Are we overestimating left ventricular abnormalities in end-stage renal disease?

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Introduction

Uraemic cardiomyopathy, defined by the presence of left ventricular hypertrophy (LVH), left ventricular (LV) dilatation or LV systolic dysfunction (LVSD), is reported to be a predictor of premature cardiovascular mortality in patients with end-stage renal disease (ESRD) [1]. Each of these LV abnormalities
cumulatively confers a poorer long term prognosis [2]. LV function, dimensions and geometry have conventionally been assessed by echocardiography. Echocardiography is well established, portable and widely available and therefore will remain a vital clinical tool. However, echocardiography has drawbacks, including operator-dependence and difficulty in obtaining satisfactory acoustic windows. A major technological limitation of echocardiography is the geometric assumption required to calculate LV mass and function. Using conventional M-mode echocardiography to assess LV mass by the Penn [3] or ASE formulae [4], ventricular dimensions are measured in the minor axis and then volumes estimated from the cube of these values, hence magnifying initial errors. These techniques assume the left ventricle to be approximately cubic and, although validated in normal hearts, patients with ESRD have a high prevalence of LV abnormalities. As LVH in ESRD is due to a combination of pressure and volume overload, both concentric and eccentric remodelling ensue, with approximately 30% of patients exhibiting eccentric remodelling, that may invalidate the use of these formulae to calculate LV mass [5]. Moreover, definition of cardiomyopathy by echocardiography is difficult, due to the large variation in intravascular (and hence intraventricular) volume that occurs in the interdialytic period and during dialysis therapy [6]. Whilst these changes should not affect haemodynamic assessments such as measurement of ejection fraction or cardiac output, any inaccuracy in defining the left ventricular internal dimensions will lead to errors in detecting the presence of LV dilatation. Overall, echocardiographic measurements are critically dependent on phase of the dialysis cycle and ability to assess dry weight. Alternative techniques, e.g. cardiac magnetic resonance imaging (CMR) offer a volume-independent assessment.

Comparisons between echocardiography and cardiac magnetic resonance imaging for measurement of LV dimensions

Using M-mode echocardiography, a 1D technique, it has been demonstrated that echocardiography overestimates left ventricular mass in ESRD compared to CMR [7]. This disparity between the two methods has also been demonstrated in other patient populations, such as patients with LVH secondary to either hypertension [8] or aortic stenosis [9]. Conversely, in one large study of healthy army recruits, echocardiography (ASE formula) consistently underestimated LV mass compared to CMR by a mean of 14.3 g [10]. These studies, in keeping with those in ESRD, suggest that in patient groups with a high prevalence of LVH (and therefore distorted LV geometry) echocardiography tends to overestimate LV mass, but the difference between the methods is minimal or likely to be reduced or reversed when larger populations with normal hearts are studied.

Uraemic cardiomyopathy as assessed by cardiac magnetic resonance imaging

In incident ESRD patients, previous studies have suggested that the echocardiographic prevalence of LVH is 50–80%, with left ventricular dilatation in 20–40% and LVSD present in approximately 16% of patients [2]. However, in a cohort of ESRD patients being assessed for renal transplantation assessed by CMR, LVH was present in 71.6% patients, LV dilatation in 11.2% and LVSD in 8.2% [11]. The lower prevalence of LVSD may reflect the fact that potential transplant recipients are a ‘healthier’ ESRD cohort. Contrast-enhanced CMR with gadolinium-DTPA based in this study identified that the presence of both LVSD and LV dilatation are essentially restricted to patients with underlying coronary artery disease. This represents the only large cohort study using CMR in ESRD and it should be noted that the cohort of patients is smaller than in previous echocardiographic studies.

