

# High-Intensity Aerobic Exercise Training Improves the Heart in Health and Disease

Ole Johan Kemi, PhD, and Ulrik Wisløff, PhD

■ Regular exercise training confers beneficial effects to the heart as well as to the entire body. This occurs partly because exercise training improves skeletal muscle work capacity and reduces resistance, thus increasing conductance in the peripheral circulation. More directly, exercise training also alters extrinsic modulation of the heart and improves the intrinsic pump capacity of the heart. Together, these effects allow for improved exercise capacity. Accumulating evidence suggests that the magnitude of these benefits increases proportionally with the intensity of individual exercise training sessions constituting the exercise training program. It has emerged that regular exercise training also confers beneficial effects to patients at risk for, or who have, established heart dysfunction and disease and, moreover, that exercise training may reduce the dysfunction of the heart itself and, at least, partly restore its ability to effectively function as a pump. The most recent studies in patients with established heart disease suggest that a high relative, yet aerobic, intensity of the exercise training improves the intrinsic pump capacity of the myocardium, an effect not previously believed to occur with exercise training. However, more and larger studies are needed to establish the safety and efficacy of such exercise training in patients with heart disease. Here, we consider the nature of the intensity dependence of exercise training and the causes of the improved heart function.

## KEY WORDS

high-intensity aerobic exercise

heart health

heart disease

**Author Affiliations:** Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, United Kingdom (Dr Kemi); and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway (Dr Wisløff).

**Corresponding Author:** Ole Johan Kemi, PhD, Institute of Biomedical and Life Sciences, University of Glasgow, West Medical Bldg, Glasgow, G12 8QQ, United Kingdom (o.kemi@bio.gla.ac.uk).

Chronic endurance exercise training brings about a number of bodily changes that benefit the entire organism in general and, in particular, the systemic circulation including the heart. Endurance exercise training improves the work capacity of the skeletal locomotor muscles; it increases blood perfusion by increasing the muscle fiber-to-capillary ratio; it improves the vasoregulatory capacity of the arterial and arteriolar vessels to effectively conduct and distribute blood to where the demand is in a manner that also reduces peripheral resistance and, thus, unloads the heart; and it improves the capacity of the heart to produce a greater cardiac output.<sup>1</sup> When integrated, these changes lead to increased maximal oxygen uptake ( $\dot{V}O_{2max}$ ) and the ability of the body to take up, transport, and utilize oxygen to fuel

aerobic work, and this in turn enables an increased work capacity and performance. In particular, improved cardiac pump capacity is integral to the effect of exercise training, and this is also highlighted by the close association between cardiac output and  $\dot{V}O_{2max}$ .<sup>1</sup> Endurance training is also associated with reduced morbidity and mortality in patients with established heart disease.

## EXERCISE INTENSITY

Exercise training and the responses to it are inherently dynamic and exist on a continuous scale ranging between the “superphysiological” and the

“pathophysiological” endpoints, that is, between extremely fit and extremely unfit. This continuum exists because the organism at the systems level is highly adaptable to both acute exercise (single exercise sessions) and chronic exercise (regular exercise training programs that are continued for months and years). Furthermore, exercise is not a static entity, but rather a dynamic event in which the exercise itself may vary with respect to intensity, duration, and frequency, with all variables existing on a continuous scale. Thus, this has far-reaching consequences because it effectively means that a high-intensity exercise leads to a greater benefit than a lower-intensity exercise, a concept that has been known for several decades,<sup>1,2</sup> and recently been linked to the exercise training-induced adaptation of the heart in both healthy subjects and patients with cardiovascular disease.<sup>3-8</sup> For instance, aerobic interval training at approximately 90% of the  $\dot{V}O_{2\max}$ , which equals to approximately 95% of maximal heart rate, increased exercise and cardiac pump capacity more than matched exercise training programs at lower intensities.<sup>4</sup> This also appears to be true in patients with severe cardiac dysfunction<sup>3,6,8,9</sup> and in situations where short bursts of very high-intense anaerobic exercise are utilized.<sup>10</sup> Therefore, the notion prevails that the effects of the exercise training depend on the intensity of the exercise training sessions; the higher the intensity, the greater the benefit. The notion is however not new but has been previously proposed.<sup>2,11</sup>

Implicitly, exercise intensity may not only dictate the magnitude of effect, but high aerobic intensity may also be a prerequisite for inducing certain aspects of the effects, at least in certain populations. A recent trial suggested that a threshold intensity over which exercise has to be executed may exist to benefit the heart intrinsically.<sup>8</sup> Exercise training at 70% of maximal heart rate did not induce any observable changes to cardiac dilatation, ejection fraction, stroke volume, or systolic parameters, whereas exercise training at 95% of maximal heart rate induced clearly observable and statistically, biologically, and clinically significant beneficial changes to those parameters. Because of this, we propose that exercise training in general, and efficacy and safety of different exercise intensities in particular, should be studied as options for prevention, treatment, and rehabilitation of heart disease in specific patient groups. A similar approach to the study of the dose-response relationships, as would be utilized in the evaluation of new drugs that are tested for efficacy and safety before they enter any market, should be employed. Only such stringent procedures can enable us to prescribe appropriately tailored exercise training programs to patients with

specific clinical backgrounds. Also, a much-understudied topic deserving attention is the interaction effects of exercise training and pharmacological drugs, since it is feasible that particular drugs may confer either additive or nonadditive effects upon the heart.

