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ORIGINAL ARTICLE

# Prediction of $VO_{2max}$ with daily step counts for Japanese adult women

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**Abstract** The purpose of the study was to develop a new non-exercise $VO_{2max}$ prediction model using a physical activity (PA) variable determined by pedometer-determined step counts (SC, steps $day^{-1}$) in Japanese women aged 20–69 years old. Eighty-seven and 102 subjects were used to develop the prediction model, and to validate the new model, respectively. $VO_{2max}$ was measured using a maximal incremental test on a bicycle ergometer. SC was significantly related to $VO_{2max}$ (partial correlation coefficient $r = 0.40$, $P < 0.001$) after adjusting for BMI (kg $m^{-2}$) and age (years). When the new prediction equation developed by multiple regression to estimate $VO_{2max}$ from age, BMI, and SC ($R = 0.71$, SEE = 5.3 ml $kg^{-1}$ $min^{-1}$, $P < 0.001$) was applied to the Validation group, predicted $VO_{2max}$ correlated well with measured $VO_{2max}$ ($r = 0.81$, $P < 0.001$), suggesting that SC is a useful PA variable for non-exercise prediction of $VO_{2max}$ in Japanese women.

**Keywords** Cardiorespiratory fitness · Maximal oxygen uptake · Pedometer · Prediction model · Physical activity · Female

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## Introduction

Cardiorespiratory fitness is an objective reproducible measure that reflects the functional consequences of physical training (Tabata et al. 1996), recent physical activity (PA) habits, disease status, genetics and mortality from cardiovascular and other causes, including cancer in middle-aged and elderly men and women (Haskell et al. 1992; Wei et al. 1999; Evenson et al. 2003; Sui et al. 2007). The relationship between low cardiorespiratory fitness and cardiovascular mortality in particular is proposed to be mediated by the development of cardiovascular disease risk factors, such as hypertension, obesity, dyslipidemia, and glucose intolerance (Bertoli et al. 2003; Fang et al. 2005). In the Exercise and Physical Activity Reference for Health Promotion 2006 (Ministry of Health Labour and Welfare Japan 2007), established by the Ministry of Health Labour and Welfare Japan in 2006, maximal oxygen uptake ($VO_{2max}$) was considered to be the most significant element of physical fitness related to health promotion and the recommended reference value for $VO_{2max}$ to prevent lifestyle-related disease was reported. Therefore, it would be important to assess cardiorespiratory fitness in a general population for the purpose of: (1) educating participants about their current health-related fitness status, (2) providing data that are helpful in developing safe and effective exercise programs, (3) collecting baseline and follow-up data that allow evaluation of the participants' progress, (4) motivating participants by establishing reasonable and attainable fitness goals, and (5) stratifying cardiovascular risk (American College of Sports Medicine 2006).

Currently, the criterion measure of cardiorespiratory fitness is the direct assessment of maximal oxygen uptake ($VO_{2max}$) during the performance of a maximal graded

exercise test (GXT). However, the direct measurement of $VO_{2max}$ is often limited to laboratory, clinical, and research settings, because it is costly and requires specialized equipment and trained personnel. The need to assess cardiorespiratory fitness in the general public has led to the development of various exercise and non-exercise prediction models. Previous investigators (Blair et al. 1989; Jackson et al. 1990; Heil et al. 1995; George et al. 1997; Malek et al. 2004a, b; Wier et al. 2006; Sanada et al. 2007) have reported valid estimates of aerobic fitness using non-exercise test variables including, age, gender, body composition (e.g., percent body fat, BMI, or skeletal muscle mass), and a self-assessed PA score. Such models are effective for use in large epidemiological cohorts in which exercise tests to predict or measure $VO_{2max}$ would be impractical. One limitation of those previous works has been the selection of a subjective self-reported PA measure to assess cardiorespiratory fitness. Self-reported PA measures can suffer from social desirability and recall biases (Tudor-Locke et al. 2004a, b), but perhaps their greatest limitation is their inability to accurately assess unstructured and incidental ambulatory PA, which may account for a greater proportion of total PA in sedentary people.

Pedometers are simple and inexpensive body-worn motion sensors that are increasingly used for objective assessment of PA behaviors. More recently, they have gained credibility as an accurate measure of ambulatory PA because they can provide a direct measure of incidental and unstructured PA (Bassett et al. 2000; Welk et al. 2000; Tudor-Locke and Myers 2001; Crouter et al. 2003; Schneider et al. 2004), and have been used in some epidemiological studies in Japan (Ministry of Health and Welfare Japan 2002) and in the USA (Centers for Disease Control and Prevention, National Center for Health Statistics 2004). Using the pedometer as a measure of PA has many other advantages. Pedometers have been shown to provide a reliable measure of PA (Welk et al. 2000; Crouter et al. 2003; Schneider et al. 2004), are sensitive to change (Tudor-Locke 2001; Crouter et al. 2003), and, unlike self-reported measures, can detect subtle changes in an individual's incidental PA (Bassett et al. 2000; Tudor-Locke and Myers 2001; Crouter et al. 2003). However, to our knowledge, there is no information on the prediction of $VO_{2max}$ using pedometer-determined step counts (SC) as an objective PA variable.

We hypothesized that pedometer-determined PA should have a good positive relationship with cardiorespiratory fitness in Japanese women. More specifically, the purpose of this study was to develop a new non-exercise $VO_{2max}$ prediction model using SC as an objective PA variable in Japanese women.

## Methods

The present investigation consists of two studies, a Prediction study and a Validation study. Outcome measurements in the Prediction study were performed in two independent institutions supervised by two coauthors NM and MH, while the validation study was done in another institution by CZ, KI, and IT (CZ).

### Subjects

The study included 189 Japanese women aged from 20 to 69 years old. None of the subjects had any chronic diseases or were taking any medications that could affect the study variables. The Prediction group included 87 healthy women, and the Validation group included 102 healthy women. All subjects provided written informed consent according to local institute policy before the measurement of physical fitness. Informed consent was obtained before the measurement of physical fitness. The research project was approved by the Ethical Committee of the National Institute of Health and Nutrition. The subjects' characteristics are described in Table 1.

### Anthropometrics

Body mass was measured using an electronic scale (Inner Scan BC-600, Tanita Co., Japan) and was determined to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using a stadiometer (YL-65, Yagami Inc., Japan). Body mass and height were measured with the subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing the body mass in kilograms by the square of height in meters (kg $m^{-2}$).

**Table 1** Physical characteristics of the study subjects

| Variable | Prediction group $n = 87$ | Validation group $n = 102$ |
|---|---|---|
| Age (years) | 45.7 ± 10.9 | 53.0 ± 14.2* |
| Height (cm) | 157.2 ± 5.6 | 155.6 ± 5.7* |
| Body mass (kg) | 52.5 ± 6.9 | 54.3 ± 7.1* |
| BMI (kg $m^{-2}$) | 21.3 ± 2.9 | 22.5 ± 2.9* |
| $VO_{2max}$ (ml $kg^{-1}$ $min^{-1}$) | 31.4 ± 7.4 | 29.8 ± 5.5 |
| SC (steps $day^{-1}$) | 9,809 ± 3,156 | 10,143 ± 3,096 |

Values are mean ± SD

*BMI* body mass index, *SC* pedometer-determined step counts

* Significant group difference between Prediction group and Validation group, $P < 0.05$

### Maximal aerobic power

$VO_{2max}$ was measured using a GXT with bicycle ergometers [Lode Excalibur (NM), Lode BV, Groningen, Netherlands; Monark Ergomedic 828E (MH, CZ), Varberg, Sweden]. The initial work load was 30–60 W, and the work rate was increased thereafter by 15 W $min^{-1}$ until the subject could not maintain the required pedaling frequency (60 rpm) (Miyachi et al. 2001). Heart rate (WEP-7404, NIHON KOHDEN Corp. Japan) and a rating of perceived exertion were monitored throughout the exercise. During the progressive exercise test, the expired gas of subjects in the Prediction group was collected, and the rates of oxygen consumption ($VO_2$) and carbon dioxide production ($VCO_2$) were measured over 30-s intervals using an automated breath-by-breath gas analyzing system [Aeromonitor AE-280S (MH), Minato Medical Science, Tokyo, Japan; Oxycon Alpha (NM), Mijnhardt b.v., The Netherlands]. The Aeromonitor AE-280S consists of a microcomputer, a hot-wire flow meter, and oxygen and carbon dioxide gas analyzers (a zirconium element-based oxygen analyzer and an infra-red carbon dioxide analyzer). Gas was sampled at the rate of 220 ml $min^{-1}$ through a filter by a suction pump through the analyzers. The Oxycon Alpha consists of a microcomputer, a capillaryline, and oxygen and carbon dioxide gas analyzers ($O_2$: differential paramagnetic; $CO_2$: infra-red absorption). Expiratory volumes were determined using a Triple V turbine volume sensor which was calibrated before each test according to the manufacturer's instructions. The systems were calibrated prior to each test with gases of known concentration. The expired air of subjects in the Validation group was collected in Douglas bags (at least three times). An oxygen and carbon dioxide mass spectrometer (Arco-1000, Arco System, Japan) was used to analyze oxygen and carbon dioxide concentrations. The volume of expired air was determined using a dry gas volume meter (DC-5, Shinagawa Seisakusho, Japan) and converted to standard temperature, pressure and dry gas (STPD). During the latter stages of the test, each subject was verbally encouraged by the test operators to give a maximal effort. Achievement of $VO_{2max}$ was accepted if two of the following conditions were met: subject's maximal heart rate (HR) was >95% age-predicted maximal HR (220—age), and the $VO_2$ curve showed a leveling off.

