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Cardiac and arterial interactions in end-stage renal disease

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Cardiac and arterial interactions in end-stage renal disease. Although cardiac hypertrophy is a frequent complication of end-stage renal disease (ESRD), relatively little is known about large arterial geometry and function *in vivo* in these patients, and the relationship between arterial changes and cardiac hypertrophy is unknown. Common carotid artery (CCA) intima-media thickness and internal diameter and left ventricular geometry and function were determined by ultrasound imaging in 70 uncomplicated ESRD patients and in 50 age-, sex-, and blood pressure-matched controls. Arterial distensibility and compliance were determined from simultaneously recorded CCA diameter and stroke changes in diameter and CCA pressure waveforms, obtained by applanation tonometry, and also by the measurement of carotid-femoral pulse wave velocity. Compared with control subjects, ESRD patients had greater left ventricular diameter ($P < 0.01$), wall thicknesses and mass ($P < 0.001$), increased CCA diameter (6.25 ± 0.87 vs. 5.55 ± 0.65 mm; $P < 0.001$), larger CCA intima-media thickness (777 ± 115 vs. 678 ± 105 μm; $P < 0.001$) and intima-media cross-sectional area (17.5 ± 4.5 vs. 13.4 ± 3.3 mm^2; $P < 0.001$). In uremic patients, arterial hypertrophy was associated with decreased CCA distensibility (17.8 ± 8.8 vs. 24.0 ± 12.7 $kPa^{-1} \cdot 10^{-3}$; $P < 0.001$) and compliance (5.15 ± 2 vs. 6.0 ± 2.5 $m^2 \cdot kPa^{-1} \cdot 10^{-7}$; $P < 0.05$), accelerated carotid-femoral pulse wave velocity (1055 ± 290 vs. 957 ± 180 cm/seconds; $P < 0.001$), early return and increased effect of arterial wave reflections (20.5 ± 15.4 vs. 9.2 ± 18.4%; $P < 0.001$). The latter phenomenons were responsible for increased pulsatile pressure load in CCA (58.3 ± 21 vs. 48 ± 17 mm Hg; $P < 0.01$) and were associated with a decreased subendocardial viability index (157 ± 31 vs. 173 ± 30%; $P < 0.001$). The CCA diameter was correlated with the left ventricular diameter ($P < 0.01$), and a significant correlations existed between CCA wall thickness or CCA intima-media cross-sectional area and left ventricular wall thicknesses and/or left ventricular mass ($P < 0.01$). In multivariate analysis, these relationships were independent regarding age, sex, blood pressure and body surface area. The present study documents parallel cardiac and vascular adaptation in ESRD, and demonstrates the potential contribution of structural and functional large artery alterations to the pathogenesis of left ventricular hypertrophy and functional alterations.

Left ventricular (LV) hypertrophy is the the most frequent cardiac alteration in end-stage renal disease (ESRD) [1, 2]. Hypertension is an important risk factor, but there are discrepancies between the level of blood pressure (BP) and the degree of hypertrophy [1, 2]. BP is usually assessed through measurements of arterial pressure in the brachial artery, and the hydraulic load is classically related to increased mean BP and peripheral resistance and hence to constriction or rarefaction of arterioles and small arteries. However, the peripheral resistance is only the static component of resistance to ventricular ejection [3, 4]. The other component of pressure load is a consequence of the heart's intermittent output, and therefore of pulsatile flow and pressure in the aorta and major arteries. Pulsatile pressure is influenced at any given time during ventricular ejection by aortic and major artery distensibility and geometry, and the intensity and timing of arterial wave reflections [3, 4]. The presence of intimal-medial thickening of large capacitance arteries, and to a lesser extent arterial lumen enlargement in human essential hypertension have recently been documented [5, 6]. Furthermore, these changes in capacitance arteries in essential hypertension parallel those in the LV, suggesting that arterial alterations and decreased distensibility contribute to the development of LV hypertrophy [5, 6].

The presence of aortic and carotid lumen enlargement and arterial wall hypertrophy has recently been documented in ESRD patients [1, 7–11]. In addition, decreased arterial distensibility and increased effect of arterial wave reflections in central arteries are observed in these patients in association with the degree of LV hypertrophy, suggesting that vascular changes contribute to the development of LV hypertophy in these patients [7–9]. However, there is little information concerning the pathogenesis of these structural alterations, and no studies have related arterial structural changes to arterial functional alterations. Furthermore, the relationship of structural changes within the arterial system and cardiac hypertrophy in ESRD is unknown.

Therefore the present study was designed in ESRD patients: (1) to evaluate the relationships between the structural and the functional alterations of large arteries; and (2) to analyze the relation between arterial alterations and LV structure and function.

Methods

Subjects

We studied 70 stable ESRD patients on hemodialysis (duration of dialysis 105 ± 85 months), and 50 age-, sex-, and BP-matched control subjects. Patients or controls with coronary artery disease, valvular heart disease, cerebral vascular disease, peripheral artery disease, heart failure, or diabetes were not included. Thirty-five ESRD patients received recombinant human erythropoietin. Twenty-two ESRD patients and 15 controls received antihypertensive therapy. ESRD patients were dialyzed 4 to 6 hours thrice weekly on AN69 membranes (Hospal, Meyzieu, France). Routine biochemical parameters were determined by standard methods

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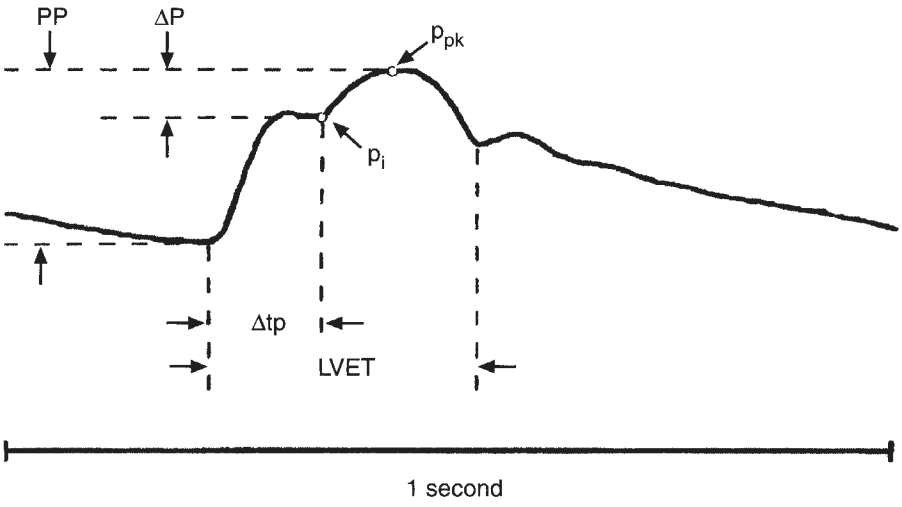

Fig. 1. *Carotid pressure waveform analysis with applanation tonometry.* Abbreviations are: PP, pulse pressure; Pi, early systolic peak; Ppk, late systolic peak; ΔP, Ppk − Pi; ΔP/PP, augmentation index; Δtp, travel time of reflected wave; LVET, left ventricular ejection time.

using autoanalyzers. All hemodynamic investigations were performed before the midweek dialysis. The study was approved by our institutional review board and all patients gave written informed consent.

