reproduction. Schonau (2004) has repeated this finding in more depth in a series of papers based upon the forearm, but other authors (Ferretti *et al.*, 2000; Rittweger *et al.*, 2000) were unable to detect the surplus bone in the lower body. The accelerated bone loss observed around menopause is predominantly due to oestrogen deficiency (Kassem *et al.*, 1996). The phase of rapid bone loss normally lasts 4–8 years, and after this period, age-related bone loss is considered to occur in women.

Although the dual-energy X-ray absorptiometry (DXA) method can be used to accurately estimate SM mass (appendicular muscle mass), it is not capable of accurate distinguish of SM mass from the trunk region. Ultrasound muscle thickness (MTH) has been widely employed for accurate measurement of SM size *in vivo* (Kawakami *et al.*, 1993; Abe *et al.*, 1997; Reimers *et al.*, 1998), and previous studies have shown it to be highly reliable and valid in measuring MTH (Kawakami *et al.*, 1993; Reimers *et al.*, 1998). These characteristics make ultrasound a useful alternative to other more expensive imaging methods for assessing changes in SM mass. Moreover, ultrasound-derived prediction equations can accurately estimate the regional SM mass involving the measurement of arm, leg and trunk muscles (Sanada *et al.*, 2006).

The present cross-sectional study investigates the relationships between regional SM mass and bone mineral indices, and examines whether regional BMC normalized to SM mass shows a similar decrease with age in young subjects through old age.

Methods

Subjects

One hundred and thirty-eight young and postmenopausal women aged 20–76 years participated in this study and were divided into three groups: 61 young women (YW: 23.7 ± 0.5, 20–39 years), 49 middle-aged postmenopausal women (MW: 58.3 ± 0.6, 40–64 years) and 28 older postmenopausal women (OW: 70.3 ± 0.7, 65–76 years). The NASA/JSC physical activity scale, a questionnaire method, was used to survey the subject's physical activity (Ross and Jacson, 1990). This scale was developed to provide an assessment score of 0–7 on a person's level of regular physical activity. There are a series of eight statements about routine physical activity.

None of the subjects smoked and they were not taking any medications, such as β-blockers, steroids or hormone replacement therapy. The subjects involved in this study were both sedentary and active women. Active young women participated in continuous aerobic exercise for at least one session per week for 1 h per session. Active postmenopausal women participated in a swimming programme for at least two sessions per week for 1 h per session. However, they were not highly trained athletes.

The purpose, procedures and risks of the study were explained to each participant prior to inclusion, and all subjects gave their written informed consent before participating in the study 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.

Whole-body DXA

Lean soft tissue mass (LSTM), fat mass, BMC and BMD were determined for the whole body using 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 their bodies. The bone densitometer delivers a very low dose of radiation (1.5 mR for the whole body) using quantitative digital radiography. Daily DXA calibration of phantoms showed a coefficient of variation of 0.35% for BMD over the past 156 measurement points. The whole-body BMC and LSTM were divided into several regions, that is, arms, legs, trunk and head. The body compositions were analysed using manual DXA analysis software (version 11.2:3). 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. To minimize inter-observer variation, all scans and analyses were carried out by the same investigator, and the day-to-day coefficient of variations of his observations were 0.72% for BMD, 2.95% for LSTM and 6.98% for fat mass in the whole body.

Blood samples

Before all measurements, fasting (> 12 h) blood samples were collected by venipuncture in EDTA-containing tubes, refrigerated immediately and centrifuged at 1500 r.p.m. for 30 min at 4 °C within 2 h. Serum samples from each participant were stored frozen at −20 °C. Estradiol was assessed by radioimmunoassay (Amersham Biosciences, Piscataway, NJ, USA). In postmenopausal women, menopausal status was confirmed by concentrations of estradiol less than $20\,\mathrm{pg\,ml^{-1}}$. In this study, estradiol concentrations were $11.4 \pm 0.3\,\mathrm{pg\,ml^{-1}}$ (range of $10.0–17.0\,\mathrm{pg\,ml^{-1}}$) in MW and $11.8 \pm 0.4\,\mathrm{pg\,ml^{-1}}$ (range of $10.0–16.0\,\mathrm{pg\,ml^{-1}}$; Table 1) in OW. Serum intact osteocalcin was measured with a sandwich enzyme immunoassay that uses polyclonal antibodies against 20 N-terminal residues (amino acids 1–20) and against seven C-terminal residues (amino acids 43–49; MBC, Tokyo, Japan). The inter- and intra-assay coefficient of variations for the estradiol and osteocalcin were <10%.

Ultrasound MTH and measurements

Muscle thickness determined by B-mode ultrasound was assessed at nine sites on the anterior and posterior surfaces of

Table 1 Physical characteristics of subjects

	Young (n = *61*)	*Middle* (n = *49*)	*Old* (n = *28*)
Age (years)	23.7 ± 0.5	58.3 ± 0.6[a]	70.3 ± 0.7[a,b]
Age at menopause (years)		50.0 ± 0.6	50.1 ± 0.9
Years since menopause		8.3 ± 0.7	20.2 ± 1.1[b]
Serum estradiol (pg ml^{-1})	86.4 ± 8.2	11.4 ± 0.3[a]	11.8 ± 0.4[a]
Osteocalcin (pg ml^{-1})	5.47 ± 0.3	9.7 ± 0.4[a]	9.9 ± 0.6[a]
Body mass (kg)	51.8 ± 0.7	55.4 ± 1.0[a]	52.6 ± 1.0[b]
BMI (kg m^{-2})	20.2 ± 0.2	23.3 ± 0.4[a]	22.6 ± 0.5[a]
Percent body fat (%)	24.6 ± 0.6	31.2 ± 0.9[a]	30.3 ± 0.7[a]
VO_2peak (ml kg^{-1} min^{-1})	33.8 ± 0.7	29.3 ± 0.7[a]	24.6 ± 0.8[a,b]
Handgrip strength (kg)	28.9 ± 0.7	27.2 ± 0.6	23.4 ± 0.7[a,b]
Leg extension power (W kg^{-1})	17.3 ± 0.6	13.8 ± 0.5[a]	12.5 ± 0.7[a]
Physical activity scale	4.2 ± 0.2	4.7 ± 0.2	4.2 ± 0.3

Abbreviations: BMI, body mass index; VO_2peak, peak oxygen uptake.
Data are presented as means ± s.e.m.
[a] Significantly different from young, $P < 0.05$.
[b] Significantly different from middle-aged, $P < 0.05$.

the body as described previously by Abe *et al.* (1994). The sites were lateral forearm, anterior and posterior upper arm, abdomen, subscapula, anterior and posterior thigh, and anterior and posterior lower leg. Ultrasonographic evaluation of MTH was performed using a real-time linear electronic scanner with a 5 MHz scanning head (SSD-500; Aloka, Tokyo, Japan). The scanning head with water-soluble transmission gel was placed perpendicular to the tissue interface at the marked sites and provided acoustic contact without depression of the skin surface. MTHs were measured directly from the screen with electronic callipers, and determined as a distance from the adipose tissue–muscle interface to the muscle–bone interface. Whole-body and regional SM mass were estimated using the equations of Sanada *et al.* (2006). MTHs were converted to mass units in kilograms by ultrasound-derived prediction equations using site-matched MTH × height, which were then used to calculate arm, trunk, thigh and lower leg SM mass. The reliability of image reconstruction and distance measurements were confirmed by comparing the ultrasonic and manual measurements of tissue thickness in human cadavers, and the coefficient of variation for the MTH measurements was 1% (Kawakami *et al.*, 1993).

Measurement of fitness values

The peak oxygen uptake (VO_2peak) was measured by an incremental cycle exercise test using a cycle ergometer (Monark, Varberg, Sweden). The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. 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 metre (NDS-2A-T; Shinagawa Dev., Tokyo, Japan). The system of mass spectrometer was calibrated during every measurement by the standard reference gas. The highest value of VO_2 during the exercise test was designated as VO_2peak.

Leg extension power was measured with an isokinetic leg power system (Anaero Press 3500; Combi wellness, Tokyo, Japan) in the sitting position. Handgrip strength of the right upper limb was measured with a hand-held dynamometer, with the subject standing and arms extended by their side.

Statistical analysis

All measurements and calculated values are expressed as the mean ± s.e.m. We compared the mean values of general criteria, bone mineral indices, body composition values and fitness values among the three age groups using one-way analysis of variance with body mass index (BMI) adjusted for the covariate. In cases with a significant F-value, a *post-hoc* test using the Newman–Keuls method was used to identify significant differences among the mean values. Pearson's product correlations were calculated between LSTM, SM mass or fitness values and bone mineral indices. The α level for testing significance was set at $P < 0.05$. All statistical analyses were performed using Stat View v5.0 for Windows (SYS Institute).

