Exercise-based cardiac rehabilitation: a systematic review

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ABSTRACT

The aim of this systematic review was to determine the effect of exercise-based cardiac rehabilitation (EBCR) on mortality, modifiable risk factors and quality of life related to health, in patients with coronary artery disease. Only Randomized Controlled Trials (RCTs) with follow up equal or higher than six months published between 1990 and 2004 were analyzed. The criteria proposed by the Clinical Practice Guideline: cardiac rehabilitation was adopted to evaluate the selected studies. Twenty-one RCTs met the inclusion criteria in a total of 2220 patients aged between 49 and 63 years of age (86% male). The majority of RCTs results were favorable to EBCR when compared to usual care (control) regarding total and cardiac mortality. This fact was also observed for the reinfarction and myocardial revascularization rates. EBCR results about the modifiable risk factors and quality of life were not conclusive when compared to control intervention, although some studies have presented statistical differences in favor of EBCR. This review confirms the benefits of EBCR therapeutic approach on coronary diseased, showing reduced rates of cardiac and all causes mortality, besides the reduced coronary events occurrence, such as myocardial revascularization and reinfarct rate. There was a favorable trend toward EBCR utilization considering the modified risk factors and quality of life. In addition, it seems that exercise *per si* constitutes the major responsible factor for the favorable intervention results related to the studied endpoints.

Keywords: Cardiac rehabilitation. Exercise-based cardiac rehabilitation. Cardiovascular mortality. Coronary artery disease.

INTRODUCTION

Cardiac rehabilitation (CR) may be defined as a sum of interventions that guarantee the improvement of the physical, psychological and social conditions of patients with post-acute and chronic diseases, enabling them by their own means, to preserve and recover their functions in society, and through health behavior minimize or revert the disease's progression[1]. Therefore, the CR objectives are to attenuate the harmful effects derived from a cardiac event, to prevent a subsequent infarct[2-3] and recurrent hospitalization[4], to reduce health costs[5], to act on the changeable risk factors associated to cardiovascular sideases[6-8], to improve life quality[9-10] of these patients and to decrease the mortality rates[2,11]. The CR is indicated to patients who received a diagnosis of acute myocardial infarct or were submitted to myocardial revascularization or cardiac transplant, and also to those with stable chronic angina and chronic cardiac insufficiency.

The CR is a complex intervention which may involve several therapies, including nutritional counseling, psychological aid and orientation about risk factors and drugs administration. Nonetheless, great part of the CR programs success is due to the physical exercise-based therapy, which is considered the central strategy of these programs[12-14]. Recent meta-analyses[13,15] demonstrated that the cardiac rehabilitation with emphasis on exercise (CREE) was associated to a decrease of 20 to 30% in the mortality rates, when compared to the usual care (without exercise). However, there is a problem in the application of these results in the clinical practice yet, enormously due to the methodological limitations and the conflicting results of the studies concerning the topic. Yet, few reviews previously published dedicated to discuss the CREE effects on the changeable cardiac risk factors and the life quality of patients with known coronary arterial disease.

The aim of this article was to determine, through a systematized review the effect of the CREE on the mortality, changeable risk factors and life quality health related in patients with coronary arterial disease.

METHODS

Search strategies

The most relevant studies originally published in English, during the beginning of the XXI century and the last decade of the XX century (January, 1990 to October, 2004), having as reference the MEDLINE database (National Library of Medicine) and the Cochrane Library were analyzed. Only the controlled and randomized clinical essays were analyzed (CRCE) with the purpose to select the studies of greater scientific evidence. Moreover, studies selected by systemized reviews, with or without meta-analysis, previously published were analyzed. The search strategy adopted the following key-words: *cardiac rehabilitation, exercise, exercise-based cardiac rehabilitation and coronary heart disease*. The following terms were applied in order to identify the studies outlines: *randomized controlled trial, review and meta-analysis*. The inclusion and exclusion criteria were freely and independently applied by two experienced reviewers who study the topic and judged the selected studies from the points raised in each item exposed (board 1).

