

# Cardiac rehabilitation in elderly myocardial infarction survivors: focus on circulatory power

Eduardo Matos Vilela<sup>1,\*</sup>, Ricardo Ladeiras-Lopes<sup>1,2</sup>, Ana João<sup>1</sup>, Susana Torres<sup>1</sup>, José Ribeiro<sup>1</sup>, Lilibeth Campos<sup>3</sup>, Fátima Miranda<sup>3</sup>, José Pedro Nunes<sup>4</sup>, Madalena Teixeira<sup>1</sup>, Ricardo Fontes-Carvalho<sup>1,2</sup>

<sup>1</sup>Cardiology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, 4434-502 Vila Nova de Gaia, Portugal

<sup>2</sup>Department of Surgery and Physiology, Cardiovascular Research Unit (UnIC), Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal

<sup>3</sup>Physical and Rehabilitation Medicine Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, 4434-502 Vila Nova de Gaia, Portugal

<sup>4</sup>Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal

\*Correspondence: [eduardomvilela@gmail.com](mailto:eduardomvilela@gmail.com) (Eduardo Matos Vilela)

DOI: [10.31083/j.rcm2203097](https://doi.org/10.31083/j.rcm2203097)

This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Submitted: 30 April 2021 Revised: 20 June 2021 Accepted: 25 June 2021 Published: 24 September 2021

Exercise-based cardiac rehabilitation (EBCR) is paramount after an acute myocardial infarction (AMI). Older individuals have been reported as having a worse prognosis after an AMI, and some series have reported differences in the functional response to EBCR. The peak circulatory power (CP), a non-invasive parameter, has been described as a surrogate for the cardiac power, showing promising results as a comprehensive measure of the cardiovascular response. Whilst this, data concerning the impact of EBCR on CP, particularly among elderly individuals, remains elusive. To address this issue, an observational, retrospective study including all patients admitted due to an AMI who completed a phase II EBCR programme between 11/2012 and 4/2017, was conducted, with CP being analysed by a symptom-limited cardiopulmonary exercise test. A total of 379 patients, 30% aged  $\geq 65$  years-old, were included. CP significantly improved after the EBCR programme (in all patients, as well as in both subgroups). Older patients presented lower CP than their younger counterparts at the beginning and the end of the programme, while presenting smaller improvements ( $122 \pm 540$  vs  $293 \pm 638$  mmHg mL/kg/min,  $p = 0.013$ ). This was maintained after adjusting for several potential confounding factors. A contemporary EBCR programme was associated with significant improvements in CP among AMI patients. Though those aged  $\geq 65$  years-old presented smaller improvements in CP than younger individuals, these still presented significant increases in this parameter. These results highlight the importance of EBCR in this challenging higher risk group of patients.

## Keywords

Cardiac rehabilitation; Secondary prevention; Myocardial infarction

## 1. Introduction

Ischaemic heart disease (IHD) is a major cause of morbidity and mortality worldwide [1, 2]. Over the years major advances have been made in its overall management, with exercise-based cardiac rehabilitation (EBCR) being central in the current management of individuals with IHD [3–5]. Exercise has a broad impact on the cardiovascular (CV) system, on both the heart and the peripheral vasculature, being associated with several beneficial effects in terms of the CV func-

tion (such as cardiac contractility and chronotropic reserve) and risk factor control, as well as having several extra-CV actions such as effects on inflammation and on metabolic pathways [6–8].

Cardiopulmonary exercise testing (CPET) can have a central role in the assessment of individuals undergoing EBCR, as to provide integrative data on the CV, pulmonary, and musculoskeletal systems, as well as their interactions [9, 10]. Indeed, beyond its role in risk stratification and exercise prescription, several studies have highlighted the association between functional parameters and CV events [11–13].

While there are currently extensive data on the beneficial effects of EBCR in the setting of IHD, there are still some caveats related to its optimal application [14, 15]. Notably, certain subgroups of individuals such as the elderly tend to be underrepresented in different series [7, 14, 16]. Importantly, this group of patients can have a worse prognosis after an acute myocardial infarction (AMI) [4, 17, 18]. In this regard, some studies have suggested the beneficial effects of EBCR among elderly individuals, in terms of functional parameters such as the peak oxygen uptake ( $pVO_2$ ) as well as events [14, 19, 20]. We have previously shown that, in a group of AMI survivors undergoing an EBCR programme, the elderly had significant improvements in functional parameters (as assessed by  $pVO_2$  and exercise duration), though these were smaller than those presented by their younger counterparts [20]. Interestingly, differences in terms of functional parameters between older and younger individuals have also been reported in other studies [21]. As such, the overall effects of EBCR in the elderly have been the focus of heightened interest [14, 22].

Beyond classical parameters such as the  $pVO_2$ , others have emerged as to try to provide a broader view of the CV system [9]. Among these, peak circulatory power (CP) has been reported as an interesting CPET parameter, being a non-invasive surrogate of the peak exercise cardiac power

[9, 23, 24]. This parameter, which incorporates both  $pVO_2$  and systolic arterial blood pressure (SBP), provides data on both central and peripheral components of cardiac work, and can thus be of interest as to provide a more comprehensive and integrative view on the CV response to exercise [23, 25]. While this parameter has previously been studied in individuals with coronary artery disease (CAD) and in heart failure (HF), data pertaining to the effect of EBCR (particularly in older individuals) remains elusive [10, 23, 26, 27]. Given this background, in the present study we aimed at assessing the effect of an EBCR programme on CP in AMI survivors, and specifically to assess the impact of age on this parameter.

