Cardiac rehabilitation

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ABSTRACT

Cardiovascular diseases are one of the majorcause of mortality globally. Coronary heart disease is the largest subset of cardiovascular disease. Although mortality rates decline during time, hospital discharge data as a measure of morbidity rates are stable, leading to larger pool of patients eligible to benefit from cardiac rehabilitation. Cardiac rehabilitation is a multi-disciplinary approach including exersize training, patient counselling, education and nutritional guidance. Despite the many known benefits of cardiac rehabilitation, refferal and participation rates remainlow and interventions to increase its use need to be developed.

Keywords: Coronary, rehabilitation, exercise

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide with annual mortality over 17 million people. It is expected that, more than 80 million individuals will be diagnosed with cardiovscular disease by 2030 worldwide [1, 2]. The increasing prevalence of CHD is due to the many risk factors that are becoming more endemic (type 2 diabetes mellitus [T2DM], obesity, sedentary lifestyle, hypertension [HTN]) and aging of the population [2].

While cardiovascular diseases' (CVD) mortality are decreasing, by improved emergency response and early intervention, medical and surgical management and to a lesser degree and risk factor reduction, it is still an important cause of disability around the world. Hospital discharge data as a measure of morbidity has been relatively stable since 2004 [3-5]. The percentage of years lived with disability has increased by 25% globally since 2005 [6].

Individuals with CVD are at high risk for subsequent major cardiac events and death [7], thus secondary prevention is very important. The impact of CVD are, increase in morbidity and mortality and the disturbing effects of secondary disability, decreased quality of life, and elevated health and social costs [8]. Cardiovascular rehabilitation (CR) is an effective and low-cost model of care for secondary prevention of CVD. It is an outpatient chronic diseasemanagement program, delivering the core components of assessment, medical risk factormanagement, structured exercise training (ET), patient educationas well as psychosocial and behavioral counselling [9].

CR consists of three phases. Phase I refers to inpatient rehabilitation during the index hospitalization. Due to the shortening durations of hospital stay, phase I CR has become less formalized. Phase II refers to physician supervised, outpatient monitored physical activity during the 2-16 weeks after discharge. Patients usually undergo up to 36 sessions in anexercise program. After this phase, patients may continue into phase III, which is an unmonitored exercise program. CR programs additionally provide nutritional, psycho-

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logical and smoking cessation counseling, besides lipid and blood pressure management.

Indications, Contraindications and Attendance

Most patients reffered for CR are eligible to participate. Common indications for CR are acute coronary syndrome, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), valve surgery, and chronic stable heart failure with reduced ejection fraction (HFrEF) (Table 1) [11-13]. HF is a relatively new addition, as there were long-standing concerns that exercise therapy (ET) would exacerbate HF. However, more recent studies by Wisløff *et al*. [14] and others [15] have shown that ET can elicit beneficial peripheral metabolic adaptations in patients with HF, resulting in a paradigm shift in favor of structured ET as a therapy for HF patients. The American Heart Association (AHA) and American College of Cardiology (ACC) decide CR is a Class I indication for these conditions. Contraindications for CR are listed in Table 2 [16]. The other preclusive reasons of participation include musculoskeletal problems, severe illnesses, co-morbid diseases, acute infections and inflammatory states that limit ET.

Despite favorable data and Class I recommendations, less than 30% of eligible CHD patients participate in CR programme. Commonly, referrals for these programs are not usually the part of routine daily care for many physicians. Frequently, access to facilities is difficult in rural areas. The other reason may be the significant advances in both medical and revascularization therapies, which have seen faster adoption by

Table 1. Indications for CR

Acute myocardial infarction
Stable angina pectoris
Coronary artery bypass graft surgery
Heart valve repair or replacement surgery
Heart valve repair or replacement surgery
Percutaneous transluminal coronary angioplasty
Chronic congestive heart failure
Peripheral arterial disease
Heart transplantation
Heart-lung transplantation

CR = cardiac rehabilitation

Table 2. Contraindications for CR

Unstable angina
Severe or symptomatic aortic stenosis
Decompensated HF
Severe obstructive cardiomyopathy
Acute cardiac mural thrombus
Acute deep venous thrombus
Pulmonary embolism

