Chapter 11
Experimental Evidences Supporting the Benefits of Exercise Training in Heart Failure

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Abstract Heart Failure (HF), a common end point for many cardiovascular diseases, is a syndrome with a very poor prognosis. Although clinical trials in HF have achieved important outcomes in reducing mortality, little is known about functional mechanisms conditioning health improvement in HF patients. In parallel with clinical studies, basic science has been providing important discoveries to understand the mechanisms underlying the pathophysiology of HF, as well as to identify potential targets for the treatment of this syndrome. In spite of being the end-point of cardiovascular derangements caused by different etiologies, autonomic dysfunction, sympathetic hyperactivity, oxidative stress, inflammation and hormonal activation are common factors involved in the progression of this syndrome.

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Together these causal factors create a closed link between three important organs: brain, heart and the skeletal muscle. In the past few years, we and other groups have studied the beneficial effects of aerobic exercise training as a safe therapy to avoid the progression of HF. As summarized in this chapter, exercise training, a non-pharmacological tool without side effects, corrects most of the HF-induced neurohormonal and local dysfunctions within the brain, heart and skeletal muscles. These adaptive responses reverse oxidative stress, reduce inflammation, ameliorate neurohormonal control and improve both cardiovascular and skeletal muscle function, thus increasing the quality of life and reducing patients' morbimortality.

Keywords Benefit • Exercise • Heart failure • Mortality • Outcomes

1 Introduction

Heart failure (HF) is a syndrome of poor prognosis in which patients present dyspnea and exercise intolerance due to the lack of the heart capacity of in maintaining the cardiac output required to preserve the metabolic needs of the organism. As a common end point for many cardiovascular diseases, more than 20 million people worldwide are estimated to have HF. This scenario tends to worse mainly because of the higher life expectancy and the increasing mean age of the population. The impairment of the cardiac function is the most classical mechanism described in this syndrome. Cardiac dysfunction can be of two types: a systolic and/or a diastolic dysfunction. Whilst most patients show both dysfunctions, there is usually a predominant pattern. The predominance of the systolic dysfunction, characterized by an inadequate emptying of the ventricle, defines a HF with reduced ejection fraction (HFREF). When the diastolic dysfunction (characterized by an inadequate relaxation and filling of the ventricle) predominates, it is called HF with preserved ejection fraction (HFPEF). Nowadays, our knowledge regarding HFREF is much wider when compared to that of HFPEF. HFPEF, however, is showing an increasing prevalence, being usually predominant in the elderly people and women. Around half of the HF patients experience HFPEF; unfortunately, none of the current therapies used to treat HFREF have shown good results in treating HFPEF patients. Besides the pharmacological therapies, aerobic exercise training has also been used to treat HF. Similar to other treatments, the current knowledge of the effects of exercise training in HF is predominantly focused in HFREF, which will be the focus of the present chapter.

This chapter will start with a brief overview on the pathophysiology of HF. Then, the effects of aerobic exercise training with focus on its benefits on neurohormonal control as well as its effects to improve cardiac and skeletal muscles functions will be discussed.

2 Overview on the Pathophysiology of the HF

The immediate response to a myocardial aggression, leading to decreased cardiac output, is the activation of compensatory neurohormonal mechanisms. Peripheral sensors, such as the baroreceptors and the cardiopulmonary receptors detect the alterations in arterial pressure, atrial distention and ventricular contractile function, which are integrated in central autonomic areas triggering the activation of several neurohormonal systems, the most important being the sympathetic nervous system, the renin-angiotensin-aldosterone system and the secretion of vasopressin [23]. In the early HF phase, these compensatory mechanisms aim to increase cardiac contractility and heart rate, in order to normalize the reduced cardiac output. However, their continuous activation induces an elevated peripheral resistance, with a consequent increase in the arterial blood pressure. Simultaneously an increased venous constriction and water/salt retention activated by the neurohormonal mechanisms, coupled with angiotensin II-induced increase in water intake, will result in a higher pre-load, activation of the Frank-Starling mechanism and increased ventricular contractility, which characterize the initial compensated phase of HF [23].

While the Frank-Starling mechanism is critically important in regulating cardiac output in normal conditions, in the presence of myocardial dysfunction its effects are greatly impaired. As the ventricle is incapable of ejecting proper volume during the systolic phase of the cardiac cycle, the heart will enter in the subsequent diastolic phase with increased residual blood volume, which, in addition to increased venous return, results in an even high pre-load. In the next cycle, again the heart is incapable of ejecting the proper systolic volume, leading the ventricle to work continuously under elevated filling pressures. In this condition, the heart works constantly in the right end of the Frank-Starling curve, showing minimal alterations in the cardiac output in response to increases in the pre-load. Additionally, the failing heart shows a decrease in the peak cardiac output of the Frank-Starling curve, further decreasing the relevance of this mechanism for the compensation of cardiac failure [147].

Along with the neurohormonal activation and the Frank-Starling mechanism, a third compensatory mechanism in HF is the ventricular hypertrophy. Left ventricle dilatation and/or sustained elevations in after-load result in higher wall stress. Both neurohormonal signaling and wall stress induce a hypertrophic response in cardiomyocytes and fibroblasts, thus leading to hypertrophy and extracellular matrix deposition. The pattern of this response depends on the type of stimulus applied to the ventricle: volume overload will result in eccentric hypertrophy with the maintenance of the wall thickness, while pressure overload results in concentric hypertrophy with increase in wall thickness [59]. While these adaptations at the beginning might help to reduce wall stress and maintain ventricular function, the exhaustion of this mechanism by the persistence of the injury triggers the chamber dilation and the reduction of its contractile function.