From a clinical perspective, there is no doubt that it will become important to employ the optimal exercise training programs in the near future to both prevent and treat heart disease. Since the human population is aging and the incidence and prevalence of heart disease is increasing,<sup>12</sup> we as a society may not be in a position to afford managing heart disease as we have done in the recent past. The burden of heart disease is already taxing societies as well as individuals and has been projected to increase in the years ahead. In this light, identifying the optimal exercise intensities for use with exercise training may be advantageous for heart disease management and, thus, should be studied in detail.

### Principles of High-Intensity Interval Training

Because the interval exercise training described above requires a high intensity as the stimulus, it has called for a different approach than the classic continuous and prolonged nature of exercise.<sup>2</sup> Despite the fact that such high-intensity exercise is still “aerobic” and, thus, below intensities corresponding to maximal heart rates or  $\dot{V}O_{2\max}$ , it is above intensity thresholds such as those where fatigue occurs within a few minutes of continued exercise, lactate and metabolites start to accumulate, intramuscular adenosine triphosphate starts to deplete, and the slow component of  $\dot{V}O_2$  kinetics or the steady increase in  $\dot{V}O_2$  during steady exercise becomes steeper. Exercise at such high intensities can therefore not be sustained for prolonged periods, and if attempted, the intensity would inevitably drop to a level that confers less benefit to the exercising subject. Thus, to accumulate time in the high-intensity zones, the principle of high-intensity interval aerobic exercise training has been introduced successfully to both normal healthy individuals<sup>2,4</sup> and patients at risk of or with established heart disease.<sup>3,6-8</sup>

The basic principle of interval exercise training is that periods of high-intensity exercise training, be it walking, running, cycling, rowing, skiing, and other activities, are interspersed by periods of lower intensities that allow for recovery, which then allow the subject to reengage in high-intensity exercise bouts, or “intervals.” It is the accumulated time in the high-intensity intervals that determine the outcome of the exercise training, whereas it is the interspersed recovery periods that allow the intervals to take place within a concentrated period. Typically, high-intensity

intervals are performed as brisk uphill walking or running at intensities close to maximal heart rate or  $\dot{V}O_2$ max for approximately 4 minutes, whereas the recovery periods consist of walking or "jogging" at considerably lower intensities (50%–60% of the intensity during the high-intensity interval) for approximately 3 minutes.<sup>3,4,6–8</sup> It is important to note that these exercise intensities are relative to the individual and that they need to be tailored individually such that 2 subjects exercising on a treadmill next to each other may look very different, 1 running very fast and the other strenuously walking, although they both are exercising at the same relative intensity of 90% of  $\dot{V}O_2$ max or 95% of maximal heart rate. The difference would be that they have different fitness levels, but they would be experiencing the same exercise stress. This also raises the point that exercise capacity, maximal heart rate, or a defined proxy must be measured in each individual before engaging with high-intensity interval exercise training to set the absolute workload to achieve the desired relative exercise intensity.

In our experience, both normal subjects and patients with heart disease express that interval training is more motivating than continuous running at lower intensities, chiefly because the effects of the high-intensity interval training are felt by the subject in terms of improved exercise capacity, and because the total exercise time is reduced. It is important, however, to acknowledge that although clear and sound beneficial effects of the abovementioned exercise regimen have been observed in several trials with subjects from different populations, the conducted trials have been small and without statistical power to fully assess safety and efficacy. The potential of this exercise training concept therefore still requires scientific scrutiny.

## MECHANISTIC BASIS FOR EXERCISE INTENSITY DEPENDENCE

Many of the exercise training-induced changes originate from adaptations in the cellular systems making up the organs, including the heart,<sup>13</sup> and since the majority of cells are plastic, they also consequently contribute to the plasticity of the systems that allows for intensity-dependent effects to occur. The cardiac muscle cell (cardiomyocyte) is the primary cell of the heart, and although it accounts only for approximately 20% of the total cell population in the heart, more than 90% of the myocardial mass is still constituted by cardiomyocytes because of the comparatively large mass of the individual cardiomyocyte.<sup>14</sup> It is the repetitive contractions of the cardiomyocytes induced by intracellular  $Ca^{2+}$  that make up the cardiac pumping

action.<sup>15</sup> Cardiomyocytes are plastic and respond to stress in both the long and short terms. They respond both to chronic exercise training programs and acutely to increased stimulation through increased frequency, amplitude, and force of the contractions, as well as the rate of relaxation.<sup>13</sup> This contributes to the Frank Starling mechanism of the whole heart, in which the heart adapts to increased loads by performing more work.

The stark effects of high-intensity exercise training on cardiomyocyte parameters of contraction in small rodents such as mice and rats provided the first clues that this type of exercise training may be substantially more effective in improving cardiac pump function than exercise training performed as continuous running at lower exercise intensities. During and after chronic exercise training programs, cardiomyocytes respond in multiple ways that encompass regulation of both size and intrinsic contractile capacity. However, the effect of daily treadmill running at approximately 90% of  $\dot{V}O_2$ max, enabled by interval exercise training, was superior to previous studies that had utilized lower intensities.<sup>16,17</sup> After the initial observation in rats,<sup>17</sup> this was confirmed in mice,<sup>16</sup> and subsequently, we showed that the cardiomyocyte effects indeed depended on the exercise intensity.<sup>18</sup> Higher intensity resulted in a greater adaptation that surpassed the effect of low-to-moderate intensity exercise training, as observed by studying cardiomyocyte hypertrophy responses and by studying contractile parameters such as fractional shortening, rates of intracellular  $Ca^{2+}$  handling, and myofilament responsiveness to  $Ca^{2+}$ .<sup>18</sup>

