see commentary on page 1711

Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging

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Patients with end stage renal failure (ESRF) have an increased risk of premature cardiovascular disease. Left ventricular (LV) abnormalities, so called 'uremic cardiomyopathy', are associated with poorer outcome. Cardiac magnetic resonance imaging (CMR) accurately defines LV dimensions and identifies underlying myocardial pathology. We studied the relationship between LV function and myocardial pathology in ESRF patients with CMR. A total of 134 patients with ESRF underwent CMR. LV function was assessed with further images acquired after gadolinium-diethylentriaminepentaacetic acid (DTPA). The presence of myocardial fibrosis was indicated by late gadolinium enhancement (LGE). Two main myocardial pathologies were identified. A total of 19 patients (14.2%) displayed 'subendocardial LGE' representing myocardial infarction, which was associated with conventional cardiovascular risk factors including a history of ischemic heart disease (IHD) ($P<0.001$), hypercholesterolemia ($P<0.05$), and diabetes ($P<0.01$). Patients with subendocardial LGE had greater LV mass ($P<0.05$), LV dilation ($P<0.01$), and LV systolic dysfunction ($P<0.001$) compared to patients with no evidence of LGE. The second pattern, 'diffuse LGE', seen in 19 patients (14.2%) appeared to represent regional areas of diffuse myocardial fibrosis. Diffuse LGE was associated with greater LV mass compared to patients without LGE ($P<0.01$) but not systolic dysfunction. In total, 28.4% of all patients exhibited evidence of myocardial fibrosis demonstrated by LGE. In contrast to published literature describing three forms of uremic cardiomyopathy – left ventricular hypertrophy (LVH), dilation, and systolic dysfunction, we have shown that LVH is the predominant cardiomyopathy specific to uremia, while LV dilation and systolic dysfunction are due to underlying (possibly silent) ischemic heart disease.

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Patients with end stage renal failure (ESRF) have a greatly increased risk of premature cardiovascular events,[1] in particular sudden cardiac death. Although there is a high prevalence of conventional cardiovascular risk factors in this population, such as hypertension, diabetes, lipid abnormalities, smoking, and inflammation, the relationship between these factors and outcome is less clear than in the general population. For example, inverse relationships exist between both cholesterol and blood pressure and mortality in dialysis patients.[2,3] However by contrast, the presence of 'uremic cardiomyopathy', described echocardiographically, defined as the presence of left ventricular hypertrophy (LVH), dilation and systolic dysfunction (LVSD), has been shown to be strongly linked with poor cardiovascular outcome.[4–7] Echocardiography, although reliable and convenient, tends to overestimate left ventricular (LV) mass in ESRF patients.[8] While echocardiography provides valuable information on myocardial dimensions, it affords less detail regarding myocardial tissue composition. The uremic heart has been associated with histological abnormalities, including increased interstitial myocardial fibrosis, described in post-mortem specimens of patients with ESRF,[9] as well as from endomyocardial biopsies of patients on renal replacement therapy.[10]

Cardiovascular magnetic imaging provides a relatively novel method for accurate definition of cardiac dimensions, and is accepted as the 'gold standard' for the assessment of ventricular dimensions.[11] Previous studies have demonstrated that this can be a useful tool in assessing cardiomyopathy in patients with ESRF.[8,12,13] Furthermore, using the extracellular contrast agent gadolinium-diethylentriaminepentaacetic acid (Gd-DTPA), the presence of myocardial fibrosis can be assessed. Contrast-enhanced cardiac magnetic resonance (CMR) imaging has already been demonstrated to provide additional insights into conditions associated with deposition of fibrosis such as myocardial infarction,[14] hypertrophic[15] and dilated cardiomyopathy,[16] as well as acute inflammatory myocarditides,[17] and other rarer cardiomyopathies.[18,19]

By applying these techniques to study the heart in ESRF, the relationship between LV geometry (with its prognostic implications) and myocardial tissue damage can be noninvasively assessed in detail. We therefore studied LV

