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REVIEW ARTICLE

Li et al: Exercise, HF, and energy metabolism

The regulatory role of exercise in heart failure and myocardial energy metabolism: A review

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ABSTRACT

Myocardial energy metabolism is crucial for maintaining optimal heart function. The heart, having limited energy storage capacity, is dependent on a continuous energy supply; any disruptions or alterations in energy metabolism pathways can lead to insufficient myocardial energy, potentially triggering heart failure (HF). Exercise, as a safe and economical non-pharmacological intervention, is widely recognized to enhance cardiovascular health and modify myocardial energy metabolism patterns. However, the specific mechanisms by which exercise regulates myocardial metabolism to prevent and treat HF remain unclear. This review aims to detail the characteristics of myocardial metabolism under normal physiological and HF conditions, to further explore the impact of different exercise modalities on myocardial metabolism, and to summarize the molecular mechanisms by which exercise protects the heart by optimizing myocardial energy metabolism. Ultimately, this article aims to provide an in-depth understanding and evidence for the application of exercise interventions in cardiac rehabilitation.

Keywords: Exercise; heart failure; HF metabolism; mitochondria; cardiac remodeling; cardiac rehabilitation

INTRODUCTION

The heart, beating billions of times and utilizing substantial Adenosine Triphosphate (ATP) daily, relies on flexible metabolic pathways due to its limited immediate energy reserves. This metabolic adaptability is crucial for maintaining cardiac function [1]. As a high-energy-consuming organ, any disruption or alteration in myocardial energy metabolism can have severe consequences on cardiac function. Thus, energy metabolism imbalance is recognized as a key pathogenic factor in the progression of heart failure (HF) [2]. Exercise, widely regarded as a safe and economical non-pharmacological intervention, provides significant cardiovascular benefits by inducing physiological ventricular remodeling and altering myocardial energy metabolism. Although exercise is known to influence myocardial metabolism, its exact protective role against HF remains unclear, potentially due to the complex nature of myocardial metabolic networks [3]. This review aims to synthesize recent research to explore myocardial energy metabolism under both physiological and pathological conditions, as well as the effects of exercise on myocardial metabolism and mitochondrial function. Ultimately, the goal is to provide a reference for the future clinical application of exercise in cardiac rehabilitation. The main points of this review are detailed in Figure 1.

HEART AND MYOCARDIAL METABOLISM

Myocardial metabolism under physiological conditions

The heart continuously generates ATP to support its high energy demands, primarily relying on mitochondrial oxidative phosphorylation. Under normal conditions, approximately 60-70% of ATP is derived from FA oxidation, 10-30% from glucose metabolism, and smaller contributions from ketone bodies, lactate, and amino acids [2, 4].

FA metabolism

FA is the primary energy source for the heart under physiological conditions. The heart obtains FA from two main sources: free fatty acids (FFA) derived from triglyceride (TG) hydrolysis by lipoprotein lipase, and non-esterified fatty acids (NEFA) bound to albumin [2, 5]. These FAs are transported into cardiomyocytes via transport proteins such as CD36, where they undergo β-oxidation to produce acetyl-CoA, which enters the TCA cycle to generate ATP [2, 5, 6].

Glucose metabolism

Glucose is absorbed via GLUT1 and GLUT4 transporters, with GLUT4 predominantly active in adults [7-9]. After uptake, glucose primarily undergoes glycolysis, forming pyruvate or lactate. Additionally, auxiliary pathways like hexosamine and pentose phosphate contribute to redox balance and biosynthesis, providing intermediates for cellular functions [2, 6].

Ketone body metabolism

Ketone bodies in the body are primarily synthesized from CoA, which is generated through the oxidation of FAs in the liver. Among these, β-hydroxybutyrate (βOHB) serves as the predominant ketone body oxidized in the heart.

βOHB is taken up into cardiac cells via the monocarboxylate transporter 1 (MCT1) and subsequently oxidized in the mitochondria [10, 11]. Within the mitochondria, β-hydroxybutyrate dehydrogenase 1 (BDH1) converts βOHB into acetoacetate, which is further activated into acetoacetyl-CoA by succinyl-CoA transferase (SCOT). This acetoacetyl-CoA is then converted into CoA through a thiolysis reaction, ultimately entering the TCA cycle to generate ATP [10, 12].

Branched chain amino acid metabolism

Branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are essential amino acids primarily derived from the diet and secondarily synthesized de novo by gut microbiota [13]. BCAAs undergo reversible transamination mediated by mitochondrial BCAA transaminase (BCAT2), producing branched-chain α-keto acids (BCKA) and glutamate. BCKAs undergo an irreversible decarboxylation process catalyzed by the BCKA dehydrogenase (BCKDH) complex, resulting in the final catabolism into acetyl-CoA and succinyl-CoA, which participate in the TCA cycle or support cellular biosynthetic pathways through anaplerosis [13]. The activity of BCKDH is regulated by inhibitory phosphorylation by BCKDH kinase (BCKDK) and activating dephosphorylation by mitochondrial protein phosphatase 2C family (PP2Cm), while BCKA can also allosterically inhibit BCKDK [14].

BCAA oxidation contributes less than 2% of the total energy supply in the heart [11]. Despite this low contribution to energy metabolism, BCAAs are metabolically significant in other physiological contexts. Additionally, the mammalian target of rapamycin (mTOR) pathway is a key signaling pathway promoting protein synthesis and cellular growth in the body.

Moreover, activation of the mTOR signaling pathway can lead to various metabolic reactions that reduce insulin sensitivity [15]. BCAAs, particularly leucine, act as effective activators of the mTOR pathway and are closely associated with insulin resistance in the body.

Substrate interactions under physiological conditions

Myocardial energy relies on glucose and FA oxidation, which interact competitively (Randle cycle) [16, 17]. Under normal conditions, FA oxidation predominates and inhibits glucose metabolism [18]. Meanwhile, increased glucose oxidation can also inhibit FA oxidation, a process regulated by hormonal signals like insulin [19]. This competition allows the heart to adapt its substrate use depending on availability and physiological demands. Additionally, ketone bodies and BCAAs can act as alternative substrates and also influence the balance between glucose and FA metabolism [19, 20].

Myocardial metabolism during HF

HF is a clinical syndrome characterized by shortness of breath and limited physical activity, caused by impaired ventricular filling or ejection [2]. It can be classified by left ventricular ejection fraction (LVEF) as: HFrEF (LVEF < 40%), HFmrEF (LVEF 40-49%), and HFpEF (LVEF ≥ 50%) [21].

The classification provides a framework to understand variations in pathophysiology and treatment responses. In HF, the heart adapts its energy pathways based on workload, substrate availability, and hormonal status [22, 23]. Studies have found that during the onset and progression of HF, adaptive or maladaptive changes in myocardial metabolism typically precede alterations in cardiac function [12, 24, 25]. Particularly during the decompensated phase, ATP production decreases by 30%, leading to an energy supply-demand imbalance and ultimately resulting in HF [26, 27]. This highlights the critical role of energy metabolism in the progression of HF. In this section, we summarize the specific metabolic changes occurring in the myocardium during HF.

FA metabolism

With the progression of heart failure, the overall energy metabolism of the myocardium gradually declines. Impaired FA oxidation energy supply has been observed in human and animal HFrEF models [2, 28, 29]. This decline in FA oxidation in animal models may be related

to the downregulation of peroxisome proliferator-activated receptor-α (PPAR-α) and peroxisome proliferator-activated receptor-γ coactivator 1 (PGC-1) signaling [6, 30]. Whether these mechanisms apply to humans is still unknown.

It is noteworthy that the phenomenon of reduced FA oxidation is not always consistent. During the compensation phase of heart failure, fatty acid uptake and oxidation do not decrease [31]. Moreover, cardiac fatty acid uptake increases in congestive heart failure [32]. This difference in fatty acid utilization patterns may be related to the type, severity, and progression of the disease. In addition, myocardial fatty acid oxidation is increased in obesity and type 2 diabetes, which may be associated with glucose utilization disorders, insulin resistance, and other factors [33, 34]. Furthermore, the fatty acid transporter protein CD36, as a downstream target of PPAR-α, can be upregulated by overexpression of PPAR-α [35]. Knockout of CD36 can accelerate the progression of heart failure induced by pressure overload, but it shows a delaying effect in the case of diabetic cardiomyopathy. These observations highlight the unclear mechanisms of fatty acid action in different pathological states, and further in-depth research is needed to uncover their potential patterns.

Increased FFA concentration is highly correlated with the risk of heart failure occurrence [36, 37]. Disrupted myocardial FA metabolism can lead to lipid accumulation within cardiomyocytes, impairing their metabolism and function [38-40]. Palmitic acid accumulation alters cardiomyocyte membranes, increases oxidative stress, and disrupts homeostasis, leading to mitochondrial dysfunction, apoptosis and insulin resistance, resulting in cardiac lipotoxicity [41-44]. Additionally, acyl-CoA, a pivotal hub molecule in lipid metabolism, has been found to be reduced in failing hearts in humans and pressure-overloaded animal models. LVAD treatment can normalize its levels through mechanical unloading, benefiting the heart. Similarly, in pressure-overload animal models, overexpression of acyl-CoA synthetase-1 (ACSL1) restores depleted acyl-CoA content, reduces lipotoxic ceramide species like palmitoyl-ceramide, and alters the ceramide profile, thereby alleviating cardiac lipotoxicity [45]. Although some studies suggest that ACSL1 overexpression can induce lipid accumulation and heart lipotoxicity, in pressure-overloaded hearts, ACSL1-mediated restoration of acyl-CoA content significantly alleviates maladaptive changes in the cardiac lipid profile. This effect outweighs potential detrimental baseline impacts under oxidative stress [46].

Glucose metabolism

To compensate for reduced fatty acid oxidation, cardiomyocytes typically enhance glucose metabolism. However, even with increased glucose uptake and utilization, its efficiency may still be insufficient to fully compensate for the decline in fatty acid oxidation, leading to an overall reduction in energy output. This energy deficit underpins the metabolic vulnerability of the failing heart. This reduction in mitochondrial function is an early manifestation of cardiac hypertrophy, which accelerates the progression of heart failure [47]. Uncoupling of glycolysis from glucose oxidation reduces energy efficiency in failing hearts. This leads to increased proton production and accumulation of glycolytic intermediates, particularly phosphoglycerate, which is strongly associated with the risk of HF [48-50]. However, a study using a canine pacing-induced HF model observed an increase in glucose oxidation [51]. This observation suggests that myocardial glucose metabolism may vary depending on experimental models or disease contexts. This discrepancy may be related to the severity of the disease or shifts in myocardial metabolism.

GLUT1 upregulation in ischemic hearts disrupts energy homeostasis and exacerbates HF [52]. The GLUT1 upregulation leading to HF has also been observed in pressure-overload models, where pressure overload activates the nuclear effector Yes-associated protein 1 (YAP). YAP interacts with TEAD1 and HIF-1α in cardiomyocytes, upregulating GLUT1 and activating glycolysis, ultimately disrupting energy homeostasis. Accumulation of glycolytic intermediates promotes ventricular remodeling [53]. On the other hand, pressure overload suppresses GLUT4 expression, impairing glucose uptake, which may exacerbate the progression of HF [54]. Similarly, GLUT4 downregulation enhances endoplasmic reticulum stress in cardiomyocytes and extracellular matrix (ECM) deposition, worsening ventricular remodeling after myocardial infarction. Additionally, dysregulation of glucose metabolism in cardiomyocytes can lead to the accumulation of advanced glycation end products (AGEs), which generate excessive reactive oxygen species (ROS), inducing oxidative stress [55]. Such oxidative stress further aggravates cardiomyocyte injury and compromises cardiac function. In contrast, in diabetic cardiomyopathy, increased GLUT4 expression to sustain myocardial glucose utilization paradoxically accelerates mitochondrial dysfunction [56]. Therefore, the role of GLUT4 differs across pathological conditions and must be considered dialectically.

Under pathological conditions, glucose engages in non-energy-related signaling pathways such as the hexosamine biosynthetic pathway, pentose phosphate pathway, and carbon cycling, producing metabolites that disrupt normal metabolic balance. These pathways generate metabolites that may contribute to cardiac hypertrophy and remodeling [57, 58]. Targeting

these dysregulated pathways may help restore energy homeostasis and mitigate myocardial remodeling [59].

Ketone body metabolism

The ketone body metabolism in failing hearts is generally considered one of the compensatory mechanisms for the reduced oxidation of other metabolic substrates. A considerable amount of high-quality research evidence has shown that the levels of circulating ketone bodies are increased in heart failure patients, and ketone body utilization in the heart is also enhanced. This finding has been consistently demonstrated in animal models [60-64]. This phenomenon occurs because ketone body utilization in the heart is directly proportional to ketone body delivery [65]. It is worth noting that ketone body levels in circulation are not elevated in HFpEF patients [66]. In recent years, many studies have shown that elevated circulating ketone body levels are strongly correlated with the worsening or adverse outcomes of HFrEF. As a result, its potential as a clinical predictive biomarker is receiving increasing attention [67-71].

In $BDH1^{-/-}$ or $SCOT^{-/-}$ animal models, impaired myocardial ketone utilization leads to exacerbated oxidative stress, mitochondrial dysfunction, and disordered myofibril ultrastructure, rendering the heart incapable of handling stress overload or ischemia, thereby accelerating the progression of cardiac decline. However, exogenous βOHB supplementation has been shown to improve pathological ventricular remodeling and slow disease progression [72, 73].

Interestingly, supplementation of βOHB within physiological concentration ranges in chronic HFrEF patients also showed an effect in enhancing cardiac output [74]. Increasing circulating ketone levels as a potential therapeutic strategy for HF has become an active area of translational research, with specific approaches including ketone infusion, ketone ester (KE) administration, or ketogenic diets, as detailed in Table 1. Although exogenous ketone therapy benefits the heart, prolonged exposure to a ketone-rich environment may lead to adverse effects such as v-ATPase proton pump degradation, contractile dysfunction, and insulin resistance [75]. Similarly, excessive βOHB accumulation in the heart may disrupt normal metabolic balance, compounding cardiac dysfunction over time. Another study on ex vivo low-flow perfused hearts found that increased βOHB accumulation in the heart also impaired the recovery of cardiac contractile function [76]. These findings highlight the complexity of ketone body roles in different pathological states, with unclear long-term effects and the potential risk of impaired cardiac function.

BCAA metabolism

In recent years, many studies have found that elevated circulating BCAA levels can serve as an independent predictor of cardiovascular events, including the onset of HF, plaque rupture, and thrombus formation, which may lead to ischemic cardiomyopathy and adverse clinical outcomes [77-82]. This correlation underscores the significance of BCAA dysregulation in cardiovascular pathology. In animal models of pressure overload and myocardial infarction, BCAA metabolism was found to be downregulated in both the compensated and decompensated phases of HF, with an intriguing pattern of increased BCAA levels observed in the heart tissue but not in plasma, suggesting localized metabolic alterations [83, 84].

To further explore the mechanisms by which BCAAs affect HF, various experimental models have been studied to elucidate their impact on cardiac metabolism and function. In a study of pressure-overloaded mice fed a BCAA-rich diet, the diet increased histone H3K23 propionylation (H3K23Pr) at promoters, downregulated electron transport chain complexes [ETC I-V], reduced mitochondrial respiration, increased myocardial fibrosis, and worsened cardiac function. In contrast, a BCAA-deficient diet produced the opposite beneficial phenotype [85]. These findings suggest that BCAA overabundance disrupts mitochondrial energy metabolism and promotes cardiac dysfunction in pathological conditions. Meanwhile, a multi-omics study revealed that downregulation of BCAA metabolism does not occur in endurance exercise-induced physiological cardiac hypertrophy, suggesting that it is a unique feature of pathological cardiac hypertrophy [86]. Interestingly, another study further found that BCAA metabolic defects do not cause HF progression, but BT2 (a potent inhibitor of BCKDK) activates systemic BCAA metabolism, particularly reducing vascular tension and lowering blood pressure, thereby preventing adverse cardiac remodeling and exerting cardioprotective effects [87].

