The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey

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Abstract

Background. Although the incidence of sudden cardiac death (SCD) is high among haemodialysis (HD) patients, there are few papers available on this topic. The aim of this study on a single-centre HD population observed over a 10 year period was to identify patient- and HD-related specific factors that might be associated with a higher risk of SCD.

Methods. The study included 123 patients (76 men; age 29–79 years) undergoing renal replacement therapy at our dialysis unit for at least 6 months. For each patient, routine laboratory tests were performed monthly, blood pressure was measured both at the start and the end of each dialysis session, haemoglobin and pre-dialysis serum K⁺ were determined weekly, serum iPTH was assessed thrice yearly, and an echocardiographic study was performed annually to determine the left ventricular mass index (LVMi). The prevalence of cardiovascular (CV) co-morbidities, and the incidence of new events were also recorded.

Results. During the 10 years, 85 patients died—16 from SCD, 30 from cardiac causes (CC) other than SCD, and 39 from other causes (OC); 38 patients were still alive (AL) at the end of the observation period. Comparative analysis of SCD, CC, OC and AL, reveals that the male prevalence (13/3) was higher in SCD than in AL, while AL were younger than the deceased patients regardless of the cause of death (P < 0.0001; ANOVA), the duration of arterial hypertension was higher in SCD (129±104 months; P = 0.0005; ANOVA), despite similar antihypertensive therapies, and the difference between LVMi at end-point and at inception (ΔLVMi) was significantly higher in SCD [+56±38 g/m² body surface area] compared with OC (−5±35), AL (−17±25) and even CC (7±30) (P < 0.0001; ANOVA); finally, the prevalence of patients with ischaemic heart disease (IHD) was higher in the SCD group (11/5; P < 0.0001, χ²). Univariate Cox regression analysis demonstrated that the factors increasing the risk of SCD were IHD (P = 0.002), the worsening of left ventricular hypertrophy (LVH) (P < 0.0001), and the presence of long-lasting arterial hypertension (P = 0.001). An increase in LVH was the sole risk factor for SCD when comparing SCD with CC patients (P = 0.003). By multivariate Cox regression analysis ΔLVMi was identified as the strongest predictor of SCD (P < 0.0001).

Conclusion. While confirming the role of common CV risk factors for SCD in dialysis patients such as IHD and arterial hypertension, this study is the first to demonstrate that the worsening of LVH is the strongest predictor of sudden death.

Keywords: haemodialysis; left ventricular hypertrophy; sudden cardiac death

Introduction

Cardiac disease is the major cause of mortality in dialysis patients, with sudden cardiac death (SCD) accounting for between 10 and 30% of deaths from all causes, according to the reports from the largest international registries [1,2]. In the general population, the incidence of SCD ranges between 0.36 and 1.28% per person/year [3], and is often preceded by other cardiovascular (CV) events, notably ischaemic heart disease (IHD) and myocardial infarction [4]. In contrast, the rate of cardiac arrest in dialysis patients is 93% at 1 year from the start of renal replacement treatment (RRT) [5]. In the two available studies of large dialysis populations, the risk of SCD was associated with the intermittent nature of haemodialysis (HD), advanced age, diabetes, the use of catethers.
for vascular access and recent hospitalization [6,7]. In view of the few investigations on SCD in the dialysis population, the aim of this study was to identify patient- and HD-related specific factors that might be associated with a higher risk of SCD in subjects receiving RRT at our dialysis unit and observed over a 10 year period.

Methods

Patients

The study included 123 patients (76 men, 47 women, age range 29–79 years) on RRT at our dialysis unit as of 1 January 1992—patients who had complete demographic and epidemiological data, who were on RRT for at least 6 months (range 6–192 months) and who had survived at least 1 year from the start of the observation. These patients were treated according to a clinical protocol aimed at improving their CV outcomes, based on strict blood pressure (BP) control, delivery of adequate dialysis doses, anaemia correction and prevention or therapy of hyperparathyroidism. Dry weight was established for each patient on a clinical basis with the aid of chest radiographs performed every 6 months to evaluate cardiothoracic index and, in certain cases, by extemporaneous echocardiography. Antihypertensive therapy, where appropriate, consisted of angiotensin converting enzyme inhibitors as the first-step drug and of GITS calcium channel blocker nifedipine and β-blocker atenolol, which were added if hypertension remained uncontrolled. Epoietin α, if needed, was used for increasing haemoglobin levels to ~10–12 g/dl. Calcium-containing phosphate binders and either intravenous or oral calcitriol were given to patients with secondary hyperparathyroidism. Each patient had HD three times weekly. Of the cohort, 82 patients had standard bicarbonate dialysis that lasted 4–4.5 h with the dialyser surface area ranging between 1.3 and 2 m², both prescribed individually as dialysis that lasted 4–4.5 h with the dialyser surface area hyperparathyroidism. Each patient had HD three times every 3 months. Kt/V was calculated every month in accordance with the urea kinetic model [10].