## 2. Methods

This was an observational, retrospective cohort study. The eligible population comprised all patients discharged from the Cardiology Department of the Gaia/Espinho Hospital Centre with the diagnosis of an AMI (according to the International Classification of Diseases, 9th Edition), between November of 2012 and April of 2017. To be included in the study, patients had to have completed a phase II EBCR programme (including at least two assessments in a consultation with a physical medicine specialist and performance of a CPET at the beginning and at the end of the programme) after discharge. The study was approved by the local Institutional Ethics Committee.

### 2.1 EBCR protocol

The EBCR programme has been previously described [15, 28, 29]. Briefly, this encompassed a predefined 8-week (three sessions per week) outpatient protocol. Before starting, patients were clinically assessed and underwent a CPET [14]. Training intensity was individually prescribed by an expert in EBCR (taking into consideration the heart rate obtained during CPET) [20, 28, 30].

#### 2.1.1 Cardiopulmonary exercise testing

Patients underwent a symptom limited CPET on a treadmill (Mortara XScribe; Mortara Instruments, Milwaukee, WI, USA) using either a modification of the Bruce protocol or a variation of this protocol (in highly deconditioned patients) [15]. CP (expressed in mmHg mL/kg/min) was defined as the product of  $pVO_2$  (mL/kg/min) and peak SBP (mmHg) [9, 23]; the  $VE/VCO_2$  slope (a measure of ventilatory efficiency, incorporating minute ventilation and  $VCO_2$ ) was derived by automatic linear regression from values obtained during the CPET [9, 10]. Data related to  $pVO_2$  and the respiratory exchange ratio (RER) have been previously reported [20]. Patients were not asked to discontinue beta-blockers before the test.

#### 2.1.2 Clinical and analytical variables

As previously detailed, patients were categorized according to age: <65 years-old (younger group) or  $\geq 65$  years-old (elderly group) [20].

**Table 1. Study population characteristics.**

	Younger group (n = 266)	Elderly group (n = 113)	p-value
Age (years)	53.5 $\pm$ 7.0	71.5 $\pm$ 5.7	<0.001
Male sex	209 (79%)	98 (87%)	0.064
STEMI	187 (70%)	68 (60%)	0.055
Revascularisation	239 (90%)	96 (85%)	0.174
Killip classification			<0.001
1	230 (87%)	79 (70%)	
2	27 (10%)	23 (20%)	
3	2 (1%)	9 (8%)	
4	5 (2%)	2 (2%)	
History of CAD	32 (12%)	28 (25%)	0.002
Arterial hypertension	120 (45%)	83 (73%)	<0.001
Dyslipidaemia	151 (57%)	82 (73%)	0.004
Diabetes mellitus	59 (22%)	41 (36%)	0.004
Smoking status			<0.001
- Current smoker	150 (56%)	23 (20%)	
- Former smoker	44 (17%)	30 (27%)	
Body mass index	26.8 $\pm$ 3.6	26.6 $\pm$ 3.1	0.569
Ejection fraction (%)	52 (44–56)	51 (45–57)	0.956
- Acetylsalicylic acid	263 (99%)	113 (100%)	0.257
- Clopidogrel	151 (57%)	75 (66%)	0.081
- Ticagrelor	111 (42%)	34 (30%)	0.033
- Anticoagulants	12 (5%)	15 (13%)	0.002
- ACEi/ARA	258 (97%)	107 (95%)	0.277
- BB	252 (95%)	101 (89%)	0.059
- Spironolactone	31 (12%)	19 (17%)	0.174
- Diuretics	32 (12%)	38 (34%)	<0.001
- CCB	11 (4%)	22 (19%)	<0.001
- Nitrates	16 (6%)	30 (27%)	<0.001
- Nicorandil	2 (1%)	5 (4%)	0.015
- Ivabradine	1 (1%)	1 (1%)	0.532
- Anti-diabetic agents	52 (20%)	35 (31%)	0.016
- Insulin	11 (4%)	4 (4%)	0.786
- Statins	264 (99%)	113 (100%)	0.355
Number of EBCR sessions	24 (17–26)	20 (16–24)	0.057

Legend: ACEi, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor blockers; BB, beta-blockers; CAD, coronary artery disease; CCB, calcium-channel blockers; EBCR, exercise-based cardiac rehabilitation; n, number of subjects; STEMI, ST-segment elevation acute myocardial infarction.

<sup>a</sup> Excluding insulin.

Data were collected for clinical, analytical, and echocardiographic variables according to the electronic health records (EHR). Arterial hypertension was defined according to the presence of this diagnosis in clinical files. Dyslipidaemia was defined according to previous diagnosis, or the use of antidiyslipidaemic medication prior to admission, or by having a low-density lipoprotein cholesterol  $\geq 190$  mg/dL [3]. Diabetes mellitus was defined according to previous diagnosis, or the use of antidiabetic agents prior to admission, or by having a glycated haemoglobin  $\geq 6.5\%$  [30]. Arterial hypertension, dyslipidaemia and diabetes mellitus were categorized as present or absent, in accordance with these criteria.

