Unexplained sudden death in patients on the waiting list for renal transplantation

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Abstract

Background. The incidence of unexplained sudden death (SD) and the factors involved in its occurrence in patients with chronic kidney disease are not well known.

Methods. We investigated the incidence and the role of comorbidities in unexplained SD in 1139 haemodialysis patients on the renal transplant waiting list.

Results. Forty-four patients died from SD of undetermined causes (20% of all deaths; 3.9 deaths/1000 patients per year), while 178 died from other causes and 917 survived. SD patients were older and likely to have diabetes, hypertension, past/present cardiovascular disease, higher left ventricular mass index, and lower ejection fraction. Multivariate analysis showed that cardiovascular disease of any type was the only independent predictor of SD (P = 0.0001, HR = 2.13, 95% CI 1.46–3.22). Alterations closely associated with ischaemic heart disease like angina, previous myocardial infarction and altered myocardial scan were not independent predictors of SD. The incidence of unexplained SD in these haemodialysis patients is high and probably a consequence of pre-existing cardiovascular disease.

Conclusions. Factors influencing SD in dialysis patients are not substantially different from factors in the general population. The role played by ischaemic heart disease in this context needs further evaluation.

Keywords: cardiovascular disease; chronic kidney disease; dialysis; sudden death; transplantation

Introduction

Sudden death (SD) is one of the most significant causes of death in patients with chronic kidney disease (CKD). It is estimated that ~20–30% of all deaths in patients treated by dialysis are sudden [1,2]. Despite its undeniable importance, it is still unclear why sudden death is prevalent in this population and what factors are involved. Part of the problem is that, by its very nature, this kind of death often does not happen in the hospital setting, so its immediate causes can only be surmised. Necropsy could shed some light on the subject [3], but it is not routinely performed today in patients dying of natural causes in most countries. To make things even more obscure, no universally accepted definition of sudden death exists [4]. Periods of up to 24, 6 and 1 h between the onset of symptoms and the event have all been used [3,5–8]. Some authors require that death be unexplained and not occurring in a hospital; others do not. For all these reasons, the factors involved in SD in dialysis patients are seldom accurately identified.

In the general population, most SDs are believed to be due to ventricular arrhythmias, usually occurring in individuals with some underlying cardiac disease, usually coronary artery disease (CAD) [5]. However, data suggest that other factors may also be important as a cause of SD or cardiac death in patients with advanced uraemia [9–12]. Many confounding factors in dialysis patients, unrelated to cardiac disease, may lead to sudden death. For instance,
metabolic/electrolyte derangements typically associated with CKD could cause cardiac arrest even in individuals with no or non-significant cardiac alterations. Therefore, it is of interest to investigate whether chronic uraemia suffices to explain the increased prevalence of sudden death of undetermined cause in an expressive number of dialysis patients or whether concomitant cardiovascular disease is also required.

In the present investigation, we used the data collected over 10 years in a registry of CKD patients, treated by maintenance haemodialysis, sent to our institution for cardiovascular assessment before being put on the waiting list for transplantation. This study addresses the following questions: What is the incidence of unexplained SD in patients on the transplant waiting list? What is the role played by co-morbidities on the incidence of SD of undetermined cause in this group of patients? Is associated cardiovascular disease a pre-condition for SD in these patients?

Materials and methods

This study was approved by the institutional ethics committee and conducted according to the Declaration of Helsinki[13]. All subjects provided a signed, written informed consent. Patients were followed up from the time of cardiovascular assessment until death or renal transplantation. Between January 1997 and December 2008, 1166 renal transplant candidates (>18 years old) from the state of São Paulo (Brazil) waiting list, scheduled to receive their first kidney graft from a deceased donor at the Renal Transplant Unit, Division of Urology, University of São Paulo Medical School, were referred to the Heart Institute (InCor) for cardiovascular assessment. We eliminated 27 patients because of incomplete data or because they were part of other studies, leaving 1139 subjects to be included. Patients were scheduled for cardiovascular investigation according to the chronological order of placement on the waiting list without any further selection criteria.

