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CARDIOVASCULAR RESPONSES TO WALKING IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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Abstract

Purposes—To assess the cardiovascular responses during constant load walking and to identify predictors of this response in peripheral artery disease (PAD) patients.

Methods—Seventy-nine patients with PAD performed a constant load treadmill test (2 mph, 0% grade). During the test, systolic blood pressure (BP), diastolic BP, and heart rate (HR) were obtained at the fourth minute to the last minute of exercise. Patients were also characterized on demographic measures, cardiovascular risk factors, baseline exercise performance and vascular measures.

Results—During constant load walking, there was a significant increase ($p<0.01$) in systolic BP (+12 ± 10 mmHg), diastolic BP (+6 ± 9 mmHg), and HR (+5 ± 5 bpm). The HR responses was negatively correlated with ischemic window ($r= -0.23$; $p<0.05$), expressed as an area under the curve of the resting ankle systolic BP and its recovery from maximal graded treadmill test, and positively correlated with the HR during the first minute of recovery from maximal graded treadmill test ($r= 0.27$; $p<0.05$). The increase in cardiovascular variables during constant load walking was greater in subjects with higher body mass index and in men ($p<0.05$).

Conclusion—Patients with PAD had an increased cardiovascular response during constant load walking, and these responses were greater in obese patients and in men. The clinical implication is that PAD patients engaged in walking training programs, particularly men and those with obesity, require frequent assessment of cardiovascular parameters to avoid exaggerated increases in BP and HR during constant load walking.

Keywords

Peripheral Vascular Disease; Intermittent Claudication; Exercise; Blood Pressure

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INTRODUCTION

Peripheral artery disease (PAD) affects a large proportion of the elderly population(27). Intermittent claudication (IC), the most common symptom of PAD, impairs ambulation(19), daily physical activity(15), and health-related quality of life(28). In addition, patients with PAD have higher prevalence of comorbid conditions(22, 27), leading to elevated rates of cardiovascular events(25, 30).

Cardiovascular responses during walking are altered in patients with PAD(3, 5). Previous studies have reported that blood pressure (BP) and heart rate (HR) both increase during constant load exercise in patients with PAD, but not in age matched controls(5). An exaggerated increase in BP and HR is an abnormal cardiovascular response to constant load exercise(4) which has been considered a potential marker for hemodynamic instability and increased cardiovascular risk in subjects with cardiac diseases(9, 23, 35).

In PAD patients, the increases in cardiovascular variables during walking might be related to a decrease in walking economy, measured as an increase in oxygen consumption during constant load exercise(17). However, it is less clear whether the severity of IC is associated with exaggerated increases in BP and HR. Furthermore, it is well established that subjects with PAD have endothelial dysfunction(6), increased arterial stiffness(34), comorbid conditions(27) and are often under drug therapy(9, 17), and whether these factors may be predictive of an exercise-induced abnormal cardiovascular response during constant load walking in patients with PAD remains uncertain. Understanding the impact of these variables on exaggerated cardiovascular responses during exercise may help identify patients who have greater cardiovascular risk during exercise.

The purposes were to assess the cardiovascular responses during constant load walking in PAD patients, and to identify predictors of cardiovascular responses during walking. The hypotheses were that BP and HR progressively increase during constant load treadmill exercise in PAD patients, and that more severe IC, greater vascular dysfunction, and presence of comorbid conditions are associated with the cardiovascular responses.

METHODS

SUBJECTS

Recruitment—Patients were evaluated in the General Clinical Research Center at the University of Oklahoma Health Sciences Center (HSC). Patients were recruited by referrals from the HSC vascular clinic, as well as by newspaper advertisements for possible enrollment into an exercise study. The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma HSC. Written informed consent was obtained from each subject prior to investigation.

