Smaller age-related alteration in cardiovascular structure and function
in physically active and fit men and women

心臓血管形態・機能の加齢変化に対する
心肺体力および身体活動の効果

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Abbreviations and Acronyms

AI = augmentation index
BP = blood pressure
baPWV = brachial-ankle pulse wave velocity
cfPWV = carotid-femoral pulse wave velocity
CHD = coronary heart disease
CRF = cardiorespiratory fitness
CVD = cardiovascular disease
DBP = diastolic blood pressure
IMT = intima media thickness
IVS = interventricular septal thickness
LPA = light intensity physical activity
LV = left ventricular
LVEDD = left ventricular end-diastolic dimension
LVESD = left ventricular end-systolic dimension
MAP = mean arterial pressure
MPA = moderate intensity physical activity
PA = physical activity
PP = pulse pressure
PWT = posterior wall thickness
RWT = relative wall thickness
SBP = systolic blood pressure
VPA = vigorous intensity physical activity
Cardiovascular diseases (CVD) account for the majority of premature morbidity and mortality in the developed world. In Japan, nearly 300,000 patients die due to heart diseases and cerebrovascular diseases each year (approximately 240 per 100,000 person-years) (1). The prevalence and death rates of CVD have been rapidly increasing in Japan, due to population aging, physical inactivity, and obesity.

Until the 1980s, Japan had a lower percentage of elderly citizens compared with any other developed countries. However, Japan is now one of the countries in which the population is aging rapidly. As of April 1, 2009 the total population of Japan
was 127.6 million and the number of elderly aged 65 or older was 28.7 million, accounting for 23% of the total population. The elderly population is expected to continue to increase rapidly and the percentage of the elderly will reach 37.6 million (40%) in 2050 (2). Life expectancy in Japan at birth has also drastically increased since World War II to 79.0 years for males and 85.8 years for females in 2006. The Japanese Cabinet Office expects that it will reach 83.3 years for males and 90.9 years for female in 2050. Thus, in the near future, Japanese society will encounter more difficult medical problems due to rapid aging, which other developed countries have never before experienced.

Infectious disease such as pneumonia, tuberculosis, and gastroenteritis were the leading causes of death in Japan until the mid 1900s. The major health problems in Japanese society have drastically changed since World War II. The morbidity and mortality rates of lifestyle-related diseases such as cancer, heart disease, stroke, and diabetes mellitus have dramatically increased. Approximately, 60% of the mortality is now attributed to lifestyle-related diseases (cancer, 31%; ischemic heart disease 16%; cerebrovascular disease 13%; diabetes mellitus 1.3%; and hypertensive disease 0.5%) and the medical costs for these diseases amounts to 10.2 trillion yen, accounting for approximately 30% of the total cost of the Japanese health insurance in 2003 (3).
Currently, heart disease and cerebrovascular disease are the second and third frequent cause of death in Japan. Clearly cost-effective strategies for preventing and managing CVD could provide important economic benefits in addition to reducing human suffering and improving quality of life.

It is now more than 50 years since the physical activity-coronary heart disease (CHD) hypothesis was launched by Morris et al. (4) with his pioneer work on London bus drivers. In the 1950s, Morris and Crawford first suggested that the rate of CHD was inversely related to the level of physical activity during occupational activities (5). In the London transportation study, sedentary bus drivers had almost twice the incidence of CHD as compared to the conductors who regularly walked up and down the stairs of double-decker buses (4). Since then, physical inactivity has been documented as a well established risk factor for CHD in Western populations; a sedentary lifestyle is associated with about two-fold increase in risk of CHD. With increasing rates of urbanization and other major changes in human behavior, the prevalence of sedentary lifestyle has further increased particularly among the young; it is estimated that children today expend approximately 600 kcal/day less than their counterparts 50 years ago (6). A sedentary lifestyle resulting from low activity levels both at work and during leisure time is associated with a significant increase in CVD
and all-cause mortality among both sexes. The associations are strong, independent of other major risk factors and illustrate the enormous preventive potential, given the high prevalence of a sedentary lifestyle in most communities (7).

Although the early work showed a consistent pattern of benefits for physical activity, the studies did not assess actual fitness. A potential benefit of evaluating cardiorespiratory fitness (CRF) is that it is an objective laboratory test and is perhaps a more accurate indication of recent physical activity habits than information provided by job classifications or self-reports of physical activity. Of course, there is a genetic component of fitness, but it is primarily determined by the individual’s habitual physical activity level. Taylor was the first to measure CRF in a large epidemiological study when he tested U.S. railroad workers with a submaximal exercise test. He and his colleagues found that the least fit one fourth of the workers were 50% more likely to develop CVD than the most fit one fourth (8) (9). Blair has spent nearly 30 years following women and men who participated in the Aerobics Center Longitudinal Study (ACLS) (10-13). These individuals received an extensive medical examination at baseline, including a maximal exercise test on a treadmill. The results show substantially lower overall risk of morbidity and mortality in persons who were at least moderately fit. A recent observation from the ACLS of an average follow-up of 12
years show that the most fit 20% had only one fourth the risk of dying compared with
the least fit 20% (14). Results from the ACLS have been remarkably consistent over
the years for a variety of fatal and non-fatal outcomes, and in both women and men of
all adult age groups. In the ACLS, low aerobic fitness is one of the strongest predictors
of mortality and also accounts for more deaths in the population than other risk
predictors, such as smoking, hypertension, elevated cholesterol, obesity, and diabetes.

Today, CVD is the leading cause of morbidity and mortality in modern
societies, and this is largely attributable to disorders of the arteries and heart.
Advancing age is a major risk factor for CVD and appears to exert its pathological
influence primarily via adverse effects on arteries and heart (15,16). Thus human aging
is associated with arterial and cardiac dysfunction and an increased risk of clinical
CVD. In contrast to age, regularly performed physical exercise in general, and CRF in
particular, are associated with enhanced arterial and cardiac function and reduced risk
of CVD. These observations suggested that higher CRF may exert its beneficial effects
on physiological function and risk of CVD with aging at least in part by minimizing or
preventing adverse changes in the structure and function of arteries and heart.

Regular exercise or training is associated with structural changes in the heart,
including increases in left ventricular (LV) chamber size, wall thickness, and mass.
Athletes involved in a high dynamic component (e.g., running) develop predominantly increased LV chamber size with a proportional increase in wall thickness caused by volume overload associated with the high cardiac output of endurance training. Endurance-trained athletes demonstrated eccentric LV hypertrophy, which is characterized by an unchanged relationship between LV wall thickness and LV radius (relative wall thickness) (17-20). Athletes involved in mainly static or isometric exercise (e.g., weightlifting) develop predominantly increased LV wall thickness with unchanged LV chamber size, which is caused by pressure overload accompanying the high systemic arterial pressure found in this type of exercise. Strength-trained athletes demonstrated concentric LV hypertrophy, which is characterized by an increased relative wall thickness (RWT) (21,22). Moreover, RWT increases with age (concentric remodeling) and it is often associated with LV systolic and diastolic dysfunctions (23) and all-cause mortality (24). However, it is not clear whether higher CRF level shows attenuate age-related cardiac remodeling.

Furthermore, regular exercise or training is also associated with structure and functional changes in the arteries. Regular aerobic exercise attenuates age-associated reductions in large elastic arterial stiffness (25-27). On the other hand, resistance training increases in arterial stiffness (28-30). Cross-sectional areas of the ascending
aorta and femoral artery are larger in endurance trained compared with sedentary peers.
Moreover, carotid intima media thickness, lumen diameter, and wall area increases
with age (arterial remodeling) and it is an independent risk factor for CVD (31,32).
However, it is not clear whether higher CRF level shows attenuate age-related arterial
remodeling.

This dissertation therefore focused on the relationships between CRF and
age-related arterial and cardiac remodeling, especially changes in the structure of
carotid arteries and left ventricle. It is important that one selects the types of exercise
suitable for their current physical fitness. By which, they can practice it safely and
effectively and also expect the positive psychological effect including having
exhilaration and relieving anxiety. Exercise and Physical Activity Guide for Health
Promotion 2006 (3) have recommended that one could start with increasing the physical
activity moderately in one’s daily life. For example, walking to school/office and
housework are the kinds of activity in which many people can readily incorporate in
their daily lives. The relationships between habitual physical activity and arterial
stiffness have not been fully understood, although the larger amount of data available.
More specifically, it remains unclear whether light intensity physical activity (LPA) is
effective to attenuate arterial stiffening.
Therefore, the purpose of this dissertation was to determine the relationships between CRF and age-related carotid artery remodeling (Chapter 2), to determine the relationships between CRF and age-related LV remodeling (Chapter 3), and to determine the relationships between the amount of LPA and arterial stiffness (Chapter 4).
Chapter 2. **Age and cardiorespiratory fitness are associated with arterial remodeling**

2-1. **Introduction**

Elastic arteries undergo remodeling with advancing age (intimal and medial thickening (33) and luminal dilation (34)). Arterial remodeling is usually an adaptive process that occurs in response to long-term changes in hemodynamic conditions, but may subsequently contribute to the pathophysiology of vascular diseases and circulatory disorders.

Carotid artery intima-media thickness (IMT) is an independent risk factor for cardiovascular disease (CVD) (31,32). On the other hand, cardiorespiratory fitness
(CRF) is independently associated with reduced risk of CVD (35,36). Thus, many previous studies focused mainly on the relationships between CRF level and the age-related increase in carotid IMT. In addition to carotid IMT, carotid artery remodeling derived from the interplay between carotid luminal dilation and wall thickening (37) is also an independent predictor of cardiovascular events (38). Previous studies suggested that dilation of lumen diameter is a typical vascular profile in patients with long-standing hypertension (39,40) and may reflect the fatiguing effects of repeated intense cyclic stress (41). Increased carotid wall area according to luminal dilation and/or wall thickening is associated with increased risk of cardiovascular events (38). Thus, when considering the pathophysiological implications of vascular disease, it is also important not to overlook changes in both age-related carotid luminal dilation and wall thickening (artery remodeling). However, the associations between CRF level and age-related carotid artery remodeling have attracted relatively little attention.

