Influence of peripheral arterial disease and supervised walking on heart rate variability

Anthony S. Leicht, PhD,[a] **Robert G. Crowther, PhD,**[a] and **Jonathan Golledge, MChir,**[b,c] *Townsville, Queensland, Australia*

Objective: **To examine the influence of peripheral arterial disease (PAD) on heart rate variability (HRV) in patients, and to examine the influence of an intense long-term (12 months) exercise program on HRV in PAD patients.**
Methods: **This study involved ambulatory patients attending a local hospital and university center. Participants were twenty-five patients with diagnosed PAD and intermittent claudication and 24 healthy, age-matched adults. Interventions involved random allocation of PAD patients to 12 months of conservative medical treatment (Conservative) or medical treatment with supervised treadmill walking (Exercise). The main outcome measures were time- and frequency-domain, nonlinear HRV measures during supine rest, and maximal walking capacity prior to and following the intervention.**
Results: **Despite significantly worse walking capacity (285 ± 190 m vs 941 ± 336 m; $P < .05$), PAD patients exhibited similar resting HRV to healthy adults. At the 12-month follow-up, Exercise patients exhibited a significantly greater improvement in walking capacity (183% ± 185% vs 57% ± 135%; $P = .03$) with similar small nonsignificant changes in HRV compared with Conservative patients.**
Conclusions: **The current study demonstrated that PAD patients exhibited similar resting HRV to healthy adults with 12 months of intense supervised walking producing similar HRV changes to that of conservative medical treatment. The greater walking capacity of healthy adults and PAD patients following supervised exercise does not appear to be associated with enhanced HRV. (J Vasc Surg 2011;54:1352-9.)**

Peripheral arterial disease (PAD) is an occlusive disease of the arteries supplying the lower limbs with a prevalence of ~5.3% for Australian males aged over 65 years.[1] The incidence of new patients with PAD is increasing by 0.85% annually, presumably due to the increasing age of the population as well as other known risk factors such as smoking and physical inactivity.[1] The most common symptom of PAD is intermittent claudication (IC), which limits walking ability and health-related quality of life.[2] Treatment options for IC include medications, lifestyle changes, supervised exercise, and endovascular or surgical interventions.[3-5] Supervised exercise has been shown to improve exercise capacity and quality of life in PAD patients[3,6]; however, the mechanisms responsible for these beneficial effects are unknown. Suggested means by which supervised exercise leads to improved walking capacity for PAD patients include improved angiogenesis and resultant improved tissue perfusion,[7] adaptation of the leg muscles to reduced blood flow,[8] or central changes such as improved cardiac performance.[9] Identification of the mechanisms by which regular exercise improves function and quality of life may lead to development of better targeted treatments for PAD patients. One such exercise-induced mechanism may be an enhanced central cardiac autonomic control. Regular exercise has been reported to increase cardiac autonomic control as assessed by heart rate variability (HRV) in older adults[10] and those with known cardiovascular disease.[11] The increased HRV and parasympathetic modulation following regular exercise have been reported to contribute to the lower incidence of future arrhythmia and cardiac risk.[12] Importantly, regular aerobic exercise has been recognized as an important nonpharmacological treatment to enhance HRV and cardiac electrical stability[13,14] that may lead to a reduction in cardiac mortality of high-risk populations.[15] It is unclear, however, whether the low intensity of exercise possible by patients with intermittent claudication can induce central autonomic changes. A 12-week exercise program was reported to increase walking capacity but not HRV in PAD patients.[16] The authors suggested the low intensity of exercise as a possible factor for the lack of HRV change for PAD patients.[16] More intense and/or longer duration exercise programs[17] may be necessary for central cardiac improvements in PAD patients, similar to that reported for healthy adults.[18]

Reduced HRV has been reported for patients with coronary artery disease[19] and those at increased risk of

From the Institute of Sport and Exercise Science,[a] the Townsville Hospital,[b] and the Vascular Biology Unit, School of Medicine and Dentistry,[c] James Cook University.

Supported by a National Health and Medical Research Council Funded Clinical Centre of Research Excellence to improve the management of peripheral artery disease. Dr Golledge is supported by a Practitioner Fellowship from the National Health and Medical Research Council and a Senior Clinical Research Fellowship from the Office of Health and Medical Research.
Competition of interest: none.
Presented at the Eleventh European Congress of Sports Sciences, Lausanne, Switzerland, Jul 5-8, 2006.