### Physical activity

PA was measured by pedometer using an acceleration sensor. Subjects wore the Kenz Lifecorder (SUZUKEN Co Ltd., Japan) for seven consecutive days. Subjects were instructed how to use the instrument, and were told to wear it on their belt or waistband in the right midline of the thigh from the moment they got up until they went to bed except while bathing or swimming. The pedometer was firmly attached to their clothes at the waist with the aid of a clip.

### Statistical analyses

Measured and calculated values are presented as means ± SD. Differences between the Prediction group and Validation group for variables were tested with Student's $t$ test for unpaired samples. Pearson's product correlations were calculated between the independent variables (age, height, body mass, BMI, and SC) and $VO_{2max}$. Hierarchical linear regression analysis was used to generate prediction formulas for $VO_{2max}$. We entered the age and BMI into the first block, SC into the second block. The prediction formulas obtained from the Prediction group were then validated in the Validation group using the Bland and Altman approach (Bland and Altman 1986) and linear regression. Measured and predicted $VO_{2max}$ values were compared using paired Student's $t$ test, standard errors, and Pearson's product correlation value ($r$) between the measured and predicted $VO_{2max}$ values. Error terms for the validation analysis were calculated as follows: the standard error of estimate $(SEE_1) = SD_y\sqrt{1-r^2}$, and total error (TE) $= \sqrt{\left(\sum (\text{measured } VO_{2max} - \text{predicted } VO_{2max})^2 / n\right)}$. All analyses were done with SPSS 16.0 J for Windows (SPSS Japan Inc., Tokyo, Japan). The statistical significance level was set at $P < 0.05$.

## Results

Results from cardiorespiratory fitness testing for $VO_{2max}$, anthropometric variables, and SC are presented in Table 1. There were significant group differences in age, height, body mass, and BMI between the Prediction group and the Validation group.

Table 2 presents Pearson correlations matrix of $VO_{2max}$ and all independent variables. These correlations between $VO_{2max}$ and all independent variables were statistically significant ($P < 0.01$) and ranged from a low of 0.21 for height to a high of −0.60 for age in the Prediction group, indicating that each independent variable was related to $VO_{2max}$. There was a statistically significant correlation between SC and $VO_{2max}$ (partial correlation coefficient $r = 0.40$, $P < 0.001$, data not shown) after adjusting for BMI and age. Table 3 shows multiple regression analysis. When estimating $VO_{2max}$ with age and BMI, the addition of SC, raised the $R^2$ from 0.40 to 0.50, a significant 10.0% increase in the explained variance of $VO_{2max}$. Multiple linear regression analysis yielded the following equation ($R = 0.71$, SEE = 5.33 ml $kg^{-1}$ $min^{-1}$, $P < 0.001$) for

**Table 2** Correlations matrix of $VO_{2max}$ and independent variables ($n = 87$)

| | $VO_{2max}$ (ml kg$^{-1}$ min$^{-1}$) | Age (years) | Height (cm) | Body mass (kg) | BMI (kg m$^{-2}$) | SC (steps day$^{-1}$) |
|---|---|---|---|---|---|---|
| $VO_{2max}$ (ml kg$^{-1}$ min$^{-1}$) | – | | | | | |
| Age (years) | −0.60** | – | | | | |
| Height (cm) | 0.21* | −0.37** | – | | | |
| Body mass (kg) | −0.26* | 0.08 | 0.22* | – | | |
| BMI (kg m$^{-2}$) | −0.37** | 0.27* | −0.31** | 0.86** | – | |
| SC (steps day$^{-1}$) | 0.26* | 0.05 | −0.18 | 0.02 | 0.10 | – |

*BMI* body mass index, *SC* pedometer-determined step counts

* $P < 0.05$; ** $P < 0.01$

**Table 3** Multiple regression analysis with $VO_{2max}$ as the dependent variable and age, BMI, and SC as the independent variables

| $VO_{2max}$ (ml kg$^{-1}$ min$^{-1}$) | Coefficients | β | SE |
|---|---|---|---|
| Model 1 | | | |
| Constant | 55.318 | | 4.682 |
| Age (years) | −0.260 | −0.54*** | 0.042 |
| BMI (kg m$^{-2}$) | −0.565 | −0.22* | 0.224 |
| Model 2 | | | |
| Constant | 49.859 | | 4.516 |
| Age (years) | −0.263 | −0.55*** | 0.039 |
| BMI (kg m$^{-2}$) | −0.641 | −0.25** | 0.207 |
| SC ($10^{-3}$ steps day$^{-1}$) | 0.734 | 0.31*** | 0.183 |

Data from Prediction group

Standard error of estimate (SEE) = 5.79 ml kg$^{-1}$ min$^{-1}$ for Model 1; SEE = 5.33 ml kg$^{-1}$ min$^{-1}$ for Model 2

*BMI* body mass index, *SC* pedometer-determined step counts, β standardized regression weights, *SE* standard error

$R^2 = 0.40$*** for Model 1; $R^2 = 0.50$*** for Model 2

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

predicting $VO_{2max}$: $VO_{2max} = 49.859 - (0.263 \times \text{Age}) - (0.641 \times \text{BMI}) + (0.734 \times 10^{-3}\ \text{SC})$, where Age = age in years, BMI = body mass index in kg m$^{-2}$, and SC = pedometer-determined walk SC per day in steps day$^{-1}$.

Figure 1 shows the relationship between the measured and predicted $VO_{2max}$ values in the Validation group. When the $VO_{2max}$ prediction equation was applied to the Validation group, predicted $VO_{2max}$ correlated well with measured $VO_{2max}$ ($r = 0.81$, $P < 0.001$), and $SEE_1$ and TE were 3.25 and 3.43 ml kg$^{-1}$ min$^{-1}$, or 10.9 and 11.5% of the average $VO_{2max}$, respectively. A slight difference was found between the measured (29.8 ± 5.5 ml kg$^{-1}$ min$^{-1}$) and predicted (29.0 ± 5.3 ml kg$^{-1}$ min$^{-1}$) $VO_{2max}$. The Bland–Altman plots display the individual subjects differences in the Validation group between the measured and predicted $VO_{2max}$ against the mean measured and predicted $VO_{2max}$ (Fig. 2). Each Bland–Altman plot displays the mean difference (dashed line) and the 95% confidence

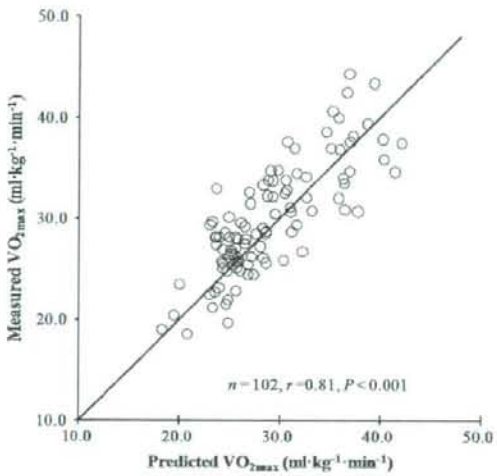


**Fig. 1** Relationship between the measured and predicted $VO_{2max}$ values in the Validation group. The *solid line* is the line of equality (measured $VO_{2max}$ = predicted $VO_{2max}$)

interval (±2SD; dotted lines). A strong agreement was found between the measured and predicted values of $VO_{2max}$. The mean difference (95% CI) between the measured and predicted $VO_{2max}$ observed in the Validation group was 0.78 (−5.92, 7.49). Three cases were outside the limits of agreement. Bland–Altman plot and linear regression showed no significant relation ($P = 0.47$) between the mean measured and predicted $VO_{2max}$ and the difference between them. The scatter on the Bland–Altman plot is distributed randomly, without signs of systematic bias.

## Discussion

This study aimed to develop a non-exercise $VO_{2max}$ prediction model using SC as a surrogate for the PA variable

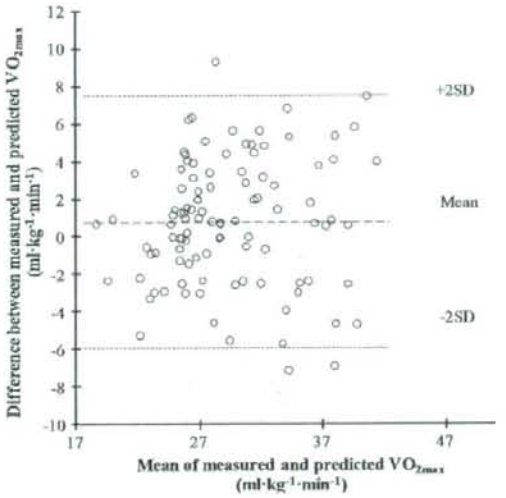


**Fig. 2** Bland–Altman plot for the Validation group: mean $VO_{2max}$ (measured and predicted) plotted against the difference (measured vs. predicted) in $VO_{2max}$. Mean difference and 95% limits of agreement (mean ± 2SD) are indicated with *dashed and dotted lines*, respectively

in Japanese women. As we hypothesized, the PA variable of SC was significantly related to $VO_{2max}$. Furthermore, the model is found to be able to predict $VO_{2max}$ with satisfactory accuracy.