CR = cardiac rehabilitation

the cardiologists, because of a combination of physician reimbursement and marketing by pharmaceutical and device companies. Although CHD is a major cause of morbidity and mortality, interest in conventional and alternative approaches to the delivery of CR has grown and adoption is increasing [17, 18]. Decreased attendance of patients has been noted especially among women, non-whites, the elderly, the rural population, and individuals with low socio-economic status [19]. Additionally, the existence of comorbidities such as higher body mass index, poor functional capacity and exercise habits, tobacco use, and depression before starting CR has been associated with lower attendance and higher dropout rates from CR programs [20, 21]. Strong recommendation from primary care physicians and CVD specialists plays a critical role in patient participation and adherence to CR programs, and helps the patient understand the value of this treatment option [22, 23]. Patients adviced to see a cardiologist or a cardiac surgeon at the time of hospital discharge had > 2-fold higher odds of being referred to CR when compared to patients adviced to see with a family physician ($p < 0.05$) [24]. The other fact is that, only 40%-60% of patients referred to these programs complete the prescribed course of CR [25].

Exercise Modes and Intensity

The exercise prescription therapy starts with a symptom limited, exercise tolerance test. Thereafter, workouts typically consist of a short warm up period, followed by supervised individualized aerobic exercise, and a short cool down phase. The aerobic exercise includes a 20-60 min workouts 3-5 days a week at 50-80% of maximal exercise capacity [26]. Relatively recent data suggest that high intensity interval training (HIIT) produces larger and more rapid in-

creases in exercise capacity [14, 27, 28]. Weston *et al.* [29] have studied ET intensity and in reviewed a collection of meta-analysis data of 1468 patients enrolled in high versus moderate intensity protocols, and conclude that the benefits of HIIT in improving cardiorespiratory fitness (CRF) exceed those gained from moderate intensity continuous training (MICT) protocols utilized as the current standard of care for CR. In a study comparing moderate intensity continuous training MICT and HIIT protocols in patients with stable ischemic cordiomyopathy demonstrated a significant increase in peak oxygen consumption (VO2MAX) in the HIIT group [30]. HIIT also improved endothelial functions, reversed left ventricular remodelling and increased ejection fraction more than continous training. Similar superior improvements have been noted in other studies too [14, 27, 28]. The differentiating factors between HIIT and MICT; that usual therapy involves continuous maintenance of workload at an intensity of 50%-65% of the peak, often measured as VO2MAX or peak HR. HIIT protocols consist of shorter high-intensity intervals (75%-95% of maximal effort) interrupted by periods of rest [31]. In a similar comparative meta-analysis including 277 patients with CHD, Elliot *et al.* [32] and colleagues demonstrated that HIIT was associated with a significantly higher VO2, which is independently associated with reduced CVD mortality.

PREhabilitation is a new approach to ET-based therapy which is suggested to optimize post-CABG outcomes. The CR programme starts pre-operatively, that is, before bypass surgery, to decrease post-CABG morbidity and mortality. In a study, implementing pre-operative ET led to improved performance on a 6-minute walk test, a shorter hospital stay, fewer pulmonary complications, and a significantly lower incidence of postoperative atrial fibrillation [33].

Additionally to ET intensity, frequency and optimal "dosing" of ET also play an important role. Michaelides *et al.* [34] found that 30 min of ET increased vascular elasticity and improved antioxidant balance; however, these benefits were lost when the ET duration was extended to 60 min. Recent data suggest that when applied to vigorous ET, more moderate amounts of ET may provide added benefits at reduced risk (< 5 h of ET per week) [35, 36]. These physiologic findings supported by a cohort study of near 13,000 patients conducted by Blair *et al.* [37]. It was found that a plateau in benefits above 9-10 metabolic equivalents (MET) above which adjusted all-cause mortality no longer improved [37]. Similarly, increases above levels of moderate ET frequency in women were not associated with reductions in the risk of vascular diseases in a prospective study of women in the United Kingdom [38]. These findings support the 2013 ACC/AHA recommendations for reducing CVD risk; 150 minutes of weekly moderate intensity exercise or 75 minutes of vigorous aerobic activity weekly in conjunction with moderate-to-high intensity muscle strengthening exercises twice per week [16].

