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Characterization of mechanical properties of adult chests during pre-hospital manual chest compressions through a simple viscoelastic model

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A R T I C L E I N F O

Keywords:
Cardiopulmonary resuscitation (CPR)
Manual chest compressions
Chest compression force
Chest compression depth
Out-of-hospital cardiac arrest (OHCA)

A B S T R A C T

Aim: The purpose of this study was to develop a simple viscoelastic model to characterize the mechanical properties of chests during manual chest compressions in pre-hospital cardiopulmonary resuscitation (CPR).
Methods: Force and acceleration signals were extracted from CPR monitors used during pre-hospital resuscitation attempts on adult patients. Individual chest compressions were identified and segmented from the chest displacement computed using the force and acceleration. Each compression-recoil cycle was characterized by its elastic coefficient k (a measure of stiffness) and its compression and recoil damping coefficients, d_c and d_r, respectively (measures of viscosity). We compared the estimated and the calculated chest displacement to assess the goodness of fit of the model. We characterized the chest of patients at the beginning of CPR in relation to sex and age, and their variation as CPR progressed.
Results: A total of 1,156,608 chest compressions from 615 patients were analysed. Mean (95% CI) coefficient of determination R^2 for the viscoelastic model was 97.9% (97.8–98.1). At the beginning of CPR, k was 104.9 $N{\cdot}cm^{-1}$ (102.0–107.8), d_c was 2.868 $N{\cdot}s{\cdot}cm^{-1}$ (2.751–2.984) and d_r was 4.889 $N{\cdot}s{\cdot}cm^{-1}$ (4.648–5.129). Damping during recoil was significantly higher than during compression. Stiffness was lower in women than in men. There were no differences in damping coefficients with sex but a higher d_r with increasing age. All model coefficients decreased with compression count, with an overall decrease after 3,000 chest compressions of 34.6%, 48.8% and 37.2%, respectively.
Conclusion: The model accurately described adult chest mechanical properties during CPR, highlighting differences between compression and recoil, sex and age, and a progressive reduction in chest stiffness and viscosity along resuscitation. Our findings may merit further investigation into whether patient-tailored and time-sensitive chest compression technique may be appropriate.

1. Introduction

Delivering high quality chest compressions is a key component of cardiopulmonary resuscitation (CPR) [1,2]. Adequate compression of the chest intends to force blood flow out of the heart to the lungs and body while allowing chest recoil enables blood to return, in order to maintain perfusion of a patient in cardiorespiratory arrest [3,4]. For more than a decade, studies have shown that rescuers' adherence to chest compression quality recommendations is good with the use of feedback devices [5–7]. However, the tendency to perform shallow clinical chest compressions even with automated feedback may be explained by factors other than the physical incapacity of the res-

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cuer [7]. Specifically, when chest compressions are applied manually, chest movement relies on patient's chest mechanical properties in response to the force applied by rescuers during compression and release.

Viscoelastic models have been proposed to explain the non-linear relationship between applied force and chest displacement during chest compressions [8], using animal data [9], data from human cadavers [10,11], or from patients in cardiorespiratory arrest [11,12]. Viscoelastic models are generally widely accepted, as they explain the elastic behaviour of the rib cage and the internal organs, as well as the damped behaviour of fluids and soft tissues within the thorax. Proposed models have been tested primarily in laboratory settings with compressions administered mechanically, with a few number of patients, or during short CPR intervals.

Previous studies have revealed that applying manual compressions for a prolonged period of time changes chest properties. [13,14]. Other studies have associated changes in chest wall mechanics with sternal and rib fractures during mechanical chest compressions, and have reported an impact on outcomes [15]. Understanding the interaction between applied force, achieved depth and patient haemodynamic response along the course of resuscitation attempts may contribute to improving treatment and outcomes.