Cardiorespiratory fitness is considered a health-related fitness component that indicates the capability of the cardiovascular and respiratory systems to provide oxygen during PA. $VO_{2max}$ is the most widely used measure of cardiorespiratory fitness, and has been shown to be strongly related to several health outcomes. Currently, direct measurement of $VO_{2max}$ in a laboratory setting using maximal GXT is the most accurate assessment. However, the use of the direct measurement of $VO_{2max}$ in epidemiological studies is limited by its high cost, by technical operational difficulties, and by the time required to measure it. Many attempts have been made to develop a non-exercise prediction model for $VO_{2max}$ (Blair et al. 1989; Jackson et al. 1990; Heil et al. 1995; George et al. 1997; Malek et al. 2004a, b; Wier et al. 2006; Sanada et al. 2007). One limitation of those previous researches has been the selection of a self-reported PA measure to assess the cardiorespiratory fitness. Self-reported PA measures suffer from social desirability and recall biases (Tudor-Locke et al. 2004a, b). Further, their greatest limitation is their inability to accurately assess unstructured and incidental ambulatory PA, which may account for a greater proportion of total PA among sedentary people. To our knowledge, only one previous study has attempted to develop a non-exercise prediction model for $VO_{2max}$ using the ratio heart rate and accelerometer-determined activity counts as an objective fitness index (Plasqui and Westerterp 2005). It was reported in this study that this fitness index contributed significantly to the explained variation in $VO_{2max}$ (the additional explained variation from the fitness index beyond that of age, gender, and body mass was 9%, partial $r = -0.48$, $P = 0.02$). The total explained variation of their non-exercise prediction model was 71%, with an SEE of 409 ml $min^{-1}$, or 13.7% of the average $VO_{2max}$. However, this prediction model may be less feasible for use in certain clinical applications because of the cost of and technical requirements for its use. Pedometers are simple and inexpensive body-worn motion sensors that are increasingly used for the objective assessment of PA behaviors. More recently, pedometers have been used in some epidemiological studies in Japan (Ministry of Health and Welfare Japan 2002) and in the USA (Centers for Disease Control and Prevention, National Center for Health Statistics 2004). Thus, there is a practical significance to the development of a non-exercise $VO_{2max}$ prediction model using SC as a surrogate for the PA variable.

Multiple regression analysis demonstrated that each of the independent variables used in this study was independently related to $VO_{2max}$. A number of studies have documented the relationship between pedometer-determined PA and $VO_{2max}$ (Ichihara et al. 1996; Michaud et al. 2002; Bjørgaas et al. 2005). The correlation of 0.26 found in this study was similar to that found in healthy adolescents (Michaud et al. 2002), and was lower than the correlation ($r = 0.48$) in people with type 2 diabetes reported by Bjørgaas et al. (2005). Differences between the subjects in these two studies (healthy vs. diabetes) may explain the inconsistent finding. Those prior studies, in conjunction with the present study, document the value of using pedometer-determined PA when estimating $VO_{2max}$.

Previously published non-exercise test prediction models reported varying success in predicting a measure cardiorespiratory fitness with SEE and $R$ values ranging from 3.44 to 8.63 ml $kg^{-1}$ $min^{-1}$ and 0.46 to 0.88, respectively (Siconolfi et al. 1985; Kohl et al. 1988; Blair et al. 1989; Jackson et al. 1990; Heil et al. 1995; Whaley et al. 1995; Rankin et al. 1996; George et al. 1997; Malek et al. 2004a, b; Jurca et al. 2005; Plasqui and Westerterp 2005, 2006; Wier et al. 2006). The values determined by the regression model in the present study were well within this range. The wide range of $R$ values reported in previous non-exercise test models may have been due in part to the differences among the studies in the type and number of predictor variables (Whaley et al. 1995). Moreover, differences in the ethnicity of the subjects between the present study (Japanese) and the previous studies (Caucasian) may explain the different correlation, because Wier et al. (2006)

reported that the addition of ethnicity to the non-exercise $VO_{2max}$ prediction models significantly raised the correlation.

The purpose of the validation analysis was to estimate the prediction model's performance by measuring Pearson's product correlation value ($r$) between the measured and predicted $VO_{2max}$ values and the error ($SEE_1$ and TE) in the Validation group. The low TE value, high $r$ value, small difference (0.18 ml $kg^{-1}$ $min^{-1}$) between TE and $SEE_1$ values for the Validation group, and slight differences between mean measured and predicted $VO_{2max}$ values all provide evidence for model stability in the present study. The present validation analysis results achieved coefficients with higher validity compared with the cross-validation results of previous studies (George et al. 1997; Malek et al. 2004b). Malek et al. (2004b) reported that the $SEE_1$ values for the Validation groups in the former non-exercise $VO_{2max}$ predictions present approximately 13.6–15.1% of the actual $VO_{2max}$, and that the TE values for the Validation groups in the former non-exercise $VO_{2max}$ predictions present approximately 23–41% of the actual $VO_{2max}$. Therefore, the $SEE_1$ and TE values in the Validation group in the present study were lower than those associated with other non-exercise methods for estimating $VO_{2max}$.

The prediction accuracy of the model can be increased by enlarging the sample size. Therefore, the data from both the Prediction and Validation groups in the present study were pooled together (combined sample, $n = 189$) to develop the non-exercise $VO_{2max}$ prediction $model_1$. Multiple regression analysis revealed that SC was a significant (partial correlation coefficient $r = 0.44$, $P < 0.001$, data not shown) contributor to the prediction of the measured $VO_{2max}$. The multiple regression $model_1$ obtained using the combined sample was the following: $VO_{2max} = 47.590 - (0.241 \times \text{Age}) - (0.540 \times \text{BMI}) + (0.672 \times 10^{-3} \text{ SC})$, $R^2 = 0.56$, SEE = 4.33 ml $kg^{-1}$ $min^{-1}$, $P < 0.001$. These results are consistent with a previous study (Wier et al. 2006) that showed an improvement in prediction accuracy, evidenced by larger $R^2$ and smaller SEE values, compared with a previous model with a smaller sample. Moreover, the PRESS (predicted residual sum of squares, Holiday et al. 1995) cross-validation statistic was similar to the regression statistic, supporting the validity of prediction $model_1$.

Many indirect methods of estimating $VO_{2max}$ based on heart rate responses to submaximal exercise have been developed, resulting in good to very good prediction accuracy (Hermiston and Faulkner 1971; Fox 1973; Akalan et al. 2008). Akalan et al. (2008) reported an $R$ value of 0.867, SEE of 4.23 ml $kg^{-1}$ $min^{-1}$, and SEE% of 10% using their multiple regression equation with six independent variables during a submaximal cycle ergometer protocol, but did not present cross-validation results. They also reported that various submaximal tests based on heart rate responses to submaximal exercise have yielded correlations ranging from $R = 0.48$–$0.97$, and found that the mean difference between YMCA, ACSM, and Astrand-Ryhming Nomogram estimated $VO_{2max}$ and observed $VO_{2max}$ was significant. Zwiren et al. (1991) validated five methods of estimating $VO_{2max}$ based on heart rate responses to submaximal exercise and reported $r =$ 0.55–0.66, and $SEE_1$% of 13–13.5%. Therefore, the $SEE_1$ values in the Validation group in the present study were lower and the $r$ values in the Validation group in the present study were higher than those reported for exercise-based prediction models. Plasqui and Westerterp (2005) developed a non-exercise model for estimating $VO_{2max}$ using a fitness index based on accelerometer counts and heart rate, and they cross-validated this model in 2006. Compared with the Plasqui and Westerterp 2006 study, our study drew on a larger sample (87 vs. 26) and achieved good model stability, as evidenced by the absence of systematic bias and smaller $SEE_1$% values. Various tests should be evaluated not only for their accuracy and validity but also for their applicability in a varied study population, their cost, and the ease and convenience of the protocol. The large number of highly varied women who obtained measurements of $VO_{2max}$ in our study helps support the generalizablity of the prediction model. In addition, because each of these predictor variables is easily obtained, it is believed that non-exercise $VO_{2max}$ prediction model using SC as a surrogate for the PA variable can be a routine component of primary healthcare examination for women in large epidemiological cohorts.

Because the outcome measurements in the Prediction and the Validation groups were performed at different institutions, the effect of institution was assessed by adding a dummy-coded institution variable and then applying a multiple regression to determine whether the institution variable provided a significant increase in the explained variance of $VO_{2max}$ over the independent variable. When the institution variable as an independent variable was added to the multiple regression, we found that the institution variable was not statistically significant ($P = 0.528$, data not shown) and did not improve the $model_1$ ($R = 0.75$, $P = 0.528$, data not shown).

This study has several limitations. First, the prediction model developed in this study may have limited generalizability because it was developed in a group of relatively healthy women 20 years of age and older. The stability of the predicted $VO_{2max}$ values using the present model is unknown in groups of individuals whose characteristics vary substantially from the range of characteristics in our Validation group (e.g., men, children and adolescents, and individuals with metabolic

syndrome). Our data showed that the correlation between pedometer-determined PA and $VO_{2max}$ of 0.26 found in this study was slightly lower than the correlation ($r = 0.48$) in people with type 2 diabetes reported by Bjørgaas et al. (2005). Further research is needed to validate the prediction model in these groups. Second, SC alone does not discriminate the intensity of movement or reflect the amount of time spent in specific intensity categories of PA, which may weaken the accuracy of our prediction model. Aadahl et al. (2007) provided evidence that the amount of daily vigorous activity (>6 MET) showed a significantly positively better relationship with $VO_{2max}$ ($P = 0.0001$, $r = 0.76$) compared with the total amount of PA done. If those indexes would encompass the prediction models, it is likely that the accuracy and validity of the prediction models would improve relative to the present prediction model. Therefore, further study is needed to investigate that possibility.

