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REVIEW | *Mechanisms of Exercise-Induced Amelioration of Cardiovascular Disease*

Revisiting the physiological effects of exercise training on autonomic regulation and chemoreflex control in heart failure: does ejection fraction matter?

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Andrade DC, Arce-Alvarez A, Toledo C, Díaz HS, Lucero C, Quintanilla RA, Schultz HD, Marcus NJ, Amann M, Del Rio R. Revisiting the physiological effects of exercise training on autonomic regulation and chemoreflex control in heart failure: does ejection fraction matter? *Am J Physiol Heart Circ Physiol* 314: H464–H474, 2018. First published November 22, 2017; doi:10.1152/ajpheart.00407.2017.—Heart failure (HF) is a global public health problem that, independent of its etiology [reduced (HFrEF) or preserved ejection fraction (HFpEF)], is characterized by functional impairments of cardiac function, chemoreflex hypersensitivity, baroreflex sensitivity (BRS) impairment, and abnormal autonomic regulation, all of which contribute to increased morbidity and mortality. Exercise training (ExT) has been identified as a nonpharmacological therapy capable of restoring normal autonomic function and improving survival in patients with HFrEF. Improvements in autonomic function after ExT are correlated with restoration of normal peripheral chemoreflex sensitivity and BRS in HFrEF. To date, few studies have addressed the effects of ExT on chemoreflex control, BRS, and cardiac autonomic control in HFpEF; however, there are some studies that have suggested that ExT has a beneficial effect on cardiac autonomic control. The beneficial effects of ExT on cardiac function and autonomic control in HF may have important implications for functional capacity in addition to their obvious importance to survival. Recent studies have suggested that the peripheral chemoreflex may also play an important role in attenuating exercise intolerance in HFrEF patients. The role of the central/peripheral chemoreflex, if any, in mediating exercise intolerance in HFpEF has not been investigated. The present review focuses on recent studies that address primary pathophysiological mechanisms of HF (HFrEF and HFpEF) and the potential avenues by which ExT exerts its beneficial effects.

autonomic control; chemoreflex drive; exercise training; heart failure

INTRODUCTION

Heart failure (HF) is a global public health problem that affects ~20% of people of >75 yr of age (3, 49). This progressive disease is generally characterized by an inability of the heart to pump sufficient blood to meet the metabolic demands of the tissues (41). Both HF with reduced ejection fraction (HFrEF; ejection fraction ≤ 40%) and HF with preserved ejection fraction (HFpEF; ejection fraction ≥ 50%) are highly prevalent (116) and are associated with similar morbidity and mortality rates (13). From an etiological standpoint, increases in sympathetic nerve activity, parasympathetic withdrawal, and activation of the renin-angiotensin system (RAS) initially act as an adaptive response to improve cardiac function (26, 120) but ultimately become maladaptive and contribute to progression of the disease (111).

Previous studies have indicated that a cardiac autonomic imbalance (sympathetic activation and vagal withdrawal) in HF results from biochemical alterations in central autonomic

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nuclei as well as altered function of peripheral autonomic reflexes (106). Several lines of evidence suggest that enhanced peripheral chemoreflex function as well as a decrease cardiac baroreflex sensitivity (BRS) contribute to the autonomic imbalance observed in HFrEF (4, 21, 65, 96, 109). Previous studies have indicated that an enhanced peripheral chemoreflex drive contributes to tonic sympathetic activation under eupneic conditions and that enhanced peripheral chemoreflex gain exacerbates sympathetic activation in response to repetitive apneas/hypopneas, which are common in HF patients (31, 98). Repetitive hypoxic/hypercapnic episodes associated with apneas and blood flow reduction to the carotid body (CB) secondary to the decrease in EF may further enhance chemoreflex gain and elicit plasticity in presympathetic neurons in the brain stem triggering sympathoexcitation and finally cardiac function deterioration (4, 21, 22, 109). In fact, previous studies have documented that chronic activation of presympathetic rostral ventrolateral medulla (RVLM) neurons in HFrEF rats is strongly associated with enhanced peripheral chemoreflex drive (21). The relative contribution of episodic hypoxia versus tonic chemoreflex activation to this phenomenon is undetermined. Mechanisms underlying autonomic imbalance in HFpEF are not as well characterized (4, 52, 106, 107). Recently, we showed that contrary to what has been described in HFrEF, central but not peripheral chemoreflex activation is a major contributor to the impairment of autonomic control in HFpEF (110). However, as well as what is observed in HFrEF, we have found increased oxidative stress, chronic hyperactivation of brain stem areas, and BRS impairment in HFpEF rats (5, 110). Hence, increased production of reactive oxidative species (ROS), which is likely associated with upregulation of the RAS, appears to contribute to sympathoexcitation in both types of HF, contributing to the progression of the disease (5, 21, 28, 29, 106, 108).

Despite the widespread use of antioxidant treatment, the relative efficacy of current therapies is limited. Thus, nonpharmacological approaches such as exercise training (ExT) may prove to be valuable adjuncts to standard therapy. Numerous studies in patients with HFrEF and in animal models have indicated that ExT has beneficial effects on cardiac function, quality of life, and survival and that these effects are associated with restoration of cardiac autonomic balance as well as attenuated oxidative stress in the brain stem (7, 10, 29, 40, 54, 71, 77, 88, 108, 117). It is unclear how changes in chemoreflex-mediated autonomic control relate to exercise tolerance in HF (81). This is of particular importance as HF patients that are exercise intolerant have a higher mortality risk (108). To date, few studies have addressed the therapeutic efficacy of ExT or the extent of exercise intolerance in HFpEF (116). This review will summarize the physiological effects of ExT in HF and discuss potential mechanisms by which ExT improves cardiac BRS, chemoreflex function, and autonomic control in HFrEF and HFpEF. In addition, we will also discuss potential mechanisms associated with exercise intolerance in HF.