Results

The physical characteristics of the subjects are presented in Table 1. The BMI and body fat percentage in MW and OW were significantly higher than those in YW ($P < 0.05$). There were no significant differences in the NASA/JSC physical activity scale among the groups. Serum estradiol in MW and OW were significantly lower than those in YW ($P < 0.05$). Serum osteocalcin in MW and OW were significantly higher than those in YW ($P < 0.05$). Handgrip strength in OW was significantly lower than that in YW and MW ($P < 0.05$). Leg extension power in MW and OW were significantly lower than those in YW ($P < 0.05$). VO_2peak (normalized to body mass) in MW and OW were significantly lower than those in YW ($P < 0.05$).

Age-related decline of body composition and bone mineral indices

Leg SM mass and LSTM in MW and OW were significantly lower than those in YW ($P < 0.05$, Table 2). Leg SM mass in OW was significantly lower than that in MW ($P < 0.05$), but there was no such difference in leg LSTM. Table 3 shows the mean BMC, BMD and bone mineral indices normalized to SM mass. The BMC and BMD in MW and OW were significantly lower than those in YW ($P < 0.05$), while BMC (whole body, arms, trunk and legs) and BMD (whole body, arms and legs) in OW were significantly lower than in those MW ($P < 0.05$). The BMC normalized to SM mass in MW and OW was significantly lower than that in YW ($P < 0.05$). The arm BMC normalized to arm SM mass and the trunk BMC normalized to trunk SM mass in OW were significantly lower than those in MW. However, whole-body and leg BMC normalized to leg SM mass were not significantly different between MW and OW. Furthermore, the interaction (age × BMI) of the age-related differences of BMD, BMC and normalized BMC was not significant.

There was significantly negative correlation between age and BMC normalized to SM mass in all women ($P<0.001$, Table 4). However, when the subjects were divided into three age groups, there was no significant correlation between age and BMC normalized to SM mass in middle-aged and older women.

Table 2 Skeletal muscle mass estimated by ultrasound and LSTM and fat mass measured by DXA

Variables	*Body segments*	*Young (n = 61)*	*Middle (n = 49)*	*Old (n = 28)*
SM mass (kg)	Whole body	14.3 ± 0.3	13.7 ± 0.3	12.0 ± 0.4[a,b]
	Arm	1.4 ± 0.0	1.4 ± 0.0	1.3 ± 0.0[a,b]
	Trunk	6.0 ± 0.0	5.8 ± 0.1	5.5 ± 0.1[a,b]
	Leg	7.3 ± 0.1	6.9 ± 0.1[a]	6.1 ± 0.2[a,b]
LSTM (kg)	Whole body	34.3 ± 0.5	34.1 ± 0.5	32.4 ± 0.6[a,b]
	Arm	3.2 ± 0.1	3.2 ± 0.1	3.1 ± 0.1
	Trunk	18.4 ± 0.2	18.8 ± 0.3	17.8 ± 0.3[b]
	Leg	12.8 ± 0.2	12.1 ± 0.2[a]	11.6 ± 0.3[a]
Fat mass (kg)	Whole body	12.8 ± 0.4	17.4 ± 0.7[a]	16.0 ± 0.6[a,b]
	Arm	1.5 ± 0.1	2.0 ± 0.1[a]	1.8 ± 0.1[a]
	Trunk	4.8 ± 0.2	9.0 ± 0.4[a]	8.1 ± 0.4[a,b]
	Leg	6.2 ± 0.2	6.3 ± 0.2	5.8 ± 0.2

Abbreviations: DXA, dual-energy X-ray absorptiometry; LSTM, lean soft tissue mass; SM mass, skeletal muscle mass.
Data are presented as means ± s.e.m.
[a] Significantly different from young, $P<0.05$.
[b] Significantly different from middle-aged, $P<0.05$.

Relationships between SM mass, muscle functions and bone mineral indices

Lean soft tissue mass was significantly correlated with site-matched BMC (arm, trunk, leg and whole body; $r=0.57$, 0.73, 0.53 and 0.47, respectively; $P<0.05$, Figure 1) and BMD (arm, L-spine, leg and whole body; $r=0.38$, 0.40, 0.60 and 0.42, respectively; $P<0.05$, Figure 2). These associations corresponded to the relationships between SM mass measured by ultrasound and the site-matched BMC (arm, trunk, leg and whole body; $r=0.53$, 0.49, 0.66 and 0.55, respectively; $P<0.05$, Figure 1) and BMD (arm, L-spine, leg and whole body; $r=0.38$, 0.44, 0.55 and 0.52, respectively; $P<0.05$, Figure 2) in all women. The BMD in YW, MW and OW is also significantly correlated with the site-matched SM mass; $r=0.29$–0.54, 0.36–0.44 and 0.46–0.60, respectively ($P<0.05$). The correlation coefficients in OW were comparatively higher than those in YW or MW. In older women, absolute VO_2peak ($\mathrm{l\,min^{-1}}$) was not significantly correlated with whole-body BMD (Table 5). Moreover, the absolute leg extension power (W) and leg extension power normalized to body mass ($\mathrm{W\,kg^{-1}}$) were significantly correlated with leg BMD, but not leg extension power normalized to leg SM mass ($\mathrm{W\,kg^{-1}}$).

Discussion

This study investigated the relationships between regional SM mass and bone mineral indices, and sought to determine whether regional BMC normalized to SM mass showed a similar decrease with age in young subjects through old age.

Table 3 Age-related differences of bone mineral density, bone mineral and bone mineral content normalized to SM mass

Variables	*Body segments*	*Young (n = 61)*	*Middle (n = 49)*	*Old (n = 28)*
BMD ($\mathrm{g\,cm^{-2}}$)	Whole body	1.12 ± 0.01	0.99 ± 0.01[a] (12%)	0.91 ± 0.01[a,b] (8%)
	Arm	0.71 ± 0.01	0.63 ± 0.01[a] (11%)	0.59 ± 0.01[a,b] (6%)
	L-spine	1.07 ± 0.02	0.92 ± 0.02[a] (14%)	0.86 ± 0.03[a] (7%)
	Leg	1.12 ± 0.01	1.01 ± 0.01[a] (10%)	0.94 ± 0.02[a,b] (7%)
BMC (g)	Whole body	1796 ± 47	1350 ± 42[a] (25%)	1175 ± 39[a,b] (13%)
	Arm	238 ± 4	199 ± 5[a] (16%)	174 ± 5[a,b] (13%)
	Trunk	551 ± 12	451 ± 12[a] (18%)	388 ± 11[a,b] (14%)
	Leg	741 ± 14	600 ± 15[a] (19%)	544 ± 16[a,b] (9%)
BMC normalized to SM mass ($\mathrm{g\,kg^{-1}}$)	Whole body	127 ± 3	99 ± 2[a] (22%)	100 ± 4[a] (−1%)
	Arm	175 ± 2	144 ± 3[a] (18%)	134 ± 3[a,b] (7%)
	Trunk	93 ± 2	78 ± 2[a] (16%)	71 ± 2[a,b] (9%)
	Leg	102 ± 2	87 ± 2[a] (15%)	91 ± 2[a] (−5%)

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; SM mass, skeletal muscle mass.
The percentage of differences were calculated from the value from young versus middle-aged and middle-aged versus old. Data are presented as means ± s.e.m.
[a] Significantly different from young, $P<0.05$.
[b] Significantly different from middle-aged, $P<0.05$.

Table 4 Correlation coefficients between age and measurement variables in young and postmenopausal women

Variables	*Body segments*	*Total (n = 138)*	*Young (n = 61)*	*Middle (n = 49)*	*Old (n = 28)*
BMD ($g\,cm^{-2}$)	Whole body	−0.73***	0.00	−0.30*	−0.52***
	Arm	−0.75***	0.13	−0.24	−0.56***
	L-spine	−0.53***	0.04	−0.28	−0.40***
	Leg	−0.64***	0.01	−0.11	−0.39***
BMC (g)	Whole body	−0.67***	−0.40***	−0.16	−0.32
	Arm	−0.66***	0.13	−0.26	−0.54***
	Trunk	−0.64***	−0.05	−0.26	−0.24
	Leg	−0.63***	0.11	−0.13	−0.42***
LSTM (kg)	Whole body	−0.16	−0.02	−0.02	−0.25
	Arm	−0.07	−0.05	0.02	−0.27
	Trunk	−0.04	0.02	−0.09	−0.27
	Leg	−0.29**	−0.03	0.06	−0.17
SM mass (kg)	Whole body	−0.35***	0.03	−0.08	−0.44***
	Arm	−0.09	0.16	−0.13	−0.55***
	Trunk	−0.32***	−0.24	−0.20	−0.35
	Leg	−0.34***	−0.02	0.00	−0.23
BMC normalized to SM mass ($g\,kg^{-1}$)	Whole body	−0.55***	−0.45***	−0.12	0.08
	Arm	−0.70***	−0.01	−0.20	−0.09
	Trunk	−0.55***	0.13	−0.14	0.02
	Leg	−0.41***	0.07	−0.12	−0.15

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; LSTM, lean soft tissue mass; SM mass, skeletal muscle mass.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.

