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Exercising heart failure patients: cardiac protection through preservation of mitochondrial function and substrate utilization?

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Current heart failure (HF) therapy remains unable to substantially improve exercise capacity. Studies have shown that exercise training has beneficial effects on the heart in both health and disease. How mitochondria respond to exercise in this setting has, however, received less attention in literature. These beneficial effects may include protective changes in mitochondrial function and adaptations in substrate utilization. This review describes exercise-induced changes in cardiac metabolism, including changes in mitochondrial function and substrate utilization and their effects on cardiac function. We conclude that exercising HF patients can improve mitochondrial function and optimize substrate utilization, eventually improving or restoring cardiac function. This suggests that exercise itself should be incorporated in the HF treatment plan, to improve cardiac function and in term exercise capacity. Extending knowledge on mechanisms by which exercise exerts protective effects could potentially lead to development of therapies directed at improving mitochondrial function and substrate utilization in HF.

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Introduction

Heart failure (HF) is a disabling syndrome in which cardiac dysfunction leads to insufficient perfusion of peripheral tissue, resulting in severe symptoms and a poor prognosis. The inability of cardiac muscle to supply the bodily tissues with oxygen (O_2) results in several maladaptive changes in cardiovascular and peripheral metabolic systems [1]. Exercise intolerance is often the first noticeable clinical manifestation of HF which arguably has the most extensive impact on the quality of life [1]. Despite an array of drugs and device-based therapies, clinicians have not been able to sufficiently improve exercise capacity in HF [2]. In current HF guidelines, exercise training is recommended for all HF patients, to improve exercise tolerance, quality of life and reduce HF rehospitalization [1]. Yet, incorporation of this type of treatment remains challenging in the clinic, and the underlying mechanisms of these beneficial effects and the role of exercise-induced cardio-protection are poorly understood [3].

In healthy hearts, exercise training has been shown to induce several physiological changes to the myocardium, including an increase in cardiac muscle mass, known as physiological cardiac hypertrophy. This adaptation is paralleled by adaptive changes to mitochondrial dynamics, which occur in order to meet the increasing cardiac mass and energy demand [4,5]. The exercise-induced mitochondrial and metabolic alterations that improve exercise performance in HF patients, however, remain incompletely understood. In this review, we therefore focus on the exercise-induced changes in cardiac metabolism and mitochondrial oxidative respiration from an experimental as well as a clinical perspective and reveal how this knowledge can potentially serve to improve cardiac function and exercise capacity in HF.

Exercise, cardiac hypertrophy, and mitochondrial function in a physiological setting

The aim of human exercise training is to expose the body to sufficient physical stimuli to induce physiological changes that subsequently improve physical performance. Cardiac mitochondrial alterations to aerobic exercise often occur in combination with an increase in cardiac muscle mass, known as physiological cardiac hypertrophy [4,5]. These adaptations are extensive and include: enhanced mitochondrial quality control through biogenesis, mitophagy, increased mitochondrial fission and/or fusion, metabolic alterations in substrate utilization, and mitochondrial

Table 1

Exercise-induced mitochondrial adaptations from preclinical and clinical studies in health and disease.

	Preclinical studies		Clinical studies	
	Author	Main findings	Author	Main findings
Health	No et al.	Mitochondrial respiratory capacity ↑	Marsh et al. Nakahara et al.	Cardiac hypertrophy ↑
	Han et al.	Mitochondrial respiratory efficiency ↑	Stewart et al.	No changes in cardiac volume
	O'Neill et al.	Cardiac hypertrophy ↑ Mitochondrial respiration ↑ ATP synthesis ↑	Lundby et al.	Total mitochondrial volume ↑
			Tarnopolsky et al.	Mitochondrial enzyme capacity ↑
			Konopka et al.	Mitochondrial biogenesis ↑ Mitochondrial dynamics ↑
			Pesta et al.	In-vivo phosphocreatine recovery ↑
			Fulghum et al.	Cardiac fuel flexibility ↑
HF				
	Emter et al.	Mitochondrial calcium-induced swelling ↓	Slimani et al. Chen et al. Haykowsky et al. Santos et al.	Cardiac systolic function ↑
	Ko et al.	Mitochondrial respiratory control rate ↑ Mitochondrial biogenesis ↑	Pearson et al.	Cardiac diastolic function ↑
	Jiang et al.	Mitochondrial respiration ↑ ATP production ↑ Cardiac fuel flexibility ↑	Fukuta et al.	No changes in cardiac systolic/diastolic function
	Burelle et al.	Cardiac fuel flexibility ↑	Hambrecht et al.	Mitochondrial enzyme activity ↑ Mitochondrial surface density ↑
			Melenovsky et al.	Cardiac fuel flexibility ↑