**Table 2. Comparison between peak circulatory power among younger and older patient groups at different stages of the exercise-based cardiac rehabilitation programme.**

	CPET1 (younger group)	CPET1 (elderly group)	<i>p</i> -value
CP (mmHg mL/kg/min)	3619 ± 1034	2999 ± 1018	<0.001
	CPET2 (younger group)	CPET2 (elderly group)	<i>p</i> -value
CP (mmHg mL/kg/min)	3911 ± 1084	3120 ± 1006	<0.001
	Delta (younger group)	Delta (elderly group)	<i>p</i> -value
CP (mmHg mL/kg/min)	293 ± 638	122 ± 540	0.013

Legend: CPET1, cardiopulmonary exercise test at the beginning of the EBCR programme; CPET2, cardiopulmonary exercise test at the end of the EBCR programme; CP, peak circulatory power.

Left ventricular ejection fraction was evaluated by the biplane Simpson's method, according to pre-discharge assessment.

## 2.2 Statistical analysis

Continuous variables were presented as mean ± standard deviation or as median [percentile 25–75, interquartile range (IQR)] according to the distribution. Categorical variables were expressed as absolute count (as well as percentage). Continuous variables were compared using unpaired or paired *t* test for those with normal distribution, or with the Mann-Whitney or Wilcoxon tests (for unmatched and matched data, respectively). The comparison of categorical variables was performed with the  $\chi^2$  test. The normality of the distribution was analysed with the Kolmogorov-Smirnov test. The Spearman correlation was used to assess the relationship between CP and the VE/VCO<sub>2</sub> slope. Linear regression analysis was used to assess if age (being ≥65 years-old) was a significant predictor of the change in CP irrespective of potential confounders. Sex, prior history of CAD, number of EBCR sessions, Killip classification, the presence of arterial hypertension, the presence of dyslipidaemia, the presence of diabetes mellitus, smoking status, and the baseline CP were forced into the model. Given that, as previously reported, RER values differed between age groups (as detailed in the Discussion), baseline RER was also included in the model [20]. Results were two-sided, and a *p* value below 0.05 was considered as significant. Statistical analysis was done using Stata 14 (Stata Corp, College Station, TX, USA).

## 3. Results

The overall study population and baseline characteristics have been previously described [20]. Briefly, a total of 379 patients (81% male gender, mean age 58.8 ± 10.6 years-old, 67% after a ST-segment elevation MI) were included in this study, of whom 30% were ≥65 years-old upon discharge (Table 1).

Patients completed a median of 22 (IQR 16–25) EBCR sessions, with older individuals attending an inferior number [20 (16–24) vs 24 (17–26), *p* = 0.057]. As previously reported, pVO<sub>2</sub> differed between groups at both the beginning and the end of the programme (19.68 ± 5.63 vs 24.15 ± 5.72 mL/kg/min and 20.47 ± 5.61 vs 25.75 ± 5.93 mL/kg/min, respectively, *p* < 0.001 for both comparisons) [20]. Peak SBP did not differ between groups at the beginning [150 (140–

**Table 3. Multivariable linear regression analysis for the evaluation of older age as a predictor of the change in peak circulatory power after an exercise-based cardiac rehabilitation programme.**

