Exercise-Based Cardiac Rehabilitation and Improvements in Cardiorespiratory Fitness: Implications Regarding Patient Benefit

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The cost of cardiovascular disease (CVD) is expected to triple in the next 20 years,[1] highlighting the need for low-cost preventive therapies to achieve improved cardiovascular health outcomes and patient value.[2] For literally millions of previously affected adults in the United States, interventions that have been shown to reduce the risk of recurrent cardiovascular events, collectively referred to as secondary prevention (Figure 1),[3] may include exercise training (ET)—based cardiac rehabilitation (CR) programs.

Numerous epidemiologic studies in men and women with and without known coronary heart disease (CHD) and varied comorbid conditions (eg, overweight/obesity, hypertension, metabolic syndrome, and type 2 diabetes mellitus) have now identified a low level of cardiorespiratory fitness (CRF), expressed as peak or maximal metabolic equivalents (METs; 1 MET equals a whole-body resting oxygen consumption of 3.5 mL/kg per min), as an independent risk factor for all-cause and cardiovascular mortality. Individuals with low CRF were approximately 2 to 5 times more likely to die during follow-up compared with their higher CRF counterparts.[4] The study by Martin et al,[5] published in the current issue of *Mayo Clinic Proceedings*, extends these analyses to a cohort of middle-aged and older men and women with documented CHD who participated in a 12-week ET-based CR program in Calgary, Alberta, Canada, examining the association between improvements in peak METs achieved through CR and subsequent mortality, with specific reference to patients in the low CRF cohort at baseline.

To assess the association among baseline, immediate postexercise-based CR (ie, after 12 weeks), and 1-year follow-up measures of peak METs on the risk of mortality in men and women with known CHD, Martin et al[5] conducted a retrospective analysis of data from the Cardiac Wellness Institute of Calgary, including 5641 patients (4282 men [76%] and 1359 women [24%]; mean ± SD age, 60.0±10.3 years) who participated in CR between July 1, 1996, and February 28, 2009. The CRF was estimated from the attained speed, grade, and duration of graded treadmill exercise testing to volitional exhaustion or adverse signs and symptoms. Patients were categorized into low (<5 METs), moderate (5-8 METs), and high (>8 METs) CRF groups. Following the baseline exercise test, patients engaged in a 12-week supervised ET regimen, 2 times per week, and were encouraged to participate in an additional 2 to 3 ET sessions on their own, using a prescribed target heart rate, MET level, and perceived exertion ("somewhat hard") as adjunctive intensity modulators. After completing the 12-week CR program, participants were educated regarding continued home-based lifestyle modification, including ET and dietary practices. A subset of the original population (3514 of 5641 [62.3%]) additionally underwent a repeated assessment at 1 year. All patients had a minimum 1-year follow-up; however, deaths in the entire study population during the full follow-up period program (approximately 13 years) were considered.

During the 12-week CR program, all subgroups demonstrated significant increases in their level of CRF ($P<.001$); however, improvements were greatest in those patients who had the lowest baseline CRF. Specifically, improvements were 1.41 METs (39% improvement), 1.01 METs (15% improvement), and 0.80 MET (8.6% improvement) for the low, moderate, and high CRF patients (at baseline), respectively. Restated, the greatest improvements occurred in those patients who were most likely to benefit most from an ET intervention, that is, those in the lowest CRF, high-risk cohort. Baseline CRF was inversely related to long-term mortality, even after adjusting for potential confounders, including age, sex, comorbid conditions, and disease severity. Improvement in CRF at 12 weeks was associated with decreased overall mortality, with the greatest reduction in mortality per MET increase (30%) among those

