Table 1. Physical Characteristics of Subjects Divided by Age and Light PA Level

	Young		Middle-Aged		Older	
Variables	High	Low	High	Low	High	Low
n	67	68	146	148	54	55
Men, n/%	40/60	41/60	37/25	38/26	8/15	8/15
Postmenopausal women, n/%	0/0	0/0	53/49	44/40	46/100	47/100
Age, y	34±0.4	34±0.5	50±0.5*	49±0.4*	63±0.3*†	64±0.4*†
Height, cm	167.3±1.0	167.3±0.8‡	159.8±0.6*	160.6±0.6*	157.7±0.8*	156.4±1.1*†
Weight, kg	62.2±1.4	62.7±1.3	57.9±0.8*	60.0±0.7*‡	55.3±1.2*	56.0±1.0*†
BMI, kg/m^2	22.1±0.4	22.3±0.4	22.6±0.2	23.3±0.3*	22.2±0.4	22.9±0.4
Body fat, %	20.7±0.8	22.8±0.7‡	26.6±0.5*	28.0±0.6*	27.9±0.7*	30.2±0.8*†‡
SBP, mm Hg	115±1	112±1	117±1	118±1*	118±2	125±2*†‡
DBP, mm Hg	69±1	67±8	73±1*	72±1*	70±1	75±2*†‡
MAP, mm Hg	86±1	84±1	90±1*	90±1*	90±1	96±2*†‡
PP, mm Hg	46±1	46±1	45±1	45±1	49±1*†	50±2*†
Plasma glucose, mmol/L	4.8±0.1	4.8±0.1	5.0±0.1*	5.0±0.1*	5.1±0.1*	5.4±0.1*†‡
Plasma insulin, μU/mL	3.9±0.2	4.0±0.2	3.9±0.2	4.6±0.2‡	3.9±0.3	4.7±0.4
Total cholesterol, mmol/L	4.75±0.10	4.72±0.09	5.44±0.07*	5.46±0.08*	5.90±0.11*†	5.87±0.12*†
HDL cholesterol, mmol/L	1.59±0.05	1.45±0.04‡	1.74±0.03*	1.63±0.03*‡	1.72±0.05	1.59±0.05
Triglycerides, mmol/L	0.88±0.06	0.87±0.05	0.98±0.05	1.05±0.05*	0.97±0.06	1.09±0.08*
n	63	66	145	142	48	40
$\dot{V}O_{2peak}$, mL/kg per min	38.8±1.0	34.6±0.8†	30.5±0.5*	29.8±0.6*	27.0±0.6*†	28.2±0.8*

Data are mean±SE. High and low indicate high-light PA level groups and low-light PA level groups; PP, pulse pressure.
*$P<0.05$ vs young.
†$P<0.05$ vs middle-aged.
‡$P<0.05$ vs high in the same age group.

Methods

Subjects

A total of 538 adults (172 men and 366 women), under the age of 40 years (young), 40 to 59 years of age (middle-aged), and over the age of 60 years (older) participated in this study (Table 1). None of the subjects smoked or were on medication for hypertension, hyperlipidemia, or diabetes mellitus. Subjects with a history of stroke, cardiac disease, or chronic renal failure, as well as those regularly engaging in weight training, were excluded from the study.[19] None of the female subjects were taking oral contraceptives or hormone replacement therapy. Subjects who were regularly engaged in swimming or cycle training were also excluded because the PA of swimming could not be measured and that of cycling may not be recorded accurately by triaxial accelerometry. The purpose, procedures, and risks of the study were explained to each participant, and all of the subjects gave their written informed consent before participating in the study, which was approved by the human research committee of the National Institute of Health and Nutrition. The study was performed in accordance with the guidelines of the Declaration of Helsinki. Before testing, subjects abstained from caffeine and fasted for ≥4 hours (a 12-hour overnight fast was used to determine arterial stiffness and blood pressure).

Arterial Stiffness and Blood Pressure

Subjects were studied under quiet resting conditions in the supine position. Carotid-femoral pulse wave velocity (cfPWV), which is an index of arterial stiffness, and blood pressure (BP) were measured with a vascular testing device (form PWV/ABI, Omron Colin). Carotid and femoral arterial pressure waveforms were stored for 30 seconds by applanation tonometry sensors attached to the left common carotid and left common femoral arteries. The value of cfPWV was calculated from the distance between the carotid and femoral artery sites divided by the transit time. The SD of the differences for interobserver reproducibility was 62 cm/s in our laboratory. Brachial BP was measured with an oscillometric device (form PWV/ABI, Omron Colin). Recordings were made in triplicate, with subjects in the supine position, and conformed strictly to American Heart Association guidelines.[20] The mean of right and left brachial BPs was used for analysis.

Physical Activity

The duration and intensity of PA were evaluated by triaxial accelerometry (Actimarker EW4800, Panasonic Electric Works). All of the subjects were asked to wear a triaxial accelerometer for 20 days; we used the data for 14 days, during which the accelerometer was worn continuously on waking until going to bed. Acceleration in the anterior-posterior (x), mediolateral (y), and vertical (z) axes were calculated using a sensor with a sample rate of 20 Hz over a range from 0 to $2\times g$. The apparatus stores the SD of the vector norm of the composite acceleration (K_m) in 3 dimensions each minute as follows:

$$K_m = \sqrt{\frac{1}{n-1}\left[\left(\sum_{k=1}^{n} x_k^2 + \sum_{k=1}^{n} y_k^2 + \sum_{k=1}^{n} z_k^2\right) - \frac{1}{n}\left\{\left(\sum_{k}^{n} x_k\right)^2 + \left(\sum_{k}^{n} y_k\right)^2 + \left(\sum_{k}^{n} z_k\right)^2\right\}\right]}$$

where n is the number of data for 1 minute ($n=1200$), and Σx, Σy, and Σz are the sums of the accelerations in each axis for 1 minute. The metabolic equivalent (MET) intensity levels of PA were calculated by simple linear regression of K_m. A previous validation study investigated the relationship between oxygen uptake ($\dot{V}O_2$) during 7 types of housework and 7 levels of walking/running speed and triaxial acceleration and confirmed that PA and $\dot{V}O_2$ were highly correlated ($r=0.93$).[21] We obtained daily PA duration corresponding with 1.1 to 2.9 METs (light), 3.0 to 5.9 METs (moderate), and ≥6.0

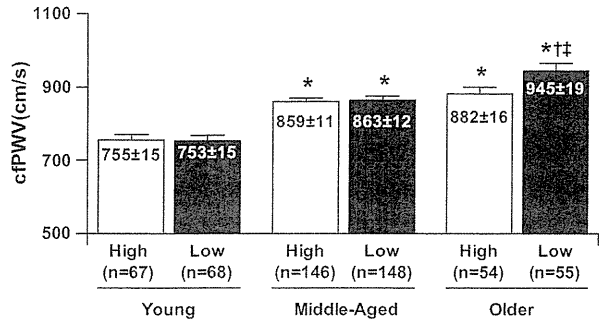

Figure 1. Arterial stiffness in high-light PA and low-light PA groups. Two-way ANOVA indicated a significant interaction between age and light PA in determining cfPWV ($P<0.05$). In older subjects, cfPWV was higher in the low-light PA group than in the high-light PA group ($P<0.01$). The differences remained significant after normalizing cfPWV for sex. *$P<0.05$ vs young; †$P<0.05$ vs middle-aged; ‡$P<0.05$ vs high in the same age group.

METs (vigorous).[22] Time spent in inactivity was defined as the sum of sedentary (<1.1 METs) and nonwearing periods, which was calculated as 1440−(daily time spent in light PA+moderate PA+vigorous PA).

To assess the effects of age and light PA on arterial stiffness, subjects in each age category were categorized into high-light PA and low-light PA groups based on the median value of the daily time spent in light PA in each age and sex category. To determine sample size of each group, we performed power calculations using nQuery Adviser version 4.0 (Statistical Solutions) before starting the study.

Cardiorespiratory Fitness

CRF, assessed from peak oxygen uptake ($\dot{V}O_{2peak}$), was measured by an incremental cycle exercise test using a cycle ergometer (Ergomedic 828E Test Cycle, Monark).[2] The incremental cycle exercise began at a work rate of 30 or 60 W for women and 60, 90, or 120 W for men, and power output was increased by 15 W · min^{-1} until the subjects could not maintain the fixed pedaling frequency (60 rpm). The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. The heart rate and rating of perceived exertion[23] were monitored on a minute-by-minute basis during exercise. $\dot{V}O_2$ was measured by the Douglas bag method during the last 30 seconds of each increase in work rate. The highest value of $\dot{V}O_2$ during the exercise test was designated as $\dot{V}O_{2peak}$. Because the test required incremental cycle exercise to exhaustion, subjects were allowed to determine whether they were willing to participate in the test; 504 of the pooled population participated in the test.

To examine whether the effects of light PA on arterial stiffness are the same in fit and unfit individuals, the subjects were categorized into high (fit) or low (unfit) CRF groups based on $\dot{V}O_{2peak}$. The $\dot{V}O_{2peak}$ reference values are provided for sex and age groups, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent lifestyle-related diseases.[24]

Blood Samples

Blood samples were taken after an overnight fast of ≥10 hours to determine fasting glucose and insulin levels. In the same session, serum samples were obtained to determine fasting total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels.

Body Composition

Body composition was determined by dual-energy X-ray absorptiometry (Hologic QDR-4500, Hologic) with subjects in the supine position.

Statistical Analyses

The data were analyzed by 2-way ANOVA (age×light PA level) and ANCOVA with sex as a covariate. In cases with a significant F value, post hoc test with the Scheffe method was used to identify significant differences among mean values. To investigate the effects of age, the groups were compared by 1-way ANOVA and Tukey post hoc test for multiple comparisons. Univariate regression and correlation analyses were used to examine the relationships between variables of interest. Spearman correlation coefficients were also used to examine the associations between the time spent in vigorous PA and cfPWV. Independent relations among the dependent variables were determined by partial correlation analysis. Stepwise multiple regression analysis was used to determine the influence of daily time spent in light, moderate, and vigorous PA on cfPWV. Colinearity was detected between daily time spent in light PA and inactivity ($r=0.97$; $P<0.001$), and the former was included in the stepwise multiple regression analysis. In all of the analyses, $P<0.05$ was considered statistically significant. Data are presented as mean±SE.

