Differential Effects of Age on Carotid Augmentation Index and Aortic Pulse Wave Velocity in End-stage Renal Disease Patients

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Background: In healthy, normotensive individuals, age-related changes in carotid augmentation index (AI) are more prominent in younger individuals (< 50 years), whereas changes in aortic pulse wave velocity (PWV) are more marked in older individuals (> 50 years). We investigated whether the differential effects of age on AI and PWV also existed in end-stage renal disease (ESRD) patients.

Methods: Two hundred and fifty-seven patients (50% male; mean age, 53.9 ± 15.0 years) with ESRD and 260 normal controls (52% male; mean age, 51.4 ± 17.8 years) received a comprehensive evaluation of cardiovascular structure and function.

Results: The percent differences in PWV between the younger and older subjects were similar in both ESRD patients (+46.2%) and normal controls (+52.5%). The percent differences in PWV between normal controls and ESRD patients were also similar in both younger (+28.2%) and older (+22.9%) subjects. In contrast, the differences in AI between the younger and older subjects were small in ESRD patients (7.3%) but large in normal controls (19.7%). Furthermore, there was a large difference in AI between normal controls and ESRD patients in the younger (+13.3%) subjects, but no difference in the older subjects (+0.8%) (interaction between study groups and age: $p < 0.001$).

Conclusion: Markedly differential effects of age on AI and PWV were observed in ESRD patients. PWV increased with age similarly in both ESRD patients and normal controls, whereas AI increased markedly in the younger but only slightly in the older ESRD patients. [*J Chin Med Assoc* 2008;71(4):166–173]

Key Words: arterial stiffness, augmentation index, end-stage renal disease, pulse wave velocity

Introduction

Cardiovascular disease accounts for approximately half the deaths among adults with end-stage renal disease (ESRD) undergoing regular dialysis.[1,2] Cardiovascular mortality in ESRD patients is 10–20 times higher than in the general population, even after stratification by age, gender, race, and presence of diabetes.[1] The excessive relative risk of cardiovascular mortality is much more pronounced in younger ESRD patients.[1,2] In the general population, cardiovascular mortality increases sharply with advancing age. In contrast, the effect of aging on cardiovascular mortality is much less obvious in patients with ESRD.[1] Children and young adults with ESRD die primarily of cardiovascular disease, and the mortality risk from cardiovascular disease is higher than that from infection or malignancy.[3,4] Several hypotheses have been proposed to explain the excess cardiovascular morbidity and mortality in young ESRD patients, including enhanced atherosclerosis,[5] uremic cardiomyopathy,[6,7] and uremic vasculopathy.[8]

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Increased arterial pulsatile load is a major cause of the high cardiovascular morbidity and mortality in ESRD patients undergoing regular hemodialysis.[9] Specifically, increased aortic stiffness determined by measurement of aortic pulse wave velocity (PWV) is a strong independent predictor of all-cause and mainly cardiovascular mortality,[10] and the insensitivity of PWV to decreased blood pressure is an independent predictor of mortality in patients with ESRD.[11] Arterial wave reflections, estimated by the carotid augmentation index (AI), play an important role in the mechanisms producing alterations in pulsatile arterial dynamics in ESRD,[12] and AI is an independent predictor of all-cause and cardiovascular mortality in these patients.[13]

In healthy, normotensive individuals, age-related changes in AI are more prominent in younger individuals (< 50 years), whereas changes in PWV are more marked in older individuals (≥ 50 years).[14] Therefore, the present study was done to investigate whether or not the differential effects of age on AI and PWV also existed in ESRD patients. The results may partly explain the observed high cardiovascular mortality in young patients with ESRD.[1]

Methods

Study subjects

A total of 257 patients with ESRD (129 males, 128 females; mean age, 53.9 ± 15.0 years) without previous history of cardiovascular disease and who had been on hemodialysis for at least 6 months were invited to participate in a comprehensive hemodynamic study; some of the data were published previously.[15–17] Patients with significant valvular heart diseases were not included. Another 260 healthy volunteers (136 males, 124 females; mean age, 51.4 ± 17.8 years) with normal renal function were enrolled as normal controls. Written informed consent approved by our Institutional Review Board was obtained from every subject before entry into the study. All ESRD patients received a 4-hour dialysis session thrice-weekly using 1.6 m^2 surface area dialyzers with bicarbonate-based dialysate (Na^+ 140 mmol/L, HCO_3^- 39 mmol/L, K^+ 2.0 mmol/L, Ca^{2+} 3.0 mmol/L and Mg^{2+} 1.0 mmol/L). Comprehensive evaluation of cardiovascular structure and function in ESRD patients was performed on a non-dialysis day. The duration on dialysis ranged from 6 to 269 months, with mean dialysis duration around 43 months. The main causes for dialysis included glomerulonephritis (41%), diabetes mellitus (16%), polycystic kidney disease (2%), hypertension (11%), and others (30%).