RESULTS

44 studies were identified, involving CR and exercise. Nonetheless, based on the criteria previously defined, only 50 were part of this review, among them 22 CRCE. The CRCE and the remaining selected studies were judged by the independent reviewers who used the evidence indices suggested by the *Clinical Practice Guideline: cardiac rehabilitation*[16] published by the *National Institute of Health* of the USA as reference. Finally, for inclusion in our analysis, only the CRCE were considered, that is, the ones that presented evidence "A" index.

Results for total mortality, cardiac mortality, re infarct, myocardial revascularization with arterial implant (MRV) and percutaneous transluminal coronary angioplasty (PTCA) – the analyzed studies involved 2,220 patients with age range between 49

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BOARD 1 Inclusion and exclusion criteria and main results	
Inclusion criteria	
Outlines	• controlled and randomized clinical essays with follow-up equal or longer than six months • revision study • systematized reviews with meta-analysis
Patients	• with myocardial infarct • myocardial revascularization through bypass implant (MRV) or through percutaneous transluminal coronary angioplasty (PTCA) • angina *pectoris* • coronary arterial disease defined through angiography
Intervention	• CREE in combination or not with conventional cardiac rehabilitation (educational and/or psychosocial orientation) • CR based on usual care without any type of exercise, although medication therapy may be included • exercise programs, supervised or not, performed in clinics, hospitals or in communities
Idiom	• only in English
Exclusion criteria	
Outlines	• unclear or badly-described randomized process • outline in which the control group also performed exercise
Patients	• inappropriate patients
Intervention	• unclear, badly-described or inadequate interventions
Publishing format	• only summarized
Main clinical-epidemiological endpoints	
• total mortality • cardiac mortality • myocardial infarct rate • occurrence of coronary revascularization procedures • changeable cardiac risk factors (smoking, systemic arterial hypertension and hypercholesterolemia) • health-related life quality	

and 63 years, being 86% from the male gender (1,913 men). The majority of the CRCE presented results favorable to the CREE when compared to the usual care, having some studies found indices of up 89% of reduction in the mortality total[2]. Such fact was also observed for the remaining coronary events considered, namely, re infarct rate and MRV and PTCA procedures performance. It is important to highlight that none of the results analyzed was significant isolated to the selected endpoints (table 1). Generally, the performed interventions were of short duration – between four to six weeks – involving a highly diverse spectrum of training protocols: some of them being of continuous characteristics and others of intervals nature, some using only cycle ergometer and others incorporating muscular strengthening as well, besides presenting different intensities and frequencies. The sample size varied from 69 to 450 patients in the 21 studies analyzed.

Total cholesterol, LDL, HDL and triglycerides – In the majority of the studies, the CREE group presented tendency to a higher total cholesterol, LDL and triglycerides reduction, and higher increase of the HDL when compared to the control group, as can be observed in the presented studies, some of which statistically significant, specially for the total cholesterol in five CRCE out of the nine selected (table 2).

DISCUSSION

Our results ratify the premise that the CREE is an efficient strategy in the recovery of coronary patients, being associated to lower mortality for all reasons[2,10-11,18-19] and for cardiovascular events[11,13,15], lower probability of re infarct[2,17,20], lower MRV rate[11,20,22] and PTCA[11,21].

The evidence support that physical exercise is closely related to the therapeutic success in the analyzed studies. The mechanisms involved in this greater cardio protection, however, are still little known[27] – probably due to its multifactor nature[4]. Among the possible benefits of the systematized practice of physical exercise are: improvement of the endothelial function with subsequent coronary vasodilatation[28-30], increase in the variability of the heart rate and an autonomous pattern more physiological[31-33], lower oxygen myocardial demand[29], development of collateral circulations[29], improvement in the lipidic profile[8,10], besides the interference in the inflammatory markers[34] and in the coagulation factors[35]. Nevertheless, some studies denote that the main effect of exercise on the mortality rates would be mediated by its indirect action over the risk factors for atherosclerosis diseases such as: smoking[36-37], dyslipidemia[7-8], body weight excess[38], arterial pressure[3,6,39] and diabetes mellitus[40-41]. It is relevant to mention the limitations of the study, that aimed to investigate the physical exercise effect on these factors such as: the methodology quality applied in the clinical essays and the inconsistent results presented, as we will discuss later on. Despite that, there is strong scientific evidence published by different research groups[26,29,42-44] that testify the importance of the physical exercise for individuals with or without known cardiac disease, justifying thus, the exercise as main focus of programs pointed to the CR.