The majority of patients with ESRD also had LVH, the mean LV mass index was approximately 65 g m$^{-2}$ less than in similar large echocardiographic studies [1]. The implication is that whilst LVH remains the prevalent form of cardiomyopathy in patients with ESRD, by using CMR, the proportion of patients with LV dilatation is reduced, as accurate definition of the ventricular chamber is allowed and systematic overestimation of LV mass is avoided. Studies performing echocardiography pre- and post-dialysis suggest that the measured LV mass index differs by 26 g m$^{-2}$, (equivalent to an approximate change in absolute LV mass of 45 g) dependent on the timing of study and the associated changes in intravascular volume [12]. With CMR, the change in LV mass before and after dialysis has been shown to be of the order of 10 g [6]. Whilst some of the reduction in LV mass post dialysis is due to changes in the water content of the interstitial tissues of the heart in volume overload, the disparity between CMR and echocardiography suggests that any error in calculation of LV mass due to changes in chamber dimension is greatly magnified when echocardiography is used. Additionally, these findings suggest that LV chamber dimensions are dependent on hydration status and have been shown by CMR to significantly vary during the inter-dialytic period in patients receiving haemodialysis [6]. Accurate definition is therefore required to discriminate between the presence of LV dilatation due to hypervolaemia and that due to underlying ischaemic, rather than uraemic, cardiomyopathy.

It is worth stressing that initial studies comparing CMR to echocardiography were performed at 1.0 Tesla providing lower resolution CMR images [7,9,10].
compared to more recent studies performed using a 1.5 Tesla scanner using a fast imaging with steady state in free precession sequence (the current convention for CMR studies) [6,9,11] allowing better contrast between the ventricular myocardium and blood pool.

Although post-mortem validation comparing *in vivo* CMR images with post mortem specimens has not been performed in humans, *ex vivo* imaging studies show close agreement between CMR measured ventricular mass and true LV mass [13]. A number of studies have shown CMR to be reproducible with low inter- and intra-observer variability (typically approximately 5%), both in normal volunteers as well as in patients with left ventricular hypertrophy, heart failure, myocardial infarction and dilated cardiomyopathy [14].

**Can CMR allow us to improve echocardiographic methods in patients with ESRD?**

Comparison of these methods and development of algorithms to improve echocardiography methods is dependent on the fundamental premise that CMR does truly represent a ‘gold standard’ for measurement of LV dimensions, i.e. a reproducible, accurate method, independent of geometric assumptions and ideally validated with post mortem specimens. No attempt has yet been made to derive a correction factor to optimise M-mode echocardiographic measures of left ventricular mass in the ESRD population. Derivation of a revised echocardiographic formula for estimation of LV mass in ESRD is an attractive concept. Data from a pilot study (Figure 1) illustrates how such a formula may be developed. The relationship between the two methods to measure LV mass is approximately linear; therefore, a revised formula may only require a simple modification to the constant in the conventional Penn cube formula. Additionally, Figure 1 demonstrates that patients with LVMI >200 g.m⁻² by echocardiography are likely to have LVH confirmed by CMR. It is only patients with lesser degrees of LVH who may be mislabelled as having ‘uraemic cardiomyopathy’ (in the form of LVH), who may in fact have normal left ventricles. A larger comparative study is required to investigate both these notions, as well as to analyse whether gender difference or remodelling pattern is of importance in revising echocardiographic formulae.

Additionally, there are fundamental differences in the methods of analysis. LV mass is calculated by planimetry using a modified Simpson’s rule (Figure 2). Conventionally, the papillary muscles are included in drawing endocardial borders to perform CMR analysis of LV mass [15]. With echocardiography, the papillary muscles are avoided for M-mode measurements and excluded from the endocardial border for bi-plane measurements. This would appear to be a crucial issue but perhaps, as both methods, echocardiography and CMR, have evolved essentially separately and been validated against post-mortem specimens, animal models and latex casts, this issue is underplayed in the literature.
Improvements to echocardiographic technique for assessment of left ventricular mass