Table 1 | Baseline patient demographics

Variable	All patients	Gadolinium negative	Gadolinium positive	Subendocardial gadolinium	Diffuse gadolinium
Number (%)	134	96 (71.6)	38 (28.4)	19 (14.2)	19 (14.2)
Age (years)	52.2±10.4	51.5±10.4	53.3±10.0	55.6±9.6	51.6±10.3
Sex (% male)	92 (68.7)	65 (67.7)	27 (71.1)	15 (78.9)	12 (63.2)
Hemodialysis (%)	93 (69.4)	72 (75)	21 (55.3)*	9 (47.4)*	12 (63.2)
Duration of RRT	12.0 (43.0)	12.0 (37.0)	12.0 (78.0)	12.0 (53.5)	21.0 (79.0)
History of IHD (%)	23 (17.2)	12 (12.5)	11 (28.9)*	10 (52.6)**	1 (5.3)
History of MI (%)	8 (5.8)	1 (1.0)	7 (19.4)***	7 (36.8)**	0 (0)
Diabetes (%)	32 (23.9)	18 (18.8)	14 (36.8)*	11 (57.9)***	3 (15.8)
Hypercholesterolemia (%)	51 (38.1)	36 (37.5)	15 (39.5)	11 (57.9)*	4 (21.1)
Smokers (%)	72 (53.7)	51 (51.3)	21 (55.3)	10 (52.6)	10 (52.6)
SBP (mmHg)	139.5±25.1	138.9±24.1	141.2±27.8	145.1±28.1	136.8±27.6
DBP (mmHg)	81.8±12.6	82.0±12.3	81.1±13.3	82.3±12.4	79.8±14.6
Cholesterol (mmol/l)	5.4±1.8	5.6±1.9	5.1±1.3	5.0±1.5	5.3±1.1
C-reactive protein (mmol/l)	15.0 (12.5)	7.0 (12)	12.0 (11.3)	12.5 (10.3)	12.0 (12.5)
Hemoglobin (g/dl)	11.8±1.7	11.7±1.7	12.0±1.6	12.2±1.4	11.9±1.9

Data are expressed as number with percent of specific subtype of late gadolinium enhancement in parenthesis; mean±standard deviation and median and intraquartile range (in parenthesis) as appropriate. Abbreviations: RRT, renal replacement therapy; MI, myocardial infarction; IHD, ischemic heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure. Tests of significance compared to patients with negative late gadolinium enhancement: *$P<0.05$, ***$P<0.01$, **$P<0.001$. χ^2 test and Fisher's exact test and parametric or non-parametric analysis of variance (as appropriate).

dimensions and function as well as myocardial composition in patients with ESRF using CMR.

RESULTS

Left ventricular dimensions

A total of 134 patients underwent CMR (68.7% male; median age 54 years, range 27–72). Baseline patient demographics are shown in Table 1. There was a high prevalence of conventional cardiovascular risk factors in this patient group with 17.2% having a history of ischemic heart disease (IHD), 23.9% of patients were diabetic (21.8% with diabetic nephropathy), 38.1% had hypercholesterolemia, and 54.7% had a positive smoking history.

The median LV mass was 172.3 g (interquartile range (IQR) 67.8) and left ventricular mass index (LVMI) was 94.4 g/m^2 (32.0). Overall, 11 (8.2%) patients had LVSD. There was a correlation between LVMI and both systolic and diastolic blood pressure (systolic blood pressure $R=0.329$, $P<0.001$; diastolic blood pressure $R=0.244$, $P=0.005$), but no significant correlation was seen between time on renal replacement therapy, or any other hematological or biochemical markers. End diastolic volume and end systolic volume also correlated with systolic blood pressure ($R=0.322$, $P<0.001$; $R=0.252$, $P<0.01$, respectively) but not diastolic blood pressure or any other hematological or biochemical markers.

Description of results of late gadolinium enhancement

Overall, 38 (28.4%) patients had evidence of LGE at CMR. In one patient, there was disparity between the two blinded observers as to the presence of LGE. This image was reviewed by a further independent observer and was considered LGE negative, and analyzed as such. Patients who had evidence of LGE (LGE positive) had greater LVMI (LGE positive – median 104.0 g/m^2, IQR 19.9; LGE negative – median 84.4 g/m^2, IQR 31.0, $P<0.001$), LV dilation (measured as end diastolic volume: LGE positive – 152.5 ml, IQR 67.5; LGE negative – 120.0 ml, IQR 56.8, $P<0.001$) and had greater evidence of LVSD (ejection fraction: LGE positive – mean 63.6%, s.d. 13.8, LGE negative – mean 70.5%, s.d. 7.0, $P=0.01$) than patients with no LGE. Further analysis of the pattern of LGE revealed crucial differences between patient groups.