Screening—Patients performed an initial progressive, graded treadmill protocol to determine study eligibility. Patients with IC were included in this study if they met the following criteria: (a) a history of IC, (b) ambulation during a graded treadmill test limited by IC(19), (c) an ankle-brachial index (ABI) ≤ 0.90 at rest(36), or an ABI ≤ 0.73 after exercise(21), and (d) ability to walk at least 8 min in a constant load treadmill test (2.0 mph/0% grade). Patients were excluded from this study under the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (d) exercise tolerance limited by factors other than leg pain (e.g., clinically significant electrocardiographic changes during exercise indicative of myocardial ischemia, dyspnea, poorly controlled blood pressure), and (f) active cancer, renal disease, or liver disease, (e) use of medications indicated for the treatment of IC (cilostazol and pentoxifylline) initiated within three months prior to investigation. The use of other types of medications were not exclusion criteria for study participation. A total of 79 patients were deemed eligible for the study.

MEASUREMENTS

Primary Outcome Assessment

Constant Load Treadmill Test: This test was the experimental protocol used to obtain the primary outcome measures consisting of changes in systolic BP, diastolic BP, HR and rate pressure product (RPP). Patients performed the constant load walking test in which the work rate was set at a constant speed of 2 mph and a grade of 0% until maximal claudication pain was attained, or for a maximum of 20 minutes(37). During the test, electrocardiogram was continuously monitored, and HR was averaged at the end of each minute. Systolic and diastolic BP were obtained every 2 minutes. RPP was obtained by multiplying systolic BP by HR.

Secondary Outcome Assessment

Medical History, Physical Examination, and Anthropometry: Demographic information, height, weight, body mass index (BMI), waist and hip circumferences(7), cardiovascular risk factors, comorbid conditions, claudication history, and a list of current medications were obtained from a medical history and physical examination at the beginning of the study. Treatment with medications was used to define cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes. There were a minority of patients who were not on medications for these disorders, and who fell outside of the normal ranges. These patients were not defined as having the risk factor because they had not been clinically diagnosed, and thus were not prescribed medications for their clinical management. Specifically, out of 28 patients who were not taking blood pressure medications, nine had blood pressure values in the pre-hypertensive or hypertensive range. Out of 31 patients who were not taking medications for dyslipidemia, 12 had abnormal blood lipid profiles. Out of 60 patients who were not taking medications for diabetes, only 4 had glucose or insulin values outside of the normal ranges. Abdominal obesity was defined as having a waist circumference > 102 cm in men and > 88 cm in women.

Ambulatory Activity Monitoring: Daily ambulatory activity was assessed using a step activity monitor (Step Watch 3, Cyma Inc., Mountlake Terrace, WA) as previously described. (15) Ambulatory activity was measured during seven consecutive days in which patients were instructed to wear the monitor during waking hours and to remove it before retiring to bed. The step activity monitor was attached to the right ankle above the lateral malleolus using elastic Velcro straps, and continuously recorded the number of steps taken on a minute-to-minute basis. The accuracy of the step activity monitor exceeds 99 ± 1% in patients with intermittent claudication.(15)

Graded Treadmill Test: The progressive, graded treadmill test used to determine study eligibility was repeated during a subsequent visit to obtain outcome measures related to peak exercise performance and HR recovery(19). The claudication onset time (COT), defined as the walking time at which the patient first experienced pain, and the peak walking time (PWT), defined as the walking time at which ambulation could not continue due to maximal pain, were both recorded to quantify the severity of claudication. Peak oxygen uptake was measured by oxygen uptake obtained during peak exercise work load with a Medical Graphics VO2000 metabolic system (Medical Graphics Inc, St. Paul, MN). During the test, a 12-lead electrocardiogram was continuously monitored, and HR was averaged at the end of each minute, while systolic and diastolic BP were obtained every 2 minutes. The peak HR and BP were considered the highest values obtained during the test. The HR at the first minute of recovery was also obtained. Using these procedures, the test-retest intraclass reliability coefficient is R = 0.89 for COT(19), R = 0.93 for PWT(19), and R = 0.88 for peak oxygen uptake(13).

ABI and Ischemic Window: As previously described, ABI measures were obtained from the more severely diseased lower extremity before and at 1, 3, 5, and 7 minutes after the graded treadmill test(19, 20). Systolic ankle BP was recorded during recovery from the graded treadmill test until baseline values were obtained. The time course of the reduction in ankle systolic BP after treadmill exercise from the resting baseline value was quantified by calculating the area under the curve, referred to as the ischemic window induced by exercise(12). Because the ischemic window is a function of both PAD severity and the amount of exercise performed, the ischemic window was normalized per meter walked.