oxidative respiratory capacity [4,5]. The exercise-induced changes in mitochondrial quality control have been described extensively before [5], yet the mechanisms of exercise-induced changes in mitochondrial function and cardiac substrate utilization are less well described. Therefore, the scope of this review will focus on mitochondrial oxidative respiration and metabolic substrate use in relation to exercise-induced physiological cardiac muscle growth and enhanced cardiac function in the setting of HF.

To supply cardiac tissue with sufficient energy to meet the demand of the continuously beating heart, the mitochondria produce tremendous amounts of energy in the form of adenosine triphosphate (ATP) from circulating fuels [6,7]. In the unstressed physiological setting, over 90% of cardiac energy production is derived through aerobic respiration [7]. Mitochondria are dependent on metabolism of various substrates, and it is generally accepted that the heart consumes approximately 20–30% of glucose (Gluc) and 40–70% of fatty acids (FAs) in this setting [7]. The transport of these substrates into the mitochondria is regulated through several transporter systems, including the glucose transporter type 4 (GLUT4) for Gluc transport into the cardiomyocyte and carnitine palmitoyltransferase 1 and 2 for transport of acetyl coenzyme A (Acyl-CoA) into the mitochondria [6,8]. During exercise, these metabolic processes including the regulation of specific transporter systems are enhanced to increase ATP production and we will elaborate on these adaptive changes to exercise in the following sections.

Cardiac mitochondrial function is maintained or improved with exercise training: evidence from animal studies

In response to chronic aerobic exercise there is a sustained increase in the demand for ATP production within cardiac as well as skeletal muscle. To meet this increased demand for ATP, beneficial cardiac growth occurs, known as physiological cardiac hypertrophy. In recent years it has become clear that mitochondrial adaptations to physiological cardiac growth are a critical yet elusive component of physiological cardiac growth [4,5]. In a study performed by No et al. the effects of 8 weeks treadmill exercise training were assessed in young (4 months) and old (20 months) rats. Interestingly, no changes were observed in the young-exercised group, and mitochondrial function was preserved. However, in the aged-exercised group, mitochondrial respiratory capacity was significantly improved [9]. This suggests that exercise causes improvements in mitochondrial oxidative capacity in ageing mice which, without exercise, would have decreased [9]. Another study involving eight weeks of treadmill exercise in mice, observed a trend towards improvements in mitochondrial respiratory capacity, expressed as state three respiration, a measure for O_2 consumption after stimulation with adenosine diphosphate. Additionally, a statistically significant increase in state four respiration and

respiratory coupling index after exercise were observed, both measures for mitochondrial respiratory efficiency [10]. A study by O'Neill et al. observed a significant increase in cardiac weight in wild-type mice after three weeks of swimming exercise [11]. This cardiac hypertrophy was associated with mitochondrial adaptations, including improved mitochondrial respiration and ATP synthesis [11]. To study the mechanistic underpinnings of improved mitochondrial function in relation to cardiac hypertrophy, the authors studied the role of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) signaling, which are essential for the cardiac growth process itself. Interestingly, they observed that PI3K, which is upstream of Akt, was essential for both cardiac growth and mitochondrial adaptations, but that Akt signaling solely played a role in the cardiac growth response [11]. A follow-up study observed results in which another downstream kinase of PI3K, phosphoinositide-dependent protein kinase-1 was also not essential for exercise-induced mitochondrial adaptations [12]. The downstream target of PI3K responsible for both cardiac growth and mitochondrial adaptations, therefore, remains unraveled. A potential target could include a protein kinase or phosphate acting upstream of Akt, an example could be A Kinase Interacting Protein 1, which has been shown to stimulate physiological cardiac growth via Akt signaling and regulate mitochondrial performance as well [13–16]. Together the above-described findings do suggest that exercise training maintains and/or enhances mitochondrial oxidative capacity in the healthy, physiological setting, alongside the increase in cardiac muscle mass (Figure 1a) (Table 1), of which the underlying mechanisms remain partially unknown.