Effects of Exercise Training on Cardiovascular Physiology

Regular physical activity (PA) has multiple effects on health, including improved endothelial function, increased maximal aerobic capacity with better oxidative efficiency, and higher anti-oxidant activity. These physiological changes are the causes of improvements in both diastolic dysfunction and contractility, lower resting blood pressure (BP) and HR, increased muscle mass and even better cognitive performance. Increased metabolic demands during ET cause upregulation of mitochondrial division and modify energy pathways within the organelles [31]. Increased mitochondrial content in muscle promotes fat oxidation especially on carbohydrate oxidation [39]. This adaptation decreases lactate as a byproduct and leads to longer duration of ET at increased aerobic capacity [40]. Additionally, ET favorably impacts cardiac remodeling and results in improvements of the performance of the myocard [41]. The mechanisms are; reversal of metabolic decoupling processes with decreases in glucose uptake in patients with metabolic syndrome and postulation of angiogenesis in working muscles mediated by β-adrenergic stimulation of capillary growth by vascular endothelial growth factors and platelet-derived growth factors [42-44]. More recent studies have shown that ET-associated post-transcriptional gene regulation via micro-RNA reduce remodeling through interactions among metabolic, contractile and epigenetic genes [45]. ET modifies sympathovagal signaling results in an increase in parasympathetic tone, leading to increased HR variability which confers a better prognosis [46, 47]. Accordingly, ET increases the threshold for ventricular ectopic activity, and controlled trials have shown that ectopic beats are less common in

trained than untrained post-MI patients [48]. Via alterations in systemic vasoconstriction, sodium and water retention, angiotensinogen II modulation, aldosterone production and decreasing aldosterone lowers sympathetic tone, complementing the effect of other ET-induced modulators of parasympathetic activity [46, 49]. The other mechanism for regulation of sympathetic tone is via adrenomodullin and atrio/brain-natriureticpeptides which are related closely to aerobic consumption. As a result BP reduction by suppressing noradrenaline and endothelin-1, and improving endothelial responsiveness and function [50-52]. ET also protects against oxidative stress and leads to increase in nitric oxide levels which have anti-hypertensive effects [53]. Ranković *et al.* [54] reported a group of patients participating in a 6-week ET program (a combination of center-based followed by home-based delivery) had C-reactive protein levels which declined by 23.7% ($p < 0.001$), and plasma vascular cell adhesion molecule-1 levels that decreased by 10.2% ($p < 0.05$) when compared to the sedentary cohort.

Many patients with CHD do not have optimal levels of lipids including high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs). Also, there is evidence to suggest that these patients may have improvement in these parameters with CR. Improvements may range between +6% and −15% and for HDL-C and TGs, respectively after CR. However, much better improvements have been seen in subgroups of patients who have more abnormal baseline lipid values [55-57]. Aditionally, it is common for individuals with CHD to have "isolated" low levels of HDL-C with relatively normal to borderline-elevated low-density lipoprotein levels (LDL-C) and/or TGs. These individuals are often thought to be resistant to non-pharmacological and pharmacological regimens. But, there is evidence to support prominent improvements in HDL-C (+17%) and LDL-C/HDL-C (−11%) following formal CR[58]. Although, most CHD patients with elevated LDL-C are already being treated by statin, from which they gain effective LDL-C reduction. That's why CR leads to smaller benefit among isolated LDL-C decrease [59-60].

