Mechanisms of Exercise-Induced Improvements in the Contractile Apparatus of the Mammalian Myocardium

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Abstract

One of the main outcomes of aerobic endurance exercise training is the improved maximal oxygen uptake, and this is pivotal to the improved work capacity that follows the exercise training. Improved maximal oxygen uptake in turn is at least partly achieved because exercise training increases the ability of the myocardium to produce a greater cardiac output. In healthy subjects, this has been demonstrated repeatedly over many decades. It has recently emerged that this scenario may also be true under conditions of an initial myocardial dysfunction. For instance, myocardial improvements may still be observed after exercise training in post-myocardial infarction heart failure. In both health and disease, it is the changes that occur in the individual cardiomyocytes with respect to their ability to contract that by large drive the exercise training-induced adaptation to the heart. Here, we review the evidence and the mechanisms by which exercise training induces beneficial changes in the mammalian myocardium, as obtained by means of experimental and clinical studies, and we argue that these changes ultimately alter the function of the whole heart and contribute to the changes in whole-body function.

Keywords: Calcium; Cardiomyocyte; Exercise Training; Health and Disease; Intensity; Myocardium.

Introduction

Physical activity and regular exercise training is a potent but cheap intervention that reduces the Western Society epidemics of lifestyle-related conditions such as heart, vascular, metabolic, and skeletomuscular diseases (e.g. American Heart Association 2003). It improves and extends individual lives as well as reduces the burden on public health and economy. In contrast, lack of physical activity and exercise training increases the prevalence, incidence, and severity of the abovementioned diseases (Blair & Church 2004). A prime example is the effect regular exercise training has on heart disease and failure patients, as it improves cardiac function, health and quality of life, and reduces morbidity and mortality to significant degrees in both sexes; in patients of all ages; and at all stages of the disease (Belardinelli et al. 1999, Blair et al. 1995, Gulati et al. 2003, Jolliffe et al. 2001, Paffenbarger et al. 1993). In line with this, recent epidemiological surveys and meta-analyses have clearly indicated that improving aerobic fitness or exercise capacity alone has the power to effectively reduce mortality, cardiac events, and hospitalization in men and women with established heart disease or with heightened risk of developing heart disease (Kodoma et al. 2009, Myers et al. 2002). Thus, the idea emerges that exercise training asserts a number of effects that benefit the subject in both health and disease. However, recommendations on physical activity in primary and secondary prevention of cardiac disease are diffuse (American College of Sports Medicine 1994, Fletcher et al. 2001) despite indisputable evidence showing that aerobic fitness is an important clinical reference point and target (Kavanagh et al. 2002, Myers et al. 2002). In order to develop optimal exercise protocols, a sound understanding of the underlying biology, including an integration of the elements from molecular to organismal physiology is required.

Exercise intensity

Although defining studies of healthy individuals are still lacking, clinical trials point to the superiority of high aerobic exercise intensity over low-to-moderate intensities to gain full effect of an exercise training program (Helgerud et al. 2007, Jensen et al. 1996, Lee et al. 2003, Rognmo et al. 2004, Shephard 1968, Tanasescu et al. 2002, Tjonna et al. 2008, Wisloff et al. 2007). This has been demonstrated while balancing lower intensity exercise programs with longer exercise times per session in order to make them isocaloric and thence isolate intensity as the sole parameter that differ between exercise training groups. Furthermore, the emergence of aerobic fitness as a continuum from health to disease supports this notion (Kavanagh et al. 2002, Myers et al. 2002). Because of the aerobic fitness-heart link (see below), cardiac adaptations may therefore also rely on the exercise intensity during long-term regular training programs also in healthy individuals, especially since it was demonstrated that stroke volume in well-trained athletes may increase continuously with increasing intensity up to maximal levels being reached around peak aerobic exercise intensity (Gledhill et al. 1994).

Maximal oxygen uptake

An important physiological characteristic in both health and disease is the maximal oxygen uptake (VO_{2max}), which assesses the maximal rate at which oxygen can be transported from ambient air to peripheral skeletal muscles where it fuels aerobic oxidative metabolism. As such, it provides a physiological measure of aerobic fitness. A majority of studies indicate that VO_{2max} is rate-limited by the cardiac pumping capacity (cardiac output), as the main drop in oxygen partial pressure occurs between the pulmonary and skeletal muscle capillaries (Richardson 1998, Richardson et al. 1999). This view has also been supported by analytical modeling, by studies showing that the cardiac pump capacity greatly differs between untrained and endurance-trained subjects, and by approaches experimentally manipulating with convective oxygen delivery (Levine 2008, Saltin & Calbet 2006, Wagner 1996). Here, we review how the

primary muscle cell of the heart; the cardiomyocyte, contributes to VO_{2max} and aerobic fitness in both health and disease and before and after exercise training programs.

The heart and the cell integrated

The beat-to-beat pump action of the whole heart originates from the coordinated equivalent beat-to-beat contraction in the cardiomyocytes (Bers 2002), and just as the stroke volume may change when exercise intensity or workload changes, the force and extent of each cardiomyocyte contraction may also change. Cardiomyocytes are the primary cells of the heart, and although they only account for ~20% of the total cell population in the heart, cardiomyocytes account for >90% of the myocardial mass because of the size of each individual cell (Bergmann et al. 2009). As such, many of the exercise training-induced chronic changes in the heart originate from cardiomyocyte adaptations (Kemi et al. 2008C), and it is also this plasticity of the systems that allows for intensity-dependent effects to occur.

Cardiomyocytes respond in multiple ways to exercise training programs, including regulation of both size and intrinsic contraction. Remarkably, the cardiomyocytes also seem to respond to exercise training in an intensity-dependent manner; higher intensities result in greater adaptation (Kemi et al. 2005). Since the objective has been to correlate VO_{2max} with cardiomyocyte function, it has required access to viable cells and tissues freshly isolated from individuals undergoing defined and controlled exercise training regimens, which cannot be accommodated by studying human subjects. We therefore adopted procedures for exercise training and testing of VO_{2max} to experimental mice and rat models (Kemi et al. 2002, Wisloff et al. 2001A). An intensity-controlled exercise training program at 90-95% of VO_{2max} was chosen to magnify any effect, and this was performed by the interval principle, in which high intensity exercise bouts (95-95% of VO_{2max}) were interspersed by moderate intensity active recovery periods at 50-60% of VO_{2max}, to

sustain and avoid a drop in the exercise intensity during the on-transients. Thus, each animal would exercise for 1-2 hours per day, 5 days per week, for a total of 8-12 weeks. This exercise training program therefore mimics human exercise programs and result in robust and reproducible adaptations that also mimic human responses to exercise training that include increased VO_{2max} and improved cardiac function, as well as vascular and skeletal muscle improvements (Kemi et al. 2002, Wisloff et al. 2001A).

Cardiomyocyte hypertrophy

Regulation of the cardiomyocyte size contributes to the cellular involvement in the regulation of pump function. The adaptive growth of the cell in response to exercise training; termed physiological hypertrophy, usually involves proportional growth in length and width (Hunter & Chien 1999). This corresponds with increased ventricular weights and chamber volumes; termed athletes' heart, and serves thus as the cellular mechanism to the organ effect (Anversa et al. 1982, Pluim et al. 2000). Cellular hypertrophy has been reported in response to various exercise training programs (Mokelke et al. 1997, Moore et al. 1993). We have reported that high intensity exercise training at 85-90% of VO_{2max} induces a proportional hypertrophic response in the length and width of cardiomyocytes that is observable already after a few weeks of exercise training; that reaches a plateau after ~2 months, and that surpasses previous studies in terms of magnitude of effect (Kemi et al. 2002, 2004, Wisloff et al. 2001A, 2001B). The greater effect is likely explained by the higher intensity of exercise training, compared to previous studies. In a more thorough comparison, we found that the magnitude of cardiomyocyte hypertrophy depends upon the intensity of exercise, as high-intensity exercise training induced a substantially larger response than moderate intensity, which in relative terms equated to almost three times greater response (Kemi et al. 2005).

