Review

Exercise and the Cardiovascular System
Clinical Science and Cardiovascular Outcomes


Abstract: Substantial evidence has established the value of high levels of physical activity, exercise training (ET), and overall cardiorespiratory fitness in the prevention and treatment of cardiovascular diseases. This article reviews some basics of exercise physiology and the acute and chronic responses of ET, as well as the effect of physical activity and cardiorespiratory fitness on cardiovascular diseases. This review also surveys data from epidemiological and ET studies in the primary and secondary prevention of cardiovascular diseases, particularly coronary heart disease and heart failure. These data strongly support the routine prescription of ET to all patients and referrals for patients with cardiovascular diseases, especially coronary heart disease and heart failure, to specific cardiac rehabilitation and ET programs. (Circ Res. 2015;117:207-219. DOI: 10.1161/CIRCRESAHA.117.305205.)

Key Words: body mass index ■ cardiovascular diseases ■ exercise ■ heart failure ■ metabolic equivalent

Despite the fact that the American Heart Association has established sedentary lifestyle as a major modifiable risk factor for cardiovascular diseases (CVD), a sizable percentage of the US population has low levels of physical activity (PA).1-3 Many organizations, including the American Heart Association and the American College of Sports Medicine, have recommended increasing PA or aerobic exercise training (ET) to increase levels of cardiorespiratory fitness (CRF) in the general population, including individuals with CVD.1-3

In this article, we review the physiology of ET and the acute and chronic adaptation, including the interaction of PA, ET, and CRF on overall CVD risk. In addition, we discuss the relative value of PA versus CRF, as well as the importance of CRF in obesity in the fitness versus fatness debate. We also review the role of formal cardiac rehabilitation and ET (CRET) programs on coronary heart disease (CHD) risk factors and morbidity and mortality in patients with CVD, including CHD and heart failure (HF). Guidance for ET dosing, as well as the potential toxicity of extremely high doses of ET, is reviewed. Finally, we provide recommendations for the routine ET prescription.

Cardiac Exercise Physiology: The Acute Response and Chronic Adaptations to Aerobic Exertion

An appropriate response to an acute aerobic exercise stimulus requires robust and integrated physiological augmentation from the pulmonary, respiratory, skeletal muscle, and cardiovascular systems. Age, sex, and genetic predispositions influence the physiological response and therefore performance during aerobic exertion. For example, with respect to maximal aerobic capacity, genetic components have been estimated to account for 20% to 40% of the variability, age causes a progressive decline, and female values are on average 25% lower than males.4 However, in apparently healthy individuals, irrespective of nonmodifiable factors, chronic, repetitive bouts of aerobic ET lead to significant improvements in physiological function and therefore performance. Although all systems (ie, pulmonary, respiratory, skeletal muscle, and cardiovascular) involved in orchestrating an appropriate response to aerobic exercise are important, the cardiovascular system, in particular cardiac systolic and diastolic function, may be thought of as the central hub. This section will provide a concise review on cardiovascular exercise physiology as it relates to both an acute response, focusing on the central response and chronic adaptations, addressing both central and peripheral responses to aerobic ET. The healthy adult model across the lifespan will be highlighted with some discussion pertaining to the effect of cardiovascular dysfunction/CVD. Finally, our emerging understanding of the potential adverse consequences of chronic aerobic ET at high volumes and intensities will be addressed.
Cardiac Response to Acute Aerobic Exercise: Focus on Augmenting Cardiac Output

Augmentation of cardiac output (CO) is the central determinant of maximal oxygen consumption ($VO_2$), as defined by the Fick equation: $VO_2 = CO \times a-vO_2$ difference, where $a-vO_2$ difference is the arteriovenous oxygen difference. At rest, CO is homogenous at $\approx 5$ L/min. However, at maximal exercise, CO varies greatly, from $\approx 20$ L/min in apparently healthy untrained individuals to $\approx 40$ L/min in elite aerobic athletes. This wide variability in CO in part explains the wide range in maximal $VO_2$, with normal values ranging from $\approx 35$ to $85$ mL O$_2$ kg$^{-1}$ min$^{-1}$. CO is the product of stroke volume (SV) and heart rate (HR), and both significantly increase during aerobic exercise. Left ventricular (LV) SV, commonly the heart chamber focal point of discussion with respect to cardiovascular exercise physiology, is augmented during aerobic exertion by a synergistic increase in end-diastolic volume (ie, preload) and myocardial contractility. Although resting SV is $\approx 50$ mL, the increases in filling volume and contractility raise SV several fold during exercise, with large variability that is influenced by age, sex, genetics, and ET status. For example, the SV at maximal exercise for 2 20-year-old men, both with a maximal HR of 200 bpm, with maximal CO of 20 and 35 L/min, respectively, will have maximal SVs of 100 mL and 175 mL, respectively. The increase in SV during exercise plateaus at $\approx 50\%$ of maximal $VO_2$. Once SV plateaus at $\approx 50\%$ of maximal $VO_2$, it is the continued linear rise in HR that drives the further increased CO. During a bout of progressive aerobic exercise to maximal capacity, HR rises in a linear fashion at a rate of $\approx 10$ bpm per 3.5 mL O$_2$ kg$^{-1}$ min$^{-1}$ increase in oxygen demand. Maximal HR during an aerobic exercise test is still commonly estimated using the 220-age equation, although considerable variability in this estimation exists (ie, SD of $\pm 12$ bpm). At maximal exercise, a high HR has the potential to decrease LV ventricular filling time possibly resulting in a reduced CO.

