Increased Systolic Pressure in Chronic Uremia
Role of Arterial Wave Reflections

Gérard London, Alain Guérin, Bruno Pannier, Sylvain Marchais, Athanase Benetos, and Michel Safar

To assess the role of arterial wave reflections in the mechanisms of systolic hypertension and altered pulsatile arterial dynamics in patients with end-stage renal disease (ESRD), 79 ESRD patients were compared with 73 age-matched control subjects with normal renal function and similar mean blood pressure. Wave reflections were investigated from the carotid pulse contour recorded by applanation tonometry using a Millar micromanometer-tipped probe. Wave reflections were quantified as the ratio (augmentation index, %) of the height of the late systolic peak to the total height of carotid pulse wave. Travel time of the reflected wave was timed from the foot of the pressure wave to the foot of the late systolic peak. Systolic and pulse pressure were increased in ESRD patients (p<0.001) and was not attributable to differences in left ventricular ejection pattern. The augmentation index was increased in ESRD patients (23.2 ±15.0 versus 9.8±15.6%; p<0.001) in association with a shorter travel time of reflected wave (109±24 versus 131 ±30 msec; p<0.001). Multiple regression analysis showed two principal factors associated (p<0.001) with the increase in augmentation index and shortened travel time of reflected wave: increased aortic pulse wave velocity and smaller stature with shorter body height in ESRD patients. The study points to the role of arterial wave reflections in the mechanisms producing alterations in pulsatile arterial dynamics in ESRD and is the first, through the mechanisms of early wave reflections, to show in humans that the increase in systolic and pulse pressures is associated with lesser body size. (Hypertension 1992;20:10-19)

KEY WORDS • blood pressure • pulse • tonometry

Clinical hypertension is usually classified on the basis of raised diastolic blood pressure (DBP).1-4 However, in recent years the extent of the systolic blood pressure (SBP) has been reconsidered as being of prime importance in producing cardiovascular morbidity and mortality.5-7 Analytical studies of arterial function treat blood pressure as a periodic phenomenon that can be divided into two components: a steady component (mean blood pressure [MBP]) and a pulsatile component (pulse pressure [PP]).8-10 The MBP is determined exclusively by cardiac output and vascular resistances.8-9 The PP represents the oscillation around this mean. The PP magnitude is determined by the interaction of the incident pressure wave generated by left ventricular ejection, and one or more reflected waves generated by the arterial system.8,9,11 The magnitude of the incident wave depends on the pattern of left ventricular ejection, the arterial stiffness, and the attenuation characteristics of the vascular tree8-14; the magnitude of the reflected waves depends on the timing and intensity of wave reflection and propagation properties of the arterial system.8-14 Altered pulsatile arterial hemodynamics have serious ill effects on heart and arteries,8-10 and several studies have shown that PP is an independent cardiovascular risk factor.15-17 The role of PP is particularly important in central arteries such as the aorta or the carotid artery.13,14,16-19 Although MBP falls only slightly in the aorta and large distributing arteries, intravascular pressure recordings have revealed major differences in the configuration and amplitude of pressure waves between central and peripheral arteries with PP and SBP amplification in the periphery.11-13,18-21 Sphygmomanometric measurements of brachial artery blood pressure may underestimate blood pressure and PP alterations in central arteries and do not provide information about the shape of pressure waves. Recent developments in high fidelity applanation tonometry allow noninvasive recording of the arterial pressure waveform and magnitude in both peripheral and central arteries and allow the effects of aging and disease states to be more accurately evaluated.19-21

Clinical and epidemiological studies have shown a high prevalence of isolated systolic hypertension in patients with end-stage renal disease (ESRD).22-24 The association of systolic hypertension and high PP in ESRD patients with an increased arterial stiffness has been noted,24 but it has also been observed that abnormal PP amplitude in ESRD patients persists even after normalization of arterial stiffness during antihypertensive treatment.25 Therefore, the mechanisms of the systolic hypertension in ESRD are not well understood, and the respective roles of the properties of the arterial...
system and alterations in the pattern of ventricular ejection remain unclear.

The objectives of the present study were to determine, using applanation tonometry, echocardiography, and measurement of aortic pulse wave velocity (PWV), the respective roles of cardiac and arterial factors in the pathogenesis of increased SBP and the altered relation between the pulsatile and steady components of blood pressure in ESRD patients compared with the control group, including normotensive and hypertensive subjects with normal renal function.

