Pre-operative echocardiographic abnormalities and adverse outcome following renal transplantation

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Abstract

Background. Premature cardiovascular disease is now the leading cause of death in renal transplant recipients. Although patients with progressive renal disease have many of the conventional risk factors for cardiovascular disease these do not have the same predictive power as they do in the general population. Echocardiographic abnormalities, notably left ventricular hypertrophy, have been shown to be associated with adverse outcome in patients on dialysis.

Methods. The echocardiograms were studied from 141 patients who were examined on the eve of renal transplantation between 1988 and 1990 to try to identify factors predicting outcome. Thirty-four patients have since died, 22 of cardiovascular disease. Ninety-three of the survivors and 27 of the dead patients had echocardiographic traces suitable for analysis.

Results. Left ventricular mass index was increased in those patients who died (median 167 vs 134 g/m²; P = 0.03), as were end-systolic (4.3 vs 3.4 cm; P < 0.01) and end-diastolic (5.8 vs 5.2 cm; P < 0.01) diameters. Systolic function was also more severely impaired (fractional shortening, 27 vs 33%; P < 0.01). Apart from age, only systolic function and end systolic diameter were independent predictors of outcome in multivariate analysis.

Conclusions. This pattern of echocardiographic abnormality is similar to that reported in long-term dialysis populations, despite the adverse effects on survival. Moreover, despite potential benefits of transplantation on cardiac function, left ventricular hypertrophy, ventricular dilatation and systolic dysfunction were all associated with adverse outcome following transplantation. We conclude that echocardiography identifies markers for premature death following transplantation and provides targets for therapeutic intervention.

Key words: echocardiography; left ventricular hypertrophy; renal transplantation; survival

Introduction

The paradox of successful advances in renal replacement is that patients with end-stage renal failure (ESRF) now die of premature cardiovascular disease rather than uraemia [1,2]. In the West of Scotland, where the prevalence of cardiovascular disease in the general population is among the highest in the world, cardiovascular complications in renal patients account for over a half of all deaths: a pattern mirrored in most northern European centres [1,2]. As a consequence, the need to address the causes and mechanisms of cardiovascular disease in patients with chronic renal failure, and particularly following renal transplantation, has become increasingly apparent.

In the general population several risk factors are well recognized and include age, dyslipidaemia, cigarette smoking and hypertension [3]. While these factors are likely to contribute to cardiovascular mortality in transplant recipients, the associations are not as clearly defined as in the general population [4]. Although this may be due to a direct effect of uraemia on cardiovascular risk it is possible that, as in essential hypertension, measurement of left ventricular mass may be more important than measurements of blood pressure. In support of this notion, left ventricular hypertrophy (LVH) has been associated with an adverse outcome in long-term dialysis patients [5]. However, the significance of echocardiographic measurements on survival in patients treated by renal transplantation has not been studied specifically.

In the present study we followed a cohort of 141 patients in whom echocardiography was performed immediately prior to renal transplantation between 1988 and 1990. The aims were to assess the influence of LV mass and other echocardiographic measurements of structure and function, on patient outcome following transplantation and to compare these with other risk factors for cardiovascular disease.

Patients and methods

Patients

Echocardiography was performed in 163 (of a possible consecutive 228) patients receiving renal transplants at the
Western Infirmary, Glasgow, between January 1988 and July 1990. The current analysis was performed in May 1996. Patients were included if they had developed end-stage renal failure in adult life and were excluded if they had diabetic nephropathy, rheumatic or congenital heart disease, or other systemic diseases involving the heart. All patients gave informed consent and the study was approved by the Western Infirmary Ethical Committee.

Of the 141 eligible patients, 34 have since died, 22 of cardiovascular causes (stroke, myocardial infarction, heart failure or sudden death). The other causes of death included sepsis, malignancy and suicide. In the analysis, the deaths have been examined as a whole group and as a subgroup of cardiovascular deaths (CVD) only.

