ARTICLE

High-Intensity Interval Training to Maximize Cardiac Benefits of Exercise Training?

Ulrik Wisløff[1,2], *Øyvind Ellingsen*[1,2], *and Ole J. Kemi*[3]

[1]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology; [2]Department of Cardiology, St. Olavs Hospital, Trondheim, Norway; and [3]Institute of Biomedical and Life Sciences, University of Glasgow, Scotland, United Kingdom

WISLØFF, U, Ø. ELLINGSEN, and O.J. KEMI. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc. Sport Sci. Rev.*, Vol. 37, No. 3, pp. 139–146, 2009. *We hypothesized that high-intensity aerobic interval training results in a greater beneficial adaptation of the heart compared with that observed after low-to-moderate exercise intensity. This is supported by recent epidemiological, experimental, and clinical studies. Cellular and molecular mechanisms of myocardial adaptation to exercise training are discussed in this review.* **Key Words:** experimental models of exercise, cardiomyocytes, pathological hypertrophy, athlete's heart, molecular adaptations to exercise training

INTRODUCTION

In medicine, exercise is often considered a unitary intervention that benefits health, and it has been common to categorize exercise training as strength or endurance, and more common to apply a relatively moderate intensity of the two exercise forms, and physiological adaptations to exercise at relatively high intensities have been less studied. In contrast, sports science has established that mode, frequency, duration, and intensity are essential for the extent of the effects of exercise training. Do these factors matter for the outcome of exercise training in prevention, treatment, and rehabilitation of cardiovascular disease and other lifestyle-related disorders? The working hypothesis based on results of several of our recent studies is that aerobic interval training at a relatively high intensity can be used in experimental and clinical settings and that this type of training induces larger beneficial effects to the heart compared with exercise training at moderate or low intensity. The combined evidence on the effects of physical activity at different intensities, ranging from large health surveys in an unselected population (*e.g.*, HUNT, www.hunt.no) via clinical studies to cellular and molecular mechanisms in experimental models outlines an integrated perspective on how regular physical activity at different intensities may be used to prevent and reverse the negative health effects of physical inactivity. A long-term goal of the reviewed research has been to study cardiac adaptation to endurance training at high versus moderate intensity relative to the individual's aerobic fitness level. In the studies, high-intensity aerobic interval training refers to walking or running intensity at bouts of 85%–90% of peak oxygen uptake or 90%–95% of peak heart rate, separated by 2–3 min of active recovery at approximately 60%–70% of peak heart rate. In humans, a training session included four 4-minute exercise bouts, plus 5–10 min warm-up and 3–5 min cooldown, whereas in animal models, the bouts lasted for 8 min and included 6–10 bouts.

EPIDEMIOLOGICAL EVIDENCE

The observation that regular physical activity protects against premature cardiovascular death is robust and consistent (18). Many studies suggest that moderate exercise intensity is sufficient to reduce the risk of cardiovascular disease in women and in older men, but there are some indications that middle-aged men need vigorous exercise to achieve protection. For instance, high exercise intensity was associated with reduced all-cause mortality in a study of health professionals, independent of the duration of activity (25), in line with a report that associated increasing exercise intensity in older well-educated men with a greater reduction in the risk of coronary heart disease (21). In addition, our group recently showed in a 16 yr of follow-up study that a single weekly bout of exercise of high intensity reduced the

Address for correspondence: Ulrik Wisløff, Ph.D., Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway (E-mail: ulrik.wisloff@ntnu.no).

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risk of cardiovascular death in both men (relative risk, 0.61; 95% confidence interval, 0.49–0.75) and women (relative risk, 0.49; 95% confidence interval, 0.27–0.89), compared with those who reported no activity. Interestingly, there was no additional benefit from increasing the duration or the number of exercise sessions per week (33). Taken together, these and other results (10) challenge the current recommendation that expenditure of at least 1000 kcal·wk^{-1} is required to achieve exercise-induced protection against premature cardiovascular mortality and indicate that exercise intensity rather than duration may be the most important factor to achieve a cardiac benefit of exercise training.