AUTONOMIC ABNORMALITIES IN HF

The autonomic nervous system is composed of two complementary systems: the sympathetic nervous system and the parasympathetic nervous system (46). Functions of the sympathetic nervous system relevant to HF include contraction of vascular smooth muscle, acceleration of heart rate (HR), and increases in cardiac contractility. In contrast, activation of the parasympathetic nervous system decreases HR and cardiac contractility (46). Autonomic imbalance, characterized by increased sympathetic drive, is one of the major pathophysiological features of HF (4, 26, 85, 109, 111). A significant amount of research has focused on the contribution of central and peripheral chemoreceptors to this increased sympathetic drive in HF (84). Indeed, in HFrEF, it has been shown that central and peripheral chemoreflex activation contributes to increases in sympathetic outflow and to progression of the disease (11, 21, 31, 52, 64, 110). In contrast, very few studies have addressed the contribution of central and/or peripheral chemoreflexes to heightened sympathetic outflow in HFpEF (5, 110). Importantly, it has been shown that, after exercise training, HFrEF animals display improved peripheral chemoreflex control that is closely related to reductions in sympathetic tone (14, 58). On the other hand, Toledo et al. (110) showed that acute activation of central chemoreceptors contributes to abnormal cardiac autonomic control and cardiac dysfunction in HFpEF rats. Although several studies have shown beneficial effects of ExT on both chemoreflex and BRS in HFrEF, the potential positive effects of ExT on chemoreflex and BRS in HFpEF has not been studied extensively. Recently, we provided the first evidence showing that ExT improves cardiac baroreflex and autonomic control in HFpEF rats (5). In addition to these findings, previous studies have shown a salutary effect of ExT on chemoreflex function in HFrEF. The potential beneficial effects of ExT on central/peripheral chemoreflex control in HFpEF are unknown.

CARDIAC AUTONOMIC IMBALANCE IN HF

It has been shown that both HFrEF and HFpEF patients display high levels of circulating norepinephrine and decreases in HR variability (HRV), confirming that autonomic dysfunction is a hallmark of HF regardless of its etiology (49, 70, 110). Several hypothalamic and brain stem areas have been identified to contribute to the development of autonomic imbalance in HF (4, 5, 21, 26, 85, 108, 109). The paraventricular nucleus (PVN) of the hypothalamus, the subfornical organ (SFO), and the RVLM are all recognized as integration sites for neural activity that controls sympathetic outflow (35, 47, 60). Interestingly, in HFrEF rats, enhanced peripheral chemoreflex drive is strongly associated with chronic activation of RVLM presympathetic neurons (21). Furthermore, ablation of the peripheral chemoreceptors normalizes RVLM neuronal activity and restores normal autonomic control in HFrEF rats (21). In addition, it has been shown that peripheral chemoreceptor stimulation activates PVN neurons in healthy rats, suggesting that the PVN may also participate in the peripheral chemoreceptor-induced sympathoexcitation observed in HFrEF (53). However, causal evidence to support this hypothesis is lacking, and future studies should address this issue. Recently, we showed that RVLM neurons are chronically active in HFpEF rats (110); however, the pathophysiological contribution of autonomic hyperreflexia and/or chronic activation of the RVLM, PVN, or SFO to heightened sympathetic activity has not been established in HFpEF (Table 1).

On the other hand, parasympathetic withdrawal is also a characteristic present in both experimental and human HF.

Table 1. *Effect of exercise training on peripheral and central chemoreflex, brain stem oxidative stress and angiotensin II, autonomic control, and cardiac function in heart failure with reduced and preserved ejection fraction*

	Chemoreflex				Autonomic Control			
	Peripheral	Central	Baroreflex	Brainstem (Oxidative Stress)	Heart rate variability	Nerve recording	Cardiac Function	Reference(s)
Heart failure with reduced ejection fraction								
Patients	ND	ND	↑	ND	↑	↑	↑	17, 33, 48, 54, 62, 63, 71, 88, 98, 114
Animal models	↑	ND	↑	↑	ND	↑	↑	14, 29, 58–60, 67, 82
Heart failure with preserved ejection fraction								
Patients	ND	ND	↑	ND	↑	ND	↑ ↓	6, 71, 91
Animal models	ND	ND	↑	↑	↑	ND	↑ ↓	5

↑, Improvement; ↓, worsening; ↑ ↓, controversial results; ND, not described in the literature.

Contrary to what is known to be related to sympathetic control in HF, the contribution of parasympathetic withdrawal on autonomic regulation and deterioration of cardiac function in HF has been poorly studied. Evidence obtained in rats subjected to myocardial infarction (leading to HFrEF) showed that vagal nerve stimulation (10 s/min) significantly reduced mortality compared with unstimulated HF rats (57). Recently, Garrott et al. (30) showed that selective activation of parasympathetic neurons reduces myocyte hypertrophy, cardiac fibrosis, and cardiac systolic and diastolic function in HFrEF rats. Much less is known about the role of parasympathetic control on autonomic imbalance, cardiac arrhythmias, and cardiac function in HFpEF. Recently, we showed that, in HFpEF rats, ExT is an effective means to improve the vagal component of HRV, decrease cardiac arrhythmias, and improve cardiac function (5). Therefore, the beneficial effects of ExT on autonomic regulation in HF are not restricted to reductions in sympathetic outflow but may also improve parasympathetic control of the heart. Further studies will need to be performed to elucidate the mechanisms underlying parasympathetic withdrawal in HF.

