

Contribution of Volume Overload and Angiotensin II to the Increased Pulse Wave Velocity of Hemodialysis Patients

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Abstract. Aortic compliance is decreased in patients with end-stage renal disease. This malfunction contributes to high aortic systolic pressures and thus to the development of left ventricular hypertrophy. It was hypothesized that besides structural vascular changes, functional changes as a result of hypervolemia and increased vasoconstrictor activity, in particular angiotensin II, play a role in decreasing aortic compliance. Nineteen hemodialysis patients were studied before and 24 h after they had been dialyzed to dry weight. Applanation tonometry of peripheral arteries was used to estimate aortic pulse wave velocity (PWV), known to depend on aortic compliance, and aortic systolic pressure augmentation (augmentation index [Aix]). Predialysis aortic PWV was increased in the dialysis patients compared with matched healthy subjects (9.9 ± 3.1 versus 7.5 ± 1.1 m/s; $P < 0.05$). The Aix was also increased (35 ± 6 versus 25 ± 10 ; $P < 0.05$). Volume reduction with dialysis had no significant effect on PWV (9.3 ± 1.5 m/s), but the Aix decreased (28 ± 7 ; $P < 0.05$). A subset of 10 patients were restudied after 1 wk of angiotensin-converting enzyme

inhibition (ACEi) with enalapril 5 mg once daily. ACEi decreased both predialysis as postdialysis BP but had no effect on pulse pressure and heart rate, which remained elevated compared with healthy subjects. ACEi also decreased predialysis aortic PWV, from 11.0 ± 3.5 to 9.1 ± 2.1 m/s ($P < 0.05$) but had no significant effect on Aix. During treatment with ACEi, the same volume reduction with dialysis decreased aortic PWV further to 8.0 ± 1.4 m/s ($P < 0.05$), a figure not different from PWV in healthy subjects. Aix decreased to an even slightly subnormal value (12 ± 23 ; $P < 0.05$). It was concluded that volume overload and angiotensin II both contribute to elevated PWV and Aix in dialysis patients. Volume reduction and ACEi both improve the aortic PWV and Aix. Combined volume reduction and ACEi has an enhanced effect that, in the present patients, was so large that PWV and Aix were no longer elevated. Monitoring and correcting of arterial pressure waves is feasible and may be an important tool in the treatment of patients with end-stage renal disease.

Hemodialysis patients have increased cardiovascular morbidity and mortality (1,2). Aortic compliance is reduced, which leads to increased aortic systolic pressures by the decreased cushioning function and by the increased pulse wave velocity (PWV) (3–5). The latter accelerates arterial wave reflections, which are summated with the propagated pressure waves (3,5). This contributes to the development of left ventricular hypertrophy (4). Tonometry of peripheral arteries, as developed by O'Rourke and colleagues (6,7), is a useful tool to measure both PWV and the summation of the propagated and reflected aortic pressure waves. Recently, increased aortic PWV was found to be an independent predictor of cardiovascular mortality in dialysis patients (8).

The cause of decreased arterial compliance and distensibility in dialysis patients is probably multifactorial. Structural changes, related to atherosclerosis and evidenced by increased

arterial wall thickness (9–11), contribute to the arterial stiffening. Functional abnormalities, such as angiotensin II-induced vasoconstriction and volume overload, also play a role. Indeed, angiotensin-converting enzyme (ACE) inhibition has been shown to reduce PWV acutely in patients with essential hypertension (12) or end-stage renal disease (ESRD) (13). Volume overload increases arterial stiffness by increasing arterial distension (Laplace's law) (14,15). Interdialytic weight gain is associated with increased aortic PWV (16). However, the few studies dedicated to this issue found no change in PWV or arterial compliance directly after volume correction by ultrafiltration (14,17). Conceivably, a favorable effect of volume correction on arterial compliance is nullified by the simultaneous stimulation of angiotensin II and thus may become apparent only if this response is inhibited. However, this has not been studied. Finally, correction of volume overload may also decrease systolic pressure augmentation by decreasing ventricular ejection duration. Indeed, it was shown recently that most patients respond with a decrease of the elevated pressure augmentation immediately after hemodialysis (5).