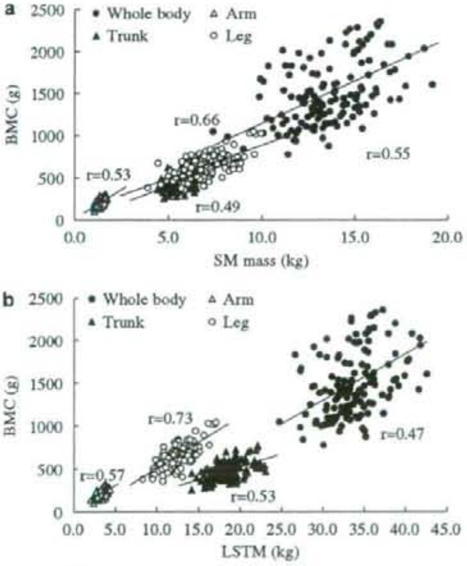

Figure 1 Relationship between SM mass estimated by ultrasound (**a**) or LSTM (**b**) measured by DXA and BMC in all subjects ($n = 138$). Whole-body and regional SM mass and LSTM were significantly correlated with BMC in all body segments ($P<0.05$). BMC, bone mineral content; DXA, dual-energy X-ray absorptiometry; LSTM, lean soft tissue mass; SM mass, skeletal muscle mass.

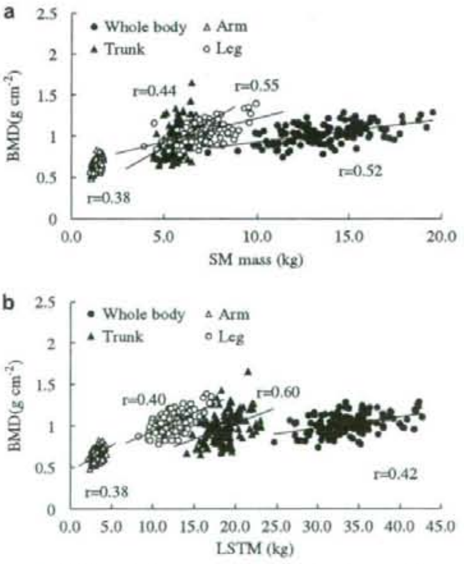

Figure 2 Relationship between SM mass estimated by ultrasound (**a**) or LSTM (**b**) measured by DXA and BMD in all subjects ($n = 138$). Whole-body and regional SM mass and LSTM were significantly correlated with BMD in all body segments ($P<0.05$). BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; LSTM, lean soft tissue mass; SM mass, skeletal muscle mass.

Table 5 Correlation coefficients between fitness value and BMD in young and postmenopausal women

	VO_2peak versus whole-body BMD			*Handgrip strength versus arm BMD*			*Leg extension power versus leg BMD*		
	Absolute ($l\,min^{-1}$)	*Normalized to body mass ($ml\,kg^{-1}\,min^{-1}$)*	*Normalized to total SM mass ($ml\,kg^{-1}\,min^{-1}$)*	*Absolute (kg)*	*Normalized to body mass ($kg\,kg^{-1}$)*	*Normalized to arm SM mass ($kg\,kg^{-1}$)*	*Absolute (W)*	*Normalized to body mass ($W\,kg^{-1}$)*	*Normalized to leg SM mass ($W\,kg^{-1}$)*
Young ($n=61$)	0.43***	0.30*	0.08	0.47***	0.37**	0.20	0.61***	0.49***	0.41***
Middle ($n=49$)	0.47***	0.17	0.09	0.34*	0.14	0.05	0.26	0.06	0.09
Old ($n=28$)	0.32	0.02	−0.18	0.42*	0.15	0.01	0.60***	0.46*	0.37

Abbreviations: BMD, bone mineral density; SM mass, skeletal muscle mass.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.

The major findings of this cross-sectional study were as follows: (1) SM mass were associated with the site-matched bone mineral indices, and these associations corresponded to the relationships between LSTM and the site-matched bone mineral indices; (2) BMC normalized to SM mass estimated by ultrasound in arm and trunk region were also significantly different with age, but not in leg and whole body in middle-aged and older postmenopausal women. These results suggest that the age-related decline of BMC normalized to SM mass was different in the body segments. Thus, the age-related differences in BMC were found to be independent of the ageing of SM mass in the arm and trunk region. However, differences in BMC measures of the leg and whole body were found to correspond to age-related decline of SM mass in postmenopausal women.

Age-related decline in SM mass and bone mineral indices

As both SM mass and bone mineral indices decrease with age, it is not yet clear how the age-related decrease in SM mass (for example, arm, leg and trunk region) affects the age-related decline of bone mineral indices in young and postmenopausal women. The age-related differences in BMC normalized to the site-matched SM mass in MW were significantly lower than those in YW (15–22%, Table 3), and serum estradiol in MW were also significantly lower than those in YW (87%, $P<0.05$, Table 1). In addition, serum estradiol in MW was significantly lower than that in YW. These results suggest that age-related decrease of BMC from youth through middle age was associated with age-related change of oestrogen deficiency (NIH Consensus Development Panel on Osteoporosis Prevention, 2001). However, when postmenopausal women were divided into MW and OW, age-related differences in whole-body and leg BMC normalized to SM mass were absent in older postmenopausal women (Table 3) with no changes in serum estradiol and osteocalcin. Furthermore, the interaction (age × BMI) of the age-related differences of BMD, BMC and normalized BMC was not significant. Therefore, the age-related differences in whole-body and leg BMC among middle-aged and older postmenopausal women were considered partly due to the age-related changes in SM mass independent of the differences of BMI. These results support that the preservation of ageing of muscles is an important factor for maintenance of leg and whole-body BMC, especially in older women.

Relationships between SM mass, muscle function and bone mineral indices

The SM mass were associated with the site-matched bone mineral indices, and these associations show equivalent to better correlations among LSTM determined by DXA and the site-matched bone mineral indices. The final outcome is so much stronger when adjusted data use independent measurements. Every DXA-derived component from BMC to FM to LSTM is likely to co-vary, since they are all derived from the same scan. These results can be applied to the future studies such as the development of prediction equation for bone mineral indices using ultrasound technique. A compact-type ultrasound machine weighs approximately 3 kg, making it easily portable. Ultrasound-derived prediction equations are capable of taking measurements in the field, and are safe and valid in predicting total and regional SM mass (Sanada *et al*., 2006).

Some investigators have shown that prolonged low-to-moderate intensity exercise is independently associated with higher BMD (Nguyen *et al*., 1998; Hagberg *et al*., 2001; Pongchaiyakul *et al*., 2004), while cardiorespiratory fitness (VO_2peak) is only slightly correlated with bone mineral indices (Henderson *et al*., 1995; Ryan and Elahi, 1998; Ryan *et al*., 1998; Lynch *et al*., 2002). In this study, VO_2peak (normalized to body mass) in young women was significantly correlated with BMD ($P<0.05$), while VO_2peak (normalized to whole-body SM mass) was not significantly associated with BMD (Table 5). These results indicate that although the present and previous studies have shown aerobic fitness to be associated with BMD, this relationship may be due to the magnitude of SM mass. However, in older women, even absolute VO_2peak ($l\,min^{-1}$) was not significantly correlated with whole-body BMD. In the same way, low grip strength is associated with low BMD and an increased risk of incident vertebral fracture (Bevier *et al*., 1989; Osei-Hyiaman *et al*., 1999; Di Monaco *et al*., 2000; Dixon *et al*., 2005). The absolute handgrip strength in older women were significantly correlated with BMD, but not normalized to body mass and SM mass, in present study. These results suggest the relation of BMD and handgrip strength associated with body mass. However, the absolute leg extension power (W) and leg extension power normalized to body mass ($\mathrm{W\,kg^{-1}}$) were significantly correlated with leg BMD, but not normalized to leg SM mass ($\mathrm{W\,kg^{-1}}$). There is no difference in leg BMC (normalized to SM) between middle-aged and older women, there may be a difference but this study does not have the power to demonstrate a difference, particularly as the numbers are much less in the older groups.

Summary

We assessed the relationship between regional SM mass and bone mineral indices, and whether BMC normalized to site-matched SM mass differed with age. This cross-sectional study concluded that whole-body and regional SM mass are associated with site-matched BMD and BMC in both young and postmenopausal women. Moreover, the age-related differences in BMC were found to be independent of the ageing of SM mass in the arm and trunk region. However, differences in BMC measures of the leg and whole body were found to correspond to age-related decline of SM mass in postmenopausal women. These results support that the preservation of ageing of SM mass is an important factor for maintenance of leg and whole-body BMC especially in older women.

