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Recent advances in exercise pressor reflex function in health and disease

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Abstract

Autonomic alterations at the onset of exercise are critical to redistribute cardiac output towards the contracting muscles while preventing a fall in arterial pressure due to excessive vasodilation within the contracting muscles. Neural mechanisms responsible for these adjustments include central command, the exercise pressor reflex, and arterial and cardiopulmonary baroreflexes. The exercise pressor reflex evokes reflex increases in sympathetic activity to the heart and systemic vessels and decreases in parasympathetic activity to the heart, which increases blood pressure (BP), heart rate, and total peripheral resistance through vasoconstriction of systemic vessels. In this review, we discuss recent advancements in our understanding of exercise pressor reflex function in health and disease. Specifically, we discuss emerging evidence suggesting that sympathetic vasoconstrictor drive to the contracting and non-contracting skeletal muscle is differentially controlled by central command and the metaboreflex in healthy conditions. Further, we discuss evidence from animal and human studies showing that cardiovascular diseases, including hypertension, diabetes, and heart failure, lead to an altered exercise pressor reflex function. We also provide an update on the mechanisms thought to underlie this altered exercise pressor reflex function in each of these diseases. Although these mechanisms are complex, multifactorial, and dependent on the etiology of the disease, there is a clear consensus that several mechanisms are involved. Ultimately, approaches targeting these mechanisms are clinically significant as they provide alternative therapeutic strategies to prevent adverse cardiovascular events while also reducing symptoms of exercise intolerance.

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Keywords

blood pressure; neural control of circulation; sympathetic overactivity; hypertension; diabetes; heart failure

1. INTRODUCTION

The autonomic nervous system plays an essential role during exercise by appropriately adjusting the circulation to meet the metabolic demands of the working muscle. Decreases in parasympathetic drive to the heart and increases in cardiac sympathetic drive increase cardiac output, while interactions between sympathetic vasoconstrictor drive to exercising and non-exercising muscle, and local metabolic factors in exercising muscle, redistribute this elevated cardiac output towards the contracting muscles. Mechanisms primarily responsible for these autonomic alterations include central command, the exercise pressor reflex, and arterial baroreflexes. Central command, a feed-forward mechanism arising from higher brain centers evokes parallel activation of locomotor activity and autonomic outflow (Eldridge et al., 1985; Goodwin et al., 1972), and is, in turn, thought to be significantly influenced by the “effort sense” of the activity (Williamson et al., 2006; Williamson et al., 2001). The exercise pressor reflex, a feed-back mechanism arising from the contracting muscle, reflexively adjusts sympathetic outflow (Alam et al., 1938; McCloskey et al., 1972) and is, in turn, greatly influenced by the metabolic milieu in the exercising muscle (Adreani et al., 1998; Kaufman et al., 1984; Rotto et al., 1988). Although exercise resets arterial and cardiopulmonary baroreflexes to a higher operating point, their sensitivity is maintained, allowing them to continue to regulate blood pressure (BP) within an optimal range during exercise (Fadel et al., 2012b; McIlveen et al., 2001; Norton et al., 1999). This review will focus on the contribution of the exercise pressor reflex in health and disease, including hypertension, diabetes, and heart failure. The literature covered is based on the symposium titled “Recent Advances in Exercise Pressor Reflex Function in Health and Disease” held at the annual meeting for the International Society for Autonomic Neuroscience in Los Angeles, July 2019.

2. THE EXERCISE PRESSOR REFLEX

The exercise pressor reflex appropriately adjusts the circulation by evoking reflex increases in sympathetic activity to the heart and skeletal muscles and decreases in parasympathetic activity to the heart, which increases BP, heart rate, and total peripheral resistance through vasoconstriction of systemic vessels (Figure 1). The fact that patients with unilateral syringomyelia or tetraplegia are unable to produce adequate cardiovascular adjustments in response to electrically evoked exercise supports the importance of this reflex mechanism (Corbett et al., 1971; Lind et al., 1968). The seminal, yet simple, experiment by Alam and Smirk (Alam et al., 1937) was the first to demonstrate that performing handgrip exercise in an ischemic state (cuff occlusion) resulted in a substantially higher BP response than performing exercise in a non-ischemic state. Moreover, the finding that BP remained elevated with sustained ischemia at the cessation of exercise suggested that metabolites produced by the contracting muscle were responsible for this response. Subsequent studies

by Coote et al. (Coote et al., 1971) demonstrated that group III and IV skeletal muscle afferents comprise the afferent arm of the reflex, and Kaufman et al. (Kaufman et al., 1983) demonstrated that individual small-diameter muscle afferents could be distinguished based on their discharge properties and sensitivity to different stimuli. Specifically, thinly myelinated group III afferents respond predominantly to mechanical stimuli and discharge vigorously at the onset of muscle contraction in proportion to tension development, with the first impulse often occurring within 200 milliseconds. Conversely, unmyelinated group IV afferents respond predominantly to metabolic stimuli and discharge in proportion to metabolite build-up with a latency of 5-30 seconds (Kaufman et al., 1983). Importantly, both stimuli, alone and in combination, are effective in evoking reflexive increases in BP (Kaufman et al., 2002; Kaufman et al., 1983). The mechanically and metabolically sensitive components of the reflex are, therefore, commonly known as the mechanoreflex and metaboreflex, respectively. It is, however, essential to note that both group III and IV afferents exhibit polymodal activity (Rotto et al., 1988; Rotto et al., 1990), and it is thus more appropriate to consider their sensitivity to mechanical or metabolic stimuli along a spectrum rather than an absolute demarcation.

2.1. The mechanoreflex

Conventional approaches used to isolate the mechanoreflex include passive exercise or stretch (human) and local blockade of mechanically gated channels (animal). Intermittent, or rhythmic, muscle contraction is also an effective stimulus of the mechanoreflex because sympathetic nerve activity becomes synchronized with tension development, which is likely due to the intermittent deformation of the myocyte plasma membrane (sarcolemma) that activates mechanically-gated channels (Copp et al., 2016a; Koba et al., 2007). Furthermore, metabolic by-products arising from muscle contraction can sensitize metabolically sensitive afferents (Rotto et al., 1988; Rotto et al., 1990). Due to the lack of commercially available specific antagonists, the receptors and channels comprising the mechanoreflex are mostly unknown. Previous studies have shown that blocking multiple mechanically-gated channels with gadolinium attenuates the pressor responses to a muscle contraction and stretch (Hayes et al., 2001; Hayes et al., 2009; Kim et al., 2007; Mizuno et al., 2011b; Smith et al., 2005b). Gadolinium blocks multiple channels, therefore the underlying targets for these effects are relatively unknown. However, recent studies have provided further insight. For example, the recent discovery of Piezo channels (two isoforms: Piezo1 and Piezo2) and the high potency of the spider toxin GsMTx-4 in blocking its mechanically activated currents have led to several investigations that suggest that cation-sensitive Piezo channels comprise, in part, the mechanically sensitive component of the exercise pressor reflex (Copp et al., 2016a; Copp et al., 2016b; Sanderson et al., 2019). Nevertheless, our understanding of the mechanoreflex is incomplete and remains an open area of active investigation, where future studies are needed to determine the exact role of mechanosensitive proteins in health and disease.

2.2. The metaboreflex

Conventional approaches to isolate the metaboreflex in humans include superimposed ischemia during exercise (cuff occlusion) and at the cessation of exercise (post-exercise muscle ischemia; PEMI), which accelerates the accumulation of metabolic byproducts of muscle contraction and traps the metabolites in the previously active muscle, respectively

(Alam et al., 1937). Furthermore, intra-arterial injection of metabolic (i.e., lactic acid, ATP, bradykinin) or chemical (i.e., capsaicin) stimuli are commonly used in animal models. Metabolites or stimuli that are known to evoke the metaboreflex include lactic acid, H⁺, potassium, bradykinin, by-products of arachidonic acid metabolism, and analogs of adenosine 5'-triphosphate (ATP) (Pan et al., 1993; Rotto et al., 1988; Rotto et al., 1990; Rotto et al., 1989; Rybicki et al., 1985; Tallarida et al., 1979). Moreover, pharmacologically blocking the corresponding receptors and channels provides further mechanistic insight into which receptors and channels are potent targets to attenuate the pressor response. Proteins thought to evoke the metaboreflex include Acid Sensing Ion Channel 1 (ASIC1) and 3 (ASIC3) (Campos et al., 2019; Hayes et al., 2008; Molliver et al., 2005), bradykinin B2 (B2) (Leal et al., 2013), and purinergic 2X (P2X) receptors (Kindig et al., 2007; McCord et al., 2010). Transient Receptor Potential Vanilloid 1 (TRPV1) receptors, which are located on group IV afferents and are excited by exogenous capsaicin and heat, are also thought to contribute to evoking the exercise pressor reflex (Smith et al., 2010). These receptors are sensitive to pH, changes in muscle temperature, and inflammatory products (Tominaga et al., 2005). However, studies investigating the functional contribution of TRPV1 receptors during exercise have been conflicting (Ducrocq et al., 2019; Kindig et al., 2005; Smith et al., 2010), and more studies are needed to clarify their role during exercise. As such, our current understanding of putative stimuli and receptors and channels responsible for the afferent arm of the metaboreflex is incomplete. Furthermore, co-operation and redundancy in mechanisms complicate these investigations and likely hinders a complete understanding of individual proteins (Stone et al., 2015). It is also important to note that most of these studies are in decerebrate animal models, which limits a direct translation to humans; however, studies in humans have supported roles played by both P2 receptors and ASIC channels (Campos et al., 2019; Greaney et al., 2014).

2.3. Role of the exercise pressor reflex during exercise

In states of inadequate oxygen delivery, the exercise pressor reflex functions as an error signal to increase oxygen delivery (Kaufman et al., 2002; O'Leary et al., 1999). However, accumulating evidence also suggests that the reflex is active and contributes to circulatory adjustments during low-intensity exercise even when oxygen delivery is adequate. Studies in humans using pharmacological blockade with intrathecal fentanyl to reduce input from group III and IV afferents from the lower limbs during mild to moderate voluntary exercise have shown that blockade of these inputs attenuates the BP, heart rate, ventilation, and blood flow responses compared with placebo conditions (Amann et al., 2010; Amann et al., 2011). Moreover, recent studies have suggested that group III and IV afferents also contribute importantly to central and peripheral fatigue during exercise (Amann, 2012; Broxterman et al., 2018), in part, by reducing motor unit recruitment, thereby limiting endurance performance (Hureau et al., 2019). Thus, the function and expression of the exercise pressor reflex largely depend on its degree of activation during exercise.

