Vascular function in patients with end-stage renal disease and/or coronary artery disease: A cardiac magnetic resonance imaging study

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Decreased arterial compliance in end-stage renal disease (ESRD) is associated with increased cardiovascular risk. Our aim was to examine aortic compliance in patients with ESRD using cardiac magnetic resonance imaging (MRI) and to compare these with patients with advanced atherosclerotic disease who are known to be at high cardiovascular risk. We examined a total of 83 subjects matched for age: 24 had ESRD and were on dialysis therapy for 3±6 years, 24 had severe coronary artery disease (CAD), 11 had both ESRD and CAD (4±5 years on dialysis therapy), and 24 healthy subjects with no evidence of CAD. Vascular and cardiac function was assessed using cardiac MRI. Aortic compliance was significantly reduced in patients with CAD compared to control subjects ($11.3 \pm 6.3\,ml \cdot 10^{-3}$/mm Hg vs $15.6 \pm 6.0\,ml \cdot 10^{-3}$/mm Hg, $P = 0.009$). Patients with ESRD also exhibited significantly reduced aortic compliance compared to healthy controls ($12.4 \pm 5.8\,ml \cdot 10^{-3}$/mm Hg vs $15.6 \pm 6.0\,ml\ 10^{-3}$/mm Hg, $P = 0.012$), whereas there was no significant difference in aortic compliance between patients with CAD and ESRD. Even in the absence of symptomatic CAD, patients with ESRD have significantly reduced aortic compliance compared to normal subjects. Patients with ESRD have equivalent aortic compliance to patients with advanced CAD. These findings suggest that a significantly reduced aortic compliance is one of many mechanisms promoting premature cardiovascular events in patients with ESRD compared to age-matched controls from the general population.

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Despite advances in renal replacement therapy, patients with end-stage renal disease (ESRD) have a greatly increased risk of premature cardiovascular morbidity and mortality.[1] Although these patients frequently have a high burden of traditional cardiovascular risk factors for coronary artery disease (CAD) such as diabetes mellitus, smoking, hypertension, and hyperlipidemia, the relationship between modifiable cardiovascular risk factors and long-term outcome is less clear than in the general population. For example, there is a U-shaped curve describing the interaction between both blood pressure and cholesterol and mortality in patients with ESRD.[2] Epidemiological and clinical studies have shown that increased arterial stiffness, most commonly assessed by measurement of pulse wave velocity (PWV) or augmentation index, is independently associated with cardiovascular morbidity and mortality in these patients.[3,4] However, although these studies are robust, using applanation tonometry as an indirect measure of central arterial function may be prone to limitations.[3]

Cardiovascular magnetic resonance imaging (MRI) accurately defines cardiac dimensions and is currently accepted as the 'gold standard' for measurement of left ventricular (LV) mass.[5,6] In addition cardiac MRI permits visualization of large arteries and blood flow. It thereby facilitates direct measurement of aortic compliance and aortic PWV.[7] Previous studies using cardiac MRI to assess PWV have focused on normal volunteers to validate the technique.[8] Given the strong relationship between vascular stiffness and outcome in ESRD we used MRI to assess cardiac and vascular function in this patient group. Furthermore, we compared subjects with ESRD with patients with advanced atherosclerotic disease at high cardiovascular risk and healthy controls.

RESULTS

Patient characteristics

Patient demographics and results from biochemical and imaging studies are depicted in Tables 1 and 2. Control subjects had lower blood pressure and C-reactive protein levels compared to all of the patient groups. Patients with

