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REVIEW

Current role and future perspectives of cardiac rehabilitation in coronary heart disease

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Abstract

Ischaemic heart disease (IHD) is a major cause of morbidity and mortality worldwide. While there have been major advances in this field, these patients are still a higher risk subgroup. As such, strategies to mitigate risk and tailor secondary prevention measures are of the utmost relevance. Cardiac rehabilitation (CR), encompassing several domains including exercise training, cardiovascular risk factor optimization, nutritional and psychological assessments, as well as other ancillary interventions has shown to be one of the pillars in the contemporary management of patients with IHD. Indeed, CR is associated with several benefits in this population, ranging from functional capacity to improvements in outcomes. Whilst this, there are still several issues concerning the optimal application of CR which are still not fully ascertained, such as lack of referral and completion, as well as questions related to programme design (particularly among patients with multiple comorbidities). In this review, we aim at presenting a pragmatic overview on the current role of CR in the management of individuals with IHD, while also discussing some of the caveats in the current data, as well as future concepts which could help improve the uptake and personalization of this pivotal time-tested intervention.

Key Words: Cardiac rehabilitation; Secondary prevention; Myocardial infarction;

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Core Tip: Ischaemic heart disease (IHD) is a leading cause of morbidity and mortality. Cardiac rehabilitation (CR) programmes have evolved over the years, as to provide comprehensive frameworks encompassing several domains of secondary prevention and forming an integral part of the contemporary management of individuals with IHD. Whilst this, the optimal application of these programmes, in diverse subsets of patients, remains an evolving and challenging field. In this review, we present a pragmatic overview on the current data concerning CR in IHD, while also discussing some of the caveats and future perspectives in this topic.

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INTRODUCTION

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality worldwide[1-3]. Ischaemic heart disease (IHD) is one of its most common presentations, and though significant advances have been made in terms of both its diagnosis and management, patients with IHD still represent a higher risk subgroup[4-6]. Given this background, strategies focused on optimizing overall secondary preventive measures have been the focus of increased interest[4,7,8].

Cardiac rehabilitation (CR) programmes are one of the pillars of the contemporary management of individuals with IHD, being associated with improvements in both morbidity and mortality[6,7,9,10]. Over the years, these programmes have evolved into comprehensive and multidimensional secondary prevention frameworks encompassing several domains ranging from exercise training (ET) to lifestyle counselling, cardiovascular risk factor (CVRF) optimization, psychological interventions, as well as nutritional support and other ancillary interventions[11,12]. While the central role of CR programmes in the management of IHD is currently consensual, there are still several hinderances concerning its optimal application, as manifest by the diversity in programme designs, availability, and patient enrolment [11,13-15]. Moreover, tailoring of these programmes for traditionally less referred subgroups of patients such as women and the elderly, as well as the role of novel strategies to improve referral and completion are also areas of intense interest[8,16-18].

In this review, we aim at presenting a focused and pragmatic overview of the role of CR programmes in the management of individuals with IHD, as well as reviewing some of the challenges and future perspectives concerning this intervention.

CR IN ISCHAEMIC HEART DISEASE

General concepts

Over the last decades, the important role of exercise in the management of individuals with IHD has come under the spotlight[19,20]. Though its potential role in the modulation of anginous symptoms is often ascribed to the classical work of Heberden in the 18th century, the first descriptions of exercise-based rehabilitation in individuals after a myocardial infarction were only reported several years later, well into the 20th century[19,21,22]. Importantly, these early pioneers had a crucial role in changing the then-current *status quo* of prolonged immobilization, by reporting on the benefits of exercise (adapted to the individual patient) in this specific setting[19]. Since these pivotal landmarks, several studies have extensively reported on the myriad benefits of ET in individuals with IHD[8,9,23,24].