Accordingly, the primary aim of the present cross-sectional study was to determine the relationships between CRF and age-related carotid artery remodeling. We hypothesized that higher CRF would be associated with reduced age-related carotid artery remodeling.

2-2. Methods
Chapter 2. ARTERIAL AGING AND CARDIORESPIRATORY FITNESS

Subjects

A total of 771 adults (180 men and 591 women), under the age of 40 (young), 40 – 59 years of age (middle-aged), and over the age of 60 (older) participated in this study (Table 1). None of the subjects smoked or were on medication for hypertension, hyperlipidemia, or diabetes. Subjects with a history of stroke, cardiac disease, chronic renal failure, or peripheral arterial disease, as well as those regularly engaged in weight training, were excluded from the study (29). 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, 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 at least 4 hours (a 12-h overnight fast was used to determine arterial stiffness and blood pressure (BP)).

Carotid artery IMT, lumen diameter and wall area

Carotid artery IMT and lumen diameter were measured from ultrasound images (vivid i; GE Medical Systems, Milwaukee, WI) equipped with a high-resolution linear array transducer, as described previously (42) (30). The longitudinal two-dimensional ultrasound images were obtained at the proximal 1- to 2-cm straight portion of the
common carotid artery. These images were first recorded on the ultrasound machine for later offline analysis, and then stored on hard disk. The carotid images were obtained by two trained investigators.

Ultrasound carotid images were analyzed using Image J image analysis software (National Institutes of Health, Bethesda, MD). Carotid IMT was defined as distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface (42). Carotid lumen diameter was defined as distance between the lumen and intima, and a near-wall boundary, corresponding to the interface of the adventitia and media. These measurements were made at end diastole as described previously (42). At least 10 measurements of IMT and lumen diameter were taken at each segment. The mean values of these 10 measurements were used for the analysis. Carotid wall area was calculated as $\rho \pi \text{IMT}^2$; where $\rho$ is the arterial wall density ($\rho = 1.06$) (43). Carotid IMT/lumen diameter ratio was calculated as $2 \times \text{IMT}/\text{lumen diameter}$ (38). The image analyses were performed by the two investigators who were blinded to the group assignment of the subjects. Intraobserver and interobserver variabilities of measurements were examined in 100 subjects. The intraobserver and interobserver variabilities of measurements were 3.7% and 4.2% for carotid IMT and 2.0% and 2.2% for the lumen diameter, respectively.
**Carotid arterial blood pressure**

The pressure waveform and amplitude were obtained from the common carotid artery with a vascular testing device (form PWV/ABI; Omron Colin, Kyoto, Japan). A multielement tonometry sensor, consisting of 15 pressure-sensitive small elements aligned side by side, was coupled to the device. The carotid tonometry sensor is compact and lightweight and can be easily attached around the neck. The sensor element located manually at the center of the carotid artery can be identified by screening the pulse pressure (PP) levels of the 15 elements provided that the sensor element size sufficiently small compared with the vessel diameter. The quality of the carotid pulse wave and the downward force were checked visually by carotid compression tonography, and pulse waves were recorded and stored over periods of 30 s. As baseline levels of BP are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial pressure (MAP) and diastolic blood pressure (DBP) to the brachial artery value (44). The intraobserver variability of measurements was 4.0% for the carotid systolic blood pressure (SBP).

**Brachial arterial blood pressure**

Brachial BP was measured with an oscillometric device (form PWV/ABI; Omron Colin) with subjects in the supine position. All measurements conformed to the American
Heart Association Guidelines(45). The mean of right and left brachial BP was used for analysis.

**Cardiorespiratory fitness (CRF)**

CRF, assessed with \( \dot{V}O_2 \text{peak} \), was measured by an incremental cycle exercise test using a cycle ergometer (Monark, Varberg, Sweden). The incremental cycle exercise began at a work rate of 30 or 60 W (60 rpm), and power output was increased by 15 W·min\(^{-1}\) until the subjects could not maintain the fixed pedaling frequency. The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. Heart rate and rating of perceived exertion (RPE) were monitored minute by minute during exercise. Oxygen uptake (\( V\text{O}_2 \)) was monitored during the last 30 s of each increase in work rate after the RPE reached 18. RPE was obtained using the modified Borg scale (46). 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 \( \dot{V}O_2 \text{peak} \) during the exercise test was designated as \( \dot{V}O_2 \text{peak} \).

To assess the effects of CRF on carotid IMT, the subjects were categorized into high (fit) or low (unfit) CRF groups on the basis of the median value of \( \dot{V}O_2 \text{peak} \) every
decade of age in each sex.

**Blood samples**

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

**Statistical analyses**

The data were analyzed by two-way ANOVA (age × fitness level) and ANCOVA, which included sex as a covariate. In cases with a significant $F$ value, a *post hoc* test with Scheffe’s method was used to identify significant differences among mean values. To investigate the effects of age, the groups were compared by one-way ANOVA and Tukey’s *post hoc* test for multiple comparisons. Univariate regression and correlation analyses were used to analyze the relationships between variables of interest. Stepwise multiple regression analysis was used to determine the independent relations of several variables to arterial stiffness. $P < 0.05$ was considered statistically significant. Data are presented as means ± SE.

**2-3. Results**

Table 1 shows the characteristics of the subjects. Brachial SBP and MAP increased
progressively with age in the unfit group but were not different between middle-aged and older in fit group. Percent body fat value was lower in the fit group than in the unfit group at all ages. Plasma glucose and total cholesterol levels increased with age.

Table 2 shows the effects of age and CRF on carotid IMT, lumen diameter, and wall area. In carotid IMT, two-way ANOVA indicated a significant interaction between age and CRF in determining carotid IMT ($P<0.01$). Carotid IMT increased progressively with age in both fitness groups. In young and middle-aged subjects, there were no significant differences in carotid IMT between the two fitness groups. Carotid IMT was lower in fit than in unfit older subjects. The differences still remained significantly after normalizing carotid IMT for sex when analyzed by ANCOVA. Two-way ANOVA indicated a significant interaction in carotid lumen diameter ($P<0.01$). Lumen diameter increased progressively with age in the unfit group but was not different among any age categories in the fit group. In middle-aged and older subjects, lumen diameter was lower in the fit group than in the unfit group. The difference remained significant after normalizing lumen diameter for sex when analyzed by ANCOVA. Two-way ANOVA indicated a significant interaction in carotid wall area ($P<0.01$). Wall area increased progressively with age in both fitness groups. In young and middle-aged subjects, there were no significant differences between the two fitness
groups. In older subjects, wall area was lower in the fit than in the unfit group. This difference remained significantly after normalizing vascular mass for sex when analyzed by ANCOVA.

Figure 1 shows the relationships between $\dot{V}O_{2\text{peak}}$ and carotid IMT (A), lumen diameter (B), and wall area (C) in each age category. Carotid IMT, luminal diameter, and wall area were correlated with $\dot{V}O_{2\text{peak}}$ in older subjects. There were no significant relationships in young or middle-aged subjects.

In older subjects, the analysis also indicated that lumen diameter was significantly correlated with weight ($r=0.36$), brachial SBP (0.43), carotid SBP (0.39), plasma glucose (0.24), plasma insulin (0.25), HDL-cholesterol (–0.16), and triglycerides (0.18). Stepwise multiple regression analysis revealed that brachial SBP ($\beta=0.38$), weight (0.32), and $\dot{V}O_{2\text{peak}}$ (–0.16) were independently correlated with lumen diameter.