Table 1 | Baseline characteristics

	Controls (*n*=24)	CAD (*n*=24)	ESRD (*n*=24)	ESRD+CAD (*n*=11)	*P*-value
Age (y)	57±10	57±10	56±9	55±10	0.950
Sex (male/female)	13/11	17/7	12/12	10/1	0.078
Time on renal replacement therapy (y)	—	—	3±6	4±5	N/A
Body mass index (kg/m^2)	26.4±2.9	29.2±5.7	25.1±3.7	26.4±5.4	0.017
Smokers, active/stopped/none	2/6/16	6/11/7	7/4/13	5/3/3	0.038
Diabetic (n)	0	4	3	5	0.002
Statin therapy (n)	1	22	6	7	<0.001
Systolic blood pressure (mm Hg)	122±15	124±14	135±35	150±24	0.001
Diastolic blood pressure (mm Hg)	76±10	72±11	79±12	87±12	0.005
Pulse pressure (mm Hg)	44 (29; 52)	48 (42; 52)	54 (40; 67)	65 (44; 84)	0.058
Total cholesterol (mmol/l)	5.5±1.3	4.2±0.8	4.8±0.9	4.8±1.1	0.001
LDL cholesterol (mmol/l)	3.3±1.2	2.1±0.6	2.9±1.0	2.8±0.8	0.001
HDL cholesterol (mmol/l)	1.5±0.5	1.1±0.4	0.9±0.2	1.1±0.3	0.001
Triglycerides (mmol/l)	1.2 (0.9; 2.0)	1.9 (1.1; 2.5)	1.9 (1.5; 2.4)	1.8 (1.4; 2.5)	0.066
C-reactive protein (mg/l)	1.4 (0.5; 2.7)	2.3 (1.1; 3.4)	5.6 (2.3; 12.0)	10.2 (2.8; 31.5)	0.001
Creatinine (μmol/l)	91±10	101±20	—	—	N/A
eGFR (ml/min/1.73m^2)	73±13	68±16	—	—	N/A

CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not available; y, year.
P-values derive from one-way analysis of variance, Kruskal–Wallis test, χ^2-test or Fisher's exact test as appropriate.

Table 2 | Vascular and cardiac structure and function measured with cardiac MRI

	Controls (*n*=24)	CAD (n=24)	ESRD (n=24)	ESRD+CAD (n=11)	*P*-value
Compliance (ml · 10^{-3}/mm Hg)	15.6±6.0	11.3±6.3	12.4±5.8	9.3±6.0	0.020
Pulse wave velocity (m/s)	7.4±1.9	7.6±1.9	8.5±2.2	8.5±3.3	0.407
Ejection fraction (%)	63.0±5.3	61.4±7.7	66.8±6.4	47.8±12.8	<0.001
Left ventricular mass (g)	98.5±27.0	111.2±31.3	153.6±59.2	208.6±59.6	<0.001
Left ventricular mass index (g/m^2)	52.6±11.2	58.6±11.9	82.0±29.1	109.2±31.7	<0.001
End-systolic volume (ml)	56.1±17.6	61.4±22.6	53.9±24.8	118.3±47.8	<0.001
End-systolic volume index (ml/m^2)	30.1±8.7	32.6±11.6	29.1±12.6	61.6±23.1	<0.001
End-diastolic volume (ml)	149.7±35.0	155.3±35.4	158.4±55.8	221.9±57.9	<0.001
End-diastolic volume index (ml/m^2)	80.3±15.9	82.7±16.1	85.2±27.6	115.6±27.7	<0.001

CAD, coronary artery disease; ESRD, end-stage renal disease; MRI, magnetic resonance imaging.
P-values derive from one-way analysis of variance.
For pulse wave velocity the number of recordings was smaller (21/19/15/7 for controls/CAD/ESRD/ESRD+CAD, respectively).

ESRD had higher C-reactive protein levels compared to subjects in the other groups. Owing to treatment with statins total cholesterol and low-density lipoprotein cholesterol levels were lower in patients with CAD than in the other groups. However, control subjects had higher high-density lipoprotein cholesterol levels compared to other groups and were more likely to be never-smokers compared to patients with CAD.

Aortic compliance

Aortic compliance was significantly reduced in patients with CAD compared to control patients (11.3±6. 3 ml · 10^{-3}/mm Hg vs 15.6±6.0 ml · 10^{-3}/mm Hg, $P=0.009$); Figure 1. Patients with ESRD also exhibited significantly reduced aortic compliance compared to healthy controls (12.4±5.8 ml · 10^{-3}/mm Hg vs 15.6±6.0 ml · 10^{-3}/mm Hg, $P=0.012$), whereas there was no significant difference in aortic compliance between patients with CAD and ESRD ($P=1.00$). The group of patients with both conditions was relatively small. However, their compliance tended to be lower than in patients with ESRD only (9.3±6.0 ml · 10^{-3}/mm Hg vs 12.4±5.8 ml · 10^{-3}/mm Hg, $P=0.15$).

