Prospective evaluation of aortic stenosis in end-stage kidney disease: a more fulminating process?

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Abstract

Background. We have previously demonstrated an increased rate of progression of aortic stenosis (AS) in patients with end-stage kidney disease (CKD 5D) compared to controls. We sought to follow prospectively a CKD 5D cohort with AS and determine major event-free survival. Follow-up was terminated once all CKD 5D subjects had undergone aortic valve replacement (AVR) or died. Our aim was to determine whether the increased rate of progression resulted in shorter major event-free (AVR or death) survival as compared to controls.

Methods. We re-matched our original CKD 5D cohort (n = 27) to a control cohort (n = 27) based on aortic valve area (AVA) at completion of the prior study. This was done...
as CKD 5D and AVA were the only statistically significant variables with respect to rate of progression.

**Results.** All the CKD 5D patients (100%) underwent surgery or died during the follow-up period. In contrast, 17 (63%) of the controls underwent surgery or died. Of the remaining 10 controls, nine remain alive and free of AVR and one was lost to follow-up.

**Conclusion.** The controls displayed greater major event-free survival (P = 0.001), suggesting a need to consider patients with CKD 5D and AS for early AVR once echocardiographic evidence of moderate to severe AS is present, regardless of symptoms.

**Keywords:** aortic stenosis; aortic valve replacement; dialysis; mortality; survival

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**Introduction**

Cardiovascular morbidity and mortality is common in patients with end-stage kidney disease (CKD 5D) [1]. Aortic valve disease occurs more often [2–6] in this population. We have previously reported an accelerated progression of AS in a CKD 5D population compared with sex-matched controls [7]. Multivariate regression analysis in that study demonstrated that the only statistically significant predictors of subsequent progression of AS were concomitant dialysis (P = 0.02) and baseline aortic valve area (AVA) (P = 0.04). Serum phosphate, calcium, calcium-phosphate product and parathyroid hormone levels did not correlate with progression in our population despite previous publications that these factors predict progression [8]. The cause of the more rapid disease progression in AS in the CKD 5D population remains unclear and is likely multifactorial.

Echocardiographically, the presence of moderate to severe calcification of the aortic valve in non-CKD 5D subjects has been demonstrated to be associated with more rapid disease progression and a shorter time to aortic valve replacement (AVR) or death [9]. In a prospective study of subjects on dialysis, baseline calcification of the AV was associated with a greater progression in stenosis severity over 12 months [10]. Unfortunately, the significant difference in valve area at baseline between the subjects with non-calcified and calcified AS limits the conclusions that can be drawn from the presence of calcification per se.

There are few prospective data in the literature regarding outcomes associated with AS in the CKD 5D population, and it is unclear whether rate of progression might be a surrogate marker for morbidity and mortality in this population. Although recent guidelines state that a high likelihood of progression is an indication for AVR in patients with severe asymptomatic aortic stenosis (level of evidence C) [11,12], whether the presence of CKD 5D should be a marker of ‘high likelihood of progression’ remains unclear.

In order to determine the natural history of AS progression in CKD 5D, we assessed the risk of death or aortic valve replacement prospectively in CKD 5D patients and controls from our original study group [7]. There is a background overall mortality rate for individuals receiving dialysis in Australia of ~12% per annum (reference anzdata.org.au).

**Materials and methods**

The original patient and control group selection has been previously described in detail [7]. Briefly, all patients with CKD 5D and an echocardiogram demonstrating AS (defined as maximal peak velocity across the aortic valve >2 m/s) between January 1999 and May 2000 were included. Each patient had two controls, with AVA, matched for gender and proximity to a CKD 5D patient study date.

Of the original CKD 5D group (n = 28), 27 had echocardiography performed at our institution. These formed the patient cohort in our current study. Matching for AVA was performed by hand to 27 of the original 56 controls. Neither gender nor age formed part of the matching process as these variables had not been found to be significant in the initial study.

Regular contact with the dialysis service at the Royal Melbourne Hospital provided updates on morbidity and mortality status. In July 2007, the study was terminated, with all of the 27 CKD 5D patients having either undergone AVR or died.

As previously published [7], at study inception the CKD 5D group had a mean age of 67 years (8.1) and a mean of 4.5 years (5.7) post-commencement of dialysis. Dialysate calcium concentration in our institution was 1.3 mM/L.

Outcomes were then established, as accurately as possible, for the control population. A medical records search was supplemented by contact with the treating doctor, the general practitioner and the Bureau of Births, Deaths and Marriages (Victoria).

Of the 27 patients with CKD 5D, none were lost to follow-up. Of the 27 controls, one was lost to follow-up. This was an elderly individual (aged 92 at recruitment) discharged from hospital 36 days after her echocardiogram for whom no further details could be obtained (including no record of death in the State of Victoria).

Major event-free survival was determined as the days that had elapsed between the echocardiogram performed at commencement of this study and the date at which the final endpoint was reached. Dates of AVR and death were collected for all participants, while those alive without surgery were censored at study end (July 2007). The final endpoint date was thus either date of AVR operation, date of death, date last seen alive or the date at the end of study.