In older subjects, the analysis also indicated that wall area was significantly correlated with brachial SBP ($r=0.29$), carotid SBP (0.28), HDL-cholesterol (–0.23), and $\dot{V}O_{2\text{peak}}$ (–0.23). Stepwise multiple regression analysis revealed that brachial SBP ($\beta=0.24$), HDL-cholesterol (–0.23), and $\dot{V}O_{2\text{peak}}$ (–0.15) were independently correlated with vascular mass.
Table 1
Subject characteristics divided by age and fitness groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th></th>
<th>Middle-aged</th>
<th></th>
<th>Older</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fit</td>
<td>Unfit</td>
<td></td>
<td>Fit</td>
<td>Unfit</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>135</td>
<td>135</td>
<td>170</td>
<td>170</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28 ± 1</td>
<td>28 ± 1</td>
<td>50 ± 1*</td>
<td>51 ± 1*</td>
<td>63 ± 1*‡</td>
<td>64 ± 1*‡</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.2 ± 0.6</td>
<td>163.9 ± 0.7</td>
<td>160.0 ± 0.6*</td>
<td>160.1 ± 0.6*</td>
<td>156.9 ± 0.7*‡</td>
<td>156.9 ± 0.7*‡</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.0 ± 0.9</td>
<td>59.3 ± 1.1</td>
<td>57.8 ± 0.8</td>
<td>61.7 ± 0.7†</td>
<td>54.2 ± 0.9*‡</td>
<td>55.9 ± 0.9*‡</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 ± 0.2</td>
<td>21.9 ± 0.3</td>
<td>22.4 ± 0.2*</td>
<td>24.1 ± 0.3**†</td>
<td>21.9 ± 0.3</td>
<td>22.6 ± 0.3‡</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>20.1 ± 0.4</td>
<td>24.8 ± 0.4†</td>
<td>23.9 ± 0.4*</td>
<td>30.4 ± 0.5**†</td>
<td>26.7 ± 0.6*</td>
<td>29.9 ± 0.5**†</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>109 ± 1</td>
<td>109 ± 1</td>
<td>118 ± 1*</td>
<td>119 ± 1*</td>
<td>120 ± 2*</td>
<td>127 ± 2††</td>
</tr>
<tr>
<td>Brachial DBP (mmHg)</td>
<td>63 ± 1</td>
<td>64 ± 1</td>
<td>72 ± 1*</td>
<td>72 ± 1*</td>
<td>71 ± 1*</td>
<td>74 ± 1*</td>
</tr>
<tr>
<td>Carotid SBP (mmHg)</td>
<td>81 ± 1</td>
<td>81 ± 1</td>
<td>91 ± 1*</td>
<td>91 ± 1*</td>
<td>92 ± 1*</td>
<td>97 ± 2††</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.8 ± 0.1</td>
<td>4.8 ± 0.1</td>
<td>5.0 ± 0.1*</td>
<td>5.1 ± 0.1**†</td>
<td>5.2 ± 0.1*‡</td>
<td>5.3 ± 0.1**‡</td>
</tr>
<tr>
<td>Plasma insulin (μU/mL)</td>
<td>5.1 ± 0.2</td>
<td>5.4 ± 0.2</td>
<td>4.1 ± 0.2*</td>
<td>5.0 ± 0.2†</td>
<td>4.3 ± 0.3</td>
<td>5.2 ± 0.5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.55 ± 0.07</td>
<td>4.66 ± 0.06</td>
<td>5.39 ± 0.07*</td>
<td>5.39 ± 0.07*</td>
<td>5.78 ± 0.08**†</td>
<td>5.80 ± 0.09**†</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.70 ± 0.03</td>
<td>1.58 ± 0.03†</td>
<td>1.76 ± 0.03</td>
<td>1.58 ± 0.03†</td>
<td>1.73 ± 0.04</td>
<td>1.64 ± 0.04</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.72 ± 0.03</td>
<td>0.83 ± 0.04†</td>
<td>0.91 ± 0.04*</td>
<td>1.09 ± 0.05**†</td>
<td>0.95 ± 0.04*</td>
<td>1.04 ± 0.05*</td>
</tr>
<tr>
<td>VO_{2peak} (mL/kg per min)</td>
<td>41.1 ± 0.40</td>
<td>31.9 ± 0.3†</td>
<td>35.4 ± 0.4*</td>
<td>26.0 ± 0.3**†</td>
<td>32.2 ± 0.5**‡</td>
<td>23.7 ± 0.4**‡</td>
</tr>
</tbody>
</table>

Data are means±SE. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL, high-density lipoprotein cholesterol; VO_{2peak}, peak oxygen uptake. *P<0.05 vs. young subjects within the same fitness group; ‡ P<0.05 vs. middle-aged subjects within the same fitness group; †P<0.05 vs. fit subjects within the same age category.
Table 2
Arterial properties divided by age and fitness groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young Fit</th>
<th>Young Unfit</th>
<th>Middle-aged Fit</th>
<th>Middle-aged Unfit</th>
<th>Older Fit</th>
<th>Older Unfit</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>0.56 ± 0.01</td>
<td>0.55 ± 0.01</td>
<td>0.66 ± 0.01*</td>
<td>0.65 ± 0.01*</td>
<td>0.69 ± 0.01*†</td>
<td>0.74 ± 0.01*‡†</td>
</tr>
<tr>
<td>Lumen diameter (mm)</td>
<td>5.88 ± 0.04</td>
<td>5.85 ± 0.04</td>
<td>5.85 ± 0.05</td>
<td>6.03 ± 0.05*†</td>
<td>5.99 ± 0.06</td>
<td>6.28 ± 0.06‡†</td>
</tr>
<tr>
<td>Wall area (mm²)</td>
<td>1.05 ± 0.02</td>
<td>1.01 ± 0.02</td>
<td>1.47 ± 0.04*</td>
<td>1.42 ± 0.03*</td>
<td>1.64 ± 0.06*†</td>
<td>1.89 ± 0.07*‡†</td>
</tr>
</tbody>
</table>

Data are means±SE. IMT, intima-media thickness; *P < 0.05 vs. young subjects within the same fitness group; ‡P < 0.05 vs. middle-aged subjects within the same fitness group; †P < 0.05 vs. fit subjects within the same age category.
Figure 1. Relationships between CRF and carotid IMT (A), luminal diameter (B), and wall area (C) in each age category.

Carotid IMT, luminal diameter, and wall area correlated with CRF in older subjects.
2-4. Discussion

The new findings of present study were as follows. First, in the older group, carotid IMT, lumen diameter, and wall area were significantly lower in the fit group than in the unfit group. Second, carotid lumen diameter increased with advancing age in the unfit group but no differences were observed among any age categories in the fit group. Third, although carotid IMT and wall area increased with age in both fitness groups, the magnitude of age-related increases was smaller in the fit group compared with the unfit group. Fourth, multiple regression analysis revealed that CRF was independently correlated with lumen diameter and wall area. These results suggested that higher CRF is associated with lower levels of age-related carotid artery remodeling.

There have been many reports regarding the relationships between age-related increases in carotid IMT and CRF levels. However, these previous studies did not focus on the age-related dilation of lumen diameter and increases in wall area, and their findings were inconsistent. Specifically, CRF level and habitual exercise have been reported to be associated with lower (47,48), no difference (49-51), or even greater (52) carotid IMT. Therefore, considering the emphasis placed on dilation of the lumen diameter and increases in wall area for prevention of CVD (38), we extended our research to the age-related luminal dilation and wall thickening. Similar to some
previous reports, the present study also showed that carotid IMT was lower in fit older subjects than their unfit counterparts. More importantly, the present study demonstrated that lumen diameter and wall area were lower in fit older subjects than in their unfit counterparts. The present findings suggested that higher CRF is associated with reduced age-related luminal dilation and wall thickening.

We can only speculate on the mechanisms responsible for the attenuation of the age-related luminal dilation and wall thickening by higher CRF. The age-related arterial remodeling is primarily an adaptive response of the arterial wall to progressive elevations in chronic arterial BP (53). The results of animal and humans studies indicated that an increase in distending pressure is a major stimulus for hypertrophy of smooth muscle cells and the synthesis of extracellular matrix in the arterial wall (54-57). Repeated intense cyclic stress may cause fracture of the load-bearing elastin fibers and thus dilation of the lumen(41). Therefore, we propose that the smaller degree of age-related luminal dilation and increase in wall area in fit groups may be due to a smaller age-related increase in BP (Table 1). Indeed, in this study, brachial SBP and carotid SBP were positively associated with lumen diameter and wall area in older subjects. However, in a stepwise multiple regression model that included these factors, \( \dot{V}O_2\text{peak} \) was independently related to lumen diameter and wall area. Mechanisms by
which the maintenance of higher CRF may directly influence lumen diameter and wall area are still speculative and include the effect of endurance-trained state on the calcium content (58) and advanced glycation end products and collagen cross-linkage in the arterial wall (59).

Our findings have a number of important implications. It has not been demonstrated previously that CRF level has beneficial effects on increases in carotid IMT. The present study showed that higher CRF was associated with smaller age-related increases in carotid IMT and wall area and dilation of the lumen. As both luminal dilation and wall thickening are risk factors for CVD (31,32,38), the maintenance of higher CRF may have a protective effect against CVD in part by attenuating age-related carotid artery remodeling. Therefore, the improvement of CRF may be important for primary prevention of CVD. Furthermore, CRF can be evaluated in any practical fields, and therefore measurement of CRF as a parameter of physical fitness may aid in the prediction of arterial remodeling.

A limitation of the present study was its cross-sectional design. Due to the design of this study, we could not evaluate individual changes in age-related carotid artery remodeling. A long-term prospective study is needed to determine the cause-and-effect relationship between CRF and age-related carotid artery remodeling.
In conclusion, the present study indicated that a higher level of CRF is associated with reduced age-related wall thickening and luminal dilation in the carotid artery.
Chapter 3. Age and cardiorespiratory fitness are associated with left ventricular remodeling

3-1. Introduction

The cardiovascular system is affected by aging. Arterial stiffness increases progressively with advancing age even in healthy men and women (15). This arterial stiffening is associated with future hypertension (60) and death from cardiovascular disease (CVD) (61). Moreover, left ventricular (LV) relative wall thickness (RWT) (ratio of wall thickness to chamber radius) also increases with age (LV remodeling) (62). The LV remodeling is often associated with LV systolic and diastolic dysfunction (23) and all-cause mortality (24). The risk of CVD in women increases sharply after menopause...
which is associated in part with the arterial stiffening, hypertension and LV remodeling (64). Accordingly, the prevention and treatment of age-related arterial stiffening, hypertension and LV remodeling in women are of great clinical importance.

Cardiorespiratory fitness (CRF) is strongly associated with risk of CVD (35) and high blood pressure (BP)(65). Previous studies indicated that age-related increases in arterial stiffness were attenuated in the higher fit adults (25,27). Moreover, the arterial stiffness and BP were negatively associated with CRF(26). When considering the pathophysiological implications of vascular stiffening, it is also important not to overlook changes in the heart to which the blood vessels are coupled. In accordance with the concept of “vascular-ventricular coupling” in that morphological and functional changes in the left ventricle and vasculature are closely coupled, we hypothesized that higher CRF is associated with the smaller age-related increases in arterial stiffness and BP, and smaller increases attenuate LV remodeling. Accordingly, the aim of the present cross-sectional study was to determine the relationships between CRF, arterial stiffness, BP, and LV structure in both pre- and post-menopausal women.

