Exercise hemodynamics in Parkinson's Disease and autonomic dysfunction

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Abstract

Aim

To clarify the characteristics of hemodynamic responses to exercise and orthostasis in Parkinson's disease patients, especially those with autonomic failure.

Methods

Clinical audit of supine cycling exercise test data (with active standing tests pre- and post-exercise) of Parkinson's patients with autonomic dysfunction. 23 patients (71±7 yr, 7 females) with a confirmed diagnosis of Parkinson's were identified.

Results

Group mean systolic blood pressure (SBP) fell during pre-exercise standing (-39±29 mmHg, P<0.001, 17 patients had orthostatic hypotension (OH)), while heart rate (HR) increased (+13±7 beats.min-1, P<0.001). SBP (P<0.001) increased during exercise with a wide variation in responses. SBP increased in 13 patients (INC; +30±14 mmHg) and either did not change or decreased in 10 patients (DEC -12±11 mmHg, P<0.001 vs INC). The increase in HR was not different between sub-groups (30±12 vs 25±10 beats.min-1, INC vs. DEC, P=0.29). The size of the pre-exercise stand SBP reduction was greater in DEC vs INC (-64±23 (10 out of 10 had OH) vs -19±16 mmHg (7 out of 13 had OH), respectively, P<0.001). The HR elevation was not different between sub-groups (13±8 vs 13±4 beats.min-1, DEC vs INC, P=0.94). Post-exercise SBP/DBP were lower for both sub-groups compared to pre-exercise and the standing SBP reduction post-exercise was not greater relative to pre-exercise in either sub-group.

Conclusion

Exercise-induced hypotension can occur in Parkinson's disease patients with autonomic failure with the magnitude of the exercise response being related to the severity of autonomic dysfunction. Exercise does not appear to worsen OH in this sample of Parkinson's patients.

Introduction

Non-motor features are increasingly recognised in Parkinson's disease, including dysfunction of the autonomic nervous system, which can have a significant impact on quality of life [1]. Cardiovascular autonomic dysfunction can result in precipitous reductions in blood pressure, particularly during various daily activities, such as the upright posture (e.g., orthostatic hypotension), and various symptoms, e.g., cognitive impairment, fatigue and fainting [2]. Cardiovascular autonomic dysfunction (defined as orthostatic hypotension and often referred to as autonomic failure) occurs in ~40% of Parkinson's patients [3], generally in the latter stages of the disease, but it can present in the earlier stages of the disorder in some patients.

Exercise is often used as an adjunct therapy in Parkinson's disease. Physical activity/exercise is also a potent stimulus of the autonomic nervous system and can threaten the appropriate maintenance of blood pressure during and/or after exercise however in individuals with compromised autonomic function, e.g., autonomic failure. In contrast to an appropriate pressor response during exercise in healthy individuals, increases in blood pressure can be blunted and/or reductions may even occur (referred to as exercise-induced hypotension) in other neurological disorders, such as Multiple System Atrophy and Pure Autonomic Failure, where autonomic failure is a key diagnostic criteria and clinical features often overlap with Parkinson's disease [4]. Furthermore, exercise can accentuate post-exercise orthostatic hypotension [5]. Analogous to the symptoms that occur during orthostatic hypotension, limited elevations and/or reductions in blood pressure during exercise can cause similar symptoms, such as dizziness, weakness and fatigue. The blood pressure responses to exercise in Parkinson's disease have been scarcely investigated however. The few previous studies that have been conducted have shown that the pressor response to maximal

exercise is blunted and that aerobic capacity is reduced in Parkinson's patients [6,7,8]. The integrity of the autonomic nervous system in those studies was not reported however, thus it was unclear if the reduced pressor response in those patients was due to autonomic dysfunction and/or another mechanism(s). In one of our previous studies, relative to aged matched healthy controls, we showed preserved exercise pressor responses in untreated idiopathic Parkinson's patients with intact cardiovascular autonomic function [9]. It is unclear, however, if blood pressure increases appropriately during exercise or if exercise accentuates orthostatic hypotension in Parkinson's disease patients with autonomic dysfunction. The aim of this study was to clarify the characteristics of hemodynamic responses to exercise and orthostasis in Parkinson's disease patients, especially those with autonomic failure.