CHEMOREFLEX AND BAROREFLEX DYSREGULATION CONTRIBUTES TO THE AUTONOMIC IMBALANCE IN HF

The Chemoreflex

Peripheral and central chemoreceptors play a pivotal role in the maintenance of arterial blood gases, pH, and cardiovascular regulation (12, 87). The CBs are the main peripheral chemoreceptors (43, 44) and play an important role in the control of cardiorespiratory function at rest and during exercise (94). The CB responds to changes in arterial P_{O_2}, P_{CO_2}, pH, glucose, and blood flow (18, 22, 24, 43, 51). The activation of type I CB glomus cells triggers a reflex response that results in increases in pulmonary ventilation, arterial blood pressure, HR, and sympathetic activity (95, 97). Several studies have demonstrated that peripheral chemoreflex function is altered in HF (4, 94, 105, 110). In HFrEF, it has been shown that the CB-mediated chemoreflex is oversensitized and plays a fundamental role in the progression of the disease (21, 75, 84). Del Rio et al. (21) showed that, in myocardial infarcted HF rats, selective CB denervation decreased sympathetic outflow to the heart and significantly reduced mortality. Recently, Niewinski et al. (76) showed that, in patients with HFrEF, unilateral CB resection restored autonomic control and partially improved peak O_2 consumption during the exercise capacity test (Fig. 1). These findings suggest that the peripheral chemoreflex plays an important role in the control of sympathetic outflow and the cardiovascular response to exercise in HFrEF.

Central chemoreceptors are located throughout the brain. However, the retrotrapezoid nucleus (RTN) located on the ventral medullary surface of the brain stem represents a major chemosensitive area (73, 104). RTN chemoreceptor neurons are pH-sensitive cells secondary to enhanced P_{CO_2} and regulate the activity of the respiratory pattern generator (35, 38, 70). Importantly, neurons from the RTN serve as an integration center for chemosensory information from other central and peripheral sites, including the CB (37). Several studies have shown that central chemoreflex function is enhanced in both animals and humans with HFrEF (52, 72). Central chemoreflex function in HFpEF is not well characterized; however, Giannoni et al. (31) showed that hypersensitivity to hypercapnia is a major predictor of mortality events in HF patients. In addition, Kristen et al. (52) showed that HFpEF rats displayed enhanced renal sympathetic nerve activity responses to hypercapnia, suggesting that an oversensitive central chemoreflex may contribute to autonomic imbalance in this HF type. Furthermore, we recently showed that central chemoreflex sensitivity is markedly increased in HFpEF rats without alterations in peripheral chemoreflex function. Perhaps more importantly, acute activation of the central chemoreflex (fraction of inspired CO_2 7%) had adverse effects on cardiac autonomic control in HFpEF rats (Fig. 2) (110). Taken together, these results sug-

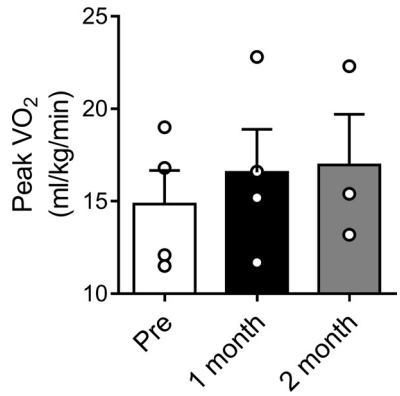

Fig. 1. Effect of unilateral carotid body resection on peak O_2 consumption ($\dot{V}_{O_2}$) during exercise in heart failure (HF) patients. Exercise capacity was assessed using treadmill spiroergometric test, and peak $\dot{V}_{O_2}$ was calculated. Note that peak $\dot{V}_{O_2}$ was increased at 1 and 2 mo after unilateral carotid body resection compared with baseline in patients with systolic heart failure (pre). [Data adapted from Niewinski et al. (76).]

gest that central chemoreceptors may contribute to exaggerated sympathoexcitation in HFpEF and that CB hyperreflexia is not enhanced, as it is in HFrEF.

The Baroreflex

Baroreceptors are strectch receptors located in the aortic arch and carotid bifurcation and sense short-term fluctuations in blood pressure (3, 4, 19, 89). Activation of baroreceptors triggers a reflex response that results in increased parasympathetic tone and decreased sympathetic tone. In contrast, unloading of baroreceptors results in sympathoexcitation (2, 67). Several studies have shown that BRS is decreased in both HFrEF and HFpEF (5, 16, 115). More importantly, it has been shown that a reduced BRS is strongly associated with mortality rate in HF (99). Indeed, HF patients with <3 ms/mmHg BRS gain had decreased survival rate compared with HF patients that showed >3 ms/mmHg BRS gain (99). Although the mechanisms underlying BRS impairment are not completely known, it is well accepted that activation of chemoreceptors results in baroreflex inhibition in HFrEF. Indeed, Del Rio et al. (21) showed that CB denervation in rats with HFrEF completely restored normal BRS. Taken together, this evidence strongly suggests that hyperactivation of peripheral chemoreceptors promotes baroreflex control impairment (83) and that both may contribute to disease progression/maintenance in HFrEF.

In HFpEF, less is known about baroreflex control impairment. Nevertheless, possible interactions between peripheral chemoreflex and BRS are less likely since the peripheral chemoreflex is not enhanced in HFpEF rats (110). However, it has been shown that HFpEF rats displayed both an increase central chemoreflex drive (21, 111) and a decrease in BRS (5, 74). Therefore, it is plausible that, in HFpEF, interactions between central chemoreceptor areas and baroreflex control-related areas within the brain stem might account for the reduction in BRS in HFpEF. Further studies should address the precise mechanisms underpinning baroreflex impairment in HFpEF.