Mode, intensity, and amount of muscle mass recruited during exercise significantly influences the activation of the exercise pressor reflex. For example, rhythmic exercise, in which accumulation of metabolites is less likely to occur as blood vessels supplying the muscle are not continuously compressed, evoke more modest cardiovascular responses than

isometric exercise, which involves more sustained compression. Furthermore, when interpreting studies involving experimental exercise, it is important to keep in mind that these studies typically employ exercise that involves a limited number of muscle groups and, except for cycling, the exercise is typically performed with only one limb. By contrast, running involves many muscles, in the arms and torso as well as in the legs, and more closely reflects whole-body exercise. Nevertheless, these studies demonstrate the importance of the exercise pressor reflex in increasing blood flow to the exercising muscle while also preventing a fall in arterial pressure due to the vasodilatation produced by local metabolites in the many active muscles (O'Leary et al., 1997; Sheriff et al., 1993). Collectively, studies support the importance of the exercise pressor reflex in evoking appropriate cardiovascular responses to exercise but also highlight the complexity surrounding its role during exercise.

Accumulating evidence has demonstrated that several cardiovascular-related diseases lead to an exaggerated exercise pressor reflex (Bacelli et al., 1999; Grotle et al., 2019a; Grotle et al., 2017; Hammond et al., 2000; Holwerda et al., 2016; Kim et al., 2019a; Negrão et al., 2001; Park et al., 2008a; Tsuchimochi et al., 2010). Although this reflex is appropriate and adaptive by evoking appropriate circulatory responses to exercise, an exaggerated BP response to exercise is maladaptive, serving as a prognostic indicator for the risk of deleterious cardiovascular events during and after exercise (Kurl et al., 2001; Laukkanen et al., 2006; Mittleman et al., 1993). Moreover, individuals with compromised cardiovascular health are at a higher risk of experiencing adverse events during physical exertion. Recent studies have shown that currently available antihypertensive treatments fail to prevent an exaggerated BP response to exercise (Chant et al., 2018). Advancing our understanding of the exercise pressor reflex in health and disease is, therefore, crucial to developing alternative strategies to lower cardiovascular risk during and after exercise.

3. EXERCISE PRESSOR REFLEX FUNCTION IN HEALTH

An essential function of the exercise pressor reflex is to facilitate increases in blood flow to the contracting skeletal muscle by evoking reflex increases in sympathetic outflow to the heart and the skeletal muscular vascular bed, which increase perfusion pressure and redistribute blood flow toward the contracting muscle. Sympathetic restraint of active skeletal muscle blood flow also serves a critical function in preventing a fall in arterial pressure as the contracting muscle has an immense capacity to vasodilate, which would outstrip cardiac output if left unrestrained (O'Leary et al., 1997; Sheriff et al., 1993). Sympathetic activity directed to the muscle is vasoconstrictor in function: cardiac cycles with single or multiple MSNA bursts lead to a peak decrease in vascular conductance after 5-6 cardiac cycles, whereas cardiac cycles without MSNA bursts lead to an increase in vascular conductance (Fairfax et al., 2013). Interpretation of microneurographic data alone is, therefore, commonly used to infer changes in vasoconstrictor drive to the skeletal muscle, but it should be emphasized that this is usually recorded from nerves supplying non-contracting muscle. Central feedforward signals and skeletal muscle afferent feedback both contribute to increasing muscle sympathetic nerve activity (MSNA) to skeletal muscles during exercise (Hajduczuk et al., 1991; Mark et al., 1985; Victor et al., 1987), and the baroreflex has a powerful influence on these adjustments (Fadel et al., 2012b). However, a complete understanding of the control of MSNA during exercise is lacking.

3.1. Mechanisms controlling muscle sympathetic nerve activity

As first demonstrated by Mark et al. (Mark et al., 1985), MSNA to non-contracting muscle increases. Both central command and the exercise pressor reflex contribute to increasing MSNA and BP during exercise. Early studies by Victor et al. (Victor et al., 1987) suggested that the metaboreflex is the primary mechanism responsible for the increase in MSNA because ischemic handgrip exercise, both isometric and rhythmic, evoked substantial increases in MSNA to the leg muscles, as recorded from the common peroneal nerve, and the increase in MSNA remained greater during PEMI compared to the non-ischemic condition. Moreover, MSNA increased during involuntary but not during voluntary muscle contraction, suggesting a minimal influence of central command (Mark et al., 1985). It is worth pointing out, though, that the involuntary contraction in the latter study was brought about by electrical stimulation of the biceps muscle, not of the forearm flexors involved in generating handgrip force. On the other hand, studies using partial neuromuscular blockade with curare to enhance the effort required to perform exercise with weakened muscles have suggested that central command primarily contributes to increasing MSNA during intense isometric muscle contractions, at ~75% MVC, as an enhanced effort at low to moderate intensities (25%, 50% MVC) showed a minimal influence on MSNA (Victor et al., 1995). Conversely, performing the same exercise in an ischemic state dramatically increased MSNA (Victor et al., 1995). Collectively, these studies support a significant contribution of the metaboreflex in increasing MSNA. However, because these studies only recorded MSNA to the non-exercising limb, it could not be determined whether MSNA is uniformly directed to both the exercising and non-exercising limb.

In 1992, Wallin et al. (Wallin et al., 1992) first proposed that MSNA may not be uniform between the exercising and non-exercising limb. Using bilateral recordings from the peroneal nerve during one-legged isometric exercise (non-ischemic) while the other leg served as a control, they showed that although there appeared to be a shared sympathetic drive at rest and during an end-expiratory apnea (which increases MSNA), as measured from the spectral power, the coherence between MSNA directed to the two legs decreased when one leg was exercising. Surprisingly, pooling the data across exercise intensities revealed no change in MSNA to non-contracting muscle, whereas there was a significant decrease in MSNA to the contracting muscle. Later it was argued that if the intensities used in the study by Wallin et al. (Wallin et al., 1992) was not sufficient to elicit an increase in MSNA to the resting muscle, then it was unlikely that the metaboreflex was activated, which could explain the lack of increase in MSNA. Therefore, in an attempt to investigate the role of metaboreflex in increasing MSNA to the contracting muscle, Hansen et al. (Hansen et al., 1994) performed a bilateral recording of MSNA to the contracting and non-contracting leg during static toe extensions at 20% MVC with and without foot ischemia. In this study, they found parallel increases of equal magnitude in MSNA to both legs only when the foot was made ischemic during exercise, an effect that remained during PEMI (Hansen et al., 1994). Thus, these findings suggested that activation of the metaboreflex is a requirement to increase MSNA to both the exercising and non-exercising leg.

3.2. Role of central command and the metaboreflex

Recently, studies have provided some novel insights into the contribution of central command and the metaboreflex in controlling sympathetic activity to the exercising and non-exercising muscle (Boulton et al., 2019; Boulton et al., 2018; Boulton et al., 2016). For example, Boulton et al. (Boulton et al., 2014) showed that MSNA to the contracting leg increases rapidly within 15 s of contraction, in an intensity-dependent manner, and remains elevated throughout the contraction. However, limb ischemia had no significant impact on the intensity-dependent increase in MSNA. Thus, these findings are in contrast with those of Wallin et al. (Wallin et al., 1992) and Hansen et al. (Hansen et al., 1994), who showed a decrease or no change in MSNA to the contracting muscle, respectively.

A follow-up study sought to provide insight into the primary mechanism mediating the increase in MSNA to the contracting muscle, by comparing changes in MSNA to the contracting muscle during electrically evoked weak (i.e., exercise pressor reflex) and voluntary (central command + exercise pressor reflex) isometric dorsiflexion muscle contractions at 5-10% MVC (Boulton et al., 2016). It is important to note that a significant issue with ipsilateral MSNA recording is the presence of EMG, the large spikes of which can swamp the nerve signal, and the presence of neural spikes generated by motor axons to the contracting muscle and of afferent activity generated by muscle spindle and Golgi tendon organ afferents. In addition, movement of the microelectrode during a contraction can lead to loss of the nerve signal, and the presence of electrical artifacts during electrically evoked contractions can further compromise the signal. Thus, to avoid electrical artifacts during electrically evoked contractions, the authors came up with a novel analytical approach to be able to quantify MSNA despite significant electrical artifacts from the muscle contraction. Specifically, they extracted negative-going sympathetic spikes from the neurogram based on the fact that sympathetic fibers are unmyelinated and generate negative-going spikes. This means they can be discriminated from the positive-going spikes generated by large-diameter myelinated axons, such as those supplying muscle spindles and Golgi tendon organs. Moreover, neural spikes are much narrower than EMG spikes, meaning the latter can be excluded through spike-discrimination. Creating post-stimulus histograms using cardiac synchronized (R-wave) negative-going spikes from the neurogram allowed for quantification of the timing and number of sympathetic spikes in the sympathetic bursts. Using this analytical approach, they found that voluntary, but not electrically-evoked, muscle contraction produced an increase in MSNA to the contracting muscle (Figure 2) (Boulton et al., 2016). Moreover, when analyzing the time-course of this increase, they found that MSNA increased around 15-30 s after onset and remained elevated throughout the contraction but quickly returned to baseline at the cessation of exercise (Figure 3). Thus, these findings contrast with those of Hansen et al. (Hansen et al., 1994) and suggest that central command, but not reflex input from the contracting muscle, contributes to increasing MSNA to the contracting muscle during low-intensity isometric contraction (Boulton et al., 2016).

However, whether these responses were uniform across the contracting and non-contracting muscles was not determined. Moreover, although the usage of mild, short, and sustained contractions is advantageous because of its minimal influence on cardiovascular responses

and, therefore, baroreflex involvement, it may not have provided a sufficient stimulus for the metaboreflex. Thus, to further investigate and maximize the involvement of the metaboreflex, MSNA to the contracting and non-contracting leg was recorded and compared using a similar analytical approach but with more extended periods of contractions (~4 min), with and without ongoing ischemia during contraction, as well as a more extended period of PEMI. Consistent with previous studies, they found that MSNA to both the contracting muscle and non-contracting muscle increased; however, ongoing muscle ischemia only enhanced MSNA to the non-contracting muscle, an effect that remained during PEMI (Figure 4). Moreover, they found that the increase in MSNA to contracting muscle occurred earlier than it did to the non-contracting muscle, which supports a significant contribution of a rapid mechanism such as central command or mechanoreflex (Boulton et al., 2018). Again, these findings contrast with those of Hansen et al. (Hansen et al., 1994) and suggest that the metaboreflex does not play a role in evoking a reflexive increase in MSNA to the contracting muscle during low-intensity isometric contractions (Boulton et al., 2018).

Interestingly, although the activation of the metaboreflex did not increase MSNA to the contracting muscle, it did significantly increase MSNA to the non-contracting muscle, which was evident by the fact that muscle ischemia significantly augmented MSNA to the non-contracting muscle (Boulton et al., 2018). Furthermore, unpublished observations from the same laboratory have also shown that MSNA to the contracting muscle increases linearly up to 50% MVC but then returns quickly to baseline during PEMI, which suggests that these effects are also present at higher intensities. Although these findings contrast with those of Hansen et al. (Hansen et al., 1994), they are consistent with Mark et al. (Mark et al., 1985) and Victor et al. (Victor et al., 1989a; Victor et al., 1987) which showed a more considerable contribution played by the metaboreflex, but not central command, in increasing MSNA to the non-contracting limb during the isometric and rhythmic exercise of the contralateral leg.

