hypertension in ESRD.1,2 It is well accepted that hypertension is an important factor in the development and maintenance of hypertension in renal failure.1

Abstract—The importance of volume status on blood pressure in hemodialysis patients has long been recognized. We hypothesized that the enhanced volume dependency of blood pressure is partly determined by ventricular stiffness at end systole. A total of 115 long-term hemodialysis patients were invited to receive a comprehensive, noninvasive cardiovascular examination. End-systolic elastance was determined by using a novel, noninvasive echo-Doppler technique. The positive ratios of the interdialytic systolic blood pressure change vs weight gain during the subsequent 25 hemodialysis sessions were averaged to obtain the volume sensitivity index (mm Hg/kg). The averaged interdialytic weight gain per fat-free mass was correlated significantly with averaged percent change in systolic blood pressure ($r=0.45$, $P<0.001$). The estimated end-systolic elastance at baseline was significantly correlated with subsequently observed volume sensitivity index (volume sensitivity index = $[1.17 \times \text{end-systolic elastance}] + 6.4$ ; $r=0.34$, $P=0.001$). End-systolic elastance was also significantly correlated with various vascular function parameters, including effective arterial elastance ($r=0.48$, $P<0.001$), pulse wave velocity ($r=0.30$, $P=0.001$), carotid augmentation index ($r=0.31$, $P<0.001$), and aortic compliance ($r= -0.49$, $P<0.001$). The results suggest that end-systolic elastance, a direct measure of left ventricular mechanical properties at end systole, is coupled to arterial mechanical properties and predicts the extent of subsequent interdialytic systolic blood pressure rise relative to weight gain. Therefore, ventricular stiffness at end systole is a determinant of the enhanced volume sensitivity of blood pressure in hemodialysis patients.

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Key Words: renal dialysis, hypertension, renovascular, blood pressure, blood volume, arteriosclerosis, cardiac function

Hypertension is present in $\approx 80\%$ to $90\%$ of patients by the time chronic renal failure progresses to end-stage renal disease (ESRD) and is one of the major risk factors that contributes to the development of cardiovascular disease in patients undergoing dialysis.1,2 A rational approach to this issue necessitates insight into the mechanisms that underlie hypertension in renal failure.1

Volume expansion has long been considered the most important factor in the development and maintenance of hypertension in ESRD.1,2 It is well accepted that hypertension can be controlled by adequate dialysis and the maintenance of dry weight in 85% to 90% of dialysis patients. In one center in Tassin, France, almost 98% of the patients were normotensive while receiving no medication by long, slow dialysis.3,4 In contrast, $\approx 50\%$ of hypertensive patients without renal function impairment are considered salt-sensitive and respond to diuretic therapy alone.5,6 Thus, it is obvious that the sensitivity of blood pressure change to volume expansion or removal in patients with ESRD is increased compared with hypertensive patients with normal renal function. The mechanisms by which volume expansion leads to an elevation in blood pressure are conventionally attributed to an increase in cardiac output and an inappropriately high systemic vascular resistance.1

We have demonstrated that arterial stiffening with age is matched by ventricular systolic stiffening, indexed by the end-systolic pressure-volume relation (ie, left ventricular end-systolic elastance, $E_{es}$).7 The two effects contribute to elevating systolic blood pressure (SBP) sensitivity to acutely altered chamber filling7 and might explain the enhanced pressure lability with diuretics and postural shifts in the elderly. Although $E_{es}$ implies the sensitivity of SBP to acute volume reduction, it is unknown whether $E_{es}$ also predicts changes in SBP with long-term volume change. On the other hand, increased arterial stiffness as a hemodynamic overload with consequent and parallel cardiac and vascular adapta-
A total of 115 patients with ESRD who had been undergoing regular hemodialysis for at least 6 months were enrolled (Table 1). They were prescribed 3 g dietary salt per day and had not been receiving any antihypertensive medication or lipid-lowering therapy for at least 2 months. All patients received 4-hour dialysis sessions 3 times weekly with a dialysate containing 140 mEq/l sodium.11

Cardiac and Vascular Structure and Function
The interdialysis supine brachial artery SBP and diastolic blood pressure (DBP) were measured with an oscillometric device. The following dimensions were measured online from the 2D, guided M-mode echocardiograph: aortic root diameter, left atrial dimension, left ventricular internal dimension at end systole and end diastole, and thickness of the interventricular septum and left ventricular posterior wall. Ejection fraction and left ventricular mass were calculated. Stroke volume (SV) was measured by pulse wave Doppler echocardiography. Cardiac index was calculated from SV and heart rate.