Vascular parameters

Supine brachial artery systolic (SBP) and diastolic blood pressures (DBP) were measured with an oscillometric device. Pulse pressure was the difference between SBP and DBP.

Echocardiography was analyzed according to the American Society of Echocardiography criteria with a SONOS 5500 system (Agilent Technologies, Andover, MA, USA) incorporated with a multifrequency transducer. Each echocardiographic parameter was the mean value of 4 consecutive measurements. The measured arterial structural parameters included aortic root and common carotid artery (CCA) diameter, and CCA intima-media thickness (IMT).[18]

The arterial functional parameters included PWV and AI. PWV was measured by recording pulse waves at the right CCA and the right femoral artery sequentially using tonometry and a simultaneous electrocardiogram.[12,16,19,20] AI was analyzed from the right CCA pressure wave contour according to the method of Murgo et al.[16,21] AI was the ratio of the augmented pressure, which was determined as the height of the late systolic peak above the inflection point, to the pulse pressure, in percentage.

Left ventricular parameters

Left atrial dimension was determined by M-mode echocardiography. Left ventricular mass and ejection fraction were calculated from M-mode measurements.[16,22] Stroke volume was measured by pulse-wave Doppler echocardiography. Left ventricular end-diastolic volume was calculated from stroke volume divided by ejection fraction. Left ventricular end-systolic volume was the difference between left ventricular end-diastolic volume and stroke volume.

Left ventricular end-systolic elastance (Ees) is a key determinant of cardiac systolic function and ventricular-arterial interaction not susceptible to loading change.[23] Ees was estimated with a recently proposed single-beat method employing SBP, DBP, SV, left ventricular ejection fraction, and an estimated normalized ventricular elastance at arterial end-diastole [E(Nd)]: $Ees = [DBP - (E(Nd) \times SBP \times 0.9)]/[E(Nd) \times SV]$, where E(Nd) was estimated from a group-averaged value adjusted for individual contractile/loading effects.[24]

Statistical analysis

Study subjects were divided into 4 groups, namely, younger normal controls (< 50 years), older normal controls (≥ 50 years), younger ESRD patients (< 50

years), and older ESRD patients (≥ 50 years). Age-related changes were calculated as the mean differences of cardiovascular parameters between the older and younger subjects divided by values in the younger subjects. Similarly, the changes related to ESRD were calculated as the mean differences in cardiovascular parameters between ESRD patients and normal controls divided by values in the normal controls. Because AI itself is a ratio expressed as a percentage, group differences in AI were calculated instead of the percent change. All continuous parameters are expressed as mean ± standard deviation. Between-group differences were assessed by *t* test. The interaction between groups was tested by general linear regression. Linear regression analyses were also performed to examine the different age-related effects on PWV and AI in ESRD patients and normal controls. Statistical significance was set at $p < 0.05$, and all tests were 2-sided.

Results

Abnormal cardiovascular structure and function in ESRD patients

The general characteristics of ESRD patients and normal controls are shown in Table 1. The normal controls and ESRD patients were similar in age and gender distribution. Compared to normal controls, ESRD patients were shorter in height, had lower body weight and smaller body mass index. Yet, ESRD patients had significantly higher SBP, DBP, pulse pressure, and heart rate than normal controls.