Study protocol

A comprehensive clinical and cardiovascular investigation was performed, including non-invasive testing for CAD with dipyridamole myocardial stress testing by SPECT with Tc-99m Sestamibi, irrespective of symptoms, in all patients. Patients had a 12-lead resting ECG and a transthoracic echocardiogram as part of their evaluation. After inception, subjects went through a study orientation and were maintained on statins, aspirin, renin-angiotensin system inhibitors (or angiotensin receptor blockers), and beta-blockers, regardless of symptoms or results of evaluation, according to current guidelines for cardiovascular therapeutic management of high-risk individuals [14].

All patients were being treated by maintenance haemodialysis performed in 4-h sessions, three times per week using bicarbonate baths, with a minimum target Kt/V of 1.5. Patients returned to the outpatient clinic 2–3 times per year for medical evaluation, and they and their families were instructed to report any significant event to the investigational team. Patients who failed to attend were contacted by phone or e-mail.

Clinical end point and follow-up

The mean follow-up was 24.4 ± 19.5 months (median, 20 months; range, 1–107 months). The primary end point was sudden death of an undetermined cause defined as death from natural causes occurring within 1 h after initiation of symptoms with no definitive assessment of its cause. The characteristics of SD were established by interviewing the physician who signed the death certificate or members of the family or by chart review.

Statistical analysis

A P-value <0.05 was considered statistically significant. Data analyses were performed with commercially available statistical software (JMP for Windows, version 6.0, SAS Institute Inc., Cary, NC, USA). The results are presented as means ± standard deviation of means unless otherwise stated. The differences between groups were assessed by Fisher’s exact test for categorical variables or the analysis of variance or median tests for continuous data. The Cox proportional model was used to verify the main factors influencing outcome. The independent variables tested were age, sex, race (Caucasian, Afro-Brazilian or Asian), smoking, dyslipidaemia (total cholesterol and/or triglycerides >200 mg/100 mL), body mass index, hypertension, diabetes, dialysis duration, and past CVD (myocardial infarction, stroke, heart failure, arteriopathy and angina). Hypertension was defined as systolic and/or diastolic blood pressure higher than 140 and 90 mmHg, respectively (means of three determinations), on inception. Arteriopathy was defined as lack of peripheral pulses or a history of gangrene or amputation.

Table 1. Baseline clinical characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sudden death (n = 44-4%)</th>
<th>Death not sudden (n = 178-16%)</th>
<th>Survivals (n = 917-80%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.2 ± 7.9</td>
<td>57.4 ± 10.0</td>
<td>52.9 ± 10.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dialysis duration, months</td>
<td>28 (1–144)</td>
<td>26 (2–292)</td>
<td>23 (4–440)</td>
<td>0.33</td>
</tr>
<tr>
<td>Males, n</td>
<td>30–68%</td>
<td>129–73%</td>
<td>537–59%</td>
<td>0.001</td>
</tr>
<tr>
<td>Caucasians, n</td>
<td>32–73%</td>
<td>127–71%</td>
<td>621–68%</td>
<td>0.74</td>
</tr>
<tr>
<td>Asians, n</td>
<td>3–7%</td>
<td>8–5%</td>
<td>45–5%</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.2 ± 5.2</td>
<td>25.1 ± 4.4</td>
<td>25.6 ± 4.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>164 ± 32</td>
<td>169 ± 36</td>
<td>159 ± 30</td>
<td>0.0004</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>96 ± 18</td>
<td>96 ± 17</td>
<td>93 ± 16</td>
<td>0.046</td>
</tr>
<tr>
<td>Dyslipidaemia, n</td>
<td>14–34%</td>
<td>60–35%</td>
<td>331–38%</td>
<td>0.69</td>
</tr>
<tr>
<td>Smoking, n</td>
<td>11–26%</td>
<td>43–24%</td>
<td>183–20%</td>
<td>0.33</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>24–55%</td>
<td>81–45%</td>
<td>309–34%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>42–95%</td>
<td>159–89%</td>
<td>762–83%</td>
<td>0.006</td>
</tr>
<tr>
<td>Angina, n</td>
<td>8–19%</td>
<td>34–19%</td>
<td>141–16%</td>
<td>0.44</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7–17%</td>
<td>15–8%</td>
<td>70–8%</td>
<td>0.17</td>
</tr>
<tr>
<td>Arteriopathy, n</td>
<td>16–38%</td>
<td>50–29%</td>
<td>172–19%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>11–26%</td>
<td>29–16%</td>
<td>66–7%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart failure, n</td>
<td>12–29%</td>
<td>29–16%</td>
<td>70–8%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Any CVD*, n</td>
<td>32–73%</td>
<td>91–51%</td>
<td>289–32%</td>
<td>0.0001</td>
</tr>
<tr>
<td>High clinical risk**, n</td>
<td>44–100%</td>
<td>167–94%</td>
<td>700–76%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Clinical previous/current angina, myocardial infarction, arteriopathy, stroke and heart failure.
**Age ≥50 years, clinical cardiovascular disease, diabetes, either alone or combined.
Results

