Altered cardiorespiratory regulation during exercise in patients with Parkinson's disease: A challenging non-motor feature

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Abstract

The incidence of Parkinson's disease is increasing worldwide. The motor dysfunctions are the hallmark of the disease, but patients also experience non-motor impairments, and over 40% of the patients experience coexistent abnormalities, such as orthostatic hypotension. Exercise training has been suggested as a coping resource to alleviate Parkinson's disease symptoms and delay disease progression. However, the body of knowledge is showing that the cardiovascular response to exercise in patients with Parkinson's disease is altered. Adequate cardiovascular and hemodynamic adjustments to exercise are necessary to meet the metabolic demands of working skeletal muscle properly. Therefore, since Parkinson's disease affects parasympathetic and sympathetic branches of the autonomic nervous system and the latter are crucial in ensuring these adjustments are adequately made, the understanding of these responses during exercise in this population is necessary. Several neural control mechanisms are responsible for the autonomic changes in the cardiovascular and hemodynamic systems seen during exercise. In this sense, the purpose of the present work is to review the current knowledge regarding the cardiovascular responses to dynamic and isometric/resistance exercise as well as the mechanisms by which the body maintains appropriate perfusion pressure to all organs during exercise in patients with Parkinson's disease. Results from patients with Parkinson's disease and animal models of Parkinson's disease provide the reader with a well-rounded knowledge base. Through this, we will highlight what is known and not known about how the neural control of circulation is responding during exercise and the adaptations that occur when individuals exercise regularly.

Keywords

Parkinson's disease, exercise pressor reflex, baroreflex, blood pressure

Introduction

Parkinson's disease (PD) prevalence is augmenting worldwide as age and life expectancy increases.[1] The first description of PD was made more than 200 years ago.[2] Currently, PD is the second most common neurodegenerative disorder.[1,3] PD is characterized by a dysfunction of dopamine-producing neurons in the substantia nigra pars compacta. This dopamine deficiency leads to motor impairments (bradykinesia, rigidity, and resting tremor), which are the classic symptoms that characterize the disease.[4] In addition, PD is also related to several non-motor symptoms, some of which precede the motor dysfunction by more than a decade.[5] Patients with PD often report symptoms, such as constipation, urinary incontinence, postprandial hypotension, heat/cold intolerance, erectile dysfunction, and orthostatic hypotension (OH),[5–8] which altogether have a significant impact on the patients' quality of life.

There is no cure for PD, and the available medications only alleviate the symptoms. In this sense, exercise is gaining attention as a potential and important way of treatment for PD. Epidemiologic studies suggest that moderate to

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vigorous exercise could be protective against developing PD.[9] Besides that, exercise-induced beneficial effects are well documented in animal models and patients with PD. For example, in animal models of PD, running wheel exercise has been shown to reduce α-synuclein aggregation and improve motor and cognitive function.[10] In humans, resistance exercise training is shown to improve several motor aspects in patients with PD,[11] and aerobic exercise training has been shown to improve baroreflex sensitivity (BRS).[12] In addition to these beneficial effects, exercise has been employed as a coping resource to manage the quality of life, motor function, physical capacity, fatigue, and disease progression[10] of patients with PD.[13–18] Despite this, in light of cardiovascular physiology, exercise prescription could be a challenging approach for exercise training in this population.

It has also been recognized that some patients with PD may eventually die unexpectedly due to cardiovascular dysfunctions.[19] Studies have shown that cardiovascular responses to exercise are generally blunted in patients with PD compared to age-matched controls.[20–24] While in healthy subjects these attenuated responses indicate a possible adaptation to chronic exercise exposure, for patients it could indicate decreased exercise efficiency. Together with the central degeneration of important cardiovascular control areas in the brain, our group[23] recently demonstrated that an altered metabolic component of the exercise pressor reflex (EPR; predominantly group III/IV afferents) contributes to the attenuated pressor responses observed during exercise in patients with PD.

