Review

Autonomic cardiovascular reflex control of hemodynamics during exercise in heart failure with reduced ejection fraction and the effects of exercise training

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Abstract

Heart failure with reduced ejection fraction is associated with increased exercise intolerance, morbidity, and mortality. Importantly, exercise intolerance in heart failure with reduced ejection fraction is a key factor limiting patient quality of life and survival. Exercise intolerance in heart failure with reduced ejection fraction stems from a multi-organ failure to maintain homeostasis at rest and during exercise, including the heart, skeletal muscle, and autonomic nervous system, lending itself to a system constantly trying to “catch-up”. Hemodynamic control during exercise is regulated primarily by the autonomic nervous system, whose operation, in turn, is partly regulated via reflexive information from exercise-stimulated receptors throughout the body (e.g., arterial baroreflex, central and peripheral chemoreceptors, and the muscle metabo- and mechanoreflexes). Persons with heart failure with reduced ejection fraction exhibit malfunctioning autonomic reflexes, which lead to exaggerated sympathoexcitation and attenuated parasympathetic tone. Chronic elevation of sympathetic activity is associated with increased morbidity and mortality. In this review, we provide an overview of how each main exercise-related autonomic reflex is changed in heart failure with reduced ejection fraction, and the role of exercise training in attenuating or reversing the counterproductive changes.

Keywords: sympathoexcitation; sympathetic nerve activity; metaboreflex; mechanoreflex; chemoreflex; arterial baroreflex; cardiac rehabilitation; HFrEF

1. Introduction

Chronic heart failure (HF) is a complex clinical syndrome [1] that 26 million people live with worldwide [2]. HF is characterized by severe exercise intolerance (i.e., low peak oxygen uptake (VO₂)) [1,3–9], which limits daily activities, reduce quality of life [6], and increase the risk of adverse events in persons living with HF with reduced ejection fraction (HFrEF; EF ≤40%) [7,8]. Patients with HFrEF classically have impaired cardiac output control and increased sympathetic outflow to muscle, vasculature, and the renal system at rest [10–15] and in response to exercise [16–19]. While sympathoexcitation increases in HFrEF, parasympathetic tone decreases, maintaining the patient in a sympatho-excited state even at rest. Thus, the HFrEF syndrome entails both myocardial and autonomic dysfunction [20], with the latter factor being the focus of this review.

The autonomic nervous system regulates cardiovascular and hemodynamic adjustments to changes in energy demand (e.g., exercise) and in times of stress. Here we will discuss the pathways and mechanisms by which the autonomic nervous system controls our hemodynamic responses to exercise, including the exercise pressor reflex (muscle metaboreflex and muscle mechanoreflex), the arterial baroreflex, and the chemoreflexes (central and peripheral) in the situation of HFrEF, i.e., autonomic dysfunction.

2. Cardiovascular reflex physiology

2.1 Brief overview of the autonomic nervous system

The autonomic nervous system has two primary branches: (1) the parasympathetic; and (2) the sympathetic nervous systems [21,22]. The balance between parasympathetic and sympathetic nerve activity modulates cardiovascular homeostasis and the response to exercise [21,23]. For example, at dynamic exercise onset, parasympathetic withdrawal causes a nearly instantaneous increase in heart rate. Conversely, increased sympathetic activation at exercise onset causes a gradual rise in heart rate. The dominant controller of heart rate thus shifts from parasympathetic activity at rest (i.e., high activity) and during initial exercise onset (i.e., withdrawal) to sympathetic activity (“sympathoexcitation”) during sustained exercise[23,24]

2.2 Autonomic dysfunction in HFrEF

Exaggerated sympathoexcitation in HFrEF may play a large role in disease progression [25] and is a marker of prognosis and survival [20,26]. At the onset of left ventricular systolic dysfunction, the balance between parasympathetic and sympathetic nerve activity shifts in response to: (a) an increase in left ventricular end-diastolic pressure; or (b) a decrease in stroke volume [20,26–28]. This shift in balance favours sympathoexcitation to temporar-
ily re-establish hemodynamic equilibrium [21]. As HFrEF advances, parasympathetic outflow progressively wanes while sympathetic outflow increases [29], independent of HFrEF etiology [30,31]. Concurrently, renin-angiotensin-aldosterone system activity increases [30,31]. These autonomic and neurohormonal responses may initially be “adaptive” to maintain cardiac function [21,30], but may subsequently and progressively become maladaptive and worsen HFrEF severity.

Autonomic dysfunction in HFrEF combines cardiac, ventilatory, neurohumoral, and vascular factors [6,28,30,32] that are also related to poor prognosis [33] and increased mortality [20,34]. Cardiac factors may include decreased tonic and reflex vagal heart rate modulation, increased resting heart rate [34,35], chronotropic incompetence [36], and decreased heart rate variability [9,36–38]. Elevated resting minute ventilation [12] and ventilation-to-perfusion mismatch are also consistently found in HFrEF [6,33,39,40]. Neurohormonal changes in HFrEF include increased venous plasma norepinephrine, cardiac and renal norepinephrine spillover, cardiac norepinephrine stores, and plasma brain natriuretic peptides [6,41]. Increased renal sympathetic nerve activity reduces renal blood flow, which may in turn exacerbate the renin-angiotensin-aldosterone system [42]. Finally, increased resting muscle sympathetic nerve activity (MSNA) burst frequency in HFrEF [9–14] elicits tonic vasoconstriction and increased peripheral resistance at rest. Exaggerated sympathoexcitation in HFrEF is most common with severe exercise intolerance [15,19] or ischemic heart disease [9].

Contrary to initial conceptual models that emphasized a generalized, non-selective increase in sympathetic nerve activity to all vasculature in response to left ventricular systolic dysfunction [27], evidence suggests a selective alteration in autonomic cardiovascular changes in the early stages of HFrEF progression (e.g., increased cardiac norepinephrine spillover versus no change in total or renal norepinephrine spillover) [28]. Autonomic dysfunction in HFrEF may be examined as the exaggeration or blunting of cardiovascular regulating autonomic reflexes in response to exercise: the exercise pressor reflex, the arterial baroreflex, and the central and peripheral chemoreflexes [21,22] (Fig. 1, Ref. [21]). The current review is focused on extracardiac reflexes, therefore, the cardiopulmonary baroreflex and cardiac chemoreflex are not discussed herein. We refer the reader to this review for further detail [43].

