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Reflex control of the cardiovascular system during exercise in disease

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The reflex control of the cardiovascular system is essential for the appropriate delivery of oxygenated blood to the exercising skeletal muscles and as such is paramount for the performance of physical activity. There is evidence for the activity of group III and IV skeletal muscle afferents being heightened in response to metabolic and/or mechanical stimulation in disease states as diverse as heart failure, hypertension, peripheral arterial disease, chronic obstructive pulmonary disease, and type II diabetes. As a consequence of this aberrant afferent activity, an inappropriate sympathetic activation and pressor response may result, along with skeletal muscle hypoperfusion, metabolic distress and exercise intolerance. The completeness and consistency of the evidence for this concept vary between disease states. Further work is required to elucidate the mechanistic basis and therapeutic targeting of this afferent pathway, with the potential to reduce cardiovascular risk and ameliorate exercise-induced fatigue in diverse patient populations.

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Introduction

Skeletal muscle adenosine triphosphate (ATP) utilization rate increases in an intensity-dependent manner during dynamic exercise. A consummate increase in oxygen delivery for aerobic ATP resynthesis is required, and provided by increases in cardiac output (secondary to elevations in stroke volume and heart rate) and the preferential redirection of peripheral blood flow to the active skeletal muscles at the expense of perfusion to certain portions of the viscera (e.g. splanchnic circulation) where oxygen consumption may also decrease [1]. Such cardiovascular responses to exercise are determined to a great extent by adjustments to the autonomic nervous system, specifically a reduction in cardiac parasympathetic nerve activity and an increase in sympathetic nerve activity (SNA) to the heart and peripheral circulation [2]. Of note, sympathetic-vascular transduction is tempered in the exercising muscle, a process known as functional sympatholysis, to allow appropriate local vasodilatation and blood flow delivery.

The autonomic cardiovascular adjustments to exercise are orchestrated by several neural mechanisms. Here we will focus on the important role played by group III and IV sensory afferents located in the skeletal muscle. Much of the recent interest in the reflex regulation of the cardiovascular system stems from reports of aberrant skeletal muscle afferent signaling in disease states as diverse as heart failure, type II diabetes and Parkinson's disease. Given the concise and focused nature of this series of articles, recent human and clinical physiology studies will be emphasized, and regrettably neither the list of clinical conditions nor the physiological outcomes described are exhaustive.

Reflex control of the cardiovascular system during exercise

Group III and IV skeletal muscle afferents are activated during exercise by intramuscular mechanical and chemical stimuli [2–4]. Group III afferents are predominantly mechano-sensitive and their experimental activation in isolation in humans (e.g. with passive exercise, passive muscle stretch, and external compression) causes reductions in cardiac parasympathetic activity, and modest increases in muscle SNA, heart rate and blood pressure (BP) (muscle mechanoreflex) [2]. Group IV afferents are predominantly metabolically sensitive to elevations in concentration of metabolites (e.g. H^+, K^+, ATP, and lactate) [5] and evoke a powerful increase in muscle SNA and BP when activated, but can also increase heart rate secondary to increases in cardiac SNA and reductions in cardiac parasympathetic nerve activity (muscle metaboreflex) [6,7]. The cardiovascular responses resulting from activation of group III and IV skeletal muscle afferents is collectively termed, the 'exercise pressor reflex' [8].

In a variety of chronic disease states augmented skeletal muscle afferent signaling has been identified. This is significant because it is purported to result in a pronounced sympathetic vasoconstriction sufficient to restrict nutritive blood flow to the active muscle causing metabolic distress, dyspnea, fatigue, cardiac autonomic imbalance, impaired

