Early echocardiographic changes and survival following renal transplantation

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Abstract

Background. Left ventricular hypertrophy, ventricular dilatation and poor systolic function prior to renal transplantation are associated with increased mortality. However, whether the improvement in these echocardiographic indices that is reported to follow renal transplantation improves patient survival has not been investigated.

Methods. We studied 67 patients who underwent renal transplantation in our unit between 1988 and 1990 and in whom echocardiography was performed immediately prior to transplant surgery and 4 months later. Pre- and post-transplantation echocardiographic parameters were compared between the 20 patients who have since died and surviving patients and a descriptive survival analysis was performed.

Results. Following transplantation there was no significant change in left ventricular mass index (LVMI) or end diastolic diameter (EDD). End systolic diameter (ESD) improved in 60% of patients (median 3.3 vs 3.7 cm; \( P = 0.031 \)) as did fractional shortening in 67% (0.33 vs 0.29; \( P = 0.001 \)). However, improvement was not associated with survival benefits. We also found that prior to transplantation, fractional shortening, ESD and EDD were strongly associated with outcome; this was no longer the case following transplantation. In contrast, LVMI provided a stronger association with adverse outcome (albeit of limited statistical significance) following transplantation.

Conclusions. In this Preliminary Report, we conclude that echocardiographic parameters are associated with adverse outcome in patients receiving renal replacement therapy (RRT). Different echocardiographic parameters are associated with adverse outcome before and after renal transplantation and improvement of pre-transplant abnormalities (e.g. poor LV systolic function) following transplantation does not necessarily confer survival benefits. Whether this is a genuine observation or a reflection of the interpretation of echocardiographic measurements in dialysis patients requires further investigation.

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

Introduction

Although patients with end-stage renal failure have a greatly increased risk of cardiovascular disease (CVD) (regardless of the mode of renal replacement therapy (RRT)), conventional risk factors for CVD are of limited prognostic value [1,2]. Recently, the prognostic importance of echocardiographic abnormalities, including left ventricular hypertrophy (LVH), ventricular dilatation and systolic dysfunction have been shown in patients on maintenance dialysis [3–5]. We have extended these findings to show that these echocardiographic abnormalities are common—and of prognostic significance—immediately prior to renal transplantation [6]. Following transplantation, most, but not all, investigators have shown improvement in systolic function and reduction in left ventricular mass (LVM) [7–12], often within a few months of surgery. However, whether improvement in echocardiographic parameters results in improved patient survival has not been investigated. We therefore studied 67 patients who underwent echocardiography immediately prior to renal transplantation at our institution (between 1988 and 1990) and in whom repeat echocardiography was performed a few months following transplant surgery. The aims of this study were to determine whether echocardiographic parameters associated with poor survival (including LVH, ventricular dilatation and systolic dysfunction) improve following transplantation, and whether improvement confers survival benefits.

Methods

Patients

In a prospective study, echocardiography was performed in 163 patients receiving renal transplants at this centre, between January 1988 and July 1990. The association between pre-
transplant echocardiographic findings and long-term survival has recently been reported [6]. In 67 patients, repeat echocardiography was performed (prospectively, as part of the study) 4 months after transplant surgery (median 4, range 3–12 months). The number of follow-up examinations was restricted to 67 for logistical reasons, as there were no data available at the time of this study on which to base either the numbers or timing of follow-up examinations. Hence, the timing and number of investigations were arbitrary. The current analysis included patients who underwent two echocardiograms, comparing the pre- and post-transplantation findings and their association with long-term survival. All patients gave informed consent and the study was approved by the local hospital Ethical Committee. The clinical and demographic features of this subset are similar to the main study population (Table 1) [6], and the overall survival similar to that previously reported at our centre [13].

Of the 67 patients studied, all commenced RRT in adult life and three had diabetic nephropathy. Twenty patients died before June 1999, when the present analysis was performed.