Procedures

The demographic and clinical parameters recorded included: age, gender, time spent on RRT, dialysis method, prevalence of diabetes and smoking habits.

Laboratory data on each patient included: weekly predialysis haemoglobin and serum K⁺ concentration, monthly assessments of serum albumin, cholesterol, HDL cholesterol, triglycerides, calcium and phosphate; iPTH was determined every 3 months. Kt/V was calculated every month in accordance with the urea kinetic model [10].

BPs were measured before the start and at the end of each dialysis session by trained personnel using a mercury sphygmomanometer with a cuff adapted to arm circumferences and with patients resting for at least 15 min. Pulse pressure (PP) was calculated as systolic–diastolic BP. Laboratory and BP data collected for the entire period of observation were averaged for each patient and presented as mean±SD.

Each patient had a standard 12-lead ECG at least every 6 months. Pre-dialysis heart rates (HRs), recorded during the 6 months before deaths or censoring events, were retrieved and averaged for each patient. Echocardiography was performed at least annually on each patient on a midweek interdialytic day. Echotracings were recorded using a two-dimensional guided M-mode echocardiograph. The criteria for the adequacy of collection, reading and reproducibility of echocardiographic measurements have been previously reported [8]. Left ventricular mass was calculated by M-mode measurements according to the modified Penn-Cube formula [11] and then indexed for body surface area (BSA) to yield the left ventricular mass index (LVMi). The difference between LVMi and at the end-point and at inception was calculated and expressed as ΔLVMi. Left ventricular geometry was defined according to previously reported criteria [12]. Dialysis hypotension was defined as the occurrence of intradialytic decrease in systolic BP to <70 mmHg during at least three HD sessions in a month. CV co-morbidities at baseline as well as CV events occurring during the 10 year observation period were recorded. CV co-morbidities and CV events were defined as: the occurrence of IHD (stable, exertional and resting angina, ischaemia on ECG or other diagnostic tests, positive coronary angiogram performed for diagnostic screening in the absence of clinical symptoms, myocardial infarction); congestive heart failure (CHF); cardiac arrhythmias; valvular disease, based on criteria issued by the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study [13].

Statistical analysis

Data are presented as mean±SD. Comparisons between groups were made by analysis of variance (ANOVA) for continuous variables. Where the F test was significant, a Newman-Keuls post hoc test for multiple comparisons was performed. For categorical variables a chi-square test was performed to assess differences between groups and Fisher’s exact test was used to assess differences between two groups considered separately.

A Cox regression analysis was used to assess significant risk factors for SCD, taking into account the duration of follow-up observations. Transplantation or transfer to CAPD was not considered a censoring event, and all patients were included in the final analysis according to an intention to treat analysis. Univariate and multivariate Cox models were used to calculate the risk associated with each variable. The multivariate regression included as covariates all significant variables from the univariate models. The statistical analysis was performed using the SPSS 11.0 software (Chicago, IL).

Results

During the 10 years of observation, 20 patients (16.3%) had successful transplantations, eight (6.5%) were transferred to a CAPD programme due to vascular access failure, while 85 (69.1%) died. Finally, 38 patients (30.9%) were still alive (AL) on 31 December 2001.
The causes of death were: SCD in 16 patients (18.8% of all causes); cardiac disease (CC) other than SCD in 30 (35.2%); 39 subjects (45.9%) died from other causes (OC), namely neoplasia (15%), cachexia (20%) or infection (8%).

Autopsy reports were available for 15 of the 16 patients who suffered SCD. The diagnoses were aortic valve rupture in one case, acute myocardial infarction in five, arrhythmia in eight and aortic aneurysm rupture in one case.

Significant differences were identified between the four groups of patients (SCD, CC, OC and AL) as far as gender and age: a male prevalence was observed in SCD as compared with AL; patients alive at the end of the observation period were younger than deceased ones, regardless of the cause of death. No significant differences were evident as a result of time spent on dialysis, the prevalence of diabetes, or smoking. Lastly, the proportions of patients treated with either standard dialysis or HDF were not significantly different between the four groups (Table 1).

Haemoglobin concentration was slightly higher in SCD and AL subjects compared to OC, while serum albumin was greater in subjects alive at the end-point than in those who had died from non-cardiac causes. No differences were detectable in the four groups of patients as far as CaxP product values, iPTH, Kt/V, serum lipids and average pre-dialysis potassium concentrations are concerned (Table 2).