To our knowledge, this study marks the first attempt to develop a non-exercise $VO_{2max}$ prediction model using SC as a surrogate PA variable that can be used in large epidemiological cohorts. This study demonstrated that SC was useful in predicting $VO_{2max}$ variance and helped the present non-exercise $VO_{2max}$ prediction model generate relatively accurate estimations of $VO_{2max}$ in Japanese women.

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#10

# ORIGINAL CONTRIBUTION
# Pulse Wave Velocity for Assessment of Arterial Stiffness Among People With Spinal Cord Injury: A Pilot Study

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**Abstract**

**Background/Objective:** The most significant complication and leading cause of death for people with spinal cord injury (SCI) is coronary artery disease (CAD). It has been confirmed that aortic pulse wave velocity (PWV) is an emerging CAD predictor among able-bodied individuals. No prior study has described PWV values among people with SCI. The objective of this study was to compare aortic (the common carotid to femoral artery) PWV, arm (the brachial to radial artery) PWV, and leg (the femoral to posterior tibial artery) PWV in people with SCI (SCI group) to able-bodied controls (non-SCI group).

**Methods:** Participants included 12 men with SCI and 9 non-SCI controls matched for age, sex, height, and weight. Participants with a history of CAD or current metabolic syndrome were excluded. Aortic, arm, and leg PWV was measured using the echo Doppler method.

**Results:** Aortic PWV (mean ± SD) in the SCI group (1,274 ± 369 cm/s) was significantly higher ($P < 0.05$) than in the non-SCI group (948 ± 110 cm/s). There were no significant between-group differences in mean arm PWV (SCI: 1,152 ± 193 cm/s, non-SCI: 1,237 ± 193 cm/s) or mean leg PWV (SCI: 1,096 ± 173 cm/s, non-SCI: 994 ± 178 cm/s) values.

**Conclusions:** Aortic PWV was higher among the SCI group compared with the non-SCI group. The higher mean aortic PWV values among the SCI group compared with the non-SCI group indicated a higher risk of CAD among people with SCI in the absence of metabolic syndrome.

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**Key Words:** Arterial stiffness; Pulse wave velocity; Spinal cord injuries; Doppler ultrasound; Coronary artery disease; Risk factors

## INTRODUCTION

Coronary artery disease (CAD) is the most significant complication and leading cause of mortality after spinal cord injury (SCI) (1). Individuals with chronic SCI have higher cardiovascular mortality rates and cardiovascular mortality occurs at earlier ages compared with the able-bodied population (2–4). Stiffening of the central or cardiothoracic arteries is a significant independent risk factor for CAD in able-bodied people (5–7). Decreases in the elastic properties of arteries reduce their buffering capacity, leading to increased pulse pressure, aortic impedance, and left ventricular wall tension, all of which augment the workload of the heart, thereby increasing CAD risk. Several indices have been used to quantify the stiffness of the peripheral and cardiothoracic arteries. These include (a) measuring pulse wave velocity (PWV); (b) relating changes in arterial diameter to distending pressure; and (c) assessing arterial pressure wave forms. Of the above indirect methods for measuring arterial stiffness, PWV is the most widely accepted technique (8). PWV has been a useful noninvasive measure to assess arterial stiffness and severity of CAD among able-bodied people in a number of previous studies (9–11).

PWV is the velocity of the blood pressure wave as it travels a known distance between 2 anatomic sites within the arterial system; it is determined by the elasticity and other properties of the artery (12). PWV values positively

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correlate with arterial distensibility and stiffness. Three locations for the measurement of PWV have been proposed: (a) trunk (aortic PWV); (b) arm (arm PWV); and (c) leg (leg PWV). Aortic PWV is the established index for measuring arterial stiffness.

Aortic PWV values have been directly linked with cardiovascular mortality, fatal and nonfatal coronary events, and fatal strokes in patients with low and high levels of traditional CAD risk factors (9–11,13–15). For example, aortic PWV values of at least 1,300 cm/s are a strong predictor of cardiac mortality among patients with hypertension (13). Among people with hypertension, a 500-cm/s increment in aortic PWV is an independent predictor of both cardiovascular mortality (odds ratio = 1.34) and all-cause mortality (odds ratio = 1.51) (14). Although leg PWV and arm PWV have not been studied to the same extent, it has been suggested that these peripheral PWV measures are insensitive to physical activity levels and/or aging compared with aortic PWV in able-bodied people (16,17).

Several CAD risk factors have been identified as determinants of PWV in the able-bodied population including obesity (18–20), diabetes mellitus (21,22), hypercholesterolemia (23) and hypertension (9,24), poor cardiorespiratory fitness (25,26), and low physical activity (27). These same CAD risk factors are common among people with SCI (28–32). In addition, people with SCI above the splanchnic outflow (T6) have autonomic dysfunction, which may contribute to disordered cardiac regulation and abnormalities of the vascular system. Thus, it was hypothesized that people with chronic SCI will have an increased risk of adverse vascular health and increased arterial stiffness as measured by PWV.

The purpose of this study was to compare aortic PWV in people with chronic SCI (SCI group) to that of age-, sex-, height-, and weight-matched able-bodied controls (non-SCI group) and to compare arm PWV and leg PWV in these same groups to determine whether differences exist in the values obtained.

## METHODS

The SCI group was made up of 15 individuals with SCI (C3–T10, ASIA A, B, and C). The non-SCI group was made up of 11 sedentary able-bodied controls matched for age, height, and weight. Individuals with SCI were recruited by a poster campaign from Toronto Rehab's Lyndhurst Centre. Non-SCI participants were recruited from the staff and friends of the authors affiliated with the Lyndhurst Centre. Participants in this study did not participate in any regular exercise or endurance-type wheelchair exercise beyond their normal activities of daily living for 6 months before enrollment. All participants were nonsmokers for at least 1 year before the study. No participants reported a prior history of CAD, pulmonary disease, diabetes mellitus, or metabolic syndrome. Each participant's current medications were recorded. No participants were taking medications known to interfere with the cardiovascular system.

A 12-lead ECG was done to screen for signs of arrhythmia or prior myocardial infarction. Fasting serum blood sugar, glycosylated hemoglobin (HbA1C), total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TG), C-reactive protein (CRP), and apolipoprotein (A and B) levels, resting blood pressure (BP), and waist circumference were measured to screen for metabolic syndrome. Heart rate and BP were recorded from the right antecubital fossa using a stethoscope and hand-held dynamometer. Metabolic syndrome was defined as per the American Heart Association Guidelines as at least 3 or more of the following criteria: abdominal obesity (waist circumference $\geq$ 102 cm for men); dyslipidemia (TC/HDL > 4 or LDL > 2.5); glucose intolerance (fasting blood sugar > 7 mmol/L); elevated CRP (>3 mg/dL); or hypertension (BP > 140/90 mmHg).

Fifteen people with SCI and 11 people without SCI were screened for enrollment in the study. Five individuals' data were excluded from the analysis; 3 individuals had metabolic syndrome; 1 individual had an arrhythmia (atrial fibrillation) that interfered with PWV measurement; and 1 individual had an incomplete assessment. In total, 12 individuals with SCI and 9 controls were included in the study. The study protocol was approved by the Toronto Rehab Research Ethics Board.

PWV was measured from the foot; blood flow waves were recorded at 2 points along the path of the arterial pulse wave. PWV was calculated from the measured wave latency and the distance traveled between the 2 arterial recording sites (Figure 1) (10,15,17,33,34). Two identical transcutaneous Doppler flowmeters (Smartdop50, Hadeco, Kanagawa, Japan) were used to obtain the PWV values at 3 locations: (a) between the carotid and the femoral arteries (aortic PWV); (b) between the femoral and posterior tibial arteries (leg PWV); and (c) between the brachial and radial arteries (arm PWV; Figure 1B). Distance traveled by the pulse was measured over the surface of the body with a tape measure as the distance (D) between recording sites (cm). A minimum of 20 sequentially recorded wave forms were analyzed and averaged. All PWV data were obtained by 2 trained technicians between 10:00 AM and 1:00 PM to avoid circadian changes in PWV values. Measurement of PWV was conducted after abstinence from caffeine and an overnight fast of at least 8 hours. Flow measurements were obtained sequentially in the arm, aorta, and leg over a 40-minute period. Arterial pulse waves were digitized for off-line analysis with signal-processing software (Chart 5.5.5, AD Instruments, New South Wales, Australia). PWV was determined over the 3 arterial segments as PWV= $D/\Delta t$ (cm/s), where $\Delta t$ was determined from time delay between the proximal and the distal foot of the wave form (Figure 1A). The foot of the wave was identified as the start of the sharp systolic

**Table 1.** Participant Characteristics

| | SCI Group | Non-SCI Group |
|---|---|---|
| N | 12 | 9 |
| Age (y) | 45.9 ± 7.8 | 44.1 ± 10.9 |
| Height (cm) | 177.6 ± 7.0 | 174.5 ± 8.2 |
| Weight (kg) | 81.1 ± 20.6 | 73.7 ± 11.5 |
| Body mass index (kg/m$^2$) | 25.5 ± 5.7 | 24.1 ± 1.9 |
| Systolic blood pressure (mmHg) | 121.0 ± 9.5 | 116.2 ± 11.4 |
| Diastolic blood pressure (mmHg) | 74.8 ± 9.3 | 71.2 ± 6.5 |
| Heart rate (beats/min) | 64.3 ± 10.5 | 65.4 ± 8.0 |

Data are means ± SD.

upstroke. All analyses were performed by a trained technician blinded to the participant's group assignment (SCI or non-SCI).