Since these observations are all based on sustained (i.e., isometric) muscle contraction, Taylor et al. (Taylor et al., 2019) sought to determine whether similar contributions exist during dynamic exercise. To do this, they measured MSNA while first performing ipsilateral isotonic rhythmic dorsiflexion of the ankle, and then subsequently performed the same exercise in the contralateral leg. This type of contraction primarily stimulates rapid-acting mechanisms such as central command and the mechanoreflex as it minimizes metabolite accumulation, given that there is essentially no load (other than the weight of the foot) on the muscles when dorsiflexing a freely rotating ankle. The results of this study showed that MSNA to the contracting leg was significantly higher compared with MSNA to the non-contracting leg. Moreover, there was a significant correlation between MSNA and electromyographic (EMG) activity, which was three times greater in the contracting leg compared with the non-contracting leg (Taylor et al., 2019). This latter finding suggests that there is a tight coupling between muscle activity and MSNA, which is likely mediated by central command. Thus, these findings are in contrast to previous studies reporting no change (Hansen et al., 1994) or a decrease (Wallin et al., 1992) in MSNA to the contracting leg but are consistent with animal studies showing parallel stimulation of locomotion and circulatory adjustments by central command (Eldridge et al., 1985; Eldridge et al., 1981).

Although the cyclic relationship between EMG activity and MSNA suggests a primary contribution of central command, it is possible that input from mechanically sensitive afferents also contributes. For example, studies have shown that passive calf muscle stretch (i.e., ankle dorsiflexion) evokes reflexive increases in MSNA to the resting leg (Cui et al., 2006) and induces renal vasoconstriction (Drew et al., 2017) in humans. Furthermore, animal studies have consistently shown that muscle afferent feedback evokes reflexive increases in MSNA to the contralateral limb (Hill et al., 1996) and renal sympathetic nerve activity (RSNA) (Koba et al., 2006; Victor et al., 1989b), and blocking mechanically-gated channels reduces mechanosensitive afferent activity, sympathetic, and pressor responses to muscle contraction (Copp et al., 2016a; Hayes et al., 2001; Hayes et al., 2009). Other studies have shown a sustained discharge of mechanically sensitive afferents throughout low levels of dynamic exercise in cats (Adreani et al., 1997; Pickar et al., 1994), in which small amounts of tension (~365 g) increased the discharge of 75% of group III afferents (Adreani et al., 1997). Furthermore, RSNA increases rapidly at onset and becomes synchronized with the developed tension during rhythmic (i.e., intermittent) contractions of the calf muscle in cats and rats (Koba et al., 2013; Koba et al., 2007; Victor et al., 1989b). However, whether the mechanoreflex also increases MSNA to the contracting muscle has not been tested. Thus, further studies are needed to clarify the role of the mechanoreflex in evoking reflex increases in MSNA to the contracting muscle.

Collectively, emerging evidence supports the conclusion that different mechanisms contribute to controlling sympathetic vasoconstrictor drive to contracting and non-contracting muscles. Specifically, central command is primarily responsible for increasing MSNA to the contracting muscle, whereas the metaboreflex plays a significant role in increasing MSNA to the non-contracting muscle. Thus, these findings suggest that the metaboreflex may primarily regulate BP by controlling sympathetic vasoconstrictor drive to non-contracting muscle, while central command may primarily prevent excessive hyperemia by increasing vasoconstrictor drive to the contracting skeletal muscle. Further studies are needed to determine whether similar effects are present in disease states.

4. EXERCISE PRESSOR REFLEX FUNCTION IN DISEASE

Although the exercise pressor reflex is essential during exercise, this exaggerated in cardiovascular diseases such as hypertension, heart failure, and reflex is diabetes (Amann et al., 2014; Baccelli et al., 1999; Grotle et al., 2019a; Grotle et al., 2017; Holwerda et al., 2016; Kim et al., 2019b; Tsuchimochi et al., 2010), and this exaggeration is a prognostic indicator of the risk of adverse cardiac events and stroke (Kurl et al., 2001; Laukkanen et al., 2006; Mittleman et al., 1993). Other diseases such as peripheral artery disease, chronic kidney disease, obesity, chronic pulmonary disease and Parkinson disease are also associated with an aberrant function of the exercise pressor reflex (Baccelli et al., 1999; Bruce et al., 2016; Kim et al., 2019b; Negrao et al., 2001; Park et al., 2008a; Sabino-Carvalho et al., 2018; Tsuchimochi et al., 2010). However, this review focuses on recent advances in our understanding of its function in hypertension, diabetes, and heart failure. Herein, we provide a general overview of these diseases and studies conducted so far in both animal and human, followed by a discussion of potential mechanisms for an exaggerated reflex. For additional and complementary reading on the effect of cardiovascular related diseases on the exercise

pressor reflex, we refer the reader to other recently published reviews (Cristina-Oliveira et al., 2020; Dombrowski et al., 2018; Grotle et al., 2019c; Mitchell, 2017; Vianna et al., 2019).

4.1. Hypertension

Hypertension is a growing health concern worldwide, affecting about 45% of the population in the US, and is a primary contributor to increased mortality from heart disease and stroke (Fryar et al., 2017; Noubiap et al., 2019). The underlying cause of hypertension is not well understood but increased dietary sodium consumption and the presence of other chronic diseases such as obesity, diabetes, and chronic kidney disease increase the prevalence of hypertension (Carretero et al., 2000). In addition to having elevated resting BP, hypertensive individuals also have an excessive BP response to exercise compared with normotensive individuals (Kahn, 1991; Kazatani et al., 1995; Pickering, 1987). This type of response significantly augments the cardiovascular strain and the risk of adverse events in hypertensive individuals (Hoberg et al., 1990; Mittleman et al., 1993; Mittleman et al., 1996). Accumulating evidence suggests that excessive activation of the exercise pressor reflex plays a significant role in causing this increased responsiveness to exercise in hypertension (Smith et al., 2015; Smith et al., 2006).

Only about 24% of hypertensive individuals have their condition under control at rest (Fryar et al., 2017; Whelton et al., 2018), and recent findings suggest that even when controlling their BP with antihypertensive medication, these medications fail to control the augmented BP responsiveness to exercise (Chant et al., 2018). Hypertension results in a chronically elevated workload on the heart at rest; thus, the lack of BP control during exercise increases this workload further and significantly increases the risk of adverse cardiovascular events during and after physical exertion. Determining the underlying mechanisms causing this exaggerated response is, therefore, crucial to develop alternative therapeutic strategies to reduce cardiovascular risk.

Animal studies—Animal studies provide valuable insight into the underlying mechanisms causing an exaggerated exercise pressor reflex. Further, these studies also allow one to study the effect of hypertension on the exercise pressor reflex without confounding variables such as antihypertensive medications and the presence of comorbidities such as obesity, diabetes, and renal disease. Decerebrate and unanesthetized animal preparations have provided insight into the isolated contribution of the exercise pressor reflex function in hypertension since the influence of central command is removed, and barodenervation procedure provide further insight into the role of baroreflexes in modulating the pressor reflex. Several animal studies using a variety of models of hypertension support an exaggerated exercise pressor reflex in this disease (Koba et al., 2013; Mizuno et al., 2013; Smith et al., 2006). These studies have shown that hypertension leads to functional alterations in both the mechanical and metabolically sensitive components of the exercise pressor reflex. For example, Smith et al. (Smith et al., 2006) showed that cardiovascular responses (mean arterial pressure; MAP, heart rate; HR) to electrically induced static contraction of the hindlimb muscles over various intensities (30-100% of maximal tension) were significantly and substantially (>2 fold) elevated in spontaneously hypertensive rats compared with normotensive rats.

The arterial baroreceptors modulate the pressor response to exercise (Bevegard et al., 1966); therefore, impairments in the buffering capacity of the baroreflex could contribute to this exaggerated response. In this study, hypertensive rats with intact baroreceptors had a higher BP response than normotensive animals with denervated baroreceptors. Denervating baroreceptors in hypertensive animals further enhanced their response, suggesting that the baroreflex modulation of the pressor response was intact in hypertensive animals and that baroreflex dysfunction is not the cause of the exaggerated responses. Importantly, postganglionic sympathetic blockade (hexamethonium) lowered baseline BP and abolished the responsiveness to exercise, supporting the idea that excessive sympathetic activity is the primary driver for BP elevations at rest and during exercise in hypertension.

To determine the contribution of the mechanoreflex and metaboreflex in evoking this exaggerated reflex, Leal et al. (Leal et al., 2008) showed using the same model and preparation that cardiovascular responses to passive tendon stretch of the hindlimb muscles, over a wide range of intensities, were significantly higher in hypertensive rats compared to normotensive rats and were positively correlated with tension development. Moreover, blocking mechanically gated channels with Gadolinium significantly attenuated the exaggerated pressor and renal sympathetic responses in hypertensive rats. Similarly, these rats also exhibited exaggerated sympathetic activity and pressor responses to ischemic exercise and graded injections of capsaicin, a TRPV1 agonist, into the local circulation of the hindlimb, whereas blocking TRPV1 receptors (Capsazepine) attenuated this response (Mizuno et al., 2011a). Spranger et al. (Spranger et al., 2017) demonstrated, in conscious dogs, that the ability of the metaboreflex to raise cardiac output is significantly reduced in hypertension due, in part, to exaggerated metaboreflex evoked coronary vasoconstriction limiting ventricular performance. This inability to sufficiently raise cardiac output, in turn, contribute to a shift in reliance on peripheral vasoconstriction to raise arterial pressure. Collectively, these findings strongly suggest that functional alterations to both mechanically and metabolically sensitive afferents contribute to the exaggerated exercise pressor reflex in hypertension.

Human studies—Accumulating data from human studies support the findings from animal studies suggesting that hypertension does indeed lead to an exaggerated exercise pressor reflex. For example, an early report by Sausen et al. (2009) showed that older hypertensive individuals, compared to older normotensives, exhibit enhanced metaboreflex sensitivity evidenced by an augmented BP response to PEMI. In a follow-up study, Delaney et al. (Delaney et al., 2010) extended these findings and showed that hypertensive individuals exhibit greater pressor and MSNA (burst frequency) responses to static handgrip exercise at 30% and 40% MVC and PEMI (Figure 5). Furthermore, pressor and MSNA responses to a non-exercise sympathoexcitatory stimulus – the cold pressor test – were not different between groups, thus suggesting that these responses were not due to a centrally generalized sympathoexcitation. However, there are conflicting data on the latter finding (Flaa et al., 2006; Lambert et al., 2004; Matsukawa et al., 1991; Schobel et al., 1998). Nonetheless, these findings do support an accentuated metaboreflex in older hypertensive individuals.