**Patient data**

Clinical history and examination findings were recorded prior to transplantation, and at the time of follow-up echocardiography. One observer (EM) measured blood pressure with a standard mercury sphygmomanometer. Follow-up data on patient and graft survival were obtained from the clinical records. Detailed information on cause of death was not available for all patients and, in view of this and the small size of the study, no attempt was made to compare cardiovascular deaths with all cause mortality [6].

**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, as previously described [6]. LVM, chamber size and volumes were calculated from the M-mode echocardiogram using methodology in use at the time of the study. The reproducibility of the pre-transplant measurements (inter- and intra-observer variability) has been reported and was not repeated for the post-transplant measurement [6]. LVM was determined from the formula of Devereux and Reichek; LVM(g) = 1.04 [(LVIDp + PWTp + IVSTp)3 – LVID3] – 13.6 [14,15]; corrected for body surface area, to give the LVM index (LVMI). In view of our previous experience of derived measurements of chamber volume and function [6], only chamber diameters are reported from which fractional shortening (FS = (EDD – ESD)/EDD) was calculated as an index of systolic function. (EDD, end diastolic diameter; ESD, end systolic diameter.)

**Analysis**

The data are presented as median (range) in Table 2. Differences between dead and surviving patients were analysed by Kruskall–Wallis analysis of variance. Comparisons between pre- and post-transplant measurements were made by Mann–Whitney U test. Differences in proportions were determined by χ2 test. Survival analysis was then performed by the method of Kaplan–Meier. In view of the small number of subjects studied, and the fact that many of the echocardiographic measurements are inter-dependent, these survival curves are largely descriptive and the data were not subjected to multivariate analysis [6]. Comparison of the survival curves above and below the median value was by the log-rank test (Figure 1). The SPSS statistics package (SPSS V7.5, SPSS Inc., USA) was used for these analyses [13,16].

**Results**

Of the 67 patients studied, 20 have since died during a median follow-up period of 9.8 years (range 0.5–11.2) following renal transplantation. The median age at transplantation was 38.3 years (range 18.7–64.5). All patients had functioning transplants (median serum creatinine at follow-up echocardiography 141 μmol/l (range 54–482)) and were treated with cyclosporin A and low dose steroids [17]. Overall survival was similar to that previously reported at our centre [13]. There was no difference in renal function at the time of repeat echocardiography in the patients who died and survivors (162 (66–394) vs 134 (54–482); P = 0.49). Age at transplantation was significantly greater in those who died (median 49.3 vs 32.5 years; P = 0.001). Median blood pressure prior to transplantation was 150/90 mmHg and fell to 137/86 mmHg at the time of the repeat echocardiography, the fall in both systolic and diastolic blood pressure being significant (P < 0.01; Table 2). There was a trend for the systolic blood pressure (SBP) to be higher in those patients who subsequently died; the difference in the pre-operative

**Table 1.** Background data. Age at transplantation (years), SBP (systolic blood pressure, mmHg), DBP (diastolic blood pressure, mmHg), Hb (haemoglobin, g/dl), LVMI (left ventricular mass index, g/m²), FS (fractional shortening, %) EDD, ESD (end diastolic and systolic diameters, cm). Three comparisons are presented. (i) Pre- and post-transplantation. (ii) Alive vs dead (pre-transplant). (iii) Alive vs dead (post-transplant). Adjacent P values represent comparison by Mann–Whitney test. All data are shown as median (range)

<table>
<thead>
<tr>
<th></th>
<th>Current population</th>
<th>Main study [6]</th>
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<tbody>
<tr>
<td>Age at transplant (years)</td>
<td>38 (19, 65)</td>
<td>39 (18, 65)</td>
</tr>
<tr>
<td>Gender</td>
<td>25 female, 42 male</td>
<td>56 female, 85 male</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3/67</td>
<td>0/141</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46/67</td>
<td>101/139</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.0 (4.8, 13)</td>
<td>9.1 (4.8, 14.6)</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>23.67 (34%)</td>
<td>28%</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>57/67 (84%)</td>
<td>83%</td>
</tr>
<tr>
<td>LVH</td>
<td>72–76% women, 67–71% men</td>
<td>63–65% women, 64–70% men</td>
</tr>
</tbody>
</table>
Echocardiography changes after renal transplantation

SBP was statistically significant ($P=0.03$; Table 2). Haemoglobin increased predictably following transplantation from a median value of 9.0–12.4 g/dl ($P=0.001$).

