Attenuated Age-Related Carotid Arterial Remodeling in Adults with a High Level of Cardiorespiratory Fitness

Yuko Gando¹, Kenta Yamamoto², Hiroshi Kawano³, Haruka Murakami², Yumi Ohmori², Ryoko Kawakami², Kiyoshi Sanada⁴, Mitsuru Higuchi³, Izumi Tabata², ⁴ and Motohiko Miyachi²

¹Sport Science Research Center, Waseda University, Saitama, Japan
²Health Promotion and Exercise Program, National Institute of Health and Nutrition, Tokyo, Japan
³Faculty of Sport Sciences, Waseda University, Saitama, Japan
⁴College of Sport and Health Science, Ritsumeikan University, Shiga, Japan

Aim: Cardiorespiratory fitness (CRF) is independently associated with a reduced risk of cardiovascular disease. Carotid arterial remodeling, which is derived from the interplay between carotid luminal dilation and wall thickening, is also an independent predictor of cardiovascular events. We hypothesized that high CRF may be associated with reduced age-related carotid arterial remodeling. This cross-sectional study was performed to determine the relationships between CRF and age-related luminal dilation and wall thickening.

Methods: A total of 771 adults (180 men and 591 women), under age 40 (young), 40-59 (middle-aged), and over age 60 (older) participated in this study. Subjects in each age category were divided into either high (fit) or low (unfit) CRF groups based on \( V·O_2 \) peak. Carotid artery intima-media thickness (IMT) and lumen diameter were measured on ultrasound images. Carotid wall mass was calculated as \( \rho L(\pi Re^2-Ri^2) \).

Results: Two-way ANOVA indicated a significant interaction (p<0.01) between age and CRF in determining IMT, lumen diameter, and wall mass. In older subjects, IMT, lumen diameter, and wall mass were significantly lower (p<0.05) in the fit than in the unfit group (IMT, 0.69±0.01 vs. 0.74±0.01 mm; lumen diameter, 5.99±0.06 vs. 6.28±0.06 mm; wall mass, 7.41±0.25 vs. 8.71±0.25 mm³). Multiple regression analysis indicated that the value of \( V·O_2 \) peak was independently correlated with carotid IMT, lumen diameter and wall mass.

Conclusion: The present study indicated that a high level of CRF is associated with reduced age-related wall thickening and luminal dilation in the carotid artery.


Key words: Aging, Fitness, Intima-media thickness, Lumen diameter, Remodeling

Introduction

Elastic arteries undergo remodeling with advancing age (intimal and medial thickening¹⁰ and luminal dilation²¹). 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)⁵.⁶. On the other hand, cardiorespiratory fitness (CRF) is independently associated with a reduced risk of CVD⁵.⁶. Thus, many previous studies focused mainly on the relationships between the CRF level and the age-related increase in carotid IMT. In addition to carotid IMT, carotid arterial remodeling derived from the interplay between carotid luminal dilation and wall thickening⁷ is an independent predictor of cardiovascular events⁸. Previous studies sug-
Table 1. Subject characteristics divided by age and fitness groups

<table>
<thead>
<tr>
<th></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>N</td>
<td>135</td>
<td>135</td>
<td>170</td>
<td>170</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Men/Women, n</td>
<td>38/97</td>
<td>38/97</td>
<td>41/129</td>
<td>41/129</td>
<td>11/69</td>
<td>11/70</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>161.0 ± 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>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>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>MAP, 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>Carotid SBP, mmHg</td>
<td>102 ± 1</td>
<td>101 ± 1</td>
<td>117 ± 2*</td>
<td>118 ± 2*</td>
<td>121 ± 3*</td>
<td>131 ± 3*††</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>LDL cholesterol, mmol/L</td>
<td>2.70 ± 0.06</td>
<td>2.91 ± 0.06†</td>
<td>3.44 ± 0.06*</td>
<td>3.59 ± 0.06*</td>
<td>3.86 ± 0.08*‡</td>
<td>3.95 ± 0.06*‡</td>
</tr>
<tr>
<td>VO₂peak, 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 the means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VO₂peak, 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.

Gestated that dilation of the lumen diameter is a typical vascular profile in patients with long-standing hypertension9,10 and may reflect the fatiguing effects of repeated intense cyclic stress11. Increased carotid wall mass according to luminal dilation and/or wall thickening is associated with an increased risk of cardiovascular events9. 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 (arterial remodeling); however, the associations between the CRF level and age-related carotid arterial 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 arterial remodeling. We hypothesized that higher CRF would be associated with reduced age-related carotid arterial remodeling.