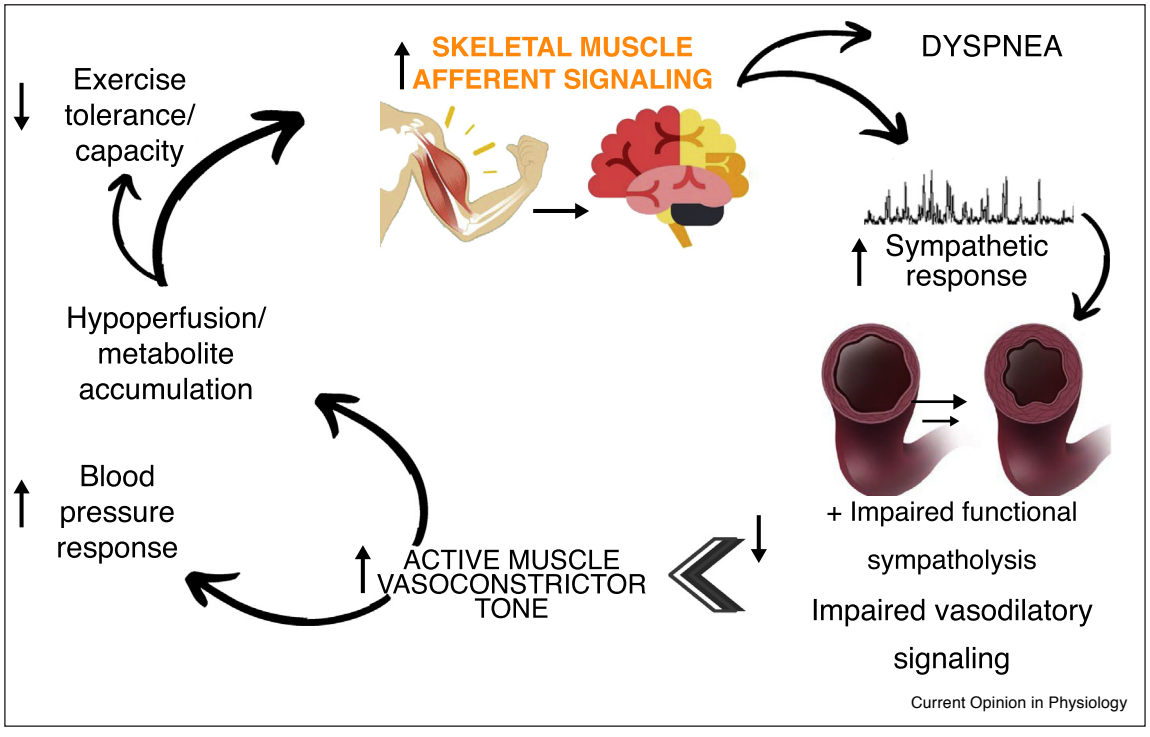
exercise capacity, and an exaggerated pressor response (Figure 1). Moreover, in this schema a positive feedback loop means that the enhanced group III and IV skeletal muscle afferent mediated increase in sympathetic vasoconstrictor tone begets more of the same by perpetuating the mismatch between oxygen supply and demand, causing further accumulation of anaerobic metabolism breakdown products and increased stimulation of metabolically sensitive skeletal muscle afferents. Conversely, in other clinical conditions, the exercise pressor reflex is diminished, which may result in an insufficient increase in heart rate, SNA and blood pressure, with deleterious implications for performance. A better understanding of the integrated cardiovascular responses to exercise has significant potential to improve exercise adherence, patient quality of life and outcomes.

Reflex control of the cardiovascular system during exercise in disease

Heart failure

Classic work by Piepoli *et al.* demonstrated that chronic heart failure patients display augmented elevations in ventilation (+169% above baseline), peripheral vascular resistance (+108%) and diastolic BP (+31%) during muscle metaboreflex activation with post-exercise ischemia, in comparison with age-matched controls (+53, 86, 23%, respectively) [9]. The underlying mechanisms and deleterious consequences of these observations are encompassed within the influential 'muscle hypothesis of heart failure' [10] that has since been further refined into an integrated multi-system model [11]. This original concept posited that left ventricular dysfunction leads to skeletal muscle underperfusion, atrophy and a shift toward faster fiber types that causes an earlier dependence on anaerobic metabolism and accelerated intramuscular acidification during exercise [10], which in turn augments the activation of metabolically sensitive skeletal muscle afferents and sets in motion the cascade of events illustrated in Figure 1. Although there has been debate regarding whether it is the metaboreflex (e.g. others have shown the metaboreflex to be blunted in heart failure [12,13]) or mechanoreflex [14] that becomes augmented in heart failure, it is clear that the exercise pressor reflex is dysfunctional in this condition. Recent evidence broadly supports and extends these earlier observations and ideas. Amman *et al.* [15] demonstrated