The inability to elevate BP could be an important component of exercise intolerance in patients with PD, as the pressor and sympathetic vasoconstrictor responses are thought to increase blood flow to the active skeletal muscles and augment brain perfusion.[25] The contribution of group III/IV afferents to increase blood flow to the exercising muscle has been demonstrated in animals[26] and humans.[27] Therefore, the ability to elevate limb/brain perfusion pressure and muscle blood flow during exercise could be particularly important for patients with PD. Of note, in 1985, Sachs et al.[20] reported a blunted BP increases during isometric exercise in patients with PD, which was accompanied by lower forearm blood flow increase. In this sense, these findings raise the necessity of a better understanding of the integrated cardiovascular responses to exercise in that population. In the present review, we have the purpose to highlight the autonomic adjustments to exercise in patients with PD.

Cardiovascular system and exercise

Regular physical exercise is beneficial for the cardiovascular system and is associated with decreased cardiovascular mortality as well as the risk of developing cardiovascular disease. Physically active subjects usually present well-controlled blood pressure (BP). The heart rate (HR) and BP increase in both dynamic and isometric/resistance exercises

are orchestrated by several neural mechanisms that work in concert to precisely control cardiovascular and hemodynamic responses that occur during exercise.[28] The marked differences between dynamic and isometric/resistance exercise is the pressor response, which occurs to a much greater extent during isometric/exercise owing to the more immediate and large increases in sympathetic nerve activity.

Neurodegenerative disorders with similar motor dysfunctions presented by PD, like multiple system atrophy (MSA) and pure autonomic failure (PAF), also present abnormal cardiovascular responses to exercise.[29] Both MSA and PAF patients present a blunted BP increase during exercise.[30,31] In dynamic and isometric exercise, patients present a markedly exercise-induced hypotension during exercise.[30,31] These abnormal responses have been attributed to decreased total vascular resistance and, in dynamic exercise, increased vasodilation in exercising muscles. Taking together with studies showing a markedly reduced muscle sympathetic activity (MSNA) in these patients,[32–34] and considering that cardiovascular responses to exercise greatly rely on MSNA, it is not surprising that these patients do not sufficiently elevate their BP.[35] This scenario is quite similar in PD, and therefore in the present section, we are going to highlight the cardiovascular responses to exercise in patients with PD.

Acute and chronic responses to exercise

Isometric/resistance exercise

Studies conducted with patients with PD showed blunted cardiovascular responses to exercise when compared to healthy controls.[20,21,23,36–39] The first pieces of evidence of an attenuated cardiovascular response to isometric exercise were demonstrated in the late 80s. Sachs et al.,[20] Ludin et al.,[21] and Turkka et al.[36] demonstrated a blunted BP increase to isometric exercise in patients with PD. However, others did not demonstrate the same response.[40,41] One could argue that the blunted cardiovascular responses to exercise in PD might be related to a lower peak workload. Sachs et al.[20] reported significantly lower maximal voluntary contraction (MVC) and pointed this out. Of note, the studies[21,36,37] that came out after did not report MVC nor discuss this point. However, our group[23] and others[39] have recapitulated the previous findings by showing a blunted increase in BP during exercise despite similar triggering stimuli (i.e. handgrip force produced). In addition, we have assessed the role of the peripheral neural mechanisms (i.e. muscle metaboreflex). Those studies that demonstrated a blunted cardiovascular response suggested an impairment of central command and/ or suggest central sympathetic dysfunction as potential mechanisms for the impaired response. During exercise, the pressor response is thought to play a crucial role in skeletal muscle perfusion.[42] Therefore, since fatigue is a common feature in patients with PD,[43] the ability to elevate BP could be an important component of exercise tolerance[44] and make

the exercise prescription a challenging approach for patients with PD.

Patients with PD also present blunted increases in BP during resistance exercise.[39] However, despite the fact that these authors suggested that resistance exercise was safe and well-tolerated by patients with PD, we believe that caution should be taken when exercise is prescribed for this patient population. Furthermore, this is because it has been reported that sudden death can occur in PD,[19] which was associated with a significant lengthening of QT interval.[45] Even in this challenging scenario, chronic exposure to resistance exercise training in patients with PD is capable of improving their motor function.[11] But literature about cardiovascular adaptation to resistance/isometric exercise is lacking. Regarding cardiovascular adaptations to chronic exercise exposure in patients with PD, Kanegusuku et al.[46] reported that, after 12 weeks of resistance training, the BP response to an orthostatic test was improved in patients with PD.