## Animal Models of Heart Disease

A much-used model of heart disease is the post-myocardial infarction (MI) heart failure (HF) model in rodents, in which the left coronary artery is permanently ligated. This procedure leads to HF characterized by pulmonary congestion; reduced reserve and pump capacity; and development of pathological hypertrophy, dilatation, and fibrosis of the heart. Increased end-diastolic and reduced systolic pressures, abnormal histology, architecture, and function of the myocardium also typify this condition, as well as reexpression of fetal genes and activation of pathological signaling pathways, with resulting compromised exercise capacity.<sup>19</sup>

Cardiomyocytes isolated from HF animals show dysfunctional excitation,  $Ca^{2+}$  handling, and contraction; abnormal cellular structure and architecture; and a pathological hypertrophy that is greater than the physiological hypertrophy observed after exercise training in healthy counterparts.<sup>20,21</sup> These changes explain the reduced ability of the cardiomyocyte and

the whole heart to perform beat-to-beat contractile work. Importantly, they are also prone to positive modulation by exercise training; in fact, regular aerobic exercise training has been demonstrated to correct and reverse at least some of the pathological alterations in the cardiomyocyte and more so after high-intensity exercise training programs at approximately 90% of  $\dot{V}O_{2\max}$  than after moderate- to low-intensity exercise training programs.

In post-MI HF rats, 2 months of high-intensity exercise training at 85% to 90% of  $\dot{V}O_{2\max}$  starting 1 month after the MI procedure resulted in several changes that lead to corrected myocardial function.<sup>21</sup> The exercise training protocol was the same exercise training program as utilized in normal animals but with lower absolute workloads to adjust for the reduced exercise capacity. The pathological hypertrophy was reversed toward normal cardiomyocyte size, and this was also associated with reduced myocardial mass and dilatation. Exercise training also corrected contractility and  $Ca^{2+}$  handling toward normal levels. Although the intensity dependence of cardiac effects after exercise training in animals with post-MI HF has not been firmly established, accumulated evidence from several studies suggests that this should be true.<sup>21–23</sup> Together, reduced pathology and improved contractility result in improved cardiac pump function that is observable during both resting and exercising conditions. The underlying intracellular and molecular mechanisms responsible for these effects are reviewed elsewhere.<sup>13</sup>

These experimental results suggest that such potential cardiac responses should receive detailed study after high-intensity exercise training programs in healthy and heart disease human populations. Together, these and similar experimental studies have provided evidence that chronic aerobic endurance exercise training leads to structural and functional changes of the cardiomyocyte, which improves contractile capacity and, thus, pump function of the heart; that the magnitude of this effect depends on the intensity of exercise training; and that this exercise training phenomenon exists in both healthy and heart disease human population.

### **An integrated View of the Cardiomyocyte and the Heart**

The above and other studies firmly support the view that cardiomyocytes respond to exercise training programs by taking on a phenotype that better serves pump function of the whole heart. Moreover, the fact that exercise training effects on  $\dot{V}O_{2\max}$  in terms of intensity dependence<sup>18</sup> and time course of training and detraining<sup>24</sup> show close similarities to the effects on cardiomyocyte contractile properties, further

suggests that the cardiomyocyte is integral to whole-body exercise capacity ( $\dot{V}O_{2\max}$ ), and that adaptations in the cardiomyocyte translate to similar adaptations of  $\dot{V}O_{2\max}$ . As demonstrated by studies of animals with post-MI HF, this concept is true both under normal circumstances and after the onset of serious heart disease. The hearts of animals with post-MI HF may normalize to levels close to healthy controls by subjecting the animal to high-intensity exercise training by means of aerobic interval treadmill running at approximately 90% of  $\dot{V}O_{2\max}$ . Thus, a line can be drawn from the intracellular environment of the cardiomyocyte to the whole heart and ultimately to the whole organism, and importantly, it appears that any changes occurring in one end of this line will also affect the phenotype at the other end.

### **EXERCISE INTENSITY IN CLINICAL TRIALS OF CARDIAC PATIENTS**

The above reports of the advantage of high-intensity exercise training over moderate-intensity modalities in experimental animal models have provided at least 2 important concepts that have been utilized in subsequent clinical exercise studies. First, as these reports elucidate the mechanisms by which exercise training reduces intrinsic cardiac dysfunction and improves inotropy and lusitropy in heart disease, they suggest that the failing human myocardium may be prone to exercise training-induced adaptation if the intensity of the exercise is sufficiently high. Second, by implication, findings from these reports suggest that high-intensity exercise training should be evaluated as a therapeutic approach in patients with post-MI HF and established heart disease. Historically, exercise training has already been studied as well as clinically utilized in these populations, but with a lower intensity of exercise than suggested by the aforementioned experimental studies.

Until recently, studies had failed to show any improvement of intrinsic heart function, but rather improved peripheral circulation and skeletal muscle function. Clinical trials had demonstrated that aerobic exercise training could be safely undertaken by patients with HF in both inpatient and outpatient settings and that exercise training improved exercise capacity, health, and quality of life. It also reduced morbidity and mortality without any adverse effects on left ventricular volume, structure, mass, or function.<sup>25–28</sup> As a result, exercise training has been recommended to patients with heart disease already for some time although not beyond a level of moderate exercise intensity.