Methods

Subjects
Seventy-nine ESRD patients (mean age ± SD, 52.7 ± 15.8 years; range, 21–85 years) undergoing maintenance hemodialysis therapy were studied. The duration of dialysis therapy was 87.7 ± 72.0 months (range, 3–249 months). No patient had a past history of cerebrovascular disease, symptomatic peripheral artery disease, or diabetes. Fifty-nine patients were normotensive and were not taking any antihypertensive therapy or vasoactive drugs. Twenty ESRD patients had hypertension (SBP greater than 160, or DBP greater than 90 mm Hg, or both) not corrected by body fluid control during dialysis. These patients stopped all antihypertensive therapy for 4 weeks before the study commenced. The patients underwent dialysis three times per week. The duration of dialysis was individually adjusted (3–6 hours) to control body fluids and blood chemistry. The dialysate was delivered by a system comprising bicarbonate delivery and ultrafiltration devices. An arteriovenous shunt was used in all patients.

Seventy-three outpatients (mean age, 51.8 ± 18.6 years; range, 17–95 years) with serum creatinine less than 0.12 mmol/l were studied as a control group. Fifteen subjects with essential hypertension (SBP greater than 160 or DBP greater than 90 mm Hg, or both) were included in the control group. They were untreated or had stopped all antihypertensive therapy at least 4 weeks before the study. No subject had a past history of cerebrovascular disease, peripheral artery disease, or diabetes.

All subjects were weighed in light clothing without shoes, and the height was measured. The trunk length was estimated as the distance between the suprasternal notch and symphysis ossis pubis and was measured with a tape measure. Each subject provided informed written consent for the study, which had been approved by our institutional review board.

Study Design
Investigations were performed in a controlled environment kept at 22±2°C. ESRD patients were studied 15–20 hours after their midweek dialysis session.

Blood Pressure
Blood pressure was measured with a random-zero mercury sphygmomanometer with cuffs adapted to arm circumference after the subjects had been recumbent for at least 15 minutes. SBP was taken as the point of appearance of Korotkoff sounds and DBP as the point of their disappearance (phase 5). MBP was determined by planimetry of radial artery PP contour determined by applanation tonometry. PP amplitude of the radial artery determined by applanation tonometry was correlated with PP measured by sphygmomanometry ($r=0.965; p<0.001$) (Figure 1). Surface under the PP curve was measured with an HP Sketch Pro Tablet Digitizer (Hewlett-Packard Company, San Diego, Calif.) and computer Zenith Z-386/25 (Zenith Data System, Nanterre, France). Total surface of the blood pressure was determined as the sum of the surface under the PP curve plus the surface calculated from DBP and the heart period. MBP was measured as the ratio between the total surface and heart period. Planimetrically determined MBP and MBP calculated as
MBP=DBP+(SBP-DBP/3)

were correlated (planimetric MBP=1.03, calculated MBP=1.9, r=0.956, p<0.001). Blood pressure was measured every minute before, during, and after pulse contours recording. Blood pressure values given in "Results" is the average value of all these measurements.

Arterial Pulse Wave Velocity

PWV, a classic index of arterial stiffness, was determined as the group phase velocity using the foot-to-foot wave velocity method.24,26 Transcutaneous Doppler flow velocity records were carried out simultaneously at the base of the neck over the common carotid artery and the right femoral artery in the groin with a non-directional Doppler unit (SEGA M842 8MHz, Société d'Electronique Générale et Appliquée, Paris) and a Gould 8188 recorder (Gould Electronique, Ballainvilliers, France) at 100 or 200 mm/sec. The foot of the flow wave was identified as the point of commencement of the sharp systolic upstroke or as a tangent drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the intersection point of these two lines.24,26 The time delay was measured between the feet of the flow waves recorded at these different points and designated as pulse transit time (t). The distance traveled by the pulse wave was measured over the body surface with a tape measure as the distance between the two recording sites (D). PWV was calculated as PWV=D/t.24,26 For the measurements of PWV between the base of the neck and the femoral artery, the distance from the suprasternal notch to the carotid was subtracted from the total distance to take into account the pulse traveling in the opposite direction; the PWV was then designated as aortic PWV. The reproducibility of the measure for aortic PWV determined as the standard deviation (expressed as percentage of the mean value) was 5.3±3.6%, as has been previously reported.24