Figure 1



Potential deleterious consequences of heightened group III and IV skeletal muscle afferent activity in disease.
Augmented skeletal muscle afferent signaling in disease states can result in a pronounced sympathetic vasoconstriction sufficient to restrict nutritive blood flow to the active muscle causing metabolic distress, particularly when accompanied by impaired functional sympatholysis. The consequences of this might include an exaggerated pressor response, fatigue, an impaired exercise capacity, and possibly dyspnea. Crucially, such augmented skeletal muscle afferent signaling begets more of the same via a powerful positive feedback loop; whereby the mismatch between oxygen supply and demand is perpetuating, causing further accumulation of anaerobic metabolism breakdown products and increased

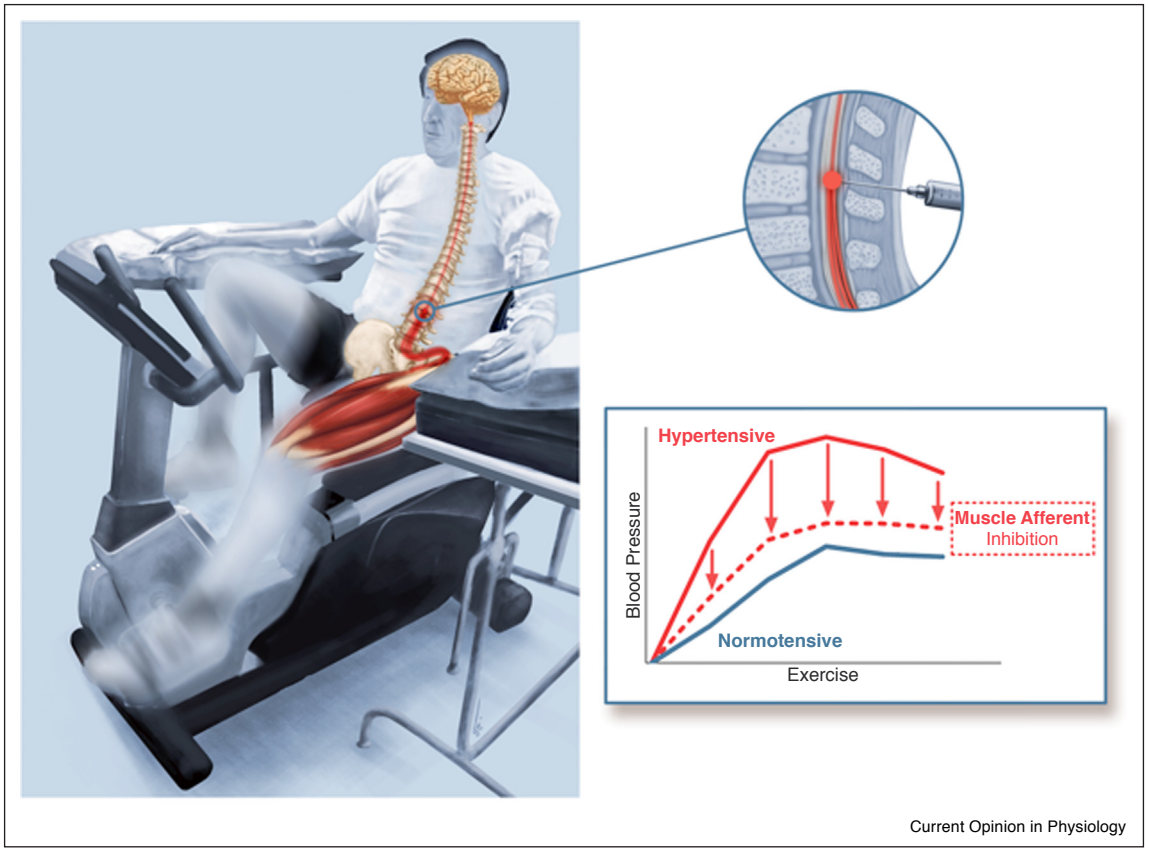
that intrathecal administration of fentanyl, a μ-opioid agonist which acts to selectively diminish group III and IV neurotransmission without affecting the ability of descending motor signals to the skeletal muscles, decreased exercising leg norepinephrine spillover (−18 to 25%), while increasing exercising leg blood flow (+10–14%) and oxygen consumption (10–17%) in heart failure patients, but not control participants. A marked reduction in leg fatigue and rating of perceived exertion were also observed.