In spite of the importance of these mechanisms in the maintenance of the organism homeostasis in the acute HF, the persistence of such aggression, leading to a chronic activation of neurohormonal systems, will result in further deterioration of the cardiac function. The excessive activation of sympathetic, renin-angiotensin-aldosterone and vasopressin systems results in maladaptive responses of the myocardium, inducing apoptosis [79] and abnormal function even in the viable myocardium. Otherwise, the viable myocardium subjected to chronic neurohormonal stimulation shows impaired calcium handling and abnormal production and use of high-energy phosphates and reactive oxygen species [23, 41]. Sympathetic hyperactivation induces desensitization, thus reducing the capacity of the heart to respond adequately to autonomic stimuli. Catecholamines, angiotensin II, aldosterone and inflammatory cytokines altogether can trigger apoptotic responses in cardiomyocytes [79]. The worsening of cardiac function causes further stimulation of the neurohumoral systems, resulting in a deleterious positive feedback mechanism. This feedback loop of progressive worsening in cardiac function and compensatory increases of neurohumoral activation will eventually reach a limit when the cardiovascular system can no longer maintain an adequate perfusion of the organism, resulting in the HF syndrome.

3 Mechanisms Conditioning the Benefits of Exercise Training in HF-Neurohormonal Systems

3.1 Autonomic Nervous System

Autonomic nervous system dysfunction is a hallmark for HF. The exaggerated sympathetic activation simultaneously with withdrawal of vagal outflow drives the organism towards progressive worsening of cardiac function. Several methods and models of HF have been used to assess and confirm sympathetic nervous system (SNS) hyperactivity in animal models of HF: sympathetic nerve recordings [39, 135], dosage of plasma cathecolamines [123], norepinephrine turnover [122], immunohistochemistry in brain autonomic areas [69], as well as functional recordings [69]. The relevance of SNS in the pathophysiology of the HF is highlighted by the great impact of blocking sympathetic hyperactivity in reducing the mortality of HF patients [22, 53]. Exercise training, on the other hand, is capable of reducing or even normalizing SNS activity in HF animals [69, 185]. Even in patients that are already in the use of β-blockers, exercise training can induce further reductions in sympathetic nerve activity [48].

Many mechanisms have been proposed to explain the SNS dysfunction in HF. Impairment of inhibitory and hyperactivation of excitatory reflexes controlling the SNS outflow were pointed as important mechanisms leading to sympathetic hyperactivity in HF. Indeed, reduced sensitivity of the sympathoinhibitory arterial baroreflex [39] and cardiopulmonary reflexes [128] and increased sensitivity from exercise pressor reflex [164] and other sympathoexcitatory reflexes such as the

carotid body chemoreflex [145] and the cardiac afferent sympathetic reflex [163] were found in animal models of HF. Exercise training can attenuate several of these reflex dysfunctions. HF animals submitted to chronic exercise training show increased baroreflex sensitivity [94, 111] through a mechanism that seems to be dependent on the parasympathetic nervous system [95]. Exercise training also ameliorates cardiopulmonary reflexes [128], attenuates carotid body afferent activity and normalizes the chemoreflex through mechanisms dependent on NO and angiotensin signalling [91]. The exercise pressor reflex driven by metaboreceptors and mechanoreceptors afferents is also attenuated by exercise training, which prevents the sensitization of those receptors [164, 165].

Second order neurons in the nucleus tractus solitarii (NTS), the first synaptic relay of peripheral receptors in the central nervous system, receive barosensitive and chemosensitive inputs and project to brainstem areas controlling vagal (nucleus ambiguus, NA, and dorsal motor of the vagus, DMV) and sympathetic (caudal and rostral ventrolateral medulla, CVLM and RVLM, respectively) outflow to heart and vessels [36, 106]. Upon loading of baroreceptors, NTS is activated and increases the firing of NA and DMV pre-ganglionic parasympathetic neurons projecting to the heart; NTS also activates gabaergic inhibitory neurons within the CVLM that project and inhibit RVLM premotor neurons projecting to sympathetic pre- and postganglionar neurons innervating the heart and vessels [108]. As a consequence, venous return, cardiac output and peripheral resistance are reduced decreasing arterial pressure, which returns to control levels [107, 108]. When peripheral chemoreceptors are activated (reduced PO_2 and pH, increased PCO_2), the firing of NTS chemosensitive neurons directly excite the RVLM premotor neurons augmenting sympathetic outflow and increasing blood pressure [130, 171]. Opposed responses are observed to baroreceptors unload and during reduced activation of peripheral chemoreceptors, respectively. Brainstem integration of cardiovascular control is continuously modulated by preautonomic neurons located in the paraventricular nucleus of hypothalamus (PVN) and other supramedullary pathways [108, 149]. Considering the role of brainstem and supramedullary autonomic nuclei in the control of sympathetic and parasympathetic activity, it makes sense that plastic and functional changes in these nuclei could condition both deleterious and benefic autonomic adaptations to HF and training, respectively.

Studies in HF animals described significant reductions in the nitric oxide content (NO, a sympathoinhibitory molecule) within the NTS [67, 140], increased expression and higher functional response to AT1 receptors blockade [166]. Indeed, augmented availability of angiotensin II was proposed to be one of the mediators of sympatoexcitation in the brain. Indeed, angiotensin converting enzyme (ACE, responsible for the conversion of angiotensin I to angiotensin II) gene and protein expression is elevated and that of angiotensin converting enzyme 2 (ACE2, which metabolizes angiotensin II to angiotensin-(1–7)) is reduced in autonomic areas of the hypothalamus (PVN) and brainstem (NTS, RVLM) of chronic HF rabbits [73]. Coherently, exercise training, by reversing ACE/ACE2 ratio, is able to attenuate the increased angiotensinergic signaling in these nuclei [73]. Other experimental studies investigating the sympathetic hyperactivity in HF found increased angiotensinergic

[182] and glutamatergic [90] and decreased GABAergic [30] and NO [177] signaling within the PVN. Again exercise training reduced sympathetic overactivity simultaneously with decreased angiotensinergic [73, 182] and glutamatergic [77] and increased GABAergic [121] and NO [181] signaling in the PVN. Similar profile was observed within the RVLM, the main nucleus controlling the sympathetic outflow to the cardiovascular system: increased glutamatergic [167] and decreased NO signaling [67] simultaneously with an imbalance between AT1 and AT2 receptors [51], which contribute to sympatoexcitation in HF animals. All these alterations are attenuated by exercise training [73].