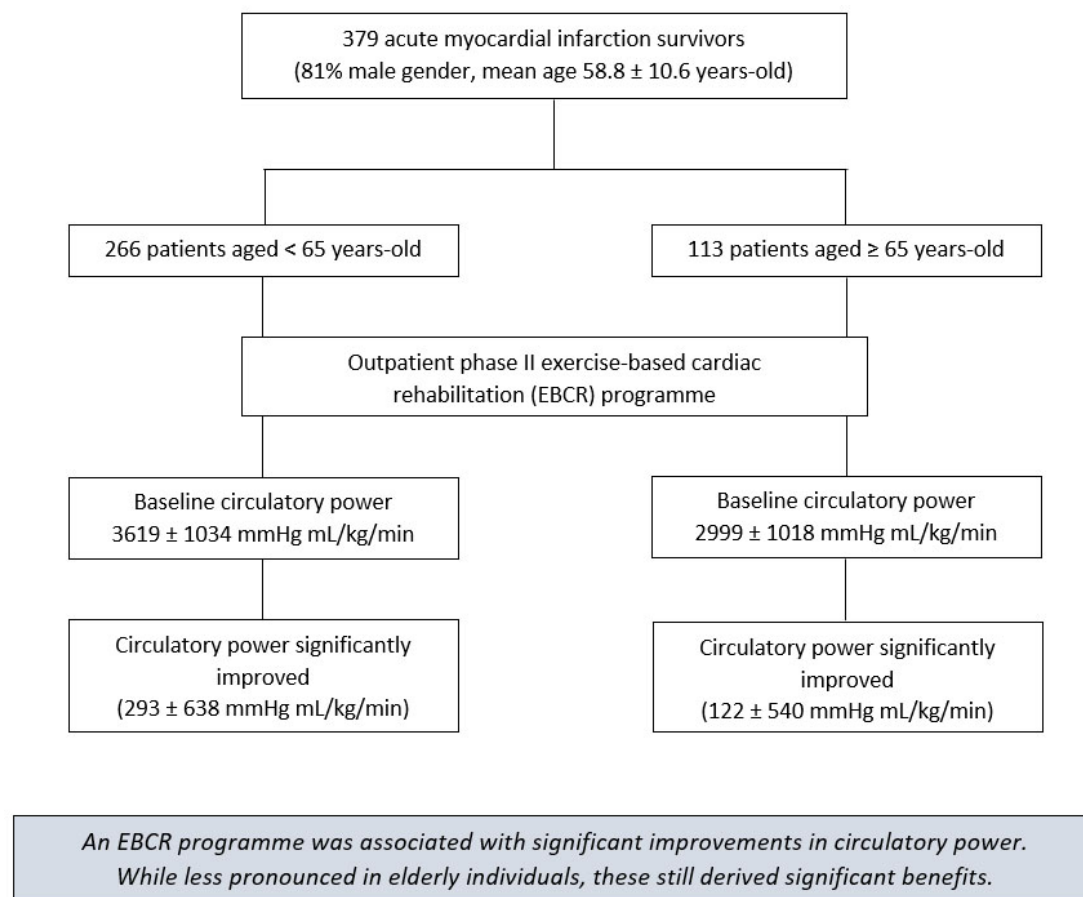
Variables	$\beta$ Coefficient	Standard error	<i>p</i> value
Sex	267.474	88.706	0.003
Age ≥65 years-old	–309.428	77.935	<0.001
Ejection fraction	41.403	70.281	0.556
Arterial hypertension	–72.074	67.512	0.286
Dyslipidaemia	131.219	68.217	0.055
Diabetes mellitus	–23.197	73.631	0.753
Smoking status	–28.980	38.881	0.457
Number of EBCR sessions	–0.658	4.716	0.889
Killip class	–87.193	55.904	0.120
Previous history of CAD	–119.542	95.022	0.209
Baseline CP	–0.209	0.036	<0.001

Legend: CAD, coronary artery disease; EBCR, exercise-based cardiac rehabilitation; CP, peak circulatory power.

160) vs 150 (140–160) mmHg, *p* = 0.289] or the end of the programme [150 (140–165) vs 150 (140–160) mmHg, *p* = 0.408], nor did its variation (*p* = 0.341).

Overall, CP significantly improved after the EBCR programme (all patients: 3676 ± 1120 vs 3434 ± 1066 mmHg mL/kg/min, *p* < 0.001; younger group: 3911 ± 1084 vs 3619 ± 1034 mmHg mL/kg/min, *p* < 0.001; older group: 3120 ± 1006 vs 2999 ± 1018 mmHg mL/kg/min, *p* = 0.018). Older individuals, however, presented lower levels of CP at both the beginning and the end of the programme (Table 2, Fig. 1). In addition, this subgroup had a smaller improvement (delta) in CP when compared to younger individuals (Table 2). The VE/VCO<sub>2</sub> slope differed between groups at both the beginning [30.0 (27.3–32.9) vs 28.3 (25.8–30.9), *p* < 0.001] and the end of the programme [29.8 (27.9–31.9) vs 28.2 (25.9–30.8), *p* < 0.001] though no difference was present in terms of its variation (delta) between groups (*p* = 0.367). No correlation was found between the variation (delta) in CP and in the VE/VCO<sub>2</sub> slope (Spearman's  $\rho$  = –0.022; *p* = 0.680).

Being aged ≥65 years-old was associated with a smaller improvement in CP irrespective of sex, prior history of CAD, Killip classification, ejection fraction, presence of arterial hypertension, dyslipidaemia, diabetes mellitus, smoking status (current or former smoking), number of EBCR sessions and



**Fig. 1. A contemporary EBCR programme was associated with significant improvements in circulatory power (CP) among a group of AMI survivors.** While the elderly had lower CP levels at the beginning and the end of the program, and had a smaller increase than younger patients, these still presented significant improvements. These results highlight the relevance of these programmes among these individuals.

baseline CP (Table 3). This result was maintained after inclusion of the baseline RER ( $p < 0.001$ ). This was also maintained after inclusion in the model of differences in medications at discharge (with an effect on blood pressure) between groups, and after including all medications potentially influencing blood pressure (i.e., angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, spironolactone, diuretics, calcium-channel blockers, nitrates, nicorandil, ivabradine;  $p < 0.001$  for both models).

#### 4. Discussion

In the current study, AMI survivors submitted to contemporary EBCR (encompassing aerobic and resistance training, in a background of optimal therapy) presented significant improvements in CP. Though older patients had lower levels of CP and had smaller increases across the programme, these still presented significant improvements.

