ORIGINAL RESEARCH

Sexual Function Is an Indicator of Central Arterial Stiffness and Arterial Stiffness Gradient in Japanese Adult Men

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***Background*—**As arterial stiffness increases in the absence of subjective symptoms, a personal indicator that reflects increased risk of cardiovascular disease is necessary. Penile erection is regulated by vascular function, and atherosclerosis affects the penile artery earlier than it affects the coronary and carotid arteries. Therefore, we hypothesized that deterioration of erectile function could be a marker of increased risk for cardiovascular disease. To test our hypothesis, we assessed erectile function and arterial stiffness in a cross-sectional study.

***Methods and Results*—**Carotid-femoral pulse wave velocity (PWV), brachial-ankle PWV, femoral-ankle PWV, and arterial stiffness gradient (PWV ratio: carotid-femoral PWV/femoral-ankle PWV) were measured as indexes of central, systemic, and peripheral arterial stiffness and peripheral organ damage, respectively, in 317 adult men. In addition, erectile function was assessed by using the questionnaire International Index of Erectile Function 5 (a descending score indicates worsening of erectile function). The scores of male sexual function were inversely correlated with carotid-femoral PWV (r_s=−0.41), brachial-ankle PWV (r_s=−0.35), femoral-ankle PWV (r_s=−0.19), and PWV ratio (r_s=−0.33). Furthermore, multivariate linear regression analyses revealed that International Index of Erectile Function 5 scores were significantly associated with carotid-femoral PWV (β=−0.22) and PWV ratio (β=−0.25), but not with brachial-ankle PWV and femoral-ankle PWV.

***Conclusions*—**Our results indicated that erectile function is independently associated with central arterial stiffness and peripheral organ damage. These findings suggest that male sexual function could be an easily identifiable and independent marker of increased central arterial stiffness and peripheral organ damage. **(*J Am Heart Assoc*. 2018;7:e007964. DOI: 10.1161/JAHA.117.007964.)**

Key Words: arterial stiffness • erectile dysfunction • predictors • sexual dysfunction • vascular function

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2015, an estimated 17.7 million individuals died from CVD, accounting for 31% of all global deaths.[1] It is now widely recognized that increased arterial stiffness, especially central arterial stiffness, is associated with future CVD events and all-cause mortality in a strong and independent manner.[2–7] Besides, it is well known that CVD is a "silent killer,"[8,9] and no subjective symptoms are present when the systemic arteries stiffen. Thus, it is necessary to establish easily identifiable markers that reflect increases in arterial stiffness.

Erectile dysfunction (ED) is characterized by the inability to attain or maintain penile erection that is sufficient for satisfactory sexual performance[10]; it is a common clinical concern worldwide, with thousands of new patients diagnosed every year.[11,12] Penile erection is regulated by an increase in arterial blood flow and a decrease in venous blood flow in the penis. Previously, it was demonstrated that atherosclerosis affects all major vascular beds to the same extent, and the penile artery, which is smaller in diameter, is affected earlier than the coronary and carotid arteries.[13–15] Therefore, penile erectile function could potentially be an early indicator of increased risk for CVD. However, this possible association remains poorly understood.

This study aimed to investigate the association between penile erectile function and arterial stiffness in adult men. We

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Clinical Perspective

What Is New?

- This study investigated whether deterioration of sexual function could be a marker of increased arterial stiffness in men.
- Deterioration of erectile function was associated with elevated central arterial stiffness and index of peripheral organ damage after adjusting by age, blood pressure, and other confounders, but not with peripheral arterial stiffness.

What Are the Clinical Implications?

- Our findings suggest that the deterioration of erectile function, as assessed by questionnaires, has the potential for being an easily identifiable and independent marker of increased central arterial stiffness and peripheral organ in men, such as in the brain and kidney.
- Because cardiovascular disease is a leading cause of death and is a "silent killer," our findings have a large clinical significance as a personal and independent indicator.
- Earlier detection of elevated central arterial stiffness by erectile function might contribute to preventive or treatment activity for cardiovascular disease.

hypothesized that erectile function is associated with arterial stiffness and that deterioration of erectile function could potentially be a marker of increased arterial stiffness. To test our hypothesis, we assessed erectile function and arterial stiffness in a cross-sectional study of adult men.

Methods

Participants

We recruited subjects through local newspaper advertisements. A total of 317 adult men (age range, 23–88 years) participated in this study. The diagnosis of hypertension was based on a brachial systolic blood pressure ≥140 mm Hg and/or treatment with antihypertensive agents, dyslipidemia was based on a low-density lipoprotein cholesterol ≥140 mg/dL and/or treatment with antihypercholesterolemic agents, and diabetes mellitus was based on a fasting blood glucose concentration ≥126 mg/dL and/or treatment with antihyperglycemic agents.[16] Participants who ate, took medicines, or smoked in the morning of the measurement day and those who were undergoing treatment for ED were excluded from this study. The study was approved by the ethics committee of the Faculty of Health and Sport Sciences at the University of Tsukuba (approval No. 27-68), and it conformed to the principles outlined in the Declaration of Helsinki. All participants were asked to provide written informed consent before inclusion in the study. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Procedures

Measurements were obtained in a quiet temperature-controlled room (24°C–26°C). First, blood samples were drawn to evaluate the blood chemistry of the participants. Subsequently, blood pressure and arterial stiffness were measured after a resting period of at least 20 minutes, after which questionnaires on male sexual function were distributed to the participants.