Apart of numerous studies confirming the role of sympathetic outflow in the genesis of cardiovascular deficits in HF, as well its withdrawal in the improvement of circulatory control in trained HF animals, the parasympathetic, the counter-regulatory axis of the autonomic nervous system whose activity is depressed in HF patients and animals [18, 69] has received much less attention. Although there is evidence that low vagal activity is a predictor of high mortality rates [34, 82], pharmacological activation of vagal outflow is not generally recommended given the several side effects of cholinergic drugs and the lack of drugs capable of specifically stimulating the vagal activity to the heart. So, the impact of the parasympathetic nervous system is not as clear as the effects of the sympathetic activity in HF. Pharmacological stimulation of parasympathetic tonus with pyridostigmine improves cardiac and circulatory parameters in HF rats [84, 137]. In chronic HF the increased vagal activity through parasympathetic nerve stimulation has shown to be effective to improve prognosis in animals [89, 179] and patients [37, 146]. However, in large randomized trials this intervention failed to show significant results [57].

Besides knowing that HF animals show alterations in parasympathetic ganglia and depressed parasympathetic activity [17], information regarding the mechanisms leading to vagal dysfunction in HF are lacking. In a recent paper we observed that decreased parasympathetic tonus in HF rats is positively correlated with the reduction of choline acetyl transferase (ChAT) positive neurons in the NA and DMV and that training-induced improvement of parasympathetic control of the heart is accompanied by a significant increase in the number and density of ChAT-positive neurons within these nuclei [69]. Figure 11.1 illustrates these findings showing in addition that elevated basal heart rate, which is driven by the increased sympathetic outflow to the heart in HF sedentary rats, is reduced and driven by the augmented parasympathetic tonus in trained HF rats. Our data also confirmed that increased sympathetic activity in HF sedentary rats is accompanied by augmented dopamine β-hydroxylase immunoreactivity (DBH*ir*) within the RVLM and that exercise training reduces both [69]. However, the correlation between sympathetic tonus and DBH*ir* within the RVLM does not attain significance [69]. These observations reinforce the potentiality of training to improve vagal control of the heart in HF individuals, with the advantage to avoid noxious side effects that accompanied pharmacological therapies. In spite of our still limited knowledge regarding the parasympathetic axis of autonomic nervous system in the treatment of chronic HF, exercise training seems to be an essential therapeutic tool to normalize vagal dysfunction in this syndrome.

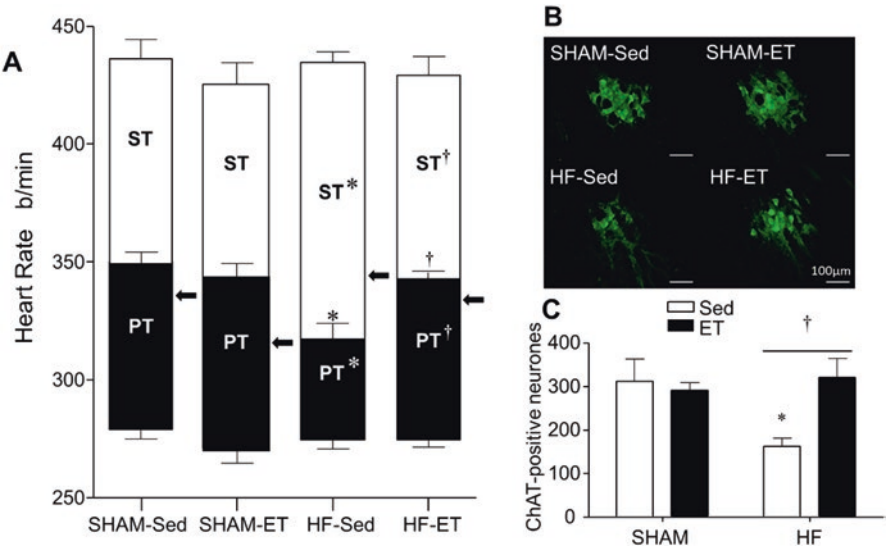

Fig. 11.1 (**a**) Comparison of cardiac sympathetic (ST, open bars) and parasympathetic tonus (PT, filled bars), intrinsic heart rate (intersection between ST and PT) and resting heart rate (indicated by arrows) in infarcted (HF) and SHAM rats submitted to sedentary (Sed) and training (ET) protocols. Significances ($P < 0.05$) * vs. SHAM; † vs. Sed. (**b**) Photomicrographs comparing the effects of heart failure and exercise training on Choline Acetyl Transferase (ChAT) immunoreactivity within the nucleus ambiguus pars sub-compacta of SHAM and HF rats submitted to sedentary (Sed) or training (ET) protocols. (**c**) Number of ChAT-positive neurones in pars sub-compacta of the nucleus ambiguus. Significant difference ($P < 0.05$): * vs. SHAM; † vs. respective Sed controls (Modified with permission from Ref. [69]

Therefore, by attenuating sympathoexcitation and by restoring the vagal control of the heart, exercise training is able to restore autonomic balance in HF individuals, even in the persistence of ventricular deficits, therefore improving its prognosis besides reducing mortality rates.