Table 1. Characteristics of study subjects*

	Normal controls (*n* = 260)	ESRD patients (*n* = 257)	*p*
Age (yr)	51.4 ± 17.8	53.9 ± 15.0	0.082
Sex (men)	136	129	0.6308
Hematocrit (%)	39.8 ± 4.1	30.1 ± 4.3	< **0.0001**
BMI (kg/m^2)	23.6 ± 3.5	22.8 ± 3.5	**0.0125**
Height (cm)	162.8 ± 8.6	159.7 ± 8.5	< **0.0001**
Weight (kg)	62.7 ± 11.9	58.2 ± 10.5	< **0.0001**
Waist circumference (cm)	79.3 ± 10.4	80.2 ± 10.5	0.3311
Systolic BP (mmHg)	118.9 ± 16.1	133.4 ± 29.8	< **0.0001**
Diastolic BP (mmHg)	68.9 ± 11.1	76.0 ± 17.1	< **0.0001**
Pulse pressure (mmHg)	50.0 ± 10.6	57.4 ± 18.9	< **0.0001**
Heart rate (beats/min)	66.9 ± 9.8	76.1 ± 13.5	< **0.0001**
Cardiac structure			
LA (mm)	32 ± 5	35 ± 6	< **0.0001**
LVEDV (mL)	61 ± 16	73 ± 28	< **0.0001**
LVESV (mL)	23 ± 9	33 ± 20	< **0.0001**
LVM (g)	144 ± 44	207 ± 68	< **0.0001**
Cardiac function			
EF (%)	74 ± 7	68 ± 12	< **0.0001**
Ees (mmHg/mL)	3.1 ± 1.1	2.8 ± 1.1	**0.003**
Vascular structure			
Aorta (mm)	30 ± 4	31 ± 4	< **0.0001**
CCA inner diameter (mm)	5.5 ± 0.6	6.3 ± 1.0	< **0.0001**
IMT (× 100) (mm)	7.2 ± 1.6	8.2 ± 1.8	< **0.0001**
Vascular function			
AI (%)	15.2 ± 19.0	22.5 ± 18.6	< **0.0001**
PWV (m/s)	8.3 ± 3.0	10.7 ± 4.6	< **0.0001**

**Data are presented as mean ± standard deviation or n. ESRD = end-stage renal disease; BMI = body mass index; BP = blood pressure; LA = left atrium; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; EF = ejection fraction; Ees = end-systolic elastance; CCA = common carotid artery; IMT = intima-media thickness; AI = carotid augmentation index; PWV = aortic pulse wave velocity.*

