Increased Arterial Stiffness in Young Adults with End-Stage Renal Disease since Childhood

JAAP W GROOTHOFF,* MARIKEN P GRUPPEN,* MARTIN OFFRINGA,† ERIC DE GROOT,‡ WILLEM STOK,§ WILLEM JAN BOS,‖ JEAN CLAUDE DAVIN,* MARC R LILIEN,|| NICOLE CAJ VAN DE KAR,‡ ERIC D WOLFF,&& and HUGO S. HEYMANS†

*Department of Pediatric Nephrology and †Department of Pediatrics, Emma Children’s Hospital, Amsterdam, the Netherlands; ‡Vascular Medicine Group, ‡Department of Physiology, Academic Medical Center, Amsterdam, the Netherlands; §St. Antonius Hospital, Nieuwegein, the Netherlands; ||Department of Pediatric Nephrology, Wilhelmina Children’s Hospital, Utrecht, the Netherlands; &&University Medical Center St. Radboud, Department of Pediatric Nephrology, Nijmegen, the Netherlands; &&Sophia Children’s hospital, Department of Pediatric Nephrology, Rotterdam, The Netherlands.

Abstract. Increased arterial stiffness is a risk factor for mortality in adults over 40 yr of age with end-stage renal disease (ESRD). As no data exist on vascular changes in young adults with ESRD since childhood, a long-term outcome study was performed. All living Dutch adult patients with onset of ESRD between 1972 and 1992 at age 0 to 14 yr were invited for carotid artery and cardiac ultrasound and BP measurements. Data on clinical characteristics were collected by review of all medical charts. Carotid ultrasound data were compared with those of 48 age-matched and gender-matched healthy controls. Carotid artery and cardiac ultrasound was performed in 130 out of 187 eligible patients. Mean age was 29.0 (20.7 to 40.6) yr. Compared with controls, patients had a similar intima media thickness but a reduced mean arterial wall distensibility DC (40.0 versus 45.0 kPa−1 · 10−3; 95% CI, −9.1 to −0.8; P < 0.001), an increased stiffness parameter β (4.2 versus 3.8; 95% CI, 0.05 to 0.68; P = 0.02), an increased elastic incremental modulus Einc (0.35 versus 0.27 kPa · 103; 95% CI, 0.02 to 0.12; P < 0.001). Multiple regression analyses in all subjects revealed that ESRD was associated with an increase in β and Einc. Arterial wall properties of patients currently on dialysis and transplanted patients were comparable. In all patients, current systolic hypertension was associated with increased Einc and decreased DC. In conclusion, carotid arterial wall stiffness is increased in young adult patients with pediatric ESRD. Hypertension is a main determinant and might be a target for treatment of these potentially lethal arterial wall changes.

Cardiovascular disease is the main cause of death in adults with end-stage renal disease (ESRD) (1–4). Cardiovascular causes of death are relatively uncommon under the age of 40 yr in the general population. Yet, cardiovascular diseases also account for most deaths in patients with ESRD aged between 25 and 44 yr (1). There are indications that even in children and young adults with ESRD since childhood, cardiovascular disease is the main cause of death, similar to older ESRD patients. We performed a long-term follow up study on the somatic, social, and psychologic outcome of children with ESRD. Over 25% of all patients had died, all of them under the age of 36 yr. We found cardiovascular disease to be the most important cause of death in the whole group, and cardiac death most prominent in those patients who died more than 10 yr after beginning renal replacement therapy (RRT) (5).

Clinical studies have shown that increased stiffness of the large arteries independently contributes to the high mortality in dialysis patients over 40 yr of age (6–8). Recently, studies performed with electron beam CT have shown coronary calcifications in adolescents and young adults with ESRD (9–11). However, these studies concern only a few patients; to date, no data exist on arterial wall distensibility in young adult patients with ESRD since childhood. The purpose of this study was to assess the prevalence and the extent of carotid arterial wall changes in young adults with ESRD since childhood to explore potential clinical determinants of vascular disease in these patients and to identify treatable causes. We also aimed to analyze the relationship between arterial wall changes on the one hand and cardiac left ventricular abnormalities and potential clinical determinants on the other.

Materials and Methods

Study Design

The study was part of a national cohort study of the Late Effects of Renal Insufficiency in Children (LERIC). It consisted of cross-sectional and retrospective parts. Arterial wall properties of the common
Data Collection

obtained from all subjects. The cross-sectional examination. The medical ethical committees of all participating centers approved the study, and informed consent was obtained from all subjects.

