THE INFLUENCE OF DIALYTIC MODALITY ON ARTERIAL STIFFNESS, PULSE WAVE REFLECTIONS, AND VASOMOTOR FUNCTION

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♦ Background: Measurements of aortic stiffness [aortic pulse wave velocity (PWV) and augmentation index (Alx)] have been established as powerful predictors of survival on hemodialysis (HD). Abnormal endothelial-dependent and endothelial-independent vascular reactivity and increased arterial stiffness are commonly described in HD patients. There is, however, a lack of information on the comparative impact of different renal replacement therapies (RRTs) on PWV and Alx, and how these different methods might influence endothelial-dependent abnormal vasodilatation.

♦ Objective: To describe in a cross-sectional design arterial compliance and distensibility in continuous ambulatory peritoneal dialysis (CAPD) versus HD versus renal transplant (RTx) patients, compared with age- and blood pressure-matched essential hypertensive controls. The PWV and aortic Alx were determined from contour analysis of arterial waveforms recorded by applanation tonometry in 40 CAPD, 41 HD, 20 RTx patients (with normal serum creatinine), and 20 controls with essential hypertension (all normotensive under treatment). Endothelial-dependent and endothelial-independent vascular reactivities were assessed by changes in Alx following challenges with inhaled salbutamol and sublingual nitroglycerin respectively.

♦ Results: CAPD patients had significantly stiffer arteries than all other categories. The PWV was 8.29 ± 1.09 m/s in second in CAPD patients, significantly higher (p < 0.05) compared to HD subjects (7.19 ± 1.87 m/s). Both dialysis subgroups had significantly higher PWV values compared to RTx patients (6.59 ± 1.62 m/s) and essential hypertensive controls (6.34 ± 1.32 m/s), p < 0.05. The Alx had a profile similar to PWV in different RRTs. All groups with the exception of CAPD subjects had a significant decrease in Alx following salbutamol. Moreover, the vasodilatation induced by either nitroglycerin or salbutamol was significantly blunted compared to HD. Overall, both dialysis categories had more abnormal responses compared to RTx patients and essential hypertensive controls.

♦ Conclusion: CAPD is associated with stiffer arteries and more profoundly abnormal endothelial-dependent vasomotor function, compared to matched HD subjects. These differences in arterial physical properties might explain differences seen in cardiac structure and function between the RRTs.


KEY WORDS: Arterial stiffness; augmentation index; endothelial vasomotor function; hemodialysis; pulse wave velocity; nitric oxide; renal transplantation.

vascular abnormalities (vascular calcifications, arteriosclerosis, severe atherosclerosis lesions) are highly prevalent in end-stage renal disease (ESRD) and are increasingly recognized for their paramount prognostic significance. In a rigid, stiff arterial tree there is an increased velocity of the pulse waveform (PWV) traveling from the heart to peripheral resistance vessels, so that the energy of the reflected wave combines with the antegrade pulse wave at an earlier time point, thus increasing the augmentation index (Alx). Recently, measures of aortic stiffness (PWV and Alx) have been shown to be powerful predictors of survival on hemodialysis (HD). For each 1-m/second increase in PWV, the all-cause mortality-adjusted risk ratio (RR) is 1.39 (95% confidence interval (CI) 1.19 – 1.62); similarly, the RR for each 10% increase in Alx, after adjustment for all confounding factors, is 1.51 (95% CI 1.23 – 1.86) for all-cause mortality and 1.48 (95% CI 1.16 – 1.90) for cardiovascular mortality (1,2). Moreover, using these measurements a renal patient may be compared with essential hypertensive (HTN) subjects, where different levels / tertiles of PWV are also significantly associated with increased risk of cardiovascular events: the RR of presenting any cardiovascular event is 1.38 (p =0.001) for the second tertile of PWV (between 10 and 12.3 m/s) and 1.90 (p =0.001) for the third tertile (> 12.3 m/s) compared with the first tertile (< 10 m/s), even after adjustment for Framingham risk factors (3).