**Patient data**

Full medical details and clinical examination findings were recorded prior to transplantation. Blood pressure was measured by one observer (EM) using a standard mercury sphygmomanometer. Routine haematological and biochemical tests were performed including serum cholesterol. Body surface area was determined from height and weight according to Boyd’s formula: 

\[
BSA = \frac{3.2 \times h^{0.725} \times w^{0.375} \times 0.01084 \times \log 2.075}{10^4 \text{m}^2}.
\]

**Echocardiography**

M-mode, two-dimensional and Doppler echocardiographic examination was undertaken by a single observer (EM) using a Hewlett-Packard ultrasound unit (model 77020A) with a 2.5 MHz transducer. Patients were studied in the left decubitus position with the probe in the third to the fifth intercostal space. All scans were recorded on video and, in the case of M-mode tracings, also on light sensitive paper at 50 mm/s. These recordings were coded and later analysed blindly by the operator (EM). Repeated echocardiographic measurements made on 10 occasions in a single subject, gave coefficients of variation of 4.9 and 4.3% for left ventricular mass and volume respectively. Independent, blinded analysis of a selection of traces by a second echocardiographer gave a correlation of 0.98 for LV mass. Traces which were suitable for determination of LV mass were analysed using a digitizing tablet (Kontron Ltd, UK) and a microcomputer (Cardio 80). Interventricular septal thickness (IVST), left ventricular internal dimension (LVID) and posterior wall thickness (PWT) were measured just distal to the tips of the mitral valve leaflets. Measurements were made over three cardiac cycles and the mean values were calculated. The timing of the cardiac cycle was assessed from simultaneous electrocardiographic recording.

Left ventricular mass (LVM) was determined from Devereux and Reichek’s formula, 

\[
LVM (g) = 1.04 (LVIDp + PWTp + IVSTp)^3 - (LVIDp)^3 - 13.6 \text{ g/m}^2.
\]

LVMI was corrected (mean ± SD) cm²/m² for BSA, to give the LVM index (LVMI). Left ventricular volumes at end-diastole (EDV) and end-systole (ESV) were estimated according to the method of Toledo et al. [7]. Values are also given for end-diastolic diameter (EDD) and end-systolic diameter (ESD). From these measurements, indices of systolic function, ejection fraction (EF = (EDV–ESV)/EDV) and fractional shortening (FS = (ESV–ESD)/EDD), were calculated.

**Analysis**

In the initial analysis, patients were divided into three groups: alive (A), dead (D) and dead from cardiovascular disease (CVD, a subgroup of D). Differences between patients in groups A vs D, and CVD vs the rest, were expressed using Wilcoxon confidence intervals for median differences between groups (for numerical data) and confidence intervals for the difference in proportions (for categorical data). These tests were performed using the MINITAB statistics package.

Survival analysis was then performed using the Cox proportional hazard model to identify factors related to cardiovascular death. Factors identified in univariate analysis were included in a multivariate analysis, and models identified using forward and backward stepwise regression. Kaplan–Meier survival curves were also generated; comparison of the survival curves above and below the median value was by the log-rank test (Figure 1). The SPSS statistics package (SPSS Inc., USA) was used for these analyses [8].

**Results**

Of 141 patients who underwent echocardiography, 120 had traces which were of adequate clarity to determine LV dimensions and mass. The summary data from all patients are shown in Table 1a. One hundred and seven patients were still alive in May 1996, a median of 7.5 years after renal transplantation and 82 of these had functioning renal allografts. Thirty-four patients had died, 22 of cardiovascular disease. The median time to death following transplantation was 2.1 years and the median age at death was 55.7 years. Overall the median follow-up was 6.5 years.

**Echocardiographic data**

Left ventricular mass measurements were increased with a median value of 144 g/m² in all patients. Although there were no normal control subjects in the present study, accepted upper limit of normal LV mass values from the Framingham population are 134–143 g/m² for men and 100–102 g/m² for women [9]. Previous studies of haemodialysis patients have demonstrated an increased prevalence of LVH. Silberberg and colleagues reported a mean LVM of 121 ± 32 (mean ± SD; range 65–198) g/m² [5]. In our series median end-diastolic diameter was increased at 5.3 (3.0–7.5) cm, and measurements of end-systolic diameter were similarly increased at 3.7 (2.1–7.1) cm consistent with Silberberg’s reported values of 3.1 ± 0.7 (mean ± SD) cm and 3.4 ± 0.7 (mean ± SD) cm respectively [5]. The median septal thickness was also increased at 1.6 (0.7–4.5) cm, although there was little difference in the posterior wall thickness, indicating that hypertrophy was asymmetrical.