The Cohort

The cohort comprises all Dutch patients who had started chronic RRT at age 0 to 14 yr between 1972 and 1992 and who were born before 1979. Patients in whom renal function recovered within 4 mo after commencing dialysis were excluded. Preemptively transplanted patients were included. Patients who started RRT after 1991 were excluded to have at least a follow-up period of 6 yr. The procedure of the cohort formation has previously been described in detail (5).

Data Collection

Between November 1998 and August 2000 members of the LE-RIC-team visited 37 hospitals in the Netherlands. They collected information on primary disease, age at beginning of RRT, the burden of hypertension, and total duration of RRT, dialysis, transplantation, use of cyclosporine. All medical charts of all patients, participants as well as nonparticipants in the cross-sectional study, were reviewed. Emigrated patients were located, and medical information was obtained from their current physician. The observation period for all variable determinants lasted from the first day of RRT until the day of chart review or examination at our hospital. All eventful periods since onset of RRT over which data could not be obtained were excluded from evaluation and recorded as missing patient-years.

Echocardiography

Echocardiography. Left ventricular end diastolic diameter (LVEDD), left ventricular mass index (LVMI), were calculated according to Devereux and Reichek (14) (see appendix). Diastolic function was assessed by measuring the early transmitral peak blood flow velocity (E) and the atrial transmitral peak blood flow velocity (A). Diastolic dysfunction was defined as an E/A ratio of less than 1. Systolic dysfunction was defined as a shortening fraction less than 28%.

Ultrasound B-Mode and M-Mode Protocol for Arterial Wall Distensibility Measurement

B-mode and M-mode echo measurements were performed on both the right and the left common carotid artery (CCA). We used an Acuson 128XP/10v (Acuson Corporation, Mountain View, CA) equipped with a small parts L7 7.0 Mhz linear array transducer. All measurements were performed on Wednesday or Thursday, which made it possible to measure all hemodialysis patients on a dialysis-free day, always preceded by a dialysis day. Two experienced sonographers scanned all subjects. Subjects were scanned in the supine position. B-mode measurements of both carotid arteries were performed 1 cm distal from the carotid bulb over a range of 1 cm of the posterior wall in a lateral transducer angle. The sonographer selected a video image of each artery wall segment. The M-mode measurements were done as follows. A B-mode image was used to direct the M-mode ultrasound beam perpendicular to the walls of the distal CCA segment. Wall motion was recorded for at least three consecutive heartbeats and then stopped using the freeze option of the instrument. B-mode and M-mode images were stored with a 4:1 compression ratio on a digital still recorder (SONY DCR-700 P) in JPEG format. An analyst, blinded to the disease-state of the subject, performed image analyses off-line with semi-automated quantitative and qualitative video image analysis software. These methods have previously been described in detail (13).

BP Measurements

Before the actual M-mode measurements, the subject was familiarized with the BP device and a test BP measurement was done. Subjects were in the supine position for at least 10 min before the first measurement. BP measurements were performed oscillometrically with an Omron 705CP before and immediately after the M-mode ultrasound measurement. The BP was assessed on the right arm or on the left arm in case of an arteriovenous shunt in the right arm.

Control Group

Forty-eight age-matched and gender-matched controls were recruited among students, hospital employees, and healthy relatives of patients for B-mode and M-mode ultrasound assessment.

Data Analyses

Analyses of the B-mode and M-mode images were performed off-line by an experienced analyst (B-mode) and a medical physiologist (M-mode), both blinded to the disease-state of the subject. Semiautomated quantitative video image analysis software was used (Etrack, Department of Physiology, Academic Medical Center, Amsterdam, the Netherlands). Etrack was built using the mathematical software package Matlab (The Mathworks, Inc). The B-mode analyses included a 2 × 2 cm ultrasound image, a quantitative assessment (the intima-media thickness measurement [IMT] of the arterial far wall) and a qualitative assessment (interface qualification, wall irregularities, plaque formation, etc.). Images were processed, using the method described by Selzer et al. (15).