Induction and maintenance of the physiological hypertrophy of the cardiomyocyte during and after a program of exercise training includes both transcriptional and translational features. Such pathways may have different temporal periods in which they occur, and may have different levels of biological importance. First, it has been convincingly demonstrated by several research groups and with various experimental approaches spanning both running and swimming exercise protocols and targeted knock-out models, that the initiation of the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is crucial for induction of the physiological hypertrophy (Kemi et al. 2008B, McMullen et al. 2003). This pathway stimulates p70S6-kinase/ribosomal protein S6 signal transduction, and it phosphorylates the eukaryotic translation initiation factor-4E binding protein-1 (4E-BP1). Accumulatively, this increases ribosomal biogenesis and activity and therefore leads to a greater translation of messenger ribonucleic acids (mRNA) and protein synthesis. Regulation of hypertrophy by this signal pathway appears to be particularly important, since the same experiments found no chronic activation of either of mitogen-activated protein kinase (MAPK) or fetal gene re-expression signals, and since a pressure-overload-induced pathological hypertrophy in contrast associated with downregulation of the PI3K/Akt/mTOR cascade (Kemi et al. 2008B). Thus, activation or inactivation levels of PI3K/Akt/mTOR signals may distinguish between physiological and pathological growth of the cardiomyocyte.

Evidence also suggests that the MAPK signal cascade (extracellular signal-regulated kinases; ERKs, p38 isoforms, c-Jun N-terminal kinases: JNKs) is transiently increased during and shortly after exercise training bouts in untrained, but not in trained rats (Iemitsu et al. 2006). This signal cascade is known to activate nuclear transcription factors such as the myocyte enhancer factor 2 (Mef-2) that initiate transcription of genes regulating cellular hypertrophy (Liang & Molkentin 2003), suggesting that MAPK

activation may facilitate induction, but not maintenance, of physiological hypertrophy. In parallel to this, exercise training also chronically increases intracellular cycling of Ca^{2+} (reviewed below), and this chronically activates Ca^{2+}/calmodulin-dependent kinase II (CaMKII) (Kemi et al. 2007A). Activated CaMKII has several downstream effects, one of which is inhibition of class II histone deacetylase (HDAC) (Bossuyt et al. 2008). Since HDAC suppresses Mef-2, reduced suppression of Mef-2 by activated CaMKII may therefore lead to chronically increased transcription of genes regulating cellular hypertrophy. However, any chronic CaMKII-induced activation of genes regulating hypertrophy may be counteracted by the fact that exercise training also reduces nuclear factor of activated T cell (NFAT) in the nucleus (Wilkins et al. 2004). In contrast to HDAC, NFAT activates Mef-2, but the exercise training effect abolishes this. However, this is debatable and requires more studies, as different studies have reported conflicting results with regard to exercise training and NFAT and its activator calcineurin (Eto et al. 2000, Wilkins et al. 2004). Alongside this, it has also recently emerged that Mef-2 also activates transcription of micro-RNAs 1 and 133, and they innately repress mRNA translation by a different molecular mechanism, namely binding and cleaving specific mRNA strands, which thereby inhibits muscle development (Liu et al. 2007). Micro-RNAs 1 and 133 are downregulated by exercise training (Care et al. 2007), such that mRNA translation is allowed to increase. It has therefore become increasingly clear that induction of physiological cardiomyocyte hypertrophy is extremely complex and that the resultant phenotype is the result of a multitude of signal cascades operating next to each other.

Maintenance of physiological hypertrophy therefore relies on the chronic activation states of the abovementioned cascades, but also by mechanisms that control and maintain the translated protein mass of the cell. This includes the molecular chaperones heat shock proteins (HSPs), of which a number of isoforms have been reported up-regulated after exercise training programs (Boluyt et al. 2006), as well as

the ubiquitin-proteasome pathway (UPS), which on the other hand is reduced after exercise training, as reported by measuring the mRNA and protein expression levels of its constituents muscle ring finger-1 (Murf-1) and muscle atrophy f-box (MAFbx) (Adams et al. 2008). Signaling mechanisms causing or maintaining physiological hypertrophy of the heart with evidence of susceptibility to exercise training are summarized in Figure 1.

Cardiomyocyte excitation, Ca^{2+} handling, and contraction

The cardiomyocyte contraction is orchestrated by a process known as Ca^{2+}-induced Ca^{2+}-release; the action potential depolarizes the plasma membrane including the transverse tubule and opens the voltage-sensitive L-type Ca^{2+} channel. This initiates an inward Ca^{2+} current through the plasma membrane that activates the ryanodine receptors (RyR2) to release 0.5-1 μM Ca^{2+} from the sarcoplasmic reticulum (SR). The following increase in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) allows for more Ca^{2+} binding to troponin C of the contractile apparatus, and this leads to a conformational change of the actin-tropomyosin-troponin complex that facilitates actin-myosin interaction and cross-bridge creation. This causes myofilament contraction, and when it occurs in a coordinated fashion as during the global transient increase in the $[Ca^{2+}]_i$, the sarcomere and the whole cell contracts (Bers 2002). The RyR2 may spontaneously open and releases small amounts of SR Ca^{2+} during diastole, but in this case the release is uncontrolled and non-coordinated and leads to potential detrimental effects such as reduced levels of SR activator Ca^{2+} and increased diastolic $[Ca^{2+}]_i$ in the cytoplasm. The cytoplasmic Ca^{2+} also activates the Na^+/Ca^{2+}-exchanger (NCX) to initiate an inward Na^+ current, and this current may induce delayed afterdepolarisations that under some circumstances cause arrhythmias and ventricular fibrillation (Venetucci et al. 2008). A tight control of the RyR2 is therefore of physiological importance. In diastole, cardiomyocyte relaxation is evoked by removal of intracellular free and troponin C-bound Ca^{2+}, mainly by

the SR Ca^{2+} ATPase (SERCA2a) that removes the bulk of the Ca^{2+}, but also by the forward-mode NCX. The SERCA2a is innately controlled by the presence of free Ca^{2+}, and more importantly for regulation of its activity, by phospholamban, which in dephosphorylated form inhibits SERCA2a, but in phosphorylated form translocates and removes the inhibition it exerts on SERCA2a. The main kinases phosphorylating PLB are protein kinase A (PKA) and CaMKII, which phosphorylate the serine-16 and threonine-17 residues of PLB, respectively. Thus, the transient increase in $[Ca^{2+}]_i$ (termed Ca^{2+} transient) constitutes the beat-to-beat cellular mechanism of the heartbeat. Several experimental approaches such as altering $[Ca^{2+}]_i$, and using models with altered $[Ca^{2+}]_i$ handling due to changed expressions of e.g. SERCA2a and PLB have demonstrated that $[Ca^{2+}]_i$ and the transient increase in $[Ca^{2+}]_i$ during systole orchestrates cellular contraction (Frampton & Orchard 1992, del Monte et al. 1999, Gomez et al. 1997). As such, the Ca^{2+} cycling frequency determines the frequency of the heartbeat, whereas the amount of Ca^{2+} released from the SR and the responsiveness of the myofilaments to Ca^{2+} determines the extent (fractional shortening) and force of the contraction (Bers 2002). Several aspects of excitation-contraction coupling are prone to exercise training, whether it be in normal or dysfunctional and failing cardiomyocytes.