**Methods**

**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 who regularly engaged in weight training, were excluded from the study12,13. Subjects who demonstrated significant IMT (> 1.5 mm), plaque formation13, ankle-brachial pressure index < 0.90, and/or characteristics of atherosclerosis were excluded. Before testing, subjects abstained from caffeine and fasted for at least 4 hours (10-h overnight fast was used to determine metabolic risk factors and blood pressure (BP)). 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.

**Carotid Artery IMT, Lumen Diameter, and Wall Mass**

Carotid artery IMT and lumen diameter were
measured from ultrasound images (vivid i; GE Medical System) equipped with a high-resolution linear array transducer, as described previously. 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 an ultrasound machine for later offline analysis, and then stored on hard disk. 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 the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface. Carotid lumen diameter was defined as the 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. At least 10 measurements of IMT and lumen diameter were taken in each segment. The mean values of these 10 measurements were used for analysis. Carotid wall mass was calculated, as previously reported, as \( \rho L (\pi R_e^2 - R_i^2) \), where \( \rho \) is the arterial wall density (\( \rho = 1.06 \), \( L \) is the length of the arterial segment (\( L = 1 \) cm), and \( R_e \) and \( R_i \) are the mean external and internal radii, respectively. Image analyses were performed by two investigators blinded to the group assignment of the subjects. Intraobserver and interobserver variabilities of measurements were examined in 100 subjects. 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 (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 is 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. Intraobserver variability of measurements was 4.0% for carotid systolic blood pressure (SBP).

**Brachial Arterial Bold Pressure**

Brachial BP was measured with an oscillometric device (PWV/ABI; Omron Colin) with subjects in the supine position. All measurements conformed to the American Heart Association Guidelines.

**Cardiorespiratory Fitness**

CRF, assessed from peak oxygen uptake (\( \dot{V}O_2 \)peak), was measured by an incremental cycle exercise test using a cycle ergometer (Ergomedic 828E Test Cycle; Monark, Varberg, Sweden) as described previously. 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 \( \dot{V}O_2 \)peak in 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), low-density lipoprotein cholesterol (LDL-cholesterol) and triglyceride levels.

**Statistical Analyses**

The data were analyzed by two-way ANOVA (age × fitness level) and ANCOVA, which included sex, brachial SBP and body fat 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. 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 remodeling values. \( P<0.05 \) was considered significant. Data are presented as the mean ± SE.

**Results**

Table 1 shows the characteristics of the subjects. Age was associated with shorter stature, greater body fat, and higher blood pressure. The percent body fat value was lower in the fit group than in the unfit group at all ages.

Table 2 shows the effects of age and CRF on
carotid IMT, lumen diameter, and wall mass. Two-way ANOVA indicated a significant interaction ($p<0.01$) between age and CRF in determining carotid IMT, lumen diameter, and wall mass. Carotid IMT and wall mass increased progressively with age in both fitness groups. Lumen diameter increased progressively with age in the unfit group but was not different at any age in the fit group. Carotid IMT and wall mass were lower ($p<0.05$) in fit than in unfit older subjects and lumen diameter was lower ($p<0.05$) in fit than in unfit middle-aged and older subjects. In the older group, these differences remained significant after normalizing for sex, brachial SBP and body fat as covariates; however, in the middle-aged group, the differences were abolished after normalizing for sex, brachial SBP and body fat. Fig. 1 shows the relationships between $\dot{V}O_2$peak and carotid IMT (A), lumen diameter (B), and wall mass (C) in each age category. Carotid IMT ($r = -0.24$, $p < 0.05$), luminal diameter ($r = -0.28$, $p < 0.01$), and wall mass ($r = -0.30$, $p < 0.01$) were correlated with $\dot{V}O_2$peak in older subjects. There were no significant relationships in young or middle-aged subjects.

In older subjects, the analysis also indicated that carotid IMT was correlated with brachial SBP ($r = 0.29$), carotid SBP (0.28), weight (0.13), $\dot{V}O_2$peak (-0.24), and HDL-cholesterol (-0.26). Stepwise multiple regression analysis revealed that brachial SBP ($\beta = 0.24$), HDL-cholesterol (-0.23), and $\dot{V}O_2$peak (-0.16) were independently correlated with carotid IMT.

In older subjects, the analysis also indicated that lumen diameter was correlated with brachial SBP ($r = 0.43$), carotid SBP (0.39), weight (0.36), $\dot{V}O_2$peak (-0.28), 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 $\dot{V}O_2$peak (-0.16) were independently correlated with lumen diameter.