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Experimental Physiology

Resistance training in men is associated with increased arterial stiffness and blood pressure but does not adversely affect endothelial function as measured by arterial reactivity to the cold pressor test

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Resistance training is a popular mode of exercise, but may result in stiffening of the central arteries. Changes in carotid artery diameter were determined using the cold pressor test (CPT), which results in production of nitric oxide via sympathetic activation and is one of the novel methods available for assessing endothelial function in the carotid artery. To investigate the effect of resistance training on endothelial function, we designed a cross-sectional study of carotid arterial vasoreactivity to CPT in men participating in regular resistance training with increased carotid arterial stiffness compared with age-matched control subjects. Twelve resistance-trained middle-aged men (age 38.7 ± 1.7 years) and 17 age-matched control subjects (age 36.8 ± 1.2 years) were studied. The direction and magnitude of changes in carotid artery diameter were measured by B-mode ultrasonography during sympathetic stress induced by submersion of the foot in ice slush for 90 s. Carotid arterial β-stiffness index, and systolic and mean arterial blood pressure were higher (7.7 ± 0.7 *versus* 6.0 ± 0.4 arbitrary units, 116 ± 2 *versus* 131 ± 4 mmHg and 86 ± 2 *versus* 95 ± 2 mmHg, respectively, all $P < 0.05$) in the resistance training group compared with control subjects. There were, however, no significant differences in the amount or percentage change in carotid artery diameter in CPT between the two groups (resistance training group, 0.33 ± 0.07 mm and 5.2 ± 1.1%; control group, 0.37 ± 0.06 mm and 5.8 ± 0.9%, respectively). These findings suggest that while carotid arterial stiffening and higher blood pressure are observed in regular resistance-trained men, these are not associated with abnormalities in carotid arterial vasoreactivity to sympathetic stimulus, which implies intact endothelial function.

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Resistance training is a popular form of exercise, and has become an integral component of exercise recommendations endorsed by a number of national health organizations (American College of Sports Medicine Position Stand, 1998; Pollock *et al.* 2000). Resistance training has favourable effects on the musculoskeletal system, thereby contributing to maintenance of functional capacity and prevention of sarcopenia and osteoporosis. In contrast, resistance training may be associated with reduction of compliance and increases in arterial stiffness in the central elastic artery (carotid artery; Bertovic *et al.* 1999; Miyachi *et al.* 2003, 2004; Cortez-Cooper *et al.* 2005; Kawano *et al.* 2006).

Increased arterial stiffness and reduced arterial compliance may be associated with endothelial dysfunction (Lind *et al.* 1999; Cheung *et al.* 2002; Nakamura *et al.* 2004). Indeed, impaired endothelial function and arterial stiffening are induced with advancing age and in the presence of cardiovascular diseases (Zeiher *et al.* 1989; O'Rourke, 1990; Taddei *et al.* 1995; Tanaka *et al.* 2000; Najjar *et al.* 2005). Therefore,

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Table 1. Subject characteristics

	Control	Resistance trained
Number of subjects	17	12
Age (years)	36.8 ± 1.2	38.7 ± 1.7
Height (cm)	171.0 ± 1.2	171.0 ± 1.8
Body weight (kg)	71.9 ± 1.9	74.9 ± 2.1
Percentage body fat (%)	19.4 ± 1.2	12.3 ± 0.9*
Total cholesterol (mmol l^{-1})	5.0 ± 0.2	4.7 ± 0.2
HDL cholesterol (mmol l^{-1})	1.3 ± 0.1	1.6 ± 0.1*
Plasma glucose (mmol l^{-1})	5.0 ± 0.1	5.1 ± 0.1
Triglycerides (mmol l^{-1})	1.5 ± 0.3	0.9 ± 0.1
Resting heart rate (beats min^{-1})	58 ± 2	56 ± 2
Maximal heart rate (beats min^{-1})	186 ± 3	183 ± 4
$\dot{V}_{O_2max}$ (l min^{-1})	2.7 ± 0.1	2.8 ± 0.1
$\dot{V}_{O_2max}$/body weight (ml kg^{-1} min^{-1})	37.7 ± 1.4	36.9 ± 1.3
Leg extension power (W)	1719 ± 91	2293 ± 155*
Handgrip (kg)	45.6 ± 1.6	51.0 ± 2.0*

Data are means ± S.E.M.; $\dot{V}_{O_2max}$, maximal oxygen consumption. *$P < 0.05$ *versus* control subjects.

impaired endothelial function is thought to be one of the physiological mechanisms underlying the reduction in carotid arterial compliance with resistance training. In this context, we hypothesized that resistance training would cause impairment of endothelial function in the carotid artery.

Local endothelial function in humans can be estimated by flow-mediated dilatation (Corretti *et al.* 2002) and/or vasoreactivity in response to medication with acetylcholine, etc. (Ludmer *et al.* 1986). Since it is difficult to determine endothelial function of the carotid artery in healthy humans using these methods, the cold pressor test (CPT), which results in production of nitric oxide (NO) via sympathetic activation (Nase & Boegehold, 1996; Tousoulis *et al.* 1997) is one of the novel methods (Rubenfire *et al.* 2000; Lavi *et al.* 2006) available for assessing endothelial function in the carotid artery.

To evaluate our hypothesis, we designed a cross-sectional study in which carotid arterial vasoreactivity to receptor-mediated sympathetic cold stimulus in regular resistance-trained men with reduced carotid arterial compliance was compared with age-matched sedentary control subjects.

Methods

Subjects

A total of 29 healthy men, 28–49 years of age, participated in the present study (Table 1). The sedentary subjects were recruited through various forms of advertisement and had not participated in a regular exercise programme for at least the previous 2 years. The resistance-trained men were recruited from various fitness clubs and had been performing vigorous resistance training for > 10 years. All resistance-trained men had been performing moderate- to high-intensity 'full-body' resistance exercise involving large muscle groups. To better isolate the effects of resistance exercise training, those who had been concurrently performing regular aerobic exercise (i.e. 'cross-training') were excluded from the study. All subjects were normotensive (< 140/90 mmHg), non-obese and free of overt chronic diseases as assessed by medical history, physical examination and complete blood chemistry and haematological evaluation. Candidates who smoked in the past 4 years, were taking medications, had ever used anabolic steroids or other performance-enhancing drugs, or who had significant femoral intima–media thickening (< 1.1 mm), plaque formation and/or other characteristics of atherosclerosis [ankle–brachial index (ABI) < 0.9] were excluded. All subjects gave their written, informed consent to participation in this study. All procedures were reviewed and 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 4 h (a 12 h overnight fast was used for determination of metabolic risk factors). All measurements were performed under comfortable laboratory conditions in the morning. Tests of resistance-trained men were conducted 20–24 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. habitually exercising) physiological state.

Body composition

Body composition was determined using dual-energy X-ray absorptiometry (DEXA; model DPX-IQ, Lunar

Radiation) with subjects in the supine position. Measurement of fat mass using DEXA has been well validated against other standards (Haarbo *et al.* 1991).

Carotid arterial intima–media thickness (IMT)

Carotid artery IMT was measured from the images obtained using a SonoSite 180 PLUS ultrasound system (SonoSite, Bothell, WA, USA) equipped with a high-resolution linear-array broad-band transducer as previously described (Miyachi *et al.* 2004). Ultrasound images were analysed using image analysis software (NIH Image 1.63, Bethesda, MD, USA). At least 10 measurements of IMT were taken at each segment, and the mean values were used for analysis. This technique has excellent day-to-day reproducibility (coefficient of variation, 3 ± 1%) for the carotid IMT.

Carotid arterial compliance

A combination of ultrasound imaging of the pulsatile common carotid artery with simultaneous applanation of tonometrically obtained arterial pressure from the contralateral carotid artery permits non-invasive determination of arterial compliance (Tanaka *et al.* 2000). The carotid artery diameter was measured from images obtained using an ultrasound system (Sonosite, Bothell, WA, USA) equipped with a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1–2 cm proximal to the carotid bulb. All image analyses were performed by the same investigator who was blinded to the group assignments.

Pressure waveforms and amplitudes were obtained from the common carotid artery with a pencil-type probe incorporating a high-fidelity strain-gauge transducer (SPT-301; Millar Instruments, Houston, TX, USA; Kelly *et al.* 1989; Tanaka *et al.* 2000). Since baseline levels of blood pressure are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic BP to the brachial artery value (Tanaka *et al.* 2000; Miyachi *et al.* 2004). In addition to arterial compliance (Van Merode *et al.* 1988), we also calculated the β-stiffness index, which provides an index of arterial compliance adjusted for distending pressure (Hirai *et al.* 1989). The arterial compliance and the β-stiffness index were calculated using the following equations:

$$\text{arterial compliance} = \frac{[(D_1 - D_0/D_0)]}{2\,(P_1 - P_0)} \times \pi \times D_0^2$$

and

$$\beta - \text{Stiffness index} = \frac{\ln\,(P_1/P_0)}{[(D_1 - D_0)\,/\,D_0]}$$

where D_1 and D_0 are the maximal and minimal diameters, and P_1 and P_0 are the highest and lowest blood pressures, respectively. The day-to-day coefficients of variation were 2 ± 1, 7 ± 3 and 5 ± 2% for the carotid artery diameter, pulse pressure and arterial compliance, respectively.