3. Exercise pressor reflex in HFrEF

Curiously, muscle pressor reflexology may play a large role in HFrEF exercise pathophysiology. First described by Alam and Smirk in 1937, the exercise pressor reflex is stimulated by skeletal muscle contraction to generate an increase in mean arterial pressure and ventilation during exercise in healthy humans [44,45]. The exercise pressor reflex is stimulated via group III and IV muscle afferents and encompasses two separate reflexes: (1) the muscle mechanoreflex (mainly group III afferents); and (2) the muscle metaboreflex (mainly group IV afferents). Their purpose is to increase sympathoexcitation during exercise to maintain the balance between cardiac output and peripheral O2 supply, thereby maintaining arterial pressure and preserving cerebral and cardiac O2 supply during exercise [46]. Indeed, an abolished exercise pressor reflex impairs the ability to increase mean arterial pressure during exercise [47]. The exercise pressor reflex is consistently exaggerated in patients with HFrEF [3,4,19,45,46,48–50].

The exercise pressor reflex is thought to be the “neural link” between peripheral muscle abnormalities and exaggerated hemodynamic responses to exercise in HFrEF [51]. When group III and IV muscle afferents were blocked via lumbar intrathecal fentanyl administration during knee extension exercise in patients with HFrEF, there was attenuated sympathetic outflow (i.e., lower total norepinephrine spillover) and lower exercise cardiac output, but there was also increased femoral blood flow and vascular conduc-
tance and less exercise fatigue [52]. Thus, the exercise pres-

tor reflex may modulate central hemodynamic control and elicit exaggerated sympathoexcitation that impairs femoral blood flow during exercise in HFrEF but not in controls [52]. The exaggerated exercise pressor response may be related to impaired muscle quality and function (e.g., muscle atrophy, altered enzyme concentrations, lower mitochondrial density, rapid exercise high energy phosphate decline [53–55]), impaired muscle O2 delivery-to-utilization matching and/or reduced muscle O2 diffusional conduc-
tance during exercise in patients with HFrEF [5,56,57]. Conversely, another report shows an exaggerated exercise pressor response not attributable to muscle O2 extraction in HFrEF, although a normal response was related to muscle O2 extraction in controls [49]. Some evidence suggests ATP and lactic acid may stimulate and sensitize group III and IV muscle afferents and thus help exaggerate sympathoexcitation in HFrEF [46]. Clinically, exaggerated sympa-

3.1 Muscle mechanoreflex in HFrEF

The muscle mechanoreflex may independently con-

tribute to HFrEF pathophysiology. Deformation of the skeletal muscle mechanoreceptors increases the muscle afferent signalling rate to the central nervous system [46]. Mechanoreceptors rapidly adjust their firing rate to changes in muscle tension consistency and respond earlier and faster than metaboreceptors [47]. The mechanoreflex elicits an increase in sympathoexcitation that increases arterial and renal vasoconstriction [58], and that debatably/negligibly increases ventilation [3,4,47]. Thus, muscle contraction indirectly increases perfusion pressure and O2 delivery to ac-
Fig. 1. Integration of exercise-related, cardiovascular autonomic reflexes in HFrEF. Afferent feedback is collected and integrated at the medulla oblongata of the brain stem (blue hexagon), where efferent signals are sent to various organs in response to the integration of the afferent and central information. Excitatory (+) and inhibitory (-) stimuli are shown for afferent feedback (black arrows), efferent sympathetic nerve activity (red arrows) and efferent parasympathetic nerve activity (green arrows). Exaggerated stimuli due to HFrEF are indicated as thick arrows, while blunted stimuli due to HFrEF are indicated as dashed thin arrows. *Note: the effects of sympathoexcitation on cardiac contractility in HFrEF are generally to increase contractility, but some research suggests stroke volume remains the same or decreases during the activation of the metaboreflex in HFrEF. **Note: the aortic bodies contain both baroreceptors and chemoreceptors, which emit contrasting afferent signals. The baroreflex stimulus is inhibitory and is blunted in HFrEF; the chemoreflex stimulus is excitatory and is exaggerated in HFrEF. Figure concept and representation of afferent and efferent pathways was inspired by figure 4 in reference [21].

3.2 Muscle metaboreflex in HFrEF

The muscle metaboreflex independently contributes to exaggerated sympathoexcitation in HFrEF [3,4,19,47,60].
The metaboreflex occurs when increased metabolite concentration (e.g., ATP [61], lactic acid, adenosine [10], phosphate, kinins, and cations [47,62]) stimulates skeletal muscle receptors, whose afferent firing rate increases to yield hemodynamic, ventilatory, and sympathetic changes [21]; these changes include increases in MSNA, peripheral vasocnstriction [47], mean arterial pressure, pulmonary vascular resistance [63], and ventilation or hyperpnea [47]. During exercise, the metaboreflex increases cardiac output via stroke volume in health [64] and potentially heart rate [65] depending on the state of exercise, recovery, or ischemia [47]. However, the presence of HFrEF alters these effects.

The metaboreflex is consistently elevated in patients with HFrEF [21,66] such that MSNA during ischemic and nonischemic handgrip exercise is greater and occurs earlier [19]; exercise ventilation is amplified due to an exaggerated metaboreflex response [3,66,67] in symptomatic but not in asymptomatic patients with HFrEF [68]; post-exercise heart rate recovery is slower [60]; and arterial pressure is elevated during post-exercise circulatory occlusion [60,64,67,69–71]. While increased arterial pressure is primarily due to increased cardiac output in health, metaboreflex activation in HFrEF elicits negligible cardiac output changes and thus elevates mean arterial pressure via peripheral vasocnstriction and elevated systemic vascular resistance [63,64,67,69–71]. A dose-response relationship for this phenomenon was recently reported across three metaboreflex exercise intensities [72]. Cardiac output was limited during metaboreflex activation because of increased coronary vasocnstriction in dogs with HFrEF, but this has yet to be confirmed in humans with HFrEF [73]. Thus, the metaboreflex mechanisms in HFrEF may be related to the impaired ability to increase stroke volume during exercise [64,70,71].