The M-mode analyses were performed as follows. From the full-screen M-mode image, a region of interest was chosen including both near and far wall structures of as many heartbeats as possible (n = 2 to 5, depending on heart rate and image quality). At a point about
three fourths in the heart interval, a gray level profile of the image was made in the vertical direction, perpendicular to the wall structures (16) (Figure 1A). This point was chosen such that all the structures of interest, i.e., the near wall periadventitia-adventitia and intima-lumen interfaces and far wall lumen-intima and media-adventitia interfaces, were clearly visible (17). Within this gray level profile, the vessel boundaries that were to be tracked were selected (Figure 1B). The tracking algorithm of the software was to a high degree insensitive to the exact placement of the boundary markers by the image analyst. From the difference in position of the near-wall and far-wall intima-lumen interfaces, the vessel diameter change over several heartbeats was calculated and the systolic and diastolic diameters were determined and averaged (Figure 1C).

Three parameters for functional arterial wall alterations were calculated: the distensibility, the stiffness parameter, and the incremental modulus of elasticity. The distensibility (DC) and stiffness parameter (\(\beta\)) of the arterial wall were calculated from the relation between BP, diastolic arterial wall diameter, and change in arterial wall diameter in systole (18,19) (see appendix). The incremental modulus of elasticity (\(E_{\text{inc}}\)) was calculated from the ratio of the carotid lumen cross-sectional area (LCSA) and the carotid intima-media cross-sectional area (IMCSA) divided by the distensibility (20) (see appendix).

**Variability of Measurements**
To validate the method of B-mode and M-mode ultrasound, we used the results of a study that was performed in our unit to analyze the components that contribute to the variability in the US measurements. The total measurement variability of the B-mode intima media thickness contributed to 25% of the total variability, whereas subject and arterial wall variability (13) caused 75% of the variability. For the M-mode distensibility and stiffness parameter, the measurement variabilities were 13.8% and 15.2%, respectively. The intra-sonographer and the intra-analyst and inter-analyst variability were less than 1%. The inter-sonographer variability accounts for most variability; therefore, our study was performed in the same unit by only two, well-trained sonographers. They were randomly assigned to patients and controls.

**Statistical Analyses**
A comparison of nominal variables of participants and nonparticipants of the cross-sectional study was performed by the \(\chi^2\) test or, if applicable, the Mann-Whitney test. Means of all outcome measures between patients and controls were compared using \(t\) test. Pearson univariate correlations were assessed between outcome measures and all potential disease determinants. All significant determinants (set at \(P < 0.2\)) identified from these analyses were studied with a linear stepwise multiple regression using the F-statistics with \(P = 0.05\) as criterion for selection. SSPS 9.0 for Windows software was used for analyses.

**Results**
**The Cohort**
The RENINE database produced a list of 251 patients who fulfilled the inclusion criteria. Checking with the local databases of all participating centers revealed the following information: one patient was mentioned twice, and three patients did not meet the inclusion criteria. By reviewing the databases of all dialysis and transplantation centers, we found two extra eligible patients. Thus, the cohort consisted of 249 patients. Of these, 62 patients (25.3%) had died by the time of cross-
sectional study. No patients were lost during follow-up. Of 187 eligible living patients, 47 (25.1%) declined to participate in the cross-sectional study, leaving 140 subjects. Reliable ultrasound data could be obtained in 130 of these 140 patients. All hemodialysis patients were treated with three 3- or 4-h dialysis sessions per week, except for two patients who received dialysis treatment at home four times per week. Antihypertensive drugs were used by 70 (53.8%) of 130 patients, of whom 26 (20%) used ACE inhibitors, 35 (26.9%) calcium blockers, and 45 (34.6%) β-blockers. No significant differences were found in age, gender, age at beginning of RRT, and therapy characteristics between participants and nonparticipants of the cross-sectional study (Table 1).

Current Status and Ultrasound Results

The mean age of the patients at the time of investigation was 29.1 yr (range, 20 to 41 yr), and of controls 28.5 yr (range, 21 to 40 yr). Of all 130 patients, 101 had a functioning renal graft at the time of investigation and 29 were on dialysis. Patients had a significantly higher mean systolic BP (Δ6.2 mmHg; 95% CI, 1.0 to 11.3) and diastolic BP (Δ10 mmHg; 95% CI, 7.3 to 12.7), a lower arterial wall distensibility (ΔDC = −5.0 kPa⁻¹ · 10⁻³; 95% CI, −9.1 to −0.8), a higher arterial wall stiffness parameter (Δβ = 0.36; 95% CI, 0.05 to 0.68), and a higher incremental modulus of elasticity of the arterial wall (ΔEinc = 0.056 kPa · 10³; 95% CI, 0.02 to 0.09; Table 2). Multiple regression analysis in all subjects, involving ESRD status, age, and BP as determinants, showed that the arterial wall stiffness parameter and incremental modulus of elasticity, but not distensibility, were independently affected by the presence of ESRD (Table 3).