Cardiac Adaptations to Chronic Aerobic ET: Mechanisms for Increased CO

Participation in a chronic aerobic ET program produces a host of positive morphological and physiological cardiovascular adaptations in apparently healthy individuals, irrespective of age and sex. Commonly reported morphological adaptations associated with chronic aerobic ET is LV dilation (ie, increased end-diastolic diameter) and hypertrophy (ie, increased wall thickness), referred to as ET-induced cardiac remodeling. These morphological LV adaptations parallel enhanced physiological function during exercise through (1) increased early diastolic filling secondary to a combination of increased preload and increased myocardial relaxation; and (2) increased contractile strength as captured by advanced imaging techniques, such as tissue Doppler and speckle-tracking imaging. Although much focus has been directed toward the LV, it is important to note that morphological adaptations also occur in the right ventricle that appear to mirror LV adaptations. The magnitude of ET-induced cardiac adaptations in apparently healthy individuals is influenced by the interplay of several factors, including age, sex, genetics, previous training status, mode of ET, and ET volume. As such, an accurate prediction of the degree of cardiac adaptations expected with a given aerobic ET program for a given individual is not feasible. Suffice to say, aerobic ET, performed within general ET prescription parameters, positively alters cardiac morphology and physiological performance. These adaptations lead to increased CO during exercise, facilitating a significantly higher maximal $VO_2$ post training. Moreover, the declines in cardiac function and, therefore, aerobic performance associated with aging are significantly attenuated by participation in an ET program across the lifespan. However, morphological changes are less pronounced in patients with CVD, which is an important distinction between young, healthy individuals, who adapt readily in terms of central adaptation, and those who have existing CVD and the elderly.

Effect of Aerobic ET on the Vasculature

Repetitive bouts of aerobic ET results in a number of favorable vascular adaptations as well, significantly attenuating deleterious adaptations precipitated by the aging process. Measures of arterial stiffness are significantly lower in individuals with a higher aerobic capacity (ie, cross-sectional analysis), as well as individuals who have recently completed an aerobic ET program (ie, longitudinal analysis). Protection against systemic oxidative stress and inflammation induced by chronic aerobic ET is posited to be a primary mechanism for the observed reductions in arterial stiffness. Enhanced endothelium-dependent vasodilation through increased production of nitric oxide is also a clear aerobic ET benefit, including
in the coronary circulation. When aerobic ET involves large muscle groups (eg, treadmill training or lower extremity ergometry), systemic vascular benefits are realized. Aerobic ET also improves endothelium-dependent vasodilation in the coronary microcirculation, again through increased production of nitric oxide.

Cardiac Disease/Dysfunction: Altered Cardiac Physiology=Diminished Aerobic Performance

Given the clear and central role normal cardiac function plays in defining maximal aerobic capacity, disease or dysfunction that detrimentally affects CO will also compromise maximal VO2. In fact, although aerobic ET is clearly safe and effective in improving functional capacity in many patient populations diagnosed with cardiac conditions, as discussed in more detail in this review, maximal aerobic capacity is unlikely to normalize if impaired cardiac physiology persists. This is readily apparent in training studies in patients diagnosed with HF, where postaerobic ET maximal VO2 values, although significantly improved compared with pre-ET, commonly do not greatly exceed 20 mL O2 kg−1 min−1, which is well below age- and sex-predicted normative values. This is not to suggest that ET is not highly beneficial in patient populations, such as HF; in fact the converse is true and CRET is considered a standard of care for individuals with HF. However, without normalization of cardiac physiology and, therefore, CO, true normalization of maximal aerobic capacity is not possible.

Effect of PA and CVD

Data from numerous epidemiological studies demonstrate that low levels of PA are associated with higher prevalence of most CVD risk factors, including hypertension, obesity, dyslipidemia, metabolic syndrome (MetS), depression, and type 2 diabetes mellitus (T2D). In addition, substantial data demonstrate a strong inverse relationship between PA levels and all-cause and CVD mortality. Several studies, mostly from Finnish cohorts, suggest that low levels of occupational PA may have an independent contribution to overall CVD mortality. High levels of PA have also been demonstrated to reduce CVD mortality risk in high-risk populations, including those with T2D and the elderly. In obesity, the consensus among studies is that high levels of PA attenuate but do not completely eliminate the increased cardiovascular mortality risk associated with obesity. In addition, increases in PA levels over time have been associated with reduced CHD and CVD mortality risk.

CRF and CVD Risk

As discussed above for PA, a low level of CRF is a well-recognized risk factor for CHD and CVD mortality, and although PA is probably the most important factor determining CRF along with non-PA inherited factors, most studies demonstrate that CRF is a more potent predictor of prognosis than is PA, at least as determined by self-report questionnaires. The potential benefits of CRF are numerous and are summarized in Table 1. Typically, CRF is expressed in metabolic equivalents (METs), which are typically estimated from workload on submaximal or maximal treadmill exercise stress tests (based on speed and incline), and this can be more precisely assessed by using cardiopulmonary exercise testing and assessing peak VO2, as well as a host of other parameters (eg, anaerobic or lactate threshold).