In HFrEF, metaboreflex sensitivity and activity are negatively related to peak VO₂ [19,67] and heart rate variability (indirect measure of cardiac autonomic regulation and associated with higher mortality [67,74]), and are positively related to the exercise ventilatory response [51,67], circulating catecholamine levels [67], and mortality risk score [68]. Further, metaboreflex activity is not related to ventricular function [67], and yet it increases as HFrEF severity worsens [51]. Metaboreflex exaggeration in HFrEF may be associated with increased peripheral, but not central, chemoreflex sensitivity and decreased arterial baroreflex regulation of heart rate, independent of left ventricular EF [67].

Some research suggests that HFrEF, perhaps only in its more severe form, attenuates [46] or has no effect on the metaboreflex [50]. Patients with mild HFrEF and controls have elevated MSNA and blood pressure during metaboreflex activation but not in those with severe HFrEF [75]. Further, one HFrEF group observed a decrease in MSNA from exercise to post-exercise ischemia while controls observed an increase [11]. The same group later published directly contrasting results in addition to earlier fatigue and greater accumulation of muscle metabolites in HFrEF, thus supporting the overall metaboreflex exaggeration in HFrEF [76]. Conflicting results on metaboreflex activity in HFrEF may result from different measured physiological indices (e.g., MSNA vs. ventilation vs. blood pressure) [77], exercise modes (e.g., rhythmic or isometric), muscle group (e.g., forearm or knee extensor), and/or HFrEF severity (e.g., muscle quality, muscle afferent sensitization or desensitization). For more on this, we refer the reader to the Wang et al. [77] and the give and take discussion between the blunted and exaggerated hypotheses. Taken together, we know muscle metaboreflex dysfunction in HFrEF alters exercise and post-exercise MSNA (mixed views on blunted vs. exaggerated responses [47]), and increases exercise and post-exercise blood pressure, vasocnstriction, and ventilation. Thus, dysfunctional metaboreflex may play a critical role in manifesting HFrEF exaggerated sympathoexcitation, early fatigue, and exercise intolerance.

4. Arterial baroreflex in HFrEF

The attenuated arterial baroreflex control of heart rate in patients with HFrEF [28,32,78–80] is associated with poor survival [81]. The arterial baroreceptors, located in the aortic arch and carotid sinuses, facilitate a negative feedback reflex that responds to stretch from a sudden increase in blood pressure by signalling afferents to the medulla oblongata. This will: (a) decrease sympathetic activity to the heart and vessels (i.e., lower heart rate, contractility, and vasocnstriction); and (b) increase parasympathetic activity to lower heart rate [22,32]. Baroreflex activation thus lowers blood pressure via cardiac output, peripheral resistance, and venous return; the opposite effects would occur with a drop in baroreceptor activity [32].

How arterial baroreflex function is altered in HFrEF is debated. Some propose that the baroreflex responds appropriately to detected decreases in stroke volume or diastolic pressure by increasing sympathoexcitation in HFrEF [21]. Others describe normal baroreflex circuits in HFrEF with, however, exaggeration of other sympatho-excitatoty reflexes that may override baroreflex function, such as the exercise pressor and chemoreflexes [82]. Conversely, somewhat conflicting evidence suggests arterial baroreflex dysfunction: heightened baroreflex sensitivity (i.e., the response magnitude when the baroreflex effectively drives the sinus node) in HFrEF [83]; reduced baroreflex sensitivity in optimally-treated patients with HFrEF [84]; reduced baroreflex sensitivity being related to pulse wave velocity and not EF, suggesting that structural alterations of the arterial wall may modulate baroreflex function [84]; and depressed baroreflex effectiveness index (i.e., the number of times the baroreflex effectively drives the sinus node) in a sample with no abnormal baroreflex sensitivity in HFrEF [85]. The baroreflex effectiveness index may be a better measure in HFrEF as it accounts for non-baroreflex con-
trol of heart rate, such as central command, ventilation, and neurohormonal factors, each of which may be abnormal in HFrEF [85]. Notwithstanding the preferred measure, a recent publication reported not only reduced baroreceptor sensitivity in patients with HFrEF, but a relationship between ejection fraction and baroreceptor sensitivity such that as ejection fraction declines, baroreceptor sensitivity declines [86]. Indeed, patients with HFrEF exhibited no such relationship nor any decline in baroreceptor sensitivity. Other functional relationships with baroreceptor sensitivity including MSNA, heart rate, and catecholamine levels [86]. Therefore, it may be surmised from the bulk of the literature that baroreflex dysfunction exists in those with HFrEF, however, the degree of dysfunction may be dependent upon the severity of the HFrEF state and level of neuroadrenergic activation.

Baroreflex modulation of heart rate, cardiac output, and blood pressure is depressed in HFrEF dogs at rest [87–91], during mild and moderate exercise [92,93], and during metaboreflex activation [94], but without effect on the baroreflex modulation of vascular resistance at rest [91]. Thus, the ability of the baroreflex to buffer the metaboreflex is diminished in HFrEF dogs [93,94]. Further, baroreflex unloading via bilateral carotid occlusion during concurrent muscle metaboreflex activation in dogs with HFrEF causes vasoconstriction in all vascular beds, non-ischemic and ischemic active tissue alike, resulting in a surge in mean arterial pressure as a result of a great pressor response [95]. This heightened sympathetic outflow as a result of baroreflex unloading in HFrEF initiates a “vicious cycle” of vasoconstriction in active tissue, which enhances the muscle metaboreflex, which causes more vasoconstriction. The authors speculate that baroreflex dysfunction coupled with muscle metaboreflex exaggeration may be a feedback loop exacerbating exercise intolerance in patients with HFrEF [95]. The interaction between these dysfunctional reflex systems in HFrEF appears to play a leading role in HFrEF pathophysiology and exercise intolerance. However, this stream of evidence comes with validity limitations. Exercise heart rate dominantly controls cardiac output in healthy dogs, whereas exercise stroke volume modulates cardiac output in HFrEF dogs [93]. This directly opposes previous work in HFrEF dogs by the same group [71], and therefore should be further investigated in patients with HFrEF of various severity and etiology.