Peripheral Vasodilator Capacity: To assess the peripheral vasodilator capacity of the affected limb, reactive hyperemic calf blood flow was performed in the more severely diseased leg by using venous occlusion mercury strain-gauge plethysmography as previously described (18).

Arterial Elasticity: Diastolic pulse contour analysis was performed to estimate arterial elasticity, referred as to the large artery elasticity index (LAEI) and small artery elasticity index measurements (SAEI). LAEI and SAEI were obtained in the morning following an overnight fast of at least 8 hours, and prior to engaging in any strenuous physical activity, as previously described (26). The test-retest intraclass reliability coefficient is R = 0.87 for large artery elasticity index and R = 0.83 for small artery elasticity index(1).

STATISTICAL ANALYSES

Measurement variables were summarized as means and standard deviations while dichotomous variables were summarized as percent with characteristic present. Gender was expressed as percent male. Change score means were examined by paired t test. Associations among pairs of variables were addressed using Pearson correlation coefficients. A forward stepwise regression procedure with p to enter set at 0.10 and p to delete after entry at 0.15 was used to select the multiple regression models. The NCSS 2000 Statistical System for Windows (NCSS, Kaysville, UT) was used for all computations.

RESULTS

The clinical characteristics of PAD patients are shown in Table I, and their baseline performance measures during graded treadmill test and clinical characteristics are shown in Table II. Patients were mostly hyperlipidemic and/or hypertensive. In this study, 66% reported pain during constant load walking test.

The cardiovascular variables at rest and during the constant load walking test are presented on Table III. All the variables had a significant increase from the fourth minute to the last minute of walking exercise ($p<0.01$). It is noteworthy that 86% of the patients had an increase in systolic BP during constant load exercise, 77% experienced an increase in HR, and 94% had an increase in RPP. The comparison of the cardiovascular responses between subjects who reported pain and subjects who did not report pain during constant load treadmill test revealed no group differences for all variables ($p>0.05$). In addition, the cardiovascular responses during treadmill test were analyzed adjusting for medication use and the results were not altered, thereby, these results were not presented.

The systolic BP and HR at 4 minute of constant load treadmill test represented, respectively, 89±11% and 83±12 % of the peak values during the graded treadmill test. By the end of the constant load treadmill test, systolic BP and HR increased to 97±11 and 86±12 % of the peak values during the graded treadmill test, respectively.

The associations between the changes in cardiovascular variables during constant load walking and clinical characteristics of PAD patients are shown in Table IV. Change scores in HR and RPP from the fourth minute to the last minute of constant load walking were negatively correlated with ischemic window (r= −0.23 and r= −0.26, respectively; $p<0.05$) and positively correlated with the HR during the first minute of recovery from maximal graded treadmill test (r= 0.27 and r= −0.24, respectively; $p<0.05$). Using multiple regression procedures (Table V), the identified predictors of the change in systolic BP during constant load walking were diabetes and statin use. The predictors of the change in HR during constant load walking were BMI, sex, statin and wafarin use. The predictors of the change in RPP during constant load walking were BMI, diabetes and wafarin use.

DISCUSSION

The major findings of this investigation are that: (i) PAD patients with IC have increases in systolic and diastolic BP, HR and RPP during constant load walking; (ii) these increases were greatest in patients with the largest ischemic window values, and in those with the highest HR values during recovery from the maximal treadmill test, and (iii) the main predictors of cardiovascular variables responses during constant load walking are sex, BMI, diabetes, as well as statin and warfarin use.