Exercise training and cardiomyocyte contraction

Aerobic exercise training performed with a high intensity (90% of VO_{2max}) over a prolonged period of time improves contractility in unloaded cardiomyocytes, measured as the fractional shortening (the shortest systolic length relative to resting diastolic length) and as the rates with which shortening and relengthening occurs, during electrical field stimulation with increasing frequencies. Fractional shortening improves by 40-50%, and contraction and relaxation rates improve by 20-40% (Kemi et al. 2004, Wisloff et al. 2001B, 2002). These changes are particularly consistent for relaxation rates throughout a series of different studies, whereas faster contraction rates have been observed in some (Kemi et al. 2004, 2005),

but not all studies (Wisloff et al. 2001B, 2002). However, increased shortening rates have also been observed in cardiomyocytes during loaded contractions that more accurately mimic physiological preload conditions of the heart (Diffee & Chung 2003). Loaded conditions also allow for studies of the development of force during each contraction cycle, with subsequent calculation of the developed power, and under those conditions, it was indicated that exercise training increased the maximal power output in the cardiomyocyte by 60%. It should though be noted that the exercise intensity applied in this study was low-to-moderate, such that direct comparisons to high intensity exercise training cannot be made as to the magnitude of effect. However, there is a clear tendency that those studies utilizing a high exercise intensity (reviewed above) during the exercise training programs report greater magnitudes of changes compared to studies utilizing lower exercise intensities or voluntary running schemes (Diffee & Chung 2003, Diffee et al. 2001, Mokelke et al. 1997, Moore et al. 1993). This has been confirmed by subjecting exercise training rats to either of high (85-90% of VO_{2max}) or moderate (65-70% of VO_{2max}) exercise intensities for 2.5 months, which found high intensity exercise to be approximately twice as effective as moderate intensity (Kemi et al. 2005). In fact, some of the studies utilizing low or voluntary exercise intensities fail to detect contractile improvements following prolonged exercise training programs (Laughlin et al 1992, Palmer et al. 1998). However, different experimental conditions while studying cellular contraction, and different electrical stimulation protocols may explain some of the differences.

Furthermore, exercise training improves contractile function also when no simultaneous changes to end-diastolic wall stress can be recorded (Schaible & Scheuer 1981), and it increases isometric force even when optimal sarcomere length is maintained (Mole 1978). This suggests that the contractile improvement of the cardiomyocyte after exercise training is independent of hypertrophy, and that the contractile response therefore relies on subcellular mechanisms that facilitate inotropy, such as adenosine

triphosphate (ATP) hydrolysis and Ca^{2+}-induced actin-myosin crossbridges. Finally, experiments with permeabilized cardiomyocytes; in which ions move freely across the plasma membrane such that the $[Ca^{2+}]_i$ can be very accurately manipulated in order to study direct Ca^{2+} effects on contractile force, have also demonstrated that force- and power outputs and the steepness of the sarcomere length-tension relationship increase in the single cell with exercise training (Diffee & Chung 2003, Diffee & Nagle 2003, Natali et al. 2002). This suggests that changes in the individual cardiomyocytes explain at least some of the Frank Starling-related mechanisms that occur with exercise training. Collectively, the cardiomyocyte contractile adaptations to exercise training reviewed above provide the cellular rationale for exercise training-induced improvements in systolic and diastolic functions and increased cardiac output in whole hearts of both humans and experimental animals (Gledhill et al. 1994, Helgerud et al. 2007, Schaible & Scheuer 1981).

Exercise training and intracellular Ca^{2+}

Since intracellular Ca^{2+} handling controls cardiomyocyte contraction (see above), it comes to no surprise that exercise training-induced changes in the cardiomyocyte contractility are chiefly caused by changes in the intracellular handling of Ca^{2+}. Indeed, the comparable changes of the rates of the Ca^{2+} transient rise and decay and the rates of contraction and relaxation suggests that changes to contractility and Ca^{2+} handling are intimately linked together. In other words, the changes in rate of Ca^{2+} cycling explain the changes in contraction-relaxation rates of the cardiomyocyte after exercise training (Kemi et al. 2004, Wisloff et al. 2001B). In short, exercise training leads to faster systolic rise and diastolic decay times of the Ca^{2+} transient, and this has been demonstrated after electrical stimulation at both low and increased frequencies that correspond to heart rates of sedentary and exercising rat and mice. Moreover and in line with the recordings of contraction-relaxation rates, the magnitude of the exercise training-induced

adaptations to rise and decay rates of the Ca^{2+} transient depends upon the exercise intensity. High intensity exercise training at 85-90% of VO_{2max} induced a ~40% change, whereas moderate intensity exercise training in contrast induced a ~20% change in the release and re-uptake rates of Ca^{2+} cycling (Kemi et al. 2005). This is in line with observations from human studies showing that high aerobic exercise intensity induces a greater cardiac adaptation than exercise training with lower intensities (Helgerud et al. 2007), and provides thus a cellular rationale for the whole heart effects. However, the concept of exercise training inducing a faster rise of the Ca^{2+} transient does not rely on unambiguous evidence, as some studies have been unable to identify a change in the rise time of the Ca^{2+} transient after exercise training, only a faster Ca^{2+} transient decay time (Wisloff et al. 2001B). Nonetheless, the majority of studies of high intensity exercise training specifically investigating Ca^{2+} transients have reported faster rise times in both mice and rats (Kemi et al. 2004, 2005, 2007A). Apart from increased rates of Ca^{2+} cycling, exercise training also reduces diastolic $[Ca^{2+}]_i$ (Kemi et al. 2007A, Wisloff et al, 2001B), compared to sedentary controls. This has several important implications. First, the likelihood of developing Ca^{2+}-linked arrhythmias is reduced. In normal hearts, this risk is already small. However, in certain pathologic conditions or mutations favoring spontaneous diastolic Ca^{2+} release, improved control of diastolic Ca^{2+} may become important. Second, reduced free intracellular diastolic Ca^{2+} also leads to a more complete relaxation and a greater recharging of the SR, which supports Ca^{2+}-induced Ca^{2+}-release by the RyR2.

In response to exercise training, $[Ca^{2+}]_i$ handling as well as contractility improves steadily over the course of the program until a plateau is reached after ~2 months; the positive inotropic effects of high intensity exercise are indistinguishable between 8 and 13 weeks of exercise training programs (Kemi et al. 2004). Two likely explanations for the plateau are either that the cardiomyocytes reach a maximal potential for improvement or that the relative exercise intensity or volume needs to be increased at this point to elicit

further development. In contrast, when a high intensity exercise training program is ceased by a return to a sedentary lifestyle (detraining), the regression of training-induced effects on cardiomyocyte $[Ca^{2+}]_i$ handling and associated contraction with a return to normal levels occurs within 2-4 weeks (Kemi et al. 2004). Hence, detraining effects occur faster than the actual training effects.

Mechanisms of Ca^{2+} control

We have in several studies provided evidence that exercise training increases the SERCA2a mRNA and protein expression levels in cardiomyocytes, but not PLB expression levels (Kemi et al. 2007A, 2008A). This upregulates the SERCA2a-to-PLB ratio and therefore allows the SERCA2a to increase activity. Concomitantly, exercise training also increases the phosphorylation status and hence chronic activation of CaMKII in the cardiomyocyte, which subsequently chronically hyperphosphorylates the threonine-17 residue of PLB (Kemi et al. 2007A). Phosphorylated PLB does not inhibit SERCA2a, in contrast to the dephosphorylated isoform. These effects suggest a faster re-uptake of free cytoplasmic Ca^{2+} by the SR and provide an explanation for the faster Ca^{2+} transient decay rate after exercise training; as reviewed above. Consequently, they also suggest that SR loading of Ca^{2+} may increase with exercise training, although this has not been measured yet. In contrast to CaMKII, PKA and its serine-16 PLB residue were unaltered by exercise training.