3.2 Renin-Angiotensin-Aldosterone System (RAAS)

Along with the autonomic nervous system, the RAAS is an essential key in the understanding of HF pathophysiology. The RAAS is a complex system composed of several regulatory and counter-regulatory molecules that act in order to control the water and salt balance and the arterial blood pressure. Viewed in the past as a hormonal circulating system, it is now accepted as an important local regulatory system present in all tissues, able to control specific tissue functions independently of the circulating RAAS. This hormonal/local system exerts its functions through 2 axes: the ACE-angiotensin II-AT1 receptor axis with vasoconstrictor, proliferative and pro-inflammatory effects and the ACE2-angiotensis-(1–7)-Mas receptor axis, with opposite vasodilator, anti-proliferative and anti-inflammatory effects. In

addition to increased angiotensin II availability within the brain leading to increased sympathetic outflow [94, 111], ACE-angiotensin II-AT1 receptor axis is hyperactivated in HF [13, 58, 73, 94, 125], the increased angiotensin II levels being responsible for fibroblasts' proliferation and myocardium hypertrophy, thus facilitating the worsening of cardiac function in an already dysfunctional heart [139].

The efficacy of RAAS blockade (renin and ACE inhibitors, AT1 receptors' antagonists, aldosterone receptors' antagonists) in reducing the neurohormonal activation of the heart and reducing mortality [83] highlight the importance of these therapeutic tools to improve prognosis in HF patients. Importantly, exercise training is effective in attenuating RAAS activity not only in the brain, but also in peripheral tissues, thus avoiding additive deleterious effects in the progression of HF. Indeed, HF animals submitted to exercise training show decreased plasma angiotensin II concentration [94] simultaneously with reduced tissue content in the heart [125], skeletal muscle [58] and brain [51, 73, 182]. Despite accumulating evidence for the importance of RAAS in HF and the benefits of exercise training in reducing its activation in several peripheral tissues, the most abundant information available was obtained in the central nervous system. Exercise training, by modulating RAAS activity can correct/normalize blunted reflexes that regulate autonomic circulatory control, such as the baroreflex [111] and the carotid body chemoreflex [91]. In addition, as described before, the enhanced angiotensinergic signaling in autonomic areas of HF individuals (increased AT1 receptors and ACE expression, decreased ACE2 expression, etc.) [61, 73, 182] determining sympathoexcitation is corrected by exercise training.

Angiotensin II-induced increases in sympathetic activity are mediated, at least in part, by increases in oxidative stress [49, 183] and exercise training has been shown to decrease sympathetic hyperactivity by reducing oxidative stress: it increases the expression of antioxidant enzymes in the brain and other tissues [50, 85, 93, 154], thus attenuating intracellular signaling triggered by angiotensin II.

Aldosterone, a mineralocorticoid secreted in response to angiotensin II signaling that is mostly known for its role in sodium reabsorption in the kidney. Nonetheless, aldosterone receptors are present in the heart [96, 124], as well as in vessels [96, 104] and brain [176]. In the heart of HF individuals, aldosterone induces marked cardiac fibrosis worsening the cardiac function [24, 133]. On the other hand, blockade of aldosterone effects by mineralocorticoid receptors antagonists has been shown to reduce mortality of HF patients [103]. There is scarce information regarding the effects of exercise training on aldosterone effects in HF. Braith et al. [21] and Wan et al. [162] have shown that exercise training reduces circulating levels of aldosterone, thus contributing to attenuate its deleterious effects in HF.

3.3 Inflammatory Response

The increased inflammatory profile also plays an important role in the pathophysiology of the HF. Plasma levels of pro-inflammatory cytokynes, such as tumor necrosis factor - alpha (TNF-α) and interleukins (IL) as IL-1β, IL-6 and IL-18, are elevated

in several tissues of HF individuals while anti-inflammatory cytokines, such as the IL-10, are reduced [60]. Intact rats chronically infused with TNF-α showed depressed cardiac function and left ventricle dilatation, a pattern that resembles the effects induced by HF [20]. These effects are partially reversed by stopping the TNFα infusion [20]. A murine model that overexpresses TNF-α in the heart also develops cardiac hypertrophy and dilatation, with reduced ejection fraction and pulmonary congestion, a phenotype very similar to HF [81]. Elevated levels of TNF-α is also related to the skeletal muscle apoptosis found in HF rats [35]. Dysfunction of human cardiomyocytes submitted to ischemia-reperfusion injury is attenuated by simultaneous inhibition of IL-1β and IL-18 [129]. In rats the chronic exposure to IL-6 induces myocardial fibrosis, cardiac concentric hypertrophy and diastolic dysfunction [102] while IL-6 knockout mice submitted to pressure overload show attenuation of both left ventricle hypertrophy and cardiac dysfunction [180].

While the relevance of the immune response in the context of HF is clear, studies aiming to modulate it with drugs administration are still ensuing. A trial using anti-TNF-α antibodies showed no improvement and had to be stopped because of increased mortality in the group receiving the higher doses of the drug [32]. As reviewed by Gullestad et al. [60], other studies using different approaches to modulate the immune response in HF showed that with few exceptions those treatments are neutral or even harmful, calling our attention for the need to expand the knowledge in this field. In contrast exercise training has shown significant effects in reducing pro-inflammatory profile in HF in rats and patients. HF rats submitted to exercise training show increases in plasma levels of the anti-inflammatory cytokine IL-10 [119] and reduction of LPS-stimulated TNFα production by macrophages [15]. Exercised HF patients show reduced plasma levels of TNF-α and its receptors (sTNF-RI and sTNF-RII), IL-6 and its receptor (sIL-6R) and of the apoptosis inducer sFasL [3]. Markers of the monocyte/macrophage system granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage chemoattractant protein-1 (MCP-1) are also reduced [2]. These findings indicate that exercise training is a better choice than recombinant antibodies and/or pharmacological blockade to modulate immune response in HF.