In contrast, it is unclear whether hypertension in humans leads to an exaggerated mechanoreflex. As noted above, mechanically sensitive afferents discharge vigorously at the onset of exercise in proportion to tension development, whereas metabolically sensitive afferents are activated later and respond in proportion to metabolites produced (Kaufman et al., 1983; Kaufman et al., 1984). The mechanoreflex, therefore, contributes to the early increase in BP as it takes time for metabolites to accumulate. Consistent with this notion, Greaney et al. (2015) analyzed changes in pressor and MSNA (peroneal nerve) over time in response to static handgrip exercise and found that older hypertensive individuals exhibit rapid onset (~10 s) pressor and MSNA responses compared with older normotensive individuals. Thus, these findings support a possible contribution of mechanically sensitive afferents in evoking the exaggerated exercise pressor reflex hypertension. However, further studies are warranted. It is essential to note that these studies all involved isometric handgrip exercise, and conflicting data suggest preserved BP and MSNA (peroneal nerve) responses to exercise and decreased metaboreflex control of MSNA during PEMI in middle-aged hypertensive individuals (Rondon et al., 2006).

To identify the role of the exercise pressor reflex during dynamic leg exercise, Barbosa et al. (Barbosa et al., 2016) compared cardiovascular responses to moderate leg cycling exercise before and after intrathecal injection of fentanyl in middle-aged hypertensive individuals. As noted above, this approach is known to reduce the contribution of the exercise pressor reflex due to its attenuation of group III and IV afferent transmission within the spinal cord without affecting force production (Amann et al., 2010; Amann et al., 2009; Amann et al., 2011; Meintjes et al., 1995). They found that hypertensive individuals exhibited an exaggerated BP response to cycling exercise starting at 1 min after initiation of exercise and lasting throughout the exercise (~5 min) (Barbosa et al., 2016). Thus, this study provides further support for increased early responsiveness to exercise (Greaney et al., 2015). Importantly, attenuating group III and IV afferent feedback in hypertensive individuals normalized these responses similar to that of normotensive individuals (Figure 6) and improved skeletal muscle blood flow (total vascular conductance). At the same time, stroke volume increased, and heart rate decreased, resulting in a maintained cardiac output (Barbosa et al., 2016). A recent study supports these findings and likewise showed that attenuating group III and IV afferent feedback with fentanyl normalized the exaggerated pressor response to single-leg knee extension exercise and improved vascular conductance to the exercising muscle (Sidhu et al., 2019). These findings provide strong evidence that the overactivation of skeletal muscle afferents is responsible for the heightened cardiovascular responsiveness to exercise in hypertension. Collectively, accumulating data support the conclusion that the exercise pressor reflex is responsible for evoking the exaggerated cardiovascular responses in hypertension. Therefore, determining underlying mechanisms for an exaggerated reflex is clinically relevant and may provide alternative therapeutic targets to reduce cardiovascular risk in this population.

Mechanisms—Potential mechanisms for an exaggerated exercise pressor reflex in hypertension likely involve both central and peripheral mechanisms. Different or similar mechanisms may also underlie the functional alterations to mechanically and metabolically sensitive afferents expressed in hypertension (Mizuno et al., 2016; Smith et al., 2015).

Plausible peripheral mechanisms include increased expression/density of channels and receptors, increased oxidative stress, and accelerated metabolite accumulation within contracting the skeletal muscle. Currently, few direct data exist implicating peripheral mechanisms in hypertension. However, some data suggest that upregulation in the expression or increased sensitivity of putative metabolically sensitive receptors, such as TRPV1 and P2 receptors, may play a role (Leal et al., 2008; Mizuno et al., 2011a). In moderately hypertensive individuals, there is evidence for a modest role played by purinergic receptors, which are found on sensory nerve endings and are activated by interstitial ATP. For example, local infusion of a non-selective purinergic (P2) receptor antagonist (pyridoxal-5-phosphate) using the bier-blocking technique partially attenuates the exaggerated sympathetic responses to metaboreflex activation (PEMI) but has no effect on responses to static handgrip exercise (Greaney et al., 2014).

Another potent peripheral mechanism is oxidative stress-mediated sensitization of peripheral afferents. Increased production of reactive oxygen species (ROS) plays a role in evoking the exaggerated exercise pressor reflex in various animal models of hypertension (Koba et al., 2013) as well as in other cardiovascular diseases associated with hypertension (Harms et al., 2017; Koba et al., 2009; Muller et al., 2012; Wang et al., 2009; Zimmerman et al., 2004). Increased activity of the renin-angiotensin-aldosterone system (RAAS) plays an essential role in the development of hypertension. Increased RAAS activity also contributes to elevating peripheral and central oxidative stress by activating NADPH oxidases (Fanelli et al., 2011; Zimmerman et al., 2004), which is a potent source of superoxide in skeletal muscle (Ferreira et al., 2016). Interestingly, NADPH mediated production of superoxide appears to be an effective stimulus of the exercise pressor reflex (Harms et al., 2017; Koba et al., 2013; Wang et al., 2009). In terms of hypertension, Koba et al. (Koba et al., 2013) showed that attenuating local production of superoxide within the contracting muscle using two superoxide scavengers (tempol and tiron) in rats with hypertension induced by Angiotensin II attenuates the pressor and renal sympathetic responses to static contraction. Moreover, both drugs attenuated the exaggerated renal SNA response to intermittent muscle contraction as well as its synchronized pattern with tension development traction, which suggests that oxidative stress may primarily sensitize mechanically sensitive afferents (Koba et al., 2013). Thus, these findings suggest that oxidative stress may contribute to evoking the exaggerated exercise pressor reflex in hypertension, in part, by sensitizing the mechanoreflex (Greaney et al., 2015; Leal et al., 2008; Mizuno et al., 2011b).

Increased accumulation of metabolites within the contracting muscle likely contributes to increased activation of the exercise pressor reflex in hypertension. Evidence suggests that functional sympatholysis is impaired in both animals (Mizuno et al., 2014; Zhao et al., 2006) and patients (Price et al., 2013; Vongpatanasin et al., 2011) with hypertension, in which reactive oxygen species (Zhao et al., 2006), angiotensin II (Vongpatanasin et al., 2011), and nitric oxide (Mizuno et al., 2014) appear to play an important role. Thus, combined with the exaggerated increase in MSNA known to occur in hypertension (Delaney et al., 2010; Greaney et al., 2015), an impaired ability to blunt the resultant vasoconstriction would likely decrease blood flow and increase metabolite accumulation in the contracting muscle causing increased activation of metabolically sensitive afferents and potentially sensitize mechanically sensitive afferents. Both exercise and disease increase muscle oxidative stress,

which impairs functional sympatholysis (Fadel et al., 2012a; Zhao et al., 2006). Moreover, oxidative stress has also been found to impair cutaneous microvascular function independently of BP in normotensive humans with salt resistance (Greaney et al., 2012), and contribute to reduce NO release and impaired vascular relaxation in rats fed a high salt diet (Zhu et al., 2007). Thus, oxidative stress may also affect the activation of skeletal muscle afferents indirectly by impairing skeletal muscle vasodilation and accelerating the production of metabolites.

Several reports also support a significant role played by central mechanisms leading to exercise pressor reflex dysfunction in hypertension. For example, directly stimulating skeletal muscle afferents at an equal magnitude resulted in a higher pressor response in hypertensive rats compared to that in normotensive rats (Mizuno et al., 2011a), which suggests altered central processing or integration of afferents feedback. Autonomic control centers in the brain are complex and highly sophisticated, with involvement and integration between several areas. The medulla oblongata in the brainstem is the primary control center for cardiovascular and respiratory control. The nucleus tractus solitarius (NTS) receives input from ascending peripheral afferents and descending central input from higher brain centers, and thus functions to integrate these signals. The rostral ventrolateral medulla (RVLM) is also thought to play a significant role in modulating the autonomic control of circulation (Potts, 2001). Moreover, both NTS and RVLM exhibit sustained activation during 2 min of static handgrip exercise and 6 minutes of PEMI (Sander et al., 2010). Ultimately, ascending and descending neural signals mediated through these structures determine the integrated autonomic response to exercise.

The exact molecular mechanisms responsible for the integration of these signals is not well understood. However, centrally derived nitric oxide (NO) within the NTS has been found to play a crucial role in cardiovascular regulation by modulating autonomic outflow, in part, by inhibiting sympathetic outflow (Cunha et al., 1993). Studies have shown that NO plays a role in buffering reflex mediated changes in BP (i.e., exercise pressor reflex and arterial baroreflex) (Li et al., 2001; Smith et al., 2005a). For example, chronically increasing nitric oxide synthase (NOS), the enzyme catalyzing the conversion of L-Arginine to nitric oxide, decrease sympathetic activity, BP, and heart rate at rest whereas suppressing nitric oxide synthase has the opposite effect (Eshima et al., 2000; Tai et al., 2004; Wu et al., 2002). Likewise, experimentally increasing NTS nitric oxide production (L-arginine infusion) attenuates the pressor response to static hindlimb contraction in cats with denervated baroreflex (Smith et al., 2005a), whereas reducing endogenous production of NTS nitric oxide (L-NAME) further increases the pressor response to mechanoreflex activation (i.e., passive tendon stretch) in hypertensive rats (Leal et al., 2012). Other studies have reported reduced basal levels of NOS activity within NTS in hypertension (Pontieri et al., 1998). Moreover, the expression of neuronal NO within areas of NTS excited by the exercise pressor reflex is lower in hypertensive compared to normotensive rats (Murphy et al., 2013).

The underlying cause of reduced NO activity in hypertension is not well understood. However, several lines of evidence have indicated that activation of the renin-angiotensin system and production of reactive oxygen species both contribute to reducing endogenous NO availability in hypertension (Eshima et al., 2000; Fanelli et al., 2011; Hirooka, 2008;

Zimmerman et al., 2004). In short, superoxide can scavenge nitric oxide, both centrally and peripherally, by reacting with NO forming peroxynitrite, which, on its own, is a powerful oxidant (Hirooka, 2008). Furthermore, increased activation of the RAAS increase sympathetic activity (Eshima et al., 2000), in part, by angiotensin II binding to its AT1R receptors, increasing the activation of NADPH oxidases, which leads to increased superoxide production in the brain stem (Fanelli et al., 2011; Hirooka, 2008; Zimmerman et al., 2004). Collectively these findings suggest that reduced nitric oxide production within the NTS impair the ability of NTS to buffer reflex increases in sympathetic activity and thus may be an underlying mechanism for an exaggerated exercise pressor reflex in hypertension.