Cardiac measurements

Echocardiographic studies of the LV were performed using a Hewlett-Packard Sonos 100 device equipped with a 2.25 MHz probe allowing M-mode, two-dimensional, and pulsed Doppler measurements. Measurements were performed blindly by two physicians according to methods of the American Society of Echocardiography [12]. Interobserver and intraobserver reproducibility have been reported previously [13]. M-mode measurements included LV posterior wall thickness (PWT), interventricular septal thickness (IVS), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD). LV mass was calculated according to the Penn convention [14], and LV mean wall thickness as (IVS + PWT)/2. The fractional shortening was calculated as [(LVEDD − LVESD)/LVEDD] × 100. LV outflow and aortic velocities were taken from the apical position, and early (E) and atrial (A) mitral inflow velocities with the signal positioned at the tip of the mitral leaflets.

Blood pressure measurement

Brachial BP was measured with a mercury sphygmomanometer after 15 minutes of recumbency. The phase I and V of Korotkoff sounds were taken as the systolic BP and diastolic BP, respectively. The mean BP was determined by integration of the radial artery pressure wave contour recorded by applanation tonometry, using an HP Sketch Pro Tablet Digitizer (Hewlett-Packard Company, San Diego, CA, USA) and a Zenith Z-425/SX computer (Zenith Data Systems, Nanterre, France) as previously described [15].

Common carotid artery pressure and pressure waveform

Common carotid artery (CCA) pressure waveform was recorded noninvasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, Houston, TX, USA) on a Gould 8188 recorder (Gould Electronique, Ballainvilliers, France) at 100 mm/second. A detailed description of this system has been published previously [5, 15, 16]. The tonometer is internally calibrated using a Millar preamplifier (TCB-500). The CCA pressure wave was analyzed according to Murgo et al (Fig. 1) [17]. The height of the late systolic peak (Ppk) above the inflection Pi (ΔP = Ppk-Pi) and the ΔP to pulse pressure (PP) ratio (ΔP/PP) defines the augmentation index (in %) which represents the effect of arterial wave reflections on BP in central arteries. The Δtp represents the travel time (ms) of the pulse wave to peripheral reflecting sites and back. LV ejection time was measured from the foot of the pressure wave to the diastolic incisura. Reproducibility of the measures have been previously published [8, 15]. Systolic BP and PP may increase from central to peripheral arteries, while the diastolic or mean BPs drops from ascending aorta to the radial artery do not exceed 2 to 3 mm Hg [3, 4, 18]. Therefore, the CCA pressure wave was calibrated assuming that brachial and carotid diastolic and mean BPs were equal. The mean BP on the CCA pressure wave was computed from the area of the CCA pressure wave in the corresponding heart period, and set equal to brachial mean BP. CCA pressure amplitude was then computed from diastolic BP and the position of mean BP on the CCA pressure wave [5, 15, 16, 19, 20], and the following parameters were determined: CCA pulse pressure, and subendocardial viability index [subendocardial viability index = DTTI/STTI in %; where STTI = systolic tension-time index (integral of pressure and time during systole), and DTTI = diastolic tension − time index (integral of pressure during diastole) [21, 22]].

Arterial measurements

Aortic diameter. The diastolic internal aortic diameter was measured by two observers at the aortic bifurcation ($Ao_{bif}D$) using 3.5 MHz transducers (Sonel 300, Compagnie Générale de Radiologie, Saint Cloud, France). Interobserver reproducibility was ± 1 mm as previously reported [13]. Reproducible data were obtained in 47 controls and 65 ESRD patients.

CCA diameter and intima-media thickness. The CCA diameter and wall motion were measured by a high-resolution B-mode (7.5 MHz transducer) echotracking system (Wall-Track system) allowing the assessment of arterial wall displacement during the cardiac cycle. A detailed description of this system has been published

previously [20, 23]. The radio frequency signal over six cardiac cycles is digitized and stored in a large memory. Two sample volumes, selected under cursor control, are positioned on the anterior and posterior walls. The vessel walls are continuously tracked by sample volumes according to phase, and the displacement of the arterial walls is obtained by autocorrelation processing of the Doppler signal. The accuracy of the system is ± 30 μm for CCA diastolic diameter (Dd) and less than ± 1 μm for stroke change in CCA diameter (Ds-Dd, where Ds is systolic diameter). The repeatability coefficient of the measurements was ± 0.273 mm for CCA diameter, and ± 0.025 mm for Ds-Dd. Measurements were done on the right CCA, two cm beneath the bifurcation. CCA-lumen cross-sectional area (LCSA) was calculated as LCSA = π(CCA diameter)^2/4. CCA intima-media thickness (IMT) was measured on the far wall at the same level as the diameter measurements with computer assisted acquisition, processing and storage. The computing equipment was linked to 80386/16 MHz processor and an imaging card providing real-time digitizing of the video analog signal from the echo recording (processing corresponding to 256 levels of grey). The IMT was automatically analyzed from changes in density on the section perpendicular to the vessel wall with dedicated software (Eurequa, TSA, Meudon, France) [24, 25]. The intima-media cross-sectional area (IMCSA) was calculated as IMCSA = π(CCA diameter/2 + IMT)^2 − π(CCA diameter/2)^2, and wall/lumen ratio as 2IMT/CCA diameter. The repeatability coefficient of the measure of IMT was ± 60 μm. A localized echostructure encroaching into the vessel lumen was considered to be a plaque if the CCA intima-media thickness was > 50% thicker than neighboring sites [5]. Measurements of CCA diameter and CCA intima-media thickness were always performed in plaque-free arterial segments.

Arterial distensibility

Carotid-femoral pulse wave velocity (PWV). Carotid-femoral PWV was determined using the foot-to-foot method [26]. Transcutaneous Doppler flow velocity recordings were carried out simultaneously at the base of the neck over the CCA and the femoral artery in the groin with a SEGA M842 8MHz Doppler unit (Sociéte d'Electronique Générale et Appliquée, Paris, France) and a Gould 8188 recorder. The time delay (t) was measured between the feet of the flow waves recorded at these different points. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites minus that from the suprasternal notch to the carotid (D). PWV was calculated as PWV = D/t. The reproducibilty of the measure has been published previously [7–9, 13].