On the other hand, as mentioned earlier, activation of the mTOR pathway can reduce insulin sensitivity and lead to insulin resistance. BCAAs can also impair insulin-stimulated glucose uptake in skeletal muscle and inhibit insulin-induced phosphatidylinositol 3-kinase activity, leading to impaired glucose uptake, insulin resistance, and subsequent metabolic disorders [88]. However, paradoxical effects of BCAA metabolism have also been observed in different contexts. In $BCATm^{-/-}$ animal models, elevated circulating BCAA levels were associated with beneficial phenotypes, such as reduced obesity and increased insulin sensitivity [89]. Furthermore, studies have shown that BCKA, rather than BCAA, is the key mediator of cardiac

insulin resistance and could serve as a target to alter cardiac insulin sensitivity [90]. In a study on pressure-overloaded PP2Cm$^{-/-}$ mouse models, Krüppel-like factor 15 (KLF15) was identified as a key upstream factor for reduced cardiac BCAA catabolism. Its loss or inhibition led to defective BCAA catabolism, resulting in elevated BCKA levels, increased superoxide production, oxidative stress damage, and worsened cardiac function [91]. Another study on BCKDH knockout/overexpression mice observed that BCKDH knockout caused increased BCKA levels, suppressed insulin-induced AKT phosphorylation, and reduced glucose uptake. Overexpression of BCKDH resulted in beneficial cardiac outcomes that were opposite to the detrimental effects observed in knockout models [92, 93]. The above animal studies collectively demonstrate that BCKA, rather than BCAA, mediates cardiac insulin resistance. Human studies have also found that elevated serum BCAA levels are a metabolic hallmark of insulin-resistant individuals, with gut microbial species such as Prevotella copri and Bacteroides vulgatus identified as key drivers of the link between BCAA biosynthesis and insulin resistance [94].

EFFECTS OF EXERCISE ON MYOCARDIAL ENERGY METABOLISM

Physical activity refers to any bodily movement that causes energy expenditure due to skeletal muscle contraction, typically exceeding a resting metabolic rate of 3.5 mL O_2/min/kg or one metabolic equivalent [95]. Specifically, exercise, a specific branch of physical activity, involves activities that are planned, structured, and repetitive actions aimed at maintaining or improving physical health [96]. Based on the form of skeletal muscle involvement during exercise, activities can be classified as dynamic or static. Dynamic exercise refers to endurance activities involving regular skeletal muscle contraction, such as swimming, jogging, and walking. The characteristic of dynamic exercise is the relative percentage of maximal oxygen uptake required for the activity, which can lead to eccentric ventricular remodeling. In contrast, static exercise refers to activities involving sustained skeletal muscle contraction to overcome resistance, such as weightlifting and deadlifts. Its defining characteristic is the relative percentage of maximum voluntary contraction, which may lead to concentric ventricular remodeling [95, 97].

Exercise and myocardial metabolism

During physical activity, which acts as a physiological stimulant, the heart's contractility and oxygen consumption rise to ten times their resting levels [98]. Increased cardiac workload during exercise induces metabolic flexibility in substrate utilization, particularly affecting FAs

and lactate metabolism [98-100]. Specifically, exercise induces a catecholamine-driven fat metabolism, elevating circulating FFAs to 2.4 mM, approximately 6-10 times the resting levels [98, 101]. This means that, at this stage, FA metabolism in the body is primarily driven by oxidative metabolism for energy supply, rather than biosynthesis, thereby reducing the risk of lipid accumulation and subsequently mitigating the potential for lipotoxicity [102]. This increase in FA oxidation, along with mitochondrial cristae density during exercise, contributes to beneficial exercise-induced physiological cardiac hypertrophy, thus amplifying the protective impact of exercise on cardiac function [103].

Due to the extensive contraction of skeletal muscles during exercise, the concentration of lactate in circulation increases significantly, approaching 10 mM [104, 105]. At the same time, the heart is one of the important consumers of lactate in the body, and its lactate utilization rate is positively correlated with the lactate concentration in circulation [106]. Interestingly, under conditions of increased circulating lactate, FA oxidation seems to increase as well, further highlighting a synergistic effect between lactate and FA, which enhances the overall energy supply in the heart under high-load conditions. Simultaneously, the reduction in glucose utilization seems to be accompanied by increased FA and lactate utilization, which may be related to the increased competition for substrates and the heart's adaptation to exercise as a response to sustained physical demand [107]. Additionally, studies have found that while acute exercise increases lactate utilization in the heart, long-term exercise has little effect on lactate oxidation capacity and related lactate dehydrogenase content, though it does increase fatty acid oxidation utilization and transport [108, 109].

Additionally, long-term exercise can enhance cardiovascular health by reducing the activity of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKB2), which suppresses glycolysis and decreases glucose utilization, thereby promoting physiological ventricular remodeling [110]. Furthermore, a study on female rats fed a high-fat, high-sugar (HFHS) diet showed that 8 weeks after exercise cessation, exercise can correct the redox imbalance caused by the HFHS diet and restore mitochondrial efficiency [111], indicating that the benefits of exercise persist even after treatment ends. Understanding the general metabolic adaptations induced by exercise sets the stage for exploring how different exercise types and intensities distinctly impact myocardial energy metabolism.

The effect of exercise type and intensity on myocardial metabolism

Different exercise intensities result in variations in cardiac metabolic responses. During low to moderate-intensity exercise, both male and female mice exhibit increased levels of ketones and lactate in their circulation. In contrast, during high-intensity exercise, male mice show elevated lactate levels without a corresponding rise in ketones, whereas female mice experience an increase in both metabolites [112]. This observation suggests that female mice's myocardial metabolism is more adaptable to physiological stresses such as exercise.

Similarly, a 12-week exercise program study involving 52 healthy participants demonstrated that high-intensity interval training (HIIT) and combined training (CT) resulted in increased levels of cardiolipin and tricarboxylic acid cycle metabolites, indicating enhanced mitochondrial activity due to aerobic training. Resistance training (RT), on the other hand, led to an increase in plasma membrane phospholipids, reflecting its protective role in maintaining cellular integrity. Notably, all three types of exercise improved insulin sensitivity and cardiac metabolic markers [113].

These findings highlight the heart's ability to flexibly select energy substrates, influenced by the type, frequency, intensity, duration, and form of exercise, as well as gender differences. Genotypes that regulate myocardial metabolism may serve as markers to distinguish between physiological ventricular remodeling from exercise and pathological remodeling resulting from disease stimuli [114]. This highlights the potential clinical applicability of exercise as a non-pharmacological intervention for the protection of cardiovascular health.

The harmful effects of exhaustive exercise on myocardial metabolism

Exhaustive exercise (EE) refers to prolonged, high-intensity exercise that exceeds the body's tolerance [115]. It has been widely studied in both human and animal models, where evidence shows that EE can induce adverse cardiovascular remodeling, including myocardial ultrastructural damage, myocardial fibrosis, malignant arrhythmias, aortic and carotid artery stiffening, and elastic lamina rupture [116-119].

Increasing evidence suggests that inflammation and oxidative stress are key mechanisms by which EE induces harmful cardiovascular remodeling [120-123]. For example, EE can elevate inflammatory factors (e.g., IL-6, IL-10, TNF-α), activate inflammatory signaling pathways such as NF-κB [124], and significantly increase ROS levels by disrupting cellular redox balance [125]. Elevated ROS levels damage mitochondria by breaking mtRNA and causing genome mismatch. ROS also disrupts mitochondrial membranes, leading to Ca^{2+} overload and

redox imbalance [125]. These changes collectively contribute to the progressive deterioration of mitochondrial structure and function.

EE also downregulates calcium-binding protein S100A1, weakening its regulatory effect on PGC-1α, thereby suppressing the expression of key proteins involved in mitochondrial biogenesis and energy metabolism, such as Ant1 and Tfam, ultimately resulting in mitochondrial dysfunction and energy metabolism imbalance [126]. Meanwhile, by inhibiting the PGC-1α/Complex I/II pathway, EE reduces mtRNA expression, upregulates mitochondrial fission-related proteins (e.g., Drp1, Fis1), and suppresses the expression of mitochondrial fusion-related proteins (e.g., Mfn2, OPA1), leading to an imbalance in mitochondrial fission and fusion dynamics [127]. This disruption further exacerbates oxidative stress and activates inflammatory pathways while inhibiting the Nrf2/HO-1 antioxidant mechanism, forming a vicious cycle that ultimately leads to cardiac metabolic dysregulation [122, 128, 129].

Additionally, as previously mentioned, GLUT4 is the most abundant glucose transporter in the myocardium. Under physiological conditions, GLUT4 is predominantly localized within intracellular vesicular structures (e.g., Golgi apparatus and microsomes). Upon stimulation by ischemia-hypoxia, insulin, or muscle contraction, GLUT4 translocates to the plasma membrane to mediate glucose transport. However, studies have shown that EE negatively correlates with GLUT4 translocation, disrupting the balance between glucose supply and demand in myocardial cells, thereby exacerbating myocardial injury [130]. AMPK plays a key role in exercise-induced mechanotransduction, and it can mediate myocardial cell autophagy, enhance mitochondrial biogenesis, and provide cardioprotective effects [131]. However, the above study also observed that EE has limited effects on AMPK activation, and its mediated cardioprotective effects are insufficient to compensate for the cardiac damage caused by EE. In contrast, moderate aerobic exercise can reverse this adverse trend. Notably, in another study involving an obese animal model, EE inhibited AMPK activation [132], while moderate aerobic exercise also showed beneficial cardioprotective effects [133]. In conclusion, EE may lead to AMPK dysregulation, reducing its ability to maintain energy homeostasis, impairing GLUT4 translocation, and exacerbating metabolic stress. Meanwhile, metabolomics studies have found that EE can induce significant changes in lipid and amino acid metabolism, such as a marked increase in the expression of metabolites like glutamate, glutamine, arachidonic acid, and myostatin. This accumulation of these substances may upregulate the PTGS2/MAOB pathway, thereby exacerbating myocardial cell inflammation and leading to further damage to the myocardium [134].

Despite these findings, the effects of EE on different age groups and exercise intensities remain unclear. Future studies should define exercise limits for various populations to optimize cardiac rehabilitation and protect cardiovascular health.

THE CONNECTION BETWEEN MYOCARDIAL ENERGY METABOLISM, EXERCISE, AND HF

In HF, cardiac metabolic adaptability declines, and energy production is restricted, further exacerbating metabolic disturbances and mitochondrial dysfunction in cardiomyocytes [5]. Such impairments are a hallmark of HF progression, emphasizing the need for targeted therapeutic strategies. Exercise, as a safe and cost-effective intervention, can enhance myocardial metabolism, regulate the expression of metabolic proteins, and reduce cardiovascular risks under various physiological conditions [135, 136]. In addition, exercise improves energy efficiency and restores mitochondrial health, making it a promising therapeutic approach. Various animal and human studies have been conducted to better understand the effects of different types of exercise on heart health. Table 2 summarizes the latest evidence regarding the cardiovascular benefits of exercise.

In a rat model of high-fat coronary artery disease, four weeks of treadmill exercise alleviated myocardial fibrosis, inflammation, and apoptosis by inhibiting NF-κB signaling. These effects collectively mitigated pathological remodeling and improved overall heart function [137]. In a myocardial infarction model, 12 weeks of resistance training failed to enhance survival rates, myocardial structure, or function [138]. Interestingly, six weeks of moderate- and high-intensity endurance training in the same model significantly increased ATP production capacity and myocardial contractility [139]. Overall, these findings suggest that exercise benefits the failing heart, but such benefits depend on the type, duration, and intensity of training. As previously discussed, the imbalance in myocardial energy metabolism is one of the central causes of HF. This section provides an overview of recent studies on how exercise addresses myocardial metabolic dysregulation to improve heart health.

The influence of exercise on myocardial metabolism

Investigating the processes through which exercise-induced metabolic alterations in cardiomyocytes confer cardiovascular benefits is a focal point of research. In a study involving 50 patients with HFpEF classified as NYHA II and III, a four-week cardiac rehabilitation program led to increased Sirt1 activity and elevated levels of βOHB, reduced oxidative stress, and this correlated with higher NAD levels and the NAD/NADH ratio, along with lower Ox-

LDL [140]. In a mouse model of coronary heart disease induced by a high-fat diet, swimming (fifty-five-minute sessions, once daily, five days a week, for eight weeks) downregulated miR-344g-5p targeting HMGCS2, thereby inhibiting ketogenesis and reducing lipid accumulation, which in turn attenuated lipotoxicity-induced myocardial fibrosis and cardiomyocyte apoptosis, and consequently cardiac dysfunction [141]. Following this, another study aimed to explore whether different forms of exercise could activate distinct molecular pathways that confer similar cardiovascular protection. Voluntary wheel running (sixty minutes per day, for eight weeks) activates the AMPK/PGC1α pathway, enhances mitochondrial phosphorylation, diminishes oxidative stress, shifts metabolism from FA to glucose oxidation, corrects metabolic disturbances in diabetic cardiomyopathy, improves cardiac function, and mitigates the adverse effects of diabetic cardiomyopathy [142]. MTP is crucial for lipid metabolism. It participates in lipid transport and facilitates the assembly of apolipoprotein B, influencing the release of chylomicrons and VLDL. Endurance training increases MTP expression in fruit flies, which leads to improved systemic lipid metabolic imbalances and cardiac dysfunctions triggered by a high-fat diet [143], as well as ameliorating age-related diastolic dysfunction and mitochondrial impairments, thereby enhancing lipid metabolism and boosting survival rates [144, 145]. These findings demonstrate that exercise can ameliorate metabolic disarray in failing cardiac muscle, thus safeguarding heart function.

GLUT4 is a key protein in the glucose uptake and transport process; previous studies have demonstrated that endurance exercise can elevate the content of GLUT4 in diabetic myocardium, thereby enhancing glucose utilization disorders in diabetic cardiomyopathy [146]. Research indicates that short-term treadmill exercise (sixty-minute sessions, once daily, five days a week, for two weeks) can reverse the decreasing trend of GLUT4 in a rat model of pulmonary arterial hypertension (PAH), regulating glucose metabolism and thus improving diastolic dysfunction caused by PAH [147]. Additionally, the research found that the short-term exercise program not only failed to reverse the declining trend in FA and amino acid metabolism but also enhanced the levels of PGC-1α and PPAR-γ, both of which are associated with FA metabolism in HF [6, 30]. Treadmill exercise (sixty-minute sessions, once daily, five days a week, for twelve weeks) can restore GLUT4 levels in female mice, thus inhibiting cellular aging, inflammation, and oxidative stress, restoring autophagy, and protecting the cardiac function of mice with high-fat diet-induced diabetes [148]. In addition to improving glucose metabolism, subsequent findings show that exercise also impacts mitochondrial function significantly through various other pathways. The variability in outcomes may be

attributable to the type of animal, disease model, and the specific exercise regimen used. Endurance training (sixty-minute sessions, once daily, five days a week, for four weeks) stimulates myocardial AMPK, which phosphorylates histone deacetylase 4. This reduces the inhibition of MEF2a in HF mice, enhances GLUT1 expression, improves glucose metabolism, and enhances heart function in mice with HF following myocardial infarction [149]. In a rat model of HF following myocardial infarction, this exercise protocol showed cardiovascular benefits, with increased FA metabolism and reduced glycolysis, potentially linked to stimulation of the AMPK/PPAR-α pathway and amelioration of mitochondrial dysfunction [150, 151]. A study comparing exercise durations (fifteen or sixty-minute sessions, once daily, five days a week, for eight weeks) found that low-intensity endurance exercise significantly enhanced Sirt3 activity more than higher doses, subsequently improving mitochondrial structure and autophagy in elderly mice with HF post-myocardial infarction, reducing apoptosis, oxidative stress, and myocardial fibrosis, thereby enhancing survival rates and cardiac function [152]. Overall, these findings underscore the potential benefits of specific exercise intensities and durations in ameliorating mitochondrial dysfunction and promoting heart health in the context of HF. Exercise enhances not only FA, glucose, and ketone metabolism in hearts failing due to various causes but also boosts BCAA metabolism. This is facilitated by upregulating mitochondrial serine-threonine PP2Cm, reducing cardiac BCAA build-up, diminishing myocardial fibrosis, apoptosis, and cardiomyocyte hypertrophy, increasing capillary density, and improving left ventricular ejection fraction, thus shielding the heart from ischemic damage [153]. Collectively, these studies highlight the critical role of tailored exercise in managing myocardial energy metabolism and mitigating HF (Figure 2).