ExT: A NONPHARMACOLOGICAL APPROACH TO IMPROVE AUTONOMIC FUNCTION IN HF

Several studies have shown that ExT mitigates sympathetic activation in animals with HFrEF (29, 65, 67, 68, 86). Masson et al. (67) showed that the beneficial effects of ExT on autonomic function in HF rats are critically dependent on the exercise paradigm used. Indeed, 8 wk of endurance ExT (70% of maximal capacity/30 min per day) and moderate-interval ExT (5 min at 80% of maximal capacity followed by 5 min at 60% of maximal capacity/30 min per day) induced similar improvements in cardiac function, but only endurance ExT (low or moderate intensity and high volume) improved cardiac autonomic control (67). In concordance with these findings, improvements in frequency and time domain components of HRV are observed in patients with HFrEF that undertake an endurance ExT program (Fig. 3 and Table 1) (40, 71, 88, 100). These findings suggest that endurance ExT is a potential therapeutic strategy to improve autonomic imbalance and cardiac function in HFrEF patients.

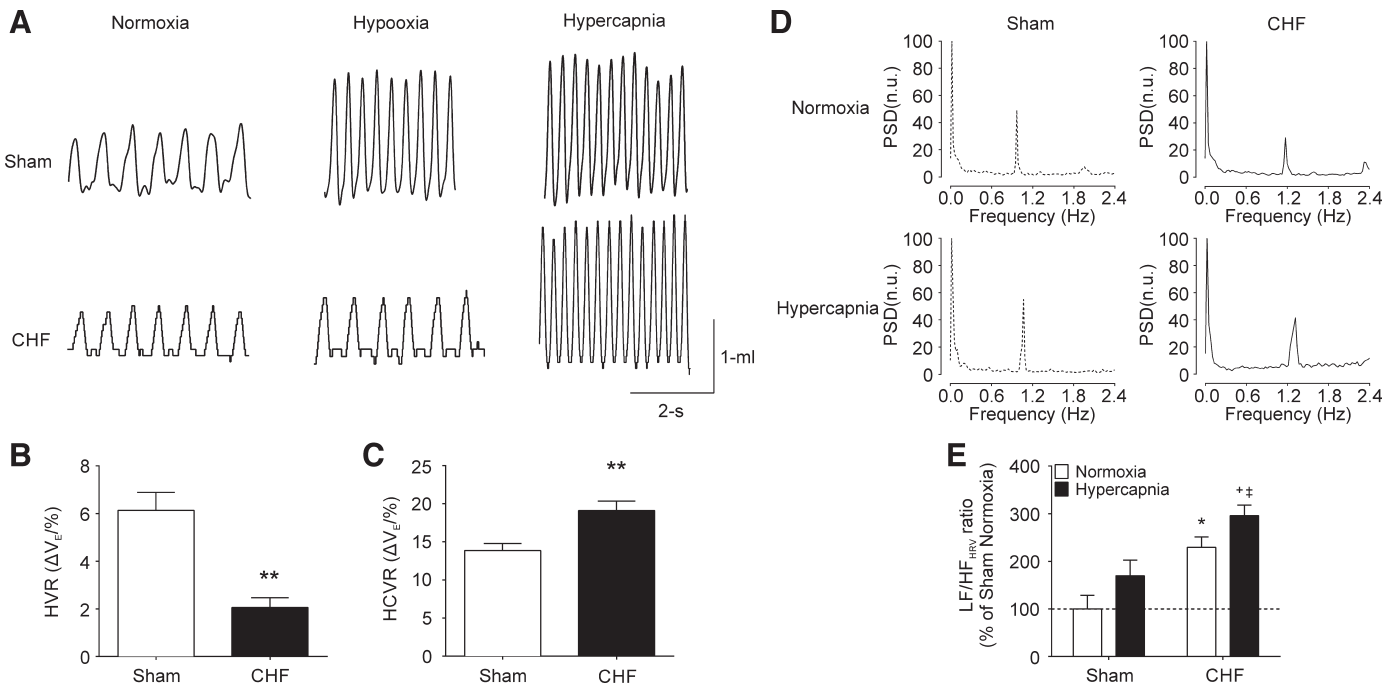

Fig. 2. Increase central chemoreflex sensitivity worsens cardiac autonomic imbalance in experimental heart failure (HF) with preserved ejection fraction (HFpEF). *A*: representative recordings of tidal volume (V_T) in normoxia (21% fraction of inspired O_2), hypoxia (10% fraction of inspired O_2), and hypercapnia (7% fraction of inspired O_2) in one sham rat and one HF rat. *B* and *C*: gain of the hypercapnic ventilatory response (HCVR) but not the hypoxic ventilatory response (HVR) was increased in HFpEF rats. $n = 6$ rats. $^{**}P < 0.01$ vs. the sham condition. *D*: representative heart rate variability (HRV) spectrums during normoxia (21% fraction of inspired O_2) and during brief hypercapnic (7% fraction of inspired O_2, 30 s) stimulation in one sham rat and one HF rat. *E*: summary data showing the effects of hypercapnia on the low-frequency (LF)/high-frequency (HF) ratio of HRV. Note that acute central chemoreflex activation worsens cardiac sympatho-vagal imbalance in HFpEF rats. $n = 4$ rats. $^{*}P < 0.01$ vs. sham + normoxia; $^{+}P < 0.05$ vs. chronic HF + hypercapnia; $^{‡}P < 0.05$ vs. sham + hypercapnia. [Modified from Toledo et al. (110) with permission.]