Reprint requests: Anthony Leicht, Associate Professor, Institute of Sport and Exercise Science, James Cook University, Townsville, Queensland, 4811, Australia (e-mail: anthony.leicht@jcu.edu.au).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.
0741-5214/$36.00

doi:10.1016/j.jvs.2011.05.027

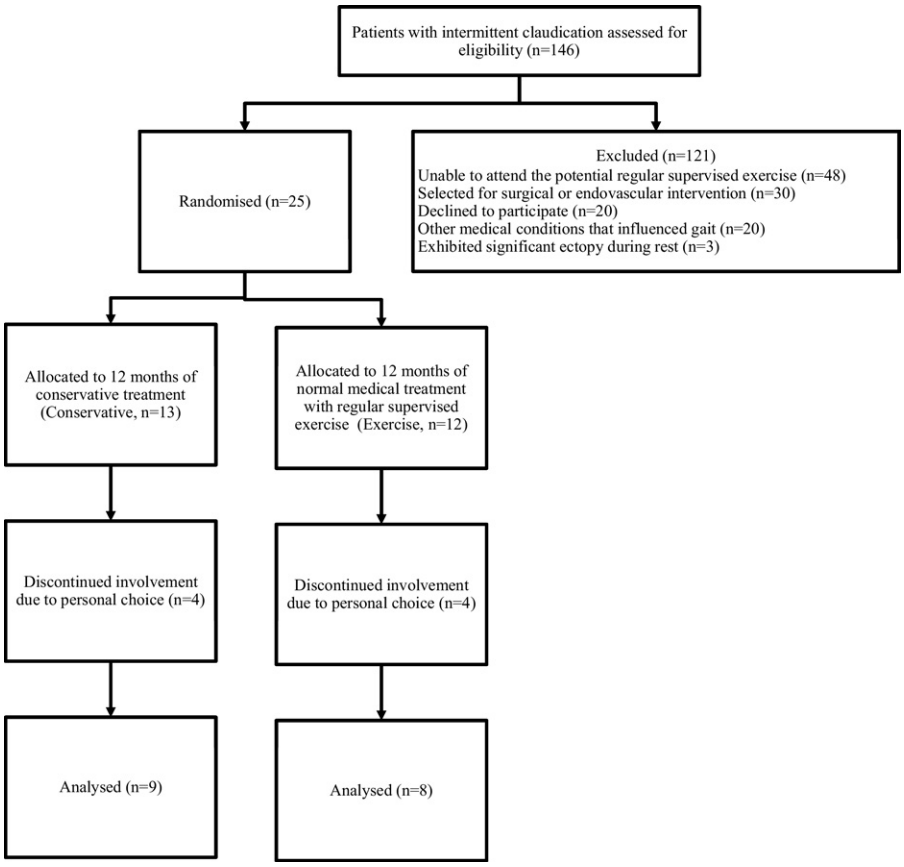

Fig. Line diagram illustrating the number of patients screened, recruited, and included within the analyses for the study.

cardiovascular death.[20] Most patients with PAD have coronary artery disease,[21] and thus it would be assumed they also have reduced HRV. However, Goernig and colleagues[22] reported that PAD patients exhibited greater parasympathetic-based HRV measures compared with patients with other cardiovascular disease and similar levels to those of healthy adults.[22] These conflicting results highlight the limited understanding of PAD and HRV that warrant further examination. The aims of the current study were: (1) to compare HRV in patients with IC and age-matched healthy adults; and (2) to examine the influence of an intense long-term (12-month) exercise program on HRV in patients with IC.

METHODS

Participants and study design

For aim 1, patients with IC and healthy, aged-matched adults (n = 24) were recruited as previously described (Fig).[4] Patients were assessed by a vascular physician. PAD was confirmed based on the absence of lower limb peripheral pulses, lower limb artery stenosis, or occlusion on duplex or computed tomographic angiography, and ankle-brachial pressure index (ABI) < 0.9.[4] All participants completed a general health questionnaire to identify medications and comorbidities (Table I). Resting HRV, ABI, and maximal walking capacity during exercise were measured in all participants. Following these assessments, IC patients were then randomly allocated to either 12 months of conservative medical treatment (Conservative; n = 13) or normal medical treatment with regular supervised exercise (Exercise; n = 12) in order to assess aim 2 (Fig). Supervised exercise consisted of treadmill walking of 3 days per week for 25 to 40 minutes per day at a workload that induced intense to maximal claudication pain.[4] Assessment of resting HRV, ABI, and maximal walking capacity were performed at recruitment (entry) for all participants and 12 months later for IC patients only. Informed written consent was obtained from all participants with all procedures undertaken in accordance with the principles outlined in the Declaration of Helsinki. Approval for the study was obtained from the local university and health district Research Ethics Committees.