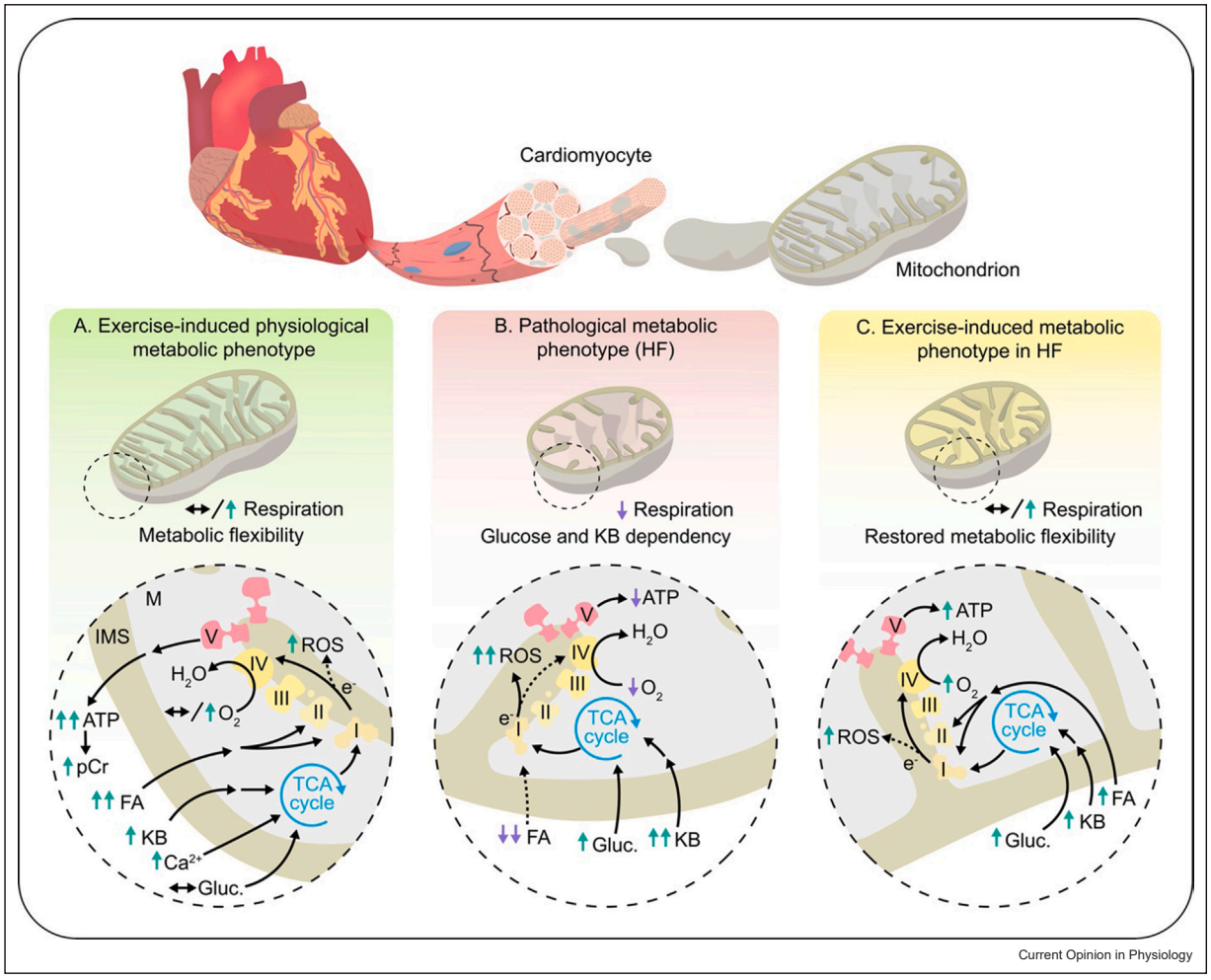
Effects of exercise on cardiac function, cardiac hypertrophy, and mitochondrial function: evidence from human studies