We studied the effect of volume withdrawal on PWV and aortic pressure augmentation with tonometry in hemodialysis patients. The interaction with angiotensin II was explored by repeating volume withdrawal during the use of an ACE inhibitor. The results were compared with measurements in matched

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healthy subjects. This format allowed us to estimate the contribution of functional factors to the decreased arterial compliance in dialysis patients.

Materials and Methods

Patients

We studied 19 patients (14 men) who were on maintenance hemodialysis. The mean age was 60 ± 9 yr (range, 49 to 74 yr), and the mean duration of hemodialysis was 13 ± 10 mo (range, 3 to 43 mo). Hypertensive medication, used by four subjects, was stopped at least 14 d before the study. In three patients, β -blockers were continued. No diabetic patients were included. All 19 patients participated in study 1, *i.e.*, vascular function before and after withdrawal of volume excess (see below). A subset of 10 patients (7 men, 1 on β -blocker) underwent additional studies during ACE inhibition (study 2). The mean age of this group was 59 ± 9 yr (range, 50 to 72 yr), and the mean duration of dialysis was 10 ± 7 mo (range, 3 to 26 mo). The data were compared with findings obtained in 13 matched healthy subjects (10 men). The age in this group averaged 59 ± 9 yr (range, 48 to 75 yr).

Study Design

The patients were dialyzed two or three times weekly with an AK-100 or AK-200 (Gambro, Stockholm, Sweden) using polysulfone triacetate membranes (Fresenius Medical Care, AG, Bad Homburg, Germany). In study 1, the patients were evaluated before and after a regular dialysis, during which volume was withdrawn until dry weight (estimated from standard criteria, *i.e.*, postdialysis BP, overt edema) was obtained. To avoid the effects of volume disequilibrium and acute vasoconstriction after ultrafiltration, the postdialysis measurements were done 24 h after dialysis. The participants were urged to maintain postdialysis weight by minimizing salt and water intake. In study 2, the patients underwent, in addition, a similar set of measurements while using an ACE inhibitor. After completion of study 1, they started enalapril 5 mg once daily and were studied again 7 to 10 d later. In three patients, who previously had been using ACE inhibition, the order of the two study phases was reversed. The healthy control subjects were evaluated once. The measurements (see below) were made in a quiet room with controlled air temperature (approximately 22°C). The protocol was approved by the institutional Ethical Committee for Studies in Humans. All participants gave their informed consent.

Measurements

Brachial artery BP was measured in the nonfistula arm with a conventional sphygmomanometer. Phase V Korotkoff sound was taken for diastolic BP. The mean of three readings was used. The mean arterial pressure (MAP) was determined by integration of the radial artery pressure wave contour recorded by applanation tonometry (see below).

The SphygmoCor system (PWV system and BP analysis system; PWV Inc., Sydney, Australia) was used to assess PWV and analyze the arterial pulse contours. Pulse contours were obtained by applanation tonometry at the carotid and radial arteries (nonfistula side) and femoral artery. With this technique, the artery is pressed gently against a hard underground (bone) (7) with a pencil-type probe that incorporates a high-fidelity strain-gauge transducer at the tip with a small pressure-sensitive ceramic sensor area (Millar Instruments, Houston, TX). To determine PWV, we recorded pressure waves at two sites sequentially: carotid-femoral for aortic PWV and carotid-radial for the brachial PWV. Wave transit time was calculated by the system software, using the R-wave of simultaneously recorded ECG

as reference frame (18). The distance traveled by the pulse wave was measured over the body surface as the distance between the recording sites at the femoral or radial artery to the suprasternal notch minus the distance from the recording site at the carotid artery to the suprasternal notch (D), as has been described by others (18). PWV was calculated as $PWV = D/t$. We measured the PWV over 10 consecutive heartbeats to cover a complete respiratory cycle. We used the average of three measurements. The reproducibility of this method is high (18).