3-2. Methods

Subjects

A total of 159 premenopausal (young) and postmenopausal women (older) participated...
in the study (Table 1). The young subjects were recruited from University and the older
subjects were recruited from the community around the National Institute of Health and
Nutrition (NIHN). The young subjects were mostly university undergraduate or
graduate students and older subjects were mostly clients of the health checkup for
postmenopausal women in the NIHN. The subjects had various physical activity levels,
and none were regularly engaged in weight training (30). None of the subjects smoked
and they were not taking steroids or hormone replacement therapy. None of the young
women were taking oral contraceptives. None of the subjects were on medication for
hypertension, hyperlipidemia, or diabetes. The purpose, procedures, and risks of the
study were explained to each subject prior to inclusion, and all 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 Declaration of Helsinki.

To assess the effects of CRF on arterial stiffness, BP and LV structure, subjects
were categorized into either low (unfit) or high (fit) CRF groups on the basis of peak
oxygen uptake ($\dot{V}O_{2\text{peak}}$). The young and older women were divided into fit and unfit
groups with median $\dot{V}O_{2\text{peak}}$ values of 33.9 ml/kg/min and 29.5 ml/kg/min, respectively.
This method is simple and straightforward. Moreover, these values are consistent with
the reference values for the maximal oxygen uptake for health promotion by gender and age, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent the lifestyle-related diseases (3).

Before testing, the subjects abstained from caffeine and fasted for at least 4 h (a 12-h overnight fast was used for determination of metabolic risk factors, arterial stiffness, wave reflection, BP and LV structure). The fitness assessment was performed after the other tests.

**Arterial stiffness and BP**

Pulse wave velocity (PWV) has been used as a noninvasive index of arterial stiffness and is reported to predict cardiovascular events (66). Carotid-femoral PWV is widely used, although complicated techniques are required to obtain an accurate pulse wave (67). Brachial-ankle PWV (baPWV) has also been developed as a simple, noninvasive index of arterial stiffness and is reported to be correlated with carotid-femoral PWV (68). Subjects were studied under quiet resting conditions in the supine position. Brachial-ankle pulse wave velocity (baPWV) and carotid augmentation index (AI), which are indexes of arterial stiffness and wave reflection, and BP were measured using a semi-automated oscillometric device (form PWV/ABI; Colin Medical Technology, Komaki, Japan) according to the method described previously(68). The device records
PWV, BP, ECG, and heart sounds simultaneously. ECG electrodes were placed on both wrists, and a heart sound microphone was placed on the left sternal border. The cuffs to measure baPWV were wrapped around both upper arms and ankles, and connected to a plethysmographic sensor that determines the volume pulse form. Volume waveforms were stored for a sampling time of 10 s with automatic gain analysis and quality adjustment. The time delay from the ascending point of the brachial artery waveform to the ascending point of each tibial artery waveform ($\Delta T_a$) was determined by the foot-to-foot method. The path lengths from the suprasternal notch to the arm ($\Delta D_a$), from the suprasternal notch to the femur ($\Delta D_b$), and from the femur to the ankle ($\Delta D_c$) were calculated to be $0.2195 \times H - 2.0734$, $0.5643 \times H - 18.381$, and $0.2486 \times H + 30.709$, respectively, where $H$ is the subject’s height in cm. The baPWV was calculated using the following formula: $(\Delta D_b + \Delta D_c - \Delta D_a) / \Delta T_a$ (cm/s). The right baPWV in each subject was used for subsequent analyses. The coefficient of variation for inter-observer reproducibility of baPWV was 4% in our laboratory.

Carotid AI, which is an index of wave reflections, was calculated as the ratio of amplitude of the pressure wave above its systolic shoulder to the total pulse pressure (PP) of carotid artery, as described previously (26,69). Carotid AI has been an independent predictor of all-cause and cardiovascular mortality (70). A multi-element
tonometry sensor, consisting of 15 pressure-sensitive small elements aligned side-by-side, was coupled to the device. The carotid tonometry sensor is compact and lightweight and can be easily attached around the neck. The sensor element manually located at the center of the carotid artery can be identified by screening the PP levels of the 15 elements, provided that the sensor element size is sufficiently small compared to the vessel diameter. The quality of the carotid pulse wave and the downward force were checked visually by carotid compression tonography, and pulse waves were recorded and stored over 30-s periods. The measured pressure waveform consists of both a “forward” or “incident” wave, and a “reflected” wave that is returning from a peripheral site. The reflected wave is superimposed on the incident wave such that the pulse and systolic pressures are increased. This increase is defined as a pressure pulse AI, and it is calculated as pressure wave above its systolic shoulder (ΔP) divided by PP (69). The shoulder was defined as the first concavity on the upstroke of the wave and separates the initial systolic pressure rise from the late systolic peak. The carotid AI has been proposed as an indicator of the magnitude of wave reflections, which is closely linked to arterial stiffness (69). In the present study, carotid AI was used as a measure of the stiffness of the central arteries. As baseline levels of BP are subject to hold down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean pressure.
arterial pressure (MAP) and diastolic blood pressure (DBP) to the brachial artery value (27,30). The coefficient of variation for inter-observer reproducibility of AI was 5% in our laboratory. Hypertension was defined as systolic blood pressure (SBP) ≥ 140, or DBP ≥ 90.

**LV dimensions and mass**

Immediately after measurement of arterial stiffness and BP echocardiographic studies were performed in each subject using an ultrasound machine equipped with a 2.5 MHz transducer (vivid i; GE Medical System, Wisconsin, USA). Ultrasound images were analyzed using computerized image analysis software (ImageJ). At least 5 measurements of M-mode images were taken at each segment, and the mean values were used for the analyses. The echocardiograms were obtained at rest with the subject in the left lateral decubitus position. Two-dimensional guided M-mode measurements of LV end-systolic dimension (LVESD) and LV end-diastolic dimension (LVEDD), interventricular septal thickness (IVS), and posterior wall thickness (PWT) were performed in accordance with the recommendations of the American Society of Echocardiography (71). LV mass was calculated according to the regression equation of Devereux et al.: \(0.80 \times (1.04 \times (LVEDD + IVS + PWT)^3) - (LVEDD)^3 + 0.6\) (72). LV dimensions and mass were normalized for the body surface area. RWT was calculated
as twice the ratio of PWT to the LVEDD (73). The coefficient of variation for inter-observer reproducibility of LV dimensions was 7% in our laboratory.

**Cardiorespiratory fitness (CRF)**

CRF, assessed from peak oxygen uptake ($\dot{V}O_{2\text{peak}}$), was measured by an incremental cycle exercise test using a cycle ergometer (Ergomedic 828E Test Cycle; Monark, Varberg, Sweden) as described previously (74).

**Blood samples**

Blood samples were taken after at least 10 h of overnight fasting to determine fasting glucose and insulin levels. In the same session, serum samples were withdrawn to determine fasting total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), and triglycerides levels. Hypercholesterolemia was defined as plasma total cholesterol $\geq 200$ mg/dl (borderline-high and high cholesterol) (75); diabetes was defined as fasting blood glucose $\geq 126$ mg/dl.

**Body composition**

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

**Statistical analyses**

Statistical analyses were performed with StatView (SAS Institute, Cary, NC). Two-way
ANOVA (age×CRF) and ANCOVA was used to compare continuous variables, and a $\chi^2$ test was used for categorical variables. When a significant $F$ value was obtained, Scheffe’s post hoc test was used to identify significant differences among mean values. When young and older women were compared within the same activity group, the data were analyzed by one-way ANOVA. Relations of interest were initially identified by simple regression analysis. Independent relations among the dependent variables were determined by multiple regression analysis. All data are shown as means±SE. Statistical significance was set a priori at $P<0.05$ for all comparisons.

3-3. Results

Plasma glucose, total cholesterol and triglycerides levels were higher ($P<0.01$) in older as compared with the young women (Table 1). HDL cholesterol was significantly higher ($P<0.05$) in the fit women as compared with their age-matched unfit peers. Although the percentages of hypertension and hypercholesterolemia were higher ($P<0.01$) in older as compared with young women, there were no significant difference between fit and unfit older groups. None of the subjects had diabetes. In both age groups, $\dot{V}O_2$peak in the fit group was approximately 11 ml/kg/min higher than in age-matched unfit peers.

Figure 1 illustrates the arterial stiffness, wave reflection and BP (baPWV, carotid AI and SBP) in unfit and fit groups. Two-way ANOVA indicated a significant
interaction between age and CRF in determining baPWV, carotid AI and BP ($P<0.01$). In both fitness groups, baPWV, carotid AI and SBP were higher ($P<0.01$) in older than in young women. In the young women, there were no significant differences in either baPWV, carotid AI or SBP between fit and unfit. In older women, baPWV, carotid AI and SBP in the fit group were significantly lower ($P<0.01$) than in their unfit peers. When ANCOVA was performed using BMI and HDL cholesterol as covariates, the difference remained statistically significant ($P<0.01$). Carotid PP was significantly higher ($P<0.01$) in unfit older women as compared to the other groups (Table 1).

LVEDD was significantly greater (young; $P<0.01$, older; $P<0.05$) in the fit women as compared with their age-matched unfit peers (Table 2). In both fitness level groups, IVS and PWT were higher in older women as compared with the young women. Although LV mass index was larger in the fit group than unfit in the young women group, there was no significant difference between the fit and unfit groups in the older women. Figure 2 illustrates the effects of age and CRF on LV structure (RWT). Two-way ANOVA indicated a significant interaction between age and CRF in determining RWT ($P<0.01$). In both fitness groups, RWT was larger ($P<0.01$) in older than in young women. In the young women, there was no significant difference in RWT between fit and unfit. In older women, RWT in the fit group were significantly thinner
(P<0.01) than in their unfit peers. When ANCOVA was performed using BMI and HDL cholesterol as covariates, the difference remained statistically significant (P<0.05). However, the difference in RWT was abolished after adjusting for baPWV or SBP.