Measuring the direct effects of exercise on cardiac mitochondrial function in the clinical setting is challenging as performing myocardial biopsies, strictly for scientific purposes in exercising healthy individuals, crosses ethical boundaries. However, several indirect techniques can be used to further explore the exercise-induced mitochondrial effects in humans. First of all, the effect of exercise on cardiac function and morphology can be assessed through cardiac imaging. Data on the effects of exercise training on cardiac volume in the clinical setting are, however, ambiguous. While some authors found evidence that three months of endurance exercise training resulted in eccentric cardiac hypertrophy and an increase in left ventricular (LV) mass in both males and females [17,18], others did not find significant changes in cardiac volumes after six months of exercise training in the healthy setting [19]. Despite this limitation, changes in metabolism and global mitochondrial performance during exercise can be determined through ^{31}Phosphorus Magnetic Resonance Spectroscopy (^{31}P MRS) of exercising skeletal muscle [20–22]. While this does not inform on cardiac metabolism itself, several of the mitochondrial changes which occur in the heart have also been shown to occur in skeletal muscle [2,23]. Using this technique, it was shown in a small study population that endurance-trained individuals had a faster phosphocreatine postexercise recovery compared to sedentary individuals, reflecting better mitochondrial oxidative capacity [24]. This study furthermore showed that intramuscular pH during recovery was higher indicating that there was less anaerobic respiration. Another way to assess exercise-induced changes in skeletal muscle mitochondria is by performing skeletal muscle biopsies. Multiple studies have shown via muscle biopsies that exercise training leads to increased mitochondrial oxidative capacity [25]. For a large part, this can be explained by the increase in total mitochondrial volume and mitochondrial enzyme activity, which occurs in response to exercise [25,26]. Interestingly, Konopka et al. showed that underlying mechanisms, such as the exercised-induced increase in key regulators associated with mitochondrial biogenesis (peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α)), mitochondrial fusion (mitofusions 1 and 2 (Mfn1 and Mfn2 respectively) and mitochondrial fission (mitochondrial fission protein 1), were present both in young (20 ± 1years) and old (74 ± 3 years) men after exposure to 12 weeks of aerobic exercise training [27]. Together, these findings suggest that endurance training can improve mitochondrial oxidative capacity in human skeletal muscle in the healthy setting (Table 1). Whether these differences could also be detected in cardiac muscle mitochondria in response to exercise training remains unknown and requires further studies.

Metabolic substrate preference: a (preserved) switch?

In the heart, exercise can increase contractile power demand and O_2 consumption by 10-fold above resting rates [28], leading to metabolic substrate changes in accordance with the intensity and duration of exercise [28]. Cardiac FA and lactate uptake are found to be increased in response to exercise [28], in contrast to findings in skeletal muscle tissue, in which fat catabolism is downregulated in this setting [29]. Prolonged exercise is associated with a postexercise rise in ketone bodies (KB) [30], but it cannot be ignored that exercise-induced changes in ketone body utilization are largely influenced by nutrition. For example, pre-exercise intake of both high concentrations of carbohydrates and KB (via ketone ester drinks) attenuate the rise in plasma β-hydroxybutyrate [30,31]. As for the long-term, chronic effects of exercise training, it was shown that mitochondrial respiration is maintained or improved by preserving or enhancing metabolic flexibility and substrate use [6–8]. These chronic effects are thought to be regulated by adenosine monophosphate-activated protein kinase (AMPK) and PGC-1α signaling, which are critical for