Recently, we developed an assay that allows us to directly study the activity levels of isolated SERCA2a proteins in the intact SR membranes of permeabilized cardiomyocytes, and this showed that the maximal rate of SERCA2a Ca^{2+} uptake increased by 30% after exercise training (Kemi et al. 2008A). This magnitude of effect compares closely with the magnitude of the exercise training-induced effect on the Ca^{2+} transient decay. In line with this, exercise training also increases the protein expression levels of

NCX (Wisloff et al. 2001B, 2002), which together with the chronic activation of CaMKII and its effect on PLB, and the increased SERCA-to-PLB ratio also explains the reduced diastolic $[Ca^{2+}]_i$. However, not all studies have been able to report that exercise training improves cardiac SR Ca^{2+} cycling or changes expression levels of SERCA2a and NCX (Lankford et al. 1998, Tate et al. 1993). The reason for this discrepancy is not clear, but may be linked to different exercise intensities, as studies of high exercise intensity have reported upregulated expression of SERCA2a and NCX, whereas those studies reporting no changes have utilized low exercise intensities in their exercise regimens. The reduction in resting diastolic $[Ca^{2+}]_i$ after exercise training could also be at least partly explained by several other factors. These include improved Ca^{2+} buffering capacity of the cytoplasm, since only a small fraction of the cytoplasmic Ca^{2+} exists as free Ca^{2+} (Bers 2002) and since exercise training increases Ca^{2+} binding and binding sites in the cardiomyocyte SR (Penpargul et al. 1977) and plasma membrane (Tibbits et al. 1989), as well as the cellular hypertrophy that may dilute cytoplasmic Ca^{2+} due to the volume expansion. Finally, mitochondrial Ca^{2+} cycling, albeit contributing very little to the overall Ca^{2+} handling of the cell, may also account for a small portion of the reduced diastolic $[Ca^{2+}]_i$ after exercise training (Beyer et al. 1984). This study indicated that the exercise trained mitochondria may increase its ability to accumulate Ca^{2+}.

In contrast to the diastolic Ca^{2+} handling, no clear and uniform mechanism that would explain why and how exercise training increases the rate of rise of the Ca^{2+} transient has yet been identified. A potential mechanism that might explain this is the indication that exercise training may chronically prolong the action potentials and thus excitation, at least in regions of the heart (Natali et al. 2002). Since the L-type Ca^{2+} channel is voltage-sensitive, this may prolong the L-type Ca^{2+} current and therefore also the Ca^{2+}-induced activation of the RyR2 on the SR; the site of the bulk systolic Ca^{2+} release. However, it is not clear whether this would lead to a faster rise time of the Ca^{2+} transient *per se*. Another mechanism that

may explain this would be if the coupling of plasma membrane excitation, L-type Ca^{2+} current across the membrane, and RyR2 on the SR membrane changed properties, for instance by reducing physical distances without hampering Ca^{2+} flux from the SR to the myofilaments. This, however, remains to be studied. Exercise training-induced changes in cardiomyocyte Ca^{2+} cycling are illustrated in Figure 2.

Ca^{2+} transient amplitude and myofilament Ca^{2+} sensitivity

Whereas the exercise training-induced increased rates of contraction and relaxation can be fully explained by the similar changes to the rise and decay rates of the Ca^{2+} transient, the larger fractional shortening that also occurs after exercise training does not appear to be fully explained by elevated peak systolic $[Ca^{2+}]_i$ or a greater amplitude of the Ca^{2+} transient (Kemi et al. 2004, 2005, Laughlin et al. 1992, Wisloff et al. 2001B, 2002), which normally would have been the first mechanism to study with relation to increased contraction. In fact, although most studies have reported no changes to the amplitude of the Ca^{2+} transient, some studies have also reported either a reduced Ca^{2+} transient amplitude or a sustained amplitude but at reduced diastolic and systolic $[Ca^{2+}]_i$ (Wisloff et al. 2001B, 2002). Thus, this suggests that other mechanisms may be at play that would explain the improved fractional shortening of the exercise trained cardiomyocyte, since systolic activator Ca^{2+} or the Ca^{2+} transient amplitude cannot provide an explanation for this phenomenon. However, if not the amplitude, the shape of the Ca^{2+} transient may still partly explain the improved magnitude of contraction, measured as increased fractional shortening after exercise training. Since the exercise training-induced increase in the decay rate of the Ca^{2+} transient was greater than the increase in the rate of rise; i.e. the Ca^{2+} transient became narrower due to the shorter duration, also means that the activator Ca^{2+} is less “smeared out” after exercise training. Because the Ca^{2+} binding to troponin C is a very short event, this consequently means that more of the available Ca^{2+} is activating contraction at the same time, such that actin-myosin contraction throughout the cell occurs more

synchronously. This would enable a greater fractional shortening, though it is very unlikely that it would explain the full exercise training effect on the fractional shortening. Thus, improved contraction appears to also result from improved myofilament responsiveness to Ca^{2+}, i.e. increased Ca^{2+} sensitivity. Higher Ca^{2+} sensitivity during submaximal, but not maximal activation of tension, after exercise training has been convincingly demonstrated, measured as a leftward shift in the tension-pCa relationship (Diffee et al. 2001, Wisloff et al. 2001B). This effectively means that the $[Ca^{2+}]_i$ that produces half-maximal tension is decreased, and it is important because most of the cardiomyocyte contraction occurs at submaximal $[Ca^{2+}]_i$. The leftward shift suggests a faster shortening, but also that a greater contraction and force output can be produced in each contraction cycle, despite the Ca^{2+} transient amplitude may not change or even when the Ca^{2+} transient duration is shortened.

Several mechanisms may explain the improved myofilament Ca^{2+} sensitivity. Recent work has implied that the exercise training-induced chronic phosphorylation (activation) of CaMKII may contribute toward this effect (Kemi et al. 2007A). Another mechanism that may explain this is the improved regulation of intracellular pH during increased stimulation frequencies (faster heart rates) (Wisloff et al. 2001B). If pH is allowed to drop by ineffective H^+ buffering, the excess H^+ will compete with Ca^{2+} for binding to troponin C, but without inducing the conformational change that induces the contraction. However, since intracellular pH is similar between exercise trained and sedentary cardiomyocytes during resting and low-frequency stimulation conditions, it can only explain improved Ca^{2+} sensitivity during increased heart rates, whereas the increased Ca^{2+} sensitivity was observed during both resting/low and high electrical stimulation frequencies. Nonetheless, it is during increased stimulation frequencies (heart rates) that the biological significance of Ca^{2+} sensitivity is highest, such that the pH effect may still exert an important adaptation to exercise training. The cause of the improved pH regulation was linked to increased mRNA

expression of the Na^+/H^+-exchanger (NHE), which removes excess H^+ from the cytoplasm (Wisloff et al. 2001B). Finally, increased expression levels of atrial myosin light chain 1 (Diffee et al. 2003), and isoform shifting of troponins (Anderson et al. 1995) and myosin heavy chains (Nakao et al. 1997) have also been proposed as candidates explaining the exercise training-induced increase in myofilament Ca^{2+} sensitivity, since such changes would associate with altered troponin-tropomyosin configurations that would alter the biophysical properties of cross-bridge creation and force production.

Experimental animal models of cardiac dysfunction and failure: post-myocardial infarction heart failure

Several experimental models of heart dysfunction, disease and failure have been developed in mice and rats that allow for studies of intrinsic heart and cardiomyocyte function under those conditions, including the associated responses to exercise training.

A commonly utilized model of heart disease is the post-myocardial infarction (MI) heart failure (HF) model in rats. The left coronary artery is permanently ligated to induce ischemia (Kemi et al. 2007B, Wisloff et al. 2002), leading to a subsequently developming HF. The condition is characterized by pulmonary congestion and compromised exercise capacity. In the heart, the symptoms include reduced reserve and pump capacity, development of pathological hypertrophy, dilatation, and fibrosis, increased end-diastolic and reduced systolic pressures, reduced function of the myocardium, and re-expression and activation of fetal genes and pathologica molecular signaling pathways (Hasenfuss 1998). Thus, this model mimics the pathology and pathophysiology of post-MI HF patients, albeit the induction of it is a sudden physical damage to an otherwise healthy organ. Hence, the etiology is different from clinical HF, but the resulting phenotype and genotype shows considerable similarities to post-MI HF in humans.

