THE IMPACT OF EXERCISE ON CARDIOVASCULAR SYSTEM: MOLECULAR SIGNALLING PATHWAY AND CARDIAC ADAPTATIONS

ABSTRACT

The purpose of this review is to describe the impact of endurance and strength physical training on the cardiovascular system by reviewing the molecular signalling pathways, which plays a key role in different muscle adaptations, and the cardiac changes in terms of metabolic and cardiac remodelling, and hemodynamics. In response to endurance-exercise, multiple signalling pathways, including Ca^{2+}-dependent pathways, reactive oxygen species (ROS), AMP-dependent protein kinase (AMPK), and mitogen activated protein kinases (p38 MAPK), are involved in the regulation of peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α), which controls the mitochondrial biogenesis. Strength training increases the insulin-like growth factor (IGF-1) which initiates the phosphatidylinositol 3-kinase (PI3-k)-(AKT)-(mTOR) signalling cascade, resulting in the synthesis of proteins and the muscle hypertrophy. In addition to the well-documented changes in skeletal muscle, a critical component of the response to exercise training is the dynamic cardiac remodelling, which is classified as either pathological or physiological depending on triggers.

Keywords: sports cardiology, exercise physiology, sports medicine

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Introduction

There is proof that exercise can improve muscular endurance, strength, and body composition, both in the general public and athletes *[1]*. While, physical activity lowers the risk of cardiovascular illnesses in the general population *[2]*, it aims to result in better performance in sport activities in athletes. However, sport activities can be very different, ranging from long distance runners to heavy weightlifters. Clearly, training in athletes should be tailored according to the type of sport, aiming to increase predominantly either muscle resistance or strength. Thus, exercise can be classified into two major categories, endurance and strength, that trigger different responses on the cardiovascular system.

Endurance training is usually performed against a little load sustained for a prolonged time frame while strength training involves movement of the musculature of the body against an opposing force, known as resistance, for a short duration *[3]*. Thus, strength training is also known as resistance training *[4]*. Pure strength and endurance training, however, are uncommon and elite sports rarely consist of only one type of exercise. For example, rowing consists of applied strength training but has endurance training elements too. Although most activities combine endurance and strength training (concurrent exercise), this review will focus on the phenotypic shift in muscle induced by endurance and strength exercises and their influence on physiology and hemodynamics.

Exercise-induced muscle signalling pathways

Muscle adaptation happens through a complicated network of various biochemical pathways that are uniquely activated during functional training *[5]*. When subjected to physiological triggers, such as during exercise training, skeletal muscle responds by remodelling in order to meet the additional demands that are imposed by the stimulus. This modification is performed by extracellular stimuli that enter the cells, engage with receptors on the cell membrane, and activate intracellular signalling pathways. These pathways affect gene transcription and protein synthesis, which triggers muscle remodelling *[6]*.

Although some pathways can be activated irrespective of the kind of exercise, different types of exercises result in different muscle signalling pathways *[7]* with endurance training and strength training predominantly affecting the capacity for substrate consumption and muscle growth, respectively *[8] [9]*. In particular, endurance training causes improved capillarization, energy metabolism, mitochondrial biosynthesis, and the conversion of fast-to-slow fibre type, while strength training causes the biosynthesis of contractile and structural proteins, which results in muscle hypertrophy and improved contraction force generation *[10] [11]*. Prior to, during, and following endurance- and resistance-based exercise, endogenous and exogenous substrate availability can modify the transcriptional activity of a subset of metabolic and myogenic genes as well as the control of signalling pathways that stimulate mitochondrial and myofibrillar protein synthesis *[12]*. Many

researchers examined the requirements behind "endurance-based" or "strength-based" activity and provided interesting data on the unique adaptations in accordance with the specific training (Figure 1.).

Endurance training

AMP-dependent protein kinase (AMPK) and mitogen activated protein kinase (MAPK), as well as Ca^{2+}-dependent pathways and reactive oxygen species (ROS), play a part in controlling skeletal muscle mitochondrial biogenesis, angiogenesis, production of cell contractile proteins, and other adaptations *[13]*. The final receptor involved in the activation of mitochondrial biogenesis and angiogenesis is peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α) and current findings indicate a crucial role for p38 MAPK in PGC-1α regulation *[14]*. However, the signalling network is much more complex, with multiple regulatory events and several cross-interactions.