Figure 1



Effects of exercise on cardiac mitochondrial function and substrate utilization in health and disease and the potential therapeutic effects in HF. Shown are: **(a)** Exercise-induced physiological metabolic phenotype, in which exercise exerts beneficial effects in cardiac mitochondria including improvements of mitochondrial respiration and metabolic flexibility. These effects are elicited by enhanced utilization of substrates, which enter the tricarboxylic acid cycle (TCA), to subsequently enter the electron transport chain for oxidative phosphorylation and in turn increase O_2 consumption and the production of ATP, which enhances overall mitochondrial function. **(b)** Pathological metabolic phenotype in the setting of HF, in which mitochondrial respiration is reduced, and substrate use is dependent on Gluc and KB. An inability to utilize FAs develops, causing a reduction of substrates entering the TCA cycle after which less O_2 is consumed and a reduction in the production of ATP is followed. Additionally, reactive oxygen species (ROS) are formed, and overall mitochondrial function is impaired. **(c)** Exercise-induced metabolic phenotype in HF, depicting the potential effects of exercise to stimulate a physiological metabolic phenotype in HF. The ability of exercise to restore or improve mitochondrial respiration as well as metabolic flexibility. Exercise causes substrates to become more available and potentially restores the inability of the failing heart to uptake circulating FAs. This restores the number of substrates entering the TCA cycle for O_2 consumption and ATP production and enhances overall mitochondrial function, which may potentially improve cardiac function in HF. IMS= inner mitochondrial space, M= mitochondrial matrix, I= complex I, II= complex II, III= complex III, IV= complex IV, V= complex V, pCr= phosphocreatinine, e^-=electron, Ca^{2+}= calcium.

mitochondrial function, overall cellular metabolism, and substrate availability in muscle tissue [32–34]. This may be accompanied by regulation of mitochondrial supercomplex assembly, improving respiratory efficiency and mitochondrial function as well [35,36].

From a preclinical perspective, several studies have been performed to identify the mechanisms associated with balancing substrate use with exercise. Generally, FA oxidation is enhanced in the exercise-adapted heart, however the results from studies focused on Gluc utilization vary widely [7,8]. This variation may be explained by the usage of different exercise models in the experimental setting [7]. A study in mice subjected to 10 weeks of different aerobic exercise regimens revealed distinct shifts in substrate utilization in relation to exercise intensity. While no changes in substrate utilization occurred during moderate-intensity training [37], high-

intensity exercise induced a switch in myocardial substrate use towards more Gluc oxidation [37]. A subsequent study focused on the alterations in Gluc metabolism observed that genetically induced lowering of Gluc oxidation (6-phosphofructo-2-kinase deficient mice) was associated with a physiological type of cardiac remodeling that occurred without exercise. This included an increase in cardiac size accompanied by an increment in capillary-to-myocyte ratio, without fibrosis formation, and with functional changes such as increased end-diastolic volume and mildly decreased wall thickness [38]. Contrarily, mice with genetically induced increases in Gluc oxidation (fructose-2,6,biphosphatase deficient mice) were accompanied by a pathological form of remodeling, including a slight increase in cardiac size, without an increase in capillary-to-myocyte ratio and with a lower ejection fraction [38]. Also, the authors showed that acute exercise was associated with reduced Gluc utilization, whereas the more adapted exercise effects included more glycolysis and phosphofructokinase activity [38]. This indicates that metabolic periodicity is of essence, and we can hypothesize that in the state of HF, with lack of metabolic flexibility, this metabolic periodicity may be lost [38]. In addition, the authors showed that inflexibility in substrate use causes reductions in mitochondrial function [38]. These findings suggest that inducing a reduction in Gluc oxidation by the heart is sufficient to induce a physiological type of remodeling. Interestingly, Wende et al. showed that GLUT4 is essential for chronic physiological cardiac adaptation in mice, suggesting Gluc metabolism is maintained or increased with chronic exercise [39]. These studies, despite variability in results on the role of Gluc utilization in chronically exercise-adapted hearts, suggest that metabolic flexibility plays a role in exercise-induced cardiac hypertrophy and mitochondrial function (Figure 1a) (Table 1). Unfortunately, the molecular mechanisms shaping his physiological metabolic phenotype remain unraveled and deserve future studies.