In addition to a stiffer arterial tree, HD and, to a lesser degree, renal transplant (RTx) patients are known to have abnormalities of endothelial-dependent and
endothelial-independent vasomotor function (4–6), as shown by several studies investigating changes in vasomotor function following intravenous drug infusion or reactive hyperemia (5,6). An abnormal endothelial-dependent vasomotor function not related to known conventional cardiovascular risk factors has also been typically described in patients on peritoneal dialysis (PD) (7). However, most of the methodology employed to study endothelial-dependent vasomotor function is difficult/impractical to export from the vascular laboratory suite to the clinical setting or to large studies, is frequently irreproducible, or uses maximal nonphysiological stimulation of arteries usually not affected by atherosclerosis (brachial artery).

Very few studies have focused on arterial wall properties in patients on PD (7–10). It has been suggested that arterial remodeling is already observed in patients at the start of continuous ambulatory peritoneal dialysis (CAPD) and this is comparable to changes seen in HD patients (11). Only one study has attempted directly to compare arterial functional parameters in PD patients with HD, transplant, or predialysis subjects (9). Furthermore, in those studies, arterial stiffness was quantified by other measurements (e.g., distensibility coefficient), rendering any meaningful perspective difficult for the practicing nephrologist.

There is a complete lack of information regarding the comparative impact of different renal replacement therapies (RRT) on PWV and AIx, and how these different methods might influence endothelial-dependent and endothelial-independent vasomotor tone.

Therefore, our first objective was to describe, in a cross-sectional design, arterial compliance properties, through concomitant measurement of PWV and AIx, in age- and blood pressure (BP)-matched subjects on CAPD versus HD versus RTx patients versus essential HTN controls. Our second objective, using a recently described, simple, noninvasive reproducible methodology — pulse wave analysis (PWA) combined with pharmacologic stimuli known to reduce wave reflection independently of endothelium (nitrovasodilatation), or by activation of the L-arginine-NO pathway (using a beta-2 agonist (6)) — was to describe endothelial-dependent and endothelial-independent vasomotor function in CAPD patients and to compare the extent of these functional abnormalities with other renal (HD and RTx) and non-renal (HTN) populations.

**PATIENTS AND METHODS**

The study included 121 patients: 40 on CAPD, 41 on HD, 20 with RTx, and 20 HTN controls. These subjects were selected from the “C.I. Parhon” University Hospital dialysis population (70 on CAPD and 170 on HD). Exclusion criteria were clinically evident overhydration, recent (previous 3 months) peritonitis, regular cardiovascular instability on dialysis (dialysis hypotension > 5% dialysis sessions over the preceding 6 months), major other illnesses (e.g., malignancy), recent (previous 6 months) myocardial infarction, unstable angina, congestive cardiac failure, recent (previous 6 months) transient ischemic attacks/cerebrovascular accidents, diabetes mellitus, and, and, current use of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin-receptor blockers in view of their potential confounding effect on the elastic properties of the arterial wall (11). Demographic data are shown in Table 1.

All HD patients [5 hours × 3/week, Kt/V > 1.4, on 60 dialyzers (Fresenius Medical Care, Bad Homburg, Germany), conductivity 135 mS, dialysate Ca2+ = 1.75 mmol/L] and all CAPD patients (4 × 2 L Fresenius CAPD solutions, total creatinine clearance > 60 L/week/1.73 m²) from the center’s renal transplantation waiting list were invited to participate. The center’s allocation policy to CAPD or HD is according to the integrated approach to ESRD suggested by Van Biesen et al. (12): if no absolute contraindication is present, patients were started on CAPD and switched to HD when PD was considered inefficient. There were no restrictions in the availability of one of the two dialysis modalities and excellent outcomes have been previously reported for our CAPD population (13). All transplant subjects were live-related RTx, with stable serum creatinine < 120 µmol/L, 3 months post transplantation, on triple regimens of cyclosporine [tailored to a 2-hour post-administration peak cyclosporine level (C2) of around 800 – 1000 ng/mL] + mycophenolate mofetil 2 g/day + prednisone 5 – 10 mg/day.