Results

Table 1 shows the physical characteristics. In young and older subjects, percentage of body fat values were higher in the low-light PA level group than in the high-light PA level group. In older subjects, SBP, DBP, and MAP were higher in the low-light PA level group than in the high-light PA level group. In older subjects, plasma glucose was higher in the low-light PA level group than in the high-light PA level group.

Figure 1 shows the effects of age and the amount of light PA on cfPWV. Two-way ANOVA indicated a significant interaction ($P<0.05$). In both light PA level groups, cfPWV was higher in middle-aged and older groups compared with the young group. In the older group, cfPWV was higher in the low-light PA level group than in the high-light PA level group ($P<0.01$). The differences remained significant after normalizing cfPWV for sex when analyzed by ANCOVA. In addition, there were no significant differences in amounts of moderate and vigorous PA between high-light PA and low-light PA in older groups (moderate: 61±3 versus 57±3 minutes/day, $P>0.05$; vigorous: 0.9±0.5 versus 1.7±0.6 minutes/day, $P>0.05$). The differences in cfPWV between the high-light PA group and low-light PA group remained significant after normalizing for amounts of moderate and vigorous PA.

Table 2 shows the PA, inactivity, and CRF of the subjects divided by age group. There were no significant differences in the number of steps among the 3 groups. $\dot{V}O_{2peak}$ decreased with age. The daily time spent in light PA was longer and the time spent in inactivity was shorter in middle-aged and older groups compared with the young group. The time spent in light PA was strongly correlated with the time spent in inactivity in all of the age groups ($r=0.97$; $P<0.001$). There were no significant differences in the daily time spent in moderate PA among the 3 groups. The daily time spent in vigorous PA was shorter in middle-aged and older groups than in the young group. The coefficients of variation in times spent in inactivity and light, moderate, and vigorous PA for 14 consecutive days were 12±1%, 17±1%, 48±3%, and 287±27%, respectively.

In the overall study population, cfPWV was weakly correlated with time spent in moderate ($r=-0.14$; $P<0.01$) or vigorous PA (Pearson $r=-0.09$; Spearman $r=0.17$; $P<0.05$)

Table 2. PA and Fitness Characteristics Divided by Age Group

Variables	Young	Middle-Aged	Older
n	135	294	109
Steps, counts per day	10 537±292	10 851±182	10 278±279
Daily time spent in PA			
Light, min/day	525±10	586±6*	592±10*
Moderate, min/day	58±2	60±1	59±2
Vigorous, min/day	4.3±0.7	2.1±0.3*	1.3±0.4*
Total, min/day	588±10	647±6*	652±10*
Inactivity, min/day	852±10	793±6*	788±10*
$\dot{V}o_{2peak}$, mL/kg per min	36.7±0.7	30.2±0.4*	27.6±0.5*†

Data are mean±SE. Total indicates (daily time spent in light PA+moderate PA+vigorous PA).

*$P<0.05$ vs young.

†$P<0.05$ vs middle-aged.

but was not significantly related to time spent in light PA or inactivity. Thus, correlations between the daily time spent in light (A), moderate (B), and vigorous (C) PA or inactivity (D) and cfPWV in each age category were analyzed (Figure 2), because cfPWV increases progressively with advancing age. In the young group, there was no relationship between daily time spent in PA and cfPWV. In the middle-aged group, cfPWV was significantly related to the daily time spent in moderate ($r=-0.21$; $P<0.01$) and vigorous ($r=-0.12$, $P<0.05$; Spearman $r=-0.19$, $P<0.01$) PA. In the older group, cfPWV was significantly related to the daily time spent in light ($r=-0.39$; $P<0.01$) and moderate ($r=-0.31$; $P<0.01$) PA and inactivity ($r=0.44$; $P<0.01$) but not in vigorous PA ($r=0.09$, $P=0.37$; Spearman $r=-0.05$, $P=0.50$). The relations remained significant after normalizing for sex in partial correlation analysis (light: $r=-0.30$; moderate: $r=-0.29$). The above results were confirmed in stepwise multiple regression analysis. In the middle-aged subjects, cfPWV was independently predicted by the daily time spent in moderate PA ($\beta=-0.22$). In the older subjects, cfPWV was independently predicted by the daily time spent in light ($\beta=-0.39$) and moderate ($\beta=-0.30$) PA. In general, qualitatively similar results (although inverse in direction) were obtained using time spent in inactivity in place of light PA.

Figure 3 shows the relationships between the daily time spent in light PA and cfPWV or MAP in unfit (n=56) and fit (n=32) older subjects. The cfPWV ($r=-0.47$; $P<0.01$) and MAP ($r=-0.30$; $P<0.05$) were correlated with the daily time spent in light PA in unfit subjects. No such relationships were observed in older fit subjects.

Discussion

The key new findings of the present study were as follows. First, in older subjects, arterial stiffness was higher in the low-light PA level group as compared with the high-light PA level group. The differences remained significant after normalizing cfPWV for amounts of moderate and vigorous PA. Second, a negative relationship between the daily time spent in light PA and arterial stiffness was observed in the older group. Third, although the daily time spent in light PA was inversely related with the arterial stiffness in unfit subjects, no such relationship was observed in fit subjects. These results suggest that the longer time spent in light PA <3 METs, such as housework or other unstructured activities, is associated with attenuation of arterial stiffening, especially in unfit older people. Our findings have important implications, because increasing light PA may be easier to achieve in the older population than increasing structured exercise training at vigorous or moderate intensities.

Little information is available regarding the relationships between light PA and arterial stiffness. Therefore, we determined the relationships between the daily times spent in inactivity and light, moderate, and vigorous PA and arterial stiffness. The strength of the present study was that daily PA levels of subjects were evaluated by triaxial accelerometry, because self-reported PA may be subject to bias and misclassification,[10] and this method allows for better determination of light PA.[16] Similar to previous findings, the present study also showed that arterial stiffness was significantly related to the daily time spent in moderate PA in middle-aged and older groups. More importantly, the present study first demonstrated that the daily time spent in light PA was inversely related with arterial stiffness in the older group, independent of the daily time spent in moderate and vigorous PA. Moreover, qualitatively similar results (although inverse in direction) were obtained using time spent in inactivity in place of light PA. The present findings suggest that replacing inactivity with light PA may be one factor associated with reduced arterial stiffening in older people.

One possible reason for the negative association between light PA and arterial stiffness is that light PA may be relatively harder for older subjects than for young and middle-aged subjects, because CRF in the older group was significantly lower than those in the young and middle-aged groups. Indeed, relative intensities (%$\dot{V}o_{2peak}$) at 3 METs in young, middle-aged, and older groups corresponded with 29%, 35%, and 38% of $\dot{V}o_{2peak}$, respectively. The relative intensity of PA may be an important factor in considering physiological adaptation of arterial stiffness, because it is strongly related with heart rate and BP responses during PA. In the present study, we found that plasma glucose was higher in the low-light PA level group than in the high-light PA level group among older subjects. Several recent studies indicated that objective measured light-intensity PA is beneficially associated with blood glucose and other metabolic risk factors.[18,25–27] Taken together, these findings suggested that the favorable effect of light PA on arterial stiffness is mediated by metabolic profile improvement. Other mechanisms by which daily light PA may influence arterial stiffness in older people are still speculative and include the effects of PA on the bioavailability of NO, vascular smooth muscle tone, connective tissue cross-linking, and gene expression.[28–30]

Our findings have a number of important practical implications. Increasing light PA may be easier to achieve in older people, especially in the unfit older population. In fact, the CRF and time spent in vigorous PA in the older group were markedly lower than those in middle-aged and young groups (Table 2). Moreover, subjects spent only a small proportion of time in moderate (59.0 minutes/day) and vigorous (1.3 minutes/day) PA. Most time spent can be categorized broadly