Exercise, cardiac hypertrophy and mitochondrial function in a pathological setting of heart failure

In the setting of HF, unremitting cardiac stress transforms the initially adaptive cardiac growth response into a maladaptive phenotype, often referred to as pathological hypertrophy. Pathological hypertrophy underlies a large number of heart diseases, including HF with both reduced or preserved LV ejection fraction (HFrEF and HFpEF, respectively) [5,40,41]. Alongside the development of pathological cardiac growth, cardiac tissue undergoes metabolic changes in which mitochondrial function decreases, and a shift occurs in substrate utilization [5,7,40,41]. The reduction in mitochondrial function is often associated with additional maladaptive processes including impaired mitochondrial quality control and an imbalance between mitochondrial biogenesis, mitophagy, and fission and fusion [5,42]. The changes in metabolic substrate use in HF have been well-described and include a defect in cardiac FA catabolism in combination with a fuel utilization switch towards Gluc utilization. Eventually, global metabolism becomes impaired as total substrates deplete in the failing heart [7,40,41]. A recent study by Flam et al. performed metabolomics in nonfailing and end-stage failing hearts and confirmed the switch to Gluc catabolism in the failing state, as well as the inability for uptake of substrates by the heart despite their circulating levels [43]. Interestingly, a study measuring arteriovenous gradients in failing and nonfailing hearts observed a switch to increased ketone body utilization rather than Gluc utilization in the failing heart [44]. An increase in ketone body consumption in failing hearts was also described in another study by Monzo et al. [45] as well as in the metabolomic study by Flam et al. [43] and could potentially be a novel metabolic switch occurring in HF (Figure 1b).

Exercise improves mitochondrial function in pathological cardiac hypertrophy: evidence from animal studies

Multiple experimental studies have focused on the role of exercise in cardiac mitochondrial function in the pathological setting. For example, in a model of HF, 15 weeks of low-intensity aerobic exercise reduced mitochondrial calcium-induced swelling, which was applied as a measure of mitochondrial function. Additionally, exercise reversed LV remodeling as well [46]. Another study employed resistance exercise in a rat model of diabetic cardiomyopathy, in which improved cardiac function as well as mitochondrial function through the respiratory control rate was observed [47]. Improved mitochondrial function was accompanied by other beneficial mitochondrial adaptations, including enhanced mitochondrial biogenesis and reduced damage to mitochondrial morphology, entailing that mitochondrial shape and cristae structure were preserved [47]. Four weeks of treadmill exercise training increased cardiac function in a HF mouse model with myocardial infarction. In this study, improvements of mitochondrial respiration and increments in ATP production were also observed in the exercised-HF mice [48]. The authors also depicted attenuation of damage to the mitochondrial morphology, in the form of cristae structure and clustering of mitochondria, in exercised HF mice compared to unexercised HF mice [48]. Hence, exercise has been shown to improve cardiac function as well as mitochondrial function in models of HF (Figure 1c) (Table 1). Of note, mitochondrial functional changes often occur in concert with additional exercise-induced mitochondrial adaptations.

Cardiac effects of exercise training in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction: evidence from human studies

Beneficial cardiac effects of exercise training have been described for the full spectrum of cardiac function in clinical HFrEF (Figure 1c). Multiple data showed that exercise training significantly improves systolic function in HFrEF by increasing LVEF as compared to the control groups [49,50]. Although both resistance and aerobic exercise training-induced improvements in exercise tolerance as previously mentioned, this was not the case for improvements in cardiac function: two meta-analyses, including a very large study with over 5000 patients showed that an increase in LVEF was present after aerobic exercise but not after resistance training [51,52]. Furthermore, improvements in diastolic function were detected in a meta-analysis including 266 HFrEF patients, with a mean difference in reduction in ratio of early diastolic transmitral velocity (E) to early diastolic tissue velocity (E′) (E/E′ ratio) with exercise training versus control of – 2.85 (95% CI –3.66 to –2.04, $p < 0.00001$) [53].