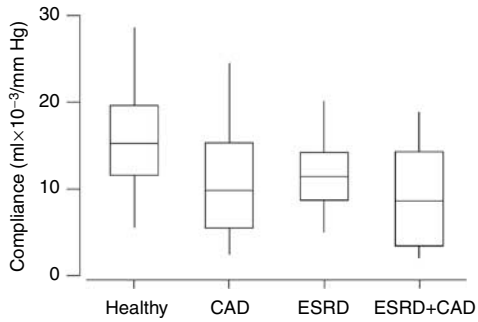

Figure 1 | Aortic compliance shown in control subjects, patients with CAD, ESRD, and ESRD + CAD, respectively; one-way analysis of variance F = 3.468, *P* < 0.02.

In the whole cohort, there was a highly significant correlation between age and compliance; aortic compliance declined with increasing age ($r = -0.498$, $P < 0.001$). Multiple stepwise linear regression analysis showed that age ($P < 0.001$), presence or absence of CAD ($P = 0.001$), and presence or absence of ESRD ($P = 0.010$) determined aortic compliance, whereas sex and mean arterial blood pressure did not enter the model (adjusted $R^2 = 0.349$).

PWV

PWV was lowest in the control group (7.4 ± 1.9 m/s) compared to patients with CAD (7.6 ± 1.9 m/s), ESRD (8.5 ± 2.2 m/s), and patients with both CAD and ESRD (8.5 ± 3.3 m/s). However, none of the comparisons between groups reached the prespecified level of significance. In the whole cohort, there was a highly significant correlation between age and PWV; PWV increased with increasing age ($r = 0.414$, $P = 0.001$). There was a significant correlation between PWV and aortic compliance in the whole study group ($r = -0.470$, $P < 0.001$).

LV mass and function

There was no significant difference in LV mass index between healthy subjects and CAD patients (58.6 ± 11.9 g/m^2, $P = 0.09$). LV mass index was significantly higher in patients with ESRD compared to healthy subjects (82.0 ± 29.1 g/m^2 vs 52.6 ± 11.2 gm^2, $P < 0.001$). In patients with CAD and ESRD, LV mass index was higher than in patients with ESRD (109.2 ± 31.7 g/m^2 vs 82.0 ± 29.1 gm^2, $P = 0.048$). LV ejection fraction was similar between patients with CAD, patients with ESRD and healthy controls (61.4 ± 7.7, 66.8 ± 6.4, 63.0 ± 5.3%, respectively; all $P = 1.00$). Ejection fraction was lower in patients with both ESRD and CAD compared to patients with ESRD (47.8 ± 12.8 vs 66.8 ± 6.4%, $P = 0.002$).

DISCUSSION

This study is to our knowledge the first report using cardiac MRI to assess aortic compliance in patients with ESRD. Our results demonstrate that even in the absence of significant coronary artery atherosclerosis, patients with ESRD have significantly reduced aortic compliance compared to normal subjects and that these patients have equivalent aortic compliance to patients with advanced CAD severe enough to require surgical revascularization. In the small group of subjects with ESRD and CAD, there was a trend towards a further reduction in aortic compliance as compared with patients with ESRD and no CAD. However, this group is too small to draw firm conclusions.

First, these findings suggest that a significant increase in arterial stiffness may be one of the many mechanisms promoting cardiovascular events in patients with ESRD. Second, even in the presence of ESRD, severe CAD is associated with reduced aortic compliance implying that impaired arterial function in these patients is a cumulative result of two factors – large artery damage, specific to uremia and further damage owing to atherosclerosis. We have also demonstrated by cardiac MRI that patients with severe CAD and normal renal function have a significant increase of arterial stiffness compared to age-matched controls.