**PULSE WAVE VELOCITY (PWV) AND AIx**

The PWV and AIx were determined from contour analysis of arterial waveforms recorded by applanation tonometry (SphygmoCor device; AtCor Medical, Westmead, Sydney, Australia), using a highly reproducible technique previously described elsewhere (14,15). Briefly, PWV was computed from carotid and femoral artery waveforms recorded consecutively, an electrocardiogram gated signal simultaneously recorded, and anthropometric distances, using a specialized software and methodology previously described and validated (16). The AIx was calculated as the difference between the first and second systolic peaks measured on the aortic pressure waveform, divided by the pulse wave height (see Figure 1 and the example in Figure 2), similarly to Refs. (14) to (18). The PWV and AIx measurements were performed 2 hours after the morning first drain in CAPD patients, predialysis (midweek dialysis sessions) in HD patients, before the morning ingestion of cyclo-
sporine A (at C0) for the RTx subjects, and before the morning administration of the antihypertensive medication in the non-renal controls. The PWV was measured with a full abdomen (normal status of a CAPD patient); however, taking into account a potential influence of the dialysis fluid on abdominal aorta wall properties, measurements were also performed in 5 patients with an empty abdomen: PWVfull abd = 8.9 ± 0.9 m/s versus PWVempty abd = 9.0 ± 0.7, p = NS. Similarly, the mean AIxfull abd = 33% versus AIxempty abd = 28%, p = NS.

TABLE 1
Demographic, Laboratory, and Medication Data in CAPD Versus Hemodialysis (HD), Renal Transplant (RTx), and Essential Hypertensive (HTN) Patients

<table>
<thead>
<tr>
<th></th>
<th>CAPD (n=40)</th>
<th>HD (n=41)</th>
<th>RTx (n=20)</th>
<th>Essential HTN (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.3</td>
<td>41.8</td>
<td>39.7</td>
<td>43.6</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21/19</td>
<td>20/21</td>
<td>10/10</td>
<td>10/10</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25±4</td>
<td>24±3</td>
<td>23±6</td>
<td>23±4</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis duration (months)</td>
<td>25.2±12.3</td>
<td>42.1±38.6</td>
<td>39.3±23.5</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>CRF etiology (Chronic GN / Interstitial nephritis / ADPKD / Unknown)</td>
<td>25/10/14</td>
<td>21/6/10/4</td>
<td>17/1/2</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.3±1.1</td>
<td>11.9±1.5</td>
<td>12.1±0.9</td>
<td>13.5±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.45±0.63</td>
<td>4.72±0.34</td>
<td>5.35±0.45</td>
<td>5.1±0.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.2±0.8</td>
<td>2.3±1.4</td>
<td>2.8±1.8</td>
<td>1.1±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP / DBP (mmHg)</td>
<td>137.4/85.9</td>
<td>130.3/81.1</td>
<td>133.2/83.9</td>
<td>129.8/85.4</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure medication</td>
<td>0</td>
<td>30c</td>
<td>3</td>
<td>0</td>
<td>&lt;0.05</td>
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<tr>
<td>No drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 class</td>
<td>4 (CCB)</td>
<td>8 (CCB)</td>
<td>14 (CCB)</td>
<td>20 (CCB)</td>
<td>NS</td>
</tr>
<tr>
<td>2 classes</td>
<td>16 (CCB +furosemide)d</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>≥ 3 classes</td>
<td>20d</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
<td>10 (20%)</td>
<td>0c</td>
<td>9 (45%)e</td>
<td>3 (15%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smokers</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = statistically nonsignificant; CRF = chronic renal failure; GN = glomerulonephritis; ADPKD = autosomal dominant polycystic kidney disease; CRP = C-reactive protein; SBP =systolic blood pressure; DBP = diastolic blood pressure; CCB = calcium channel blockers; ACEI = angiotensin-converting enzyme inhibitors.

a Significant difference HD versus CAPD (p < 0.05).
b Significant difference HTN subjects versus RTx subjects.
c Significant difference HD versus other categories.
d Significant difference CAPD versus other categories.
e Significant difference RTx versus other categories.