In this context, the aim of this observational study was to apply a simple and innovative viscoelastic model to describe the chest mechanical properties observed during manual chest compressions in out-of-hospital cardiac arrest (OHCA) adult cases. The model accommodates differences in the viscosity of the chest between compression and recoil phases. We assessed the accuracy of the model in the estimation of instantaneous chest displacement from exerted force. We characterized chest model parameters at the beginning of the intervention and evaluated the model behaviour over the duration of resuscitation. The simplicity of the model allowed estimation of the dynamic behaviour of the chest along the course of CPR for different populations. The observed differences could support the appropriateness of a patient-adapted and time-sensitive chest compression technique, moving away from the current standardized approach during resuscitation.

2. Materials and methods

2.1. Data collection

Force and acceleration signals were extracted from monitor-defibrillators (Heartstart MRx, Phillips Healthcare, USA) equipped with chest compression monitors (Q-CPR®) used during adult prehospital cardiac arrest episodes attended by Tualatin Valley Fire & Rescue (TVF&R), a single first response advanced life support (ALS) emergency medical service (EMS) agency (Tigard, Oregon, USA), from 2013 through 2017. The database is a part of the Portland Resuscitation Outcomes Consortium Epidemiological Cardiac Arrest Registry, approved by the Institutional Review Board (IRB00001736) of the Oregon Health & Science University (OHSU). Patient personal information is not included in the records. TVF&R crews provided continuous chest compressions with interposed ventilations every 10th compression regardless of airway type. Responders benefited from real-time feedback on chest compression quality including rate, depth and completeness of release. For this study, we selected cases of adult patients who received at least 200 chest compressions.

2.2. Theory: description of the chest model

Our model relies on the classical assumption that the applied force during chest compressions can be decomposed into the sum of an elastic force and a damping force, that is, the chest is modelled with a spring and a damper in parallel disposition [8,11]. Accordingly, the instantaneous applied force $F(t)$ is the sum of the elastic force $F_e(t)$, being proportional to the chest displacement $x(t)$, and the damping force $F_d(t)$, being proportional to the chest velocity $v(t)$:

$$F(t) = F_e(t) + F_d(t) = k \cdot x(t) + d \cdot v(t) \tag{1}$$

where k is the elastic coefficient, $x(t)$ the chest displacement, d is the damping coefficient and $v(t)$ the chest velocity. The elastic coefficient allows to characterize the stiffness of the chest, or its inverse, the elasticity. We can refer to either term interchangeably, with the understanding that the behaviour of one reflects the inverse behaviour of the other.

In order to accommodate the anticipated differences in viscosity between chest compression and recoil phases we introduced separated damping coefficients in our model:

$$F_c(t) = k \cdot x_c(t) + d_c \cdot v_c(t) \tag{2}$$

$$F_r(t) = k \cdot x_r(t) - d_r \cdot v_r(t) \tag{3}$$

where $F_c(t)$ and $F_r(t)$ are the instantaneous exerted forces during compression and release, achieving displacements $x_c(t)$ and $x_r(t)$, respectively. Coefficients d_c and d_r are the compression and recoil damping coefficients, respectively. The negative sign in Equation (3) indicates the opposite direction of the chest movement during recoil. With this model, we characterized each chest compression by its elastic coefficient k (a measure of stiffness), and its compression and recoil damping coefficients (measures of viscosity).

2.3. Calculation: data annotation and estimation of the model parameters

Chest displacement and velocity signals were calculated from acceleration [16]. Individual chest compressions were automatically detected using force and depth signals [13]. Fig. 1 shows an overview of a selected interval of our database (panel A) along with the annotation detail of each compression (B). Each compression was segmented into compression and recoil phases using the beginning and end points and the instant of maximum downward chest displacement D_{max} (Fig. 1). Locations and values of the maximum compression velocity (CV), maximum recoil velocity (RV), and maximum compression force (F_{max}) within each compression were annotated.

The ratio F_{max}/D_{max} allowed for computing the elastic coefficient k. This relationship can be referred to as stiffness, in line with the terminology used by other authors [13,17]. Henceforth, the behaviour of the coefficient k directly describes the behaviour of the stiffness of the chest. For simplification, we ignored the lag between the instant of maximum force and the instant when the chest reaches the maximum depth [13]. For computing the compression damping coefficient d_c we used CV and the concurrent force and displacement employing Equation (2). Similarly, for computing the recoil damping coefficient d_r we used RV and the concurrent force and displacement employing Equation (3).