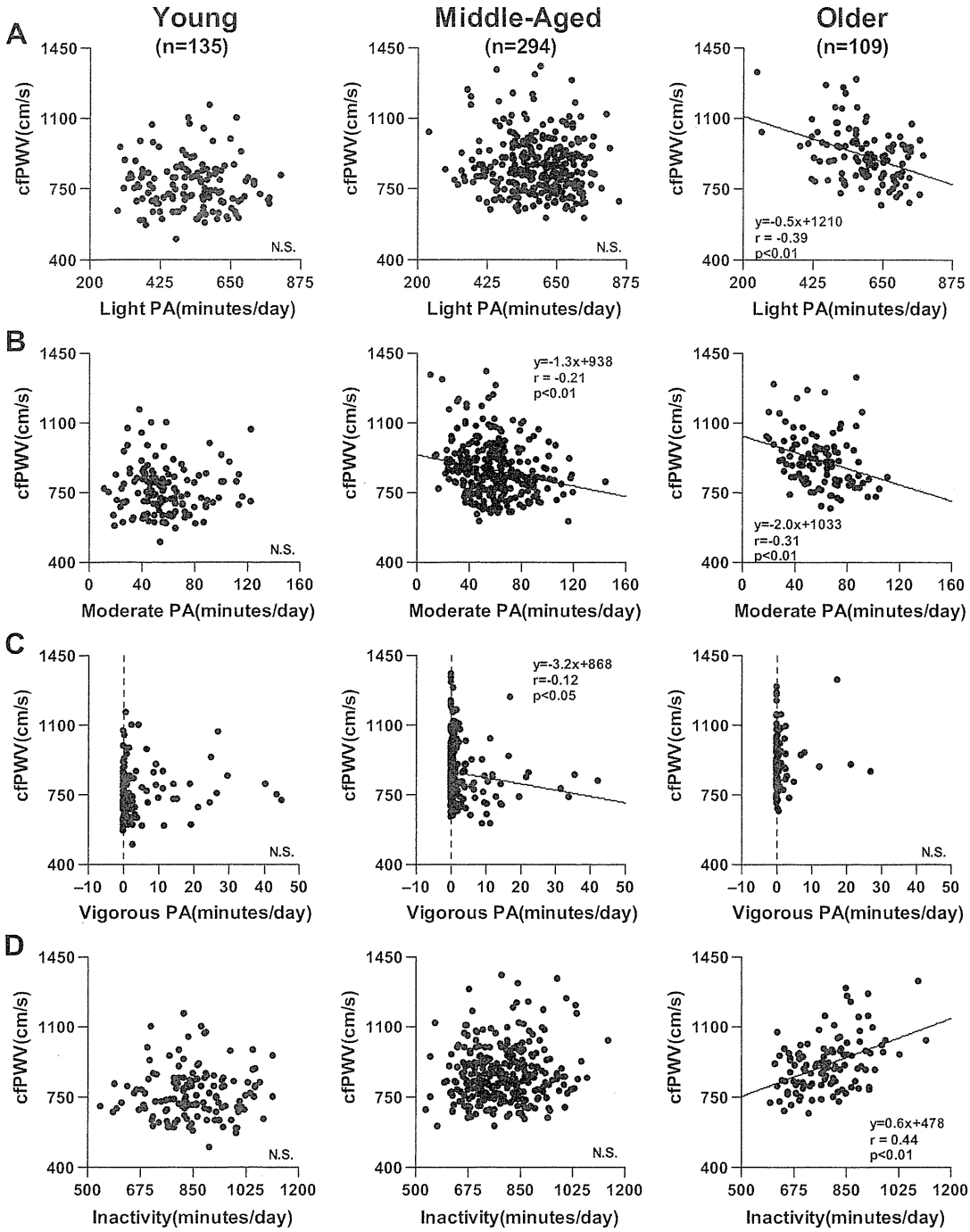

Figure 2. Relationships between daily time spent in each PA intensity and cfPWV. In the older group, cfPWV was significantly related to the daily time spent in light PA ($r=-0.39$; $P<0.01$), moderate PA ($r=-0.31$; $P<0.01$), and inactivity ($r=0.44$; $P<0.01$).

into 2 distinct modes: light PA and inactivity (mostly sedentary and sleeping time). Those who spent more time in light PA must, therefore, spend less time in sedentary behaviors. A recent prospective study suggested that increased time spent in sedentary activities is associated with elevated fasting insulin levels regardless of the amount of time spent in moderate-vigorous PA.[31] Substituting light PA for sedentary behavior may be a practical and achievable preventive strategy in older people. Light PA can be achieved through household tasks and other nonexercise activities, which need not be fitness-enhancing activities. The modes of PA that are common at the population level are primarily unstructured forms, and our data indicated that elevated energy expenditure through less-defined modes of PA is likely to be important in the primary prevention of arterial stiffening. On the other hand, we should emphasize that structured exercise training from moderate to vigorous intensity is an important way in which arterial stiffening may be prevented.

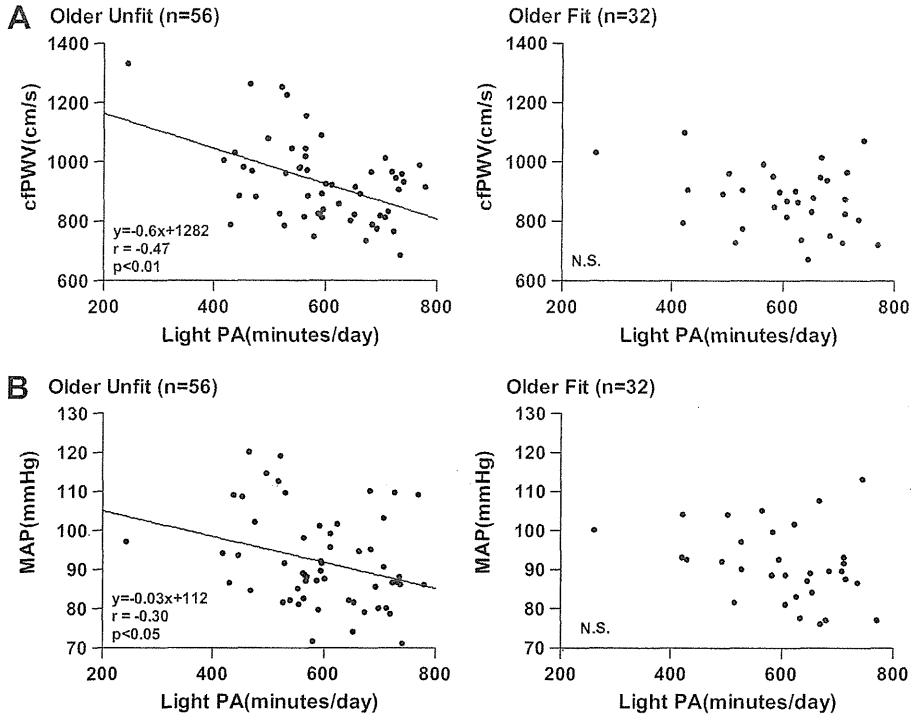

Figure 3. Relationships between daily time spent in light PA and cfPWV (A) and MAP (B) in unfit and fit older subjects. The cfPWV ($r=-0.47$; $P<0.01$) and MAP ($r=-0.30$; $P<0.05$) were correlated with the daily time spent in light PA in unfit subjects.

As the initial approach to determine the relationships between the PA at various intensities or CRF and arterial stiffness, we used a cross-sectional study design. Because of the limitations associated with this design, we attempted to isolate the influence of light PA level as much as possible. To do so, low-light and high-light PA groups were carefully matched for age, number of males, and menopausal status. In addition, to isolate the effects of light PA, per se, we performed 2-way ANCOVA (age×light PA level) with these covariates. However, because of the design of this study, we could not evaluate individual changes in age-related arterial stiffness. A prospective study is needed to determine the cause-and-effect relationships between PA at various intensities and arterial stiffness. Moreover, in the present study, the time spent in light PA included all of the activities under 3 METs, for example, intermittent unstructured activities and continuous slow walking, and also included daily variations attributed mainly to changes in work-leisure balance. Although we will be able to clarify the type, duration, frequency, and daily variation of activity by analyzing the data accumulated with the accelerometer, the analysis will be very difficult. Therefore, further studies are required to make definitive conclusions regarding which pattern of activity is the most beneficial.

Perspectives

The present study indicated that time spent in light PA is negatively associated with arterial stiffness in older people. The association was especially evident in unfit subjects. Moreover, qualitatively similar results (although inverse in direction) were obtained using time spent in inactivity. These findings suggested that replacing inactivity with light PA, such as household tasks and other unstructured activities, may be an effective means of preventing age-related arterial stiffening. The underlying mechanisms and practical implications of these findings warrant further investigation.

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Disclosures

None.

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ORIGINAL ARTICLE

A cross-sectional study of sarcopenia in Japanese men and women: reference values and association with cardiovascular risk factors

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Abstract In this study of Japanese men and women, we determine reference values for sarcopenia and test the hypothesis that sarcopenia is associated with risk factors for cardiovascular disease, independent of waist circumference. A total of 1,488 Japanese men and women aged 18–85 years participated in this study. Appendicular muscle mass (AMM) was measured by dual-energy X-ray absorptiometry. Reference values for classes 1 and 2 sarcopenia (skeletal muscle index: AMM/height^2, kg m^{-2}) in each sex were defined as values one and two standard deviations below the sex-specific means of reference values obtained in this study from young adults aged 18–40 years. The reference values for class 1 and class 2 sarcopenia were 7.77 and 6.87 kg m^{-2} in men and 6.12 and 5.46 kg m^{-2} in women. In subjects both with class 1 and class 2 sarcopenia, body mass index and % body fat were significantly lower than in normal subjects. Despite whole-blood glycohaemoglobin A1c in men with class 1 sarcopenia was significantly higher than in normal subjects, and brachial-ankle pulse wave velocity in women both with class 1 and class 2 sarcopenia were significantly higher than in normal subjects, using one-way ANCOVA with adjustment for the covariate of waist circumference. Although sarcopenia is associated with thin body mass, it is associated with more glycation of serum proteins in men and with greater arterial stiffness in women, independent of waist circumference.

Keywords CVD risk · Japanese · Obesity · Reference value · Sarcopenia

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Introduction

Sarcopenia, the decline of muscle mass with age, causes several disabilities (Alexander et al. 1995; Judge et al. 1993; Wolfson et al. 1995) and lifestyle-related diseases (Karakelides and Nair 2005; Roubenoff 2004; Schrager et al. 2007; Walsh et al. 2006). Although many potential mechanisms of sarcopenia have been investigated such as the level of physical activity, hormone deficiency and dietary protein intake, chronic inflammation and production of catabolic cytokines have been reported to be one such mechanism (Schrager et al. 2007). This chronic inflammation is a typical phenomenon linked to ageing and is considered the major risk factor for age-related chronic diseases (Licastro et al. 2005). For example, skeletal muscle, which is the main consumer of glucose and target of insulin activity, is important for glucose metabolism and could be a good target for the treatment of metabolic disorders such as insulin resistance, reduced glucose

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tolerance, and type 2 diabetes mellitus (DeFronzo 1988; Shepherd and Kahn 1999). The metabolic effects of sarcopenia include a decrease in resting metabolic rate secondary to decreased fat-free mass and decreased physical activity, leading to a higher prevalence of insulin resistance, type 2 diabetes mellitus, dyslipidemia, and hypertension (Karakelides and Nair 2005).