Reactive oxygen species (ROS)

Muscles produce ROS in different ways (e.g., NADPH oxidases, xanthine oxidases, mitochondria), which modulate several signalling pathways, including AMPK and MAPK, as a result of physical exercise, which affects several physiological changes. Increasing glucose uptake, mitochondriogenesis, and hypertrophy are outcomes of these pathways in skeletal muscle after physical exercise *[15]*. A change in the redox relationship in working muscles is caused by increased levels of ROS *[16]*. During eccentric contractions or highly intensive exercise, ROS can act as intracellular messengers by activating redox-sensitive transcription factors and signalling cascades.

There is evidence that the PGC-1 expression and metabolic adaptation brought on by endurance exercise in skeletal muscle are significantly influenced by ROS *[17]*. Most studies point toward hydrogen peroxide (H_2O_2), a non-radical ROS, considered a crucial signalling molecule for metabolic changes in skeletal muscle, and it has been shown that PGC-1 overexpression requires the H_2O_2 generated by contracting skeletal muscle cells *[18]*. Furthermore, the observation that H_2O_2 administration decreased cellular ATP levels, activated AMPK, and elevated PGC-1 mRNA suggested that H_2O_2 can stimulate PGC-1 production via AMPK *[19]*. In contrast, exercise-induced elevation of PGC-1 has been suppressed along with decreased phosphorylation of p38 MAPK by pharmacological suppression of xanthine oxidase using allopurinol *[20]*, supporting the hypothesis that in vivo contraction-induced activation of p38 MAPK and consequent modulation of PGC-1 expression are mediated by ROS.

Signalling modulated by Ca^{2+} and calmodulin

Contractions of skeletal muscles cause the Ca^{2+}/calmodulin-dependent protein kinases to become active (CAMK). In particular, CAMKII, the main CAMK isoform, is phosphorylated (activated) by endurance training, while CAMKK is in control of muscle tissue contraction-induced activation of AMPK *[21] [22]*. Because exercise regulates p38 MAPK and AMPK activation, respectively (see below), CAMKII and CAMKK may operate as upstream kinases in the control of PGC-1.

AMP-dependent protein kinase (AMPK)

A crucial regulator of the metabolism of skeletal muscle, AMPK serves as an intracellular sensor of ATP utilisation. Active AMPK includes three subunits: α, β, and γ. There are several isoforms of each AMPK subunit. The majority of AMPK activation brought on by vigorous exercise is accounted for by the subtypes α2/β2/γ3 *[23]*. The interaction of these subunits with the nucleotides (AMP, ADP and ATP) provides AMPK with the capacity to determine the condition of cellular energy. Repeated muscular contractions and exercise greatly activate AMPK in skeletal muscle due to its function as a cellular energy sensor.

During energy stress, the concentration of intracellular AMP increases (i.e., ATP/AMP ratio lowers) as a sign of decreased energy and 5'-AMP binds to two domains of the γ subunits which activates AMPK. Hence, when the AMP level in the muscle rises during contraction, the activating effect progresses. As a result, ATP-producing catabolic activities are promoted, while ATP-consuming anabolic processes are inhibited *[24]*. Eventually, as a metabolic sensor, AMPK controls PGC-1 expression and stimulates mitochondrial biogenesis in skeletal muscle *[25]*.

Mitogene activated protein kinases (p38 MAPK)

The protein kinases are activated by different forms of exercise. Among these kinases, p38 MAPK is most likely involved in the control of PGC-1 through transcription factors that bind to the PGC-1 promoter *[26]* and is essentially required for the regulation of PGC-1 brought on by endurance exercise. In this context, it has been shown that PGC-1 gene expression and skeletal muscle adaptability are facilitated by contractile activity-induced activation of the p38 MAPK pathway *[27]*. Of note, while the p38γ MAPK/PGC-1α regulatory axis is necessary for the exercise-induced angiogenesis and mitochondrial biogenesis, it has no role on fiber type transformation *[15]*.

Peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α)

Increased mitochondrial content and functional exercise capacity are two features of endurance training adaptation that are recapitulated by overexpressing PGC-1α in skeletal muscle. As a result, PGC-1α is considered the "master regulator of mitochondrial biogenesis" and is a crucial element of the adaptations brought on by exercising with endurance training *[28]*. In reaction to metabolic stress, both p38 MAPK and AMPK are activated, investigations in cell culture and in vitro have shown that they may directly phosphorylate and activate PGC-1 *[15]*. PGC-1α is a transcriptional coactivator and a fundamental regulator of mitochondrial biogenesis in muscle and It has been defined that acute endurance exercise led to a 54% increase in nuclear PGC-1α protein *[24], [28]*.