Excessive salt intake is associated with increased risk of developing hypertension, reduced cardiovascular function, and central sensitization of autonomic pathways responsible for BP regulation (Adams et al., 2009; Adams et al., 2007; Pawloski-Dahm et al., 1993). Emerging evidence suggests that increased salt intake also enhances the exercise pressor reflex (Figure 7) (Yamauchi et al., 2014). Studies have shown that increasing plasma osmolality by intravenous infusion of hypertonic saline (3% NaCl) increases MSNA in healthy conscious humans (Farquhar et al., 2006). Moreover, increased dietary salt intake resulted in more considerable BP variability in salt-resistant rats, an effect that was observed at night when rats are more physically active (Simmonds et al., 2014). Conversely, a recent study showed that increased dietary salt intake over ten days did not affect BP variability in healthy young adults (Migdal et al., 2020). It is possible, however, that prolonged high salt intake alters baroreflex control of BP, which, in turn, could impair the ability of baroreflex to modulate exercise-induced increases in BP (Grassi et al., 2002; Huang et al., 1994). Accumulating evidence also supports a role of high dietary salt intake in increasing BP and sympathetic responsiveness to various non-exercise stimuli (e.g., electrical stimulation of afferent nerves, exogenous Angiotensin II and insulin administration, and aortic depressor nerve activation). Thus, these findings suggest that high exogenous sodium concentration in the brain induces central sensitization of the sympathetic nervous system.

The underlying mechanisms for this sensitization are not well understood but likely involve an interaction between brain regions responsible for sodium sensing and cardiovascular regulation. Putative areas include organum vasculosum laminae terminalis (OVLT) and subfornical organ (SFO), which play a significant role in behavioral and autonomic responses to hyperosmolarity (Guyenet, 2017; Kinsman et al., 2017). Interestingly, injection of physiologically relevant concentrations of NaCl into these areas elicits increases in sympathetic activity and BP (Kinsman et al., 2017), and neural signals from OVLT transmits to the paraventricular nucleus of the hypothalamus, which has direct projections to brain stem area responsible for cardiovascular regulation such as RVLM and NTS (Guyenet, 2017; Jänig, 2006).

Investigations on the effect of salt loading on the reflexive cardiovascular responses to exercise are in the early stages. However, one animal study clearly shows that healthy rats fed high sodium containing diet (chow: 5% NaCl) over 2-3 weeks have a significantly higher pressor response to static hindlimb contraction compared to healthy rats fed a low sodium diet (chow: 0.1%). Furthermore, a recent human study found that salt restriction lowered resting and exercise BP in patients with hypertension without impacting central and

peripheral hemodynamics during arm or leg exercise. However, BP responsiveness (change values) was not altered in this salt restriction study (Ratchford et al., 2019).

Summary and significance—Collectively, these findings provide strong evidence that hypertension leads to an exaggerated exercise pressor reflex. Moreover, alterations to both mechanically sensitive and metabolically sensitive afferents contribute to this exaggeration. The underlying mechanisms for this exaggeration likely include both peripheral and central mechanisms in which dietary salt consumption appears to play a significant role. Advancing our understanding of these mechanisms is clinically essential to develop alternative therapeutic strategies as currently available medications are not protective of an exaggerated BP response during exercise (Chant et al., 2018).

4.2. Diabetes

Diabetes is the 7th leading cause of death and affects more than 30.3 million in the US (Bommer et al., 2017; Boyle et al., 2001; Wild et al., 2004). The majority of these cases are type 2 diabetes mellitus (T2DM), whereas type 1 diabetes mellitus (T1DM) accounts for ~5%. However, epidemiological studies suggest that the prevalence of T1DM is also increasing worldwide (Maahs et al., 2010). Importantly, the overall prevalence of diabetes and pre-diabetes in young adults is increasing, and more than 25% of older adults have diabetes (Mayer-Davis et al., 2017; Prevention, 2018). Individuals with diabetes also have a higher prevalence of comorbidities, such as atherosclerosis, hypertension, and diabetic peripheral neuropathy, and prevalence increase with age and the progression of the disease (Prevention, 2018). There is, therefore, a great urgency to develop effective treatments considering that risk of complications and cardiovascular disease (CVD) increases with the duration of diabetes (Song, 2016). Exercise is recommended as a treatment strategy in diabetes as it has a multitude of cardiometabolic benefits. However, in recent years, accumulating evidence indicates that diabetics may be at an elevated risk of experiencing adverse cardiovascular events during exercise. Accumulating evidence suggests that sympathetic and BP responses to exercise are exaggerated in diabetes, in part, due to an exaggerated exercise pressor reflex (Holwerda et al., 2016; Karavelioglu et al., 2013; Kim et al., 2019a; Scott et al., 2008). The underlying mechanisms causing this exaggerated response are not known. This section will, therefore, discuss recent advancements in the role of the exercise pressor reflex in T1DM and T2DM. Due to a recent review covering the majority of these advancements in T2DM (Grotle et al., 2019c), we only discuss these studies concisely.

Type 1 diabetes mellitus

Animal studies: Since few human studies have comprehensively assessed the effect of T1DM on the reflexive control of the circulation, animal studies provide critical insight. Importantly, these can isolate effects in a more homogenous population, which is useful since patients with diabetes often vary widely in the severity and progression of the disease. Grotle et al. (Grotle et al., 2017) were the first to show that untreated T1DM results in an exaggerated reflex pressor response to electrically induced static exercise in the early stage of the disease (Figure 8). Recently, another study extended these findings and showed that short-term T1DM leads to exaggerated sympathetic responsiveness to static muscle contraction, in part, due to the sensitization of group IV afferents (Ishizawa et al., 2020).

Furthermore, the pressor responses to both tendon stretch (Grotle et al., 2019b; Ishizawa et al., 2020) and local injection of capsaicin (Ishizawa et al., 2020) into the hindlimb vasculature are likewise exaggerated, suggesting that short-term T1DM alters the expression of the mechanoreflex and the metaboreflex. In contrast, the reflex pressor response to static muscle contraction became attenuated towards the later stage of the disease (Grotle et al., 2017), suggesting that the expression of the reflex may change as a result of the progression of the disease.

Interestingly, this temporal pattern mimics the symptoms during the progression of sensory neuropathy and may thus suggest that similar mechanisms exist. A typical early symptom of sensory neuropathy includes mechanical allodynia, characterized as increased pain to a normally non-painful stimulus (Pop-Busui et al., 2017). It is reasonable that similar changes could occur to mechanically sensitive afferents responsible for evoking the exercise pressor reflex. Consistent with this hypothesis, the pressor response to tendon stretch was significantly and substantially higher one week after T1DM onset compared with non-diabetic controls (Grotle et al., 2019b). Preliminary findings also suggest that the pressor response to intermittent muscle contraction (i.e., simulated dynamic muscle contraction) is likewise exaggerated. Collectively, these data support the concept that T1DM leads to an altered reflexive control of the circulation during exercise, which may be expressed differently depending on the progression of the disease. Moreover, increased sensitivity of both mechanically and metabolically sensitive afferents play a significant role in evoking the exaggerated reflex in the early stage of the disease.

Human studies: Although there are a lack of studies investigating the effect of T1DM on the reflexive control of the circulation in humans during exercise, one study reported augmented systolic BP responses to dynamic exercise in middle-aged T1DM patients (Matteucci et al., 2006). Furthermore, another study reported that young T1DM individuals demonstrated abnormal hemodynamic responses to exercise, which was attributed to an altered expression of the metaboreflex (Roberto et al., 2012). Other studies suggest that T1DM increases basal sympathetic nerve activity and systolic BP in children and adolescents with T1DM, which in turn is associated with increased risk of cardiovascular complications later in life (da Costa Rodrigues et al., 2006; Mueller, 1984; Mueller et al., 1982; Pop-Busui et al., 2004; Zorena et al., 2010). Moreover, these responses likely vary depending on glycemic control (Duvernoy et al., 2016). Thus, varying levels of glucose control, time of disease onset, and duration of disease in human cohorts make it difficult to comprehensively assess the effects of T1DM on the reflexive control of the circulation. More studies are needed to understand further the effect of T1DM on the exercise pressor reflex in humans.

Mechanisms: The mechanisms underlying abnormal cardiovascular responses to exercise in T1DM are not known. Given that sensory neuropathy is prevalent in diabetes and that it affects group III and IV afferents, it is reasonable that similar mechanisms are involved (Kaufman et al., 1983; Khan et al., 2002; Sun et al., 2012). Thus, alterations causing sensitization of group III and IV sensory afferents evoking neuropathic pain may also evoke an exaggerated exercise pressor reflex in T1DM (Janig, 2011; Khan et al., 2002; Orstavik et

al., 2006; Pitcher et al., 2000; Xu et al., 2015). Altered activation patterns or changes in protein expression of nociceptive channels and receptors mediate, in part, an increased sensitization of group III and IV afferents (Delliaux et al., 2009; Eijkelkamp et al., 2013; Lolignier et al., 2015). However, the specific channels and receptors involved are not well understood. Recently, a study showed that T1DM leads to increased sensitization of group IV afferents in vitro, potentially due to increased activity of PKC signaling (Ishizawa et al., 2020). Emerging evidence also supports a role of mechanically gated Piezo channels (Eijkelkamp et al., 2013; Grotle et al., 2019b; Szczot et al., 2018). Piezo channels are rapidly adapting mechanically gated channels that respond to changes in tension applied to the lipid bilayer and, once opened, allow cations such as calcium to flow into the cell, causing depolarization (Bagriantsev et al., 2014). Specifically, enhanced Piezo mechano-transduction plays a role in evoking pain to usually non-painful stimuli (i.e., mechanical allodynia) (Bagriantsev et al., 2014; Eijkelkamp et al., 2013; Fermo et al., 2017; Park et al., 2008b). Importantly, recent studies have suggested that these channels also play a role in evoking the exercise pressor reflex (Copp et al., 2016a) and the exaggerated mechanoreflex in early-stage T1DM (Grotle et al., 2019b). For example, blocking these channels with GsMTx-4 attenuates the exaggerated pressor response to mechanoreflex activation (i.e., tendon stretch) in T1DM rats (Figure 9) (Grotle et al., 2019b). Preliminary findings support these findings and suggest that these channels also play a role in evoking the exaggerated pressor response to simulated dynamic muscle contraction in T1DM rats. Collectively, these findings suggest that mechanically gated Piezo channels play a role in evoking the exaggerated exercise pressor reflex in T1DM, and thus identifies a potential therapeutic target to reduce the heightened cardiovascular risk associated with T1DM.