Cold pressor test

The CPT was performed by submersion of the right foot up to the ankle in ice slush for 90 s, a modification of the method published previously (Corretti *et al.* 1995*b*; Rubenfire *et al.* 2000). The foot was chosen to maximize the haemodynamic and sympathetic responses (Seals, 1990). Subjects were instructed to avoid breath-holding, muscle contractions and Valsalva's manoeuvre. Measurements of carotid arterial geometry were obtained before (baseline) and for 10 s during CPT. The day-to-day coefficient of variation for the change in carotid arterial diameter response to CPT was 4 ± 1%.

Maximal oxygen uptake

We measured maximal oxygen consumption ($\dot{V}_{\mathrm{O_2 max}}$) 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).

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 with enzymatic techniques (Tanaka *et al.* 2000).

Arterial blood pressure at rest

Chronic levels of arterial blood pressure at rest were 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).

Muscle strength

Leg extension power was determined using a dynamometer (Anaero Press 3500; Combi Wellness, Tokyo, Japan) in the sitting position. The subjects were fastened with a seat belt to a chair. In the starting position, the feet were placed on a sliding plate with the knee angle adjusted to 90 deg. Subjects were advised to vigorously extend their legs. 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 (Yoshiga *et al.* 2002).

Table 2. Cardiovascular measures

	Control	Resistance trained
Brachial systolic BP (mmHg)	116 ± 2	131 ± 4*
Brachial mean BP (mmHg)	86 ± 2	95 ± 3*
Brachial diastolic BP (mmHg)	71 ± 2	74 ± 3
Brachial PP (mmHg)	45 ± 1	57 ± 2*
Carotid systolic BP (mmHg)	104 ± 2	123 ± 5*
Carotid PP (mmHg)	33 ± 2	48 ± 4*
Carotid artery diameter (mm)	6.4 ± 0.1	6.2 ± 0.1
Carotid artery IMT (mm)	0.64 ± 0.02	0.65 ± 0.03

Data are means ± S.E.M.; BP, blood pressure; PP, pulse pressure; IMT, intima–media thickness. $^*P < 0.05$ *versus* control subjects.

Handgrip strength of the right arm was measured with a hand-held dynamometer, 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.

Statistics

Statistical analyses were performed using statistical software (StatView, SAS, Cary, NC, USA). All data are presented as means ± S.E.M. Mean differences between resistance-trained and control men were examined using Student's unpaired *t* test. Analysis of covariance (ANCOVA) was used to test for differences in carotid arterial compliance and β-stiffness index between resistance-trained men and control subjects, with mean arterial blood pressure as a covariate.

Statistical significance was set *a priori* at $P < 0.05$ for all comparisons.

Results

Subject characteristics are presented in Table 1. Body fat was lower in the resistance-trained men compared with the control subjects. Although all metabolic risk factors were well within clinically normal levels in both groups, high-density lipoprotein (HDL) cholesterol levels were higher in resistance-trained men compared with control subjects. Muscle strength, assessed by leg extension power and handgrip strength, was higher in resistance-trained men than in the control subjects. There were no significant differences in other parameters between the two groups.

Table 2 shows cardiovascular measures. With the exception of diastolic blood pressure in the brachial artery, blood pressure parameters of brachial and carotid arteries were higher in resistance-trained men compared with control subjects. Ankle–brachial index was lower in resistance-trained men than control subjects. There were no significant differences in the diameter or IMT in the carotid artery between the two groups.

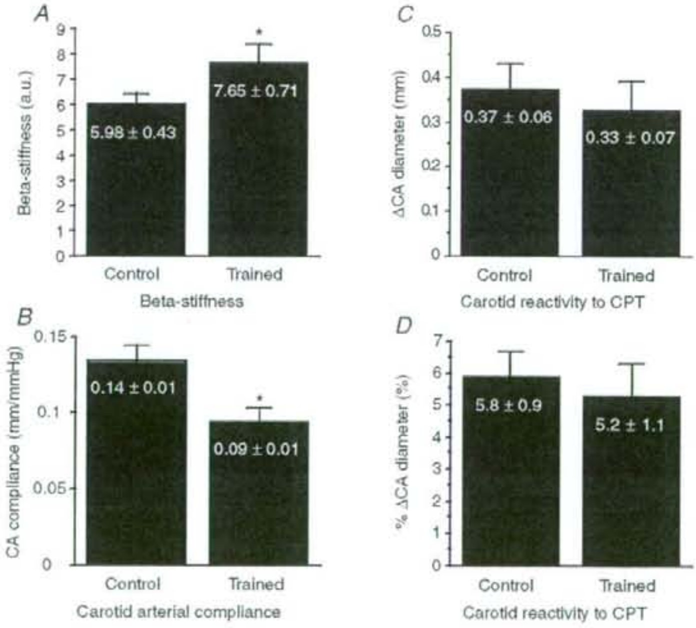

Figure 1. Carotid arterial β-stiffness index (*A*), carotid arterial (CA) compliance (*B*), and amount (*C*) and percentage change (*D*) in carotid artery diameter in response to CPT in resistance-trained men and control subjects

Values are means ± S.E.M. $^*P < 0.05$ *versus* control subjects.

Carotid arterial β-stiffness (Fig. 1*A*) was higher and compliance (Fig. 1*B*) was lower in resistance-trained men compared with control subjects. There were no significant differences in the amount (Fig. 1*C*) or percentage change (Fig. 1*D*) of carotid artery diameter in response to CPT between resistance-trained men and control subjects. The differences in carotid arterial compliance and β-stiffness index between resistance-trained men and control subjects disappeared after normalizing carotid arterial compliance and β-stiffness index relative to mean arterial blood pressure (ANCOVA; $P = 0.081$ and $P = 0.101$, respectively).

Discussion

The results of the present study indicated that, although the carotid arterial compliance was lower in resistance-trained men compared with age-matched control subjects, there were no significant differences in the amount or percentage change of carotid arterial diameter in CPT between resistance training and control groups. In contrast to our original hypothesis, these findings suggest that while regular resistance training can increase carotid arterial stiffness, this is not associated with abnormalities of carotid arterial vasoreactivity to sympathetic physiological stress induced by cold.

The endothelial function of conduit arteries is one of the vascular functions, and has been identified as a primary target of injury from mechanical forces and processes that increase cardiovascular risk, such as hypertension (Moyna & Thompson, 2004). Owing to the clinical and functional importance of health of the endothelium, we examined the impact of resistance training on endothelial function. As a primary approach to resolve this issue, we performed a cross-sectional study. To isolate the effects of resistance training as much as possible, resistance-trained men and control subjects were carefully matched for age, height, body weight, aerobic capacity and metabolic risk factors. Although subjects were recruited carefully, as described in the Methods, blood pressure in resistance-trained men was higher than that in the control subjects. As a result, we found a 30% reduction in central arterial compliance in resistance-trained men compared with control subjects. These results are consistent with those of a previous cross-sectional study (Bertovic *et al.* 1999). Differences in carotid arterial compliance and β-stiffness index between resistance-trained men and control subjects were affected after normalizing carotid arterial compliance and β-stiffness index relative to mean arterial blood pressure. Given this association between blood pressure and arterial compliance, higher blood pressure may lead to lower arterial compliance in resistance-trained men than in control subjects due to equation using arterial distensibility and blood pressure. However, we feel that the higher blood pressure in resistance-trained men may be induced by greater arterial stiffening associated with the resistance training. Nevertheless, despite the higher arterial stiffness and blood pressure in resistance-trained men than in control subjects, there was no difference in carotid arterial vasoreactivity to CPT between the two groups.

The response of conduit arteries to systemic cold may be the result of the balance between adrenergic vasoconstriction and vasodilatation, with the latter being mediated by endothelial function (Nabel *et al.* 1988; Zeiher *et al.* 1989; Vita *et al.* 1992; Corretti *et al.* 1995*a*). The normal coronary vasodilator response to CPT can be blocked by competitive inhibition of L-arginine, a substrate for NO synthase (Tousoulis *et al.* 1997), and L-arginine can normalize the vasoconstrictor response to CPT in coronary artery disease (Gellman *et al.* 1996). In addition, both endogenous NO and exogenously administered NO donors suppress sympathetic outflow at the prejunctional level, and NO may exert a tonic influence on the discharge of sympathetic efferents (Zanzinger *et al.* 1994; Nase & Boegehold, 1996). Therefore, the endothelial function, via NO, may play an important role in changing the conduit artery diameter response to sympathetic stimulation by the CPT. We first examined the impact of resistance training with arterial stiffening on endothelial function of the carotid artery using CPT, and found that there were no significant differences in the amount or percentage change in carotid arterial diameter in response to CPT between resistance-trained men and control subjects. Our results were consistent with those of a previous study, which demonstrated that resistance training did not affect endothelial function in the peripheral muscular artery evaluated by flow-mediated dilation (FMD) (Rakobowchuk *et al.* 2005). These findings are consistent with the posit that regular resistance training may protect against the adverse effects of resistance load associated hypertension by preserving arterial endothelial function (Jurva *et al.* 2006).

