Effect of Aging on Human Circulatory System in Normotensive Healthy Subjects

Mike Lin, MD^{1,2,3,*} Shoa-Lin Lin, MD^{3,4,*} Kuei-Liang Wang, MD³ Hsien-Wen Kuo, MD, PhD⁵
Tahir Tak, MD, PhD, FACC⁶

¹ Department of Medicine, Gou-Hsin Hospital, Pingtung City, Taiwan

² National Kaohsiung Marine University, Kaohsiung City, Taiwan

³ An-Fa Institution of Preventive Medicine, Taipei, Taiwan

⁴ Division of Cardiology, Department of Internal Medicine, Yuan's General Hospital, Kaohsiung City, Taiwan

⁵ Department of Medicine, Institute of Environmental Medicine, National Yang-Ming University, Taipei, Taiwan

⁶ Department of Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota

*These authors contributed equally to this work.

Address for correspondence Tahir Tak, MD, PhD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905 (e-mail: tak.tahir@mayo.edu).

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Abstract

Aging is associated with degenerative changes in cardiac and endothelial function (EF). This study was done to assess whether age-related changes take place on EF, carotid intima-media thickness (IMT), blood pressure (BP), and echocardiographic measurements. All volunteers were healthy normotensive healthy subjects. They were divided into three groups. Group 1, young adults: < 40 years old; Group 2, middle age: between 40 and 60 years old; Group 3, elderly: > 60 years old. High-frequency vascular ultrasound was used to assess the baseline brachial artery dimension and flow velocity after reactive hyperemia. The carotid IMT and echocardiographic measurements including Doppler variables were recorded in all subjects. Systolic BP, left ventricular mass, and left ventricular end-diastolic volume increased progressively with age ($p < 0.001$). Left ventricular ejection fraction decreased progressively with age (male, $p = 0.034$; female, $p = 0.001$); E/A ratio of the left ventricular flow spectrum declined with age ($p < 0.001$). The ultrasonic EF variables of flow increased during reactive hyperemia and IMT increased with age ($p < 0.001$). Our study demonstrates that BP, body weight, and ultrasonic variables changed significantly with age. The aging-associated changes provide insight into progression to atherosclerosis.

Keywords

- ▶ endothelial function
- ▶ intima-media thickness
- ▶ elderly population
- ▶ flow-mediated dilation
- ▶ left ventricular mass
- ▶ echocardiography

Increased carotid intima-media thickness (IMT) is a measure of structural atherosclerosis. It correlates with the severity of coronary atherosclerosis¹ and predicts cardiovascular events.² Decreased carotid elasticity represents early functional atherosclerosis. It has been implicated as an independent predictor for cardiovascular mortality in high-risk individuals.² The brachial artery flow-mediated dilation (FMD) using a noninvasive ultrasound method has been used to study endothelial function (EF).³ Previous reports have claimed that impairment of the FMD may predict

cardiovascular events,⁴ while preserved EF is associated with favorable cardiovascular outcome.⁵

Several articles have described that the arterial and left ventricular structure and function may change progressively with age. Aging is an important risk factor for atherosclerosis.^{6,7} Woo et al have reported that endothelium-dependent dilation in older subjects is similar to the arteries of healthy young Chinese and white adults.⁸ With older age, Chinese subjects are less susceptible to impaired EF.⁸ The study of Woo et al is the only study of EF relevant to Chinese population.

However, whether this phenomenon that Chinese subjects are less susceptible to impaired EF applies to all Chinese age groups still needs further investigation. Of note, the study of Woo et al did not include subjects > 70 years of age.

This study planned to include apparently healthy subjects including those with age older than 80 years old. Thus, the aim of this study was to assess the impact of age on the clinical variables including body weight, body mass index (BMI), and blood pressure (BP), echocardiographic variables including cardiac size and function, and ultrasonic endothelial functional variables obtained from brachial artery.

Materials and Methods

Study Population

A total of 126 healthy volunteers (63 males and 63 females) aged 18 to 84 years were recruited to receive 1-day complete health screenings from our institutions between January 2006 and December 2010. All were normotensive subjects, non-smokers, nondiabetic, without any cardiovascular risk factors, and not on any specific medications. Only subjects with normal sinus rhythm were included. This study was approved by the Institutional Review Board. Informed consents were obtained from all participants. Study subjects were divided into three groups according to age: young-to-adult group: age < 40, $n = 42$; middle age group: age 40 to 60, $n = 42$; and elderly group: age > 60 years old, $n = 42$. For each group, there were 21 males and 21 females.