The influence of exercise on mitochondria

Building on the benefits of exercise-induced metabolic changes, the impact of physical activity on mitochondrial dynamics is a critical component that further enhances cardiovascular protection. Mitochondria, as the main site of metabolism, are highly dynamic organelles and a crucial factor in cell death and survival during the development of cardiovascular diseases [154]. The dynamics of mitochondria—biogenesis, fusion, fission, and autophagy—are vital for preserving their integrity, positioning, size, and function, and are therefore critical for cardiovascular health [155]. Exercise dynamically modulates mitochondrial shape and biogenesis, sustains mitochondrial homeostasis, optimizes myocardial metabolic substrates, and safeguards cardiovascular health [155-157]. While it remains unclear how exercise affects mitochondrial dynamics [158], research indicates that treadmill running (sixty-minute sessions,

once daily, five days a week, for four weeks) activates the SIRT1/PGC-1α/PI3K/Akt pathway, boosts antioxidant defenses and mitochondrial function, thereby reducing myocardial fibrosis and enhancing heart function in aged rats after myocardial infarction [159]. Treadmill running (sixty-minute sessions, once daily, five days a week, for four weeks) increases AMPKα2 activity, boosts respiratory chain complex I activity, activates mitochondrial autophagy, and combats DOX-induced cardiac injury [160]. In the myocardium, there are mainly intermyofibrillar and subsarcolemmal (SS) mitochondrial populations. Exercise is more adept at regulating the redox balance and iron management of SS mitochondria, thus adjusting mitochondrial homeostasis [161].

HIIT, known for its time efficiency, is increasingly being studied for its potential benefits in cardiovascular protection compared to more traditional exercise regimens such as moderate-intensity continuous training (MICT). In particular, the function of mitochondria in these protective mechanisms has become a key area of investigation. A randomized controlled trial involving obese individuals demonstrated that both MICT and HIIT enhance mitochondrial respiratory functions. However, HIIT was found to be more effective than MICT in increasing mitochondrial numbers and enhancing cardiac contractility, highlighting its superior benefits for mitochondrial health [162, 163]. This suggests that different forms of aerobic exercise may provide distinct mitochondrial benefits depending on their intensity. Moreover, HIIT enhances mitochondrial size and morphology and decreases mitochondrial fragmentation due to prolonged sitting, thus preserving mitochondrial integrity [164].

Exercise impacts not only mitochondrial dynamics—including biogenesis, fusion, and fission—but also other key aspects of mitochondrial health. Treadmill training (sixty-minute sessions, once daily, five days a week, for twelve weeks) significantly enhances levels of mitochondrial-derived peptide in the heart, which improves myocardial contraction and tends to enhance diastolic function [165]. Treadmill running (forty-five-minute sessions, once daily, five days a week, for five weeks) significantly boosts endothelial nitric oxide synthase (eNOS) activity in mitochondria, elevates nitric oxide production, enhances S-nitrosylation, decreases oxidative stress, improves mitochondrial function, and fortifies the heart's capacity to manage ischemic hypoxia [166]. Telomerase reverse transcriptase (TERT) within mitochondria performs functions beyond simply maintaining telomeres. Voluntary wheel running (4350 ± 685 meters per day, for three weeks) was found to increase TERT activity in hearts under pressure overload, leading to improved complex-I activity, enhanced antioxidant response, and prevention of mitochondrial dysfunction, ultimately exerting an anti-hypertrophic effect [167].

Exercise impacts not only during its performance but also afterward, as studies show that rats on a high-fat diet maintain the benefits of enhanced mitochondrial respiratory efficiency, increased antioxidant response, and reduced inflammation even up to 8 weeks after stopping exercise [111]. Moreover, the genetic backdrop is critically influential in the cardiac response to exercise; under specific genetic conditions, exercise fails to offer cardioprotective benefits. In a model of arrhythmogenic cardiomyopathy with a desmoglein-2 mutation, prolonged swimming sessions (ninety-minute sessions, five days a week, for eleven weeks) unexpectedly led to adverse outcomes. These included calcium overload, activation of calpain-1, and the cleavage of mitochondria-associated apoptosis-inducing factor. These processes consequently and ultimately worsen cardiac pathology and function in DSG2mut/mut mice by promoting cellular damage and apoptosis [168]. In contrast, treadmill running (forty-five-minute sessions, once daily, five days a week, for eight weeks) did not decrease blood pressure, left ventricular hypertrophy, or myocardial fibrosis in aged spontaneously hypertensive rats (SHR), showing no change in mitochondrial dynamics; however, it effectively reduced blood pressure in younger SHR rats [169]. Interestingly, swimming (forty-five-minute sessions, twice daily, five days a week, for eight weeks), by activating AKT, increased the phosphorylation of glycogen synthase kinase-3β, enhanced mitochondrial dynamics and spatial distribution, lowered ANP levels, and improved cardiac contractility [170]. These contrasting research findings broaden our comprehension of exercise's impacts on the cardiovascular system, highlighting the complexity and the essential need for tailored exercise programs for diverse patient populations to optimize cardiovascular health protection (Figure 3).

The influence of exercise on exerkines

Exerkines are described as fluid factors that respond to both acute and chronic exercise, playing a crucial role in conferring various cardiac metabolic benefits. Recently discovered exerkines such as FGF21, BAIBA, and Irisin, provide new insights into how exercise yields both immediate and long-term cardiovascular benefits [171].

FGF21

FGF21 was initially discovered to be secreted by the liver, and later it was also found that skeletal muscle, the pancreas, and brown adipose tissue are capable of secreting it as well [172]. A study on FGF21$^{-/-}$ mice found that overexpression of FGF21 can protect myocardial mitochondrial dynamics and improve cardiac dysfunction caused by its deficiency [173]. While it was traditionally believed that the heart is its primary effector organ, recent findings suggest

that myocardial cell damage can lead to the release of FGF21 in an autocrine manner, exerting cardioprotective effects [174]. Moreover, other tissues, such as the liver and brown adipose tissue, secrete FGF21 in a paracrine manner to inhibit ventricular remodeling and protect the heart [175, 176].

In mice with cardiomyocyte β-klotho knockout, endurance exercise increased β-klotho expression in cardiomyocytes, which then upregulated FGF21. This cascade activated AMPK, leading to FOXO3 phosphorylation and increased SIRT3 expression, which ultimately prevented mitochondrial dysfunction and improved cardiac function in diabetic cardiomyopathy [177].

Additionally, studies have found that FGF21 has significant predictive value in distinguishing between mild and severe HF caused by T2DM and can serve as an independent predictor of late-stage HF in patients with HFrEF, HFpEF, HFmrEF, and T2DM [178-180]. In parallel, preclinical studies on the application of FGF21 are also continuously improving. For example, in a study involving insulin-resistant mice, long-term FGF21 treatment activated the FAO signaling pathway, improving cardiac metabolism, alleviating insulin resistance, enhancing FGF21 sensitivity, and improving cardiac dysfunction [181].

Irisin

Irisin, produced during skeletal muscle exercise and activated by PGC-1α, is derived from the cleavage of the membrane protein FNDC5, and serves as a mediator of exercise-induced metabolic adaptations [182-184]. Recent studies have also found that Irisin can be secreted in various tissues, such as the heart, brain, liver, and fat. However, its expression is highest in skeletal muscle. As a myokine, it plays a key role in enhancing energy expenditure and exerts its effects through both autocrine and paracrine mechanisms.

In a study examining various exercise modalities—including endurance, weight resistance, vibration, and electrical stimulation—all forms were shown to increase Irisin/FNDC5 levels in the myocardium, thereby promoting mitochondrial autophagy. Among these modalities, weight resistance exercise had the most pronounced effect, significantly activating the PINK1/Parkin-LC3/P62 pathway, thereby suppressing oxidative stress and improving cardiac function [185].

In models of radiation-induced heart injury, treadmill running (thirty-minute sessions, once daily, five days a week, for three weeks) increased the expression of Irisin, selectively activated mitochondrial autophagy, and improved heart function [186]. The phenomenon of induced

protective mitochondrial autophagy also ameliorates cardiac hypertrophy from TAC and apoptosis caused by Ang II [187, 188]. Iditarod, related to FNDC5, is produced by the body as a reaction to exercise, modulating amounts of myocardial autophagy and enhancing resistance to cardiac stress from exercise [189]. In a type 2 diabetes mellitus model, treadmill training (forty-five-minute sessions, once daily, five days a week, for eight weeks) increased Irisin levels, which inhibited excessive mitochondrial fission due to DRP1 [190]. Research has found that Irisin can serve as a biomarker to predict the long-term clinical prognosis of HFpEF patients with low or near-normal NT-proBNP levels [191]. Moreover, it can also predict the outcomes of chronic heart failure caused by T2DM and its acute decompensated heart patients with acute myocardial infarction [192]. Furthermore, the expression of the precursor FNDC5 of Irisin increases in HF patients with better aerobic exercise performance, suggesting that FNDC5 is related to exercise performance in heart failure patients [193].

Other exerkines

BAIBA, a valine metabolite consisting of L-BAIBA and D-BAIBA isomers. It is produced by skeletal muscles during exercise and reaches other organs through paracrine/autocrine signaling to exert its effects [194]. In particular, studies have shown that BAIBA can improve diabetic cardiomyopathy, atrial fibrillation caused by obesity, and atrial remodeling by inhibiting oxidative stress, reducing inflammation, and increasing insulin sensitivity. These mechanisms collectively contribute to its cardiac protective effects [195, 196]. It is increased by endurance training (sixty-minute sessions, once daily, five days a week, for eight weeks). The increase in β-aminoisobutyric acid (BAIBA) elevates miR-208b expression and enhances AMPK phosphorylation. These changes reduce myocardial apoptosis and mitochondrial dysfunction, ultimately improving heart function after myocardial infarction [197]. Research on humans has found that an increase in circulating BAIBA concentration is negatively correlated with various cardiac metabolic risk factors, including elevated blood pressure, cholesterol levels, and insulin resistance [198].

CCDC80 is a signal peptide, and there is evidence supporting its presence in various types of cells [199-201]. However, the understanding of its functions and secretion mechanisms remains complex, requiring additional studies to provide clearer insights into the underlying mechanisms [199]. Swimming (sixty-minute sessions, once daily, five days a week, for twelve weeks) induces the body to produce Coiled-coil domain-containing protein 80 (CCDC80). CCDC80 selectively inhibits the kinase activity of JAK2 and the STAT3 signaling pathway,

thus reducing Angiotensin II-induced cardiac fibrosis and hypertrophy in mice, and preserving heart function [202]. Moreover, the study found that the circulating concentration of CCDC80 also increased after exercise in healthy individuals. However, the study did not extend its analysis to include the circulating concentration of CCDC80 in populations with pathological conditions such as heart failure, which would be crucial for understanding its role in various health contexts. Further research is required in the future to investigate whether it can predict individual responses to exercise in HF patients, particularly in terms of metabolic and cardiorespiratory health.

In conclusion, exerkines such as FGF21, Irisin, BAIBA, and CCDC80 promote cardiac protection and the recovery of heart function through various mechanisms (as illustrated in Figure 4). Given that heart failure patients are characterized by exercise intolerance, these exerkines demonstrate significant potential as exercise substitutes. Research on their preclinical mechanisms continues to progress, though there is currently no direct evidence for their application in heart failure patients. Nevertheless, this remains promising overall.

CONCLUSION

HF represents the final stage of multiple cardiovascular diseases and poses a significant global public health challenge that urgently requires effective solutions. While numerous treatment strategies are continually researched, a critical gap remains in identifying effective treatments. The health benefits of exercise, particularly for the cardiovascular system, are widely recognized. Exercise confers substantial protective benefits to the cardiovascular system by removing pathological factors, correcting myocardial metabolic imbalances, reducing oxidative stress and inflammation, minimizing cell death, and safeguarding mitochondrial function and dynamics. Consequently, maintaining normal heart function is critically dependent on optimal myocardial metabolism. Pathological disruptions in energy supply or substrate scarcity can cause a mismatch between myocardial energy demands and supply, ultimately resulting in HF. Exercise not only elevates myocardial metabolic demands but also dynamically alters the metabolic environment. Recent research emphasizes that exercise primarily acts by rectifying metabolic disorders, enhancing glucose and lipid transport, preserving mitochondria, and generating beneficial exerkines.

Recent meta-analysis evidence shows that exercise has a positive impact on the quality of life (QoL), aerobic capacity, and cardiac function in elderly HF patients. However, exercise variables such as frequency, volume, and duration did not significantly improve the LVEF

indicator [203]. This result underscores the complexity of optimizing exercise programs for heart failure patients, as factors beyond exercise variables or interactions between exercise variables may play a crucial role in determining improvements in cardiac function. Additionally, the studies included in the meta-analysis displayed considerable heterogeneity, likely due to differences in the severity of heart failure, exercise modalities, and the presence of comorbidities. Such heterogeneity may affect the clarity of the dose-response relationship between exercise variables and LVEF improvement. Furthermore, resistance exercise has been found to have a more significant impact on improving patients' aerobic capacity compared to aerobic exercise, while combined training shows no significant difference in its effects on LVEF compared to the other two approaches. This suggests that exercise prescriptions for heart failure patients should be personalized to ensure both safety and efficacy in those with impaired cardiac function. At the same time, while evidence suggests that improvements in LVEF after exercise intervention do not appear to be significantly related to exercise variables, it is crucial to recognize that metabolic adaptations induced by exercise—such as improvements in mitochondrial function and reduced metabolic dysfunction—could still contribute significantly to overall cardiac health. Future research should integrate metabolomics and molecular analysis to clarify the mechanisms by which exercise enhances cardiac health and provide additional support to traditional examinations such as echocardiography.

Current evidence shows that moderate to low-intensity aerobic exercises are beneficial for the heart, but exhaustive exercises can reduce myocardial contractility, cause myocardial damage, and even deteriorate heart function. This deterioration is closely associated with the type, intensity, and frequency of the exercise [204-207]. Hence, defining the dosage limits of exercise is crucial. In clinical settings, exercise intolerance continues to be a major symptom in individuals with HF, greatly diminishing their quality of life. The mechanisms behind exercise intolerance are likely related to aging, reduced pulmonary reserve, and respiratory or skeletal muscle dysfunction, among other complex factors [208]. While current methods to mitigate exercise intolerance are limited, an increasing body of research indicates that exercise itself benefits HF and can alleviate exercise intolerance [209]. Thus, further studies on the dosage and timing of exercise interventions are essential for optimizing the application of exercise therapy in cardiac rehabilitation, with significant clinical and societal implications.

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REFERENCES

[1] Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of Metabolic Flexibility in the Failing Heart. Frontiers in Cardiovascular Medicine. 2018;5:68.

[2] Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac Energy Metabolism in Heart Failure. Circulation Research. 2021;128(10):1487-513.

[3] Gibb AA, Hill BG. Metabolic Coordination of Physiological and Pathological Cardiac Remodeling. Circulation Research. 2018;123(1):107-28.

[4] Kolwicz SC, Purohit S, Tian R. Cardiac Metabolism and its Interactions With Contraction, Growth, and Survival of Cardiomyocytes. Circulation Research. 2013;113(5):603-16.

[5] Da Dalt L, Cabodevilla AG, Goldberg IJ, Norata GD. Cardiac lipid metabolism, mitochondrial function, and heart failure. Cardiovascular Research. 2023;119(10):1905-14.

[6] Ritterhoff J, Tian R. Metabolic mechanisms in physiological and pathological cardiac hypertrophy: new paradigms and challenges. Nature Reviews Cardiology. 2023;20(12):812-29.

[7] Shao D, Tian R. Glucose Transporters in Cardiac Metabolism and Hypertrophy. In: Prakash YS, editor. Comprehensive Physiology. 1 ed: Wiley; 2015. p. 331-51.

[8] Wei J, Duan X, Chen J, Zhang D, Xu J, Zhuang J, et al. Metabolic adaptations in pressure overload hypertrophic heart. Heart Failure Reviews. 2023;29(1):95-111.

[9] Szablewski L. Glucose transporters in healthy heart and in cardiac disease. International Journal of Cardiology. 2017;230:70-5.

[10] Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac Energy Metabolism in Heart Failure. Circ Res. 2021;128(10):1487-513.

[11] Wei J, Duan X, Chen J, Zhang D, Xu J, Zhuang J, et al. Metabolic adaptations in pressure overload hypertrophic heart. Heart Fail Rev. 2024;29(1):95-111.