Strength Training

Strength training causes neuromuscular adaptations that improve muscle strength and power, increase in muscle cross sectional area, and changes in connective tissue stiffness. Mechanotransduction involves converting a mechanical signal into a biochemical event and can activate this pathway, which is crucial to the hypertrophic process because it coordinates the molecular foundation for both protein production and degradation *[29]*.

In order to control rates of protein synthesis and/or breakdown and, over a lengthy period of time (weeks to months), muscular hypertrophy, strength exercise increases the activity of the phosphatidylinositol 3-kinase (PI3-k)-(AKT)-(mTOR) signalling cascade *[12]* resulting in the synthesis of proteins and the development of muscle *[9]*. A sequential activation cascade is initiated by a rise in insulin-like growth factor (IGF-1) or its splice variant mechano growth factor (MGF). Following this rise, AKT (Protein kinase B) activates two distinct pathways:

- mammalian target of rapamycin (mTOR);
- glycogen synthase kinase-3β (GSK3β),

both of which are essential for skeletal muscle growth *[5], [6]*.

Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin complex 1 (mTORC1) is a kinase that when activated causes cell growth and proliferation through phosphorylation cascades *[30]*. Two physically and functionally different complexes known as the mammalian target of rapamycin complex 1 (mTORC1) and the mammalian target of rapamycin complex 2 (mTORC2) are formed by the mTOR protein.

When hypophosphorylated, the eIF4E-binding protein 1 (4EBP1) attaches to eIF4E (Eukaryotic translation initiation factor 4E) to block it from interacting with eIF4G (Eukaryotic translation initiation factor 4G), which would otherwise assist in enhancing ribosome recruitment to mRNAs. Hence, it has the ability to inhibit the initiation of mRNA translation. When mTORC1 is activated by AKT, protein synthesis is promoted by direct phosphorylation of 4E-BP1 and Ribosomal protein S6 kinase beta-1 (S6K1) *[31]*. By phosphorylating 4E-BP1 at multiple sites, mTORC1 promotes its dissociation from eIF4E allowing the formation of the eIF4F (Eukaryotic initiation factor 4F) complex and the initiation of cap-dependent translation *[32]*.

Glycogen synthase kinase-3 beta (GSK3β)

AKT is associated with an alternative pathway, running concurrently with mTOR, that induces hypertrophy via phosphorylating GSK-3β *[33]*. When GSK3β is phosphorylated, eIF2B (Eukaryotic translation initiation factor 2B) activity is reduced, facilitating the translation initiation process *[34]*. In particular, studies have demonstrated that strength training enhances GSK-3β phosphorylation, which blocks eIF2B, both immediately and three hours after, confirming the notion that this pathway is involved in the stimulation of protein synthesis brought on by strength training *[5], [6], [35]*.

Link between endurance and strength exercise

The cross-talk between the two signalling pathways (endurance and strength training) is based on the tuberous sclerosis complex (TSC) signalling and in particular on two TSC proteins (TSC1 and TSC2) that form a functional complex and inhibit phosphorylation of S6K1 and 4EBP1. In particular, TSC2 is a GTPase-activating protein (GAP) toward Ras homolog enriched in the brain (RHEB). The GTP-bound form of RHEB

stimulates cell growth and proliferation within the cell because it functions as an activator for mTORC1.TSC2 enhances the intrinsic GTPase activity of the GTP-binding protein RHEB, facilitating RHEB's conversion to its GDP-bound inactive state *[36], [37]*. Thus, TSC2 would operate as a RHEB GAP to inhibit RHEB GTP from activating mTORC1.

TSC2 is also influenced by AMPK which phosphorylates TSC2 at two locations, which is the proposed mechanism by which it inhibits TOR and, consequently, protein synthesis and muscle hypertrophy *[38], [39]*. This is supposed to increase the GAP activity, transforming the GTP-bound form into the GDP-bound form that no longer activates mTOR *[39]*. Furthermore, AKT phosphorylates TSC2 in response to mitogen stimulation, which lowers RHEB GAP activity and increases RHEB-GTP levels and, as a result, mTOR kinase activity *[40]*.

While strength training triggers the activation of AKT, which specifically reduces the inhibitory effects of the TSC on mTOR, thus activating mTOR in response to growth stimuli *[37]*, on the other hand aerobic exercise AMPK decreases protein synthesis via lowering mTORC1 activity *[5], [7]*.

The impact of exercise on cardiac adaptations

Metabolic remodelling (Figure 2.)