The underlying mechanisms of the attenuated pressor response to exercise observed in patients with PD are unclear, but certain aspects may be taken into account. It is likely that Lewy bodies (abnormal aggregates of protein that are widely distributed in the hypothalamus), sympathetic centers (intermediolateral nucleus of the thoracic cord and sympathetic ganglia), and parasympathetic centers (dorsal vagal and sacral parasympathetic nuclei) could disrupt the central component of autonomic reflex arches, which are involved in autonomic regulation.[4] We recently advanced this body of knowledge by showing in humans that the EPR could be a potential mechanism that contributes to the impaired cardiovascular response to exercise in PD patients.[23] The blunted metaboreflex-mediated increases in BP are explained through a lower increase in total peripheral resistance (TPR). In addition, patients with PD are known to exhibit an inverse relationship between resting MSNA and age.[35,47,48] Accordingly, patents with PD have displayed lower MSNA responses to mental stress;[35,48] however, MSNA responses to exercise were not assessed yet, which would provide a more direct measurement of the efferent postganglionic sympathetic outflow. Since older men are highly reliant on sympathetic nerve activity for beat-to-beat control of BP,[49] the lower increase in TPR could indicates a lower efferent sympathetic activity to the vasculature during exercise and isolated metaboreflex activation. Studies have also shown that PD patients present loss of sympathetic cardiac nerves,[8,47,50] lower norepinephrine release,[51] and lower alpha-adrenergic responsiveness,[52] which altogether may explain the attenuated cardiovascular responses to isometric/resistance exercise.

Dynamic exercise

Dynamic exercise is characterized by rhythmical contractions that change both muscle length and joint angle of the working muscles. This intermittent pumping of skeletal muscle (i.e. muscle pump) contributes to increases in muscle blood flow.

Similar to what is reported during isometric/resistance exercise, patients with PD also present blunted cardiovascular responses to dynamic exercise. Reuter et al.[53] demonstrated a significant difference in systolic BP increase between patients with PD and controls in an incremental exercise test using a cycle ergometer. Patients with PD showed a slight increase in systolic BP at lower intensity levels and a more pronounced blunted increase at higher intensities compared to healthy controls. Similar findings were reported by Werner et al.[54] in a modified Bruce protocol. The authors demonstrated a lower systolic BP at the peak of exercise. In addition, the same group extended the results demonstrating that the BP increase is significantly lower in patients than in healthy controls, regardless of whether subjects were on their Parkinson medication.[55] In 2016, Kanegusuku et al.[22] tested submaximal and maximal cardiovascular responses in patients with PD during an incremental test through analysis of the anaerobic threshold and the respiratory compensation point. The authors demonstrated blunted cardiovascular responses at both the submaximal and the maximal phase of the incremental test. Noteworthy, patients with PD had lower oxygen consumption, HR, and systolic BP at respiratory compensation point and at peak exercise.

Despite the well-known beneficial effects of chronic aerobic exercise exposure to the autonomic and cardiovascular function, just few studies investigated whether those effects are also presented in patients with PD.[13,56] Evidence shows that treadmill training may improve VO_{2peak}.[57] More importantly, the baroreflex control of the BP is shown to be improved after 4 weeks of treadmill training.[12] However, more studies with larger sample sizes are warranted to provide more information regarding the beneficial effects of chronic dynamic exercise on autonomic function, their possible interaction with PD medications, and in disease progression.