2.4. Validation of the model

To assess the accuracy of the model, we estimated the instantaneous chest displacement from the model parameters calculated for each single compression and compared it with the chest displacement computed from the chest acceleration. For this purpose, the instantaneous chest displacement was estimated by solving this variable in Equation (2) and Equation (3):

$$\widetilde{x}_c(t) = \frac{F_c(t) - d_c \cdot v(t)}{k} \tag{4}$$

$$\widetilde{x}_r(t) = \frac{F_r(t) + d_r \cdot v(t)}{k} \tag{5}$$

where $\widetilde{x}_c(t)$ and $\widetilde{x}_r(t)$ are the estimated chest displacement during compression and recoil, respectively.

For comparison purposes, we also estimated the chest displacement using a simplified purely elastic model as:

$$\widetilde{x}(t) = \frac{F(t)}{k} \tag{6}$$

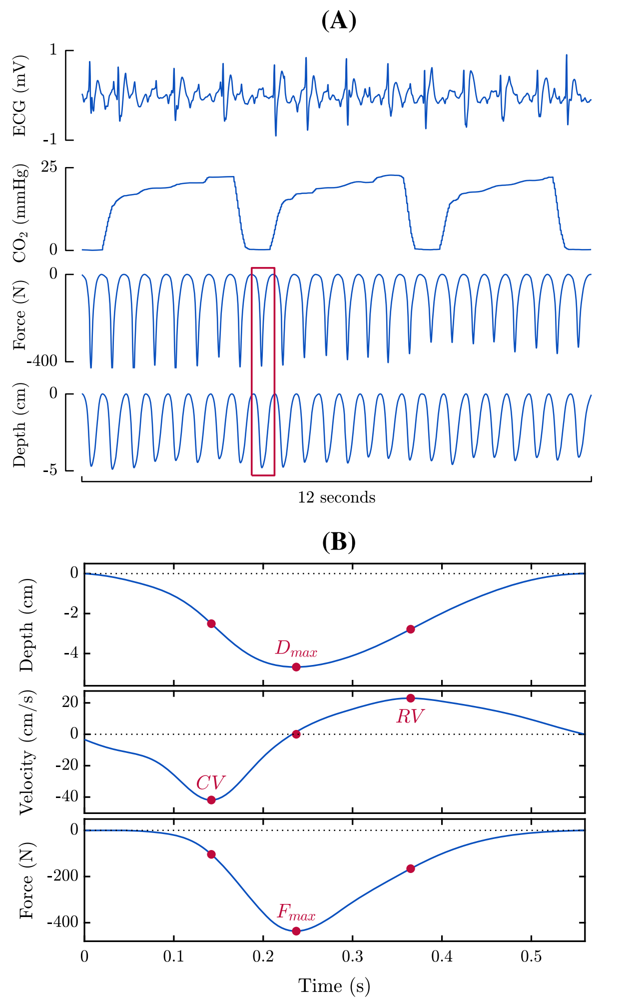

Fig. 1. Example of data annotation. Panel A: overview of a selected interval of our database. Panel B: Annotations on the depth, velocity and force signals for an individual chest compression.

2.5. Statistical analysis

We evaluated the goodness of fit of the chest model through the coefficient of determination R^2 of the difference between the measured and the estimated chest displacement signals per individual chest compression using the expression:

$$R^2 = 1 - \frac{\Sigma_{i=1}^{N}[x(t_i) - \tilde{x}(t_i)]^2}{\Sigma_{i=1}^{N}[x(t_i) - \bar{x}]^2} \tag{7}$$

where N is the number of samples for each individual chest compression; t_i is the time instant corresponding to the sample i; $x(t_i)$ is the measured (observed) displacement at t_i; $\tilde{x}(t_i)$ is the displacement estimated by the model at t_i and $\bar{x}$ is the mean value of the measured displacement along each individual chest compression.