Table 2. Age-related and end-stage renal disease (ESRD)-related changes

	< 50 yr (n = 231)		≥ 50 yr (n = 286)		Age-related		ESRD-related		p*
	Normal (n = 125) a	ESRD (n = 106) b	Normal (n = 135) c	ESRD (n = 151) d	Normal (c – a)/a (Δ%)	ESRD (d – b)/b (Δ%)	Younger (b – a)/a (Δ%)	Older (d – c)/c (Δ%)	
Hematocrit (%)	40.5 ± 4.3	30.1 ± 4.8	39.1 ± 3.6	30.0 ± 4.0	–3.5†	–0.5	–25.7†	–23.3†	0.1330
BMI (kg/m^2)	23.3 ± 3.9	21.8 ± 3.7	23.8 ± 3.1	23.5 ± 3.2	2.0	8.0†	–6.7†	–1.2	**0.0368**
Height (cm)	164.3 ± 8.5	162.1 ± 8.3	161.4 ± 8.4	158.0 ± 8.2	–1.8†	–2.5†	–1.3	–2.1†	0.3987
Weight (kg)	63.3 ± 13.2	57.5 ± 11.8	62.2 ± 10.6	58.8 ± 9.5	–1.7	2.2	–9.2†	–5.6†	0.2354
Waist circumference (cm)	77.0 ± 10.6	76.1 ± 10.9	81.6 ± 9.7	83.2 ± 9.2	6.1†	9.3†	–1.1	1.9	0.1920
Systolic BP (mmHg)	113.9 ± 14.3	134.7 ± 29.4	123.6 ± 16.4	132.5 ± 30.2	8.5†	–1.6	18.3†	7.2†	**0.0051**
Diastolic BP (mmHg)	66.5 ± 11.7	80.6 ± 20.1	71.1 ± 10.0	72.7 ± 13.8	6.8†	–9.8†	21.2†	2.3	< **0.0001**
Pulse pressure (mmHg)	47.4 ± 9.2	54.0 ± 14.3	52.5 ± 11.1	59.8 ± 21.3	10.8†	10.6†	14.1†	13.9†	0.0818
Heart rate (beats/min)	68.9 ± 9.5	77.7 ± 13.8	65.0 ± 9.7	75.0 ± 13.2	–5.7†	–3.5	12.8†	15.5†	0.5520
Cardiac structure									
LA (mm)	30 ± 4	33 ± 6	33 ± 5	36 ± 6	9.7†	8.7†	10.7†	9.7†	0.9905
LVEDV (mL)	62 ± 15	77 ± 27	59 ± 16	70 ± 28	–4.8	–8.7	23.2†	18.1†	0.3570
LVESV(mL)	23 ± 8	34 ± 19	22 ± 9	32 ± 20	–5.2	–3.8	44.5†	46.7†	0.9816
LVM (g)	128 ± 42	203 ± 69	158 ± 42	210 ± 67	23.0†	3.4	57.9†	32.8†	**0.0237**
Cardiac function									
EF (%)	71.8 ± 6.9	67.9 ± 11.2	75.0 ± 6.5	68.6 ± 12.7	4.5†	1.1	–5.4†	–8.5†	0.1460
Ees (mmHg/mL)	2.8 ± 0.8	2.6 ± 1.0	3.4 ± 1.2	3.0 ± 1.2	19.4†	15.3†	–8.5	–11.6†	0.2380
Vascular structure									
Aorta (mm)	28 ± 3	31 ± 3	31 ± 4	32 ± 4	10.0†	3.1†	9.3†	2.5	**0.0037**
CCA inner diameter (mm)	5.3 ± 0.5	5.9 ± 0.8	5.7 ± 0.7	6.5 ± 1.0	7.5†	8.5†	11.3†	12.3†	0.2380
IMT (× 100) (mm)	6.4 ± 1.2	7.4 ± 1.4	8.0 ± 1.5	8.8 ± 1.8	26.1†	18.7†	16.7†	9.8†	0.3255
Vascular function									
AI (%)	5.0 ± 19.6	18.3 ± 21.8	24.7 ± 12.3	25.5 ± 15.2	19.7†‡	7.3†‡	13.3†‡	0.8‡	< **0.0001**
PWV (m/s)	6.5 ± 1.3	8.4 ± 2.7	10.0 ± 3.1	12.3 ± 4.9	53.8†	46.4†	29.2†	23.0†	0.4665

**Interaction between aging and uremic effects; †$p < 0.05$; ‡difference in means rather than percent difference in means as in other parameters. BMI = body mass index; BP = blood pressure; LA = left atrium; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; EF = ejection fraction; Ees = end-systolic elastance; CCA = common carotid artery; IMT = intima-media thickness; AI = carotid augmentation index; PWV = aortic pulse wave velocity.*

ESRD patients had obvious abnormalities in cardiovascular structure and function. They had greater left atrial and ventricular chamber size and left ventricular mass, decreased left ventricular systolic function, greater aortic and CCA diameters and IMT, and increased AI and PWV, as compared to normal controls.

Age-related changes in cardiovascular structure and function

In both ESRD patients and normal controls, subjects ≥ 50 years had shortened height, enlarged waist circumference, and increased pulse pressure, left atrial dimension, Ees, aorta and CCA diameters, IMT, and AI and PWV, as compared to subjects aged < 50 years. No significant changes in body weight, and left ventricular end-diastolic and end-systolic dimensions were observed in both groups. On the other hand, body mass index increased significantly with age in ESRD patients but not in normal controls. SBP, DBP, left ventricular mass, and aortic diameter significantly increased with age in normal controls but not in ESRD patients (Table 2).

Differential effects of age on AI and PWV

In both men and women, younger and older, ESRD patients had increased PWV compared to their respective normal controls (Figure 1A). In subjects < 50 years old, the ESRD-related percent difference in PWV was greater in females than in males ($p = 0.0017$). There was no significant interaction between age-related changes and ESRD-related changes in PWV in men ($p = 0.5452$) and women ($p = 0.0789$). In contrast, in both men and women, there was a prominent ESRD-related change in AI in subjects aged < 50 years (Figure 1B). The interaction between age-related changes and ESRD-related changes in AI was significant in both men ($p = 0.0062$) and women ($p < 0.0001$).