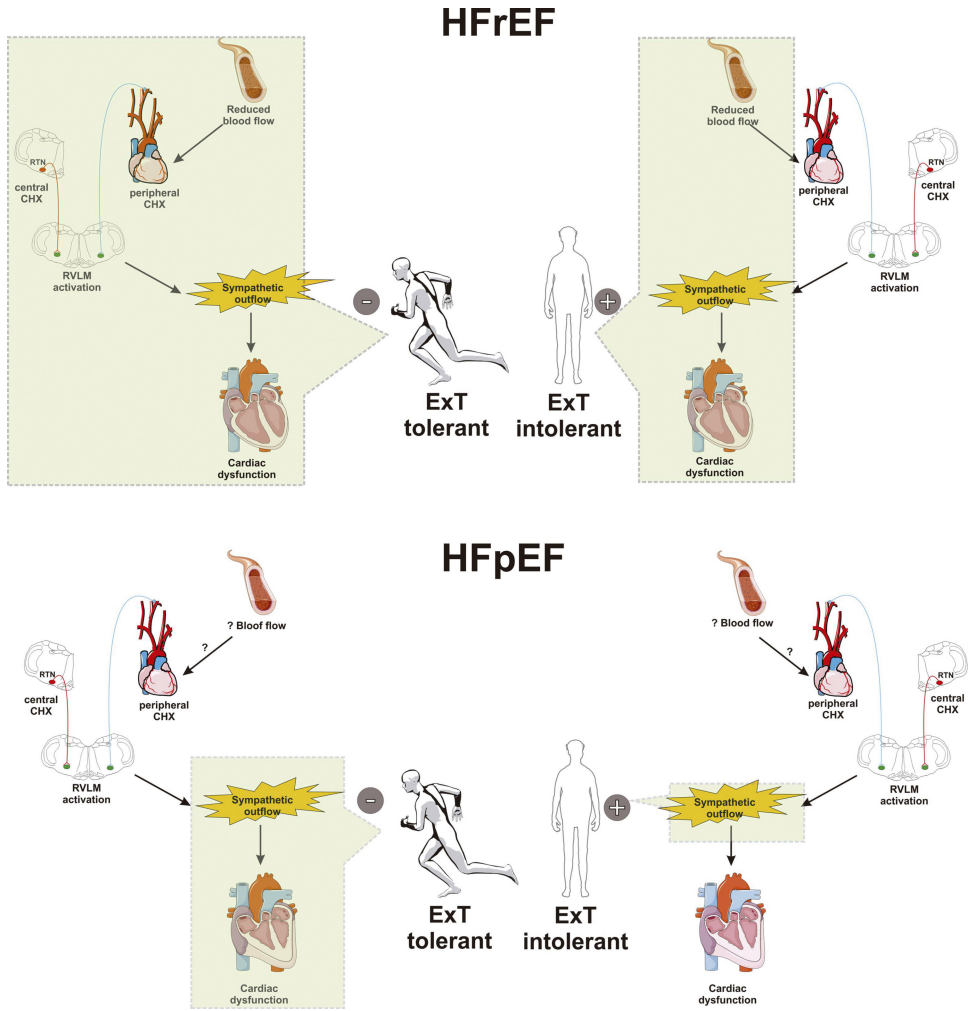

Fig. 3. Effect of exercise training (ExT) on the pathophysiology of heart failure (HF) with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF). HF is characterized by augmented central and peripheral chemoreflex drive, activation of brain stem autonomic control nuclei (i.e., rostral ventrolateral medulla), and sympathoexcitation, which all promote cardiac dysfunction, worsening quality of life and lifespan. In exercise-tolerant HFrEF animals and patients, ExT restores blood flow to the muscle, brain, and carotid body chemosensitive cells, normalizing peripheral chemoreflex drive. On the contrary, in the HFrEF exercise-intolerant population, no effect of ExT on blood flow is can be found, and peripheral chemoreflex drive remains potentiated, promoting sympathoexcitation and cardiac dysfunction. Less is known about the role of ExT on HFpEF progression. Indeed, the effect of ExT on blood flow and chemoreflex sensitivity has not been studied. However, recent evidence showed in experimental HFpEF that ExT restored autonomic control in exercise-tolerant animals. Interestingly, HFpEF patients with exercise intolerance display a further deterioration in cardiac autonomic imbalance during ExT. In summary, ExT may hasten HF pathophysiology in the exercise-intolerant population, an effect that is independent of HF ethiology. The mechanism associated with exercise tolerance in HF deserves future investigation.

The effects of ExT on autonomic control in HFpEF patients have not been studied extensively (Fig. 3 and Table 1) (1). Murad et al. (71) showed that ExT imparts less robust improvements in HRV (SD of all normal RR intervals) compared with its effects in HFrEF. This study strongly suggests that ExT (1 h/day, 3 days/wk per 16 wk at 60% of HR reserve) in groups with similar demographic characteristics (age: 68.0 ± 40.8 yr and NYHA: New york Heart Association II and III) but with different HF etiology (HFrEF and HFpEF) has a differential effect on autonomic function (71). Recently, we showed that 6 wk of endurance ExT results in improvements in cardiac systolic function and cardiac arrhythmogenesis in rats with HFpEF (5). We also observed that sympathetic activation, parasympathetic withdrawal, and BRS impairment were all restored after ExT (5). To date, there are no comprehensive studies addressing the effects of ExT on autonomic control in HFpEF patients; however, there have been a number of randomized control trials examining the general effect of ExT on HFpEF patients (23). Interestingly, several of these studies have suggested that ExT elicits only minor improvements in HFpEF and does not improve cardiac diastolic function or exercise capacity (23, 80). In concordance with this evidence, we observed no effect of ExT on cardiac diastolic function in experimental HFpEF (5). Importantly, Angadi et al. (6) showed that the beneficial effects of ExT in patients with HFpEF appear to be critically dependent on the exercise paradigm. Four weeks of high-intensity interval training (85–90% of peak HR/4 × 4 min followed by 3 min of active recovery) but not moderate-intensity aerobic continuous training (70% peak HR/30 min per day) resulted in a marked improvement in peak O_2 consumption and diastolic function in HFpEF patients (6). Future studies should address the possible contribution of different ExT programs on autonomic regulation in HFpEF patients.