This study was approved by the Royal Melbourne Hospital Human Research and Ethics Committee.

**Statistics**

As variables were normally distributed, two-sample t-tests were used to compare continuous variables between study groups and Pearson’s chi-square tests were used to compare categorical variables. Time to endpoint was non-normally distributed and thus described non-parametrically as median (interquartile range). Kaplan–Meier survival analysis and log-rank tests were used to compare major event-free survival time between patients and controls. Hazard ratios and 95% confidence intervals of major events in patients compared with control were derived using Cox proportional hazard models. Two-sided P-values <0.05 indicated statistical significance. All the statistical analyses were done using SPSS version 17. Graphs were created using GraphPad Prism, version 4.0c.

**Results**

**Baseline characteristics**

The two groups were hand matched for AVA (mean AVA = 1.14 cm²) (Table 1). The mean age was not different between the groups, but the patients in the CKD 5D group were more likely to be male (P = 0.09), consistent with the broader Australian dialysis population (reference to anzdata.org.au website).
The ESKD cohort had biochemical variables available at the time of the original echocardiogram. These results demonstrated mean Ca$^{2+}$ of 2.32 mmol/L (0.22), mean PO$_4^{-}$ of 1.71 mmol/L (0.33), mean PTH of 35.66 pg/mL (34.40) and a calcium-phosphate product of 3.68 (1.35). As a group, lipid profile data demonstrated mean cholesterol of 4.9 mmol/L (1.13) and triglycerides of 2.34 mmol/L (2.0).

**Outcomes**

Within the CKD 5D group, there were 15 deaths and 12 AVRs. In contrast, in the control group there were 11 deaths, six AVRs and nine subjects surviving free of an AVR. As described, one patient was lost to follow-up in this group.

We had predetermined that the study would end once all CKD 5D patients had either undergone an AVR or died. Over this time period, nine (33%) of the control population remained operation-free and alive (Figure 1).

**Major event-free survival**

Major event-free survival time was significantly greater in the control group compared with the CKD 5D group [median 1316 vs 426 days; P log-rank test = 0.001, HR and 95% CI: 2.83 (1.50–5.33); Figure 1].

**Outcomes in the severe AS population**

It is likely that symptoms will appear earlier in people with more severe AS, resulting in either death or surgical referral. We thus also looked at outcomes according to whether severe AS was present at the baseline echo study, with severe AS defined as being present when any of the following criteria were met: a mean gradient >40 mmHg, an AVA <1.0 cm$^2$ or $V_{max}$ >4 m/s [11]. Subjects with any of those criteria on the initial echocardiogram were classified as subjects having severe AS.

These criteria identified 12 subjects in the CKD 5D and 14 subjects in the control cohort with severe AS. In the CKD 5D group, AVA was <1.0 cm$^2$ in 12 subjects, mean gradient was >40 mmHg in six subjects and $V_{max}$ was >4 m/s in six subjects. In the control group, AVA was <1.0 cm$^2$ in 12 subjects, mean gradient was >40 mmHg in six subjects and $V_{max}$ was >4 m/s in six subjects.

Table 2 and Figure 2 details the baseline results for the subgroups of each cohort classified as having severe AS according to current guidelines.

Baseline echocardiographic variables between the severe AS subgroups within each cohort were not statistically significantly different, as was expected given that these pre-determined criteria identified them. However, individuals with CKD 5D had a subsequent rapid progression to operation or death.

**Characteristics at time of surgical referral**

A total of 18 patients underwent AVR. The 12 patients within the CKD 5D cohort had a preoperative AVA of 0.96 cm$^2$ (0.26), with a mean gradient of 46 mmHg (9.8) and a peak gradient of 78 mmHg (17.8). Maximum velocity recorded through the aortic valve was 4.4 m/s (0.5). The six controls had a preoperative AVA of 0.84 cm$^2$ (0.09), with a mean gradient of 52 mmHg (11) and a peak gradient of 81 mmHg (19.2). Maximum velocity recorded through the aortic valve was 4.5 m/s (0.5). There was no statistical difference in any echocardiographic measure of AS severity between the two groups prior to surgical referral for AVR.

**Age**

The mean age at recruitment of those who underwent surgery was younger in both the control and CKD 5D cohorts than the mean age of those who died [AVR: 57.2 years (12.7) (controls) and 61.8 years (8.6) (CKD 5D) compared to those who died: 69.9 years (9.1) and 72.9 years (3.7), respectively]. The difference in age between the control patients who had an AVR and those who died was not statistically significant (P = 0.07). The difference in age between the CKD 5D patients who had an AVR and those who died was statistically significant (P = 0.003).

The age at final outcome did not differ between the cohorts, despite the longer time to outcome in the controls, because the control cohort was slightly younger at recruitment than the CKD 5D patients (Table 2, P = ns).