E es is a key determinant of cardiac systolic function and ventriculo-arterial interaction not susceptible to loading changes.12 E es was estimated with a recently proposed single-beat method.13,14 The right common carotid artery diameter at diastole and the intimal-medial thickness of the posterior wall were measured from the 2D echocardiographic images.15 Various aspects of the function of large arteries were indexed by the trunk pulse wave velocity,15 aortic compliance (AC), effective arterial elastance (E a ), and carotid augmentation index (AI).11 AC was the ratio of SV to pulse pressure.15 E a was the ratio of end-systolic pressure (P es ) to SV.16 Additionally, peripheral vascular resistance was calculated as the ratio of mean blood pressure to cardiac output.

Hydration Status
Inferior vena cava diameter was measured by 2D-guided M-mode echocardiography.17 Total body water and fat-free mass were measured by the multifrequency bioimpedance method.18

Volume Sensitivity of Arterial Pressure
Predialysis (final interdialysis blood pressure) and postdialysis (initial interdialysis blood pressure) seated blood pressure and body weight were recorded for 25 consecutive dialysis sessions with a mercury sphygmomanometer and a beam scale.10 For each interdialysis session, the ratio of blood pressure gain per body weight gain was calculated. The average of all positive ratios (average, 16 sessions) during the 25 sessions represented the observed volume sensitivity index (V inx) for the individual. Patients were grouped as having high or low volume sensitivity when their values of V inx were in the upper or lower tertile, respectively.

In a subset of 34 patients, ambulatory blood pressure was monitored for 48 hours including the entire interdialysis period and one dialysis session within 1 week after the cardiovascular examination was performed. The device was programmed to measure blood pressure at 20-minute intervals during the daytime (7 AM to 11 PM) and at 30-minute intervals during the nighttime (11 PM to 7 AM).

Statistical Analysis
Data are presented as mean±SD. Correlations between interdialytic weight gain and blood pressure change and between V inx and the parameters of cardiovascular hemodynamics were performed with simple and multiple linear regression analyses. Between-group comparisons were performed with unpaired Student t tests. Statistical significance was set at the level of P<0.05.

An expanded Methods section can be found in an online supplement available at http://www.hypertensionaha.org.

Results
Volume Dependency of Interdialytic Blood Pressure Change
Significant volume dependency of blood pressure was observed in these patients. The interdialytic weight gain, averaged from all 25 hemodialysis sessions, was correlated significantly with the average percent change in SBP (r=−0.35, P=0.001), mean blood
pressure ($r=0.32$, $P=0.003$), and DBP ($r=0.25$, $P=0.018$). Similarly, the average interdialytic weight gain per fat-free mass was also correlated significantly with average percent change in SBP ($r=0.45$, $P<0.001$), mean blood pressure ($r=0.42$, $P<0.001$), and DBP ($r=0.36$, $P=0.001$). The observed $V_{\text{inx}}$ ranged from 1.84 to 20.56 mm Hg/kg. The distribution of $V_{\text{inx}}$ across the study population is displayed in Figure 1.

**Ees and Volume Dependency of SBP**

The estimated $E_{\text{es}}$ at baseline could predict the subsequently observed values of $V_{\text{inx}}$: $V_{\text{inx}}=(1.17 \times E_{\text{es}})+6.4$ ($r=0.34$, $P<0.001$; Figure 2). The correlation between $E_{\text{es}}$ and $V_{\text{inx}}$ persisted after age and SBP were accounted for ($P=0.034$).

**Coupled Cardiac and Arterial Stiffness**

$E_{\text{es}}$ was significantly correlated with $E_{\text{es}}$ ($r=0.48$, $P<0.001$), pulse wave velocity ($r=0.30$, $P=0.001$), AI ($r=0.31$, $P<0.001$), and AC ($r=-0.49$, $P<0.001$).

**Volume Sensitivity and Hemodynamics**

$V_{\text{inx}}$ was not correlated with any blood pressure values measured in either the interdialysis or intradialysis period. In the subgroup of 34 patients who had undergone 48-hour ambulatory blood pressure monitoring, predialysis SBP was correlated significantly with 48-hour mean SBP ($r=0.59$, $P<0.001$), 48-hour daytime SBP ($r=0.62$, $P<0.001$), and 48-hour nighttime SBP ($r=0.49$, $P<0.001$). Similarly, postdialysis SBP was correlated with 48-hour mean SBP, daytime SBP, and nighttime SBP ($r=0.36$, 0.58, and 0.46, respectively; all $P<0.001$). However, $V_{\text{inx}}$ was not correlated with any of the ambulatory blood pressure measurements.