[12] Matsuura TR, Puchalska P, Crawford PA, Kelly DP. Ketones and the Heart: Metabolic Principles and Therapeutic Implications. Circ Res. 2023;132(7):882-98.

[13] McGarrah RW, White PJ. Branched-chain amino acids in cardiovascular disease. Nat Rev Cardiol. 2023;20(2):77-89.

[14] White PJ, McGarrah RW, Grimsrud PA, Tso SC, Yang WH, Haldeman JM, et al. The BCKDH Kinase and Phosphatase Integrate BCAA and Lipid Metabolism via Regulation of ATP-Citrate Lyase. Cell Metab. 2018;27(6):1281-93 e7.

[15] Fine KS, Wilkins JT, Sawicki KT. Circulating Branched Chain Amino Acids and Cardiometabolic Disease. J Am Heart Assoc. 2024;13(7):e031617.

[16] Randle PJ, Garland PB, Hales CN, Newsholme EA. THE GLUCOSE FATTY-ACID CYCLE ITS ROLE IN INSULIN SENSITIVITY AND THE METABOLIC DISTURBANCES OF DIABETES MELLITUS. The Lancet. 1963;281(7285):785-9.

[17] Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. American Journal of Physiology-Endocrinology and Metabolism. 2009;297(3):E578-E91.

[18] Bertrand L, Horman S, Beauloye C, Vanoverschelde J-L. Insulin signalling in the heart. Cardiovascular Research. 2008;79(2):238-48.

[19] Renguet E, Ginion A, Gélinas R, Bultot L, Auquier J, Robillard Frayne I, et al. Metabolism and acetylation contribute to leucine-mediated inhibition of cardiac glucose uptake. American Journal of Physiology-Heart and Circulatory Physiology. 2017;313(2):H432-H45.

[20] Cox Pete J, Kirk T, Ashmore T, Willerton K, Evans R, Smith A, et al. Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes. Cell Metabolism. 2016;24(2):256-68.

[21] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Journal of Heart Failure. 2016;18(8):891-975.

[22] Chen L, Song J, Hu S. Metabolic remodeling of substrate utilization during heart failure progression. Heart Failure Reviews. 2019;24(1):143-54.

[23] Lopaschuk GD. Metabolic Modulators in Heart Disease: Past, Present, and Future. Canadian Journal of Cardiology. 2017;33(7):838-49.

[24] van Bilsen M, Smeets PJ, Gilde AJ, van der Vusse GJ. Metabolic remodelling of the failing heart: the cardiac burn-out syndrome? Cardiovasc Res. 2004;61(2):218-26.

[25] Lopaschuk GD. Metabolic Modulators in Heart Disease: Past, Present, and Future. Can J Cardiol. 2017;33(7):838-49.

[26] Ingwall JS, Weiss RG. Is the Failing Heart Energy Starved?: On Using Chemical Energy to Support Cardiac Function. Circulation Research. 2004;95(2):135-45.

[27] Bottomley PA, Panjrath GS, Lai S, Hirsch GA, Wu K, Najjar SS, et al. Metabolic Rates of ATP Transfer Through Creatine Kinase (CK Flux) Predict Clinical Heart Failure Events and Death. Science Translational Medicine. 2013;5(215).

[28] Flam E, Jang C, Murashige D, Yang Y, Morley MP, Jung S, et al. Integrated landscape of cardiac metabolism in end-stage human nonischemic dilated cardiomyopathy. Nature Cardiovascular Research. 2022.

[29] Previs MJ, O'Leary TS, Morley MP, Palmer BM, LeWinter M, Yob JM, et al. Defects in the Proteome and Metabolome in Human Hypertrophic Cardiomyopathy. Circulation: Heart Failure. 2022;15(6).

[30] Scarpulla RC, Vega RB, Kelly DP. Transcriptional integration of mitochondrial biogenesis. Trends in Endocrinology & Metabolism. 2012;23(9):459-66.

[31] Funada J, Betts TR, Hodson L, Humphreys SM, Timperley J, Frayn KN, et al. Substrate utilization by the failing human heart by direct quantification using arterio-venous blood sampling. PLoS One. 2009;4(10):e7533.

[32] Taylor M, Wallhaus TR, Degrado TR, Russell DC, Stanko P, Nickles RJ, et al. An evaluation of myocardial fatty acid and glucose uptake using PET with [18F]fluoro-6-thia-

heptadecanoic acid and [18F]FDG in Patients with Congestive Heart Failure. J Nucl Med. 2001;42(1):55-62.

[33] De Jong KA, Lopaschuk GD. Complex Energy Metabolic Changes in Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction. Can J Cardiol. 2017;33(7):860-71.

[34] Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation. 2004;109(18):2191-6.

[35] Finck BN, Kelly DP. Peroxisome proliferator-activated receptor alpha (PPARalpha) signaling in the gene regulatory control of energy metabolism in the normal and diseased heart. J Mol Cell Cardiol. 2002;34(10):1249-57.

[36] Djoussé L, Benkeser D, Arnold A, Kizer JR, Zieman SJ, Lemaitre RN, et al. Plasma Free Fatty Acids and Risk of Heart Failure: The Cardiovascular Health Study. Circulation: Heart Failure. 2013;6(5):964-9.

[37] Voros G, Ector J, Garweg C, Droogne W, Van Cleemput J, Peersman N, et al. Increased Cardiac Uptake of Ketone Bodies and Free Fatty Acids in Human Heart Failure and Hypertrophic Left Ventricular Remodeling. Circ Heart Fail. 2018;11(12):e004953.

[38] Wei J, Nelson MD, Szczepaniak EW, Smith L, Mehta PK, Thomson LE, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women. Am J Physiol Heart Circ Physiol. 2016;310(1):H14-9.

[39] McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, et al. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. Circulation. 2007;116(10):1170-5.

[40] Nyman K, Graner M, Pentikainen MO, Lundbom J, Hakkarainen A, Siren R, et al. Cardiac steatosis and left ventricular function in men with metabolic syndrome. J Cardiovasc Magn Reson. 2013;15(1):103.

[41] Listenberger LL, Schaffer JE. Mechanisms of lipoapoptosis: implications for human heart disease. Trends Cardiovasc Med. 2002;12(3):134-8.

[42] Adrian L, Lenski M, Todter K, Heeren J, Bohm M, Laufs U. AMPK Prevents Palmitic Acid-Induced Apoptosis and Lipid Accumulation in Cardiomyocytes. Lipids. 2017;52(9):737-50.

[43] Choi RH, Tatum SM, Symons JD, Summers SA, Holland WL. Ceramides and other sphingolipids as drivers of cardiovascular disease. Nat Rev Cardiol. 2021;18(10):701-11.

[44] Stratford S, Hoehn KL, Liu F, Summers SA. Regulation of insulin action by ceramide: dual mechanisms linking ceramide accumulation to the inhibition of Akt/protein kinase B. J Biol Chem. 2004;279(35):36608-15.

[45] Goldenberg JR, Carley AN, Ji R, Zhang X, Fasano M, Schulze PC, et al. Preservation of Acyl Coenzyme A Attenuates Pathological and Metabolic Cardiac Remodeling Through Selective Lipid Trafficking. Circulation. 2019;139(24):2765-77.

[46] Tsushima K, Bugger H, Wende AR, Soto J, Jenson GA, Tor AR, et al. Mitochondrial Reactive Oxygen Species in Lipotoxic Hearts Induce Post-Translational Modifications of AKAP121, DRP1, and OPA1 That Promote Mitochondrial Fission. Circ Res. 2018;122(1):58-73.

[47] Zhang L, Jaswal JS, Ussher JR, Sankaralingam S, Wagg C, Zaugg M, et al. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. Circ Heart Fail. 2013;6(5):1039-48.

[48] Becerra-Tomas N, Ruiz-Canela M, Hernandez-Alonso P, Bullo M, Li J, Guasch-Ferre M, et al. Glycolysis Metabolites and Risk of Atrial Fibrillation and Heart Failure in the PREDIMED Trial. Metabolites. 2021;11(5).

[49] Sant'Ana PG, Tomasi LC, Murata GM, Vileigas DF, Mota GAF, Souza SLB, et al. Hypoxia-Inducible Factor 1-Alpha and Glucose Metabolism during Cardiac Remodeling Progression from Hypertrophy to Heart Failure. Int J Mol Sci. 2023;24(7).

[50] Fillmore N, Levasseur JL, Fukushima A, Wagg CS, Wang W, Dyck JRB, et al. Uncoupling of glycolysis from glucose oxidation accompanies the development of heart failure with preserved ejection fraction. Mol Med. 2018;24(1):3.

[51] Recchia FA, McConnell PI, Bernstein RD, Vogel TR, Xu X, Hintze TH. Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. Circ Res. 1998;83(10):969-79.

[52] Rosenblatt-Velin N, Montessuit C, Papageorgiou I, Terrand J, Lerch R. Postinfarction heart failure in rats is associated with upregulation of GLUT-1 and downregulation of genes of fatty acid metabolism. Cardiovasc Res. 2001;52(3):407-16.

[53] Kashihara T, Mukai R, Oka SI, Zhai P, Nakada Y, Yang Z, et al. YAP mediates compensatory cardiac hypertrophy through aerobic glycolysis in response to pressure overload. J Clin Invest. 2022;132(6).

[54] Zhang B, Jiang H, Wu J, Cai Y, Dong Z, Zhao Y, et al. m6A demethylase FTO attenuates cardiac dysfunction by regulating glucose uptake and glycolysis in mice with pressure overload-induced heart failure. Signal Transduct Target Ther. 2021;6(1):377.

[55] Binsch C, Barbosa DM, Hansen-Dille G, Hubert M, Hodge SM, Kolasa M, et al. Deletion of Tbc1d4/As160 abrogates cardiac glucose uptake and increases myocardial damage after ischemia/reperfusion. Cardiovasc Diabetol. 2023;22(1):17.

[56] Wende AR, Schell JC, Ha CM, Pepin ME, Khalimonchuk O, Schwertz H, et al. Maintaining Myocardial Glucose Utilization in Diabetic Cardiomyopathy Accelerates Mitochondrial Dysfunction. Diabetes. 2020;69(10):2094-111.

[57] Mylonas N, Drosatos K, Mia S. The role of glucose in cardiac physiology and pathophysiology. Curr Opin Clin Nutr Metab Care. 2023;26(4):323-9.

[58] Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. 2013;113(6):709-24.

[59] Ritterhoff J, Young S, Villet O, Shao D, Neto FC, Bettcher LF, et al. Metabolic Remodeling Promotes Cardiac Hypertrophy by Directing Glucose to Aspartate Biosynthesis. Circ Res. 2020;126(2):182-96.

[60] Murashige D, Jang C, Neinast M, Edwards JJ, Cowan A, Hyman MC, et al. Comprehensive quantification of fuel use by the failing and nonfailing human heart. Science. 2020;370(6514):364-8.

[61] Mizuno Y, Harada E, Nakagawa H, Morikawa Y, Shono M, Kugimiya F, et al. The diabetic heart utilizes ketone bodies as an energy source. Metabolism. 2017;77:65-72.

[62] Bedi KC, Jr., Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, et al. Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure. Circulation. 2016;133(8):706-16.

[63] Qian N, Wang Y. Ketone body metabolism in diabetic and non-diabetic heart failure. Heart Fail Rev. 2020;25(5):817-22.

[64] Abdurrachim D, Teo XQ, Woo CC, Chan WX, Lalic J, Lam CSP, et al. Empagliflozin reduces myocardial ketone utilization while preserving glucose utilization in diabetic hypertensive heart disease: A hyperpolarized (13) C magnetic resonance spectroscopy study. Diabetes Obes Metab. 2019;21(2):357-65.

[65] Li X, Hui S, Mirek ET, Jonsson WO, Anthony TG, Lee WD, et al. Circulating metabolite homeostasis achieved through mass action. Nat Metab. 2022;4(1):141-52.

[66] Hahn VS, Petucci C, Kim MS, Bedi KC, Jr., Wang H, Mishra S, et al. Myocardial Metabolomics of Human Heart Failure With Preserved Ejection Fraction. Circulation. 2023;147(15):1147-61.

[67] Song J-P, Chen L, Chen X, Ren J, Zhang N-N, Tirasawasdichai T, et al. Elevated plasma β-hydroxybutyrate predicts adverse outcomes and disease progression in patients with arrhythmogenic cardiomyopathy. Science Translational Medicine. 2020;12(530):eaay8329.

[68] Niezen S, Connelly MA, Hirsch C, Kizer JR, Benitez ME, Minchenberg S, et al. Elevated Plasma Levels of Ketone Bodies Are Associated With All‐Cause Mortality and Incidence of Heart Failure in Older Adults: The CHS. Journal of the American Heart Association. 2023;12(17):e029960.

[69] Flores‐Guerrero JL, Westenbrink BD, Connelly MA, Otvos JD, Groothof D, Shalaurova I, et al. Association of beta‐hydroxybutyrate with development of heart failure:

Sex differences in a Dutch population cohort. European Journal of Clinical Investigation. 2021;51(5):e13468.

[70] Oyetoro RO, Conners KM, Joo J, Turecamo S, Sampson M, Wolska A, et al. Circulating ketone bodies and mortality in heart failure: a community cohort study. Frontiers in Cardiovascular Medicine. 2024;11:1293901.

[71] Kashiwagi Y, Nagoshi T, Inoue Y, Tanaka Y, Takahashi H, Oi Y, et al. Close linkage between blood total ketone body levels and B-type natriuretic peptide levels in patients with cardiovascular disorders. Scientific Reports. 2021;11(1):6498.

[72] Schugar RC, Moll AR, Andre d'Avignon D, Weinheimer CJ, Kovacs A, Crawford PA. Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. Mol Metab. 2014;3(7):754-69.

[73] Horton JL, Davidson MT, Kurishima C, Vega RB, Powers JC, Matsuura TR, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight. 2019;4(4).

[74] Nielsen R, Moller N, Gormsen LC, Tolbod LP, Hansson NH, Sorensen J, et al. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. Circulation. 2019;139(18):2129-41.

[75] Wang S, Neumann D, Westenbrink BD, Schianchi F, Wong LY, Sun A, et al. Ketone Body Exposure of Cardiomyocytes Impairs Insulin Sensitivity and Contractile Function through Vacuolar-Type H(+)-ATPase Disassembly-Rescue by Specific Amino Acid Supplementation. Int J Mol Sci. 2022;23(21).

[76] Lindsay RT, Dieckmann S, Krzyzanska D, Manetta-Jones D, West JA, Castro C, et al. beta-hydroxybutyrate accumulates in the rat heart during low-flow ischaemia with implications for functional recovery. Elife. 2021;10.

[77] Lim LL, Lau ESH, Fung E, Lee HM, Ma RCW, Tam CHT, et al. Circulating branched‐chain amino acids and incident heart failure in type 2 diabetes: The Hong Kong Diabetes Register. Diabetes/Metabolism Research and Reviews. 2020;36(3):e3253.

[78] Jiang W, Lu K, Zhuang Z, Wang X, Tang X, Huang T, et al. Mendelian Randomization Analysis Provides Insights into the Pathogenesis of Serum Levels of Branched-Chain Amino Acids in Cardiovascular Disease. Metabolites. 2023;13(3):403.

[79] Du X, Li Y, Wang Y, You H, Hui P, Zheng Y, et al. Increased branched-chain amino acid levels are associated with long-term adverse cardiovascular events in patients with STEMI and acute heart failure. Life Sciences. 2018;209:167-72.

[80] Ahmad T, Kelly JP, McGarrah RW, Hellkamp AS, Fiuzat M, Testani JM, et al. Prognostic Implications of Long-Chain Acylcarnitines in Heart Failure and Reversibility With Mechanical Circulatory Support. Journal of the American College of Cardiology. 2016;67(3):291-9.

[81] Hunter WG, Kelly JP, McGarrah RW, Khouri MG, Craig D, Haynes C, et al. Metabolomic Profiling Identifies Novel Circulating Biomarkers of Mitochondrial Dysfunction Differentially Elevated in Heart Failure With Preserved Versus Reduced Ejection Fraction: Evidence for Shared Metabolic Impairments in Clinical Heart Failure. Journal of the American Heart Association. 2016;5(8):e003190.

[82] Kouzu H, Katano S, Yano T, Ohori K, Nagaoka R, Inoue T, et al. Plasma amino acid profiling improves predictive accuracy of adverse events in patients with heart failure. ESC Heart Failure. 2021;8(6):5045-56.