Hypertension

Exaggerated BP responses to exercise can increase the risk of acute cardiovascular and cerebrovascular events [16] and may be particularly concerning for populations in whom the prevailing BP is already elevated. Notably, hypertensive patients in whom resting BP is controlled still exhibit an exaggerated increase in BP response to exercise, possibly due to a heightened muscle metaboreflex sensitivity [17••]. Delany *et al.* [18] first demonstrated that hypertensive patients have augmented muscle SNA and mean BP responses to muscle metaboreflex activation with post-exercise ischemia in comparison to normotensive controls. However, such exaggerated muscle SNA responses have not been consistently observed [19]. More recently, Barbosa *et al.* [20] observed that an exaggerated BP response to leg cycling in hypertensive patients was normalized following intrathecal administration of fentanyl (Figure 2). These findings demonstrate that a key mechanism driving an increased cardiovascular risk in hypertensive patients can be corrected, with potential application for the development of treatments for this abnormal response to exercise.

The mechanisms underpinning the heightened activation of group III and IV skeletal muscle afferents in human hypertension are not as well synthesized as for heart failure, although there are several areas of active exploration [21]. Structural remodeling and functional impairments in skeletal muscle blood flow regulation, including heightened peripheral SNA-mediated vasoconstriction and impaired vasodilatory signaling may be lead to hypo-perfusion and excessive accumulation of anaerobic metabolites during exercise [22]. While this might reasonably be expected to

Figure 2



Exaggerated exercise pressor reflex in hypertension.
Schematic illustration of the work of Barbosa *et al.* [20] demonstrating that intrathecal administration of fentanyl, a μ-opioid agonist which acts to selectively diminish group III and IV neurotransmission without affecting the ability of descending motor signals to the skeletal muscles, abolished the exaggerated pressor response observed at the onset of dynamic exercise in hypertensive patients.

augmented group III and IV skeletal muscle afferent stimulation *per se*, alterations in their sensitivity, for example via an upregulation of purinergic [23] and TRPV1 [21] signaling pathways, may also be important. Impaired functional sympatholysis may augment neural-vascular transduction in hypertension [24], although this is not a consistent observation [25]. Finally, alterations in central autonomic reflex control may also be influential, with diminished nitric oxide signaling and augmented oxidative stress at the nucleus tractus solitarius shown to be important for the overactive muscle mechanoreflex observed in the hypertensive rat [26].

Peripheral arterial disease

Peripheral arterial disease (PAD) is characterized by a hypo-perfusion of the extremities caused by atherosclerosis and leading to intermittent claudication. Chronic femoral artery ligation has been shown to enhance the exercise pressor reflex in decerebrated rats, an effect attenuated by administration of the peripheral μ-opioid receptor antagonism [27]. Similarly, PAD patients present with large, early, and sustained BP responses to both low-intensity one-legged plantar flexion and electrically evoked leg contraction (a maneuver to isolate the mechanically sensitive skeletal muscle afferents) [28]. This augmented pressor response was evident before the onset of claudication-related pain. More recently, Miller *et al.* [29••] showed that leg revascularization in PAD attenuates the exercise pressor reflex and increases coronary blood flow during exercise.