Conversely, in abdominal obesity, increased macrophage infiltration occurs in adipose tissue, which also contributes to chronic inflammation and insulin resistance (Oparil and Oberman 1999; Gasteyger and Tremblay 2002). The deleterious effect of abdominal obesity is believed to be due to visceral adipose tissue, the amount of which is strongly correlated with traditional cardiovascular disease (CVD) risk factors: total cholesterol, low high-density lipoprotein (HDL)-cholesterol, triglycerides, blood pressure, glycation of serum proteins, and arterial stiffness (Johnson et al. 1992; Lear et al. 2007; Pouliot et al. 1994). Therefore, the combination of sarcopenia and abdominal obesity may promote inflammation, possibly further accelerating the progression of CVD. However, it is not clear whether sarcopenia is associated with CVD risk factors independent of abdominal obesity in either men or women.

Reference data are available from the New Mexico Elder Health Survey (Baumgartner et al. 1998), in which appendicular muscle mass was measured by dual-energy X-ray absorptiometry (DXA) in 883 randomly selected elderly Hispanic and white men and women. Sarcopenia was defined as a muscle mass 2 standard deviations (SD) below the mean for young healthy participants in the Rosetta Study (Wang et al. 1989). We, therefore, performed the present study in Japanese men and women, to determine reference values for sarcopenia and test the hypothesis that sarcopenia is associated with CVD risk factors independent of waist circumference.

Methods

Subjects

Healthy Japanese men ($n = 434$) and women ($n = 1{,}054$) aged 18–85 years participated in this study. The study population included young adults (266 men and 263 women) aged 18–40 years, examined to define the reference values, and those aged 41 years or older (168 men and 791 women). Subjects were recruited from the community near the National Institute of Health and Nutrition (Tokyo, Japan). All subjects were active and free of overt CVD as determined using a medical history questionnaire. All assessments were conducted at the National Institute of Health and Nutrition between February 2004 and February 2009 (Miyatani et al. 2008).

The subjects were not taking any medications such as beta-blockers, steroids or hormone replacement therapy. The study population included both sedentary and active men and women. Active subjects participated in a swimming program involving at least two sessions per week, 1 h per session, however, they were not highly trained athletes.

The purpose, procedures and risks of the study were explained to all participants prior to inclusion, and all subjects gave their written informed consent before participating in the study. The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the Human Research Committee of the National Institute of Health and Nutrition, Tokyo, Japan.

Analysis of blood samples

All blood samples were drawn with the subject in the seated position. Fasting (>12 h) blood samples were collected by venepuncture in tubes with or without ethylenediamine tetraacetic acid (for plasma or serum), refrigerated immediately and centrifuged at 1,500 rpm for 30 min at 4°C within 2 h. These samples were stored at –20°C. Serum concentrations of total cholesterol and triglyceride were determined using commercial kits (Mitsubishi Chemical Medience, Tokyo, Japan). Serum HDL-cholesterol was measured by an enzymatic method (Mitsubishi Chemical Medience). Serum low-density lipoprotein (LDL) cholesterol levels were calculated as follows: total cholesterol (mg dL^{-1}), HDL-cholesterol (mg dL^{-1}), triglyceride (mg dL^{-1}) × 0.2 (Friedewald et al. 1972). Plasma glucose was measured using the glucose dehydrogenase method (Kuan et al. 1977). Whole-blood glycohaemoglobin A1c (HbA1c) was measured by an enzymatic method (Glycohemoglobin A1c kit; Mitsubishi Chemical Medience).

Analysis of arterial blood pressure at rest

Systolic blood pressure and diastolic blood pressure were measured at rest using a vascular testing device (Form PWV/ABI; Colin Medical Technology, Komaki, Japan). Chronic arterial blood pressure levels at rest were measured with the same device over the brachial and dorsalis pedis arteries. Recordings were made in triplicate with subjects in the supine position. The brachial-ankle pulse wave velocity (baPWV), which provides qualitatively similar information to that derived from central arterial stiffness (Sugawara et al. 2005), was measured by the volume plethysmographic method.

In addition to accumulation of visceral fat (waist circumference ≥85 cm in men, ≥90 cm in women), subjects with one or more of the following risk factors were considered to have metabolic syndrome: high systolic and diastolic blood pressure (≥130 mmHg for systolic blood pressure and/or ≥85 mmHg for diastolic blood pressure), abnormal serum lipids (≥150 mg dL^{-1} for triglyceride and/or <40 mg dL^{-1} for HDL cholesterol), and high plasma glucose level (≥110 mg dL^{-1}).

Measures of whole-body DXA

Lean soft tissue mass and bone mineral density (BMD) were determined for the whole body using DXA (Hologic QDR-4500A scanner; Hologic, Waltham, MA, USA). Participants were positioned for whole-body scans in accordance with the manufacturer's protocol. Participants lay in the supine position on the DXA table with limbs close to the body. To minimize interobserver variation, all scans and analyses were carried out by the same investigator, and the day-to-day CVs of these observations were <0.8% for (whole-body BMD) (BMD taken over the whole body) (Sanada et al. 2009a). The whole-body lean soft tissue mass was divided into several regions, i.e., the arms, legs and trunk. Body composition was analysed using manual DXA analysis software (version 11.2:3). Reference values (skeletal muscle index (SMI): appendicular muscle mass (AMM)/height^2, kg m^{-2}) for class 1 and class 2 sarcopenia in each sex were defined as values 1 and 2 SD below the sex-specific means of the study reference data for young adults aged 18–40 years, respectively.

Measures of fitness

The maximum oxygen uptake ($\dot{V}O_2$ max) was measured by incremental exercise testing using a cycle ergometer. The incremental cycle exercise began at a work rate of 90 W (60 rpm), and power output was increased by 30 W min^{-1} until the subjects could not maintain the fixed pedalling frequency. During the ergometer test, the subjects were encouraged to exercise at as high an intensity as possible. Rating of perceived exertion was obtained using the modified Borg scale (Borg 1982). Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O_2 and CO_2 gas concentrations were measured by mass spectrometry (WSMR-1400; Westron, Chiba, Japan), and gas volume was determined using a dry gas meter (NDS-2A-T; Shinagawa Dev., Tokyo, Japan). The highest value of $\dot{V}O_2$ during the exercise test was designated as $\dot{V}O_2$ max.

Handgrip strength of the right upper limb was measured using a handheld dynamometer. In the standing position, with the arms straight by the sides, the subject gripped the dynamometer as hard as possible for 3 s without pressing the instrument against the body or bending at the elbow. Values (kilogram) were recorded as the average of two trials.

Leg extension power was measured with an isokinetic leg power system (Anaero Press 3500; Combi Wellness, Tokyo, Japan) in the sitting position.

Statistical analysis

All measurements and calculated values are expressed as mean ± SD. We compared the mean values of general criteria, body composition values, fitness values and CVD risk between normal and sarcopenia groups by one-way ANCOVA with adjustment for the covariate of waist circumference. In addition, we tested the interaction of sarcopenia and gender on risk factors for CVD by two-way ANCOVA with adjustment for the covariate of waist circumference (sarcopenia and gender). Student unpaired t test was used for testing significance among the normal subjects, class 1 sarcopenia and class 2 sarcopenia. The alpha level for testing significance was set at $P < 0.05$. All statistical analyses were performed using StatView v5.0 for Windows (SAS Institute, Cary, NC, USA).

Results

The physical characteristics of young men and women (age ≤ 40 years) are shown in Table 1. The SMI in young men and women aged 18–40 years were 8.67 ± 0.90 and 6.78 ± 0.66 kg m^{-2}, respectively. Therefore, the reference values for class 1 sarcopenia (1 SD below the

Table 1 Physical characteristics of young men and women (age ≤ 40 years)

	Men (age ≤ 40 years) $n = 266$	Women (age ≤ 40 years) $n = 263$
Age (years)	28.2 ± 7.4	28.0 ± 7.0
Body height (cm)	173.4 ± 5.5	160.4 ± 5.8
Body mass (kg)	68.9 ± 9.1	53.5 ± 7.5
BMI (kg m^{-2})	23.0 ± 3.0	20.8 ± 2.6
%fat (%)	16.6 ± 4.8	23.9 ± 5.8
AMM (kg)	26.1 ± 3.1	17.5 ± 2.3
SMI (kg m^{-2})	8.67 ± 0.90	6.78 ± 0.66
VO_2max (ml kg^{-1} min^{-1})	41.6 ± 9.6	36.1 ± 6.5
Handgrip strength (kg)	44.8 ± 7.1	29.8 ± 5.3
LEP (W)	1,834 ± 452	952 ± 254

Data are presented as mean values ± SD

BMI body mass index, *AMM* appendicular muscle mass, *SMI* skeletal muscle index, *BMD* bone mineral density, *LEP* leg extension power

sex-specific means) in Japanese men and women were 7.77 and 6.12 kg m^{-2}, respectively. Similarly, the reference values of class 2 sarcopenia (2 SD below the sex-specific means) in Japanese men and women were 6.87 and 5.46 kg m^{-2}, respectively. The prevalence rates of class 1 and class 2 sarcopenia in subjects 70–85 years of age were 6.7 and 56.7% in men and 6.3 and 33.6% in women, respectively.

Comparisons between physical characteristics of subjects and sarcopenia in adult men and women (age $\geq$ 41 years) by one-way ANCOVA with adjustment for the covariate of waist circumference are shown in Table 2. In subjects both with class 1 and class 2 sarcopenia, body mass index (BMI) and % body fat were significantly lower than in normal subjects. Whole-body and regional BMD (arm, lumbar spine and leg) were significantly lower in men and women both with class 1 and class 2 sarcopenia than in normal subjects ($P < 0.05$). Handgrip strength in men and women both with class 1 and class 2 sarcopenia were significantly lower than in normal subjects ($P < 0.05$). The values of $\dot{V}O_2$ max (normalised to body mass) in men and women with class 1 sarcopenia were significantly lower than in normal subjects ($P < 0.05$).

The waist circumference was significantly lower in men and women both with class 1 and class 2 sarcopenia than in normal subjects ($P < 0.005$). Comparisons between subjects' risk factors for CVD and sarcopenia in adult men and women (age $\geq$ 41 years) by one-way ANCOVA with adjustment for the covariate of waist circumference are shown in Table 3. The HbA1c in men with class 1 sarcopenia was significantly higher than in normal subjects ($P < 0.0001$). The baPWV were significantly higher in women both with class 1 and class 2 sarcopenia than in normal subjects ($P < 0.0001$).