[83] Sansbury BE, DeMartino AM, Xie Z, Brooks AC, Brainard RE, Watson LJ, et al. Metabolomic analysis of pressure-overloaded and infarcted mouse hearts. Circ Heart Fail. 2014;7(4):634-42.

[84] Lai L, Leone TC, Keller MP, Martin OJ, Broman AT, Nigro J, et al. Energy metabolic reprogramming in the hypertrophied and early stage failing heart: a multisystems approach. Circ Heart Fail. 2014;7(6):1022-31.

[85] Yang Z, He M, Austin J, Sayed D, Abdellatif M. Reducing branched-chain amino acids improves cardiac stress response in mice by decreasing histone H3K23 propionylation. Journal of Clinical Investigation. 2023;133(22):e169399.

[86] Kwon HK, Jeong H, Hwang D, Park ZY. Comparative proteomic analysis of mouse models of pathological and physiological cardiac hypertrophy, with selection of biomarkers of pathological hypertrophy by integrative Proteogenomics. Biochim Biophys Acta Proteins Proteom. 2018.

[87] Murashige D, Jung JW, Neinast MD, Levin MG, Chu Q, Lambert JP, et al. Extra-cardiac BCAA catabolism lowers blood pressure and protects from heart failure. Cell Metabolism. 2022;34(11):1749-64.e7.

[88] Tremblay F, Krebs M, Dombrowski L, Brehm A, Bernroider E, Roth E, et al. Overactivation of S6 kinase 1 as a cause of human insulin resistance during increased amino acid availability. Diabetes. 2005;54(9):2674-84.

[89] She P, Reid TM, Bronson SK, Vary TC, Hajnal A, Lynch CJ, et al. Disruption of BCATm in mice leads to increased energy expenditure associated with the activation of a futile protein turnover cycle. Cell Metab. 2007;6(3):181-94.

[90] Uddin GM, Karwi QG, Pherwani S, Gopal K, Wagg CS, Biswas D, et al. Deletion of BCATm increases insulin-stimulated glucose oxidation in the heart. Metabolism. 2021;124:154871.

[91] Sun H, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, et al. Catabolic Defect of Branched-Chain Amino Acids Promotes Heart Failure. Circulation. 2016;133(21):2038-49.

[92] Biswas D, Dao KT, Mercer A, Cowie AM, Duffley L, El Hiani Y, et al. Branched-chain ketoacid overload inhibits insulin action in the muscle. J Biol Chem. 2020;295(46):15597-621.

[93] Yu J-y, Cao N, Rau CD, Lee R-P, Yang J, Flach RJR, et al. Cell-autonomous effect of cardiomyocyte branched-chain amino acid catabolism in heart failure in mice. Acta Pharmacologica Sinica. 2023;44(7):1380-90.

[94] Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BA, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016;535(7612):376-81.

[95] Martinez MW, Kim JH, Shah AB, Phelan D, Emery MS, Wasfy MM, et al. Exercise-Induced Cardiovascular Adaptations and Approach to Exercise and Cardiovascular Disease. Journal of the American College of Cardiology. 2021;78(14):1453-70.

[96] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports (Washington, DC: 1974). 1985;100(2):126-31.

[97] Morganroth J. Comparative Left Ventricular Dimensions in Trained Athletes. Annals of Internal Medicine. 1975;82(4):521.

[98] Fulghum K, Hill BG. Metabolic Mechanisms of Exercise-Induced Cardiac Remodeling. Frontiers in Cardiovascular Medicine. 2018;5:127.

[99] Yalçınkaya BH, Genc S, Yılmaz B, Özilgen M. How does exercise affect energy metabolism? An in silico approach for cardiac muscle. Heliyon. 2023;9(6):e17164.

[100] Saltin B, Åstrand P. Free fatty acids and exercise. The American Journal of Clinical Nutrition. 1993;57(5):752S-8S.

[101] Lopaschuk GD, Ussher JR, Folmes CDL, Jaswal JS, Stanley WC. Myocardial Fatty Acid Metabolism in Health and Disease. Physiological Reviews. 2010;90(1):207-58.

[102] Kostić M, Korićanac G, Tepavčević S, Stanišić J, Romić S, Ćulafić T, et al. Low-intensity exercise diverts cardiac fatty acid metabolism from triacylglycerol synthesis to beta oxidation in fructose-fed rats. Archives of Physiology and Biochemistry. 2023;129(4):922-32.

[103] Chen Z, Zhou Z, Peng X, Sun C, Yang D, Li C, et al. Cardioprotective responses to aerobic exercise-induced physiological hypertrophy in zebrafish heart. The Journal of Physiological Sciences. 2021;71(1):33.

[104] Drake AJ, Haines JR, Noble MIM. Preferential uptake of lactate by the normal myocardium in dogs. Cardiovascular Research. 1980;14(2):65-72.

[105] Kaijser L, Berglund B. Myocardial lactate extraction and release at rest and during heavy exercise in healthy men. Acta Physiologica Scandinavica. 1992;144(1):39-45.

[106] Gibb AA, Hill BG. Metabolic Coordination of Physiological and Pathological Cardiac Remodeling. Circ Res. 2018;123(1):107-28.

[107] Schulman-Geltzer EB, Collins HE, Hill BG, Fulghum KL. Coordinated Metabolic Responses Facilitate Cardiac Growth in Pregnancy and Exercise. Curr Heart Fail Rep. 2023;20(5):441-50.

[108] Fulghum KL, Rood BR, Shang VO, McNally LA, Riggs DW, Zheng YT, et al. Mitochondria-associated lactate dehydrogenase is not a biologically significant contributor to bioenergetic function in murine striated muscle. Redox Biol. 2019;24:101177.

[109] Riehle C, Wende AR, Zhu Y, Oliveira KJ, Pereira RO, Jaishy BP, et al. Insulin receptor substrates are essential for the bioenergetic and hypertrophic response of the heart to exercise training. Mol Cell Biol. 2014;34(18):3450-60.

[110] Gibb AA, Epstein PN, Uchida S, Zheng Y, McNally LA, Obal D, et al. Exercise-Induced Changes in Glucose Metabolism Promote Physiological Cardiac Growth. Circulation. 2017;136(22):2144-57.

[111] Tocantins C, Martins JD, Rodrigues ÓM, Grilo LF, Diniz MS, Stevanovic‐Silva J, et al. Metabolic mitochondrial alterations prevail in the female rat heart 8 weeks after exercise cessation. European Journal of Clinical Investigation. 2023;53(11):e14069.

[112] Fulghum K, Collins HE, Jones SP, Hill BG. Influence of biological sex and exercise on murine cardiac metabolism. Journal of Sport and Health Science. 2022;11(4):479-94.

[113] Pataky MW, Kumar AP, Gaul DA, Moore SG, Dasari S, Robinson MM, et al. Divergent Skeletal Muscle Metabolomic Signatures of Different Exercise Training Modes Independently Predict Cardiometabolic Risk Factors. Diabetes. 2024;73(1):23-37.

[114] Strøm CC, Aplin M, Ploug T, Christoffersen TEH, Langfort J, Viese M, et al. Expression profiling reveals differences in metabolic gene expression between exercise‐induced cardiac effects and maladaptive cardiac hypertrophy. The FEBS Journal. 2005;272(11):2684-95.

[115] Wan DF, Pan SS, Tong YS, Huang Y. Exercise Preconditioning Promotes Autophagy to Cooperate for Cardioprotection by Increasing LC3 Lipidation-Associated Proteins. Front Physiol. 2021;12:599892.

[116] Rubies C, Batlle M, Sanz-de la Garza M, Dantas AP, Jorba I, Fernandez G, et al. Long-Term Strenuous Exercise Promotes Vascular Injury by Selectively Damaging the Tunica Media: Experimental Evidence. JACC Basic Transl Sci. 2022;7(7):681-93.

[117] Guo YP, Pan SS. Exercise preconditioning improves electrocardiographic signs of myocardial ischemic/hypoxic injury and malignant arrhythmias occurring after exhaustive exercise in rats. Sci Rep. 2022;12(1):18772.

[118] Costa ADS, Ghouri I, Johnston A, McGlynn K, McNair A, Bowman P, et al. Electrically stimulated in vitro heart cell mimic of acute exercise reveals novel immediate cellular responses to exercise: Reduced contractility and metabolism, but maintained calcium cycling and increased myofilament calcium sensitivity. Cell Biochem Funct. 2023;41(8):1147-61.

[119] Eijsvogels TMH, Aengevaeren VL. Exercise at the Extremes: Unraveling the Mechanisms of Deleterious Cardiovascular Adaptations. JACC Basic Transl Sci. 2022;7(7):694-6.

[120] Meza-Ramos A, Alcarraz A, Lazo-Rodriguez M, Sangüesa G, Banon-Maneus E, Rovira J, et al. High-Intensity Exercise Promotes Deleterious Cardiovascular Remodeling in a High-Cardiovascular-Risk Model: A Role for Oxidative Stress. Antioxidants (Basel). 2023;12(7).

[121] Yehya M, Boulghobra D, Grillet PE, Fleitas-Paniagua PR, Bideaux P, Gayrard S, et al. Natural Extracts Mitigate the Deleterious Effects of Prolonged Intense Physical Exercise on the Cardiovascular and Muscular Systems. Antioxidants (Basel). 2023;12(7).

[122] Mizokami T, Suzuki K. Involvement of neutrophils and macrophages in exhaustive exercise-induced liver, kidney, heart, and lung injuries. Exerc Immunol Rev. 2024;30:49-62.

[123] Gebhardt K, Hebecker A, Honekamp C, Nolte S, Barthkuhn M, Wilhelm J, et al. Respiratory and Metabolic Responses of CD4 + T Cells to Acute Exercise and Their Association with Cardiorespiratory Fitness. Med Sci Sports Exerc. 2024;56(10):1882-92.

[124] Zhang J, Luo Z, Zhang Z, Zhao M, Tong C, Cong P, et al. Protective effect and mechanism of cannabidiol on myocardial injury in exhaustive exercise training mice. Chem Biol Interact. 2022;365:110079.

[125] Li M, Ning B, Wang T. The mechanism and prevention of mitochondrial injury after exercise. J Physiol Biochem. 2021;77(2):215-25.

[126] Yang M, Xiao Z, Chen Z, Ru Y, Wang J, Jiang J, et al. S100A1 is Involved in Myocardial Injury Induced by Exhaustive Exercise. Int J Sports Med. 2022;43(5):444-54.

[127] Xiong Y, Xu J, Cao W, Zhang J, Feng Z, Cao K, et al. Hydroxytyrosol improves strenuous exercise-associated cardiac pathological changes via modulation of mitochondrial homeostasis. Food Funct. 2022;13(16):8676-84.

[128] You B, Cheng J, Dun Y, Ripley-Gonzalez JW, Liu J, Li D, et al. Rhodiola pre-conditioning reduces exhaustive exercise-induced myocardial injury of insulin resistant mice. Sci Rep. 2022;12(1):20277.

[129] Zhang H, Liu M, Zhang Y, Li X. Trimetazidine Attenuates Exhaustive Exercise-Induced Myocardial Injury in Rats via Regulation of the Nrf2/NF-kappaB Signaling Pathway. Front Pharmacol. 2019;10:175.

[130] Guo YP, Pan SS, Chen TR, Huang Y, Wan DF, Tong YS. Exercise preconditioning promotes myocardial GLUT4 translocation and induces autophagy to alleviate exhaustive exercise-induced myocardial injury in rats. J Mol Histol. 2023;54(5):453-72.

[131] Zhou XH, Luo YX, Yao XQ. Exercise-driven cellular autophagy: A bridge to systematic wellness. J Adv Res. 2025.

[132] Li Z, Tian Z. Restoration of autophagy activity by dipsacoside B alleviates exhaustive exercise-induced kidney injury via the AMPK/mTOR pathway. Nat Prod Res. 2024:1-7.

[133] Dun Y, Hu Z, You B, Du Y, Zeng L, Zhao Y, et al. Exercise prevents fatal stress-induced myocardial injury in obese mice. Front Endocrinol (Lausanne). 2023;14:1223423.

[134] Li T, Wang L, Wu L, Xie Y, Chang M, Wang D, et al. Integrated Metabolomics and Network Pharmacology Investigation of Cardioprotective Effects of Myricetin after 1-Week High-Intensity Exercise. Nutrients. 2023;15(6).

[135] Mi S, Jiang H, Zhang L, Xie Z, Zhou J, Sun A, et al. Regulation of Cardiac-Specific Proteins Expression by Moderate-Intensity Aerobic Exercise Training in Mice With

Myocardial Infarction Induced Heart Failure Using MS-Based Proteomics. Frontiers in Cardiovascular Medicine. 2021;8:732076.

[136] Mota GAF, De Souza SLB, Vileigas DF, Da Silva VL, Sant'Ana PG, Costa LCDS, et al. Myocardial proteome changes in aortic stenosis rats subjected to long‐term aerobic exercise. Journal of Cellular Physiology. 2024;239(4):e31199.

[137] Zhang S, Yu G, Ping M, Du Q, Guo X. Effects of aerobic exercise on myocardial injury, NF-B expression, glucolipid metabolism and inflammatory factors in rats with coronary heart disease. Clinics. 2024;79:100386.

[138] Rodrigues E, Lima A, Gomes M, Souza L, Pontes T, Pagan L, et al. Influence of Isolated Resistance Exercise on Cardiac Remodeling, Myocardial Oxidative Stress, and Metabolism in Infarcted Rats. Antioxidants. 2023;12(4):896.

[139] Stølen T, Shi M, Wohlwend M, Høydal MA, Bathen TF, Ellingsen Ø, et al. Effect of exercise training on cardiac metabolism in rats with heart failure. Scandinavian Cardiovascular Journal. 2020;54(2):84-91.

[140] Corbi G, Conti V, Troisi J, Colucci A, Manzo V, Di Pietro P, et al. Cardiac Rehabilitation Increases SIRT1 Activity and β -Hydroxybutyrate Levels and Decreases Oxidative Stress in Patients with HF with Preserved Ejection Fraction. Oxidative Medicine and Cellular Longevity. 2019;2019:1-10.

[141] Li S, Qian X, Gong J, Chen J, Tu W, Chen X, et al. Exercise Training Reverses Lipotoxicity-induced Cardiomyopathy by Inhibiting HMGCS2. Med Sci Sports Exerc. 2021;53(1):47-57.

[142] Wang SY, Zhu S, Wu J, Zhang M, Xu Y, Xu W, et al. Exercise enhances cardiac function by improving mitochondrial dysfunction and maintaining energy homoeostasis in

the development of diabetic cardiomyopathy. Journal of Molecular Medicine. 2020;98(2):245-61.

[143] Peng T, Ding M, Yan H, Li Q, Zhang P, Tian R, et al. Exercise Training Upregulates Cardiac mtp Expression in Drosophila melanogaster with HFD to Improve Cardiac Dysfunction and Abnormal Lipid Metabolism. Biology. 2022;11(12):1745.

[144] Peng T, Ding M, Yan H, Zhang P, Tian R, Guo Y, et al. Endurance exercise upregulates mtp expression in aged Drosophila to ameliorate age‐related diastolic dysfunction and extend lifespan. Physiological Reports. 2024;12(3):e15929.

[145] No M-H, Heo J-W, Yoo S-Z, Kim C-J, Park D-H, Kang J-H, et al. Effects of aging and exercise training on mitochondrial function and apoptosis in the rat heart. Pflügers Archiv - European Journal of Physiology. 2020;472(2):179-93.

[146] Osborn BA, Daar JT, Laddaga RA, Romano FD, Paulson DJ. Exercise training increases sarcolemmal GLUT-4 protein and mRNA content in diabetic heart. Journal of Applied Physiology. 1997;82(3):828-34.

[147] Morais F, Nogueira-Ferreira R, Rocha H, Duarte JA, Vilarinho L, Silva AF, et al. Exercise training counteracts the cardiac metabolic remodelling induced by experimental pulmonary arterial hypertension. Archives of Biochemistry and Biophysics. 2022;730:109419.

[148] Ko J, Jang YC, Quindry J, Guttmann R, Cosio-Lima L, Powers SK, et al. Exercise-Induced Antisenescence and Autophagy Restoration Mitigate Metabolic Disorder–Induced Cardiac Disruption in Mice. Medicine & Science in Sports & Exercise. 2023;55(3):376-88.