EVIDENCE FROM SPORTS SCIENCE

It is well known that highly trained endurance athletes have increased cardiac dimensions. Consistent findings also suggest that exercise with relatively high exercise intensity improves cardiac function in humans. For instance, Cox *et al.* (6) found adaptive changes in left ventricular (LV) dimensions after 7 wk of intense endurance training in previously sedentary subjects, with a program consisting of six alternating days per week of continuous cycling (40 min) and interval running (5 × 5-min bouts at 85%–90% of maximal oxygen uptake [$\dot{V}O_{2max}$]). In line with this, we demonstrated that aerobic interval training at 90%–95% of maximal heart rate (~4 × 4 min) increased $\dot{V}O_{2max}$ by 18% and LV mass by 12% and increased LV contractility during exercise by 13% in previously untrained female subjects (24). It was recently shown in healthy male subjects that improvements in $\dot{V}O_{2max}$ and stroke volume were intensity dependent, with the highest response in those who trained with the highest exercise intensity (90%–95% of maximal heart rate) when compared with the effect of performing isocaloric exercise programs at lower exercise intensities but longer duration (11). Other types of more anaerobic interval training with shorter durations than used in our studies have demonstrated that high-intensity training is more effective

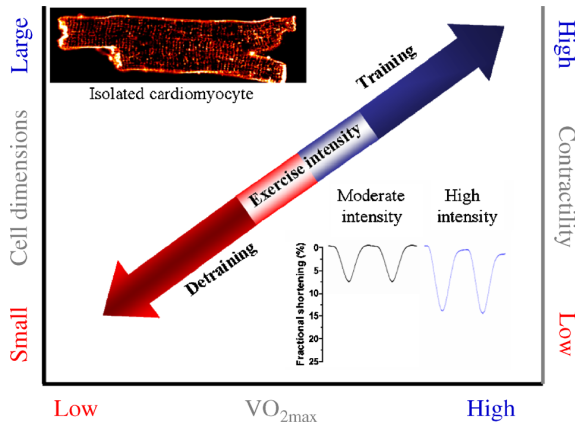

Figure 1. The extent of exercise-induced adaptation of maximal oxygen uptake ($\dot{V}O_{2max}$) and cardiomyocyte function/structure depends on exercise intensity.

(normalized for training volume) for improving aerobic fitness than moderate-intensity training (2,28). The close link between exercise intensity and improvement in $\dot{V}O_{2max}$ is important (Fig. 1) because $\dot{V}O_{2max}$ seems to be a better prognostic marker for cardiovascular disease than any other established risk factor (18).

EXPERIMENTAL APPROACH

Although there seems to be agreement that endurance training leads to beneficial cardiac adaptations, less is known about the cellular adaptations underlying these improvements. Because myocardial tissue from trained humans is unlikely to become available, most data on the cellular level will come from experimental models. To gain more insight into training-induced adaptation in isolated heart muscle cells (cardiomyocytes) from the left ventricle, we established experimental models with which to study cardiac adaptation in both rats and mice (referred in [16,17,31]) that mimicked human responses to exercise training, involving increased $\dot{V}O_{2max}$, improved running economy, reduced resting heart rate, improved systolic and diastolic LV function, as well as increased LV size.

Maximal Oxygen Uptake ($\dot{V}O_{2max}$)

We have observed that, in line with human data (11,28,29,34), the improvement in $\dot{V}O_{2max}$ is intensity dependent (16). The effect of regular high-intensity interval training at 85%–90% of $\dot{V}O_{2max}$ in rats amounted to about twice that of moderate exercise intensity at 65%–70% of $\dot{V}O_{2max}$.

Exercise Training Improves Cardiomyocyte Contractile Function

Several studies have provided evidence that chronic aerobic exercise training improves the contractile capacity of the cardiomyocyte by increasing the extent and the rates with which it shortens during systole and relaxes during diastole and by improving its ability to generate force, independent of neurohormonal influences.

Regular high-intensity aerobic exercise at 85%–90% of $\dot{V}O_{2max}$ improves the maximal extent of shortening in unloaded cardiomyocytes during electrical field stimulation. Fractional shortening increases by 40%–50%, whereas contraction and relaxation rates improve by 20%–40% (15–17,30–34). The improvement is particularly consistent for relaxation rates, but faster contraction rates also have been observed in several studies (16,17). Similarly, faster velocity of shortening also has been observed in cardiomyocytes under loaded contractions (8). The experiments also indicated that maximal power output in the cardiomyocyte increased by 60% after exercise training.