ExT MODULATES CHEMOREFLEX AND BAROREFLEX FUNCTION IN HF

Recent studies have indicated that altered chemoreceptor and baroreceptor functions, especially an enhanced peripheral chemoreflex and decreased BRS, both play an important role in the progression of HF (21, 31, 92, 99) and may contribute to exercise intolerance (75). Niewinski et al. (76) showed that unilateral CB resection results in decreased peripheral chemosensitivity, decreased sympathetic activity, and partial improvement in exercise tolerance (Fig. 1). Importantly, HF patients that underwent CB resection displayed a significant improvement in exercise times (566 ± 73 vs. 642 ± 70 s, P = 0.03, baseline vs. 6 mo after CB resection, respectively) (76). However, no change in BRS was observed (76). These results

strongly suggest that peripheral chemoreflex dysfunction, and not baroreflex control, contributes to reductions in exercise tolerance in HFrEF. Despite the finding that CB resection is a feasible approach to treatment of HFrEF patients, it has been proposed that ExT may have better results than CB denervation since ExT also improves endothelial function and increases blood flow to many vascular beds (45). Moreover, previous studies have indicated that ExT can also reduce the increases in tonic peripheral chemoreflex activity and improve BRS (Table 1) (17, 58, 65, 86). Indeed, in rabbits with pacing-induced HFrEF, it has been shown that endurance ExT (8 m/min followed by 20 min at 13 m/min and a subsequent cooldown period of 8 m/min for 5 min, 5 days/wk) partially reverses the chemoreflex-mediated increases in sympathetic tone to the heart and to the kidney (58, 65). In addition, Calegari et al. (14) showed that in rats with myocardial infarction-induced HFrEF, the pressor response elicited by intravenous potassium cyanide, a peripheral chemoreceptor stimulant, was reduced after ExT (16 m/min, 60 m/day, 5 days/wk, 8 wk). Taken together, these studies suggest that the beneficial effects of ExT on autonomic control in HFrEF are partially mediated by the restoration of normal peripheral chemoreflex function. However, it is worth noting that these studies did not determine whether the effect of ExT on chemoreflex control and sympathetic activation occurred in tandem or whether one lead to the other. Contrary to what is known in HFrEF, the effect of ExT on peripheral and/or central chemoreflex function in HFpEF has not been studied extensively (Table 1) (4, 116).

Toledo et al. (110) previously reported that central chemoreflex function, but not peripheral chemoreflex function, is enhanced in HFpEF. Furthermore, they showed that acute activation of the central chemoreflex worsens cardiac autonomic function, cardiac arrhythmogenesis, and cardiac diastolic function in HFpEF rats (Fig. 2). Determining whether ExT has any effect on the enhanced central chemoreflex and/or cardiac autonomic dysfunction observed in HFpEF is an important area of study to be addressed in the future.

MECHANISMS UNDERLYING CHEMOREFLEX DYSFUNCTION IN HF

Some of the purported mechanisms underlying enhanced CB chemoreflex activation and consequently autonomic dysfunction in HFrEF include oxidative stress in the CB and both oxidative stress and chronic hyperactivation in RVLM-C1 neurons (21, 24, 58). It has been postulated that the primary stimulus for these biochemical changes in the CB and RVLM is the reduction of blood flow secondary to decreased cardiac output in HFrEF (24). In support of this notion, blood flow reduction per se is sufficient to recapitulate many physiological and biochemical aspects of the enhanced chemoreflex drive observed in HFrEF (24). In contrast, in rats with HFpEF, the primary mechanism associated with altered chemoreflex function is not related to blood flow restrictions to the CB (22). Indeed, we observed that HFpEF rats showed normal CB blood flow and no sensitization of the CB-mediated chemoreflex (22). Nevertheless, we found that HFpEF rats displayed an enhanced central chemoreflex drive, suggesting that factors other than blood flow reduction are involved in the altered chemoreflex drive and autonomic imbalance in HFpEF (110). Interestingly, Rosin et al. (91) showed bilateral anatomic connections between RTN and RVLM-C1 neurons. Several groups have shown that acute stimulation of central chemoreceptor triggers sympathoexcitation in humans (103), rats (79), and cats (69). Importantly, we showed that hypercapnic stimulation (fraction of inspired CO_2: 7%) induces a HRV disturbance in HFpEF rats characterized by a shift in the spectral components toward a more sympathetic predominance (110). Therefore, it is plausible to hypothesize that in HFpEF, sympathoexcitation may result from increased activity of central RTN chemoreceptor neurons projecting to RVLM-C1 sympathetic neurons. Is important to note that ExT normalizes cardiac autonomic balance in HFpEF rats (5). Thus, it is plausible that ExT may also restore normal central chemoreflex sensitivity as a result of normalizing RTN/RVLM cross-talk in HFpEF. The effects of ExT on central chemoreflex drive in HFpEF require further study.