Exercise can have a profound impact on the cardiovascular (CV) system, both in the heart as well as in the peripheral vasculature[10,20,25-27]. Interestingly, though its effect on left ventricular systolic function *per se* can vary (depending on factors such as the population under study, timing of introduction and type of protocol), data concurs as to the improvements in functional capacity [as assessed by surrogates such as the peak oxygen consumption (pVO2)][20,28-30]. In addition, its impact on other sites such as the pulmonary and musculoskeletal systems should also be kept in mind, particularly when analysing data related to overall functional capacity as well as its impact in the face of the complex multimorbidity patient[20,31-33]. Moreover, and given recent reports illustrating the putative role of inflammation in IHD, the potential modulation of inflammatory pathways by physical activity has also been postulated as being one of the mechanisms underlying the benefits of exercise-based CR[25,34]. Of note, however, that while some mechanistic as well as clinical data have supported this hypothesis, further research is still needed to fully ascertain the potential relative contribution of inflammatory modulation and metabolic substrate utilization to the overall improvements in individuals undergoing CR[25,34-36].

The role of exercise in preventing CVD has been extensively explored, as depicted by the data showing its relevance in reducing the incidence of several pathologies such as heart failure (HF) and mortality[4,37,38]. Interestingly, though some reports have explored the notion that intense ET could potentially lead to detrimental CV effects, as manifest by phenomena ranging from elevations in cardiac biomarkers (such as cardiac troponin and natriuretic peptides) to coronary artery calcification and myocardial fibrosis, data has consistently shown the beneficial effects of moderate regular exercise[27,38-41]. As such, though these factors should be taken into consideration, particularly in terms of exercise prescription and personalization, the plethora of benefits associated with ET should be further highlighted, namely in the setting of IHD[9,10,42] (Figure 1).

CURRENT EVIDENCE CONCERNING CR

As discussed above, there are several potentially beneficial biological effects of ET[25,38,43] (Figure 1). In accordance with these data, it has become one of the central components in the management of IHD[4,6-8]. While the contribution of ET is undisputable, CR programmes have progressively incorporated increasingly different facets, as to provide a comprehensive approach to the individual patient[8,11,12,44]. This progression mirrors the growing complexity of both patients (including multiple comorbidities, the inclusion of older individuals as well as differences in terms of socio-cultural backgrounds) as well as of therapeutic modalities, and as such the need to provide an ever more patient-centred intervention, as to improve outcomes[11,44-46]. Interestingly, as the concept of global CV risk (comprising different CVRF, as well as modulators which could have varying levels of influence) becomes paramount in the CV assessment, the utility of CR in tackling different components of CVD gains additional relevance[4,8,11]. Indeed, reports have shown the benefits of comprehensive programmes, when compared to isolated interventions[44,47]. These concepts are reflected in the current recommendations by different societies, which reinforce the need for CR programmes to include multiple components, as to provide optimal risk management strategies[11,48-50]. In this regard, the European Association of Preventive Cardiology (EAPC) has recently provided guidance on the core components of CR programmes in individuals with IHD (as well as in other CVD), while also presenting a position statement concerning standardization of this intervention[8,11].

Different studies have assessed the impact of CR programmes in the setting of IHD [9,23,51,52]. A meta-analysis performed by Anderson *et al*[23] reported on significant benefits in terms of CV mortality, hospitalizations, and quality of life. Subsequently, and as to address the relevance of this intervention in a contemporary setting, the CROS-II meta-analysis (including only individuals enrolled by 1995 or later) provided further evidence on CR, as attested by reductions in mortality[9]. The benefits for patients undergoing CR in this setting have also been reported in observational real-word studies[53-55]. Importantly, the CROS-II study also reinforced the need for standardization across different programmes, as to allow further assessments[9,51]. This point should be particularly taken into consideration when analysing data from studies which do not report on benefits in terms of outcomes[51,56-58], as differences in programme design, ET compliance and intensity could (at least partially) explain some of these discrepancies[59-63]. This latter point should be further considered, and

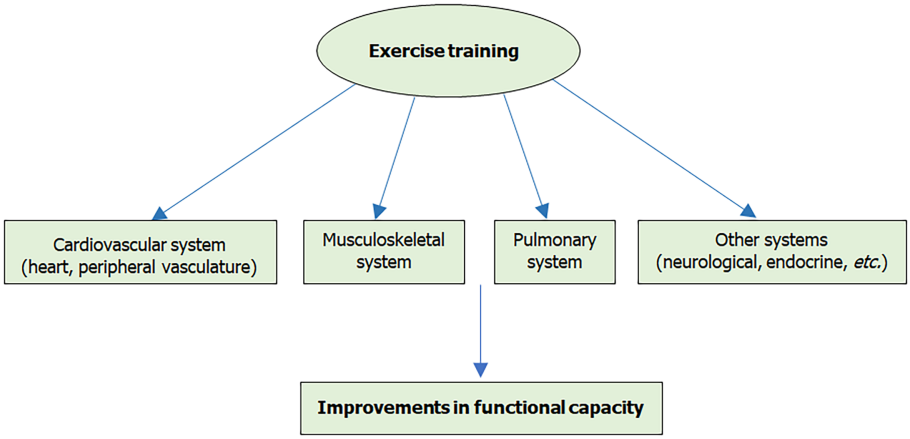

Figure 1 Overview of some of the sites related to the overall effects of exercise training.