The test–retest variability of PWV measures in our laboratory was established by sequential measurement of 9 able-bodied men (21–39 years) on 2 separate days. The intraclass correlation coefficients for test–retest reliability were 0.730 to 0.972 for each PWV value. The mean PWV combined for the 3 sites was 1,095 ± 238 vs 1,057 ± 210 cm/s for Trial 1 vs Trial 2 (not significant).

Statistical analyses were performed using StatView (Version 5.0) software. Demographic, anthropometric, and PWV data are expressed as mean ± SD. Participants with and without SCI were compared by the nonparametric Mann-Whitney *U* test because of the small group size. A 2-sided $P < 0.05$ was considered significant.

## RESULTS

There were no significant differences between groups in the baseline demographic or anthropometric parameters including age, height, weight, heart rate, and BP (Table 1). The mean duration of injury of the participants with SCI was 20 ± 13 years (SD). Mean aortic PWV in the SCI group (1,274 ± 369 cm/s) was significantly higher ($P < 0.05$) than that of the non-SCI group (948 ± 110 cm/s; Figure 2A). There were no statistically significant differences between the SCI group and the non-SCI group (Figure 2B and C) in either arm PWV (SCI: 1,152 ± 193 cm/s, non-SCI: 1,237 ± 193 cm/s; $P = 0.434$) or leg PWV (SCI: 1,096 ± 173 cm/s, non-SCI: 994 ± 178 cm/s) values ($P = 0.145$).

## DISCUSSION

Aortic PWV values in the SCI group were higher than those of able-bodied controls (non-SCI group), whereas there were no significant differences between the SCI and non-SCI groups in arm PWV and leg PWV values. Recently reported aortic PWV values in healthy able-bodied individuals 24 to 62 years of age ranged from 600 to 1,000 cm/s (8). Among hypertensive study participants, aortic PWV values ranged from 1,100 to 1,500 cm/s (8).

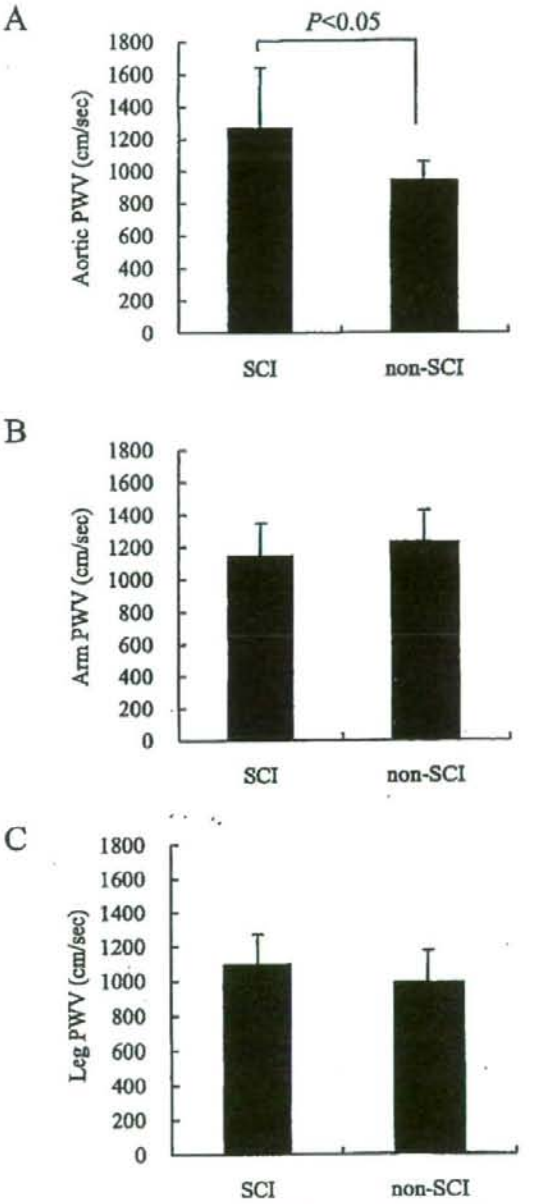


**Figure 2.** *Aortic PWV (A), arm PWV (B), and leg PWV (C) in participants with SCI and able-bodied controls (non-SCI).*

Arm and leg PWV values in healthy able-bodied individuals ranged from 840 to 1,200 and from 920 to 1,050 cm/s, respectively (8). The values for PWV documented herein are comparable with those previous-

ly reported for able-bodied individuals within the same age range.

Additionally, we found that aortic PWV values among healthy SCI participants were higher than those of the age-matched non-SCI participants. Aortic PWV values in the SCI group were equally high compared with the values (>1,300 cm/s) associated with an increased risk of developing CAD in the report of Blacher et al (13). These results suggest that the SCI group has a high risk of CAD. Screening protocols to diagnose and prevent CAD related mortality are urgently needed.

In contrast to the aortic PWV result, there were no significant differences between the SCI and non-SCI groups in either arm PWV or leg PWV. These results concur with a prior study reporting that aortic PWV is sensitive to daily activity and aging, whereas leg and arm PWV values are not (16,17). This sensitivity of the PWV of central vs peripheral arteries may be related to their distinct roles in hemodynamic regulation. Compared with the central arteries whose cushioning function damps fluctuations in flow, the peripheral arteries do not exhibit the same extent of pulsatile changes in diameter (35) and, as such, may not undergo the adaptations leading to a loss of elasticity. However, previous studies, which investigated femoral arterial stiffness by augmentation index (AI) (36) and arterial compliance (37,38) among people with SCI, showed that stiffness of the femoral artery in people with SCI was higher than that of able-bodied people. The reasons for this discrepancy is not clear; however, the use of the PWV methodology as opposed to the AI and arterial compliance to assess arterial stiffness may in part explain the discrepancy between our finding of normal leg PWV values and prior publications reporting elevated femoral AI and decreased arterial compliance values among patients with SCI. The PWV method measures pulse wave latency over the femoral and posterior tibial arteries as opposed to the femoral artery alone when assessing AI or arterial compliance.

Although there are no prior studies determining PWV in people with SCI, 3 previous studies investigated arterial stiffness using other measures of arterial stiffness: the AI (36) and arterial compliance (37,38) and compared them with those of able-bodied controls. de Groot et al (37) and Schmidt-Trucksass et al (38) reported that arterial compliance of the superficial femoral and carotid artery were significantly lower in people with SCI compared with people without SCI. Wecht et al (36) reported that arterial stiffness evaluated by AI was high in a group of people with paraplegia compared with an able-bodied group. Moreover, premature and advanced coronary atherosclerosis was found in persons with SCI compared with able-bodied people using electron beam tomography (39). Our observation of increased aortic arterial stiffness supports prior reports of premature CAD in the SCI population.

Mechanisms that may potentially account for higher aortic PWV among people with SCI include (a) structural changes in the vessel as a result of long-term sympathectomy and increased collagen content in the vascular wall (40) or (b) functional changes in the endothelium caused by decreased regional blood flow. Decreased regional blood flow as a result of inactivity impedes endothelium function and subsequently inhibits NO production, which is a mediator of endothelium dilatation (38). Although the relative importance of structural and functional changes in vascular tone is unknown, these may relate to both disordered cardiac regulation and inactive lifestyles after SCI. The mechanism(s) that account for these results are unknown.

This study has limitations that require caution when interpreting and generalizing the findings reported herein. First, the reliability of PWV values for people with SCI has not been reported. Second, this pilot study had a small sample size. Third, adjustments for confounding variables including the participant's injury level, duration of injury, and physical activity levels, which impact CAD risk, were not done. Future studies may want to use validated measures such as the Physical Activity Recall Assessment for People with SCI (PARA-SCI) (31) to quantify activity and explore the relationship between PWV and activity. Last, it is uncertain if the high PWV values reported reflect the presence of CAD among the subjects' in this study. Further studies with larger representative samples of participants with SCI are needed to determine the relationship between the increased arterial stiffness and the development/onset of atherosclerotic and asymptomatic CAD among people with SCI.

## CONCLUSION

To our knowledge, this is the first study describing aortic PWV in people with SCI. High aortic PWV values were found in study participants with SCI compared to age-, sex-, height-, and weight-matched able-bodied participants, indicating a higher risk of CAD among individuals with SCI. Arm PWV and Leg PWV were found to be insensitive to the differences between the 2 groups. PWV is potentially a good screening test to assess CAD risk among people with chronic SCI. However, this pilot study merely measured PWV among people with SCI. Further study is needed to confirm the reproducibility of PWV measures among people with SCI. Further study of the PWV method's reliability, validity, and responsiveness while considering the potential confounding effects of: age, duration of injury, impairment, and physical activity on PWV among individuals with SCI are needed.