LV hypertrophy was considered present when the LV mass indexes were \( \geq 110 \) g/m\(^2\) for women (72). Increased RWT was present when this ratio was \( \geq 0.45 \) (73). Normal geometry was present when LV mass index and RWT were normal, increased RWT and normal LV mass index identified concentric remodeling, increased LV mass index with normal RWT identified eccentric hypertrophy, and increases of the 2 variables identified concentric hypertrophy (76). In the present study, older, fit women with LV concentric hypertrophy or remodeling (N=8/30) were significantly (P<0.05) fewer in number than was the case with unfit peers (N=17/30). Table 3 shows the arterial stiffness, BP and fitness parameters in subjects of different LV hypertrophy patterns. In normal geometry group, baPWV, carotid AI and BP were lower (P<0.01) than concentric hypertrophy and remodeling group.

Univariate correlation analyses were performed to determine which physiological variables were most closely associated with RWT. To eliminate the effect of age, the data was divided into young and older women. In older women, RWT was significantly related to SBP (\( r=0.57, P<0.01 \)), MAP (\( r=0.58, P<0.01 \)), DBP (\( r=0.46, \))
Chapter 3. CARDIAC AGING AND CARDIORESPIRATORY FITNESS

\[ P<0.01 \], carotid PP \( (r=0.57, P<0.01) \), baPWV \( (r=0.46, P<0.01) \), carotid AI\( (r=0.29, P<0.05) \), \( VO_{2\text{peak}} \ (r=-0.32, P<0.05) \). In the young women, they were not significant correlations, except for weak correlation between RWT and SBP \( (r=0.21, P<0.05) \).

RWT was not significantly related to BMI and HDL cholesterol in both age groups.

Figure 3 shows the relationships between RWT and selected correlates of interest in overall, young and older women. In overall study population, a multiple regression analysis revealed that the association between RWT and baPWV was not significant after adjustment for age and SBP as covariates.
**Table 1**

**Subject Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th></th>
<th>Older</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unfit</td>
<td>Fit</td>
<td>Unfit</td>
<td>Fit</td>
</tr>
<tr>
<td>N</td>
<td>49</td>
<td>50</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24 ± 1</td>
<td>23 ± 1</td>
<td>61 ± 1*</td>
<td>58 ± 1*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.4 ± 0.8</td>
<td>162.9 ± 0.9†</td>
<td>155.9 ± 0.8*</td>
<td>155.6 ± 1.1*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.0 ± 1.2</td>
<td>55.0 ± 1.0</td>
<td>55.7 ± 1.4</td>
<td>52.0 ± 1.0†</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.54 ± 0.01</td>
<td>1.58 ± 0.01</td>
<td>1.55 ± 0.01</td>
<td>1.49 ± 0.01†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.2 ± 0.4</td>
<td>20.7 ± 0.3</td>
<td>22.9 ± 0.6*</td>
<td>21.5 ± 0.3†</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>104 ± 1</td>
<td>107 ± 1</td>
<td>130 ± 4*</td>
<td>117 ± 3*†</td>
</tr>
<tr>
<td>Brachial DBP (mmHg)</td>
<td>60 ± 1</td>
<td>60 ± 1</td>
<td>76 ± 2*</td>
<td>69 ± 1*†</td>
</tr>
<tr>
<td>Brachial MAP (mmHg)</td>
<td>77 ± 1</td>
<td>78 ± 1</td>
<td>100 ± 3*</td>
<td>89 ± 2*†</td>
</tr>
<tr>
<td>Carotid PP (mmHg)</td>
<td>38 ± 1</td>
<td>37 ± 1</td>
<td>60 ± 5*</td>
<td>49 ± 3†</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.8 ± 0.1</td>
<td>4.9 ± 0.1</td>
<td>5.3 ± 0.1*</td>
<td>5.1 ± 0.1*</td>
</tr>
<tr>
<td>Plasma insulin (µU/mL)</td>
<td>5.6 ± 0.4</td>
<td>5.8 ± 0.4</td>
<td>4.7 ± 0.6</td>
<td>4.2 ± 0.5*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.69 ± 0.09</td>
<td>4.54 ± 0.11</td>
<td>5.50 ± 0.16*</td>
<td>5.68 ± 0.12*</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.68 ± 0.05</td>
<td>1.85 ± 0.05†</td>
<td>1.68 ± 0.07</td>
<td>1.88 ± 0.07†</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.73 ± 0.04</td>
<td>0.66 ± 0.04</td>
<td>0.98 ± 0.07*</td>
<td>0.87 ± 0.07*</td>
</tr>
<tr>
<td>VO₂peak (mL/kg per min)</td>
<td>29.9 ± 0.4</td>
<td>41.4 ± 0.7†</td>
<td>23.0 ± 0.7*</td>
<td>34.2 ± 0.6*†</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>0</td>
<td>0</td>
<td>33*</td>
<td>13*</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>0</td>
<td>0</td>
<td>63*</td>
<td>80*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are means ± SE. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HDL, high-density lipoprotein; VO₂peak, peak oxygen uptake. *P<0.05 vs. young women in the same fitness group; †P<0.05 vs. unfit women in the same age group; NS, not significant.
### Table 2
LV Dimensions and Mass

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young Unfit</th>
<th>Young Fit</th>
<th>Older Unfit</th>
<th>Older Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm/m²)</td>
<td>29.0 ± 0.3</td>
<td>29.9 ± 0.3†</td>
<td>28.4 ± 0.5</td>
<td>30.5 ± 0.4†</td>
</tr>
<tr>
<td>LVESD (mm/m²)</td>
<td>17.7 ± 0.3</td>
<td>18.5 ± 0.3†</td>
<td>16.4 ± 0.4*</td>
<td>17.1 ± 0.3*</td>
</tr>
<tr>
<td>IVS (mm/m²)</td>
<td>5.14 ± 0.1</td>
<td>5.42 ± 0.1†</td>
<td>6.80 ± 0.3*</td>
<td>6.56 ± 0.2*</td>
</tr>
<tr>
<td>PWT (mm/m²)</td>
<td>5.47 ± 0.10</td>
<td>5.64 ± 0.10</td>
<td>6.70 ± 0.3*</td>
<td>6.35 ± 0.2*</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>76.0 ± 1.4</td>
<td>90.0 ± 2.4†</td>
<td>103.0 ± 6.6*</td>
<td>102.0 ± 4.0*</td>
</tr>
</tbody>
</table>

Data are means ± SE. LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PWT, posterior wall thickness; RWT, relative wall thickness. *P<0.05 vs. young women in the same fitness group; †P<0.05 vs. unfit women in the same age group.
### Table 3

Arterial stiffness, BP and fitness parameters in subjects of the different LV hypertrophy patterns

<table>
<thead>
<tr>
<th>Variables</th>
<th>Concentric hypertrophy</th>
<th>Concentric remodeling</th>
<th>Eccentric hypertrophy</th>
<th>Normal geometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>12</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>baPWV (cm/sec)</td>
<td>1450 ± 69</td>
<td>1309 ± 52</td>
<td>1124 ± 43†</td>
<td>1104 ± 14*</td>
</tr>
<tr>
<td>Carotid AI (%)</td>
<td>32.8 ± 3.5</td>
<td>21.7 ± 3.8</td>
<td>6.7 ± 6.1†</td>
<td>3.6 ± 1.7*</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>141 ± 8</td>
<td>124 ± 4†</td>
<td>108 ± 3*</td>
<td>108 ± 1*</td>
</tr>
<tr>
<td>VO₂peak (mL/kg per min)</td>
<td>27.3 ± 2.8</td>
<td>29.1 ± 1.4</td>
<td>40.4 ± 2.5*</td>
<td>33.6 ± 0.6‡</td>
</tr>
</tbody>
</table>

Data are means ± SE. baPWV, brachial pulse wave velocity; AI, augmentation index; SBP, systolic blood pressure; VO₂peak, peak oxygen uptake. *P<0.05 vs. concentric hypertrophy and remodeling group; †P<0.05 vs. concentric hypertrophy group; ‡P<0.05 vs. eccentric hypertrophy group.
Figure 1. Arterial stiffness and BP in unfit and fit women.

Two-way ANOVA indicated a significant interaction between age and CRF in determining baPWV, carotid AI and BP \((P<0.01)\). In both fitness groups, baPWV, carotid AI and SBP were higher \((P<0.01)\) in older than in young women. In older women, baPWV, carotid AI and SBP in the fit group were significantly lower \((P<0.01)\) than in their unfit peers. baPWV, brachial-ankle pulse wave velocity; AI, augmentation index; SBP, systolic blood pressure. *\(P<0.01\) vs. young women in the same fitness group; †\(P<0.01\) vs. unfit women in the same age group.
Figure 2. RWT in unfit and fit women.
Two-way ANOVA indicated a significant interaction between age and CRF in determining RWT ($P<0.01$). In older women, RWT in the fit group were significantly thinner ($P<0.01$) than in their unfit peers. RWT, relative wall thickness. *$P<0.01$ vs. young women in the same fitness group; †$P<0.05$ vs. unfit women in the same age group.
Figure 3. Relationships between RWT and SBP or baPWV overall (A and B), and in younger (C and D) and older (E and F) women.

RWT, relative wall thickness; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure.
3-4. Discussion

The main findings of the present study were as follows. First, arterial stiffness and BP in the fit older women were lower than in their unfit counterparts. Second, RWT in the fit older women were also lower than in their unfit counterparts. Third, RWT was strongly related to BP and arterial stiffness in the older women. Forth, there were no such differences and relationships in young women. These results suggest that higher CRF attenuates arterial stiffening and LV concentric remodeling in older women.

