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Resting energy expenditure in subjects with and without intermittent claudication

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Abstract

Subjects with peripheral arterial disease and intermittent claudication have ischemia of the lower extremities, but little is known how this influences resting energy expenditure. The objective of the study was to compare the resting energy expenditure of subjects with and without intermittent claudication. One hundred six subjects limited by intermittent claudication and 77 controls who did not have peripheral arterial disease and intermittent claudication participated in this study. Subjects were assessed on resting energy expenditure, body composition, ankle/brachial index (ABI), and calf blood flow. Subjects with intermittent claudication had a lower resting energy expenditure (1585 ± 251 vs 1716 ± 277 kcal/d, P = .019), higher body fat percentage (33.4% ± 10.7% vs 29.6% ± 7.7%, P = .016), higher fat mass (29.6 ± 10.6 vs 24.2 ± 8.9 kg, P = .011), and lower ABI (0.66 ± 0.20 vs 1.19 ± 0.12, P < .001). Resting energy expenditure was predicted by fat-free mass (P < .001), ABI (P = .027), and calf blood flow (P = .040). Resting energy expenditure remained lower in the subjects with intermittent claudication after adjusting for clinical characteristics plus fat-free mass (1611 ± 171 vs 1685 ± 209 kcal/d, P = .035), but was no longer different between groups after further adjustment for ABI and calf blood flow (1622 ± 165 vs 1633 ± 185 kcal/d, P = .500). Subjects with intermittent claudication have lower resting energy expenditure than controls, which is partially explained by ABI and calf blood flow.

1. Introduction

Intermittent claudication is a symptom of peripheral arterial disease (PAD) and is associated with elevated rates of mortality [1-4] and morbidity [5]. Intermittent claudication afflicts 5% of the US population older than 55 years [6] and occurs during ambulation when the peripheral circulation is inadequate to meet the metabolic requirement of the active leg musculature. Consequently, patients with intermittent claudication have ambulatory dysfunction [7,8], thereby limiting daily physical activities [9] and negatively affecting health-related quality of life [10].

The ambulatory dysfunction and lower physical activity level of patients with intermittent claudication place them at greater risk for disuse atrophy of the lower extremity musculature [11] than is typically observed with normal aging [12]. Because fat-free mass is the largest contributor to resting energy expenditure [13], patients with intermittent claudication may have relatively low whole-body resting energy expenditure because of ischemia of the lower extremity musculature and consequent muscle denervation and atrophy [14], leading to an energy imbalance favoring fat accumulation. This energy imbalance increases the risk of developing metabolic syndrome, obesity, and abdominal obesity, all of which negatively impact intermittent claudication, physical function, health-related quality of life, and peripheral circulation [15,16]. Subjects with PAD have either lower [17] or similar [18] oxygen uptake of the more affected calf musculature at rest than controls and a slower hemoglobin oxygen saturation kinetics at the onset of exercise, indicative of impaired ability to use oxygen [19,20]. However, whole-body resting energy expenditure of subjects with intermittent claudication has not been examined.

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The primary purpose of this study was to compare the resting energy expenditure of subjects with and without intermittent claudication. We hypothesized that the resting energy expenditure is lower in subjects with intermittent claudication, primarily because of ischemia of the lower extremity musculature.

2. Methods

2.1. Subjects

2.1.1. Recruitment

Subjects participated in this study in the Geriatrics, Research, Education, and Clinical Center at the Maryland Veterans Affairs Health Care System (MVAHCS) at Baltimore. Subjects were recruited from the Vascular Clinic at the site of the Baltimore MVAHCS, as well as by newspaper advertisements for a free evaluation of peripheral vascular function and physical function. The procedures used in this study were approved by the Institutional Review Boards at the University of Maryland and the MVAHCS at Baltimore. Written informed consent was obtained from each subject before investigation.

2.1.2. Screening of the intermittent claudication group

Subjects were included in this study if they had *Fontaine stage II PAD* [21] defined by the following inclusion criteria: (*a*) a history of intermittent claudication, (*b*) an ankle/brachial index (ABI) less than or equal to 0.90 [22], and (*c*) *nonsmoking status* defined as not having smoked over the preceding year and confirmed by having the patients breathe into a 2000 Series Ecolyzer carbon monoxide analyzer (National Draeger, Pittsburgh, PA) to assess the concentration of carbon monoxide in the expired air. Subjects were excluded from this study for the following conditions: (*a*) absence of PAD (ABI > 0.90) [22]; (*b*) inability to obtain an ABI measure due to noncompressible vessels; (*c*) asymptomatic PAD; (*d*) current smoking; (*e*) use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline); (*f*) exercise tolerance limited by factors other than leg pain (eg, severe coronary artery disease, dyspnea, poorly controlled blood pressure); and (*g*) active cancer, renal disease, or liver disease. A total of 106 subjects with intermittent claudication were deemed eligible for this investigation, whereas 84 subjects were ineligible.