CCA distensibility and compliance. CCA compliance and CCA distensibility were determined from changes in CCA diameter during the systole and simultaneously measured CCA pulse pressure (ΔP) according to following formulas: CCA compliance = [πDd(Ds-Dd)/2]/ΔP($m^2 \cdot kPa^{-1} \cdot 10^{-7}$); and CCA distensibility = 2[(Ds-Dd)/Dd]/ΔP($kPa^{-1} \cdot 10^{-3}$) [6, 20, 23]. The repeatability coefficient of the measurement was ± 1 $kPa^{-1} \cdot 10^{-3}$ for CCA distensibility and 0.52 $m^2 \cdot kPa^{-1} \cdot 10^{-7}$ for CCA compliance. While distensibility provides information about "elasticity" of the artery as a hollow structure, the incremental modulus of elasticity (Einc) provides information on the properties of the wall material, independent of the geometry. Einc was calculated = 3(1 + LCSA/IMCSA) · 1/CCA distensibility [27].

Table 1. Baseline clinical characteristics

Parameters	Controls $N = 50$	ESRD $N = 70$
Clinical parameters		
Age *years*	46.7 ± 14.2	50.8 ± 15.0
Sex (M/F ratio)	1.40 ± 0.49	1.38 ± 0.48
Body surface area m^2	1.85 ± 0.25	1.68 ± 0.20[b]
Body mass index kg/m^2	26.03 ± 4.70	23.20 ± 4.40[b]
Systolic BP *mm Hg*	141.0 ± 22.2	146.0 ± 28.7
Diastolic BP *mm Hg*	84.0 ± 14.5	82.4 ± 13.6
Mean BP *mm Hg*	103.5 ± 15.6	103.7 ± 16.6
Ankle/arm systolic BP (ratio)	1.10 ± 0.10	1.09 ± 0.09
Blood chemistry		
Total cholesterol *mmol/liter*	5.40 ± 1.15	5.23 ± 1.29
HDL cholesterol *mmol/liter*	1.32 ± 0.35	1.06 ± 0.30[c]
LDL cholesterol *mmol/liter*	3.82 ± 1.40	3.68 ± 0.83
Triglyceride *mmol/liter*	1.15 ± 0.70	1.89 ± 1.00[c]
Blood urea *mmol/liter*	6.4 ± 1.0	24.3 ± 2.0[c]
Hemoglobin *g/dl*	14.9 ± 1.3	11.0 ± 1.7[c]
Calcium *mmol/liter*	2.46 ± 0.08	2.45 ± 0.12
Phosphates *mmol/liter*	1.03 ± 0.21	1.88 ± 0.38[c]
Smoking status		
Current smokders	$N = 9$	$N = 6$
Lifelong dose (pack · years)[a]	9.7 ± 12.0	10.6 ± 15.1
History of hypertension	$N = 23$	$N = 46$
Known duration of hypertension *years*	6.7 ± 6.0	8.0 ± 7.0
Current antihypertensive treatment	$N = 15$	$N = 22$
Ca blockers	6	9
ACE inhibitors	6	8
β blockers	3	5

[a]Whether smoking or not at the time of the study
[b] $P < 0.01$; [c] $P < 0.001$

Statistical analysis

Data were expressed as mean ± SD. Student's t-test was used for comparison of controls and ESRD patients. Qualitative data were compared with the χ^2 test. Gender was used as a dummy variable (1-male, 2-female). Multiple stepwise regression analysis was used to assess the determinants of cardiac and arterial parameters and interactions. Statistical analysis was done on the NCSS 5.0 software [28]. Repeatability and reproducibility of the methods were defined as recommended by the British Standard Institution [29].

Results

Characteristics of the populations are presented in Table 1. The two groups were similar regarding age, sex ratio, and blood pressure. Twenty-three control subjects (46%) and 44 ESRD patients (63%) had a past history of hypertension, and 15 controls and 22 ESRD patients were treated with antihypertensive drugs during the study period. ESRD patients had lower body surface area ($P < 0.01$) and body mass index ($P < 0.01$). The total and LDL cholesterol levels were similar in the two groups, while increased triglycerides ($P < 0.001$) and decreased HDL cholesterol ($P < 0.001$) were observed in ESRD patients. ESRD patients had lower hemoglobin levels ($P < 0.001$). Smoking habits were not different in the two groups.

Comparison of LV and carotid artery structure and function

LV dimensions, and LV mass were increased in ESRD patients ($P < 0.001$). LV outflow velocity integral and aortic flow velocities were increased in ESRD ($P < 0.01$), and were inversely correlated with hematocrit and/or hemoglobin ($r = -0.35$; $P < 0.01$). Mitral inflow velocities were increased in ESRD patients ($P < 0.01$) but

Table 2. Cardiac measurements

Parameters	Controls	ESRD
LV end-diastolic diameter *min*	5.00 ± 0.43	5.35 ± 0.66[b]
LV end-systolic diameter *mm*	3.05 ± 0.42	3.45 ± 0.60[c]
LV mean wall thickness *cm*	0.90 ± 0.11	1.06 ± 0.19[c]
LV mass *g*	192 ± 41	271 ± 118[c]
LV mass index g/m^2	104 ± 17	160 ± 65[c]
% Shortening	38.6 ± 5.2	35.5 ± 6.1[b]
E *cm/second*	66 ± 14	73 ± 22[a]
A *cm/second*	51 ± 14	77 ± 24[c]
E/A *ratio*	1.34 ± 0.37	0.98 ± 0.34[c]
Heart period *ms*	950 ± 146	866 ± 149[b]
LV ejection time *ms*	303 ± 26	292 ± 34
LV outflow velocity integral *cm/beat*	21.4 ± 3.3	26.1 ± 7.6[c]
Aortic maximum flow velocity *cm/second*	106 ± 12	125 ± 26[c]

Abbreviation is: LV, left ventricular
[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$

Table 3. Arterial structure and function

Parameters	Controls	ESRD
CCA pulse pressure *mm Hg*	48.0 ± 17.0	58.3 ± 21.0[b]
Augmentation index %	9.2 ± 18.4	20.5 ± 15.4[b]
Travel time of reflected wave *ms*	126 ± 28	112 ± 26[b]
Subendocardial viability index %	173 ± 30	157 ± 31[b]
Ao_{bif} diameter *mm*	15.0 ± 1.8	17.0 ± 2.6[c]
CCA diameter *mm*	5.55 ± 0.65	6.25 ± 0.87[c]
CCA intima-media thickness *μm*	678 ± 105	777 ± 115[c]
CCA wall/lumen (ratio)	0.24 ± 0.03	0.25 ± 0.03
CCA intima-media cross-sectional area mm^2	13.4 ± 3.3	17.5 ± 4.5[c]
Stroke changes in CCA diameter *μm*	405 ± 145	380 ± 135
CCA distensibility $KPa^{-1} \cdot 10^{-3}$	24.0 ± 12.7	17.8 ± 8.8[b]
CCA compliance $m^2 \cdot KPa^{-1} \cdot 10^{-7}$	6.00 ± 2.50	5.15 ± 2.00[a]
CCA elastic incremental modulus $KPa \cdot 10^3$	0.46 ± 0.23	0.61 ± 0.35[b]
Carotid-femoral PWV *cm/second*	957 ± 180	1055 ± 290[a]

Abbreviations are: CCA, common carotid artery; Ao_{bif}, aorta at bifurcation level; PWV, pulse wave velocity.
[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$

the E/A ratio was lower than that in controls ($P < 0.001$). Shortening fraction was in the normal range in ESRD patients. The heart period was shorter in ESRD patients ($P < 0.01$), while the LV ejection time was similar in both groups (Table 2).