Baroreflex sensitivity is improved after exercise training in HFrEF [30] and after simulating exercise training with electrical stimulation of the peroneal and tibial nerves [96]. Baroreflex activation therapy (carotid sinus stimulation) safely improved exercise capacity, functional class, and quality of life, and reduced NT-proBNP levels in patients with HFrEF already optimally treated with guideline therapy [97]. Vagal nerve stimulation therapy in NYHA class II–III HFrEF patients yielded similar but inconsistent findings to baroreflex activation therapy, with no apparent benefit to survival or heart function [98–100]. Recently, a series published in the Lancet reviewed baroreceptor stimulation as a non-pharmacological treatment of autonomic dysfunction in heart failure, however, outcomes were minimal, showing improved exercise capacity but no improvement in cardiac function, and trial control patient groups were not included [101], lending themselves to low-impact findings and implications. To summarize, baroreflex control of heart rate is impaired in HFrEF, however, the mechanisms may be outside the baroreceptors themselves [21,82] or related to arterial stiffness [32,84]. Improved arterial baroreflex sensitivity impacts exercise tolerance and quality of life [82,97] but not necessarily prognosis.

5. Chemoreflex in HFrEF

The chemoreflex may be exaggerated in patients with HFrEF, observed as abnormal ventilation at rest [102] and blunted vasodilation during exercise due to exaggerated MSNA [12]. The chemoreflex modulates homeostasis under conditions of hypercapnia, acidosis, or hypoxemia [32]. The chemoreflex has two levels: (1) the central chemoreflex; and (2) the peripheral chemoreflex. The chemoreceptors respond to hypoxemia and/or hypercapnia by stimulating increases in ventilation and sympathetic outflow, with the goal of increasing tissue perfusion, O2 delivery and utilization, and CO2 mobilization and expiration [32]. Interestingly, increased ventilation partially buffers sympathetic nerve activity via competition between pulmonary stretch afferents (not discussed here) and the chemoreflexes [103,104]; however, in patients with HFrEF, increased ventilation and exaggerated sympathoexcitation commonly coexist [13]. Conceptually, patients with HFrEF commonly have lower cardiac output and organ perfusion, which would increase glycolytic metabolism. Thus, elevated CO2 and H+ levels and decreased O2 levels in the blood may exaggerate the chemoreflexes over time [32]. Further, patients with HFrEF exhibit blunted muscle vasodilation during both central and peripheral chemoreflex activation compared to controls, likely attributable to the greater increase in MSNA observed in the patients [12]. Both central and peripheral chemosensitivity may contribute to exercise hyperventilation in HFrEF [83], which may compensate hemo-dynamically by increasing cardiac output via heart rate in health and HFrEF [105].

5.1 Central chemoreflex in HFrEF

The central chemoreceptors are located adjacent to the respiratory centres in the medulla oblongata and detect blood CO2 and pH levels. When blood CO2 levels rise (“hypercapnia”), there is more CO2 in the interstitial space surrounding the central chemoreceptors, triggering afferent signals to the respiratory centres in the medulla oblongata. The respiratory centres respond by raising ventilation. Studies targeting the central chemoreflex activate the CO2-sensitive central chemoreceptors while simultane-
ously deactivating the O2-sensitive peripheral chemoreceptors by breathing hyperoxic hypercapnic gas (93% O2 and 7% CO2 [83]). Patients with HFpEF have greater ventilation [13], heart rate [13], and MSNA [12,13] and decreased forearm blood flow [12] during resting hyperoxic hypercapnia compared to controls. Further, symptomatic patients have greater MSNA and ventilation and attenuated sympathoinhibition during hyperoxic hypercapnia compared to asymptomatic HFpEF patients [106]. These findings are clinically relevant as blood CO2 levels increase during exercise and/or sleep apnea, therefore, in patients with HFpEF, elevated blood CO2 levels exaggerate the central chemoreflex and exacerbate the already elevated sympathoexcitation. Clinically, hyperventilation is more prognostic than peak VO2 in HFpEF [83], although both are meaningful endpoints. Abnormal exercise hyperventilation in HFpEF is often due to high ventilation-to-perfusion mismatch and increased VCO2 due to greater bicarbonate buffering of lactic acid [107]. Even so, there is more data on the peripheral rather than central chemoreflex during exercise in HFpEF.

5.2 Peripheral chemoreflex in HFpEF

Exaggerated peripheral chemoreflex activity is common in HFpEF and may contribute to exaggerated sympathoexcitation, hyperventilation, breathing instability (e.g., Cheyne-Stokes) [102,108], and autonomic dysfunction in HFpEF [30]. The peripheral chemoreceptors ("glomus cells") in the carotid bodies and aortic arch detect blood O2 levels. When blood O2 levels fall, the chemoreceptors depolarize the glossopharyngeal and vagus nerves, signaling the medulla oblongata to increase ventilation [102], increase heart rate [103], and increase vasoconstriction to maintain perfusion pressure [12,102]. The peripheral chemoreflex is investigated using steady-state (10% O2 and 90% N2 [12]) or transient (100% N2 [109]) hypoxia. Titrating CO2 uptake maintains arterial isocapnia to minimize central chemoreflex activity [12].

Hypoxemia increases ventilation at rest and during exercise, and decreases the peak work rate but not peak VO2 in HFpEF [39], the latter suggesting greater work of breathing with hypoxia. Patients with HFpEF had greater MSNA and reduced forearm blood flow compared to controls during resting isocapnic hypoxia [12]. Carotid chemoreceptor inhibition via dopamine caused resting hindlimb vasodilation in HFpEF but not healthy dogs, while both groups experienced similar exercise vasodilation [110]. By adding alpha-adrenergic blockade with phentolamine, carotid chemoreceptors accounted for roughly 1/3rd of the sympathetic tone during exercise in healthy dogs [110] while this additional blockade abolished exercise vasodilation in HFpEF dogs [110]. Notably, carotid body denervation in two healthy dogs abolished the exercise vasodilation [110]. Thus, peripheral chemoreflex sensitivity is exaggerated in HFpEF [102]. Indeed, animal models indicate that the transformation from normal, tonic chemoreceptor activity to HFpEF-characteristic chemoreceptor hyperactivity may occur in a matter of weeks [102].