In keeping with the experimental studies, 3 small trials have been published that utilize the high-intensity

aerobic exercise training programs (~90% of  $\dot{V}O_2\text{max}$ ) either in patients with post-MI HF with symptoms indicating New York Heart Association classes I–III severity of HF<sup>8</sup> or in patients with coronary artery disease.<sup>3,6</sup> Common to each study were findings of cardiac benefits of high-intensity exercise training performed at 90% to 95% of peak heart rate (corresponding to ~90% of  $\dot{V}O_2\text{max}$  and easier to assess than  $\dot{V}O_2\text{max}$ ), and that the effect was considerably larger than that of moderate exercise intensity, for example, 50% to 70% of peak heart rate (Table 1). Several aspects stemming from these studies deserve further consideration.

First, these results show that patients with heart disease due to MI or coronary artery disease are capa-

ble of performing treadmill walking/running to an intensity reaching 90% to 95% of peak heart rate. This exercise intensity was achieved and sustained during 4-minute interval bouts as described above, which were performed 3 times per week for a total period of 3 months. For each exercise training session, 4 intervals were performed, each interspersed with a 3-minute period of lower-intensity exercise for purposes of recovery. For all 3 studies, each exercise session was supervised by experienced researchers or technicians, and the exercise was continuously monitored with absolute workload adjusted to maintain the relative exercise intensity.<sup>3,6,8</sup> The high-intensity aerobic interval exercise training group was compared

**Table 1 • SUMMARY OF CLINICAL STUDIES COMPARING HIGH-INTENSITY AND MODERATE-INTENSITY EXERCISE TRAINING PROGRAMS<sup>a</sup>**

Parameter	Condition	High-intensity exercise	Moderate-intensity exercise
Maximal oxygen uptake	Heart failure <sup>8</sup>	46% <sup>b</sup>	14% <sup>b</sup>
	CAD <sup>3,6</sup>	18% <sup>b</sup>	8% <sup>b</sup>
	Metabolic syndrome <sup>7</sup>	35% <sup>b</sup>	16% <sup>b</sup>
	Obesity <sup>30</sup>	33% <sup>b</sup>	16% <sup>b</sup>
LV diastolic diameter	Heart failure <sup>8</sup>	-12% <sup>b</sup>	No effect
	CAD <sup>3</sup>	No effect	No effect
LV systolic diameter	Heart failure <sup>8</sup>	-15% <sup>b</sup>	No effect
LV end-diastolic volume	Heart failure <sup>8</sup>	-18% <sup>b</sup>	No effect
	CAD <sup>3</sup>	No effect	No effect
LV end-systolic volume	Heart failure <sup>8</sup>	-25% <sup>b</sup>	No effect
Pro-brain natriuretic peptide	Heart failure <sup>8</sup>	-40% <sup>b</sup>	No effect
LV ejection fraction	Heart failure <sup>8</sup>	35% <sup>b</sup>	No effect
LV stroke volume	Heart failure <sup>8</sup>	17% <sup>c</sup>	No effect
	CAD <sup>3</sup>	No effect	No effect
LV global contractility	Heart failure <sup>8</sup>	22% <sup>b</sup>	No effect
LV ejection velocity	Heart failure <sup>8</sup>	19% <sup>b</sup>	No effect
LV relaxation early diastole	Heart failure <sup>8</sup>	49% <sup>b</sup>	No effect
LV filling pressure	Heart failure <sup>8</sup>	-26% <sup>b</sup>	-15% <sup>b</sup>
LV isovolumic relaxation rate	Heart failure <sup>8</sup>	22% <sup>b</sup>	No effect
Strain rate early diastolic function	CAD <sup>3</sup>	40% <sup>b</sup>	No effect
Strain rate mitral annular velocities	CAD <sup>3</sup>	No effect	No effect
Strain rate mitral filling velocities	CAD <sup>3</sup>	6% <sup>c</sup>	18% <sup>c</sup>
Systolic blood pressure	Heart failure <sup>8</sup>	No effect	No effect
	CAD <sup>3,6</sup>	No effect	No effect
	Metabolic syndrome <sup>7</sup>	-9 mm Hg <sup>c</sup>	-10 mm Hg <sup>c</sup>
	Obesity <sup>30</sup>	No effect	No effect
	Heart failure <sup>8</sup>	No effect	No effect
Diastolic blood pressure	CAD <sup>3,6</sup>	No effect	No effect
	Metabolic syndrome <sup>7</sup>	-6 mm Hg	-6 mm Hg <sup>d</sup>
	Obesity <sup>30</sup>	-6 mm Hg <sup>c</sup>	-8 mm Hg <sup>c</sup>
	Heart failure <sup>8</sup>	No effect	No effect

Abbreviations: CAD, coronary artery disease; LV, Left ventricle.

<sup>a</sup>Summary of the heart-related effects of high- and moderate-intensity exercise training programs piloted in patients with postmyocardial infarction heart failure or coronary artery disease or in subjects at increased risk of developing heart disease due to the metabolic syndrome or obesity. Values indicate magnitude of effects. No effect indicates  $P > .05$ .

<sup>b</sup>Effects are statistically significant both within- and between-group analyses.

<sup>c</sup>Effect is statistically significant only for within-group analysis.