Subjects and Methods

We conducted a clinical audit of data from autonomic function exercise tests that are routinely performed in our Units on patients with suspected autonomic dysfunction. Suspected was characterised by the referring clinician and/or the Autonomic Unit consultants surmising that the patient had probable cardiovascular autonomic dysfunction based on the symptoms that they reported, for example, dizziness or visual disturbances and/or paracervical and suboccipital ("coat hanger") ache while upright, fainting or near fainting episodes, and/or weakness, lethargy or fatigue. We identified records of 23 patients (71 ±7 yr, 7 females) that had a confirmed diagnosis of Parkinson's disease (4.4 ± 3.7 yr) and had completed the exercise test protocol [10]. Patients were on the following medications; dopamine agonists (78%), dopaminergic adjunct therapy (61%, e.g., catechol-O-methyl transferase inhibitors, DOPA decarboxylase inhibitors, monoamine oxidase inhibitors), statins (35%), volume expanders/adrenergic agonists for orthostatic intolerance (30%), proton pump inhibitors for gastrointestinal dysfunction (22%), selective serotonin reuptake inhibitors (26%) and anti-hypertensives (13%). The exercise test protocol involves supine cycling (Lode Angio, Lode B.V., Groningen, Netherlands), e.g., no gravity and orthostatic stress, at 3 incremental stages (25, 50 and 75 watts) for 3 min each [9]. A 5 min active stand test was conducted before and after the exercise protocol to assess orthostatic hypotension and symptoms pre- and post-exercise. Blood pressure and heart rate were intermittently recorded throughout the protocol using upper arm sphgymomanometry (Dinamap Pro 400, GE Healthcare, Chalfont St Giles, UK).

ANOVA or paired t tests were performed for comparisons over time within the exercise test and within or between the pre- and post-exercise stand tests. When the ANOVA revealed a

significant difference, Tukey's post-hoc testing was performed to determine the location of the specific differences. For any sub-group analyses performed, differences between sub-groups were assessed with student's t test or Chi-square where appropriate. Pearson’s product correlation was used for studying relationships between variables. Values are presented as means ± SD. Statistical significance was set at a p value of <0.05. Ethical approval was waived as the study did not require ethical approval because it was a retrospective chart review of routine clinical tests.

Results

Both systolic (142±18 vs 104±30 mm Hg, P <0.05) and diastolic (78±9 vs 65±14 mm Hg, P <0.05) blood pressure decreased on standing and heart rate increased (65±10 vs 78±10 beats.min^{-1}, P <0.05) in the whole group. 17 of the 23 patients fulfilled the criteria for orthostatic hypotension indicating autonomic failure. 4 out of the other 6 patients (-5±11 mm Hg) displayed reductions in blood pressure during orthostasis. Not all patients (9 out of 23) were able to complete all 3 stages of the exercise protocol due to fatigue or motor dysfunction. There were no differences between those that did and didn't complete the exercise test with regards to pre-exercise supine and head-up tilt blood pressure (both P >0.05) or the peak exercise blood pressure response (P >0.05) or with regards to age or disease duration (both P >0.05). The group mean systolic blood pressure increased during exercise (P <0.05) but there was a wide variation in the responses however (see Figure 1A). A similar trend was evident for diastolic blood pressure (P <0.05). Heart rate increased during exercise (P <0.05, see Figure 1B). Resting supine blood pressure was lower (systolic 134±15 and diastolic 75±11 mm Hg, both P <0.05 vs. pre-exercise supine) and heart rate was higher (69±11 beats.min^{-1} vs. pre-exercise supine, P <0.05) post-exercise. During post-exercise standing, both systolic and diastolic blood pressure decreased and heart rate increased in the whole group (all P <0.05). The same 17 patients that fulfilled the criteria for orthostatic hypotension on pre-exercise standing also met the criteria on post-exercise standing.

On further inspection of the blood pressure responses to exercise, systolic blood pressure increased in 13 patients and either did not change or decreased in 10 patients. We therefore further examined these 2 sub-groups that did increase (INC) and those that did

not increase or in fact decreased (DEC) systolic blood pressure during exercise. Resting blood pressure was higher in DEC ($P < 0.05$, see Figure 1C). By definition, blood pressure (systolic and diastolic) in the INC group increased during exercise whereas in the DEC group blood pressure was either maintained or reduced ($P < 0.05$ vs INC, see Figure 1C). There were no differences between sub-groups in the elevation in heart rate during exercise ($P > 0.05$, see Figure 1D).

The pre- and post-exercise stand data were also re-analysed (see Figure 2). Supine blood pressure was higher in the DEC group ($P < 0.05$ vs INC). There was no difference in supine heart rate between the sub-groups (65±12 vs 65±8 beats.min^{-1} for INC and DEC, respectively, $P > 0.05$). The size of the pre-exercise stand systolic and diastolic blood pressure reductions were greater in DEC vs INC however (both $P < 0.05$ vs INC, see Figure 2A). The entire DEC group had orthostatic hypotension and 7 of the 13 INC group had orthostatic hypotension (100 vs 54%, respectively, $P<0.05$). The increase in heart rate during standing was not different between the sub-groups (13±8 vs 13±4 beats.min^{-1}, $P > 0.05$). The magnitude of the change in blood pressure during exercise was also significantly correlated with the magnitude of orthostatic hypotension ($R^2 = 0.53$, $P<0.001$).