Pulse Wave Analysis

We used the SphygmoCor system for analysis of the radial and carotid pressure wave contour. The average of three recordings was used. Radial systolic and diastolic BP was assumed to be equal to brachial systolic and diastolic BP. Mean BP was calculated as the area under the curve of the radial pressure waveform. The ascending aortic pressure waveform was constructed with a validated transfer function from the carotid pressure wave contour (19) assuming a similar MAP throughout the arterial system (6). The augmentation index was calculated as the height of the late systolic peak above the inflection point, divided by the aortic pulse pressure (18). Cardiac supply was estimated by calculating the diastolic pressure time index (*i.e.*, the integral of pressure during diastole), which has been shown to be related to coronary oxygen supply potential (20). Cardiac demand was estimated by calculating the systolic tension time index (*i.e.*, the integral of pressure and time during systole), which has been shown to be related to cardiac oxygen consumption (20). The balance between supply and demand is represented by the ratio of diastolic pressure time index/systolic tension time index, the subendocardial viability index (11,20).

Statistical Analyses

Data are expressed as mean \pm SD. Paired two-sided *t* tests were used for comparison of the results at the different points in time. $P < 0.05$ was taken to indicate statistical significance. The main target of this study was to determine whether the elevated aortic PWV in dialysis patients can be improved. A measure for the clinical relevance of the magnitude of a PWV decrease is the finding by Blacher *et al.* (8) that the relative risk for an increased mortality in hemodialysis patients is 1.4/1 m per s PWV increase. The reported SD (which has been confirmed by us) of the difference between two repeated PWV measurements on different days is 0.69 (21), indicating that a decrease in aortic PWV similar to this SD is clinically relevant. Using this value, it can be calculated that the power of detecting a clinically relevant and statistically significant difference in 10 subjects is 0.80.

Results

Study 1: Effects of Volume Reduction Alone

As indicated in Table 1, central and brachial BP and pulse pressure, heart rate, aortic PWV, and AIx all were significantly elevated compared with the healthy subjects. The viability index was decreased. The mean brachial PWV was high as well, but the difference with the healthy subjects was not significant ($P = 0.17$). Volume reduction with hemodialysis resulted in a decrease in body weight; central and brachial systolic, mean, and diastolic BP; pulse pressure; ejection duration; and AIx. However, central and brachial systolic BP and pulse pressure remained elevated compared with the healthy control subjects. Mean aortic PWV decreased, but this change was not significant ($P = 0.16$). Brachial PWV was unchanged.

Table 1. Study 1: 19 patients studied before and 24 h after hemodialysis^a

Parameter	Before HD	After HD	Control Subjects
Weight (kg)	76.8 ± 11.2	74.8 ± 10.6 ^c	76.8 ± 10.2
Height (cm)	173 ± 10	—	177 ± 7
SBP (mmHg)	148 ± 17 ^b	132 ± 13 ^{b,c}	122 ± 10
MAP (mmHg)	105 ± 17 ^b	95 ± 11 ^c	92 ± 7
DBP (mmHg)	83 ± 17 ^b	76 ± 10 ^c	75 ± 5
PP (mmHg)	65 ± 15 ^b	56 ± 12 ^{b,c}	47 ± 8
CSBP (mmHg)	132 ± 15 ^b	120 ± 15 ^c	112 ± 10
CDBP (mmHg)	82 ± 16	76 ± 10 ^c	75 ± 6
CPP (mmHg)	50 ± 16 ^b	45 ± 13 ^b	37 ± 8
Heart rate (BPM)	71 ± 12 ^b	74 ± 11 ^b	60 ± 6
Ejection duration (ms)	325 ± 32	303 ± 25 ^c	323 ± 81
Aortic PWV (m/s)	9.9 ± 3.1 ^b	9.3 ± 2.5 ^b	7.5 ± 1.1
Radial PWV (m/s)	9.1 ± 1.6	9.1 ± 1.5	8.4 ± 1.2
Augmentation index	35 ± 6 ^b	28 ± 7 ^c	25 ± 10
Viability index	1.39 ± 0.30 ^b	1.48 ± 0.28 ^b	1.69 ± 0.18

^a Data are compared with matched healthy subjects. HD, hemodialysis; SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP; PP, pulse pressure; C, central; PWV, pulse wave velocity.