Arterial Pressure Pulse Waveform

The aortic or central artery PP waveform in humans has been well characterized and generally shown to manifest an inflection point that divides the pressure wave into an early (P^1) and mid-to-late systolic peak (P^2) (Figure 2). The measured pressure waveform consists of both a forward or incident wave and a backward or reflected wave.11,18,19 P^1 is taken to be the result of the reflected wave returning from peripheral site (or sites) and causing an increase of the PP and SBP.11-13,18,19,23 This increase is the height of the P^1 above P (ΔP in millimeters of mercury).11 ΔP/PP ratio defines an augmentation index (ΔP/PP in percent).11,19,20 As previously demonstrated, the time (Δtp) from the foot of the pressure wave to the foot of late systolic peak has been interpreted to represent the travel time of the pulse wave to peripheral reflecting site (or sites) and its return11-13 (Figure 2). Study of the relation between the aortic pressure waveform and aortic input impedance has shown that a larger secondary rise of PP is associated with an enhanced oscillatory impedance spectrum due to differences in the magnitude of wave reflections or interaction of reflection for different sites, or both.11-13

Radial and carotid artery pressure waveform and amplitude were recorded noninvasively with a pencil-type19-21 probe incorporating a high fidelity Millar strain gauge transducer in the tip of the probe (model SPT-301, Millar Instruments, Houston, Tex.). The Millar strain gauge transducer possesses a small pressure-sensitive ceramic sensor (0.5x1.0 mm) incorporating piezoresistive elements forming two arms of a Wheatstone bridge. The frequency response of the sensor is more than 2 kHz coplanar with a larger area (7 mm diameter) of flat surface, which is in contact with the skin overlying the arterial pulse. The tonometer is internally calibrated (1 mV=1 mm Hg) using a conventional Millar preamplifier (TCB-500, Millar Instruments). Waveforms were recorded on a Gould 8188 recorder (Gould Electronic) at 100 or 200 mm/sec. The instrument is based on the principles of applplanation tonometry as used in ocular tonometry for measuring intraocular pressure.20 In theory, applplanation of a curved surface of a pressure-containing structure equalizes the circumferential stress of the structure wall and allows the sensor to measure true intra-arterial pressure. The accuracy of the probe has been validated in humans by comparing direct intra-aortic pressure recordings with indirectly recorded carotid pressure waves, and directly and indirectly recorded radial artery pressure. Comparisons making use of spectral analysis showed an excellent correlation between direct intra-arterial and indirect recordings.20 Tonometry recordings show a pressure wave with harmonic content that does not significantly differ from that of intra-arterially
recorded waves. In 16 subjects undergoing cardiac catheterization for suspicion of coronary artery disease, we measured blood pressure simultaneously by two methods: invasively at the aortic arch and noninvasively with the Millar micromanometer at the site of the common carotid artery. Significant correlation existed between the carotid and aortic PP (carotid PP 1.05, aortic PP -0.40; r=0.922; p<0.001). In the present study the carotid pressure wave contour was taken to be representative of the pressure wave contour in the ascending aorta and central arteries, since similarity of noninvasive carotid and invasive ascending aortic pulses in individual subjects has also been reported by others. Applanation tonometry requires training to obtain accurate and reproducible waveforms without producing artifacts. Such artifacts can be produced by inadequate angulation between the probe and the vessel axis, transducer movement caused by movement of the patient's or operator's hands, and finally by inappropriate hold-down pressure as described by Kelly et al.

A hand-held probe was placed over the carotid and radial arteries, after localization of the point of maximal arterial pulsation. In ESRD patients the radial artery pulse contour and blood pressure were studied on the arm not wearing arteriovenous shunt. An optimal hold-down pressure was applied to the artery to obtain a readily reproducible waveform of maximal and stable amplitude. For the analysis of the carotid pulse contour, the probe was placed as near as possible to the base of the neck, and the blood pressure and heart rate were measured during the application of the Millar probe. Ten to 15 consecutive pulses were analyzed for each subject.

The late systolic fluctuation occurs later in peripheral arteries than in central vessels, contributing little or nothing to the systolic peak and PP amplitude. The radial artery waveform was therefore analyzed only as regards amplitude and was compared with PP sphygmomanometric values (Figure 1).