In addition to the alterations in skeletal muscle that are well-documented, an essential part of the response to exercise training is the dynamic cardiac remodelling needed to match peripheral demand with an adequate cardiac output. During exercise and the first few hours following exercise, the heart's ability to use glucose through glycolysis is diminished. Genes that are important for metabolic remodelling, transcription, cell division, differentiation, proliferation, and contraction appear to be regulated by changes in metabolism brought on by phosphofructokinase (PFK). To activate transcriptional pathways directing heart development and hypertrophy, exercise-induced alterations in PFK activity are required. PFK activity in the myocardium is controlled by exercise, and the consequent changes in metabolism are sufficient to trigger a transcriptional pathway that affects exercise-induced cardiac development *[41]*.

Declines in PFK activity appear to be particularly critical for directing the exercise gene program by upregulating Cited4 levels and downregulating Cebpb expression, as well as for coordinating glucose-derived carbon for anabolic activities. Additionally, the metabolic periodicity brought on by exercise may affect mitochondrial dynamics and support the maintenance of healthy mitochondrial pools. Lower intensity exercise appears to promote myocardial glucose catabolism, but relatively high intensity, sustained exercise may decrease myocardial glucose catabolism, start mitochondrial fission, and improve mitochondrial function *[42]*.

Cardiac remodeling (Figure 3.)

The geometrical pattern of the left ventricle is categorised based on LV mass and relative wall thickness (RWT = (2 x posterior wall thickness) / (LV internal diameter at end-diastole). Individuals with normal LV mass may have either normal geometry (RWT <0.42) or concentric remodeling (RWT >0.42). An increased LV mass identifies subjects with left ventricular hypertrophy (LVH) and according to the RWT they can be divided into concentric (RWT >0.42) or eccentric (RWT <0.42) LVH *[43], [44]*.

Left ventricular morphology can change during life time due to changes in myocardial wall thickness and/or left ventricular dimensions. Eventually, LVH (i.e., increased myocardial mass) may develop. According to the triggers, this process can be classified as either physiological or pathological *[42]*.

Mechanical stress and neurohumoral stimulation are the two main factors that cause cardiac hypertrophy. These factors influence a number of cellular processes, involving sarcomere construction, protein synthesis, gene expression, and cell metabolism, which eventually trigger and sustain the hypertrophic process *[45], [46], [47]*.

Physiological cardiac remodeling

Physiological LVH is characterised by normal cardiac anatomical structure and architecture, with normal or increased contractility *[48]*. Exercise triggers a growth program without inducing the fetal-gene program, which is different from pathological remodelling. It also causes an increase in energy metabolic capacity that can meet the higher energy needs induced by continuous activity. The latter regimen keeps the heart function within normal limits *[49]*.

In sports with high-dynamic and low-static demand (for instance, tennis) LVH is mostly eccentric, while high-static demand sports, like weightlifting, induce mostly concentric LVH. In activities like cycling that require both high-dynamic and high-static demands, the hypertrophy is balanced and mixed *[50], [51]*. These morphological changes could be reversed after a detraining period from one to three weeks *[52]* but the return to a full “normal” heart dimension is still unclear *[53]*.

In some cases, the morphology of an athlete's heart may resemble the one in people with hypertrophic cardiomyopathy. Given that hypertrophic cardiomyopathy is a frequent reason for sudden mortality in athletes, differentiating this condition from the normal athlete’s heart is of paramount importance, however there are significant challenges, in particular in subjects with LV wall thickness of 13-15 mm, who represent a grey zone. In this subset, several features can be considered to support the diagnosis of an athlete’s heart, including LV cavity >55 mm, normal LV filling pattern, decrease wall thickness with deconditioning, max VO2 >45 ml/Kg/min *[54]*.

Pathological cardiac remodelling

The pathological hypertrophic remodeling differs from the physiological LVH in its transcriptional markers *[55]*. The expression of genes involved in fuel metabolism and bioenergetics is reprogrammed in a recognized way during the development of pathological cardiac hypertrophy and in the failing heart. Expression of nuclear and mitochondrial genes implicated in several mitochondrial energy transduction and respiratory pathways is downregulated, and the capacity to burn the major fuel (fatty acids) is decreased *[56]*. The cardiomyocyte starts a growth program as a reaction to hypertension or pressure overload that is defined by the activation of a “fetal” gene program that includes altered sarcomere isoform gene expression and enhanced natriuretic peptide production *[49]*. The coordination between the growth of the cardiomyocytes and angiogenesis in the heart is dysregulated during the the progression of heart failure from adaptive cardiac

hypertrophy, and angiogenesis is necessary for the anatomical and functional development of the heart *[48], [57]*.

