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Alteration of proximal aorta biophysical properties in patients with end stage renal disease

A P Patrianakos, D N Karakitsos, E de Groot, F I Parthenakis, E K Daphnis and P E Vardas

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LINE

Objective: To present a novel, non-invasive echocardiographic application to assess the structural and functional properties of the complex composition of the proximal aorta in patients with end stage renal disease (ESRD).

Methods: 71 haemodialysis patients (mean (SD) age 61.3 (9.3) years, dialysis duration 79.2 (51.6) months) and 62 age matched controls were studied. From the suprasternal view, the distance between ascending and descending aorta was measured with two dimensional ultrasound. The aortic flow wave transit time was measured with pulsed wave Doppler. M mode echocardiography, with simultaneous blood pressure estimates, was used to assess the diameters of the aortic annulus and of the ascending aorta. Pulse pressure, pulse wave velocity (PWV), pressure strain elastic modulus, characteristic impedance, and β index were calculated.

Results: Patients had increased pulse pressure (68.0 (7.2) v 51.4 (5.0) mm Hg, p < 0.001), PWV (6.1 (1.1) v 3.9 (0.6) m/s, p < 0.001), characteristic impedance (174 (58) v 111 (31) m/s cm², p < 0.001), pressure strain elastic modulus (872 (254) v 541 (140) mm Hg, p < 0.001), and β index (8.9 (3.4) v 5.5 (1.4), p < 0.001) compared with controls. In patients PWV was correlated with age and time on haemodialysis (r = 0.44, p < 0.001, and r = 0.51, p < 0.001, respectively). **Conclusion:** A novel application of duplex ultrasound of the proximal aorta showed that patients with

Conclusion: A novel application of duplex ultrasound of the proximal aorta showed that patients with ESRD have impaired proximal aortic function compared with controls. The data indicate that these non-invasive measurements can be used to describe status and change in aortic biophysical properties and may be used as a marker for cardiovascular disease risk.

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mpaired biophysical properties of the large peripheral arteries,^{1,2} in particular of the aorta,^{2,3} are common in renal failure and appear to contribute greatly to cardiovas-cular morbidity and mortality in these patients.^{3,4}

Although invasive and non-invasive methods for quantifying vascular biophysical properties have been explored,^{5–7} they pose considerable challenges. Invasive methods⁸ use manometer tipped catheters, which enable precise measurement of vascular stiffness at specific regions of vessels, but these approaches have limited clinical utility.

Arterial stiffness can be assessed non-invasively by indirect measurement of pulse wave velocity (PWV) based on the time that it takes the pulse wave to travel a specific distance along the vasculature. These measurements can be made with the echocardiographic Doppler foot to foot method,⁹ applanation tonometry,¹⁰ and magnetic resonance imaging (MRI).¹¹

Critical points of these methods are the precise measurement of the pulse transit time and the path length. MRI is still rather expensive, time consuming, and not readily available in daily clinical practice.

We have developed a novel ultrasound application that uses widely available echocardiographic Doppler (duplex) techniques as a tool for the assessment of the biophysical properties of the proximal aorta. We evaluated our technique in healthy control subjects and in a cohort of patients with end stage renal disease (ESRD), as it is well documented in the literature that these patients have altered aortic biophysical properties.

METHODS

Study group

Seventy one haemodialysis patients derived from a cohort of 168 patients with ESRD met the inclusion criteria of this

cross sectional study. Patients were eligible for entry into the study when they had been on haemodialysis for more than nine months. Exclusion criteria were atrial fibrillation, uncontrolled blood pressure (defined as predialysis blood pressure greater then 140/90 mm Hg), moderate or severe aortic valve disease, chronic pulmonary disease, ascending aortic dilatation > 45 mm, any symptoms indicating acute inflammatory disease, and hospitalisation (during the previous six months) for unstable angina or myocardial infarction. All patients stopped their antihypertensive treatment one week before entry into the study to avoid the acute effect of antihypertensive medication. Blood pressure was controlled with so called "dry weight" methods.12 Dry weight is defined as the body weight below which a normal albuminaemic patient experiences hypotension or muscle cramps, or postural hypotension is clinically manifest.