The results of the present study indicated that carotid arterial compliance in resistance-trained men was lower than that in control subjects, and blood pressure was significantly higher in resistance-trained men compared with control men. In contrast, HDL cholesterol level was higher in resistance-trained men than in control subjects, and there were no differences in other lipid profiles or IMT between the two groups. Considering the relationships between reduction in arterial compliance and impaired endothelial function, hypertrophied IMT or abnormal lipid profile with advancing age and/or the presence of cardiovascular disease (Zeiher *et al.* 1989; O'Rourke, 1990; Taddei *et al.* 1995; Tanaka *et al.* 2000; Najjar *et al.* 2005), the decrease in carotid arterial compliance induced by resistance training may be different from vascular alterations seen in ageing or in the presence of cardiovascular disease. Arterial compliance is affected by endothelial function as well as by sympathetic vascular tone, arterial calcification, elastin-to-collagen ratio and IMT, and correlates with clinical parameters, such as aerobic capacity, age, blood pressure, body fat, waist circumference and lipids (Nichols & O'Rourke, 1998; Tanaka *et al.* 2000). The degree to which these other factors affect the relationship between training-associated decrease in arterial compliance independent of endothelial function will require further studies in a larger cohort.

Rubenfire *et al.* (2000) reported that the direction and magnitude of the change in carotid artery diameter in response to CPT are altered based on the presence of risk factors and coronary disease independent of IMT. The carotid artery vasoreactivity to CPT may have a valuable role in coronary risk assessment and in predicting response to therapy. The present study revealed that there were no significant differences in carotid arterial vasoreactivity to CPT and IMT between resistance-trained men and control subjects, suggesting that regular resistance training may not affect at least two of the cardiovascular disease risk factors. In addition, HDL cholesterol, leg extension power and handgrip strength were higher in resistance-trained men than in control subjects. Given these functional and physiological benefits of resistance training, we should emphasize that the practice of resistance training should not be discouraged.

Limitations

Endothelial function assessed by FMD should optimally be adjusted by shear stress, shear rate or blood flow velocity (Pyke & Tschakovsky, 2005; Rakobowchuk *et al.* 2005). However, it is technically difficult to determine the blood velocity or shear stress during the relatively short period (90 s) of CPT used in our study. Further, in contrast to the occlusion release technique for assessing brachial endothelial function, the carotid artery vasoreactivity to CPT is a complex interaction between clinical, adrenergic nerve and hormonal responses and endothelial function.

Conclusion

The results of the present study showed that regular resistance training is associated with reduction of central arterial compliance as measured using a combination of ultrasound images and applanation tonometry. However, there were no differences in carotid arterial vasoreactivity to CPT between resistance-trained men and sedentary control subjects. These findings suggest that while carotid arterial stiffening and higher blood pressure are observed in regular resistance-trained men, they are not associated with impaired vasoreactivity to sympathetic stimulus, which implies intact endothelial function. Nevertheless, the results of the present cross-sectional study must be confirmed in future prospective exercise intervention studies.

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Original Article

Attenuated Increases in Blood Pressure by Dynamic Resistance Exercise in Middle-Aged Men

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The present study was performed to test the hypothesis that the blood pressure (BP) response to resistance exercise in middle-aged men with stiffening arteries is greater than that in young men with compliant arteries. The BP responses to acute dynamic resistance exercise (leg press) at individual relative (low, moderate and high) and absolute intensities were investigated in both young and middle-aged men. A total of 21 sedentary healthy normotensive men, 21–25 years of age (young) and 41–59 years of age (middle-aged), were included in the study. At rest, the arterial compliance (simultaneous ultrasound and applanation tonometry) and muscle strength (leg press) were lower, and indices of arterial stiffness and BP were higher in the middle-aged men than in the young men (p<0.05). There were no significant differences in height, body mass, or heart rate between the two groups. During exercise, the systolic BP of the middle-aged men at 80% one-repetition maximum (1RM) was significantly lower than that of the young men for the last half of the exercise period (p<0.05). The amounts of change in systolic and diastolic BP from baseline to the end of resistance exercise were lower in the middle-aged men than in the young men at individual relative intensities (p<0.05) and at individual absolute intensity. In contrast to our hypothesis, these findings indicated that the BP response during dynamic resistance exercise using large muscle groups may be attenuated in middle-aged men relative to young men. (*Hypertens Res* 2008; 31: 1045–1053)

Key Words: **aging, resistance exercise, blood pressure, pressor, arterial stiffening**

Introduction

Regular physical activity is regarded as an important component of prevention and treatment of age-related increases in cardiovascular disease (*1, 2*). Aerobic exercise in particular is recommended by major health organizations, including the American Heart Association and American College of Sports Medicine (*3, 4*), because it shows favorable effects on cardiovascular functions in young, middle-aged, and older men (*5–8*). In recent years, resistance exercise, another common exercise modality, has gained widespread acceptance in exercise prescription and cardiopulmonary rehabilitation programs and has become an integral component of comprehensive health programs endorsed by the major health organizations (*3, 9*). However, there is very little information on the potential influence of resistance training on non-musculoskeletal components, in particular the cardiovascular system. Systolic and diastolic blood pressures (BPs) rise rapidly to extremely high values during heavy weight-lifting exercise (*10*), and BPs are extreme even when exercise is performed with a relatively small muscle mass (*11, 12*). Most previous studies

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have focused on the BP responses to resistance exercise in young adults (*13–15*), and thus have provided little information regarding BP responses in middle-aged and older individuals (*12*, *16*). Furthermore, the interaction between age and BP response for dynamic resistance exercise using large muscle groups has not been reported in middle-aged men with stiffening arteries or young men with compliant arteries.

The stiffness of the large central arteries in the cardiothoracic region increases with advancing age in sedentary humans (*6*, *17*, *18*). This physiological alteration reduces the buffering capacity of the arteries, leading to increased pulse pressure, peripheral vessel resistance, and left ventricular wall tension (*19*, *20*), all of which augment the workload of the heart. Generally, it can be assumed that middle-aged and older men with advanced arteriosclerosis would show attenuated pressor buffering function during resistance exercise. Accordingly, we hypothesized that the BP response to dynamic resistance exercise in middle-aged men with stiffening arteries would be larger than that in young men with compliant arteries. The present study was performed to clarify the differences in BP response to acute dynamic resistance exercise at individual relative or absolute intensities between young and middle-aged men.

Methods

Subjects

Twelve young (21–25 years) and nine middle-aged men (41–58 years) were recruited through various forms of advertisement or by posting on bulletin boards at our university, and had not participated in a regular exercise program for at least the previous 2 years. Only male subjects were included in the study to ensure that the interpretation of differences between the two age groups would not be confounded by the possible influence of sex. All subjects were normotensive (<140/90 mmHg), non-obese (body mass index <30 kg/m^2), and free of overt chronic diseases as assessed by medical history and physical examination. Subjects taking cardiovascular-acting medications, such as anabolic steroids, or with significant intima-media thickening, plaque formation, and/or other characteristics of atherosclerosis (*e.g.*, ankle-brachial index [ABI] <0.9) were excluded from the study. All subjects gave their written informed consent to participation in the study, and all procedures were reviewed and approved by the Institutional Review Board.

Measurements at Rest

Brachial-Ankle Pulse Wave Velocity and BP

The brachial-ankle pulse wave velocity (baPWV) and BP were assessed using a form PWV/ABI device (Colin Medical Technology, Komaki, Japan). Subjects were examined in the supine position after a rest of at least 5 min. The cuffs were wrapped on both sides of the brachium and ankle, and contained a plethysmographic sensor that determined the waveform data, including BP measurements by the oscillometric method. The baPWV was calculated as distance/time (cm/s) between the brachium and ankle. The time delay between the arrival of the pulse wave at the brachium and ankle was obtained automatically by gating the pulse wave to the peak of the R wave of the electrocardiogram. The distance was estimated from the subject's height as $L = L_a - L_b$ (L_a: path length from the heart to the ankle; L_b: path length from the heart to the brachium). Then, we used the mean of the right and left baPWV values for analysis. The measurements of baPWV and BP were performed three times per day, and the three values were averaged. The reproducibility of baPWV measurement has been validated in our laboratory (coefficient of covariance, 2±1%) and in other studies (*21*, *22*).