High levels of CRF, like higher PA, are associated with reduced prevalence of many CHD and CVD risk factors, including hypertension, obesity, MetS, and T2D. More importantly, considerable data have demonstrated the powerful prognostic effect of CRF, including in the general population, patients at high risk of CVD, as well as in CVD populations, such as CHD and HF.

A recent high-profile meta-analysis by Kodama et al observed that a 1-MET increase in CRF was associated with 13% and 15% reductions, respectively, in all-cause and CHD/CVD mortality. In addition, this meta-analysis defined age- and sex-specific normal levels of CRF associated with lower event rates in both men (40 years: 9 METs; 50 years: 8 METs; at 60 years: 7 METs) and women (40 years: 7 METs; 50 years: 6 METs; 60 years: 5 METs).

Even in high-risk individuals with MetS, pre–diabetes mellitus or T2D, high levels of CRF are associated with good prognosis, typically better than the prognosis in unfit individuals without these conditions. Berry et al have demonstrated the importance of high CRF to protect against lifetime CVD risk, as these authors found that those with a high burden of traditional CVD risk factors but a high level of CRF had lifetime CVD mortality rates that were similar or lower than those with a low burden of traditional CVD risk factors, suggesting the importance of CRF in those with otherwise high CVD risk.

Several studies have also focused on changes in CRF over time and the impact on CVD morbidity and mortality. Blair and colleagues, using data from the Aerobics Center Longitudinal Study (ACLS; n=9777), reported that men classified as unfit (ie, bottom 20th percentile of CRF based on age and sex of the entire ACLS population) at their first examination but fit at their second examination several years later had a 52% reduction in CVD mortality compared with men classified as unfit on both examinations. Lee et al also using the

Table 1. Potential Benefits of Cardiorespiratory Fitness on Prognosis

<table>
<thead>
<tr>
<th>Physiological benefits</th>
<th>Clinical benefits</th>
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<tbody>
<tr>
<td>Reduced blood pressure</td>
<td>Improved insulin sensitivity</td>
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<td>Improved heart rate variability</td>
<td>Decreased myocardial oxygen demands</td>
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<td>Increased myocardial infarction</td>
<td>Maintain lean mass</td>
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<td>Improved endothelial function</td>
<td>Reduced visceral adiposity</td>
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<td>Reduced blood and plasma viscosity</td>
<td>Increased capillary density</td>
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<td>Increased mitochondrial density</td>
<td>Improved mood and psychological stress</td>
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<td>Reduced systemic inflammation</td>
<td>Improved sleep</td>
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<td>Reduced risk of developing</td>
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<tr>
<td>Hypertension</td>
<td>Osteoporosis</td>
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<td>Depression</td>
<td>Osteoarthritis</td>
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<tr>
<td>Metabolic syndrome</td>
<td>Dementia and Alzheimer disease</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Breast, colon, and other cancers</td>
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ACLS data (n=14345) evaluated the long-term (mean follow-up, 11.4 years) effects of changes in CRF on CVD mortality and observed significant reductions in CVD mortality of 27% and 42%, respectively, in those who had either no change or improvements in CRF at their second examination on average 6.3 years later. For every 1-MET increase in CRF over time, all-cause and CVD mortality were reduced by 15% and 19%, respectively. Moreover, in the fitness versus fatness debate, discussed below, these improvements persisted after adjusting for changes in body mass index (BMI). Others have also reported favorable effect of CRF changes over time and subsequent mortality.3,51

**CRF Versus BMI**

Several authors of this review and others have evaluated the independent effects of CRF and adiposity on subsequent CVD mortality, and considerable evidence suggests that high levels of CRF eliminate or significantly attenuate the CVD mortality risk in overweight and obese individuals, which has been demonstrated in the general population, in those with dyslipidemia and in T2D.1,4,2,4,5 Therefore, CRF seems to markedly alter the relationship between adiposity and subsequent prognosis.

Barry et al42 recently performed a meta-analysis of 10 major studies and quantified the combined effect of CRF and obesity on mortality. They demonstrated that compared with normal weight and fit individuals, unfit individuals had double the mortality regardless of BMI, whereas an obese but fit individual had similar survival compared with normal weight individuals. In a study from the ACLS of 3148 healthy adults, changes over time in both body fatness and CRF predicted the development of hypertension, MetS, and dyslipidemia, but changes in CRF were superior to increases in body fatness for predicting future risk of these disorders.53 As reviewed earlier, after adjustment for changes in CRF, BMI changes over time no longer were associated with CVD or all-cause mortality.50 Therefore, the constellation of these data indicate that CRF is more important than obesity on long-term prognosis.