Anthropometric Measurements

A digital scale was used to measure the body weight of the participants to the nearest 0.1 kg. A wall-mounted stadiometer was used to measure their height to the nearest 0.1 cm. Body mass index was calculated by dividing the weight (kg) of the participants by their height (m^2). Waist circumference was directly measured on the skin at the level of the umbilicus, with the participant in a standing position. Measurements were made in duplicate to the nearest 0.1 cm.

Blood Biochemistry

Blood samples were collected from each participant after a 12-hour overnight fast, in the morning. Serum concentrations of triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol and plasma concentrations of glucose and glycosylated hemoglobin were determined using standard enzymatic techniques. Serum total testosterone levels were measured using chemiluminescent immunoassay by a commercial laboratory (LSI Medience Corp, Ibaraki, Japan).

Heart Rate, Blood Pressure, Arterial Stiffness, and Arterial Stiffness Gradient

After a resting period of at least 20 minutes, heart rate, blood pressure, and arterial stiffness were measured in a quiet temperature-controlled room (24°C–26°C). Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, carotid-femoral pulse wave velocity (cfPWV), brachial-ankle PWV (baPWV), and femoral-ankle PWV (faPWV) were measured using a previously described noninvasive vascular profiling system (form PWV/ABI; Colin Medical Technology, Komaki, Japan).[17,18] Of the direct carotid-femoral distance, 80% was applied to calculate cfPWV.[19] Carotid and femoral artery pulse waves were simultaneously obtained using 2 applanation tonometers incorporating an array of 15

micropiezoresistive transducers. Bilateral brachial and posterior tibial arterial pressure waveforms were recorded using extremity cuffs connected to air plethysmographic sensors wrapped on both arms and ankles of the participants. The distances traveled by the pulse waves were assessed in triplicate with a random zero-length measurement over the surface of the body using a nonelastic tape measure. Pulse wave transit time was determined from the time delay between the proximal and distal "foot" waveforms. The foot of the wave was automatically identified and detected as the commencement of a sharp systolic upstroke. PWV was assessed in duplicate and was calculated as the distance divided by the transit time. In addition, arterial stiffness gradients (PWV ratio: central arterial stiffness/peripheral arterial stiffness) were calculated by dividing cfPWV by faPWV. Recently, it was reported that the PWV ratio is a better predictor of mortality than the classic cfPWV is,[20] and it reflects peripheral organ damage.[21,22]

Male Sexual Function

Male erectile function was assessed by using 2 questionnaires, the International Index of Erectile Function (IIEF) 5 and the Aging Males' Symptoms (AMS), because questionnaires are not objective methods.

The IIEF questionnaire, which was developed and validated in 1997, was adopted as the gold standard for the assessment of ED.[23,24] The IIEF5 is the short form of the IIEF, and its scores range from 5 to 25 points, in which descending scores indicate worsening of erectile function. According to previous studies, individuals with 5 to 7 points on the IIEF5 were diagnosed as having severe ED; those with 8 to 11 points, as having moderate ED; those with 12 to 16 points, as having mild to moderate ED; those with 17 to 21 points, as having mild ED; and those with 22 to 25 points, as having no ED.[25,26]

The AMS questionnaire contains 17 self-rating symptom-based questions, according to 3 subscales; 7 of the questions are somatic, 5 are psychological, and 5 are sexual.[27] The total sum of all subscales provides a total score, and the sum of the scores of somatic, psychological, and sexual types of questions is also calculated. Contrary to the IIEF5 scores, the ascending scores indicate worsening of each function in the AMS.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of all parameters. Data were expressed as the means±SD or frequency counts (for categorical data). Moreover, values were analyzed using Spearman's rank correlation coefficients (r_s) and Kruskal-Wallis nonparametric tests with post hoc paired comparisons, as appropriate. The variables of skewed distributions were log transformed to obtain normal distributions before multivariate linear regression analyses. Independent correlates of log-transformed cfPWV, faPWV, and PWV ratio were examined using multivariate linear regression analyses. The frequencies of principal risk factors, medications, and medical histories were analyzed using χ^2 tests. Statistical significance was set at $P<0.05$ for all comparisons. Statistical analyses were performed using JMP Pro version 12 (SAS Institute).

Results

The number of participants who took antihypertensive, antihypercholesterolemic, and antihyperglycemic agents was 80 (25.2%), 41 (12.9%), and 16 (5.0%), respectively. Moreover, 9 participants (2.8%) had a history of angina, 3 (0.9%) had a history of myocardial infarction, and 7 (2.2%) had a history of stroke. Twenty-one participants (6.6%) were current smokers. The mean values of body mass index (23.8 kg/m^2), total cholesterol (207 mg/dL), high-density lipoprotein cholesterol (61 mg/dL), low-density lipoprotein cholesterol (122 mg/dL), triglycerides (115 mg/dL), glucose (103 mg/dL), glycosylated hemoglobin (5.5 mg/dL), testosterone (20.6 nmol/L), systolic blood pressure (127 mm Hg), and diastolic blood pressure (79 mm Hg) were within the normal ranges (Table 1).

