Am J Cardiovasc Dis 2020;10(4):367-375
www.AJCD.us /ISSN:2160-200X/AJCD0116265

Original Article

Differential impact of a cardiac rehabilitation program in functional parameters according to patient gender

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Received June 14, 2020; Accepted August 24, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: Introduction: Exercise-based cardiac rehabilitation (EBCR) programs are of paramount importance in the management of acute myocardial infarction (AMI) survivors. Albeit this, female patients tend to be less referred for these programs, while also having a poorer prognosis. We aimed at assessing the impact of a contemporary EBCR program on functional parameters after an AMI, and specifically the impact of gender on its potential benefits. Methods: Observational, retrospective cohort study including all patients admitted to a tertiary center due to an AMI who completed a phase II EBCR program after discharge, between November 2012 and April 2017. Functional parameters were assessed by a symptom-limited cardiopulmonary exercise test (CPET). Patients were dichotomized according to gender. Results: A total of 379 patients were included, 19% of whom were women. After the program, peak oxygen uptake (pVO2) and exercise duration increased significantly ($P<0.001$). Though female patients presented a lower pVO2 and completed a shorter CPET at both the beginning and end of the study, there were no differences in the magnitude of improvement in these parameters between both groups [pVO2 delta 1.37 ± 3.08 vs 1.31 ± 2.62 mL/kg/min, $P=0.876$; CPET duration delta 120 (60-167) vs 85 (60-146), $P=0.176$]. Conclusions: A contemporary EBCR program was associated with significant improvements in functional parameters, as assessed by CPET. Though female patients had lower levels of pVO2, the benefits of this program were similar among groups. These results highlight the importance of EBCR among this higher risk subset of patients.

Keywords: Acute myocardial infarction, cardiac rehabilitation, secondary prevention

Introduction

Exercise-based cardiac rehabilitation (EBCR) programs have a central role in the optimal management of patients after an acute myocardial infarction (AMI) [1, 2]. This notion stems from several studies which highlight the important benefits associated with EBCR, in terms of both morbidity and mortality [3-5]. Exercise can exert a plethora of physiological effects in the cardiovascular, pulmonary and musculoskeletal systems, being associated with several changes ranging from improvements in cardiac contractility, microvascular function and modulation of endothelium-derived relaxation, to anti-inflammatory effects and improvements in both metabolic substrate utilization and overall aerobic capacity [6-9].

Though the current role of EBCR programs in the setting of AMI is consensual [1, 2], there are still important hinderances concerning their optimal application [1, 4, 10]. Notably, women tend to be less referred than men for these programs and to complete a shorter number of sessions [11-13]. This is particularly important given that several studies have also shown that women tend to be offered less guideline-directed optimal management strategies than men [2, 13, 14]. Given the potential worse prognosis of female patients after an AMI (a fact partially explained by differences in overall cardiovascular risk profiles, presentation and therapy), optimizing secondary prevention measures is of paramount relevance among this subgroup of patients [2, 15-18]. As such, there has been considerable interest in the potential role of

EBCR in the mitigation of residual risk among this particularly challenging and higher-risk patient population [6, 11, 12].

Cardiopulmonary exercise testing (CPET) can provide a comprehensive and global assessment of the impact of EBCR as it can provide detailed data pertaining to several of its target actions (namely in terms of the cardiovascular, pulmonary and musculoskeletal systems, as well as their interactions) [19, 20]. Several studies have also reported on the association between higher levels of overall physical capacity (sometimes described as cardiorespiratory fitness), as assessed by functional parameters [such as the peak oxygen consumption (pVO2)] and cardiovascular events, in different clinical settings [19, 21].

Given this background, we hypothesized that a contemporary EBCR program would be of significant benefit among female patients in terms of functional parameters, though these could differ from that in male patients. As such, we designed the present study in order to assess the impact of an EBCR program in functional parameters among AMI survivors, and specifically the potential differences according to patient gender.

Materials and methods

This was an observational, retrospective cohort study. The eligible population comprised all patients discharged from the Cardiology Department of the Gaia/Espinho Hospital Center (a tertiary care hospital in Portugal) with the diagnosis of an AMI (according to the International Classification of Diseases, 9th edition), between November 2012 and April 2017. In order to be included, patients had to have completed a phase II EBCR program (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 program). The study was approved by the local Institutional Ethics Committee.

EBCR protocol

The EBCR program has been previously described [20-23]. Briefly, this consisted of a predefined eight-week (three sessions per week) outpatient protocol, including endurance and resistance training. Training intensity was individually prescribed by a physical medicine specialist expert in EBCR, and fatigue was measured with the Borg scale [22].