4 Mechanisms Conditioning the Benefits of Exercise Training in HF – Cardiovascular System

4.1 Heart

As commented above, impairment of cardiac function is a hallmark of HF. The progression of the syndrome induces progressive deleterious remodeling of the heart leading to dilation of the chambers and loss of its elliptical shape [78]. Exercise training is able to prevent most of these alterations. Some studies have shown amelioration of cardiac function or reverse remodeling in trained HF animals [77, 182] and patients [42, 64, 157]. Others have found no significant effects in both animals

and patients [61, 73, 94, 136, 143]. These discrepancies could result from differences in the intensity, duration and type of the exercise protocol used [169]. Therefore, the beneficial effects of exercise training on myocardial remodeling and function seems to be only mild. Nonetheless, exercise training is capable improve other deficits induced by HF.

The impaired coronary blood flow and coronary reserve in HF are improved by exercise training, which activates myocardial angiogenesis [87, 143]. This finding is of relevance since the high coronary flow reserve has significant prognostic value in the context of HF [132]. Decreased coronary blood flow in HF is related to an increased production of reactive oxygen species in the coronary arteries and decreased levels of antioxidant enzymes [31], leading to increased NO scavenging and impaired endothelial NO synthase (NOS) function [16, 168]. Excessive oxidative stress, as demonstrated by increased levels of reactive oxygen species and decreased levels of antioxidant enzymes, also affects the myocardium itself [65, 66, 70]. The consequences of this dysfunction is the injury of cardiomyocytes, with contractile abnormalities [72], impairment of the proteasome, leading to accumulation of misfolded proteins [46], and eventually culminating in cell death. Exercise training induces cardioprotection through the reduction in oxidative stress simultaneously with the increase of antioxidant enzymes [12], thus restoring the cellular protein quality control [29].

Another feature of HF is impaired Ca^{2+} handling. The calcium homeostasis within cardiomyocytes is regulated by several proteins. Special attention has been given to those responsible for the control of the Ca^{2+} uptake and release within the sarcoplasm and sarcolemma. Those include the sarcoplasmic reticulum Ca^{2+}ATPase (SERCA2) and its regulator phospholamban (PLN), the ryanodine receptor, Ca^{2+} channels, and the Na^{+}/Ca^{2+} exchanger. While it is consensual that HF leads to Ca^{2+} handling dysfunction and excitation-contraction uncoupling, the mechanisms leading to those alterations are very complex and studies show conflicting results [11, 98]. Nonetheless, it seems that exercise training is able to ameliorate the HF-induced Ca^{2+} handling alterations, whichever directions they occur [76, 101, 134, 152, 170].

The heart in HF, submitted to excessive sympathetic signaling, show β-adrenergic receptor desensitization [56]. This results from a reduction in the density of β_1-adrenergic receptor, a decreased β_1 / β_2 ratio [26] and uncoupling of β_1-adrenergic receptor from the G_s protein caused by enhanced βARK expression [156]. Exercise training can attenuate this desensitization thus increasing β-adrenergic response [87], likely through increases in the expression of β_1-adrenergic receptors and cAMP levels [38, 87]. Therefore, exercise training can restore cardiac contractility reserve in HF.

HF also results in a dysfunction of the sinus node pacemaker cells leading to decreased intrinsic pacemaker heart rate (see Fig. 11.1) [69, 141, 174]. This sinus node dysfunction is characterized by increased recovery time and intrinsic cycle length, a caudal shift of the pacemaker location and slower sinoatrial conduction [141]. Molecular alterations that might explain these alterations include widespread changes in the expression of ion channels, gap junction channels, Ca^{2+}, Na^{+}, and H^{+}-handling proteins and receptors [174]. This sinus node dysfunction, along with

the β-adrenergic desensitization, lead the organism to require a higher sympathetic activation to maintain a similar heart rate when compared to normal subjects [69]. Exercise training also reverses this dysfunction, restoring intrinsic pacemaker heart rate of HF rats to similar levels when compared to control animals [69]. Whether the other mechanisms (for instance the anatomical change in the pacemaker location) are also corrected it remains to be investigated.

4.2 Endothelium

Impaired endothelium-derived vasodilatation is characteristic of HF [80]. This dysfunction is caused by reduced production of endothelial-derived relaxing factors, most notably NO [74, 131] and increased levels of endothelin [88]. Increased production of both reactive oxygen species (that inactivates NO) [16] and pro-inflammatory cytokines (such as the TNF-α that decreases endothelial NOS activity) [4, 172] are among the mechanisms that lead to the depletion of NO. The relevance of endothelial dysfunction in HF is of great importance and its severity can predict deleterious outcomes [105]. Exercise training increases NOS expression, restores NO production and decreases oxidative stress [75, 158] improving endothelium-mediated dilation and attenuating deleterious alterations. Exercise can also restore the number and function of endothelial progenitor cells [142, 144] and increase the levels of proangiogenic cytokines, such as the vascular endothelial growth factor (VEGF) and the stromal cell-derived factor (SDF-1) [144], suggesting that exercise also ameliorates angiogenesis.