The contour of the carotid artery pressure wave was described according to Murgo et al., and the following parameters were measured: PP, P1, late systolic peak amplitude (ΔP=P1-P, in millimeters of mercury), augmentation index (ΔP/PP in percent), and travel time of the reflected wave from the foot of the pressure wave to the inflection point (Δtp) (Figure 2). The left ventricular ejection time (LVET) was measured from the foot of the pressure wave to the diastolic incisure. The pressure wave parameters were analyzed by visual inspection of 10-15 consecutive waves. The analysis was done "blindly" by the same two observers. Intraobserver reproducibility, determined as the standard deviation (expressed as percentage of the mean value) was 4.3% for Δtp and 5.5% for the augmentation index. Interobserver reproducibility was, respectively, 6.1% and 11.2%.

In 32 randomly selected ESRD patients, the carotid pulse contour analysis and aortic PWV were also measured after brief closure (1 minute) of arteriovenous shunt with a cuff inflated 20 mm Hg above SBP.

Echocardiographic Measurements

As previously described, two-dimensionally directed M-mode echocardiography was performed using a Roche Kontron RT 400 apparatus (Roche Lab, Nutley, N.J.), an IRREX ultrasonograph with a 2.25 MHz transducer (Irrex, Kontron Instruments, Montigny le Bretonneux, France) and a Cardio 80 computer (Hewlett-Packard, Elkhart, Ind.). Measurements of aortic root diameter, left ventricular end-diastolic diameter, end-systolic diameter, percent shortening, and velocity of fiber shortening were made according to American Society of Echocardiography recommendations. Left ventricular ejection fraction was estimated by the Teichholz equation. All echocardiographic records were read blindly by the same two observers. The reproducibility of the measures has previously been published.

Statistical Analysis

Data were expressed as mean±SD. Student's t test for unpaired and paired data was used for comparisons. To assess the combined influence of variables on arterial parameters, stepwise linear regression analysis with forward and backward elimination procedures was used. For the multiple regression analysis, control subjects and ESRD patients were pooled and the presence or absence of ESRD was expressed by a dummy variable (1, No; 2, yes). A value of p<0.05 was considered significant. The statistical analysis was performed on a Zenith Z-386/25 computer running ncss 5.1 program.

Results

Subjects

Table 1 shows clinical characteristics of the control subjects and ESRD patients. ESRD patients had a lower weight (p<0.001), were smaller in stature (p<0.001), and had a shorter trunk (p<0.01). The height-to-trunk ratio was similar in ESRD and control subjects. Although DBP and MBP were not statistically different, SBP and brachial artery PP were increased in ESRD patients (p<0.001).

Aortic Pulse Wave Velocity and Carotid Pressure Waveform

The aortic PWV was increased in ESRD patients (1,035±238 versus 930±196 cm/sec; p<0.01) (Table 2). Aortic PWV was correlated with age (r=0.680; p<0.001) and MBP (r=0.396; p<0.001). Radial artery PP determined by applanation tonometry was higher in
Table 2. Carotid Pulse Wave Analysis in End-Stage Renal Disease Patients and in Control Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control subjects</th>
<th>ESRD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial artery PP (mm Hg)*</td>
<td>60.7±16.1</td>
<td>73.7±22.0†</td>
</tr>
<tr>
<td>Carotid artery PP (mm Hg)*</td>
<td>57.3±19.6</td>
<td>73.2±25.7†</td>
</tr>
<tr>
<td>Carotid PP/radial PP (ratio)*</td>
<td>0.93±0.14</td>
<td>0.99±0.15†</td>
</tr>
<tr>
<td>P† (mm Hg)</td>
<td>47.4±14.2</td>
<td>53.6±15.8§</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>7.5±10.5</td>
<td>19.0±15.2†</td>
</tr>
<tr>
<td>∆PP/PP (%)</td>
<td>9.8±15.6</td>
<td>23.2±15.0‡</td>
</tr>
<tr>
<td>Atp (msec)</td>
<td>131±30</td>
<td>109±24†</td>
</tr>
<tr>
<td>Heart period (msec)</td>
<td>909±149</td>
<td>840±145§</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>300±26</td>
<td>310±31</td>
</tr>
<tr>
<td>Aortic PWV (cm/sec)</td>
<td>930±196</td>
<td>1,035±2385</td>
</tr>
</tbody>
</table>

Values are mean±SD.