<sup>d</sup>Effect did not reach statistical significance, but the magnitude of change is similar to the effect of high-intensity exercise training, which did reach statistical significance.

with 2 other groups: a control group that adhered to the guidelines offered by the family physician and a second exercise intervention group that performed continuous exercise training by walking or running at moderate exercise intensities corresponding to 50% to 70% of peak heart rate. To balance the caloric expenditure between the exercise intervention groups and, thus, isolate exercise intensity as a parameter, the moderate-intensity exercise group exercised for a longer period per session than the high-intensity exercise group throughout the studies. When subjects were asked to characterize the exercise sessions according to the 6 to 20 Borg Scale, continuous exercise sessions scored approximately 12, whereas high-intensity interval exercise sessions scored approximately 17.

No meaningful data on safety, morbidity, or mortality were available from these trials because the sample sizes were small. Nonetheless, no adverse events were observed during the course of these studies that could be attributed to the high-intensity exercise regimen. Overall, more than 85% of the prescribed exercise training sessions were performed by the intervention groups, with no differences between groups. Furthermore, dropout rates were not different among the 3 groups, and the informal feedback from patients in the exercise intervention groups was that continuous moderate-intensity exercise was "somewhat boring," whereas the high-intensity interval exercise training was perceived as more "motivating, albeit challenging."

### **High-Intensity Exercise Training in Patients With HF**

In evaluating high-intensity exercise training in HF patients, stable patients with post-MI HF of both sexes were randomized to control, continuous moderate-intensity, or high-intensity interval exercise training programs that each lasted 3 months.<sup>8</sup> Nine subjects completed participation in each group. Patients were classified with New York Heart Association classes I–III symptoms, were  $75 \pm 11$  years old, had reduced ejection fractions less than 0.40 (mean 0.29), and were otherwise on optimal treatment plans that included  $\beta$ -blockers and angiotensin-converting enzyme inhibitors. Exclusion criteria included unstable angina pectoris, MI within the last month prior to participation, complex arrhythmias, or orthopedic or neurological limitations to exercise.

The aerobic high-intensity interval exercise training program increased  $\dot{V}O_{2\max}$  by 46%, which was paralleled by reduced left ventricular dilatation and mass; and increased ejection fraction (from 0.28 to 0.38), stroke volume, and systolic and diastolic flow; and motion parameters, as well as reduced levels of pro-brain natriuretic peptide (Table 1). Moreover,

quality of life also increased with the exercise training program. In contrast, moderate-intensity exercise training induced only a 14% increase in  $\dot{V}O_{2\max}$ , but had no effect on the measured cardiac parameters, apart from a small effect on diastolic filling pressure. Blood pressure was not affected by exercise training. No changes occurred in the control group that was subject to exercise recommendations from the family physician according to the current guidelines for exercise training in patients with HF.<sup>8</sup> This was the first study to show that exercise training, if performed at high intensity, could confer benefit to the heart itself, even in patients with HF and severely compromised heart function. Although the safety and efficacy require more study, this study provides proof-of-concept that high-intensity interval exercise training may be feasible in patients with post-MI HF and that its effect may surpass previous exercise regimens applied to this patient population.

In contrast, the recently finished HF-ACTION trial, the largest study of exercise training in patients with HF and reduced ejection fraction, could not detect any significant benefits as to the primary and secondary endpoints all-cause mortality and all-cause hospitalizations or to other clinical measures of health outcome.<sup>29</sup> It should be noted, however, that this study utilized a moderate exercise intensity and is therefore not comparable to high-intensity exercise programs. Moreover, HF-ACTION did show that moderate-intensity exercise could be safely conducted in this population of patients similar to the smaller trial<sup>8</sup> of utilizing high-intensity exercise. These trials,<sup>8,29</sup> therefore, pave the way for a larger, multicenter study of the safety and efficacy of high-intensity exercise training in patients with heart disease such as those with post-MI HF.

### **High-Intensity Exercise Training in Patients With Coronary Artery Disease**

Analogous to patients with post-MI HF, high-intensity exercise training using aerobic intervals at approximately 90% to 95% of peak heart rate has also been piloted in patients with coronary artery disease.<sup>3,6</sup> This was also a small single-center trial that provided proof-of-concept evidence that such exercise may also be utilized in coronary artery disease as a treatment option, although it was not powered to assess efficacy or safety. The experimental design was similar to the post-MI HF trial<sup>8</sup> described above, including high-intensity interval and moderate-intensity continuous exercise groups. Both male and female patients aged approximately 62 years were recruited and all had stable coronary artery disease. Excluded were patients with left main coronary artery disease, unstable angina pectoris, claudication, recent MIs or coronary

interventions, complex arrhythmias, ejection fractions of less than 0.40, or other complications rendering exercise training being difficult, such as orthopedic or neurological problems.

The exercise training programs lasted 10 weeks and led to increases in  $\dot{V}O_{2\max}$  of 18% and 8% after high- and moderate-intensity exercise training, respectively (Table 1). This is considerably less than that experienced by the patients with post-MI HF undergoing similar exercise training programs. The difference likely arose from the fact that patients with post-MI HF had much lower baseline levels of  $\dot{V}O_{2\max}$  and exercise capacity than patients with coronary artery disease and, thus, had a greater potential for relative improvement. Increased  $\dot{V}O_{2\max}$  was also associated with increased exercise capacities, measured by treadmill test speed and duration. Although inconclusive and with limited statistical power, echocardiographic evaluation of heart function by strain rate and tissue imaging suggested that high-, but not moderate-, intensity exercise improved early diastolic myocardial relaxation rate in patients with coronary artery disease.<sup>3</sup> This is comparable with results from the experimental studies reviewed above, suggesting that diastolic function is particularly prone to exercise changes at the level of the single cardiomyocyte.<sup>13</sup> Early mitral filling velocities increased, however, with both exercise intensities, whereas blood pressure remained unaltered, and no adverse effects were observed in these studies.