Type 2 diabetes mellitus

Animal studies: Several recent animal studies have advanced our understanding of the exercise pressor reflex in T2DM. Potential confounding variables such as medications, varying disease onset, and level of glycemic control often confound human studies making animal studies advantageous. Kim et al. (Kim et al., 2019b) were the first to provide evidence that T2DM negatively impacts neural cardiovascular control. In this study, they used a high-fat diet, low-dose streptozotocin-induced T2DM rat model, and isolated the exercise pressor reflex by electrically stimulating a static contraction of the hindlimb muscles. Central command was also isolated by electrically stimulating the mesencephalic locomotor region (MLR) in decerebrate rats. In this study, they showed that T2DM leads to exaggerated pressor and renal sympathetic responses to both static contraction and MLR stimulation (Kim et al., 2019b), suggesting that both the exercise pressor reflex and central command contribute to the exaggerated cardiovascular responses in T2DM. In this study, however, they did not explore the role of onset and duration of diabetes. Therefore, to further explore the effects of duration of diabetes on the exercise pressor reflex, as well as the role of the mechanoreflex, Grotle et al. (Grotle et al., 2019a) determined the effect of disease progression on the pressor response to static contraction and tendon stretch. Unlike the previous study, this study used a rodent model (UC Davis- Type 2 Diabetes Mellitus) that develops T2DM naturally (untreated) over time with more similar pathophysiology as that seen in humans and showed that as T2DM rats progressed with the disease, the expression of the exercise pressor reflex changed. Specifically, 31 weeks after diabetes onset, but not at 21

weeks, the pressor response to static contraction was exaggerated in T2DM rats compared to non-diabetic controls (Figure 10). Interestingly, at the same time point, the T2DM rats had an exaggerated pressor response to tendon stretch (Grotle et al., 2019a). Thus, these findings suggest that T2DM, dependent on disease progression, leads to an exaggerated exercise pressor reflex. Furthermore, increased responsiveness of mechanically sensitive afferents may, in part, be responsible for causing an exaggerated exercise pressor reflex in T2DM.

Human studies: Several studies have indicated that T2DM leads to an exaggerated BP response to exercise in humans. These studies have shown that adolescents (Pinto et al., 2014), middle-aged adults (Regensteiner et al., 2009; Scott et al., 2008), and older adults with T2DM (O'Connor et al., 2015) exhibit an exaggerated BP response to both maximal and moderate-intensity dynamic exercise. However, the underlying mechanisms for these responses are not known. In this regard, Holwerda et al. (Holwerda et al., 2016) provided some critical insight. In this study, they had middle-aged normotensive and hypertensive T2DM individuals perform static handgrip exercise at 30% and 40% MVC followed by a period of PEMI to isolate the metaboreflex contribution while measuring MSNA and BP. They found that T2DM individuals, independent of the presence of hypertension, exhibit an exaggerated pressor and sympathetic response to isometric handgrip exercise, an effect sustained during PEMI compared to healthy age-matched controls (Figure 11). Furthermore, there was a significant relationship between MSNA responses and the severity of T2DM. Thus, these findings are consistent with those in animals suggesting that the severity or duration of disease significantly impacts the expression of the exercise pressor reflex (Holwerda et al., 2016).

Mechanisms: The underlying mechanisms for an exaggerated exercise pressor reflex in T2DM are not known. Possible mechanisms include increased production of metabolites, alterations in expression and sensitivity of receptors and channels present on group III and IV afferents as well as increased oxidative stress. Studies have shown that T2DM individuals exhibit increased sympathetic activity (Holwerda et al., 2016; Kim et al., 2019b) and attenuated blood flow during exercise (Groen et al., 2019; Kingwell et al., 2003; Lalande et al., 2008), which suggests that accelerated muscle ischemia increases the production of metabolites potentially contributing to an exaggerated metaboreflex (Holwerda et al., 2016). Other studies suggest that these alterations may occur early in the disease as blood flow responses to supine cycling exercise (60% $\text{VO}_{2\text{peak}}$) and acetylcholine injection is lower in pre-diabetic individuals compared to age, weight, and $\text{VO}_{2\text{peak}}$ matched controls (Kingwell et al., 2003). T2DM is also associated with increased production of vasoconstrictors such as endothelin-1 and thromboxane A2 (Frisbee et al., 2019; Oguri et al., 2009; Reynolds et al., 2017; Stepp et al., 2002), which may further accentuate muscle ischemia at rest or during exercise. Whether T2DM leads to impairments in functional sympatholysis is unclear and may be dependent on the severity of endothelial dysfunction (Bock et al., 2019; Thaning et al., 2011). Nonetheless, these studies do suggest that accelerated muscle ischemia may contribute to increased activation of metabolically sensitive while possibly sensitizing mechanically sensitive afferents, thereby causing an exaggerated exercise pressor reflex in T2DM.

Other possible mechanisms include alterations to group III and IV afferents. For example, the most common complication in diabetes is sensory neuropathy, which is associated with increased sensitization or damage of group III and group IV afferents. Mechanical allodynia, a common early symptom of sensory neuropathy, has been found to involve overactivation of mechanically sensitive afferents (Janig, 2011; Khan et al., 2002; Orstavik et al., 2006; Pitcher et al., 2000; Xu et al., 2015). Thus, these findings are consistent with an exaggerated mechanoreflex in T2DM rats (Grotle et al., 2019a). Lastly, an increased presence of oxidative stress and inflammatory mediators within the contracting muscle may also contribute to the overactivation of group III and IV sensory afferents (Grotle et al., 2019c). Collectively, these findings suggest that multiple mechanisms may contribute to exaggerating the exercise pressor reflex in T2DM. Future investigations are, therefore, warranted to further dissect the potential contribution of these mechanisms as well as the possible interplay between them.

Summary and significance: Several studies have indicated that T2DM leads to an exaggerated exercise pressor reflex, which increases their risk of adverse cardiovascular events during and after exercise. Moreover, these findings also highlight the importance of appropriate and supervised exercise prescription in this population, especially in individuals with poorly controlled diabetes. The underlying mechanisms for these responses are poorly understood and require further investigation. These investigations are, in turn, of great urgency to develop effective therapeutic strategies to lower the immediate cardiovascular risk associated with exercise in this population.

4.3. Heart failure

Heart failure (HF) is a leading cause of mortality worldwide, and prevalence increases with aging and with other comorbidities such as diabetes, hypertension, and obesity. Generally, two subtypes of HF exist and are diagnosed based on whether ventricular ejection fraction is preserved (HFpEF) or reduced below 40% (HFrEF) (Metra et al., 2017). Although the etiology and mechanisms underlying these two subtypes may differ, both subtypes present with structural and functional abnormalities of the heart and skeletal muscle, causing sympathetic overactivity, tachycardia, and excessive vasoconstriction at rest which worsens with exercise contributing to exercise intolerance (Floras, 1993; Silber et al., 1998; Thomas et al., 1978). Accumulating evidence suggests that these abnormal responses are caused mainly by the overactivation of skeletal muscle afferents (Andrade et al., 2018; Ansorge et al., 2005; Hammond et al., 2000; Kaur et al., 2015; Vanhees et al., 1994). The current paradigm “the muscle hypothesis of HF” first described in classical work by Coats and Piepoli 1994 (Coats et al., 1994), suggests that skeletal muscle abnormalities (muscle atrophy/wasting, reduced capillary density, muscle fiber type changes) underlie exercise intolerance, in part, due to its resultant effect on the activation of skeletal muscle afferents (Coats et al., 1994; Magnusson et al., 1997; Piepoli et al., 2006; Ponikowski et al., 2001). Other compensatory responses are also involved. These include increased activation of hormonal systems (i.e., vasopressin, atrial natriuretic peptide, and renin-angiotensin-aldosterone), enhanced central and peripheral chemoreflex function, and perhaps altered arterial baroreflex function (Del Rio et al., 2013; Gao et al., 2004; Zucker et al., 2015).

The mechanisms mediating an abnormal exercise pressor reflex function in HF are not well understood; however, several studies support that alterations in mechanically and metabolically sensitive skeletal muscle afferents play a significant role. Paradoxically, the overactivation of skeletal muscle afferents may initially be a compensatory response to a failing ability to raise cardiac output (Vanhoutte, 1983). However, over time, a positive feedback scenario arises in which impaired cardiac and active skeletal muscle blood flow leads to further activation of muscle afferents while accelerating the onset of fatigue, and symptoms of exercise intolerance (Amann et al., 2014; Coutsos et al., 2013; Kaur et al., 2015). Herein, we discuss animal and human studies investigating the role of the exercise pressor reflex in HF, and potential underlying mechanisms for an overactivation of the exercise pressor reflex in HF.

Animal studies—Animal models of HF provide valuable insight as the effect of HF on neural cardiovascular regulation can be studied independently of medications and in a more homogenous study population. Several studies have shown in rodents and in conscious dogs that induction of HF causes an exaggerated reflexive increase in sympathetic activity in response to static and dynamic exercise as well as stretching the hindlimb muscle (Hammond et al., 2000; Hammond et al., 2001; Koba et al., 2008; Smith et al., 2005b). Studies suggest that alterations to both mechanically sensitive and metabolically sensitive afferents mediate the exaggerated exercise pressor reflex in HF (Wang et al., 2010). For example, direct electrophysiological evidence shows altered group III and IV afferent function in HF in which group III afferents exhibit exaggerated responsiveness, whereas group IV afferents exhibit a blunted responsiveness (Wang et al., 2010). Other studies have shown that HF exaggerates renal and lumbar sympathetic nerve activity, which responded synchronously with tension development during rhythmic muscle contraction (Koba et al., 2008). Moreover, blocking mechanically sensitive channels with gadolinium attenuated cardiovascular responses to static exercise to a greater magnitude in coronary artery ligation induced HF in rats (Smith et al., 2005b). Thus, these findings support a significant role played by the mechanoreflex in HF.

The exaggerated increase in sympathetic-mediated vasoconstriction in HF likely accelerates the accumulation of metabolites, increasing the responsiveness of metabolically sensitive skeletal muscle afferents. A significant role of the metaboreflex is to function as an error signal to increase perfusion to active skeletal muscle in the face of increased metabolic demands during exercise (O'Leary et al., 1999; Rowell et al., 1990). In healthy conditions, metaboreflex activation evokes increases in BP predominantly by increasing cardiac output, in part, due to effective arterial baroreflex modulation of peripheral vasoconstriction (Kim et al., 2005). However, HF impairs both the ability of the metaboreflex to raise cardiac output and the ability of the arterial baroreflex to inhibit metaboreflex-induced peripheral vasoconstriction (Hammond et al., 2001; Kaur et al., 2018a). A series of studies measuring cardiovascular responses to voluntary dynamic exercise during metaboreflex activation (step-wise reduction in hindlimb blood flow) in conscious dogs before and after inducing heart failure by ventricular pacing (moderate heart failure), eloquently demonstrated how HF alters the strength and mechanisms of the metaboreflex (Ansorge et al., 2005; Hammond et al., 2000; Kim et al., 2005). For example, Hammond et al. (Hammond et al., 2000) showed

that HF results in a shift in reliance on peripheral vascular resistance as opposed to cardiac output to increase BP. Moreover, they showed that HF lowers the threshold for metaboreflex activation and exacerbates its activation at heavier workloads, which, in turn, coincided with increases in neuroendocrine response (plasma norepinephrine, renin, and vasopressin) and progressive restriction of renal blood flow (Hammond et al., 2000; Hammond et al., 2001).