The average IIEF5 score (descending scores indicate worsening of erectile function) was lowered, whereas the AMS sexual score (ascending scores indicates worsening of erectile function) was elevated, for each age group, which indicated that erectile function decreases with advancing age (Figure 1). In addition, age was significantly correlated with cfPWV (r_s=0.61, $P<0.001$), baPWV (r_s=0.69, $P<0.001$), faPWV (r_s=0.34, $P<0.001$), and PWV ratio (r_s=0.45, $P<0.001$). cfPWV was significantly correlated with baPWV (r_s=0.75, $P<0.001$), faPWV (r_s=0.38, $P<0.001$), and PWV ratio (r_s=0.85, $P<0.001$); baPWV was significantly correlated with faPWV (r_s=0.71, $P<0.001$) and PWV ratio (r_s=0.40, $P<0.001$); and faPWV was significantly correlated with PWV ratio (r_s=−0.12, P=0.032). The IIEF5 scores were negatively correlated with cfPWV (r_s=−0.41, $P<0.001$), baPWV (r_s=−0.35, $P<0.001$), faPWV (r_s=−0.19, $P<0.001$), and PWV ratio (r_s=−0.33, $P<0.001$) in all participants, and with cfPWV (r_s=−0.28, $P<0.001$), baPWV (r_s=−0.17, P=0.027), and PWV ratio (r_s=−0.24, P=0.001) in older participants (Figure 2). Similarly, the scores of the AMS sexual subscale were positively correlated with cfPWV (r_s=0.39, $P<0.001$), baPWV (r_s=0.39, $P<0.001$), faPWV (r_s=0.26, $P<0.001$), and PWV ratio (r_s=0.28, $P<0.001$) in all participants; with cfPWV (r_s=0.35, P=0.036) and baPWV (r_s=0.37, P=0.024) in young participants; and with cfPWV (r_s=0.23, P=0.004), baPWV (r_s=0.20, P=0.014), and PWV ratio (r_s=0.16, P=0.040) in older participants (Figure 3).

Table 1. Characteristics of Studied Men (n=317)

Characteristics	Value
Age, y	59±15
Height, cm	168.0±6.7
Body mass, kg	67.4±11.7
Body mass index, kg/m^2	23.8±3.4
Waist circumference, cm	85.3±10.3
Total cholesterol, mg/dL	207±36
HDL cholesterol, mg/dL	61±15
LDL cholesterol, mg/dL	122±33
Triglycerides, mg/dL	115±66
Glucose, mg/dL	103±19
HbA1c, mg/dL	5.5±0.5
Testosterone, nmol/L*	20.6±6.9
Hemodynamics	
Systolic blood pressure, mm Hg	127±15
Diastolic blood pressure, mm Hg	79±11
Mean arterial pressure, mm Hg	99±13
Pulse pressure, mm Hg	48±9
Heart rate, bpm	61±10
cfPWV, cm/s	909±206
baPWV, cm/s	1466±274
faPWV, cm/s	957±108
PWV ratio	0.95±0.21
Male functions	
IIEF5 score, points	17±6
AMS total, points†	29±8
AMS somatic, points†	12±4
AMS psychological, points†	7±2
AMS sexual, points†	11±4
Principal risk factors, n (%)	
Hypertension	116 (36.6)
Dyslipidemia	115 (36.3)
Diabetes mellitus	31 (9.8)
Medications, n (%)	
Antihypertensive	80 (25.2)
Antihypercholesterolemic	41 (12.9)
Antihyperglycemic	16 (5.0)
Medical history, n (%)	
Angina	9 (2.8)
Myocardial infarction	3 (0.9)
Stroke	7 (2.2)
Current smoking, n (%)	21 (6.6)

Table 1. Continued

Data are shown as the mean±SD or frequency count (percentage), as appropriate. AMS indicates Aging Males' Symptoms; baPWV, brachial-ankle PWV; bpm, beats per minute; cfPWV, carotid-femoral PWV; faPWV, femoral-ankle PWV; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IIEF5, International Index of Erectile Function 5; LDL, low-density lipoprotein; and PWV, pulse wave velocity.
*Data are available in 304 individuals.
†Data are available in 253 individuals.

To investigate the further associations between arterial stiffness and each of the IIEF5 scores and AMS sexual scores, we separately applied multivariate linear regression analyses. We observed that the log-transformed IIEF5 scores were significantly associated with cfPWV (β=−0.22, P<0.001) and PWV ratio (β=−0.25, P<0.001), but not with baPWV (β=−0.05, P=0.230) and faPWV (β=0.03, P=0.590) (Table 2). Similarly, the log-transformed AMS sexual scores were significantly associated with cfPWV (β=0.11, P=0.043).

Table 3 and Figure 4 show the characteristics of participants classified by the severity of ED by IIEF5 score. The value