Ultrasound Endothelial Function Study

Ultrasound EFs of right brachial artery were assessed for each subject. After an initial 15 minutes rest period, baseline recordings of brachial artery diameter and flow velocity were performed using a 7.5 MHz high-resolution vascular ultrasound transducer attached to a Hewlett-Packard SONOS 7500 (SONOS 7500 imaging system, Philips Medical Systems, Andover, MA) ultrasound machine. A pressure cuff over the forearm was inflated to at least 50 mm Hg above the systolic BP (SBP) for 5 minutes. Flow velocity was measured with the sample volume reduced to the smallest possible size (1 mm) and located at the center of the vessel. B-mode images of the same segment were collected for 1 minute after cuff release for subsequent off-line analysis. Internal diameter of brachial artery at the R wave of electrocardiogram was acquired for calculation of FMD according to the previous method.^{3,9} The Doppler spectral flow signals were obtained at baseline and during peak reactive hyperemia, similar to previous method.^{3,10} Maximal brachial artery diameter and peak and mean systolic velocity were measured subsequently. The mean value of three cardiac cycles was used.

Ultrasound of Carotid Arteries

The right common carotid artery was examined by two-dimensional (2D) ultrasound images with a 7.5 MHz linear transducer (Hewlett Packard Sonos 7500 system). The transducer was positioned appropriately to achieve longitudinal pictures of right common carotid artery. Transmit zone, depth, and gain were set up to optimize serial images of the lumen-arterial interface. Vascular images were magnified

with the resolution box function. Machine operating parameters were not changed during the study. Measurements of right common carotid artery IMT were obtained from each subject according to standard protocols.^{2,11} The ultrasonic vascular images were required at end diastole throughout the study. The mean value of three measurements was used.

Cardiac Functions and Structures Measurements

Echocardiography was performed using a 2.25 MHz transducer (Hewlett Packard Sonos 7500 system) in the lateral decubitus position. The measurements were obtained from 2D-guided M-mode recordings, which include the following parameters: aortic root (AoR) diameter, left atrial (LA) dimension, left ventricular mass (LVM), relative wall thickness, end-diastolic volume (EDV), end-systolic volume (ESV), interventricular septal thickness, left ventricular posterobasal wall thickness (PWT), and left ventricular internal dimensions at end diastole and left ventricular internal dimensions at end systole (LVIDd and LVIDs). Cardiac systolic function variables including stroke volume (SV) and left ventricular ejection fraction (LVEF) were assessed according to the American Society of Echocardiography recommendations.^{12,13} Left ventricular diastolic inflow profile was obtained from the apical four-chamber view, with the sample volume positioned at the tips of mitral leaflets. The Doppler beam was aligned to produce the narrowest possible angle between the beam and the blood flow vector. The peak flow velocity during rapid passive filling phase (E), peak flow velocity during atrial contraction (A), and ratio between E and A velocities (E/A) were studied according to the previous method.¹⁴

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation. The differences in the categorical values were evaluated using chi-square test. The differences of continuous values were studied using unpaired *t*-test. Pearson correlation coefficient analyses were used to examine the relationships between two parameters. One-way ANOVA was used to compare data among the three age groups. Post hoc Scheffes test was also used to detect the differences utilizing triple group comparison. A probability value of $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (Version 12).

Results

All 126 subjects received basic clinical evaluations, echocardiography, and ultrasonic vascular examinations. No subject was excluded due to a poor recording or narrow acoustic window.

Age-Related Changes

► **Table 1** lists basic clinical information in three different age groups. The SBP measured at brachial artery of men increased progressively with age: it was 108.4 ± 10.8 mm Hg in the young-to-adult group, 115.8 ± 12.3 mm Hg in the middle aged group, and 125.4 ± 11.5 mm Hg in the elderly group