There were significant increases in BP, HR and RPP during constant load walking, indicating that patients with IC experience an increase in cardiovascular intensity during constant load walking. Interestingly, the HR and BP at 4 minutes of the constant load treadmill test represented more than 80% of the peak cardiovascular responses in the maximal treadmill test. At the end of constant load treadmill test these variables were similar and in some cases greater than peak responses in during the graded treadmill test. These results suggest that cardiovascular responses during constant load exercise are exaggerated in patients with PAD. Previous studies have shown that cardiovascular responses during constant load exercise are greater in PAD patients than in healthy subjects (3, 4). In addition, changes in HR and BP described in subjects with left ventricular dysfunction (2) were lower than the ones observed in this study. Although the mechanisms underlying the increases in cardiovascular variables during constant load test in PAD patients were not addressed in this study, some hypotheses might explain the results. We have recently shown that patients with IC have significant increases in VO_2 during painful ambulation(17), suggesting that during constant load walking exercise, painful ambulation becomes more challenging in these patients. Hence, the exaggerated cardiovascular responses observed in this study might reflect the increases in the metabolic demand of exercise. However, since the cardiovascular variables increased in almost all patients, while only 66% of them reported pain, other mechanisms might also be involved in the abnormal cardiovascular responses during walking in PAD patients. As endothelial dysfunction(6) and an increase in arterial stiffness(34) have been reported in patients with PAD, it is possible that a blunted vasodilatatory capacity of arteries led to an progressive increase in blood pressure in these patients(32). However, the main factor that might be related to the increase in cardiovascular variables during constant load exercise in patients with PAD is the activation of pressor reflex (3). Exercise pressor reflex is activated during physical activity mediated by stimulation of mechanically and metabolically sensitive primary afferent neurons, which reflexively augment BP and HR(3).

In the present study the cardiovascular responses for all variables were similar between subjects that reported pain and subjects that did not report pain during constant load treadmill test. In fact, at the beginning of exercise (4 minute) the BP and HR were already high, which suggest that exaggerated cardiovascular response precede the occurrence of pain. The lack of association between exercise induced changes in systolic BP and the claudication pain is in agreement with previous studies (3, 4). Although pain reflects the occurrence of ischemia, it is a late perceptual response of ischemia. In addition, pain is affected by several acute and chronic factors, which includes exercise. Interestingly, the increases in cardiovascular variables were not correlated with ABI and arterial elasticity and reactive hyperemic blood flow. It suggests that the impact of the disease in the conduit arteries did not affect the magnitude of the increases in cardiovascular variables during constant load exercise. Although reactive hyperemic blood flow represents micro-vessel distribution, it was obtained under basal conditions, such as ABI and arterial elasticity. Therefore, it is not surprising that these variables are not closely correlated with the cardiovascular responses during constant load exercise. Although, this finding is in contrast with studies which found that endothelial dysfunction(33) and increased arterial stiffness(31) were related to an exaggerated blood pressure response to exercise in hypertensive subjects, this discrepancy suggests that these factors are less important in explaining cardiovascular responses during exercise in PAD patients who have much greater atherosclerotic burden and local muscle ischemia than hypertensive subjects.

Patients with greater increases in HR and RPP during constant load walking were more ischemic in the legs after the maximal treadmill test and had slower HR recovery. Ischemic window represents both macro-vessel and micro-vessel function in the active musculature following treadmill exercise, and a greater ischemic window after standardized exercise has been related with a faster deoxygenation of active muscle during exercise(16), probably leading to a greater activation of pressor reflex. Slow HR recovery after exercise has been considered a marker of poor cardiac autonomic control caused by the lack of capacity to reestablish parasympathetic nervous activity(8). The greater increases in cardiovascular variables during constant load walking in subjects with slow HR recovery suggest that an impaired heart autonomic control might also be involved in these abnormal responses.

The increase in cardiovascular variables during walking was greater in subjects with higher BMI. It is well described that obese subjects present altered lipid profile, insulin resistance, and endothelial dysfunction(29). In PAD patients, obesity is related to higher mortality rates (14), lower COT(10), and a longer hemodynamic recovery(10). In addition, during walking at a constant load, obese PAD subjects perform a greater amount of work compared to non-obese PAD patients(10). All these factors might have contributed to the greater increases in HR and RPP during constant load exercise in obese PAD patients. The present study also showed that men experienced greater increases in HR during constant load walking than women. Previous studies have observed a higher rate of acute cardiovascular events(38) and a greater prevalence of hospitalization associated with vascular procedures(11) in men. Moreover, a recent study also observed that after constant load treadmill walking, men with PAD presented a slower HR recovery than women(24). Taking together, the available evidence suggests a worse cardiovascular control in men with PAD, which might be related to the greater cardiovascular responses during the constant load walking. However, the role of gender on cardiovascular variables in patients with PAD has been poorly studied and further investigations are necessary to clarify this issue.