In the group as a whole, fractional shortening was low at 31 (5–53)%, although the calculated ejection fraction was not with a median value of 54 (26–83)%.

The median E:A ratio, a measure of diastolic dysfunction, was 0.84 (0.37–5.07), suggesting that diastolic dysfunction is not of major importance in this population, although it is present in some patients.
Outcome and echocardiographic measures

Comparison of the echocardiographic findings in survivors and non-survivors (summarized in Table 1), revealed that median LVMI was significantly higher in the patients who died (167 vs 134 g/m², respectively). The LVMI of patients who died from cardiovascular causes was highest (177 g/m²). Ventricular dimensions showed a similar pattern: EDD was increased with a median value of 5.9 cm (CVD) and 5.8 cm (all deaths), compared with 5.2 cm in the survivors. The corresponding values for ESD were 4.7, 4.3 and 3.4 cm. Interestingly, there were no differences in the derived measurements of LV volume, which in view of the large observed differences in LV diameter could reflect the different accuracies in measurement of the appropriate ventricular axes or deficiencies in this method of assessment in patients with renal failure. Not surprisingly, in view of these findings, the comparison of the survival curves is arbitrary, but we examined the survival of patients subdivided into two groups by the median value of left ventricular mass index. Kaplan–Meier survival curves are shown in Figure 1A (LVMI, P < 0.01). Echocardiographic ventricular diameter and FS were also related to survival in a similar fashion (Figure 1B, C: FS, P < 0.01; ESD, P < 0.01).

Other risk factor data

It is essential to examine the role of echocardiographic measurements in the context of other recognized risk factors for cardiovascular death such as hypertension, hyperlipidaemia, cigarette smoking and previous cardiac disease. These data are also shown in Table 1. The most striking difference in any parameter was age at the time of transplantation. As has previously been reported [5] this was the most significant difference with an overall median value of 39 years; 37 years in...
the survivors, 53 years in the patients who died and 53 years in those who died of cardiovascular disease ($P<0.01$ dead vs alive and $P<0.01$ CVD vs rest).

There were no significant differences in the other recognized cardiovascular risk factors (Table 1b); hypertension, blood pressure measurements or in either total cholesterol or triglycerides (although these data are incomplete). The proportion of cigarette smokers was high at 37% overall, 37% in the survivors, 39% in the dead group, 38% in the CVD. The proportion of patients who had had a previous myocardial infarction was low, and there was no significant difference between the groups. Finally, there were no significant differences in the sex ratio, body mass index or haemoglobin. The latter measurement is of particular relevance as the severity of anaemia [11] is one factor known to influence LVMI.

**Multivariate analysis**

Since age is an irremediable risk factor we therefore attempted, as others have done [5], to determine the relative importance of all parameters including echocardiographic measurements on outcome using the Cox proportional hazards method [8]. These data are shown in Tables 2 and 3. In the initial analysis of cardiovascular deaths (CVD) six factors (of those listed in Table 1) were shown to be significantly associated with survival: age, ESD, FS, EDD, LVMI and EF. These findings are similar to those of Silberberg et al. [5] in a dialysis population. Stepwise regression analysis [8], to identify independent determinants of outcome (Table 3), revealed that age was the most important association. ESD and systolic function (FS) were also independent predictors of outcome.

**Discussion**

In this study we have examined the prognostic importance of echocardiographic left ventricular dimensions, mass and function at the time of renal transplantation in a cohort of patients followed for a median of 7.5 years.