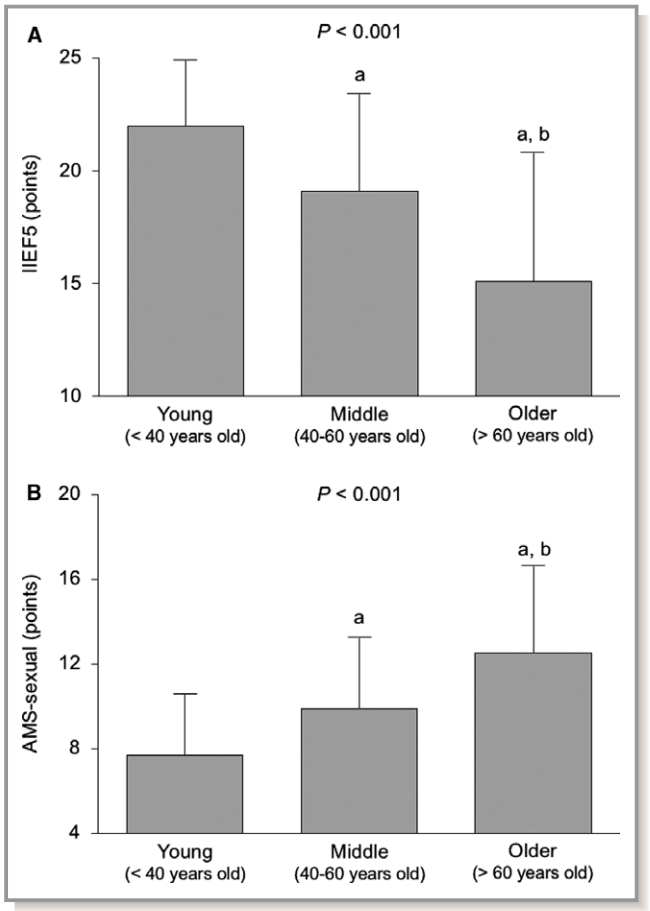

Figure 1. Age-related differences in the International Index of Erectile Function 5 (IIEF5) scores (A) and the Aging Males' Symptoms (AMS) sexual scores (B). Data available in 253 individuals in AMS sexual score. Data are expressed as mean±SD. [a]P<0.05 vs young-aged group, [b]P<0.05 vs middle-aged group.

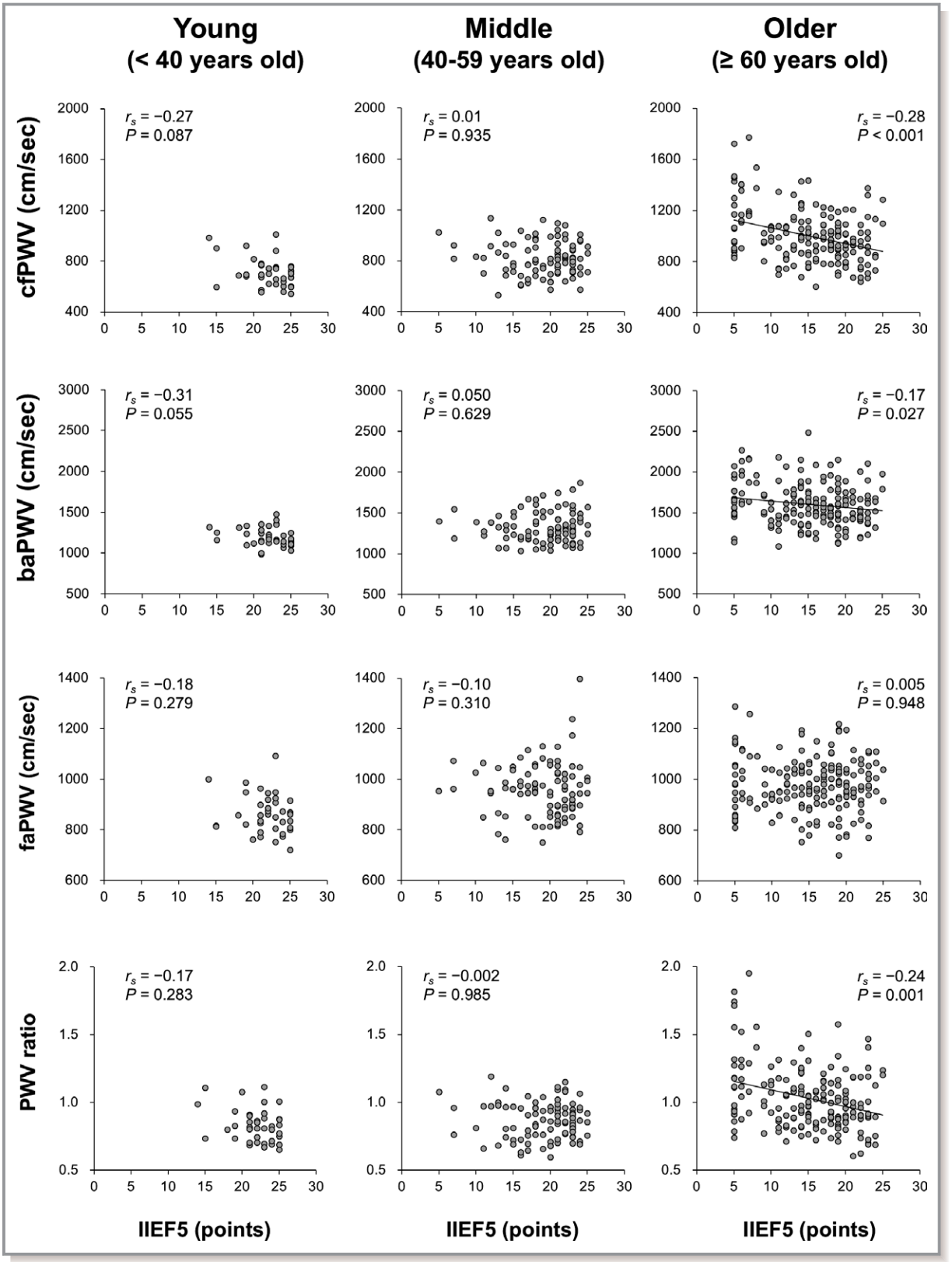

Figure 2. Correlations between the International Index of Erectile Function 5 (IIEF5) scores and carotid-femoral pulse wave velocity (cfPWV), brachial-ankle PWV (baPWV), femoral-ankle PWV (faPWV), and PWV ratio in each age group (young-aged, n=40; middle-aged, n=97; older-aged, n=180).