To characterize patients chests at the beginning of CPR, the model parameters were estimated from the first 100 chest compressions using generalized linear mixed effects (GLME) with patient as random effect, and sex, age, and receipt of bystander CPR as fixed effects when assessing for differences. Age was used as a continuous variable and as a categorical variable: <50, 50–80, and >80 years old. Results were reported using the estimated mean and 95% confidence intervals (CI), and the p values from the GLME analysis. We considered non-overlapping 95% CI intervals as statistically significant. The Kruskal-Wallis test was used to study differences between age groups, for which p values below

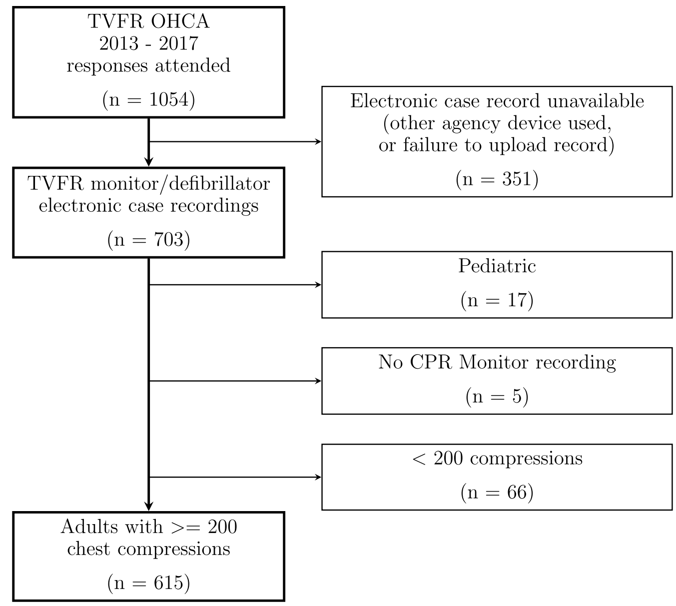

Fig. 2. Decision tree for the inclusion/exclusion of case studies from the TVF&R emergency responses, 2013–2017.

0.017 were considered significant (after Bonferroni correction for three comparisons).

Values were grouped every 100 chest compressions and normalised to the median of the case's first 100 compressions for analysing the model evolution with compression count. [14] Significance of trends with compression count were assessed with Jonckheere-Terpstra tests [18]. We considered p_{trend} (from tests for trend) values below 0.05 to be statistically significant. Signal processing and statistical analyses were performed with custom Matlab® (Natick, MA, USA) programs, using version R2021a. The results of all tests performed are reported.

3. Results

TVF&R responded to 703 cases between 1 January 2013 and 31 December 2017 in which defibrillator/monitor recordings were acquired. Of them, 615 were from adult patients that received at least 200 chest compressions (Fig. 2).

A total of 1,156,608 chest compressions were annotated from 615 adult OHCA patients, with a median (IQR) of 1,720 (1,036–2,609) compressions per patient, ranging from 200 to 5,849. Patient characteristics are reported in Table 1. Median age was 66 (53–77) years and 34% of the patients were female. Restoration of spontaneous circulation (ROSC) at any time occurred in 40% of the patients and bystander CPR was provided in 68% of the patients. Median (IQR) compression depth was 5.1 cm (4.5–5.6), and median compression rate was 118 min^{-1} (114–122).

Overall, mean R^2 was 97.9 (95% CI 97.8–98.1) significantly higher than the R^2 obtained with the pure elastic model (85.8, 95% CI 85.3–86.5), $p < 0.001$.

3.1. Characterization of patient's chest at the beginning of chest compressions

Table 2 shows the values of the model parameters at the beginning of chest compressions (first 100 chest compressions). Overall mean elastic coefficient k was 104.9 N·cm^{-1} (95% CI 102.0–107.8). Mean compression damping coefficient d_c was 2.868 N·s·cm^{-1} (95% CI 2.751–2.984). Mean recoil damping coefficient d_r was 4.889 N·s·cm^{-1} (95% CI 4.648–5.129), much higher than the compression damping coefficient ($p < 0.001$).