We tested the interaction of sarcopenia and gender on risk factors for CVD by two-way ANCOVA with adjustment for the covariate of waist circumference (Table 4). The effect of the interaction between sarcopenia (normal vs. class 1) and gender on HbA1c was significant on two-way ANCOVA ($P = 0.010$). Therefore, we analysed separately for sarcopenia and gender groups. Consequently, the HbA1c was significantly lower in normal men than in men with class 1 sarcopenia and in all women (normal and class 1 sarcopenia) by student unpaired t test ($P < 0.05$). However, the effect of sarcopenia (normal vs. class 1) on HbA1c was not approached significance on two-way ANCOVA (sarcopenia and gender). On the other side, the effect of the interaction between sarcopenia (normal vs. class 1 and class 2 sarcopenia) and gender on baPWV was not approached significance on two-way ANCOVA ($P = 0.166$). Although the effect of sarcopenia (normal vs. class 1) on baPWV after adjustment for waist circumference was not approached significance on two-way ANCOVA (sarcopenia and gender), the effect of sarcopenia (normal vs. class 2 and class 1 vs class 2) on baPWV were significant ($P < 0.05$).

Discussion

This cross-sectional study of Japanese men and women was performed to investigate the reference values for sarcopenia and examine whether sarcopenia is associated with CVD risk independent of waist circumference. The major findings of this study were as follows: (1) the reference values for class 1 and class 2 sarcopenia were 7.77 and 6.87 kg m^{-2} in Japanese men and 6.12 and 5.46 kg m^{-2} in Japanese women, respectively; (2) sarcopenia is associated with lower BMI and % body fat. However, among the subjects with class 1 sarcopenia, men had significantly elevated glycation of serum proteins and women had significantly elevated arterial stiffness independent of waist circumference.

Reference values for sarcopenia

Sarcopenia is important because a loss of more than 40% of muscle mass is associated with death, and muscle loss can contribute to diminished strength, functional limitation, and disability in the elderly (Roubenoff and Hughes 2000) and in those with chronic inflammatory conditions (Helliwell and Jackson 1994; Stucki et al. 1994). Baumgartner et al. (1998) measured AMM by DXA in elderly Hispanic and white men and women, and reported cut-off values for sarcopenia. Sarcopenia was defined as muscle mass 2 SD below the mean for young healthy participants in the Rosetta Study (Wang et al. 1989). These authors established values for sarcopenia (AMM/height^2) of 7.26 kg m^{-2} for men and 5.45 kg m^{-2} for women. The prevalence rate increased from 13.5 to 24% in subjects less than 70 years of age, and was slightly greater in Hispanic subjects than in non-Hispanic white subjects. To our knowledge, previous studies of reference data for sarcopenia were limited to subjects of Caucasian and African American ethnicity (Baumgartner et al. 1998; Janssen et al. 2002). Our results showed that the cut-off values for sarcopenia were 6.87 and 5.46 kg m^{-2} in Japanese men and women, respectively, and the prevalence rates of class 1 and class 2 sarcopenia in subjects 70–85 years of age were 6.7 and 56.7% in men, and 6.3 and 33.6% in women, respectively. These values are lower than those in other ethnic groups because Japanese people are thinner than the populations of the USA and Western Europe (Flegal et al. 2002; Mokdad et al. 2003; Seidell 1997; Yoshiike et al. 2002).

Table 2 Physical characteristics of adult men and women (age ≤ 41 years)

	Men (age ≤ 41 years)						Women (age ≤ 41 years)					
	Normal ($n = 100$)	Class 1 sarcopenia ($n = 63$)	Class 2 sarcopenia ($n = 5$)	*P* value by one-way ANCOVA			Normal ($n = 613$)	Class 1 sarcopenia ($n = 156$)	Class 2 sarcopenia ($n = 22$)	*P* value by one-way ANCOVA		
				Normal versus class 1	Normal versus class 2	Class1 versus class 2				Normal versus class 1	Normal versus class 2	Class1 versus class 2
Age (years)	64.9 ± 7.5	65.0 ± 14.0	67.0 ± 16.9	0.442	0.641	0.583	59.8 ± 8.6	60.8 ± 10.9	62.5 ± 11.4	0.275	0.198	0.419
BMI (kg m^{-2})	25.0 ± 2.2	21.9 ± 1.8	20.2 ± 2.0	0.000	0.003	0.605	23.5 ± 3.0	20.4 ± 1.6	19.4 ± 2.0	0.000	0.000	0.023
% body fat (%)	22.3 ± 3.8	20.9 ± 5.2	21.8 ± 2.9	0.007	0.000	0.001	29.8 ± 5.6	29.0 ± 4.4	30.7 ± 6.0	0.000	0.000	0.005
AMM (kg)	23.6 ± 2.2	21.0 ± 1.6	18.4 ± 2.5	0.000	0.001	0.020	16.4 ± 1.9	14.1 ± 1.0	12.5 ± 1.1	0.000	0.000	0.000
SMI (kg m^{-2})	8.53 ± 0.53	7.48 ± 0.21	6.51 ± 0.16	0.000	0.000	0.000	6.84 ± 0.51	5.89 ± 0.17	5.25 ± 0.14	0.000	0.000	0.000
Whole-body BMD (g cm^{-2})	1.04 ± 0.08	0.96 ± 0.09	0.92 ± 0.15	0.000	0.021	0.675	0.86 ± 0.09	0.81 ± 0.09	0.77 ± 0.05	0.000	0.000	0.075
Arm BMD (g cm^{-2})	1.58 ± 0.10	1.48 ± 0.11	1.42 ± 0.08	0.000	0.000	0.359	1.27 ± 0.13	1.21 ± 0.13	1.18 ± 0.08	0.000	0.000	0.307
Lumbar spine BMD (g cm^{-2})	1.15 ± 0.18	1.05 ± 0.18	0.89 ± 0.16	0.029	0.025	0.260	0.97 ± 0.18	0.90 ± 0.16	0.82 ± 0.11	0.000	0.001	0.031
Leg BMD (g cm^{-2})	2.51 ± 0.21	2.31 ± 0.20	2.13 ± 0.20	0.000	0.001	0.191	2.08 ± 0.22	1.95 ± 0.20	1.87 ± 0.09	0.000	0.001	0.108
VO_2max (ml kg^{-1} min^{-1})	29.0 ± 4.4	33.4 ± 5.2	30.3 ± 2.1	0.016	0.691	0.890	29.4 ± 6.2	27.1 ± 4.9	21.3 ± 1.2	0.000	0.002	0.016
Handgrip strength (kg)	37.6 ± 5.5	35.5 ± 6.3	31.7 ± 6.2	0.012	0.020	0.194	26.4 ± 4.7	23.2 ± 4.1	21.4 ± 4.9	0.000	0.000	0.083
LEP (W)	1,222 ± 365	1,050 ± 401	883 ± 569	0.018	0.120	0.538	778 ± 224	630 ± 190	483 ± 153	0.000	0.000	0.001

Data are presented as mean values ± SD

Waist C waist circumference

Table 3 Comparisons between subjects' risk factors for cardiovascular disease and sarcopenia in adult men and women (age ≤ 41 years) by one-way ANCOVA with adjustment for the covariate of waist circumference

	Men (age ≤ 41 years)						Women (age ≤ 41 years)					
	Normal ($n = 100$)	Class 1 sarcopenia ($n = 63$)	Class 2 sarcopenia ($n = 5$)	*P* values by one-way ANCOVA			Normal ($n = 613$)	Class 1 sarcopenia ($n = 156$)	Class 2 sarcopenia ($n = 22$)	*P* values by one-way ANCOVA		
				Normal versus class 1	Normal versus class 2	Class1 versus class 2				Normal versus class 1	Normal versus class 2	Class1 versus class 2
Waist C (cm)[a]	88.6 ± 7.5	83.3 ± 6.5	76.9 ± 9.5	**0.000**	**0.004**	0.075	83.7 ± 9.4	77.6 ± 7.7	75.3 ± 6.4	**0.000**	**0.000**	0.191
SBP (mmHg)	131.7 ± 15.5	130.1 ± 21.3	134.1 ± 29.1	0.284	0.359	0.370	124.7 ± 19.2	123.9 ± 19.8	132.6 ± 16.5	0.283	**0.008**	**0.026**
MBP (mmHg)	102.8 ± 13.5	98.6 ± 15.7	100.0 ± 17.5	0.941	0.690	0.445	95.3 ± 14.7	94.7 ± 15.2	98.8 ± 10.9	0.197	**0.043**	0.115
DBP (mmHg)	82.0 ± 10.5	75.3 ± 8.7	79.3 ± 14.7	**0.029**	0.877	0.212	72.6 ± 10.2	72.0 ± 11.4	74.7 ± 8.9	0.299	0.064	0.165
baPWV (cm s^{-1})	1,501 ± 248	1,534 ± 324	1,660 ± 322	0.087	0.162	0.184	1,340 ± 219	1,452 ± 355	1,593 ± 290	**0.000**	**0.000**	0.061
FPG (mg dl^{-1})	95.6 ± 8.4	94.8 ± 10.3	100.5 ± 5.2	0.513	0.099	0.073	94.0 ± 8.8	96.1 ± 9.0	95.0 ± 11.7	0.137	0.186	0.432
HgA1c (%)	4.99 ± 0.29	5.26 ± 0.46	5.25 ± 0.39	**0.000**	0.059	0.568	5.15 ± 0.36	5.17 ± 0.41	5.29 ± 0.37	0.124	**0.023**	0.131
TG (mg dl^{-1})	124.2 ± 81.9	109.4 ± 66.3	98.0 ± 36.6	0.973	0.633	0.931	102.2 ± 56.4	103.9 ± 65.9	97.0 ± 57.0	0.142	0.796	0.896
TC (mg dl^{-1})	188.2 ± 39.0	171.3 ± 35.4	189.3 ± 10.8	**0.021**	0.828	0.316	210.3 ± 45.7	207.9 ± 45.9	212.8 ± 44.8	0.796	0.488	0.538
HDLC (mg dl^{-1})	56.1 ± 13.5	57.9 ± 14.7	66.3 ± 29.5	0.253	0.787	0.834	65.6 ± 14.7	69.1 ± 15.3	69.0 ± 19.8	0.427	0.980	0.697
TC/HDLC ratio	3.53 ± 1.02	3.14 ± 0.98	3.29 ± 1.33	0.478	0.520	0.303	3.36 ± 1.01	3.14 ± 0.90	3.22 ± 0.83	0.565	0.706	0.402
MetS no.	1.71 ± 1.05	0.75 ± 0.50	1.10 ± 1.03	0.588	0.950	0.531	0.84 ± 0.87	0.63 ± 0.82	0.76 ± 0.77	0.155	**0.024**	0.189