The nine controls that survived free of operation were of a similar age at study commencement as those controls that died [71.6 (11.2)]. Although their AVA was larger [1.3 cm$^2$ (0.5)] compared to the rest of the control popula-

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**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD 5D (n = 27)</th>
<th>Controls (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.0 (8.3)</td>
<td>68.5 (12.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>AVA (cm$^2$)</td>
<td>1.14 (0.41)</td>
<td>1.14 (0.41)</td>
<td>0.87</td>
</tr>
<tr>
<td>Male (%)</td>
<td>74 (0.41)</td>
<td>52 (0.41)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

This table shows the mean (standard deviation) values for age and baseline aortic valve area (AVA) and percent of males in the end-stage kidney disease (CKD 5D) group and controls.

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**Fig. 1.** Major event-free survival.
Table 2. Baseline measures in the subjects with severe aortic stenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD 5D (n = 12)</th>
<th>Controls (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at recruitment (years)</td>
<td>68.5 (8.5)</td>
<td>67.1 (12.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Baseline AVA (cm²)</td>
<td>0.80 (0.13)</td>
<td>0.81 (0.14)</td>
<td>1.0</td>
</tr>
<tr>
<td>Baseline mean gradient (mmHg)</td>
<td>39.1 (15.6)</td>
<td>34.8 (14.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline $v_{max}$ (m/s)</td>
<td>67.4 (25.8)</td>
<td>58.1 (22.2)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Comparison between the subgroups with severe AS in the end-stage kidney disease (CKD 5D) and control cohorts. Age at recruitment (years), baseline aortic valve area (AVA) (cm²), baseline aortic valve mean gradient (mmHg) and the baseline maximum velocity gradient ($v_{max}$) (m/s) through the aortic valve are all described as mean (standard deviation).

Our findings suggest that the guidelines for AVR timing in CKD 5D patients should be reconsidered. The median time (5 months) to either death or AVR in the CKD 5D patients with severe AS suggests that echocardiographic diagnosis of severe AS should be sufficient to initiate consideration of early AVR. Concern has been raised that these patients might not be considered for surgery unless in extremis [13]. In keeping with this concern, a recent large ($n > 100000$) retrospective analysis of AVR alone (without concomitant bypass surgery) in the USA shows an increase in the percentage of patients with preoperative renal failure but no change in the percentage of patients on dialysis undergoing AVR over a 10-year period. This suggests a possible bias against considering AVR in CKD 5D patients [14].

Currently, the criteria for ‘rapid progression’ in the guidelines for AVR are defined as age, valvular calcification and coronary artery disease [12]. We therefore propose that dialysis be added to this list as another predictive criterion of rapid progression.

Discussion

Our data confirm the clinical impression that AS is a more fulminant disease process in individuals with CKD 5D. This was evident in our study across the spectrum of AS severity. Thus, within a time frame by which all CKD 5D patients had either undergone AVR or died, one-third of the control cohort remained free of either of these endpoints. Within the subgroups with severe AS, median progression to either death or AVR took 2.1 times longer in the control cohort, and most individuals with CKD 5D and severe AS had progressed to death or AVR within a couple of years.

Current guidelines for surgical intervention in severe AS [12] suggest referral at the time of symptom development; thus, our data may represent either earlier occurrence of symptoms attributable to severe AS (possibly unmasked by the haemodynamic challenges of dialysis) or a clinical tendency to refer earlier in the CKD 5D population because of concern about more rapid disease progression.

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Unfortunately, timing of surgery is not the only clinical challenge faced in the care of stage CKD 5D patients with AS. Published literature suggests that concern about bioprosthetic valve degeneration should not play a role in choice of valve prosthesis type [15], with the largest study in CKD 5D patients undergoing valve replacement suggesting that prosthesis type had no effect on patient survival [16]. Though anecdotal in nature and small in number, both the literature [17] and our own clinical experience have noted occasional rapid disease progression in a bio-prosthetic AVR in a CKD 5D patient. Choice of prosthetic AVR raises the challenge of managing anticoagulation whilst on dialysis [13]. In addition, both valve types are susceptible to infection, an important issue in view of the increased occurrence of infective endocarditis in CKD 5D [18,19]. In recognition of the difficulties in decision-making regarding valve prosthesis choice, the latest (2008) AHA Guidelines Update on Valvular Heart Disease refrains from being prescriptive in the CKD 5D population [12].

The strengths of this study include its relatively large size compared with other prospective studies of AS in dialysis patients, the long duration of follow-up and the near-complete ascertainment of outcomes. It is, however, nonetheless a small observational study, and other limitations include the limited baseline data available and the lack of information on other outcomes.

Conclusion

This prospective study has demonstrated that AS is a more fulminant disease process in people with CKD 5D, particularly when it is severe. As a result, individuals with CKD 5D and AS should be considered high risk and considered for early surgical referral in the setting of severe aortic stenosis on echocardiography prior to symptom development.

Conflict of interest statement. None declared.

References

Role of haemodialysis on left ventricular dyssynchrony

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Role of haemodialytic therapy on left ventricular mechanical dyssynchrony in patients with end-stage renal disease quantified by speckle-tracking strain imaging

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Abstract

Background. Abnormal myocardial loading can contribute to left ventricular (LV) mechanical dyssynchrony in patients with end-stage renal disease (ESRD). The aims of this study were to characterize and quantify LV function and mechanical dyssynchrony in patients with...