Table 1
Patient characteristics (n = 615). Values are reported as median (IQR) or as number (percentage).

Characteristic	Observed value
Age (y)	66 (53–77)
Female	68 (53–80)
Male	65 (53–75)
Sex, n (%)	
Female	208 (34)
Male	407 (66)
ROSC/no ROSC, n (%)[1]	225 (40) / 338 (60)
Female	72 (39) / 115 (61)
Male	153 (41) / 223 (59)
Bystander/no bystander, n (%)[1]	351 (68) / 166 (32)
Female	117 (69) / 53 (31)
Male	234 (67) / 113 (33)
Chest compression quality	
Depth (cm)	5.1 (4.5–5.6)
Rate (min^{-1})	118 (114–122)

ROSC: restoration of spontaneous circulation, it refers to any ROSC event.
[1] Of known.

Table 2
Parameters of the viscoelastic model calculated from the first 100 compressions of each patient, given as mean (95% CI).

Characteristic	n	k (N·cm^{-1})	d_c (N·s·cm^{-1})	d_r (N·s·cm^{-1})
Overall	615	104.9 (102.0–107.8)	2.868 (2.751–2.984)	4.889 (4.648–5.129)
Sex				
Female	208	96.84 (92.57–101.1)[1]	2.788 (2.598–2.977)	5.004 (4.652–5.437)
Male	407	109.2 (105.3–112.7)	2.909 (2.761–3.056)	4.809 (4.506–5.112)
Age (years)				
<50	115	102.4 (95.42–109.1)	2.766 (2.481–3.050)	4.099 (3.655–4.544)[2]
50–80	384	104.7 (101.1–108.3)	2.844 (2.735–3.032)	4.863 (4.552–5.173)
>80	116	108.1 (101.4–114.9)	2.916 (2.667–3.165)	5.759 (5.179–6.332)
Bystander CPR				
Yes	351	107.9 (104.0–111.7)	3.032 (2.876–3.187)	5.027 (4.718–5.337)
No	166	106.2 (100.6–117.1)	2.789 (2.575–3.002)	5.044 (4.583–5.504)

k: elastic coefficient; d_c: compression damping coefficient; d_r: recoil damping coefficient. CPR: cardiopulmonary resuscitation. d_r was significantly higher than d_c in all groups.
[1] k was lower in women than in men.
[2] d_r increased with age.

Regarding sex, k (stiffness) was lower in women (96.84, 95% CI 92.57–101.1) than in men (109.2, 95% CI 105.3–112.7) ($p < 0.001$) (Table 2). No differences between damping coefficients for compression and for recoil were found between the sexes ($p = 0.34$, $p = 0.36$, respectively. Age did not influence k ($p = 0.57$) or d_c ($p = 0.51$), although d_r increased with age ($p < 0.001$), and was clearly different among the three age groups studied ($p < 0.001$ for the three two-by-two combinations of the age groups studied after Kruskal-Wallis test). Regarding patients receiving bystander CPR or not, we did not observe statistically significant differences in any of the three model parameters at the beginning of EMS intervention ($p = 0.62$, $p = 0.08$ and $p = 0.95$ for k, d_c, and d_r, respectively).

3.2. Evolution of the model parameters with compression count

First, we assessed the goodness of fit of the model as CPR progressed. The correlation coefficient R^2 kept stable with compression count at an average of 98.9% with little variation as CPR progressed ($p_{trend} = 0.034$, Fig. 3). In contrast, R^2 for the purely elastic model increased from an initial 86.3% to 91.5% after 3,000 chest compressions ($p_{trend} < 0.001$). This increase was notably monotonic after approximately 1,000 chest compressions.