The mechanisms responsible for increased arterial stiffness in ESRD are both complex and incompletely understood. Arterial abnormalities in ESRD are heterogeneous and associate atherosclerosis and remodelling with aging and hemodynamic alterations.[9] Major architectural abnormalities are fibroelastic intimal thickening, calcification of elastic lamellae, increased extracellular matrix with more collagen, and relatively less elastic fiber content.[10,11] Factors most frequently quoted in association with increased arterial stiffness in patients with ESRD are altered calcium and phosphate metabolism and parathyroid activity.[10] Arterial calcification is a common complication in ESRD,[10,12] and the extent of arterial calcification is predictive of subsequent cardiovascular mortality beyond established risk factors.[13,14] Calcification occurs in two different parts of the vessel wall, the media and the intima, and previous reports have suggested that patients with intimal calcifications are older and have a burden of traditional cardiovascular risk factors such as smoking and dyslipidemia, whereas medial calcification is seen in younger patients and may therefore be a finding more unique to uremia.[14] We were unable to demonstrate any correlation between calcium, phosphate, or time on dialysis and arterial stiffness, but in keeping with other studies we did find that age was associated with a significant reduction in arterial compliance (data not shown). Together with age, other factors such as presence or absence of atherosclerosis and/or renal disease seem to be important predictors of aortic compliance.

The group of patients with normal renal function and severe CAD represents the largest cohort of patients with coronary atherosclerosis studied by cardiac MRI. We have confirmed with this technique that CAD patients are characterized by a significant reduction in arterial compliance compared to age-matched controls. Additionally, as these patients were treated with aggressive lipid lowering therapy, it is not possible to draw any conclusions regarding serum cholesterol or inflammatory markers, both being ameliorated by statin therapy.[15–17]

Our study also highlights some limitations of this technique. First, although it is highly likely that vascular stiffness is the chief mechanism for reduced aortic compliance, cardiac MRI is unable to display calcific lesions owing to their absence of water (and hence proton) content. This compares relatively unfavourably with multi-slice computed tomography, which has emerged as a tool for assessing cardiac calcification.[18] However, multi-slice computed tomography is not able to accurately distinguish between intimal and medial calcification and requires ionizing radiation. Therefore making serial scans to test a therapeutic intervention a less attractive option, than using cardiac MRI surrogate measures of calcification. Second, calculation of aortic compliance is based on cross-sectional volume of the vessel wall and pulse pressure. It should be noted that for practical

reasons, direct aortic blood pressure measurement has been substituted by non-invasive indirect brachial blood pressure measurement.[19–21] Another important limitation of our study is the small number of patients with both conditions, ESRD and CAD. This is mainly owing to the rigorous definition of angiographically confirmed CAD. Comorbid cardiovascular disease is prevalent in approximately 30% of dialysis patients at initiation of therapy.[22] However, this may be ill defined, owing to poor correlation between symptoms, angiographic findings, and outcome. We chose to define CAD angiographically in patients with ESRD using similar criteria as in the CAD group and this has limited our numbers. Non-invasive tests for CAD have a high false-positive rate in this population.[23]

In conclusion, a MRI scan offers a 25-min examination of both vascular and cardiac function. Cardiac MRI is currently widely used as a high fidelity research method for the assessment of LV mass and function[24] and is being increasingly used in clinical practice.[25] By assessing vascular function in the same examination as an LV study, we have demonstrated that it is possible to acquire important additional data. We have shown significant abnormalities in patients with a high burden of atherosclerotic disease and with ESRD. Cardiac MRI measures of aortic compliance may represent potential targets for therapeutic interventions in patients with ESRD who are at a very high risk of cardiovascular events.