Data are presented as mean values ± SD. Bold values are $P < 0.05$ and *P* values by Student unpaired *t* test

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *baPWV* brachial-ankle pulse wave velocity, *TG* triglycerides, *TC* total cholesterol, *HDLC* high-density lipoprotein cholesterol, *FPG* fasting plasma glucose, *MetS No.* number of risk factors of metabolic syndrome

[a] Mean ± SD is unadjusted

Table 4 Comparisons between subjects' risk factors for cardiovascular disease and sarcopenia in adult men and women (age ≥ 41 years) by two-way ANCOVA with adjustment for the covariate of waist circumference (*P* values)

	Interaction of sarcopenia (normal vs. class 1) and gender			Interaction of sarcopenia (normal vs. class 2) and gender			Interaction of sarcopenia (class 1 vs. class 2) and gender		
	Sarcopenia effect	Gender effect	Interaction	Sarcopenia effect	Gender effect	Interaction	Sarcopenia effect	Gender effect	Interaction
SBP (mmHg)	0.188	0.106	0.926	0.153	0.871	0.875	0.056	0.509	0.841
MBP (mmHg)	0.143	0.125	0.328	0.206	0.702	0.760	0.068	0.565	0.771
DBP (mmHg)	0.172	0.389	**0.011**	0.794	0.923	0.590	0.442	0.638	0.635
baPWV (cm s^{-1})	0.128	0.184	0.166	**0.009**	0.699	0.670	**0.024**	0.320	0.564
FPG (mg dl^{-1})	0.158	0.253	0.582	0.252	0.860	0.446	0.677	0.340	0.186
HgA1c (%)	0.258	0.347	**0.010**	0.782	0.910	0.599	0.760	0.232	0.991
TG (mg dl^{-1})	0.592	0.066	0.449	0.496	**0.006**	0.702	0.521	0.606	0.918
TC (mg dl^{-1})	0.419	0.445	**0.047**	0.856	0.342	0.676	0.591	0.874	0.596
HDLC (mg dl^{-1})	0.726	**0.046**	0.281	**0.009**	**0.032**	0.931	**0.022**	0.241	0.539
TC/HDLC ratio	0.399	0.166	0.559	0.078	0.233	0.819	0.116	0.328	0.629
MetS no.	0.554	**0.000**	0.365	0.232	**0.016**	0.518	0.289	**0.004**	0.859

Bold values are $P < 0.05$

Relationship between sarcopenia and CVD risk factors

A major purpose of this study was to test the hypothesis that in Japanese men and women sarcopenia is associated with CVD risk independent of waist circumference. Ageing is accompanied by changes in body composition characterised by a relative decline of muscle mass (Aniansson et al. 1983) and an increase in fat mass (Lara-Castro et al. 2002). In certain individuals, these changes are extreme and produce a combination of substantial overweight and muscle weakness, a condition recently termed "sarcopenic obesity" (Roubenoff 2000; Roubenoff and Hughes 2000). Schrager et al. (2007) reported that global obesity and, to a greater extent, central obesity directly affect inflammation, which in turn negatively affects muscle strength, contributing to the development and progression of sarcopenic obesity. These findings suggest that proinflammatory cytokines may be critical in both the development and progression of sarcopenic obesity. However, the results of the present study indicated that sarcopenia is associated with lower BMI and % body fat, it is associated with more glycation of serum proteins in men independent of waist circumference independent of waist circumference (Table 3). Thus sarcopenia in men may be associated with higher glycation of serum proteins regardless of the presence of abdominal obesity. Moreover, the effect of the interaction between sarcopenia (normal vs.. class 1) and gender on HbA1c after adjustment for waist circumference was significant (Table 4). Therefore, we analysed separately for sarcopenia and gender groups. Consequently, the HbA1c in normal men was significantly lower than in men with class 1 sarcopenia and in all women (normal, class1 and class 2 sarcopenia). These results suggest that non sarcopenic men who are maintained muscle mass could stay low glycation of serum proteins. However, the effect of sarcopenia on HbA1c after adjustment for waist circumference was not approached significance on two-way ANCOVA (sarcopenia and gender). For this reason, we think that the number of subject in women is comparatively larger than in men. In fact the HbA1c in women was not significantly difference between sarcopenia and normal subject on one-way ANCOVA (Table 3).

Muscle mass may decline by 25% between the ages of 50 and 75 years (Balagopal et al. 1997), which translates into atrophy or a decrease in the number of type II fibres and a tendency toward an increase or maintenance of type I fibres (Doherty 2003). Hence, because type II fibres are recognized as glycolytic and insulin-resistant (Tanner et al. 2002), a decrease in their number and size may explain how sarcopenia positively alters glucose metabolism. Diabetes mellitus is associated with severe muscle wasting, and insulin increases body cell mass and body nitrogen in diabetics (Walsh et al. 1976). It is not clear to what extent loss of the anticatabolic effect of insulin occurs in nondiabetic subjects as they age, but insulin resistance could certainly play a role in the development of sarcopenia (Roubenoff and Hughes 2000). Stephen and Janssen reported that sarcopenic obesity, identified based on muscle strength but not muscle mass, was modestly associated with increased CVD risk (Stephen and Janssen 2009). These findings imply that strength may be more important than muscle mass for protection against CVD in old age. However, the reference values for sarcopenia in this study were determined by bioimpedance analysis. The relationship between sarcopenia on DXA and CDV risk factors was not studied.

Conversely, although there was no significantly difference in serum concentrations of triglyceride, the total cholesterol in sarcopenic men was significantly lower than that in normal subjects, independent of waist circumference. Aubertin-Leheudre et al. (2006) demonstrated that obese women had a far worse lipid profile, including a lower HDL cholesterol and higher triglycerides, than did sarcopenic-obese postmenopausal women. In addition, obese women ingested significantly more animal and less vegetable protein, although both groups had a similar total protein intake in their study. We did not evaluate dietary intake in this study. However, the lower total cholesterol in sarcopenic men may be associated with a difference in the components of their protein intake.

The baPWV is a recognized indicator of arterial stiffness (Asmar et al. 1995) and arterial compliance (Bank and Kaiser 1998) and has been regarded as a marker reflecting vascular damage (Cohn 1999). Substantial evidence has accumulated indicating that arterial stiffness and increased baPWV are important independent predictors of CVD events (Laurent et al. 2006). The amount of visceral fat is an independent predictor of PWV, and could be considered a risk factor for CVD (Lu et al. 2008). Our recent study shows that the age-related increase baPWV is attenuated in men trained to row, who retained lean soft tissue mass as measured by DXA (Sanada et al. 2009b). However, the relationship between sarcopenia and arterial stiffness is not clear. Our findings in this study show that baPWV is significantly higher in women both with class 1 and class 2 sarcopenia than in normal controls, independent of waist circumference (Table 3). A previous study indicated that greater leg lean mass was the most important determinant of lower arterial stiffness (Snijder et al. 2004). These results suggest that sarcopenia in women is positively associated with arterial stiffness regardless of waist circumference. On the other side, the effect of the interaction between sarcopenia (normal vs. class 1 and class 2 sarcopenia) and gender on baPWV was not approached significance on two-way ANCOVA (Table 4). In addition, although the effect of sarcopenia (normal vs. class 1) on baPWV after adjustment for waist circumference was not approached significance, the effect of sarcopenià (normal vs. class 2 and class 1 vs. class 2) on baPWV were significant. These results suggest that class 2 sarcopenia had higher baPWV than normal and class 1 sarcopenia independent of gender.

Summary

This study provided reference values for sarcopenia in Japanese men and women. Using these values, we tested the hypothesis that sarcopenia is associated with risk factors for CVD, independent of waist circumference. Although sarcopenia is associated with thin body mass, it is associated with more glycation of serum proteins in men and with greater arterial stiffness in women, independent of waist circumference.

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ORIGINAL ARTICLE

Greater forearm venous compliance in resistance-trained men

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Abstract Greater venous compliance is associated with attenuation of the tolerance response to orthostatic stress and reduced incidence of venous diseases. Resistance training induces tolerance to orthostatic challenge and the growth of capillaries, which may lead to negative and positive effects on venous compliance, respectively. It has not been confirmed, however, whether habitual resistance training positively or negatively affects venous compliance. We compared the forearm venous compliance in resistance-trained men with age-matched controls. Eleven resistance-trained middle-aged men (37.7 ± 1.5 years) and 12 age-matched sedentary controls (36.7 ± 1.6 years) were studied. Forearm venous compliance was measured in subjects in the supine position by inflating a venous collecting cuff placed around the upper arm to 60 mmHg for 8 min and then decreasing cuff pressure to 0 mmHg at a rate of 1 mmHg/s. Forearm venous compliance was determined using the first derivative of the pressure–volume relation during cuff pressure reduction (compliance = $\beta_1 + 2\beta_2 \times$ cuff pressure). Forearm venous compliance at 20 mmHg cuff pressure was 16% greater in the resistance-trained group than in the age-matched sedentary controls (0.097 ± 0.005 vs. 0.083 ± 0.004 ml/dl/mmHg, $P < 0.05$). Forearm venous compliance was positively related to forearm venous volume ($r = 0.643$, $P = 0.0009$), but not forearm muscle mass ($r = 0.391$, $P = 0.0648$). In conclusion, the present study suggests that (1) the resistance-trained men have greater forearm venous compliance than age-matched controls, and (2) the higher forearm venous compliance in the resistance-trained men may be explained by greater forearm venous capacitance.