^b $P < 0.05$ compared with control subjects.

^c $P < 0.05$ compared with predialysis.

Volume correction tended to increase heart rate ($P = 0.06$) and viability index ($P = 0.07$).

Study 2: Effects of Volume Reduction and ACE Inhibition

The studied patients were a subset from study 1, and predialysis data were comparable as in study 1 (Table 2). The changes induced by volume reduction alone in this subset were similar as seen for the whole group. The numerical decrease in aortic PWV was greater in this subset, but again, this change did not reach significance ($P = 0.09$). Repetition of the study during treatment with the ACE inhibitor enalapril showed the following effects. First, predialysis data, *i.e.*, in the absence of volume correction, showed that ACE inhibition tended to decrease central and brachial systolic, mean, and diastolic BP (P values between 0.05 and 0.09) but had no effect on pulse pressure. Despite the latter, ACE inhibition decreased aortic PWV and brachial PWV. ACE inhibition also decreased AIx, without changing the viability index. Second, when volume reduction was applied during ACE inhibition, there was a further decrease in BP parameters, including pulse pressure, and a further reduction of aortic PWV, without change in brachial PWV. The AIx decreased further, and the viability index increased. The changes induced by the combination of volume correction and ACE inhibition were so large that, in fact, the systolic BP, pulse pressure, aortic PWV, and AIx became normal. Differences with the healthy control subjects were that heart rate remained increased, diastolic pressure had decreased below normal, and the viability index remained somewhat decreased.

PWV and pulse pressure are measured independently, and both are related to arterial compliance. We therefore also studied their interrelation. We assumed that ACE inhibition

could influence this relation, because it reduced MAP while having relatively little influence on BP. Close correlations were found for PWV and brachial pulse pressure ($r = 0.72$, $P < 0.0001$; Figure 1). During ACE inhibition, this relation ($r = 0.71$, $P < 0.001$) tended to be shifted to a lower level of BP, but the difference between the relations was not significant. Similar relations were found for aortic pulse pressure and PWV ($r = 0.62$, $P < 0.0001$; during ACE inhibition, $r = 0.71$, $P < 0.0001$).

Discussion

The main findings of this study are that (1) aortic PWV and AIx measured with tonometry are elevated in hemodialysis patients, (2) both volume correction and ACE inhibition decrease the aortic PWV and AIx, (3) the effect of volume correction on aortic PWV becomes apparent especially if performed during ACE inhibition, and (4) the largest reductions in aortic PWV and AIx are found after simultaneous volume correction and ACE inhibition. In the present subjects, the effects of combined volume reduction and ACE inhibition were so large that PWV and AIx were no longer increased compared with healthy matched subjects.

The group of London and Safar in Paris showed convincingly that arterial compliance, measured with echo Doppler techniques or tonometry, is decreased in patients with ESRD (3,4). The significance of this abnormality lies in its prediction of cardiovascular mortality (8,22). There is little doubt that besides structural changes (9–11), hypervolemia and increased activity of the renin-angiotensin system can play a role (11,13,16,23) and that acute volume changes will influence renin activity. However, we are not aware of systematic studies of short-term volume correction on vascular function without and with ACE inhibition in hemodialysis patients.