Chronic obstructive pulmonary disease

Exercise dyspnea is evident in patients with chronic obstructive pulmonary disease (COPD), a disease of chronic irreversible and diffuse airflow obstruction. Bruce *et al.* [30] showed that ventilation remained significantly elevated during skeletal muscle metaboreflex activation via post-exercise ischemia in COPD patients, while it returned to baseline in a control group. No between-group differences were noted for heart rate and BP. As discussed in heart failure, skeletal muscle dysfunction associated with a premature acidification and fatigue during exercise may contribute to the exaggerated ventilatory drive from the muscle metaboreflex in COPD [31]. Strikingly, intrathecal administration of fentanyl to patients with COPD enhanced endurance to constant work-rate cycling exercise, while delaying the increase in mean BP, ventilation, dyspnea, and leg fatigue [32]. However, it should be acknowledged that the contribution of group III and IV skeletal muscle afferents to steady-state exercise hyperpnoea remains controversial [33]. Nevertheless, these observations provide an encouraging insight into the exciting potential for the therapeutic targeting of skeletal muscle afferents in chronic diseases, such as COPD.

Type II diabetes

Holwerda *et al.* [34] reported that mean BP and muscle SNA responses to muscle metaboreflex activation with post-exercise ischemia in patients were augmented in patients with type II diabetes (Figure 3). The reason for this remains to be determined, but muscle SNA responses were positively correlated with fasting glucose and HBA1c, suggesting that the severity of type II diabetes may be a factor in determining muscle metaboreflex sensitivity. Of note, the muscle SNA, but not BP, responses to a cold pressor test were heightened in type II diabetics, perhaps indicative of a generalized heightening of sympathetic reflexes in this condition.