Keywords Resistance training · Venous compliance · Venous capacitance · Muscle mass

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Introduction

Venous compliance of the extremities is a major determinant of the amount of blood that may be translocated to the central region, because small changes in peripheral blood volume can greatly impact cardiac filling pressure and subsequently cardiac output (Rowell 1993). Indeed, greater venous compliance is associated with intolerance during orthostatic stress (Olsen and Lanne 1998). In contrast, venous compliance was negatively related to venous thromboembolism, suggesting that decreased venous

compliance may reflect status of venous thromboembolism, such as varicose veins and deep vein thrombosis (Turner et al. 2000). Previous studies indicated that the reduction in venous compliance was preserved to a greater extent in endurance-trained men than in their sedentary peers (Hernandez and Franke 2004; Monahan et al. 2001), suggesting that habitual endurance training may reduce the tolerance response to orthostatic challenge and decrease risk of venous diseases.

Resistance exercise has become an integral component of exercise recommendations endorsed by a number of national health organizations for prevention of sarcopenia (ACSM 1998), cardiovascular diseases (Williams et al. 2007), diabetes mellitus (American Diabetes Association 2000) or weight gain (Donnelly et al. 2009). However, it has been reported that there are negative effects on vascular function in that resistance-trained men have arterial stiffening and high blood pressure (Kawano et al. 2008; Miyachi et al. 2003), although this is not a universal finding (Rakobowchuk et al. 2005a). It is thought that increased arterial stiffness is caused by marked pressor responses during resistance exercise (MacDougall et al. 1985) via ischemia of capillaries caused by muscle contraction. Venous pressure may also be increased during resistance exercise, leading to enhancement of mechanical stress. In addition, it was reported that resistance-trained men show tolerance of cardiovascular responses to lower body negative pressure (Smith and Raven 1986). Thus, it is possible that habitual resistance training may decrease venous compliance.

On the other hand, due to the increased number of capillaries with resistance training (Hather et al. 1991; Hepple et al. 1997; Schantz 1982), muscle hypertrophy caused by resistance training may induce greater volume and density in veins, leading to greater venous capacitance. As greater venous compliance is associated with the larger venous volume induced by functional muscular hypertrophy, habitual resistance training may increase venous compliance, and greater venous compliance may be associated with higher venous capacitance and muscle mass.

Therefore, to evaluate these contrasting hypotheses, we compared venous compliance in resistance-trained men with age-matched controls, and determined whether there were any associations between venous compliance and venous capacitance or muscle mass.

Methods

Subjects

Eleven resistance-trained men aged 37.7 ± 1.5 years and 12 age-matched sedentary controls aged 36.7 ± 1.6 years participated in this study. The control subjects were recruited through various forms of advertising and had not participated in a habitual exercise program for at least the previous 2 years. The resistance-trained men (bodybuilders) were recruited from several fitness clubs. They had been performing muscular strength training at least three times per week using the whole body and involving large muscle groups at moderate to high intensity (mainly with high numbers of repetitions and low weight) to increase muscle volume without aerobic exercise for 10 years or more. Before testing, 31 participants including trained and control men were recruited. Twenty-three subjects were suitable for this study according to several election criteria outlined below. All subjects in the present study were non-obese and free of overt chronic diseases based on medical history, physical examination and complete blood chemistry and haematological evaluation. In addition, subjects who had smoked in the previous 4 years, were taking medications, had used anabolic steroids or other performance-enhancing drugs or who had significant femoral intima-media thickening (1.1 mm or more), plaque formation and/or other characteristics of atherosclerosis [ankle-brachial index (ABI) 0.9 or less] were excluded from the study. All subjects gave informed consent to participation in the study, which was approved by the Human Research Committee of the National Institute of Health and Nutrition.

Measurements

Before testing, subjects abstained from caffeine and fasted for at least 12 h overnight. All measurements were performed in the laboratory under comfortable conditions in the morning. Tests for the resistance-trained men were conducted 24–28 h after their last exercise training session to avoid the immediate (acute) effects of exercise, but they were still considered to be in their normal (i.e., regular exercising) physiological state.

Venous compliance plethysmography

Subjects rested in the supine position for 30 min before data acquisition. They were given instructions to facilitate simultaneous measurement of left forearm volume change (strain gauge plethysmography) and venous collecting cuff pressure. To promote venous drainage, the left forearm was placed slightly above heart level and the arm and wrist were supported. After resting and following instructions, forearm venous compliance was measured using the technique developed by Halliwill et al. (1999). The venous collecting cuff was inflated to 60 mmHg and held constant for 8 min. During this time, all subjects were instructed to remain relaxed and not to move the arm being tested. After

the 8-min inflation period, the collecting cuff pressure was reduced at a rate of 1 mmHg/s from 60 to 0 mmHg while changes in forearm volume were recorded. Changes in forearm volume were measured non-invasively by mercury strain gauge plethysmography (EC-5R; D.E. Hokanson Inc., Bellevue, WA, USA). The point of maximal left forearm circumference was measured and marked to determine appropriate size and placement of the strain gauge. Mercury-in-silastic strain gauges were calibrated to determine changes in left forearm volume relative to baseline. A venous collecting cuff (D.E. Hokanson) was placed around the left upper arm 5 cm proximal to the antecubital crease. The venous collecting cuff was connected to a rapid cuff inflator (EC-20; D.E. Hokanson) that was attached to an external air source.

Metabolic risk factors for coronary heart disease

To screen for the presence of coronary heart disease, concentrations of fasting serum lipids and plasma glucose were determined using enzymatic techniques (Tanaka et al. 2000).

Arterial blood pressure at rest

Arterial blood pressure at rest (coefficient of variation, 3 ± 1%) was measured with a semi-automated device (Form PWV/ABI; Colin Medical, Komaki, Japan) over the brachial and dorsalis pedis arteries. Recordings were made in triplicate with subjects in the supine position (Miyachi et al. 2005).

Body composition

The percentage of whole body fat mass and the lean soft mass of the left forearm were measured using a dual-energy X-ray absorptiometry (DEXA) scanner (Hologic QDR-4500; Hologic Inc., Waltham, MA, USA) with subjects in the supine position. The body regions were delineated according to specific anatomical landmarks using manual DEXA analysis software (version 11.2.3). The lean soft tissue mass of extremities assessed using DEXA was assumed to represent appendicular skeletal muscle mass along with a small and relatively constant amount of skin and underlying connective tissues (Miyatani et al. 2008). The reliability of small lean soft tissue mass region assessed by DEXA has been confirmed previously (Burkhart et al. 2009).

Muscle strength

Muscle strength was assessed by leg extension power and handgrip strength as described previously (Kawano et al. 2008). Briefly, leg extension power (coefficient of variation, 2 ± 1%) was determined using a dynamometer (Anaero Press 3500; Combi Wellness, Tokyo, Japan) in the sitting position. The subjects were secured in a chair using a seat belt. In the starting position, the feet were placed on a sliding plate with the knee angle adjusted to 90°. Five trials were performed at 15-s intervals and the average of the two highest recorded power outputs (in W) was taken as the definitive measurement.

Handgrip strength (coefficient of variation, 2 ± 1%) was measured with a handheld dynamometer (Grip-D; Takei Instruments, Niigata, Japan), with the subject standing and the arms extended by their sides. The subjects then gripped the dynamometer as strongly as possible for 3 s without pressing the instrument against their body or bending at the elbow, and values (in kg) were recorded as the averages of two trials for each arm. The two values for the right and left arms were averaged to obtain the value of handgrip strength.

Maximal oxygen uptake

We measured maximal oxygen consumption ($\dot{V}O_{2max}$) during incremental cycle ergometer exercise (Miyachi et al. 2001). Oxygen consumption (coefficient of variation, 4 ± 1%), heart rate and ratings of perceived exertion were measured throughout the protocol (Miyachi et al. 2001).

Data analysis

Data for evaluation of forearm venous compliance (coefficient of variation, 4 ± 1%) were collected after analogue-to-digital conversion at 1,000 Hz (PowerLab; AD Instruments, Bella Vista, NSW, Australia) onto a personal computer for later analysis. Reproducibility of forearm venous compliance in our laboratory was determined by another group of present subjects. To characterize compliance, the relationship between forearm volume and cuff pressure was compared as the cuff pressure decreased at a rate of 1 mmHg/s from 60 to 0 mmHg after being held at 60 mmHg for 8 min. This method assumes that cuff pressure is equal to intravenous pressure, which has been verified experimentally (Halliwill et al. 1999). Data below 10 mmHg were excluded due to the ambiguity of true venous pressure at low cuff pressures. Pressure–volume curves were compared by the quadratic regression model $(\Delta\text{limb volume}) = \beta_0 + \beta_1(\text{cuff pressure}) + \beta_2(\text{cuff pressure})^2$. For the model, Δlimb volume was equal to limb volume at a given cuff pressure minus baseline limb volume. Regression models were calculated using the general linear model procedure (Excel 2007; Microsoft Inc., Redmond, WA, USA). The pressure–volume relation is not linear; therefore, a single number is not sufficient to characterize the slope of the pressure–volume curve. Thus,

the group-averaged regression parameters β_1 and β_2, determined from the pressure–volume curves for each participant in the relevant group, were used together as an estimate of compliance, such that compliance $= \beta_1 + 2\beta_2$ (cuff pressure) or the derivative of the pressure–volume curve (Halliwill et al. 1999; Monahan et al. 2001). Venous compliance is only reported over the pressure range of 10–60 mmHg, thus avoiding ambiguous results obtained when lower pressures are used because venous pressure is unknown. Previous studies, focusing on venous compliance at arbitrary pressure, assessed the value of compliance at 20 mmHg (Halliwill et al. 1999; Monahan et al. 2001). Although determining compliance values over the range of 10–60 mmHg, we considered the physiological range to be 10–20 mmHg in the supine position. Therefore, to explore the relation between venous compliance and subject characteristics, comparison of venous compliance between the two groups and univariate correlations were determined using values for forearm venous compliance at an arbitrary pressure of 20 mmHg (i.e., $\text{Compliance}_{20\ \text{mmHg}} = \beta_1 + 2\beta_2 \times 20$).