Exercise has been recommended as the first line therapy in patients with PAD(22). Although the risk of cardiovascular events was not directly assessed in this study, our data indicate that cardiovascular responses increase during constant-load walking in most patients with PAD, which, theoretically, might represent an increase in cardiovascular risk during exercise. The clinical implication of this result is that PAD patients have impaired cardiovascular control during walking, indicating that cardiovascular variables should be periodically assessed during constant load walking to avoid reaching an excessively high cardiovascular workload. This assessment should be more frequently performed in obese patients and in men because these groups have even greater cardiovascular responses during constant load walking. Another clinical implication of this result is that exaggerated cardiovascular responses during exercise may indicate that medication therapy needs adjustment for more optimal cardiovascular control.

This study has limitations that should be considered in the interpretation of the results. The cross-sectional design does not allow causality to be established and the correlations should be interpreted with caution. Furthermore, the design does not allow us to assess the long-term cardiovascular consequences of the increased cardiovascular responses to exercise in PAD patients. In addition, we did not include an age-matched, non-PAD control group, which does not permit us to attribute the responses obtained during exercise to the disease. Patients with severe cardiac disease were excluded in the screening, therefore, the results of this study can only generalize to our current sample of patients, which consisted of PAD patients limited by IC who were able to walk at least 8 minutes during a constant load exercise test and did not present severe cardiac disease. Finally, the constant load walking protocol employed a fixed speed and grade, and therefore represents a different relative exercise intensity among subjects. An individualized protocol using a different speed and grade for each subject could have been used to standardize the relative exercise intensity among patients. However, since all patients were able to walk al least 8 minutes, the constant load protocol represented a relatively low intensity for all subjects.

In conclusion, patients with PAD have an exaggerated cardiovascular response to a constant load walking exercise, and these responses are greater in both obese and male patients. The clinical implication is that PAD patients with IC have impaired cardiovascular control during exercise and require frequent assessment of cardiovascular parameters to avoid exaggerated increases in BP, HR and RPP during constant work load walking, especially men and those with obesity.

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Table I

Clinical characteristics of patients with intermittent claudication (n=79).

Variables	Values Mean (SD)
Age (yrs)	65.9 (10.7)
Body mass index (kg/m^2)	29.1 (6.2)
Waist girth (cm)	103.9 (16.4)
Ankle-brachial index	0.81 (0.2)
Sex (% men)	62%
Race (% Caucasian)	71%
Pain during constant load treadmill test (% yes)	66%
Medical history	
Current smoking (% yes)	27%
Diabetes (% yes)	29%
Hypertension (% yes)	76%
Hyperlipidemia (% yes)	81%
Abdominal obesity (% yes) (n=78)	41%
Obesity (% yes) (n=78)	41%
Lower extremity revascularization (% yes)	44%
Medications	
Diuretics (% yes)	42%
Beta-blockers (% yes)	34%
Calcium channel blockers (% yes)	32%
Alpha receptor blockers (% yes)	20%
Statins (% yes)	61%
ASA (% yes)	61%
Plavix (% yes)	2%
Trental (% yes)	9%
Pletal (% yes)	9%
Warfarin (% yes)	9%
Metformin (% yes)	19%
Insulin (% yes)	9%

Values are means (SD) or percentage of patients.

Table II

Performance and clinical characteristics in patients with intermittent claudication.