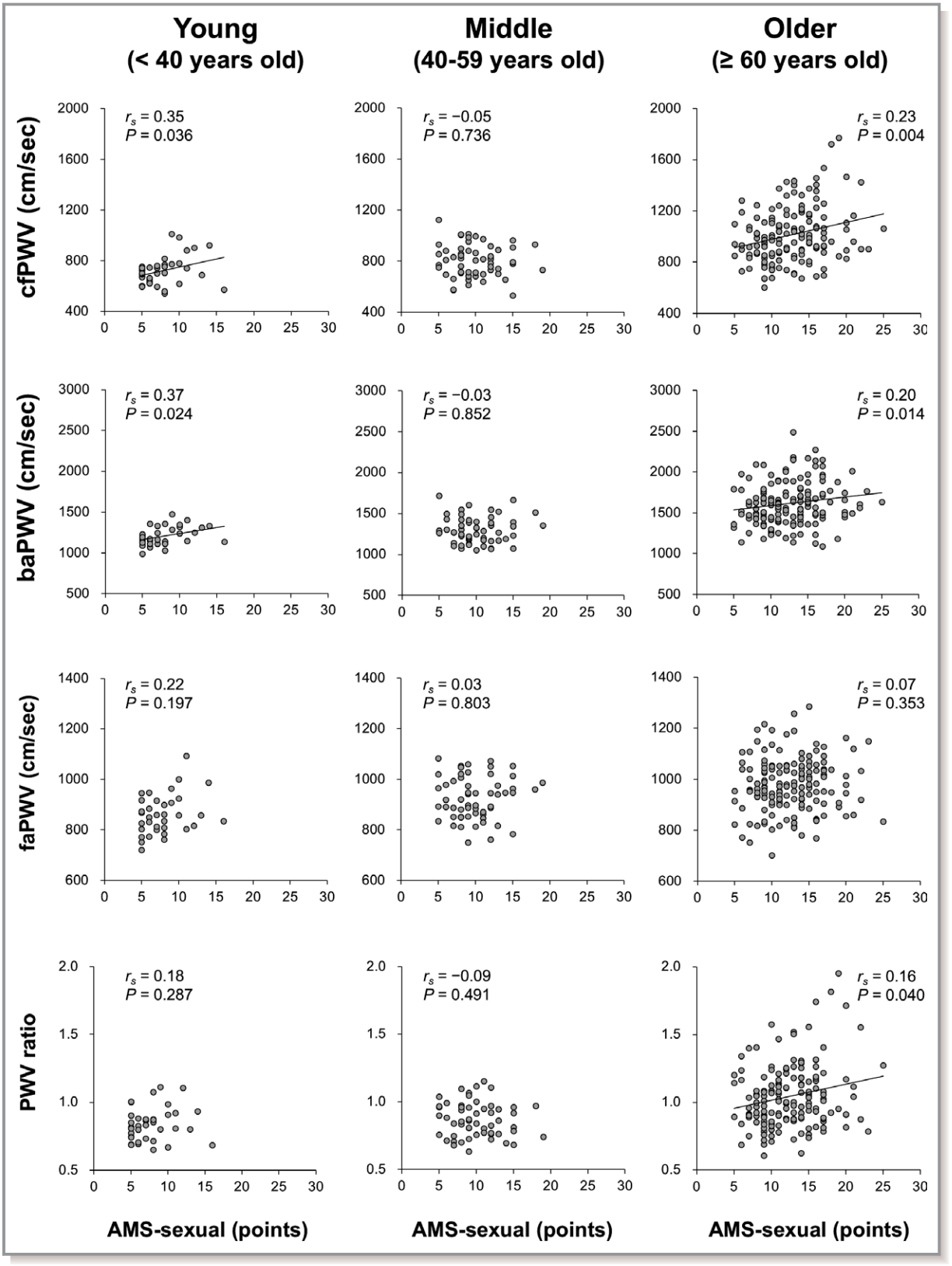

Figure 3. Correlations between the Aging Males' Symptoms (AMS) sexual scores and carotid-femoral pulse wave velocity (cfPWV), brachial-ankle PWV (baPWV), femoral-ankle PWV (faPWV), and PWV ratio in each age group (young-aged, n=37; middle-aged, n=57; older-aged, n=159).