The differential effects of age on AI and PWV in patients with ESRD were also obvious when the relationships of age versus AI and age versus PWV were directly analyzed by linear regression (Figure 2). PWV was linearly correlated with age in both ESRD patients ($PWV = 0.13 \times age + 3.07$; $r = 0.2418$, $p < 0.0001$) and normal controls ($PWV = 0.09 \times age + 3.77$; $r = 0.4268$, $p < 0.0001$) in men, and the slope was slightly steeper in ESRD patients ($p = 0.049$ for the interaction of the slopes) (Figure 2A). Similarly, PWV was linearly correlated with age in both ESRD patients ($PWV = 0.12 \times age + 4.83$; $r = 0.1125$, $p = 0.0001$) and normal controls ($PWV = 0.14 \times age + 1.18$; $r = 0.4967$, $p < 0.0001$) in women without significant interaction of the slopes ($p = 0.43$) (Figure 2B). In contrast, although AI was linearly correlated with age in both ESRD patients ($AI = 0.37 \times age - 2.79$; $r = 0.1009$, $p = 0.0003$) and normal controls ($AI = 0.69 \times age - 25.21$; $r = 0.3778$, $p < 0.0001$) in men, the slope was significantly steeper in normal controls ($p = 0.01$ for the interaction of the slopes) (Figure 2C). Furthermore, AI was linearly correlated with age in normal controls only ($AI = 0.60 \times age - 10.28$; $r = 0.3812$, $p < 0.0001$) and not in ESRD patients ($AI = 0.08 \times age + 23.45$; $r = 0.0047$, $p = 0.4435$) in women ($p = 0.0001$ for the interaction of the slopes) (Figure 2D).

Discussion

Age-related increases in arterial stiffness and wave reflection are partly responsible for increased cardiovascular morbidity and mortality in the elderly. In the healthy population, age-related changes in AI are more prominent in younger subjects, whereas changes in large artery stiffness are more marked in older subjects.[14] The present study demonstrates that differential effects of age on AI and PWV exist in ESRD

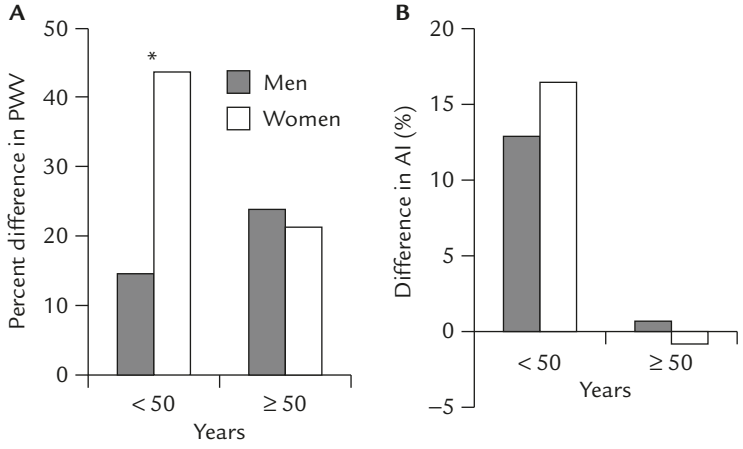

Figure 1. Differential end-stage renal disease (ESRD)-related changes in carotid augmentation index (AI) and aortic pulse wave velocity (PWV) in subjects < 50 years and ≥ 50 years old. (A) Percent difference in PWV between patients with ESRD and normal controls in men and women, younger and older. (B) Difference in AI between patients with ESRD and normal controls in men and women, younger and older. *Significant difference between men and women ($p = 0.0017$).