Previous studies indicated that age-related arterial stiffening is attenuated in fitter adults (25,27), and that central arterial stiffness and BP are negatively associated with CRF (26). We also found that older, fit women demonstrated lower baPWV and AI when compared with older, unfit peers. CRF is a major determinant of overall physiological functional capacity, and low levels of CRF have been identified as a risk factor for cardiovascular, as well as all-cause mortality (35). Thus, the present and previous findings suggest that arterial stiffness may be one factor responsible for the inverse relationship between premature mortality and CRF in those who are middle-aged and older.

In the present study, older, fit women demonstrated lower arterial stiffness. One possible reason for this finding is that BP does not increase as much with age in women
who are very fit. Indeed, we found that the differences in baPWV and AI between
groups were qualitatively similar to the differences in BP (Figure 1). Another possibility
is that higher CRF minimizes age-related structural changes in the arterial wall. In this
regard, the endurance-trained state has been shown to be associated with an elevated
overall content of elastin and a reduced calcium content, (58) and reduced formation of
advanced glycation endproducts and collagen crosslinking in the arterial wall (77). A
third possibility is that higher CRF may act to maintain endothelium-dependent
vasodilation with age, as reported previously (78).

LV wall thickness increases with age not only in subjects with hypertension but
also in normotensive adults (62). Moreover, physiological hypertrophy (“the athlete’s
heart”), characterized by an increase in LV chamber size and mass, is observed in adults
with a high level of CRF (79). Given this, it is reasonable to hypothesize that both age
and CRF are associated with increased LV wall thickness and mass. Gates et al.
(80) reported that the highest mean values for these LV characteristics were observed in
older, endurance-trained men, suggesting an additive effect of aging and exercise
behavior. In contrast to the previous findings, our results indicated that RWT in old, less
fit women was significantly thicker than in fit peers. Moreover, older, fit women with
LV concentric hypertrophy or remodeling (N=8/30) were fewer in number than was the
case in less fit peers (N=17/30). Taken together, in contrast to the men’s results, LV hypertrophy and remodeling are attenuated in older women with a high level of CRF. These sex-specific differences may be partly explained by concentrations of endogenous anabolic and sex hormones (81).

Long-term athletic training produces alterations in cardiac structure that result in an increase in calculated LV mass without concentricity (79). Mortality and the frequency of cardiovascular events are highest in patients with concentric hypertrophy (73) which is often a maladaptive response to provocative stimuli, such as hypertension and arterial stiffness. In the present study, fit young women had higher LV mass than their unfit counterparts, without LV concentricity; neither fit nor unfit young women had high levels of BP or arterial stiffness. Thus, we thought that although fit young women had higher LV mass, this is not unfavorable hypertrophy induced by provocative stimuli.

What physiological mechanisms might explain attenuating LV concentric remodeling in the fit-older women? LV remodeling is commonly conceptualized as an adaptive response to increased cardiac afterload caused by vascular loading such as arterial stiffening and hypertension. The results of \textit{in vitro} studies indicate that mechanical stretching is the primary stimulus responsible for induction of increased
cardiac myocyte protein synthesis and hypertrophy (82). We therefore hypothesized that removal of the excess mechanical stimulus applied to the LV is one of the mechanisms responsible for attenuation of remodeling. Indeed, in the current study, when ANCOVA was performed using baPWV and SBP as covariates, the difference in RWT was abolished. Moreover, arterial stiffness and BP were strongly and significantly related to RWT in older women but not in younger women, which is consistent with the previous report by Schillaci et al. (83). Thus, high CRF is associated with lower arterial stiffness, BP, and RWT in older women. Other possible mechanisms may be that regular aerobic exercise modulates selective age-associated impairments in the autonomic nervous system (84), suppression of myocardial collagen cross-linking (85), and attenuation of gene expression of atrial natriuretic peptides (86). It is possible that maintenance of higher CRF contributes to the attenuation of age-related LV remodeling by removal of the various factors that cause loading of the LV.

Epidemiological study have indicated that highly fit men and women have a lower incidence of CVD in comparison with their sedentary peers (87). Although the mechanisms underlying this protective effect probably include favorable changes in traditional risk factors (88), an additional possibility is that a high level of CRF is associated with attenuated LV remodeling through the control of increases in arterial
stiffening, particularly in middle-aged and older adults. Recent study in hypertensive rats indicated that exercise training attenuates the development of heart failure and increased survival and attenuates LV concentricity without a reduction in LV mass (89). Similar to these findings, RWT in our fit older group was thinner than in the unfit, without a reduction in LV mass. These results suggest that aerobic exercise has a direct beneficial effect on LV concentric remodeling.

Antihypertensive treatment also reduces LV mass and decreases the prevalence of LV hypertrophy and concentric remodeling (90). However, unlike antihypertensive drugs, which are costly, have effects that are largely limited to BP control, and often have adverse effects, aerobic exercise training is a relatively safe and inexpensive form of therapy with favorable effects on a broad spectrum of CVD antecedents and outcomes. Our findings suggest that in addition to antihypertensive medications (90) and salt restriction (91), maintenance of higher CRF may also be effective in partial attenuation of LV remodeling in middle-aged and older women. Therefore, the improvement of CRF may be an important tool for the primary prevention of CVD.

The present study have several limitations. First, as an initial approach to determine the relation between CRF, arterial stiffness, BP and LV remodeling, we used a cross-sectional study design. Due to the design of this study, we could not evaluate
individual changes in age-related arterial stiffness, BP and LV structure. Although fitter older women had both lower BP and lower PWV than their unfit counterparts, the cross-sectional design of the study does not allow us to clarify whether fitness favorably affects BP (and consequently stiffness) and/or stiffness (and consequently BP). As this type of study design has a number of well-recognized limitations, we attempted to isolate the influence of CRF as much as possible. To do so, both young and older women were carefully matched for differences in \( \dot{V}O_{2\text{peak}} \) between the groups of fit and unfit individuals (11 ml/kg/min). In addition, to isolate the effect of CRF per se, subjects taking drugs for hypertension, diabetes, or hyperlipidemia were excluded from the study. However, the results of the present cross-sectional study must be confirmed in future long-term prospective studies.

Second, estimation of LV mass may not be accurate because M-mode echocardiography does not consider LV long-axis length. On the other hand, there are insubstantial differences in LV internal diameter, wall thickness, and calculated RWT, whatever method is used. Indeed, a previous study indicates that RWT increases with age, whereas LV mass does not change (62). Consistent with the previous study, we observed an age-related increased in RWT. In contrast to that study, we observed age-related increases in LV mass. Therefore, although the M-mode calculation is
sufficient to assess RWT, the calculations of LV mass should be confirmed by the 2D area-length method (92) and magnetic resonance imaging (93).

Third, we used baPWV as a measure of arterial stiffness. The value of baPWV includes stiffness derived from the combination of large arteries and peripheral arteries. Compared with central elastic arteries, peripheral arteries are generally considered to be of less clinical significance. However, baPWV is strongly related to aortic PWV (68) and may provide qualitatively similar information to central arterial stiffness. Nevertheless, the results of baPWV determinations need to be confirmed by aortic PWV in the future.
Chapter 4. Longer time spent in light physical activity is associated with reduced arterial stiffness in older people

4-1. Introduction

Age-related arterial stiffening is associated with higher incidences of cardiovascular mortality and cardiovascular events (94). High levels of cardiorespiratory fitness (CRF) (74) and habitual physical activity (PA) from moderate to vigorous intensity have been shown to attenuate arterial stiffening (25,95). However, it is not clear whether light intensity physical activity (LPA) is also effective to attenuate arterial stiffening.

Many previous studies indicated the impact of PA on arterial stiffness. PA
evaluation in these studies was performed by self-reported questionnaires (96-98). However, subjective interpretation of questions and perception of PA may lead to misclassification of the magnitude of activity (99). Several studies performed using uniaxial accelerometers indicated the impact of PA on arterial stiffness (95,100). Sugawara et al. (95) reported that moderate physical activity (MPA) and vigorous physical activity (VPA) have favorable effects on arterial stiffness, although LPA had no such effect.

Previous studies demonstrated a stronger correlation between counts obtained with triaxial accelerometry and energy expenditure measured in a metabolic chamber in comparison with counts from uniaxial accelerometry (101-103) and validated the predicted energy expenditure in LPA obtained with triaxial accelerometry (103,104). LPA, such as housework (i.e., sweeping, mopping, and window washing), has a relatively high energy cost during daily living (101,105).

Therefore, we hypothesized that the amount of LPA may be associated with arterial stiffness. Moreover, it is also uncertain whether the effects of LPA are the same in fit and unfit individuals. Evidence of an effect of such differences in fitness level would suggest possibilities for targeted prevention. Accordingly, we examined the relationships between PA at various intensities obtained with triaxial accelerometry,
CRF, and arterial stiffness in a cross-sectional study.

4-2. Methods

Subjects

A total of 522 adults (167 men and 355 women), under the age of 40 (young), 40 to 59 years of age (middle-aged), and over the age of 60 (older) participated in this study (Table 1). None of the subjects smoked or were on medication for hypertension, hyperlipidemia, or diabetes. Subjects with a history of stroke, cardiac disease, or chronic renal failure, as well as those regularly engaged in weight training were excluded from the study (30). 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 be not recorded accurately by triaxial accelerometry. 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, 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 at least 4 hours (a 12-hour overnight fast was used to determine arterial stiffness and blood pressure (BP)).
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 BP were measured with a vascular testing device (form PWV/ABI; Omron Colin, Kyoto, Japan). Carotid and femoral arterial pressure wave forms were stored for 30 s 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 standard deviation 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(45). The mean of right and left brachial BP was used for analysis.