Assessments

Participants arrived at the laboratory following an overnight fast and 24-hour absence from physical activity. Medications were withheld on the testing morning. Height was measured using a stadiometer (Seca 202,

Table I. Characteristics of patients with intermittent claudication and healthy, aged-matched adults

	Intermittent claudication (n = 25)	*Healthy adults (n = 24)*
Age (years)	66.9 ± 8.0	65.2 ± 7.7
Height (cm)	166.7 ± 8.5	168.1 ± 7.1
Mass (kg)	80.5 ± 16.3	75.0 ± 12.2
Body fat (%)	32.9 ± 8.2	33.5 ± 7.6
Male	14 (56)	10 (42)
Waist girth (cm)	97.3 ± 14.0	86.9 ± 10.5[b]
Hip girth (cm)	106.5 ± 10.8	100.9 ± 7.5[a]
Waist:hip ratio	0.91 ± 0.09	0.86 ± 0.09[a]
Ankle-brachial index – worst	0.61 ± 0.16	1.14 ± 0.14[c]
Ankle-brachial index – best	0.85 ± 0.24	1.20 ± 0.15[c]
Current smoker	7 (28)	0 (0)[b]
Former smoker	15 (60)	8 (33)[b]
Diabetes	6 (24)	0 (0)[a]
Hypertension	10 (40)	6 (25)
Myocardial infarction	8 (32)	0 (0)[b]
Beta-blocker	6 (24)	1 (4)
Angiotensin-converting enzyme inhibitor	6 (24)	4 (17)
Statin	10 (40)	3 (13)
Antiplatelet	12 (48)	1 (4)[a]
Intermittent claudication distance (m)	114 ± 86	
Maximal walking distance (m)	285 ± 190	941 ± 336[c]
Peak aerobic capacity (mL · kg^{-1} · min^{-1})	18.6 ± 7.2	34.5 ± 7.9[c]

Values are mean ± SD or number (%).
[a]$P < .05$ vs intermittent claudication.
[b]$P < .01$ vs intermittent claudication.
[c]$P < .001$ vs intermittent claudication.

Seca, Hamburg, Germany), and body mass and body fat percentage were determined using bioelectrical impedance scales (Tanita TBF 521, Tanita Corp. of America, Arlington Heights, IL). Waist and hip girths were assessed using a steel tape to the nearest millimeter in accordance with international standards.[23] Participants were then connected to a metabolic analysis system (Powerlab 8M; ADInstruments Pty Ltd, Bella Vista, Australia) for the continuous monitoring of heart rate (HR; Lead II) and respiration during supine rest and exercise. Participants initially rested supine for 5 minutes prior to measurement of supine resting HRV and respiration. Then, ABI of both legs were assessed as previously described.[4] Finally, participants undertook a graded walking test on a motorized treadmill commencing at 3.2 km/hr and incline of 0%. The incline increased by 2% every 2 minutes until voluntary exhaustion or a maximum time of 25 minutes, as previously described.[4] Participants were allowed to breathe spontaneously at their own rate throughout all assessments, as HRV has been reported to be similar during normal resting breathing frequencies.[24] All HR and respiratory data were recorded using Chart (ADInstruments) at a sampling rate of 1 kHz and stored for later analysis.

Data analysis

Respiration. Throughout rest and exercise, expired air was analyzed every 15 s for oxygen consumption (VO_2), ventilation (V_E), respiratory rate (R_R), and tidal volume (T_V) via indirect calorimetry (Powerlab 8-M Metabolic System).[4]

HRV. A 5-minute electrocardiogram (ECG) recording during supine rest was reviewed with beats identified as either normal or ectopic using an automatic R wave threshold detector within Chart and then reviewed manually. Normal-to-normal RR intervals only (>94% of recording) were utilized for HRV analyses with ectopic beats replaced using linear interpolation of the previous and succeeding normal intervals. All RR intervals were exported and analyzed using customized software (Kubios HRV v2.0 software, Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland).[25] The RR interval series was interpolated at 4 Hz and detrended using a smoothness priors regularization procedure[26] prior to the calculation of the following default time-domain and geometrical parameters: HR; standard deviation of all normal-normal RR intervals (SDNN); root mean square of successive differences in normal-normal RR intervals (RMSSD); percentage of successive normal-normal RR intervals different by more than 50 ms (pNN50); and HRV triangular index (area of RR interval histogram divided by the height of the histogram).[27] Frequency-domain components of HRV (low frequency, [LF] 0.04-0.15 Hz; high frequency, [HF] 0.15-0.4 Hz) were obtained via power spectral analysis of the data using an autoregressive model of 20 and expressed in absolute units (ms^2) and normalized units (nu), while the LF/HF ratio was calculated as a measure of sympathovagal balance.[27] Nonlinear HR dynamics were also examined, as these measures have been reported to be superior to conventional time- and frequency-domain HRV measures to document HR behavior.[28] The default nonlinear measures examined included the short (SD1, reflecting short-term instantaneous RR modulation) and long (SD2, long-term RR modulation) axes of the Poincare plot, Sample-entropy (SampEn), and short- (α_1) and long-term (α_2) fractal scaling exponents.[25] Fractal scaling components were conducted via detrended fluctuation analyses that calculated the slope of the relationship between the (log) integrated and detrended fluctuation and (log) window size. The $\alpha 1$ and $\alpha 2$ values were computed based on window sizes of four to 16 beats and 16 to 64 beats, respectively.[25] Heart rate complexity or randomness was determined via SampEn with input variables of m (length of compared runs at each time point of the time series) = 2 and r (tolerance for judging the similarity of runs) = 20%.[25] SampEn has been demonstrated to be independent of recording length and exhibit less bias compared with other measures such as approximate entropy.[29,30] Linear and nonlinear HRV measures have previously been reported to be reproducible during short-term recordings of supine rest.[31,32]

