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Therapeutic potential of cycling high-intensity interval training in patients with peripheral artery disease: A pilot study

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ARTICLE INFO

Intermittent claudication severely limits both exercise performance and walking ability in patients with lower-extremity peripheral artery disease (PAD). The ESC has declared that the evidence supporting exercise therapy for the treatment of claudication is sufficiently robust to merit a Level I recommendation [1]. The walking outcomes of treadmill exercise have so far been found to be superior to the outcomes of several other lower extremity exercises, namely, cycling, stair climbing, and static and dynamic leg exercises [2]. It remains unclear, however, whether the current protocol of treadmill exercise sufficiently improves oxygen uptake (VO_2) and other measures of cardiorespiratory fitness (CRF) in PAD patients [3]. Better CRF leads to better survival outcome in patients with cardiovascular disease [4]. The treatment goals of exercise therapy in PAD should therefore extend beyond ameliorated limb symptoms and walking distance to improved CRF and exercise tolerance, and ultimately to a reduced incidence of cardiovascular events.

High-intensity interval training (HIIT) is established to be superior to moderate-intensity continuous training (MICT) in improving CRF in both athletes and the general population. A meta-analysis has also confirmed the efficacy and safety of HIIT relative to continuous training in patients with cardiometabolic diseases [5], whereas no previous reports have assessed HIIT as an exercise therapy for PAD. We therefore performed a pilot study to investigate the degree to which HIIT with a bicycle ergometer improved the parameters of cardiopulmonary exercise testing (CPET) in PAD patients participating in a cardiovascular rehabilitation (CR) program. The institutional review board of our hospital approved the protocol. The investigation conformed to the principles of the Declaration of Helsinki.

Six patients with bilateral lower-extremity PAD were introduced to a HIIT protocol on a bicycle ergometer in the outpatient CR program at Showa University Fujigaoka Rehabilitation Hospital between May and November 2015. A symptom-limited CPET was performed before and after the CR program as previously described [6]. We decided to evaluate the peak work rate and cycling exercise time as surrogate parameters of walking ability, as previous reports have shown significant correlations between the peak work rate and 6-minute walking distance [7] and between the training-induced changes in maximal cycle and treadmill times [3]. The changes in CPX parameters were assessed as endpoints, and the non-parametric Wilcoxon signed-rank test was used for the statistical analysis. All data were expressed as the median (range) unless indicated otherwise.

All of the patients had been diagnosed with PAD based on findings of atherosclerosis obliterans and Fontaine class-II. The patient characteristics are shown in Table 1. All of the patients had multiple vascular risk factors and were receiving medications for the same. The blood metabolic profile of the population was as follows: BS, 111 (89–139) mg/dl; HbA1C, 6.9 (6.0–8.6) %; LDL-cholesterol, 122.5 (72–151) mg/dl; HDL-cholesterol, 47.0 (31.0–63.0) mg/dl; triglyceride, 189.5 (97.0–348) mg/dl. Coronary artery disease was a comorbidity in half of the patients, whereas none of the patients had history of heart failure. Ejection fraction documented by echocardiography was normal range in all the PAD patients.

Every patient exhibited an ankle-brachial index of <0.9 in both ankles. Ultrasound examinations revealed either obstructive arterial lesions or stenotic (>50% stenosis), with multiple atherosclerotic lesions detected throughout the arteries of the lower extremities. All the patients were treated with anti-platelet agents including cilostazol. Although one patient had history of the femoral to popliteal artery bypass surgery, the graft was occluded several years before participation in the CR program.

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Table 1
Baseline characteristics.

Patient characteristics										Lower limb lesion							
	Gender	Age, yr	DM	HT	DLP	Smoking	CKD	CAD	COPD	ABI rt	ABI lt	CIA	SFA	BK	CLZ	The other anti-PLT drugs	History of RVT
Case 1	Male	66	+	+	+	+				0.53	0.65	+	+	+		PG	
Case 2	Male	75	+	+	+			+		0.47	0.69	+		+	+	AS	
Case 3	Female	70	+	+				+		0.85	0.63		+	+		AS, TP	
Case 4	Male	63	+	+	+	+	+	+		0.46	0.88		+	+	+	TP	
Case 5	Male	79		+	+	+	+			0.78	0.6		+	+	+	TP	+
Case 6	Female	67		+		+			+	0.86	0.66	+	+	+	+		
	Male 4 (67%)	68.5[a]	4 (67%)	6 (100%)	4 (67%)	4 (67%)	2 (33%)	3 (50%)	1 (17%)	0.66[a]	0.66[a]	3 (50%)	5 (83%)	6 (100%)	4 (67%)	NA	1 (17%)

DM, diabetes mellitus. HT, hypertension. DLP, dyslipidemia. CKD, chronic kidney disease. CAD, coronary artery disease. COPD, chronic obstructive pulmonary disease. ABI, ankle-brachial index. IA, iliac artery. SFA, superficial femoral artery. BK, below knee arteries. CLZ, cilostazol. PLT, platelet. PG, oral prostaglandin E1 derivative. AS, aspirin. TP, thienopyridine. RVT, revascularization therapy.