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# Low-intensity resistance training with slow movement and tonic force generation increases basal limb blood flow

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## Summary

Metabolic syndrome is associated with reductions in basal limb blood flow. Resistance training increasing muscle mass and strength increases basal limb blood flow. Low-intensity resistance exercise with slow movement and tonic force generation (LST) has been proposed as one of the effective methods of resistance training increasing muscle mass and strength. The hypothesis that LST training increases basal femoral blood flow as well as traditional high-intensity resistance training at normal speed (HN) was examined. Thirty-six healthy young men without a history of regular resistance training were randomly assigned to the LST [~55–60% one repetition maximum (1RM) load, 3 s lifting and 3 s lowering with no relaxation phase, n = 12], HN (~85–90% 1RM, 1 s lifting and 1 s lowering with 1 s relaxation, n = 12) or sedentary control (CON, n = 12) groups. Participants in the training groups underwent two whole-body training sessions per week for 13 weeks. Basal femoral blood flow increased significantly by +18% in LST and +35% in HN (both $P<0.05$), while there was no such change in CON. There were no significant differences between these increases induced by LST and HN, although the increase in LST corresponded to about half that in HN. In conclusion, not only resistance training in HN but in LST as well, were effective for increasing basal limb blood flow, and that this effect was evident even in healthy young men.

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## Introduction

Basal limb blood flow decreases with advancing age in healthy men and women (Dinenno et al., 2001a,b, Moreau et al., 2003; Miyachi et al., 2005), which is related to corresponding reductions in leg fat-free mass and estimated leg oxygen demand (Dinenno et al., 2001a,b). Reductions in peripheral blood flow have been suggested to be mechanistically involved in metabolic syndrome, a cluster of disease states including hyperinsulinemia, dyslipidaemia and hypertension (Lind & Lithell, 1993). Accordingly, the prevention and treatment of age-related reductions in basal femoral blood flow may be of clinical importance.

Habitual aerobic exercise is regarded as an important component of preventing and treating cardiovascular disease and functional disability (Pate et al., 1995). However, habitual aerobic exercise does not appear to modulate the age-related reductions in basal limb blood flow (Dinenno et al., 2001a,b). Several recent studies showed that resistance training, which increases muscle mass and strength (MacDougall et al., 1977; Staron et al., 1984), is associated with increased basal femoral blood flow in middle-aged men and women (Miyachi et al., 2005; Anton et al., 2006). Resistance training is known to have some additional favourable health promoting effects aside from muscular hypertrophy and strength gain, such as improving insulin sensitivity (Dela & Kjaer, 2006). Increasing basal femoral blood flow by resistance training is considered one such favourable effect.

In general, traditional high-intensity (~80% 1RM) resistance training has been regarded as optimal for gaining muscular size and strength (McDonagh & Davies, 1984). However, such strenuous exercise may be associated with a risk of orthopaedic injury. In addition, a marked increase in systolic blood pressure (over 300 mmHg) has been reported to occur during high-intensity resistance exercise (~8RM) involving large muscle groups (MacDougall et al., 1985; Fleck, 1988). These problems must be considered in high-intensity resistance exercise regimens especially for high-risk populations.

Relatively low-intensity (~50–60% 1RM) resistance training with slow movement and tonic force generation (LST) is another method of resistance exercise. Previously, we reported that LST training resulted in a significant increase in muscular size and strength as high-intensity (~80–90% 1RM) resistance training with normal speed (HN) in knee extension training (Tanimoto & Ishii, 2006) and in a whole-body training regimen (Tanimoto et al., 2008), and LST was not associated with either generation of large force or marked elevation of blood pressure (Tanimoto & Ishii, 2006). Therefore, LST would be one of the useful methods of resistance training for promoting muscular hypertrophy and strength gain, which is relatively safe for a larger population.

With regard to the hypothesis of the effects of LST in promoting muscle hypertrophy, LST exercise movement was configured to achieve continuous force generation throughout the exercise movement. Continuous force generation at >40% maximum voluntary contraction has been shown to suppress both blood inflow to and outflow from the muscle due to an increase in intramuscular pressure (Bonde-Petersen et al., 1975). Resistance training regimens with restricted muscular blood flow were considered to induce increases in muscular size and strength mediated by the following processes due to oxygen insufficiency in muscle: (i) stimulated secretion of growth hormone by intramuscular accumulation of metabolic by-products, such as lactate (Takarada et al., 2000a); (ii) moderate production of reactive oxygen species promoting tissue growth (Takarada et al., 2000b); and (iii) additional recruitment of fast-twitch fibres under hypoxic conditions (Shinohara & Moritani, 1992).

The present study was performed to investigate whether resistance training even in LST also increases basal femoral blood flow as well as in HN, and whether resistance training in LST and HN increase basal femoral blood flow even in healthy young men.

The present study examined whether LST training can safely increase basal limb blood flow in healthy young people as a preventive effect, before such investigations are carried out in patients with metabolic syndrome or others and in older people as a curative effect.

## Methods

### Subjects

Thirty-six healthy young men without a history of regular exercise training volunteered as subjects in the present study. All subjects were non-smokers, normotensive (blood pressure <140/90 mmHg), non-obese (body mass index <30 kg m$^{-2}$) and free of overt chronic diseases as assessed by medical history, physical examination and complete blood chemistry and haematological evaluation. Candidates showing signs of peripheral artery disease [ankle-brachial index (ABI) <0·90] were excluded. The subjects were assigned at random into three experimental groups (n = 12 for each group: LST, HN, CON defined below). Groups were matched for physical parameters, such as height, weight and age (Table 1). All subjects were fully informed about the experimental procedures as well as the purpose of the study, and each subject provided written informed consent before participating in the study. The study protocol was approved by the Ethics Committee for Human Experiments, National Institute of Health and Nutrition.

### Regimens for exercise training

The subjects in each training group performed whole-body resistance training regimens consisting of five types of exercise: vertical squat, chest press, latissimus dorsi pull-down, abdominal bend and back extension, as described previously (Tanimoto et al., 2008). The subjects performed the following training regimens.

LST group: low-intensity (55~60% of 1RM) training with slow movement and tonic force generation [3 s for concentric

**Table 1** Characteristics of the subjects.

| | LST | | HN | | CON | |
|---|---|---|---|---|---|---|
| | Pretraining | Post-training | Pretraining | Post-training | Pretraining | Post-training |
| Age, year | 19·0 ± 0·2 | | 19·5 ± 0·1 | | 19·8 ± 0·2 | |
| Height, cm | 174·1 ± 1·6 | | 174·8 ± 1·2 | | 174·3 ± 2·1 | |
| Body mass, kg | 62·5 ± 1·4 | 64·1 ± 1·5 | 63·8 ± 1·2 | 65·3 ± 1·2 | 64·2 ± 1·2 | 64·7 ± 1·1 |
| LSTM, kg | 53·9 ± 3·9 | 55·2 ± 3·7[a,b] | 53·7 ± 3·0 | 55·6 ± 3·4[a,c] | 54·6 ± 2·7 | 55·2 ± 2·6[a] |
| %Fat, % | 13·7 ± 3·6 | 13·7 ± 3·8 | 15·7 ± 3·2 | 14·8 ± 2·9[a] | 14·8 ± 3·6 | 14·6 ± 3·5 |
| Left leg muscle mass, kg | 8·82 ± 0·21 | 9·07 ± 0·19[a,b] | 8·80 ± 0·19 | 9·19 ± 0·21[a,c] | 8·89 ± 0·18 | 8·98 ± 0·18 |

Values are means ± SE; n = 12 for each group.
LST, low-intensity exercise with slow movement and tonic force generation; HN, high-intensity exercise with normal speed; CON, sedentary control; LSTM, lean soft tissue mass.
[a]Significant difference ($P<0·05$) between pretraining and post-training.
[b]Increase in LST was significantly higher ($P<0·05$) than that in CON.
[c]Increase in HN was significantly higher ($P<0·05$) than that in CON.

 

(lifting phase) and eccentric (lowering phase) actions, and no relaxation phase; LST].

HN group: high-intensity (85~90% 1RM) training with normal speed (1 s for concentric and eccentric actions and 1 s for relaxation; HN). CON group: sedentary controls.

The training intensity was determined at 8RM in both LST and HN. 8RM means the load which person is only able to perform 8 correct form repetitions with. Subjects performed each type of training with 8RM intensity. Exercise intensities of LST and HN were adjusted to the same RM (8RM). Mechanical load in LST training was much lower than that in HN training (~55–60% 1RM in LST versus ~80–90% 1RM in HN). The difference in mechanical load under the same 8RM intensity between the two groups may have been due to differences in the type of movement. Subjects performed one warm-up set and three regular sets with an interest rest period of 60 s for each type of exercise. A 3-min rest was taken between exercise events. Training sessions were performed twice a week for 13 weeks.

All subjects were advised to maintain their usual physical activity and dietary habits to avoid any influence of physical activity outside the training session and nutritional influence.

## Measurements

Before they were tested, subjects abstained from caffeine and alcohol, and fasted for 12 h overnight. All testing, except muscular strength testing, was conducted under comfortable laboratory conditions early in the morning. Subjects were studied 4 or 5 days after their last exercise session to avoid any acute effects of exercise.