Carotid Artery Intima-Media Thickness

The right common carotid artery intima-media thickness (IMT) was measured from images obtained using an ultrasound machine equipped with a high-resolution linear-array broad-band transducer as described previously (*23*, *24*). Ultrasound images were analyzed using computerized image analysis software (NIH Image 1.63). At least 10 measurements of IMT were taken at each segment, and the mean values were used for analysis. This technique has excellent day-to-day reproducibility (coefficient of variance, 3±1%) for the carotid IMT.

Carotid Artery Compliance and Stiffness

A combination of ultrasound imaging of the pulsatile right common carotid artery with simultaneous applanation of tonometrically obtained arterial pressure from the contralateral carotid artery permits noninvasive determination of arterial compliance (*23–25*). The carotid artery diameter was measured from images obtained using an ultrasound machine equipped with a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1–2 cm distal to the carotid bulb. All image analyses were performed by the same investigator who was blinded to the group assignments.

Pressure waveforms and amplitudes were obtained from the common carotid artery with a pencil-type probe incorporating a high-fidelity strain-gauge transducer (SPT-301; Millar Instruments, Houston, USA) (*26*). As baseline levels of BP are subject to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic BP to the brachial artery value (*23–25*). In addition to arterial compliance (*27*), we also calculated the β-stiffness index, which provides an index of arterial compliance adjusted for distending pressure (*28*). Arterial compliance and the β-stiffness index were calculated using the equations $[(D_1 - D_0)/D_0]/[2(P_1 - P_0)](P_1 - P_0) \times \pi \times (D_0)^2$ and $[\ln(P_1/P_0)]/[(D_1 - D_0)/D_0]$, where D_1 and D_0 are the maximal and minimum diameters, and P_1 and P_0 are the highest and lowest BPs, respectively (*23–25*). The day-to-day coefficients of variation were 2±1%, 7±3%, and 5±2% for the carotid artery diameter, pulse pressure, and arterial compliance, respectively.

Measurements during Dynamic Resistance Exercise

Radial BP and ECG

To determine circulatory response, radial BP and ECG were recorded simultaneously in the sitting position at baseline, during exercise, and during the recovery period. ECG and radial BP waveforms were determined using arterial tonometry (JENTOW-7700; Colin Medical Technology) and standard lead electrocardiography (Life Scope 11; Nihon Kohden, Tokyo, Japan), respectively. Both ECG and arterial BP waveforms were sampled at 1,000 samples per second by connecting each device to a computer using an A/D converter (PowerLab; AD Instruments, Colorado Springs, USA). The principle of arterial tonometry is that BP at the radial artery can be obtained by measuring the reaction forces produced by flattening the radial artery. Recently, this method has become preferred over the conventional finger photoplethysmographic method (Finapres), and it has been confirmed that the accuracy and reliability of BP measured by tonometry are greater than those of BP measured by the intra-arterial method. A tonometric sensor was attached to the left wrist, and the wrist was placed on a padded platform at the level of the heart. The oscillometric calibrations were carried out for accurate tonometric measurement before, and sometimes during the main experiment (29).

Strength Testing

Maximal muscular strength was assessed with a leg press machine using air pressure (Keiser; Fitness Apollo Japan Co., Ltd. Tokyo, Japan). A one-repetition maximum (1RM) was determined by having the subjects perform single repetitions with progressively heavier weights, resting 2–3 min between attempts; the heaviest weight that subjects could lift once through a complete range of movement was considered their 1RM. The day-to-day coefficient of variation for 1RM strength in our laboratory is 4±2%.

Exercise Protocol I

Subjects rested under quiet conditions before beginning the leg press exercise. After a 60-s baseline period, all subjects randomly performed 10 repetitions of the leg press exercise for 40 s at each of 40%, 60%, and 80% 1RM, followed by an 80-s recovery period. One repetition was performed for 4 s (2 s for concentric and 2 s for eccentric contraction). To measure radial BP accurately, the subject's left arm was supported on an adjustable table during measurement. Subjects were stabilized in the apparatus during exercise using their right hand to hold the support handle on the seat. The left arm was allowed to rest freely by their side to avoid interference with the recording of radial BP from this arm. The subjects were encouraged to avoid deep inhalations while performing the Valsalva maneuver during the exercise. Exercise measurements were performed randomly in a day. The interval time between exercises was controlled at 10 min.

Table 1. Subject Characteristics

	Young	Middle-aged
N	12	9
Age, years	21.4±0.5	47.8±1.9
Height, cm	170.6±1.7	170.1±2.1
Body mass, kg	65.3±2.1	67.7±2.9
Resting heart rate, bpm	52.3±1.7	60.8±4.4
Brachial systolic BP, mmHg	118±3	123±4
Brachial diastolic BP, mmHg	67±2	80±3*
Brachial mean BP, mmHg	82±4	96±4*
Brachial PP, mmHg	55±4	43±2*
Carotid systolic BP, mmHg	109±2	119±6
Carotid diastolic BP, mmHg	67±2	80±3*
Carotid PP, mmHg	42±2	38±3
Carotid diastolic diameter, mm	5.9±0.1	6.7±0.3*
Carotid intima-media thickness, mm	0.48±0.02	0.63±0.02*
Carotid arterial compliance, mm^2/mmHg	0.17±0.01	0.11±0.01*
Carotid β-stiffness index, a.u.	3.95±0.28	7.30±0.76*
Brachial-ankle PWV, cm/s	1,092±38	1,291±46*
Augmentation index, %	−6.9±5.7	19.6±5.8*
Leg press maximum, kg	350±11	286±19*

Data are mean±SEM. BP, blood pressure; PP, pulse pressure; PWV, pulse wave velosity. Leg press maximum was evaluated by air pressure machine (Keiser; Fitness Apollo Japan Instruments). *Significant at $p<0.05$ *vs.* young.

Exercise Protocol II

Eleven young men and nine middle-aged men were studied using protocol II. All subjects performed 10 repetitions of the leg press exercise at individual absolute intensity (145 kgw) 10 min after the end of protocol I. Protocol II was performed using a procedure similar to that in protocol I.

Data Analysis

In the baseline period, during the leg press exercise and recovery periods, waveforms of ECG and radial BP were recorded continuously and simultaneously on a personal computer (iBook G3; Apple Computer, Cupertino, USA). Heart rate and systolic, diastolic, and mean BP were calculated using the Chart5 software package (AD Instruments). Baseline values of BP were taken as the average of the baseline period (1 min) before exercise. Average values every 4 s for one repetition and peak values of BP were obtained during the 40-s exercise period. Eight BP values in the recovery period were averaged at 0–4, 4–8, 16–20, 36–40, 56–60, 76–80, 96–

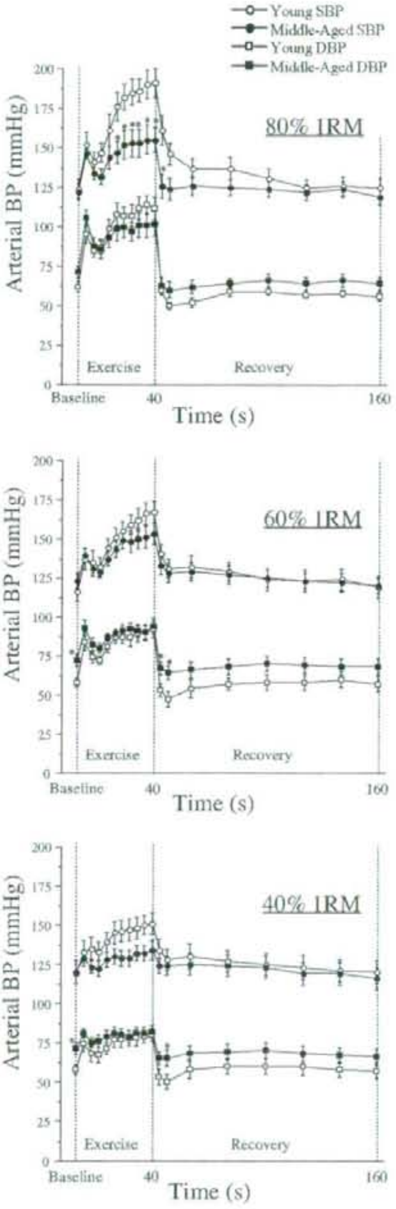

Fig. 1. *Systolic (circles) and diastolic (squares) blood pressure responses during resistance exercises and recovery periods at 40% (bottom), 60% (middle), and 80% (top) of 1RM in young (white) and middle-aged (black) men. Values are means±SEM.* $*p<0.05$ *vs. young men.*