During follow-up, 44 patients died from SD of an undetermined cause, 178 died from other causes and 917 survived. SD corresponded to 20% of all deaths (44/222) with a rate of 3.9 deaths/1000 patients per year. Tables 1 and 2 compare the baseline characteristics of the three groups. Compared with survivors, patients who died suddenly were older, predominantly males, with higher systolic and diastolic blood pressure, and with an increased prevalence of diabetes, hypertension, heart failure, arteriopathy, past history of stroke, and current/previous cardiovascular disease of any type at baseline. Also, left ventricular mass index was higher, ejection fraction lower and abnormal myocardial scan (fixed/transient defect) more frequent among patients dying suddenly. Finally, all SD patients were classified as of high clinical risk, according to the American Society of Transplantation risk stratification algorithm for patients awaiting kidney transplantation [15]. This algorithm considers at high risk for transplant patients aged 50 years or more and individuals with diabetes and associated cardiovascular disease, alone or in combination.

Contrary to that, angina and previous myocardial infarction as well as duration of dialysis treatment, race, body mass index, dyslipidaemia and smoking did not correlate with SD.

There were also differences between patients dying suddenly and those who died from other causes (Tables 1 and 2). These differences were restricted to cardiovascular diseases of any type (73% versus 51%, P = 0.01), which was more frequent in patients with SD, and compromised (<50%) baseline left ventricular ejection fraction (31% versus 12%, P = 0.005), which was reduced in patients with SD. The prevalence of heart failure tended to be higher in SD patients, but the difference did not achieve statistical significance (29% versus 16%, P = 0.07).

Multivariate analysis (Cox proportional model, Table 3) showed that cardiovascular disease of any type, assessed at baseline, was the only independent predictor of sudden unexplained death (P = 0.0001; HR = 2.13, 95% CI 1.46–3.22). Age, diabetes and altered myocardial stress testing were not independent predictors of sudden death. Other variables associated with outcome on univariate analysis, such as ejection fraction, hypertension, LV mass index and heart failure, were not included in the model because they were part of the concept of cardiovascular disease.

Discussion

In our cohort, the incidence of unexplained SD was 3.9 deaths/1000 patients per year corresponding to 20% of all deaths. Comparison with data in the literature is difficult because no universal accepted definition of sudden death exists [3–8]. In spite of this shortcoming, it is clear that the incidence of SD in our patients is higher than the overall incidence in the general population, the latter ranging between 0.36 and 1.28 per 1000 habitants per year [16]. However, when comparing the incidence of SD among diverse populations, age and co-morbidities must be taken into account because these variables have a significant impact on the probability of SD. For instance, a recent Canadian study found that the incidence of sudden cardiac death, occurring within 24 h after the onset of symptoms, for individuals of age similar to that in our cohort (55–59 years old), was 1.8/1000 patients/year [8]. More importantly, when one considers only patients with any clinically recognized heart disease in the general population, the incidence of SD goes up to 5.98/1000 subjects/year [17], an incidence higher than that observed in our study. It is possible that the marked differences in SD rates between CKD patients and the general population reported in the literature would be significantly reduced after adjusting for confounding factors like age and concomitant cardiovascular disease.

In dialysis patients, the US Renal Data System reported an incidence of cardiac arrest much higher than that observed in our cohort, of the order of 62/1000 patients per year [1,18]. Our figures are also lower than...
those reported by Genovesi et al. [2] in Europe who observed an incidence of SD in haemodialysis patients close to 22/1000 patients/year. These differences are too large to be explained only by discordant criteria utilized to define SD and may reflect a higher prevalence of elderly patients and individuals with co-morbidities in the US and European dialysis populations. There are indeed considerable variations in mortality rates of patients on dialysis across diverse populations that are significantly influenced by the cardiovascular mortality rates in the respective general populations [18,19]. The fact that our patients were considered for transplant may also have influenced the results, because individuals with more serious ailments are usually excluded from transplant waiting lists. On the other hand, the estimated relative contribution of SD to all-cause mortality in our cohort (20%) was not far from those reported in other studies, varying between 19% and 29% [1,2,18].