Table 1 Clinical variables of three different age groups

Variables	Gender	Young-to-adult, Group 1 < 40 y (range)	Middle age, Group 2 40–60 y (range)	Elderly, Group 3 > 60 y (range)	p-Value	Post hoc Scheffes
Age (y)	M	30 ± 7 (60–84)	50 ± 6 (41–59)	70 ± 7 (19–39)	< 0.001	1–2, 1–3, 2–3
	F	30 ± 7 (60–88)	49 ± 5 (40–58)	71 ± 8 (18–39)	< 0.001	1–2, 1–3, 2–3
BH (cm)	M	168 ± 8 (157–179)	168 ± 7 (156–185)	166 ± 6 (155–188)	0.501	
	F	160 ± 3 (146–170)*	160 ± 5 (152–174)*	157 ± 7 (154–166)*	0.099	
BW (kg)	M	63 ± 9 (49–78)	66 ± 10 (46–85)	65 ± 8 (46–87)	0.527	
	F	52 ± 6 (44–68)*	54 ± 6 (40–67)*	58 ± 7 (46–67)*	0.060	
BSA (M ²)	M	1.69 ± 0.15 (1.43–1.94)	1.73 ± 0.16 (1.39–2.03)	1.69 ± 0.12 (1.42–2.11)	0.519	
	F	1.51 ± 0.08 (1.35–1.73)*	1.54 ± 0.09 (1.31–1.71)*	1.57 ± 0.13 (1.42–1.71)*	0.254	
BMI (kg·M ⁻²)	M	22.3 ± 2.3 (19.9–27.0)	23.4 ± 2.6 (18.1–27.0)	22.7 ± 4.3 (18.1–25.8)	0.428	
	F	20.3 ± 2.3 (17.2–26.6)*	21.0 ± 1.8 (17.3–25.2)*	23.3 ± 2.3 (18.0–25.6)	< 0.001	1–2, 1–3
Brachial artery						
SBP (mm Hg)	M	108.4 ± 10.8 (106–142)	115.8 ± 12.3 (98–140)	125.4 ± 11.5 (90–130)	< 0.001	1–2, 1–3
	F	101.5 ± 11.3 (100–140)*	105.4 ± 10.4 (88–122)*	118.4 ± 13.1 (84–130)*	< 0.001	1–2, 1–3
DBP (mm Hg)	M	67.7 ± 7.4 (60–90)	72.1 ± 9.9 (56–100)	73.1 ± 8.9 (60–90)	0.081	
	F	67.2 ± 6.9 (54–92)	67.6 ± 5.7 (56–80)	68.1 ± 11.3 (52–80)	0.347	
Ankle artery						
SBP (mm Hg)	M	121.5 ± 15.2 (120–170)	139.2 ± 7.3 (110–170)	150.6 ± 13.8 (100–150)	< 0.001	1–2, 1–3, 2–3
	F	110.5 ± 12.4 (120–170) ^a	125.6 ± 14.1 (100–156)*	138.5 ± 15.8 (90–140)*	< 0.001	1–2, 1–3, 2–3
DBP (mm Hg)	M	75.2 ± 8.9 (70–110)	83.0 ± 9.3 (64–100)	86.3 ± 9.9 (60–90)	< 0.001	1–3, 2–3
	F	71.1 ± 7.7 (70–110)	77.0 ± 7.4 (60–96)	84.0 ± 10.3 (60–90)	< 0.001	1–3, 2–3
A/B index	M	1.12 ± 0.07 (1.00–1.67)	1.20 ± 0.09 (0.97–1.38)	1.20 ± 0.13 (1.00–1.27)	0.101	
	F	1.09 ± 0.09 (0.98–1.45)	1.19 ± 0.10 (1.08–1.44)	1.17 ± 0.14 (0.96–1.25)	0.231	

Abbreviations: AA, (right) ankle artery; A/B index, ankle SBP divided by brachial SBP; BA, (right) brachial artery; BMI, body mass index; BSA, body surface area; BW, body weight; DBP, diastolic blood pressure; F, female; H, body height; M, male; SBP, systolic blood pressure.

Notes: Comparison of data between male and female: * $p < 0.05$; ** $p < 0.01$. Post hoc Scheffes: Comparison of data between three groups: "1–2," "1–3," and "2–3" indicates mean significant difference of average values of Group 1 versus Group 2, Group 1 versus Group 3, and Group 2 versus Group 3, respectively.

(post hoc Scheffes: 1/2, 1/3, $p < 0.001$). A similar phenomenon, SBP increasing progressively with age, also appeared in women (post hoc Scheffes: 1/2, 1/3, $p < 0.001$). However, we found no difference in diastolic BP measured at brachial artery among the three groups (► **Table 1**). As for BP measured at ankle artery, the SBP of men also increased progressively with age: it was 121.5 ± 15.2 mm Hg in the young-to-adult group, 139.2 ± 7.3 mm Hg in the middle aged group, and 150.6 ± 13.8 mm Hg in the elderly group (post hoc Scheffes: 1/2, 1/3, 2/3, $p < 0.001$). SBP increasing progressively with age also appeared in women (post hoc Scheffes: 1/2, 1/3, 2/3, $p < 0.001$). However, we found no difference of diastolic BP measured at the level of the ankle artery among the three groups. No significant difference was seen in body weight, body height, body surface area, and A/B index among the different age groups (► **Table 1**).

Comparison of Echocardiographic Variables

► **Table 2** shows the baseline echocardiographic variables of interventricular septum (IVS), PWT, LVIDd, LVIDs, LA, AoR, left ventricular EDV (LVEDV), left ventricular ESV (LVESV), and LVM of three different groups. Higher values of IVS, PWT, LVEDV, and LVM appeared in males ($p < 0.05$) for all comparisons.