In HFpEF on the other hand, cardiac effects of exercise training are more ambiguous: in a meta-analysis of seven randomized controlled trials (RCT's) in HFpEF patients, both the improvement in systolic or diastolic function was not present [54]. Other studies, including a meta-analysis of 204 HFpEF patients, did find improvements of diastolic function (E/E′) after exercise intervention (MD of –2.38 (95% CI –3.47 to –1.28, $p < 0.0001$) [53] (Table 1). While improvements in peak VO_2 are similar to improvements in HFrEF, the changes in (systolic) cardiac function are less evident in this patient cohort.

Effects of exercise training on oxidative metabolism

Oxidative mitochondrial function and effects of exercise in HF have profoundly been studied in skeletal muscle. Skeletal muscle biopsies in HF studies show a decrease in expression of critical regulators of mitochondrial quality control, including citrate synthase and Mfn2, as well as a reduced density in mitochondrial cristae [42,55]. These findings were associated with measures of exercise performance [42,55]. Interestingly, both HFrEF and HFpEF are characterized by impairment of in-vivo oxidative mitochondrial function [56,57]. In three studies in HFrEF, the rate of phosphocreatine level depletion was higher and postexercise recovery of these levels was significantly lower compared to healthy individuals, which indicates that oxidative mitochondrial function was impaired in the lower leg muscles [56–58]. Also, mitochondrial oxidative function was impaired in HFpEF compared to controls [57]. It is important to notice that in these three functional in-vivo studies, exercise was tested by plantar flexion or arm flexor exercises, which focus on using isolated skeletal muscles in absence of a cardiopulmonary exercise load. In HFrEF, Hambrecht et al. showed that six months of exercise training led to enhanced oxidative enzyme activity and an increase in surface density of mitochondria [59]. Based on the positive effects of exercise in HFpEF and the positive effect of endurance training on phosphocreatine recovery in health [24], it can be hypothesized that exercise could be a potential beneficial intervention for mitochondrial function in HF(pEF) [60]. These findings suggest that targeting skeletal muscle oxidative mitochondrial metabolism may allow to improve exercise capacity in HF (Table 1). New studies are required to further discover therapeutic targets, but a potential target could include the erythropoietin receptor in skeletal muscle, which has been shown to regulate mitochondrial biogenesis and physiological exercise [61].

Metabolic substrate preference: a switch?

Contrary to the exercised heart, pathological stress induces a switch in substrate utilization, which is associated with re-expression of the fetal gene program and upregulation of molecular pathways involved [7,40,41]. As exercise can improve mitochondrial function in the failing heart, the question remains whether this is accompanied by reversing or improving the pathological switch in substrate utilization. Therefore, Jiang et al. who described improved cardiac and mitochondrial function in exercised-HF mice, investigated Gluc metabolism in these mice. Interestingly, the authors observed an increase in Gluc use, primarily regulated through increased expression of glucose transporter type 1 (GLUT1) and inhibition of histone deacetylase 4 [48]. In a model of diabetic cardiomyopathy, resistance exercise improved cardiac and mitochondrial function. As in the previously described study, these beneficial effects were also associated with improved GLUT4 and pyruvate dehydrogenase E1-alpha protein expression but reductions in carnitine palmitoyltransferase-1 alpha (CPT-1α) and peroxisome proliferator-activated receptor alpha (PPARα) [47]. A study performed with sedentary and 10-week treadmill exercise-trained rats, which developed cardiac hypertrophy, showed that when subjected to ischemia/reperfusion injury, trained rats offered metabolic cardio protection through an increase in Gluc utilization as well as palmitate oxidation [62]. Several studies have shown that enhancement of mitochondrial supercomplex assembly can improve mitochondrial function as well as overall substrate availability in a HF setting [63,64]. Together these findings indicate that exercise exerts beneficial effects on metabolic substrate use (Figure 1c), it remains questionable whether exercise solely refuels the heart by improving Gluc, FA, and/or ketone metabolism or whether it can also preserve the maladaptive switch from FA to Gluc metabolism.