The magnitude of improvement depends on exercise intensity (Fig. 1). The effects after high-intensity aerobic exercise training at 85%–90% of $\dot{V}O_{2max}$ are twice those of moderate exercise intensity at 65%–70% of $\dot{V}O_{2max}$ (16). Contractility improves steadily during the course of the exercise training program until a plateau is reached after approximately 2 months; the positive inotropic effects of

high-intensity exercise are indistinguishable between 8 and 13 wk of exercise training programs (17). This correlates with the extent of changes in $\dot{V}O_{2max}$ ($r = 0.98$, $P < 0.02$) and cardiomyocyte hypertrophy ($r = 0.99$, $P < 0.01$). Two likely explanations for the plateau are either that the cardiomyocytes reach a maximal potential for improvement or that the relative exercise load (intensity or volume) needs to be increased at this point for further development. In contrast to the observed time course of training-induced adaptation to a high-intensity exercise program, the regression of training-induced effects back to baseline levels occurs within 2–4 wk when training is stopped by a return to a sedentary lifestyle (17). Hence, detraining occurs faster than training effects.

Exercise Training Improves Cardiomyocyte Calcium Handling

The myofilament actin-myosin binding and sarcomere shortening that constitutes the cardiomyocyte contraction is initiated by binding of intracellular free Ca^{2+} to the Ca^{2+}-binding subunit of troponin (TnC) of the troponin-tropomyosin complex. The intracellular free Ca^{2+} is made available through a process called Ca^{2+}-induced Ca^{2+} release, whereby action potential-evoked depolarization of the cardiomyocyte plasma membrane activates the L-type Ca^{2+} channel, which allows a small influx of Ca^{2+}. Also, a smaller amount of Ca^{2+} enters the cell via Na^+/Ca^{2+}-exchanger (NCX) that is working in a reversed mode during the action potential. The Ca^{2+} entry stimulates the ryanodine receptor (RyR2) of the membrane of the sarcoplasmic reticulum (SR) to release approximately 500 nM Ca^{2+} from the SR to evoke a contraction. During the cellular relaxation, the TnC-bound and free Ca^{2+} is resequestered back to the SR through the cardiac isoform of SR Ca^{2+} ATPase (SERCA2a); the rate-control of this process is by the free Ca^{2+} and phospholamban (PLN), whereas the extracellular and intracellular [Ca^{2+}] is balanced by the plasma membrane Ca^{2+} ATPase and the NCX that both extrude Ca^{2+} from the cell. This process controls cardiomyocyte contractility, and several aspects of it have been identified as susceptible to change by exercise training (Fig. 2). The "similar" changes of Ca^{2+} transients and contraction-relaxation velocities suggest an interdependent relationship, indicating that the changes in rate of Ca^{2+} cycling are associated with the changes in contraction-relaxation rates of the cardiomyocyte after exercise training and detraining (17,31). Exercise training results in a faster systolic rise and faster diastolic decay of the Ca^{2+} transient, with magnitude of contractility corresponding to the extent of cell shortening and relaxation rates. These effects also depend on exercise intensity (16). They may at least partly be caused by exercise training-induced activation of the Ca^{2+} calmodulin-dependent protein kinase II with subsequent phosphorylation of the threonine-17 residue of PLN that increases the activity of the SERCA2a during diastole and a concomitant upregulation of the SERCA2a-to-PLN ratio (13,14). These changes increase the rate of Ca^{2+} reuptake into the SR, noted after exercise training by directly studying the SERCA2a component of free Ca^{2+} removal in the cytosol of the cardiomyocyte, which then improves not only relaxation but also loading of the SR with Ca^{2+} (13).