Cardiopulmonary exercise testing

At the beginning and at the end of the program, 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) [20, 24]. The following variables were calculated: pVO2 measured in mL/kg/min; percent-predicted pVO2 (according to reference values by Wasserman/Hansen [25]); peak respiratory exchange ratio (RER), defined by the ratio of CO_2 production to O_2 consumption at peak effort; exercise duration expressed in seconds. Patients were not asked to discontinue betablockers before the test.

Clinical, analytical and echocardiographic variables

Data were collected for clinical, analytical, and echocardiographic variables according to the electronic health records. Patients were dichotomized according to gender (female vs male patients).

Arterial hypertension was defined according to the presence of this diagnosis in clinical files. Dyslipidemia was defined according to previous diagnosis, or the use of anti-dyslipidemic medication prior to admission, or by having a low-density lipoprotein cholesterol ≥ 190 mg/dL [1]. Diabetes mellitus was defined according to previous diagnosis, or the use of antidiabetic agents prior to admission, or by having a glycated hemoglobin ≥ 6.5% [26]. Left ventricular ejection fraction (EF) was evaluated by the biplane Simpson's method and collected according to pre-discharge assessment.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median (percentile 25-75, interquartile range [IQR]) according to the normality of the distribution. Categorical variables were expressed as absolute count and percentage. Continuous variables were compared using unpaired or paired t tests for those with normal distribution, or with the

Table 1. Study population characterization

	All patients (n=379)	Male sex (n=307)	Female sex (n=72)	*p* value#
Age (years)	58.8 ± 10.6	59.0 ± 10.6	58.2 ± 10.8	0.581
STEMI	255 (67%)	207 (67%)	48 (67%)	0.902
Revascularization	335 (88%)	278 (91%)	57 (79%)	0.007
Killip classification				0.042
1	309 (82%)	257 (84%)	52 (73%)	
2	50 (13%)	35 (11%)	15 (21%)	
3	11 (3%)	10 (3%)	1 (1%)	
4	7 (2%)	4 (1%)	3 (4%)	
History of CAD	60 (16%)	48 (16%)	12 (17%)	0.829
Arterial hypertension	203 (54%)	160 (52%)	43 (60%)	0.244
Dyslipidemia	233 (61%)	198 (65%)	35 (49%)	0.013
Diabetes mellitus	100 (26%)	81 (26%)	19 (26%)	0.999
Smoking status				<0.001
Current smokers	173 (46%)	144 (47%)	29 (40%)	
Former smokers	74 (20%)	73 (24%)	1 (1%)	
Body mass index	26.7 ± 3.5	26.7 ± 3.4	26.8 ± 3.7	0.774
Ejection fraction (%)	52 (44-56)	52 (44-57)	52 (44-56)	0.959
Medication at discharge				
Acetylsalicylic acid	376 (99%)	305 (99%)	71 (99%)	0.525
Clopidogrel	226 (60%)	189 (62%)	37 (51%)	0.113
Ticagrelor	145 (38%)	113 (37%)	32 (44%)	0.230
Anticoagulants	27 (7%)	22 (7%)	5 (7%)	0.948
ACEi/ARB	365 (96%)	300 (98%)	65 (90%)	0.003
BB	353 (93%)	284 (93%)	69 (96%)	0.315
Spironolactone	50 (13%)	42 (14%)	8 (11%)	0.562
Diuretics	70 (18%)	55 (18%)	15 (21%)	0.566
CCB	33 (9%)	24 (8%)	9 (13%)	0.205
Nitrates	46 (12%)	37 (12%)	9 (13%)	0.917
Nicorandil	7 (2%)	5 (2%)	2 (3%)	0.515
Ivabradine	2 (1%)	1 (1%)	1 (1%)	0.262
Anti-diabetic agents*	87 (23%)	72 (23%)	15 (21%)	0.634
Insulin	15 (4%)	8 (3%)	7 (10%)	0.005
Statins	377 (99%)	305 (99%)	72 (100%)	0.492
Number of EBCR sessions	22 (16-25)	23 (17-26)	21 (15-24)	0.041

Abbreviations: ACEi = angiotensin-converting enzyme inhibitors; ARB = 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; * excluding insulin; # comparison between male and female patients.