Relation between Cardiac Left Ventricular Dimensions and Arterial Wall Properties

Decrease in E/A ratio was associated with a decrease in the arterial wall distensibility (R = 0.17; P = 0.05), increase in incremental modulus of elasticity (R = −0.24; P = 0.006), and increase in the arterial stiffness parameter (R = −0.29; P = 0.001) in all patients. Increase in the left ventricular mass index was associated with a decrease in the arterial wall distensibility (R = −0.22; P = 0.01) and an increase in the incremental modulus of elasticity (R = 0.18; P = 0.05). An increase of the

Table 1. Patient characteristics of participants and nonparticipants

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Nonparticipants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>130</td>
<td>57</td>
</tr>
<tr>
<td>Male (n)</td>
<td>70 (53.8%)</td>
<td>33 (57.9%)</td>
</tr>
<tr>
<td>Primary disease (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glomerulopathy</td>
<td>46 (35.4%)</td>
<td>18 (31.6%)</td>
</tr>
<tr>
<td>obstructive uropathy</td>
<td>37 (28.5%)</td>
<td>18 (31.6%)</td>
</tr>
<tr>
<td>congenital renal malformation</td>
<td>28 (21.5%)</td>
<td>13 (22.8%)</td>
</tr>
<tr>
<td>HUS</td>
<td>10 (7.7%)</td>
<td>5 (8.8%)</td>
</tr>
<tr>
<td>metabolic diseaseb</td>
<td>3 (2.3%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>other</td>
<td>6 (4.6%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Age at onset of RRTc (yr)</td>
<td>10.6 (range, 3.2 to 14.9)</td>
<td>11.0 (range, 1.9 to 14.9)</td>
</tr>
<tr>
<td>Age at time of investigation (yr)</td>
<td>29.0 (range, 20.7 to 40.6)</td>
<td>30.4 (range, 21.3 to 41.8)</td>
</tr>
<tr>
<td>Tx at time of investigation (n)</td>
<td>101 (78%)</td>
<td>48 (84%)</td>
</tr>
<tr>
<td>Dialysis at time of investigation (n)</td>
<td>29 (22%)</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Duration of RRT (yr)</td>
<td>18.1 (range, 6.2 to 30)</td>
<td>16.0 (range, 0.3 to 30.0)</td>
</tr>
<tr>
<td>Duration of dialysis (yr)</td>
<td>4.5 (range, 0 to 25.7)</td>
<td>3.7 (range, 0.2 to 18.3)</td>
</tr>
<tr>
<td>Duration of transplantation (yr)</td>
<td>13.5 (range, 0 to 28.9)</td>
<td>15.1 (range, 1.8 to 26.9)</td>
</tr>
<tr>
<td>Start RRT 1972 to 1981 (n)</td>
<td>69 (53.1%)</td>
<td>36 (63.2%)</td>
</tr>
</tbody>
</table>

a Renal dysplasia, cystic disease, Alport syndrome, nephronophthisis, congenital nephrotic syndrome.
b Oxalosis (3), cystinosis (5).
c RRT, renal replacement therapy.
left ventricular mass–left ventricular volume ratio was associated with a decrease in the distensibility ($R = -0.27; P < 0.001$) and an increase of the incremental modulus of elasticity ($R = 0.18; P = 0.02$) (Table 4).

**Determinants of Arterial Wall Properties**

Multiple regression analysis revealed that aging was associated with an increase in IMT, a low arterial distensibility, and a high incremental modulus of elasticity and stiffness parameter of the arterial wall. A high incremental modulus of elasticity and a low arterial distensibility were both strongly associated with a high current systolic BP ($\beta = 0.55, P < 0.001$; $\beta = -0.64, P < 0.001$, respectively). As the data on the prescription of calcium-containing phosphate binders and parathormone were incomplete, we could not analyze these determinants. Univariate and multivariate associations between changes in arterial wall integrity and determinants of disease are shown in the Tables 5 and 6.