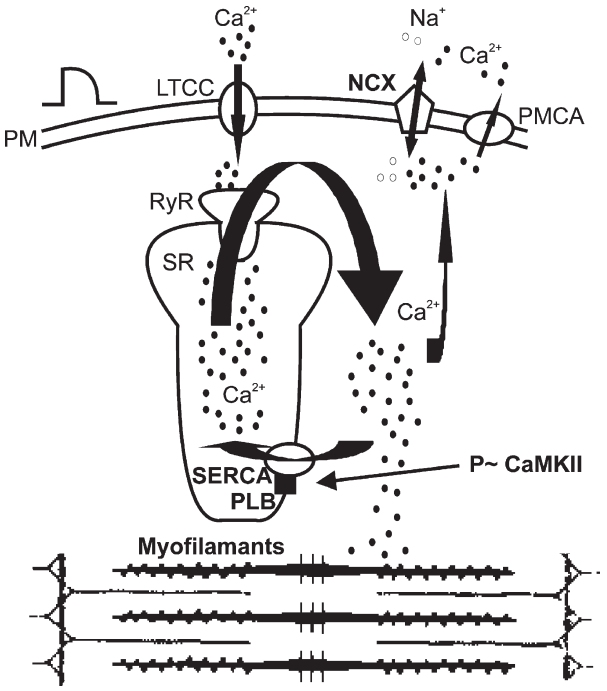

Figure 2. Schematic model of excitation-contraction coupling in cardiomyocytes with *broad arrows* indicating sites in which exercise training–induced adaptations have been evidenced. For details, see text. PM indicates plasma membrane; LTCC, L-type calcium channel; Ca^{2+}, calcium; Na^+, sodium; NCX, sodium-calcium exchanger; PMCA, plasma membrane calcium ATPase; RyR, Ryanodine receptor; SR, sarcoplasmic reticulum; SERCA, sarcoplasmic reticulum Ca ATPase 2a; PLB, phospholamban; P~-CaMKII, calcium/calmodulin-dependent kinase IIdelta phosphorylation.

Exercise training does not necessarily seem to increase the $[Ca^{2+}]_i$ transient amplitude, but the shorter duration of the $[Ca^{2+}]_i$ transient after exercise training implies that more Ca^{2+} is available for activating a synchronous contraction of the whole cell at any given time during the systole, compared with the $[Ca^{2+}]_i$ transient in cardiomyocytes from sedentary animals that in comparison is lower and lasts longer. Because these changes may not fully account for the cardiomyocyte shortening after exercise training, improved contractility may also result from improved myofilament responsiveness to Ca^{2+}. Higher myocardial Ca^{2+} sensitivity during submaximal but not maximal activation of tension after exercise training has been demonstrated in rats (9). Exercise training produced a leftward shift in the tension-pCa relation. This is important because almost all of the cardiac contraction occurs at submaximal $[Ca^{2+}]_i$. Hence, it suggests an improved activation with greater force output in the myocardium on a beat-to-beat basis. Higher myofilament Ca^{2+} sensitivity also has been indicated in mice (14), but this species has been less thoroughly studied.

An interesting subsidiary observation was the response of permeabilized cells to altered pH at constant [Ca^{2+}]. Acid pH decreased and alkaline pH increased myofilament shortening in cardiomyocytes from sedentary and trained animals (31).

In an analogous way to intracellular [Ca^{2+}], this indicates that a component of the exercise training–induced enhancement of the cardiomyocyte contractility could be attributed to the more alkaline intracellular pH in the cardiomyocytes from trained rats at high stimulus frequencies. However, because enhanced shortening was observed at stimulus rates with comparable intracellular pH (2 Hz or less), it means that the altered intracellular pH cannot constitute a complete explanation. Further work is required to fully characterize this effect, but altered pH sensitivity may accompany the altered Ca^{2+} sensitivity of the myofilaments in the trained animals. Our data indicated that the acidic shift in pH correlated with the rise of intracellular [Ca^{2+}] and was dependent on glycolysis. Whether the difference between the trained and sedentary groups is due to increased pH buffering capacity, reduced intracellular [Ca^{2+}] or increased amount and/or activity of proteins involved in intracellular Ca^{2+} regulation, contraction, or pH regulation has yet to be determined. Na^+/H^+-exchanger messenger RNA (mRNA) was markedly higher in trained cardiomyocytes (130%) when assayed immediately after exercise (31). These examples suggest that other aspects of intracellular physiology of regulation outside Ca^{2+}-induced Ca^{2+} release may contribute to exercise training–induced adaptation of the heart.

Physiological Cardiomyocyte Hypertrophy

Although the contractile function of the cardiomyocyte as well as the whole heart largely depends on excitation, Ca^{2+}-induced Ca^{2+} release, and contraction of myofilaments, this is not the only contributing factor. A balanced growth of the cardiomyocyte and the whole heart, as well as chamber dilatation, also contributes to increase the contractile pump function. This is termed *physiological hypertrophy* and occurs during pregnancy and exercise training.