The mechanisms underlying these blunted responses presented by patients with PD are thought to be in part mediated by cardiac impairment.[58] In a cohort study, Palma et al. demonstrated that chronotropic insufficiency may be present at least 4 years before the onset of motor dysfunction. Of note, patients with established motor dysfunction also exhibited cardiac autonomic dysfunction, which may account for the blunted responses present by patients with PD. Studies are showing low myocardial radioactivity concentrations after injection of different sympathoneural imaging agents (heart 123I-metaiodobenzylguanidine and 6-[^{18}F] fluorodopamine; Figure 1),[59] suggesting an early, cardioselective, postganglionic denervation in patients with PD, and this denervation of sympathetic fibers to the heart has been shown in patients with and without OH and even in early PD.[60] Patients with PD and OH also present lower basal leg vascular resistance compared to those without OH and controls.[61]
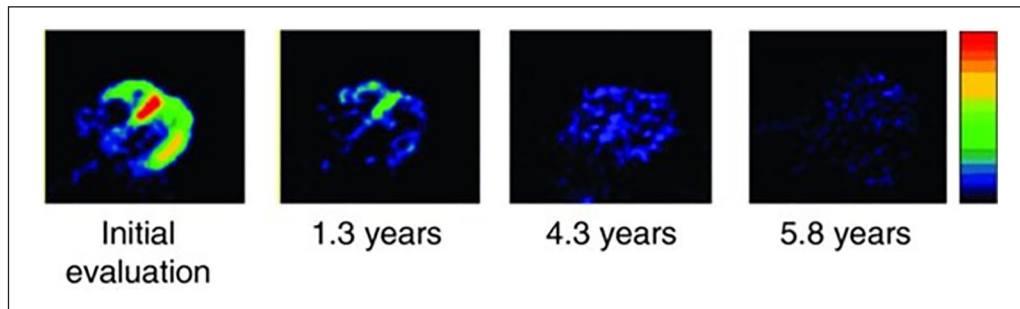
Figure 1. Progression of cardiac denervation in a patient with PD. The patient had partial loss of myocardial ^{18}F-DA-derived radioactivity upon initial evaluation, with normal anterobasal septal radioactivity. Loss of ^{18}F-DA-derived radioactivity progressed rapidly thereafter.
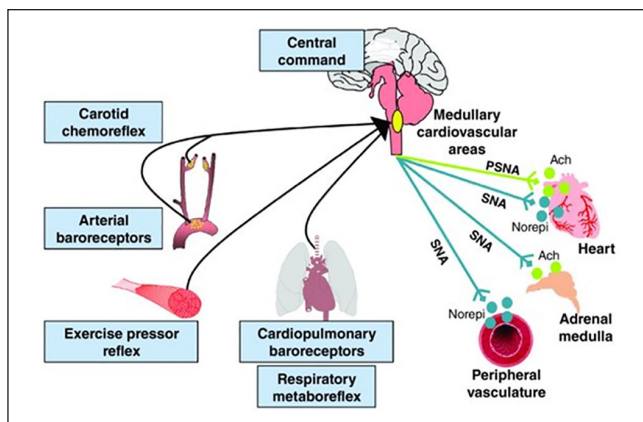Source: Reprinted, with permission, from Goldstein.[6]

Figure 2. Schematic summarizing the mechanisms involved in mediating the autonomic adjustments to exercise. Neural signals originating from higher brain centers (i.e. central command), chemically sensitive receptors in the carotid and aortic bodies (i.e. arterial chemoreflex), stretch receptors in the carotid and aortic arteries (i.e. arterial baroreflex), mechanically and metabolically sensitive afferents from skeletal muscle (i.e. exercise pressor reflex), mechanically sensitive stretch receptors in the cardiopulmonary region (i.e. cardiopulmonary baroreflex), and metabolically sensitive afferents from respiratory muscles (i.e. respiratory metaboreflex) are processed within brain cardiovascular control areas that influence efferent sympathetic and parasympathetic nerve activity. The alterations in autonomic outflow elicited by these inputs during exercise evoke changes in cardiac and vascular function, as well as release of catecholamines from the adrenal medulla.
Source: Reprinted, with permission, from Fisher et al.[28]

Autonomic reflex dysfunctions in PD

The cardiovascular response to exercise is controlled by both central and peripheral mechanisms that modulate parasympathetic and sympathetic activity to the heart and blood vessels in an intensity-dependent manner (Figure 2). In this section, we will highlight some of the neural mechanisms participating in this cardiovascular regulation during exercise, specifically: (1) the arterial baroreflex, which represents a closed-loop, negative feedback control system

involved in BP regulation in a beat-to-beat basis; (2) the EPR, which plays a pivotal role in generating the cardiovascular response to exercise via a feedback mechanism originating in skeletal muscle comprising of group III and IV skeletal muscle afferents that respond to both mechanical and metabolic stimuli; and (3) the chemoreflex, which exerts a powerful influence on breathing via changes in blood O_2 and CO_2 tension sensed by specific receptors located at both central and peripheral level.[28]