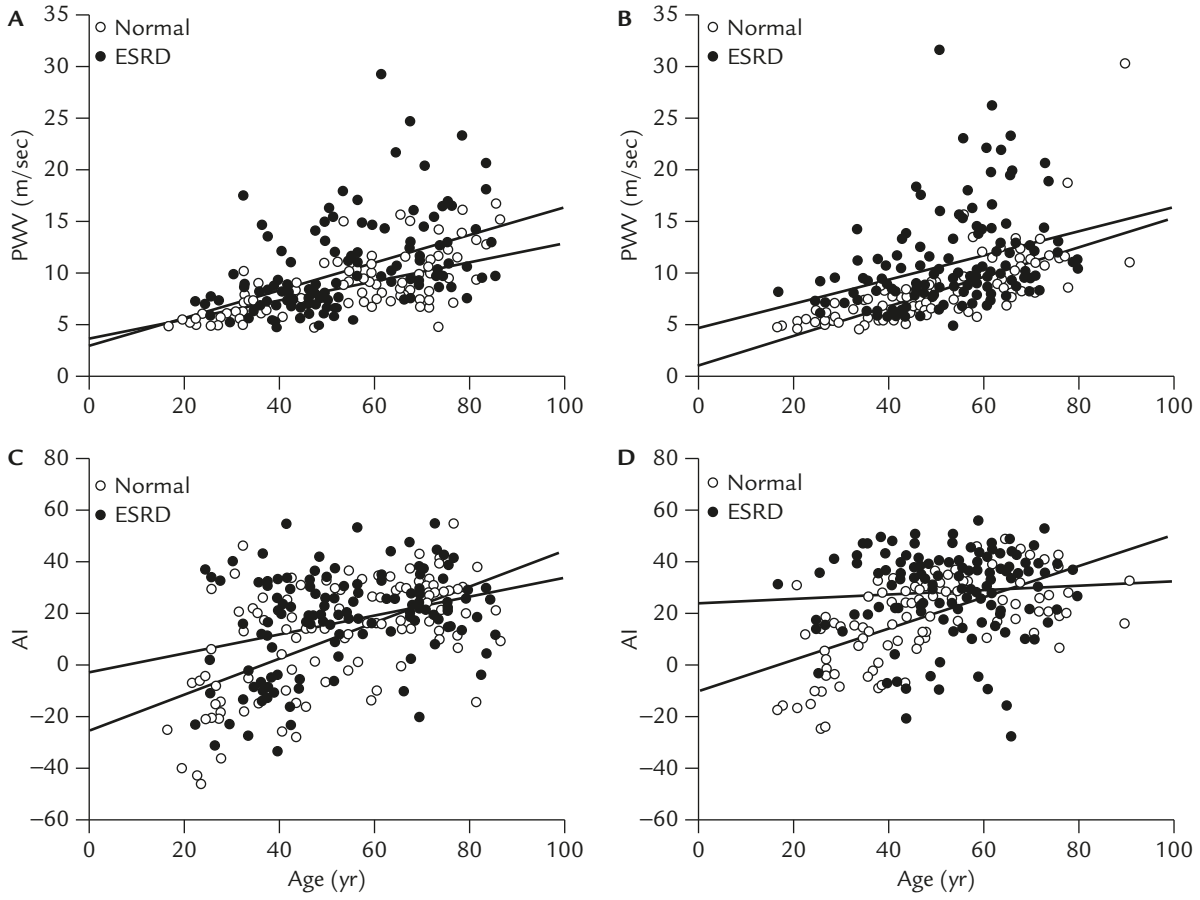

Figure 2. Linear regression analyses of aortic pulse wave velocity (PWV) and carotid augmentation index (AI) on age in end-stage renal disease (ESRD) patients (black circles and solid lines) and normal controls (white circles and dashed lines): (A) PWV in men; (B) PWV in women; (C) AI in men; (D) AI in women.

patients. PWV increased with age similarly in both ESRD patients and normal controls. In contrast, AI increased markedly in the younger but only slightly in the older ESRD patients, so age-related increase in AI was blunted in ESRD patients, especially in women. The results may partly explain the observed high cardiovascular mortality in younger patients with ESRD.[1]

Younger patients with ESRD suffer from excessive cardiovascular mortality, which is increased 700-fold in 25–34-year-old patients undergoing dialysis.[1,25] Goodman et al demonstrated that coronary artery calcification is common and progressive in young adults with ESRD who are undergoing dialysis.[8] Oh et al reported that young adults with childhood-onset chronic renal failure have a high prevalence of arteriopathy associated with indicators of microinflammation, hyperparathyroidism, calcium phosphate overload and hyperhomocysteinemia, but not traditional atherogenic risk factors.[25] A particular phenotype of coronary atherosclerosis has been described in uremic patients, characterized by preferential thickening and calcification of the tunica media.[25,26] It appears that the mechanisms underlying uremic arteriopathy may be distinct from those causing atherosclerosis as part of the aging process.[25] Guerin et al showed that the presence of vascular calcifications in ESRD patients was associated with increased stiffness of large-capacity, elastic-type arteries, like the aorta and CCA.[11] In addition, increased arterial stiffness in young adults with ESRD since childhood has been recognized.[27] Therefore, it is reasonable to speculate that increased pulsatile load may be an important determinant of cardiovascular mortality in younger patients with ESRD.