### High-Intensity Exercise Training in Patients at Risk of Developing Heart Disease

Finally, we have also conducted 2 small trials in which patients without heart disease, but with increased risk of developing heart disease, were subjected to the same interval high-intensity or continuous moderate-intensity exercise training programs as described above.<sup>7,30</sup> These patients were at risk because of the metabolic syndrome<sup>7</sup> or obesity without additional features of the syndrome such as elevated blood pressure, dyslipidemia, or impaired glycemic control. Currently, this syndrome affects about 25% of the adult US population and is increasing worldwide.<sup>31</sup>

The study populations consisted of men and women aged 45 to 55 years who participated in the high- or moderate-intensity exercise training programs for 12 to 16 weeks or served as controls. All of the metabolic syndrome patients<sup>7</sup> fulfilled the criteria as defined by the World Health Organization,<sup>32</sup> whereas the obese patients<sup>30</sup> all presented with a body mass index in excess of 30 kg/m<sup>2</sup>. Exclusion criteria included unstable angina pectoris, MI and HF, or other heart, pulmonary, or kidney disease, uncontrolled

hypertension, and orthopedic or neurological limitations to exercise. The results from these studies confirmed that high-intensity exercise training is more effective at increasing work capacity, function, and health parameters. High-intensity interval exercise training increased  $\dot{V}O_{2\max}$  by 30% to 35%, whereas moderate-intensity continuous exercise training increased  $\dot{V}O_{2\max}$  by 15% to 16%, respectively (Table 1). Thus, increasing exercise intensity from 60% to 70% of maximal heart rate to approximately 90% lead to a doubling of the exercise effect in patients without symptoms of heart disease or cardiac dysfunction, but who were at increased risk of developing such disease.<sup>7,30</sup> The same trend was true for other parameters measured, such as exercise capacity, blood profiles, insulin action, blood pressure, and function of the arterial blood vessel endothelium and skeletal muscle contractile apparatus.

Although heart structure and function could not be assessed in these studies, it is likely that the intensity dependence of effects would be true also for the heart, especially because the cardiac pump function is closely related to  $\dot{V}O_{2\max}$ <sup>1</sup> and because animal models of obesity and the metabolic syndrome have indicated that the cardiac effects of exercise training depend on the exercise intensity.<sup>23</sup> Body mass remained unchanged in both of the studies, possibly because of their short duration. Remarkably though, at the end of the exercise training periods in the study of metabolic syndrome patients, 46% of the high-intensity exercising patients and 37% of the moderate-intensity exercising patients were no longer diagnosed with the metabolic syndrome.<sup>7</sup> Thus, both exercise regimens had the power to reduce the prevalence of the metabolic syndrome, though with a greater effectiveness after high-intensity exercise training. Exercise training also tended to reduce both systolic and diastolic blood pressures in these patients but no intensity-dependent effects were observed.

Finally, epidemiological surveys in both the United States and Europe have also confirmed that the benefit of exercise training and higher fitness for populations with established or increased risk of developing heart disease appears to increase with increasing exercise intensities.<sup>4,27,28,33-37</sup> This was true also in populations on optimal pharmacological medication and when adjusted for other risk factors such as the presence of pulmonary disease, hypertension, obesity, diabetes, and high cholesterol levels.

### APPLICATION TO PRACTICE

The above discussion of the current state of exercise training in patients with established or increased risk of