Table 2. Independent Correlates of cfPWV, baPWV, faPWV, and PWV Ratio

	cfPWV (R^2=0.53, P<0.001)*		baPWV (R^2=0.61, P<0.001)*		faPWV (R^2=0.39, P<0.001)*		PWV Ratio (R^2=0.31, P<0.001)*	
Variable	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age, y*	0.411	<0.001	0.396	<0.001	0.246	<0.001	0.305	<0.001
Height, cm	0.173	<0.001	−0.097	0.027	0.019	0.727	0.174	0.003
Waist circumference, cm*	−0.127	0.013	−0.061	0.190	0.024	0.681	−0.157	0.012
Systolic blood pressure, mm Hg*	0.213	<0.001	0.373	<0.001	0.431	<0.001	0.003	0.965
HDL cholesterol, mg/dL*	−0.006	0.912	−0.013	0.778	0.001	0.990	−0.010	0.871
LDL cholesterol, mg/dL*	−0.020	0.660	−0.045	0.285	−0.001	0.976	−0.017	0.754
Triglycerides, mg/dL*	0.023	0.662	−0.007	0.891	0.055	0.362	−0.004	0.951
Glucose, mg/dL*	0.183	<0.001	0.086	0.055	0.011	0.843	0.187	0.002
Testosterone, nmol/L*	0.072	0.107	0.051	0.208	−0.020	0.701	0.086	0.113
Medications								
Antihypertensive, yes/no	0.158	0.001	0.165	<0.001	0.120	0.031	0.108	0.064
Antihypercholesterolemic, yes/no	−0.022	0.622	−0.060	0.147	−0.021	0.685	−0.015	0.792
Antihyperglycemic, yes/no	−0.001	0.988	0.016	0.718	−0.020	0.722	0.008	0.898
Medical history								
Angina, yes/no	0.031	0.478	0.014	0.724	−0.003	0.946	0.039	0.458
Myocardial infarction, yes/no	−0.027	0.524	−0.043	0.264	−0.101	0.039	0.025	0.623
Stroke, yes/no	−0.039	0.362	0.051	0.192	0.050	0.313	−0.064	0.224
Current smoking, yes/no	−0.051	0.226	−0.054	0.157	−0.035	0.461	−0.037	0.467
IIEF5 score, points*	−0.226	<0.001	−0.053	0.230	0.030	0.590	−0.254	<0.001

Covariates included in the multiple linear regression models were age, height, waist circumference, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, testosterone, antihypertensive medication, antihypercholesterolemic medication, antihyperglycemic medication, medical history of angina, myocardial infarction, and stroke, current smoking, and IIEF5 scores. baPWV indicates brachial-ankle PWV; cfPWV, carotid-femoral PWV; faPWV, femoral-ankle PWV; HDL, high-density lipoprotein; IIEF5, International Index of Erectile Function 5; LDL, low-density lipoprotein; and PWV, pulse wave velocity.

*Log-transformed.

of cfPWV was significantly higher in participants with mild ED, mild to moderate ED, moderate ED, and severe ED than in participants with no ED. In addition, cfPWV was significantly higher in participants with severe ED than in those with mild ED and mild to moderate ED (Figure 4A). Besides, the value of PWV ratio was significantly higher in participants with mild to moderate ED, moderate ED, and severe ED than in participants with no ED. In addition, PWV ratio was significantly higher in participants with severe ED than in those with mild ED and mild to moderate ED (Figure 4B).

Discussion

In the present study, we investigated the association between penile erectile function and arterial stiffness in adult men. We found significant negative correlations between IIEF5 scores and cfPWV, baPWV, faPWV, and PWV ratio. Multivariate linear regression analyses demonstrated that IIEF5 scores were significantly associated with cfPWV and PWV ratio, but not with baPWV and faPWV. Similar trends were found for AMS sexual scores. These results suggest that the deterioration of erectile function, as assessed by questionnaires, has the potential for being an easily identifiable and independent marker of increased central arterial stiffness and peripheral organ damage in men. Earlier detection of elevated central arterial stiffness by erectile function might contribute to the preventive or treatment activity for CVD.

The association between male erectile function and CVD has been demonstrated in many epidemiological studies,[25,28–31] and a previous meta-analysis has revealed that, compared with reference groups, men with ED exhibited significantly increased risk of CVD (48%), coronary heart disease (46%), and stroke (35%).[32] These associations could be attributed to endothelial dysfunction[33] and the artery size hypothesis.[13–15] According to the artery size hypothesis, atherosclerosis affects all major vascular beds to the same extent, and penile arteries, which are smaller in diameter than coronary and carotid arteries, are affected earlier by atherosclerotic plaques of the same size. Systemic endothelial dysfunction may cause the inability to regulate blood flow