TESTS OF ENDOTHELIAL VASOMOTOR FUNCTION

Endothelial-dependent and endothelial-independent vascular reactivities were assessed by the maximum changes in AIx following challenges with inhaled salbutamol and sublingual nitroglycerin respectively, as described by Wilkinson et al. (18,19). In these previous studies, the beta-2 agonist and sublingual nitroglycerin both significantly and consistently reduced the AIx (19,20). Inhalation of a beta-2 agonist was consistent with the endothelial-dependent activation of the L-arginine-NO pathway, since it was substantially inhibited by L-NMMA and correlated to that of intra-arterial acetylcholine (19). A detailed presentation of the technique in renal patients is presented elsewhere (14,15).

DATA ANALYSIS

The response to inhaled salbutamol, or nitroglycerin, was defined as the maximum change in each parameter after drug administration. Data were analyzed by SPSS software (version 9.0; SPSS Inc., Chicago, Illinois, USA). For inter-group comparisons, t-test was used with Bonferroni correction, and Fisher’s exact test for the analysis of variance. All values represent mean ±SD, and a p value less than 0.05 was considered significant.

RESULTS

Demographic and laboratory data, BP levels, and antihypertensive regimens are shown in Table 1. Relevant data on factors recognized from previous
studies as potential confounders of arterial stiffness parameters [age, gender, body size, smoking, cholesterol levels (16–19), inflammation status (10,21), BP levels and ACEI (22), and statin use (23)] are also presented.

The CAPD patients had significantly stiffer arteries than all other categories: PWV was 8.29 ± 1.09 m/s in CAPD patients and was significantly higher (p < 0.05) compared to HD patients (7.19 ± 1.87 m/s). Both dialysis subgroups had significantly higher PWV values compared to RTx patients (6.59 ± 1.62 m/s) and essential HTN controls (6.34 ± 1.32 m/s), p < 0.05. A comparison of AIx between pre-HD, CAPD, RTx, and essential HTN is presented in Table 2. Again, the highest AIx was recorded in CAPD patients.

EVALUATION OF ENDOTHelial-DEPendeNT AND ENDothelial-INDEPendeNT VASOMOTOR FUNCTION (TABLE 2)

In CAPD patients, the vasodilatations induced by both nitroglycerin and salbutamol were significantly blunted (decrease in AIx values from baseline levels of 55% and 13% respectively) compared to HD patients (decrease in AIx values of 129% and 45% respectively, p < 0.05). Most importantly, it appears that in CAPD patients the endothelium-dependent component of the vasomotor response is the most affected, since this is the only category that has similar AIx values following salbutamol (30.8 ± 17.9%) compared to baseline AIx levels (35.3 ± 18.3%, p = NS). Overall, both dialysis categories had more abnormal responses following salbutamol and nitroglycerin compared to RTx patients and HTN controls.

DISCUSSION

This is the first systematic study to examine the differences in arterial stiffness between cohorts of chronic kidney disease patients treated either by PD.
or HD, or by RTx. It complements our previous findings of blunted endothelium-dependent vasoreactivity in HD patients (14) and our longitudinal study of the effect of RTx on arterial stiffness (15).

In this study, we found that the subjects on CAPD had stiffer arteries and more profoundly abnormal vasomotor function than the subjects on HD, despite a shorter period on RRT. The CAPD subjects’ results are more abnormal even than the HD patients when studied immediately prior to a HD session. In marked contrast, subjects who had undergone RTx displayed marked improvements in vascular structure and function, to an extent similar to subjects with just essential HTN.