Although less widely used to estimate LV mass than the M-mode method, 2D echocardiography is more accurate and reproducible than M-mode methods. However, one study using these methods in patients with hypertension suggests that this technique also suffers from intra-observer variability and wide limits of agreement compared to CMR [16]. Using intravenous contrast combined with harmonic Doppler imaging has been shown to improve the accuracy of LV mass measurements with echocardiography. Finally, 3D echocardiography measures of LV mass show close correlation with CMR measures, although there are relatively few comparative studies [18]. It should therefore be remembered that the deficiencies in using echocardiography to define LVH reflect the assumptions used to calculate LV mass rather than the technique itself. The more complex echocardiographic techniques compare much more closely with CMR for measurements. These benefits may come at the expense of the ease and convenience of conventional echocardiography.

Limitations of CMR

CMR is obviously less widely available than echocardiography and is more expensive. To develop from a research tool into a more widely used clinical investigation, reduction in scan time is required, at least to perform a routine study of cardiac mass and function. Automated analysis software will allow the results of such studies to be rapidly processed. A number of patients will be unable to undergo scanning, due to standard contraindications to MRI such as claustrophobia, presence of a pacemaker or implantable cardiac defibrillator or other implanted ferromagnetic objects. Additionally, although contrast-enhanced CMR with gadolinium-based contrast agents offered some promising insights into myocardial tissue abnormalities in ESRD [11], the recent association between use of these contrast agents and development of nephrogenic systemic fibrosis will make further study using these agents impossible, until this safety issue is resolved [20].

Implications for treatment of uraemic cardiomyopathy

The prognostic implications of uraemic cardiomyopathy defined by CMR have not yet been reported. Although echocardiography may overestimate the prevalence of LVH, survival studies suggest that normal LV dimensions measured by echocardiography are associated with good long-term outcome [2]. As LVH is associated with poor outcome in ESRD, regression of LVH remains a therapeutic target. The ability to accurately detect small non-artefactual changes in LV mass by CMR allows smaller sample size in clinical trials of regression of LVH. One prospective study, comparing the effect of conventional versus nocturnal hemodialysis on LV mass, estimates that a total sample size of 38 patients (19 per limb allowing for patient dropout) will be required to detect a 10 g reduction in LV mass [19]. Potentially, such studies may be conducted in a single centre, reducing the costs and organisational support. Ultimately to reduce cardiovascular risk in patients with ESRD, better definition of cardiac dimensions is required to facilitate identification of targets for intervention. Whether this is by expanded use of CMR, 3D echocardiography or optimization of conventional echocardiography remains to be seen. Hopefully, these novel developments in cardiac imaging will translate into detection of superior methods of regression of LVH in appropriately powered clinical trials, either in patients with ESRD, or preferably, in patients with less severe chronic kidney disease, when regression of LVH is likely to be a more achievable goal.

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References

Agonistic antibody-triggered stimulation of Angiotensin II type 1 receptor and renal allograft vascular pathology

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Introduction

Despite the substantial improvements in post-transplantation management and novel immunosuppressive modalities that have resulted in improved overall survival, rejection with vascular involvement remains a challenging problem in organ allotransplantation. Acute vascular rejections have an aggressive clinical course and frequently lead to a loss of allograft [1]. The histopathology of vascular rejection applies to a wide variety of vascular lesions in the allograft, ranging from thrombosis, fibrinoid vascular necrosis and endarteritis to myointimal proliferation with fibrosis [2]. A definitive causal relationship that would explain whether overwhelming anti-donor T-cell response, or alloantibodies, or both are responsible for the development of vascular allograft lesions is still missing. Resistance to therapy with anti-lymphocyte antibody preparations or steroids [3], implicates the contribution of anti-donor humoral reactivity against human leukocyte antigens (HLA) and vascular rejection. Donor-specific anti-HLA alloantibodies initiate rejection through complement-mediated and antibody-dependent, cell-mediated, cytotoxicity [4]. The accumulation of the complement degradation product, C4d, is generally regarded as a marker for an antibody-mediated allosresponse and is associated with poor