5 Mechanisms Conditioning the Benefits of Exercise Training in HF – Skeletal Muscle

5.1 Skeletal Myopathy

The HF-related skeletal myopathy can induce a severe syndrome known as cardiac cachexia. This syndrome is defined by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and that leads to progressive muscle functional impairment. This severe clinical complication is also observed in many other chronic disease conditions, such as cancer, diabetes and HIV infection, affecting different types of skeletal muscles that are involved not only in force production, but also in posture maintenance and respiration. Epidemiological data demonstrate that in comparison with non-cachectic patients, the average stay at the hospital for cachectic patients is twice longer, and cost 70% more [7]. Thus, the reduced muscle mass and muscle dysfunction in HF are strongly associated with a reduced quality of life and a poor prognosis. Curiously, no specific

therapy are current available to block or attenuate the process of HF-related skeletal myopathy, leading the patients to develop cardiac cachexia.

In addition to muscle mass loss and decreased muscle function, HF-related skeletal myopathy has been characterized by capillary rarefaction, mitochondrial dysfunction, altered myofiber phenotype (causing a shift from type I slow twitch toward type II fast twitch myofibers) and reduced muscle endurance [160]. Together, these features contribute to the increased fatigability leading patients to dyspnea, fatigue and exercise intolerance.

The sustained hyperactivities of SNS and RAAS, described in the previous topics are directly associated with the pathogenesis of HF, can directly contribute to the changes in morphofunctional features related to skeletal myopathy. One of the main pharmacological therapies of HF is the blockade of the sympathetic and RAAS hyperactivity, through the use of β-blockers and ACE inhibitors or AT1 receptor antagonists, respectively; however, the effect of these treatments on skeletal myopathy has not been clarified yet. In contrast, it was already demonstrated that aerobic exercise training (AET) emerges as a potent non-pharmacological strategy to counteract HF-related skeletal myopathy and the evidences from basic science are strong enough to recommend it as an adjuvant therapy.

5.2 Sympathetic Hyperactivity and Skeletal Myopathy

The sympathetic activation in skeletal muscle tissue is mediated by β-adrenergic receptors (β-AR) and this activation can improve muscle regeneration process [151], increase force production, promote a shift toward type II glycolytic myofibers and increase muscle mass [99]. This hypertrophic response was described by studies which used β-AR agonists, such as *clenbuterol* and *formoterol* (selective β_2-AR agonists) and *isoproterenol* (a nonselective β-AR agonist) [71, 99, 173]. The cellular mechanisms involved in this process include, an inhibition in muscle proteolysis, mainly by ubiquitin-proteasome system (UPS), concomitantly with an increased protein synthesis, mainly associated with Insulin Like Growth Factor1/Phosphoinositide-3-kinase/Akt-protein kinase B/mammalian-mechanistic Target Of Rapamycin (IGF-1/PI3K/Akt/mTOR) signaling pathway [114–116].

Based on aforementioned hypertrophic effect, β-AR activators were prescribed to counteract the HF-related muscle myopathy in late 80's decade. In fact, some beneficial effects of β-AR agonists on muscle mass were observed; however, tachycardia was reported as a side effect [110]. Tachycardia occurred due to the β_1-AR related cardiac effect, while the hypertrophic effect of β-AR activators was demonstrated to be specific to selective β_2-AR agonists which would be more efficient to combat skeletal myopathy [52]. In this sense, our group observed that β_2-AR knockout mice displayed exercise intolerance and a severe muscle atrophy after myocardial infarction induced-HF [161]. One possible explanation is that in previous stages of HF, increased sympathetic activity through the activation of β_2-AR could be able to delay the onset of muscle proteolysis.

This seems to be the case in a mice model of sympathetic hyperactivity induced-HF, which was largely used in many studies of our group. At 3 months of age, although no signs of HF were present, these animals displayed sympathetic hyperactivity associated with *plantaris* muscle hypertrophy mediated by β_2-AR activation [10]. In the same mouse model, when HF syndrome turned severe, the *plantaris* atrophy and skeletal myopathy became evident. Therefore, while activation of β_2-AR by β_2-agonists seems to counteract skeletal myopathy in early stages of the syndrome, long-term and sustained activation of SNS leads to HF-related skeletal myopathy, which might be related to β_2-AR desensitization and downregulation reducing its anabolic effects. In fact, sympathetic hyperactivity besides being one hallmark of HF, it also contributes to the development of the skeletal myopathy [136].

5.3 Renin-Angiotensin-Aldosterone System Hyperactivity and Skeletal Myopathy

Angiotensin II (Ang II) is the main effector molecule of the system and its high levels are also a hallmark of HF leading to vasoconstriction, pro-inflammatory effects and reduced muscle regenerative capacity [45, 175]. High levels of Ang II induce protein breakdown and decrease the levels of skeletal muscle protein synthesis, leading to cardiac cachexia [47]. In addition to its direct effects on skeletal muscle, the indirect effects of Ang II can also contribute to muscle atrophy, due to its role in regulating circulating hormones and inflammatory cytokines. In this sense, Ang II increases interleukine-6 (IL-6) cytokine levels leading to an imbalance in the ratio between skeletal muscle protein synthesis and protein degradation by inhibiting IGF-I/Akt/mTOR signaling pathway while activating UPS [178]. It was observed that Ang II, when infused in rodents through osmotic pumps for up to 2 weeks, significantly decreased systemic IGF-I levels. In addition, the animals presented reduction in body weight and daily food intake, which are directly related to cardiac cachexia [25].

In addition to ACE inhibitors or AT1 receptor blockers, vasodilator agents are commonly used as hypertensive therapy in HF syndrome. However, it was shown that only the compounds that act directly in RAAS are able to block the changes in circulating IGF-I and body weight reduction, indicating that Ang II induces cardiac cachexia through a pressor-independent mechanism [5, 25].

Thus, pharmacological inhibition of RAAS can be recommended to avoid exercise intolerance and increasing the quality of life related to an attenuated skeletal muscle myopathy. In fact, HF treatment with ACE inhibitors increases respiratory muscle strength in humans [33] and partially prevents HF-induced muscle myopathy in rodents [184]. The same features were observed for AT1 receptor blockers which, at least in part, can attenuate the reduced muscle force in HF syndrome [44].