ESRD, end-stage renal disease; PP, pulse pressure; P†, pressure at inflection point; ∆P=Pµ−P†, amplitude of late systolic peak; ∆PP/PP (%)=(Pµ−P†)/PP, augmentation index, where AP is amplitude of late systolic peak, Pµ is mid-to-late systolic peak, and P† is early systolic peak; Atp, travel time of reflected wave; LVET, left ventricular ejection time; PWV, pulse wave velocity.

*Measurements performed with Millar micromanometer. \( p<0.05; \spadesuit p<0.02; \triangle p<0.01; \diamondsuit p<0.001.\)

ESRD patients (73.7±22.0 versus 60.7±16.1 mm Hg; \( p<0.001).\) Carotid PP was lower in the control group than in the ESRD group (57.3±19.6 versus 73.2±25.7 mm Hg; \( p<0.001).\) Although carotid PP in the control group was lower than radial PP (57.3±19.6 versus 60.7±16.1 mm Hg; \( p<0.001),\) carotid and radial PP were similar in the ESRD group (73.2±25.7 versus 73.7±22.0 mm Hg). The carotid-to-radial PP ratio was lower in the control group than in the ESRD group (0.93±0.14 versus 0.99±0.15; \( p<0.02).\) A positive correlation was observed between age and carotid-to-radial PP ratio (\( p<0.001).\) (Figure 3). The analysis of parameters of the carotid pulse wave contour is shown on Table 2. The ∆Pp was shorter in ESRD patients (109±24 versus 131±30 msec; \( p<0.001).\) The duration of ∆Pp was correlated with aortic PWV (\( p<0.001).\) (Figures 4 and 5), and the presence of ESRD (Table 3).

Discussion

The major conclusions from the present study are 1) that the pulsatile component of blood pressure is increased in patients with ESRD, especially in central arteries; 2) that the increase in PP in the carotid artery (ESRD patients (53.6±15.8 versus 47.4±14.2 mm Hg; \( p<0.01).\) In the two groups a correlation was observed between P† and aortic PWV (\( r=0.624; p<0.001).\) The ∆P was increased in ESRD patients in comparison with control subjects (19.0±15.2 versus 7.5±10.5 mm Hg; \( p<0.001).\) The ∆P/PP was 23.2±15.0% in ESRD patients versus 9.8±15.6% in control subjects (\( p<0.001).\) The ∆P/PP was correlated with aortic PWV, body height, LVET, and the presence of ESRD (Table 4). The LVET was longer in ESRD patients (\( p<0.05\)) despite a shorter heart period (\( p<0.01).\) The ∆P/PP was correlated with the age of patients, but this correlation was dependent on the age-related increase in aortic PWV (Table 4).

Brief closure of arteriovenous shunt induced an increase in blood pressure, in heart period (Nicoladoni-Branham's sign) and LVET (\( p<0.001)\) (Table 5). Carotid PP and ∆P/PP increased during arteriovenous shunt closure, in parallel with an increase in aortic PWV and shortening of ∆Pp. All these alterations were small but significant (\( p<0.001).\)

Echocardiographic Measurements

Results of echocardiographic measurements are given in Table 6. ESRD patients showed a significant increase in left ventricular end-diastolic diameter and aortic diameter (\( p<0.001).\) The percentage of shortening and the velocity of circumferential fiber shortening were lower in ESRD patients but were in the normal range. No correlation was observed between PP, P†, or ∆P/PP and percentage of shortening or ejection fraction. The ∆P/PP was positively correlated with LVET (\( r=0.389; p<0.001).\)

Discussion

The major conclusions from the present study are 1) that the pulsatile component of blood pressure is increased in patients with ESRD, especially in central arteries; 2) that the increase in PP in the carotid artery
in ESRD patients is principally related to increased late systolic peak due to increased pulse wave reflections; and 3) that increased wave reflections in ESRD patients are associated with an increase of aortic PWV and a diminished body height.