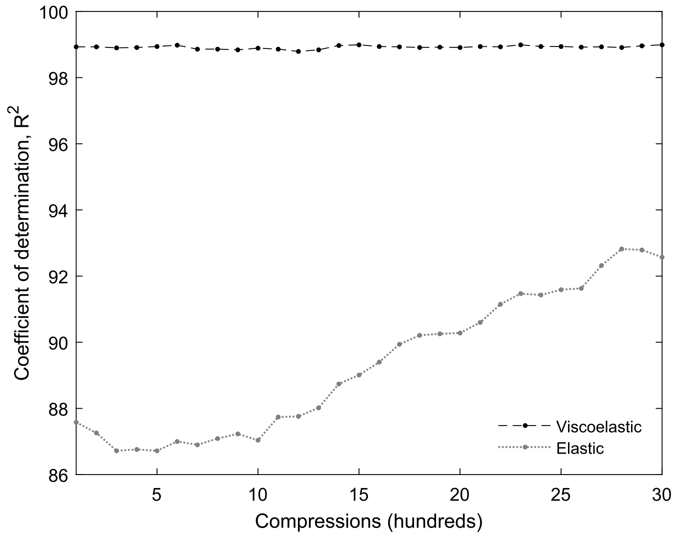

Fig. 3. Evolution of the coefficient of determination R^2 with compression count, for the viscoelastic model and for the pure elastic model. Although far from the more accurate viscoelastic model, resemblance of the chest to a pure spring increased after the first 1,000 compressions.

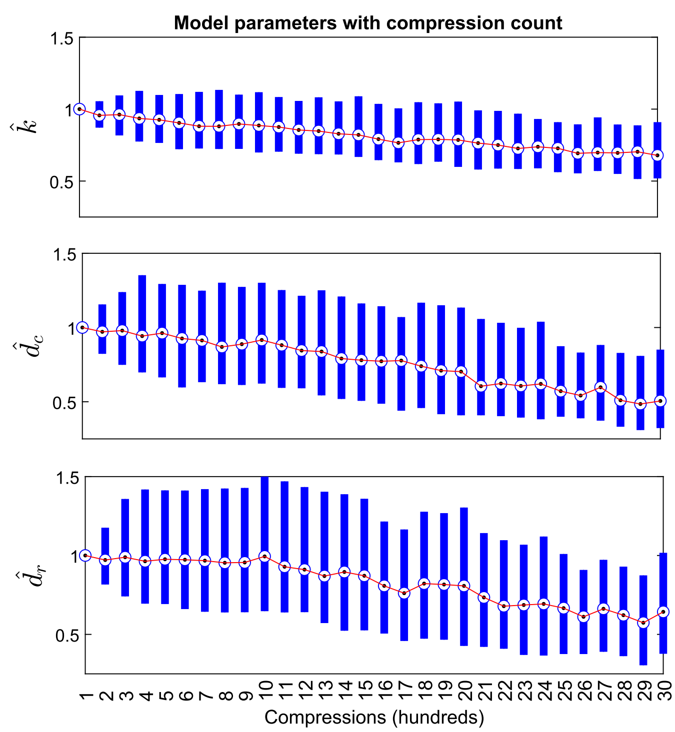

Fig. 4. Evolution of the model parameters with compression count for all patients. Values were averaged every 100 compressions and normalized to the first 100 compressions. The red line joins the median values for each set of 100 compressions, the bars represent the 25th and 75th percentiles for each set. Decreasing trends with compression count were statistically significant ($p_{trend} < 0.001$). k: elastic coefficient (stiffness); d_c: compression damping coefficient; d_r: recoil damping coefficient.

Fig. 4 shows the evolution of the model parameters with compression count, normalised to the first 100 compressions, for all patients. Significant decreasing trends were observed in the median values for the elastic and damping coefficients in all cases, regardless of patient age and sex, or receipt of bystander CPR ($p_{trend} < 0.001$). Total percentage change of the viscoelastic model parameters after 3,000 chest compressions is reported in Table 3. For all patients, the elastic coeffi-

Table 3
Total percentage change of the viscoelastic model parameters after 3,000 chest compressions.