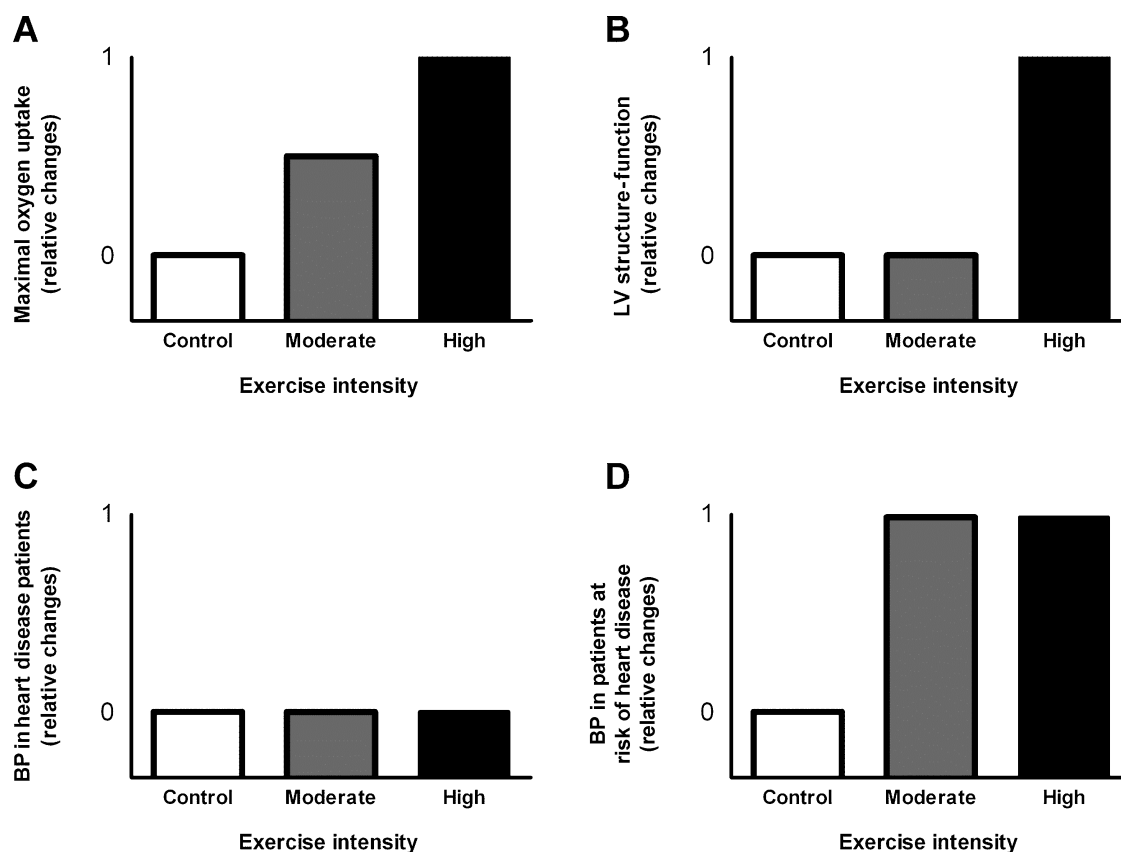
heart disease and its reliance on the intensity of individual exercise training sessions is important when considering its clinical use. It is recognized that exercise training as recommended in national and international guidelines is safe and beneficial to patients and society.<sup>38,39</sup> However, exercise training of moderate intensity appears to have only limited effects on intrinsic heart function, such as inotropy and lusitropy.

Exercise training programs that utilize high exercise intensities, however, have demonstrated reduced left ventricular dilatation and mass and increased ejection fraction, stroke volume, and systolic and diastolic parameters of cardiac pump function (Table 1). However, it should be reiterated that studies are small and have limited power to detect efficacy and no power to detect safety. Thus, this area of investigation is in need of larger, multicenter trials that could confirm these initial results. Nonetheless, these early studies hold promise that exercise training may deliver optimal prevention and treatment and are supported by experimental studies

in appropriate animal models that confirm the intensity dependence of exercise training. Nonetheless, extreme caution should be exercised when interpreting available results. Conversely, given the worldwide heart disease pandemic and the inadequate strategies currently employed to prevent and treat heart disease, we should be investigating management strategies that are both effective and affordable. Effective and safe exercise training programs that are easy to manage, coupled with other lifestyle interventions with clear clinical benefits, would clearly contribute toward this goal. *We, however, wish to stress that increasing exercise intensity is recommended in healthy individuals to maximize benefit.*<sup>40</sup>

## SUMMARY AND CONCLUSIONS

Several recent studies have demonstrated that the beneficial effects of aerobic exercise training are intensity dependent, high aerobic intensity is superior



**Figure 1.** The trials reviewed here have identified several different patterns of adaptation in response to high- or moderate-intensity exercise programs. Maximal oxygen uptake displayed a dose-response behavior with respect to exercise intensity (A), whereas LV structure and function parameters improved after high-, but not moderate-intensity exercise training (B). In heart disease (post-myocardial infarction heart failure or coronary artery disease), exercise training had no effect on blood pressures (C), but in contrast, both moderate- and high-intensity exercise trainings were equally effective at reducing blood pressures in patients at increased risk of developing heart disease due to the metabolic syndrome or obesity (D). BP indicates blood pressure; LV, left ventricular.



to low to moderate intensity. This is true in healthy subjects, in patients with established heart disease such as post-MI HF or coronary artery disease, and in patients at increased risk of developing heart disease due to obesity and the metabolic syndrome. Moreover, the trials reviewed here identified several different patterns of response to programs utilizing high or moderate exercise intensities in patients with established heart disease or at increased risk of developing heart disease (Figure 1). First, a true dose-response relationship regarding exercise intensity was observed for  $\dot{V}O_{2\max}$  in all studies; high-intensity exercise training conferring about twice the benefit of moderate-intensity exercise training (panel A). Second, measurements of left ventricular structure and function parameters indicated that high-intensity exercise training may be required for the effect to occur (panel B). In patients with post-MI HF, a reversal of the pathological remodeling and systolic and diastolic improvements were observed only after high-intensity exercise training. However, this should be confirmed by more sensitive methods or larger studies with a greater power to detect small differences, since animal studies<sup>13</sup> have indicated that the response pattern in the myocardium to exercise training resembles the dose-response scenario presented in panel A. Nonetheless, this suggests that various heart-related parameters prone to exercise training adaptation may either show dose-response relationships or display various levels of intensity-thresholds for adaptation. Exercise training effects on blood pressure showed mixed effects. In patients with established heart disease, such as post-MI HF or coronary artery disease, no effects of exercise training were observed (panel C). However, both moderate- and high-intensity exercise training similarly reduced blood pressures in those at increased risk of developing heart disease due to the metabolic syndrome and obesity, although only diastolic, but not systolic, blood pressure decreased in obesity without metabolic syndrome (panel D).