CENTRAL MECHANISMS CONTRIBUTING TO AUTONOMIC DYSFUNCTION IN HF

Oxidative stress plays an important role in the progression of HF (112). Increases in ROS formation in the brain stem are a major contributor to sympathoexcitation in HF (5, 111). Several studies have shown that, independent of HF etiology, there is a marked change in the balance between pro- and antioxidant enzyme expression and/or activation that contributes to increased systemic (9), cardiac (15), and central nervous system ROS production (29, 31, 110). Intracellular redox balance in the brain stem is significantly shifted in a prooxidative direction by alterations in pro-/antioxidant enzyme expression in HFrEF. NADPH oxidase (NOX) is upregulated, whereas CuZn-superoxide dismutase (CuZn-SOD) and manganese-superoxide dismutase (Mn-SOD) are both downregulated, in the RVLM of HFrEF animals (29, 93). Less is known about the cellular and molecular mechanisms associated with sympathoexcitation in HFpEF. We recently showed that ROS formation in RVLM neurons of HFpEF rats is increased (5, 110) and that this is associated with increased phosphorylation of the $p47^{phox}$ subunit of NOX (5). In contrast to findings in HFrEF rats, CuZn-SOD enzyme expression in the RVLM was not decreased in HFpEF rats (5). These results suggest that a prooxidative shift in redox balance within the RVLM of HFpEF rats is related to NOX activation rather than downregulation of CuZn-SOD. The effects of ExT on other antioxidant enzymes (i.e., Mn-SOD) during the progression of HFpEF deserve further study.

Besides the RVLM, other brain regions have been also described as potential contributors to sympathoexcitation in HF (8, 78, 119). Indeed, the nucleus of the tractus solitarius (NTS), which represents the primary central integration site for peripheral chemoreceptor and baroreceptor activity, has been identified as a master regulator of chemoreflex and baroreflex function (36). Interestingly, in both HFrEF and HFpEF, there is a significant overexpression of the angiotensin II type 1 receptor in the NTS, suggesting an inflammatory process and oxidative stress in this area (90, 101, 118). In addition, it has been shown that the PVN and SFO are both hyperactive in HFrEF and contribute to impairment of autonomic function (119). The role of the NTS, PVN, and SFO in HFpEF pathophysiology remains largely unknown. Future studies are needed to deter-

mine the contribution of these areas in the progression and maintenance of altered autonomic function in HFpEF.

ExT AND MUSCLE BLOOD FLOW REGULATION IN HF

It has been proposed that chronic reductions in blood flow to various tissues in the body contribute to autonomic dysregulation and the progression of both HFrEF and HFpEF (14, 24, 56). Reductions in blood flow in HF are mediated, at least in part, by reduced cardiac output and increases in peripheral vascular resistance associated with increased sympathetic outflow to blood vessels (2, 102). In addition to contributing to autonomic dysregulation, blood flow reduction to exercising muscle likely contributes to exercise intolerance in both HFrEF and HFpEF (25, 56). Indeed, leg blood flow during single-leg knee extension exercise is reduced in HFrEF patients (2). Thus, chronic blood flow reduction may contribute to enhanced peripheral and central chemoreflex drive in HFrEF and HFpEF, which in turn may further exacerbate reductions in muscle blood flow associated with reduced cardiac output. While there is some evidence to suggest that hyperactivation of the sympathetic nervous system in HF contributes to exercise intolerance, there is currently no evidence about the contribution of altered chemoreflex function on sympathetically mediated increases in peripheral vascular resistance in either HFrEF and HFpEF.

Mechanistically, the cellular and molecular effects of chronic blood flow reduction are likely due to altered expression of several transcription factors or activation of signaling pathways that are sensitive to shear stress. Kruppel-like factor 2 (KLF2) is a mechanosensitive transcription factor that responds to alterations in blood flow and shear stress (20), which may be a viable link between chronic blood flow reduction and biochemical changes that lead to autonomic dysregulation in HF. HFrEF rats have significantly lower KLF2 expression in tissue from the peripheral chemoreceptors (39). Importantly, statin treatment, a known inducer of KLF2 expression, restores CB KLF2 expression, reduces chemoreflex sensitivity, and normalizes autonomic dysfunction (39). This evidence strongly suggests that KLF2 expression plays a pivotal role in HFrEF pathophysiology. It is unknown whether or not expression of KLF2 or any of its downstream targets play an important role in mediating muscle blood flow during exercise or exercise tolerance in general.

Finally, it is well established that resting blood flow to several organs is improved after completion of an ExT program in HF (65, 86, 100); however, the effects of ExT on muscle blood flow in HFpEF are not well established. Based on our previous studies, it is reasonable to hypothesize that ExT exerts its beneficial effects on CB function in HFrEF through the upregulation of CB KLF2. Further investigations are needed to determine whether this pathway is a primary target of ExT. Currently, there are no studies addressing blood flow reduction in the central nervous system or any potential beneficial effect of ExT on central nervous system blood flow in HFpEF.

EXERCISE INTOLERANCE IN HF

It has been shown that both HFrEF and HFpEF patients have severe exercise intolerance (113), which is considered one of the initial points in the pathogenesis and diagnosis of HF (34). Exercise intolerance is characterized by reduced exercise capacity and the presence of dyspnea during daily activities, symptoms that worsen the quality of life (107). Importantly, Tabet et al. (108) showed that HFrEF patients who are unable to complete ExT have increased mortality rates compared with patients that were able to complete ExT. The ExT protocol consisted of 5 sessions/wk for 4−8 wk (30 min of segmental gymnastics and 40 min of cycling on a cycle ergometer). Patients that improved <2 ml·kg^{-1}·min^{-1} in O_2 consumption had a lower survival rate compared with the exercise-tolerant patients (108). Importantly, exercise tolerance appears to be independent of the degree of cardiac failure since tolerant and intolerant HF patients display similar initial values of HF deterioration (108). It is worth noting that no determinations of autonomic control and chemosensitivity between tolerant versus intolerant HF patients were addressed by Tabet et al. (108). Taking into account that unilateral CB resection improved peak O_2 consumption and improved exercise capacity in HFrEF patients (75), it is possible to hypothesize that exercise intolerance in HF may be related to the peripheral chemoreflex dysfunction. Indeed, it has been suggested that impairments in O_2 transport from the blood to muscle in both HFrEF and HFpEF play a key role in the development of exercise intolerance (25). Therefore, it is possible that increases in vascular resistance result from the enhanced peripheral/central chemoreflex drive in HF and that any ExT-mediated improvements in peripheral/central chemoreflex function could potentially improve exercise tolerance.