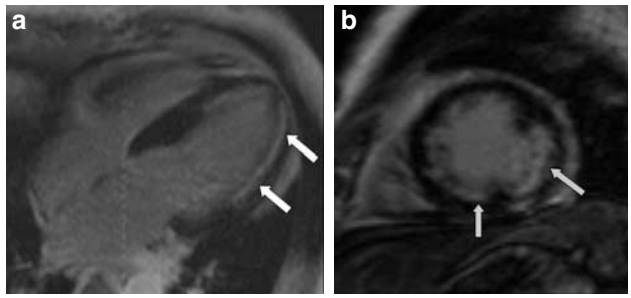

Figure 1 | (a) Horizontal long axis view of the left ventricle of a diabetic patient on peritoneal dialysis. There is a discrete area of bright subendocardial late gadolinium enhancement (LGE) representing a large infero-lateral myocardial infarction (arrowed). Signal intensity of this area is 44.0 compared to the 5.9 for the LGE-negative area. (**b**) Short axis view of the same patient as (**a**). The subendocardial gadolinium enhancement representing an inferior myocardial infarction is arrowed.

Broadly speaking, there were two patterns of LGE. Firstly, discrete (subendocardial) LGE involving the subendocardium was seen in 19 patients (14.2%). This finding is in keeping with the pattern of LGE previously described in patients with myocardial infarction and is shown in Figure 1a and b. This finding was associated with conventional cardiovascular risk factors and was found in significantly higher numbers in patients with a history of IHD, hypercholesterolemia, and diabetes but was not associated with gender, smoking history, or a difference in blood pressure. While a history of IHD was significantly associated with subendocardial LGE, nine patients (6.7% of the whole study cohort, 47.3% of the

patients with subendocardial LGE) had CMR evidence of myocardial infarction indicated by subendocardial LGE despite no antecedent history of IHD. Description of the clinical demographics of the patients with each type of LGE is shown in Table 1.

The second pattern – diffuse LGE was less intense, without subendocardial dominance. This diffuse LGE was seen in 19 patients (14.2%). While this pattern was still 'patchy' and was therefore regional, this appears to represent regional areas of diffuse fibrosis, within the left ventricle (Figure 2a and b). There was no association between the presence of diffuse LGE and the presence of cardiovascular risk factors, nor was this associated with significant differences in time on renal replacement therapy or blood pressure at the time of scanning. These two patterns were not mutually exclusive and one patient, with severe LVH, diabetes, and coronary artery disease had both patterns of LGE.

Owing to the subjective nature of classification of pattern of gadolinium enhancement, objective measurement was made to compare signal intensity (or pixel intensity on the analyzed images), of the region of interest of LGE compared to that of nulled myocardium. The mean signal intensity of nulled myocardium was 6.6 (s.d. 1.7), with that of subendocardial LGE significantly higher than that of diffuse LGE (32.7 SD 13.1 vs 18.6 s.d. 6.4, $P<0.001$), demonstrating the distinct presence of diffuse LGE separate from any artefact in the acquisition of images as well as the different tissue properties of subendocardial and diffuse LGE (Table 2, Figure 3).

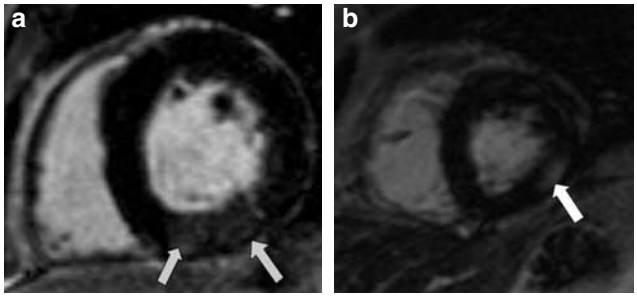

Figure 2 | (a) Short axis view of the left ventricle of hemodialysis patient demonstrating a diffuse area of gadolinium enhancement in the inferior wall of the left ventricle (arrowed). Signal intensity of this area is 17.6 compared to the 6.9 for the LGE-negative area. (**b**) Short axis view of the left ventricle of another hemodialysis patient demonstrating a diffuse area of gadolinium enhancement in the lateral wall of the left ventricle. Signal intensity of the area of late gadolinium enhancement is 32.0 compared to 8.4 for the LGE-negative area. This patient had normal coronary arteries at angiography performed as transplant assessment.