Baroreflex failure

The baroreflex is comprised of mechanically sensitive receptors located in the carotid body and aortic arch that relay information to the brainstem regarding beat-to-beat changes in BP. The resultant neural feedback provides critical information to modulate HR (cardiac baroreflex) or peripheral vasoconstrictor outflow (sympathetic baroreflex), which maintains pressure homeostasis at rest and in response to perturbations such as orthostatic stress. A failure of arterial baroreflex function, assessed by the BRS, has been associated with cardiac mortality in several diseases.[62] In addition, the arterial baroreflex system plays a pivotal role in counteracting transient falls in BP during the execution of activities of daily living. Thus, a failure of arterial baroreflex is probably a key mechanism associated with OH.[63,64] Approximately 40% of the patients with PD experience coexistent abnormalities, such as OH.[63,65] The OH induces additional incapacitating symptoms[7] (Figure 3) that may contribute to the increased risk of falls, which have a significant impact on patient's quality of life. Therefore, the interest to better understand the baroreflex function in patients with PD starts to increase.

Most of the studies that have assessed the baroreflex function in patients with PD report impaired values of BRS compared to age-matched controls.[23,51,66–68] The majority of the studies have used spontaneous fluctuations of BP[23,68,69] or Valsalva maneuvers[51,66,67,70] to assess the baroreflex function in those patients. In addition, most of these studies assess the cardiac BRS in patients with advanced age, and
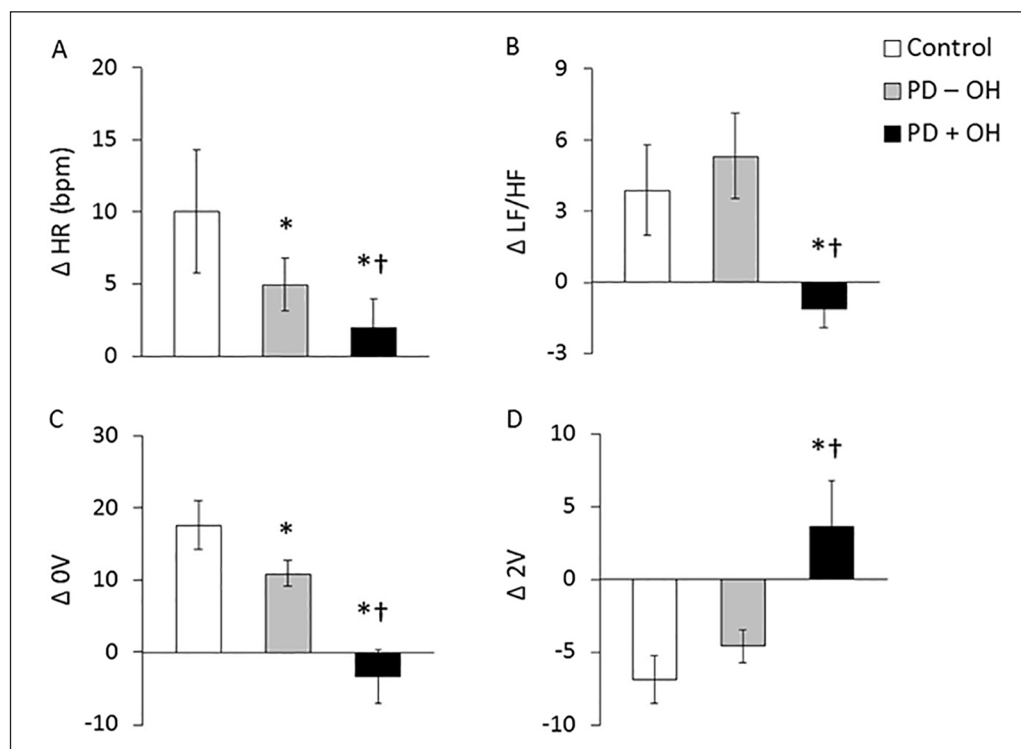
Figure 3. Heart rate and sympathovagal balance in response to active standing in controls and patients with PD with (PD + OH) and without (PD – OH) orthostatic hypotension (panels A and B, respectively). Nonvariable (0V—a proxy of sympathetic activity, panel C) and very variable (2V—a proxy of parasympathetic activity, panel D) category of symbolic dynamics analyses of heart rate variability. *$p < 0.05$ compared with the control group. †$p < 0.05$ compared with PD – OH group. Mean data from Vianna et al.[7]

not used the gold standard technique for baroreflex function assessment. The rapid changes in BP induced by sequential boluses of vasoactive drugs (i.e. modified Oxford technique) were not conducted until now, given the severity of disease in advanced age patients. In this sense, studies should use the gold standard method in order to have a big picture of the baroreflex function. The modified Oxford technique allows the analysis of the ups and downs of the baroreflex function, providing an overall understanding of which arm (for increase or fall in BP) is most impaired.