it has also been explored when addressing different training methodologies[62,63]. In this regard, albeit high-intensity interval training (HIIT) showed interesting results when compared to moderate continuous training, three large randomized controlled trials in coronary artery disease (CAD), HF with reduced and preserved ejection fractions (respectively) failed to show an advantage of HIIT in terms of the pVO2[62-64]. Importantly, exercise prescription played a pivotal role, as acknowledged by the authors, reinforcing the need for a personalized and highly integrated approach[62,63]. It should also be recalled that the number of CR sessions performed can influence results, as illustrated by data showing that performing a smaller number can lead to worse outcomes[65,66]. These concepts had previously been elegantly raised by Sandercock *et al*[56] by comparing the case of ET to the prescription of pharmacological therapies, where in both cases dosing issues could affect the overall results of the intervention.

Differential responses should also be further explored, as studies have shown that the functional response to CR (namely as expressed by the pVO2) can be associated with outcomes[67,68]. In this regard De Schutter *et al*[67], assessing data from 1171 individuals with coronary heart disease (CHD) who underwent a phase II CR programme, showed significant differences in mortality when comparing those who had improvements in pVO2 to those who did not. When assessing pVO2 as a continuous variable, a 1 mL/kg/min improvement in pVO2 was reported as being associated with a 10% reduction in mortality[67]. Recently, Carbone *et al*[68] also reported that among individuals with CHD undergoing CR, pVO2 at the end of the CR programme was a predictor of mortality. Notably, associations between pVO2 and CV events have also been reported in other settings, further reiterating the need for rigorous programme designs, namely in terms of exercise prescription[8,11,68,69]. Of mention, the timing of CR initiation (after an acute event) should also be taken into consideration as this can be associated not only with reduced uptake and completion but can also influence the response to ET[10,28,29,70].

Another issue which should be discussed pertains to the cost-effectiveness of CR[8,23]. Some studies have suggested the cost-effectiveness of CR among individuals with IHD, while an analysis by Hinde *et al*[70] also supports potential benefits in expanding overall CR coverage[71-73]. Though these data concur as to the relevance of CR, as discussed by Barradas-Pires, differences in terms of programmes and population under study should also be noted, as standardization of CR programmes (as discussed above) would allow further analysis of the best ways to optimize this intervention, while potentially streamlining patient care[71,74]. Beyond this, it should also be referred that differences in terms of overall policies (when comparing world regions) could also influence CR programmes (namely in terms of accessibility and uptake), a factor which should also be acknowledged[13,14].

While the abovementioned caveats should be kept under consideration, the wealth of data supporting the relevance of CR in individuals with IHD in terms of both morbidity and mortality reinforces its role in this group of patients. This is reflected by current guidelines by both the European Society of Cardiology and the American Heart Association/American College of Cardiology, which attribute these programmes high levels of recommendation in this setting, highlighting the paramount role of contemporary CR in the optimal management of IHD[4,6,7,75,76].

CHALLENGES TO CR

As stated above, CR programmes are endorsed as part of the standard management strategy of IHD[4,6,7,75]. Whilst this, data has shown that CR is often underutilized and that even in those who are referred for this intervention, many do not complete the pre-specified programme[8,13,14,77,78]. Notably, while the issue of CR underutilization can affect a substantial number of individuals, as illustrated by data from the ESC-EORP EUROASPIRE V study where less than half of individuals with CAD were referred for CR, this can particularly affect certain subgroups such as women and older patients[77-81].