Sixty two people with no history of cardiovascular or renal disease, matched for age, sex, and body surface area, served as the control group. Patients were dialysed through a fistula. This procedure was done with the same standardised technique, including synthetic membrane haemodialysers matched for patient's body surface area, bicarbonate dialysis fluid, and controlled ultrafiltration rate. The duration of dialysis sessions was tailored (four hours, three times weekly) to achieve a mean (SD) total dialysis dose (Kt/V) > 1.2 (1.39 (0.18)). Information compiled from the questionnaire filled out at enrolment included personal and

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Abbreviations: AO_D, aortic diastolic diameter; AO_S, aortic systolic diameter; CI, confidence interval; DBP, diastolic blood pressure; E_P, pressure strain elastic modulus; ESRD, end stage renal disease; MABP, mean arterial blood pressure; MRI, magnetic resonance imaging; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; Z_{CS}, characteristic impedance corrected for ascending aorta diameter

family history, smoking habits, and history of coronary heart disease, hypertension, and diabetes mellitus. All pertinent information was stored on our database. The study conformed to the principles outlined in the Declaration of Helsinki13 and was approved by the institutional ethics committee. All patients gave written informed consent.

Ultrasound study

Standard M mode, two dimensional echocardiography and Doppler measurements of left ventricular function, according to the recommendations of the American Society of Echocardiography,14 and blood pressure measurement (sphygmomanometry of phase I (systolic blood pressure (SBP)) and phase V (diastolic blood pressure (DBP)) Korotkoff sounds) were taken during the same session for each of the study participants.

The baseline measurements were made during the two weeks after inclusion, on the morning before the midweek haemodialysis. Blood pressure was measured in the arm contralateral to the arteriovenous shunt with a mercury sphygmomanometer and a cuff of appropriate size. Pulse pressure (PP) was estimated as PP = SBP - DBP and mean arterial blood pressure (MABP) as MABP = DBP + PP/3. Subjects were in the supine position for at least 15 minutes before the first measurement. Blood pressure was measured five times, at two minute intervals, and averaged for statistical analysis. The heart rate was determined from the three lead orthogonal ECG. A baseline echocardiogram was recorded with a Hewlett Packard Sonos 2500 (Andover, Massachusetts, USA) ultrasound device with a 2.5 or 2.0 MHz wide angle phased array transducer. All examinations were recorded on videotape for subsequent offline data analysis.

The aortic annulus was measured at the level of the valve leaflets. From the suprasternal view a pulsed wave Doppler tracing of the ascending aorta was recorded at a sweep speed of 100 mm/s. The sample volume was placed in the centre of the ascending aorta adjacent to the right pulmonary artery. Time 1 (T_1) was measured from the R wave of the QRS complex to the onset of the pulsed wave Doppler aortic flow. The sample volume was then placed as distally as possible in the centre of the descending aorta. The Doppler tracing was again recorded and time 2 (T2) was measured from the R wave of the QRS complex, which was used as a fixed reference time point, to the onset of the pulsed wave Doppler descending aortic flow. Aortic length was measured on two dimensional ultrasound images. It was defined as the distance from the pulsed wave Doppler sample volume in the descending aorta to the anatomical landmark of the ascending aorta adjacent to the right pulmonary artery (fig 1). The Doppler tracings in the ascending and descending aorta were recorded within 10 seconds of each other, thus minimising confounding effects of heart rate changes. From the two dimensional image, an M mode recording was made of the ascending aorta, about 3 cm from the level of the aortic annulus. Aortic systolic (AO_S) and diastolic diameters (AO_D) were measured from the leading edges of the ultrasound interfaces. Wall thickness was not measured, as its thickness is gain dependent. The Doppler tracings and two dimensional images were obtained during 10 cardiac cycles and averages of the measurements were used for the statistical analyses. The following calculations were used: transit time = $T_2 - T_1$; PWV = aortic length/transit time (m/s); aortic crosssectional area = $\pi \times (aortic annulus/2)^2 (cm^2)$; characteristic impedance corrected for ascending aorta diameter (Z_{CS}) = PWV $\times \rho/AO_s$ cross sectional area (where $\rho = 1.06$); pressure strain elastic modulus $(E_P) = (SBP - DBP)/[(AO_S)$ - AO_D)/ AO_D]; and arterial wall stiffness β index = ln (SBP/ $DBP)/[(AO_S - AO_D)/AO_D].$

Figure 1 (A) Two dimensional echocardiogram of the aortic arch from the suprasternal view showing the aorta length measured as the distance from the pulsed wave Doppler sample volume in the descending (DESC) to the ascending (ASC) aorta adjacent to the right pulmonary artery

(RPA). (B) Time 1 (T_1) was measured from the R wave of the QRS complex to the onset of aortic flow at the level of the RPA. (C) Time 2 (T_2) was measured with the same method, with the sample volume placed in the descending aorta as distally as possible. Transit time (TT) was measured as T_2-T_1 . Here is an example from a control subject, in which pulse wave velocity (PWV) was calculated as aorta length/TT = (7.5 cm/20 ms) 3.78 m/s.