Alterations in pulsatile component of blood pressure have been observed in ESRD patients. The increased PP results principally from an increase in SBP, but as shown in previous study, a concomitant small decrease in DBP could also be observed. The tendency for the higher SBP seen in ESRD patients corroborates other clinical and epidemiological observations, including those using conventional and ambulatory blood pressure recordings. In contrast with the gradual decline in the incidence of systolic-diastolic hypertension after a few years of dialysis treatment, the prevalence of systolic hypertension increases over the years. The systolic hypertension is not improved during hemodialysis despite an adequate fluid volume control and is not corrected during the interdialytic period despite antihypertensive treatment.

Measurement of carotid PP and wave contour by applanation tonometry reveals that the alteration in the pulsatile component of blood pressure in ESRD patients is underestimated by sphygmomanometric measurements of brachial artery blood pressure. Indeed, in the control group the radial artery PP is higher than carotid artery blood pressure, whereas in ESRD patients, carotid and radial PP do not differ, and the carotid-to-radial PP ratio is significantly increased in ESRD. The contour of the aortic pressure wave alters as it travels toward the peripheral arteries. In normotensive subjects (27–41 years of age), the PP amplification between aorta and brachial artery is 18–31% and that between aorta and radial artery averages 46%. Changes in PP between central and peripheral arteries depend principally on the nonuniform arterial elasticity and on peripheral wave reflections. With advancing age there

FIGURE 4. Scatterplot shows correlation between aortic pulse wave velocity and travel time of the reflected wave (Δt). ESRD, end-stage renal disease.

FIGURE 5. Scatterplot shows correlation between the patient height and travel time of the reflected wave (Δt). ESRD, end-stage renal disease.
### TABLE 3. Correlation Matrix and Stepwise Regression Analysis for Travel Time of the Reflected Wave (Δtp) as Dependent Variable and Related Variables

<table>
<thead>
<tr>
<th>Related variables</th>
<th>Aortic PWV</th>
<th>Height</th>
<th>ESRD</th>
<th>Heart period</th>
<th>Age</th>
<th>Δtp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic PWV</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>r=0.191</td>
<td>r=-0.221</td>
<td>p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>r=-0.145</td>
<td>r=0.285</td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart period</td>
<td>r=0.680</td>
<td>r=-0.201</td>
<td>r=0.026</td>
<td>r=0.021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>r=-0.598</td>
<td>r=0.561</td>
<td>r=-0.370</td>
<td>r=0.318</td>
<td>r=-0.497</td>
<td></td>
</tr>
<tr>
<td>Δtp</td>
<td>r=0.0001</td>
<td>r=0.0001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Related variables:**
- YES: Aortic PWV (cm/sec), Height (cm), ESRD (1, no; 2, yes), Heart period (msec), Age (yr)
- NO: Atp

**t value:**
- Aortic PWV (cm/sec): -12.1
- Height (cm): 11.3
- ESRD (1, no; 2, yes): -3.0
- Heart period (msec): 1.0
- Age (yr): 0.2

**Probability:**
- Aortic PWV (cm/sec): <0.00001
- Height (cm): <0.00001
- ESRD (1, no; 2, yes): 0.0004
- Heart period (msec): 0.3000
- Age (yr): 0.8063

**%RMSE:**
- Aortic PWV (cm/sec): 42.3
- Height (cm): 37.1
- ESRD (1, no; 2, yes): 2.7
- Heart period (msec): 0.0
- Age (yr): 0.3

**R squared (R^2):** 0.680 (p<0.0001)
**F ratio:** 108.7 (p<0.0001)
**RMSE:** 15.7

Dependent variable, Δtp. Δtp, travel time of reflected wave; PWV, pulse wave velocity; ESRD, end-stage renal disease; RMSE, root mean square error.

### TABLE 4. Correlation Matrix and Stepwise Regression Analysis for Augmentation Index (ΔP/PP %) as Dependent Variable and Related Variables

<table>
<thead>
<tr>
<th>Related variables</th>
<th>Aortic PWV</th>
<th>Height</th>
<th>LVET</th>
<th>ESRD</th>
<th>Age</th>
<th>ΔP/PP %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic PWV</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>r=0.100</td>
<td>r=-0.073</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVET</td>
<td>r=0.191</td>
<td>r=-0.221</td>
<td>r=0.138</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>r=0.05</td>
<td>r&lt;-0.01</td>
<td>r&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>r=0.680</td>
<td>r=-0.201</td>
<td>r=0.285</td>
<td>r=-0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔP/PP %</td>
<td>r=0.493</td>
<td>r=-0.437</td>
<td>r=0.389</td>
<td>r=0.378</td>
<td>r=0.482</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Related variables:**
- YES: Height (cm), Aortic PWV (cm/sec), LVET (msec), ESRD (1, no; 2, yes), Age (yr)
- NO: ΔP/PP %