Functional correlates of late gadolinium enhancement

Patients with subendocardial LGE had had greater LV mass, LV dilation indicated by end diastolic volume, and poorer systolic function indicated by reduced LV ejection fraction

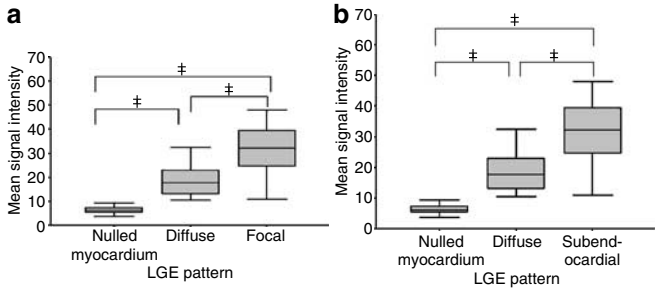

Figure 3 | (a–b) Box plots demonstrating the mean signal intensity (with 95% confidence intervals) for each area of gadolinium enhancement. ‡$P<0.001$ compared to areas of alternate patterns of LGE (paired samples *t*-test).

Table 2 | Results of left ventricular dimensions and late gadolinium enhancement

Variable	All patients	Gadolinium negative	Gadolinium positive	Subendocardial gadolinium	*Diffuse Gadolinium*
LVH (%)	96 (71.6)	61 (63.5)	35 (92.1)**	17 (89.5) *	18 (94.7)***
LV dilatation (%)	15 (11.2)	5 (5.2)	10 (27.7)***	7 (36.8)***	3 (15.8)
LVSD (%)	11 (8.2)	0 (0)	11 (57.9)**	8 (44.4)**	3 (15.8)**
EF (%) (s.d.)	68.5±9.9	70.5±7.0	63.6±13.8*	59.7±13.9**	67.5±12.9
LV mass (g)	172.3 (67.8)	154 (64.0)	186.5 (50.8)**	185.0 (66.0)*	195 (47)***
LV mass/BSA (g/m^2)	94.4 (32.0)	84.4 (31.0)	104.0 (19.9)**	100.5 (27.9)	105.0 (16.0)***
ESV (ml)	43.1 (30.2)	34.2 (21.5)	57.7 (41.7)**	64.0 (33.0)**	50.7 (34.3)*
ESV/BSA (ml/m^2)	23.5 (14.0)	19.0 (12.5)	30 (21.9)**	35.5 (21.0)**	22 (17.9)
EDV (ml)	131.8 (64.6)	120 (56.8)	152.5 (67.5)**	174.0 (57.0)***	140.0 (78.0)*
EDV/BSA (ml/m^2)	71.9 (30.8)	69.0 (29.7)	84.0 (32.3)***	89.6 (32.5)**	74.0 (31.8)
Mass of LGE	—	0	9.0±4.9	9.3±6.2	8.7±3.4
Signal intensity of myocardium	—	6.6±1.7	24.4±12.3**	30.6±13.6**	18.2±6.9**
Signal intensity index	—	1	3.8±1.9	2.8±0.10**	5.3±1.8**
Normal angiogram (%)	20 (40.8)	13 (56.5)	7 (26.9)	0 (0)	7 (58.3)
No. of patients with mild/moderate CAD (%)	10 (20.4)	6 (26.1)	4 (15.4)	0 (0)	4 (33.3)
No. of patients with severe CAD (%)	19 (38.8)	4 (17.4)	15 (57.7)***	14 (100)**	1 (8.3)

Data are expressed as number with percent of specific subtype of late gadolinium enhancement (LGE) in parenthesis; all data are median and intraquartile range (in parentheses) except where mean±standard deviation are shown as appropriate. Percentages shown are as a proportion of that subtype of LGE and as percentage of patients undergoing angiography with that subtype of LGE. Tests of significance compared to patients with negative LGE: *$P<0.05$, ***$P<0.01$, **$P<0.001$. Abbreviations: LVH, left ventricular hypertrophy; LV, left ventricle/ventricular; LVSD, left ventricular systolic dysfunction; EF, ejection fraction; BSA, body surface area; EDV, end diastolic volume; ESV, end systolic volume; LGE, late gadolinium enhancement; CAD, coronary artery disease.