Table 3. Characteristics of Subjects Classified by the Severity of ED

Characteristics	No ED (IIEF5 Score >21)	Mild ED (IIEF5 Score 17–21)	Mild to Moderate ED (IIEF5 Score 12–16)	Moderate ED (IIEF5 Score 8–11)	Severe ED (IIEF5 Score <8)	*P* Value
Number	85	108	71	21	32	. . .
Age, y	49±16	57±13	64±12	67±7	72±9	<0.001
Height, cm	169.7±6.3	169.3±6.3	165.4±6.9	167.5±5.9	164.7±6.6	<0.001
Body mass, kg	68.2±11.6	69.3±12.1	65.3±11.1	65.9±11.6	63.8±11	0.080
Body mass index, kg/m^2	23.7±3.6	24.1±3.6	23.8±3.2	23.4±3.4	23.4±3.0	0.807
Waist circumference, cm	84.1±10.5	86.5±11.4	84.7±8.7	86.6±10.4	84.7±8.6	0.325
Total cholesterol, mg/dL	203±34	209±36	208±36	216±36	207±45	0.769
HDL cholesterol, mg/dL	61±16	62±15	60±15	65±18	60±16	0.856
LDL cholesterol, mg/dL	119±31	123±33	123±36	125±25	121±35	0.915
Triglycerides, mg/dL	108±59	115±67	119±78	127±67	118±54	0.533
Glucose, mg/dL	99±18	104±15	103±17	110±38	107±19	0.010
HbA1c, mg/dL	5.4±0.6	5.5±0.6	5.6±0.5	5.7±0.6	5.6±0.5	0.017
Testosterone, nmol/L*	21.3±7.2	20.1±5.2	20.6±6.0	22.0±9.6	19.3±10.0	0.479
Hemodynamics						
Systolic blood pressure, mm Hg	124±15	128±14	126±14	129±17	135±16	0.001
Diastolic blood pressure, mm Hg	77±12	81±10	79±9	78±11	81±10	0.129
Mean arterial pressure, mm Hg	95±13	100±12	99±11	99±13	105±13	0.001
Pulse pressure, mm Hg	47±8	47±8	47±9	51±10	54±12	0.007
Heart rate, bpm	61±11	62±11	60±10	60±8	63±10	0.731
baPWV, cm/s	1359±230	1438±251	1515±277	1529±275	1695±295	<0.001
faPWV, cm/s	934±111	956±109	965±97	958±84	999±123	0.059
Principal risk factors, n (%)						0.556
Hypertension	18 (21.1)	42 (38.9)	26 (36.6)	7 (33.3)	23 (71.9)	<0.001
Dyslipidemia	24 (28.2)	40 (37.0)	28 (39.4)	9 (42.9)	14 (43.8)	0.423
Diabetes mellitus	6 (7.1)	10 (9.3)	6 (8.5)	2 (9.5)	7 (21.9)	0.185
Medications, n (%)						
Antihypertensive	11 (12.9)	28 (25.9)	20 (28.2)	5 (23.8)	16 (50.0)	0.002
Antihypercholesterolemic	4 (4.7)	18 (16.7)	9 (12.7)	5 (23.8)	5 (15.6)	0.065
Antihyperglycemic	2 (2.4)	5 (4.6)	2 (2.8)	1 (4.8)	6 (18.8)	0.006
Medical history, n (%)						
Angina	3 (3.5)	2 (1.9)	3 (4.2)	0 (0)	1 (3.1)	0.801
Myocardial infarction	1 (1.2)	0 (0)	0 (0)	0 (0)	2 (6.3)	0.021
Stroke	0 (0)	2 (1.9)	3 (4.2)	1 (4.8)	1 (3.1)	0.395
Current smoking, n (%)	6 (7.1)	4 (3.7)	7 (9.9)	2 (9.5)	2 (6.3)	0.556

Data are shown as the mean±SD or frequency count (percentage), as appropriate. baPWV indicates brachial-ankle pulse wave velocity; bpm, beats per minute; ED, erectile dysfunction; faPWV, femoral-ankle pulse wave velocity; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IIEF5, International Index of Erectile Function 5; and LDL, low-density lipoprotein.
*Data are available in 304 individuals.

in the corpora cavernosa of the penis. However, the mechanisms underlying the association between male erectile function and CVD are not fully understood. In the present study, we demonstrated that male erectile functions were significantly associated with arterial stiffness. Moreover, after adjusting by covariance for differences in age and other factors, male erectile functions were significantly associated with cfPWV, but not with baPWV and faPWV. Thus, our results provide possible new explanations for the association between erectile function and CVD. To the best of our

knowledge, this was the first study to suggest that decreased erectile function is an independent indicator of increased central arterial stiffness in men.

In the present study, we demonstrated that erectile function was significantly associated with central arterial stiffness. Similarly, Vlachopoulos et al have reported that central arterial stiffness was higher in patients with hypertension who had ED than in those without ED.[34] These results suggest that men with ED exhibit higher central arterial stiffness than that exhibited by men without ED. On the contrary, only in patients with ED, Vlachopoulos et al investigated whether central arterial stiffness predicts major adverse cardiovascular events.[35] In their study, they concluded that higher central arterial stiffness is associated with increased risk for a major adverse cardiovascular event in patients with ED,[35] which suggested that the risk for major adverse cardiovascular events varied even in these patients. In the present study, we stratified the participants into 5 groups according to the severity of ED. As a result, the no ED group had the lowest values of cfPWV (822±170 cm/s), and cfPWV was significantly higher in participants with mild ED (879±160 cm/s), mild to moderate ED (927±191 cm/s), and moderate ED (982±222 cm/s) than in participants without ED. The differences in the values were 57, 105, and 160 cm/s, respectively. Moreover, participants with severe ED had the highest values of cfPWV (1147±252 cm/s), and the difference in the values between participants with severe ED and no ED was 325 cm/s. In a meta-analysis involving 15 longitudinal studies, Vlachopoulos et al indicated that an increase in aortic PWV by 100 cm/s was significantly associated with an increased risk of 14% and 15% in total CVD events and CVD mortality, respectively.[36] These results suggest that detailed classification is effective for creating an awareness about the increased risk for CVD.

Recently, it was reported that the arterial stiffness gradient, which is the ratio of central arterial stiffness/peripheral arterial stiffness, is a better predictor of mortality than the classic cfPWV is.[20] In addition, the loss or reversal of stiffness gradient leads to transmission of a highly pulsatile pressure wave into the microcirculation, causing peripheral organ damage.[21,22] In the present study, we found that the severity of ED was significantly associated with PWV ratio. These results support our speculation that male sexual function has the potential for being a personal indicator of increased CVD risk in men. In addition, sexual function may reflect peripheral organ damage in men, such as in the brain and kidney.