In a clinical study in 61 HF patients and 25 healthy controls, Melenovsky et al. compared circulating fuel concentrations pre- and postexercise and demonstrated that HF patients experienced a lower serum pyruvate postexercise, which was associated with peak VO_2 [65]. Also, postexercise Gluc levels were associated with an increased risk for an adverse outcome in HF, suggesting that Gluc dependency also plays a major role in the exercising HF patient. Interestingly, postexercise concentrations of metabolites (including free FA (FFA), Gluc, lactate, and β-hydroxybutyrate), except for pyruvate, were not related to cardiac performance. Suggesting, that metabolic flexibility induced by exercise may allow to improve cardiac performance for exercise (Table 1).

Future perspectives for exercise in the treatment of heart failure

Many experimental studies have evaluated the effect of exercise on mitochondrial function, substrate utilization, and cardiac function in health and disease. In the disease setting, the focus of many studies is shifting towards discovering novel substrates that can refuel the heart, for example the use of KB, short-chain FAs, and branch-chain amino acids in the treatment of HF [66–68]. However, these studies are still in the initial phases, and studies in the light of exercise have not been performed, and it therefore remains unknown whether exercise can synergize the beneficial effects of these type of substrates. Additionally, studies focused on the molecular mechanisms of exercise-induced improved mitochondrial function and substrate utilization in HF remain limited. Potentially, mechanisms regulating physiological cardiac growth interact with those regulating mitochondrial function and substrate utilization, as well as those involved in mitochondrial quality control.

Investigating the direct effects of exercise on metabolic and mitochondrial function in the clinical setting remains challenging. Considering the recent developments in the assessment of extensive metabolomics, future research could provide valuable information on changes in substrate metabolism during exercise in the failing and nonfailing heart. Additionally, studies using ^{31}P MRS measurements have solely been performed in the absence of a cardiopulmonary exercise load. Considering that symptoms of HF are most profound in the setting of endurance exercise, study protocols using ^{31}P MRS should ideally assess mitochondrial function by using an exercise protocol with a cardiopulmonary exercise component.

Despite the knowledge that exercise programs have beneficial cardiac effects in HF patients, implementing an exercise program in treatment of HF patients remains challenging. Interestingly however, a meta-analysis by Slimani et al, describing RCT's with HF exercise programs in 2409 (predominantly HFrEF) patients, showed that neither duration of intervention, duration of single session nor weekly frequency were of large influence on the beneficial effects of exercise on cardiac systolic function [49], suggesting that solely participating in any kind of exercise intervention can already provoke beneficial cardiac effects.

Conclusion

Taken together, these findings suggest that exercise induces physiological cardiac hypertrophy accompanied by preservation or improvement in mitochondrial function as well as optimization of metabolic substrate use in health and HF. Therefore, exercise training results in cardiac protection in HF, and implementing exercise regimens more intensively in treatment programs could serve a beneficial role in HF treatment. In addition, future studies focused on the physiological molecular mechanisms may lead to the discovery of novel therapeutic targets to rewire cardiac metabolism from a pathological to a physiological phenotype and may allow us to improve cardiac function and exercise capacity in HF.

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CRediT authorship contribution statement

KTN, SNV, PSA & BDW were responsible for the article drafting and revising. All authors approved the final version of the manuscript, all authors met the criteria for authorship, and all who qualify for authorship are listed.

Data Availability

No data was used for the research described in the article.

Declaration of Competing Interest

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The review by Voorrips et al. discusses the pathophysiological mechanisms that are responsible for exercise intolerance in HF and elaborates on the potential SGLT2-inhibitor-mediated effects on these phenomena. Providing an up-to-date overview of existing studies on the effect of SGLT2 inhibitors on clinical outcome parameters that are relevant to the assessment of exercise capacity, this review elaborates on current gaps in evidence and potential future perspectives on the effects of SGLT2 inhibitors on exercise intolerance in chronic HF.

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