We have also addressed the effect of CRF to alter the relationship between obesity status and subsequent prognosis in the obesity paradox that has been described in patients with CVD,52 particularly CHD,54 and HF.55 Although obesity adversely affects most CVD risk factors and increases the risk of most CVD, considerable evidence during the past 15 years has indicated an obesity paradox, where the overweight and obese individuals with most CVD seem to have a better outcome than do their leaner counterparts with the same CVD, as has been reviewed in detail elsewhere.52,54,55 In a study of 9563 patients with CHD, only those in the bottom tertile of age- and sex-related CRF demonstrated an obesity paradox, with leaner patients by BMI, body fat percentage, and even waist circumference or central obesity had a higher all-cause and CVD mortality than did heavier patients who were unfit.56 On the other hand, those patients with CHD who were more fit had a favorable prognosis, regardless of their level of adiposity. Likewise, in 2066 patients with systolic HF who had CRF assessed by cardiopulmonary exercise testing, the HF patients with low CRF (ie, peak VO₂<14 mL O₂ kg⁻¹ min⁻¹) had a poor prognosis, and survival was related to BMI, showing a typical obesity paradox where the best survival occurred in obese with BMI ≥ 30 kg/m², worst survival with BMI 18.5 to 24.9 kg/m², and intermediate survival in the overweight BMI.57 As demonstrated in patients with CHD, HF patients with more preserved CRF (ie, peak VO₂>15 mL O₂ kg⁻¹ min⁻¹) had a good survival, regardless of BMI, and no obesity paradox was evident. Therefore, these data indicate that CRF also markedly affects the obesity paradox.

**Effect of ET on CRF and CVD Risk Factors**

Although genetic hereditability is a determinant of CRF,6 the most important contribution to CRF is PA and ET. Many studies indicate significant improvements in CRF associated with moderate aerobic ET, but more vigorous ET seems to confer equal or enhanced health and CVD benefits, as well as greater improvements in CRF.3,56

In addition, ET affects many of the standard CVD risk factors, including plasma lipids, especially high-density lipoprotein cholesterol,57-59 adiposity,60,61 fasting glucose levels and T2D control,62,63 and blood pressure–lowering and hypertension control64; however, for all of these parameters, the effect of ET may be statistically significant, but the effect is overall modest, often <3% to 5%.

**Benefits of ET and Secondary CVD Prevention**

Several observational studies, as well as randomized control trials have established the benefits of PA and ET in cohorts with CVD, including CHD and HF.1 Perhaps the most impressive evidence of the benefits of ET is in formal CRET programs of patients after major CHD events (Table 2).3

**Effect of CRET on Obesity**

Considering the high prevalence of overweight and obesity in society and in particular in patients with CHD, there are potential benefits of formal CRET in the promotion of weight loss and weight maintenance.65 Despite the extensive data on the obesity paradox in CVD, including CHD, briefly discussed above,55 support still exists for the benefits of at least purposeful (as opposed to nonpurposeful) weight loss in patients with CHD.65

In patients with CHD, CRET has produced an impressive 37% reduction in the prevalence of MetS.66 Moreover, in patients who successfully lost weight in CRET programs (eg, >5% or mean 10%), statistically greater improvements in CRF and plasma lipids were noted compared with those who did not lose weight.67 In a study of 377 patients from the Mayo Clinic, weight loss was associated with reductions in total mortality plus major CVD events, even among CHD patients with a BMI of <25 kg/m², as well as in those with higher BMI.68 Ades et al48,69 demonstrated that greater weight loss with CRET occurred using a high-calorie expenditure program, in the range of 3000 to 3500 kcal per week, which was associated with reductions in insulin resistance, improvements in high-density lipoprotein cholesterol, and triglycerides, as well as reduced blood pressure and plasminogen activator inhibitor I. In a recent large meta-analysis in patients with CHD, weight loss was associated with a 30% increase in major CVD end points; however, this was because of observational weight loss in 10 cohorts who had a 62% increase in major events, compared with presumed intentional weight loss in 4 cohorts, who had a 33% reduction in major events.65 Therefore, the magnitude of
data still suggests benefits of purposeful weight loss, ideally through the synergistic implementation of ET and a healthy, calorically appropriate, diet, during CRET.

**Effect of CRET on Lipids and Inflammation**

Although improvements in low-density lipoprotein cholesterol with CRET are minimal, improvements in high-density lipoprotein cholesterol and triglycerides are more substantial (mean changes, +6% and −15%, respectively), with relatively greater improvements in those with remarkably abnormal baseline values.3,70,71

We have recently reviewed the potential of PA and ET to improve levels of high-sensitive C-reactive protein (hs-CRP).72 In patients with CHD, hs-CRP fell by ≈40% in those who completed CRET, with no improvement noted in control patients with CHD who did not attend CRET (Figure 1).73 Patients with MetS had nearly 2-fold higher levels of hs-CRP compared with those without MetS, and both groups received substantial improvements in hs-CRP after CRET.74 Lean patients with CHD and obese patients with CHD who did not lose weight had only minor improvements in hs-CRP after CRET, whereas obese patients with weight loss had marked reductions in hs-CRP.74

**Effects of CRET on Psychological Risk Factors**

One of the most important effects of CRET may be in the area of psychological stress, including levels of depression, anxiety, hostility, and total psychological stress.75 Patients with CHD have a high prevalence of psychological stress, with marked benefits after formal CRET (Figure 2).76 In addition, CHD patients with depression who completed CRET had 70% reductions in 3-year mortality (8% versus 30%; P<0.0001) compared with a control group of depressed patients with CHD who did not attend CRET.77 Because CRET involves other aspects of therapeutic lifestyle changes besides ET, we divided patients into those who did not improve peak $V_O^2$, those who had mild improvements in peak $V_O^2$ (≤10%), and in those with more marked improvements (>10%) and demonstrated that improvements in depression and depression-related increased mortality only occurred in those who improved CRF, although the improvements were similar in those who had mild and more marked improvements in peak $V_O^2$.77,78