Testosterone is a male sex hormone and is associated with both cardiovascular function and erectile function.[37–39] Indeed, we have previously reported that lifestyle modification induced-increased circulating testosterone levels were significantly associated with improved cardiovascular functions in overweight and obese men.[40,41] However, in the present study, no significant association was observed between serum testosterone levels and both arterial stiffness and severity of ED. These inconsistent results may be caused by the differences in circulating testosterone levels. Akishita et al have demonstrated that men with circulating total testosterone levels <14.2 nmol/L had an ≈4-fold higher CVD risk than men with higher circulating testosterone levels,[38] and Vlachopoulos et al have reported that circulating testosterone level was significantly associated with arterial stiffness in normal men and in those with testosterone deficiency (the average testosterone levels were 14.9 nmol/L).[37] In addition, in our previous studies, the average levels of circulating testosterone at baseline were ≈11.1 and 12.3 nmol/L in overweight and obese men, respectively.[40,41] In the present study, the average levels of serum testosterone were 20.6 nmol/L, and circulating testosterone levels of the participants were higher than those reported in other previous studies. These results implied that low circulating

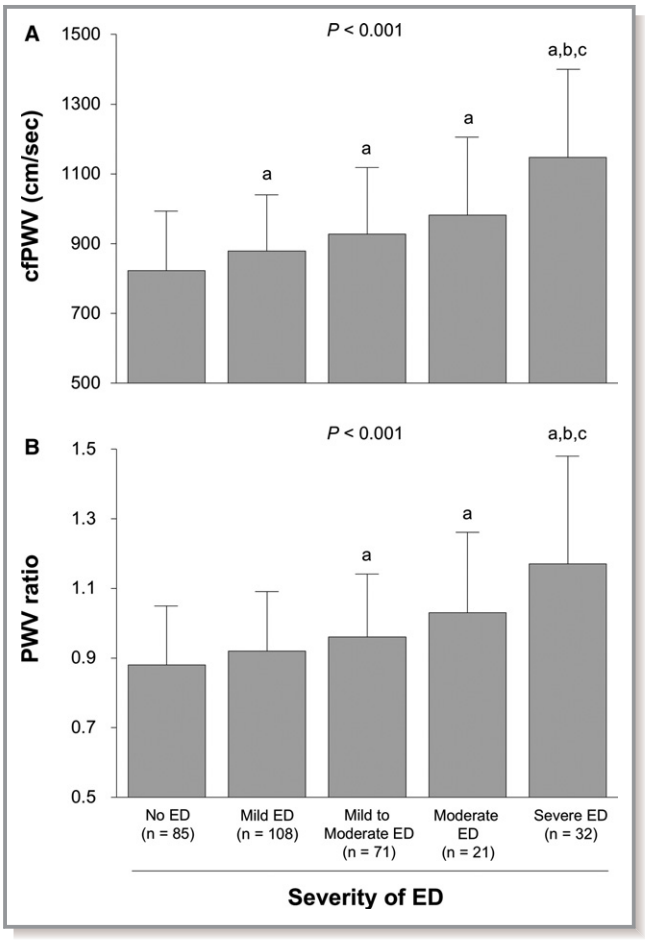

Figure 4. Association between severity of erectile dysfunction (ED) classified by International Index of Erectile Function 5 score and carotid-femoral pulse wave velocity (cfPWV; A) and PWV ratio (B). Data are expressed as mean±SD. [a]$P<0.05$ vs no erectile dysfunction, [b]$P<0.05$ vs mild ED, [c]$P<0.05$ vs mild to moderate ED.

testosterone levels might be associated with impaired cardiovascular and sexual functions in men.

A previous study has reported that ED is an independent predictor of peripheral artery disease, as determined by ankle-brachial index.[42] However, in the present study, ED was not associated with faPWV as an index of peripheral arterial stiffness. This discrepancy could be explained by the locations of the arteries. In human circulation, blood flows from the heart to the penile artery through the central and not the peripheral artery. Thus, penile erectile function was not influenced by peripheral arteries. Another explanation could be the characteristics of peripheral artery. Central arterial stiffness significantly increases with aging, whereas peripheral arterial stiffness remains unchanged[21] or slightly decreases with aging.[43] Thus, faPWV, as an index of peripheral arterial stiffness, may underestimate the aging-induced structural changes in arteries.

The present study has several limitations. First, we did not measure the inflammation levels, although the markers, such as C-reactive protein and interleukin-6, were associated with vascular functions, including erectile function.[34,44,45] Second, we did not measure peripheral organ function, such as that of the brain and kidney, and assessed only the PWV ratio as an index of peripheral organ damage. This issue will be addressed in our future study. Finally, we could not reveal the cause of ED and the causal relationship between arterial stiffness and male sexual function because of the cross-sectional study. A future longitudinal study will be necessary to reveal the causal relationship.

In the present study, we investigated the association between penile erectile function and arterial stiffness in adult men. There were significant negative correlations between IIEF5 score and cfPWV, baPWV, faPWV, and PWV ratio. Moreover, multivariate linear regression analyses demonstrated that IIEF5 scores were significantly associated with only cfPWV and PWV ratio, but not with baPWV and faPWV. Similar trends were found for AMS sexual scores. Therefore, our results suggest that deterioration of erectile function, as assessed using questionnaires, has the potential for being a personal and independent indicator of increased central arterial stiffness.

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Disclosures

None.

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