Mann-Whitney or Wilcoxon tests (for unmatched and matched data, respectively). Categorical variables were compared with the χ^2 test. Normality of distribution was assessed using the Kolmogorov-Smirnov test. Linear regression analysis was used to evaluate if gender was a significant predictor of the change in pVO2 irrespective of potential confounders. Age (patients dichotomized as being 65 years-old or older vs under 65 years-old), revascularization, Killip classification, arterial hypertension, dyslipidemia, diabetes mellitus, smoking status, number of EBCR sessions, baseline pVO2 and RER were forced into the model. Though different cut-offs for age have been used for dividing younger and older patients, given data which support 65 years old as having an impact on functional parameters [24], this value was used in the present model.

All results were two-sided, and a *p* value <0.05 was considered as significant. Statistical analysis (as described above) was done using Stata 14 (Stata Corp, College Station, TX, USA).

Results

Study population characterization

A total of 381 events were included. Two patients were represented twice (given that they suffered an AMI on two distinct occasions), and in these only the first event was considered for the analysis; as such a total of 379 patients were represented, 19% of whom were women (**Table 1**). Significant differences between female and male patients were present in terms of revascularization, Killip classification, the presence of dyslipidemia, smoking status and number of EBCR sessions attended (**Table 1**). As for medications at discharge,

Table 2. Comparison between male and female patients in terms of functional parameters, at different stages of the exercise-based cardiac rehabilitation program

	CPET1 (male sex)	CPET1 (female sex)	*p* value
Peak VO2 (mL/kg/min)	23.79 ± 5.88	18.70 ± 4.91	<0.001
Percent-predicted peak VO2	78.38 ± 16.55	82.99 ± 17.79	0.037
RER	1.08 ± 0.13	1.02 ± 0.12	<0.001
Duration (seconds)	600 (480-660)	480 (368-593)	<0.001
	CPET2 (male sex)	CPET2 (female sex)	*p* value
Peak VO2 (mL/kg/min)	25.16 ± 6.21	20.01 ± 4.94	<0.001
Percent-predicted peak VO2	82.72 ± 16.77	88.57 ± 17.44	0.009
RER	1.08 ± 0.11	1.05 ± 0.11	0.036
Duration (seconds)	720 (600-780)	548 (480-662)	<0.001
	Delta (male sex)	Delta (female sex)	*p* value
Peak VO2 (mL/kg/min)	1.37 ± 3.08	1.31 ± 2.62	0.876
Percent-predicted peak VO2	4.34 ± 9.62	5.58 ± 12.89	0.359
RER	0.002 ± 0.114	0.030 ± 0.102	0.054
Duration (seconds)	120 (60-167)	85 (60-146)	0.176

Abbreviations: CPET1 = cardiopulmonary exercise test at the beginning of the EBCR program; CPET2 = cardiopulmonary exercise test at the end of the EBCR program; RER = respiratory exchange ratio.

there were significant differences between groups in the prescription of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARB) and insulin (**Table 1**).

Overall impact of the EBCR program in functional parameters

After the EBCR program [median 22 (16-25) sessions] there were significant improvements in pVO2 (24.18 ± 6.31 vs 22.82 ± 6.04 mL/kg/min, P<0.001), percent-predicted pVO2 (83.83 ± 17.04 vs 79.25 ± 16.87%, P<0.001) and CPET duration [661 (540-780) vs 542 (480-660) s, P<0.001]. There were no differences in the RER (1.08 ± 0.11 vs 1.07 ± 0.13, P=0.212). These significant improvements were present in both male [pVO2 25.16 ± 6.21 vs 23.79 ± 5.88 mL/kg/min, percent-predicted pVO2 82.72 ± 16.77 vs 78.38 ± 16.55%, CPET duration 720 (600-780) vs 600 (480-660) s; P<0.001 for all comparisons] and female patients [pVO2 20.01 ± 4.94 vs 18.70 ± 4.91 mL/kg/min, percent-predicted pVO2 88.57 ± 17.44 vs 82.99 ± 17.79%, CPET duration 548 (480-662) vs 480 (368-593) s; P<0.001 for all comparisons]. There were no differences in the RER for male patients (1.08 ± 0.11 vs 1.08 ± 0.13, P=0.779), whereas these were present for female patients (1.05 ± 0.11 vs 1.02 ± 0.12, P=0.015).