High-intensity exercise training at 85%–90% of $\dot{V}O_{2max}$ induces a hypertrophic response in the cardiomyocytes that is observable already after a few weeks and reaches a plateau after approximately 2 months (16,17,31). The magnitude of cardiomyocyte hypertrophy depends on the intensity of exercise because high-intensity exercise training induced a substantially larger response than moderate intensity: 14% versus 5% longer cells, respectively (16). Moreover, detraining after exercise training induces a regression of the hypertrophy that occurs over a much quicker time scale than it takes to induce the training adaptations (17). Cell width is more variable because some (16,17) but not all studies (31) of rats show increased width with exercise training, whereas mice studies also show increased width. It is apparent that longitudinal cardiomyocyte growth is sufficient to explain the effect of exercise training on the myocardial mass, and it provides a cellular mechanism for the eccentric ventricular hypertrophy that is elicited by programs of aerobic exercise in humans as well as animals. Accumulated evidence has indicated that the molecular regulation of physiological hypertrophy is multifaceted and occurs at all levels, from transcription to translation and posttranslational modification as well as maintenance of the synthesized proteome. In contrast to pathological hypertrophy, physiological hypertrophy seems to rely less on induction of hypertrophy-regulating genes because genetic profiling has demonstrated that pathological hypertrophy is associated with a greater number of genes differentially expressed than physiological hypertrophy after exercise training (3,19). This suggests that exercise-induced physiological hypertrophy depends more on translation of mRNA, including its efficiency (protein synthesis per transcribed mRNA), and on maintenance of synthesized proteins. To elucidate this, we studied if induction of physiological hypertrophy of the heart after high-intensity aerobic exercise training is associated with activation of the phosphoinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signal transduction pathway because it has been implicated in swim-induced hypertrophy (22) and because it is activated by insulin-like growth factors (14), which also increase with exercise training. The mTOR phosphorylates and hence activates both 70S6-kinase and thus ribosomal protein S6, and the eukaryotic translation initiation factor-4E–binding protein-1 (4E-BP1). Together, this increases ribosomal biogenesis and translation of mRNA and hence induces higher ribosomal activity and protein synthesis in the cardiomyocyte, in a process that does not necessitate an increase in mRNA transcription. Exercise training in mice induced a hyperphosphorylation, and thus activation, of Akt and mTOR, including the downstream targets of mTOR such as 70S6-kinase, ribosomal protein S6, and 4E-BP1 (14). In contrast, pressure overload–induced hypertrophy after aortic constriction was associated with reduced phosphorylation levels of the Akt-mTOR pathway compared with normal control mice and was associated with reexpression of the fetal gene program.

Exercise-induced increase in the maintenance of the protein mass has been suggested by several studies. For instance, upregulation of the heat shock proteins (HSP; especially HSP70 and HSP72 but also other isoforms) has been demonstrated after endurance exercise training, including a possible link to reduced apoptosis after exercise training (23).

Physiological hypertrophy also has been associated with genetic regulation. An important regulator of gene transcription that induces hypertrophy of the heart is the mitogen-activated protein kinase (MAPK) system, and this signaling pathway has been identified to contribute toward endurance exercise training-induced hypertrophy (12). Because this was observed transiently after single exercise bouts in untrained but not in chronically trained hearts, it suggests that MAPK-activated gene expression may contribute to initiation of physiological hypertrophy but not to the maintenance of it. The transcription factor myocyte-enhancing factor-2 (Mef2) may be involved, as it acts downstream of MAPK signaling and is also under calcium/calmodulin-dependent kinase–mediated histone deacetylace control. Both Mef2 and calcium/calmodulin-dependent kinase have been indicated to be activated by exercise training (15,20). The Mef2 transcriptional activity was transiently upregulated at a similar time course as MAPK signaling (12). Finally, downregulation of microRNA-1 and microRNA-133 has been shown after high-intensity exercise training (5). These microRNAs are innate regulators of hypertrophy-associated mRNA translation because they

silence transcribed mRNA sequences and thereby inhibit hypertrophy of the heart. Thus, a downregulation of microRNA-1 and microRNA-133 contribute to increase the rate of mRNA translation and protein synthesis. As shown in Figure 3, the development of physiological hypertrophy of the heart is controlled by transcriptional, translational, and posttranslational regulatory mechanisms.