In line with the pieces of evidence for impaired BRS in patients with PD, animal studies are trying to further clarify the baroreflex function in PD through BP changes induced by injections of vasoactive drugs.[71–74] However, there is no consensus between the studies. For example, Fleming et al.[71] demonstrated a lower BRS to nitroprusside-induced hypotension but preserved BRS to phenylephrine-induced hypertension in mice overexpressing human wild type alpha-synuclein. In another type of PD model, induced by bilateral infusion of 6-hydroxydopamine, Falquetto et al.[72] demonstrated lower BRS to increases in BP, but similar for falling in BP. Recently, the same group published the opposite effect[74] showing similar BRS responses to increases in BP, but lower for falling in BP, which is in line with our proposed hypothesis. In addition, one study demonstrated similar BRS to increases and fall in BP.[73]

Of note, these incongruences might be explained by the fact that there are no perfect animal models that genuinely recapitulate the age-dependent PD phenotype, α-synuclein pathology, and pathophysiology. Animal models of PD are also insufficient to mimic non-motor symptoms such as the olfactory dysfunction, constipation, depression, and cognitive impairments.[75] Therefore, until the ideal animal model is not created, these results should be interpreted with caution. In addition, the BRS analysis and the way of drug administration is not consistent within studies.[72,74]

EPR

The peripheral feedback from the skeletal muscle is known as EPR.[76] These peripheral signals originate from group III, predominately mechanically sensitive, and group IV, predominately metabolically sensitive, skeletal muscle afferent nerve endings in response to muscular contractions.[77,78] A plethora of studies have indicated that the metabolic component of EPR (i.e. metaboreflex) has a predominant role in regulating the sympathetically mediated increases in peripheral resistance, cardiac contractility, stroke volume (SV), HR, and BP during exercise.[28,79] Several chronic disease states with altered skeletal muscle afferent signaling have been identified.[44] Recently, the contribution of the EPR, via its metabolic component, to the blunted cardiovascular
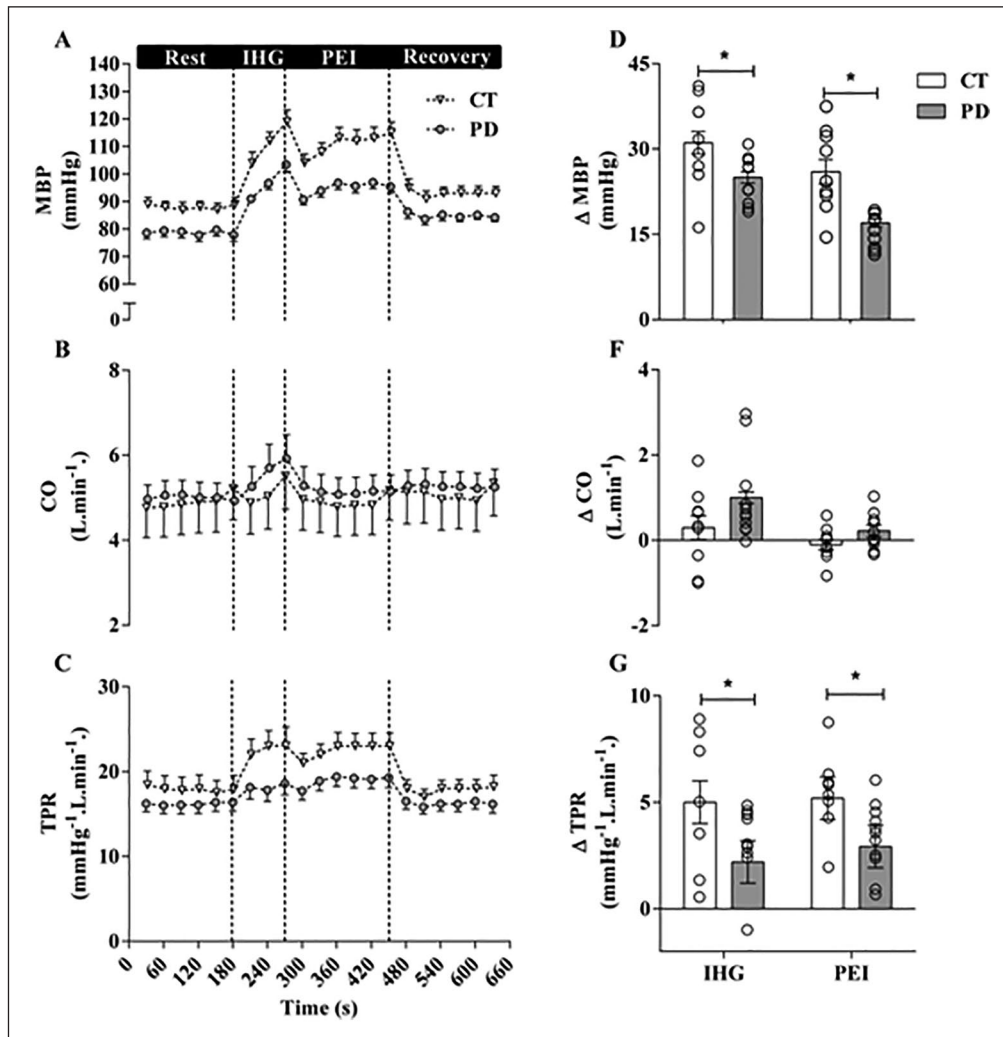
Figure 4. The attenuated cardiovascular responses to isometric handgrip (IHG) exercise in patients with Parkinson's disease (PD) are, at least in part, attributable to an altered skeletal muscle metaboreflex. Mean and individual data from Sabino-Carvalho et al.[23] demonstrated that mean BP (MBP) responses 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.