Except for $E_{\text{es}}$, $V_{\text{inx}}$ was not correlated with any of the cardiac function variables. On the other hand, $V_{\text{inx}}$ was correlated significantly with most of the vascular function variables, including AC ($r=-0.22$, $P=0.016$), $E_{\text{es}}$ ($r=0.24$, $P=0.009$), AI ($r=0.21$, $P=0.025$), and total peripheral resistance (TPR) ($r=0.29$, $P=0.019$). In a stepwise multiple regression analysis including $E_{\text{es}}$, AC, $E_{\text{es}}$, AI, and TPR as independent variables, only $E_{\text{es}}$ remained significantly associated with the dependent variable $V_{\text{inx}}$ ($P=0.001$).

**Volume Sensitivity and Hydration Status**

$V_{\text{inx}}$ was correlated significantly with total body water ($r=-0.32$, $P<0.001$), percent total body water ($r=-0.22$, $P<0.001$), and fat-free mass ($r=-0.32$, $P=0.001$) but not with other hydration status variables. After controlling for age and SBP, total body water ($P=0.001$) and fat free mass ($P=0.001$) remained significantly related to $V_{\text{inx}}$. In a stepwise multiple regression analysis including $E_{\text{es}}$, total body water, and fat-free mass as independent variables, $E_{\text{es}}$ ($P=0.001$) and fat-free mass ($P=0.002$) remained significantly associated with the dependent variable $V_{\text{inx}}$.

**Comparison Between High and Low Volume–Sensitivity Groups**

The high volume–sensitivity group had significantly higher predialysis SBPs ($P<0.05$) than did the low volume–sensitivity group (Table 2). However, both groups appeared to have similar ambulatory blood pressure profiles recorded for a consecutive 48 hours (Table 2). Although both groups had comparable cardiovascular structures, the high-sensitivity group appeared to have stiffer left ventricular chamber properties, as reflected by significantly greater $E_{\text{es}}$ ($P<0.001$;
by guest on August 29, 2017

The association between Ees and V inx is a determinant of chronic volume dependency of SBP in interdialytic SBP rise relative to weight gain and therefore is first time that Ees predicts the extent of the subsequent totally noninvasive technique, we have demonstrated for the pressure regulation in hemodialysis patients. With a novel, blood pressure rise is directly related to the interdialytic

In this study, we have demonstrated that the interdialytic hypertension. Because Ees is a measure of left ventricular mechanical properties at end systole and is coupled to arterial mechanical properties, our results support the hypothesis that the enhanced volume sensitivity of blood pressure in ESRD patients is due partly to the coupled systolic-ventricular and vascular stiffening in these patients.

Discussion

The high-sensitivity group also had stiffer large arteries, as reflected by the significantly greater AI (P=0.005) and Ees (P=0.013), and significantly lower AC (P=0.03). TPR was also higher in the high-sensitivity group compared with the low-sensitivity group (P=0.002). The high volume–sensitivity group had significantly smaller interdialysis body weight (P=0.015), body surface area (P=0.014), fat-free mass (P=0.003), and total body water (P=0.004; Table 4).

### Ventricular-Vascular Coupling in ESRD

The arterial system in ESRD patients undergoes structural remodeling similar to changes with aging and is characterized by diffuse dilation, hypertrophy, and stiffening of the aorta and major arteries.8,19–22 Arterial stiffening results in increased left ventricular systolic stress and left ventricular hypertrophy.23 Previous studies have demonstrated that the alteration of arterial structure and function is coupled to cardiac structural adaptation, mainly left ventricular hypertrophy.8 Our data broaden the established cardiac and arterial interactions in ESRD by demonstrating the association between Ees and various arterial functional parameters. Ees is traditionally considered a measure of contractility, as it directly varies in response to inotropic agents and is less influenced by volume and resistance load.24 However, conceptually, Ees is also a measure of chamber stiffness at end systole. Ees depends on both active contraction and on diastolic and passive structural factors.7,25 The association of Ees with Ees and other arterial stiffness indices indicates that the arterial stiffening in ESRD is also coupled to left ventricular systolic stiffening, similar to that observed in normal aging.7 Combined ventricular-vascular stiffening could potentially have important consequences on the cardiac response to varied filling volume, because a stiff heart-arterial system generates a greater systolic pressure change for a given change in ventricular volume. By varying loading acutely with occlusion of the inferior vena cava during cardiac catheterization, we have demonstrated that aging-related systolic-ventricular and vascular stiffening contributes to the greater sensitivity of blood pressure to volume change.7