Table II. HRV and respiratory measures during supine rest for patients with intermittent claudication and healthy, aged-matched adults

	Intermittent claudication (n = 25)	*Healthy adults (n = 24)*
Time-domain HRV		
Heart rate (beats · min^{-1})	68.0 ± 10.1	63.2 ± 8.0
Standard deviation of RR (NN) intervals (ms)	25.6 ± 13.2	30.4 ± 16.1
Square root of the mean squared differences of successive RR intervals (ms)	27.4 ± 20.5	28.2 ± 21.6
Percentage of successive NN intervals >50 ms (%)	10.5 ± 18.4	8.2 ± 15.5
HRV triangular index	6.6 ± 2.9	7.8 ± 3.8
Frequency-domain HRV		
Low frequency (ms^2)	336 ± 336	466 ± 365
High frequency (ms^2)	337 ± 462	448 ± 895
Low frequency (nu)	57.0 ± 23.1	62.6 ± 20.0
High frequency (nu)	43.0 ± 23.1	37.4 ± 20.0
Low frequency/high frequency	2.08 ± 1.80	2.64 ± 2.33
Nonlinear HRV		
SD1 - short axis of Poincare plot (ms)	19.6 ± 14.6	20.2 ± 15.3
SD2 - long axis of Poincare plot (ms)	49.5 ± 20.8	52.4 ± 18.0
Sample entropy	1.39 ± 0.36	1.41 ± 0.28
α_1 (short-term fractal scaling exponent)	1.10 ± 0.31	1.15 ± 0.29
α_2 (long-term fractal scaling exponent)	1.02 ± 0.25	0.91 ± 0.30
Respiratory variables		
Tidal volume (L)	0.7 ± 0.5	0.8 ± 0.3
Respiratory rate (breaths · min^{-1})	15.2 ± 3.8	13.0 ± 3.1[a]
Ventilation (L · min^{-1})	8.8 ± 4.8	7.7 ± 1.9
Oxygen consumption (mL · kg^{-1} · min^{-1})	3.5 ± 1.8	3.5 ± 0.8

HRV, Heart rate variability; *nu*, normalized units.
Values are mean ± SD.
[a]$P \leq .05$ vs intermittent claudication.

Walking capacity. Distance to the onset of claudication pain (ICD), maximal walking distance (MWD), and peak aerobic capacity (VO_{2peak}) were recorded as previously described.[4]

Statistical analysis

Data were expressed as mean ± standard deviation and analyzed using the Statistical Package for the Social Sciences (SPSS v17; SPSS Inc, Chicago, Ill). Data normality was determined using the Kolmogorov-Smirnov statistic with a Lilliefors significance correction. To assess aim 1, differences between PAD patients and healthy adults were examined via independent *t* tests or Mann Whitney *U* tests, where appropriate. To assess aim 2, variables at baseline (0 months) and 12-month changes in variables were compared between groups via independent *t* tests or Mann Whitney *U* tests, where appropriate. Changes in variables were examined in absolute terms (outcome at 12 months compared with entry) or as a percentage (outcome at 12 months minus entry/entry value × 100) to account for any potential differences at baseline and the nature of the variable (ie, some variables were expressed either as a ratio or a percentage and therefore absolute differences were more appropriate). Relationships between HRV and ICD, MWD, and VO_{2peak} were determined via Spearman rank (ρ) correlation coefficients. A $P < .05$ was set as the level of significance for all analyses.

RESULTS

Comparison between patients with intermittent claudication and healthy adults. Compared with healthy adults, PAD patients exhibited a larger waist and hip girth; a larger waist:hip ratio; a greater frequency of current and former smoking; a greater frequency of diabetes mellitus; a greater history of prior myocardial infarction; a greater use of antiplatelet medication; and lower ABI, MWD, and VO_{2peak} (Table I). All other descriptive characteristics were similar between IC patients and healthy adults (Table I).

During supine rest, PAD patients and healthy adults exhibited similar time-domain, frequency-domain, and nonlinear measures of HRV (Table II), while PAD patients breathed at a greater rate compared with healthy adults (Table II).

Effect of supervised exercise on HRV. HRV recordings were not available for all IC patients at the 12-month follow-up examination, as eight patients withdrew from the study. The characteristics of patients with complete HRV analyses are shown in Table III. The characteristics of these IC patients were similar to the original group of recruited IC patients ($P > .31$).