Further proof of this comes from studies showing that post-MI HF animals also die from progressive pump failure or sudden arrhythmic events, in line with clinical cases in humans (Myles et al. 2008). The model therefore has been used to study the mechanistic basis of post-MI HF both before and after exercise training. Indeed, and similar to humans, cardiomyocytes isolated from hearts of post-MI HF rats are characterized by dysfunctional and reduced excitation, Ca^{2+} handling, and contraction, and abnormal cellular structure and architecture, including a pathologically enlarged size (Bers 2002, Loennechen et al. 2002, Wisloff et al. 2002). A metabolic myopathy contributes toward the cellular dysfunction (Kemi et al. 2007B), but factors intrinsic to the Ca^{2+} handling, such as reduced NCX and SERCA2a also explain the dysfunction (Wisloff et al. 2002). Furthermore, altered gene transcription and translation, including re-expression of embryonic fetal genes also contribute to the pathology (Hunter & Chien 1999). Functionally, failing cardiomyocytes show reduced fractional shortening and reduced rates of contraction and relaxation, reduced Ca^{2+} transient amplitude and rise and decay rates, and increased diastolic $[Ca^{2+}]_i$ (Loennechen et al. 2002, Wisloff et al. 2002). Taken together, these changes have the potential to explain the reduced ability of the cardiomyocyte to perform beat-to-beat contractile work, and importantly, they also constitute a set of parameters that are prone to positive modulation by exercise training; as detailed above. Thus, this opens up the possibility that exercise training may reverse the contractile dysfunction of the cardiomyocyte and restore a more normal pump function of the heart through a cellular route. Indeed, 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 85-90% of VO_{2max} than after moderate to low exercise intensity training programs.

Post-MI HF and exercise training

Several ameliorating effects to the heart have been observed when post-MI HF rats are subjected to 2-3 months of daily high intensity exercise training at 85-90% of VO_{2max} starting one month after the induction of MI. Thus, this is the same exercise training program as described above for healthy animals, though with lower absolute workloads to adjust for the reduced exercise capacity. First, the arterial dysfunction is reversed by virtue of restored production of nitric oxide (NO) in the endothelium of the vessel wall, a change facilitated by adaptive changes in the endothelial NO synthase (eNOS), its activation by Akt, and by reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase-generated reactive oxygen species (ROS) scavenging of NO (Adams et al. 2005, Hambrecht et al. 2003). Thus, the normalized arterial function stems from changes intrinsic to the artery endothelium and is not driven by the heart. However, a net effect is that it unloads the heart and thus improves hemodynamics and pressure characteristics. Secondly, and even more important for the heart, exercise training also reduces the intrinsic dysfunction of the heart, leading to an improved ability of the myocardium and the cardiomyocyte to perform beat-to-beat contractions, independent of peripheral vascular feedback to the heart as well as neurohormonal regulation.

The exercise training partly, but not fully, reversed the pathological hypertrophy, observed as reduced cell length and width (Wisloff et al. 2002). The cellular remodeling was also paralleled by reduced myocardial mass and left ventricular dilatation, as measured by echocardiography. The mechanism of the reverse remodeling remains unknown, but it was associated with reduced mRNA levels of atrial natriuretic peptide (ANP). This does not prove a cause-effect relationship between reverse remodeling and ANP, but it does demonstrate that whatever the mechanism is, it is reflected in both the phenotype and the molecular marker of this phenotype.

In parallel to the reverse remodeling, exercise training also restored the rates of contraction and relaxation and the amplitude of the fractional shortening toward normal levels (Wisloff et al. 2002). Normalized rates of contraction and relaxation were explained by increased rates of rise and decay of the Ca^{2+} transient, which also reverted toward normal levels. Mechanistically, this was associated with normalized NCX and SERCA2a, which in post-MI HF are pathologically altered, suggesting that diastolic removal of cytoplasmic Ca^{2+} was shifted from the plasma membrane to the SR. This also implies that SR Ca^{2+} loading was normalized, which would benefit the RyR2 release of SR Ca^{2+}, measured as the amplitude or the rise time of the Ca^{2+} transient. Therefore, this supports cardiomyocyte inotropy and may likely also reduce the potential for developing arrhythmic events, since a Ca^{2+} flux across the plasma membrane leads to an inward Na^{+} current through the NCX that under some circumstances may induce delayed afterdepolarizations (Venetucci et al. 2008). Nonetheless, although faster contraction and relaxation rates can be fully explained by faster Ca^{2+} cycling in its entirety, the normalized fractional shortening after exercise training cannot be solely explained by the Ca^{2+} transient, since the changes in the amplitudes of the fractional shortening and the Ca^{2+} transient do not fully correspond to each other. The narrowing of the Ca^{2+} transient due to the changes to the Ca^{2+} cycling rates may increase fractional shortening (see fuller explanation above), but it is unlikely that this fully explains the normalized fractional shortening. It is therefore likely that myofilament Ca^{2+} sensitivity also contributes toward the correction of the inotropy. Indeed, experiments in permeabilized cardiomyocytes subject to increasing [Ca^{2+}] reveal that exercise training counteracts and corrects the post-MI HF-associated reduction in Ca^{2+} sensitivity (Wisloff et al. 2002). In parallel to reduced Ca^{2+} sensitivity, intracellular pH is also chronically reduced in post-MI HF (Kemi et al. 2006), and this has been associated with the reduction of myofilament Ca^{2+} sensitivity and the restoration by exercise training, which improved both Ca^{2+} sensitivity and pH regulation of the cardiomyocyte (Wisloff et al. 2002). These changes were at least partly associated with myocardial NHE,

rendering an improved ability to buffer intracellular H^+ after exercise training in post-MI HF. However, the concept of myofilament Ca^{2+} sensitivity in post-MI HF has yet to be fully explored. For instance, a recent study observed that myofilament Ca^{2+} sensitivity increased in post-MI HF mice; possibly to compensate for contractile failure, but in this study, exercise training reversed the post-MI HF-associated increase in the myofilament Ca^{2+} sensitivity, in a PKA-dependent manner (de Waard et al. 2007). The reason for this controversy is unknown.

Finally, post-MI HF is also associated with a metabolic cardiomyopathy, as evidence by reduced activities and levels of enzymes involved in myocardial energy metabolism, such as creatine and adenylate kinases, creatine synthase, cytochrome c oxidase (COX), lactate dehydrogenase, as well as reduced levels of the master transcription factor for mitochondrial biogenesis; the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) (Kemi et al. 2007B). The intervention with high intensity exercise training reversed the abnormal metabolic status and close-to-normalized myocardial energetics. This may have served to improve the abnormal Ca^{2+} cycling and inotropy, because SERCA2a, actin-myosin ATPase, and actin-myofilament sliding all require ATP to function normally (Kuum et al. 2009).

Several other studies have also confirmed that exercise training has the potential to improve the cardiomyocyte contractile capacity in HF (Musch et al. 1989). Interestingly, very high anaerobic exercise intensities, as achieved by repeated short bursts of treadmill running sprints, have also shown a potential for reversing and correcting the pathological abnormalities induced by post-MI HF (Zhang et al. 1998, 2000). However, the applicability of this exercise training regimen for HF patients remains controversial, as no clinical trials have repeated this in human patients. In fact, the effect of different exercise intensities in HF has not been explicitly studied, such that it remains unknown whether or not the intensity-

dependence of exercise training in post-MI HF is similar to that during normal conditions. However, the available data suggest that the adaptation to exercise training, including its dependence on exercise intensity, remains similar between normal and HF conditions. This assertion is based upon several factors. First, the intensity-dependence of exercise training adaptation exists in clinical trials, as evaluated by echocardiography in the whole-heart (Amundsen et al. 2008, Wisloff et al. 2007), and secondly, effect size is greater in studies utilizing high intensity exercise training compared to studies using low or moderate intensity exercise training, which in most cases only exert modest or no effects (Wisloff et al. 2002, Musch et al. 1989).