Intraobserver and interobserver variability

The short term reproducibility of the method was assessed in 98 patients (49 controls and 49 haemodialysis patients). The sonographer who recorded the initial scans repeated the ultrasound measurements 48 hours after the initial measurement. A second experienced sonographer also cross checked the scans. Interobserver and intraobserver variability of PWV measurements was estimated.

Blood chemistry

Blood samples were taken in the morning after an overnight fast on a non-dialysis day. Whole blood was used for packed cell volume, EDTA-plasma for total, low density lipoprotein, and high density lipoprotein cholesterol and triglycerides, and serum for other biochemical assays, including creatinine and albumin.

Statistical analysis

Summary data are expressed as mean (SD). Correlations between continuous variables were assessed by the Pearson correlation coefficient. For ordinal data the Spearman rank correlation was used.

Histories of diabetes, hypertension, coronary heart disease, and smoking were entered as dichotomous variables (0 = no, 1 = yes).Backward stepwise linear regression analysis was used to assess which of the significant correlations between variables were independently correlated with PWV.

Groups were compared by the unpaired Student's *t* test or the Mann-Whitney U test, as appropriate.



 Table 1
 Characteristics and ultrasound measurements of the study population

	Patients with ESRD (n = 71)	Controls (n = 62)
Age (years)	61.32 (9.38)	58.39 (8.31)
Men/women	42/29	35/27
Duration of dialysis at inclusion		
(months)	79.2 (51.6)	NA
Coronary heart disease	29.6%	NA
Diabetes mellitus	26.8%	NA
Hypertension	63.4%	NA
Tobacco use	50.7%	61.3%
Serum total cholesterol (mmol/l)	5.57 (0.42)	4.37 (0.30)*
Serum LDL (mmol/l)	3.99 (0.18)	2.32 (0.27)*
Serum HDL (mmol/l)	1.1 (0.11)	1.25 (0.17)*
Serum trialycerides (mmol/l)	1.71 (0.33)	1.09 (0.1)*
Parathyroid hormone (mmol/l)	315.3 (143.6)	39.8 (14.23)*
Serum albumin (a/l)	37.2 (4.3)	40.6 (2.6)*
Haemoalobin (mg/l)	13.15 (0.6)	14.18 (0.8)*
$LVMI (a/m^2)$	148.27 (27.5)	93.83 (12.01)
Body surface area (m ²)	1.7 (0.14)	1.67 (0.22)
SBP (mm Ha)	138.4 (9.1)	125.3 (4.7)*
MABP (mm Hg)	93.7 (8.1)	91.05 (7.5)
Pulse pressure (mm Ha)	68.03 (7.23)	51.45 (5.03)*
AO_{S} (cm)	3.27 (0.4)	3.07 (0.13)*
AO _D (cm)	3.06 (0.42)	2.79 (0.14)*
Aortic length (cm)	8.1 (1.1)	8.1 (0.9)
Transit time (ms)	13.8 (2.4)	21.04 (3.2)*
Pulse wave velocity (m/s)	6.07 (1.06)	3.94 (0.57)*
Characteristic impedance (m/s·cm ²)	174.34 (57.71)	110.9 (30.6)*
Pressure strain elastic modulus		
(man Ha)	872.5 (254.5)	540.6 (140.1)
(mm Fig)	0 0 /2 //	5 5 (1 1)*

Agreement between repeated intraobserver and interobserver measurements was evaluated by the agreement analysis method of Bland and Altman.¹⁵ Bias and 95% confidence intervals (CIs) were also calculated as described by Bland and Altman.¹⁵ A two tailed p = 0.05 was considered significant. Data were analysed with a commercially available statistical package (SPSS for Windows 11.0; SPSS Inc, Chicago, Illinois, USA).

applicable; SBP, systolic arterial blood pressure

RESULTS

Table 1 shows the characteristics of the study population. All patients were receiving recombinant human erythropoietin and phosphate binders. Antihypertensive treatment was administered to 39.4% of the patients (46.4% angiotensin converting enzyme inhibitor, 28.5% calcium antagonist, 21.4% β blocker, and 3.5% combination treatment) and 16 patients (22.5%) were taking statins.