2.1.3. Screening of the control group

Control subjects were included in this study if they met the following criteria: (*a*) no history of intermittent claudication, (*b*) no other ambulatory leg pain, (*c*) an ABI greater than 0.90, and (*d*) current nonsmoking status. Controls were excluded from this study for the following conditions: (*a*) history of any type of leg pain; (*b*) an ABI less than or equal to 0.90; (*c*) inability to obtain an ABI measure due to noncompressible vessels; (*d*) poorly controlled hypertension (resting systolic blood pressure >200 mm Hg or resting diastolic blood pressure >120 mm Hg); (*e*) current smoking; (*f*) history of cardiovascular disease, myocardial infarction, or stroke; (*g*) history of dyspnea; (*h*) history of angina; and (*i*) active cancer, renal disease, or liver disease. A total of 77 control subjects were deemed eligible for this investigation, whereas 30 subjects were ineligible.

2.2. Measurements

2.2.1. Medical history

Demographic information, height, weight, cardiovascular risk factors, comorbid conditions, claudication history, and a list of current medications were obtained during a physical examination and medical history interview. Body mass index was calculated as weight in kilograms divided by height in square meters.

2.2.2. Resting energy expenditure

On a subsequent visit, subjects arrived at the laboratory and were tested between 7:00 and 9:00 AM after a 12-hour overnight fast. A Plexiglas ventilated hood was placed over the subjects' heads as they rested supine in a darkened, quiet room maintained at 24°C. Oxygen consumption and carbon dioxide production were determined over 45 minutes of supine rest with a computerized open-circuit indirect calorimeter (Deltatrac Sensormedics Metabolic Monitor model 125, Anaheim, CA) [23]. The first 15 minutes of the test habituated subjects to the instrumentation and testing procedures. During the final 30 minutes of the test, oxygen consumption and carbon dioxide production values were obtained and used to calculate resting energy expenditure [24].

2.2.3. Body composition

Percentage body fat was determined after a 12-hour overnight fast by a total body scan with dual-energy x-ray absorptiometry (model DPX-L; LUNAR Radiation, Madison, WI) in the supine position [11]. All scans were analyzed using the LUNAR Version 1.3 DPX-L extended analysis program for body composition [11].

2.2.4. Ankle/brachial index

After 10 minutes of supine rest, ankle systolic pressure was measured with a Parks Medical Electronics nondirectional Doppler flow detector (Model 810-A, Aloha, OR), a pencil probe (9.3 MHz), and standard-sized ankle blood pressure cuffs (10-cm width). Measurements were taken from the posterior tibial and dorsalis pedis arteries in both legs. The higher of the 2 arterial pressures from the more severely diseased leg was recorded as the ankle systolic pressure. Brachial blood pressures were measured from both arms with a Critikon Dinamap Vital Signs Monitor (Model 1846-SX, Tampa, FL), using either a standard adult–sized blood pressure cuff (14-cm width) or a large adult–sized cuff (17-cm width). Brachial systolic pressure and diastolic pressure were recorded from the arm yielding the higher systolic pressure. From these measures, ABI was calculated as ankle systolic pressure/brachial systolic pressure [25]. The test-retest intraclass reliability coefficient is R = 0.96 for ABI [7].

2.2.5. Calf blood flow

After the measurement of ABI, calf blood flow in the more severely diseased leg was obtained by venous occlusion strain gauge plethysmography. A mercury strain gauge was placed around the calf at the maximal circumference, and arterial blood flow to the foot was temporarily occluded by an ankle cuff inflated to 300 mm Hg. Calf blood flow was measured by inflating a thigh cuff to a venous occlusion pressure of 50 mm Hg. The ankle and thigh cuffs were deflated immediately after the calf blood flow measurement was obtained, and this measurement was repeated 5 times. The average of the 5 trials was calculated and used for calf blood flow [26]. The test-retest intraclass reliability coefficient is $R = 0.86$ for calf blood flow [26].