**t value:**
- Height (cm): -7.7
- Aortic PWV (cm/sec): 6.8
- LVET (msec): 5.2
- ESRD (1, no; 2, yes): 3.1
- Age (yr): 0.7

**Probability:**
- Height (cm): <0.00001
- Aortic PWV (cm/sec): <0.00001
- LVET (msec): <0.00001
- ESRD (1, no; 2, yes): 0.0023
- Age (yr): 0.4617

**%RMSE:**
- Height (cm): 18.4
- Aortic PWV (cm/sec): 14.7
- LVET (msec): 8.8
- ESRD (1, no; 2, yes): 3.0
- Age (yr): 0.2

**R squared (R^2):** 0.5830 (p<0.0001)
**F ratio:** 39.7 (p<0.0001)
**RMSE:** 10.6

Dependent variable, ΔP/PP (%). ΔP/PP (%) = Pₗₗ - Pₑₑ / Pₑₑ, augmentation index where ΔP is amplitude of late systolic peak, Pₗₗ is mid-to-late systolic peak, and Pₑₑ is early systolic peak; PWV, pulse wave velocity; LVET, left ventricular ejection time; ESRD, end-stage renal disease; RMSE, root mean square error.
TABLE 5. Effects of Arteriovenous Shunt Occlusion on Carotid Artery Pulse Pressure and Dynamics

<table>
<thead>
<tr>
<th>Variables</th>
<th>A-V shunt open</th>
<th>A-V shunt occluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>148.3±22.6</td>
<td>152.8±24.9*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78.7±13.8</td>
<td>82.9±16.2*</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>102.2±15.4</td>
<td>105.0±18.1*</td>
</tr>
<tr>
<td>Radial artery PP (mm Hg)†</td>
<td>70.3±21.0</td>
<td>71.7±21.6‡</td>
</tr>
<tr>
<td>Carotid artery PP (mm Hg)†</td>
<td>69.1±22.1</td>
<td>73.4±22.2*</td>
</tr>
<tr>
<td>ΔP/PP (%)</td>
<td>20.8±13.6</td>
<td>23.7±13.9*</td>
</tr>
<tr>
<td>Δtp (msec)</td>
<td>114±25</td>
<td>110±25.3*</td>
</tr>
<tr>
<td>Heart period (msec)</td>
<td>826±98</td>
<td>865±100*</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>311±24</td>
<td>316±25*</td>
</tr>
<tr>
<td>Aortic PWV (cm/sec)</td>
<td>1,011±243</td>
<td>1,064±247*</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=32.

A-V, arteriovenous; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; ΔP/PP (%)=Pmax−Pmin/PP, augmentation index, where ΔP is change in pressure, Pmax is mid-to-late systolic peak, and Pmin is early systolic peak; Δtp, travel time of reflected wave; LVET, left ventricular ejection time; PWV, pulse wave velocity.

†Measurements performed with Millar micromanometer.

*p<0.05; †p<0.001.

and the ratio between carotid and radial PP correlates positively with age. Nevertheless, in comparison with the control group, ESRD patients have an increased carotid-to-radial PP ratio. Since these two groups were similarly aged, these results suggest an acceleration of the age-associated degenerative changes of the aorta in ESRD.

The higher carotid PP is due to an increase in both Pj and late systolic peak (ΔP). The initial pressure rise to the inflection point (Pj) is greater in ESRD, but the magnitude of these alterations in the PP augmentation is limited, accounting for about 35% of the difference in PP observed between the two groups. According to the “waterhammer formula,” which relates pressure fluctuation to flow fluctuation in the absence of wave reflections, the amplitude of Pj depends on the ventricular ejection and the stiffness of the artery.8-11 The higher initial pressure rise in ESRD was not related to differences in the pattern of ventricular ejection but was associated with an increased stiffness of central arteries as suggested by the positive correlation observed between Pj and aortic PWV.