We have previously assessed the differential impact of an EBCR programme among elderly individuals in terms of classical CPET parameters such as the  $pVO_2$ , exercise test duration and the RER [20]. The current results on CP concur with our previous observations, by depicting an overall gap be-

tween age strata, while also reinforcing the beneficial effects of a contemporary EBCR programme among both subgroups of patients [20]. Briefly, our prior data showed that although older individuals had lower functional capacity (namely a lower  $pVO_2$  and exercise duration), these also derived significant benefits from this intervention [20]. In this analysis, we have focused on CP, a parameter which could reflect the overall performance of the cardiac pump, and thus provide a non-invasive estimate of the cardiac power [23, 31, 32]. Given the data reporting the relationship between CP and CV events, we believe these results are of relevance to the current literature on this topic. This parameter, first described in 2002 by Cohen-Solal *et al.*, has been mainly explored in the setting of HF, where it has emerged as a potentially important component of the overall CPET prognostic assessment [9, 23, 31–33]. Indeed, while the central role of  $pVO_2$  in the assessment of CV disease is consensual [11, 14], CP has been reported as being able to provide additional ancillary data, namely among individuals with HF under beta-blocker therapy [34]. Interestingly, a recent report by Lala *et al.* [32] on advanced HF patients found that CP was a strong predictor of a composite outcome encompassing death, durable mechanical circu-



latory support implantation or cardiac transplantation (at 1 year). Notably, whilst its assessment in the setting of HF has expanded over the years, data on the impact of EBCR on CP remains to be further ascertained, specifically in terms of data among elderly individuals [27, 35, 36].

Ageing is associated with several changes in both the CV system and other sites, with decreases in overall functional capacity being described in different clinical settings [37, 38]. This concept has been particularly studied in terms of  $pVO_2$ , being also described in CP (which incorporates the former in its calculation) [37, 39]. The fact that similarly to the results concerning  $pVO_2$  [20], the differences in CP were maintained even after adjusting for several potential confounders highlights the concept that these could (at least partially) be attributed to differences in terms of the overall physiologic response between groups. Furthermore, a higher CV burden in the background of imbalances in terms of CV risk factors (such as arterial hypertension, dyslipidaemia, and diabetes, significantly more prevalent in older individuals) as well as of prior CAD could also be related to these findings. As reviewed by Fleg *et al.* a plethora of CV changes (potentially modulated by risk factor exposure) could be associated with pathological imbalances in the elderly, whereas extra-CV adaptations should also be kept in mind [40, 41]. As elegantly reviewed by Giallauria *et al.*, ageing is a risk factor for frailty, a multifactorial condition involving different mechanistic pathways and having numerous manifestations, being associated with impaired quality of life, lower functional capacity, and worse outcomes [18, 41–44]. In this regard, data from the SILVER-AMI study, assessing 3041 individuals aged  $\geq 75$  years-old with an AMI, reinforced this notion by reporting that mobility impairment was able to modulate the association between age and outcomes [18]. One analysis from this study also showed that in-hospital mobility was an important predictor of functional decline in this population [43]. Interestingly, a prior study on elderly individuals, addressing the potential role of pre-infarction angina, also showed that among patients with this clinical manifestation prior physical activity could affect in-hospital CV outcomes [45]. Notably, and in accordance with the current results, EBCR has been shown to be able to lead to significant improvements in functional capacity among elderly individuals, reinforcing its pivotal role in this higher risk subset of patients [20, 21, 36].

The current study assessed CP by a CPET, as a product of  $pVO_2$  and SBP, as described in the current recommendations [9, 23]. Though the use of mean arterial blood pressure has also been described, given the concordance between measurements described by Hulkkonen *et al.* [24], we believe this should not limit the interpretation of the current data. Differences in the RER should also be taken into consideration [20]. However, while this differed between groups, the mean values obtained ( $1.09 \pm 0.10$  vs  $1.09 \pm 0.13$  in the younger group;  $1.05 \pm 0.11$  vs  $1.03 \pm 0.11$  in the older group) as well as the incorporation of this parameter in the regression model should not hinder the overall assessment of the

data on CP. Another point which should be acknowledged relates to the lack of data on musculoskeletal parameters, which could have influenced test termination and as such overall assessment. Given the differences in terms of muscle mass and function associated with ageing, as well as the potential role of exercise in mitigating these changes, further studies should focus on these parameters, as to provide a broader overview on the adaptations leading to functional impairment [14, 41, 46, 47]. In addition, though the programme comprised 24 sessions, elderly patients completed a shorter number (as shown in Table 1). This is in accordance with previous reports and highlights the need for further strategies to promote both referral and overall uptake of EBCR programmes in the elderly [16, 48, 49]. Though this point should be acknowledged, given the lack of significant differences between groups and the inclusion of this parameter in the regression model, this should not preclude the interpretation of the overall results.

Interestingly, a seminal study reported on a correlation between CP and the VE/ $VCO_2$  slope [50]. While differences in terms of overall patient characteristics (particularly when considering functional capacity and ejection fraction) should be taken into consideration, the current findings concerning the VE/ $VCO_2$  slope reinforce the complexity of responses, while also reinforcing the need for further data on the overall determinants of functional capacity in this patient population. Finally, given the recently reported findings by Anand *et al.* [51] on peak stress cardiac power (as assessed by stress echocardiography) in terms of mortality and HF development among individuals with an ejection fraction above 50%, it would be interesting to have data on stress echocardiography. Given the morphological and functional changes associated with ageing, additional echocardiographic parameters (encompassing both left ventricular size and potential hypertrophy as well as diastolic function) could also be of interest [28, 38, 40]. While these points should be acknowledged and pondered with, the current results provide a pragmatic assessment on the impact of a contemporary EBCR programme on CP among elderly individuals, showcasing the relevance of this intervention among this challenging group of patients.