The carotid chemoreflex interacts with the muscle metaboreflex to regulation minute ventilation in a breathing frequency dependent manner in patients with HFpEF, potentially contributing the exercise hyperventilation and exercise intolerance in HFpEF [111]. In other words, the activation of the muscle metaboreflex worsens the effects of the already hyperactive carotid chemoreflex in patients with HFpEF; as exercise stimulates both reflexes, this interaction may be a key player in functionally limiting exercise tolerance, which in turn is related to quality of life and mortality in HFpEF. The interaction between these situationally distant reflexes poses a therapeutic problem pharmacologically, however, exercise therapy (see section 1.6) may be used to address both reflexes individually and thus improve the nature of their interaction in patients with HFpEF.

Carotid body ablation, resection, or denervation have demonstrated improved autonomic function (reduced renal sympathetic nerve activity or MSNA, increased renal blood flow, increased heart rate variability, reduced peripheral chemosensitivity, increased baroreflex sensitivity) in animal HFpEF models [112–114]. A 2017 first-in-man study demonstrated that carotid body resection (4 patients unilateral resection, 6 patients bilateral resection) in HFpEF decreased both MSNA and peripheral chemosensitivity and improved exercise tolerance 1-month post-resection [115]. However, safety concerns arose in those with bilateral resection who trended lower of oxygen saturation at night [115]; carotid bodies stimulate protective reactions to hypoxia, therefore, further investigation balancing patient safety and clinical benefit is required prior to wider usage of carotid body resection or alteration. Although still debated, hemodynamic, neurohumoral, and local metabolic mechanisms underlying HFpEF pathophysiology may collectively progress peripheral chemoreceptor sensitization [102]. Despite the high O2 supply to peripheral chemoreceptors in health, it is speculated that relatively reduced O2 supply in HFpEF may play a role in peripheral chemoreceptor sensitization [102]. As previously mentioned, hyperventilation, sleep apneas, and Cheyne-Stokes respiration are common in patients with HFpEF and are secondary to peripheral chemoreflex exaggeration, not vice versa [102]. However, these ventilatory abnormalities may also exacerbate the mechanisms of chemoreflex exaggeration [102]. Oxidative stress may stimulate carotid chemoreceptor sensitization in HFpEF [32,102]. Chronic exposure to intermittent hypoxemia, as is common in HFpEF, sensitizes the carotid chemoreceptors to be more “excitable” to acute hypoxemia in HFpEF rats, likely due, in part, to greater carotid body oxidative stress [116]. Angiotensin II, a pro-oxidant, is chronically elevated in ~45–50% of patients with severe HFpEF (NYHA class III–IV) despite ACE inhibitor treatment [117,118] and is associated with poor prognosis in HFpEF [117]. The NADPH-angiotensin II-superoxide
pathway may increase carotid body chemoreceptor sensitivity to hypoxemia in humans with HFrEF [119]. Finally, co-morbidities common in HFrEF are also related to increased oxidative stress and may exacerbate carotid body sensitization [32]. Therefore, the role of oxidative stress remains an essential component of HFrEF pathophysiology. In summary, the peripheral chemoreflex is exaggerated in patients with HFrEF and contributes to abnormal ventilation.

6. The role of exercise training on reflex control of cardiovascular hemodynamics

Exercise training is a highly effective therapy that increases not only functional capacity, but enhances quality of life, resting heart rate, ventilatory efficiency, and ejection fraction, as well as reduces the incidence of major cardiovascular events, hospitalizations, and cardiac mortality [120–122] and thus shows promise as an effective therapy for autonomic dysfunction [42]. Further, exercise training reduced the rate of new-onset atrial arrhythmias, but not ventricular arrhythmias, in patients with HF. Indeed, lower peak VO\textsubscript{2} scores were predictive of greater mortality risk and new-onset atrial arrhythmias in trained patients with HF [122]. This remains significant as the presence of atrial fibrillation is associated with lower pre-training peak VO\textsubscript{2}, greater hospitalization and mortality risk [123]. Arrhythmias are associated with cardiac related death in patients with HFrEF, and low ejection fraction, as such found in patients with HFrEF, remains the only consistent predictor of sudden cardiac death in patients with ischemic heart disease [124]. Thus, coupling exercise with the current anti-arrhythmic therapies, such as cardiac resynchronization therapy, may further reduce arrhythmias and subsequent cardiac death. In the same vein, chronotropic incompetence, characterized by the inability to adequately increase heart rate in response to exercise, is mediated by sympathovagal balance and commonly found in patients with HFrEF [125]. Evidence indicates that exercise training may partially ameliorate chronotropic incompetence in patients with HFrEF [125]; it is therefore reasonable to infer that exercise training may be coupled with implantable device therapy to collectively improve sympathovagal balance, chronotropic incompetence, and outcomes. However, this has yet to be fully investigated.

A recent meta-analysis (study \( n = 16 \)) by Pearson and Smart [126] reported exercise training improved short-term heart rate variability (study \( n = 11 \); 2 studies with HF with preserved ejection fraction), decreased MSNA (study \( n = 6 \)), and increased heart rate recovery at 1-min post-exercise (study \( n = 5 \)) in exercise-trained patients with HFrEF compared to non-exercise trained HFrEF controls. Several animal HFrEF models have reported decreased sympathetic activation or improved hemodynamic control following exercise training [113,127–132]. Exercise training in rat models of HFrEF increased parasympathetic tone and intrinsic heart rate compared to untrained rats with HFrEF, such that post-training values achieved no difference with healthy sham rats [133]. Further, normalized parasympathetic activity was related to training-induced preservation of preganglionic vagal neurons [133]. Early evidence in patients with HFrEF exhibited a shift from sympathetic to parasympathetic dominance after 5–8 weeks of exercise training [134–136]. Similarly, 9 months of exercise training shifted the sympathovagal balance toward a greater parasympathetic tone in patients with HFrEF, but this effect required a long time course as it was not seen at 3 months [137]. Improved sympathovagal balance, as measured by a decrease in the ratio of low frequency to high frequency with power spectral heart rate analysis, was inversely correlated with increased peak VO\textsubscript{2} as a result of exercise training in patients with HFrEF [138]. Improvement in both time and frequency domains of heart rate variability [30,126,134,137,139–141] and reduced sympathetic nerve activity following exercise training in patients with HFrEF has been well documented [43,142]. This section will therefore focus on individual autonomic reflex-specific improvements following exercise training in HFrEF for a mechanistic approach (Fig. 2).