Animal models of cardiac dysfunction and increased risk of developing HF

Several experimental models exist that also allow for studies of conditions that either show myocardial dysfunction with different etiologies to post-MI, or show an increased risk of developing heart disease. These include a mouse model of type 2 diabetes mellitus induced by an inactivating mutation in the gene encoding leptin that presents with a metabolic and contractile cardiomyopathy (db/db mice), and a rat model of metabolic syndrome, a condition that presents with a cluster of risk factors adjourned together that precede heart disease, such as abdominal obesity, hypertension, insulin resistance or glucose intolerance, and dyslipidemia (Tjonna et al. 2008). Included in this syndrome is also a reduced amount of key proteins required for normal mitochondrial function, suggesting that it is linked to an abnormal metabolic state (Wisloff et al. 2005). Studies of exercise training in these models have supported the hypothesis that exercise training positively modulates intrinsic cardiomyocyte contractile function and that it may correct abnormal and reduced contractility to the degree that normal or close-to-normal contractile function is achieved.

High intensity exercise training was performed in the same way as described above for normal and post-MI HF rats and mice, but this time by mice with diabetic cardiomyopathy due to diabetes type 2-like symptoms and rats with the metabolic syndrome. First, diabetic cardiomyopathy was associated with reduced cardiomyocyte contractility and Ca^{2+} handling and abnormal cellular architecture (Stolen et al. 2009), reminiscent of post-MI HF. Exercise training restored normal contraction and Ca^{2+} transients, reduced spontaneous Ca^{2+} leak by the RyR2 and increased SERCA2a activity which thus also reduced diastolic $[Ca^{2+}]_i$, normalized transverse tubule density which was reduced in diabetic cardiomyopathy and corrected therefore the abnormal synchrony of Ca^{2+} release throughout the cell, and reversed the pathological hypertrophy. Figure 3 illustrates these phenomena. These changes were precipitated by altered activity levels of CaMKII and PKA, but in contrast to normal cardiomyocytes, exercise training reduced phosphorylation of threonine-17 of PLB and cytoplasmic CaMKII and increased phosphorylation of serine-16 PLB, the PKA-dependent residue (Stolen et al. 2009). The cause of this controversy is unknown, but it suggests that CaMKII may have differential downstream effects that under some circumstances may incur a benefit and under other circumstances incur adverse effects. Normalization of diabetic metabolic parameters was however ruled out as a mechanism restoring myocardial inotropy. Secondly, the metabolic syndrome was also associated with reduced contractility and Ca^{2+} handling, and pathological remodeling of cell size (Haram et al. 2009, Wisloff et al. 2005). In this case, exercise training also reversed the pathological changes and normalized the contractility of the cardiomyocytes, although the underlying explanatory mechanisms have been studied less rigorously. It is though clear that positive modulation of intracellular Ca^{2+} cycling at least partly leads to this, but so may also the partial correction of metabolic pathways in the cell (Wisloff et al. 2005). In both models, exercise training-induced improvements to cardiomyocyte contractile capacity are also associated with improved whole-heart functions and exercise capacities, measured as VO_{2max}.

Intact responses to exercise training during cardiac dysfunction and failure

The studies described above collectively suggest that the ability to respond to exercise training is sustained even during the development of a cardiac myopathy and failure due to either of MI, type 2 diabetes, and the metabolic syndrome, and that this ability remains equivalent to that observed in healthy animals. Importantly, since the majority of the measurements described above were performed in isolated cardiomyocytes, it furthermore suggests that exercise training corrects inotropy and lusitropy via mechanisms intrinsic to the cardiomyocyte and does not rely on extrinsic modulatory factors.

It has become clear that exercise training not only regulates single genes and molecular pathways, but also networks of a large number of genes throughout the genome (Bye et al. 2008), but the significance and exact implication of this is incompletely understood. For instance, post-MI HF and salt-induced pathological hypertrophy is associated with a much larger number of differentially expressed myocardial genes than exercise training (Beisvag et al. 2009, Kong et al. 2005). Nonetheless, this suggests that separate genetic networks may be responsible for the pathological development of the heart and the changes that occur in response to exercise training, and hence, this may explain why the ability to respond to exercise training remains intact despite a pathological phenotype and genotype in the heart. However, this remains to be investigated in more details.

The reviewed research strongly indicates that the function of the cardiomyocytes determines the function of the whole heart and ultimately the function of the whole body, and this relationship is maintained during the whole spectrum of conditions from disease to high fitness levels. Whole heart changes usually correlate well with changes in VO_{2max} after exercise training, and this relationship has now also been

confirmed between individual cardiomyocytes and VO_{2max} (Kemi et al. 2004). Changes in cardiomyocyte size (volume), contractility (fractional shortening and rates of contraction and relaxation) and systolic and diastolic Ca^{2+} handling correlate well with the changes in VO_{2max} in the same animals. The same phenomena have also been observed in human populations, though these studies only allow studies of whole hearts and not cardiomyocytes (Pelliccia et al. 2002). Thus, changes occurring in the cardiomyocyte have the power to substantially alter exercise capacity, function, and health not only in normal individuals, but also in those developing or living with heart disease. As reviewed below, it is reasonable to assert that these phenomena also extend from small rodents to humans, also under conditions of heart disease or an increased risk of developing heart disease.

Exercise training in clinical trials of heart dysfunction and disease: cardiac effects

The above research provides the mechanisms by which exercise training reduces intrinsic cardiac dysfunction and improves inotropy and lusitropy, and it provides a rationale for studying the effects of high intensity exercise training in patients with post-MI HF and established heart disease, as well as in patients with increased risk of developing heart disease. Currently, clinical trials and practice has only emphasized the use of moderate exercise intensities in the management of patients with established or increased risk of developing heart disease, as safety and efficacy has only been assessed after moderate exercise intensities (Hambrecht et al. 2000, 2003, Kodoma et al. 2009, Tanasescu et al. 2002). However, recent trials have suggested that high intensity aerobic exercise training programs at ~90% of VO_{2max} may also be beneficial to patients with either post-MI HF (Wisloff et al. 2007), coronary artery disease (Amundsen et al. 2008, Rognmo et al. 2004), and increased risk of developing heart disease (Schjerve et al. 2008, Tjonna et al. 2008). Common for these trials is that they report cardiac benefits of high intensity exercise training performed at 90-95% of peak heart rate (which corresponds to ~90% of VO_{2max}), and that

this effect is considerably larger than the effect of moderate exercise intensity at 70% of peak heart rate, in which exercise capacity increased, but no changes were observed in the heart. In the high intensity exercise groups, patients were able to run strenuous intervals at high exercise intensities on a treadmill 3 times per week for several months. This resulted in 30-50% increased VO_{2max}, and was paralleled by reduced left ventricular dilatation and mass, and increased ejection fractions, stroke volumes, and systolic and diastolic intracardiac flow and ventricular wall motion parameters, especially in those with compromised myocardial function. In contrast, no effects occurred in the control groups that were subjected to recommendations from the family physician following current guidelines for exercise training and physical activity, and only minor to no effects were observed after energy-matched moderate intensity exercise training. It should though be emphasized that these trials were small and not powered to assess safety or efficacy of exercise training. In line with the above, the largest trial of exercise training in HF patients conducted so far (HF-ACTION) could not detect any mortality or re-hospitalization benefits of exercise training; likely due to the use of low and moderate intensities and avoidance of high intensity in the chosen exercise training programs (O'Connor et al. 2009). Epidemiological surveys have however confirmed that the benefit of exercise training for populations with established or increased risk of developing heart disease increases with increasing exercise intensities, even when adjusted for other prevalent risk factors such as hypertension, obesity, diabetes and high cholesterol, or for pharmacological medication (Lee et al. 2003, Kavanagh et al. 2002, Kodoma et al. 2009, Moholdt et al. 2008, Myers et al. 2002, O'Neill et al. 2005, Paffenbarger et al. 1993, Tanasescu et al. 2002).