A seminal work derived from the European Cardiac Rehabilitation Inventory Survey showed that asymmetries could affect different phases of CR, while also noting geographical differences[14]. This latter issue was also reported on a study assessing CR availability worldwide, showing important differences according to location[13]. Though outside the scope of the present report, several factors encompassing patient-related, physician-related, and system-related barriers can affect CR referral as well as completion[5,14,82-84] (Table 1). As such, and as reviewed by Chindhy *et al*[83], strategies directed at each of these components should be the focus of further tailoring, as to allow increased CR uptake. Strategies such as physician and patient education on the benefits of CR, automatic patient referral, flexible hours as well as optimization of expense coverage and early appointments after hospital discharge have been among some of the modalities postulated as to tackle some of these barriers[14,83,85]. Additionally, the potential utilization of alternative modalities should also be reflected upon, to mitigate some of these barriers[82,86-88]. Interestingly, and as discussed below, home-based CR (HBCR) as well as the incorporation of different technologies (such as sensors) could also be of interest, as to address some of these gaps[82,83,89,90]. As detailed in a statement concerning HBCR, this could be an option to overcome several barriers to CR such as scheduling, access, and transportation issues, as well as enrolment delays, though pitfalls such as less intensive training, monitoring and safety concerns related to higher risk patients have also been noted as some of its potential disadvantages[89,91,92]. Importantly, data has shown that this strategy can be performed safely while providing several benefits[89,91,93]. Whilst this, differences in programme designs (including patient characteristics as well as programme duration and frequency) should be considered when analysing comparisons with centre-based CR[89]. Interestingly, although older individuals have traditionally been less represented, a study has shown that a home-based programme was associated with significant functional benefits among the elderly, thus showcasing its possible relevance in this subgroup[92,94]. Notwithstanding the major advances facilitated by the growing digitalization of healthcare, adaptation of facilities as to provide the different facets of contemporary CR (including not only ET but also testing, educational sessions and other interventions) should also be reflected upon, as to maximize resource utilization[11,95].

One important aspect pertains to the presence of multiple comorbidities among individuals with IHD[8,96,97]. Indeed, as patients present with increasingly complex clinical contexts (such as in the elderly, as well as those with HF and polyvascular disease), tailoring of CR programmes can be particularly challenging[8,96-98]. Notably, ET can be associated with functional improvements such as walking distance in patients with peripheral artery disease (PAD), being recommended as an important part of the management of individuals with intermittent claudication[8,99]. Whilst this, studies have shown that functional benefits can differ when comparing patients with CAD with those who present with both CAD and PAD[96,98,100]. Another frontier field which is rapidly expanding relates to cardio-oncology rehabilitation[8,101]. Importantly, attending to the specificities related both to CV pathophysiology as well as to the potential impact of the oncologic disease and its associated treatments, the most adequate programme should be highly individualized and structured on a multidisciplinary setting[101-104]. Given these backgrounds, optimization of CR programmes in these frontier fields should be the focus of further research.

As mentioned above, the response to CR is an important aspect, as this has been shown in some studies to be associated with outcomes[67,68]. While some factors such as age and gender have been associated with modulation of the response to CR, several others have been postulated as having a role in explaining some of the differences in this response[17,25,67,81]. As expertly reviewed by Gevaert *et al*[25], the overall determinants to the complex individual response to CR should be further ascertained, as to allow improvements in its application. In this context, both clinical research as well as translational data, supplemented by the possible inclusion of insights gained from the application of novel instruments such as artificial intelligence

Table 1 Some of the challenges concerning cardiac rehabilitation uptake and completion

Suboptimal referral rates
Limited access (centre availability, geographical issues, transportation, *etc.*)
Challenges concerning programme design (working hours, participant characteristics, *etc.*)
Low participation of different subsets of patients (women, elderly, patients with multiple comorbidities, *etc.*)
Language barriers
Socio-economic issues
Low motivation and/or low self-efficacy
Challenges in the patient/provider relationship
Lack of knowledge concerning cardiac rehabilitation

and multi-omics technologies could improve current knowledge on the pathways involved in the response to CR in different individuals[25,105].

FUTURE PERSPECTIVE

As detailed in the current review, contemporary CR provides an ample secondary prevention framework, able to provide a comprehensive approach to the complex patient with IHD[4,6,8,10]. Nevertheless, questions related to the optimal application of CR among distinct subsets of patients (with a focus on those with different comorbidities) as well as the asymmetries in patient referral and completion still present highly important challenges.