The Effect of CR on Mortality
In the early era of CR, two pilot meta-analyses, which involved 10 to 22 randomized clinical trials and > 4000 participants revealed that ET-based CR was as-

sociated with significant reductions in all-cause and CVD mortality of ~20%-25% as compared with usual care. However, these early studies primarily included smaller trials that involved mostly middle-aged male post-MI survivors. Women and elderly populations were largely absent from the analyses, which limited the generalizability of these reports [61, 62]. In subsequent systematic reviews and meta-analyses, higher risk patients and improved methodology and reporting were employed. These demonstrated a similar reduction in mortality rates associated with CR, as high as 13%-27% for all-cause mortality and 26%-36% for CVD mortality [63-66]. A large meta-analysis of 25 randomized and non-randomized studies from 1995 onward evaluating 219,702 patients supported the benefit of CR in overall mortality reduction in patients who were post-acute coronary syndrome, post-CABG, and in mixed CHD populations [67]. In a recent Cochrane review and meta-analysis of 63 RCTs between 1970 and 2014, including 14,486 CHD patients, CR was associated with an absolute risk reduction for CVD mortality from10.4% to 7.6% with no difference in all-cause mortality [68, 69]. Another meta-analysis that only involved RCTs from 2010 to 2015 (18 trials, 7691 patients) supported the impact of supervised ET programs on CVD mortality (Hazard risk 0.58, 95% CI 0.21-0.88), but also did not find a significant effect on all-cause mortality. Interestingly, the investigators also showed that a subgroup analysis of trials involving comprehensive CR programs (i.e., ET program along with close monitoring and management of major risk factors for CHD) both all-cause and CVD mortality were significantly decreased [70]. Cardiac rehabilitation was found effective on reducing Tpe interval, Tpe/QT and Tpe/QTc which is related with ventricular arrythmia and sudden cardiac death [71].

In different group of patients, the effect of CR on all-cause and CVD mortalitysuch as stable CHD or stable angina and acute coronary syndrome, including unstable angina, ST elevation MI and non-ST elevation MI, with or without revascularization, remains unclear. A few randomized control trials (RCT) have focused on these subcategories of CHD, because of the small number of cases that are too small to studymortality effects, benefits are unclear. Studies about individuals those with impaired left ventricular function, and patients with incomplete coronary revascularization will be important in determining optimal

therapy for those at high risk of decompensation and death. Aditionally, most previous studies followed patients for 12-36 months, which may not have allowed enough time to observe the associated mortality benefits from CR. As the healthcare fundings are shrinking, it will be crucial to identify the types of patients who will benefit from CR, as this will improve resource utilization in the long-term management of CVD patients [16].

Cardiac Rehabilitation and Rehospitalization

There are a little number of trials that investigated the hospital readmissions during the early studies of CR. Heran *et al.* [66] showed that total readmission rates were reduced in patients who underwent ET-based CR when compared with usual care in studies that followed patients for up to 12 months. A Cochrane review reported rehospitalization risk reduction with CR from 30.7% to 26.1% [68].Some recent trials and observational studies confirmed that, optimal medical management and early intervention may have a major impact on reducing recurrent hospitalizations in CHD and CR failed to show any benefit of CR. In contrast, the benefit of CR in reducing hospitalization has been shown for HF patients [67].

Cardiac Rehabilitation and Non-fatal Myocardial Infarction

In previous, some meta-analyses and systematic reviews did not show benefit of CR on recurrent non-fatal MI rates [62, 64-66]. Only two meta-analyses demonstrated a reduction by 47% in non-fatal MI rates [63, 72]. A lack of benefit in the prevention of recurrent non-fatal MI in the CR group was reported by others [67, 68]. It was thought that this was due to the conversion of fatal to non-fatal MIs, thereby decreasing mortality rates once CR was incorporated into routine cardiac care.

Van Halewijn *et al.* [70] reported the reduction of MI rates by 30% in ET-based CR as compared with usual care, and that cerebrovascular events were decreased by 60%, with the number needed to treat being 45 and 82 for MI and cerebrovascular events, respectively. This study was the first to show a significant reduction in stroke rates in this population after CR; however, this may be due to more comprehensive CV care, medication optimization, and improvements in CVD risk factors, such as BP control, smoking cessation, and reduced cholesterol levels, rather than the effects of ET alone [70].