compared to patients with no evidence of LGE. In these patients it appears that myocardial interrogation using LGE reveals that underlying ischemia, in particular myocardial infarction, is the cause for cardiomyopathy. In patients with subendocardial LGE, there was an inverse correlation between mass of subendocardial LGE and LV ejection fraction (Pearson's $R = -0.675$, $P = 0.002$).

By contrast, patients with diffuse LGE had no or minimal impairment of systolic function, compared to those without LGE. However, diffuse LGE was associated with significantly greater LV mass compared to patients without LGE, and while the presence of LGE was also associated with a greater LV dilatation indicated by increased end diastolic volume and end systolic volume, this did not appear to have a negative impact on systolic function, with no overall reduction in ejection fraction. Unlike subendocardial LGE, there was no significant correlation between the mass of diffuse LGE and LV dimensions or function. In patients with diffuse LGE, there was a trend towards a negative correlation between overall LVMI and hemoglobin (Spearman's $R = -0.40$, $P = 0.09$), but no significant correlations with other biochemical or hematological parameters. The functional characteristics of the classifications of LGE are shown in Table 2.

Correlation of CMR with coronary angiography

In all, 49 patients underwent coronary angiography, of which only 22 (40.8%) had normal coronary arteries (Table 2). Patients with subendocardial LGE, consistent with previous infarction, had a significantly higher burden of severe coronary artery disease ($P < 0.001$ compared to LGE-negative patients). While more than half the patients with diffuse LGE had normal coronary arteries, only one patient with diffuse LGE had a significant stenosis in one vessel, suggesting that diffuse LGE is unlikely to be directly linked to large vessel coronary artery disease.

DISCUSSION

This is the first report using this technique to assess cardiac function in patients with ESRF. We have used a widely applied protocol,[20] which represents a descriptive study using CMR in ESRF to assess cardiac function and myocardial tissue composition using Gd-DTPA to identify myocardial fibrosis.

Published literature has categorized uremic cardiomyopathy into three subtypes – LVH, ventricular dilatation, or systolic dysfunction (or a combination of these patterns)[4–7] with each pattern associated with cumulatively worse survival.[6] By contrast, we propose, based on CMR findings, that there are only two types of uremic cardiomyopathy. Firstly, that due to underlying IHD, where LV dilation and systolic dysfunction are due primarily to previous myocardial infarction revealed by CMR as subendocardial LGE. The second form, diffuse LGE found in patients with more severe LVH, is in keeping with a process, which we speculate may be more specific to uremia and therefore represents a separate entity.

Gadolinium-DTPA is an extracellular contrast agent that diffuses into the interstitial space between cells and exhibits its effect by shortening the T_1 relaxation of tissue in a magnetic field. There is greater space for Gd-DTPA accumulation both in areas of myocardial fibrosis and edema. In areas of ischemia or infarction, gadolinium leaks into the surrounding fibrotic, or edematous, tissue resulting in LGE on CMR imaging. However, the presence of LGE is not specific and further subjective assessment of the pattern of LGE is required. LGE has also been described in patients with myocarditis,[17] dilated cardiomyopathy,[16] and other cardiomyopathies.[18,19] Importantly, LGE has been shown to represent collagen deposition in hypertrophic cardiomyopathy.[15]

We have demonstrated two patterns of LGE in patients with ESRF. The first pattern – subendocardial LGE, consistent with that described in myocardial infarction, follows a primarily subendocardial distribution.[20] This reflects the perfusion of the sub-endocardium by end-arteries. Therefore, we have shown a high prevalence of myocardial infarction in our patient group indicated by subendocardial LGE. Patients with subendocardial LGE had greater evidence of LV systolic dysfunction, clearly highlighting the importance of underlying ischemic heart disease as the cause for ventricular impairment in these patients. While this was associated with a history of IHD, 6.7% of the patients studied had CMR evidence of myocardial infarction, despite no preceding history, in keeping with studies suggesting that ESRF patients are likely to have silent myocardial ischemia.[21] Although we found more evidence of myocardial ischemia in patients on peritoneal dialysis, this is likely to be due to the higher number of diabetics on this modality (15.1% of hemodialysis patients were diabetic compared to 43.9% on peritoneal dialysis, χ^2 $P < 0.001$).