Echocardiographic data

Prior to transplantation LVM was increased with around two thirds of the population fulfilling the Framingham criteria for LVH [6,10] (Table 1). Following transplantation there was no improvement in LVM; LVMI decreased in 53% and increased in 47% of patients during the median period of 4 months between investigations. There was no significant difference in the median value which increased from 143 to 145 g/m$^2$ ($P=0.71$). EDD also failed to show a consistent pattern, EDD decreased in 51% of patients and there was no significant reduction in the median value (5.1 vs 5.2 cm; $P=0.980$). There was, however, a significant decrease in ESD (3.3 vs 3.7 cm; $P=0.031$), which improved in 60% of patients. Systolic function also showed a more consistent trend, with an increase in median FS following transplantation (0.33 vs 0.29; $P=0.001$), and improvement in 68% of patients.

Outcome and echocardiographic measures

In view of the small number of patients, and the fact that echocardiographic parameters are inter-related, we limited survival analysis to a simple descriptive level [6]. The patients were subdivided by the median value of echocardiographic parameters in a Kaplan–Meier analysis [3,6] but were not subjected to multivariate analysis (Figure 1). There were significant differences in the pre-transplantation FS, EDD and ESD curves ($P=0.005$, 0.008 and $<0.001$ respectively, log-rank test) but there was no significant influence of LVMI ($P=0.130$).

The post-transplant analysis revealed a different pattern. There were no significant differences in patient survival in the curves for FS or EDD subdividing the population by the median value of each of these parameters ($P=0.446$ and 0.996 respectively, log rank test) and ESD achieved only borderline significance ($P=0.042$). An increased LVMI ($P=0.092$) showed a trend towards adverse outcome but did not achieve statistical significance.

A simple comparison of echocardiographic parameters between survivors and those who died (Table 1) shows a similar pattern to the Kaplan–Meier curves. Prior to transplantation, the major differences between patients who died and survivors were in end diastolic and systolic dimensions (EDD 5.6 vs 5.0 cm; $P<0.01$; ESD 4.1 vs 3.4 cm; $P<0.01$; dead vs alive), and systolic function (FS 0.25 vs 0.32, $P=0.02$). However, there were no significant differences in any of these parameters following transplantation between survivors and patients who died (Table 2). Although a higher LVMI was observed both prior to transplantation and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Tx</th>
<th>Post-Tx</th>
<th>$P$</th>
<th>Pre-Tx</th>
<th>Post-Tx</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38.3 (18.7, 64.5)</td>
<td>35.8 (18.0, 64.5)</td>
<td>&lt;0.01</td>
<td>35.8 (18.0, 64.5)</td>
<td>35.8 (18.0, 64.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150 (104, 200)</td>
<td>144 (104, 200)</td>
<td>0.03</td>
<td>144 (104, 200)</td>
<td>144 (104, 200)</td>
<td>0.03</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90 (60, 125)</td>
<td>86 (60, 125)</td>
<td>&lt;0.01</td>
<td>86 (60, 125)</td>
<td>86 (60, 125)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.0 (4.8, 13.0)</td>
<td>12.4 (8.3, 17.5)</td>
<td>&lt;0.01</td>
<td>8.8 (5.0, 13.0)</td>
<td>10.2 (4.8, 12.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ct (u/l)</td>
<td>162 (66, 394)</td>
<td>134 (54, 482)</td>
<td>0.49</td>
<td>134 (54, 482)</td>
<td>134 (54, 482)</td>
<td>0.49</td>
</tr>
<tr>
<td>LVMI (g/m$^2$)</td>
<td>143 (61, 483)</td>
<td>145 (62, 483)</td>
<td>0.71</td>
<td>145 (62, 483)</td>
<td>145 (62, 483)</td>
<td>0.71</td>
</tr>
<tr>
<td>FS (%)</td>
<td>29.3 (5.2, 52)</td>
<td>33.0 (9, 55)</td>
<td>&lt;0.01</td>
<td>33.0 (9, 55)</td>
<td>33.0 (9, 55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>5.2 (3.0, 7.5)</td>
<td>5.1 (3.0, 7.0)</td>
<td>0.98</td>
<td>5.0 (3.0, 7.3)</td>
<td>5.6 (4.9, 7.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>3.7 (2.1, 5.4)</td>
<td>3.3 (2.0, 5.4)</td>
<td>0.03</td>
<td>3.3 (2.0, 5.4)</td>
<td>3.3 (2.0, 5.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