The E/A ratio of mitral flow spectrum of men decreased progressively with age: it was 1.59 ± 0.23 in the young-to-adult group, 1.13 ± 0.25 mm Hg in the middle aged group, and 0.87 ± 0.20 in the elderly group ($p < 0.001$, post hoc Scheffes: 1/2, 1/3, 2/3). A similar phenomenon of E/A ratio decreasing progressively with age was also seen in women ($p < 0.001$, post hoc Scheffes: 1/2, 1/3, 2/3). These findings suggest that left ventricular diastolic function deteriorated with aging. The LVEF also showed progressive decrease with age in women: 73.1 ± 5.3 in the young-to-adult age group, 69.8 ± 4.9 in the middle aged group, and 65.2 ± 6.7 in the elderly group ($p < 0.001$, post hoc Scheffes: 1/2, 1/3, 2/3). Also, LVEF decreased progressively with age in men ($p = 0.034$, post hoc Scheffes: 1/3) (► **Table 2**). This indicates that the decrease in left ventricular systolic function is inversely related to increase in age. LVIDd, LVIDs, LA, LVEDV, and LVESV increased progressively with increase in age. ($p \leq 0.01$ in all comparisons) Similarly, IVS, PWT, and LVM also increased progressively with age ($p < 0.05$ in all comparisons) (► **Table 2**).

Vascular Endothelial Function Variables

Vascular EF variables regarding IMT, flow increased during reactive hyperemia (FIRH), FMD, and peak blood flow (PBF) of pre- and postphysiologic compression test among the three groups are listed in ► **Table 3**. The PBFs of the ultrasonic measurements of radial arteries in male were significantly greater than those of female gender, which presented both at pre- and postphysiologic compression test ($p < 0.05$ in all comparisons). In addition, as age increased, the values of FIRH and FMD exhibited a significant decrease ($p < 0.05$ in all comparisons, the post hoc Scheffes: 1/2, 1/3, 2/3 results of IMT showed progressive increase with age and were present in both genders ($p < 0.001$, post hoc Scheffes: 1/2, 1/3, 2/3). The data of PBF prephysiologic compression test in men also

decreased progressively with age; 48.6 ± 5.0 for the young-to-adult age group, 45.3 ± 6.0 for the middle age group, and 40.6 ± 5.7 for the elderly group ($p = 0.005$, the post hoc Scheffes: 1/2, 1/3). Similarly, the PBF prephysiologic compression test in women and postphysiologic compression test in both genders decreased progressively with age ($p < 0.001$ in all comparisons) (► **Table 3**).

Correlation of Clinical Variables to the Body Height, Body Weight, and BMI in Male Gender

Blood Pressure Variables

The BP variables correlated positively with BMI: BA-SBP (BA, brachial artery; $r = 0.366$, $p < 0.01$), BA-diastolic blood pressure (DBP) ($r = 0.294$, $p < 0.01$), AA-SBP (AA, ankle artery; $r = 0.449$, $p < 0.01$), and AA-DBP ($r = 0.410$, $p < 0.01$). A/B index did not reveal any significant correlation to body weight, body height, and BMI. Only AA-SBP exhibited positive correlation with body weight ($r = 0.287$, $p < 0.001$). There was no significant correlation of body height to any of the BP variables (► **Table 3**).

Echocardiographic Variables

All echocardiographic variables except E/A ratio and LVEF correlated positively with BMI ($p \leq 0.01$ in all comparisons). E/A ratio and LVEF exhibited negative correlations with BMI with correlation coefficient of -0.318 ($p < 0.01$) and -0.308 ($p < 0.05$), respectively (► **Table 4**). Body weight demonstrated similar trends that it correlated with most echocardiographic variables except E/A ratio and LVEF ($p \leq 0.01$ in all comparisons). Body weight also had negative correlations with E/A ratio and LVEF with a correlation coefficient of -0.171 ($p < 0.05$) and -0.244 ($p < 0.05$), respectively. However, there was no significant correlation between body height and any of the echocardiographic variables (► **Table 4**).

Vascular Ultrasound Variables

The IMT had a positive correlation with BMI ($p < 0.05$). BMI revealed inverse correlation with vascular EF data of FIRH and FMD, the correlation coefficient of BMI with FIRH and FMD was -0.318 ($p < 0.01$) and -0.351 ($p < 0.01$), respectively. BMI had a positive correlation with PBF post-physiologic compression test ($p < 0.05$) but no correlation with baseline PBF.

Correlations of Age, Body Height, Body Weight, and BMI to the Ultrasonic Measurements

Left ventricular systolic function (presented by LVEF) exhibited a strong negative correlation with age not only in female ($r = -0.450$, $p < 0.01$) but also in male gender ($r = -0.334$, $p < 0.01$). Left ventricular diastolic function (E/A ratio) also showed similar trend with age in both genders ($p < 0.01$). In terms of vascular functions, FIRH showed the most strong inverse correlation with age either in male status ($r = -0.763$, $p < 0.01$) or in female status ($r = -0.665$, $p < 0.01$). FMD also showed this phenomenon but the correlation coefficients were lower ($p < 0.01$). On the contrary, IMT exhibited a positive correlation with age on both gender ($p < 0.01$).