Table 3 depicts the BP and cardiological data of our patients. BPs, both pre- and post-dialysis, were not significantly different between the four groups, nor were the prevalence of intradialytic hypotensive episodes, the values of LVMi, or the various patterns of left ventricular geometry, although a slight, but not significant, prevalence of eccentric Left Ventricular Hypertrophy (LVH) was observed among the deceased patients, regardless of the cause of death (Table 3). An increase in LVMi, however, was observed in SCD and CC, while a reduction of LVMi was evident in OC and AL—though no differences were detectable in the prevalence of patients treated with antihypertensives and in the magnitude of such therapy between the four groups. Moreover, the increase of LVMi observed in SCD patients during the 10 years of observation was significantly greater than that observed in subjects who had died from cardiac causes other than SCD (Table 3). Furthermore, the duration of exposure to arterial hypertension was higher in SCD patients than in subjects in groups AL and OC. Finally, a higher incidence of new CV events during the observation period was documented in patients who had died from cardiac causes when compared with living subjects; and among CV co-morbid conditions, a higher prevalence of IHD was evident in patients who had suffered SCD as compared both with living subjects or patients who had died from non-cardiac diseases (Table 3).

### Table 1. Demographic and epidemiological data for 16 dialysis patients deceased from SCD, for 38 living at the end of 10 years of observation (AL), for 39 deceased from causes other than cardiac (OC) and for 30 deceased from other cardiac causes (CC)

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
<th>AL</th>
<th>OC</th>
<th>CC</th>
<th>Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>16</td>
<td>38</td>
<td>39</td>
<td>30</td>
<td>ANOVA &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±10a</td>
<td>53±15</td>
<td>69±12a</td>
<td>69±7a</td>
<td>ANOVA</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialytic age (months)</td>
<td>46±49</td>
<td>56±45</td>
<td>39±40</td>
<td>36±36</td>
<td>ANOVA</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/3b</td>
<td>19/19</td>
<td>24/15</td>
<td>20/10</td>
<td>Chi-square</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis (standard/HDF)</td>
<td>11/5</td>
<td>20/18</td>
<td>20/10</td>
<td>20/10</td>
<td>Chi-square</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>3/13</td>
<td>6/32</td>
<td>9/30</td>
<td>7/23</td>
<td>Chi-square</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>9/7</td>
<td>16/22</td>
<td>11/28</td>
<td>8/22</td>
<td>Chi-square</td>
<td>NS</td>
</tr>
</tbody>
</table>

*aIndicates significant difference compared with AL, P<0.01 at least, Newman-Keuls post hoc test.

**Table 2.** Laboratory parameters for 16 dialysis patients deceased from SCD, for 38 living at the end of 10 years of observation (AL), for 39 deceased from causes other than cardiac (OC) and for 30 deceased from other cardiac causes (CC)

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
<th>AL</th>
<th>OC</th>
<th>CC</th>
<th>Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>16</td>
<td>38</td>
<td>39</td>
<td>30</td>
<td>ANOVA</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>10.8±1.4a</td>
<td>10.7±1.2a</td>
<td>9.7±1.3</td>
<td>10.2±1.2</td>
<td>ANOVA</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.1±0.3</td>
<td>4.2±0.4a</td>
<td>3.8±0.5</td>
<td>4.1±0.4</td>
<td>ANOVA</td>
<td>0.0087</td>
</tr>
<tr>
<td>CaxP (mg^2/dl^2)</td>
<td>58.5±11.3</td>
<td>64.5±7.9</td>
<td>58.8±14.0</td>
<td>56.2±13.1</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>237±213</td>
<td>359±257</td>
<td>264±272</td>
<td>277±288</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.16±0.11</td>
<td>1.18±0.12</td>
<td>1.20±0.15</td>
<td>1.19±0.18</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>195±37</td>
<td>183±28</td>
<td>185±48</td>
<td>187±38</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>192±81</td>
<td>183±57</td>
<td>195±91</td>
<td>173±62</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>61±14</td>
<td>59±18</td>
<td>63±18</td>
<td>55±11</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
<tr>
<td>Average pre-HD serum K^+ (mEq/l)</td>
<td>5.6±0.6</td>
<td>5.7±0.5</td>
<td>5.4±0.6</td>
<td>5.5±0.5</td>
<td>ANOVA</td>
<td>NS</td>
</tr>
</tbody>
</table>

*aIndicates significant difference compared with OC, P<0.05 at least, Newman-Keuls post hoc test.
Univariate Cox regression models demonstrated that the significant predictors of the risk of SCD were: increase in LVMi (a 2% increase in risk for each 1 g of LVMi increase; \(P < 0.0001\)), long-lasting arterial hypertension (0.7% increase in risk for each month of exposure to inadequate BP control; \(P = 0.001\)) and IHD (5-fold increased risk; \(P = 0.002\)) (Figure 1).

Multivariate Cox model results are presented in Table 4. By this analysis the worsening of LVH and the duration of arterial hypertension remained the significant predictors of SCD in our population (Table 4).