Differential impact of the EBCR program according to gender

Female patients presented lower levels of pVO2 and completed a shorter duration of CPET at both the beginning and the end of the EBCR program (**Table 2**). Female patients also presented lower levels of RER, as compared with male patients (beginning of the EBCR program: 1.02 ± 0.12 vs 1.08 ± 0.13, P<0.001; end of the EBCR program: 1.05 ± 0.11 vs 1.08 ± 0.11, P= 0.036). Notably, female patients presented higher levels of percent-predicted pVO2 at both time points of the EBCR program. When assessing the variation (delta) in terms of pVO2 and CPET duration, there were no differences between female and male patients (**Table 2**). The same result was present with regards to the variation in the RER (**Table 2**). In the linear regression analysis model, after adjustment for several potential confounders, gender was not significantly associated with a differential response in terms of improvement in pVO2 (**Table 3**).

Discussion

In this study on a contemporary cohort of AMI survivors, we found significant improvements in functional parameters after an EBCR program. Notably, although female patients had lower levels of pVO2 and complete a shorter duration of CPET at both the beginning and end of the EBCR program, there were no differences in the magnitude of improvement in these parameters between both groups of patients.

The present results, and specifically those concerning female patients, add to the current evidence-base on the role of EBCR after an AMI [2, 13, 27]. Given studies suggesting a worse prognosis among women after an AMI [14-16], and the myriad of data concerning the association between pVO2 and cardiovascular events [10, 19, 21, 28], we believe these results could be

Table 3. Multivariable linear regression analysis for the evaluation of gender as a predictor of the change in peak VO2 after an exercise-based cardiac rehabilitation program

Variables	β Coefficient	Standard error	*p* value	95% confidence interval
Age ≥ 65 years-old	-1.592	0.382	<0.001	-2.344 to -0.841
Arterial hypertension	-0.878	0.331	0.008	-1.529 to -0.227
Diabetes mellitus	-0.010	0.364	0.977	-0.727 to 0.706
Gender	0.810	0.435	0.063	-0.046 to 1.666
Revascularization	0.528	0.487	0.279	-0.430 to 1.485
Killip class	-0.307	0.262	0.242	-0.823 to 0.209
Dyslipidemia	0.683	0.319	0.033	0.056 to 1.309
Smoking status	-0.300	0.188	0.112	-0.670 to 0.070
Number of EBCR sessions	0.008	0.023	0.725	-0.037 to 0.053
Baseline pVO2	-0.158	0.033	<0.001	-0.224 to -0.092
Baseline RER	-1.155	1.337	0.388	-3.784 to 1.475

Abbreviations: EBCR = exercise-based cardiac rehabilitation; pVO2 = peak VO2; RER = respiratory exchange ratio.

of clinical importance. The degree of improvements in pVO2 observed in the present report is within the range described in other studies as being of clinical relevance, as elegantly reviewed by Franklin et al. [19]. As described in a seminal study by Kavanagh et al., reporting on 2380 women who were referred for cardiac rehabilitation due to coronary heart disease (CHD), a 1 mL/kg/min improvement in pVO2 (when assessed as a continuous variable) was associated with a 10% reduction in cardiac mortality [29]. Indeed, a recent observational study on patients with CHD again highlighted this notion, showing that improvements of 1 mL/kg/min in pVO2 were associated with a 10% reduction in all-cause mortality [28]. Interestingly, in this study (were 73% of patients were males), female patients were less likely to be responders to the cardiac rehabilitation program (a finding possibly explained by differences in terms of overall patient characteristics) [28]. Another study reporting on patients who attended EBCR due to CHD (24% of whom were women) also showed significant functional improvements (for both genders), while there were no differences in the magnitude of improvement [1.5 ± 1.2 metabolic equivalents of task (METs) in men vs 1.2 ± 1.1 METs in women, P=0.08] [30].

In our study, women presented lower levels of functional capacity (in terms of pVO2) at both timepoints of the EBCR program (18.70 ± 4.91 vs 23.79 ± 5.88 at the beginning, 20.01 ± 4.94 vs 25.16 ± 6.21 mL/kg/min at the end; P<0.001 for both comparisons). The present data are also in accordance with the current literature, which describes pVO2 values (as expressed in relation to body weight) circa 15 to 30% lower in women than in men [10, 27]. Several potential mechanistic pathways for this finding have been proposed, relating both to differences in terms of the cardiovascular system *per se* as well as differences in the musculoskeletal system (both in terms of fibre type and contractility), overall nutritional balance (and nutrient homeostasis), and other pathways relating to diverse mechanisms such as the endocrine response to exercise training and the levels of sex hormones [27]. Importantly, however, in the present study the percent-predicted pVO2 was higher in female patients at both time points (**Table 2**). These results once more showcase the importance of taking into consideration the potential physiological differences between groups, being in accordance with other data which report on higher levels of percent-predicted pVO2 in women submitted to exercise, as compared to their male counterparts [31]. The same notion should be kept in mind when interpreting the results of the linear regression analysis. Indeed, the results of the linear regression analysis (accounting for multiple potential confounding factors) further stress the hypothesis that the results relating to pVO2 may be, at least in part, related to physiological differences between groups as well as their possible toll of the overall cardiovascular response and associated risk factors. As recently extensively reviewed by Witvrouwen et al., there are multiple physiological differences between genders which could have a possible impact on the response to exercise training [10, 27]. Additionally, there were significant differences between groups in terms of the RER. Although these should be kept in mind, given their absolute levels (as well as their inclusion in the regression model), we believe these results should not hinder the interpretation of the present data.