Exercise Training in Heart Failure

In rats with heart failure after myocardial infarction (post-MI), treadmill running induced substantial beneficial adaptations in $\dot{V}O_{2max}$, work economy, myocardial mass, and LV cardiomyocyte dimensions. $\dot{V}O_{2max}$ increased on average 10% per week until it leveled off at weeks 5–6, whereas the total improvement in work economy was 16% in trained animals (30). These results are similar to those observed after exercise training healthy rats and suggest that, although $\dot{V}O_{2max}$ may be reduced in post-MI heart failure compared with healthy individuals, the adaptability to exercise training remains intact. In fact, it is preserved to the level that exercise-trained post-MI heart failure rats may even show higher $\dot{V}O_{2max}$ than sedentary healthy rats. The studies rigorously controlled the extent and intensity of exercise and applied higher aerobic exercise intensity than other previously published exercise training programs. This may be the reason why the improvement in $\dot{V}O_{2max}$ was markedly higher than previous findings of training in post-MI heart failure rats, in which average improvements were 15% after 8–10 wk of endurance training.

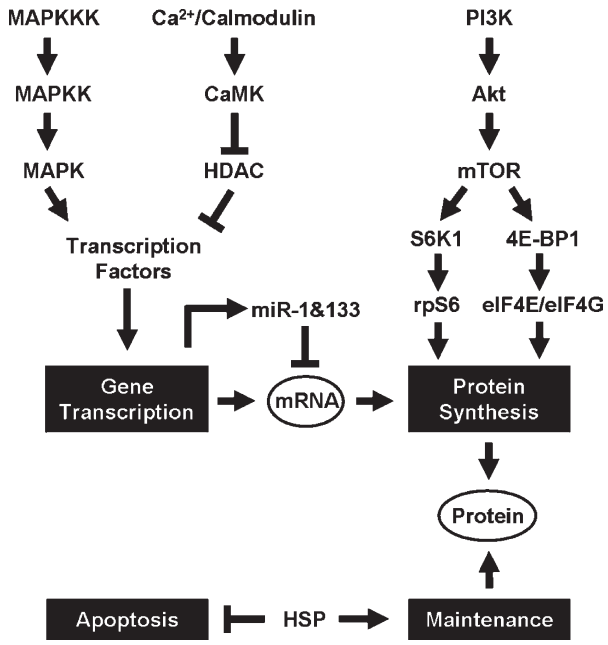

Figure 3. Putative molecular mechanisms associated with exercise-training induced physiological hypertrophy of the heart, supported by evidence from our and other laboratories. For details, see text. MAPKKK indicates mitogen-acitivated protein kinase kinase kinase; MAPKK, mitogen-activated protein kinase kinase; MAPK, mitogen-activated protein kinase; CaMK, calcium/calmodulin-dependent kinase II; HDAC, histone deacetylase; miR, microRNA; PI3K, phospho inositide 3-kinase; mTOR, mammalian target of rapamycin; S6K1, ribosomal protein S6 kinase-1; 4E-BP1, 4-E-binding protein 1; eIF4E/eIF4G, eukaryotic translation initiation factor; rpS6, ribosomal protein S6; HSP, heat shock protein.

Post-MI heart failure reduced contraction and slowed relaxation in isolated cardiomyocytes. In post-MI heart failure rats, 2 months of high-intensity exercise training at 85%–90% of $\dot{V}O_{2max}$ (starting 4 wk after inducing the MI) restored fractional shortening and the rate of relaxation in cardiomyocytes, to levels comparable to sedentary healthy controls. The restoration of the rate of relaxation with exercise training was closely associated with improved rates of $[Ca^{2+}]_i$ handling, which reverted toward healthy levels (30). In the same study, exercise training reduced the levels of resting diastolic $[Ca^{2+}]_i$ and restored the $[Ca^{2+}]_i$ transient amplitude. Some of the mechanisms for restoring contractile dysfunction with exercise training seemed to be due to normalized myocardial levels of SERCA2a and NCX (30). These findings are similar to those observed in myocytes from anaerobically interval-trained post-MI rats (35).