### Arterial blood flow

A duplex ultrasound machine (model 180 Plus; Sonosite, Bothell, WA, USA) equipped with a high-resolution (5–10 MHz) linear-array transducer was used to measure vessel diameter and blood velocity on the left common femoral artery and right common carotid artery, as described previously (Dinenno *et al.*, 1999, 2001a,b; Ozdemir *et al.*, 2006). Mean blood velocity measurements were performed with an insonation angle $<60^{\circ}$. The mean diameter [$D = D(\text{systole}/3) + D(\text{diastole } 2/3)$] based on the relative time periods of the systolic (1/3) and diastolic (2/3) blood pressure phases was used to represent the cross-sectional area. Femoral blood flow was calculated as: mean blood velocity (MBV) $\times \pi \times$ (femoral arterial radius)$^2 \times 60$. The data reported were time averages of 10 measurements for all variables and were analysed by the same investigator, who was blinded to the identity of the subject. Vascular conductance and resistance were calculated as arterial blood flow/mean blood pressure and mean blood pressure/arterial blood flow, respectively. In our laboratory, the day-to-day reproducibility of the measurements for arterial diameter, mean blood velocity and absolute blood flow were $3 \pm 1$, $7 \pm 2$ and $6 \pm 2\%$ (average $\pm$ SD), respectively.

### Arterial blood pressure at rest

Arterial blood pressure at rest was measured with a semiautomated device (Form PWV/ABI; Colin Medical Technology, Komaki, Japan) over the brachial and dorsalis pedis arteries. Recordings were made in triplicate with subjects in the supine position. ABI was then calculated and used as a measure of atherosclerosis in leg arteries.

### Left ventricular function

Echocardiography was used to measure left ventricular (LV) function, according to established guidelines (Sahn *et al.*, 1978; Cheitlin *et al.*, 2003). Stroke volume (SV) was measured from LV end-diastolic and end-systolic volumes calculated from LV internal dimensions (Miyachi *et al.*, 2004). Cardiac output was calculated as SV × heart rate. Systemic vascular resistance was calculated by the following formula: brachial mean blood pressure/cardiac output. All image acquisition and image analyses were performed by the same investigator, who was blinded to the group assignment of subjects. At least 10 measurements of cardiac output were taken and the mean values were used for analysis.

## Muscle thickness by B-mode ultrasound imaging

The muscle thickness (MT) was measured by B-mode ultrasound (5 MHz scanning head) at six sites from the anterior and posterior surfaces of the body, in principle following the standard method described by Abe *et al.* (Abe *et al.*, 1994). The sites were: chest, anterior and posterior upper arm, abdomen, subscapula and anterior and posterior thigh. Six anatomical landmarks for the sites were noted in our previous study (Tanimoto *et al.*, 2008).

Muscle thickness was scanned using a real-time linear electronic scanner with a 5 MHz scanning head (SSD-500; Aloka, Tokyo, Japan). The scanning head was prepared with water-soluble transmission gel that provided acoustic contact without depression of the skin surface. The scanner was placed perpendicular to the tissue interface at the marked sites.

### Body composition determined by dual energy X-ray absorptiometry scan

Lean soft tissue mass (LSTM: body mass minus bone and fat mass) and fat mass were determined for the whole body using dual energy X-ray absorptiometry (DXA) (Hologic QDR-4500A scanner; Hologic, Waltham, MA, USA). Subjects were positioned for whole-body scans according to the manufacturer's protocol. Participants lay in the supine position on the DXA table with the limbs close to the body. To minimize interobserver variation, all scans and analyses were carried out by the same investigator. The whole body was divided into several regions, i.e. arms, legs, trunk and head. The body compositions were analysed using manual DXA analysis software (version 11.2:3; Waltham, MA, USA). The arm region was defined as the region extending from the head of the humerus to the distal tip of the fingers. The reference point

between the head of the humerus and the scapula was positioned at the glenoid fossa. The leg region was defined as the region extending from the inferior border of the ischial tuberosity to the distal tip of the toes. The whole body was defined as the region extending from the shoulders to the distal tip of the toes. A reference point that could be visualized clearly on the DXA system terminal was selected.

### Muscular strength

Maximal muscular strength was tested with the five types of exercise used in the training regimen. Values were obtained for 1RM according to the established guidelines (Baechle et al., 2000).

### Metabolic risk factors for coronary heart disease

To screen for the presence of coronary heart disease, fasting plasma concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and glucose were determined with enzymatic techniques (Tanaka et al., 2000).

### Statistical analyses

All values are expressed as means ± SE. One-way analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD) was used to determine the significance of any differences among the initial parameters of the three groups. Two-way ANOVA repeated measures (group × period) with Newman-Keuls method was used to examine differences in changes in any parameters between groups. For all statistical tests, $P<0.05$ was considered significant.

## Results

Before the intervention period, there were no significant differences in any of the variables among the three groups.

### Changes in muscle mass and strength

The percent changes in total MT in ultrasound imaging, defined as the sum of the values for all six measurement sites, after the experimental period were +6·8 ± 3·4% in LST, +9·1 ± 4·2% in HN and +1·3 ± 2·2% in CON. The absolute changes in LSTM (body mass minus fat and bone mass) in DXA were 1·4 ± 0·4 kg in LST, 1·8 ± 0·4 kg in HN and 0·6 ± 0·2 kg in CON. The percent changes in left leg LSTM, defined as leg muscle mass, were 3·0 ± 1·0% in LST, 4·4 ± 1·0% in HN and 1·1 ± 0·8% in CON. On measurement of muscular strength, the percent changes in total 1RM strength, defined as the sum of values for all five types of exercise used in the training regimen, were +33·0 ± 8·8% in LST, +41·2 ± 7·8% in HN and +1·3 ± 2·4% in CON. For all changes in muscle mass and strength shown above, increases in the LST and HN groups after the experimental period were significantly greater than those in CON, and there were no significant differences between the changes in LST and HN. Our previous study provided detailed data regarding changes in muscle mass and muscular strength (Tanimoto et al., 2008).

### Metabolic risk factors for coronary heart disease

There were no significant changes in fasting plasma concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose or ABI (Table 2). All metabolic risk factors were well within clinically normal levels in all subjects. Brachial blood pressure, cardiac output and systemic vascular resistance (total peripheral resistance: TPR) did not change in any group (Table 3).

### Changes in arterial blood flow

Figure 1 shows basal femoral (top) and carotid (bottom) blood flow and basal femoral blood flow per unit volume of leg muscle mass (middle) in the three groups before and after the experimental period. Figure 2 shows femoral and carotid vascular conductance (upper) and both femoral and carotid vascular resistance (lower).

In the LST and HN groups, basal femoral blood flow increased significantly after the experimental period, while there was no such change in CON. The percent changes in basal femoral blood flow were +18·0 ± 4·7% in LST and +34·8 ± 8·3% in HN. There were no significant differences between these changes induced by LST and HN, although the increase in basal

**Table 2** Metabolic risk factors

| | LST | | HN | | CON | |
|---|---|---|---|---|---|---|
| | Pretraining | Post-training | Pretraining | Post-training | Pretraining | Post-training |
| Total cholesterol, mg dl$^{-1}$ | 185·9 ± 7·2 | 182·3 ± 9·8 | 164·4 ± 6·3 | 162·4 ± 5·4 | 162·6 ± 7·4 | 153·1 ± 7·4 |
| HDL cholesterol, mg dl$^{-1}$ | 63·2 ± 2·3 | 62·3 ± 3·7 | 61·4 ± 5·3 | 63·1 ± 4·1 | 56·3 ± 3·0 | 56·3 ± 3·7 |
| LDL cholesterol, mg dl$^{-1}$ | 106·8 ± 5·4 | 104·2 ± 5·8 | 90·2 ± 5·5 | 88·0 ± 5·1 | 93·5 ± 6·0 | 84·9 ± 5·1 |
| Triglycerides, mg dl$^{-1}$ | 79·6 ± 6·5 | 79·6 ± 9·9 | 64·0 ± 7·4 | 56·9 ± 6·3 | 63·9 ± 7·6 | 59·8 ± 5·1 |
| Fasting glucose, mg dl$^{-1}$ | 88·1 ± 1·7 | 87·4 ± 1·4 | 90·1 ± 1·5 | 89·0 ± 1·8 | 87·2 ± 1·3 | 84·8 ± 1·1 |

Values are means ± SE; n = 12 for each group.
LST, low-intensity exercise with slow movement and tonic force generation; HN, high intensity exercise with normal speed; CON, sedentary control.