The program design consisted of 24 sessions. Albeit this, patients completed a median of 22 (16-25) sessions. In accordance with previous data [11, 13], female patients completed a shorter course of EBCR [21 (15-24) vs 23 (17-26), P=0.041]. This showcases the need for ancillary strategies to promote not only the referral of women for these programs (as supported by the present data on functional parameters) but also on bridging the gap concerning compliance to these interventions [11-13]. Several issues have previously been described as barriers to both enrolment and completion of EBCR programs, namely among female patients [11-13]. Also, though patients were enrolled briefly after discharge, specific data concerning timing of referral was not available for the present study [6]. It should also be considered that data on body composition and nutritional status were also not available for the present analysis. Given the previously described differences between genders [27], it would be of interest for future studies to explore the effect of EBCR on these parameters, as to allow a better clarification on the role of EBCR as a whole in this group of patients, while also allowing adequate tailoring in order to fully address present unmet needs among this higher risk subset of individuals.

Limitations

Several caveats should be taken into consideration when interpreting the present results. Firstly, this was an observational retrospective study, with no control group. Also, only patients who completed an EBCR program were included. However, given current data from both randomized controlled trials as well as subsequent meta-analysis showing the beneficial effects of EBCR [3-5, 22], this should not hinder the interpretation of the present data. Secondly, we did not assess the variation in EF during the program. Though we believe these data could be of interest, the absence of differences between groups in terms of EF should be considered in the face of this limitation. In addition, several studies have previously extensively addressed this issue [6, 20]. Thirdly, and in accordance with previous studies which show that women tend to be less represented in these programs [4, 11-13], female patients comprised 19% of the total individuals. While this caveat should be acknowledged, both the contemporary setting of this study (as depicted in **Table 1**) and the rigorous and robust assessment of functional capacity (by a symptom-limited CPET), as well as the inclusion of several potential confounders in the multivariable linear regression analysis, should be considered when interpreting the present results. Fourthly, this study concerned AMI survivors treated at a single tertiary center, who were discharged under optimal medical therapy and most of whom were subjected to revascularization during hospitalization. Therefore, generalization to other settings should be done with caution [1, 2, 13].

Finally, we aimed at assessing the impact of an EBCR program on functional parameters. Though data in terms of cardiovascular events was not present, given contemporary reports on EBCR [3-5], and the important association between functional parameters and cardiovascular events (as discussed above) [19, 21, 28], this should not negatively affect the interpretation of the present findings. As highlighted in the Discussion, there are several important physiological differences between genders, and these can have an important interaction with both the expression of cardiovascular disease as well as the response to exercise training [10, 13, 27]. Given these specificities, it would be of interest for future studies to address the role of additional interventions in the modulation of these parameters. Also, data on psychological items as well as on quality of life measures were not present. Though these issues have been subjected to previous study [12, 13, 27, 32], it would be of relevance to have further data in order to allow further personalization of these programs, a notion which has been gaining the spotlight [27]. Furthermore, although advice on a healthy lifestyle (encompassing issues related to physical exercise and diet) was part of the overall management by the attending physician, no specific protocol was present. Though these limitations should be considered, patients who attended the EBCR program presented significant improvements in functional parameters, highlighting the relevance of this intervention among a contemporary subset of AMI survivors.

Conclusions

The performance of a phase II EBCR program was associated with significant functional benefits among a contemporary cohort of AMI patients. These were present among both female and male patients. Although female patients presented a worse functional capacity (as assessed by pVO2 and CPET duration) at the beginning and at the end of the program, they presented the same functional benefits as their male counterparts. These results highlight the importance and relevance of EBCR programs among this higher risk subset of patients.

Disclosure of conflict of interest

None.

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