**Effect of CRET on CRF**

Probably, the most important improvement in CRET is on CRF, which has recently been reviewed in detail.1 In a review of >18,000 patients with CHD in 9 studies, where CRF was assessed by several methods (estimated METs, peak $V_O^2$, walking distance, and 6-minute walk test), improvements in CRF were strongly associated with reductions in all-cause and CVD mortality.1 For patients with stable CHD, every 1-MET increase in CRF was associated with an 8% to 35% (median, 20%) reduction in CVD mortality.1

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**Table 2. Benefits of Formal Cardiac Rehabilitation and Exercise Training Programs**

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<tr>
<th>Benefit</th>
<th>Before Rehabilitation</th>
<th>After Rehabilitation</th>
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<tr>
<td>Improvement in exercise capacity</td>
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<td>Estimated metabolic equivalents, +35%</td>
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<td>Peak oxygen consumption, +15%</td>
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<td>Peak anaerobic threshold, +11%</td>
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<tr>
<td>Improvement in lipid profiles</td>
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<td>Total cholesterol, −5%</td>
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<td>Triglycerides, −15%</td>
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<td>HDL-C, +6% (higher in patients with low baseline)</td>
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<td>LDL-C, −2%</td>
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<td>LDL-C/HDL-C, −5% (higher in certain subgroups)</td>
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<td>Reduction in inflammation</td>
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<td>hs-CRP, −40%</td>
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<td>Reduction in indices of obesity</td>
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<td>BMI, −1.5%</td>
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<td>fat, −5%</td>
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<td>Metabolic syndrome, −37%</td>
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<td>Improvements in behavioral characteristics</td>
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<td>Somatization</td>
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<td>Overall psychological distress</td>
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<td>Reduction in stress-related increased mortality</td>
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<td>Improvements in quality of life and components</td>
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<td>Improvement in autonomic tone</td>
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<td>Increased heart rate recovery</td>
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<td>Increased heart rate variability</td>
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<td>Reduced resting pulse</td>
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<td>Improvements in blood rheology</td>
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<td>Reduction in hospitalization costs</td>
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<td>Reduction in major morbidity and mortality</td>
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BMI indicates body mass index; hs-CRP, high-sensitive C-reactive protein; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Reprinted from Swift et al1 with permission of the publisher. Copyright ©2013, The Japanese Circulation Society.
16%) reduction in mortality. Considering the typical 15% improvement in peak VO₂ and 35% increase in estimated METs after CRET, these benefits translate into substantial reductions in subsequent mortality.

**Effects of CRET on Morbidity and Mortality**

One of the first major meta-analyses of CRET programs by O’Connor et al. in 1989 included 22 randomized control trials in 4551 patients with CHD who had post–myocardial infarction and demonstrated reductions in total and CVD mortality of 20% and 25%, respectively, at 3-year follow-up after CRET. A more recent meta-analysis of 8440 participants in 32 randomized control trials demonstrated a 31% reduction in CVD mortality after CRET. Although most of the benefits from CRET in CHD have been described in patients with post–myocardial infarction, a recent study from Olmsted County Registry in 2395 postpercutaneous coronary intervention patients demonstrated a 45% reduction in all-cause mortality after CRET. Although most of the benefits from CRET in CHD have been described in patients with post–myocardial infarction, a recent study from Olmsted County Registry in 2395 postpercutaneous coronary intervention patients demonstrated a 45% reduction in all-cause mortality at 6-year follow-up in those attending CRET. In another study from the Olmsted County Registry that included 846 patients who underwent coronary artery bypass grafting, all-cause mortality was reduced by 46% during 10-year follow-up in those who attended CRET. The benefits of CRET on mortality have also recently been noted in a large cohort of elderly Medicare beneficiaries. Although there are no data on ET on mortality in patients with HF, the study by Edelmann et al. assessed the effect of structured ET, including supervised endurance ET/resistance programs, on exercise capacity (peak VO₂), LV diastolic function, and quality of life in 64 patients with HFP EF compared with 44 patients who received usual care, demonstrating similar improvements with ET in HFP EF as noted in most of the smaller ET studies in patients with systolic HF.

**Benefits of ET in HF**

The potential benefits of PA, ET, and increased CRF in the prevention and treatment of HF have recently been reviewed. Berry et al. showed that although higher CRF is associated with a 10% lower risk of myocardial infarction in men (and only nonsignificant 3% lower risk in women), each 1-MET increase in CRF was associated with a 20% reduction in HF risk. Pandey et al. recently assessed changes in midlife CRF over time, demonstrating that every 1-MET improvement in midlife CRF was associated with a 17% lower risk of developing HF later in life. In addition, substantial evidence indicates that PA, ET, and CRF markedly affect the prognosis of patients with established HF. Most ET studies in HF have demonstrated 15% to 17% improvements in peak VO₂, which have translated into reductions in hospitalization and mortality of 28% to 35%. Probably, the most well-known study of ET in HF is the recent Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION trial), which assessed 2333 patients with class II–IV systolic HF. Although this trial hypothesized a 10% to 15% improvement in peak VO₂ with ET, only a 4% average improvement was noted, reflective of the relatively low adherence of ET in the intervention group, which unfortunately was because of the fact that only 30% exercised to their target training level minutes per week. After a median of 30-month follow-up, a nonsignificant 7% reduction was noted in the combined end point of hospitalization and all-cause mortality; however, after adjustment for preselected mortality predictors in HF, the primary end point was significantly lowered in the ET group by 11%. In addition, there was a close relationship between ET volume and clinical prognosis, with a 30% reduction in the primary end point among subgroups who achieved their ET prescription.