Summary and conclusions

Experimental and clinical studies have demonstrated that high intensity aerobic exercise training is beneficial for the intrinsic pump capacity of the heart, independent of whether it is a healthy or

dysfunctional or failing heart, or at an increased risk of developing dysfunction and failure. This phenomenon is by large intensity-dependent, since high aerobic exercise intensity leads to greater effects than low- to moderate exercise intensities. At the cellular level in the heart, exercise training leads to improved inotropy due to contractile and hypertrophy changes. The improvement of contractility in the cardiomyocyte is tightly regulated by intracellular handling of Ca^{2+} and the cell's ability to flux Ca^{2+} to and from the myofilaments that constitute the contraction, as well as the myofilaments' response to Ca^{2+}. These processes are down-regulated in heart disease, but exercise training has the ability to correct the abnormalities. Thus, the ultimate adaptation of the cardiomyocyte to chronic exercise training is to increase the pump capacity of the heart, which again ultimately increases the work capacity and functionality of the whole body. In other words, the function of the cardiomyocyte is integral to the whole-body exercise capacity (VO_{2max}). The cellular physiology reviewed above therefore makes best sense when appreciating the role cellular changes have for the integrated physiology of the mammalian, and it does not matter whether the mammal is a small rodent or man.

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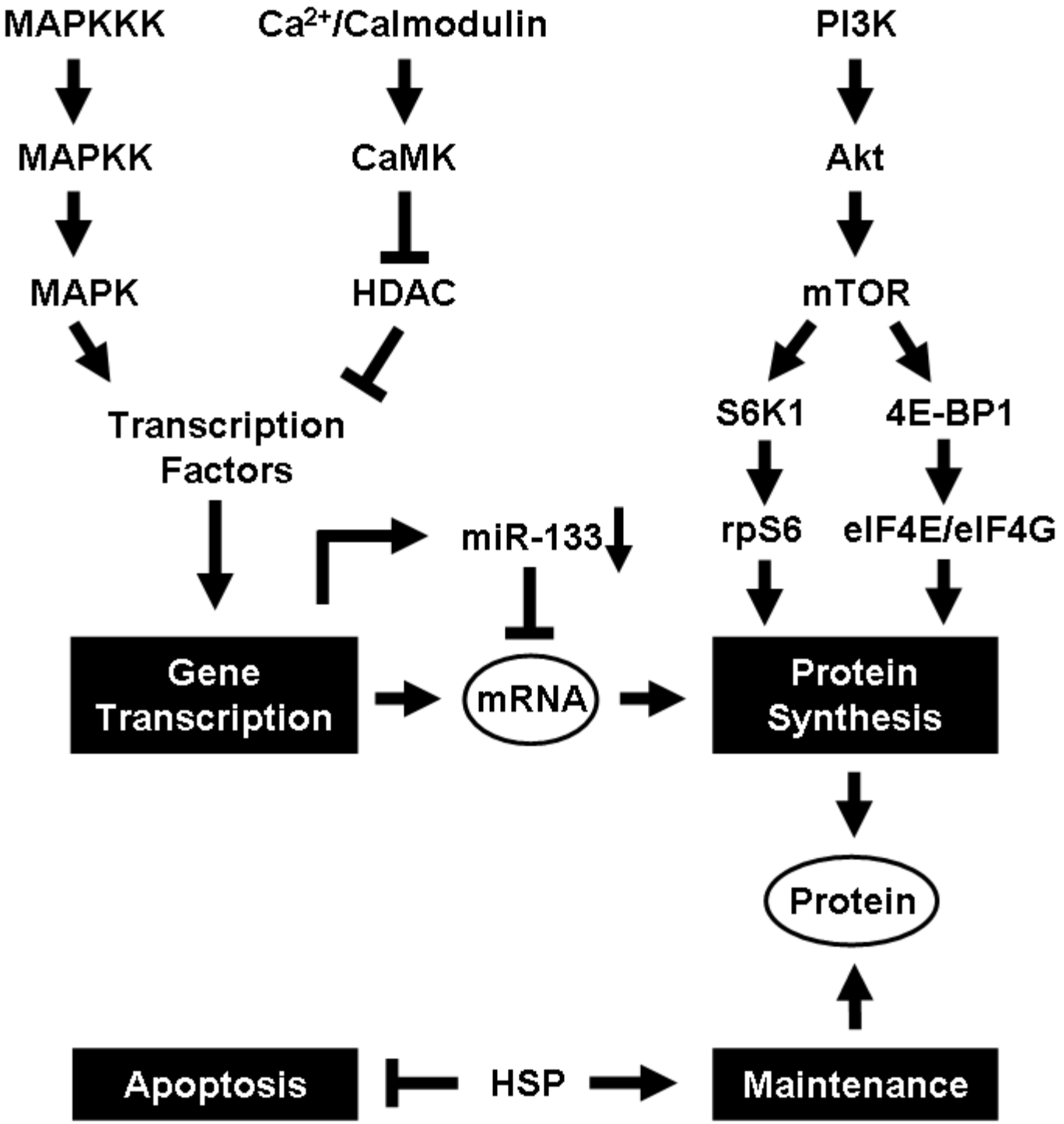
Figure legends

Figure 1: Schematic of signaling pathways that cause or maintain exercise training-induced hypertrophy of the cardiomyocyte. Details are provided in the text. MAPKKK: mitogen-activated protein kinase kinase kinase, MAPKK: mitogen-activated protein kinase kinase, MAPK: mitogen-activated protein kinase, CaMK: Ca^{2+}/calmodulin-dependent protein kinase, HDAC: histone deacetylase, miR-133: micro-ribonucleic acid-133, mRNA: messenger ribonucleic acid, PI3K: phosphoinositide 3-kinase, Akt: protein kinase B, mTOR: mammalian target of rapamycin, S6K1: ribosomal protein S6-kinase-1, rpS6: ribosomal protein S6, 4E-BP1: 4E binding protein-1, eIF4E/eIF4G: eukaryotic translation initiation factors 4E and 4G, HSP: heat shock protein. Reproduced with permission from Wisloff et al. 2009.

Figure 2: Schematic of excitation-contraction coupling and Ca^{2+} cycling in cardiomyocytes, with broad arrows indicating exercise training-induced changes. Details are provided in the text. PM: plasma membrane, LTCC: L-type Ca^{2+} channel, NCX: Na^{+}/Ca^{2+} exchanger, PMCA: plasma membrane Ca^{2+} ATPase, RyR: ryanodine receptor, SR: sarcoplasmic reticulum, SERCA: SR Ca^{2+} ATPase, PLB: phospholamban, P~CaMKII: phosphorylated Ca^{2+}/calmodulin-dependent protein kinase II. Reproduced with permission from Wisloff et al. 2009.

Figure 3: Schematic of Ca^{2+} transients (top), transverse (t)-tubule networks (middle), and synchrony of systolic Ca^{2+} release (bottom) in cardiomyocytes from sedentary (left) and exercise trained (right) mice with type 2 diabetes mellitus. The figure illustrates that less systolic Ca^{2+} is available for contraction in sedentary mice; that t-tubules appear disorganized and less dense in sedentary mice, and that the synchrony of the stimulated Ca^{2+} release during systole is reduced in sedentary mice, compared to exercise trained mice.