Even though the therapy with inhibitors of RAAS has demonstrated some positive outcomes in HF-related skeletal myopathy, AET also emerges as a potential non-pharmacological adjuvant therapy modulating RAAS.

5.4 *Aerobic Exercise Training: An Important Non-pharmacological Treatment for HF-Induced Skeletal Myopathy*

The aerobic exercise training (AET) have been studied in its basis for more than 50 years and nowadays it is recognized as an efficient and safe strategy in order to prevent and/or treat several cardiovascular diseases [43]. The beneficial effects of AET in HF have been demonstrated in heart, neurohumoral systems and skeletal muscle tissue. Therefore, both European [40] and American [68] guidelines have agreed upon the recommendation of AET in combination with an adequate pharmacological treatment. Interestingly, the responsiveness of skeletal muscle to AET is higher than to pharmacological therapy, which highlights the importance of the AET as strategy to counteract HF-related muscle myopathy. As will be described below, data from basic science provide strong evidence for AET as a prominent strategy to prevent and/or revert muscle metabolic and contractile dysfunction in HF.

5.5 *Effects of AET in the Metabolism and Function of the Skeletal Muscle*

HF causes many metabolic changes in the skeletal muscle tissue [100, 127]. Those changes, such as a switch toward type II glycolytic myofibers and decreased mitochondrial density and function, trigger a reduced aerobic capacity leading to muscle fatigue and exercise intolerance. Indeed, a decrease in protein expression of PGC-1α (peroxisome proliferator-activated receptor gamma), a potent regulator of mitochondrial biogenesis, was observed in animal models of HF [159]. In contrast, AET is able to modulate those metabolic changes due to its capacity to improve the production and the utilization of energy substrates by the muscle cells in a more efficient way. Such improvements in muscle substrate supply and uptake are optimized by the enhanced blood supply to skeletal muscle tissue, once AET prevents HF-induced capillary rarefaction [62]. In addition, AET promotes a shift toward oxidative type I myofibers in skeletal muscle tissue, which improves its oxidative features [10].

Due to the HF-related cachexia, the skeletal muscle contractile function is also impaired in HF and these features are strongly associated with changes in Ca^{2+} handling. In fact, rodents with HF displayed low levels of sarcoplasmic Ca^{2+} associated with reduced rate of sarcoplasmic reticulum Ca^{2+} release and reuptake [97, 126]. These findings are also observed in patients, since a reduced Ca^{2+} release and reuptake associated with decreased dihydropyridine receptors and sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA)2a protein expression in *vastus lateralis* was observed [109].

Herein, AET shows its effectiveness by improving skeletal muscle Ca^{2+} handling. In fact, our group have demonstrated that AET at moderate intensity can improve

the net balance of Ca^{2+} handling proteins in *soleus* and *plantaris* muscle from sympathetic hyperactivity induced-HF mice, culminating in a better muscle function [28]. Interestingly, Ca^{2+} handling is also observed in HF patients since leg extension training was able to reduce Ca^{2+} leaking through ryanodine receptors in *vastus lateralis* muscle [112].

5.6 *Effects of AET in Neurohumoral Hyperactivity and for the Control of Skeletal Muscle Mass*

As previously mentioned, cardiac cachexia is considered an independent predictor of morbidity and mortality in HF patients and animal models. This syndrome is triggered by neurohumoral hyperactivity in association with impaired muscle function. Besides no specific therapy is available until now for treating muscle wasting in HF syndrome, AET can counteract the muscle myopathy by improving muscle function and metabolism (direct effect) or by attenuating neurohumoral hyperactivity (indirect effect).

Regarding neurohumoral hyperactivity, it was demonstrated that a 4-month period of moderate intensity AET leads to a significant reduction in muscle sympathetic nerve activity in HF patients [136]. Although the mechanisms behind this reduction are a topic under current investigation, some potential candidates were identified, such as afferent autonomic control coordinated by arterial baroreceptors, cardiopulmonary receptors and chemoreceptors [27, 150]. In fact, it was observed that AET is able to improve metaboreflex and mechanoreflex [6]. In addition, reduced AT1 receptors and normalized ACE levels in the brain of HF rodent models have been proposed as one of the possible mechanisms of reducing sympathetic hyperactivity by AET [186]. Indeed, it was demonstrated that AET reduces serum Ang II levels, and such effect is related to a lower sympathetic activity in HF [58, 117].

The neurohumoral hyperactivity is also associated with high concentrations of pro-inflammatory cytokines and muscle *redox* imbalance, which are involved in muscle catabolism. In fact, increased circulating TNF-α levels (a pro-inflamatory cytokine) were observed in patients with atrophy and muscle weakness [118]. Moreover, the increased muscle TNF-α expression contributes to the local protein degradation. The effects of TNF-α on HF-related skeletal muscle myopathy are mediated through the activation of a family of transcription factors known as nuclear factor kappa B (NF-kB), which regulate UPS [1]. Interestingly, AET is able to reduce serum TNF-α levels and plasma inflammatory markers in HF patients [2]. This response is accompanied by a reduced atrophy and improved muscle function. In addition, AET also reduces muscle expression of pro-inflammatory cytokines in HF patients [54].

The high levels of TNF-α in HF triggers an increase in reactive oxygen species (ROS) production which will ultimately lead to protein degradation by the UPS [92]. UPS is up regulated in HF due to its action in degradation of damaged proteins

in skeletal muscle [8]. The key effectors of the UPS are the enzymes known as E3-ligases (ubiquitin ligases), which couples activated ubiquitin to lysine residues on protein substrates conferring specificity to the system [92]. Two of these E3-ligases (Atrogin-1 and MuRF1) were already well described and their transcriptional activities are elevated in skeletal muscle tissue under various atrophic conditions; therefore, making them good markers of atrophy being known as *atrogenes* [86]. In fact, it was observed that AET reduces Atrogin-1 mRNA levels and normalizes proteasome activity in skeletal muscle from both rodent models and HF patients, highlighting the importance of AET to prevent UPS hyperactivity in HF [55].