In rats, higher myofilament Ca^{2+} sensitivity and improved pH regulation also are putative mechanisms for improved contractile function. The cellular basis for these changes is not known, but multiple biochemical alterations of the contractile proteins may be involved, including isoform switching of troponin T and suppression of α-myosin and increased β-myosin heavy chain expression. Whereas myofilament Ca^{2+} sensitivity was depressed in sedentary rats with post-MI heart failure, this effect was not evident after exercise training. Thus, exercise training seems to normalize myofilament Ca^{2+} sensitivity. The responses to altered pH at constant $[Ca^{2+}]$ in permeabilized cardiomyocytes isolated from exercise-trained rats with post-MI heart failure were less than in cardiomyocytes isolated from sedentary counterparts and had responses similar to healthy sedentary rats. Further work is required to fully characterize this effect, but altered pH sensitivity may accompany the altered Ca^{2+} sensitivity of the myofilaments in the trained post-MI heart failure animals, as also observed in healthy trained rats.

de Waard and colleagues (7) demonstrated that 8 wk of voluntary exercise (starting within 24 hours after inducing MI) in post-MI mice improved LV fractional shortening, rate of contraction (dP/dt), and reduced pulmonary congestion, as well as improved cardiomyocyte shortening. They found no effects of exercise training on Ca^{2+} transients but attributed the improvement in cardiomyocyte shortening to a normalization of Ca^{2+} sensitivity. Contrary to our studies (30), the study found that cardiomyocytes from MI mice had increased Ca^{2+} sensitivity and that exercise training returned it to levels comparable to healthy control mice. This effect of exercise was protein kinase A–mediated and likely because of improved β1-adrenergic signaling, as suggested by the increased β1-adrenoceptor protein (48%) and cyclic adenosine monophosphate levels (36%). Exercise prevented the MI-induced decrease in maximum force-generating capacity of skinned cardiomyocytes. Furthermore, exercise reduced diastolic Ca^{2+} concentrations but did not change SERCA2a and PLN expression and phosphorylation status. Whether the discrepancy in the results are due to different species, exercise regimens or the time points of cardiomyocyte

experiments with regard to induction of MI (2 wk in this study and 4 wk in previous studies) is currently not known.

Reversed Cardiac Hypertrophy

In contrast to observations in healthy rats, we found a significant reduction of pathological hypertrophy as $\dot{V}O_{2max}$ increased, evidenced by reduction in ventricular weights and cardiomyocyte dimensions. These results are similar to those reported in anaerobically trained MI rats (35). Reduced ventricular hypertrophy in trained post-MI rats is consistent with reduced expression of atrial natriuretic peptide mRNA, a known marker of pathological cardiac hypertrophy (30). By directly reducing cell length in post-MI failing cardiomyocytes, aerobic interval training acts to minimize ventricular remodeling in post-MI and is thus anticipated to prevent the development of dilated cardiomyopathy. Our data show that increased cell length not necessarily improves maximal extent of shortening, as was the case in healthy rats (30). Thus, different types of hypertrophic stimuli (training vs MI) might yield qualitatively different adaptations in cardiomyocyte shortening, despite the marked hypertrophy in both situations. In contrast to healthy rats, increased $\dot{V}O_{2max}$ was associated with reduced cell dimensions and improved maximal extent of cardiomyocyte shortening in heart failure.

Cardiac Dysfunction in Metabolic Syndrome

The strong statistical association between fitness and premature cardiovascular disease in man suggests a link between impaired oxygen metabolism and disease. To directly test this hypothesis, we selected rats on the basis of low versus high intrinsic exercise performance (low-capacity runners (LCR) vs high-capacity runners (HCR)) over accumulating generations and hypothesized that they also would differ in $\dot{V}O_{2max}$, mitochondrial oxidative pathways, and cardiovascular risk factors (32). After 11 generations, rats with low aerobic capacity (LCR) scored high on 12 cardiovascular risk factors that constitute the metabolic syndrome. Additionally, these rats had impaired cardiomyocyte function, including suppressed Ca^{2+} handling that makes them suitable as an experimental model for studying cellular mechanisms for cardiac dysfunction in individuals with the metabolic syndrome.