Several forms of overloads to the left ventricle may be brought on by cardiovascular disorders. Whereas volume overload is frequent in individuals with mitral regurgitation, aortic regurgitation, dilated cardiomyopathy, and chronic coronary artery disease, pressure overload is typical in cases of arterial hypertension and aortic stenosis. Typically, cardiac conditions such myocardial infarction and dilated cardiomyopathy coexist with ventricular dilatation and an increase in cardiomyocyte length which leads to the development of pathological eccentric hypertrophy *[48]*. In contrast, pathological concentric hypertrophy typically arises in conditions like hypertension or aortic stenosis where cardiomyocytes ordinarily thicken more than they lengthen *[48], [58]*.

Changes in hemodynamics

Every type of exercise has a different hemodynamic impact, which triggers separate cardiac adaptation (Table 1).

Endurance exercises

The body responds to aerobic exercise by increasing oxygen uptake (VO2), heart rate, cardiac output, and stroke volume, which peaks initially before plateauing. At rest, skilled endurance athletes' cardiac output can range between 5 and 6 liters per minute and up to 40 liters per minute during maximal exertion *[59]*. Along with an increase in cardiac output, blood pressure also rises, but not as much as it would during strength training. As a result, the heart of an endurance athlete must adjust to both volume and pressure overload. Because volume load plays a major role in endurance training, the heart grows eccentrically after exercise *[60]*, with new sarcomeres sequentially added to those that already exist. As a result, the inner diameter of the left ventricle increases and the wall thickness increases as well *[61]*.

Endurance exercise also reduces blood pressure at rest with a more pronounced effect on hypertensive compared with normotensive individuals *[62]*. Wide pulse pressure (rising systolic blood pressure, coupled with a decline in diastolic blood pressure) and a little rise in mean pressure are the results of decreasing peripheral vascular resistance *[63]*.

Strength exercises

Compared to athletes with endurance training, strength athletes have different cardiovascular adaptations. Elite level resistance exercise is linked to abrupt and strong pressure reactions which translates into a markedly elevated systolic and diastolic blood pressure, with little effect on the stroke volume and only a slight increase in heart rate *[64]*. During a strength exercise VO2 barely increases; however, with a higher workload the increases in the intrathoracic pressure due to the Valsalva manoeuvre results in lower venous return and low cardiac output. To sustain cardiac output and blood pressure, a reflex increase in heart rate and vasoconstriction, respectively, occurs *[63]*.

In weightlifting athletes, due to the elevated afterload, high intraventricular pressure is required to open the aortic valve, which may cause an abrupt elevation in blood pressure *[65]*. High afterload and intraventricular pressure during the ejection phase enhance myocardial wall stress, which is the principal trigger of cardiac hypertrophy in the pressure-overloaded heart *[66]*. The concentric LVH that occurs in the heart of a resistance-trained athlete in response to a rapid, intense pressure overload may occasionally be accompanied by an enlargement of the left ventricular diameter *[67]*.

Ageing heart and the effects of exercise

It is well known that physical activity prevents or delays chronic diseases *[68]*. Compared to other recognized components of cardiovascular disease risk, capacity for exercise is a more accurate predictor of death in males *[69]*. Furthermore, in patients with postinfarction heart failure, exercise intensity was a key determinant in reversing LV remodeling and enhancing quality of life, endothelial function, and aerobic capacity *[70]*. In individuals with heart failure who are clinically stable, aerobic exercise training, particularly long-term (6 months) length, reverses left ventricular remodelling which was evaluated using the ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV). Strength training in contrast did not alter or exacerbate ventricular remodelling, whether it was done alone or in conjunction with aerobic exercise *[71]*.

CONCLUSIONS

In this article we have reviewed the effects of different forms of exercise on the cardiovascular system by evaluating the molecular signalling pathways, which are crucial for muscle adaptations. Adaptation to endurance exercises mainly occurs through PGC-1α, which regulates mitochondrial biogenesis, and is regulated by biochemical processes such as Ca2+-dependent pathways, reactive oxygen species (ROS), AMP-dependent protein kinase (AMPK), and mitogen activated protein kinases (p38 MAPK). Strength training, on the other hand, raises levels of insulin-like growth factor (IGF-1), which starts the PI3-k-(AKT)-(mTOR) signalling cascade.

Furthermore, we described the changes in the metabolism, geometric pattern, and cardiac hemodynamics induced by different types of physical training. Endurance training via volume overload combined with pressure load induces eccentricLVH, in contrast to the strength exercise that mainly induces pressure load on the heart causing concentric LVH. There is still a “grey area” in differentiating between hypertrophic cardiomyopathy and athlete's heart which could be solved by thorough investigation of LV cavity, LV filling pattern and wall thickness after deconditioning.