6.1 Role of exercise programming on autonomic reflex function in HFrEF

It is imperative to consider that improved exercise capacity, cardiac function, and/or skeletal muscle function does not equal improved autonomic function. Similar to how exercise regime (moderate intensity continuous training, high intensity interval training, resistance training, etc.) yields different health and clinical benefits improve autonomic function, although the majority include some form of aerobic training. Low intensity cardiac rehabilitation in patients with HFrEF [143], whether or not the exercise regime improves autonomic function in HFrEF may depend greatly on the mode, duration, and intensity of exercise [30]. Nonetheless, it appears that a wide variety of regimes restored autonomic tone and reactivity to sympathetic and parasympathetic stimuli in patients with HFrEF [137]. An aerobic, resistance-band training study targeting each muscle group one at a time lowered circulating catecholamine levels at rest and during exercise in HFrEF patients [144]. Combined interval and resistance training had statistically similar effects on respiratory drive compared to interval training alone in patients with HFrEF, but data indicated that combined training may have improved resting and exercise breathing pattern indices and \( P_{ETCO_2} \) more than intervals alone [145]. Inspiratory muscle training has produced benefits to exercise tolerance and potentially autonomic function in patients with HFrEF [146]. Clearly, exercise training program parameters (frequency, intensity, type, and time) are highly varied among autonomic studies in patients with HFrEF. Therefore, studies explicitly evaluating autonomic measures and mechanisms are required in and above clinical outcomes.
6.2 Exercise pressor reflex function after exercise training in HFrEF

Exercise training alters both the muscle metaboreflex and the muscle mechanoreflex in patients with HFrEF [147,148]. Six weeks of forearm training reduced the systolic and diastolic pressure, minute ventilation, respiration rate, and leg vascular resistance responses and increased the leg blood flow response to post-handgrip exercise circulatory occlusion in patients with HFrEF more so compared to healthy controls [148]. Further, these changes were accompanied by a decrease in sympathetic activation but without change in parasympathetic activation as measured by power spectral analysis of blood pressure low frequency components [148]. Antunes-Correa et al. [147] reported lower resting MSNA following exercise training (4-months combined aerobic, resistance, and flexibility training) compared to an untrained control HFrEF group; interestingly, however, the nature of the metaboreflex improvement further complicates the known literature surrounding muscle metaboreflex dysfunction in patients with HFrEF. During muscle metaboreflex activation via post-exercise circulatory occlusion, exercise trained patients with HFrEF reported heightening MSNA as well as increased transient receptor potential vanilloid type-1 (TRPV1) receptors and cannabinoid receptor type-1 (CB1) in the vastus lateralis (trained muscle) whereas the untrained group saw no change in MSNA or the expression of either receptor compared to baseline testing [147]. This latter finding suggests that the blunted muscle metaboreflex response, found in some HFrEF studies [11,75,149] but not all [21,47,51,66,148], and confirmed at baseline testing in this study, is augmented with exercise training, thereby returning muscle metaboreflex dysfunction closer to normal function. It may be that HFrEF severity dictates the nature of muscle metaboreflex dysfunction [75], such that mild cases (e.g., NYHA class I–II) exhibit exaggerated responses that deteriorate as disease severity worsens, resulting in a blunted muscle metaboreflex response in more severe HFrEF conditions (e.g., NYHA class III–IV). In addition to muscle metaboreflex isolation, authors isolated the mechanoreflex with passive exercise and found decreased MSNA and expression of cyclooxygenase-2 (COX-2), prostaglandin-E2 receptor-4, and thromboxane-A2 receptors [147], each of which is involved in the COX pathway, a hypothesized mechanism behind mechanoreflex dysfunction in HFrEF. Recently, 6-months of exercise training cardiac rehabilitation in patients with HFrEF not only improved peak VO2, resting and low-intensity exercising MSNA, but also attenuated...
the exaggerated MSNA during muscle metaboreflex activation compared to pre-training levels, although remained greater than healthy controls both pre- and post-training [150]. Aside from these high-impact data, little research has focused on the effect of exercise training on the exercise pressor reflex, the isolated muscle metaboreflex, or the isolated muscle mechanoreflex in patients with HFrEF. However, inferences may be made from animal HFrEF studies.

Two studies by Wang et al. [151,152] demonstrated that exercise training targets both the muscle metaboreflex and mechanoreflex in rat HFrEF models. Exercise training normalized pre-exercise blunted muscle metaboreflex (isolated via capsaicin injection) and decreased the pre-exercise exaggeration of the muscle mechanoreflex (isolated via contraction and passive stretch) in rats with HFrEF, with no effects seen in sham rats post-training [152]. Mechanistically, exercise training improved the sensitization of both group III and IV afferents in the HFrEF rat models, corresponding to improved function of certain muscle metaboreflex (TRPV1) and mechanoreflex (P2X) receptors [151]. A review by the same group discussed the discrepancy between the observations of both blunted and exaggerated muscle metaboreflex responses in HFrEF, as well as potential mechanisms underlying the improved exercise pressor reflex response after exercise training, to a greater detail than may be covered herein [77].

6.3 Arterial baroreflex function after exercise training in HFrEF

The effect of exercise training on baroreflex function in patients with HFrEF is, surprisingly, vastly understudied in humans. To the knowledge of the authors, the only known study in human patients with HFrEF showing improved baroreflex sensitivity post-exercise training lacked a control group [153]. Fortunately, 6-months of combined aerobic and circuit training significantly improved baroreflex sensitivity with concomitant improvements in heart rate variability, cardiac presynaptic sympathetic innervation, increases in myocardial blood flow where it was reduced pre-training, however, without a statistically significant increase in peak VO₂, in 12 NYHA class II–III HFrEF patients [153]. The very small sample and lack of a patient control group still enforce the need for updated evidence in baroreflex function post-exercise training in patients with HFrEF. Similarly, simulating exercise training with peroneal and tibial nerve electrical stimulation (transcutaneous electrical nerve stimulation; TENS) in patients with HFrEF effectively improved baroreflex sensitivity [96,154]. In contrast to the TENS groups, however, brief (2-day) exercise “training” had no effect on baroreflex sensitivity [96] and two weeks (4–6 sessions, 75-min each) of exercise training still failed to significantly improve baroreflex sensitivity in patients with HFrEF [154].