**Table 2.** BP, B-mode Intima Media Thickness and M-mode distensability of the common carotid arteries of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients $n = 130$</th>
<th>Controls $n = 48$</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, % male subjects</td>
<td>47.9</td>
<td>53.6</td>
<td>NS</td>
</tr>
<tr>
<td>Age at time of investigation, yr (range)</td>
<td>29.1 (21–40)</td>
<td>28.1 (21–40)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>128.1 (±21.5)</td>
<td>121.9 (±12.3)</td>
<td>6.2 (1.0 to 11.3)$^b$</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>80.9 (±13.2)</td>
<td>70.9 (±5.0)</td>
<td>10 (7.3 to 12.7)$^c$</td>
</tr>
<tr>
<td>Mean IMT$^a$, carotis communis, mm (SD)</td>
<td>0.58 (±0.07)</td>
<td>0.56 (±0.06)</td>
<td>0.02 (−0.007 to 0.04)</td>
</tr>
<tr>
<td>Arterial distensibility kPa$^{-1} \cdot 10^{-3}$ (SD)</td>
<td>40.0 (±13.1)</td>
<td>45.0 (±10.5)</td>
<td>−5.0 (−9.1 to −0.8)$^b$</td>
</tr>
<tr>
<td>Arterial wall stiffness parameter $\beta$ (SD)</td>
<td>4.2 (±1.2)</td>
<td>3.8 (±0.8)</td>
<td>0.36 (0.05 to 0.68)$^b$</td>
</tr>
<tr>
<td>Elastic incremental modulus kPa $\cdot 10^3$ (SD)</td>
<td>0.36 (±0.14)</td>
<td>0.28 (±0.09)</td>
<td>0.08 (0.02 to 0.12)$^c$</td>
</tr>
</tbody>
</table>

$^a$ IMT, intima media thickness.
$^b$ $P = 0.02$.
$^c$ $P < 0.001$.

**Discussion**

As far as we know, this is the first report on arterial wall properties in a large cohort of young adults with ESRD since childhood. In this study, we aimed to assess the extent of carotid arterial wall changes in young adults with ESRD since childhood to explore clinical determinants that could be associated with arterial damage and to identify treatable causes.

To establish the extent of arterial wall stiffness, we calculated the wall distensibility, the stiffness parameter, as well as the incremental modulus of elasticity, and compared the values of our patients for these parameters with the values in healthy controls. The distensibility reflects the direct relation between pulse pressure and change in wall dimension and provides information on the elasticity of the artery as a hollow structure. However, it is directly dependent on the actual BP, also in healthy subjects, and is therefore a less reliable indicator to

**Table 4.** Univariate analysis: correlation ($R$) between arterial wall properties and anatomic and functional characteristics of the cardiac left ventricle of all patients$^1$

<table>
<thead>
<tr>
<th></th>
<th>DC$^b$</th>
<th>E$_{inc}$$^c$</th>
<th>$\beta^d$</th>
<th>IMT$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of investigation</td>
<td>$-0.37^i$</td>
<td>0.23$^i$ 0.41$^i$</td>
<td>0.31$^i$</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>$-0.64^i$</td>
<td>0.54$^j$ 0.47$^j$</td>
<td>0.15$^g$</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>$-0.42^h$</td>
<td>0.21$^i$ 0.21$^h$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ ESRD, end-stage renal disease (transplanted and dialysis patients).
$^b$ DC, distensibility.
$^c$ E$_{inc}$, arterial wall incremental modulus of elasticity.
$^d$ $\beta$, arterial wall stiffness parameter.
$^e$ IMT, intima media thickness.
$^f$ Standardized coefficient.
$^i$ $P < 0.05$.
$^j$ $P < 0.01$.
$^k$ $P < 0.001$.

$^1$ Only significant associations are given (set at $P < 0.2$).
establish structural wall changes in hypertensive subjects. Hayashi et al. (18) showed a linear relation between the logarithm of the wall pressure and the internal wall diameter of extracranial and intracranial arteries in the physiologic pressure range. The slope of this relation, the stiffness parameter $\beta$, combines information on the intrinsic wall material as well as changes in wall dimensions under a given relative pressure. This measure is independent of the actual BP in normotensive subjects (18,19). Finally, the incremental modulus of elasticity ($E_{inc}$) provides direct information about the arterial wall material, independent of its geometry (20).

We found low arterial wall distensibility, a high arterial stiffness parameter, and a high incremental modulus of elasticity in all patients compared with age-matched and gender matched healthy controls. The increase in the carotid incremental modulus of elasticity and the stiffness parameter were both associated with ESRD, independent of other determinants. Low arterial wall distensibility was only associated with current hypertension. We found no differences in arterial properties between patients currently on dialysis and transplanted patients. As expected, an increase in arterial stiffness was associated with an increase in ventricular mass but more strongly with a loss of diastolic function of the cardiac left ventricle. To our surprise, we found only a small increase in IMT in female patients compared with age-matched and gender-matched controls and no increase at all in male patients compared with controls. We found signs of plaque formation and arterial wall irregularities in only one patient.