ESRD patients had an increased CCA pulse pressure (58.3 ± 21.0 vs. 48 ± 17 mm Hg, $P < 0.05$), due to increased wave reflections (augmentation index 20.5 ± 15.4% in ESRD vs. 9.2 ± 18.4% in controls, $P < 0.001$) and early return of reflected waves (Δtp 112 ± 26 in ESRD vs. 126 ± 28 ms in controls; $P < 0.01$). The subendocardial viability index was lower in ESRD (157 ± 31 vs. 173 ± 30%; $P < 0.01$). Aortic diameter and CCA diameter were increased in ESRD ($P < 0.001$; Table 3). Multivariate analysis in ESRD and controls showed that CCA diameter was positively correlated with age ($P < 0.001$), CCA pulse pressure ($P < 0.001$), and sex ($P < 0.001$), and in ESRD patients only also with LV outflow velocity integral ($P < 0.001$; Table 4 and Fig. 2). CCA intima-media thickness and intima-media cross-sectional area were increased in ESRD patients ($P < 0.001$; Table 3). In both groups CCA intima-media thickness was positively correlated with age ($P < 0.001$), body surface area ($P = 0.003$), CCA diameter ($P = 0.007$), smoking ($P = 0.028$), and CCA pulse pressure ($P = 0.008$; Table 4). The increased wall thickness in ESRD was principally related to larger diameter ($P < 0.001$). The CCA wall-to-lumen ratio was similar in both groups. In control subjects the wall to lumen ratio was positively correlated to CCA pulse pressure ($r = 0.38$; $P < 0.05$), but this correlation was not significant in ESRD patients ($r = 0.09$; NS).

Systolic expansion in CCA diameter were similar in both groups, despite higher distending pressure in ESRD patients, and CCA distensibility ($P < 0.01$) and CCA compliance ($P < 0.05$) were reduced in ESRD (Table 3). In parallel with reduced CCA distensibility, ESRD patients had higher carotid-femoral-PWV ($P < 0.05$). In both groups the CCA distensibility and carotid-femoral-PWV were strongly correlated ($r^2 = 0.81$; $P < 0.0001$). The principal factors correlated with CCA distensibility and CCA compliance, and carotid-femoral-PWV in control subjects were age ($P < 0.001$) and CCA pulse pressure ($P < 0.001$). In ESRD patients carotid-femoral-PWV was positively correlated with CCA pulse pressure ($P = 0.0012$), and independently of pressure and age ($P = 0.062$; Table 4) positively correlated with CCA intima-media cross-sectional area and/or intima-media thickness ($P < 0.001$; Fig. 3). Carotid pulse pressure ($P < 0.001$), age ($P < 0.001$), and CCA intima-media cross-sectional area were also independently associated with CCA compliance and/or CCA distensibility (Fig. 3 and Table 4). The incremental modulus of elasticity (Einc) was higher in ESRD patients than in controls (0.61 ± 0.38 vs. 0.46 ± 0.23 kPa · 10^3; $P < 0.01$). Independently from age or blood pressure, a positive correlation was observed between CCA distensibility and the subendocardial viability index ($P < 0.01$; Fig. 4). CCA alterations were not associated with duration of dialysis, blood lipid abnormalities, and routine biochemical parameters.

Relations between cardiac and arterial structure

In the ESRD patients, there were significant relationships between comparable cardiac and arterial parameters (Table 5). Independently from age or body surface area, CCA diameter was correlated with aortic diameter and both were correlated with LV end-diastolic diameter (Fig. 5; $P < 0.001$). A significant correlation was observed between CCA intima-media thickness (or intima-media cross-sectional area) and CCA diameter and LV wall thickness and/or LV mass (Fig. 5; $P < 0.001$). These correlations remained significant after adjustment for age and pressure (Table 5). A significant correlation ($P < 0.01$) was observed between mitral E/A ratio and carotid-femoral-PWV and CCA distensibility, but this correlation was related to common influence of age on LV and arterial stiffness.

Discussion

In ESRD patients, alterations in LV geometry and function have been well documented [1, 2, 30, 31], but structural and functional alterations of the arterial system *in vivo* are less documented [7, 10, 11]. The present study demonstrates that in ESRD arterial system undergo significant structural remodeling, characterized by dilation of major arteries and wall hypertrophy. These changes in arterial geometry were associated with increased arterial stiffness and early arterial wave reflections responsible for an increased pulsatile pressure load in central arteries. These arterial abnormalities were associated with LV geometry alterations similar to the arterial changes, and decreased subendocardial viability index. These findings were independent of age, sex, body size, and systemic BP.

Table 4. Multivariate relations of CCA structure and function in ESRD patients

Parameters		T value	Sequential r^2	*P*	%RMSE	Single r^2
Dependent variable: CCA diameter						
Sex (M/F)		−4.6	0.115	<0.0001	12.5	0.114
Age *years*		4.6	0.327	<0.0001	12.2	0.216
CCA pulse pressure *mm Hg*		3.4	0.488	0.0011	6.6	0.190
LV outflow velocity integral *cm/beat*		2.4	0.525	0.0184	3.1	0.180
Total variance explained %	52.5					
Root mean square error (RMSE)	0.63					
F ratio	19.6	($P < 0.0001$)				
Dependent variable: CCA intima-media thickness						
Age *years*		4.43	0.399	<0.0001	13.4	0.398
Body surface area m^2		3.84	0.517	0.003	10.1	0.202
CCA diameter *mm*		2.79	0.617	0.007	5.1	0.420
CCA pulse pressure *mm Hg*		2.73	0.657	0.008	4.9	0.242
Smoking status *pack · year*		2.03	0.685	0.028	2.7	0.185
Total variance explained %	65.7					
Root mean square error (RMSE)	69.5					
F ratio	23.7	($P < 0.0001$)				
Dependent variable: Carotid-femoral PWV						
CCA intima-media cross-sectional area mm^2		4.38	0.442	<0.0001	12.8	0.442
CCA pulse pressure *mm Hg*		3.38	0.524	0.0012	7.5	0.385
Age *years*		1.96	0.537	0.062	1.8	0.247
Total variance explained %	53.7					
Root mean square error (RMSE)	209.7					
F ratio	25.7	($P < 0.0001$)				
Dependent variable: CCA compliance						
CCA pulse pressure *mm Hg*		−4.8	0.242	<0.0001	15	0.242
Age *years*		−4.1	0.324	<0.001	11.1	0.190
CCA intima-media cross-sectional area mm^2		−2.9	0.399	0.006	5.3	0.055
Total variance explained %	38.5					
Root mean square error (RMSE)	1.64					
F ratio	14.6	($P < 0.0001$)				

Abbreviations are: CCA, common carotid artery; LV, left ventricular; PWV, pulse wave velocity.