Health-related Quality of Life and Psychosocial Stress in Cardiac Rehabilitation

The role of CR in enhancing patients' wellness is related to restoring or improving functional capacity. This relates to both physical work capacity and cognitive function. The latter is important because ~25% of CVD events are associated withphyscosocial stress (PSS), which has been shown to be associated with prolonged hospitalization, delayed return to work, and

Table 3. Mechanisms by which moderate-to-vigorous exercise training may reduce the risk for nonfatal and fatal cardiovascular events

Cardioprotective mechanisms of physical activity				
Psychologic	Anti-arrhytmic	Anti-thrombotic	Anti-atherosclerotic	Hemodynamics
↑Social interactions	↑Heart rate variability	↑Fibrinolysis	↑Insulin sensitivity	↑Cardiac remodelling
↓Psyhcosocial stress	↓Adrenergic activity	↓Platelet adhesion	↑HDL/LDL	↑Coronary flow
↓Depression	↑Vagal tone	↓Fibrinogen	↓Triglycerides	↑EPC's and CAC'S
		↓Blood viscosity	↓Blood pressure	↓Myocardial O2 demand
			↓Adiposity	↓Endothelial dysfunction
			↓Inflammation	↑Nitric oxide

BP = blood pressure, EPCs = endothelial progenitor cells, CACs = cultured/circulating angiogenic cells, ↑ = increased, ↓ = decreased, O2 = oxygen. *Nitric oxide also has antithrombotic effects.

increased mortality. The effects of PSS is inversely related to health-related quality of life [73-75]. A cohort study showed a tendency to return to work earlier than those in the conventional care group [76].

Cardioprotective Effect of Cardiac Rehabilitation

A meta-analysis of CHD patients, lipid profile including total cholesterol and LDL-C levels were significantly lower in patients in the comprehensive CR group, but not the ET-only group. Another meta-analysis based on this population demonstrated reductions in total cholesterol and triglycerides, without improvements in LDL-C and HDL-C levels [64, 65]. Additionally, patients' systolic BP significantly reduced following CR. Similarly, another RCTs demonstrated significant reductions in LDL-C and systolic BP values [70]. Kasapoglu Aksoy *et al*. [77] found that CR was found to be effective and safe in terms of functional capacity, daily life activities and anxiety in both obese and non-obese patients. In addition, one RCT that addressed $\geq$ 6 CVD risk factors during CR demonstrated a reduction in overall mortality, but no differences in overall mortality were present in studies that addressed fewer risk factors. According to these findings, the improvement in CHD risk factors are closely related with concomitant medical management during the ET-based programs, suggesting a critical role of risk factor modification in the secondary prevention. The overall benefits of CR programs for CHD are summarized in Table 3 [16, 70].

Complications of Exercise Therapy

Vigorous physical exercise is a CV stressor, it it can trigger both non-fatal and fatal arrhythmias, especially in patients with known or occult CVD. The 2007 American Heart Association scientific statement on exercise and acute CVD events, the risk of any major CV complication (sudden cardiac death, total mortality or MI) is 1/60.000 - 80.000 patient-hours [78]. In a study of > 25,000 patients participating in 65 CR centers, there was one CVD event for every 8,484 exercise tests performed, one CVD event for every 50,000 patient hours of ET, and 1.3/million cardiac arrests for every patient hours of ET [79]. In a review of 4,846 CHD patients enrolled in interval and continuous CR regimens in Norway, the difference in event rates were 1 in 129,456 h of moderate ET and 1 in 23,182 h of high intensity ET [80]. Although the benefits of structured CR clearly outweigh the risks, additional data on risk stratification and prophylactic strategies (e.g., value of warm-up/cool-down, education of warning signs or symptoms) may help reduce the infrequent, ET-related CVD events. These efforts are already under-way with the development of the Physical Activity Intelligence score, a validated physiologic metric that predicts CVD and all-cause mortality based on aerobic capacity; this is discussed further elsewhere in this issue [81].

CONCLUSION

CR is a cost effective strategy in secondary prevention of CVD. CR has been widely used for over forty yearsin different countries worldwide, with a robust evidence, effective improvements in cardiopulmonary fitness, PSS, quality of life and reduction in morbidity and mortality. It is also a strategy for reducing hospital readmitions. Despite these evidences, CR still remain underutilized not only because of the low patient referral, but also high discontinuation rates. Further randomized controlled research is necessary to evaluate long-term outcomes to assess the persistence of change observed in supervised CR of relatively short duration. Finally, a vigilant approach to primary prevention utilizing the expertise found in CR programs is needed.

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