responses presented during exercise in patients with PD was investigated by our group. Sabino-Carvalho et al.[23] 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 ± 1 mmHg) when compared to healthy control participants (+26 ± 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.

This is significant because in an integrative perspective, a failure to increase sympathetic activity to important compliant regions, such as splanchnic circulation, will certainly impair the blood flow redistribution to the muscles during exercise. Therefore, the quantitative significance of vasoconstriction in these vascular beds with respect to how much blood per minute can be redistributed to working muscle and how much BP can be altered by such vasoconstriction. This scenario could lead to a blunted pressor response and, consequently, to lower increase blood flow to the active muscle, which may lead to metabolic distress, tissue/brain hypoperfusion, fatigue, cardiac autonomic imbalance, and an impaired exercise capacity (Figure 5). Moreover, this hypothetical model means that the attenuated group III and IV skeletal muscle afferent fibers, together with central degeneration of important cardiovascular areas, mediated the blunted increase in sympathetic activity, perpetuating the mismatch between oxygen supply and demand, causing deleterious implications for exercise in these population. Therefore, a better understanding of the integrated cardiovascular responses to exercise has a significant role in
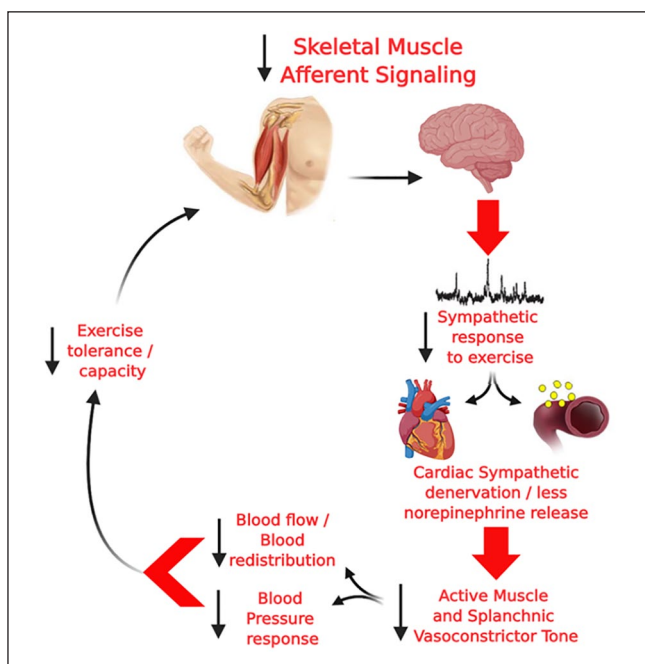
Figure 5. Potential deleterious consequences of altered group III and IV skeletal muscle afferent activity in disease. Diminished skeletal muscle afferent signaling, together with central degeneration in PD, can result in a blunted sympathetic vasoconstriction leading to a blunted pressor response and, consequently, to lower increase blood flow to the active muscle, which may lead to metabolic distress, tissue/brain hypoperfusion, fatigue, cardiac autonomic imbalance, and an impaired exercise capacity.

improving exercise adherence, security, and patient's quality of life.