These differences in arterial physical properties might explain some of the differences reported in cardiac structure and function between the renal replacement methods. Indeed, recent studies, in sharp contrast with older literature, described more severe left ventricular hypertrophy in CAPD patients compared to their HD (24,25) or RTx counterparts (26). This was related in a cross-sectional manner to latent overhydration and volume overload in CAPD patients (24,26), but not necessarily to worse BP control (24). The three major determinants of preload and afterload are volume status, BP level, and stiffness / distensibility of large arteries (27). Increased stiffness of large arteries and impaired endothelial-dependent vasorelaxation have been linked, in non-renal and HD patients (17,27), to an increased left ventricular mass. We provide solid evidence that these major components of the cardiac structure equation are more abnormal in CAPD patients. Future studies should explore the relative contribution of all these major players: hydration status, well-characterized BP levels (through ambulatory BP measurement), and arterial stiffness / distensibility. Finally, the aortic PWV and aortic BP AIx have also been shown to be powerful survival markers in essential HTNs (3,28) and in HD patients (1,2).

As this is the first substantial report of these parameters in CAPD patients, it is not certain that they will carry the same importance, but the relevance of their impact on hard end points should be the focus of future investigations. Nevertheless, in a recent prospective trial with a mean follow-up of 63 months (29), a PWV comparable to that recorded in our CAPD patients (8.3 m/s) was associated with significantly higher cardiovascular and overall mortalities than in those subjects with PWV < 8.2 m/s. Moreover, according to receiver-operating characteristic curve analyses for AIx (1), the best cutoff value for all-cause mortality is 25% (sensitivity 83%); our CAPD patients had baseline mean AIx values greater than 35%, 20% higher than in essential HTN controls and RTx subjects, that is, a potential increase in mortality of 100%, according to Blacher et al. (1).

Our findings suggest that CAPD patients have more affected vasorelaxation, and possibly more abnormalities in endothelial-dependent vasomotor function. In some studies, salbutamol-mediated vasorelaxation was only partly attenuated by L-NAME (30,31), supporting alternative NO-independent mechanisms for the effects of beta-2 stimulation. Nevertheless, the predominant endothelial dysfunction is supported by data from van Guldener et al. (7): Using a different methodology (percentage increase in ultrasound-derived brachial artery diameter after

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td><strong>Comparison of Augmentation Index (AIx) Between Baseline and Post Intervention in Peritoneal Dialysis (CAPD) Versus Hemodialysis (HD), Renal Transplant (RTx), and Essential Hypertensive (HTN) Patients</strong></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CAPD</strong></td>
</tr>
<tr>
<td>Baseline AIx (%)</td>
</tr>
<tr>
<td>Post-SAL AIx value (%)</td>
</tr>
<tr>
<td>Amplitude of change in AIx (from baseline) post SAL (%)</td>
</tr>
<tr>
<td>Hemodynamic changes from baseline post SAL</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Post-NTG AIx value (%)</td>
</tr>
<tr>
<td>Amplitude of change in AIx (from baseline) post NTG (%)</td>
</tr>
<tr>
<td>Hemodynamic changes from baseline post NTG</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
</tr>
</tbody>
</table>

SAL =inhaled salbutamol; MAP = mean arterial pressure; HR = heart rate; NTG = sublingual nitroglycerin.
^a Significant difference from HD, RTx, and essential HTN (p < 0.05).
^b Significant difference from RTx and essential HTN (p < 0.05).
^c Significant difference from basal (i.e., pre-intervention) values (p < 0.05).
^d Significant difference from essential HTN (p < 0.05).
reactive hyperemia), they found that only the endothelial-dependent vasodilatation and not the endothelial-independent component, was abnormal in PD patients compared to well-matched controls.