During submaximal dynamic exercise in healthy subjects, the metaboreflex facilitates increases in skeletal muscle and coronary blood flow (O'Leary et al., 1998). However, the altered strength and mechanism of metaboreflex activation in HF restrict skeletal muscle and coronary blood flow (Ansorge et al., 2005; Coutsos et al., 2013; Kaur et al., 2015). For example, metaboreflex activation in HF results in exaggerated sympathetic mediated vasoconstriction within the ischemic contracting muscle causing further amplification of the reflex, in which α_1 -adrenergic blockade with prazosin abolished this response (Figure 12) (Kaur et al., 2018b). Likewise, metaboreflex activation in HF elicits vasoconstriction in the coronary circulation, thereby reducing cardiac performance, in which α_1 -adrenergic blockade abolished this response (Figure 13) (Ansorge et al., 2005; Coutsos et al., 2013). Thus, these findings suggest that HF exaggerates the metaboreflex, which, in turn, restricts both muscle and cardiac blood flow leading to exercise intolerance (Ansorge et al., 2005; Coutsos et al., 2013; Hammond et al., 2000; Hammond et al., 2001; Kaur et al., 2018b). Collectively, studies in animal models of HF support the concept of that exaggerated activation of skeletal muscle afferents leads to excessive sympathoexcitation and abnormal circulatory adjustments to exercise.

Human studies—Studies in humans support that activation of the exercise pressor reflex in HF patients causes an exaggerated reflexive increase in sympathetic activity and altered cardiovascular responses to dynamic and static exercise (Amann et al., 2014; Barretto et al., 2009; Ives et al., 2016; Negrão et al., 2001; Notarius et al., 2001; Piepoli et al., 1999). Most studies have utilized passive exercise and ischemic exercise with post-exercise ischemia to investigate the role of the mechanoreflex and metaboreflex, respectively. Consistent with animal studies, studies have shown that sensitization of mechanically sensitive afferents mediates an exaggerated exercise pressor reflex. For example, Ives et al. (Ives et al., 2016) showed that reducing group III and IV afferent activity with intrathecal fentanyl, a μ -opioid receptor antagonist, during passive leg exercise lowered norepinephrine spillover, increased femoral vascular conductance, and muscle oxygenation. In contrast, there was no effect on ventilation, HR, stroke volume, and thus cardiac output. Likewise, several studies have shown that the BP response to metaboreflex activation (PEMI) is similar or slightly attenuated in HF patients.

Consistent with animal studies, studies have shown that the mechanism by which the metaboreflex raises BP is markedly different. For example, Crisafulli et al. (Crisafulli et al., 2007) demonstrated that HFrEF patients raised BP primarily by increasing systemic vascular resistance, whereas healthy individuals primarily raised BP by increasing cardiac output. This shift in reliance on systemic vascular resistance appears to be also true for HFpEF, and coronary artery disease patients (Magnani et al., 2018; Roberto et al., 2017) and likely is an adaptive response to preserve BP. However, the resultant peripheral vasoconstriction may cause further stimulation of the exercise pressor reflex, ultimately leading to a positive

feedback scenario causing premature fatigue and exercise intolerance. In support of this concept, studies have shown that activation of the metaboreflex by ischemic rhythmic handgrip exercise fails to restore blood flow to the exercising muscle in HF patients compared to that seen in healthy (Crisafulli et al., 2007; Shoemaker et al., 1999). Importantly, reducing group III and IV afferent feedback with intrathecal fentanyl during single-leg knee extensor exercise (20/50/80% peak workload), reduced norepinephrine spillover and contributed to a 25% increase in active skeletal muscle vascular conductance while attenuating end-exercise fatigue by 30%, all despite a 4% and 8-13% reduction in BP and cardiac output, respectively (Amann et al., 2014).

The contribution of mechanically sensitive and metabolically sensitive afferents in this dysregulation is controversial and an open area of debate (Middlekauff et al., 2007). Notably, there are conflicting data on whether the metaboreflex is accentuated or attenuated in human HF. For example, Sterns et al. (Sterns et al., 1991) showed similar MSNA and pressor responses to static handgrip exercise in HF patients and healthy controls. In contrast, the MSNA response to PEMI quickly returned to baseline in HF, whereas it remained elevated in healthy controls. Another study showed that HF patients had an earlier onset enhanced MSNA response to rhythmic handgrip exercise and increased MSNA responsiveness to passive exercise with reduced central command (Middlekauff et al., 2004b). Furthermore, mechanoreflex activation in HF results in exaggerated renal vasoconstriction (Middlekauff et al., 2001). Thus, these findings suggest that the mechanoreflex plays a significant role in mediating the exaggerated exercise pressor reflex in HF.

Conversely, several studies by Piepoli and colleagues suggest that the metaboreflex primarily mediates the exaggerated exercise pressor reflex in HF (Piepoli et al., 1996; Piepoli et al., 1999; Piepoli et al., 2008; Scott et al., 2000). For example, Scott et al. (Scott et al., 2000) showed an exaggerated ventilatory response to dynamic leg exercise with circulatory occlusion but not to passive exercise. Although these findings are clinically significant, as dyspnea is a hallmark characteristic of HF, the contribution of the mechanoreflex may be masked when using ventilatory responses as the primary outcome. In support of this notion, Ives et al. (Ives et al., 2016) showed that reducing group III and IV afferent activity with intrathecal fentanyl during passive leg exercise lowered norepinephrine spillover, increased femoral vascular conductance, and muscle oxygenation. In contrast, there was no effect on ventilation, HR, stroke volume, or cardiac output.

The conflicting findings are likely due, in part, to differences in disease severity, exercise capacity, and the protocol used to investigate exercise pressor reflex function (i.e., mode of exercise, static vs. dynamic exercise, muscle group, intensity) (Negrão et al., 2001; Notarius et al., 2001; Piepoli et al., 2006; Ponikowski et al., 2001). For example, Negrão et al. (Negrão et al., 2001) reported preserved MSNA responses to PEMI in mild HF patients, whereas patients with severe HF had diminished responses. Interestingly, in the early study by Stern et al. (Sterns et al., 1991) which showed attenuated MSNA responses to PEMI, 8 out of the 9 patients had LVEF% below 20% whereas in the study by Piepoli and colleagues which showed exaggerated metaboreflex-ventilatory responses, the mean LVEF% was 30%, and all patients had well-controlled HF. Whether or not ejection fraction explains some of

these differences is unclear, and further studies are warranted. Group III and IV afferents also exhibit significant polymodal activity and redundancy. It is therefore reasonable that the effect on these afferents likely depends on factors such as the severity and length of muscle hypoperfusion, in which metabolite sensitization of mechanically sensitive afferents may be an adaptive response to facilitate an increase in perfusion. Whether the metaboreflex is accentuated or attenuated may also depend on how the reflex is measured. For example, if assessing the metaboreflex by its ability to raise arterial BP or cardiac output, one could conclude that the reflex is attenuated whereas if assessing the reflex by its ability to raise peripheral vasoconstriction one could conclude that the reflex is accentuated (Dombrowski et al., 2018; Hammond et al., 2000). Further studies are warranted to comprehensively determine the effect of disease progression on the expression of mechanoreflex and metaboreflex activation before a complete synthesis is possible. Collectively, these findings support that HF leads to an exaggerated exercise pressor reflex. Moreover, this exaggerated activation restricts active skeletal muscle perfusion and thereby accelerates symptoms of exercise intolerance, including muscle fatigue and dyspnea.

Mechanisms—The underlying mechanisms for an exaggerated exercise pressor reflex in HF are not well understood but likely involve increased production of metabolites, inflammatory markers, and reactive oxygen species. The chronic hypoperfusion in HF likely also leads to alterations in the expression and sensitivity of receptors and channels present on group III and IV afferents. Furthermore, studies in conscious dogs suggest that HF also alters the arterial baroreflex-metaboreflex interaction. Although the arterial baroreflex resets to a higher operating point, it continues to be a powerful modulator of arterial BP during exercise, in part, by buffering metaboreflex evoked systemic vasoconstriction (Kim et al., 2005; Sheriff et al., 1990). However, studies have shown that HF reduces the strength of the arterial baroreflex (Kim et al., 2004). Recently, Kaur et al. (Kaur et al., 2018a) demonstrated that this reduced strength of the baroreflex also impairs its ability to modulate metaboreflex evoked systemic vasoconstriction during dynamic exercise in conscious dogs. Specifically, baroreceptor unloading (bilateral carotid occlusion) during metaboreflex activation in HF caused substantial systemic vasoconstriction, including in the exercising muscles of which the metaboreflex originated (Figure 14). Thus, impaired metaboreflex-arterial baroreflex interaction in HF limits rather than facilitates the restoration of active skeletal muscle blood flow (Kaur et al., 2018a). In other words, induction of HF likely reduces the ability of baroreceptors to buffer metaboreflex evoked vasoconstriction of the active skeletal muscle, including the very ischemic muscle from which the metaboreflex arises. This metaboreflex positive feedback normally acts with limited gain and amplifies the metaboreflex responses (Kaur et al. 2018b). However with impaired baroreflex buffering of the muscle metaboreflex, as workload rises and muscle becomes progressively under-perfused due to the limited cardiac output, the positive feedback may spiral towards infinite vasoconstriction as metaboreflex activation causes ever increasing vasoconstriction in the ischemic muscle causing more metaboreflex activation, etc. This may contribute to the vicious sympathetic storms often seen during exercise in HF and hasten exercise intolerance.

The chronic and acute hypoperfusion in HF likely leads to alterations in the expression and sensitivity of receptors and channels present on group III and IV afferents. Potent candidates

for mechanoreflex sensitization in HF are cyclooxygenase products (COX) such as prostaglandins and thromboxane, which play a significant role in modulating inflammation and pain. For example, inhibiting cyclooxygenase production (indomethacin) in the exercising arm abolished the MSNA response to 3 min of low-intensity rhythmic exercise, a protocol used to minimize any influence of the metaboreflex. In contrast, MSNA responses to PEMI was not different after blockade (Middlekauff et al., 2004a). A later study showed that COX-2, but not COX-1, pathway contribute to mechanoreflex sensitization in HF (Morales et al., 2012). These findings are also supported by a recent study showing improved mechanoreflex control of MSNA after a period of exercise training (4 mo), which corresponded to a significant reduction in protein expression of COX-2 in the skeletal muscle (Antunes-Correa et al., 2014). Another potent candidate for mechanoreflex sensitization is ATP, which can sensitize group III afferents via purinergic 2X receptors (Kindig et al., 2007; Li et al., 2008). For example, studies have shown that intra-arterial injection of α,β -methylene-ATP into the hindlimb enhance the pressor response to tendon stretch by 72%, a response dependent on the severity of myocardial infarction (Gao et al., 2007; Li et al., 2004). Importantly, blocking P2X receptors (PPADS) attenuated the response of group III afferents to static contraction and tendon stretch to a greater magnitude in HF rats than in healthy rats (Wang et al., 2009) and HF increases the protein expression of P2X receptors in the DRG (Gao et al., 2007; Wang et al., 2010). Collectively, these studies suggest that metabolite-induced sensitization of muscle afferents contributes to the exaggerated exercise pressor reflex in HF.