The discovery of this high prevalence of myocardial infarction in ESRF patients is important given the poor long-term survival of these patients post infarction and general trend towards under treatment in these patients. Under use of cardioprotective therapy is common despite the recognized benefits of secondary prevention in the general population[22–25]; and with ongoing studies and emerging evidence for cardioprotective drugs in ESRF.[26–28] Thus, the diagnosis of subclinical myocardial infarction with CMR is likely to have prognostic and therapeutic implications and may be an indication for further assessment with angiography, particularly if the patient is being considered for transplantation. Furthermore, in patients with coronary artery disease requiring intervention, CMR can assess myocardial viability prior to revascularization, allowing optimal identification of patients likely to benefit from coronary intervention.[20]

The second pattern of gadolinium enhancement demonstrated was a pattern of diffuse, less intense, LGE. This was an unexpected finding. This diffuse gadolinium enhancement is less striking than that seen in, for example, myocardial infarction or hypertrophic cardiomyopathy. However, it was

reproducible and not due to artefact in the imaging process, and was associated with features of uremic cardiomyopathy, most notably LVH. Diffuse gadolinium enhancement implies an additional pathological process, other than large vessel myocardial infarction. It may reflect diminished capillary blood supply with associated fibrosis,[29] which is a prominent histopathological finding in the uremic heart, or low-grade ischemia.[30] It may be that small vessel disease is also present in patients who have epicardial atherosclerosis. Alternatively, this pattern of enhancement may most likely represent fibrosis throughout the hypertrophic ventricle, being evident in severe hypertrophy. Overall, the presence of gadolinium enhancement may not be because of a single process and to address this issue a larger study of gadolinium enhancement in patients with LVH because of hypertension and normal renal function is necessary. There are common factors in the development of hypertrophy and vascular disease in patients with renal failure including hypertension, arterial stiffness, vessel calcification,[31] hyperparathyroidism,[32] and anaemia.[33] Although speculative, the association with gadolinium enhancement with myocardial fibrosis is consistent with histopathological reports of fibrosis in post-mortem specimens of hypertrophic hearts of patients with ESRF.[9]

Uremic cardiomyopathy has been previously defined by LV mass and chamber dimensions based on echocardiography. The echocardiographic assessment of chamber volume and both calculated systolic function and LV mass are highly dependent on the phase of dialysis cycle. Thus, calculated LV mass may fall by approximately 10 g in post-dialysis, compared to pre-dialysis assessment.[13] CMR does not have this limitation and previously we have been unable to demonstrate significant systolic dysfunction in healthy dialysis patients, although LVH is common,[12] in keeping with other studies showing only a slightly higher prevalence of LVSD of 14.8% in unselected ESRF patients.[6] In this study, systolic dysfunction and ventricular dilatation are not present in the absence of LGE and it is only patients with focal gadolinium enhancement that have significant ventricular dilatation and systolic dysfunction. This suggests that only LVH is truly associated with uremia (and presumably is a consequence of hypertension and other factors associated with renal failure), while systolic dysfunction is not because of uremia, but to underlying IHD. Therefore, CMR represents an advance as additional investigation to guide invasive assessment, particularly in asymptomatic patients, undergoing evaluation for renal transplantation. The implication is that patients with systolic dysfunction require investigation of coronary heart disease.

Our study has some limitations. We studied patients being considered for renal transplantation, who are fitter than the majority of patients with ESRF, and hence found a lower prevalence of systolic dysfunction than expected. To fully appreciate the burden of cardiovascular disease in patients with ESRF, it would be necessary to study the entire dialysis population. Therefore, we cannot exclude selection bias, and expect a higher prevalence of LVSD (but also an even higher prevalence of IHD) in an unselected cohort of dialysis patients. Coronary angiography (and endomyocardial biopsy) in all patients would provide additional information regarding the relationship between LGE and coronary artery disease, but is invasive, and as a pilot study direct correlation with angiography was not sought. Hence, correlation between angiographic and CMR findings should be interpreted with caution. Finally, in analysis of LGE, using signal intensity, greater discrimination between nulled myocardium and areas of LGE (using a signal intensity of LGE >2 standard deviations higher than the mean intensity of an area of reference myocardium) would give greater distinction in image analysis, but may exclude definite areas of LGE. Future use of computer software to automatically detect areas of LGE will optimize detection of enhancement.