### Volume Factor and Pressor System

The role of volume overload in the pathogenesis of hypertension in hemodialysis patients was questioned recently, and the role of pressor systems was emphasized.1,2,9 TPR has been shown to be substantially greater in hypertensive compared

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**Table 3. Cardiovascular Structure and Function Variables in Patients With Low and High Observed Volume Sensitivity**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Sensitivity (n=38)</th>
<th>High Sensitivity (n=39)</th>
<th>All Subjects (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS, mm</td>
<td>12.2 ± 2</td>
<td>11.2 ± 2</td>
<td>12.2 ± 2</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>11.2 ± 2</td>
<td>11.1 ± 2</td>
<td>11.2 ± 2</td>
</tr>
<tr>
<td>LVId d, mm</td>
<td>51.7 ± 2</td>
<td>51.5 ± 5</td>
<td>51.6 ± 2</td>
</tr>
<tr>
<td>LVIds, mm</td>
<td>30.7 ± 2</td>
<td>29.5 ± 5</td>
<td>30.6 ± 2</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>140.4 ± 46</td>
<td>139.3 ± 35</td>
<td>138.3 ± 38</td>
</tr>
<tr>
<td>LVM, g</td>
<td>229.7 ± 76</td>
<td>216.5 ± 56</td>
<td>219.1 ± 10</td>
</tr>
<tr>
<td>Ees mm Hg/mL</td>
<td>2.6 ± 0.9</td>
<td>3.1 ± 1.1*</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>71.1 ± 10</td>
<td>72.8 ± 7</td>
<td>72.9 ± 2</td>
</tr>
<tr>
<td>Cl, L/min/m²</td>
<td>3.4 ± 0.8</td>
<td>3.2 ± 0.8</td>
<td>3.2 ± 0.9</td>
</tr>
</tbody>
</table>

**Table 4. Anthropometric and Hydration Variables in Patients With Low and High Observed Volume Sensitivity**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Sensitivity (n=38)</th>
<th>High Sensitivity (n=39)</th>
<th>All Subjects (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.61 ± 0.07</td>
<td>1.58 ± 0.09</td>
<td>1.59 ± 0.08</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.4 ± 11.8</td>
<td>55.7 ± 8.2*</td>
<td>58.0 ± 10.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 ± 3.5</td>
<td>22.4 ± 3.3</td>
<td>22.9 ± 3.2</td>
</tr>
<tr>
<td>Waist-to-thi ratio</td>
<td>0.87 ± 0.07</td>
<td>0.84 ± 0.07</td>
<td>0.85 ± 0.07</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.64 ± 0.17</td>
<td>1.55 ± 0.14*</td>
<td>1.59 ± 0.16</td>
</tr>
<tr>
<td>Renin, ng/L/s</td>
<td>8.62 ± 8.62</td>
<td>5.56 ± 3.06</td>
<td>6.95 ± 10.56</td>
</tr>
<tr>
<td>Aldosterone, mmol/L</td>
<td>780 ± 740</td>
<td>600 ± 770</td>
<td>730 ± 780</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>38.7 ± 12.1</td>
<td>31.7 ± 7.0*</td>
<td>34.1 ± 10.1</td>
</tr>
<tr>
<td>Total body water, kg</td>
<td>29.0 ± 8.3</td>
<td>24.3 ± 4.9*</td>
<td>25.9 ± 6.8</td>
</tr>
<tr>
<td>Percent total body water, %</td>
<td>47.9 ± 9</td>
<td>44.7 ± 7</td>
<td>45.8 ± 8</td>
</tr>
<tr>
<td>Total body water/fat-free mass, %</td>
<td>75 ± 2</td>
<td>77 ± 8</td>
<td>78 ± 26</td>
</tr>
<tr>
<td>IVC diameter index, mm²</td>
<td>7.7 ± 2.6</td>
<td>8.1 ± 2.6</td>
<td>7.7 ± 2.6</td>
</tr>
</tbody>
</table>

Cl indicates cardiac index; LVId d, left ventricular internal dimension at end diastole; LVIds, left ventricular internal dimension at end systole; LVMi, left ventricular mass index; and PWT, left ventricle posterior wall thickness. All other abbreviations are as defined in text.

*P<0.05. †P<0.01.
with normotensive ESRD patients. The reasons for such inappropriate elevations of peripheral vascular resistance in hypertensive ESRD patients are unclear. Although the importance of the volume factor in blood pressure regulation in hemodialysis patients has been clearly demonstrated in the present study, our results also support the presence of the pressor systems and their possible contribution to the observed volume sensitivity: TPR was significantly related to \( V_{\text{vas}} \) and patients with high volume sensitivity had significantly higher TPR than did patients with low volume sensitivity. Our results suggest that with similar volume gain in the interdialysis period, blood pressure rises more in patients with higher TPR.