Figure 1


MAPKKK
Ca2+/Calmodulin
PI3K
MAPKK
CaMK
Akt
MAPK
HDAC
mTOR
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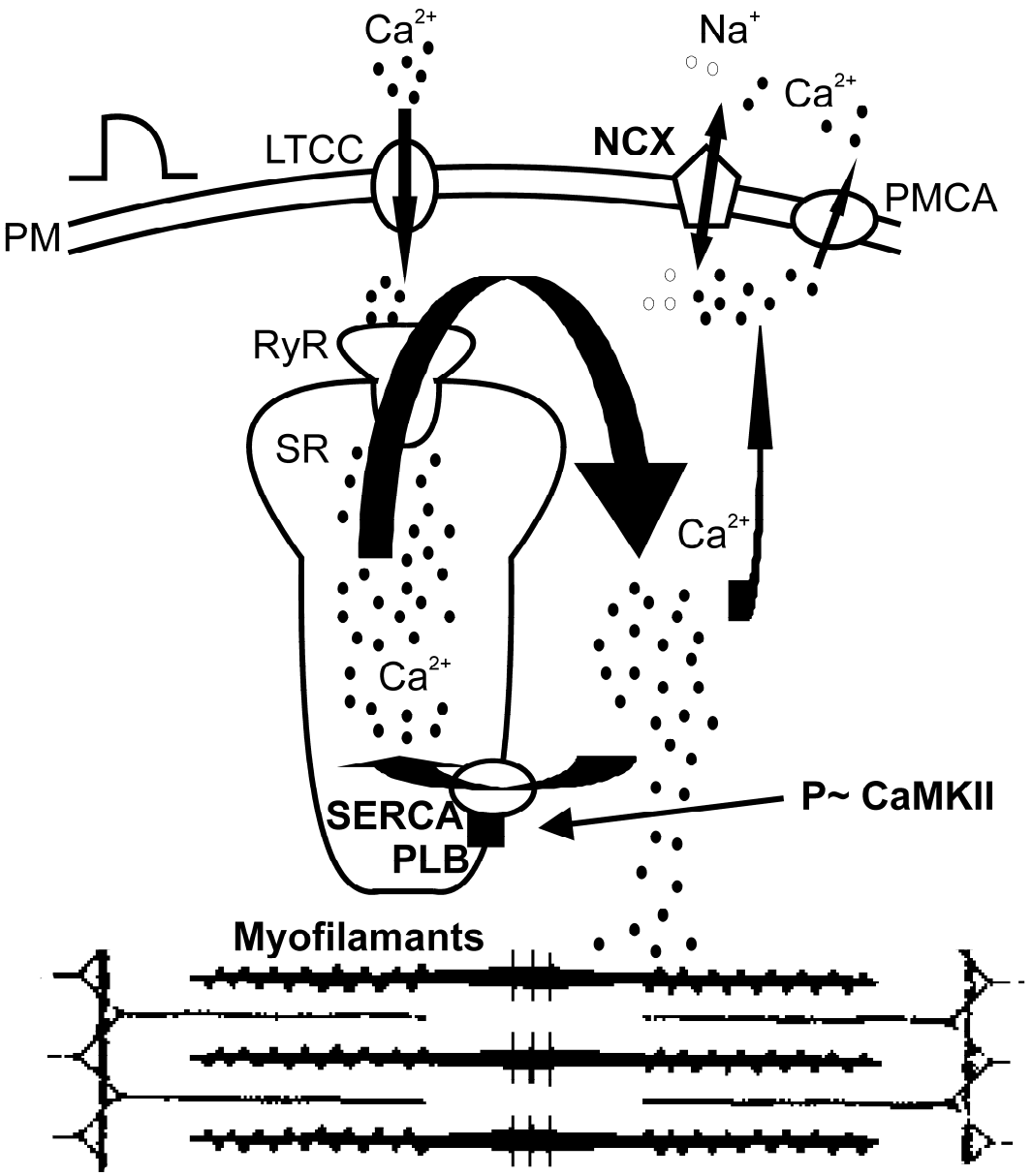
Protein Synthesis
Protein
Apoptosis
HSP
Maintenance

Figure 2


Ca2+
Na+
Ca2+
LTCC
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RyR
SR
Ca2+
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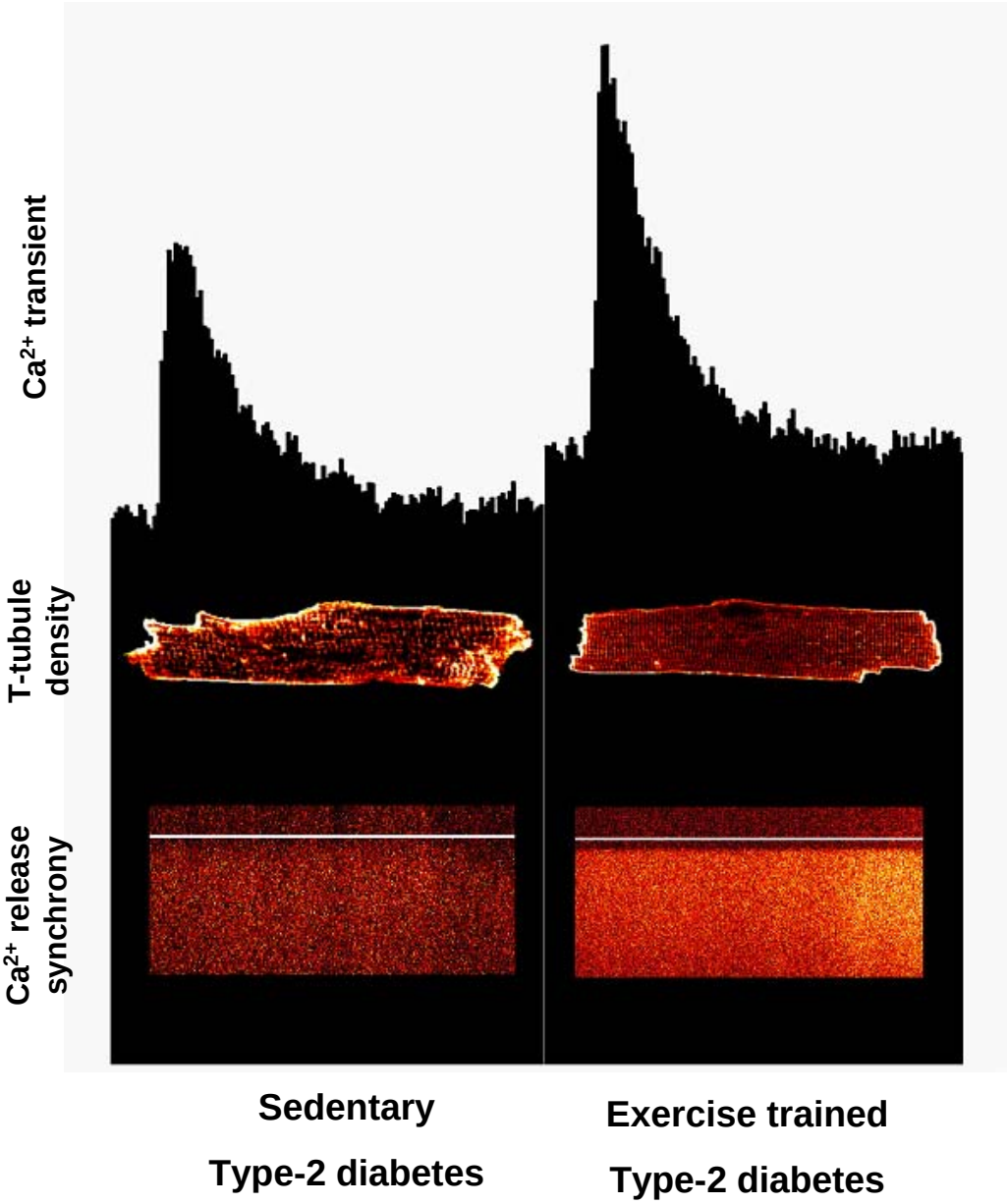
Myofilamants

Figure 3


Ca2+ transient
T-tubule density
Ca2+ release synchrony
Sedentary
Type-2 diabetes
Exercise trained
Type-2 diabetes