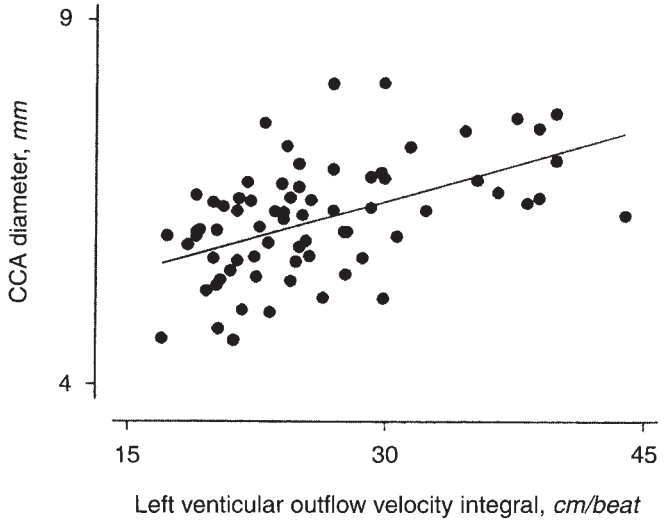

Fig. 2. *Correlation in ESRD patients between the left ventricular outflow velocity integral and common carotid artery (CCA) diameter.* $r = 0.44$; $P < 0.0001$.

Arterial changes that occurs with aging and disease include two distinct conditions even though they are often associated. The first (atherosclerosis) is focal, non-uniformly distributed, primarily intimal, inducing occlusive lesions and compensatory focal enlargement of arterial diameters [3, 4, 32]. The second (arteriosclerosis) is primarily medial, characterized by diffuse dilation and stiffening of major arteries, and occurs with aging and hypertension [3, 4, 32]. Confirming published data [7, 10, 11], CCA and aortic diameter and CCA intima-media thickness were increased in ESRD patients. These alterations were non-focal and diffuse, including major capacitive arteries. The determinants of aortic and CCA diameters in controls and ESRD patients were age, blood flow velocity (Fig. 2), CCA pulse pressure and sex (all other factors being equal, arterial dimension were lower in women; Table 4) [20, 32, 33]. Besides the effect of age, body size or sex, arterial walls are exposed to the influence of mechanical factors such as flow and pressure stresses that act as mechanical stimuli for arterial remodeling. Changes in blood flow and flow velocity alter the tangential stress (shear stress) while changes in pulsatile blood pressure alter the circumferential tensile stress. Experimental and clinical studies have shown that chronically increased arterial flow and/or flow velocity and shear stress led to increased internal arterial dimensions and arterial wall remodeling [34–36]. In ESRD, features such as anemia, arteriovenous shunts and overhydration are associated with increased systemic and regional blood flow and flow velocity, creating conditions for arterial remodeling. The relationships between CCA diameter and aortic flow velocity and hemoglobin level, as well as the influence of fluid removal by dialysis on decrease in CCA diameter [10] suggest that

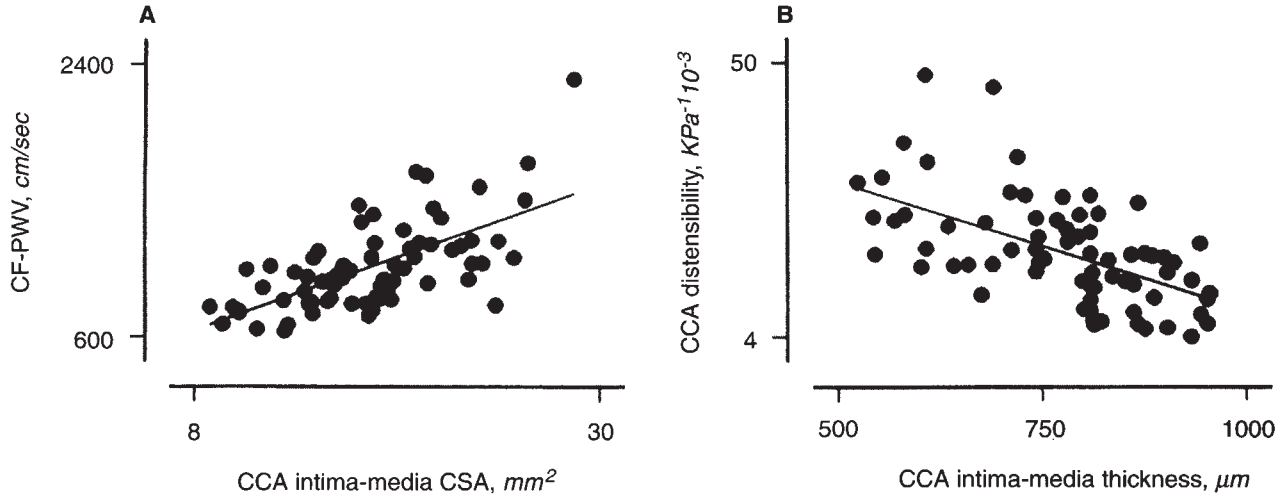

Fig. 3. *Correlations in ESRD patients between common carotid artery (CCA) intima-media cross-sectional area (CSA) and carotid-femoral pulse wave velocity (CF-PWV) (***A.** *$r = 0.66$, $P < 0.0001$) and CCA distensibility (***B**, *$r = 0.56$, $P < 0.0001$).*

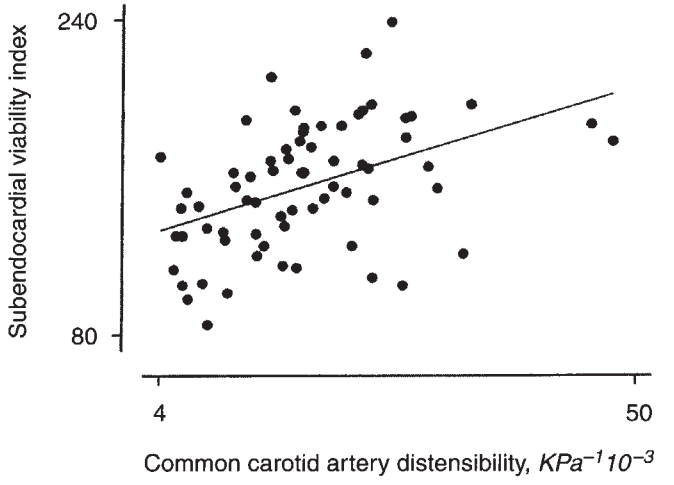

Fig. 4. *Correlations in ESRD patients between Common carotid artery distensibility and subendocardial viability index.* $r = 0.44$; $P < 0.001$.

the arterial enlargement observed in ESRD results from chronic volume and flow overload.