Total and cardiac mortality – our results suggest that the CREE is related to a bigger protection factor for the total and cardiac mortality endings. Moreover, some studies have presented expressive indices for the reduction risk index in the total mortality[2]. A recent meta-analysis[13] of 48 CRCE, involving 8940 patients, comparing CREE and usual care, demonstrated through a combined analysis, that CREE was associated to a reduction of 20% in the total mortality and of 26% in the cardiac mortality. These results agree with other previously published reviews which found between 20 and 30% of reduction in the mortality in coronary patients in a time when the therapeutic clinical and surgical arsenal was less developed[15,45-46]. It is interesting to highlight that the group led by Dr. Taylor[13] did not observe difference between the conventional cardiac rehabilitation versus that performed with emphasis on exercise, when analyzed related to its dose or the follow-up duration. Likewise, Jolliffe *et al.*[15] demonstrated in their meta-analysis that the CREE versus usual care were significantly different for all the mortality causes [OR combined = 0,73 (IC95% = 0,54 to 0,98)]. Moreover, this same author calls attention in his study that the conventional cardiac rehabilitation, compared to the usual care, did not present such difference [OR combined = 0,87 (0,71 to 1,05)], emphasizing thus, the importance of the CREE. Yet, the presented studies in this and other reviews did not support the claim that the conventional rehabilitation is significantly better than the CREE, since the methodological limitations and differences concerning these studies do not allow us to reach to a more definite conclusion. Based on this idea, it is possible to infer that there are no expressive advantages in terms of mortality, in the adoption of other complementary measures, besides the regular practice of physical exercise, which seems to be directly responsible for positive results in the intervention in relation to the selected endpoints.

Changeable factors – The CREE seems to be associated to a bigger reduction in the total cholesterol[6-8,10,23], and in smaller degree for the LDL[7] and triglycerides[6,10] and to a slight increase in the HDL[3,6,8], even though not always with statistical significance for a given study. *A priori*, our review data seem to corroborate other studies that, through a combined analysis, found differences in these reductions for the total cholesterol and triglycerides, favorable to the CREE group, with indices of –0,37 (IC95% of the combined estimate = –0,63 to –0,11 mmol/L) and –0,23 (IC95% of the combined estimate = –0,39 to –0,07 mmol/L), respectively[13]. On the other hand, the majority of the CREE did not observe any significant effect of the CREE over the LDL and HDL cholesterol,

TABLE 1
Summary of the studies and their main results for total mortality, cardiac mortality, re infarct, MRV and PTCA (CREE vs. usual care)