**Echocardiographic data**

Left ventricular mass was increased before renal transplantation with a median value of 144 g/m$^2$. Although there were no normal control subjects, accepted upper limits of LV mass in the Framingham population are 131–143 g/m$^2$ for men and 100–102 g/m$^2$ for women [9]. These cut-off values would categorize 64–70% of men and 63–65% of women in the present study as having LVH. Previous reports in patients on dialysis have demonstrated an increased prevalence of LVH. Silberberg and colleagues reported mean values of LV mass of $121\pm32$ (mean $\pm$ SD); range (65–198) g/m$^2$ [5]. In a more recent study of 438 haemodialysis patients Parfrey et al. reported LVH in 41% [12]. The present study confirms these observations with LVMI values for men and women of 163(47, 507) and 116(61,
Table 2. Crude associations for CVD

<table>
<thead>
<tr>
<th>Variable</th>
<th>β (95% CI)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.083 (1.09, 1.04-1.13)</td>
<td>1.01-1.13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESD</td>
<td>0.797 (2.22, 1.51-3.27)</td>
<td>1.51-3.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FS</td>
<td>-8.17 (2.82 × 10⁻⁴, 2.31 × 10⁻⁶-0.31)</td>
<td>2.31×10⁻⁶-0.31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EDD</td>
<td>0.822 (2.27, 1.34-3.86)</td>
<td>1.34-3.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVMII</td>
<td>0.0045 (1.0045, 1.000-1.0008)</td>
<td>1.000-1.0008</td>
<td>0.03</td>
</tr>
<tr>
<td>EF</td>
<td>5.2621 (197, 1.1-3510)</td>
<td>1.1-3510</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 3. Independent associations following stepwise regression analysis, Cox proportional hazards model, for CVD

<table>
<thead>
<tr>
<th>Variable</th>
<th>β (95% CI)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.081 (1.08, 1.02-1.15)</td>
<td>1.02-1.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESD</td>
<td>0.768 (2.16, 1.27-3.66)</td>
<td>1.27-3.66</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FS</td>
<td>-7.40 (6.09 × 10⁻⁴, 1.14 × 10⁻⁶-0.32)</td>
<td>1.14×10⁻⁶-0.32</td>
<td>0.02</td>
</tr>
</tbody>
</table>

β represents the co-efficient [11]. RR the relative hazard ratio with 95% confidence intervals and P-value in adjacent columns.
following a short, pre-transplant treatment. CAPD patients are less subject to shifts in fluid status, yet might not have been at their ideal dry weight when studied. Although the absolute LV dimensions might have been affected, the conclusions of the study are unlikely to be altered.

**Outcome**

Of the original cohort of patients, 34 have died. Left ventricular mass index was significantly higher, by about 30 g/m\(^2\), in the patients who died compared with who are still alive (Table 1). When patients were stratified according to LVMII there were twice as many deaths in the group with LVMII above the median (Figure 1A). Subdivision of patients by LVMII, or other echocardiographic parameters is arbitrary. Silberberg used a value of 125 g/m\(^2\) for LVMII [5], close to the mean value for their patient group, while Parfrey used Framingham figures of 132 g/m\(^2\) for men and 100 g/m\(^2\) for women [8,12] both demonstrated a clear effect of increased LVMII and adverse outcome. Our data confirm these previous findings in dialysis populations but show that despite any possible beneficial effects of renal transplantation on the left ventricle [15,16]. The presence of increased left ventricular diameter and mass, and reduced fractional shortening, on the eve of renal transplantation is associated with a poor outcome. Fractional shortening was significantly less in patients who died, with a median value of just 23% in the patients who died of cardiovascular causes. The importance of poor systolic function is demonstrated in Figure 1B which depicts the effect on survival of subdividing the patients by the median FS. The end-systolic and end-diastolic dimensions were also increased in patients who subsequently died (Table 1) consistent with previous reports [5,12]. The effect of ESD on survival is shown in Figure 1C. Measurements of chamber diameter, and mass measurements derived from these, are obviously interrelated and it may be inappropriate to assess these parameters independently. Thus, although our data may be interpreted as showing the three patterns of ‘cardiomyopathy’ described by Parfrey et al. [12], these may be artificial subdivisions reflecting inter-related underlying abnormalities.

At the outset, the primary aim of this study, was to examine the role of LVH (LVMII) on outcome. However, the analysis (Tables 2, 3) identified ESD as a more significant and independent predictor of CVD. Previous studies have also shown that increased ESD is associated with adverse outcome [5,13] although this just failed to achieve statistical significance in the study of Silberberg and colleagues [5]. Ventricular dilatation may contribute to the higher calculated LVMII [6] and may conceivably be the most important abnormality. Further studies will be required to validate the measurements of LVMII made using echocardiography in patients on dialysis and to compare this method with other techniques such as magnetic resonance imaging. A related observation is that, although chamber diameter and FS were clearly abnormal and related to outcome, measurements of chamber volume and estimated ejection fraction (Table 1), and E/A ratio (a measure of diastolic dysfunction) did not exhibit the same strength of relationship. This may reflect the unreliable nature of derived echocardiographic indices in this population, and also the available technology at the time when this study was performed. It is possible that measurements of left ventricular volume and function using today’s echocardiographic equipment and analytical software would provide more consistent results [17].