[149] Jiang H, Jia D, Zhang B, Yang W, Dong Z, Sun X, et al. Exercise improves cardiac function and glucose metabolism in mice with experimental myocardial infarction through

inhibiting HDAC4 and upregulating GLUT1 expression. Basic Research in Cardiology. 2020;115(3):28.

[150] Wang L, Gao K, Wang D. Exercise training has restorative potential on myocardial energy metabolism in rats with chronic heart failure. Iranian Journal of Basic Medical Sciences. 2018(Online First).

[151] Kraljevic J, Marinovic J, Pravdic D, Zubin P, Dujic Z, Wisloff U, et al. Aerobic interval training attenuates remodelling and mitochondrial dysfunction in the post-infarction failing rat heart. Cardiovascular Research. 2013;99(1):55-64.

[152] Zhao D, Sun Y, Tan Y, Zhang Z, Hou Z, Gao C, et al. Short‐Duration Swimming Exercise after Myocardial Infarction Attenuates Cardiac Dysfunction and Regulates Mitochondrial Quality Control in Aged Mice. Oxidative Medicine and Cellular Longevity. 2018;2018(1):4079041.

[153] Wu G, Guo Y, Li M, Li C, Tan Y, Li Y, et al. Exercise Enhances Branched-Chain Amino Acid Catabolism and Decreases Cardiac Vulnerability to Myocardial Ischemic Injury. Cells. 2022;11(10):1706.

[154] Boulghobra D, Coste F, Geny B, Reboul C. Exercise training protects the heart against ischemia-reperfusion injury: A central role for mitochondria? Free Radic Biol Med. 2020;152:395-410.

[155] Gu C, Yan J, Zhao L, Wu G, Wang Y-l. Regulation of Mitochondrial Dynamics by Aerobic Exercise in Cardiovascular Diseases. Frontiers in Cardiovascular Medicine. 2022;8:788505.

[156] Zhang F, Lin JJ, Tian HN, Wang J. Effect of exercise on improving myocardial mitochondrial function in decreasing diabetic cardiomyopathy. Experimental Physiology. 2023:EP091309.

[157] Viloria MAD, Li Q, Lu W, Nhu NT, Liu Y, Cui ZY, et al. Effect of exercise training on cardiac mitochondrial respiration, biogenesis, dynamics, and mitophagy in ischemic heart disease. Front Cardiovasc Med. 2022;9:949744.

[158] Lim AY, Chen Y-C, Hsu C-C, Fu T-C, Wang J-S. The Effects of Exercise Training on Mitochondrial Function in Cardiovascular Diseases: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences. 2022;23(20):12559.

[159] Jia D, Hou L, Lv Y, Xi L, Tian Z. Postinfarction exercise training alleviates cardiac dysfunction and adverse remodeling via mitochondrial biogenesis and SIRT1/PGC‐1α/PI3K/Akt signaling. Journal of Cellular Physiology. 2019;234(12):23705-18.

[160] Wang L, Qiao Y, Yu J, Wang Q, Wu X, Cao Q, et al. Endurance exercise preconditioning alleviates ferroptosis induced by doxorubicin-induced cardiotoxicity through mitochondrial superoxide-dependent AMPKα2 activation. Redox Biology. 2024;70:103079.

[161] Montalvo RN, Boeno FP, Dowllah IM, Moritz CEJ, Nguyen BL, Doerr V, et al. Exercise and Doxorubicin Modify Markers of Iron Overload and Cardiolipin Deficiency in Cardiac Mitochondria. International Journal of Molecular Sciences. 2023;24(9):7689.

[162] Jeremic N, Weber GJ, Theilen NT, Tyagi SC. Cardioprotective effects of high‐intensity interval training are mediated through microRNA regulation of mitochondrial and oxidative stress pathways. Journal of Cellular Physiology. 2020;235(6):5229-40.

[163] Vaccari F, Passaro A, D'Amuri A, Sanz JM, Di Vece F, Capatti E, et al. Effects of 3-month high-intensity interval training vs. moderate endurance training and 4-month follow-

up on fat metabolism, cardiorespiratory function and mitochondrial respiration in obese adults. European Journal of Applied Physiology. 2020;120(8):1787-803.

[164] Pasmiño G, Paredes M, Silva H. Effects of High-Intensity Swimming Interval Training on Area, Perimeter, Circularity Index and Phenotype of Cardiac Mitochondrial Ultrastructure in Sprague Dawley Rats. Life. 2024;14(8):984.

[165] Yuan J, Wang M, Pan Y, Liang M, Fu Y, Duan Y, et al. The mitochondrial signaling peptide MOTS-c improves myocardial performance during exercise training in rats. Scientific Reports. 2021;11(1):20077.

[166] Boulghobra D, Dubois M, Alpha-Bazin B, Coste F, Olmos M, Gayrard S, et al. Increased protein S-nitrosylation in mitochondria: a key mechanism of exercise-induced cardioprotection. Basic Research in Cardiology. 2021;116(1):66.

[167] Li S, Xin Q, Fang G, Deng Y, Yang F, Qiu C, et al. Upregulation of mitochondrial telomerase reverse transcriptase mediates the preventive effect of physical exercise on pathological cardiac hypertrophy via improving mitochondrial function and inhibiting oxidative stress. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2024;1870(1):166859.

[168] Chelko SP, Keceli G, Carpi A, Doti N, Agrimi J, Asimaki A, et al. Exercise triggers CAPN1-mediated AIF truncation, inducing myocyte cell death in arrhythmogenic cardiomyopathy. Science Translational Medicine. 2021;13(581):eabf0891.

[169] Quiroga C, Mancilla G, Oyarzun I, Tapia A, Caballero M, Gabrielli LA, et al. Moderate Exercise in Spontaneously Hypertensive Rats Is Unable to Activate the Expression of Genes Linked to Mitochondrial Dynamics and Biogenesis in Cardiomyocytes. Frontiers in Endocrinology. 2020;11:546.

[170] Godoy Coto J, Pereyra EV, Cavalli FA, Valverde CA, Caldiz CI, Maté SM, et al. Exercise-induced cardiac mitochondrial reorganization and enhancement in spontaneously hypertensive rats. Pflügers Archiv - European Journal of Physiology. 2024;476(7):1109-23.

[171] Jin L, Diaz-Canestro C, Wang Y, Tse MA, Xu A. Exerkines and cardiometabolic benefits of exercise: from bench to clinic. EMBO Molecular Medicine. 2024;16(3):432-44.

[172] Zhang Y, Liu D, Long XX, Fang QC, Jia WP, Li HT. The role of FGF21 in the pathogenesis of cardiovascular disease. Chin Med J (Engl). 2021;134(24):2931-43.

[173] Yan B, Mei Z, Tang Y, Song H, Wu H, Jing Q, et al. FGF21-FGFR1 controls mitochondrial homeostasis in cardiomyocytes by modulating the degradation of OPA1. Cell Death Dis. 2023;14(5):311.

[174] Zhao Z, Cui X, Liao Z. Mechanism of fibroblast growth factor 21 in cardiac remodeling. Front Cardiovasc Med. 2023;10:1202730.

[175] Ruan CC, Kong LR, Chen XH, Ma Y, Pan XX, Zhang ZB, et al. A(2A) Receptor Activation Attenuates Hypertensive Cardiac Remodeling via Promoting Brown Adipose Tissue-Derived FGF21. Cell Metab. 2018;28(3):476-89 e5.

[176] Sun JY, Du LJ, Shi XR, Zhang YY, Liu Y, Wang YL, et al. An IL-6/STAT3/MR/FGF21 axis mediates heart-liver cross-talk after myocardial infarction. Sci Adv. 2023;9(14):eade4110.

[177] Jin L, Geng L, Ying L, Shu L, Ye K, Yang R, et al. FGF21–Sirtuin 3 Axis Confers the Protective Effects of Exercise Against Diabetic Cardiomyopathy by Governing Mitochondrial Integrity. Circulation. 2022;146(20):1537-57.

[178] Ianos RD, Iancu M, Pop C, Lucaciu RL, Hangan AC, Rahaian R, et al. Predictive Value of NT-proBNP, FGF21, Galectin-3 and Copeptin in Advanced Heart Failure in

Patients with Preserved and Mildly Reduced Ejection Fraction and Type 2 Diabetes Mellitus. Medicina (Kaunas). 2024;60(11).

[179] Ianos RD, Cozma A, Lucaciu RL, Hangan AC, Negrean V, Mercea DC, et al. Role of Circulating Biomarkers in Diabetic Cardiomyopathy. Biomedicines. 2024;12(9).

[180] Fan L, Gu L, Yao Y, Ma G. High serum fibroblast growth factor 21 levels were related to the prognosis and ventricular remodeling of heart failure patients with mildly reduced and reduced ejection fraction. Perfusion. 2024;39(2):285-93.

[181] Tanajak P, Sa-Nguanmoo P, Wang X, Liang G, Li X, Jiang C, et al. Fibroblast growth factor 21 (FGF21) therapy attenuates left ventricular dysfunction and metabolic disturbance by improving FGF21 sensitivity, cardiac mitochondrial redox homoeostasis and structural changes in pre-diabetic rats. Acta Physiol (Oxf). 2016;217(4):287-99.

[182] Bao J-F, She Q-Y, Hu P-P, Jia N, Li A. Irisin, a fascinating field in our times. Trends in Endocrinology & Metabolism. 2022;33(9):601-13.

[183] Liu S, Cui F, Ning K, Wang Z, Fu P, Wang D, et al. Role of irisin in physiology and pathology. Frontiers in Endocrinology. 2022;13:962968.

[184] Aydin S, Kuloglu T, Aydin S, Eren MN, Celik A, Yilmaz M, et al. Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: Cardiac muscle produces more irisin than skeletal muscle. Peptides. 2014;52:68-73.

[185] Li H, Qin S, Liang Q, Xi Y, Bo W, Cai M, et al. Exercise Training Enhances Myocardial Mitophagy and Improves Cardiac Function via Irisin/FNDC5-PINK1/Parkin Pathway in MI Mice. Biomedicines. 2021;9(6):701.

[186] He W, Tang Y, Li C, Zhang X, Huang S, Tan B, et al. Exercise Enhanced Cardiac Function in Mice With Radiation-Induced Heart Disease via the FNDC5/Irisin-Dependent Mitochondrial Turnover Pathway. Frontiers in Physiology. 2021;12:739485.

[187] Li R, Wang X, Wu S, Wu Y, Chen H, Xin J, et al. Irisin ameliorates angiotensin II‐induced cardiomyocyte apoptosis through autophagy. Journal of Cellular Physiology. 2019;234(10):17578-88.

[188] Li R-L, Wu S-S, Wu Y, Wang X-X, Chen H-Y, Xin J-j, et al. Irisin alleviates pressure overload-induced cardiac hypertrophy by inducing protective autophagy via mTOR-independent activation of the AMPK-ULK1 pathway. Journal of Molecular and Cellular Cardiology. 2018;121:242-55.

[189] Cobb T, Hwang I, Soukar M, Namkoong S, Cho U-S, Safdar M, et al. Iditarod , a Drosophila homolog of the Irisin precursor FNDC5 , is critical for exercise performance and cardiac autophagy. Proceedings of the National Academy of Sciences. 2023;120(39):e2220556120.

[190] Wang B, Zhao C, Wang Y, Tian X, Lin J, Zhu B, et al. Exercise ameliorating myocardial injury in type 2 diabetic rats by inhibiting excessive mitochondrial fission involving increased irisin expression and AMP‐activated protein kinase phosphorylation. Journal of Diabetes. 2024;16(1):e13475.

[191] Berezina TA, Berezin OO, Novikov EV, Lichtenauer M, Berezin AE. Irisin Predicts Poor Clinical Outcomes in Patients with Heart Failure with Preserved Ejection Fraction and Low Levels of N-Terminal Pro-B-Type Natriuretic Peptide. Biomolecules. 2024;14(12).

[192] Hsieh IC, Ho MY, Wen MS, Chen CC, Hsieh MJ, Lin CP, et al. Serum irisin levels are associated with adverse cardiovascular outcomes in patients with acute myocardial infarction. Int J Cardiol. 2018;261:12-7.

[193] Lecker SH, Zavin A, Cao P, Arena R, Allsup K, Daniels KM, et al. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure. Circ Heart Fail. 2012;5(6):812-8.

[194] Jung TW, Hwang HJ, Hong HC, Yoo HJ, Baik SH, Choi KM. BAIBA attenuates insulin resistance and inflammation induced by palmitate or a high fat diet via an AMPK-PPARdelta-dependent pathway in mice. Diabetologia. 2015;58(9):2096-105.

[195] Qin X, Liu P, Jin L, Zhu K, Yang Y, Hou Z, et al. Exerkine beta-aminoisobutyric acid protects against atrial structural remodeling and atrial fibrillation in obesity via activating AMPK signaling and improving insulin sensitivity. Biomed Pharmacother. 2024;171:116137.

[196] Gur FM, Aktas I. The ameliorative effects of thymoquinone and beta-aminoisobutyric acid on streptozotocin-induced diabetic cardiomyopathy. Tissue Cell. 2021;71:101582.

[197] Yu Y, Chen W, Yu M, Liu J, Sun H, Yang P. Exercise-Generated β-Aminoisobutyric Acid (BAIBA) Reduces Cardiomyocyte Metabolic Stress and Apoptosis Caused by Mitochondrial Dysfunction Through the miR-208b/AMPK Pathway. Frontiers in Cardiovascular Medicine. 2022;9:803510.

[198] Roberts LD, Bostrom P, O'Sullivan JF, Schinzel RT, Lewis GD, Dejam A, et al. beta-Aminoisobutyric acid induces browning of white fat and hepatic beta-oxidation and is inversely correlated with cardiometabolic risk factors. Cell Metab. 2014;19(1):96-108.

[199] Liu Y, Monticone M, Tonachini L, Mastrogiacomo M, Marigo V, Cancedda R, et al. URB expression in human bone marrow stromal cells and during mouse development. Biochem Biophys Res Commun. 2004;322(2):497-507.

[200] Okada T, Nishizawa H, Kurata A, Tamba S, Sonoda M, Yasui A, et al. URB is abundantly expressed in adipose tissue and dysregulated in obesity. Biochem Biophys Res Commun. 2008;367(2):370-6.

[201] O'Leary EE, Mazurkiewicz-Munoz AM, Argetsinger LS, Maures TJ, Huynh HT, Carter-Su C. Identification of steroid-sensitive gene-1/Ccdc80 as a JAK2-binding protein. Mol Endocrinol. 2013;27(4):619-34.

[202] Yin A, Yuan R, Xiao Q, Zhang W, Xu K, Yang X, et al. Exercise-derived peptide protects against pathological cardiac remodeling. eBioMedicine. 2022;82:104164.

[203] Slimani M, Ramirez-Campillo R, Paravlic A, Hayes LD, Bragazzi NL, Sellami M. The Effects of Physical Training on Quality of Life, Aerobic Capacity, and Cardiac Function in Older Patients With Heart Failure: A Meta-Analysis. Front Physiol. 2018;9:1564.

[204] Li T, Wang L, Wu L, Xie Y, Chang M, Wang D, et al. Integrated Metabolomics and Network Pharmacology Investigation of Cardioprotective Effects of Myricetin after 1-Week High-Intensity Exercise. Nutrients. 2023;15(6):1336.

[205] Shi M, Dong Z, Zhao K, He X, Sun Y, Ren J, et al. Novel insights into exhaustive exercise-induced myocardial injury: Focusing on mitochondrial quality control. Frontiers in Cardiovascular Medicine. 2022;9:1015639.

[206] Costa ADS, Ghouri I, Johnston A, McGlynn K, McNair A, Bowman P, et al. Electrically stimulated in vitro heart cell mimic of acute exercise reveals novel immediate cellular responses to exercise: Reduced contractility and metabolism, but maintained calcium

cycling and increased myofilament calcium sensitivity. Cell Biochemistry and Function. 2023;41(8):1147-61.

[207] Tóth ME, Sárközy M, Szűcs G, Dukay B, Hajdu P, Zvara Á, et al. Exercise training worsens cardiac performance in males but does not change ejection fraction and improves hypertrophy in females in a mouse model of metabolic syndrome. Biology of Sex Differences. 2022;13(1):5.