Investigations of the effect of BP on arterial diameters in the general population have produced inconsistent results, the most recent studies indicating that CCA diameter was increased in untreated essential hypertensive patients, principally in relation to increased pulsatile pressure [5, 6, 20]. The present results are in agreement with these data and indicate that in ESRD patients the increase in CCA diameter is significantly associated with higher local distending pressure.

In comparison with controls, the CCA intima-media thickness and intima-media cross-sectional area were increased in ESRD patients. In control subjects and ESRD patients, CCA intima-media thickness increased with age, body surface area, CCA diameter, distending pressure, and smoking habits. Arterial diameter's influence on arterial wall thickness is a logical consequence of Laplace's law, whereby wall tension is directly proportional to arterial radius and intraarterial pressure, and inversely proportional wall thickness [3, 4]. The increase in CCA intima-media thickness and similar CCA wall-to-lumen ratio in ESRD would be an appropriate response to the arterial dilation in conditions of similar local pressure. However, in ESRD patients the wall-to-lumen ratio was similar to controls in the presence of higher CCA distending pressure. In normal young and middle-aged subjects, systolic BP and pulse pressure are amplified by 15 to 30% as the pressure wave travels from the aorta to brachial and peripheral arteries, due to the geometric and viscoelastic nonuniformity of the arterial tree and appropriate timing of arterial wave reflections [3, 4]. In ESRD, pressure wave transmission and amplification is altered resulting in attenuation of central-to-peripheral pulse pressure amplification [7–9] due to an early return an increased effect of reflected waves in central arteries. For these reasons the pulse and systolic pressure in central arteries are higher than that of control subjects with similar brachial BP. In ESRD, even if brachial BP is comparable to that of controls and remains in the normotensive range, the CCA pulse (and systolic) pressure is higher and closer to values observed in essential hypertensive patient [7–9]. Therefore, in the presence of increased CCA diameter and higher distending pressure, the carotid wall/lumen ratio should be increased in ESRD patients. The reasons why it is not observed are not clear. It is possible that conduit arteries have a limited capacity to respond adequately to a combined flow and pressure overload. This was observed on radial artery on the side of arteriovenous fistula in ESRD patients [34] and in experimental conditions. Indeed, in vein grafts subjected to separate mechanical factors such as circumferential stretching and changes in blood velocity, Dobrin, Littooy and Endean [37] demonstrated that changes in flow influences the intimal thickening, whereas medial thickening respond to changes in wall stress. Intimal thickening occurs in response to low flow velocity, whereas medial thickening occurs in response to increased parietal tension. The present result indicates that in ESRD patients, a high flow velocity occurring simultaneously with high pulsatile pressure results in an unchanged wall-to-lumen ratio.

In ESRD, the increase in CCA intima-media thickness (Fig. 3) is associated with decreased arterial distensibility, increased

Table 5. Multivariate relations of arterial and cardiac structures in ESRD patients

Parameters			T value	Sequential r^2	P	%RMSE	Single r^2
Dependent variable: LV mean wall thickness							
CCA intima-media thickness μm			4.70	0.416	<0.0001	15.3	0.416
Age *years*			2.60	0.482	0.0120	4.4	0.076
CCA diameter *mm*			2.07	0.530	0.042	2.5	0.336
CCA pulse pressure *mm Hg*			2.00	0.558	0.050	2.1	0.249
Total variance explained %	55.8						
Root mean square error (RMSE)	0.16						
F ratio	22.4	($P < 0.0001$)					
Dependent variable: LV end-diastolic diameter							
CCA diameter *mm*			2.54	0.124	0.013	4.1	0.124
Body surface area m^2			2.34	0.189	0.022	3.3	0.122
Total variance explained %	18.9						
Root mean square error (RMSE)	0.57						
F ratio	7.8	($P = 0.01$)					
Dependent variable: Ao_{bif} diameter							
CCA diameter *mm*			6.46	0.456	<0.0001	28.7	0.456
Body surface area m^2			4.15	0.578	0.001	12.3	0.286
Total variance explained %	57.8						
Root mean square error (RMSE)	1.65						
F ratio	41.8	($P < 0.0001$)					

Abbreviations are: LV, left ventricular; CCA, common carotid artery; Ao_{bif} aorta at the bifurcation level.

PWV, and early return of wave reflections. Arterial distensibility decrease with increased blood pressure. In essential hypertensive patients, Laurent et al [38] have shown that decrease in CCA distensibility was primarily due to higher distending blood pressure rather than to structural modifications. In the present study the blood pressure was similar in controls and ESRD patients, and the higher carotid pulse pressure in uremic patients could be the cause as well as the consequence of decreased distensibility [3, 4]. Moreover, as the relationships between increased CCA intima-media thickness and carotid-femoral-PWV or CCA compliance were independent from age and blood pressure the present results suggest that decreased arterial distensibility in ESRD patients results directly from arterial wall hypertrophy. This could be related to qualitative changes in arterial wall (alterations in intrinsic elastic properties) or to quantitative changes (increased amount of wall material). The fact that incremental modulus of elasticity was increased in ESRD patients is more in favor of altered intrinsic elastic properties as observed in experimental uremia and *in vitro* in arteries of uremic patients, namely fibroelastic intimal thickening, calcification of elastic lamellae and ground substance deposition [39, 40].

In the present ESRD patients a moderate increase in LV end-diastolic diameter and wall thickening were observed, and LV hypertrophy (LV mass index $\geq$ 132 g/m^2 in men and $\geq$ 110 g/m^2 in women [41]) was present in 43 patients (61.4%). Among the ESRD patients, significant relationships existed between comparable cardiac and vascular parameters (Table 5). The LV diameters and arterial diameters correlated (Fig. 5). Similarly, significant correlations were observed between the CCA intima-media thickness and intima-media cross-sectional area and LV wall thickness and/or LV mass (Fig. 5). Therefore, there appeared to be a "volume effect" and "wall effect" involving both the LV and CCA, but in reality these two effects interacted as indicated by the significant correlation between CCA diameter and LV wall thicknesses. Although these interrelationships between comparable cardiac and vascular parameters could be largely influenced by common factors such as age, body surface area, sex, anemia, and flow overload, the correlations persisted independently of these factors, suggesting that other mechanisms could be involved, particularly abnormalities related to the altered function of large conduit arteries. The important factors relating the pressure load to LV hypertrophy and altered LV function are the peak and end-systolic pressures in the aorta and central arteries [32], which are critically dependent on arterial distensibility and the intensity and timing of arterial wave reflections, that is, on the physical properties of arteries [3, 4, 32]. Previous studies have shown that LV hypertrophy in ESRD was correlated to increased pulsatile pressure load due to increased arterial stiffness and wave reflections [7–9]. However, the significant correlation between CCA diameter and LV wall thickness also suggests the existence of a direct link between arterial dilation and LV hypertrophy. Indeed, the inertial effects are greater in enlarged arteries since larger blood-filled arteries require the heart to produce excess work in order to accelerate blood against larger inertial forces during ejection [42].