Physical activity

The duration and intensity of PA were evaluated by triaxial accelerometry (Actimarker EW4800; Panasonic Electric Works, Osaka, Japan). All subjects were asked to wear a triaxial accelerometer for 20 days. 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 × g. The apparatus stores the standard deviation of the vector norm of the composite acceleration ($K_m$) in the three dimensions each minute as follows:

$$
K_m = \sqrt{\frac{1}{n-1} \left[ \left( \sum_{i=0}^{n} x_i^2 + \sum_{i=0}^{n} y_i^2 + \sum_{i=0}^{n} z_i^2 \right) - \frac{1}{n} \left\{ \left( \sum_{i=0}^{n} x_i \right)^2 + \left( \sum_{i=0}^{n} y_i \right)^2 + \left( \sum_{i=0}^{n} z_i \right)^2 \right\} \right]}
$$

where $n$ is the number of data for 1 min ($n = 1200$), and $\Sigma x$, $\Sigma y$, and $\Sigma z$ are the sums of the accelerations in each axis for 1 min. 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 the seven types of housework and seven levels of walking/running speed and triaxial acceleration, and confirmed that PA and $\dot{V}O_2$ were highly correlated ($r = 0.93$) (106).

We obtained daily PA duration corresponding to 1.1–2.9 metabolic equivalents (METs) (light), 3.0 – 5.9 METs (moderate), and ≥ 6.0 METs (vigorous) (107).

To assess the effects of age and LPA on arterial stiffness, subjects in each age category were categorized into high – LPA and low – LPA groups on the basis of the median value of the daily time spent in LPA in each age category.

**Cardiorespiratory fitness (CRF)**

CRF, assessed from peak oxygen uptake ($\dot{V}O_{2\text{peak}}$), was measured by an incremental
cycle exercise test using a cycle ergometer (Ergomedic 828E Test Cycle; Monark, Varberg, Sweden) (74). As the test requires incremental cycle exercise to exhaustion, subjects were allowed to determine whether they were willing to participate in the test; 435 of the pooled population participated in the test.

To examine whether the effects of LPA on arterial stiffness are the same in fit and unfit individuals, the subjects were categorized into high (fit) or low (unfit) CRF groups on the basis of \( \dot{V}\text{O}_{2}\text{peak} \). The \( \dot{V}\text{O}_{2}\text{peak} \) reference values are provided for gender and age group, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent lifestyle-related diseases (3).

**Blood samples**

Blood samples were taken after at least 10 h of overnight fasting to determine fasting glucose and insulin levels. In the same session, serum samples were obtained to determine fasting total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), and triglyceride levels.

**Body composition**

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

**Statistical analyses**
The data were analyzed by two-way ANOVA (age × LPA level) and ANCOVA, which included sex as a covariate. In cases with a significant $F$ value, a post hoc test with Scheffé’s method identified significant differences among mean values. To investigate the effects of age, the groups were compared by one-way ANOVA and Tukey’s post hoc test for multiple comparisons. Univariate regression and correlation analyses were used to analyze the relationships between variables of interest. Independent relations among the dependent variables were determined by partial correlation analysis. Stepwise multiple regression analysis was used to determine the influence of step counts, daily time spent in LPA, MPA, and VPA on cPWV. $P < 0.05$ was considered statistically significant. Data are presented as means ± SE.

4-3. Results

Table 1 shows the physical characteristics of the subjects. In each age category, percent body fat values did not differ between the high – LPA and the low – LPA level groups. In older subjects, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were higher in the low – LPA than in the high – LPA level groups, respectively. In older subjects, plasma glucose was also higher in the low – LPA than in the high – LPA level groups.

Figure 1 shows the effects of age and the amount of LPA on cPWV. Two-way
ANOVA indicated a significant interaction \( (P < 0.05) \). In both LPA 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 – LPA level group than in the high – LPA level group \( (P < 0.01) \). The differences remained significant after normalizing cfPWV for sex when analyzed by ANCOVA.

Table 2 shows the PA and CRF of the subjects divided by age categories. There were no significant differences in the number of steps among the three groups. \( \dot{V}_{O_2\text{peak}} \) decreased with age. The daily time spent in LPA was longer in middle-aged and older groups compared with the young group. There were no significant differences in the daily time spent in MPA among the three groups. The daily time spent in VPA was shorter in older subjects than in the young and middle-aged groups.

Figure 2 shows the relationships between the daily time spent in LPA (A), MPA (B), or VPA(C) PA and cfPWV in each age category. 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 MPA \( (r = -0.21, P < 0.01) \) and VPA \( (r = -0.12, P < 0.05) \) PA. In the older group, cfPWV was significantly related to the daily time spent in LPA \( (r = -0.30, P < 0.01) \) and MPA \( (r = -0.32, P < 0.01) \) but not in VPA. The relations remained significant after normalizing for sex in partial
correlation analysis (LPA, \( r = -0.20 \); MPA, \( r = -0.30 \)). 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 MPA (\( \beta = -0.21 \)). In the older subjects, cfPWV was independently predicted by the daily time spent in LPA (\( \beta = -0.27 \)) and MPA (\( \beta = -0.29 \)) PA.

Figure 3 shows the relationships between the daily time spent in LPA and cfPWV or MAP in unfit (n=48) and fit (n=29) older subjects. The cfPWV (\( r = -0.41, P < 0.01 \)) and MAP (\( r = -0.36, P < 0.05 \)) were correlated with the daily time spent in LPA in unfit subjects. No such relationships were observed in older fit subjects.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Young High</th>
<th>Young Low</th>
<th>Middle-aged High</th>
<th>Middle-aged Low</th>
<th>Older High</th>
<th>Older Low</th>
</tr>
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<td>N</td>
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<td>67</td>
<td>147</td>
<td>147</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 ± 0.3</td>
<td>34 ± 1</td>
<td>50 ± 0.5*</td>
<td>49 ± 0.4*</td>
<td>63 ± 0.3*</td>
<td>64 ± 0.5*</td>
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<tr>
<td>Height (cm)</td>
<td>165.5 ± 1.0</td>
<td>169.1 ± 0.7</td>
<td>158.1 ± 0.5*</td>
<td>162.3 ± 0.7*†</td>
<td>155.5 ± 0.8*</td>
<td>157.5 ± 1.1*‡</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.2 ± 1.4</td>
<td>64.7 ± 1.3†</td>
<td>56.4 ± 0.7*</td>
<td>61.5 ± 0.8*†</td>
<td>53.2 ± 1.1*</td>
<td>57.4 ± 1.4*‡</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.9 ± 0.4</td>
<td>22.5 ± 0.3</td>
<td>22.5 ± 0.2</td>
<td>23.3 ± 0.3†</td>
<td>22.0 ± 0.4</td>
<td>23.1 ± 0.5</td>
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<td>Body Fat (%)</td>
<td>21.6 ± 0.8</td>
<td>21.9 ± 0.7</td>
<td>27.5 ± 0.5*</td>
<td>27.1 ± 0.6*</td>
<td>28.4 ± 0.7*</td>
<td>29.2 ± 0.8*</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>113 ± 1</td>
<td>114 ± 1</td>
<td>117 ± 1</td>
<td>118 ± 1*</td>
<td>120 ± 2*</td>
<td>126 ± 3*†</td>
</tr>
<tr>
<td>Brachial DBP (mmHg)</td>
<td>67 ± 1</td>
<td>68 ± 8</td>
<td>72 ± 1*</td>
<td>73 ± 1*</td>
<td>70 ± 1</td>
<td>76 ± 2*†</td>
</tr>
<tr>
<td>Brachial MAP (mmHg)</td>
<td>84 ± 1</td>
<td>85 ± 1</td>
<td>90 ± 1*</td>
<td>91 ± 1*</td>
<td>91 ± 1*</td>
<td>97 ± 2*†</td>
</tr>
<tr>
<td>Brachial PP (mmHg)</td>
<td>46 ± 1</td>
<td>46 ± 1</td>
<td>45 ± 1</td>
<td>45 ± 1</td>
<td>49 ± 1*†</td>
<td>50 ± 2*†</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.8 ± 0.1</td>
<td>4.8 ± 0.1</td>
<td>5.0 ± 0.1*</td>
<td>5.1 ± 0.1*</td>
<td>5.0 ± 0.1*</td>
<td>5.4 ± 0.1*‡</td>
</tr>
<tr>
<td>Plasma insulin (μU/mL)</td>
<td>3.9 ± 0.2</td>
<td>4.0 ± 0.2</td>
<td>3.8 ± 0.2</td>
<td>4.7 ± 0.2*</td>
<td>3.6 ± 0.3</td>
<td>4.5 ± 0.4</td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.73 ± 0.09</td>
<td>4.74 ± 0.10</td>
<td>5.43 ± 0.07*</td>
<td>5.46 ± 0.08*</td>
<td>5.99 ± 0.12*</td>
<td>5.95 ± 0.12*‡</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.64 ± 0.04</td>
<td>1.40 ± 0.04†</td>
<td>1.77 ± 0.03*</td>
<td>1.59 ± 0.03*†</td>
<td>1.75 ± 0.05</td>
<td>1.66 ± 0.06*</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.78 ± 0.06</td>
<td>0.97 ± 0.06†</td>
<td>0.93 ± 0.04</td>
<td>1.10 ± 0.05*†</td>
<td>0.96 ± 0.05</td>
<td>1.05 ± 0.07</td>
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<td>63</td>
<td>146</td>
<td>141</td>
<td>42</td>
<td>35</td>
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<tr>
<td>VO₂peak (mL/kg per min)</td>
<td>37.4 ± 1.0</td>
<td>36.0 ± 0.9</td>
<td>29.8 ± 0.5*</td>
<td>30.5 ± 0.6*</td>
<td>27.0 ± 0.6*</td>
<td>28.0 ± 0.8*‡</td>
</tr>
</tbody>
</table>

