown that chronotropic incompetence in other cardiac populations[3] is more associated with a trend toward impaired norepinephrine release, post-synaptic β-receptor, and reduced exercise capacity than with β-blocker treatment. Consequently, chronotropic incompetence could be reverted with exercise training irrespective of β-blocker treatment. It seems that both the enhanced baroreceptor response and decrease in sympathetic outflow and plasma catecholamines may be the intermediary physiological mechanisms for improving flow-mediated vasodilation. This, in turn, is considered a key factor to appropriately increase HR when cardiac demands are raised.[3] Hence, it may suggest that β-blocker treatment combined with HIIT does not compromise the effect of exercise training. The question remains, however, regarding whether MI patients with normal left ventricular ejection fraction, who usually exercise and have a normal physiological HR response during exercise and recovery, should be considered for β-blocker treatment.

The findings of this study highlight the clinical importance of MI patients receiving long-term supervised exercise training, instead of only unsupervised recommendations, to reduce major adverse cardiovascular events. Heart rate response, although a surrogate of sympathovagal response, is an easy and practical variable to assess prognosis and exercise intolerance, and to optimize and adapt exercise training design.

There are some limitations to this study that should be mentioned. Firstly, the small sample size. There were 115 participants excluded from the 224 who were assessed for eligibility because they did not meet inclusion criteria and another 39 who refused to participate. Secondly, the technological resources needed to monitor unsupervised physical activity in the AC group were unavailable. Finally, the AC group presents fewer participants compared to the HIIT groups. Consequently, any small change in just one participant could skew the mean of the results.

In conclusion, the present study documented that a 16-week exercise intervention with both low and high-volume HIIT elicited similar improvements in chronotropic responses after MI, independently of β-blocker treatment. Supervised HIIT training was more effective than giving physical activity recommendations alone, leading to better autonomic balance. Low-volume HIIT is presented as a potent and time-efficient exercise strategy that could enhance sympathovagal balance in this population.

Acknowledgments The authors thank the participants for their commitment. Our special thanks to Jessica Werdenberg for reviewing the manuscript, Peter H. Brubaker for his valuable advice, and Rodrigo Gallardo and Tatiana Matajira as cardiologists of the project.

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Supplemental Digital Content 1

Figure. Flow diagram of the INTERFARCT study from recruitment to the end of the intervention

Supplemental Digital Content 2

Figure. HR recovery change of different groups after intervention program.

AC: Attention Control group; HIIT: High-Intensity Interval Training. Data are expressed as mean absolute recovered heart rate. Statistically significant differences (P<0.05) expressed as: ***** = between T1 and T2. Error bars at 95%CI.