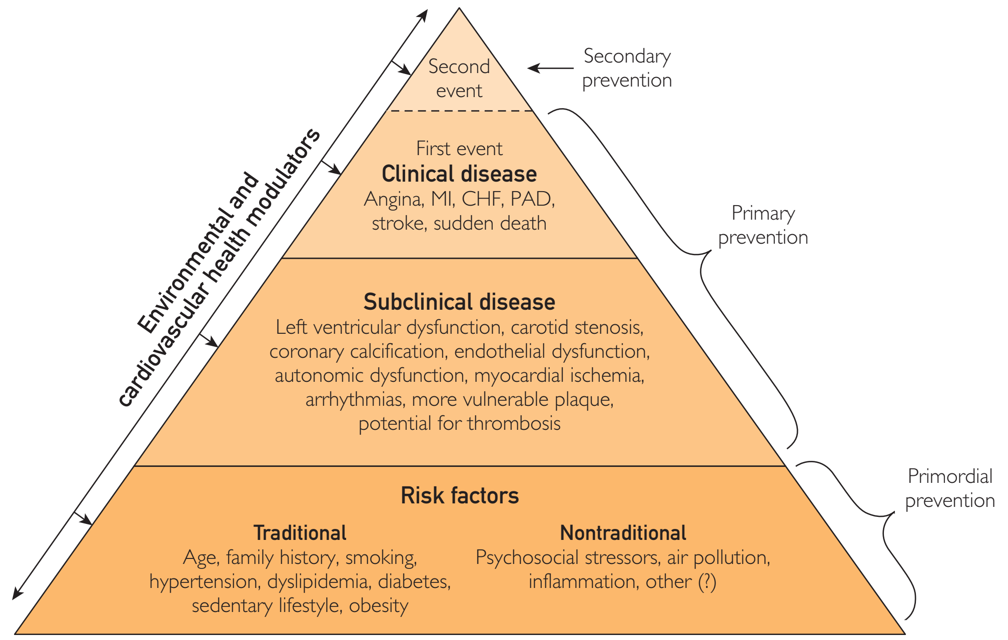

FIGURE 1. Risk factor framework and the progression of cardiovascular disease, with types of prevention interventions: primordial (prevention of risk factors), primary (treatment of risk factors), and secondary (prevention of recurrent cardiovascular events). Environmental and cardiovascular health modulators include dietary and physical activity practices, cigarette smoking, pharmacotherapies (eg, aspirin, β-adrenergic blockers, statins, and angiotensin-converting enzyme inhibitors) when indicated, and coronary revascularization when appropriate. CHF = congestive heart failure; MI = myocardial infarction; PAD = peripheral arterial disease. From *Circulation*,[3] with permission.

patients with the lowest baseline CRF levels (<5 METs). At 1 year, each 1-MET increase in CRF was associated with a 22% reduction in overall mortality for the entire cohort ($P<.001$). In view of the very modest changes in conventional risk factors (eg, cholesterol level, triglyceride value, and body mass index), even at 1 year, the investigators concluded that a significant mortality benefit of CR is due to the ET component of the program, whether it is medically supervised, home based, or both. This study may be somewhat limited by the lack of information regarding the ET habits after completing the CR program and underrepresentation of women, common problems in many such studies.

Fitness or Exercise Tolerance and Mortality in Secondary Prevention

Vanhees et al[6] reported the prognostic significance of peak oxygen uptake ($\dot{V}O_2$) in 527 men with CVD who were referred to an outpatient CR program. Peak $\dot{V}O_2$ on a cycle ergometer was directly measured by open-circuit spirometry a mean ± SD of 12.9±2.7 weeks after acute myocardial infarction (MI; n=312) or coronary artery bypass surgery (n=215). All tests were terminated at a comparable end point, that is, volitional fatigue (exhaustion). During a mean follow-up of 6.1 years, 33 and 20 patients died of cardiovascular and noncardiovascular causes, respectively. Those with the highest cardiovascular and all-cause mortality averaged 4.4 METs or less. In contrast, no deaths occurred among patients who averaged 9.2 METs or more. Similarly, long-term findings from the National Exercise and Heart Disease Project among post-MI patients demonstrated that every 1-MET increase in CRF after a training period was associated with a reduction in mortality from any cause that ranged from 8% to 14% during a 19-year follow-up.[7]

Kavanagh et al[8,9] evaluated the predictive value of cardiopulmonary exercise testing in

12,169 men (55.0±9.6 years old) and 2380 women (59.7±9.5 years old) with known CHD who were followed up for a mean of 7.9 and 6.1 years, respectively. Directly measured peak $\dot{V}O_2$ on a cycle ergometer at program entry proved to be a powerful predictor of cardiovascular and all-cause mortality. The cutoff point, above which there was a marked benefit in prognosis, was 13 mL/kg per minute (3.7 METs) in women and 15 mL/kg per minute (4.3 METs) in men. For each 1-mL/kg per minute increase in peak $\dot{V}O_2$, there was a 10% reduction of cardiovascular mortality in women vs 9% in men. The investigators concluded that men and women referred to CR who achieve only modest gains in CRF could nevertheless obtain significant prognostic and functional benefits.