At study entry, Conservative and Exercise patients exhibited similar time-domain and nonlinear measures of HRV, while lower LF (ms^2), and a trend toward lower LF (nu) and LF/HF, and greater HF (nu), were evident for Exercise patients compared with Conservative patients (Ta-

Table III. Characteristics of patients with intermittent claudication randomized to either 12 months of conservative medical treatment (Conservative) or medical treatment with regular supervised walking (Exercise)

	Conservative (n = 9)	*Exercise (n = 8)*
Age (years)	65.0 ± 8.7	68.3 ± 6.1
Height (cm)	164.9 ± 9.5	165.8 ± 9.3
Mass (kg)	73.6 ± 21.0	81.6 ± 13.9
Body fat (%)	30.8 ± 7.8	33.7 ± 8.3
Male	5 (56)	4 (50)
Waist girth (cm)	91.8 ± 16.9	96.2 ± 10.6
Hip girth (cm)	99.9 ± 12.2	109.3 ± 9.2
Waist: hip ratio	0.91 ± 0.10	0.88 ± 0.09
Ankle-brachial index – worst	0.55 ± 0.12	0.62 ± 0.17
Ankle-brachial index – best	0.79 ± 0.28	0.87 ± 0.22
Current smoker	2 (22)	1 (13)
Former smoker	6 (67)	6 (75)
Diabetes	2 (22)	1 (13)
Hypertension	4 (44)	1 (13)
Myocardial infarction	2 (22)	1 (13)
Beta-blocker	4 (44)	1 (13)
Angiotensin-converting enzyme inhibitor	4 (44)	1 (13)
Statin	2 (22)	3 (38)
Antiplatelet	3 (33)	4 (50)
Intermittent claudication distance (m)	107 ± 93	116 ± 58
Maximal walking distance (m)	244 ± 172	296 ± 150
Peak aerobic capacity ($mL \cdot kg^{-1} \cdot min^{-1}$)	20.0 ± 5.7	19.2 ± 7.6

Values are mean ± SD or number (%).

ble IV). At the 12-month follow-up assessment, Exercise patients had a smaller increase of body fat percentage compared with the Conservative group (1.2 ± 4.1 vs 2.5 ± 2.3; $P = .06$). The Exercise group had a greater increase in MWD compared with Conservative (183% ± 185% vs 57% ± 135%; $P = .03$) at follow-up. The change in resting ABI over 12 months was similar for the Exercise and Conservative patients (ABI-worst: -2.6% ± 37.5% vs -4.6% ± 36.5%; ABI-best: -5.6% ± 16.7% vs -2.1% ± 27.6%; $P > .76$). All time- and frequency-domain HRV measures changed similarly for Exercise and Conservative patients (Table V). However, the Exercise group had a greater increase in SD2 compared with the Conservative group (Table V). No significant relationships were exhibited between changes in HRV and changes in ICD, MWD, and VO_{2peak} between entry and 12 months.

DISCUSSION

The new findings from the current study are two-fold. First, IC patients exhibited comparable HRV to healthy age-matched adults during supine rest. Second, 12 months of supervised treadmill did not influence HRV in IC patients despite significant improvements in walking capacity. These findings suggest that changes in autonomic cardiac control are not responsible for the improved walking capacity stimulated by supervised exercise in IC patients.

Influence of PAD on HRV. The current findings confirm that PAD has minimal impact on supine HRV and cardiac autonomic control. This was an interesting finding given that IC patients also exhibited a prior incidence of other cardiovascular/metabolic conditions and risk factors reported to reduce HRV.[11,33] The IC patients for the current study were suitable for supervised exercise and thus were unlikely to have marked cardiac dysfunction. It is possible that significant cardiac dysfunction may be necessary for measurable reductions in HRV and autonomic control.[15] The reported greater HRV for PAD patients compared with patients with known cardiac disease[22] indicates further that HRV is reduced by significant coronary artery disease only. Whether the similar HRV denotes that IC patients have better prognosis in terms of the risk of subsequent cardiac events remains to be clarified.

Influence of a 12-month supervised walking program on HRV. Regular exercise has been promoted as a key component for the treatment of PAD[21] with significant improvements in walking capacity and quality of life reported following regular exercise for PAD patients.[3-6,34] The mechanisms for these improvements are still unknown, with improved HRV a possibility. Significant improvements in HRV have been noted following 8 to 26 weeks of regular exercise in healthy young adults,[18] older adults,[10] dogs susceptible to cardiac arrhythmias,[14] and patients with cardiovascular disease,[11] but not in PAD patients.[16] The current, long-term study demonstrated that changes in most HRV measures were statistically similar for patients undertaking either conservative or exercise treatments despite a significantly greater improvement in MWD for those undertaking regular exercise. Although statistically similar, the HRV changes were chiefly positive for Exercise and predominantly negative for Conservative patients, suggesting a tendency for improved cardiac autonomic control for Exercise patients. Further, Exercise patients exhibited an increased SD2 compared with Conservative patients, reflecting reduced long-term sympathetic modulation[35] following the supervised exercise program. However, the lack of significant and consistent HRV improvements with regular supervised exercise fails to support HRV enhancement as a contributing mechanism to greater walking capacity. Further, minimal changes in resting ABI following regular exercise for the current and other studies[36] fail to support improved lower limb blood flow as a significant contributor to improvement in walking capacity. It is likely that other mechanisms are responsible for improved walking capacity.