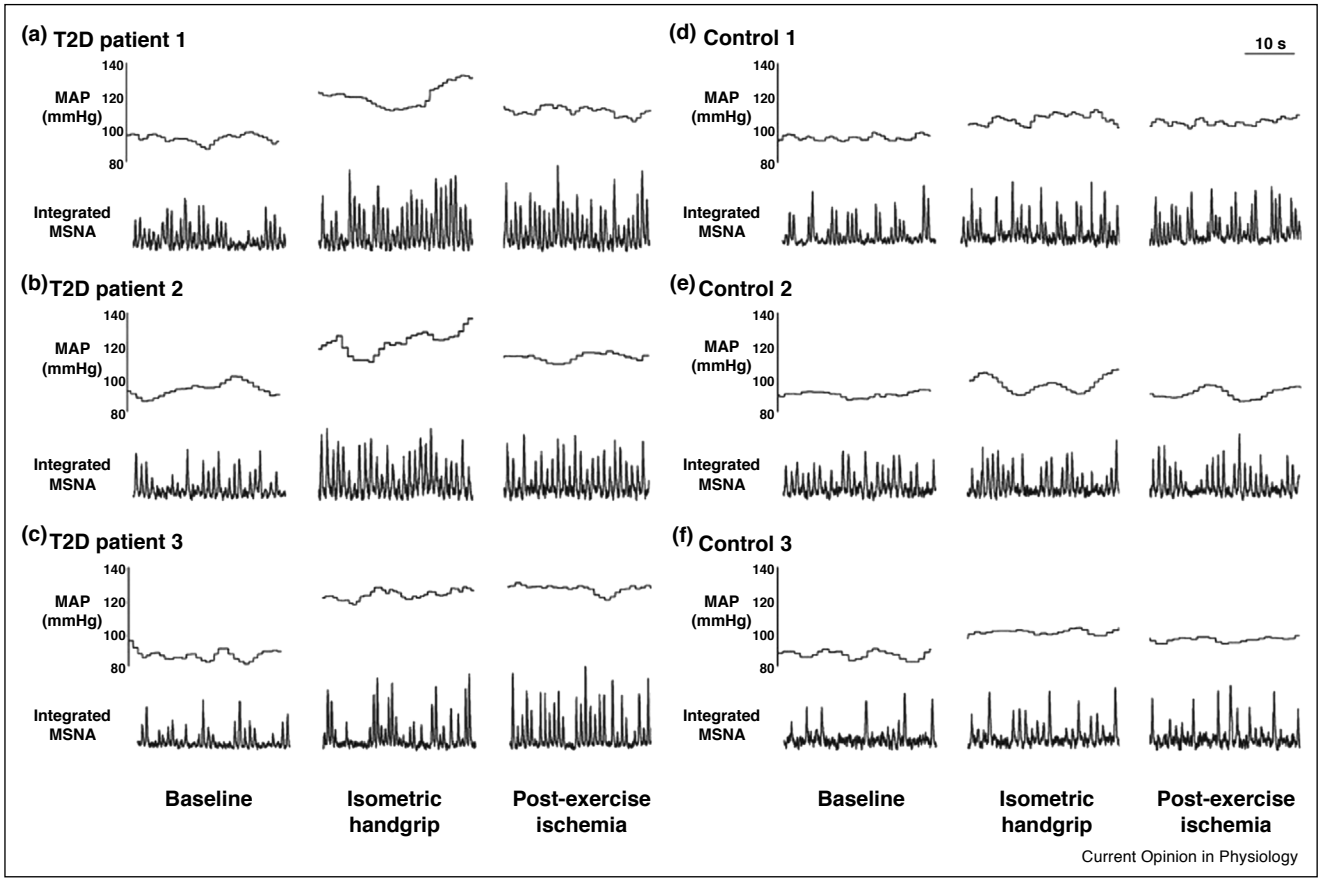
Renal disease

Exercise intolerance is evident in patients with chronic kidney disease (CKD) and associated with uremic myopathy, physical deconditioning and abnormal neuro-cardiovascular responses [35]. Park *et al.* [36] demonstrated that patients with end-stage renal disease have exaggerated BP increases to moderate intensity handgrip exercise, post-exercise ischemia (metaboreflex activation) and passive hand movement (mechanoreflex activation), but not during the cold pressor test. Intriguingly, abnormal exercise pressor reflex control in those patients was accompanied by similar or blunted increases in muscle SNA. However, equalizing the BP responses by infusing sodium nitroprusside in the patients with CKD during exercise, thereby equalizing baroreflex-mediated restraint of SNA to that of controls, revealed an augmented muscle SNA response to exercise in patients with CKD [37]. In addition, recent evidence suggest that endothelial dysfunction and nitric oxide bioavailability may contribute to the exaggerated pressor response in CKD [38••].

Obesity

Heightened muscle SNA and increased peripheral vasoconstriction at rest are fairly well-established in obesity; however, it remains controversial how obesity influence the neuro-cardiovascular responses to exercise. Negrao *et al.* [39] reported that although obese normotensive women have a greater mean BP and muscle SNA response to exercise than lean normotensive women, during muscle metaboreflex activation with post-exercise ischemia, surprisingly muscle SNA was significantly lower in obese women ($+3.8 \pm 0.82$ versus $+9.4 \pm 1.03$ bursts/min) despite similar BP and forearm vasoconstrictor responses, when compared to lean counterparts. Interestingly, weight loss with a hypocaloric diet or a hypocaloric diet and exercise, augmented the muscle metaboreflex in these individuals [40]. Conversely, Limberg *et al.* [41] observed a comparable increase in muscle SNA and BP during isometric handgrip and muscle metaboreflex activation with post-exercise ischemia in adults with metabolic syndrome and control participants. These discrepancies may be due, at least in part, to the presence

Figure 3



Exaggerated exercise pressor reflex in type II diabetes (T2D).
Original sympathetic neurograms and mean BP recordings illustrating the exaggerated cardiovascular responses to exercise and isolated muscle metaboreflex activation during post-exercise ischemia.

and/or absence of other factors, such as: hypertension, diabetes, and sarcopenia.