Study	Patients*	Intervention and method	ENDPOINTS				
			Total mortality OR (IC95%)**	Cardiac mortality OR (IC95%)**	Myocardial re infarct OR (IC95%)**	MRV OR (IC95%)**	PTCA OR (IC95%)**
Bethell *et al.* (1990)[17]	• 229 male patients after AMI • IG = 113 (54) • CG = 116 (53)	• IG – exercise 3 times/ week during 3 months; aerobic exercises between 70 to 85% of the HRmax and of muscular strengthening • Randomized after 5 days of AMI • *Follow-up* of 5 years	1.43 (0.64 a 3.18)	1.13 (0.49 a 2.59)	0.63 (0.26 a 1.52)	–	–
Fridlund *et al.* (1991)[18]	• 127 patients after AMI (101 – M and 25 – F) • IG = 86 (53) • CG = 41 (63)	• IG –1 hour of exercises/ week during 6 months • *Follow-up* of 1 and 5 years	0.15 (0.02 a 1.48)	–	–	0.91 (0.43 a 1.91)	1.33 (0.34 a 5.11)
Oldridge *et al.* (1991)[19]	• 201 patients after AMI (177 – M and 24 – F) • IG = 99 (53) • CG = 102 (53)	• IG – 50 min of exercise 2 times/week to 65% HRmax during 8 weeks • Stratified by status • 1 year *follow-up*	0.77 (0.17 a 3.51)	–	–	–	–
PRECOR (1991)[2]	• 121 male patients after AMI • IG = 60 (51) • CG = 61 (49)	• IG – exercise 3 times/ week during 6 weeks • Randomized after 30 and 60 days of MI • 2 years *follow-up*	0.11 (0.01 a 2.01)	–	0.65 (0.18 a 2.45)	2.07 (0.18 a 23.44)	–
Schuler *et al.* (1992)[20]	• 96 male patients • IG = 43 (54) • CG = 53 (54)	• IG – exercises at least 2h/week; daily exercises (20 min/day) • Randomized after angiography • *Follow-up* annually performed during 6 years	0.74 (0.22 a 2.45)	2.70 (0.50 a 14.52)	0.75 (0.16 a 3.51)	0.51 (0.17 a 1.55)	1.59 (0.42 a 5.97)
Heller *et al.* (1993)[21]	• 450 patients after AMI (323 – M and 127 – F) • IG = 213 (59) • CG = 237 (58)	• IG – the information on the exercise practice was obtained through a questionnaire • Randomized by groups • 6 months *follow-up*	2.26 (0.56 a 9.15)	–	–	0.91 (0.53 a 1.55)	0.75 (0.34 a 1.66)
Fletcher *et al.* (1994)[8]	• 91 male patients • IG = 44 (62) • CG = 47 (63)	• IG – exercises performed 5 days/week (20 min/day) in a cycle during 6 months with control by telephone (telemetry) • Randomized until the time of the study • 6 months *follow-up*	0.79 (0.17 a 3.73)	–	–	–	–
Holmback *et al.* (1994)[22]	• 69 patients after AMI (67 – M and 2 – F) • IG = 34 (55) • CG = 35 (55)	• IG – exercises with intervals performed for 2 days/week (45 min) during 12 weeks • Randomized after 6 weeks from the AMI • 1 year *follow-up*	1.03 (0.06 a 17.16)	–	5.46 (0.25 a 118.06)	0.33 (0.01 a 8.47)	–
Haskell *et al.* (1994)[6]	• 300 patients (259 – M and 41 – F) • IG = 145 (58) • CG = 155 (56)	• IG – exercises performed at home • Randomized after angiography • 4 years *follow-up*	1.07 (0.21 a 5.39)	3.23 (0.13 a 79.89)	9.89 (0.53 a 185.35)	7.64 (0.39 a 149.18)	3.35 (0.89 a 12.64)
Specchia *et al.* (1996)[11]	• 256 patients (182 – M and 18 – F) • IG = 125 (51) • CG = 131 (54)	• IG – exercises performed 5 days/week (30 min of cycle) at 75% maximal work ability during 4 weeks. After hospital outgoing daily callisthenic exercises plus 30 min walk every 2 days • Randomized after hospital outgoing • 34 months *follow-up*	0.41 (0.14 a 1.21)	0.38 (0.13 a 1.09)	–	1.71 (0.64 a 4.56)	0.52 (0.05 a 5.81)

TABLE 1 (continuation)

Study	Patients*	Intervention and method	ENDPOINTS				
			Total mortality OR (IC95%)**	Cardiac mortality OR (IC95%)**	Myocardial re infarct OR (IC95%)**	MRV OR (IC95%)**	PTCA OR (IC95%)**
Carlsson *et al.* (1997)[7]	• 168 patients (126 – M and 42 F) • IG = 87 (62) • CG = 81 (62)	• IG – exercises performed from 2 to 3 days/week during 10 to 12 weeks • Randomized 4 weeks after hospital outgoing • 1 year *follow-up*	0.99 (0.14 a 7.16)	–	–	–	–
Yu *et al.* (2003)[10]	• 112 patients (89 – M and 23 – F) • IG = 72 (62) • CG = 40 (61)	• IG – exercises performed 2 days/week during 8 weeks between 65 and 85% of the maximal work ability • Randomized after AMI or PTCA • 2 years *follow-up*	0.80 (0.68 a 0.93)	–	–	–	–

* = IG (Intervention group) = number of individuals (age average in years) and CG (Control group) = number of individuals (age average in years); HRmax = Maximal heart rate; AMI = acute myocardial infarct; M = male; F = female; ** = OR – *Odds ratios* related to cardiac rehabilitation with emphasis in exercise vs. usual care (indices based in the meta-analysis published by Taylor et al. Am J Cardiol 2004;116:682-92)[13].