Despite the surprising lack of controlled, exercise training trials in patients with HFrEF on baroreflex sensitivity, evidence strongly suggests that exercise therapy improves baroreflex function in patients on the pre-HFrEF spectrum (e.g., hypertension, coronary artery disease, post-myocardial infarction, etc. [155,156]) as well as in animal HFrEF models [128,129,157–159], and thus strongly warrants clinical trials investigating the efficacy of improved baroreflex function and corresponding health benefits from exercise. However, given the lack of patient evidence, this section of the review will focus on animal based HFrEF studies.

Exercise training improved arterial baroreflex control of both renal sympathetic nerve activity and heart rate in HFrEF rabbits [158] and rats [160]. The latter finding was accompanied by improved aortic depressor nerve activity sensitivity following exercise training in rats with HFrEF [160], suggesting a role not only of carotid baroreceptors but of aortic baroreceptors in modulating heart rate and sympathetic outflow in HFrEF. Indeed, work by Liu et al. [159] demonstrated that atropine and metoprolol infusion modulated baroreflex control of heart rate through increased vagal tone, rather than reduced sympathetic outflow, following exercise training in HFrEF.

Exercise training normalized sympathetic outflow (resting renal sympathetic nerve activity) and arterial baroreflex function (attenuated maximum gain of heart rate and renal sympathetic nerve activity curves) in rabbits with HFrEF [128,157]. Further, angiotensin II type 1 receptor blockade in non-exercise trained HFrEF rabbits raised baroreceptor sensitivity approximating that of those exercise-trained rabbits with HFrEF; exercise in HFrEF rabbits also lowered circulating angiotensin II levels [157]. Mousa et al. [158] attributed their observed reduction in renal sympathetic nerve activity and elevation in baroreflex sensitivity in rabbits with HFrEF to concurrent reduction in circulating angiotensin II and angiotensin receptors in the central nervous system that occurs following exercise training. Thus, angiotensin II and the RAAS pathway is mechanistically tied to the dysfunctional pathophysiology of the arterial baroreflex in HFrEF. In rats, only endurance training improved cardiac autonomic control (increased baroreflex sensitivity) compared to moderate interval training, despite improved cardiac function and exercise capacity in both programs [129].

6.4 Chemoreflex function after exercise training in HFrEF

Patients with HFrEF following carotid body resection exhibited significantly improved exercise time compared to pre-resection exercise time, reduced MSNA, and decreased peripheral chemosensitivity [115]. Although these are encouraging findings in human patients, this approach has been contested, for many reasons, in favour of exercise training [161]. Exercise training poses a less-invasive, more cost-effective, and in most cases, simpler alternative that may produce similar or better results, as well as more global physiological and health benefits (endothelial func-
tion, peripheral blood flow distribution, skeletal muscle factors, and metabolic factors associated with reduced mortality).

Animal models have confirmed the efficacy of exercise training on attenuating exaggerated chemoreceptor sensitivity in HFrEF. Exaggerated peripheral chemosensitivity was attenuated by exercise training in rabbits with HFrEF [162]. Renal blood flow is classically reduced in the HFrEF condition due to exaggerated renal sympathetic nerve activity and consequent renal vasoconstriction, mediated in part by heightened peripheral chemoreceptor sensitivity. Exercise training attenuated peripheral chemoreflex-mediated tonic reductions in renal blood flow in rabbits with HFrEF, as assessed by compared carotid-body chemoreceptor denervated animals with carotid-body intact animals; further, exercise training also attenuated hypoxia induced reductions in renal blood flow in the same HFrEF sample [163]. Along with improved exercise capacity, rabbits with pacing-induced HFrEF returned to pre-pacing levels of renal blood flow and vascular conductance during acute hypoxia after exercise training [127]. Thus, animal models have demonstrated that exercise training attenuates exaggerated peripheral chemoreceptor sensitivity found in HFrEF and improves physiological functions (increased peripheral blood flow) and autonomic signalling (reduced renal sympathetic nerve activity, increase baroreflex sensitivity). Unfortunately, in human patients with HFrEF, data supporting direct involvement and improvement of peripheral chemoreceptor function is lacking. Both interval training and combined interval and resistance training improved respiratory drive in patients with HFrEF [145]. Coats et al. [134] demonstrated reduced minute ventilation and the ventilation-carbon dioxide production slope post-exercise training, along with improved heart rate variability and reduced catecholamine levels, indicative of a shift in sympathovagal from sympathetic toward greater vagal tone, in patients with HFrEF.

7. Central command

Central command is critical to the autonomic response to exercise initiation in healthy humans and is involved in arterial baroreflex resetting during exercise [164]. Despite the instrumental difficulty in differentiating between changes in central command from changes originating in other autonomic reflex segments (e.g., the mechanoreflex), evidence suggests central command is a modifiable and trainable portion of the autonomic control centre [165]. Using electrically evoked skeletal muscle contractions to isolate central command, routine exercise training was shown to decrease central command input during exercise without a concomitant change in exercise pressor reflex in healthy humans [165]. However, evidence of central command changes and the effects of exercise training in HFrEF is limited. Central command was shown to contribute to the exaggerated sympathetic nerve activity during exercise that is characteristic of HFrEF by simulating exercise with mesencephalic locomotor region stimulation in decerebrate, ischemic HFrEF rats, and observing fictional-exercise-induced elevated renal and lumbar sympathetic nerve activity [166]. In humans with severe HFrEF, the methodology was unable to differentiate between central command and the mechanoreflex as the primary driver of elevated MSNA during exercise [75]. Interestingly, central command in patients with HF and preserved ejection fraction (HFrEF) was not different from healthy controls despite a lower exercise heart rate [167]; however, the such investigations to better understand the role of central command on exercise pathophysiology in patients with HFrEF is lacking and merits further attention.