SBP was statistically significant ($P=0.03$; Table 2). Haemoglobin increased predictably following transplantation from a median value of 9.0–12.4 g/dl ($P=0.001$).
Fig. 1. Kaplan–Meier survival curves. Left column, pre-transplantation and right column, post-transplantation. Each graph shows survival curves for 12 years following renal transplantation dividing the population by the median of each parameter. Solid lines indicate subjects below the median, dashed lines those above the median value (Table 2). *P* values (log-rank test): LVMI (pre) 0.130, LVMI (post) 0.092; EDD (pre) 0.008, EDD (post) 0.996; ESD (pre) <0.001, ESD (post) 0.042; FS (pre) 0.005, FS (post) 0.446.
in the follow-up measurement in the patients who died, this was of borderline significance (median 168 vs 131 g/m²; \( P = 0.05 \)) prior to transplantation, compared with the highly significant differences in ESD, EDD and FS. In contrast, LVMI was the only significantly different echocardiographic parameter following transplantation (166 vs 132 g/m²; \( P = 0.04 \)).

One of the aims of the present study was to determine whether improvement in pre-transplant echocardiographic parameters associated with poor outcome, results in a reversal of these prognostic influences. Overall, LVMI, ESD, EDD and FS improved in 53%, 60%, 51% and 67% of patients respectively. However, a benefit on survival was not seen. In the patients whose LVMI decreased, 34% died, compared with 26% in the group whose LVMI increased. The corresponding values for ESD, EDD and FS were 34%, 35% and 35% in those whose measurements improved and 20%, 24% and 19% in those whose measurements worsened. Similarly, the data in Table 2 shows that there were only significant differences in these echocardiographic parameters (between survivors and those patients who have died) prior to transplantation.

**Discussion**

In a recent study we found that echocardiographic abnormalities present immediately prior to renal transplantation (specifically increased chamber diameter, increased LVMI and reduced FS) were associated with adverse outcome [6]. In this study, we have followed a smaller group of patients in whom echocardiography was performed before and a few months after renal transplantation, and have examined the influence of pre- and post-transplantation parameters and changes therein on patient survival. Although previous studies have reported changes in echocardiographic parameters following transplantation [7–12] we believe this is the first study that attempts to relate these to patient outcome.

LVMI did not change significantly following transplantation. Although the time interval between studies was short, regression of LVH may occur over such a period in patients with essential hypertension and good blood pressure control and has previously been observed following renal transplantation [10]. Most other studies showing a reduction in LVMI following renal transplantation have been conducted in smaller cohorts of patients but at a longer interval following renal transplantation [7–12]; and reduction in LVMI has not been a universal observation [11]. Such variability may be due to the balance of determinants of blood pressure following successful transplantation, although it may reflect the variability of echocardiographic measurements of LVM in dialysis patients [6]. While some factors such as intravascular volume should return to normal, others including immunosuppressive therapy and correction of anaemia, may contribute to a rise in blood pressure and thus increased LVMI. Correction of anaemia may have dual effects, contributing to an increase in blood pressure but also helping to regress LVH by improving oxygen delivery [18]. In our study, there was no change in LVM despite reduction in blood pressure and improved haemoglobin. Although we do not have information on intravascular volume, nor on other potential confounding factors such as spontaneous closure of haemodialysis access, it is probable that a longer interval between transplantation and repeat echocardiography would be required to establish the natural history of LVH in this population. Alternatively, the use of magnetic resonance imaging (MRI) may provide a better method for the assessment of cardiac structure and function and independent of intravascular volume [4,19] permitting a definitive analysis in a small group of patients.