In older patients, increased arterial stiffness is mostly accompanied by an increased IMT (21,22). Oh et al. (11) also found an increase in IMT of the carotid artery in 39 patients with ESRD since childhood, contrary to our results. Mean age at time of investigation and the total duration of ESRD for the patients of their study were the same as in our study. However, their patients had spent more time on average on dialysis than our patients had (45% versus 24.8% ESRD time). Only 39 of 141 living patients participated in their study; therefore, a selection of patients with a relatively long time on dialysis could explain the difference between the studies. They also measured the presence of coronary calcifications by means of electron-beam CT and found significant calcifications in 92% of all patients. Contrary to the carotid artery IMT, which increased dramatically with age in the patient group in their study, these calcifications were seen as frequent and to the same extent in patients aged 19 to 27 yr as in those aged 28 to 43 yr (11). This finding and the absence of an evident increase in IMT in our patients suggests that, at least in these very young adults with ESRD since childhood, arterial stiffening

### Table 5. Univariate analysis: correlation (R) between arterial wall properties and potential determinants in all patients

<table>
<thead>
<tr>
<th></th>
<th>DC a</th>
<th>$E_{inc}$ b</th>
<th>$\beta$ c</th>
<th>IMT d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>$-0.40^{m}$</td>
<td>$0.18^{k}$</td>
<td>$0.23^{l}$</td>
<td>$0.12^{j}$</td>
</tr>
<tr>
<td>Height</td>
<td>$-0.15^{j}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis at time of investigation e</td>
<td>$0.20^{k}$</td>
<td>$-0.27^{m}$</td>
<td>$-0.13^{j}$</td>
<td>$-0.10^{j}$</td>
</tr>
<tr>
<td>Systolic BP f</td>
<td>$-0.58^{m}$</td>
<td>$0.50^{m}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>$-0.44^{m}$</td>
<td>$0.44^{m}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burden hypertension g</td>
<td>$-0.14^{j}$</td>
<td>$0.23^{k}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration RRT ih</td>
<td>$-0.20^{k}$</td>
<td>$0.19^{k}$</td>
<td>$0.33^{m}$</td>
<td>$0.30^{m}$</td>
</tr>
<tr>
<td>Duration hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration peritoneal dialysis</td>
<td></td>
<td>$0.15^{j}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration transplantation</td>
<td>$-0.12^{j}$</td>
<td></td>
<td>$0.14^{j}$</td>
<td>$0.21^{k}$</td>
</tr>
<tr>
<td>GFR &lt;25ml/min per 1.73m$^2$ i</td>
<td>$0.14^{j}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of RRT j</td>
<td></td>
<td></td>
<td>$-0.16^{l}$</td>
<td></td>
</tr>
<tr>
<td>Age at time of investigation</td>
<td></td>
<td>$-0.24^{j}$</td>
<td>$0.12^{j}$</td>
<td>$0.40^{m}$</td>
</tr>
<tr>
<td>Current use cyclosporine</td>
<td></td>
<td></td>
<td></td>
<td>$0.30^{m}$</td>
</tr>
<tr>
<td>Duration cyclosporine use</td>
<td></td>
<td>$0.16^{j}$</td>
<td>$-0.16^{l}$</td>
<td></td>
</tr>
</tbody>
</table>

a DC, distensibility.
b $E_{inc}$, incremental modulus of elasticity.
c $\beta$, arterial wall stiffness parameter.
d IMT, intima media thickness.
e Dialysis as RRT modality at time of investigation versus functioning renal graft.
f BP, blood pressure.
g Total duration of mean BP $>p95$.
h RRT, renal replacement therapy.
i Patients with GFR < 25 ml/min per 1.73m$^2$, including dialysis patients.
j $p < 0.2$.
k $p < 0.05$.
l $p < 0.01$.
m $p < 0.001$.
n Only significant associations are given (set at $P < 0.2$).
can occur even in the absence of evident atherosclerotic plaque formation. Epidemiologic studies confirm the important role of arteriosclerosis in arterial stiffening. These studies indicate that the combination of arterial wall damage as a result of chronic overhydration and hypertension, and a high serum calcium-phosphate product is the most important etiologic factor in arterial stiffening (7,23). Like Oh et al. (11), Goodman et al. (10) showed that coronary calcifications occur in hemodialysis patients under the age of 30 yr and that the calcium load and not the serum cholesterol levels were determinant factors for these calcifications. Blacher et al. (7) found the incremental elastic modulus to be independent of serum lipids in ESRD patients, which supports the hypothesis that arteriosclerosis plays a dominant role in arterial stiffening. The association of coronary calcifications with a high CRP and Chlamydiae pneumoniae seropositivity, especially in the transplanted patients, as found by Oh et al. (11), suggest that microinflammation might also play an important role in the development of uremic arteriosclerosis (11).