Changes in arterial structure and function are associated with decreased subendocardial viability ratio (Fig. 4), an index of the propensity for myocardial ischemia when there are altered hemodynamic forces in the absence of occlusive arterial lesions [21, 22]. Canine studies have shown that aortic stiffening directly decreased subendocardial blood flow despite an increase in mean coronary flow, and that chronic aortic stiffening reduced cardiac transmural perfusion and aggravated subendocardial ischemia [43]. Due to decreased arterial distensibility and increased PWV, wave reflections return earlier and impact on the incident wave during the systole, increasing aortic and CCA pressures, and increasing the LV systolic stress and the systolic tension-time index, an index of LV oxygen and blood demand. On the other hand, the impact of the reflected wave in the systole decreases the mean and telediastolic pressures, decreasing the diastolic tension-time index, which is an index of LV perfusion capacity [21, 22].

In conclusion, the present study documents parallel cardiac and vascular adaptations in ESRD and demonstrates the potential contribution of structural and functional large artery alterations to

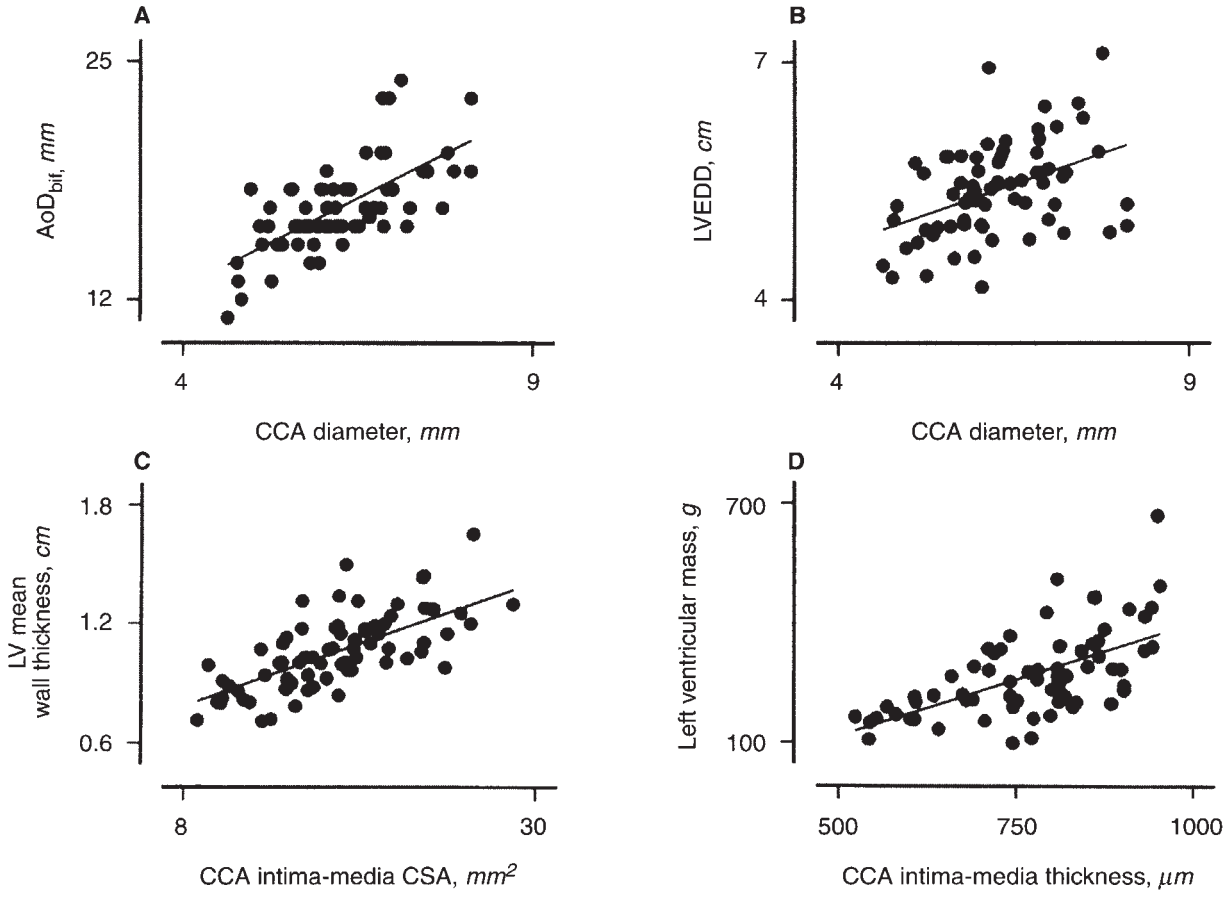

Fig. 5. *Correlations in ESRD patients between common carotid artery (CCA) diameter (A) and aortic bifurcation diameter (AoDbif;* r = 0.67; P < 0.0001), and (**B**) left ventricular end-diastolic diameter (LVEDD) (r = 0.42; P < 0.001), and (**C**) CCA intima-media cross-sectional area (CSA) and left ventricular mean wall thickness (r = 0.68; P < 0.0001), and (**D**) CCA intima-media thickness and left ventricular mass (r = 0.62; P < 0.0001).

the pathogenesis of left ventricular hypertrophy and functional alterations.