Other studies in animals have shown that HF alters the responsiveness of metabolically sensitive afferents. For example, rats with HF exhibit attenuated group IV afferent activity and pressor responses to intra-arterial injection of a TRPV1 receptors agonist (capsaicin), which corresponded to attenuated protein expression of TRPV1 in DRG (Li et al., 2004; Smith et al., 2005c; Wang et al., 2010). A recent human study indirectly supports these findings by demonstrating improved metaboreflex control of MSNA after a period of exercise training (4 mo), which was accompanied by increased protein expression of TRPV1 receptors in skeletal muscle (Antunes-Correa et al., 2014). Thus, these findings suggest that HF alters the responsiveness to chemically sensitive proteins.

Other possible mechanisms include increases in peripheral and central oxidative stress, which may contribute to evoking an exaggerated exercise pressor reflex by sensitizing muscle afferents and impairing the central modulation of sensory afferent feedback, respectively (Gao et al., 2004; Koba et al., 2009). For example, reducing superoxide production in the exercising muscle attenuated the pressor and renal sympathetic response to static and intermittent muscle contraction in HF rats but not in healthy rats (Koba et al., 2009). Other studies suggest that increased activity of central angiotensin II and NADPH derived superoxide play a role in sympathoexcitation in HF, in part, due to its effect on arterial baroreflex function (Gao et al., 2004; Liu et al., 1999). Moreover, exercise training effectively reduces sympathoexcitation, in part, by enhancing baroreflex function mediated by an angiotensin II-dependent mechanism (Mousa et al., 2008). A recent study demonstrated that impaired interaction between the metaboreflex and arterial baroreflex in HF contributes to further amplification of the metaboreflex (Figure 14) (Kaur et al., 2018a). Thus, these findings may suggest that alterations in central signaling of angiotensin II and

superoxide play a role in impairing this interaction and could be targeted with exercise training or pharmacological blockade to reduce the activation of the metaboreflex in HF. However, further studies are needed to test this hypothesis and to determine the role of oxidative stress and angiotensin II in modulating the exercise pressor reflex in human HF.

Summary and significance—Collectively, these studies support the notion that HF leads to an exaggerated exercise pressor reflex. Alterations in both mechanically sensitive and metabolically sensitive afferents likely contribute to this response. Importantly, emerging evidence suggests that impaired metaboreflex-arterial baroreflex interaction contributes significantly to the exaggerated activation of the reflex by restricting oxygen delivery to the ischemic muscle. Thus, targeting this interaction may prevent excessive hypoperfusion during exercise, which could prevent alterations to receptors and channels responsible for evoking the exercise pressor reflex. Importantly, investigations into underlying mechanisms responsible for an exaggerated exercise pressor reflex can lead to therapeutic interventions with the potential to improve cardiovascular function during exercise while reducing symptoms of exercise intolerance in heart failure.

5. CONCLUSION

The exercise pressor reflex appropriately adjusts the circulation by evoking reflex increases in sympathetic activity and decreases in parasympathetic activity, which increases BP, heart rate, and systemic vasoconstriction. In this review, we have discussed recent advancements in our understanding of the reflex function in health and diseases. Specifically, we discuss emerging evidence in healthy conditions suggesting that the reflex contribution controlling MSNA is different in the contracting and non-contracting muscles. We also provide an extensive overview of advances in our understanding of the reflex function in chronic diseases such as hypertension, diabetes, and heart failure, which exhibit an exaggerated exercise pressor reflex.

5.1. Future directions and significance

This review highlights many avenues for future research. We discussed emerging evidence suggesting that central command and the metaboreflex exhibit differential control over sympathetic vasoconstrictor drive to contracting and non-contracting muscles, respectively. However, since these studies only used a small muscle mass and low-intensity contractions, future studies are needed to determine whether similar effects are present using larger muscle mass and increasingly higher intensity contractions. More studies are also required to isolate the contribution of the mechanoreflex in making these adjustments. Importantly, given the adverse effects of disease states on the exercise pressor reflex, in part due to mechanoreflex sensitization, further insight into how disease states such as hypertension, diabetes, and heart failure alter the expression of the exercise pressor reflex is needed. Although the underlying mechanisms for an exaggerated reflex in these diseases are complex, multifactorial, and dependent on the etiology of the disease, it is clear that several mechanisms are involved. Further studies are therefore needed to clarify each mechanism's role and the interplay between them. Ultimately, approaches targeting these mechanisms are

clinically significant as they provide alternative therapeutic strategies to prevent adverse cardiovascular events while also reducing symptoms of exercise intolerance.

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Figure 1.

Exercise Pressor reflex. Afferent (green) and efferent (red) mechanisms. Taken from Mitchell et al. (Mitchell, 2017).

Figure 2.

Experimental records from one subject during electrical stimulation of tibialis anterior (A) and during weak voluntary contraction at a matched intensity (B). A section of the “nerve” channels during electrical stimulation has been expanded to reveal the raw neural signal between electrical artifact and sympathetic spikes that have been identified with an asterisk (*). The “nerve” channel during voluntary contraction has also been expanded for comparison. Taken from Boulton et al. (Boulton et al., 2016).

Figure 3. MSNA at 15 s intervals during voluntary (closed circles) and electrically-evoked (open circles) contractions. *significant main effect of condition ($P < 0.03$). ^Significant interaction of time and condition ($P < 0.01$). Taken from Boulton et al. (Boulton et al., 2016).

Figure 4.

MSNA responses to contracting and non-contracting legs. Grouped MSNA responses to the contracting (open circles) and non-contracting (closed circles) legs at 1 min intervals during dorsiflexion (...) and ischaemia (—). A significant main effect of time is indicated with an asterisk. (* $P < 0.05$). Data are indicated as mean $\pm$ SE. Taken from Boulton et al. (Boulton et al., 2018).

Figure 5.

The change from baseline in mean arterial pressure (MAP) and heart rate (HR) in normotensive (NTN, closed circles) and hypertensive (HTN, open circles) subjects during the 30% MVC trial (A and B) and during 40% MVC trial (C and D). Data are a 30-s average of handgrip exercise (HG) and 30-s averages during post-exercise muscle ischemia (PEMI; I1-I4). Values are means $\pm$ SE. * $P < 0.05$ vs. NTN. The HTN group had a greater MAP response during exercise, and these differences persisted during the PEMI period. There were no group differences in HR response. Taken from Delaney et al. (Delaney et al., 2010).

Figure 6.

Representative original data. Blood pressure tracing from one hypertensive subject during the trials of cycling before and after intrathecal fentanyl administration. Subject exercised for 5 minutes at 40 W and 60 rpm and trials were interspersed by 30 min. Leg cycling exercise was initiated 51-58 min following fentanyl administration. Taken from (Barbosa et al., 2016).

Figure 7.

The pressor (A), cardioaccelerator (B), and tension-time-index (TTI; C) responses to static contraction of rats fed low NaCl (0.1%; black bars; n=22) or high NaCl (4.0%; white bars; n=26). #Significant differences (P<0.05) between 0.1% vs. 4.0% NaCl rats. Values inside bars represent baseline values (means ± standard errors). MAP, mean arterial pressure; HR, heart rate; bpm, beats/min. Taken from Yamauchi et al. (Yamauchi et al., 2014).

Figure 8.

Raw data traces show the change in blood pressure (BP), mean arterial pressure (MAP), and heart rate (HR; in beats/min (bpm)) before and during a 30-s static contraction of the hindlimb muscles in one female control (CTL) rat and one female streptozotocin-induced type 1 diabetic (STZ) rat (B) 3 wk after diabetes induction. The peak change in MAP was exaggerated in the STZ rat (26 ± 5 mmHg) compared with that in CTL rat (17 ± 3 mmHg). Taken from Grotle et al. (Grotle et al., 2017).

Figure 9.

Original data trace from 1 male streptozotocin (STZ)-induced type 1 diabetes mellitus rat showing blood pressure (BP), heart rate (HR, beats/min), mean arterial pressure (MAP), and tension during 30 s of static tendon stretch before (A) and after (B) injection of GsMTx-4. Peak MAP values before and after GsMTx-4 injection were 157 and 120 mmHg, respectively. Taken from Grotle et al. (Grotle et al., 2019b).

Figure 10.

Means $\pm$ SE (n, number of rats) and individual data showing that statically contracting the hindlimb muscles evoked an exaggerated peak pressor response in the 31-wk compared with the responses in 21-wk type 2 diabetes mellitus (T2DM) and nondiabetic rats (A). Peak changes in heart rate were not different among the groups (B). Developed tensions [tension-time index (TTI)] were similar among groups (C). * $P < 0.05$ (1-way ANOVA) indicates statistically greater response compared with nondiabetic rats. # $P < 0.05$ (1-way ANOVA) indicates statistically greater pressor response compared with 21-wk T2DM rats. MAP, mean arterial pressure; HR, heart rate; bpm, beats/min. Taken from Grotle et al. (Grotle et al., 2019a).

Figure 11.

Original recordings of muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) in 3 type 2 diabetes patients (T2D; A-C) and 3 control subjects (D-F) at baseline, during 30% maximal voluntary contraction (MVC) isometric handgrip, and during post-exercise muscle ischemia (PEMI). Taken from Holwerda et al. (Holwerda et al., 2016).

Figure 12.

Average mean arterial pressure (top) and hindlimb resistance (bottom) responses ($n=6$) during free-flow exercise, metaboreflex threshold, and maximal metaboreflex activation in control (open circles) and α_1 -adrenergic blockade (closed circles) experiments in normal animals (left) and after induction of heart failure (right). * $P < 0.05$ vs. mean arterial pressure or hindlimb resistance at the previous setting in the same experiment. † $P < 0.05$ vs. control. ‡ $P < 0.05$ vs. normal. Taken from Kaur et al. (2018b).

Figure 13.

Left ventricular hemodynamic and function responses: coronary blood flow (CBF), coronary vascular conductance (CVC), maximal rate of left ventricular pressure change (dP/dt_{max}), and preload recruitable stroke work (PRSW) and during Ex and Ex + MMA in control (A) and heart failure (B) before (black bars) and after α_1 -blockade conditions (striped bars). Symbol definitions: *Between bars, significant pairwise comparison ($P < 0.05$); †significant change from the previous setting; *brackets, significant effect of settings or conditions (horizontal: rest, Ex, MMA; vertical: control, α_1 -blockade). Taken from (Coutsos et al., 2013).

Figure 14.

Average hemodynamic data at rest, during mild exercise (Ex), muscle metaboreflex activation (MMA), and bilateral carotid occlusion (BCO) during MMA in normal animals and after the induction of heart failure. * $P < 0.05$ vs. previous setting; † $P < 0.05$ vs. normal. Horizontal brackets reflect a significant effect of settings; vertical brackets reflect a significant effect of heart failure. MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; NIVC, nonischemic vascular conductance; RVC, renal vascular conductance; HVC, hindlimb vascular conductance; dP/dt_{max} and dP/dt_{min}, maximal rates of rising and fall, respectively, in left ventricular pressure. Taken from Kaur et al. (Kaur et al., 2018a).