## 5. Limitations

Several points should be taken into consideration when interpreting the present results. As previously mentioned, this was a retrospective single-centre study, including only those individuals who completed the EBCR programme, with no control group [20]. While this should be acknowledged, prior data from randomized controlled trials in the field should be considered in the face of this caveat [27, 28]. Furthermore, patients were under optimized medical therapy (as shown in Table 1), with most being submitted to revascularization. As such, generalization of these findings to other settings should be done cautiously. Secondly, data concerning parameters such as the presence of atrial fibrillation, renal function, and haematological parameters (namely

haemoglobin) were not available for the current analysis [52]. Of note, measures of frailty could also be of interest, as this syndrome could lead to limitations in terms of functional assessments as well as EBCR uptake [42, 43]. In this regard, methodologies such as the 5-meter gait speed test and the Timed Up and Go test have been proposed as potential ancillary tools in the evaluation of these individuals [43, 44]. Given these points, further studies focusing on these parameters could allow additional tailoring of EBCR programmes among the elderly [14, 41, 44, 47]. Arterial hypertension was defined (as described in the Methods section) according to the presence of this diagnosis in the EHR. As such, some individuals under medication due to left ventricular systolic dysfunction or angina could have been missed in this categorization, whereas the lack of ambulatory blood pressure monitoring could also have been of relevance, as to appraise the potential presence of “white-coat” hypertension [4, 53]. Albeit these issues, the maintenance of the present results after inclusion of different medications (which could affect blood pressure) on the model should be considered, as further reinforcing the current findings. Thirdly, we dichotomized patients as below or  $\geq 65$  years-old. As previously discussed [20], though several definitions have been used to define elderly individuals, this cut-off was chosen given its utilization in different studies [21, 36, 45, 53], with data reporting on its importance in terms of events [54]. Whilst this, the fact that only 3.7% of individuals were aged  $\geq 80$  years-old should be considered, as further studies should specifically focus on addressing different responses according to age substrata. Finally, data on CV outcomes was not present, as our aim was to assess the impact of an EBCR programme on functional capacity, as expressed by CP. This information, along with the incorporation of serial echocardiographic assessments (namely stress echocardiography, as explored in the Discussion) should be the focus of future research, as to refine the role of CP in this setting. We believe, however, that while these hindrances should be pondered with, the current study provides novel and relevant data on the CV response to a contemporary EBCR programme among AMI survivors, with a special focus on elderly individuals, thus providing a useful framework for further studies exploring the relationship between CP improvements, potential EBCR programme design personalization and overall CV events.

## 6. Conclusions

A contemporary EBCR programme was associated with significant improvements in CP among AMI survivors. Patients aged  $\geq 65$  years-old presented significant improvements in CP, though these were less pronounced than those among younger individuals, even after adjustment for several potential confounding factors.

These results highlight the importance of EBCR among elderly individuals, given its physiological and functional benefits, in this challenging higher risk group of individuals.

## Author contributions

EMV, AJ, ST, JR, LC, FM, MT were involved in the study's conceptualization and methodology. EMV, MT were involved in the data collection. EMV, RLL, JPN were involved in the statistical analysis. EMV, RLL, MT were involved in the writing of the first draft. EMV, MT, JPN, RFC were involved in the review and editing of the study. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the local Ethics Committee (approval number: 229/2017-1).

## Acknowledgment

Not applicable.

## Funding

This study received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

## Availability of datasets

The datasets generated and/or analysed during the current study are not publicly available.

## References

- [1] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, *et al.* Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021; 143: e254–e743.
- [2] Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, *et al.* European Society of Cardiology: Cardiovascular Disease Statistics 2019. *European Heart Journal*. 2020; 41: 12–85.
- [3] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*. 2016; 37: 2315–2381.
- [4] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2018; 39: 119–177.
- [5] Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf M, Hackbusch M, *et al.* Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *European Journal of Preventive Cardiology*. 2020; 27: 1756–1774.