Table 2. Study 2: paired data of 10 patients studied before and 24 h after hemodialysis, in the absence or presence of ACE inhibition

Parameter	Before HD	After HD	Before HD + ACEi	After HD + ACEi	Control Subjects
Weight (kg)	74.4 ± 13.0	72.4 ± 12.4 ^c	73.9 ± 13.0	72.4 ± 13.0 ^{c,f}	76.8 ± 10.2
Height (cm)	173 ± 11	—	—	—	177 ± 7
SBP (mmHg)	152 ± 18 ^b	133 ± 12 ^{b,c}	139 ± 16 ^b	120 ± 12 ^{c,e,f}	122 ± 10
MAP (mmHg)	108 ± 18 ^b	95 ± 10 ^c	95 ± 11	87 ± 10 ^{c,f}	92 ± 7
DBP (mmHg)	84 ± 19	75 ± 11 ^c	73 ± 10	67 ± 6 ^{b,c,f}	75 ± 5
PP (mmHg)	67 ± 19 ^b	58 ± 15 ^{b,c}	66 ± 18 ^b	53 ± 11 ^{c,f}	47 ± 8
CSBP (mmHg)	136 ± 18 ^b	117 ± 12 ^c	122 ± 17	106 ± 12 ^{c,f}	112 ± 10
CDBP (mmHg)	85 ± 19	75 ± 10 ^c	73 ± 10	68 ± 6 ^{b,c,f}	75 ± 6
CPP (mmHg)	54 ± 20 ^b	46 ± 16	52 ± 20 ^b	39 ± 10 ^{c,f}	37 ± 8
Heart rate (bpm)	76 ± 11 ^b	77 ± 9 ^b	73 ± 11 ^b	77 ± 8 ^b	60 ± 6
Ejection duration (ms)	318 ± 21	301 ± 24 ^c	322 ± 29	291 ± 29 ^c	323 ± 81
Aortic PWV (m/s)	11.0 ± 3.5 ^b	9.8 ± 3.0 ^b	9.1 ± 2.1 ^{b,d}	8.0 ± 1.4 ^{c,e,f}	7.5 ± 1.1
Brachial PWV (m/s)	9.4 ± 1.4	9.0 ± 1.3	8.3 ± 1.0 ^d	8.2 ± 1.8 ^{e,f}	8.4 ± 1.2
Augmentation index	33 ± 6	27 ± 7 ^c	26 ± 14	12 ± 23 ^{c,f}	25 ± 10
Viability index	1.27 ± 0.24 ^b	1.40 ± 0.21 ^{b,c}	1.31 ± 0.18 ^b	1.46 ± 0.18 ^{b,c,f}	1.69 ± 0.18

^a Data are compared to matched healthy subjects. HD, hemodialysis; ACEi, angiotensin-converting enzyme inhibition; SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP; PP, pulse pressure; C, central; PWV, pulse wave velocity.

^b $P < 0.05$ compared with control subjects.

^c $P < 0.05$ postdialysis compared with predialysis.

^d $P < 0.05$ compared with predialysis without ACEi (effect of ACEi before volume reduction).

^e $P < 0.05$ compared with postdialysis without ACEi (effect of ACEi after volume reduction).

^f $P < 0.05$ compared with predialysis without ACEi (combined effect of volume reduction and ACEi).

The assumption that acute variations of angiotensin II activity affect arterial compliance is in line with the observation by others that a single dosage of the ACE inhibitor quinapril can decrease the elevated aortic PWV of hypertensive hemodialysis patients in parallel with BP (11). This acute effect of quinapril must be distinguished from the favorable effects that long-term ACE inhibition may have on structural arterial abnormalities that increase arterial stiffness (24,25). Our present observation that a few days of enalapril also induced a fall in aortic PWV probably is an acute functional effect as well, because this period will be too short to cause significant structural vascular remodeling. It has been hypothesized that the relative lack of significant arterial changes during diuretic therapy (26,27) is due to the opposing effect of vasoconstrictor stimulation (23). Although this chronic model is a different situation than acute volume correction with hemodialysis, the principle is the same in that the effect of volume correction on arterial function can be counteracted by vasoconstrictors.