On the other hand, protein synthesis is essential to the positive control of the skeletal muscle mass. Since IGF-I muscle levels are reduced in HF [63], the activation of IGF-I/Akt/mTOR signaling pathway could be considered a good strategy to counteract HF-induced muscle atrophy. In fact, it was demonstrated that muscle-specific IGF-I transgenic expression or gene transfer procedure in muscles can sustain muscle hypertrophy [113] and prevent muscle mass loss in different animal models of muscle atrophy, such as Duchenne dystrophy [14], dexamethasone injection [138], immobilization [155], Ang II infusion [153], and HF [148]. In this same line, it is known that Akt gene transfer procedure in skeletal muscles from rodents can induce hypertrophy and improve the regenerative process [120]. In addition, transgenic mice with muscle-specific overexpression of Akt displayed around 40% of increase in skeletal muscle mass accompanied by an improvement in force development [19]. Therefore, another possible strategy to increase the expression of elements from IGF-I/Akt/mTOR could be through AET, since it is able to revert the reduced muscle IGF-I expression in HF patients [148].

These results highlight the fact that AET re-establishes the skeletal muscle homeostasis attenuating atrophy, and this was recently demonstrated by our group using a mice model of sympathetic hyperactivity induced-HF. In order to verify whether AET could ameliorate the HF-related skeletal muscle myopathy, mice underwent to moderate intensity AET (5 days a week for 8 weeks) were evaluated. As expected, HF mice displayed atrophic *soleus* muscle in both type I and type IIa myofibers. Interestingly, AET was effective in attenuating this atrophy. This protective effect against muscle atrophy was associated with a reversion in exercise intolerance and an increase in motor performance. In addition, it was suggested, at least in part, that one of the possible mechanisms related with that improvement in skeletal muscle mass and function was the reestablished level of some components of IGF-I/Akt/mTOR signaling pathway [9]. However, up to now, no study investigated the real role of Akt, mTOR and any other downstream related proteins of that signaling pathway in skeletal muscle tissue during the development of HF.

Collectively, it has been demonstrated that AET is able to promote remarkable beneficial adaptations in skeletal muscle tissue during the development of HF syndrome. Therefore, it can be considered the hypothesis that AET is a powerful non-pharmacological therapy in order to prevent the onset of the HF-related skeletal myopathy and to avoid cardiac cachexia.

6 Conclusions

HF syndrome in different experimental models is accompanied by autonomic dysfunction, neurohormonal hyperactivity, oxidative stress and inflammation that trigger progressive worsening of the cardiac function and a severe skeletal myopathy, that leads to the loss of functional capacity and poor quality of life. These chronic deleterious HF-induced alterations are responsible for the high mortality rates exhibited by HF patients. Experimental studies have provided ample evidence regarding the benefits of aerobic exercise training in this pathology, as summarized in Fig. 11.2. Exercise training is highly efficient in ameliorating HF-induced dysfunctions by acting in the same pathways targeted by current standard pharmacological care (i.e. β-blockers, ACE inhibitors and angiotensin receptor blockers, aldosterone-receptor antagonists). In addition, exercise training has been shown to correct vagal outflow, inflammatory response and skeletal myopathy, improvements not yet obtained through available pharmacological therapy. These findings support the efficacy of aerobic exercise training in the treatment of chronic HF with of the advantage of avoiding side effects.

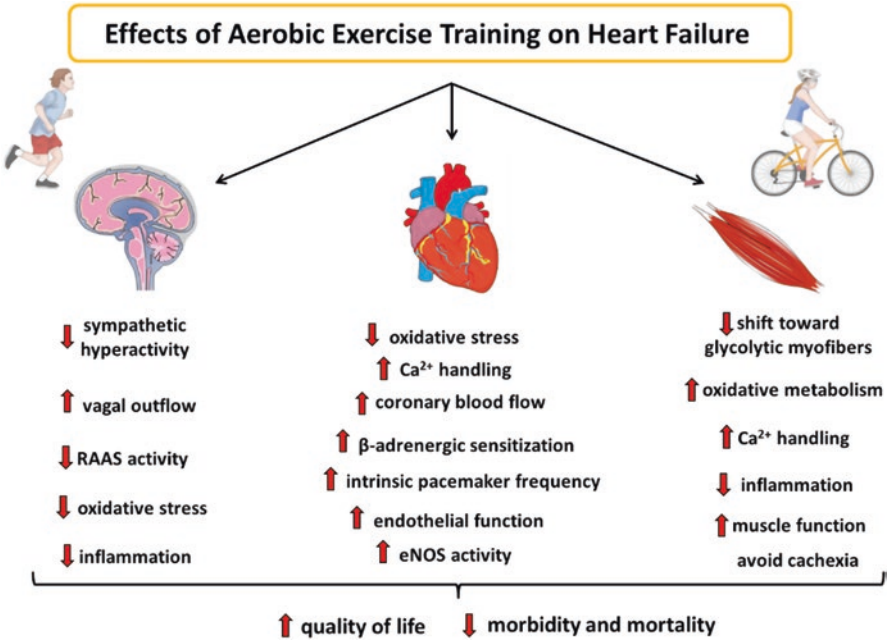

Fig. 11.2 The effects of aerobic exercise training on heart failure patients. eNOS, endothelial nitric oxide synthase, RAAS, renin-angiotensin-aldosterone system

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