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FIGURE LEGENDS

1. Figure 1. Simplified molecular signalling pathways involved in endurance and strength exercise training.

   4EBP1 – Eukaryotic translation initiation factor 4E-binding protein 1; AKT – Protein kinase B; AMP – Adenosine monophosphate; AMPK - 5' AMP-activated protein kinase; ATP – Adenosine triphosphate; CAMKII - Ca2+/calmodulin-dependent protein kinase II; CAMKK - Ca2+/calmodulin-dependent

protein kinase kinase; eIF2 – Eukaryotic initiation factor 2; eIF2B – Eukaryotic translation initiation factor 2B; eIF4E – Eukaryotic translation initiation factor 4E; eIF4G – Eukaryotic translation initiation factor 4G; eIF4F – Eukaryotic initiation factor 4F; IGF-1 – Insulin-like growth factor; GSK3β – Glycogen synthase kinase-3β; MGF – Mechano growth factor; mTORC1 - Mammalian target of rapamycin complex 1; p38γ MAPK – p38 Mitogen Activated Protein Kinase; PGC-1α – Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K - Phosphoinositide 3-kinases; RHEB GDP - Ras homolog enriched in brain in its Guanosine Diphosphate-bound form; RHEB GTP - Ras homolog enriched in brain in its Guanosine Triphosphate-bound form; ROS - Reactive oxygen species; S6K1 - Ribosomal protein S6 kinase beta-1; TSC1 - Tuberous sclerosis complex 1; TSC2 - Tuberous sclerosis complex 2.

2. Figure 2. Cardiac remodelling from a metabocentric perspective.

BCAAs (Branched-chain amino acids); C/EBPB (CCAAT/enhancer-binding protein beta) is a transcription factor, participating in cell proliferation, differentiation and development; Cited4 (CBP/p300-Interacting transactivator with E (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain); KLF15 (Krüppel-like factor 15) is a critical transcriptional regulator of BCAA metabolism; it inhibits mTOR(mammalian target of rapamycin) activity; PFK – Phosphofructokinase.

3. Figure 3. Left ventricular geometrical patterns of cardiac remodelling.

Left ventricular mass index = LVM (left ventricular mass)/body surface area; Relative wall thickness = 2 x posterior wall thickness / LV internal diameter at end-diastole

Abbreviations

4EBP1 = Eukaryotic translation initiation factor 4E-binding protein 1;

AKT = Protein kinase B;

AMP = Adenosine monophosphate;

AMPK - 5' = AMP-activated protein kinase;

ATP = Adenosine triphosphate;

CAMKII = Ca2+/calmodulin-dependent protein kinase II;

CAMKK = Ca2+/calmodulin-dependent protein kinase kinase;

eIF2 = Eukaryotic initiation factor 2;

eIF2B = Eukaryotic translation initiation factor 2B;

eIF4E = Eukaryotic translation initiation factor 4E;

eIF4G = Eukaryotic translation initiation factor 4G;

554 eIF4F = Eukaryotic initiation factor 4F;

555 IGF-1 = Insulin-like growth factor;

556 GSK3β = Glycogen synthase kinase-3β;

557 MGF = Mechano growth factor;

558 mTORC1 = Mammalian target of rapamycin complex 1;

559 p38γ MAPK = p38 Mitogen Activated Protein Kinase;

560 PGC-1α = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K =
561 Phosphoinositide 3-kinases;

562 RHEB GDP = Ras homolog enriched in brain in its Guanosine Diphosphate-bound form;

563 RHEB GTP = Ras homolog enriched in brain in its Guanosine Triphosphate-bound form;

564 ROS = Reactive oxygen species;

565 S6K1 = Ribosomal protein S6 kinase beta-1;

566 TSC1 = Tuberous sclerosis complex 1;

567 TSC2 = Tuberous sclerosis complex 2.

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Figure 1. Simplified molecular signalling pathways involved in endurance and strength exercise training