Variables	Mean (SD)
Time to onset pain during graded treadmill test (sec) (n=77)	326 (213)
Time to maximal pain during graded treadmill test (sec) (n=77)	661 (251)
Peak systolic blood pressure during graded treadmill test (mmHg) (n=75)	155 (20)
Peak diastolic blood pressure during graded treadmill test (mmHg) (n=75)	85 (11)
Peak heart rate during graded treadmill test (bpm) (n=76)	121 (20)
Peak oxygen uptake ($mL*kg^{-1}*min^{-1}$) (n=76)	14.7 (3.6)
Ischemic Window ($mmHg*min^{-1}*m^{-1}$) (n=77)	−0.21 (0.31)
Heart rate recovery 1st minute (bpm) (n=73)	91 (18)
Reactive hyperemic blood flow (%/min) (n=76)	5.1 (3.5)
Large artery elasticity index (mL/mmHg*10) (n=62)	14.3 (6.6)
Small artery elasticity index (mL/mmHg*100) (n=62)	4.2 (2.3)
Physical activity level (strides/day) (n=73)	3867 (1720)

Values are means and standard deviation (SD).

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Table III

Cardiovascular responses to constant load walking in patients with intermittent claudication. Values are means (SD).

Variables	Resting	4 min	Final	Δ (final – 4 min)	% subjects who increased
SBP (mmHg)	131 (20)	137 (16)	149 (18)	+12 (10)*	86
DBP (mmHg)	76 (10)	78 (9)	83 (12)	+6 (9)*	68
MBP (mmHg)	94 (11)	98 (9)	105 (10)	+8 (7)*	83
HR (bpm)	79 (13)	99 (15)	103 (17)	+5 (5)*	77
RPP (bpm*mmHg)	10304 (2136)	13531 (2742)	15420 (3335)	+1920 (1435)*	94

SBP – Systolic Blood pressure; DBP – Diastolic Blood Pressure; MBP – Mean Blood Pressure; HR – Heart Rate; RPP - Rate pressure product.

*p<0.01

Table IV

Associations between the changes in cardiovascular variables during constant load walking and clinical characteristics of patients with intermittent claudication.

Variables	Δ SBP (final – 4 min)	Δ HR (final – 4 min)	Δ RPP (final – 4 min)
Continuous variables (values are Pearson correlation coefficients)			
Age	−0.02	−0.11	−0.11
Body mass index	0.03	0.18	0.16
Peak Oxygen Uptake	−0.20	0.17	−0.05
Ankle-brachial index	−0.14	−0.02	−0.10
Ischemic Window	−0.14	−0.23*	−0.26*
HR recovery 1st minute	0.02	0.27*	0.24*
Reactive hyperemic blood flow	0.11	0.08	0.12
Large artery elasticity index	0.05	0.01	0.02
Small artery elasticity index	−0.13	0.10	−0.02
Time to onset of pain	0.02	−0.05	−0.02
Physical activity	0.07	−0.09	−0.03
Categorical Measures (Values are difference in mean between categories)			
Obesity (non-obese –obese)	−1.80	−1.70	−485.01
Hypertension (non hypertense –hypertense)	−0.13	−1.03	−146.54
Diabetes (non diabetic –diabetic)	+4.77	−1.20	+272.61
B-blockers (no– yes)	+1.62	+0.51	+399.03

SBP – Systolic Blood pressure; HR – Heart Rate; RPP - Rate pressure product.

*p<0.05

Table V

Multiple regression models predicting abnormal cardiovascular responses to constant load walking.

Dependent variables	Independent variabes	Regression coefficient	95% CI	Standard coefficient	p
Δ SBP (final – 4 min)	Diabetes *	−4.55	− 9.37 to 0.27	−0.21	0.064
	Statin *	−4.25	−8.77 to 0.26	−0.21	0.065
Δ HR (final – 4 min)	BMI (kg/m^2)	0.22	0.05 to 0.40	0.26	0.015
	Male *	2.59	0.37 to 4.81	0.24	0.023
	Statin *	2.66	0.47 to 4.84	0.25	0.018
	Warfarin *	4.63	0.87 to 8.40	0.26	0.017
Δ RPP (final – 4 min)	BMI (kg/m^2)	63	8 to 119	0.27	0.025
	Diabetes *	−630	−1371 to 112	−0.20	0.095
	Warfarin *	1488	412 to 2563	0.30	0.007

SBP – Systolic Blood pressure; HR – Heart Rate; RPP - Rate pressure product.

* The reference group for each regression coefficient for the independent variables is the group without the condition (non-diabetic subjects, those not taking statins, women, and those not taking warfarin, respectively).