In older subjects, the analysis also indicated that wall mass was correlated with brachial SBP ($r = 0.45$), carotid SBP (0.41), weight (0.33), $\dot{V}O_2$peak (-0.30), HDL-cholesterol (-0.24), plasma insulin (0.23), plasma glucose (0.19), and triglycerides (0.16). Stepwise multiple regression analysis revealed that brachial SBP ($\beta = 0.42$), weight (0.28), and $\dot{V}O_2$peak (-0.19) were independently correlated with wall mass.

### Discussion

The key new findings of the present study were as follows. First, in the older group, carotid IMT, lumen diameter, and wall mass were significantly lower in the fit group than in the unfit group. Second, although carotid IMT and wall mass increased with age in both fitness groups, the magnitude of age-related increases was smaller in the fit group than in the unfit group. Third, carotid lumen diameter increased with advancing age in the unfit group but no differences were observed at any age in the fit group. Fourth, multiple regression analysis revealed that $\dot{V}O_2$peak was independently correlated with carotid IMT, lumen diameter, or wall mass. These results suggested that higher CRF is associated with lower levels of age-related carotid arterial 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 the lumen diameter and increases in wall mass, and their findings were inconsistent. Specifically, the CRF level and habitual exercise have been reported to be associated with lower$^{22-24}$, no difference$^{25-27}$, or even greater$^{28}$ carotid IMT. Similar to previous findings by Galetta et al.$^{29}$, the present study also showed that a high level of CRF is related to an attenuation of age-related carotid arterial remodeling. An advantage of our study was the considerable number of subjects with a wide age range. Moreover, the strength of the present study was that CRF levels of all subjects were evaluated by maximal exercise testing. Considering the emphasis
placed on dilation of the lumen diameter and increases in wall mass for prevention of CVD\textsuperscript{8}, we extended our research to 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 in their unfit counterparts. More importantly, the present study demonstrated that lumen diameter and wall mass 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 age-related luminal dilation and wall thickening by higher CRF. Age-related arterial remodeling is primarily an adaptive response of the arterial wall to progressive elevations in chronic arterial BP\textsuperscript{30}. The results of animal and human 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\textsuperscript{31-34}. Repeated intense cyclic stress may cause fracture of the load-bearing elastin fibers and thus dilation of the lumen\textsuperscript{11}. Therefore, we propose that the smaller degree of age-related luminal dilation and increase in wall mass in fit groups may be due to a smaller age-related increase in blood pressure. Indeed, in this study, brachial SBP and carotid SBP were positively associated with carotid IMT, lumen diameter or wall mass in older subjects. However, in a

Fig. 1. Relationships between CRF and carotid IMT (A), lumen diameter (B), and wall mass (C) in each age category.
stepwise multiple regression model that included these factors, \( \dot{V}O_{2\text{peak}} \) was independently related to carotid IMT, lumen diameter, or wall mass. Park et al.\(^{25}\) reported that wall internal area and wall thickness area of the aorta were increased by menopause and improved by regular exercise in an animal study. As noted by Park et al., eNOS and endothelin-1 in the aorta tissue may participate in these mechanisms. Moreover, the mechanisms by which the maintenance of higher CRF may directly influence lumen diameter and wall mass are still speculative and include the effect of an endurance-trained state on the calcium content\(^{36,37} \) and advanced glycation end products and collagen cross-linkage in the arterial wall\(^{37} \). Exercise ameliorated the progression of endothelial dysfunction\(^{38} \) and atherosclerotic lesion formation with a strong negative correlation between atherosclerotic areas and the mean running distance per day\(^{39} \).

Our findings have a number of important implications. The present study showed that higher CRF was associated with smaller age-related increases in carotid IMT and wall mass and dilation of the lumen. As both luminal dilation and wall thickening are risk factors for CVD\(^{3,4,8} \), the maintenance of higher CRF may have a protective effect against CVD in part by attenuating age-related carotid arterial remodeling; therefore, the improvement of CRF may be important for primary prevention of CVD.

A major 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 arterial remodeling. A recent prospective study by Kozakova et al.\(^{22} \) reported that a period of vigorous activity influenced the 3-year IMT progression in a young to middle-aged population (30-60 yr). More research will be needed to determine cause-and-effect relationships in the older population (over 60 yr).

In conclusion, the present study indicated that a high level of CRF is associated with reduced age-related wall thickening and luminal dilation in the carotid artery.

**Grants**

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**Disclosure**

The authors declare no conflicts of interest.

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