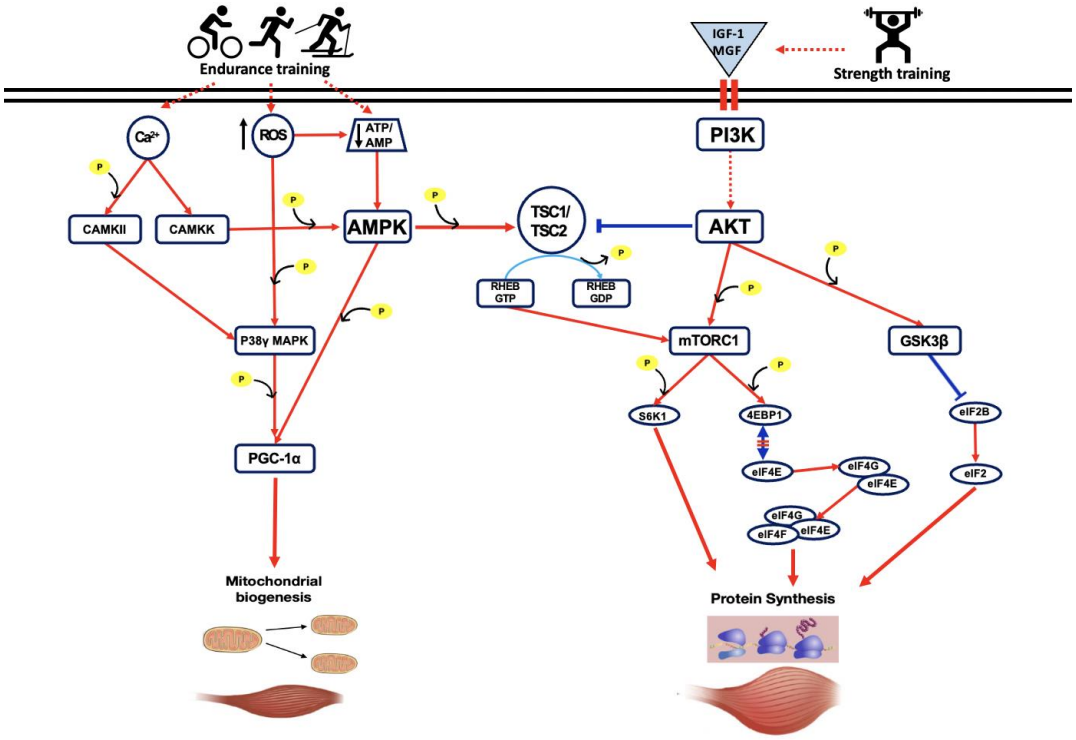


Figure 2. Cardiac remodelling from a metabocentric perspective

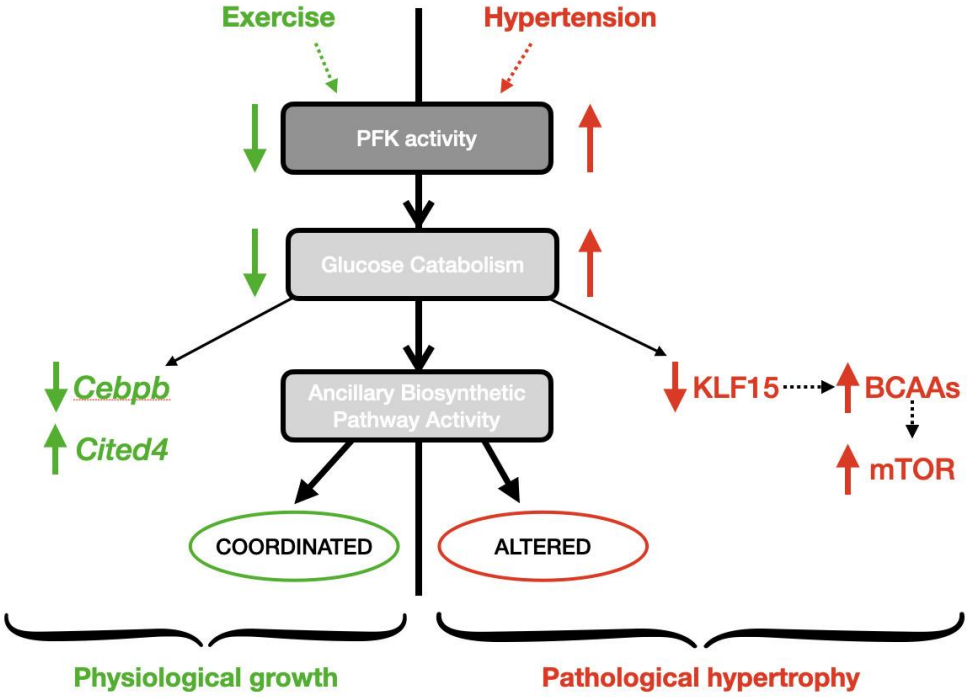
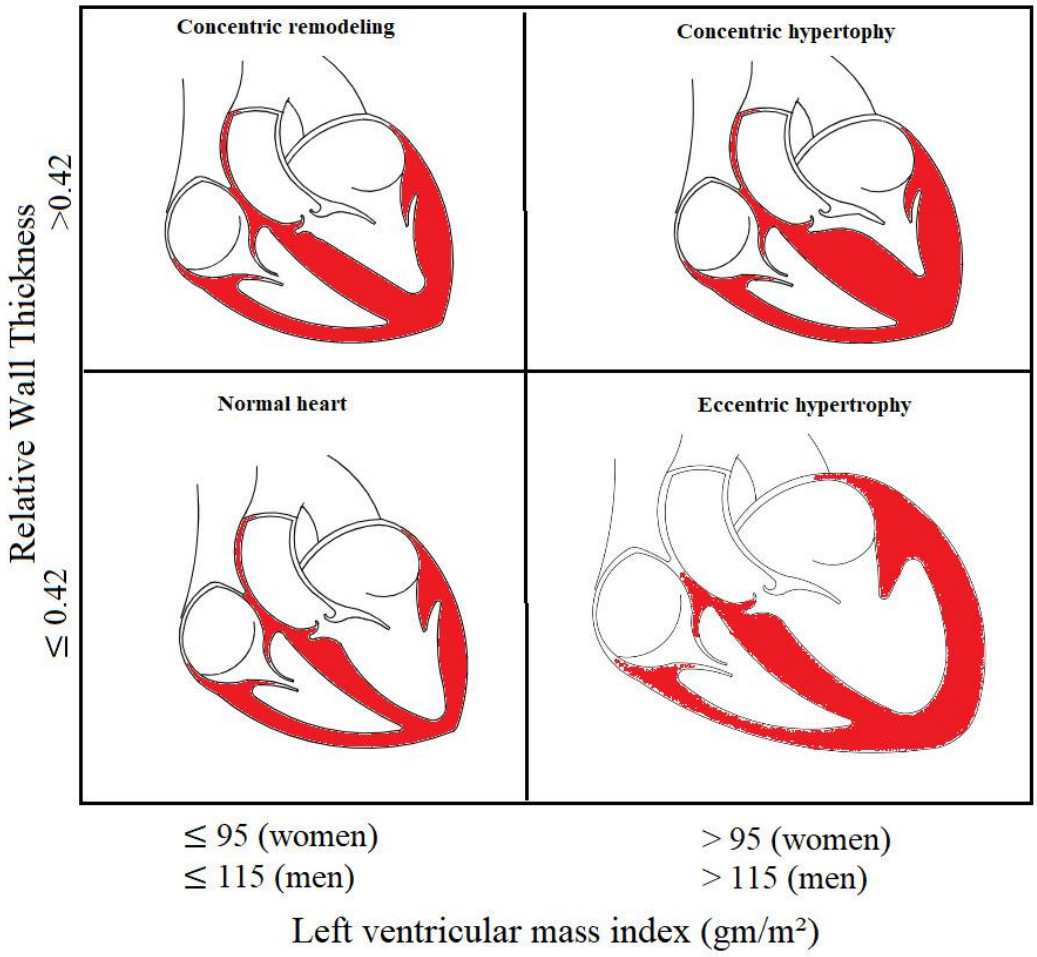


Figure 3. Left ventricular geometrical patterns of cardiac remodelling



579 **Table 1.** Hemodynamic response to different types of training
580

	Endurance exercise	Strength exercise	Comments
VO_2 max	increase	increase/stable	Endurance exercise increases the body's ability to absorb oxygen (VO_2), in contrast VO_2 rarely rises during a strength training session.
Resting heart rate	decrease	stable	As long as cardiac output at rest doesn't change, the rise in stroke volume is followed by a commensurate decline in heart rate.
Stroke volume	increase	stable	The LV end-diastolic volume is increased with endurance training, which results in an increase of the stroke volume.
Maximal cardiac output	increase	stable	With a maximum exercise effort, the rise in SV causes a considerable increase in cardiac output.
Systolic BP (rest)	Decrease or stable	stable	Systolic and diastolic BP increases during resistance exercise, but not endurance. Blood pressure of people with arterial hypertension drops toward normal as they exercise more, regardless of type of the exercise. This is brought on by a decrease in the artery's overall peripheral resistance as well as an improvement in flexibility of smooth muscles of blood vessels.
Diastolic BP (rest)	Decrease or stable	stable	
LV hypertrophy	Asymmetric	Symmetric	Strength training mostly causes concentric LVH, whereas endurance training primarily causes eccentric LVH. Balanced and mixed hypertrophy is seen in concurrent exercise demands.

Overload state	Volume > pressure	Pressure > volume	Endurance exercise induces volume overload on the heart, while strength exercise induces pressure overload and volume overload

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582 ***(****Modified from [63])*

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