Table 2 Comparisons of echocardiographic variables of three groups

Variables	Gender	Young-to-adult, Group 1 < 40 y (range)	Middle age, Group 2 40–60 y (range)	Elderly, Group 3 > 60 y (range)	p-Value	Post hoc Scheffes
IVS (mm)	M	9.71 ± 1.49 (7–13)	10.84 ± 1.90 (8–14)	11.96 ± 1.21 (10–14)	< 0.001	1–2, 1–3, 2–3
	F	8.81 ± 1.52 (6–11)**	8.83 ± 1.34 (6–11)**	10.93 ± 1.22 (9–13)**	< 0.001	1–2, 1–3, 2–3
PWT (mm)	M	9.33 ± 1.66 (6–13)	10.16 ± 1.74 (7–15)	10.72 ± 1.60 (8–14)	0.018	1–3
	F	8.44 ± 1.55 (6–11)**	8.63 ± 1.50 (7–11)**	10.20 ± 1.74 (8–13)*	0.004	1–2, 1–3
LVIDd (mm)	M	43.6 ± 4.2 (36–52)	45.9 ± 4.7 (37–53)	48.1 ± 5.9 (32–58)	0.01	1–3
	F	41.8 ± 5.8 (35–58)	42.5 ± 4.0 (34–50)	46.8 ± 5.0 (38–55)	0.008	1–2, 1–3
LVIDs (mm)	M	25.8 ± 3.9 (20–34)	27.9 ± 4.7 (20–39)	30.4 ± 5.5 (19–42)	0.005	1–3
	F	23.5 ± 3.4 (19–32)	25.6 ± 2.8 (20–33)	30.0 ± 5.1 (20–37)	< 0.001	1–2, 1–3
LA (mm)	M	27.0 ± 4.4 (22–35)	32.9 ± 4.4 (24–42)	34.8 ± 5.3 (24–44)	< 0.001	1–3, 2–3
	F	26.2 ± 5.1 (19–35)	29.2 ± 3.4 (21–35)	34.2 ± 3.4 (29–42)	< 0.001	1–2, 1–3
AoR (mm)	M	27.7 ± 3.8 (23–35)	32.0 ± 3.2 (25–38)	34.0 ± 3.2 (27–39)	< 0.001	1–3, 2–3
	F	25.9 ± 3.5 (20–32)	29.0 ± 2.8 (23–35)	31.7 ± 3.5 (28–40)	< 0.001	1–3, 2–3
LVEDV (mL)	M	86.8 ± 19.5 (55–127)	95.5 ± 23.2 (57–135)	108.9 ± 29.6 (41–162)	0.008	1–2, 1–3, 2–3
	F	73.4 ± 16.5 (51–105)**	84.4 ± 16.8 (46–114)**	102.1 ± 28.1 (60–150)*	0.001	1–2, 1–3, 2–3
LVESV (mL)	M	24.7 ± 9.7 (13–47)	31.0 ± 14.0 (14–66)	36.8 ± 15.2 (15–78)	0.008	1–3, 2–3
	F	19.6 ± 7.3 (12–41)*	21.4 ± 6.6 (13–43)*	36.1 ± 15.3 (13–54)	< 0.001	1–2, 1–3, 2–3
LVEF (%)	M	71.8 ± 6.4 (54–83)	68.7 ± 7.8 (51–82)	66.3 ± 7.4 (52–77)	0.034	1–3
	F	73.1 ± 5.3 (61–82)	69.8 ± 4.9 (60–80)	65.2 ± 6.7 (54–77)	0.001	1–2, 1–3, 2–3
E/A ratio	M	1.59 ± 0.23 (1.14–2.06)	1.13 ± 0.25 (0.73–1.67)	0.87 ± 0.20 (0.50–1.24)	< 0.001	1–2, 1–3, 2–3
	F	1.64 ± 0.27 (1.23–2.18)	1.30 ± 0.24 (0.82–2.03)*	0.84 ± 0.20 (0.51–1.27)	< 0.001	1–2, 1–3, 2–3
LVM (g)	M	91.1 ± 20.5 (57.8–133.4)	100.3 ± 24.4 (59.9–141.8)	114.3 ± 31.1 (43.1–170.1)	0.005	1–2, 1–3, 2–3
	F	77.1 ± 17.3 (53.6–110.3)**	85.5 ± 17.6 (46.3–119.7)*	107.2 ± 29.5 (63.0–157.5)*	0.001	1–2, 1–3, 2–3

Abbreviations: AoR, aortic root; E/A ratio, E flow divided by A flow (mitral valve); IVS, interventricular septum; LVIDd, left ventricular internal dimensions at end-diastole; LVIDs, left ventricular internal dimensions at end-systole; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; PWT, posterior wall thickness.