**Table 3** Hemodynamic characteristics.

| | LST | | HN | | CON | |
|---|---|---|---|---|---|---|
| | Pretraining | Post-training | Pretraining | Post-training | Pretraining | Post-training |
| Brachial systolic BP, mmHg | 111·3 ± 1·6 | 111·4 ± 2·8 | 108·3 ± 1·8 | 110·3 ± 1·3 | 108·4 ± 2·1 | 107·6 ± 2·6 |
| Brachial mean BP, mmHg | 80·3 ± 1·6 | 80·0 ± 2·2 | 77·8 ± 0·9 | 81·3 ± 1·4 | 77·8 ± 1·9 | 77·9 ± 2·0 |
| Brachial diastolic BP, mmHg | 60·7 ± 1·5 | 60·3 ± 2·4 | 59·4 ± 1·7 | 61·8 ± 1·9 | 59·3 ± 1·7 | 60·0 ± 1·5 |
| Femoral artery lumen diameter, mm | 8·5 ± 0·2 | 8·7 ± 0·2 | 8·4 ± 0·1 | 8·6 ± 0·2 | 8·3 ± 0·2 | 8·5 ± 0·2 |
| Femoral artery IMT, mm | 5·4 ± 0·8 | 5·6 ± 0·8 | 5·4 ± 0·7 | 5·4 ± 0·8 | 5·2 ± 0·7 | 5·3 ± 0·5 |
| Femoral artery MBV, cm $s^{-1}$ | 13·9 ± 0·8 | 15·2 ± 0·7[a,b] | 12·2 ± 0·8 | 15·7 ± 1·4[a,c] | 15·3 ± 1·5 | 14·7 ± 0·8 |
| Carotid artery lumen diameter, mm | 6·1 ± 0·1 | 6·1 ± 0·1 | 6·2 ± 0·1 | 6·1 ± 0·1 | 6·1 ± 0·1 | 6·2 ± 0·1 |
| Carotid artery IMT, mm | 4·8 ± 0·5 | 4·9 ± 0·3 | 4·7 ± 0·4 | 4·9 ± 0·5 | 4·7 ± 0·4 | 4·7 ± 0·5 |
| Carotid artery MBV, cm $s^{-1}$ | 31·0 ± 1·3 | 32·5 ± 1·0 | 29·3 ± 1·1 | 32·1 ± 1·1 | 31·0 ± 1·2 | 31·3 ± 1·3 |
| Cardiac output, l $min^{-1}$ | 3·7 ± 0·6 | 3·8 ± 0·6 | 3·9 ± 0·7 | 4·1 ± 0·9 | 4·2 ± 0·8 | 3·9 ± 0·7 |
| systemic vascular resistance, U | 22·4 ± 3·4 | 21·4 ± 4·4 | 20·8 ± 1·1 | 21·0 ± 1·7 | 19·4 ± 1·4 | 20·4 ± 0·8 |

Values are means ± SE; n = 12 for each group.
LST, low-intensity exercise with slow movement and tonic force generation; HN, high-intensity exercise with normal speed; CON, sedentary control; MBV, mean blood velocity; IMT, intima-media thickness.
[a]Significant difference ($P<0·05$) between pretraining and post-training.
[b]Increase in LST was significantly higher ($P<0·05$) than that in CON.
[c]Increase in HN was significantly higher ($P<0·05$) than that in CON.

femoral blood flow in LST corresponded to about half that in HN.

Basal femoral blood flow per unit volume of leg muscle mass changed after the experimental period in a manner similar to the basal femoral blood flow changes described above. The percent changes in basal femoral blood flow per unit volume of leg muscle mass were +15·0 ± 4·8% in LST and +29·1 ± 8·2% in HN. Percent changes in leg muscle mass after the experimental period were not related to those in basal leg blood flow in either training group (LST and HN; Fig. 3). Furthermore, percent changes in cardiac output after the experimental period were not related to those in basal leg blood flow in ether training group (LST and HN; Fig. 4).

These changes were associated with a significant increase in femoral vascular conductance and a significant reduction in femoral vascular resistance in the LST and HN groups, respectively. The increases in femoral blood flow in the LST and HN group were primarily dependent on an increase in mean blood velocity, not on artery lumen diameter (see Table 3). There were no significant changes in any carotid parameter (blood flow, vascular conductance or vascular resistance) after the experimental period in any of the three groups.

## Discussion

The present randomized-control intervention study is the first to document the effect of low-intensity (~50–60% 1RM) resistance training with slow movement and tonic force generation (LST) on basal femoral blood flow and vascular conductance. The salient findings of the present study were that basal femoral blood flow and vascular conductance significantly increased even after 13 weeks of LST training, as well as after 13 weeks of traditional high-intensity (~85–90% 1RM) resistance training with normal speed (HN) in young men.

In addition, LST resulted in increases in muscular size and strength comparable to those associated with HN (Tanimoto et al., 2008). LST met the requirement of the primary purpose of resistance training, which is to be effective for gaining muscular size and strength. Meeting this requirement is essential for any study investigating the additional effects of resistance training methods.

These findings extend our understanding of the relation between resistance training and basal limb blood flow in at least two additional ways. First, by establishing that traditional high-intensity resistance training is effective for increasing basal femoral blood flow (Miyachi et al., 2005; Anton et al., 2006), the findings presented here indicate that resistance training even in LST, which used a relatively low mechanical load, is effective for increasing basal femoral blood flow. However, we should emphasize that although not significantly different, the change in basal femoral blood flow in LST corresponded to about half that in HN. Second, by establishing that resistance training increases basal femoral blood flow in middle-aged men and women whose basal femoral blood flow decreases with the advancing age (Dinenno et al., 2001a,b; Moreau et al., 2003), the findings of the present study indicated that in both the LST and HN groups, resistance training increases basal femoral blood flow even in young men. With regard to the intergenerational differences in basal femoral blood flow changes, changes in basal femoral blood flow in young men caused by resistance training in the present study (15% in LST and 29% in HN) were lower than those in middle-aged men and women in the previous study (over 50%). This age-related difference would be due to differences in the baselines of basal femoral blood flow before the training intervention period. These findings suggest that LST training may be one of the effective strategies for increasing basal limb perfusion, and that regular resistance training from a

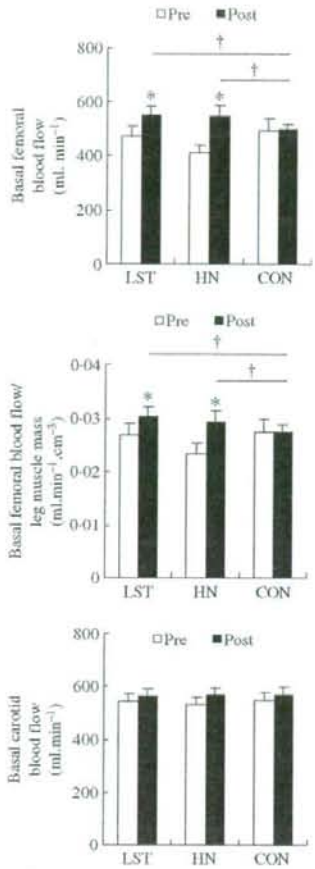


**Figure 1** Basal femoral and carotid blood flow before and after the intervention period. Means ± SE ($n = 12$ for each group) in basal femoral blood flow (top), femoral blood flow/leg muscle mass (middle) and basal carotid blood flow (bottom). *Significant difference ($P<0·05$) between pretraining and post-training values. †Significant differences ($P<0·05$) between groups. Absolute basal femoral blood flow and that per unit volume of leg muscle mass in both training groups (LST and HN) increased significantly after experimental period.

young age may contribute to preservation of basal limb blood flow.

## Potential mechanisms

What are the physiological mechanisms that would explain the increases in basal limb blood flow following resistance training? A previous study indicated that leg oxygen demand and leg muscle mass are associated with basal femoral blood flow (Dinenno et al., 2001a,b). Therefore, it was initially hypothesized that resistance training, which promotes muscular hypertrophy, increases basal femoral blood flow because muscle mass is strongly related to energy consumption (Evans & Cyr-Campbell, 1997). However, in the present study, increases in leg muscular size (3·0% in LST, 4·4% in HN) were much lower than the increases in basal femoral blood flow (18% in LST, 35% in HN), and percent changes in leg muscle mass after the experimental period were not related to those in whole-leg basal blood flow in the two training groups (LST and HN, $r = -0·05$; Fig. 3). Moreover, increases in the relative blood flow to leg muscle mass in the two training groups were quantitatively the same as increases in whole-leg blood flow (Fig. 1). These findings suggest that qualitative changes in leg muscles by resistance training (LST and HN) have a more immediate and/or potent influence than quantitative changes (gain in muscle mass).

The muscle metabolic rate and capillary density may be qualitative factors contributing to increased basal femoral blood flow. Resistance training is known to be a strong stimulus that increases skeletal muscle turnover (syntheses and degradation) (Hasten et al., 2000) and basal metabolic demands (Ades et al., 2005), which may have acted to increase blood flow independent of muscle mass. Muscular metabolic rate was not measured, while basal metabolic rate (BMR) was measured. BMR increased after the experimental period in HN ($P<0·01$) and in LST ($P<0·1$) (data not shown).

An additional possible cause of the changes in leg blood flow is that peripheral blood flow may be a simple reflection of changes in systemic blood flow (cardiac output) (Leithe et al., 1984). However, there were no obvious changes in cardiac output or TPR after the intervention period, and there was no significant relation between percent changes in cardiac output and those in basal whole-leg blood flow in either training group (LST and HN, $r = 0·19$; Fig. 4). Furthermore, basal carotid blood flow did not increase after LST and HN training. These findings suggest that the increase in basal femoral blood flow after both types of resistance training was affected not by systemic cardiovascular changes but by peripheral vascular and metabolic adaptations.

## Physiological and practical implications

The present findings have potentially important physiological and practical implications. Traditional high-intensity resistance training increases muscle mass and strength. It is widely accepted that such training also facilitates performance of daily tasks, and promotes spontaneous physical activity especially in the elderly and in subjects with low physical capacity (Borst, 2004; Hunter et al., 2004). Several recent studies showed the beneficial influence of high-intensity resistance training on vascular function, contributing to increases in basal whole leg blood flow (Miyachi et al., 2005; Anton et al., 2006). The present study in healthy young men suggested that the resistance training program in the LST group promoted muscular hypertrophy without high mechanical load and increased basal femoral blood flow as efficiently as the regimen performed by the HN group. The LST regimen was not associated with either the generation of large force or marked elevation of blood