During post-exercise standing blood pressure decreased and the size of the systolic and diastolic blood pressure reductions were greater in DEC vs INC (both $P < 0.05$ vs INC, see Figure 2B). Similar, to pre-exercise, the entire DEC group had orthostatic hypotension and 7 of the 13 INC group had orthostatic hypotension. The increase in heart rate during standing was not different between the sub-groups (12±9 vs 13±7 beats.min^{-1}, $P > 0.05$). The size of the changes in blood pressure were not greater relative to pre-exercise for both sub-groups

(all P >0.05). Symptoms were generally more prevalent on post-exercise standing despite smaller reductions in blood pressure however. There was no difference in age (70 ± 7 vs 72 ± 6 yr for INC vs DEC, respectively, P=0.42) or disease duration (3.5 ± 2.7 vs 5.5 ± 4.6 yr for INC vs DEC, respectively, P=0.54) between the sub-groups. There were also no statistical differences in dopaminergic pharmacotherapy between the INC and DEC sub-groups (dopamine agonists; 69 vs 90%, respectively, P>0.05; dopaminergic adjunct therapy; 46 vs 80%, respectively, P>0.05). More patients in the DEC group were on medications for orthostatic intolerance however (8 vs 60%, P <0.05).

Discussion

The aim of this study was to clarify the characteristics of hemodynamic responses to exercise and orthostasis in Parkinson's disease patients, especially those with autonomic failure. The main findings were that the exercise pressor response is blunted and blood pressure can even decrease during exercise in Parkinson's disease patients with autonomic dysfunction and the extent of the blunting/decrease in blood pressure during exercise is related to the severity of autonomic dysfunction. Furthermore, exercise did not exacerbate orthostatic hypotension in this group of patients. Finally, this is the first study to document reductions in blood pressure, e.g., exercise-induced hypotension, in Parkinson's disease patients with autonomic failure.

Cardiovascular autonomic dysfunction is a key non-motor feature of Parkinson's disease. The integrity of cardiovascular autonomic function during exercise in Parkinson's disease has not been thoroughly investigated however. In the few previous studies that have examined the hemodynamic responses to exercise in Parkinson's, the blood pressure responses to maximal exercise were reduced [6,7,8] and the pressor responses to sub-maximal exercise were preserved in Parkinson's patients [9,11]. In the former studies the integrity of autonomic function of the patients was not reported and the reduced blood pressure response may have been a result of the lower aerobic capacity and peak power output achieved. In the latter studies, autonomic function, as assessed using a standard screening protocol or just a head-up tilt test, appeared normal. In the present study 17 of the 23 patients had orthostatic hypotension indicating autonomic failure. 10 of the 23 patients exhibited no change or a reduction in blood pressure during exercise (e.g., the DEC group). All patients in this sub-group displayed orthostatic hypotension and greater reductions in blood pressure on orthostasis relative to the remainder of the patients that exhibited an

increase in blood pressure during exercise (e.g., the INC group). OH was present in 7 of the 13 patients of the INC group, however, suggesting that this, e.g., autonomic failure, may not explain the differences in the exercise pressor response between the 2 groups. However, blunted exercise pressor responses were still evident in the INC group given that the definition of this group was simply an increase (of any magnitude) in SBP during exercise, thus, patients who exhibited mild to moderate elevations of blood pressure that are considered sub-normal were included. Furthermore, when examining the whole patient group, the magnitude of the systolic blood pressure change during exercise was also significantly correlated with the magnitude of orthostatic hypotension on pre-exercise standing. These findings strongly suggest that the exercise pressor response (or lack of) in Parkinson's disease patients with autonomic dysfunction is associated with the severity of their cardiovascular autonomic dysfunction, which is consistent with other autonomic failure disorders that display orthostatic and exercise-induced hypotension (e.g., Multiple System Atrophy, Pure Autonomic Failure and Spinal Cord Injury) [4]. Because our primary focus was the examination of the exercise cardiovascular responses in PD patients with suspected autonomic dysfunction we looked to assess those responses first and then further analyse those data (e.g., DEC vs INC) according to the level of autonomic dysfunction rather than start with a comparison of those with and without autonomic failure (e.g., OH). Regardless, if the data are analysed with this latter approach (e.g., those with OH vs. those without OH) then the findings are the same; the blunted/absent pressor responses to exercise are magnified and more prevalent in patients with autonomic failure and the extent of the blunted/absent pressor response is directly related to the severity of autonomic dysfunction/failure (e.g., OH).