Notes: Comparison of data between male and female: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Post hoc Scheffes: Comparison of data between three groups: "1–2," "1–3," and "2–3" indicates mean significant difference of average values of Group 1 versus Group 2, Group 1 versus Group 3, and Group 2 versus Group 3, respectively.

Table 3 Vascular endothelial function variables and IMT of three groups

Variables	Young-to-adult, Group 1 < 40 y (range)	Middle age, Group 2 40–60 y (range)	Elderly, Group 3 > 60 y (range)	p-Value	Post hoc Scheffes
IMT (mm)	M 0.57 ± 0.10 (0.42–0.80)	0.80 ± 0.18 (0.60–1.58)	0.89 ± 0.09 (0.75–1.05)	< 0.001	1–2, 1–3, 2–3
	F 0.55 ± 0.10 (0.42–0.70)	0.73 ± 0.08 (0.60–0.90)	0.90 ± 0.11 (0.70–1.06)	< 0.001	1–2, 1–3, 2–3
FMD (%)	M 17.47 ± 4.89 (9.6–26.7)	10.70 ± 1.60 (6.6–21.1)	8.59 ± 1.75 (5.9–12.5)	0.01	1–2, 1–3, 2–3
	F 17.50 ± 4.03 (9.5–24.5)	11.88 ± 2.61 (7.7–20.2)	8.75 ± 1.98 (5.3–13.3)	0.008	1–2, 1–3, 2–3
FIRH (%)	M 241.3 ± 76.1 (134–360)	156.4 ± 52.7 (108–310)	131.1 ± 22.4 (91–178)	0.018	1–2, 1–3, 2–3
	F 245.4 ± 77.9 (125–450)	168.7 ± 48.5 (110–261)	128.0 ± 40.7 (85–188)	0.004	1–2, 1–3, 2–3
Pre-PBF (mL/min)	M 48.6 ± 5.0 (39.4–58.9)	45.3 ± 6.0 (33.6–56.4)	40.6 ± 5.7 (29.8–50.0)	0.005	1–2, 1–3
	F 41.1 ± 5.1 (30.3–49.0)*	40.0 ± 4.1 (31.2–48.5)*	36.6 ± 4.8 (29.1–46.0)*	< 0.001	1–3
Post-PBF (mL/min)	M 71.9 ± 26.7 (49.0–161.3)	55.1 ± 10.7 (40.8–83.6)	42.1 ± 12.6 (22.6–68.6)	< 0.001	1–3
	F 97.6 ± 26.7 (57.5–157.5)*	64.6 ± 19.9 (27.8–100.5)*	48.9 ± 14.4 (25.6–76.3)*	< 0.001	1–3, 2–3

Abbreviations: FIRH, flow increased during reactive hyperemia; FMD, flow-mediated dilation; IMT, intima-media thickness; PBF, peak blood flow; Pre-, Post-, pre- or post-physiologic compression test.
Notes: Comparison of data between male and female: * $p < 0.05$. Post hoc Scheffes: Comparison of data between three groups: “1–2,” “1–3,” and “2–3” indicate mean significant difference of average values of Group 1 versus Group 2, Group 1 versus Group 3, and Group 2 versus Group 3, respectively.

All major variables from echocardiography and ultrasound measurements except IMT exhibited negative correlations with BMI in both genders ($p < 0.05$ in all comparisons). IMT exhibited a positive correlation with BMI on both genders ($p < 0.01$).

Relation of IMT to Clinical and Ultrasonic Variables in Total Subjects

IMT exhibited a weak positive correlation with body weight ($r = 0.168$, $p < 0.05$). It also showed a positive correlation with age ($r = 0.337$, $p < 0.001$). BA-SBP, BA-DBP, AA-SBP, AA-DBP, and A/B index also correlated positively with IMT as shown in ▶Table 5 (A). As to echocardiographic variables, all items exhibited positive correlations with IMT ($p < 0.001$ in all correlations). On the contrary, LVEF and E/A ratio revealed negative correlations with IMT, the correlation coefficients were -0.392 ($p < 0.001$) and -0.746 ($p < 0.001$), respectively, ▶Table 5 (B). The vascular endothelial variables of FIRH, FMD, and PBF pre- and post-PCT demonstrated inverse correlations with IMT ($p < 0.05$ in all correlations).

Discussion

This study revealed that SBP measured at brachial artery increased progressively with age in both genders ($p < 0.002$ in all comparisons). The mean SBP measured from brachial artery for the elderly group was 125.4 ± 11.5 mm Hg for men and 118.4 ± 13.1 for women, which were still in the normal range (▶Table 1).