TABLE 2
Summary of the studies and their main results for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (CREE vs usual care)

	Total cholesterol			LDL cholesterol			HDL cholesterol			Triglycerides		
	IG*	CG*	(IC95%)**	IG*	CG*	(IC95%)**	IG*	CG*	(IC95%)**	IG*	CG*	(IC95%)**
Schuler *et al.* (1992)[20]	–0.39 (1.03) [40]	–0.25 (0.85) [50]	–0.14 (–0.54 a 0.26)	–0.24 (0.80) [40]	0.03 (0.63) [50]	–0.27 (–0.57 a 0.03)	0.14 (0.28) [40]	0.11 (0.30) [50]	0.03 (–0.09 a 0.15)	–0.33 (0.87) [40]	–0.39 (1.34) [50]	0.06 (–0.37 a 0.49)
Engblom *et al.* (1992)[23]	–0.91 (1.72) [98]	0.11 (0.79) [82]	–1.02*** (–1.40 a –0.64)	–0.90 (1.57) [98]	–0.75 (1.57) [82]	–0.15 (–0.65 a 0.35)	0.03 (0.37) [98]	0.03 (0.37) [82]	0.00 (–0.11 a 0.11)	–1.14 (3.81) [98]	–0.65 (4.35) [82]	–0.49 (–1.71 a 0.73)
Haskell *et al.* (1994)[6]	–0.99 (0.83) [118]	–0.09 (0.63) [127]	–0.90*** (–1.09 a –0.71)	–0.95 (0.81) [118]	–0.16 (0.59) [127]	–0.79 (–0.97 a 0.61)	0.14 (0.23) [118]	0.06 (0.17) [127]	0.08*** (0.03 a 0.13)	–0.34 (0.87) [118]	0.01 (0.97) [127]	–0.35*** (–0.58 a –0.12)
Wosornu *et al.* (1996)[24]	0.00 (0.94) [27]	–0.30 (0.95) [26]	0.30 (–0.21 a 0.81)	–0.10 (0.79) [27]	–0.40 (0.79) [26]	0.30 (–0.12 a 0.27)	0.00 (0.26) [27]	–0.16 (0.26) [26]	0.10 (–0.04 a 0.24)	0.10 (0.95) [27]	0.10 (1.08) [26]	0.00 (–0.54 a 0.54)
Carlsson *et al.* (1997)[7]	–0.79 (0.97) [75]	0.11 (0.79) [67]	–0.90*** (–1.19 a –0.61)	–0.96 (0.83) [75]	–0.01 (0.75) [67]	–0.95*** (–1.21 a –0.69)	–	–	–	–	–	–
Fletcher *et al.* (1994)[8]	–0.18 (1.34) [41]	0.41 (1.30) [47]	–0.59*** (–1.14 a –0.04)	–	–	–	–0.13 (0.38) [41]	0.16 (0.41) [47]	–0.29*** (–0.46 a –0.12)	–	–	–
Toobert *et al.* (2000)[25]	–0.23 (0.82) [14]	–0.54 (1.37) [11]	0.31 (–0.61 a 1.23)	–0.49 (0.57) [14]	–0.18 (0.98) [11]	–0.31 (–0.96 a 0.34)	0.07 (0.31) [14]	–0.03 (0.28) [11]	0.10 (–0.13 a 0.33)	0.07 (1.11) [14]	0.18 (2.71) [11]	–0.11 (–1.81 a 1.59)
Belardinelli *et al.* (2001)[3]	0.59 (0.74) [59]	0.77 (0.99) [59]	–0.18 (–0.50 a 0.14)	0.43 (0.96) [59]	0.26 (0.91) [59]	0.17 (–0.17 a 0.51)	1.47 (0.95) [59]	0.26 (0.91) [59]	1.21*** (0.87 a 1.55)	0.07 (1.11) [59]	0.18 (2.71) [59]	–0.11 (–1.81 a 1.59)
Yu *et al.* (2003)[10]	–0.30 (0.72) [72]	–0.50 (0.72) [40]	–0.37*** (–0.63 a –0.11)	0.00 (0.87) [72]	–0.50 (0.88) [40]	–0.20 (–0.53 a 0.12)	0.20 (0.24) [72]	0.20 (0.20) [40]	0.05 (–0.03 a 0.14)	–0.40 (0.88) [72]	0.10 (0.84) [40]	–0.50*** (–0.83 a –0.17)