Statistics

Statistical analyses were performed using statistical software (StatView; SAS, Cary, NC, USA). Mean differences between the resistance-trained group and the control group were examined using Student's unpaired t test. Stepwise multiple-regression analysis was used to determine the influences of maximal oxygen uptake, muscle mass and forearm venous capacitance on forearm venous compliance. Statistical significance was set at $P < 0.05$, with all data presented as mean ± SEM.

Results

Subject characteristics are presented in Table 1. Percentage body fat was lower in the resistance-trained group compared with the control group ($P < 0.05$). Forearm lean soft tissue mass evaluated by DEXA and muscle strength assessed by leg extension power and handgrip strength was higher in the resistance-trained group than in the control group (all $P < 0.05$). With the exception of diastolic blood pressure measured in the brachial artery, blood pressure parameters of the brachial artery were higher in the resistance-trained group compared with the control group (all $P < 0.05$). There were no differences in other parameters between the two groups.

In the resistance-trained group, the pressure–volume curve derived from the forearm was steeper than that in the control group, indicating greater venous compliance (Fig. 1a; Table 2; interaction: $P < 0.0001$). In the resistance-trained group, maximal change in forearm volume (at 60 mmHg cuff pressure) from baseline (at 0 mmHg cuff pressure) was higher than that in the control group (Figs. 1a, 2a; $P < 0.05$), indicating greater venous capacitance in the forearm. As venous compliance is pressure-dependent, comparison between resistance-trained men and sedentary peers as controls were determined using values for forearm venous compliance at an arbitrary pressure of 20 mmHg ($\text{Compliance}_{20\ \text{mmHg}} = \beta_1 + 2\beta_2 \times 20$). Forearm venous compliance at 20 mmHg cuff pressure was 17% greater in the resistance-trained men compared with the age-matched sedentary controls (0.097 ± 0.005 vs. 0.083 ± 0.004 ml/dl/mmHg, $P < 0.05$) (Fig. 2b).

Univariate correlation was also determined using forearm venous compliance at an arbitrary pressure of 20 mmHg. In all subjects pooled, forearm venous compliance was positively related to forearm venous volume ($r = 0.643$, $P = 0.0009$), but not forearm lean soft tissue ($r = 0.391$, $P = 0.0648$) (Fig. 3). Stepwise multiple-regression analysis revealed that among all parameters, forearm venous volume was only the independent correlate of forearm venous compliance ($\beta = 0.627$).

Table 1 Subject characteristics

	Control	Resistance-trained
N	12	11
Age (years)	36.7 ± 1.6	37.7 ± 1.5
Height (cm)	171.6 ± 1.6	171.3 ± 1.9
Body weight (kg)	73.4 ± 1.9	75.6 ± 2.2
Fat (%)	21.6 ± 0.8	15.1 ± 0.6*
Forearm lean soft tissue mass (g)	1,231 ± 39	1,513 ± 45*
Total cholesterol (mg/dl)	194 ± 12	180 ± 8
HDL cholesterol (mg/dl)	51 ± 3	60 ± 4
Plasma glucose (mg/dl)	90 ± 2	92 ± 3
Triglycerides (mg/dl)	150 ± 35	81 ± 13
Resting heart rate (bpm)	59 ± 2	55 ± 2
Brachial systolic BP (mmHg)	116 ± 3	132 ± 4*
Brachial mean BP (mmHg)	85 ± 2	95 ± 3*
Brachial diastolic BP (mmHg)	70 ± 2	75 ± 3
Brachial PP (mmHg)	46 ± 2	57 ± 2*
Maximal heart rate (bpm)	185 ± 3	184 ± 4
$\dot{V}O_{2max}$ (l/min)	2.6 ± 0.1	2.7 ± 0.1
$\dot{V}O_{2max}$/body weight (ml/kg/min)	35.9 ± 1.7	36.3 ± 1.3
Leg press power (W)	1,654 ± 99	2,344 ± 161*
Leg press power/body weight (W/kg)	23.1 ± 1.6	31.0 ± 1.9*
Handgrip strength (kg)	44 ± 2	53 ± 1*

Data are mean ± SEM

N no. of subjects, *BP* blood pressure, *PP* pulse pressure, $\dot{V}O_{2max}$ maximal oxygen consumption

* Significant at $P < 0.05$ versus control

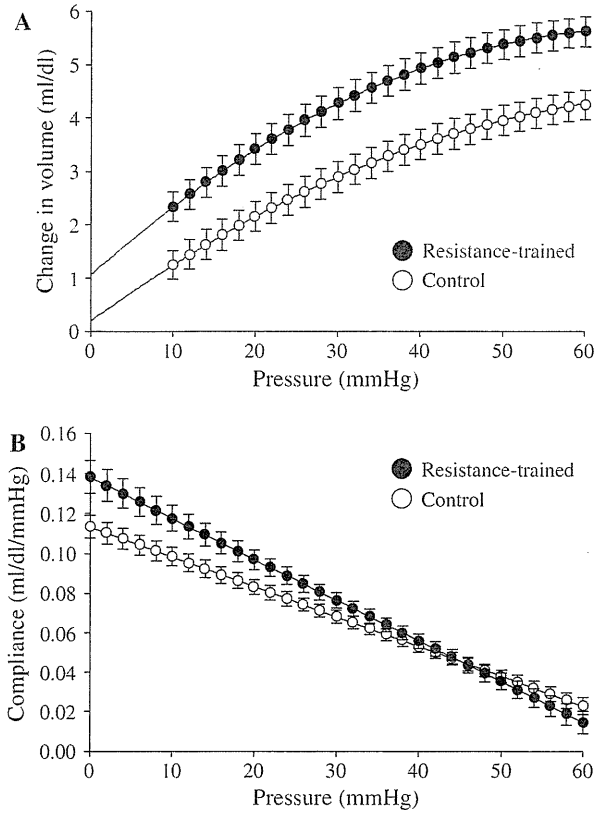

Fig. 1 Pressure–volume (**a**) and pressure–compliance relations (**b**) in the resistance-trained men and age-matched controls. Values are mean ± SEM

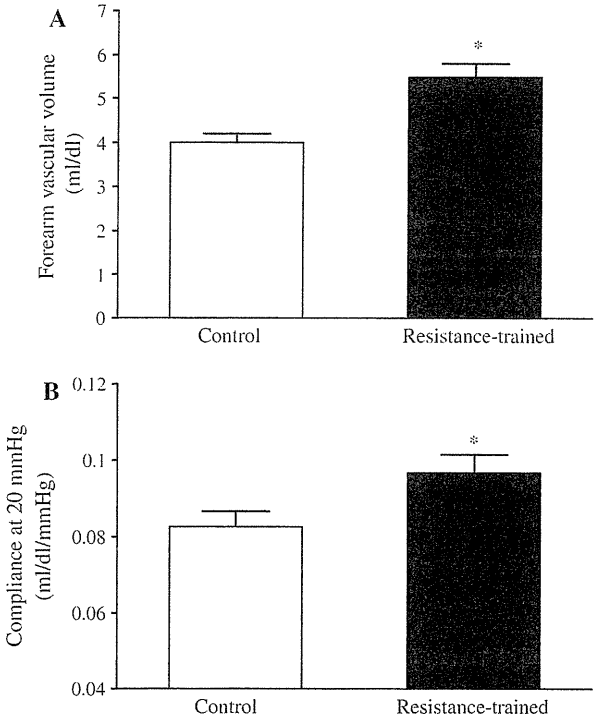

Fig. 2 Forearm venous volume (**a**) and forearm venous compliance at 20 mmHg cuff pressure (**b**) in the resistance-trained men and age-matched controls. Values are mean ± SEM

Discussion

This study was performed to investigate the association between habitual resistance training and venous compliance. We found that the resistance-trained group showed greater venous compliance in the forearm compared with the age-matched controls, and that the forearm venous compliance was associated with forearm venous volume (i.e., capacitance), but not with forearm muscle mass. To our knowledge, this is the first study designed to assess the association between resistance training and venous compliance. The present findings may expand our understanding of the alterations in vascular function caused by habitual exercise.

Reason for determining venous compliance in the forearm

We determined upper limb venous compliance in the resistance-trained group, although previous studies have emphasized the importance of lower limb blood volume in relation to orthostatic stress, and indirectly assessed the effects of resistance training on venous compliance using lower body negative pressure (Lightfoot et al. 1994; Smith and Raven 1986). As the resistance-trained men in the present study performed whole-body strength training, it was presumed that their forearms would have generated tonic force in most resistance exercises, including lower limb exercise. Moreover, the lower limbs were exercised daily through light to moderate physical activity, such as walking or jogging (i.e., aerobic exercise), but the upper limbs were not. Accordingly, we assumed that greater

Table 2 Pressure–volume regression parameters

	ΔLimb volume $= \beta_0 + \beta_1$(cuff pressure) $+ \beta_2$(cuff pressure)^2
Control	ΔLimb volume $= 0.172 \pm 0.273 + 0.113 \pm 0.006$(cuff pressure) $- 0.00076 \pm 0.00007$(cuff pressure)^2
Resistance-trained	ΔLimb volume $= 1.048 \pm 0.285^* + 0.138 \pm 0.008^*$(cuff pressure) $- 0.00103 \pm 0.00010^*$(cuff pressure)^2

Data are mean ± SEM

* Significant at $P < 0.05$ versus control