Aging is associated with several structural and functional changes of the arterial wall media (hypertrophy, extracellular matrix accumulation, calcium deposits) and the vascular endothelium (decrease in the release of vasodilators and increased synthesis of vasoconstrictors) that are associated with increased vascular stiffness.^{15,16} With aging, an increase in collagen content, collagen cross-linking, and fraying of elastin fibrils occur in the medial layer,¹⁷ all of which reduce arterial distensibility and increase stiffness. Besides the pathologic changes, nitric oxide (NO) secretion from the endothelium is also decreased with age. Several animal studies have found that NO production and NO levels decline with aging, likely as a result of a decline in the level of endothelial NO synthase.¹⁸ Furthermore, increase in angiotensin II (Ang-II) levels as well as significantly increased Ang-II signaling in aged arterial walls,¹⁹ both of which are thought to play a pivotal role in arterial aging, and these effects can explain the increase in the SBP with advanced age.

This study also demonstrated that IVS, PWT, and LVM increased progressively from young-to-adult group, middle age group, and finally to the elderly group ($p < 0.05$ in all comparisons) (▶Table 2). It indicated that the cardiac size and mass were significantly expanded with age. A previous autopsy-based study suggested that cardiac mass increased significantly with aging.²⁰ Another echocardiographic studies in normal volunteers found that increasing age correlated with an increase in left ventricular wall thickness.²¹ Furthermore, aging is the major determinant factor of the E/A ratio as shown in previous investigations.^{1,11,22} Deposition of

Table 4 Correlation of clinical variables to the body height, body weight, and BMI in male gender

Variables	BH	BW	BMI
Blood pressure indices			
BA-SBP (mm Hg)	−0.120	0.176	0.366**
BA-DBP (mm Hg)	−0.148	0.090	0.294**
AA-SBP (mm Hg)	−0.015	0.287**	0.449**
AA-DBD (mm Hg)	−0.082	0.190	0.410**
A/B index	0.151	0.212	0.214
Echocardiographic variables			
IVS (mm)	0.012	0.471**	0.597**
PWT (mm)	0.235*	0.481**	0.483**
LVIDd (mm)	0.147	0.321**	0.323**
LVIDs (mm)	0.114	0.301**	0.359**
RV (mm)	0.200	0.346**	0.291**
LA (mm)	0.192	0.468**	0.504**
AoR (mm)	0.045	0.361**	0.436**
LVEDV (mL)	0.128	0.317**	0.316**
LVESV (mL)	0.092	0.337**	0.364**
LVEF (%)	0.011	−0.244*	−0.308**
E/A ratio	0.114	−0.171*	−0.318**
LVM (g)	0.134	0.333**	0.332**
Vascular ultrasound variables			
IMT (mm)	−0.121	0.102	0.245**
PBF-baseline	0.210	0.074	−0.152
PBF-post-PCT	0.045	−0.202	−0.369**
FIRH (%)	0.005	−0.259	−0.392**
FMD (%)	−0.026	−0.266	−0.374**

Abbreviations: AA, (right) ankle artery; A/B index, ankle SBP divided by brachial SBP; AoR, aortic root; BA, (right) brachial artery; BH, body height; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; E/A ratio, E flow divided by A flow (mitral valve); FIRH, flow increased during reactive hyperemia; FMD, flow-mediated dilation; IMT, intima-media thickness; IVS, interventricular septum; LVIDd, left ventricular internal dimensions at end-diastole; LVIDs, left ventricular internal dimensions at end-systole; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; PBF, peak blood flow; PWT, posterior wall thickness; SBP, systolic blood pressure.

Notes: * $p < 0.05$; ** $p < 0.01$.

collagen in the LV could induce diastolic dysfunction which may partly explain this mechanism.^{1,11} Schulman et al²³ first described that the LV diastolic filling rate progressively slow after the age of 20 years, by 80 years, the ratio is reduced on average, up to 50%.²⁴ In the Framingham Study of apparently healthy subjects, a high correlations between age and Doppler indexes of LV diastolic function with correlation coefficient of -0.80 ($p < 0.0001$) was noted.²⁵ Hence, the age-associated decrease in the Doppler transmitral E/A ratio is identical not only in Framingham Study but also in the Taiwanese participants.