The intensity of walking that can be undertaken by patients may limit the ability of exercise to alter HRV in PAD patients.[16] Previously, we reported that HRV changes were training-intensity dependent for healthy young adults.[18] Subsequently, Exercise patients in the current study undertook exercise at a level of maximal claudication pain and presumably above their anaerobic threshold.[37] Walking was completed at an average intensity of 95% to 100% peak HR per session for the entire 12 months, with this intensity failing to improve HRV. Supervised exercise was undertaken over a long duration as is recommended for

Table IV. HRV measures for patients with intermittent claudication prior to 12 months of conservative medical treatment (Conservative) or medical treatment with regular supervised walking (Exercise)

	Conservative (n = 9)	*Exercise (n = 8)*
Time-domain HRV		
Heart rate (beats · min^{-1})	65.8 ± 10.1	70.1 ± 10.6
Standard deviation of RR (NN) intervals (ms)	29.5 ± 15.2	21.7 ± 10.4
Square root of the mean squared differences of successive RR intervals (ms)	30.8 ± 22.4	25.9 ± 19.2
Percentage of successive NN intervals >50 ms (%)	13.0 ± 18.9	9.5 ± 21.1
HRV triangular index (ms)	7.5 ± 3.2	5.9 ± 2.1
Frequency-domain HRV		
Low frequency (ms^2)	470 ± 393	170 ± 196[a]
High frequency (ms^2)	430 ± 549	245 ± 242
Low frequency (nu)	61.3 ± 17.3	42.4 ± 22.8
High frequency (nu)	38.7 ± 17.3	57.6 ± 22.8
Low frequency/high frequency	2.35 ± 2.34	1.03 ± 0.86
Nonlinear HRV		
SD1 - short axis of Poincare plot (ms)	22.0 ± 16.0	18.5 ± 13.7
SD2 - long axis of Poincare plot (ms)	55.7 ± 21.3	48.0 ± 25.8
Sample entropy	1.44 ± 0.22	1.39 ± 0.41
α_1 (short-term fractal scaling exponent)	1.15 ± 0.25	0.92 ± 0.27
α_2 (long-term fractal scaling exponent)	1.06 ± 0.08	1.12 ± 0.26

HRV, Heart rate variability; *nu*, normalized units.
Values are mean ± SD.
[a]$P < .05$ vs Conservative.

Table V. Change in HRV measures for patients with intermittent claudication during 12 months of conservative medical treatment (Conservative) or medical treatment with regular supervised walking (Exercise)

	Conservative (n = 9)	*Exercise (n = 8)*
Time-domain HRV		
Heart rate (%)	1.2 ± 11.3	−8.1 ± 14.8
Standard deviation of RR (NN) intervals (%)	−16.0 ± 23.2	3.0 ± 28.8
Square root of the mean squared differences of successive RR intervals (%)	−9.1 ± 31.5	4.3 ± 31.6
Percentage of successive NN intervals >50 ms (abs)	2.2 ± 11.3	−2.8 ± 8.7
HRV triangular index (%)	−7.1 ± 27.2	4.3 ± 15.7
Frequency-domain HRV		
Low frequency (ms^2, %)	−32.6 ± 45.2	34.2 ± 103.7
High frequency (ms^2, %)	−1.7 ± 61.5	2.6 ± 42.8
Low frequency (nu, abs)	−6.8 ± 15.4	1.8 ± 11.4
High frequency (nu, abs)	−6.8 ± 15.4	1.8 ± 11.4
Low frequency/high frequency (abs)	0.70 ± 2.74	0.30 ± 1.05
Nonlinear HRV		
SD1 - short axis of Poincare plot (%)	−9.4 ± 31.1	4.5 ± 31.3
SD2 - long axis of Poincare plot (%)	−20.2 ± 23.2	7.9 ± 31.1[a]
Sample entropy (abs)	0.14 ± 0.19	0.01 ± 0.43
α_1 (Short-term fractal scaling exponent) (abs)	−0.06 ± 0.34	0.07 ± 0.17
α_2 (Long-term fractal scaling exponent) (abs)	−0.05 ± 0.22	0.00 ± 0.29

abs, Absolute; *HRV,* heart rate variability; *nu*, normalized units.
Values are mean ± SD.
[a]$P < .05$ vs Conservative.