Characteristic	n	$\frac{\Delta k}{k}$ (%)	$\frac{\Delta d_c}{d_c}$ (%)	$\frac{\Delta d_r}{d_r}$ (%)
Overall	615	↓34.6 (33.0–36.1)	↓48.8 (46.8–50.9)	↓37.2 (34.2–40.2)
Sex				
Female	208	↓38.6 (36.5–40.6)	↓54.9 (51.7–58.2)	↓48.2 (44.0–52.4)
Male	407	↓33.6 (31.8–35.5)	↓46.1 (43.9–48.3)	↓33.5 (30.6–36.4)
Age (years)				
<50	115	↓31.5 (29.7–33.3)	↓46.3 (41.6–50.9)	↓34.1 (28.3–39.9)
50–80	384	↓35.1 (32.7–37.5)	↓48.0 (45.7–50.2)	↓35.7 (32.7–38.7)
>80	116	↓38.6 (36.2–41.0)	↓49.6 (44.7–54.5)	↓50.9 (44.8–57.0)
Bystander CPR				
Yes	351	↓37.8 (36.4–39.1)	↓51.4 (49.0–53.9)	↓39.2 (36.0–42.4)
No	166	↓31.5 (28.7–34.4)	↓45.3 (40.4–50.1)	↓31.3 (27.2–35.4)

k: elastic coefficient (stiffness); d_c: compression damping coefficient; d_r: recoil damping coefficient. CPR: cardiopulmonary resuscitation. In parentheses, the 95% CI.

cient, k, decreased by 34.6%. This decrease was greater in women, in patients over 80 years old, and in patients having received bystander CPR ($p < 0.001$). The compression damping coefficient, d_c, decreased by 49%; more in women than in men, in patients between 50–80 years old and for bystander CPR patients ($p < 0.001$). The compression recoil coefficient, d_r, decreased by 37%, much more in women, in patients over 80 years old and for bystander CPR patients ($p < 0.001$).

4. Discussion

The importance of adequate chest compressions has been highlighted by resuscitation guidelines over the years. However, the well-established and universal chest compressions goals for depth, rate and recoil involve adapting manual chest compressions to wide variations of human chest characteristics among patients and during the course of resuscitation efforts. The motivation of our study was to propose a simple model to characterize the mechanical properties of adult human chest and to study how these properties vary during the course of resuscitation efforts and to facilitate comparative population analysis.

There are several studies proposing mathematical models for human chest characterization in order to better understand its response to exerted force during CPR. From studies using manikins or test bench, animal or human data, viscoelastic models which support that human chest behaves as a spring in parallel with a damper are the most widely accepted. These studies have had an impact on the design of more realistic training manikins but their mathematical complexity has made it difficult to apply them in the context of prolonged CPR.

The non-linear relationship between force and chest displacement during chest compressions shows a characteristic hysteresis [8,12,17,19], which supports the need for differentiating compression and recoil phases. Our model was effective by introducing separated damping coefficients, and fitted well to the characteristics of individual patients, irrespective of sex, age and of chest changes as compressions were prolonged (R^2 of 97.9, 95% CI 97.8–98.1). As expected, the viscoelastic model outperformed the pure elastic model in all criteria evaluated.

Damping was notably higher during recoil than during compression. During compression the chest follows the responder's action. During decompression, two phases can be distinguished [14]: one extending from the exerted peak force to the instant when the responder releases the force almost completely and the following phase, when the chest recoils unopposed. This particular feature during decompression may explain the large difference between the values of compression and recoil damping coefficients.

We found differences in the model parameters among patients at the beginning of EMS chest compressions, indicating that physiological differences may also deserve attention in CPR science. Our results suggest that chests are more elastic (less stiff) in women than in men, tend to be stiffer with age and notably more viscous during recoil in older patients.