On the basis of considerable body of evidence, the recent American College of Cardiology Foundation/American Heart Association Guidelines for HF recognized ET at a class I level and the Center of Medicare and Medicaid Service recently approved formal CRET programs for patients with systolic HF.

**ET in Heart Failure**

**Preserved Ejection Fraction**

Although the majority of the early ET studies in HF concentrated on patients with significant systolic dysfunction, ≥50% of patients with HF have heart failure preserved ejection fraction (HFP EF), which is particularly common in older patients with HF and in women. Recently, Edelmann et al. assessed the effect of structured ET, including supervised endurance ET/resistance programs, on exercise capacity (peak VO₂), LV diastolic function, and quality of life in 64 patients with HFP EF compared with 44 patients who received usual care, demonstrating similar improvements with ET in HFP EF as noted in most of the smaller ET studies in patients with systolic HF, with improvements in peak VO₂ of >16% after ET. In addition, ET resulted in improvements in diastolic function, as determined by E/e′ and left atrial volume indices and improvements in the physical dimensions quality of life component.

Although there are no data on ET on mortality in patients with HFP EF, the study by Edelmann et al. and others has established proof-of-concept for the potential benefits of ET not only for HF or systolic dysfunction but also for the full spectrum of HF.
of HF, including those with HFrEF. Considering the cost of HF on society, particularly the effect of HFrEF in old patients with HF and in women,95–97 future large studies are needed to assess the effect of ET in various ET modalities (including resistance training and high-intensity interval training or [HIIT] on cost, quality of life, and major HF morbidity and mortality).95–97,99,100

Mechanisms of ET Benefits in HF

In patients with HFrEF, as well as in patients with systolic cardiac dysfunction, the degree of exercise intolerance is not directly related to the degree of cardiac weakness but somewhat surprisingly, the symptoms of dyspnea and fatigue in HF or often directly related to abnormalities of skeletal muscle.102 Clearly, patients with chronic HF have decreased muscle bulk compared with healthy subjects, and HF patients have a shift in muscle fiber type, from slow twitch, oxidative type I fibers to fast twitch, glycolytic type IIb fibers, which have been correlated with reduced exercise capacity, such as peak VO₂.97,102 In addition, there is evidence of a systemic inflammatory response in HF, which involves the skeletal muscle and contributes importantly to the skeletal myopathy in HF. There is also decreased capillary numbers per muscle fiber, rapid depletion of high energy phosphates, and rapid decrease in muscle pH during ET, with decreased mitochondria density and oxidative enzyme content. Each of these features has been correlated with reduced exercise capacity in patients with chronic HF.102 In addition, sympathetic nerve activation typifies many chronic diseases, such as renal failure, lung disease, as well as HF, which are all characterized by systemic inflammation and skeletal myopathy.102

Certainly, deconditioning contributes to the skeletal myopathy of HF; PA and ET reverse many of the features of skeletal myopathy, particularly the elevated sympathetic nerve activation and increase level of inflammation.95,102 Clearly, skeletal muscle functions somewhat as an endocrine organ, as skeletal muscle has been shown to produce and release cytokines (myokines), with interleukin-6 being the prototype and the first cytokine present in the circulation during ET.103 Many studies indicate anti-inflammatory effects of ET and interleukin-6, which may be particularly applicable to the benefits of ET in chronic diseases, such as HF.95,102,103 Nevertheless, deconditioning is not the only mechanism for the skeletal muscle dysfunction in HF; so, ET would not be expected to completely reverse the adverse effects. However, there are numerous potential effects of ET that benefit patients with HF, in addition to producing improvements in skeletal muscle function, including those with systolic dysfunction as well as HFrEF (Table 3).99 Although most of the studies of ET in HF have focused on aerobic ET, considering the skeletal muscle deficiency in quantity and function in HF, resistance ET, which improves cardiovascular risk factors and prognosis, may be particularly applicable for patients with HF.104

Potential Role of HIIT

Moderate-intensity continuous ET (MICT) has become part of the standard care for most patients with CVD, including for CHD and HF. Recently, however, evidence has emerged demonstrating that HIIT may be performed safely and results in improvements in functional capacity, including peak VO₂ and quality of life, leading some to intimate that HIIT, as opposed to the more traditional MICT, should be the preferred clinical approach to ET in patients with CVD.99,100 In fact, in studies of patients with CHD and HF, as well as in cohorts with obesity and MetS, HIIT has been typically superior to MICT for improving CRF, determined by peak VO₂, and for more positive adaptations in cardiac structure and function, including hemodynamics, cardiac biomarkers, and various echocardiographic parameters.99,100 This has led some to call for a paradigm shift, which may be controversial, particularly considering the theoretical increases in adverse CVD events associated with ET at higher intensities. We recently reviewed data in >100 patients with HF that assessed the efficacy and safety of HIIT for patients with HF.99 Although the initial evidence demonstrating the benefits of HIIT in patients with CVD, including CHD and HF, is compelling, we feel that currently there is still insufficient evidence to supplant an MICT approach with HIIT. This recommendation is not based on the findings of any one study, which have generally all been positive up to this point in time, but rather the relatively small body of collective evidence demonstrating the efficacy of HIIT that is currently available. For example, in our current analysis of HIIT and HF, we were only able to analyze just over 100 subjects with HF in the HIIT arms, and there is relatively little information on long-term safety, training compliance, and no data on long-term clinical events.