PAD patients.[17] Despite undertaking supervised walking at a greater intensity and duration than previously reported,[16,17] HRV change was similar for both the Exercise and Conservative groups. These findings imply that it is unlikely that any treadmill-walking regimen that can be undertaken by most IC patients will alter HRV.

In the current study, walking resulted in minimal HRV benefits for IC patients. Whether other modes of exercise, such as upper limb exercise, may be more effective in stimulating central cardiac changes is unknown. To date, walking has been the most examined and recommended mode for PAD patients due to its functionality and applicability to enhancement of quality of life.[17,21] However, other modes may be more beneficial for HRV improvements for PAD patients. For example, 12 to 24 weeks of upper body ergometry or strength training improved MWD similar to that of treadmill walking,[38,39] while 6 weeks of combined walking, cycling, and circuit/resistance exercise improved MWD and VO_{2peak} to a greater extent than walking or upper body resistance training alone.[40]

These results indicate that walking capacity can be improved with alternative exercise modes that may be less painful,[39] with the impact of these modes on central cardiac improvements such as HRV still to be clarified. Further studies are needed to assess whether other modes of exercise can improve cardiac autonomic control and cardiovascular function in PAD patients. The impact of these exercise regimens on long-term mortality for PAD patients is required, as the current results indicate that currently recommended walking regimens do not significantly enhance HRV that may lower the risk of future cardiac events.

Limitations. The main limitation of the current study was the small sample size, particularly the number of patients followed up to 12 months. While studies with greater patient numbers may provide further evidence for the impact of PAD on HRV, comparable results between the current and prior studies[16,22] involving larger patient numbers (n = 13-27 per group) provide support for the limited influence of PAD on HRV.

In conclusion, the current study demonstrated that PAD and healthy aged adults exhibited similar HRV measures during supine rest, and that 12 months of intense supervised walking failed to improve HRV measures for IC patients. It seems unlikely that cardiac autonomic changes play any important role in the beneficial effect of supervised exercise on walking capacity in patients with IC.

The authors would like to thank Fiona Young for her technical assistance with the HRV analyses, and Dr Kunwarjit Sangla, Associate Professor Frank Quigley, and Associate Professor Warwick Spinks for their assistance with the study.

AUTHOR CONTRIBUTIONS

Conception and design: AL, JG
Analysis and interpretation: AL, RC, JG
Data collection: AL, RC
Writing the article: AL, JG
Critical revision of the article: AL, RC, JG
Final approval of the article: AL, RC, JG
Statistical analysis: AL
Obtained funding: AL, JG
Overall responsibility: AL