In summary, CMR represents a novel method for detailed investigation of myocardial function and tissue composition in ESRF. By confirming a high burden of (potentially silent) myocardial infarction indicated by subendocardial LGE, we have demonstrated the importance of recognition and treatment of atherosclerotic vascular disease in this population and further investigation with angiography where appropriate. By contrast, the presence of diffuse LGE suggests that an additional process is present, perhaps specific to uremia and related to fibrosis in the hypertrophic left ventricle. Further study of this entity is required to assess its clinical and pathological correlates, as well as CMR-based studies with regression of LVH as a goal of treatment. Moreover, the implications for survival merit investigation. With increasing availability, CMR may become a vital instrument for the assessment of cardiovascular disease in patients with ESRF and permits repeated non-invasive screening during the long and uncertain wait for cadaveric transplants.

MATERIALS AND METHODS

Patients

We prospectively studied 134 patients (median (range) age 54 (27–72) years; 67.6% male) with ESRF established on renal replacement therapy, undergoing cardiological assessment prior to consideration of renal transplant listing. All patients gave written, informed consent and the study was approved by the local ethics committee. All patients underwent conventional cardiovascular risk factor assessment including history, clinical examination, ECG as well as routine hematology, biochemical, and lipid profile. A history of IHD was defined as previous myocardial infarction or angina pectoris, and hypercholesterolemia was defined as fasting total serum cholesterol >5.0 mmol/l or use of statin therapy. The decision to list a patient for transplantation was not influenced by CMR findings, and was taken on the basis of clinical findings and additional investigations such as myocardial perfusion scanning and coronary angiography as clinically indicated.

Exclusion criteria

Exclusion criteria were contraindications to magnetic resonance scanning (permanent pacemaker, implanted ferromagnetic objects, pregnancy, and extreme claustrophobia). We also screened and

excluded two otherwise eligible patients with a documented history or echocardiographic evidence of hypertrophic cardiomyopathy and one further patient with a history of thalassemia and repeated blood transfusions; both of which have been associated with characteristic CMR findings.[15,34] There was no evidence of other cause of cardiomyopathy (e.g. amyloidosis, Fabry's disease, sarcoidosis, iron overload) in study patients based on clinical (original renal disease, serum ferritin, and clinical review) and echocardiographic findings.

CMR technique

All patients underwent gadolinium CMR using a 1.5 Tesla MRI scanner (Sonata, Siemens, Erlangan, Germany). CMR was performed on the post–dialysis day in hemodialysis patients. Patients on peritoneal dialysis were studied at their 'dry weight', according to clinical charts. A fast imaging with steady-state precession (true FISP) sequence was used to acquire cine images in long axis planes (vertical long axis, horizontal long axis, left ventricular outflow tract) followed by sequential short axis LV cine loops (8 mm slice thickness, 2 mm gap between slices) from the atrioventicular ring to the apex. Imaging parameters, which were standardized for all subjects, included repetition time (TR)/echo time (TE)/flip angle/voxel size/field of view (FoV) = 3.14 ms/1.6 ms/60°/ $2.2 \times 1.3 \times 8.0$ mm/340 mm. Further images were acquired 10 min after an intravenous bolus of Gd-DTPA (0.2 mmol/kg) using a breath-hold segmented turbo fast low angle shot (FLASH) inversion-recovery sequence, using identical slice positions as the cines. Standardized settings were used for contrast-enhanced imaging in all subjects. Specific parameters included TR/TE/flip angle/voxel size/FoV/number of segments = 11.6 ms/4.3 ms/20°/ $2.2 \times 1.3 \times 8.0$ mm/23. Inversion time for the TurboFLASH sequence was optimized on an individual patient basis. Successful nulling of normal myocardium was deemed to have been achieved once the LV myocardium appeared black and homogenous. Generally, an inversion time of between 240 and 280 ms was required. Overall, scan time was approximately 30–40 min.