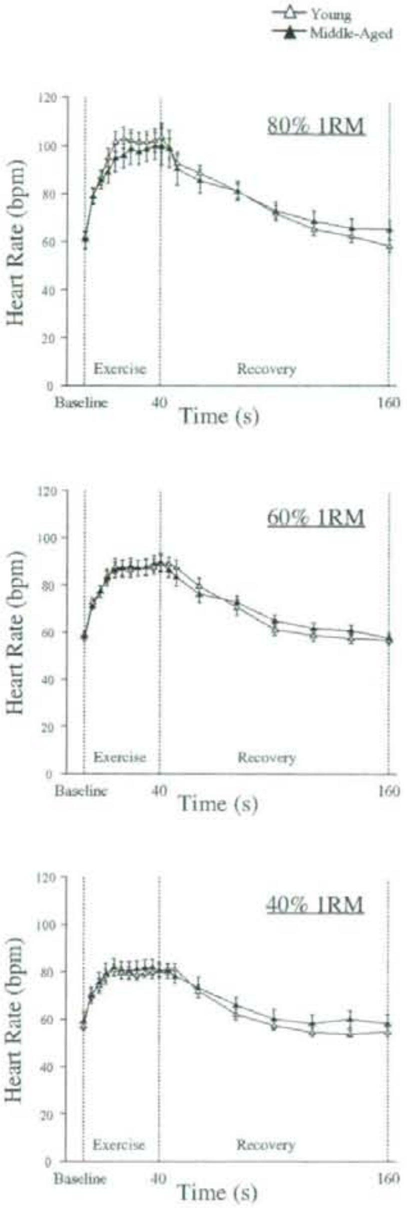

Fig. 2. *Heart rate responses during resistance exercises and recovery periods at 40% (bottom), 60% (middle), and 80% (top) of 1RM in young (white) and middle-aged (black) men. Values are means±SEM.*

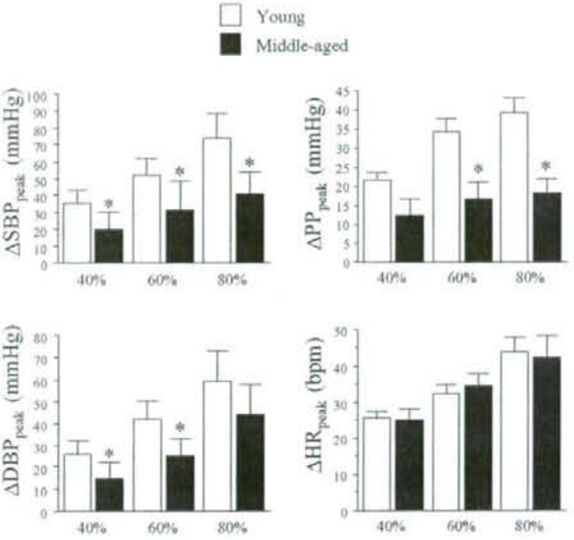

Fig. 3. *The amounts of change in systolic (SBP; top left) and diastolic (DBP; bottom left) blood pressure, pulse pressure (PP; top right) and heart rate (HR; bottom right) responses to resistance exercises at 40%, 60%, and 80% of 1RM in middle-aged (black bar) and young (white bar) men. Values are means±SEM.* $^*p < 0.05$ *vs. young men at the same intensity.*

100, and 116–120 s. Heart rate was calculated as the peak value during exercise.

Statistical Analysis

Changes during the leg press exercise were assessed by two-way analysis of variance (group × time) with repeated measures. In the case of significant F-values, a post hoc test (Newman-Keuls method) was used to identify significant differences among mean values. Peak values were analyzed using the t-test. All data are presented as the means±SEM. Statistical significance was set at $p < 0.05$ for all comparisons.

Results

Subject Characteristics

Subjects' characteristics at rest are shown in Table 1. There were no significant differences in height, weight, heart rate, or carotid BP between young and middle-aged men in the present study. Brachial diastolic and mean BP and carotid diastolic diameter were higher in the middle-aged men than in the young group ($p < 0.05$). Brachial systolic BP and carotid pulse pressure were not significantly different between the two groups. β-Stiffness, augmentation index, and baPWV in the middle-aged men were significantly higher than those in the young group ($p < 0.05$). The carotid arterial compliance and leg press maximum of the middle-aged men were significantly lower than those of the young men ($p < 0.05$).

Exercise Protocol I

Radial systolic and diastolic BP responses during the exercise and recovery periods are shown in Fig. 1. Baseline values of radial diastolic BP under the 40% and 60% 1RM conditions were higher in middle-aged than in young men, and there were no significant differences between groups in other baseline BP values. Systolic BP for 20–40 s during exercise in the middle-aged men at only 80% 1RM was significantly lower than that in the young group ($p < 0.05$). There were no significant differences in heart rate response to resistance exercise between middle-aged and young men at any intensity examined (Fig. 2). Systolic and diastolic BP returned to the baseline values within 60 s during the recovery period. The amounts of change in systolic and diastolic BP and pulse pressure from baseline to the peak response during resistance exercise were significantly lower in the middle-aged men than in the young group at all exercise intensities examined, but there was no significant difference in Δ heart rate (Fig. 3).

Exercise Protocol II

The amounts of change in systolic and diastolic BP and pulse pressure from baseline to the peak response during resistance

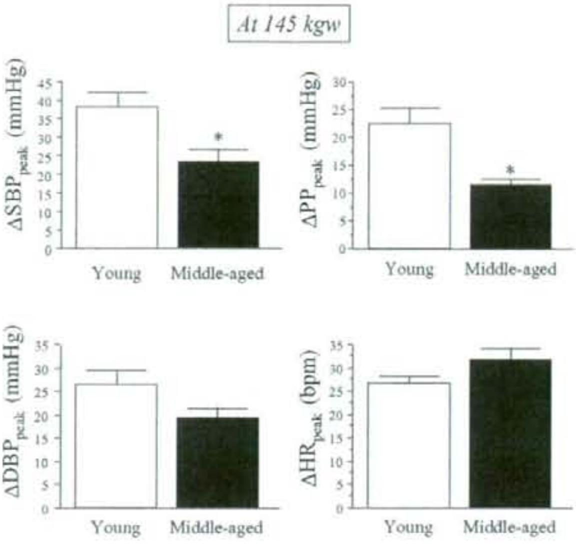

Fig. 4. *The amounts of change in systolic (SBP; top left) and diastolic (DBP; bottom left) blood pressure, pulse pressure (PP; top right) and heart rate (HR; bottom right) responses to resistance exercise at 145 kgw in middle-aged (black bar) and young (white bar) men. Values are means±SEM.* *$^*p < 0.05$ vs. young men.*

exercise were lower in the middle-aged men than in the young men at individual absolute intensity, but there was no significant difference in Δheart rate (systole, $p=0.019$; diastole, $p=0.091$; pulse pressure, $p=0.003$; Fig. 4).

Discussion

The major findings of the present study were as follows. 1) The absolute value of BP response to dynamic resistance exercise at 80% 1RM was lower in middle-aged men with stiffening arteries than in young men with compliant arteries. 2) At all relative intensities, the amounts of change in peak BP response to resistance exercise were lower in middle-aged than in young men. 3) At individual absolute intensity, the amounts of change in peak systolic BP response to resistance exercise were lower in middle-aged than in young men. In contrast to our hypothesis, these results suggest that BP responses during dynamic resistance exercise may be attenuated with advancing age at either individual relative or absolute intensity, despite age-related stiffening of the arteries.

Previous studies have suggested that the arteries of middle-aged men appear to be stiffer than those of young men based on measurements of carotid arterial compliance, β-stiffness, augmentation index, and baPWV (*5, 6, 22, 23, 30*). Our results also showed that arterial stiffening develops at a greater rate in middle-aged men than in young men. However, remarkable hypertrophy (>1.1 mm) of IMT, which is a characteristic of atherosclerosis, was not observed in any of the subjects in the present study. The maximal muscle strength estimated by the leg press exercise was lower in middle-aged men than in young men. These results indicate that the middle-aged men in the present study had developed arteriosclerosis without atherosclerosis and had lower maximal muscle strength than the young men. Although all BP values at rest in middle-aged men were higher than those in young men, all subjects were normotensive (<140/90 mmHg). Carotid diastolic diameter in middle-aged men was higher than that in young men. This result was consistent with the results of a previous epidemiological study (*31*). This alteration may be a physiological adaptation to suppress marked reductions in arterial compliance and vessel diameter induced by hypertrophied IMT with advancing age.

Dynamic resistance exercise is mainly used for health promotion and strength conditioning as it has greater effects on strength and volume of skeletal muscle in comparison with static (isometric) exercise (*32*). Understanding the pressor response during dynamic resistance exercise using large muscle groups is essential for exercise prescription. However, most previous studies have focused on static resistance exercise (*11, 12, 16, 33*), and have provided little information regarding the cardiovascular response during dynamic resistance exercise (*10*), or the interaction between age and BP response to dynamic resistance exercise using large muscle groups. We found that pressor responses during dynamic