[208] Del Buono MG, Arena R, Borlaug BA, Carbone S, Canada JM, Kirkman DL, et al. Exercise Intolerance in Patients With Heart Failure. Journal of the American College of Cardiology. 2019;73(17):2209-25.

[209] Nijholt KT, Sánchez‐Aguilera PI, Voorrips SN, De Boer RA, Westenbrink BD. Exercise: a molecular tool to boost muscle growth and mitochondrial performance in heart failure? European Journal of Heart Failure. 2022;24(2):287-98.

[210] Berg-Hansen K, Christensen KH, Gopalasingam N, Nielsen R, Eiskjær H, Møller N, et al. Beneficial Effects of Ketone Ester in Patients With Cardiogenic Shock. JACC: Heart Failure. 2023;11(10):1337-47.

[211] Wodschow HZ, Davidovski FS, Christensen J, Lassen MCH, Skaarup KG, Nygaard H, et al. Oral ketone esters acutely improve myocardial contractility in post-hospitalized COVID-19 patients: A randomized placebo-controlled double-blind crossover study. Frontiers in Nutrition. 2023;10:1131192.

[212] Takahara S, Soni S, Phaterpekar K, Kim TT, Maayah ZH, Levasseur JL, et al. Chronic exogenous ketone supplementation blunts the decline of cardiac function in the failing heart. ESC Heart Failure. 2021;8(6):5606-12.

[213] Thai PN, Miller CV, King MT, Schaefer S, Veech RL, Chiamvimonvat N, et al. Ketone Ester D‐β‐Hydroxybutyrate‐(R)‐1,3 Butanediol Prevents Decline in Cardiac Function in Type 2 Diabetic Mice. Journal of the American Heart Association. 2021;10(19):e020729.

[214] Yurista SR, Eder RA, Welsh A, Jiang W, Chen S, Foster AN, et al. Ketone ester supplementation suppresses cardiac inflammation and improves cardiac energetics in a swine model of acute myocardial infarction. Metabolism. 2023;145:155608.

[215] Yurista SR, Matsuura TR, Silljé HHW, Nijholt KT, McDaid KS, Shewale SV, et al. Ketone Ester Treatment Improves Cardiac Function and Reduces Pathologic Remodeling in Preclinical Models of Heart Failure. Circulation: Heart Failure. 2021;14(1):e007684.

[216] Berg-Hansen K, Gopalasingam N, Christensen KH, Ladefoged B, Andersen MJ, Poulsen SH, et al. Cardiovascular Effects of Oral Ketone Ester Treatment in Patients With Heart Failure With Reduced Ejection Fraction: A Randomized, Controlled, Double-Blind Trial. Circulation. 2024;149(19):1474-89.

[217] Williams AS, Crown SB, Lyons SP, Koves TR, Wilson RJ, Johnson JM, et al. Ketone flux through BDH1 supports metabolic remodeling of skeletal and cardiac muscles in response to intermittent time-restricted feeding. Cell Metabolism. 2024;36(2):422-37.e8.

[218] Oka S-i, Tang F, Chin A, Ralda G, Xu X, Hu C, et al. β-Hydroxybutyrate, a Ketone Body, Potentiates the Antioxidant Defense via Thioredoxin 1 Upregulation in Cardiomyocytes. Antioxidants. 2021;10(7):1153.

[219] Weis EM, Puchalska P, Nelson AB, Taylor J, Moll I, Hasan SS, et al. Ketone body oxidation increases cardiac endothelial cell proliferation. EMBO Molecular Medicine. 2022;14(4):e14753.

[220] Byrne NJ, Soni S, Takahara S, Ferdaoussi M, Al Batran R, Darwesh AM, et al. Chronically Elevating Circulating Ketones Can Reduce Cardiac Inflammation and Blunt the Development of Heart Failure. Circulation: Heart Failure. 2020;13(6):e006573.

[221] Gopalasingam N, Moeslund N, Christensen KH, Berg‐Hansen K, Seefeldt J, Homilius C, et al. Enantiomer‐Specific Cardiovascular Effects of the Ketone Body 3‐Hydroxybutyrate. Journal of the American Heart Association. 2024;13(8):e033628.

[222] Liao S, Tang Y, Yue X, Gao R, Yao W, Zhou Y, et al. β-Hydroxybutyrate Mitigated Heart Failure with Preserved Ejection Fraction by Increasing Treg Cells via Nox2/GSK-3β. Journal of Inflammation Research. 2021;Volume 14:4697-706.

[223] Oneglia AP, Young BE, Cipher DJ, Zaha V, Nelson MD. Acute effects of β-hydroxybutyrate on left ventricular function in young, healthy adults. Journal of Applied Physiology. 2023:japplphysiol.00630.2023.

[224] Qi H, Gu L, Xu D, Liu K, Zhou M, Wang Y, et al. β-Hydroxybutyrate inhibits cardiac microvascular collagen 4 accumulation by attenuating oxidative stress in streptozotocin-induced diabetic rats and high glucose treated cells. European Journal of Pharmacology. 2021;899:174012.

[225] Chu Y, Hua Y, He L, He J, Chen Y, Yang J, et al. β-hydroxybutyrate administered at reperfusion reduces infarct size and preserves cardiac function by improving mitochondrial function through autophagy in male mice. Journal of Molecular and Cellular Cardiology. 2024;186:31-44.

[226] Liu Y, Wei X, Wu M, Xu J, Xu B, Kang L. Cardioprotective Roles of β-Hydroxybutyrate Against Doxorubicin Induced Cardiotoxicity. Frontiers in Pharmacology. 2021;11:603596.

[227] Seefeldt JM, Libai Y, Berg K, Jespersen NR, Lassen TR, Dalsgaard FF, et al. Effects of ketone body 3-hydroxybutyrate on cardiac and mitochondrial function during donation after circulatory death heart transplantation. Scientific Reports. 2024;14(1):757.

[228] Ji L, He Q, Liu Y, Deng Y, Xie M, Luo K, et al. Ketone Body β-Hydroxybutyrate Prevents Myocardial Oxidative Stress in Septic Cardiomyopathy. Oxidative Medicine and Cellular Longevity. 2022;2022:1-14.

[229] Homilius C, Seefeldt JM, Axelsen JS, Pedersen TM, Sørensen TM, Nielsen R, et al. Ketone body 3-hydroxybutyrate elevates cardiac output through peripheral vasorelaxation and enhanced cardiac contractility. Basic Research in Cardiology. 2023;118(1):37.

[230] Kim YJ, Kim HJ, Lee SG, Kim DH, In Jang S, Go HS, et al. Aerobic exercise for eight weeks provides protective effects towards liver and cardiometabolic health and adipose tissue remodeling under metabolic stress for one week: A study in mice. Metabolism. 2022;130:155178.

[231] O'Neill CC, Locke EJ, Sipf DA, Thompson JH, Drebushenko EK, Berger NS, et al. The Effects of Exercise Training on Glucose Homeostasis and Muscle Metabolism in Type 1 Diabetic Female Mice. Metabolites. 2022;12(10):948.

[232] Pejon TMM, Scariot PPM, Selistre-de-Araujo HS, Gobatto CA, Cornachione AS, Beck WR. Effects of Moderate–Intensity Physical Training on Skeletal Muscle Substrate Transporters and Metabolic Parameters of Ovariectomized Rats. Metabolites. 2022;12(5):402.

[233] Ruberti OM, Sousa AS, Viana LR, Pereira Gomes MF, Medeiros A, Gomes Marcondes MCC, et al. Aerobic training prevents cardiometabolic changes triggered by myocardial infarction in ovariectomized rats. Journal of Cellular Physiology. 2021;236(2):1105-15.

[234] Morra EA, Rodrigues PL, Jesus ICGD, Do Val Lima PR, Ávila RA, Zanardo TÉC, et al. Endurance training restores spatially distinct cardiac mitochondrial function and myocardial contractility in ovariectomized rats. Free Radical Biology and Medicine. 2019;130:174-88.

[235] Khoshkhouy F, Farshbaf A, Mahmoudabady M, Gholamnezhad Z. Effects of moderate exercise on lipopolysaccharide-induced inflammatory responses in rat's cardiac tissue. Cytokine. 2021;138:155409.

[236] Kindlovits R, Bertoldi JMCRJ, Rocha HNM, Bento‐Bernardes T, Gomes JLP, De Oliveira EM, et al. Molecular mechanisms underlying fructose‐induced cardiovascular disease: exercise, metabolic pathways and microRNAs. Experimental Physiology. 2021;106(5):1224-34.

[237] Rami M, Rahdar S, Ahmadi Hekmatikar A, Awang Daud DM. Highlighting the novel effects of high-intensity interval training on some histopathological and molecular indices in the heart of type 2 diabetic rats. Frontiers in Endocrinology. 2023;14:1175585.

[238] Bode D, Rolim NPL, Guthof T, Hegemann N, Wakula P, Primessnig U, et al. Effects of different exercise modalities on cardiac dysfunction in heart failure with preserved ejection fraction. ESC Heart Failure. 2021;8(3):1806-18.

[239] Kar S, Shahshahan HR, Hackfort BT, Yadav SK, Yadav R, Kambis TN, et al. Exercise Training Promotes Cardiac Hydrogen Sulfide Biosynthesis and Mitigates Pyroptosis to Prevent High-Fat Diet-Induced Diabetic Cardiomyopathy. Antioxidants. 2019;8(12):638.

[240] Fathi R, Nasiri K, Akbari A, Ahmadi-KaniGolzar F, Farajtabar Z. Exercise protects against ethanol-induced damage in rat heart and liver through the inhibition of apoptosis and activation of Nrf2/Keap-1/HO-1 pathway. Life Sciences. 2020;256:117958.

[241] Sun S, Zhang H, Kong Z, Shi Q, Tong TK, Nie J. Twelve weeks of low volume sprint interval training improves cardio-metabolic health outcomes in overweight females. Journal of Sports Sciences. 2019;37(11):1257-64.

[242] Praksch D, Sandor B, Kovacs D, Petrovics P, Kovacs K, Toth K, et al. Impact of home- and center- based physical training program on cardio-metabolic health and IGF-1 level in elderly women. European Review of Aging and Physical Activity. 2019;16(1):13.

[243] Mora-Rodriguez R, Ortega JF, Morales-Palomo F, Ramirez-Jimenez M. Weight loss but not gains in cardiorespiratory fitness after exercise-training predicts improved health risk factors in metabolic syndrome. Nutrition, Metabolism and Cardiovascular Diseases. 2018;28(12):1267-74.

[244] Gripp F, Nava RC, Cassilhas RC, Esteves EA, Magalhães COD, Dias-Peixoto MF, et al. HIIT is superior than MICT on cardiometabolic health during training and detraining. European Journal of Applied Physiology. 2021;121(1):159-72.

[245] Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. Circulation. 2007;115(24):3086-94.

[246] Patten RK, McIlvenna LC, Levinger I, Garnham AP, Shorakae S, Parker AG, et al. High-intensity training elicits greater improvements in cardio-metabolic and reproductive outcomes than moderate-intensity training in women with polycystic ovary syndrome: a randomized clinical trial. Human Reproduction. 2022;37(5):1018-29.

[247] Guzel Y, Atakan MM, Areta JL, Turnagol HH, Kosar SN. Ten weeks of low-volume walking training improve cardiometabolic health and body composition in sedentary postmenopausal women with obesity without affecting markers of bone metabolism. Research in Sports Medicine. 2024;32(2):331-43.

[248] Yu P, Zhu Z, He J, Gao B, Chen Q, Wu Y, et al. Effects of high-intensity interval training, moderate-intensity continuous training, and guideline-based physical activity on cardiovascular metabolic markers, cognitive and motor function in elderly sedentary patients with type 2 diabetes (HIIT-DM): a protocol for a randomized controlled trial. Frontiers in Aging Neuroscience. 2023;15:1211990.

[249] Dun Y, Thomas RJ, Smith JR, Medina-Inojosa JR, Squires RW, Bonikowske AR, et al. High-intensity interval training improves metabolic syndrome and body composition in outpatient cardiac rehabilitation patients with myocardial infarction. Cardiovascular Diabetology. 2019;18(1):104.

[250] Lechner K, Kia S, Von Korn P, Dinges SM, Mueller S, Tjønna A-E, et al. Cardiometabolic and immune response to exercise training in patients with metabolic syndrome: retrospective analysis of two randomized clinical trials. Frontiers in Cardiovascular Medicine. 2024;11:1329633.

[251] Sakurai S, Murata M, Yanai S, Nitta S, Yamashita Y, Shitara T, et al. Three Weeks of Inpatient Cardiac Rehabilitation Improves Metabolic Exercise Data Combined With Cardiac and Kidney Indexes Scores for Heart Failure With Reduced Ejection Fraction. Circulation Reports. 2023;5(6):231-7.

TABLES AND FIGURES WITH LEGENDS

Table 1. Evidence supporting the cardiovascular advantages of supplementing ketones

Form	Disease	Object	Key discoveries	Reference

KE (0.5 g/kg)	CS	Human	CO↑; Tissue oxygenation↑;Glycemic ↓	[210]
KE (395 mg/kg)	COVID-19	Human	GLS↑	[211]
KE (0.38 g/mL)	TAC	Mice	Cardiomyocyte hypertrophy↓;Elevated cardiac periostin↓;CO↑;Fibrosis ↓	[212]
KE (20%)	DCM	Mice	SCOT↑;BDH1↑;ACAT 1↑;ROS↓; Complex-II↑;Complex-IV↑Complex-V↑	[213]
KE (550 mg/Kg,2 occ/d)	AMI	Pig	Inflammation↓;Apoptosis↓;Oxidative stress↓	[214]
KE (10%/15%)	TAC/MI post-MI HF	Mice Rat	LVEF↓;Fibrosis↓;Cardiomyocyte hypertrophy↓;SCOT↑	[215]
KE (25 g/occ,4 occ/d,14 d)	HFrEF	Human	CO↑;LVEF↑;FP↓;NT-proBNP↓;Cardiac volumes↓	[216]
TRF	BDH1$^{-/-}$	Mice	Ventricular remodeling↓;Mitochondrial bioenergetics↑	[217]

Ketogenic diet(10%protein,90 %fat,5d)	Trx1 KD	PCMs Mice	Trx1↑;Oxidative stress↓;Ventricular remodeling↓	[218]
Ketogenic diet (10.4 kcal protein,0.1 kcal carbohydrates,89.5 kcal fat)	TAC	Mice MCEC	Angiogenesis↑	[219]
$SCOT^{-/-}$ in skeletal muscle	TAC	Mice	NLPR3↓;Inflammation↓	[220]
D -βOHB/L -βOHB(0.36 mg/kg)	Normal	Pig	Coronary artery dilation↑;Afterload↓;CO↑	[221]
βOHB(10 mmol/kg,1 occ/w,15 w)	HFpEF	Mice	NOX2/GSK-3β↓;Treg cell↑;Inflammation↓;Ventricular remodeling↓	[222]
βOHB(483 mg/Kg,4 occ/h)	Normal	Human	CO↑	[223]
βOHB(160,200,240 mg/Kg/d;10 w)	Diabetes	Rat HCMECs	COL4↓;Cu/Zn-SOD↑;NT↓;Microvascular fibrosis↓	[224]
βOHB(10 mmol/kg)	I/R	Mice	mTOR pathway(-);Mitophagy↑;Infarct size↓; Oxidative stress↓	[225]
βOHB(10 mmol/Kg/d,5 occ/d,5 d)	DOX cardiotoxicity	C57BL/6 H9C2	Fibrosis↓;apoptosis↓;Oxidative stress↓;Mitochondrial membrane integrity↑	[226]

βOHB(360 mg/kg/h)	Heart transplantation	Pig	SV↑;Arterial elastance↓;CO↑;dP / dt↑	[227]
D-βOHB(3 mg/g,1 occ/d)	Septic cardiomyopathy	Mice H9C2 cell	FoxO3a/MT2↑;Mitochondrial dysfunction↓;ROS↓	[228]
Cardiac perfusion βOHB(3/10 mM)	Normal	Rat	CO↑;LVEF↑;SV↑;dP / dt_{max}↑;Vascular resistance↓	[229]