Finally, we wish to reiterate that efficacy and safety of high-intensity exercise training remain to be fully established in well-defined patient groups, such that until further notice, the clinical applicability remains unknown. The available results are, however, encouraging and call for larger multicenter studies that are powered to clarify this issue. In the interim, we reiterate that high-intensity exercise training requires further study and that one should move forward only with extreme caution.

## References

1. Astrand PO, Rodahl K. *Textbook of Work Physiology*. New York, NY: McGraw-Hill; 2003.
2. Shephard RJ. Intensity, duration and frequency of exercise as determinant of the response to a training regime. *Int Z Angew Physiol*. 1968;26:272–278.
3. Amundsen BH, Rognmo O, Hatlen-Rebhan G, Slordahl SA. High-intensity aerobic exercise improves diastolic function in coronary artery disease. *Scand Cardiovasc J*. 2008;42:110–117.
4. Helgerud J, Hoydal K, Wang E, et al. Aerobic high-intensity intervals improve  $\dot{V}O_{2\max}$  more than moderate training. *Med Sci Sports Exerc*. 2007;39:665–671.
5. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS Jr. Relative intensity of physical activity and risk of coronary heart disease. *Circulation*. 2003;107:1110–1116.
6. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004;11:216–222.
7. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118:346–354.
8. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115:3086–3094.
9. Warburton DE, McKenzie DC, Haykowsky MJ, et al. Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*. 2005;95:1080–1084.
10. Burgomaster KA, Howarth KR, Phillips SM, et al. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J Physiol*. 2008;586:151–160.
11. Barinaga M. How much pain for cardiac gain? *Science*. 1997;276:1324–1327.
12. American Heart Association. *Heart Disease and Stroke Statistics—2003 Update*. Dallas, TX: American Heart Association; 2003.
13. Kemi OJ, Ellingsen O, Smith GL, Wisloff U. Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. *Front Biosci*. 2008;13:336–346.
14. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324:98–102.
15. Bers DM. Cardiac excitation-contraction coupling. *Nature*. 2002;415:198–205.
16. Kemi OJ, Loennechen JP, Wisloff U, Ellingsen O. Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. *J Appl Physiol*. 2002;93:1301–1309.
17. Wisloff U, Helgerud J, Kemi OJ, Ellingsen O. Intensity-controlled treadmill running in rats:  $\dot{V}O_{2\max}$  and cardiac hypertrophy. *Am J Physiol Heart Circ Physiol*. 2001;280:H1301–H1310.
18. Kemi OJ, Haram PM, Loennechen JP, et al. Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. *Cardiovasc Res*. 2005;67:161–172.
19. Hasenfuss G. Animal models of human cardiovascular disease, heart failure, and hypertrophy. *Cardiovasc Res*. 1998;39:60–76.
20. Loennechen JP, Wisloff U, Falck G, Ellingsen O. Cardiomyocyte contractility and calcium handling partially recover after early deterioration during post-infarction failure in rat. *Acta Physiol Scand*. 2002;176:17–26.
21. Wisloff U, Loennechen JP, Currie S, Smith GL, Ellingsen O. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility,  $Ca^{2+}$  sensitivity and SERCA-2 in rat after myocardial infarction. *Cardiovasc Res*. 2002;54:162–174.
22. de Waard MC, van der Velden J, Bito V, et al. Early exercise training normalizes myofilament function and attenuates left

- ventricular pump dysfunction in mice with a large myocardial infarction. *Circ Res*. 2007;100:1079–1088.
23. Haram PM, Kemi OJ, Lee SJ, et al. Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. *Cardiovasc Res*. 2009;81:723–732.
  24. Kemi OJ, Haram PM, Wisloff U, Ellingsen O. Aerobic fitness is associated with cardiomyocyte contractile capacity and endothelial function in exercise training and detraining. *Circulation*. 2004;109:2897–2904.
  25. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L; ELVD-CHF Study Group. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure. *Circulation*. 2003;108:554–559.
  26. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA*. 2000;283:3095–3101.
  27. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women. *JAMA*. 2009;301:2024–2035.
  28. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA*. 2001;288:1994–2000.
  29. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure. *JAMA*. 2009;301:1439–1450.
  30. Schjerve IA, Tyldum IA, Tjonna AE, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clin Sci*. 2008;115:283–293.
  31. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.
  32. World Health Organization. *Report of a WHO Consultation: Definition of the Metabolic Syndrome, Diagnosis, and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization, Department of Non-Communicable Disease Surveillance; 1999.
  33. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002;666:671.
  34. Moholdt T, Wisloff U, Nilsen TI, Slordahl SA. Physical activity and mortality in men and women with coronary heart disease: a prospective population-based cohort study in Norway (the HUNT study). *Eur J Cardiovasc Prev Rehabil*. 2008;15:639–645.
  35. Myers J, Prakash H, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *New Engl J Med*. 2002;346:793–801.
  36. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. *Circulation*. 2005;111:2313–2318.
  37. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med*. 1993;328:538–545.
  38. Balady GJ, Williams MA, Ades PA, et al. AHA/AACVPR scientific statement. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update. *Circulation*. 2007;115:2675–2682.
  39. European Society of Cardiology, Heart failure Association of the ESC (HFA), European Society of Intensive Care Medicine (ESICM); Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933–989.
  40. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendations for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093.