We found in study 1 that volume correction alone had no effect on aortic PWV, even though BP decreased. In the subgroup of study 2, volume correction caused a numerical decrease in aortic PWV, but this was not significant. It is unlikely that the lack of a significant decrease in aortic PWV was due to the small number of patients, because the power of this observation was only 0.31 in study 2 and similarly low (0.17) with twice as many patients of study 1. Instead, a significant decrease in aortic PWV was found when volume correction was carried out during treatment with an ACE

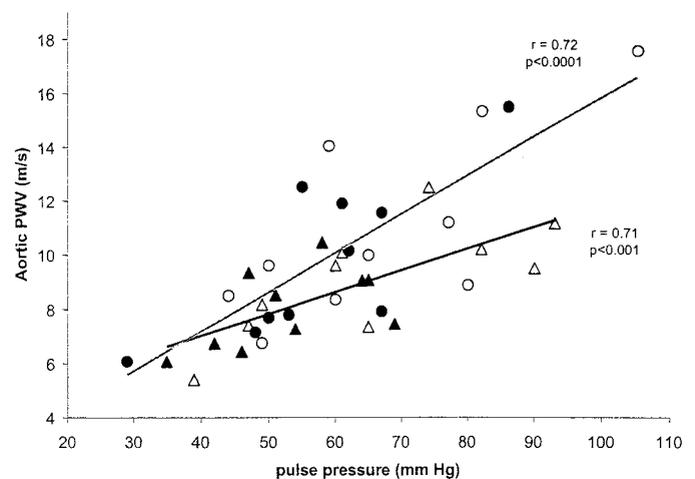


Figure 1. Relationship between brachial pulse pressure and aortic pulse wave velocity. Data were obtained in 10 patients without angiotensin-converting enzyme (ACE) inhibition before (○) and after (●) volume reduction with dialysis (■; $r = 0.72$, $P < 0.0001$) and with ACE inhibition before (△) and after (▲) volume reduction with dialysis (—; $r = 0.71$, $P < 0.001$). The difference between the two correlations is not significant.

inhibitor. The power of that observation was 0.87, in agreement with our prediction of power to find a consistent change of approximately 1 m/s in a group of 10 patients. These findings suggest that volume correction by itself may indeed

reduce the elevated PWV but that this effect is opposed by concomitant changes in angiotensin II, yielding inconsistent individual results. Conceivably, baroreflex-induced adrenergic stimulation by volume withdrawal may similarly oppose effects on arterial function. Adrenergic activity also often is increased in patients with ESRD (28,29). In this respect, it is relevant that ACE inhibition can normalize this adrenergic overactivity but that such treatment leaves the function of the arterial baroreflex intact (29). Our findings may explain why previous studies showed no significant decrease in aortic PWV before and after dialysis (17). A similar mechanism may account for the lack of improvement after ultrafiltration of the reduced carotid artery compliance and distensibility as assessed with echo Doppler (14), because that is also controlled acutely by angiotensin II (30). To what extent the effects of enalapril were due to stimulation of bradykinin rather than impaired angiotensin II production is unclear. This question awaits studies with angiotensin II receptor blockers. Our data do not suggest that volume reduction alone cannot improve arterial function. To be able to show this probably requires larger volume corrections.

Brachial artery pulse pressure, like PWV, is a strong independent predictor of cardiovascular mortality (31,32). Central pulse pressure is correlated with left ventricular mass (5,11). We found a close correlation between changes in pulse pressure and aortic PWV. This underscores the idea that both depend on aortic compliance (6). Because these variables are measured independently, this association can be regarded as an internal control on the study results. During ACE inhibition, the correlation tended to be shifted to lower PWV, probably reflecting a lower absolute level of BP.

Brachial artery PWV was slightly increased, but the difference with healthy control subjects was not significant. A slight or insignificant increase in brachial PWV was also found by others (33,34). This artery is considered to remain free from atherosclerosis, and its reported decreased distensibility in patients with essential hypertension relates to the increased distending BP rather than to structural changes (35). However, in patients with chronic renal failure, the compliance of the brachial artery may be decreased as a result of altered intrinsic elastic properties (36), associated with fibroelastic intimal thickening and calcifications (9). In the present study, volume reduction had no effect on brachial artery PWV, even when it was applied during ACE inhibition and caused a decrease in BP. However, ACE inhibition itself induced a consistent decrease to a completely normal value. This indicates that also in this artery, functional changes can contribute to a decrease in compliance and that the role of angiotensin II may exceed its effect on BP.