- [6] Vilela EM, Bastos JCC, Rodrigues RP, Nunes JPL. High-sensitivity troponin after running—a systematic review. *Netherlands Journal of Medicine*. 2014; 72: 5–9.
- [7] Fontes-Carvalho R, Vilela EM, Gonçalves-Teixeira P. The Effect of Exercise Training in Systolic and Diastolic Function. In Watson RR, Zibadi S (eds). *Lifestyle in Heart Health and Disease* (pp 153–162). Amsterdam: Elsevier. 2018.
- [8] Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. *Frontiers in Cardiovascular Medicine*. 2018; 5: 135.
- [9] Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *European Heart Journal*. 2018; 39: 1144–1161.
- [10] Mezzani A. Cardiopulmonary Exercise Testing: Basics of Methodology and Measurements. *Annals of the American Thoracic Society*. 2017; 14: S3–S11.
- [11] Ross R, Blair SN, Arena R, Church TS, Després J, Franklin BA, *et al*. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: a Case for Fitness as a Clinical Vital Sign: a Scientific Statement from the American Heart Association. *Circulation*. 2016; 134: e653–e699.
- [12] De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, *et al*. Cardiac rehabilitation fitness changes and subsequent survival. *European Heart Journal. Quality of Care & Clinical Outcomes*. 2018; 4: 173–179.
- [13] Mikkelsen N, Cadarso-Suárez C, Lado-Baleato O, Díaz-Louza C, Gil CP, Reeh J, *et al*. Improvement in  $VO_{2peak}$  predicts readmissions for cardiovascular disease and mortality in patients undergoing cardiac rehabilitation. *European Journal of Preventive Cardiology*. 2020; 27: 811–819.
- [14] Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, *et al*. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. a position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *European Journal of Preventive Cardiology*. 2020; 28: 460–495.
- [15] Vilela EM, Ladeiras-Lopes R, Ruivo C, Torres S, Braga J, Fonseca M, *et al*. Different outcomes of a cardiac rehabilitation programme in functional parameters among myocardial infarction survivors according to ejection fraction. *Netherlands Heart Journal*. 2019; 27: 347–353.
- [16] Brouwers RWM, Houben VJG, Kraal JJ, Spee RF, Kemps HMC. Predictors of cardiac rehabilitation referral, enrolment and completion after acute myocardial infarction: an exploratory study. *Netherlands Heart Journal*. 2021; 29: 151–157.
- [17] Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clinics in Geriatric Medicine*. 2009; 25: 563–77.
- [18] Gupta A, Tsang S, Hajduk A, Krumholz HM, Nanna MG, Green P, *et al*. Presentation, Treatment, and Outcomes of the Oldest-Old Patients with Acute Myocardial Infarction: the SILVER-AMI Study. *American Journal of Medicine*. 2021; 134: 95–103.
- [19] Eijssvogels TMH, Maessen MFH, Bakker EA, Meindersma EP, van Gorp N, Pijnenburg N, *et al*. Association of Cardiac Rehabilitation with all-Cause Mortality among Patients with Cardiovascular Disease in the Netherlands. *Journal of the American Medical Association*. 2020; 3: e2011686.
- [20] Vilela E, Ladeiras Lopes R, Torres S, João A, Ribeiro J, Primo J, *et al*. Differential Impact of a Cardiac Rehabilitation Program on Functional Parameters in Elderly versus Non-Elderly Myocardial Infarction Survivors. *Cardiology*. 2020; 145: 98–105.
- [21] Menezes AR, Lavie CJ, Forman DE, Arena R, Milani RV, Franklin BA. Cardiac rehabilitation in the elderly. *Progress in Cardiovascular Diseases*. 2014; 57: 152–159.
- [22] Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation*. 2010; 121: 63–70.
- [23] Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. *European Heart Journal*. 2002; 23: 806–814.
- [24] Hukkonen J, Aatola H, Pälve K, Lehtimäki T, Hutri-Kähönen N, Viikari JS, *et al*. Determinants of exercise peak arterial blood pressure, circulatory power, and exercise cardiac power in a population based sample of Finnish male and female aged 30 to 47 years: the Cardiovascular Risk in Young Finns Study. *BMC Cardiovascular Disorders*. 2014; 14: 35.
- [25] Hirashiki A, Adachi S, Nakano Y, Kamimura Y, Shimokata S, Takeshita K, *et al*. Circulatory power and ventilatory power over time under goal-oriented sequential combination therapy for pulmonary arterial hypertension. *Pulmonary Circulation*. 2017; 7: 448–454.
- [26] Castello-Simões V, Minatel V, Karsten M, Simões RP, Perseguini NM, Milan JC, *et al*. Circulatory and Ventilatory Power: Characterization in Patients with Coronary Artery Disease. *Arquivos Brasileiros de Cardiologia*. 2015; 104: 476–485.
- [27] Santos-de-Araújo AD, Bassi-Dibai D, Veiga TP, Caruso FCR, Mendes RG, Júnior JCB, *et al*. Circulatory and ventilatory power in diabetic patients: Secondary analysis of a randomized controlled trial. *Physiotherapy Research International*. 2020; 25: e1830.
- [28] Fontes-Carvalho R, Azevedo AI, Sampaio F, Teixeira M, Bettencourt N, Campos L, *et al*. The Effect of Exercise Training on Diastolic and Systolic Function after Acute Myocardial Infarction: a Randomized Study. *Medicine*. 2015; 94: e1450.
- [29] Vilela EM, Ladeiras-Lopes R, Joao A, Braga J, Torres S, Ribeiro J, *et al*. Differential impact of a cardiac rehabilitation program in functional parameters according to patient gender. *American Journal of Cardiovascular Disease*. 2020; 10: 367–375.
- [30] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, *et al*. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European Heart Journal*. 2020; 41: 255–323.
- [31] Laoutaris ID, Piotrowicz E, Kallistratos MS, Dritsas A, Dimaki N, Miliopoulos D, *et al*. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. *European Journal of Preventive Cardiology*. 2020; zwaa091.
- [32] Lala A, Shah KB, Lanfear DE, Thibodeau JT, Palardy M, Ambardekar AV, *et al*. Predictive Value of Cardiopulmonary Exercise Testing Parameters in Ambulatory Advanced Heart Failure. *Journal of the American College of Cardiology*. 2021; 9: 226–236.
- [33] Goulart CDL, Dos Santos PB, Caruso FR, Arêas GPT, Marinho RS, Camargo PF, *et al*. The Value of Cardiopulmonary Exercise Testing in Determining Severity in Patients with both Systolic Heart Failure and COPD. *Scientific Reports*. 2020; 10: 4309.
- [34] Tabet JY, Metra M, Thabut G, Logeart D, Cohen-Solal A. Prognostic value of cardiopulmonary exercise variables in chronic heart failure patients with or without beta-blocker therapy. *American Journal of Cardiology*. 2006; 98: 500–503.
- [35] Aguiar Rosa S, Abreu A, Marques Soares R, Rio P, Filipe C, Rodrigues I, *et al*. Cardiac rehabilitation after acute coronary syndrome: do all patients derive the same benefit? *Revista Portuguesa De Cardiologia*. 2017; 36: 169–176.
- [36] Prescott E, Eser P, Mikkelsen N, Holdgaard A, Marcin T, Wilhelm M, *et al*. Cardiac rehabilitation of elderly patients in eight rehabilitation units in western Europe: Outcome data from the EU-CaRE multi-centre observational study. *European Journal of Preventive Cardiology*. 2020; 27: 1716–1729.
- [37] Hawkins S, Wiswell R. Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. *Sports Medicine*. 2003; 33: 877–888.
- [38] Roh J, Rhee J, Chaudhari V, Rosenzweig A. The Role of Exercise in Cardiac Aging: from Physiology to Molecular Mechanisms. *Circulation Research*. 2016; 118: 279–295.