Interestingly, all the model parameters decreased as CPR progressed. Decreasing of the elastic coefficient (by 35%) implies that the chest becomes less stiff with compression count, in line with previous research on this topic [13,17]. Damping coefficients decreased with compressions, especially during the compression phase (49%), validating the decrease in chest viscosity and the progressive resemblance of the chest to a spring in prolonged CPR. We confirmed this effect since the goodness of fit of the viscoelastic model was not affected by prolonged CPR, but the coefficient of determination for the pure elastic model increased with compressions, that is, the elastic component of the chest becomes more relevant in extended CPR. Decreasing of chest stiffness and viscosity with compression count was higher in women than in men, and with increasing age, particularly noticeable in oldest patients (see details in Table 3). Therefore, in the course of resuscitation, differences between patients are compounded by changes caused by prolonged exposure to the compression-decompression nature of CPR.

Responders from the ALS EMS agency providing the cases for this study benefited from real-time feedback on chest compression rate, depth and complete release. Despite differences between patients and changes of chest properties during the resuscitation effort, responders were able to adapt the exerted force to maintain consistency in compression depth and rate [13,14]. In fact, little improvement in chest compression depth was observed but a decrease in the maximal exerted force was observed as CPR was prolonged. This is compatible with the idea reflected in our model, that the reduction in stiffness and viscosity makes it easier to achieve the desired depth and that responders reduce their force consequently.

Several studies have put the spotlight on the fact that the significant decrease in chest stiffness with time could be due to rib or sternal fractures which commonly occur during CPR [15,17]. Recently, it has been suggested that high force variations during mechanical CPR are associated with ribcage injuries and worse outcomes [15]. We confirmed the significant decrease in chest stiffness as manual CPR progressed, but since rescuers could adapt their manoeuvre, we hypothesize that the incidence of rib cage injuries could be lower with manual CPR. In any case, evidences relating changes in chest properties and CPR-related injuries and lower outcomes may support further investigation into whether patient-tailored and time-sensitive CPR is necessary.

An issue that may deserve further investigation is that we found no differences at the beginning of EMS CPR between patients who did or did not receive bystander CPR beforehand. This was unexpected, as we anticipated that stiffness would have decreased in response to the bystander CPR. This finding may indicate that bystander CPR was not sufficient to consider this group of patients outside the general group chest characteristics. This might reflect poor quality of bystander chest compressions in terms of compression depth or chest recoil. Of note we did observe more changes with EMS CPR in patients that had received bystander CPR over time suggesting that this does indeed impact chest properties over time.

4.1. Limitations

Cases included in the study came from a single ALS EMS agency. Using our model with data from bystander CPR using AEDs could extend the results and reinforce the conclusions, although it would be necessary to equip current AEDs with the ability to record force and acceleration signals during CPR. In addition, rescuers benefited from real-time feedback on the quality of chest compressions and could administer an "adaptive" CPR to adhere to the recommendations. It might be interesting to apply our model during prolonged CPR in the absence of real-time feedback. Another limitation is that we did not have information to control change of rescuers and to assess consistency from the beginning to the end of individual chest compression series. Finally, we had no information about possible deformities or injuries during the course of CPR, or about patient chest size and body mass index. Having this information would provide valuable information to support or discourage the idea of adapting the compression manoeuvre to each patient.

5. Conclusions

Adult human chests can be accurately characterized with a simple viscoelastic model accounting for differences in compression and recoil phases. Using the model parameters we have been able to characterize differences in chest properties at the beginning of EMS-CPR. As a general rule, damping (viscosity) was higher during recoil than during compression. Women's chests were less stiff than men's, and damping during recoil increased with age. No differences were observed between patients who did or did not receive bystander CPR. Interestingly, chest stiffness and viscosity decreased as CPR progressed, more in women than in men, more as age increased and more in patients having received bystander CPR. Our findings support further investigation into whether patient-tailored and time-sensitive CPR is of value.

Declaration of competing interest

Author Digna María González-Otero is employed by Bexen Cardio, a Spanish medical device manufacturer. Bexen Cardio had no role in study funding, or study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors Sofía Ruiz de Gauna, Jose Julio Gutiérrez, Camilo Leonardo Sandoval, James Knox Russell, Izaskun Azcarate, José Antonio Urigüen, and Mohamud Ramzan Daya declare no conflict of interest.

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