In 2008, Kavanagh et al[10] compared changes in CRF, as measured by peak $\dot{V}O_2$, vs improvement in walking distance in predicting prognosis after acute MI and/or coronary artery bypass surgery in 6956 men who completed a 12-month walking-based CR program. After a median 9-year follow-up, improvement in walking distance was a strong independent predictor and a more accurate guide to prognosis than gains in peak METs. Each 1-mile increase in walking distance conferred a 20% reduction in cardiovascular mortality in this cohort of men with CHD. More recently, others have reported that distance walked on a 6-minute walk test predicted subsequent cardiovascular events during an 8-year follow-up in patients with stable CHD.[11]

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training randomized controlled trial in patients with chronic heart failure with reduced left ventricular ejection fraction (≤35%) found that ET was associated with a decreased incidence (11%) of combined all-cause mortality or hospitalization after adjusting for baseline prognostic variables.[12] Interestingly, the mean postconditioning improvement in directly measured peak $\dot{V}O_2$ was only 0.7 mL/kg per minute. In another investigation of 600 patients with CVD who were referred to a 12-week CR program, participants performed both entry-level and exit-level submaximal treadmill workloads, using fixed target heart rate ranges and perceived exertion ratings. After adjusting for age, each 1-MET increase in exit training level was associated with a 28% decrease in all-cause mortality.[13]

Collectively, the aforementioned referenced studies (Table 1) and other recent reports[14] support the hypothesis that CRF provides a strong, graded inverse association with cardiovascular and all-cause mortality in patients with and without CHD, irrespective of sex, body mass index, major risk factors, heart failure, and other comorbid conditions. An exercise capacity of less than 5 METs correlates with a higher mortality group, whereas 9 to 10 METs or more generally identifies a cohort with an excellent long-term prognosis, regardless of the underlying extent of CHD. These data and the results of other investigations[15] also suggest an "asymptote of gain" beyond which further improvements in CRF (ie, beyond 9-10 METs) convey little or no additional survival benefit. The findings of Martin et al[5] reinforce the notion of small gains yielding big results and suggest that CHD patients with low CRF should be particularly targeted in CR programs to increase their functional capacity in an effort to reduce their heightened mortality.

Cardioprotective Effects of Regular ET and/or Improved CRF

Numerous mechanisms may be responsible for the decreased mortality associated with ET-based CR, including antiatherosclerotic, antiischemic, antiarrhythmic, antithrombotic, and psychologic effects (Table 2).[4] Because more than 40% of the risk reduction associated with ET cannot be accounted for by changes in traditional risk factors, Green et al[16] proposed a cardioprotective "vascular conditioning" effect, including enhanced nitric oxide vasodilator function, improved vascular reactivity, altered vascular structure, or combinations thereof. This adaptation may explain, at least in part, the significantly higher event-free survival in a cohort of patients (n=101) with obstructive CHD who were randomized to 12 months of ET or percutaneous coronary intervention with stenting (88% vs 70% in the percutaneous coronary intervention group; P=.02).[17] Whereas percutaneous coronary intervention treats a very short segment of the diseased coronary tree, it was suggested that ET exerts beneficial effects on endothelial function and disease progression in the entire arterial bed.[16,17] Decreased vulnerability to arrhythmias and increased resistance to threatening ventricular arrhythmias have also been postulated to reflect exercise-related autonomic adaptations

TABLE 1. Relation of Fitness or Exercise Tolerance to All-Cause or Cardiovascular Mortality in Secondary Prevention[a]