8. Clinical implications

Exaggerated sympathoexcitation and depressed vagal tone, as a result of exercise autonomic reflex dysfunction, are proven contributors to prognosis, exercise intolerance, and survival in patients with HFrEF [21,32,47]. It may be clinically prudent to treat the cause(s) of the sympathoexcitation in HFrEF rather than, or at least in addition to, its consequences (e.g., increased MSNA, vasoconstriction, blood pressure) [47,48]. As discussed, potential mechanisms for each reflex may include skeletal muscle abnormalities, arterial stiffness, chronic or intermittent hypercapnia, respiratory acidosis or hypoxemia, and chronic oxidative stress. Exercise training may target some or all of these potential causes forafferent dysfunction, and may attenuate or reverse chronic sympathoexcitation and enhance vagal tone [21]. Other therapies targeting afferent, central, and efferent portions of the reflex loop (Fig. 1) are emerging [21].

9. Future needs and directions

Exercise training is an effective and low-cost non-pharmacologic therapeutic option for people living with HFrEF. Exercise training improves exercise capacity, which is related with better outcomes in patients with HF [168,169]. This non-invasive, affordable, and readily accessible therapy has the potential to be more successful compared to devices and medications for a number of reasons, including but not limited to (a) the effects of exercise target multiple organs and signaling systems, resulting in a “global” improvement; (b) regular exercise improves perceived quality of life and mental health, and (c) exercise training impacts not only the HFrEF sequelae, but other comorbidities and thus lifts the overall burden of health.

The effect of exercise training on the function of each reflex [170], rather than the physiological consequence (e.g., MSNA, heart rate variability, heart rate recovery, etc. [126]) is relatively understudied and not completely known. For example, the recent meta-analysis reports only heart rate recovery, MSNA, and heart rate variability: all indirect measures of autonomic nervous system activity and not used to differentiate between sympathetic and parasympathetic activity, nor tied to any one reflex pathway [126].
This may be due to the technical difficulty and invasiveness in obtaining direct measures, coupled with the challenge of obtaining meaningful data across a wide variety of comorbidities (e.g., a recent mean of 5 comorbidities [169]) that often accompany HFrEF. Medication usage presents another challenge with evaluating the effectiveness of exercise training trials as certain medications (e.g., beta-blockers) may negate or mask favourable sympathovagal shifts. The effect of exercise training on peripheral chemoreflex function and regulation of cardiovascular hemodynamics is understudied in humans with HFrEF. Further, Pearson and Smart [126] report that the majority of studies and randomized controlled trials on exercise therapy on autonomic function in HFrEF lack sufficient allocation concealment, intention-to-treat analysis, control group physical activity monitoring, and considerations regarding relative exercise intensity and accurate energy expenditure. Clearly, both study design and the primary outcome have room for improvement in future randomized controlled trials in exercise training effects on autonomic function in patients with HFrEF.

Mechanistic animal studies have yet to be confirmed in patients with HFrEF; cardiac catheterization during exercise reflex activation may determine the extent of reflex modulation of coronary vasoconstriction and altered ventricular function during exercise in HFrEF [73]. As well, despite the mounting evidence supporting oxidative stress involvement in chemoreflex exaggeration, there is limited data on the effects of exercise training on chemoreflex function and oxidative stress in patients with HFrEF [30]. Other therapies currently under or for future investigation that modulate reflex physiology may include carotid body resection, ablation or desensitization (early findings suggest unilateral vs. bilateral for patient safety [115]), arterial baroreceptor stimulation, vagal nerve stimulation, central acting parasympathetic-mimicking or sympathetic-modulatory medications, efferent renal nerve ablation, acetylcholinesterase inhibition, nicotinic receptor agonists, and beta-adrenergic receptor blockers [21].

Randomized controlled trials are still needed to phenotype autonomic dysfunction to select the appropriate therapeutic approach in HFrEF. The issue of autonomic dysfunction in HFrEF becomes more complicated when comorbidities that also relate to autonomic dysfunction (e.g., hypertension, obesity, diabetes, etc.) [126,171] are added to the equation. The combined effects of multiple morbidities are not well understood and thus requires larger spectrum of inclusion criteria in experimental designs to increase our body of evidence. Patient sex is often overlooked in heart failure research despite the well-acknowledged fact that cardiovascular health and autonomic function is different in females compared to males. As the majority of heart failure studies are primarily male participants, future trials with sex-based comparisons are needed to elucidate any potential sex differences to better treat female patients in the future. Finally, HFrEF and mid-range ejection fraction (HFmEF) are increasingly clinically recognized and studied. However, the evidence around autonomic dysfunction is vastly disproportionally in patients and animals with HFrEF compared to their phenotypic counterparts. Future research should address the gap in literature surrounding HFrEF and HFmEF autonomic function, as well as phenotype-based studies to liken and differentiate the diseases from one another so as to improve future therapy targets on a phenotype-specific basis.

10. Conclusions

Fundamentally, reflex dysfunction may be adaptive at the onset of cardiac failure, but inter-reflex coordination is progressively lost, and thus autonomic dysfunction occurs. The exercise pressor reflex is exaggerated and enhances mean arterial pressure, MSNA, peripheral and likely cardiac vasoconstriction during exercise in HFrEF. Conversely, the exercise pressor reflex may be attenuated in more severe HFrEF. Baroreflex control of heart rate is blunted in HFrEF, as is its ability to buffer the metaboreflex, resulting in elevated resting and exercise heart rate and mean arterial pressure. Chemoreflex hyperactivity induces respiratory disorders, elevated heart rate, and greater vasoconstriction at rest and during exercise. Cumulatively, cardiovascular autonomic reflex dysfunction in HFrEF ex-aggerates sympathoexcitation to cardiac, respiratory, renal, vascular, and skeletal muscular tissues. The cardiovascular autonomic reflex dysfunction thus critically contributes to exercise intolerance and prognosis in HFrEF patients.

Author contributions

Conceptualization—NGB, DDM, HH, and CRT; methodology—NGB, DDM, HH, and CRT; investigation—NGB; data curation—NGB; writing—NGB; review and editing—NGB, DDM, HH, and CRT; visualization—NGB and CRT; supervision—CRT; funding acquisition—NGB and CRT. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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Conflict of interest
The authors declare no conflict of interest.

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