The increased effect of arterial wave reflections on the aorta and central arteries causes increased pressure during systole and decreased DBP and/or diastolic tension-time index.[28] These alternations increase left ventricular oxygen requirements and predispose to left ventricular hypertrophy and decreased coronary perfusion with relative subendocardial ischemia.[29,30] London et al showed that the association of ESRD patients' mortality with wave reflection (indexed by

AI) was independent of arterial stiffening estimated as PWV.[13] The present study further suggests that the excessive increase in AI in the younger ESRD patients may partly explain the excessive cardiovascular mortality in these patients. This is supported by the accentuated increase in left ventricular mass and aorta diameter parallel to the change in AI in the younger ESRD patients in this study. In ESRD patients, the relation between early arterial wave reflection and left ventricular hypertrophy in long-term dialysis has already been defined, and the arterial wave reflection may alter cardiac structure, resulting in left ventricular hypertrophy independently of other factors.[31]

AI is affected by age, PWV, traveling distance of pressure waves (body height), left ventricular ejection time, and reflective properties of the arterial system.[31,32] PWV is directly related to aortic stiffness by the Bramwell-Hill equation.[32,33] The associations between AI and age and between PWV and age in the general population are well-recognized.[14,32] In our younger subjects, there were no significant differences in height and the aging effect on PWV between the normal controls and ESRD patients. Hence, the accentuated increase in AI in young ESRD patients was likely due to the accentuated increase in the reflective properties of the vascular tree, which could be altered independently of stiffening of the large arteries.[32]

Similar aging effects on PWV and pulse pressure in both normal controls and ESRD patients suggest uniform central vascular stiffening with aging since childhood. The incremental effects of age and uremia on aortic stiffness may provide a sound basis for PWV as a strong independent predictor of all-cause and mainly cardiovascular mortality in patients with ESRD.[10,11] On the other hand, aortic stiffening may not be the cause of the excessive cardiovascular mortality in the younger ESRD patients because PWV in the younger ESRD patients was not higher than that in the older normal controls, and the highest PWV appeared in the older ESRD patients.

IMT is an early marker of atherosclerosis and a predictor of vascular events.[34,35] Oh et al reported that IMT was significantly increased in young adults with childhood-onset chronic renal failure compared with matched control subjects, and it was associated with ESRD duration, cumulative dialysis time, and cumulative serum calcium, phosphate and calcium phosphate product.[25] In contrast, Groothoff et al showed that IMT was not significantly increased in young adults with ESRD compared to controls.[27] In our study, IMT seemed to increase with the presence of ESRD and advancing age, and the highest IMT occurred in the older ESRD patients.[8,25] The results may suggest that accelerated atherosclerosis is not the main cause of the excessive cardiovascular mortality in the younger ESRD patients, and may further underscore the importance of pulsatile load as indexed by AI in these patients.

In the normal population, young females are protected from cardiovascular mortality compared to young males.[1] The advantage of female gender on cardiovascular mortality disappears in patients with ESRD.[1] In this study, the most striking findings were that AI was very high in younger female ESRD patients and AI did not increase with age as observed in normal controls and male ESRD patients. These results may suggest that increased wave reflection is also a possible explanation for the high cardiovascular mortality in the young female ESRD patients.

The present study used a cross-sectional design, with its inherent limitations. Therefore, any conclusions from this study should be considered as hypothesis generation. Other factors, such as duration of renal insufficiency and hemodialysis, history of hypertension and diabetes, and presence of left ventricular dysfunction and hyperparathyroidism may also affect AI and PWV and may have confounded our results. Left ventricular ejection fracture usually remains unchanged with advancing age in the normal population. In the present study, the slightly but statistically significantly increased ejection fraction in the normal controls ≥ 50 years old as compared with normal controls < 50 years old was probably due to chance and did not have any clinical significance.

In conclusion, markedly differential effects of age on AI and PWV were observed in ESRD patients. PWV increased with age similarly in both ESRD patients and normal controls, whereas AI increased markedly in the younger but only slightly in the older ESRD patients. The differential effects of age on AI and PWV appeared to be more prominent in female ESRD patients. These results suggest that increased pulsatile load may play an important role in the high cardiovascular mortality in the younger, especially female, ESRD patients.

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