Therefore, despite the theoretical benefits of HIIT in patients with CVD, including HF, we think that further studies of long-term efficacy, safety, compliance, and clinical event data are needed before this supplants MICT as the ET modality of first choice in the prevention and treatment of CVD.99,100

<table>
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<td>Improved skeletal muscle function</td>
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<td>Reduced all-cause mortality</td>
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Importance of ET in Muscular Fitness

Although this review mostly emphasizes the importance of aerobic ET to improve CRF and CVD prognosis, muscular fitness (MF) and muscle strength are also important, as MF has been shown to have substantial effect on CVD risk factors and prognosis.104 Moreover, MF also is a major determinant of frailty and cachexia, which is particularly important for patients with advanced HF and in the elderly.105 Frailty is defined as a biological syndrome characterized by declining overall function and loss of resistance to stresses,
and this is known to be associated with increased morbidity, mortality, and healthcare utilization, especially in elderly and patients with advanced HF. In those with advanced HF, cachexia and wasting seem to be independent predictors of increased mortality. On the other hand, we and others have demonstrated an obesity paradox in many groups of patients with CVD,\textsuperscript{52,53} including CHD\textsuperscript{54} and HF,\textsuperscript{55} demonstrating the importance of maintaining higher levels of lean muscle mass,\textsuperscript{106} which are associated with greater MF and muscle strength.\textsuperscript{104} In fact, an obesity paradox has been noted with better prognosis with higher body fat in CHD\textsuperscript{54,106–109} and HF,\textsuperscript{110} possibly because of the fact that patients with higher body fat also generally have higher MF and muscle strength.\textsuperscript{111} Although generally ET increases both CRF and MF, specifically resistance training may be especially helpful to improve MF and maintain lean muscle mass in elderly patients and those with advanced HF.\textsuperscript{104}

**Exercise Dosing**

The PA Federal Guidelines call for a minimum of 150 minutes per week of aerobic PA at 75 minutes per week of vigorous aerobic PA; the Institute of Medicine suggests 60 minutes daily of some aerobic PA.\textsuperscript{1–3,56,112} However, recent evidence suggests that more than half of American adults still do not meet these minimal requirements based on self-report, and only 10% of American adults meet these minimal guidelines based on objective accelerometry.\textsuperscript{1–3,113,114} In addition, recent evidence suggests that substantial benefits are obtained with ET doses much lower than these guidelines.\textsuperscript{115–117} Clearly, efforts to have individuals who lead a completely sedentary lifestyle engage in regular PA, even if not meeting the target levels described above, is of paramount importance.

For example, in a study 416 175 individuals from Taiwan, a dose–response relationship between aerobic PA and mortality is noted, with progressive reductions in mortality noted ≤90 daily minutes of moderate PA and ≤40 daily minutes of vigorous PA (defined as 6.5–8.5 METs; Figure 3).\textsuperscript{115} Even those who did only 15 minutes of ET daily had a 14% reduction in all-cause mortality and a 3-year longer life expectancy. In a recent study of 55 000 people from the ACLS, including 13 000 runners and 42 000 nonrunners followed on average for 15 years, runners had impressive reductions in all-cause and CVD mortality of 30% and 45%, respectively, with an average increase in life expectancy of 3 years.\textsuperscript{116} Persistent runners had the greatest reduction in risk, whereas those who began running but stopped or vice versa received about half of the benefit. However, when dividing runners into quintiles (Q) of exercise volumes (ie, miles per week, times per week, and min per week), Q1 (<6 miles per week, 1–2 times per week, and <51 minutes per week) had similar all-cause and CVD mortality risk reductions as Q2 to Q4 and a slight trend toward greater benefit than Q5 (Figure 4).\textsuperscript{116} These results suggest that with running, as a common and convenient method of ET, maximal benefit on all-cause and CVD mortality occurs at low doses, including ET doses well below the current major PA guidelines.\textsuperscript{112}

Figure 3. Daily physical activity duration and all-cause mortality reduction. Reprinted from Wen et al\textsuperscript{115} with permission of the publisher. Copyright ©2011, Elsevier.

Figure 4. Central illustration: hazard ratios (HRs) of all-cause and cardiovascular mortality by running characteristic (weekly running time, distance, frequency, total amount, and speed). Participants were classified into 6 groups: nonrunners (reference group) and 5 quintiles of each running characteristic. All HRs were adjusted for baseline age (years), sex, examination year, smoking status (never, former, or current), alcohol consumption (heavy drinker or not), other physical activities except running (0, 1–499, or ≥500 metabolic equivalent [MET] minutes/week), and parental history of cardiovascular disease (yes or no). All P values for HRs across running characteristics were <0.05 for all-cause and cardiovascular mortality except for running frequency of ≥6 times/week (P=0.11) and speed of <6.0 miles per hour (P=0.10) for cardiovascular mortality. Reprinted from Lee et al\textsuperscript{116} with permission of the publisher. MET indicates metabolic equivalents. Copyright ©2014, Elsevier.
Dangers of Excessive Endurance ET