MATERIALS AND METHODS

Subjects

We examined a total of 83 subjects. Group 1 consisted of 24 patients with triple-vessel CAD confirmed by coronary angiography who were about to undergo elective coronary artery bypass graft surgery on the following day at the Department of Cardiothoracic Surgery, Western Infirmary, Glasgow. Group 2 comprised 24 patients with ESRD in whom CAD has been ruled out by coronary angiography or exercise tolerance test. Group 3 consisted of 11 patients with ERSD and CAD defined by stenosis $\geqslant$70% of at least one epicardial coronary artery at coronary angiography. The renal patients were recruited from the Renal Unit, Western Infirmary, Glasgow. Twenty-four subjects with no history of angina, CAD, or peripheral artery disease, who were recruited from a local health club and from surgical wards at Gartnavel General Hospital, Glasgow, served as controls. Blood samples were collected on the day of the MRI scan. Plasma total cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, high-sensitivity C-reactive protein, and serum creatinine were assessed using standard biochemical methods. The Modification of Diet in Renal Disease formula was used for the estimation of glomerular filtration rate in CAD patients and healthy volunteers.[26]

All subjects in the four groups were matched for age (within 3 years). The study was approved by the West Glasgow Ethics Committee and all subjects gave written informed consent.

Cardiac MRI technique

All study participants underwent cardiac MRI using a 1.5. Tesla MRI scanner (Sonata, Siemens, Erlangen, Germany). MRI was performed 1 day before bypass graft surgery in the CAD patients. In patients on hemodialysis imaging was performed on the post-dialysis day whereas patients on peritoneal dialysis were studied at their 'dry weight'. Overall scan time was approximately 25 min.

To measure aortic compliance, cine MR images in the transverse plane of the ascending aorta were obtained at the level of the main pulmonary artery (Figure 2), utilizing true fast imaging with steady-state precession (true FISP) sequence (repetition time 3.2 ms, echo time 1.6 ms, flip angle 60°, field of view 276 × 340 mm, pixel dimensions 2.3 × 1.3 mm, slice thickness 7 mm). The approximately 10 s breath-hold MRI resulted in prospective images with a temporal resolution of 22.5 ms. During compliance measurement, brachial systolic and diastolic blood pressures were measured within the scanner, using an MRI-compatible oscillometric device (Schiller Magscreen monitoring system, Schiller AG, Baar, Switzerland).

Although aortic compliance was the primary focus of this study, we measured PWV in a subset of patients ($n = 62$). A fast low angle shot gradient-echo pulse sequence (repetition time 41 ms, echo time 3.2 ms, flip angle 30°, field of view 192 × 256, pixel dimensions 1.5 × 1.5, slice thickness 5 mm) was applied perpendicular to the aorta at two levels: at the level of the crossing of the pulmonary artery through the ascending (in the same plane as the compliance sequence) and descending aorta and at the level of the diaphragm (Figure 3). This resulted in multiphase image pairs of modulus- and velocity encoded images with a temporal resolution of approximately 20.7 ms throughout the cardiac cycle.

LV mass and function were measured using a true FISP sequence to acquire cine images in long axis planes (vertical long axis, horizontal long axis, and LV outflow tract) followed by sequential short axis LV cine loops (8-mm slice thickness, 2 mm gap between slices) from the atrioventricular ring to the apex. Imaging parameters, which were standardized for all subjects, included the following: repetition time 3.2 ms, echo time 1.6 ms, flip angle 20°, field of view 276 × 340 mm, pixel dimensions 2.3 × 1.3 mm, and slice thickness 8 mm.

Image analysis and calculations

To calculate compliance, aortic volumes were measured by manual tracing of the cross sectional area of the vessel lumen using analysis software (Argus VA60C 2004, Siemens, Erlangen, Germany) which was multiplied by the slice thickness (Figure 2). Aortic compliance was calculated according to the following formula:

$$\text{Compliance} = [(\text{Aortic volume})_{\max} - (\text{Aortic volume})_{\min}]/\Delta P$$

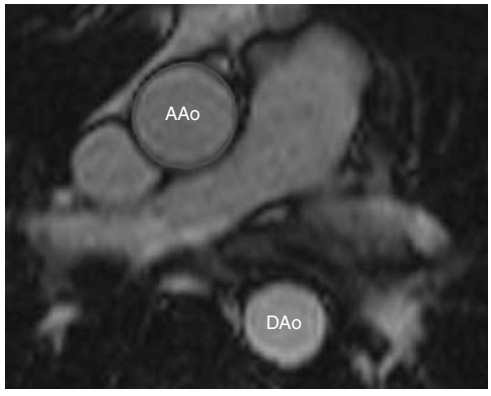

Figure 2 | Ascending aorta (AAo) and descending aorta (DAo) shown in cross section, with ascending aortic contour traced for compliance measurement.