- [39] Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, *et al.* Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2009; 16: 249–267.
- [40] Fleg JL, Strait J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. *Heart Failure Reviews*. 2012; 17: 545–554.
- [41] Vigorito C, Abreu A, Ambrosetti M, Belardinelli R, Corrà U, Cupples M, *et al.* Frailty and cardiac rehabilitation: a call to action from the EAPC Cardiac Rehabilitation Section. *European Journal of Preventive Cardiology*. 2017; 24: 577–590.
- [42] Giallauria F, Di Lorenzo A, Venturini E, Pacileo M, D'Andrea A, Garofalo U, *et al.* Frailty in Acute and Chronic Coronary Syndrome Patients Entering Cardiac Rehabilitation. *Journal of Clinical Medicine*. 2021; 10: 1696.
- [43] Hajduk AM, Dodson JA, Murphy TE, Tsang S, Geda M, Ouellet GM, *et al.* Risk Model for Decline in Activities of Daily Living among Older Adults Hospitalized with Acute Myocardial Infarction: the SILVER-AMI Study. *Journal of the American Heart Association*. 2020; 9: e015555.
- [44] Mone P, Pansini A. Gait Speed Test and Cognitive Decline in Frail Women with Acute Myocardial Infarction. *American Journal of the Medical Sciences*. 2020; 360: 484–488.
- [45] Abete P, Cacciatore F, Morte DD, Mazzella F, Testa G, Galizia G, *et al.* Joint effect of physical activity and body mass index on mortality for acute myocardial infarction in the elderly: role of preinfarction angina as equivalent of ischemic preconditioning. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2009; 16: 73–79.
- [46] Distefano G, Goodpaster BH. Effects of Exercise and Aging on Skeletal Muscle. *Cold Spring Harbor Perspectives in Medicine*. 2018; 8: a029785.
- [47] Kitzman DW, Whellan DJ, Duncan P, Pastva AM, Mentz RJ, Reeves GR, *et al.* Physical Rehabilitation for Older Patients Hospitalized for Heart Failure. *The New England Journal of Medicine*. 2021. (in press)
- [48] Young L, Zhang Q, Lian E, Roberts K, Weintraub N, Dong Y, *et al.* Factors Predicting the Utilization of Center-Based Cardiac Rehabilitation Program. *Geriatrics*. 2020; 5: 66.
- [49] Martin BJ, Hauer T, Arena R, Austford LD, Galbraith PD, Lewin AM, *et al.* Cardiac rehabilitation attendance and outcomes in coronary artery disease patients. *Circulation*. 2012; 126: 677–687.
- [50] Tabet J, Beauvais F, Thabut G, Tartière J, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO<sub>2</sub> slope in chronic heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2003; 10: 267–272.
- [51] Anand V, Kane GC, Scott CG, Pislaru SV, Adigun RO, McCully RB, *et al.* Prognostic value of peak stress cardiac power in patients with normal ejection fraction undergoing exercise stress echocardiography. *European Heart Journal*. 2021; 42: 776–785.
- [52] Takano N, Amiya E, Oguri G, Nakayama A, Taya M, Nakajima T, *et al.* Influence of atrial fibrillation on oxygen uptake and exercise tolerance in cardiovascular patients; close association with heart rate response. *International Journal of Cardiology*. 2019; 22: 84–91.
- [53] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Journal of Hypertension*. 2018; 39: 3021–3104.
- [54] Frengley JD, Sansone GR, Alba A, Uppal K, Kleinfeld J. Influence of Age on Rehabilitation Outcomes and Survival in Post-Acute Inpatient Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2011; 31: 230–238.