Generally, autonomic dysfunction presents in the latter stages of Parkinson's disease [12] but it can occur early and even before the hallmark motor dysfunction presents [13]. The proposed mechanisms of cardiovascular autonomic dysfunction in Parkinson's disease generally involve lewy body accumulation and cell loss in various key areas of the autonomic nervous system, such as, autonomic regulatory areas including the hypothalamus, medulla, locus coeruleus and raphe, pre-ganglionic parasympathetic and sympathetic regions including the dorsal vagal motor nuclei of the glossopharyngeal and vagal nerves, autonomic and sympathetic ganglia, as well as post-ganglionic sympathetic denervation [1] that ultimately affect control of blood pressure through baroreflex impairment and loss of sympathetic innervation.

The mechanisms for the blunted/absent exercise pressor responses, as well as the more severe cardiovascular autonomic dysfunction/failure, in the DEC group are likely related to impairments in the ability to control cardiac output and/or total peripheral resistance. The similar heart rate responses to orthostasis and exercise in the INC and DEC groups might suggest that the ability to increase/maintain cardiac output was not the likely mechanism contributing to the impaired blood pressure control in the DEC group, consistent with other autonomic failure disorders that display a preserved cardiac output, yet impaired blood pressure, response to exercise [14, 15]. That said, stroke volume (and cardiac output) was not assessed in the present study, cardiac sympathetic denervation is common in Parkinson's disease [1], and an impaired cardiac contractility during exercise has also been reported in PD patients with cardiac sympathetic denervation [11] suggesting that an impaired cardiac output response may have occurred in the DEC group. In contrast, it is possible that the control of total peripheral resistance is impaired in the DEC group.

Typically, total peripheral resistance is decreased during dynamic exercise due to the large vasodilation that occurs in the active musculature despite vasoconstriction in other non-active vascular beds. It is therefore possible that an excessive muscle vasodilation and/or impaired elevations in vascular resistance in quiescent vascular beds (e.g., splanchnic circulation) causes an exacerbated decrease in total peripheral resistance and caused a reduced blood pressure during exercise in the DEC group. Although absolute DBP was not different between the INC and DEC groups during exercise, the change in DBP was significantly different in the DEC group (e.g., an increase in INC and no change in DEC). This hypothesis is consistent with other autonomic failure disorders that display blunted elevations in splanchnic vascular resistance and blood pressure during exercise [14, 15]. Alternatively, it might be a combination of an impaired cardiac output and a blunted total peripheral resistance response is responsible for the blunted exercise pressor response in DEC. A recent study has indicated that both impaired cardiac innervation and total peripheral resistance responses cause OH in PD [16]. Although it is not known whether these findings explain the blunted exercise pressor response in PD patients with autonomic dysfunction, the overlap between the cardiovascular control mechanisms during orthostasis and exercise suggest that this might be likely.

Previous studies have shown that exercise exacerbates orthostatic hypotension in autonomic failure disorders [9]. In contrast in the present study, exercise did not accentuate the fall in blood pressure during orthostasis. The reasons for this are unclear but might be related to the lower supine blood pressure prior to standing, thus limiting the potential size of the reduction in blood pressure during orthostasis, the relatively high severity of

autonomic dysfunction/failure already evident in this group of patients and/or a specific mechanism related to Parkinsonism as opposed to the other autonomic failure disorders (e.g., Multiple System Atrophy, Pure Autonomic Failure) where exacerbated orthostatic hypotension has previously been documented [9]. Although exercise did not worsen orthostatic hypotension in this sample of Parkinson's patients, it did increase orthostatic symptoms (based on patient reporting; data not presented) which were likely due to the lower pre-standing blood pressure causing blood pressure to fall to symptomatic lower limits quicker and/or a greater peripheral displacement of blood due to the previous exercise bout.

In conclusion, these data indicate that exercise-induced hypotension can occur in Parkinson's disease patients with autonomic failure, the magnitude of the exercise blood pressure response in Parkinson's disease patients with autonomic dysfunction is related to the severity of their cardiovascular autonomic dysfunction and exercise does not appear to worsen orthostatic hypotension in this sample of Parkinson's patients but lowers resting blood pressure. These findings have implications for clinicians and their management of Parkinson's patients.

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Figure 1. Mean (± 1 SD) blood pressure (upper line systolic, lower line diastolic) and heart rate during exercise for the whole group (A and B, respectively) and for the sub-groups that did (INC) and didn't (DEC) display a pressor response to exercise (C and D). *P<0.05 vs 0 watts, #P<0.05 vs INC.

Figure 2. Mean (± 1 SD) absolute systolic and diastolic blood pressure supine prior to 5 min active stand test (left side) and the changes in systolic and diastolic blood pressure during the 5 min active stand test (right side) pre- (upper panel A) and post-exercise (lower panel B) for the sub-groups that did (INC) and didn't (DEC) display a pressor response to exercise. #P<0.05 vs INC.