As Hippocrates said centuries ago, “Everything in excess is opposed to nature.”118 We and others have reviewed the potential adverse effects of high levels of exercise,119,120 although these dangers have also been disputed.121

There are many potential adverse effects of excessive endurance ET (EEE) on cardiac structure and function (Figure 5).119 Acutely, EEE increases markers of myocardial injury, such as cardiac troponin and B-type natriuretic peptide, as well dilation of cardiac chambers, especially the atrium and the right ventricle, and reduction in right ventricular function.119–121 Chronically, there is concern that these levels of EEE can lead to detrimental cardiac remodeling and fibrosis, as well as nonlethal arrhythmias, particularly increased risk of atrial fibrillation, and potentially more lethal ventricular arrhythmias, which have been especially noted with vigorous EEE in animals, with some suggestion of the same finding in humans.119,120,122,123 Recent studies have also suggested that longer distance runners, despite having more favorable overall CHD risk profiles, may have increased levels of atherosclerosis and CHD.124,125

In a recent study of 24,000 patients with CHD with personal history of myocardial infarction, those doing more ET had progressive reductions in CVD mortality, up to a point (Figures 6 and 7).126 However, at running doses of >30 miles per week or walking >46 miles per week, there seems to be substantial loss of the ET benefit on CVD mortality.

Although clearly from a population perspective, lack of PA is much more prevalent than is EEE, with the potential for much greater adverse effects on overall and CVD health at the societal level.1,119,121,127 However, these studies also point to the fact that more does not seem to be better, and even low doses of ET, particularly for running, seem to be beneficial for conferring long-term CVD health and longevity.1,127

Exercise Prescription

Based on a constellation of data, the current recommendation of 150 minutes per week of moderate aerobic PA or 75 minutes per week of vigorous aerobic PA based on the Federal PA Guidelines seems reasonable,112 realizing that substantial benefits occur at levels of PA well below this, indicating that some PA is always better than no PA.115–117,128 In addition, as reviewed above, with some more vigorous PA (eg, running), maximal benefits seem to occur at quite low levels.116,117,128

Figure 5. Proposed pathogenesis of cardiomyopathy in endurance athletes. BNP indicates B-type natriuretic peptide; CK-MB, creatine kinase MB; LV, left ventricle; RA, right atrium; RV, right ventricle; and SCD, sudden cardiac death. Reprinted from O’Keefe et al119 with permission of the publisher. Copyright ©2012, Elsevier.

Future Consideration

Although resistance ET was not reviewed in detail in this report, exercises, such as weight lifting, will improve muscular strength, which is an important predictor of CVD risk factors and prognosis.104 Resistance ET will also help to improve insulin insensitivity and will also prevent or reverse sarcopenia—a pernicious and progressive problem that commonly affects individuals as they age. Therefore, including resistance ET for at least 15 to 20 minutes twice weekly and including frequent repetition exercises of the large muscle groups, combined with aerobic PA/ET, would be ideal,3,104 particularly to maintain MF and muscle strength in elderly and in patients with advanced HF who are at risk of frailty and cachexia.

Figure 6. Categorical model. Cox proportional survival analyses of the risk of cardiovascular disease (CVD)–related mortality vs metabolic equivalent of task-h/d (MET-h/d) run or walked. Relative risk is calculated for 1.07 to 1.8, 1.8 to 3.6, 3.6 to 5.4, 5.4 to 7.2, and 7.2 MET-h/d or more relative to the inadequate exercisers (<1.07 MET-h/d). All CVD-related mortality includes both CVD as an underlying cause and CVD as a contributing cause for some other underlying cause. Significance levels are coded as follows: *P<0.05; †P<0.01; ‡P<0.001. The significance levels for 7.2 MET-h/d or more vs <1.07 MET-h/d were all nonsignificant, that is, P=0.99 for all-cause mortality, P=0.68 for all CVD-related mortality, and P=0.46 for CVD as the underlying cause of death. Reprinted from Williams et al126 with permission of the publisher. Copyright ©2014, Elsevier.
Figure 7. Continuous model. Cox proportional survival analyses of the risk of cardiovascular disease (CVD)-related mortality vs metabolic equivalent of task-h/d (MET-h/d) run or walked. In the model αMET-h/d (βMET-h/d if MET-h/d ≥7.2, 7.2 otherwise)+covariates, the hypothesis β=0 tests whether the hazard ratio (HR) is increased significantly above 7.2 MET-h/d relative to the HR at 7.2. Shown is the 15.4% average decrease in the risk for CVD-related mortality per MET-h/d between 0 and 7.2 MET-h/d (95% confidence [CI], 8.9%–21.5%; P<0.001) and a 2.62-fold risk increase above 7.2 MET-h/d relative to the risk at 7.2 MET-h/d (95% CI, 1.29- to 5.06-fold; P=0.009). Reprinted from Williams et al126 with permission of the publisher. Copyright ©2014, Elsevier.

Disclosures

Dr Lavie has served as a consultant and speaker on fitness/obesity for the Coca-Cola Company and has published a book on the obesity paradox with potential royalties. Drs Church and Blair have served as consultants for weight loss and fitness companies and for the Coca-Cola Company, which has also provided them unrestricted research grants. The other authors report no conflicts.

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