REFERENCES

1. Lakshmanan R, Hyde Z, Jamrozik K, Hankey GJ, Norman PE. Population-based observational study of claudication in older men: the Health in Men Study. Med J Aust 2010;192:641-5.
2. Izquierdo-Porrera AM, Gardner AW, Bradham DD, Montgomery PS, Sorkin JD, Powell CC, et al. Relationship between objective measures of peripheral arterial disease severity to self-reported quality of life in older adults with intermittent claudication. J Vasc Surg 2005;41:625-30.
3. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. JAMA 2009;301:165-74.
4. Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J, et al. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. J Vasc Surg 2008;47:303-9.
5. Gardner AW, Montgomery PS, Flinn WR, Katzel LI. The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. J Vasc Surg 2005;42:702-9.
6. Milani RV, Lavie CJ. The role of exercise training in peripheral arterial disease. Vasc Med 2007;12:351-8.
7. Figoni SF, Kunkel CF, Scremin AM, Asher A, Banks NL, Rivera A, et al. Effects of exercise training on calf tissue oxygenation in men with intermittent claudication. PM R 2009;1:932-40.
8. Hiatt WR, Regensteiner JG, Wolfel EE, Carry MR, Brass EP. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. J Appl Physiol 1996;81:780-8.
9. Helgerud J, Wang E, Mosti MP, Wiggen ØN, Hoff J. Plantar flexion training primes peripheral arterial disease patients for improvements in cardiac function. Eur J Appl Physiol 2009;106:207-15.
10. Schuit AJ, van Amelsvoort LG, Verheij TC, Rijneke RD, Maan AC, Swenne CA, et al. Exercise training and heart rate variability in older people. Med Sci Sports Exerc 1999;31:816-21.
11. Lucini D, Milani RV, Costantino G, Lavie CJ, Porta A, Pagani M, et al. Effects of cardiac rehabilitation and exercise training on autonomic regulation in patients with coronary artery disease. Am Heart J 2002;143:977-83.
12. Tsuji H, Larson MG, Venditti FJ, Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94:2850-5.
13. Billman GE. Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention. J Appl Physiol 2002;92:446-54.
14. Billman GE, Kukielka M. Effect of endurance exercise training on heart rate onset and heart rate recovery responses to submaximal exercise in animals susceptible to ventricular fibrillation. J Appl Physiol 2007;102:231-40.
15. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-62.
16. Sandercock GRH, Hodges LD, Das SK, Brodie DA. The impact of short term supervised and home-based walking programmes on heart rate variability in patients with peripheral arterial disease. J Sports Sci Med 2007;6:471-6.
17. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. Sports Med 2004;34:983-1003.
18. Leicht AS, Allen GD, Hoey AJ. Influence of intensive cycling training on heart rate variability during rest and exercise. Can J Appl Physiol 2003;28:898-909.
19. Huikuri HV, Niemelä MJ, Ojala S, Rantala A, Ikäheimo MJ, Airaksinen KE, et al. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. Circulation 1994;90:121-6.
20. Stein PK, Barzilay JI, Chaves PH, Mistretta SQ, Domitrovich PP, Gottdiener JS, et al. Novel measures of heart rate variability predict cardiovascular mortality in older adults independent of traditional cardiovascular risk factors: the Cardiovascular Health Study (CHS). J Cardiovasc Electrophysiol 2008;19:1169-74.
21. Stoyioglou A, Jaff MR. Medical treatment of peripheral arterial disease: a comprehensive review. J Vasc Interv Radiol 2004;15:1197-207.
22. Goernig M, Schroeder R, Roth T, Truebner S, Palutke I, Figulla HR, et al. Peripheral arterial disease alters heart rate variability in cardiovascular patients. Pacing Clin Electrophysiol 2008;31:858-62.
23. Norton K, Whittingham N, Carter L, Kerr D, Gore C, Marfell-Jones M. Measurement Techniques in Anthropometry, In: Norton K, Olds T (eds). Anthropometrica. Sydney: UNSW Press; 2000, p. 27-75.
24. Bloomfield DM, Magnano A, Bigger JT Jr, Rivadeneira H, Parides M, Steinman RC. Comparison of spontaneous vs. metronome-guided breathing on assessment of vagal modulation using RR variability. Am J Physiol 2001;280:H1145-50.
25. Tarvainen MP, Niskanen JP, Kubios HRV. Version 2.0 User's guide. Kuopio; Finland; Biosignal Analysis and Medical Imaging Group (BSAMIG) University of Kuopio; 2008.
26. Tarvainen MP, Ranta-aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. IEEE Trans Biomed Eng 2002;49:172-5.

27. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-65.
28. Tulppo MP, Hughson RL, Mäkikallio TH, Airaksinen KE, Seppänen T, Huikuri HV, et al. Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. Am J Physiol Heart Circ Physiol 2001;280:H1081-7.
29. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000;278:H2039-H49.
30. Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. Am J Physiol Regul Integr Comp Physiol 2002;283:R789-97.
31. Maestri R, Pinna GD, Porta A, Balocchi R, Sassi R, Signorini MG, et al. Assessing nonlinear properties of heart rate variability from short-term recordings: are these measurements reliable? Physiol Meas 2007;28: 1067-77.
32. Kowalewski MA, Urban M. Short- and long-term reproducibility of autonomic measures in supine and standing positions. Clin Sci (Lond) 2004;106:61-6.
33. Bonaduce D, Petretta M, Marciano F, Vicario ML, Apicella C, Rao MA, et al. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. Am Heart J 1999;138: 273-84.
34. Imfeld S, Singer L, Degischer S, Aschwanden M, Thalhammer C, Labs KH, Jaeger KA. Quality of life improvement after hospital-based rehabilitation or home-based physical training in intermittent claudication. VASA 2006;35:178-84.
35. De Vito G, Galloway SD, Nimmo MA, Maas P, McMurray JJ. Effects of central sympathetic inhibition on heart rate variability during steady-state exercise in healthy humans. Clin Physiol Funct Img 2002;22:32-8.
36. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on haemodynamics in intermittent claudication: a systematic review of randomized controlled trials. Sports Med 2010;40:433-47.
37. Ritti-Dias RM, de Moraes-Forjaz CL, Cucato GG, Costa LA, Wolosker N, de Fatima N, et al. Pain threshold is achieved at intensity above anaerobic threshold in patients with intermittent claudication. J Cardiopulm Rehabil Prev 2009;29:396-401.
38. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. Vasc Med 2009;14:203-13.
39. Ritti-Dias RM, Wolosker N, de Moraes Forjaz CL, Carvalho CR, Cucato GG, Leão PP, et al. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. J Vasc Surg 2010;51:89-95.
40. Parr BM, Noakes TD, Derman EW. Peripheral arterial disease and intermittent claudication: efficacy of short-term upper body strength training, dynamic exercise training, and advice to exercise at home. S Afr Med J 2009;99:800-4.

Submitted Apr 7, 2011; accepted May 14, 2011.