Another objective of this work was to verify the role played by co-morbidities on the incidence of SD of undetermined cause in this group of patients. We found that associated cardiovascular disease is likely the decisive factor predisposing to SD, echoing findings in the general population. Also, the main baseline characteristics of patients dying suddenly were similar to those observed in patients dying from other causes, the groups differing only in the severity of cardiac disease that was more accentuated in patients with SD.

We observed that angina, abnormal myocardial scan and previous myocardial infarction were not predictors of SD in our patients. That was unexpected because coronary events are by far the most important cause of sudden death in the general population [3,5,7,20]. It is possible that the small number of events in our study influenced this result. Other interpretations should, however, be considered. One possibility is that other cardiovascular events were involved as an important cause of SD, thereby reducing the relative importance of ischaemic heart disease. It is of interest that a Japanese autopsy study found that stroke was the most frequent cause of SD in dialysis patients followed by cardiac disease [21]. Alternatively, a coronary event could be caused by the rupture of a non-obstructive plaque that would go undetected by myocardial scan. Even so, that does not explain the lack of association of SD with previous myocardial infarction. Nephrologists have expressed their discomfort in the face of the negative results of the 4D study [9], regarding the effect of statins on cardiac outcomes (including SD), of patients with CKD [22]. This work is notable because it suggests that ‘classical coronary artery disease in dialysis patients is either not responsible for SD or not responsive to statins’ [22]. Our results are of interest because our patients besides being treated with statins were also systematically assessed for CAD. Considering the ambiguities surrounding the subject, it is clear that more work is needed to clarify the exact role played by ischaemic heart disease as a cause of SD in dialysis patients.

Our study has some limitations. Firstly, our results apply only to a subgroup of patients with CKD evaluated for transplant and cannot be generalized to the whole population of patients with chronic renal disease. Finally, the number of patients with events is small, and this was not a prospective study.

In conclusion, the incidence of unexplained SD in this cohort of haemodialysis patients evaluated for transplantation is high and probably a consequence of pre-existing cardiovascular disease. In this sense, factors influencing SD in dialysis patients are not substantially different from those occurring in the general population. The relative role played by ischaemic heart disease needs further evaluation.

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Conflict of interest statement. None declared.

References
The increased risk of post-transplant diabetes mellitus in peritoneal dialysis-treated kidney allograft recipients

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Abstract

Background. Post-transplant diabetes mellitus (PTDM) is a common metabolic complication in kidney allograft recipients, significantly contributing to the elevated cardiovascular morbidity after renal transplantation and increased risk of chronic transplant dysfunction. The aim of the present investigation was to evaluate the factors influencing PTDM development. Under particular consideration were the elements, existing before the transplantation, especially the modality of dialysis treatment significance, i.e. haemodialysis (HD) versus peritoneal dialysis (PD).

Methods. Three hundred and seventy-seven consecutive outpatients who underwent renal transplantation (RTx) in our institution between January 2003 and December 2005 were analysed. PTDM was diagnosed according to the current American Diabetic Association/World Health Organization criteria. Statistical inference was conducted by means of univariate methods (one factor versus PTDM) and multivariate methods in frames of generalized linear model.

Results. In the study group, 72 patients (23.4%) developed PTDM after RTx (55 HD and 17 PD patients). PTDM incidence at 3, 6 and 12 months was 15.9%, 22.1% and 23.4%, respectively. The mean interval from transplantation to the onset of PTDM was 3.08 ± 2.73 months. In univariate analysis, the factors associated with the elevated risk of PTDM appearance were older recipient age, positive family history of diabetes, hypertensive nephropathy as end-stage renal disease cause, higher body mass index at transplantation, treatment by PD, and the graft from an older donor. In multivariate verification, statistical significance remained: older recipient age (P < 0.001), positive family history of diabetes (P = 0.002), and treatment by PD (P = 0.007).

Conclusions. Treatment by PD appears to be a possible novel factor, not yet reported, which may increase the risk of PTDM development.

Keywords: modality of dialysis treatment; peritoneal dialysis versus haemodialysis; post-transplant diabetes mellitus; pre-transplant risk factors