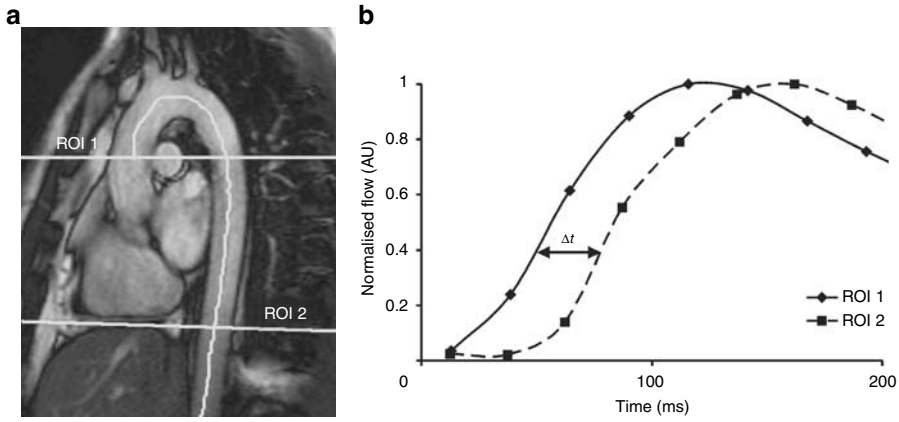

Figure 3 | Measurement of aortic pulse wave velocity. (**a**) Sagittal view of the aorta displaying regions of interest (ROI) 1 and 2 at points where velocity encoded flow images are acquired. The central line derived by skeletonization algorithm to generate aortic length is indicated. (**b**) Flow curves showing normalized blood flow at ROIs 1 and 2 with time delay (Δt) also indicated.

where $(\text{Aortic volume})_{\max}$ and $(\text{Aortic volume})_{\min}$ are the maximal and minimal calculated aortic volumes obtained during the cardiac cycle, respectively, and ΔP is the pulse pressure.

PWV was computed based on the upstroke difference of the velocity time curves at two different regions:

$$\text{PWV} = \Delta x/\Delta t,$$

where Δx is the length, and Δt is the time difference of initial flow acceleration between two regions of interest. To calculate distances between levels, views of the complete aortic arch were loaded into an off-line analysis programme (Cardiowarp, in-house software). A skeletonization algorithm was applied to the aorta shape in order to extract a midline of the section of interest (Figure 3a). The upstroke flow curves were normalized to their own maximum value using off-line analysis software (Origin 6.1, OriginLab Corporation, Northampton, MA, USA). In the region between 0.2 and 0.5 the curves were consistently linear and parallel and therefore the time delay could be computed directly (Figure 3b).[8]

LV function and mass were analyzed as previously described in detail.[27] In brief, from short axis cine loops LV epicardial and endocardial contours were manually traced in end systole and end diastole and LV mass and ejection fraction calculated using analysis software.

Statistical analysis

All of the statistical analyses were performed using SPSS software package (SPSS for Windows 12.0, SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test for normal distribution of the data. Data are expressed as mean $\pm$ s.d. or median (interquartile range) as appropriate. Categorical variables are presented as frequency counts, and intergroup comparisons were analyzed by χ^2-test for smoking, sex, and medication with statins. Statistical analysis of prevalence of diabetes was performed with Fisher's exact test. For continuous variables, the differences between the groups were evaluated using unpaired Student's t-test or Mann–Whitney U test as appropriate. All of the comparisons of compliance and PWV between the four groups were made in paired age-matched samples as age is a major determinant of aortic stiffness in both healthy and diseased populations.[8,20,28–32] Pearson's correlation coefficients are given where indicated. $P<0.05$ (two tailed) was considered significant and was corrected for multiple comparisons using the Bonferroni method where appropriate.

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