Endothelial Dysfunction, Aging, and Atherosclerosis

Our data further demonstrate that the IMT increased progressively with age, which were presented in both genders ($p < 0.001$ in both genders). It is consistent with previous

experience that aging itself had an increase in the IMT thickness; it correlated with vascular endothelial dysfunction (ED) significantly.⁵ The FIRH and FMD represent the vascular EF in response to reactive hyperemia. This study showed that the data of FIRH and FMD exhibited a significant decrease in both genders with increasing age ($p < 0.05$ in all comparisons). It also shows progressive ED with increasing age (►Table 3), which does not support the previous report that Chinese subjects are not susceptible to ED.⁹ Our study population (asymptomatic) showed progressive impairment of ED as demonstrated by results of FIRH and FMD. ED impairs the ability to regulate inflammation and thrombosis.¹¹ Damaged or “perturbed” endothelial cells lining can lose or impair their ability to maintain thromboresistance and can actually promote thrombosis and atherosclerosis.⁵ Previous studies using either the acetylcholine test or measurements of FMD

Table 5 Relation of IMT to clinical and ultrasonic variables in total subjects ($n = 126$)

(A) Clinical data/IMT		(B) Echo variables/IMT		(C) Vascular variables/IMT	
H (cm)	−0.056	IVS	0.516***	FIRH	−0.726***
BW (kg)	0.168*	PWT	0.471***	FMD	−0.385***
BSA (m ²)	0.114	LVIDd	0.456***	PBF (baseline)	−0.231*
BMI	0.278**	LVIDs	0.422***	PBF (post-PCT)	−0.680***
Age	0.337***	RV	0.516***		
BA-SBP	0.460***	LA	0.351***		
BA-DBP	0.309***	AoR	0.567***		
BAPP	0.336***	LVEDV	0.433***		
AA-SBP	0.574***	LVESV	0.420***		
AA-DBP	0.540***	LVM	0.455***		
AAPP	0.429***	LVEF	−0.392***		
A/B index	0.355**	E/A ratio	−0.746***		

Abbreviations: AA, (right) ankle artery; AAPP, ankle artery pulse pressure; A/B index, ankle SBP divided by brachial SBP; AoR, aortic root; BA, (right) brachial artery; BAPP, brachial artery pulse pressure; BH, body height; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; E/A ratio, E flow divided by A flow (mitral valve); FIRH, flow increased during reactive hyperemia; FMD, flow-mediated dilation; IMT, intima-media thickness; IVS, interventricular septum; LVIDd, left ventricular internal dimensions at end-diastole; LVIDs, left ventricular internal dimensions at end-systole; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; PBF, peak blood flow; PWT, posterior wall thickness; SBP, systolic blood pressure.

Notes: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

or FIRH demonstrated endothelial dysfunction in patients with coronary risk factors in absence of angiographic or ultrasound evidence of structural CAD, and this was also observed in apparently healthy aging subjects.^{3,25–27} These results and our data suggest that ED is present in the early stages of atherosclerosis.

Aging and the Vascular System

IMT has been used as the indicator of human atherosclerosis for a long time. Age-associated vascular remodeling occurs through intimal and medial thickening, vascular stiffening, luminal dilation, and ED.^{2,27} Previous reports have demonstrated a positive correlation between increased IMT of the common carotid artery and hypertension.^{28,29} Furthermore, several studies have shown a significant association of IMT with cerebrovascular disease and clinical CAD.^{30,31} Our study found that the IMT measured from carotid artery correlated significantly with BMI ($r = 0.278$, $p < 0.01$), age ($r = 0.337$, $p < 0.001$), and data of SBP, DBP, and pulse pressure of brachial artery and ankle artery measurements ($p < 0.001$) (► **Table 5**). In addition, IMT exhibited strong negative correlations with vascular functions such as FIRH, FMD, and PBF postphysiologic compression test ($p < 0.001$ in all correlations) as well as cardiac diastolic function using E/A ratio ($r = -0.746$, $p < 0.001$) (► **Table 5**). On the basis of the previous investigators and our clinical observation, we may summarize the concepts as follows: vascular aging and vascular disease are inseparable partners; each contributes specific components of what is presently referred to as “vascular disease.” What epidemiology now refers to as vascular disease should probably be regarded as the “vascular aging-vascular disease interaction.” Aging blood vessels and

heart provide the milieu in which cardiovascular disease can flourish. Hence, vascular aging can be regarded as a risk factor for atherosclerotic cardiovascular disease.

Conclusion

The subjects in the present study were individuals who underwent a “health screen” and were apparently healthy without any evidence of cardiovascular risk factors. These data provide us with insights into the aging process and ED that may govern the atherosclerotic process before the development of any clinical abnormality. Besides, our study suggests that vascular thickness (IMT) is closely related to cardiac function and BP. The BP, body weight, and ultrasonic variables alter dynamically with age, which possibly causes the progression in atherosclerosis, even in the Taiwanese population.

Study Limitation

Although our study is prospective, the sample size is relatively small. Further investigations including large scale healthy subjects are needed to address the normal ranges of LVEF, IMT, and vascular EF. Moreover, additional studies are needed to assess the effect of therapeutic interventions by following the changes in the LV systolic and diastolic function, vascular EFs, and IMT, which may be useful in highlighting the atherosclerosis progression or regression.

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