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References

1. London GM, Marchais SJ, Guérin AP, Fabiani F, Métivier F: Cardiovascular function in hemodialysis patients, in *Advances in Nephrology* (vol 20), edited by Grünfeld JP, Bach JF, Funck-Brentano JL, Maxwell MH, St. Louis, Mosby Year Book Publishers, 1991, pp 249–273
2. Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS: Risk factors for the development of left ventricular hypertrophy in a prospective followed cohort of dialysis patients. *J Am Soc Nephrol* 4:1486–1490, 1994
3. O'Rourke MF: Vascular impedance: The relationship between pressure and flow, in *Arterial Function in Health and Disease*, Edinburgh, Churchill Livingstone Publisher, 1982, pp 94–132 and pp 185–243
4. Nichols WW, O'Rourke MF: Contour of pressure and flow waves in arteries, in *McDonald's Blood Flow in Arteries: Theoretic, Experimental and Clinical Principles* (3rd ed), London, Edward Arnold Publishers, 1991, pp 216–250
5. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, Alderman MH, Devereux RB: Parallel cardiac and vascular adaptation in hypertension. *Circulation* 86:1909–1918, 1992
6. Boutouyrie P, Laurent S, Girerd X, Benetos A, Lacolley P, Abergel E, Safar M: Common carotid artery stiffness and patterns of left ventricular hypertrophy in hypertensive patients. *Hypertension* 25(part 1):651–659, 1995
7. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K, London AM: Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 37:137–142, 1990
8. Marchais SJ, Guérin AP, Pannier BM, Levy BI, Safar ME, London GM: Wave reflections and cardiac hypertrophy in chronic uremia. Influence of body size. *Hypertension* 22:876–883, 1993
9. London GM, Guerin AP, Pannier B, Marchais SJ, Benetos A, Safar ME: Increased systolic pressure in chronic uremia: Role of arterial wave reflections. *Hypertension* 20:10–19, 1992
10. Barenbrock M, Spieker C, Laske V, Rahn K-H: Studies of the vessel wall properties in hemodialysis patients. *Kidney Int* 45:1397–1400, 1994
11. Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48:820–826, 1995
12. Sahn DJ, de Maria A, Kisslo J, Weyman A: Recommendations

regarding quantitation in M-mode echocardiographic measurements. *Circulation* 58:1072–1083, 1978
13. London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, Froment L: Salt and water retention and calcium blockade in uremia. *Circulation* 82:105–113, 1990
14. Devereux RB, Reichek N: Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. *Circulation* 55:613–618, 1977
15. London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JL: Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease: Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 90:2786–2796, 1994
16. Kelly R, Daley J, Avolio A, O'Rourke M: Arterial dilation and reduced wave reflection: Beneficial effects of Dilevalol in essential hypertension. *Hypertension* 14:14–21, 1989
17. Murgo JP, Westerhof N, Giolma JP, Altobelli SA: Aortic input impedance in normal man: Relationship to pressure wave forms. *Circulation* 62:105–116, 1980
18. Krooker EJ, Wood EH: Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. *Circ Res* 3:623–632, 1955
19. Armentano R, Megnien JL, Simon A, Bellenfant F, Barra J, Levenson J: Effects of hypertension on Viscoelasticity of carotid and femoral arteries in humans. *Hypertension* 26:48–54, 1995
20. Benetos A, Laurent S, Hoeks AP, Boutouyrie P, Safar ME: Arterial alterations with aging and high blood pressure: A noninvasive study of carotid and femoral arteries. *Arterioscler Thromb* 13:90–97, 1993
21. Buckberg GD, Fixler DE, Archie JP, Hoffman JIE: Experimental subendocardial ischemia after cardiopulmonary bypass. *Circ Res* 30: 37–81, 1972
22. Buckberg GD, Towers B, Paglia DE, Mulder Dg, Maloney JV: Subendocardial ischemia after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 64:669–687, 1972
23. Hoeks APG, Brands PJ, Smeets FA, Reneman RS: Assessment of distensibility of superficial arteries. *Ultrasound Med Biol* 16:121–128, 1990
24. Touboul PJ, Prati P, Scarabin PY, Adrai V, Thibout E, Ducimetière P: Use of monitoring software to improve the measurement of carotid wall thickness by B-mode imaging. J Hypertens 10(Suppl 5):S37–S41, 1992
25. Bonithon-Kopp C, Ducimetière P, Touboul JP, Fève JM, Billaud E, Courbon D, Héraud V: Plasma converting-enzyme activity and carotid wall thickening. *Circulation* 89:952–954, 1994
26. Avolio AO, Chen SG, Wang RP, Zhang Cl, Li MF, O'Rourke MF: Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 68:50–58, 1983
27. Laurent S, Girerd X, Mourad JJ, Lacolley P, Beck L, Boutouyrie P, Mignot J-P, Safar M: Elastic modulus of the radial artery wall material is not increased in patients with essential hypertension. *Arterioscler Thromb* 14:1223–1231, 1994
28. Hintze JL: *NCSS, 05–02-1987. User Manual*. Kaysville, Utah, 1987
29. British Standard Institution: *Precision of Test Methods. 1: Guide for the Determination of Reproducibility for a Standard Test Method*. London, British Standard Institution, 1979, BS 5497, part 1
30. Hüting J, Kramer W, Schütterle G, Wizemann V: Analysis of left-ventricular changes associated with chronic hemodialysis. A noninvasive follow-up study. *Nephron* 49:284–290, 1988
31. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barré PE: The prognostic significance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 5:2024–2031, 1995
32. Nichols WW, O'Rourke M: *MacDonald's Blood Flow in the Arteries*. London, Edward Arnold Publisher, 1990, pp 283–329
33. Vasan RS, Larson MG, Levy D: Determinants of echocardiographic aortic root size. The Framingham study. *Circulation* 91:734–740, 1995
34. Girerd X, London G, Boutouyrie P, Mourad JJ, Laurent S, Safar M: Remodelling of radial artery and chronic increase in shear stress. (abstract) *Hypertension* 26:561, 1995
35. Kamiya A, Togawa T: Adaptative regulation of wall shear stress to flow change in the canine carotid artery. *Am J Physiol* 239:H14–H21, 1980
36. Langille BL, O'Donnell F: Reductions in arterial diameters produced by chronic decrease in blood flow are endothelium-dependent. *Science* 231:405–407, 1986
37. Dobrin PB, Littooy FN, Endean ED: Mechanical factors predisposing to intimal hyperplasia and medial thickening in autogeneous vein grafts. *Surgery* 105:393–400, 1989
38. Laurent S, Caviezel B, Beck L, Girerd X, Billaud E, Boutouyrie P, Hoeks A, Safar M: Carotid artery distensibility and distending pressure in humans. *Hypertension* 23(part 2):878–883, 1994
39. Ibels LS, Alfrey AL, Huffer WE, Craswell PW, Anderson JT, Weil R: Arterial calcification and pathology in uremic patients undergoing dialysis. *Am J Med* 66:790–796, 1979
40. Amann K, Neusüb R, Törnig J, Irzyniec T, Mall G, Ritz E: Pressure independent changes of elastic peripheral arteries and veins in uremia. (abstract) *Am J Hypertens* 8(part 2):101A, 1995
41. Devereux RB, Lutas EM, Casale RN, Kligfield P, Eisenberg RR, Hammond IW, Miller DH, Reis G, Alderman RH, Laragh JH: Standardization of M-Mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 4:1222–1230, 1984
42. Womersley JR: Oscillatory flow in the arteries: The constrained elastic tube as a model of arterial flow and pulse transmission. *Phys Med Biol* 2:178–187, 1957
43. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y: Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol* 21:1497–1506, 1993