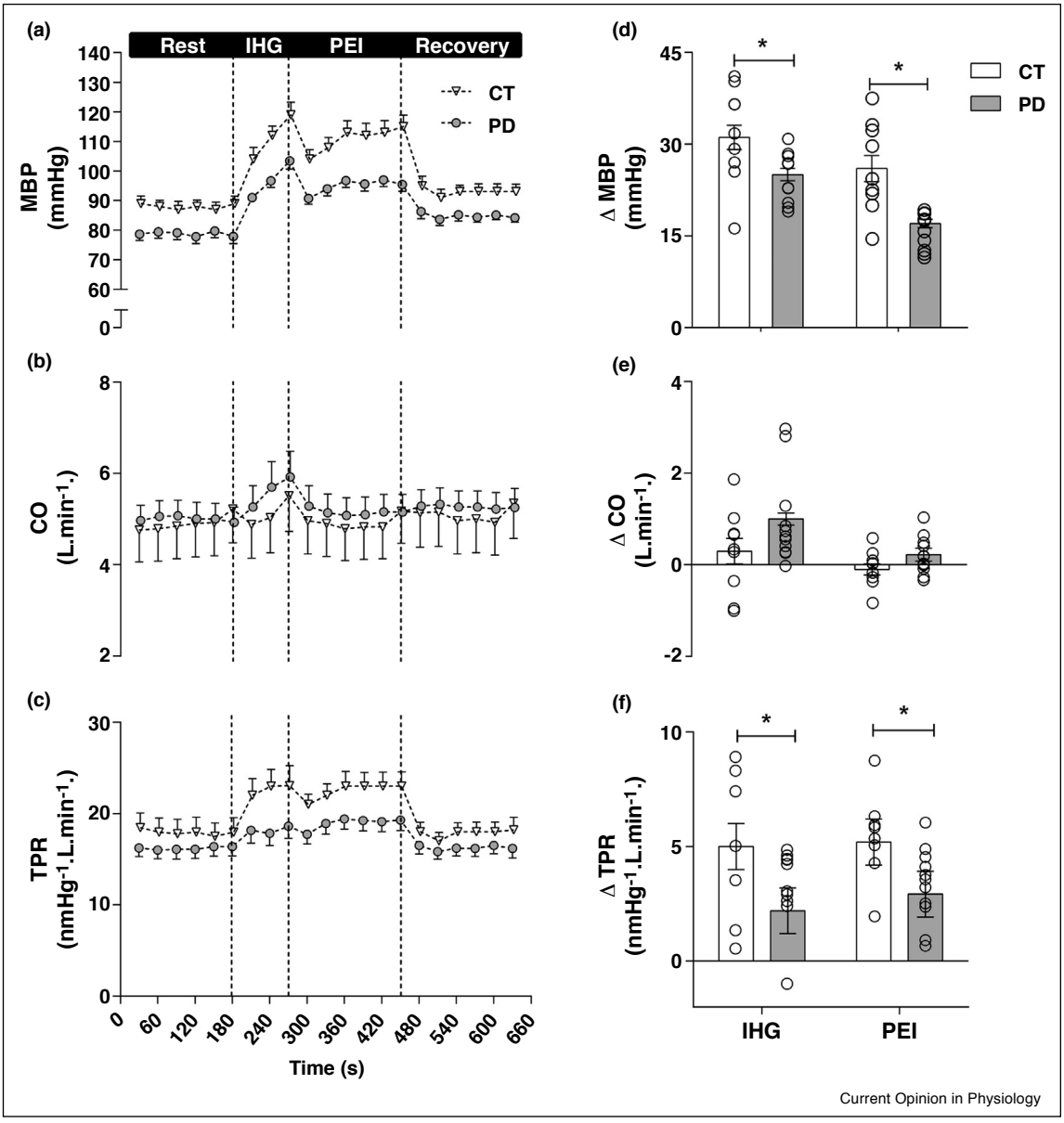
Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder and although the motor function abnormalities are well documented, PD patients also experience non-motor symptoms, such as those associated with autonomic or cardiovascular system dysfunction. Sabino-Carvalho *et al.* [42••] demonstrated that isometric handgrip at 40% maximum voluntary contraction followed by post-exercise ischemia evoked a blunted increase in mean BP in patients with PD ($+17 \pm 1$ mmHg) when compared to healthy control participants ($+26 \pm 1$ mmHg) (Figure 4). Responses to a cold pressor test did not differ between groups, suggesting no group differences in generalized sympathetic responsiveness. These findings support the concept that attenuated cardiovascular responses to exercise observed in patients with PD are, at least in part, explained by an altered skeletal muscle metaboreflex.