Patients had lower haemoglobin (p < 0.001), serum albumin (p < 0.001) and high density lipoprotein (p < 0.001) and higher low density lipoprotein, total cholesterol and triglyceride concentrations (all p < 0.001) than controls. Patients had greater PP (p < 0.001), ascending aortic diameter (p < 0.001), PWV (p < 0.001), Z_{CS} (p < 0.001), β index (p < 0.001), and left ventricular mass index (p < 0.001) than controls (table 1).

PWV was correlated with age (r = 0.44, p < 0.001; fig 2), time on haemodialysis (r = 0.51, p < 0.001; fig 2), PP (r = 0.35, p = 0.002), left ventricular mass index (r = 0.29, p = 0.01), and history of smoking (r = 0.29, p = 0.02), diabetes (r = 0.45, p < 0.001), and hypertension (r = 0.43, p < 0.001).

According to their time on haemodialysis, patients were classified into three groups: group A (haemodialysis duration 1-5 years, 25 patients), group B (haemodialysis duration 6-9 years, 26 patients), and group C (haemodialysis duration 1-5 years, 20 patients). Patients in groups B and C had greater PWV than group A (6.31 (1.02) and 6.58 (0.59) v 5.42 (1.09) m/s, p = 0.004 and p < 0.001, respectively), whereas no significant differences were found between groups B and C (p = 0.29). In haemodialysis patients PWV thus measured was found to correlate with the ascending aorta M mode measurements of E_P (r = 0.56, p < 0.001), β index (r = 0.58, p < 0.001), and Z_{CS} (r = 0.38, p = 0.001). No significant correlation between PWV and SBP (r = 0.14, p = 0.22), DBP (r = -0.14, p = 0.22), MABP (r = 0.04, = 0.69), or biochemical parameters was found. р

Patients were divided according to median values of SBP (138 mm Hg), DBP (70 mm Hg), and MABP (92.6 mm Hg). This subgroup analysis showed no significant differences in PWV.

Stepwise backward linear regression analysis showed that among the variables that were correlated with PWV, the time on haemodialysis (b = 0.45, p = 0.001, 95% CI 0.21 to 0.88) and history of diabetes (b = 0.38, p = 0.01, 95% CI 0.44 to 1.31) were independent predictors of PWV.







Figure 3 Bland-Altman plots showing the differences between the intraobserver (left) and interobserver (right) PWV measurements (on the y axis) plotted against the mean value of the measurements (x axis). The continuous line indicates zero bias.

Reproducibility

The mean repeated intraobserver PWV measurements performed initially and 48 hours later were 4.88 (1.49) and 4.93 (1.56) m/s, respectively. Bland-Altman analysis (figs 3 and 4) showed that bias was 0.052 (95% CI 0.002 to 0.102) and 95% limits of agreement of intraobserver variation were -0.44and -0.54. Mean interobserver PWV measurements made by observers A and B were 4.8 (1.4) and 5.0 (1.6) m/s. The Bland-Altman analysis (figs 3 and 4) showed that bias was 0.12 (95% CI 0.056 to 0.184) and 95% limits of agreement of interobserver variation were -0.50 and -0.745.

DISCUSSION

In this study we combined existing two dimensional cardiac ultrasound and Doppler techniques to develop a novel tool for the non-invasive assessment of regional aortic biophysical properties in adults. This technique takes into account the diversity of the proximal aorta and can describe its properties.

Since several epidemiological and clinical studies have shown that damage of large elastic arteries in patients with ESRD is enhanced independently of age and blood pressure¹⁶ and is a major contributing factor to the high cardiovascular morbidity and mortality in these patients,^{3 17} such a population is particularly appropriate for the validation of our method for examining the stiffness in the proximal aorta.

A new finding in our study was that patients with ESRD exhibited increased regional aortic stiffness as documented by increased regional PWV, E_P , Z_{CS} , and β index compared



Figure 4 Box plots of intraobserver and interobserver measurements of PWV plotted versus the initial measurements.

with controls. PWV as measured by the above method was correlated with M mode measurements of aortic stiffness.

Ultrasound assessment of aortic stiffness

This novel method estimates the regional aortic PWV. An analogous method has been used in a paediatric population.¹⁸ In adults PWV in this aortic region has been measured by MRI techniques.^{11 19} Our values for the control group were analogous to the estimated values (3.94 (0.57) v 3.8 (0.7) m/s) of the MRI technique used by Groenink *et al.*¹⁹ As stated by the Moens-Koerteweg equation, PWV, which is proportional to the square root of Young's elastic modulus, travels faster in stiffer arteries.⁵ London *et al*² have reported increased PWV in patients with ESRD compared with controls. The new finding of the present study was that, apart from increased PWV along the aorta in patients with ESRD, there is evidence of increased regional PWV compared with controls.