CS: cardiogenic shock; CO: cardiac output; KE: ketone ester; TRF: time-restricted feeding; AMI: acute myocardial infarction; I/R: ischemia/reperfusion; CHFrEF: chronic heart failure with reduced ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; SV: stroke volume; HR: heart rate; LVEF: left ventricular ejection fraction; FP: filling pressure; GLS: global longitudinal strain; TRF: time-restricted feeding; PCMs: primary cardiomyocytes; TAC: transverse aortic constriction; DCM: diabetic cardiomyopathy; CS: citrate synthase; EMPA: empagliflozin; DAPA: dapagliflozin; SOTA: sotagliflozin; LVDF: left ventricular diastolic function; LVV: left ventricular volume; LVM: left ventricular mass; LVSF: left ventricular systolic function; DBP: diastolic blood pressure; SBP: systolic blood pressure

Table 2. Evidence for the cardiovascular benefits of exercise

Form of exercise	Rate and strength	Disease	Key discoveries	Reference

Voluntary wheel running(8 w)	-	HFD	Bodyweight↓;Insulin resistance↓;Mitochondrial dysfunction↓;White fat browning↑	[230]
Treadmill exercise(5 d/w,4 w)	10-15 m/min,60 min/d	T1D	Glucose transport↓;Ketone body metabolism↓;FA metabolism↑;Insulin resistance↑	[231]
Swimming exercise(5 d/w,12w)	80% of the critical load intensity,30min/d	OVX	CD36↑;GLUT4↑;TG↓	[232]
Treadmill exercise(5 d/w,4 w)	60-75%Vmax,60 min/d	OVX+MI	Decreased pro-inflammatory cytokines↓;Inflammation↓;IL-10↑;Dimethylamine↓	[233]
Treadmill exercise(5 d/w,12w)	50-60%V_{max},60min/d	OVX	Nox4↓;SERCA2↑;Mitochondrial dysfunction↓;Myocardial contractility↑	[234]
Treadmill exercise(5 d/w,9 w)	30 min/d,15 m/min	LPS model	NO↓;TNF-α↓;IL-1β↓;CRP↓;CAT↑;Apoptosis↓	[235]
Treadmill exercise(4 d/w,8 w)	50-75%Vmax,60 min/d	HFrD model	p-p70S6K↑;p-ERK↑;IRβ-PI3K-AKT pathway activation	[236]

Treadmill exercise(5 d/w,8w)	HIIT:(6-12)×2min,2-6 m/min	T2DCM	B-catenin↓;c-Myc↓;GSK3B↑;Apoptosis↓;Fibrosis↓	[237]
Treadmill exercise(3-5 d/w,8 w)	MICT:60%V_{O2max},60min/d;40-50%V_{O2max}10min HIIT:90%V_{O2max},4×4min; 60%V_{O2max} 3min	Advanced HFpEF	Ca^{2+} leak↓;SV↑	[238]
Treadmill exercise(5 d/w,20 w)	30-50 min/d,10-15 m/min	HFpEF	H_2S↑;Apoptosis↓;Insulin resistance↓;Diastolic function↑;BGC↓	[239]
Treadmill exercise(3 d/w,8 w)	65%V_{max},60 min/d	AICM	Nrf2/Keap1/HO1 pathway activation;Apoptosis↓	[240]
Cycling exercise(12 w,3 d/w)	MICT and HIIT:4w-400kJ+8w-300kJ MICT:60%V_{O2max},61min HIIT:90%V_{O2max},9×4min/occ SIT:100%V_{O2max},80×6s/occ	Overweight women	$\dot{V}_{O2max}$↑;Body weight↓;Insulin sensitivity↑	[241]
Exercise(12 w,3 d/w)	50-70%V_{O2max},35-40 min	Postmenopausal women	LDL↓;TG↓;HgbA1c↓;IGF-1↑	[242]
Exercise(16 w,3 d/w)	43 min	MetS	Body weight↓;Waist circumference↓;MAP↓	[243]

Running exercise(8 w,3 d/w)	MICT:60-75%V_{O2max},3500 m-5000 m HIIT:85-100%V_{O2max},7×200-10×200 m	Obesity	BMI↓;Visceral fat↓;SBP↓;TC↓;BGC↓;TG↓s	[244]
Running exercise(3 d/w,12 w)	AIT:warm-up 50%-60%V_{O2max}10min;exercise:90%-95%V_{O2max} 4min,4occ;50%-70%V_{O2max} 3min,4occ;38min/occ MIT:70%-75%V_{O2max},47min/occ	post-MI heart failure	BNP↓;LVEDV↓;LVESV↓;BNP↓;Vasodilation	[245]
Cycling exercise(3 d/w,12 w)	MICT:60-75%HRmax,45min/occ; HIIT:90-100%HRmax,ex 1min,12occ,2occ/w;90-95%HRmax,4min,8occ,1occ/w	PCOS	V_{O2max}↑;Insulin sensitivity↑;Aerobic capacity↑	[246]
Running exercise(3 d/w,10 w)	70% HRmax，40min/occ；	PMW	Body weight↓;Fat mass↓;Resting glucose↓;HbA1c↓;V_{O2max}↑	[247]
Running exercise(3 d/w,12 w)	MICT:30% HRmax,5min/occ;65-75% HRmax,35min/occ	T2D	HbA1c↓;BDNF↑;Blood lipids↓;Blood glucose↓	[248]

	HIIT:50-60%HRmax,10min;85-95% HRmax,exercise1min,10 occ			
Running exercise /Cycling exercise(3 d/w,12 w)	RPE12-14,≥20 min,1 w; HIIT: RPE15-17,2-4 min/occ,5-8 occ; MICT:RPE12-14,20-45 min/occ	MI+ MetS	Waist circumference↓;Blood glucose↓;TG↓;DBP↓	[249]
Running exercise(12-16 w,2 d/w)	MICT:35-50% HRmax,10min/occ; Low-HIIT:35-50%HRmax,19min/occ;80-90%HRmax,4min/occ; High-HIIT;35-50%HRmax,40min/occ;80-90% HRmax,4min/occ，4occ;	MetS	Leukocyte counts↓;TG↓;V_{O2max}↑	[250]
Cycling exercise (3 w,5 d/w)	30 min,2 occ/d	HFrEF	MECKI↑;CVE incidence↓	[251]

MI: myocardial infarction; OVX: ovariectomy; LPS: lipopolysaccharide; HF: heart failure; PDC: pyruvate dehydrogenase complex; GLUT: glucose transporter; PGC-1: peroxisome proliferator-activated receptor γ coactiva-tor-1; CRP: C-reactive protein; BNP: brain natriuretic; PAH: pulmonary arterial hypertension; HFD: high-fat diet; T1D: type 1 diabetes; HFrD: high-fructose diet; T2DCM: type 2 diabetic cardiomyopathy; SV: stroke volume; BGC: blood glucose concentration; AICM:

alcohol-induced cardiomyopathy; MetS: metabolic Syndrome; MAP: mean arterial pressure; TC: total cholesterol; SBP: systolic blood pressure; CVE incidence: cardiovascular events incidence; PCOS: polycystic ovary syndrome; PMW: postmenopausal women; HRmax: peak heart rate; DBP: diastolic blood pressure; TG: triglycerides

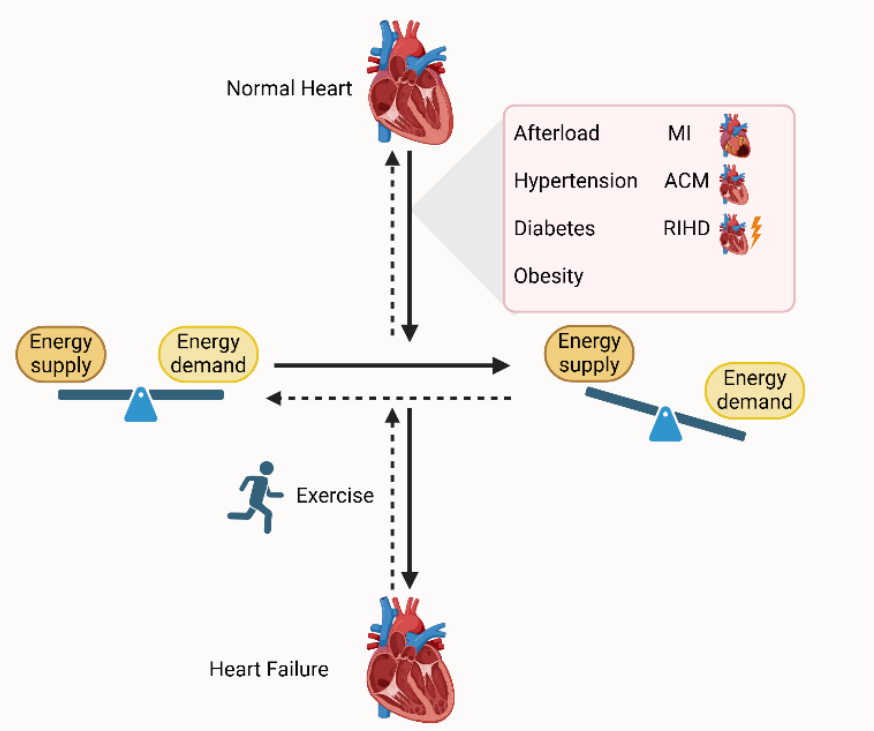

Figure 1. Exercise regulates myocardial metabolic imbalance to improve cardiac function.

Pathological factors such as hypertension, increased afterload, diabetes, obesity, MI, ACM, and RIHD can lead to an imbalance in myocardial energy metabolism supply and demand, ultimately resulting in heart failure. However, exercise can help optimize this condition by improving cardiac function. MI: myocardial infarction; ACM: arrhythmogenic cardiomyopathy; RIHD: radiation-induced heart disease.

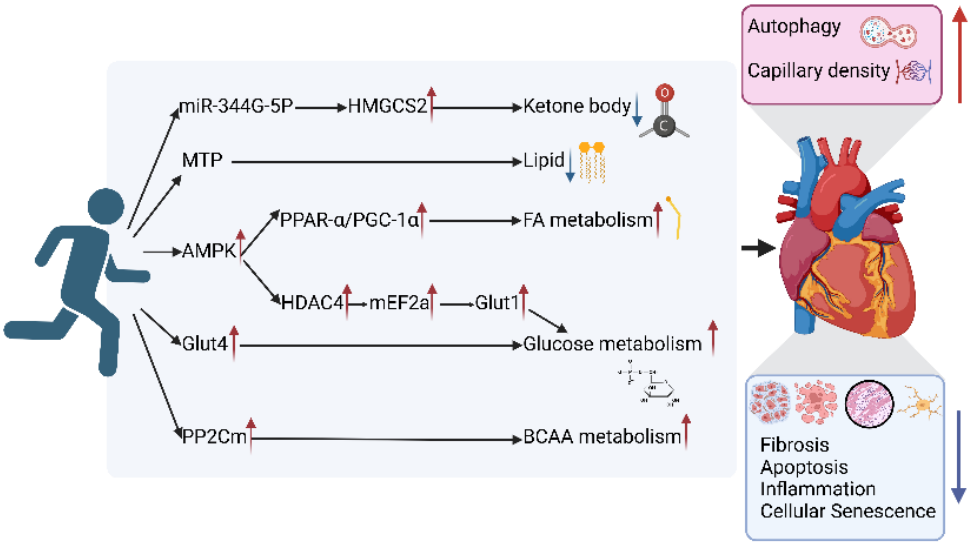

Figure 2. Mechanisms of how exercise regulates myocardial metabolism and enhances heart function.

Exercise can activate various pathways in the body, thereby improving fatty acid metabolism, glucose metabolism, and BCAA metabolism, while also reducing ketone bodies and lipids. As a result, this ultimately leads to increased autophagy of cardiomyocytes and higher capillary density in the myocardium, which is accompanied by decreased aging, apoptosis, fibrosis, and inflammation in cardiomyocytes, collectively enhancing cardiac function. HMGCS2: 3-hydroxy-3-methylglutaryl-CoA synthase 2; MTP: microsomal triglyceride transfer protein; PPAR-α: peroxisome proliferator-activated receptor-alpha; HDAC4: histone deacetylase 4; MEF2A: Myocyte enhancer factor 2A; GLUT1: Glucose transporter type 1; GLUT4: Glucose transporter type 4; PP2Cm: protein phosphatase 2Cm; AMPK: AMP-activated protein kinase.

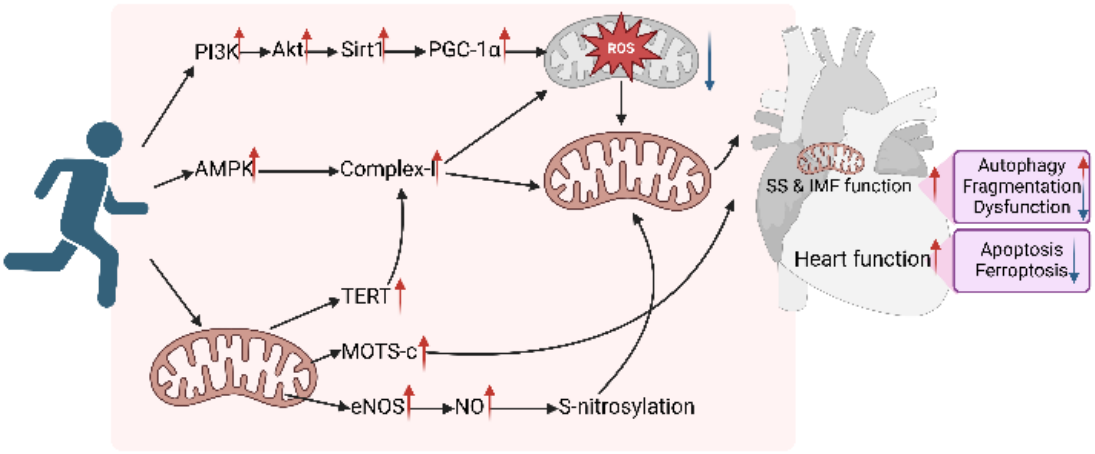

Figure 3. Mechanisms through which exercise modulates mitochondria to enhance heart function.

Exercise can activate the SIRT1/PGC-1α/PI3K/Akt pathway and the AMPK/complex-I pathway in the body, as well as stimulate mitochondria to enhance the activity of MOTS-c, eNOS, and TERT. Consequently, these actions collectively promote overall mitochondrial function, increase mitochondrial autophagy, alleviate mitochondrial fragmentation and dysfunction, reduce cardiomyocyte apoptosis and ferroptosis, and ultimately improve cardiac function. PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; Sirt1: Sirtuin 1; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-α; Complex I: NADH dehydrogenase; TERT: Telomerase reverse transcriptase; MOTS-c: mitochondrial-derived peptide; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; SS: Subsarcolemmal mitochondrial populations; IMF: Intermyofibrillar mitochondrial populations.

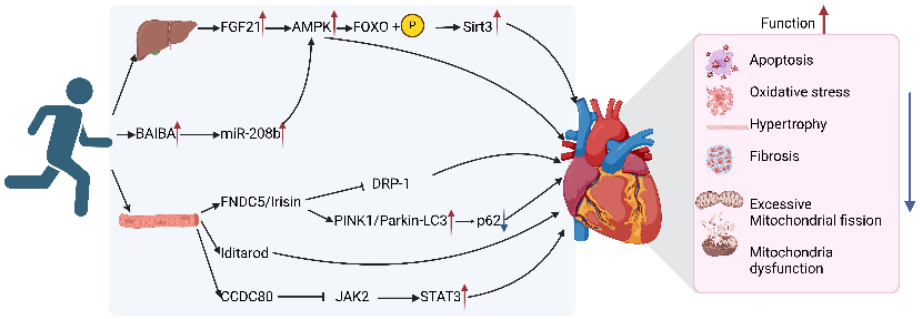

Figure 4. Mechanisms of how exerkines enhance heart function.

Exercise can stimulate the body to secrete various exerkines, such as FGF21, BAIBA, Irisin, Iditarod, and CCDC80, which in turn collectively reduce adverse factors such as cardiomyocyte apoptosis, oxidative stress, hypertrophy, fibrosis, excessive mitochondrial fission, and dysfunction, thereby enhancing cardiac function. FGF21: fibroblast growth factor 21; AMPK: AMP-activated protein kinase; FOXO3: forkhead Box O3; Sirt3: sirtuin 3; BAIBA: β-Aminoisobutyric Acid; miR-208b: microRNA-208b; FNDC5: fibronectin type III domain-containing protein 5; DRP1: dynamin-related protein 1; PINK1: PTEN-induced kinase 1; CCDC80: coiled-coil domain containing 80; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3.