We also studied aortic pressure augmentation. In dialysis patients, AIx is increased as a result of a combination of increased stroke volume and ejection time (determinants of the antegrade pressure wave) and the increased PWV (determinant of the retrograde pressure wave) (3,4,11). The elevated AIx is a major determinant of the cardiac afterload and therefore for the development of left ventricular hypertrophy (4,5,11,33). Pressure augmentation has a negative effect on the cardiac

oxygen supply and demand ratio (22). This ratio, or (subendocardial) viability index, is decreased in hemodialysis patients (11,37). Baseline AIx was clearly elevated in the present patients, too. In fact, the AIx was even underestimated as a result of the higher heart rate, which tends to decrease AIx (approximately 4% per 10 beats/min increase (38)). A recent study showed a decrease in AIx in most patients immediately after dialysis (5). However, in fewer than half of the patients, this decrease was still present at 24 h after dialysis, which was the time that we did our measurements. Another recent study showed a slight increase in viability index during a regular hemodialysis-ultrafiltration session (37). This change depended entirely on reduction of oxygen demand, associated with a fall in systolic pressure, and ejection time (37). We found similar changes after dialysis-induced volume correction, *i.e.*, a decrease in AIx, and increase in viability index. Two points deserve attention. First, volume correction improved AIx and the viability index also in the absence of ACE inhibition. Because PWV did not decrease significantly in this situation, the observed decrease in ventricular ejection time was probably critical for this effect (37). Second, ACE inhibition improved the AIx and the viability index further. This can be explained by the decrease in PWV and perhaps also by decreased intensity of the aortic reflected wave (13).

Perhaps the most striking result in our study was that when volume correction was applied during the use of enalapril, aortic PWV became normal. This was an unexpected finding. It is widely known that patients with end-stage renal failure have structural arterial abnormalities (9–11), which correlate with decreased arterial compliance and increased aortic PWV (11). As recently reported, the increased aortic PWV in dialysis patients is correlated with the intensity of aortic calcifications (24,39). It is excluded that a short course of ACE inhibition can restore these structural abnormalities, and therefore we had expected at least some residual arterial dysfunction. Some points may be relevant. First, the combination of volume control and ACE inhibition adequately controlled the hypertension in our patients. In fact, the diastolic pressure was a little below normal. Studies in patients with essential hypertension have shown that arterial distensibility, although elevated at high BP levels, is not different from that in normotensive individuals at the same BP range (35,40). This suggests that arterial wall hypertrophy, present in the large majority of patients with chronic hypertension, is not necessarily a determinant of arterial stiffness (41). To what extent this holds in patients with end-stage renal failure is unclear. For solving this question, larger numbers of patients have to be studied. Second, it should be realized that the healthy control subjects in our study did not use an ACE inhibitor.

We should realize that the methodology of estimating aortic pressure changes from peripheral artery tonometry is an indirect one, and this, in fact, may be regarded as a limitation of our study. The small number of subjects, perhaps not comprising the whole range of vascular dysfunction that exists in patients with ESRD, is another limitation. Nonetheless, it is very clear that aortic PWV and AIx respond quite favorably to volume correction and ACE inhibition. It is also clear that

increased PWV and AIx, measured with peripheral artery tonometry as performed in our study, are strong predictors of cardiovascular mortality in patients with ESRD (5,8). Therefore, we suggest that monitoring and, if possible, normalizing artery pressure waves may be an important new tool in the treatment of patients with ESRD.

In conclusion, both volume overload and angiotensin II contribute to the decreased arterial compliance and increased AIx in hemodialysis patients. Both volume correction and ACE inhibition improve these abnormalities to some extent, but when applied in combination, the best result, even normalization in our patients, is obtained. Monitoring and correction of arterial pressure waves may prove to be an important issue in the treatment of patients with ESRD.

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