There has been only one comparable study (9) addressing differences in arterial wall properties between HD, CAPD, and matched controls (RTx patients were not included). Konings et al. (9) compared 36 PD patients, 18 HD patients, and 25 controls, and found that the distensibility coefficient of the right common carotid artery was similar in PD patients and controls but significantly lower in HD patients. Relevant from a physiopathological perspective is the fact that part of this difference might occur because, in HD patients, the prevalence of diabetes, smoking, and macrovascular disease was greater compared with PD patients. We excluded, by design, diabetics and patients with macrovascular disease. Additionally, discrepancies between the two studies may be explained by the important difference in age (>10 years), biochemical parameters (less anemic and better dialyzed patients in our HD cohort), and different methodology (distensibility coefficient of the common carotid artery as marker of arterial stiffening) used by Konings et al. (9). We consider that the PWV — as a direct measurement combined with a measurement assessing disturbed wave reflections — AIx, and pulse wave contour analysis following different stimuli are more comprehensive. Importantly, the present technique has been demonstrated to be reproducible (14,15,18) and offers more meaningful data / parameters in the context of outcome studies discussed (1–3, 28) (see above).

Our data do not extend to elucidate the marked differences between the two otherwise well-matched dialysis cohorts, although potentially relevant factors have been explored. There are numerous factors in renal disease and dialysis that could impinge upon arterial structure and function, including demographic characteristics (32), atherosclerosis and arteriosclerosis (8,21), vessel calcification (33), hyperhomocysteinemia (7), dyslipidemia (19,29,34), dysautonomia (29,30), chronic volume overload (31), and high circulating endothelin (14), angiotensin II (32), and NO-inhibitor levels (32).

Particular reasons for the markedly more abnormal vascular function results recorded in the CAPD cohort could include older age, a higher body mass index and/or body surface area, a worse BP control, and differences in low-grade inflammatory status (10,21). However, in our comparative cross-sectional analysis, there were no significant differences in these parameters between CAPD subjects and other categories, which is in line with previous data (7). Previously it has been shown that certain medications may favorably influence the elastic properties of the arterial wall and endothelial function, particularly ACEI (21,22) and statin use (23); again, in our study the better vasomotor function seen in HD patients compared to CAPD patients was not attributable to these factors (see exclusion criteria in Methods, and Table 2).

Additional explanations not explored are the marked hyperinsulinemia that the glucose load associated with PD induces — insulin has been shown to have a vasomotor action (35). Equally, dyslipidemia has been associated with increased aortic stiffness (19,29) but not with progressive increase in PWV in CAPD patients (8). Nevertheless, cholesterol levels were significantly higher in our CAPD cohort than in HD patients. Dysautonomia (34) and vascular calcifications (33) — potential contributors to increased arterial stiffness — have been associated more frequently with CAPD compared to other RRT. Finally, subtle differences in hydration status (26), the recently recognized chronic volume overload of CAPD patients (24,26) or the effect of intra-peritoneal fluid on aortic hemodynamics (32), are other potential explanations for these findings.

Our study has limitations. A cross-sectional comparative analysis, despite carefully correcting for all known potential confounders, cannot exclude the possibility of baseline differences between the two dialysis populations. Clearly, the important prognostic significance of our novel findings requires confirmation by future longitudinal studies investigating changes in PWV, AIx, and vasomotor function, according to the renal replacement modality.

In conclusion, we describe for the first time that CAPD is associated with stiffer arteries, increased arterial pulse wave reflections, and more abnormal vasomotor function compared to matched HD subjects. Irrespective of the type of dialysis treatment, ESRD patients have rigid arteries and abnormal vasorelaxation compared to transplanted subjects and hypertensives with normal renal function. Since some of these differences may be already present at dialysis initiation, further longitudinal studies are urgently required to confirm these abnormalities, to investigate etiopathogenetic mechanisms, and to see if these differences persist and contribute to end-organ damage and mortality (as one would expect them to, from existing almost exclusively HD data).

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