* IG = intervention group; CG = Control group: Average in mmol/L (standard deviation) [number of patients]; ** = average difference, in mmol/L; *** significative ($p < 0.05$).

although some evidence point to a significant increase of HDL, reaching indices of 1,21 mmol/L. An important point to be highlighted is that several of these results may have been disguised or compromised by the concomitant use and currently ordinary of drugs which act directly on the lipidic profile of these patients.

The increased systolic arterial pressure, another changeable and important factor due to its great prevalence, seems to decrease as consequence of the CREE[6,8,13,25,37,47], as demonstrated by Taylor *et al.*[13], in a combined analysis [–3,19 (IC95% = –5,44 to –0,95)]. Although there is a significant difference from the statistical point of view, the clinical relevance is only modest. Concerning the diastolic arterial pressure, the impact tends to be even smaller or absent with the CR[6,13,25].

Smoking significantly contributes to a greater morbidity and mortality, being almost always associated to an important cardiovascular dysfunction[48]. The CREE seems to be associated to a better protection in relation to smoking deleterious effects, such as the data observed by Dr. Lisspers' group[36] from Stockholm, showing protection of 82% derived from the CREE, when compared to the control, being these results corroborated by other re-

search centers[6-7,20,37]. However, these results are not unanimous. Dinnes *et al.*[49] demonstrated through their systematized review that there is no effect of the exercise-based therapy on this factor, contrasting with the great majority of the studies presented here. It is important to mention that the referred authors did not perform the meta-analysis strategy of the studies mentioned in their review, limiting hence, their inference. Another important point would be the possible interaction between medical counseling and smoking prohibition in hospitals[4], being able thus, to greatly contribute with the results obtained by such studies.

Health-related life quality – the great majority of research centers[3,9-10,36,50-53] that investigate the CR effects on the health related- life quality demonstrated considerable improvement in this variant, despite its occurrence in the control group as well at a certain extent. Therefore, it seems that the results of these studies did not show clear evidence about the specific benefits of the therapy with emphasis on exercise for the life quality of coronary patients, probably due to its multi factor nature. Moreover, Furthermore, there are two important aspects to be highlighted in the methodology applied in these studies: firstly, the diversity, sensitivity and specificity of the existing instruments to evaluate this topic; second its reduced sample size, two critical points for the obtained results comparison[13,15,54].

Limitations of the clinical essays – Great part of the analyzed studies have been inconclusive and specially unclear due to countless and substantial factors which may interfere in the presented results and consequently, their interpretation and comparison, namely: 1) poor quality of the applied methodological guidelines; 2) large variation in the follow-up timing (six months to six years); 3) reduced sample size of some studies affecting the statistical and clinical relevance of the clinical essay; 4) short time of intervention besides a diverse intervention methodology, involving different types, intensity and training frequency; 5) unclear description of the randomization process and patients' placement; 6) follow-up loss, some studies registering up to 20% of loss; 7) post-randomization exclusion of patients, with no following explanation about the reason which determined those patients' exclusion; 8) use of drugs which may interact or not with the effect; 9) the majority of the analyzed patients were men and middle-aged, minimizing the inferential power or results' generalization for other populations; 10) there is a a higher prevalence of coronary arterial disease in populations of low social-economical status and, paradoxically, there is an expressive number of clinical essays showing the extreme opposite of such scale. These factors affect not only the internal but also the external validation of these studies.

CONCLUSION

This review confirms the benefits of the CREE in the therapeutic approach of coronary patients, reducing their cardiac mortality indices and for all reasons, besides contributing to the decrease of the occurrence of other coronary events, such as the myocardial revascularization and the re infarct rate.. The CREE results about the changeable factors and the life quality are not conclusive due to methodological limitations of the observed studies, despite a favorable tendency to this strategy's use. Moreover, this study corroborates the impression that regular physical exercise *per si* constitutes in the main component and responsible for the favorable results of the intervention in relation to the studied endpoints.

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