**Characteristics of ESRD Patients With High and Low Volume Sensitivity**

Patients with high volume sensitivity appeared to be thinner than their low volume–sensitivity counterparts. Both groups had similar cardiovascular structures, but the volume-sensitive patients had distinctly stiffer large arteries and left ventricles at end systole. The high volume–sensitivity patients had higher SBP at predialysis, yet their 48-hour ambulatory blood pressure profiles were similar to those of the low volume–sensitivity patients, implying greater blood pressure lability owing to the demonstrated cardiovascular stiffening in the former.

The volume sensitivity of blood pressure has been previously assessed with different techniques. The volume factor has been manipulated or estimated by using salt loading, interdialytic weight change, bioelectric impedance analysis to measure predialysis total body water or postdialysis extracellular fluid volume, ultrasound for determining the inferior vena cava diameter, or intradialytic decrease in plasma volume calculated from predialysis and postdialysis total plasma protein concentrations. In the present study, we used interdialytic weight gain to estimate the interdialytic fluid accumulation, which did not assess postdialysis volume status. However, we complemented our methods with measurements of total body water and inferior vena cava diameter during the interdialytic period, which suggested that postdialysis volume overload should have been minimal in our patients. Furthermore, the demonstration of significant volume sensitivity of blood pressure supports the adequacy of the current methodology in the present study.

In addition to predialysis and postdialysis blood pressures, ambulatory blood pressure has also been used to assess volume sensitivity in previous studies. Although ambulatory blood pressure is considered the “gold standard” for diagnosing hypertension and monitoring treatment in ESRD patients, a 2-week, averaged, dialysis-unit blood pressure (6 measurements) either before or after dialysis, can provide a reliable guide to the presence of hypertension or its control. On the other hand, the predictive power of average monthly values (12 measurements) of predialysis blood pressure for left ventricular mass is not inferior to that of ambulatory blood pressure monitoring. In the present study, we averaged blood pressure measurements for 25 dialysis sessions to demonstrate the volume dependency of interdialytic blood pressure change. Furthermore, to calculate \( V_{\text{vas}} \), we purposefully eliminated those sessions when the initial blood pressure was lower than the final blood pressure, so that \( V_{\text{vas}} \) would be less affected by factors other than volume that also modulate the variability in blood pressure values over the intradialytic and interdialytic intervals. Although intradialysis ambulatory blood pressure monitoring data could be used to calculate \( V_{\text{vas}} \), the \( V_{\text{vas}} \) by ambulatory blood pressure monitoring from one dialysis session would not necessarily be superior to the \( V_{\text{vas}} \) by routine predialysis and postdialysis blood pressures from an average of 16 sessions (across a period of ~2 months). Monitoring for an entire interdialytic and/or intradialytic session measures the blood pressure variation for that session only and does not account for the significant variability among different sessions. On the other hand, although the variability and measurement errors for predialysis and postdialysis blood pressure can attenuate or even mask potential associations with other variables, increasing the number of measurements might reduce the attenuation of association.

Mechanisms other than volume are involved in blood pressure regulation in patients with uremia, such as the renin-angiotensin system, adrenergic activity, renal vasodilators, and other potential, novel effector mechanisms. In this study, we did not measure baroreceptor function or plasma norepinephrine levels, and we had only one measurement of plasma rennin activity during the interdialysis day. Therefore, we were unable to explore the interaction of volume sensitivity with other mechanisms in blood pressure regulation. However, the demonstration of increased volume sensitivity caused by cardiovascular stiffening in ESRD patients is not contradictory, and might be complementary, to those established and potential mechanisms. For example, orthostatic changes in blood pressure in the elderly are related to decreased baroreceptor sensitivity. However, cardiovascular stiffening with the resultant volume sensitivity in the elderly might also contribute to postural hypotension, probably through the relative hypovolemia with the pooling of blood volume in the lower body on assuming the upright posture. In addition, it has been shown that decreased arterial compliance might be responsible for the declined baroreceptor function in the elderly.

**Perspectives**

This study demonstrates the possible role of cardiovascular stiffening in blood pressure regulation in patients with ESRD. Future studies are required to explore the potential benefit of intervention on cardiovascular stiffening in these patients.

**Acknowledgments**

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Volume Status and Blood Pressure During Long-Term Hemodialysis: Role of Ventricular Stiffness

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