2.3. Statistical analyses

Unpaired *t* tests were used to compare differences between the subjects with and without intermittent claudication for parametric measures, and Mann-Whitney *U* tests were used to compare the groups for nonparametric measures. Stepwise multiple regression was performed to identify predictors of resting energy expenditure. Analysis of covariance was then used to assess group differences in resting energy expenditure after adjusting for baseline clinical characteristics and predictor variables. All analyses were performed using the SPSS-PC (Chicago, IL) statistical package. Statistical significance was set at *P* less than .05. Measurements are presented as means ± standard deviations.

3. Results

The clinical characteristics of the subjects with and without intermittent claudication are shown in Table 1. The subjects with intermittent claudication had higher values than the controls for body mass index (P = .021); prevalence of obesity (P = .014); waist circumference (P = .032); waist-hip ratio (P = .004); and prevalence of diabetes (P < .001), hypertension (P = .004), and dyslipidemia (P = .046). As shown in Table 2, subjects with intermittent claudication had lower values than the controls for resting energy expenditure (P = .019), ankle systolic blood pressure (P < .001), and ABI (P < .001), and higher values for body fat percentage (P = .016) and fat mass (P = .011).

The prediction of resting energy expenditure from body composition and peripheral hemodynamic measures in subjects with and without intermittent claudication is shown in Table 3. Variables entered the model in the following order: fat-free mass, ABI, and calf blood flow. The final model for the prediction of resting energy expenditure is shown in the following regression equation: resting energy expenditure (in kilocalories per day) = 87.6 + (25.2 × fat-free mass) + (125.1 × ABI) + (19.9 × calf blood flow); $R = 0.80$, $R^2 = 0.64$, standard error of estimate = 191 kcal/d, P less than .001.

The adjusted resting energy expenditure of subjects with and without intermittent claudication is displayed in Table 4. Resting energy expenditure remained lower in the subjects with intermittent claudication after adjusting for clinical characteristics (model 1, P = .024) and for clinical characteristics plus fat-free mass (model 2, P = .035). Resting energy expenditure was no longer different between the subjects with intermittent claudication and

Table 1
Clinical characteristics of subjects with intermittent claudication and controls

Variables	Control group (n = 77)	Intermittent claudication group (n = 106)	*P* value
Age (y)	64 (10)	67 (8)	.077
Weight (kg)	81.0 (15.5)	88.6 (13.3)	.011
Body mass index	28.3 (4.7)	29.6 (4.0)	.021
Waist girth (cm)	98.7 (9.4)	101.8 (11.1)	.032
Hip girth (cm)	108.5 (9.9)	106.1 (10.0)	.531
Waist-hip ratio	0.91 (0.08)	0.96 (0.07)	.004
Sex (% male)	82	87	.314
Race (% white)	62	54	.117
Diabetes (% yes)	10	33	<.001
Hypertension (% yes)	42	66	.004
Dyslipidemia (% yes)	43	56	.046
Abdominal obesity (% yes)	35	47	.021
Obesity (% yes)	29	42	.014

Values are means (SD) or percentages. *Abdominal obesity* was defined as having a waist girth greater than 88 cm in women and greater than 102 cm in men. *Obesity* was defined as having a body mass index greater than or equal to 30 kg/m^2.

Table 2
Resting energy expenditure, body composition, and peripheral hemodynamic measures of subjects with intermittent claudication and controls

Variables	Control group (n = 77)	Intermittent claudication group (n = 106)	*P* value
Resting energy expenditure (kcal/d)	1716 (277)	1585 (251)	.019
Respiratory exchange ratio	0.83 (0.05)	0.82 (0.05)	.778
Body fat (%)	29.6 (7.7)	33.4 (10.7)	.016
Fat mass (kg)	24.2 (8.9)	29.6 (10.6)	.011
Fat-free mass (kg)	53.8 (9.9)	56.1 (11.3)	.130
Ankle systolic blood pressure (mm Hg)	155 (23)	91 (30)	<.001
ABI	1.19 (0.12)	0.66 (0.20)	<.001
Calf blood flow (%/min)	3.49 (1.58)	3.41 (1.30)	.788

Values are means (SD).

Table 3
Prediction of resting energy expenditure from body composition and peripheral hemodynamic measures in subjects with intermittent claudication and controls

Step	Independent variable	Cumulative *R*
1	Fat-free mass	0.74
2	ABI	0.78
3	Calf blood flow	0.80

Table 4
Adjusted resting energy expenditure of subjects with intermittent claudication and controls

Variables	Control group (n = 77)	Intermittent claudication group (n = 106)	*P* value
Model 1: adjusted resting energy expenditure (kcal/d)	1707 (229)	1593 (210)	.024
Model 2: adjusted resting energy expenditure (kcal/d)	1685 (209)	1611 (171)	.035
Model 3: adjusted resting energy expenditure (kcal/d)	1633 (185)	1622 (165)	.500

Values are means (SD). Model 1: resting energy expenditure is adjusted for age, body mass index, waist-hip ratio, sex, race, current smoking, diabetes, hypertension, dyslipidemia, abdominal obesity, and obesity. Model 2: resting energy expenditure is adjusted for the variables in model 1 plus fat-free mass. Model 3: resting energy expenditure is adjusted for the variables in models 1 and 2 plus ABI and calf blood flow.

controls after further adjustment for ABI and calf blood flow (model 3, P = .500).