Reference	Population/follow-up period	Fitness measurement	All-cause or cardiovascular mortality
Vanhees et al,[6] 1994	Male patients ≥4 wk after MI (n=312) or CABG (n=215) for 6.1 y	Peak $\dot{V}O_2$	71% Decrease per 1-L/min increase
Dorn et al,[7] 1999	315 Post-MI men randomized to a 6-mo exercise program; patients were followed up for 19 y	Peak METs	8%-14% Decrease per 1-MET increase
Kavanagh et al,[8] 2002	12,169 Men with CVD referred for exercise-based CR; median follow-up was 7.9 y	Peak $\dot{V}O_2$	9% Decrease per 1-mL/kg/min increase
Kavanagh et al,[9] 2003	2380 Women with CVD referred for exercise-based CR; mean follow-up was 6.1 y	Peak $\dot{V}O_2$	10% Decrease per 1-mL/kg/min increase
Kavanagh et al,[10] 2008	6956 Men with CVD completing a 12-mo walking-based training regimen; median follow-up was 9.0 y	Walking distance	20% Decrease per 1-mile improvement
O'Connor et al,[12] 2009	2331 Medically stable outpatients with heart failure and reduced EF (≤35%), randomized to exercise training or usual care; median follow-up was 30 mo	Peak $\dot{V}O_2$	11% Decrease per 0.7-mL/kg/min increase
Feuerstadt et al,[13] 2007	600 Men and women with CVD who were referred to a 12-wk exercise-based CR program; mean follow-up was 4.4 y	Exit training MET level	34% Decrease per 1-MET increase; 28% decrease per 1-MET increase[b]
Beatty et al,[11] 2012	556 Outpatients with stable CHD; median follow-up was 8.0 y for cardiovascular events (heart failure, MI, and death)	6MWT	Each SD decrease in 6MWT distance (104 m) was associated with a 30%[c] to 55%[d] higher rate of cardiovascular events
Martin et al,[5] 2013	5641 Patients with CHD who participated in a 12-wk exercise-based CR program; ≥1 y follow-up for all patients	Peak METs	22% Decrease per MET increase (entire cohort) and a 30% decrease per MET increase in those with low baseline fitness (<5 METs)

[a]CABG = coronary artery bypass graft surgery; CHD = coronary heart disease; CR = cardiac rehabilitation; CVD = cardiovascular disease; EF = ejection fraction; MET = metabolic equivalent (where 1 MET equals 3.5 mL/kg/min); MI = myocardial infarction; 6MWT = 6-minute walk test; $\dot{V}O_2$ = oxygen consumption.
[b]After adjustment for age.
[c]Adjusted for potential confounders.
[d]Unadjusted.

(eg, increased vagal tone and decreased adrenergic activity).[18]

Another benefit of ET-based CR includes improvements in psychological dysfunction, which is common in patients with CHD.[19,20] Studies have reported nearly 50% reductions in adverse behavioral scores and the prevalence of psychological disorders, including depression, anxiety, hostility, and overall stress, after formal CR.[19,20] Moreover, CHD patients with depression and/or psychological distress seem to derive the greatest mortality benefits from CR, especially in those who achieve only modest improvements in CRF (<10%). Such patients commonly demonstrate significant reductions in the prevalence of depression and depression-related mortality, similar to that achieved with more marked improvements in peak METs.[21] Even greater reductions in depression-related mortality were noted in very high-risk heart failure patients after CR.[22] Thus, major benefits of CR programs may be related to improving levels of CRF in patients with abnormal psychological profiles.[23]

Exercise Recommendations for Patients With CHD

Patients with CHD should be counseled to participate in 30 to 60 minutes of moderate-intensity aerobic physical activity, such as brisk walking, at least 5 days and preferably 7 days per week, complemented by resistance training 2 or more days per week and an increase in daily lifestyle activities (eg, walking breaks at work, gardening, and household work).[24,25] A major goal is to improve CRF and move patients out of the lowest CRF, least active, high-risk cohort.[24]

The threshold intensity for training to improve CRF in exercise-based CR has been

TABLE 2. Potential Cardioprotective Effects of Regular Physical Activity

	Antiatherosclerotic	Psychological	Antithrombotic	Anti-ischemic	Antiarrhythmic
Increase in	HDL-C and insulin sensitivity	Social support	Fibrinolysis	Coronary flow, EPCs, CACs, and nitric oxide	Vagal tone and heart rate variability
Decrease in	total cholesterol, LDL-C, blood pressure, and inflammation	Depression and stress	Platelet adhesiveness, fibrinogen, and blood viscosity	Myocardial oxygen demand, endothelial dysfunction	Adrenergic activity

CAC = cultured/circulating angiogenic cells; EPC = endothelial progenitor cells; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

suggested to approximate 45% of the oxygen uptake reserve,[26] which is the difference between resting and peak METs, using a level of metabolism that starts at a resting level (ie, 1 MET) rather than at zero. To illustrate, if a patient has an aerobic capacity of 5 METs, the minimum intensity for training would be calculated as 45% of the range between rest and his/her functional capacity, that is, $([5 - 1] \times 0.45) + 1 = 2.8$ METs. In the absence of a baseline peak or symptom-limited exercise test, the threshold intensity for training in CR can be approximated by the patient's standing resting heart rate plus 20 to 30 beats/min,[27,28] using perceived exertion (fairly light to somewhat hard) as an adjunctive intensity modulator.