The use of novel technologies has steadily made an impact across different fields of Medicine, including CR[25,90,105-107]. Though the interest in HBCR has been present over the years, with data showing that this could be an interesting option in different subsets of patients, the recent COVID-19 pandemic has markedly expanded the interest in novel models (including hybrid ones) of CR[89,90,108,109]. In this background, models which incorporate concepts of telehealth (namely encompassing different technologies) have been proposed as to allow continuity of care, while minimizing risk[110,111]. Of note, beyond this transitioning phase, these have been postulated as being of potential use to allow for future improvements in overall CR access[90]. Though the use of tele-rehabilitation has made great strides over the last years, as to mitigate some of the barriers associated with CR (particularly in terms of transportation, timing, and potentially cost), questions related to the relative role of hybrid models, as well as of the individuals who could benefit most from these, should be the focus of further study[90,94,109,112]. Moreover, the inclusion of digital tools such as mobile applications as well as sensors (to address not only data related to ET but also to different physiological facets including weight and diet as well as possible CVRF control) should also be a cornerstone of research[90,106,113,114]. Interestingly, some studies highlight the potential in the use of digital applications (often included in the broader concept of mHealth, as the use of wireless technologies with the aim of improving health outcomes) in CR[114]. These could improve access to CR (namely when applied in the framework of HBCR) and allow for more intensive monitoring of different parameters (such as CVRF and physical activity)[90,106,114]. Indeed, some reports have shown that telemonitoring could be of interest in IHD, namely being associated with benefits in functional capacity, whereas the integration of other modalities could allow additional options to address psychological parameters[113,115,116]. In this regard, a randomized study comparing the use of a wrist heart rate monitor with standard training showed that this could be associated with similar increases in pVO2 at twelve weeks, whereas another randomized study (the REMOTE-CR trial, assessing 162 individuals with CHD) showed that cardiac telerehabilitation could lead to comparable results in terms of pVO2[117,118]. While highly promising, questions related to the optimal application of mHealth in CR, particularly in terms of its inclusion across different moments in the CR continuum, should be the focus of additional research[110,114,118,119]. Beyond this, studies aimed at defining the most adequate platforms for a given programme (as well as their comparison to standard methodologies and subsequent validation) and further large, randomized trials would also be of importance, as to allow for an increasingly personalized approach[90,94,120-

122].

Another aspect worthy of mention pertains to the functional assessment methodology. While this point has been comprehensively reviewed in a position statement by the EAPC, novel insights (as discussed above) could also add interesting data[11,42,120,121]. While exercise testing (namely cardiopulmonary exercise stress testing) has a central role, other methods have also been described as of potential interest[11,42,90,123,124]. In this regard, the use of the 6-min walk test in assessing exercise progression has been proposed, whereas another recent study (albeit in a small number of individuals) reported on the use of the 200-m fast walking test in tailoring exercise in low to moderate risk CHD patients undergoing HBCR[123,124]. The relative role of these parameters (namely in the face of data derived from digital platforms) should also be further ascertained[121,125].

Finally, the concept of programme standardization will continue to have a central place when addressing the data for CR[8,11,12]. Data from different CVD shows that there are still variances across CR programmes in ET prescription, a fact which should be considered[126,127]. As mentioned above, standardization (and potential certification) of CR programmes could be of marked importance as to allow benchmarking and process optimization, across varied settings[11,12]. In this regard, also the evolution of preventive cardiology as a highly specialized area of Cardiology, as endorsed by the recently published core curriculum in Preventive Cardiology by the EAPC, could allow for further developments in this specific setting[11,128-130].

CONCLUSION

While substantial advances have been made in the management of IHD, this remains a major cause of morbidity and mortality. Contemporary CR programmes encompass a broad range of interventions, aimed at providing a comprehensive secondary prevention approach to these challenging individuals. Though differences in programme design and application should be considered, data has shown its relevance in improving outcomes, across different contexts. Importantly, the optimal strategy in different groups of patients (such as the elderly and other traditionally less represented individuals) remains an evolving field.

As the complexity of IHD in terms of patient characteristics and different therapeutic strategies (with an increasing focus on mitigating residual risk) grows, the central role of CR as a highly tailored intervention will grow ever more relevant, in the era of precision-based personalized medicine.

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