Correction of intravascular volume homeostasis would be expected to reduce ESD and EDD. Surprisingly, only ESD was reduced, a change that is likely to reflect improved systolic function (FS) in some patients. The failure of EDD to improve may reflect some irreversible condition, such as dilated cardiomyopathy, as has previously been described by Parfrey and colleagues [4,5,7]. Again, the balance of evidence from published studies is for a major improvement in systolic function following renal transplantation, associated with reduction in intravascular volume and cardiac chamber diameters. Improved FS is likely to be a consequence of correction of anaemia and uraemia [7,18]. Thus overall, with the exception of LVMI, most of the echocardiographic parameters measured in this study showed a trend towards improvement consistent with previous reports [7–12]. To determine whether such changes confer survival benefits we compared variables between survivors and patients who died in a limited survival analysis (Figure 1; Table 2).

There were differences in the relationship between pre- and post-transplant echocardiographic parameters and outcome. Prior to transplantation, ventricular dilatation (ESD and EDD) and poor systolic function were associated with a poor outcome. Pre-transplant LVMI was also higher in the patients who died (168 vs 131 g/m²) but achieved only borderline significance (\( P = 0.05 \)). This confirms our previous findings in a larger and related study [6] and the findings reported for patients on dialysis programmes [1,3–5]. However, following transplantation we observed a different relationship between echocardiographic parameters and outcome. There was a slightly stronger relationship between increased LVMI, which was significantly increased in patients who died (166 vs 132 g/m²; \( P = 0.04 \)), but with a clearer pattern in the Kaplan–Meier curves (Figure 1; Table 2). In contrast to the pre-transplantation findings, chamber diameters and systolic function post-transplantation showed almost no association with outcome (Figure 1; Table 2). These observations reinforce the prognostic importance of echocardiographic measurement and show that different parameters are likely to be important at different stages in the lives of patients on renal replacement.
programmes. Moreover, our findings demonstrate that, although there may be improvement in some echocardiographic parameters following transplantation (specifically ESD and FS), this may not necessarily improve outcome. This probably reflects the fact that the patients who died had poorer starting echocardiographic indices and were thus more likely to show improvement. However, it also implies that it is important to address and correct echocardiographic abnormalities when they develop [20,21], and before the development of irreversible structural changes [21], rather than assume that they will regress following transplantation [7–10,12].

In conclusion, although this is a small-scale study using dated echocardiographic methodology, it is the first to relate changes in echocardiographic parameters around the time of transplantation to patient outcome. We have found that ventricular dilatation and poor systolic function prior to transplantation, but not following transplantation, are associated with an adverse outcome. In contrast, the presence of LVH may be a marker for outcome following transplantation. To our disappointment, improvement in echo parameters following transplantation did not appear to improve survival, albeit in this small study with relatively few end-points. However, the insensitivity of echocardiographic measurements of LVM and function (which have never been specifically validated in this population) [13,14,19,22] is likely to have contributed. Further studies are required using modern methodology [19], such as cardiac MRI [22], to identify abnormalities in cardiac structure and function in patients on renal replacement therapy and to develop novel strategies for their correction [23].

References

11. Huting J. Course of left ventricular hypertrophy and function in end-stage renal disease after renal transplantation. Am J Cardiol 1992; 70: 1481–1484

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