[a] Age and ABI were expressed as medians.

The outpatient CR program consisted of exercise training in supervised sessions 1 to 2 times a week for 5 months and daily home exercise consisting of brisk walking at a prescribed heart rate. In the first 2 to 4 weeks of the program, exercise training on the cycle ergometer was performed at a workload intensity around the anaerobic threshold (AT) obtained in a symptom-limited CPET performed at the beginning of the program. The HIIT protocol was then performed on a bicycle ergometer at a workload corresponding to >70% of the peak VO_2. An exercise session consisted of a warm-up period, a cool-down period, and four 4-minute intervals of high intensity cycling. Each interval was separated by a 3-minute active pause consisting of cycling at 15 or 20 watts. The levels of exercise intensity were gradually increased when the patients tolerated it, with constant monitoring of the heart rate and the rate of perceived exertion. The final workload in the high-intensity interval was 86 (71–95) % of the peak VO_2.

The PAD patients exhibited impaired exercise tolerance in the CPET analysis at the beginning of the CR program (Table 2). After completion of the 5-month CR program with cycling HIIT, the patients' self-reported walking distance and daily activity improved. In CPET analysis, the AT ($p = 0.09$) and peak VO_2 ($p < 0.05$) both at follow-up increased compared with those at baseline, though the ventilatory efficiency was not significantly improved. In previous our observation, there were no differences in the peak VO_2 levels between at the pre- and post-CR program with the use of cycling MICT (below the AT levels) in other patients with bilateral PAD ($n = 6$, 14.0 to 14.3 ml/min/kg) although it was not adequate to compare those patients with the subjects in the present study because of differences in the backgrounds. The present HIIT protocol also significantly improved the peak work rate and cycling exercise time ($p < 0.05$, respectively). Thus, the cycling HIIT is likely to improve both the CRF and walking ability even in the bilateral PAD.

A meta-analysis from a previous report [5] has demonstrated that HIIT is more beneficial to the CRF and other physiological parameters than MICT in patients with lifestyle-induced cardiometabolic disease. Previous studies also identified significant increases in PGC-1α, indicating improved mitochondrial biogenesis in the skeletal muscle of the subjects who underwent HIIT [5]. The effect of HIIT on exercise capacity was also mediated by improved microvascular oxygen delivery-to-utilization matching in skeletal muscle [8]. With exercise, stenotic/occlusive lesions in the arterial supply of the leg muscles of PAD patients with claudication limit the increase in blood flow, causing a mismatch between the oxygen supply and metabolic demand of the muscle [9]. Acquired metabolic abnormalities of the muscles of the lower extremity contribute to the reduced exercise performance and capacity [9,10]. One report has also shown evidence of an ischemia-related myopathy in calf skeletal muscle consisting of calf muscle atrophy associated with mitochondrial dysfunction [10]. Taking these findings in sum, HIIT appears to be a suitable and useful exercise mode for patients with PAD.

Results of the present study indicate that the incorporation of HIIT on a bicycle ergometer into a cardiovascular rehabilitation program enables patients with PAD to more readily reach a level of exercise that enhances CRF and walking ability. Cycling exercise also seems to be safer, as it supplants exercise performed on a treadmill, an apparatus from which elderly PAD patients are prone to fall. Cycling HIIT, thus, may be an effective alternative to treadmill exercise in exercise therapy for patients with PAD. However, a larger randomized-controlled trial will be necessary to confirm our observation.

Conflict of interest

None declared.

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Table 2
Changes of CPX parameters.

CPX parameters	Baseline	Follow-up	P
RMR (ml/min/kg)	3.3 (2.9–4.1)	3.5 (3.0–4.2)	0.63
AT (ml/min/kg)	9.7 (7.8–12.7)	10.4 (8.4–13.8)	0.09
Peak VO_2 (ml/min/kg)	12.6 (11.3–15.8)	14.5 (11.7–16.6)	0.03
VE/VCO_2 slope	36.0 (34.7–38.6)	36.3 (29.2–42.8)	1
Peak WR (watt)	58 (54–83)	69.5 (62–88)	0.03
Cycling time (*sec*)	329 (276–483)	404 (303–513)	0.03

RMR, resting metabolic rate. AT, anaerobic threshold. WR, work rate.
All data were expressed as medians (range). The non-parametric Wilcoxon signed-rank test was used to assess the changes in CPX parameters between the pre- and post-CR program. P values of <0.05 were considered significant.

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