Another mechanism that may contribute to the development of exercise intolerance in HF is parasympathetic withdrawal. Indeed, recent evidence obtained in healthy animals revealed that optogenetic silencing of vagal neurons from the dorsal motor vagal nucleus significantly reduces exercise capacity (61). Importantly, studies of both experimental and human HF have shown a marked decrease in cardiac vagal tone. Thus, future studies should focus on the role of decreased parasympathetic activity in the development of exercise intolerance in HF.

Alterations in cerebral blood flow have been also proposed to participate in exercise tolerance in HF (12, 27, 32). HFrEF patients display brain hypoperfusion and reduced cerebral metabolism (55). Indeed, Koike et al. (50) demonstrated the presence of cerebral hypoperfusion during an incremental symptom-limited maximal exercise test in HF patients. In addition, Fu et al. (27) showed that altered cerebral hemodynamics were associated with the reduced functional capacity displayed by HF patients, suggesting that the attenuated cerebrovascular response to exercise contributes to the decline in functional capacity. Taking into account that brain hypoperfusion is related to sympathoexcitation (66), reductions in blood flow to the brain in HF may be mediated at least in part by the enhanced sympathetic activity that, in turn, contributes to exercise intolerance during the progression of the disease. Also, recent evidence obtained in healthy rats shows that purinergic signaling mediates RTN central chemoreceptor gain by regulating blood vessel dilation during hypercapnic stimulation (42). Interestingly, in HFpEF, there is a significant increase in central chemoreflex gain. Therefore, it is plausible to hypothesize that disruption of the normal purinergic signaling in the RTN may take place in HF to potentiate the central chemoreflex. Thus, ExT may improve central chemoreflex in HFpEF by normalizing vasodilation in the RTN. HF patients

that are intolerant of ExT may not show exercise-induced vasodilation in the RTN and thus no restoration of normal chemoreflex drive or autonomic balance would be expected to occur. These novel hypotheses deserve further investigation.

FUTURE PERSPECTIVES

ExT has been shown to be an effective treatment to improve autonomic control, cardiac function, arrhythmogenesis, and survival in HFrEF patients (10, 29, 40). However, little is known about the effects of ExT on the outcome of HFpEF patients. Recently, we showed that ExT positively impacts autonomic control and cardiac function in HFpEF rats (5). Interestingly, the beneficial effects of ExT on HF are associated with the level of tolerance/intolerance to physical exercise (108). Exercise intolerance is a predictor of hospital readmission and mortality in HF (107). Common factors are involved in exercise intolerance that appear to be independent of HF etiology. Factors such as sympathovagal imbalance and reductions in brain and muscle blood flow have all been associated with exercise intolerance in patients and animal models of HF (12, 27, 56). The precise mechanism by which ExT improves HF outcome is a still a matter of debate. Future studies should address the effects of ExT on peripheral/chemoreflex function and brain stem autonomic control areas and their relationship with exercise tolerance in both HFrEF and HFpEF.

CONCLUSIONS

HFpEF or HFrEF is characterized by a marked impairment in cardiac autonomic control, which ultimately hastens cardiac function deterioration. ExT has been proposed as an effective means to restore/improve autonomic control. Indeed, it has been shown that ExT normalizes cardiac autonomic control in experimental HFrEF and HFpEF. The mechanisms associated with the beneficial effects of ExT on autonomic regulation are still a matter of debate, but it seems that in both HFrEF and HFpEF, ExT is able to significantly reduce oxidative stress in key brain stem areas related to sympathetic control. Other mechanisms (i.e., cerebral blood flow normalization) can certainly contribute to reduce sympathoexcitation in HF after ExT, but causal links are missing. Importantly, sympathoexcitation and parasympathetic withdrawal appear to be linked to an increased sensitivity of peripheral and central chemoreceptors and decreased BRS in HFrEF and HFpEF. Therefore, ExT may also exert beneficial effects on cardiac autonomic function through the normalization of both chemoreflex drive and cardiac BRS. Whether or not this effect is cause or consequence of the improvements in cardiac function after ExT still remains to be determined. Ultimately, exercise intolerance is of major importance in HF, and addressing the mechanisms underlying it may improve prognosis in HFrEF and HFpEF populations. Importantly, there is no evidence showing the precise mechanisms associated with exercise tolerance in HF. It is plausible that altered chemoreflex function in HF may provide an explanation for this phenomenon, but this hypothesis requires further study.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.C.A., C.T., and H.SD prepared figures; D.C.A., A.A.-A., C.T., H.S.D., and R.D.R. drafted manuscript; D.C.A., A.A.-A., C.T., H.S.D., C.L., R.Q., H.D.S., N.J.M., M.A., and R.D.R. edited and revised manuscript; D.C.A., A.A.-A., C.T., H.S.D., C.L., R.Q., H.D.S., N.J.M., M.A., and R.D.R. approved final version of manuscript.

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