4. Discussion

The main findings of this investigation were that (*a*) resting energy expenditure was lower in subjects with intermittent claudication than in controls and remained lower after adjusting for baseline clinical measures and fat-free mass, (*b*) ABI and calf blood flow were predictors of resting energy expenditure, and (*c*) resting energy expenditure was no longer different between groups after further adjusting for ABI and calf blood flow.

This is the first investigation to examine the resting energy expenditure in subjects with PAD and intermittent claudication. Resting energy expenditure was 131 kcal/d lower in subjects with intermittent claudication than in controls and remained 74 kcal/d lower after adjusting for fat-free mass, possibly because of lower oxygen uptake of the lower extremities [17]. The metabolic impact of subjects with intermittent claudication having a lower adjusted resting energy expenditure of 74 kcal/d is further compounded by their 42% lower daily physical activity level of 259 kcal/d [9], thereby lowering their total daily energy expenditure by more than 330 kcal/d and increasing the risk of fat gain. Indeed, the subjects with intermittent claudication had a higher prevalence of obesity and abdominal obesity than the controls.

Fat-free mass was the primary predictor of resting energy expenditure, thus supporting previous work [13]. However, fat-free mass only partially explained the lower resting energy expenditure of the subjects with intermittent claudication, as their resting energy expenditure remained lower than the controls after adjustment for fat-free mass and clinical characteristics (model 2). This finding suggests that other factors in addition to fat-free mass are predictive of resting energy expenditure, supporting previous studies [27,28]. One possibility is that the muscle mass of the lower extremities is not as metabolically active in subjects with intermittent claudication. This is supported by previous work demonstrating a 50% reduction in oxygen uptake of the calf musculature in subjects with PAD measured by near-infrared spectroscopy [17]. Previous reports also have found that PAD is associated with impaired muscle oxygen utilization during the onset of exercise [19,20], as well as a higher percentage of angular fibers, indicative of muscle denervation [14,29]. These factors could contribute to lower resting energy expenditure after adjustment for fat-free mass.

The ABI was a predictor of resting energy expenditure, even after adjustment for fat-free mass, suggesting that resting energy expenditure decreases in more severe PAD. This finding supports previous work that resting energy expenditure is not entirely explained by fat-free mass and body composition [27,28]. The findings from the current investigation suggest that having impaired circulation to the lower extremities, as measured by ABI, is an additional factor related to resting energy expenditure after adjusting for fat-free mass. Interestingly, calf blood flow was a predictor of resting energy expenditure after adjustment for both fat-free mass and ABI. Although subjects with intermittent claudication had similar calf blood flow at rest as the controls, our data suggest that small difference in calf blood flow explains additional variance in resting energy expenditure. After adjusting for fat-free mass, ABI, and calf blood flow (model 3), the resting energy expenditure was similar between the subjects with intermittent claudication and controls; and no additional measurements were predictive of resting energy expenditure.

There are several limitations to this study. The cross-sectional design comparing subjects with and without intermittent claudication does not allow causality to be established, as it is possible that subjects with intermittent claudication had lower resting energy expenditure before the development of symptoms or that other comorbid conditions not evaluated in this study were related to their lower resting energy expenditure. The present findings are also limited to PAD subjects with intermittent claudication and may not be generalized to subjects with less severe and more severe symptoms. However, a relatively high proportion of subjects were African American; and the subjects with intermittent claudication had the typical high prevalence of risk factors for PAD, including diabetes, hypertension, dyslipidemia, and obesity. Thus, the findings of the present study are generalizable to most subjects with intermittent claudication who typically have numerous comorbid conditions.

In conclusion, subjects with intermittent claudication have lower resting energy expenditure than controls, which is partially explained by ABI and calf blood flow. The lower resting energy expenditure of subjects with intermittent claudication, combined with their lower daily physical activity [9], suggests that they may be at higher risk for long-term positive energy balance than control subjects. Future studies are needed to determine whether resting energy expenditure is modifiable through interventions that may increase peripheral circulation in subjects with intermittent claudication.

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