Experimental studies have shown that local PWV reflects well the distribution and severity of atherosclerotic lesions and altered stiffness in the local aortic region in which pulse waves travel.²⁰ We can speculate that the ensuing aortic wall stiffness in ESRD is due to arteriosclerosis, a process that manifests as generalised medial degeneration causing dilatation and stiffening of the arteries, in combination with atherosclerosis that typically disturbs conduit function.²¹

Furthermore, we found that patients who were on haemodialysis for more than five years had increased PWV compared with the other patients with ESRD. This observation coincides with previous reports^{22 23} and, although arteriosclerosis is multifactorial in patients with ESRD, dialysis itself apparently may have a role in the progression of proximal aortic stiffness.

To date aortic PWV has been estimated non-invasively mainly with pulsed wave Doppler echocardiography (foot to foot method) and MRI. However, in the foot to foot method a precise determination of the transit time and the length of the vascular segments are crucial factors, whereas measurement of the aortic length over the body surface is little more than an approximation, especially in subjects who, like patients with ESRD, have tortuous vessels.⁷ This superficial measurement of the aortic length is also influenced by other factors, such as the effects of fat, breast size, and thoracic or spinal abnormalities. On the other hand, MRI is not a bedside examination and is difficult to use for series follow up in daily clinical practice.

Our method is a novel application of a widely available ultrasound technique and can be easily performed with existing echocardiographic equipment with no need of advanced technology. The method allows precise determination of aortic path length and it uses well defined anatomical reference points. To our knowledge, this duplex ultrasound technique has not been applied before to studying the biophysical properties of the aorta in adult patients. The method saves time, is easily applied to routine clinical practice, and has acceptable reproducibility and repeatability.

We studied this aortic region of interest, which has a complex vascular structure that includes a section of the ascending aorta, the aortic arch, and a part of the descending aorta. The aorta is well documented to be regionally heterogeneous, since the ratio of elastic fibres to collagen changes from 3.1:1 in the proximal ascending aorta to 2.8:1 in the mid thoracic region and to 0.8:1 in the abdominal region.²⁴ Alterations of the biophysical properties of the proximal aortic region can affect cardiovascular coupling. Our results showed a relation between PWV and left ventricular mass index as London *et al*²⁵ also previously reported. The most important factor in developing cardiac hypertrophy is increased end systolic wall stress,²⁶ which is influenced not only by the geometric properties of the ventricle but also by aortic stiffness.²⁷

We also observed, as previously reported, that diabetes was an independent factor associated with increased aortic PWV^{10 28} and that in haemodialysis patients arterial blood pressure is not related to aortic PWV.^{16 27} The fact that PWV is at least partially independent of blood pressure suggests that this index of arterial stiffness is probably not merely a surrogate of blood pressure and may reflect the consequences of disease induced structural changes of the arterial wall.²⁹

Patients on long term haemodialysis have a high prevalence of calcified heart valves that may be correlated with aortic stiffness. However, as our primary end point was to validate our method, we did not assess the burden of aortic valve calcification.

The above echocardiographic method may be widely used in the future to assess the risk of cardiovascular diseases. However, the long term significance and predictive value of our technique still needs to be established.

Technical considerations

Although we can accurately measure the length of the aorta in this region, the time interval we can measure with a sweep speed recording of 100 mm/s is 5 ms. Given that the patients' measured transit time was 13.8 (2.45) ms because of the rapid velocities in this region, a 5 ms error potentially makes a large difference in an individual patient's results. To ameliorate this error we averaged measurements over 10 cycles. Despite the above technical considerations, our PWV measurements for the control group were analogous to the results obtained by others with MRI methods.19 Moreover, we have documented significant differences between patients with ESRD and the control group, as others also reported.² ²⁸ Our values were not analogous to the values obtained by the foot to foot method. Foot to foot PWV measures the high frequency components responsible for the sharp inflexion at the foot of the aortic pulse wave and should therefore be compared with the phase velocity predicted for the higher frequencies. Therefore, our PWV values were not similar to the PWV values obtained by the foot to foot method, as they correspond to different phase velocities.5 30

Conclusions

We investigated a novel application of duplex ultrasound of the proximal aorta in patients with clinically defined ESRD and in unaffected subjects. We found that patients with ESRD have impaired proximal aortic function compared with controls. Therefore, our data indicate that these non-invasive assessments can be used to describe status and change in aortic biophysical properties and may be used as a marker for cardiovascular disease risk.

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Neither the corresponding author nor any of the contributing authors have any competing interests.

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