Data analysis

LV function was analyzed by two observers, blinded to patient clinical characteristics, from short axis cine loops using manual tracing of epicardial and endocardial end-systolic and end-diastolic contours with end-systolic and end-diastolic volumes and LV mass calculated using analysis software (Argus, Siemens, Erlangen, Germany). LVSD was defined as LV ejection fraction (LVEF) $<55\%$, with LVH defined as left ventricular mass index (LV mass/body surface area; LVMI) >84.1 g/m^2 (male) or >76.4 g/m^2 (female) and LV dilation defined as end diastolic volume/body surface area >111.7 ml/m^2 (male) or 99.3 ml/m^2 (female) or end systolic volume >92.8 ml (male) or 70.3 ml (female) based on based on mean normal LV dimensions for healthy volunteers plus 2 standard deviations.[35]

Contrast-enhanced image analysis

Myocardial fibrosis was documented as indicated by the presence of LGE as previously described,[14,15] with each image reviewed by two blinded observers. Images were assessed for the presence, pattern, and volume of gadolinium enhancement. Patients were classed as having positive LGE, if LGE was seen on at least two (of three) views: short axis view, long axis view, and reverse phase sequences, to exclude artefact. Artefact on the contrast-enhanced images was excluded by the acquisition of 'reverse phase' images through slice planes which appeared to demonstrate intramyocardial contrast enhancement. This technique involves the reversal of the phase-encoding and frequency-encoding directions as the phase-encoding direction is particularly prone to artefacts caused by cardiac motion or chest wall movement. Only areas of contrast enhancement that persisted on these reversed phase images were included in subsequent quantification of areas of contrast enhancement.

Areas of contrast enhancement were first identified visually and this area was contoured by manual planimetry to calculate volume of enhanced myocardial tissue. Mean signal intensities ($\pm$s.d.) for areas of contrast enhancement and for an adjacent reference area of non-enhancing myocardium were then determined using the Siemens Argus software. LGE was defined as an area of visually identified contrast enhancement with a mean signal intensity that was greater than one standard deviation higher than the mean signal intensity of an adjacent area of reference ventricular myocardium, which although nulled had a mean signal intensity significantly above zero. No manual alteration of image brightness/intensity settings was made during this process to ensure objective visual assessment of LGE. We subsequently analyzed patterns of gadolinium enhancement both subjectively and objectively based on mean signal intensity. LGE volume was determined by manual planimetry of any areas of contrast enhancement meeting these criteria. As dynamic scaling occurs for all images, to ensure internal consistency a mean signal intensity index was calculated as

$$\text{Mean signal intensity index} = \frac{\text{Mean intensity of region of LGE}}{\text{Mean intensity of nulled myocardium}}$$

LGE mass was calculated by multiplying LGE volume by myocardial density (1.05 g/cm^3) and is used as the absolute measured value of contrast-enhancing tissue seen.

Coronary angiography

A total of 49 patients underwent coronary angiography as part of assessment for renal transplant listing. Decision to perform angiography and interpretation of the angiogram was made by a cardiologist blinded to CMR findings, and was made on clinical grounds, based on symptoms, LVSD, or positive stress test (exercise test or myocardial perfusion scanning). CMR was performed within 3 months (before or after) of angiography. Patients were classified as having normal coronary arteries, mild/moderate coronary artery disease (presence of coronary plaque or up to 70% stenosis of any epicardial coronary artery), or severe coronary artery disease (presence of $>70\%$ stenosis of any epicardial coronary artery).

Statistical analysis

We compared the prevalence of conventional cardiovascular risk factors and LV abnormalities between those patients with, and without, the presence of myocardial fibrosis indicated by CMR by χ^2 or Fisher's exact test (as appropriate) for categorical data and paired *t*-test and Mann–Whitney –*U* testing for parametric or non-parametric data, respectively, for continuous data. Correlations between LV structure and biochemical (corrected calcium, albumin, glucose, cholesterol, urea reduction ratio in hemodialysis patients), hematological (hemoglobin), and demographic (age, blood pressure, time on renal replacement therapy) data were assessed using Pearson and Spearman correlation coefficient for parametric and non-parametric data, respectively. Analyses were performed using SPSS Version 11.5 (SPSS Inc., Chicago, IL, USA).

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