Conclusions and future directions

In this short article, we have attempted to highlight the range of conditions in which alterations in the reflex control of the cardiovascular system have been identified. In many cases, the underlying mechanisms remain incompletely understood. Moreover, the pathophysiological basis of the conditions described is diverse and the extent to which the aberrant cardiovascular reflex control identified is attributable to equally diverse disease-specific phenomena or a common etiology (e.g. physical deconditioning), remains to be determined. This issue is further complicated when one considers that patients commonly present with multiple co-morbidities, with potentially conflicting effects on the exercise pressor reflex (e.g. obesity, hypertension). Nevertheless, as our understanding of how varying disease processes influence and interact in the regulation of the cardiovascular system new insights are provided about the fundamental control pathways, with implications beyond the individual conditions studied.

Figure 4



The attenuated cardiovascular responses to isometric handgrip (IHG) exercise in patients with Parkinson's disease (PD) is, at least in part, attributable to an altered skeletal muscle metaboreflex.
Mean and individual data from Sabino-Carvalho *et al*. [42••] demonstrated that mean BP (MBP) responses to exercise and post-exercise ischemia (PEI) are blunted in patients with Parkinson's disease when compared to healthy control (CT) participants. CO, Cardiac output; TPR, total peripheral resistance.

An important issue not covered in depth here is the ability of group III and IV skeletal muscle afferent activation to impinge upon the circulations of multiple organs (e.g. heart, kidney, brain, and lung) and how this may be affected in diverse disease states. For example, Brassard and Gustaffson [43] have provocatively posited that exercise intolerance in heart failure may result from a lower cerebral perfusion and oxygenation, in part as a consequence of increased muscle metaboreflex sensitivity, a hyperventilation induced fall in arterial carbon dioxide tension (P_aCO_2) and augmented cerebral vasoconstriction, which increases sense of effort and reduces descending motor drive. This challenging idea highlights how the reflex regulation of cardiorespiratory function during exercise might be intimately integrated with a host of other bodily processes (e.g. motor control, skeletal muscle function). Work is required to fully understand the interaction between the exercise pressor reflex and other

reflexes (e.g. chemoreflex [44], diving reflex [45,46]) in diverse disease states. Finally, the influence of age, sex and habitual activity pattern on the exercise pressor reflex in disease states requires exploration.

In conclusion, there is accumulating evidence that in a diverse range of disease states the reflex control of the cardiovascular system is dysregulated. In several conditions a heightened activity of group III and IV skeletal muscle afferents has been identified that may lead to inappropriately high pressor response, exaggerated sympathetic vasoconstriction and hypoperfusion, resulting in metabolic distress, fatigue and exercise intolerance. Treatment of abnormal exercise pressor reflex activity in the disease states highlighted could enhance the efficacy of exercise prescription as a medical therapy. Further work is required to elucidate the molecular basis and therapeutic targeting of this afferent pathway.

Conflict of interest statement

Nothing declared.

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