Finally, in the comparison using the univariate Cox model of SCD patients with subjects who had died from cardiac causes other than SCD, LVMi remained the sole predictor of SCD in this subgroup selected for cardiac disease (\(P = 0.003\)).

**Discussion**

Reports from the Framingham cohort have demonstrated that LVH is associated with an increased risk of SCD in the general population [14].

The major finding of our study is that the worsening of pre-existing LVH, independent of the absolute LVMi values at inception, is the strongest predictor of the risk of SCD in dialysis patients. In this population, LVH has been found to be associated with lower actuarial survival rates [15] probably...
because LVH is progressive and continues after the initiation of dialysis treatment [16]. In our patients, long-lasting arterial hypertension and pre-existing IHD were demonstrated to also be correlates of SCD. However, the worsening of LVH turned out to be the most significant predictor when all the putative factors were examined together by multivariate analysis. This result reflects a peculiar picture of dialysis patients, since the increase in LVMi is even a stronger predictor of SCD than IHD itself, which, on the contrary, is associated with SCD in ~80% of cases in the general population [17]. Indeed the pathogenesis of LVH is multifactorial, similar to that of SCD in uraemic patients. Although no differences in some predictors of both LVH and SCD, like anaemia, BP or prevalence of diabetes, were detected between the four groups of patients, we cannot exclude the possibility that any one factor may have played different roles—maybe due to different individual susceptibilities of patients—either causing their LVH to worsen or predisposing them to SCD.

A further interesting feature of our study is that the increase of LVH is the only significant factor associated with the risk of SCD when comparing SCD patients with all subjects who had died from all the other cardiac causes. A reliable explanation could be the discrepancy between the increased oxygen demand of a hypertrophied myocardium and the impaired coronary reserve. This mechanism may be active because the growth of the coronary vascular bed is not proportionate to the increase in myocardial mass, resulting in myocardial ischaemia, despite normal coronary arteries [18]. In addition, a higher tendency toward electrical instability due to the increased myocardial mass and the presence of intermyocardiac fibrosis may play a role, possibly leading to life-threatening ventricular arrhythmias [19,20].

In our patients, a relationship was demonstrated between SCD and IHD while no correlation was present between SCD and the prevalence of arrhythmic events. This is in contrast with previous observations that premature ventricular depolarizations and episodes of non-sustained ventricular tachycardia were associated with an increased risk of SCD in patients with recent myocardial infarction [21]; however, it is consistent with more recent observations that such arrhythmias did not provide prognostic information about the risk of SCD in heart failure [22]. Also, we cannot rule out the possibility that abnormalities in HR variability and in the QT interval dispersion, which have been deemed to be associated with the risk of SCD in dialysis [23,24], were present in our patients. Finally, no differences were detected between groups in predialysis HRs, thereby perhaps excluding a role for cardiac autonomic neuropathy in predicting SCD in our patients. In our population, the exposure to long-lasting arterial hypertension was a powerful predictor of the risk of SCD. This finding is in keeping with previous reports on the predictive role of arterial hypertension with regards to unfavourable CV outcomes among dialysis patients [25]. Indeed, arterial hypertension has been associated with LVH both in the general population [26] and in dialysis patients [27,28]; its arrhythmogenic effect, which might play a role in inducing SCD, is probably worsened by concomitant LVH [29]. Older ages at inception and the male gender were prevalent among SCD patients relative to living subjects, a finding that confirms previous well-established data in SCD patients [30]. And last, a surprising finding of our study is the lack of any relationship between haemoglobin concentration and SCD, though anaemia has been previously deemed as a clinical correlate of cardiac death in dialysis patients [31]. The haemoglobin levels of our patients were kept at ~10–12 g/dl by epoetin treatment, and that is likely to have reduced the risk of death for CV causes in our population.

In conclusion, the worsening of LVH seems to be the main predictor of the risk of SCD. This is consistent with previous data from our group demonstrating that the incidence of major adverse CV events was higher in subjects with worsening LVH, notwithstanding antihypertensive therapy with ACE inhibitors [32]. Moreover, LVH regression, particularly induced by ACE inhibitor therapy [8,9,32] has been deemed to have a positive effect on the survival of dialysis patients [33].

One limit of this study is that it is retrospective and based upon a relatively small number of patients. Additionally, new indexes that have recently emerged as suitable markers of SCD in the general population, such as homocysteine and CRP [34] were not part of our database. However, this is the first clinical survey that has attempted to identify factors and mechanisms responsible over the longer term for SCD in dialysis patients, and it is the first to demonstrate that the worsening of pre-existing LVH is the most important predictor of the risk of sudden death in this population. According to our data, while awaiting the discovery and application of reliable and low cost biohumoral predictors of the risk of SCD, efforts must be made to adjust for the worsening of LVH, and possibly to reverse it, in patients on RRT, in order to prevent catastrophic events and perhaps to provide better CV prognoses to them.

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