The principal modification causing the increased PP in ESRD patients is the increase of the late systolic peak. This change in the carotid late systolic peak accounted for 65% of the difference in PP between the control and ESRD groups. As has been demonstrated by the comparison of ascending aortic pulse wave contour and aortic input impedance,11-13 the development and amplitude of late systolic peak in central arteries depend on the timing and intensity of wave reflections. In the present study, the increase in late systolic peak was associated with an early return of reflected pressure wave with a significantly shorter travel time (Δtp). The Δtp is theoretically determined by the distance (L) of the pulse travel to the reflecting site (or sites) and the PWV as11:

L=PWV×Δtp/2

where fmin is the frequency of the first minimum of the modulus of systemic input impedance. From these equations

1/(2Δtp)=fmin

can be derived. In the present study Δtp was correlated with aortic PWV and with the patients' height. Experimental studies have shown that the frequency of fmin is determined by the PWV and the distance between the recording and lower body reflecting sites8,9 and that there is an inverse relation between this frequency and body length.32 The Δtp was shorter in ESRD patients in comparison with control subjects and could be attributable to two factors: 1) a difference in body size with lesser body height and smaller distance to the reflecting sites in ESRD patients and 2) a higher aortic PWV in ESRD patients.

Shorter height observed in ESRD patients is related to growth retardation often observed in azotemic children and in adults with nephropathies starting in childhood.

The mechanisms responsible for the increased aortic stiffness in ESRD patients are not clear. The principal determinants of the PWV are age and blood pressure,8,24-26 but the increase in PWV in ESRD patients cannot be explained by differences in age or blood pressure. Alterations in aortic stiffness are not related to the common metabolic disturbances observed in ESRD.24-25 Avolio et al8 have shown that high salt intake by itself could be a factor increasing arterial stiffness. The possibility is that salt and water retention, which is a frequent complication of ESRD, could independently of blood pressure induce cardiovascular alteration, including increased arterial stiffness.

The increase of the late systolic peak was associated with longer LVET (Table 4). The longer LVET in ESRD patients could be the consequence of increased wave reflections8,9 and their effect on increased late systolic pressure and end-systolic stress. On the other
hand, a longer systolic ejection time could be a favorable condition for the reflected waves to merge with the late systolic part of the ejection wave and for an amplification. Therefore, the association between LVET and ΔP/PP ratio could be the consequence as well as one of the causes of the PP amplification.

According to Murogo et al,11 the higher late systolic peak was associated with more oscillatory impedance spectra due to more intense arterial wave reflections. An increase in peripheral resistances enhances the wave reflections.12 The peripheral resistances were not increased in ESRD patients since MBP was similar to the control group and cardiac output was higher (increased heart rate and higher ejection volume) due to arteriovenous shunt and anemia.37 It has been shown that opening of arteriovenous shunt in central vessels creates an "open-end" reflecting site close to the heart with wave reflections occurring too early to be apparent in the central arteries, and the shunt had little effect on pressure wave contour and amplitude.38 Results of the present study are in agreement with this observation. Indeed, the closure of a peripheral arteriovenous shunt in ESRD patients induced minimal changes in arterial pressure wave contour and amplitude.38 The reflection coefficient was not estimated in the present study, but changes in aortic diameters24 and stiffness support the view that the reflection coefficient could be altered in ESRD, accounting for the independent association of ΔP/PP with ESRD (Table 4).

In conclusion, the present study shows that the pulsatile component of blood pressure is abnormal in ESRD patients and that, for the same MBP, the PP and SBP are increased in these patients. The increased carotid PP observed in ESRD is related to an increased wave reflection and an early return of the reflected wave, causing an increase in the late systolic peak. The principal factors associated with PP amplification observed in ESRD patients are: 1) an increased aortic PWV due to an increased stiffness of the arterial walls and 2) a lesser body height resulting in a reduced "effective" length of the vasculature.

References

34. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF: Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: Comparison between urban and rural communities in China. Circulation 1985; 71:202–210
Increased systolic pressure in chronic uremia. Role of arterial wave reflections.
G London, A Guerin, B Pannier, S Marchais, A Benetos and M Safar

*Hypertension.* 1992;20:10-19

doi: 10.1161/01.HYP.20.1.10

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/20/1/10

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/