Several questions arise from the echocardiographic abnormalities identified: (a) what are the mechanisms underlying the echocardiographic abnormalities? (b) how do they contribute to mortality? (c) can they be corrected? and (d) how do they relate to other risk factors for cardiovascular disease?

In the general population, the major determinants of LV mass are blood pressure and age [9]. There were no relationships between mean BP and LV mass or between age and LV mass in our study. The lack of relationship with BP may reflect the inadequacy of casual recordings and 24 h ambulatory monitoring may be more informative as it is following transplantation [18] and in progressive renal disease [19]. Alternatively, there may be other echocardiographic techniques such as magnetic resonance imaging. The importance of poor systolic function is associated with adverse outcome [5,13] although this may reflect the unreliable nature of derived echocardiographic indices in this population, and also the available technology at the time when this study was performed. It is possible that measurements of left ventricular volume and function using today’s echocardiographic equipment and analytical software would provide more consistent results [17].

Sudden death is the most common mode of death in patients on RRT, reflecting the increased susceptibility of the dilated or hypertrophied heart to develop arrhythmias. Alternatively, repeated and excessive ventricular dilatation may produce intractable left ventricular failure, which is known to be associated with adverse outcome in patients on dialysis [12].

The final question relates to the place of echocardiographic findings with other known risk factors for CVD. As in previous studies, age was the strongest determinant of outcome in the univariate analysis and
in the multivariate survival analysis was shown to be an independent risk factor (Tables 2, 3). However, the median age of the patients who subsequently died was just 53 years at the time of surgery—an age at which it would be impossible to deny transplantation—making it essential to identify other remediable risk factors. There were no differences in the prevalence of conventional risk factors: treated hypertension, the available cholesterol, and triglyceride measurements and, although cigarette smoking was significant in the univariate analysis, it was not an independent predictor of outcome. These observations are in general agreement with the literature [3,21]. Of the other factors included in the multivariate survival analysis only the echocardiographic measurements of ESD and EF were independent predictors. Therefore, it appears that these are of more prognostic value than conventional risk factors.

Studies are urgently required to determine whether the cardiovascular risk associated with echocardiographic abnormalities can be reversed before and following transplantation, and whether this translates into improved patient survival. It is likely that this will require revised targets for blood pressure control, stricter control of intravascular volume and perhaps the use of specific antihypertensive agents [22].

In conclusion, these findings suggest that patients with echocardiographic LV dilatation, hypertrophy or impaired cardiac function are at increased risk of cardiovascular death following renal transplantation, despite the possible cardiac benefits for that transplantation might confer. Such abnormalities are common in dialysis patients selected for renal transplantation and may contribute to the very high cardiovascular mortality in this group.

Cardiovascular risk in patients treated by renal transplantation is likely to be cumulative and to reflect different influences and risk factors during progressive renal disease, dialysis and transplantation. In each phase different potential risk factors are important including hypertension, hyperlipidaemia, immunosuppressive therapy and the uraemic state. Thus, the present study is only a ‘snap-shot’ of risk albeit immediately prior to transplantation, the major event in the life of most patients on RRT. The present study confirms that echocardiographic abnormalities are an independent predictor of outcome following transplantation and it is likely that targeting such factors will save more lives than foreseeable developments in dialysis and immunosuppressive therapy. Moreover, cardiac pathology develops progressively over the course of renal disease. Left ventricular hypertrophy has recently been reported in patients with normal renal function in the early stages of primary renal disease [10], and irreversible features such as interstitial fibrosis are present prior to dialysis [20]. Whilst it may be possible to regress some of the cardiac abnormalities in dialysis patients or following transplantation strategies must be developed to prevent their development beginning at the first clinic visit of patients with progressive renal disease.

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