**The Consequences of Arterial Wall Changes**

The high incidence of coronary calcifications in young adults with ESRD since childhood as found by Oh et al. (11) by electron-beam CT is alarming (11). However, the impact on clinical outcome of lesions found by this fascinating new technique has yet to be established. In older ESRD patients, arterial wall stiffening has been recognized as an independent mortality risk factor (6–8). Physiologically, an increase in arterial wall stiffness, and hence a reduction of its distensibility, induces an increase in the pulsatile pressure load of the cardiac left ventricle, forcing it to extra exertion to maintain normal tissue perfusion (21,25). The direct consequences are left ventricular hypertrophy, an increase in systolic BP, and a decrease in diastolic BP (26,27). The combination of a higher demand for coronary flow as a result of the left ventricular hypertrophy and the reduced supply due to a decrease in diastolic BP lead to an increased susceptibility to coronary ischemia (28–30). The potential lethal risk of these physiologic consequences of the arterial wall changes in ESRD, as well as in nonrenal diseased subjects, has been confirmed in clinical observations of dialysis patients, renal transplanted patients, and nonrenal patients with coronary artery disease (7,8,23,31). Blacher et al. (7) have identified the incremental elasticity modulus of the carotid artery as a strong predictor of mortality in dialysis patients. Barenbrock et al. (32) also found in older renal transplanted patients an independent relation between a reduction of the carotid artery distensibility and cardiovascular events. From the American Registry studies, it is well known that cardiovascular disease is the most prevalent cause of death even in young ESRD patients aged between 25 and 44 yr (1). Yet, it is unknown how many of these patients suffered from ESRD since childhood. Previously, we found a high cardiac mortality in our cohort of patients with ESRD since childhood at a mean age of 17.5 yr, the oldest being 36 yr (5). To establish the specific impact of the increased arterial stiffness on mortality in our patients, a follow-up of this cohort is imperative.

**Targets for Intervention**

We tried to identify treatable causes for the deteriorated arterial wall properties. Current hypertension appeared to be the only treatable risk factor for arterial stiffening in our patients. Guerin et al. (8) showed that treatment with ACE inhibitors was associated with a decrease in mortality. A prospective study is needed to establish beneficial effects on wall distensibility and mortality of rigorous anti-hypertensive intervention.

**Limitations of the Study**

Measurement variability is an intrinsic problem of all quantitative ultrasound studies. We found that the inter-sonographer variability accounted for most variability and that the intra-sonographer and the inter-analyst and intra-analyst variability was less than 1%. It was logistically inevitable to have all patients measured by at least two sonographers; therefore, we randomized all patients and controls over two experienced sonographers to avoid the inter-sonographer bias. No 24-h BP measurements were performed, because we learned that submitting subjects to more than 1 do in investigation would have dramatically reduced the participation in the project. As we could not obtain reliable data on calcium-containing phosphate binders or on Vitamin D prescription or serum calcium, parathormone, phosphate, CRP, and cholesterol levels, we could not analyze the effects of these parameters on the arterial wall properties in our patients. Guerin et al. (24) showed that the extent of arterial stiffening and calcifications in older ESRD patients increased with the use of calcium-containing phosphate binders. However, the role of parathyroid activity in the arterial calcification remains controversial. Some have ob-

---

**Table 6. Multiple regression analysis of determinants of carotid artery wall distensibility (DC), incremental modulus of elasticity (E inc.), stiffness parameter (β), and intima media thickness (IMT) in all patient**

<table>
<thead>
<tr>
<th></th>
<th>DC βa</th>
<th>E inc β</th>
<th>β</th>
<th>IMT β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>−0.64c</td>
<td>0.55c</td>
<td>0.26b</td>
<td>0.36c</td>
</tr>
<tr>
<td>Age</td>
<td>−0.32c</td>
<td>0.30c</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a β, standardized regression coefficient.

b P < 0.01.

c P < 0.001.

d Only significant associations are given (set at P < 0.05).
served an association between high (33), others between normal or low parathormone levels and arterial stiffening in dialysis patients (24,25). Oh et al. (11) found coronary calcifications to be associated with a high parathormone level. A prospective study in children and young adults with ESRD is needed to evaluate the role of disturbances in calcium-phosphate metabolism on arterial wall stiffening.