Chemoreflex

Central and peripheral chemoreflex continually modulate breathing and, through a synergically powerful negative feedback loop, maintain arterial blood gas homeostasis in the body. Chemically sensitive receptors, located primarily peripherally in the carotid bodies, sense changes in blood chemical composition (e.g. carbon dioxide (CO_2), hydrogen ions ($H+$)), and discharge afferent information to medullary regions via the carotid sinus and vagus nerve. On the other hand, receptors located centrally in many brain stem areas, including the nucleus tractus solitarii (NTS), raphe nuclei, locus coeruleus, pre-Bötzinger complex, and the retro trapezoid nucleus (RTN), are also important regions for sense central $CO_2/H+$ changes.

Cardiorespiratory dysfunction is the leading cause of death in PD,[80] attributed to the disease-producing chronic immobilization and debilitation. Recent studies have suggested that the attenuated chemoreflex response plays an important role in the respiratory function of patients with PD,[81] rather than impairment of the ventilatory muscle function. Serebrovskaya et al.[82] reported that male patients with

PD under Sinemet-250 medication, which control to any peripheral dopamine influence, presented a reduced ventilatory response during severe isocapnic hypoxia. Of note, the patients presented normal voluntary hyperventilation, which suggests that the motor impairment of the ventilatory muscles does not explain the reduced response to isocapnic hypoxia.[83]

Regarding the central chemoreceptors, animal models of PD provide a better understanding of the impact of PD on the central chemoreflex.[84] Bilateral lesions of the striatum with 6-hydroxydopamine led to a massive degeneration of important areas like raphe nuclei, locus coeruleus, pre-Bötzinger complex, and the RTN.[84] In these rats, breathing was attenuated at rest and also in response to hypercapnia. From a translational perspective, studies have assessed the chemoreflex-induced ventilatory responses to hypercapnia in patients with PD, and the results remain controversial. In contrast to the impaired hypercapnia-induced ventilatory response presented in the animal models, Onodera et al.[85] showed a preserved response to hypercapnia and a blunted hyperventilatory response to isocapnic hypoxia in patients at an early stage of PD. While Seccombe et al.[81] demonstrated a marked impairment of the ventilatory response to hypercapnia in patients with PD, however, the authors did not compare the responses with a matched control group, but rather with normative data.

Conclusion

Currently, the pharmacological approach is the primary resource for symptomatic control of PD during early to severe stages. The current literature supports that exercise may provide a low-cost approach for PD symptom management and for the overall patient health. However, more studies should be conducted in light of the non-motor symptoms presented by patients with PD. The present review highlighted the cardiovascular responses to different types of exercises. Noteworthy, a plethora of studies are showing beneficial effects of exercise in several aspects of PD, and that exercise training should be recommended to all patients with PD. However, some aspects pointed out in the present review should be taken into account. (1) The attenuated cardiovascular responses observed in patients with PD during exercise must be interpreted carefully, since it may represent an inability to increase sympathetic activity rather than a chronic adaptation of exercise. Several aspects play a role in this impairment, such as sympathetic cardiac denervation, central degeneration, and altered muscle metaboreflex; (2) A baroreflex failure appears to be a key element in the OH presented by patients with PD. Therefore, strategies to improve BRS could be warmly welcomed in this clinical setting.[86] Non-invasive transcutaneous vagus nerve stimulation via the auricular branch of the vagus nerve appears to improve baroreflex function;[87] and (3) the chemoreflex function of patients with PD seems to be an open avenue for research. Despite

the growing evidence of animal models, it seems that animal models do not entirely reproduce clinical symptoms and pathology of human PD. Therefore, well-controlled studies in the field are lacking. Studying the effects of interventions such as exercise training on the neural control of BP in patients with PD will provide clinical insights with important implications for exercise management as a beneficial therapeutic approach. Collectively, this review contributes to a more comprehensive understanding of the mechanisms underlying the cardiorespiratory responses to exercise in patients with PD.

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