Although numerous studies have reported modest improvements in CRF and selected CHD risk factors with standard exercise-based CR, other investigations have sought to determine the amount of physical activity (kilocalories per week) needed to attenuate the progression of coronary atherosclerotic lesions and/or promote greater weight losses and even more favorable cardiometabolic risk profiles (Figure 2).[29,30] Comparing coronary angiographic findings at baseline and after 12 months of an exercise intervention, Hambrecht et al[29] reported that CHD patients with moderate (1533±122 kcal/wk) and high levels (2204±237 kcal/wk) of leisure-time physical activity showed no change and regression of coronary atherosclerotic lesions, respectively, whereas those with the lowest level of leisure-time physical activity (1022±142 kcal/wk) demonstrated progression of disease ($P<.005$). Similarly, Ades et al[30] noted profound reductions in body weight and fat stores and marked improvements in cardiometabolic risk factors in overweight CHD patients who underwent a high-calorie energy expenditure (3000 to 3500 kcal/wk) CR program compared with a standard CR control group. These data suggest that CHD patients who are able to adopt a more aggressive training regimen (ie, approximating 5-6 hours per week of vigorous ET) are likely to derive even greater benefits.

Implications for Health Care Professionals

Although the inverse association between aerobic capacity and cardiovascular and all-cause mortality has been widely promulgated among physiologists and epidemiologists, the medical community has been less sanguine in embracing CRF as one of the strongest and most consistent prognostic markers in patients with and without CHD. For patients with stable CHD, each 1-MET increase in CRF is associated with an 8% to 35% (median, 16%) reduction in mortality, which compares favorably with the survival benefit conferred by the most commonly prescribed cardioprotective medications.[31] Because CRF is such a powerful prognostic indicator, measurement of peak METs should be considered to be a standard assessment for patients with CVD or high CVD risk. The findings of Martin et al[5] clearly demonstrate

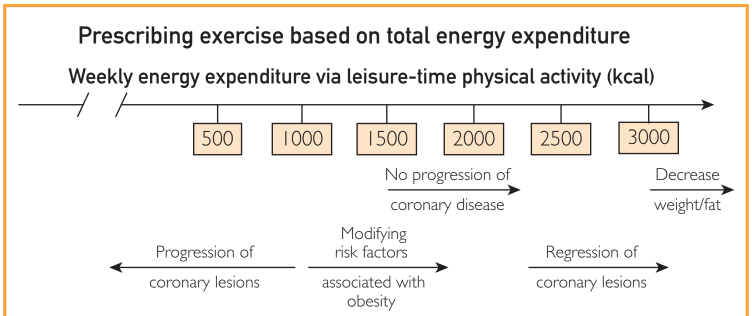

FIGURE 2. Impact of the amount of physical activity (kilocalories per week) on angiographic, risk factor, and weight loss outcomes associated with exercise-based cardiac rehabilitation.

that CHD patients with low CRF can especially benefit from prescribed CR to improve functional capacity and survival. Unfortunately, for too many patients with CHD, the ET prescription remains underfilled.[31-34]

Areas of Continued Research

First, viable systems to assist patients in continuing their secondary prevention efforts, including ET, need to be developed. A disease management system, similar to one developed at the Mayo Clinic, has been demonstrated to be effective.[35] Second, new techniques of ET, including high-intensity interval ET, which may provide greater improvements in CRF and endothelial function than does moderate-intensity ET, should be further evaluated in larger numbers of patients with CVD, including CHD.[36] Finally, enhancing the referral, enrollment, and completion of formal CR for all patients, especially women, elderly populations, and those from rural areas, is urgently needed.[37,38]

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Abbreviations and Acronyms: **CHD** = coronary heart disease; **CR** = cardiac rehabilitation; **CRF** = cardiorespiratory fitness; **CVD** = cardiovascular disease; **ET** = exercise training; **MET** = metabolic equivalent; **MI** = myocardial infarction; $\dot{V}O_2$ = oxygen uptake

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