Conclusions
Young adults with ESRD since childhood, both transplanted patients and patients on dialysis, are at risk for arterial wall stiffening. These wall changes are associated with an increased mortality risk. Current hypertension and prolonged renal replacement therapy are independent risk factors, and a more vigorous therapeutic approach toward hypertension might improve the prospects of these patients.

Acknowledgments
Hannah Coutinho, Bella Drost, Janneke van den Broek, and Anouk van der Graaf, all medical students, contributed to the data collection. Data collection was made possible by the co-operation of the following physicians: RJ Hene, Medical Center University Utrecht; JJ Ho- man van der Heide, Academic Hospital Groningen; M Kooistra, Dianet, Utrecht; JW van der Pijl, Medical Center University Leiden; EJ Rischen-Vos, Dijkzigt Hospital, Rotterdam; S Surachmo, Academic Medical Center, Amsterdam; AJ Apperloo, St. Elisabeth Hospital, Tilburg; M Boekker, Rijnland Hospital, Leiderdorp; J Boonakker, Reinier de Graaf Gasthuis, Delft; MHL Christiaans, Academic Hospital, Maastricht; PPNM Diederik, St Fransiscus Gasthuis, Rotterdam; MA van Dorp, St Clara Hospital, Rotterdam; WT van Dorp, Ken- nemer Gasthuis, Haarlem; WJ Fagel, Medical Center Leeuwarden PG Gerlag, St Joseph Hospital, Veldhoven; A van Es, Dialysis Center ‘t Gooi, Hilversum; AB Geers, St Antonius Hospital, Nieuwegein; EG Hagen, Hospital De Lichtenberg, Amersfoort; SJ Hoorn, Catharina Hospital, Eindhoven; RM Huisman, Dialysis Center Groningen; K Jie, Groene Hart Hospital, Gouda; GMTh de Jong, Drechtsteden Hospital, Dordrecht; AJ Hoitsma, St. Radboud Hospital Nijmegen; G Kolster, Isala Clinics, Zwolle; I Keur, Dianet Buitenveldert, Amsterdam; WAH Koning-Mulder, Medical Spectre Twente, Enschede; AG Lieve- erse, Diaconessenhuis, Eindhoven; PB Leurs, Oostschelde Hospital, Goes; N vd Lely, Reinier de Graaf Gasthuis, Delft; MJ Nube, Medical Center Alkmaar; C Oldenbroek, Westfries Gasthuis, Hoorn; MJM Smit, Juliana Children’s Hospital, The Hague; G Vestenburg, Scheper Hospital, Emmen; RM Valentijs, Red Cross Hospital, The Hague, AE v Wijk, Hospital Free University, Amsterdam. We thank Gavín ten Tusscher for his stylistic advice and John Kastelein for his advice concerning the methods of vascular wall research. Financial Support for the study was provided by the Dutch Kidney Foundation (Niers- tichting Nederland).

References


Appendix

Calculation of the distensibility (DC), the incremental modulus of elasticity (E_{inc}), and the stiffness parameter (\beta) of the carotid wall and of the left ventricular mass (index).

\[ DC = 2(D\Delta D)/\Delta P \]

\[ \beta = (\ln [SBP/DBP])/(D\Delta D) \]

\[ E_{inc} = 3(1+[LCSA/IMCSA])/DC \]

\[ \Delta P = \text{systolic BP} - \text{diastolic BP} \]

\[ LCSA = \pi D^2/4 \]

\[ IMCSA = \pi(D/2 + IMT)^2 - \pi(D/2)^2 \]

\[ LVM = ([LVEDD/10 + IVST/10 + PWT/10]^3 \times 1.04) - ([LVEDD/10]^3 - 13.6) \]

\[ LVMI = LVM/v(weight \times length/3600) \]

D, arterial diastolic diameter; \Delta D, change in arterial diameter; \Delta P, pulse pressure; LCSA, carotid lumen cross-sectional area; IMCSA, carotid intima-media cross-sectional area; IMT, intima media thickness of the carotid artery; SBP, systolic BP; DBP, diastolic BP; LVM, left ventricular mass; LVMI, left ventricular mass index; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVEDD, left ventricular end-diastolic diameter.