Consistent with a low tolerance for exercise, the sedentary LCR rats had a 58% lower $\dot{V}O_{2max}$, a 16% lower economy of running (*i.e.*, higher oxygen cost of running), 23% less LV weight, and shorter and wider LV cardiomyocytes compared with the sedentary HCR rats (32). Moreover, cardiomyocytes from sedentary LCR rats had poorer systolic and diastolic function relative to the HCR counterparts. In response to training, both the LCR and HCR rats showed significant improvement in all 12 of the measures of cardiovascular risk factors but with a uniformly greater training response in the HCR relative to the LCR rats for each measure. Genomically, the cardiac-specific transcription patterns are also different between HCR and LCR rats, suggesting that this at least partly causes the different phenotypes. However, only approximately 5%–6% of the screened genes from cardiac tissue samples were identified as differentially regulated between the LCR and HCR rats, by the use of microarray technology (4). This does not seem to account for the full phenotype difference, such that other regulatory mechanisms may also be important for creating the difference and/or that the genome scan is not sensitive enough to provide transcription patterns with the highest temporal or spatial resolution. The genome-wide scan did, however, suggest that cardiac energy production is shifted from lipid to glucose metabolism in LCR hearts compared with HCR counterparts, which suggests a more pathological phenotype in LCR than HCR. This method did not detect any induction of cardiac gene expression in the two strains of rats by program of high-intensity exercise training (4).

CLINICAL ARRIVAL

Results from several studies indicate that endurance training in chronic heart failure patients NYHA classes II and III is safe and results in significant improvements in cardiovascular function, quality of life and survival, with no deleterious effects on LV volume, function, or wall thickness. Based on the experimental studies in rodents (13–17,30), and two clinical studies involving patients with coronary artery disease (1), we performed a study in patients with postinfarction heart failure to determine whether we could observe similar beneficial effects of high-intensity exercise (walking 4 × 4–min intervals on a treadmill at an exercise intensity corresponding to 90%–95% of peak heart rate, 3 times per week for 12 wk). In line with what we observed in rats, we found that VO_{2peak} increased more with high-intensity interval training than moderate continuous training at 70% of peak heart rate (training volume was equalized so that patients in the two exercise groups used the same amount of kilocalories each training) (46% vs 14%, $P < 0.001$) and was associated with reverse LV remodeling. LV end-diastolic and end-systolic volumes declined with high-intensity training only, by 18% and 25%, respectively; LV ejection fraction increased by 35%, and pro brain natriuretic peptide decreased by 40%. Improvement in endothelial function (brachial artery flow-mediated dilation) was larger, and mitochondrial function in lateral vastus muscle (peroxisome proliferator-activated receptor-γ coactivator 1a expression) increased with high-intensity training only. Plasma inflammatory markers remained largely unchanged. MacNew global score for quality of life in cardiovascular disease increased in both exercise groups. No changes occurred in the control group (34). In patients with metabolic syndrome, high-intensity aerobic interval training (4 × 4 min at 90%–95% of peak heart rate for 40 min) yielded superior effects on general cardiovascular health compared with endurance training involving moderate exercise intensity (continuous moderate exercise intensity at 70% of peak heart rate for 47 min; difference in exercise duration to equalize training volume) (26).

A central unanswered question in the literature yet is "how little can I get away with, and at what intensity" and, implicitly, "achieve protection against premature cardiovascular morbidity and mortality." We recently showed that acute exercise at relatively high intensity (90%–95% of peak heart rate) completely prevented the normal postprandial

reduction in endothelial function in apparently healthy individuals (27). These findings should motivate for future studies examining also whether adaptations in the heart occurs after a single bout of exercise as this reminds to be studied in detail. Additionally, there is a need of larger multicenter studies applying aerobic interval training at 90%–95% of peak heart rate that look into the safety issue of this type of endurance training, especially in the population of patients with established cardiovascular disease. So far, we have approximately 2000 hours with interval training in our laboratory in various patient groups, including heart failure, metabolic syndrome, coronary artery disease, and hypertension, without any negative outcome (Rognmo, O., unpublished manuscript/observations, 2009).

CONCLUSIONS AND FUTURE PERSPECTIVES

Recent advances in studies of exercise physiology have substantially improved our knowledge about the cellular and molecular mechanisms underlying adaptation to exercise training. The studies indicate that high intensity may be an important success factor for designing effective exercise programs and that high intensity may be particularly critical for improving cardiac function. These experimental data seem to translate into clinical studies in humans. Despite the fact that exercise at high relative intensity seems to induce larger beneficial adaptation in the cardiovascular system, we do not know whether this type of training is safe in larger patient cohorts and whether it affects complication rates in patients more favorably than exercise at low-to-moderate intensity.

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