Data are means ± SE. High and Low, high – LPA level groups and low – LPA level groups; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HDL, high-density lipoprotein; VO₂peak; peak oxygen uptake. *P < 0.05 vs. young; ‡P < 0.05 vs. middle-aged; †P < 0.05 vs. high in the same age group.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th>Middle-aged</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steps (counts/day)</td>
<td>10537 ± 292</td>
<td>10851 ± 182</td>
<td>10691 ± 289</td>
</tr>
<tr>
<td>Daily time spent in PA (minutes/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PA</td>
<td>588 ± 10</td>
<td>647 ± 6*</td>
<td>658 ± 11*</td>
</tr>
<tr>
<td>Light (LPA)</td>
<td>525 ± 10</td>
<td>586 ± 6*</td>
<td>597 ± 10*</td>
</tr>
<tr>
<td>Moderate (MPA)</td>
<td>58 ± 2</td>
<td>60 ± 1</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Vigorous (VPA)</td>
<td>4.3 ± 0.7</td>
<td>2.1 ± 0.3*</td>
<td>1.3 ± 0.4*</td>
</tr>
<tr>
<td>VO\textsubscript{2}peak (mL/kg per min)</td>
<td>36.7 ± 0.7</td>
<td>30.2 ± 0.4*</td>
<td>27.4 ± 0.5*</td>
</tr>
</tbody>
</table>

Data are means ± SE. PA, physical activity; LPA, light intensity physical activity; MPA, moderate intensity physical activity; VPA, vigorous physical activity; VO\textsubscript{2}peak; peak oxygen uptake. *P < 0.05 vs. young; ‡ P < 0.05 vs. middle-aged.
Figure 1. Arterial stiffness in high – LPA and low – LPA groups.
Two-way ANOVA indicated a significant interaction between age and LPA in determining cfPWV ($P < 0.05$). In older subjects, cfPWV was higher in low – LPA than in high – LPA groups ($P < 0.01$). The differences remained significant after normalizing cfPWV for sex. LPA, light intensity physical activity; cfPWV, carotid–femoral pulse wave velocity. *$P < 0.05$ vs. young; ‡$P < 0.05$ vs. middle-aged; †$P < 0.05$ vs. high in the same age group.
Chapter 4. LIGHT PHYSICAL ACTIVITY AND ARTERIAL AGING

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 LPA ($r = -0.30$, $P < 0.01$). LPA, light intensity physical activity; MPA, moderate intensity physical activity; VPA, vigorous intensity physical activity; cfPWV, carotid – femoral pulse wave velocity.
Chapter 4. LIGHT PHYSICAL ACTIVITY AND ARTERIAL AGING

Figure 3. Relationships between daily time spent in LPA and cfPWV (A) and MAP (B) in unfit and fit older subjects.

The cfPWV ($r = -0.41, P < 0.01$) and MAP ($r = -0.36, P < 0.05$) were correlated with the daily time spent in LPA in unfit subjects. LPA, light intensity physical activity; cfPWV, carotid – femoral pulse wave velocity; MAP, mean arterial pressure.
4-4. Discussion

The key new findings of the present study were as follows. First, in older subjects, arterial stiffness deteriorated in the low-LPA level groups as compared with the high-LPA level groups. Second, a negative relationship between the daily time spent in LPA and arterial stiffness was observed in the older group. Third, although the daily time spent in LPA was inversely related with the arterial stiffness in unfit subjects, no such relationships were observed in fit subjects. These results suggest that LPA < 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 LPA may be easier to achieve in the older population than increasing structured exercise training at vigorous or moderate intensities.

Previous studies indicated that high levels of CRF (74) and regular PA from moderate to vigorous intensity attenuate arterial stiffening (25) (95). However, little information is available regarding the relationships between LPA and arterial stiffness. Therefore, we determined the relationships between the daily time spent in LPA, MPA, and VPA 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 (99) and this method allows better
determination of LPA (104). Similar to previous findings (25) (95), the present study also showed that arterial stiffness was significantly related to the daily time spent in MPA in middle-aged and older groups. More importantly, the present study first demonstrated that the daily time spent in LPA was inversely related with arterial stiffness in the older group. Furthermore, the relationship was clear in unfit older people. The present findings suggested that the daily time spent in LPA may be one important factor associated with arterial stiffening in unfit older people.

In the present study, the daily time spent in LPA was negatively associated with arterial stiffness in the older group. One possible reason for this finding is that light PA, such as housework and slow walking, 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 (%\(\dot{V}O_2\text{peak}\)) at 3 METs in young, middle-aged, and older groups corresponded to 29%, 35%, and 38% of \(\dot{V}O_2\text{peak}\), 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 blood pressure responses during PA. Another possibility is that longer daily time spent in LPA may minimize age-related changes in the arterial wall. The advanced glycation end products accumulate slowly on
long-lived proteins, such as collagen and elastin, to stiffen the arteries, and reducing these cross-links can enhance vessel compliance in experimental animals (59,108). In the present study, we found that plasma glucose was higher in the low – LPA level than in the high – LPA level groups in older subjects. Taken together, these findings suggested that the favorable effect of LPA on arterial stiffness is mediated by BP reduction and metabolic profile improvement. Other mechanisms by which daily LPA may influence arterial stiffness in older people are still speculative and include the effects of PA on the bioavailability of nitric oxide, connective tissue cross-linking, vascular smooth muscle tone, and gene expression (109-111).

Our findings have a number of important clinical implications. Increasing LPA may be easier to achieve in older people, especially in the unfit-older population. In fact, the CRF and time spent in VPA in the older group were markedly lower than those in middle-aged and young groups (Table 2). LPA can be achieved through household tasks and other non-exercise 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.

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. Due to 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.

The present study indicated that time spent in LPA is negatively associated with arterial stiffness in older people. The association was especially evident in unfit subjects. These findings suggest that the daily time spent in LPA, such as household tasks and other unstructured activities, may be effective in prevention of age-related arterial stiffening. The underlying physiological mechanisms and clinical implications of these finding warrants further investigation.
The purpose of this dissertation was to determine the relationships between cardiorespiratory fitness (CRF) and age-related carotid artery and left ventricular (LV) remodeling. In addition, we examined the relationships between arterial stiffness and time spent in light intensity physical activity (LPA) obtained with triaxial accelerometry which may not affect CRF.

In chapter 2, Carotid intima-media thickness (IMT), lumen diameter and wall area in fit older subjects were significantly lower ($P<0.05$) than unfit counterparts (IMT; 0.69+/−0.01 vs 0.74+/−0.01mm, lumen diameter; 5.99+/−0.06 vs 6.28+/−0.06mm, wall
area; 1.64+/−0.06 vs 1.89+/−0.07mm²). These results suggest that high level of CRF is associated with smaller age-related carotid artery remodeling. In chapter 3, relative wall thickness (RWT) in fit older women was lower ($P<0.05$) than in their unfit counterparts (0.42+/−0.08 vs 0.47+/−0.04mm.) This result suggests that high level of CRF is associated with smaller age-related LV remodeling.

Collectively, these findings support the view that maintenance of higher CRF is an effective strategy for combating several adverse physiological changes associated with arterial and cardiac aging, especially carotid artery and LV remodeling. In addition, previous studies conducted on hypertensive individuals have indicated that arterial stiffness and blood pressures may be causally linked with RWT (112). The findings from chapters 2 and 3 extend these concepts gained in clinical medicine to the functional status of CRF in healthy people. Specifically, in the current studies, we found that poor-fit older men and women demonstrated a higher central arterial stiffness and thickness and a higher RWT. Moreover, arterial stiffness was significantly related to the RWT. Taken together, these results raise the possibility that chronic stiffening and thickening of the central arteries may contribute, at least in part, to the concentric LV hypertrophy observed in cardiorespiratory unfit men and women. Our present findings are consistent with the concept of “vascular-ventricular coupling” in
Chapter 5. SUMMARY AND CONCLUSION

that morphological and functional changes in the left ventricle and vasculature are closely coupled (113,114). This modulatory influence may explain in part why cardiorespiratory fit adults have a lower prevalence of cardiovascular disease (CVD).

In chapter 4, carotid-femoral pulse wave velocity (cfPWV) in the low-LPA level older group was higher ($P < 0.01$) than in their high counterparts (952 +/- 21 vs 857 +/- 16 cm/s). This result suggests that LPA is associated with attenuation of arterial stiffening. The finding first suggests that it is not only higher CRF and habitual physical activity from moderate to vigorous intensity but also LPA is independently associated with reduced arterial stiffness. Although the guideline for physical activity of Japan (3) and other countries (115) have never been mentioned LPA under 3METs, it may be necessary to consider whether the LPA should be recommended for health promotion in future.

Studies in this dissertation have several limitations. As initial approach to determine the relationships between CRF, arterial remodeling, and LV remodeling (chapter 2 and 3) and LPA and arterial stiffness (chapter 4), we used a cross-sectional study design. These present cross-sectional studies provided only associations. The results of these cross-sectional studies must be confirmed in future long-term prospective studies (e.g., to examine the association between CRF and cardiac and
arterial remodeling in a large cohort) and randomized intervention studies (e.g., to examine the effect of LPA on arterial stiffness). The current guideline for physical activity of Japan and other country is not enough yet. Given the expected future increase in cardiovascular events, additional beneficial prevention strategy is necessary. We believe that our on-going studies will become one of the prevention strategies of CVD.

As the populations in Japan and other modern societies get aging, greater resources will be required to meet health care needs. The associated costs and demand pose a real and increasingly imminent threat to our health care systems. A key strategy will be delaying the onset and development of age-associated physiological dysfunction and disease. Habitual exercise and habitual physical activity can be a powerful tool to achieve this goal. The prevalence of CVD will rapidly increase in the next decades in many industrialized countries, including Japan. Much of the etiology of CVD is attributable to disorders of the arteries and heart. As such, the use of regular exercise and physical activity to delay and prevent the development of arterial and cardiac dysfunction and disease can play a key role in promoting healthy aging.
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