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Journal of Electrocardiology xx (2016) xxx – xxx

JOURNAL OF Electrocardiology

www.jecgonline.com

Review article

Sudden cardiac death in haemodialysis: clinical epidemiology and mechanisms☆

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Abstract Sudden cardiac death, which causes premature loss of lives on haemodialysis of the elderly, youths and even children; cannot be prevented, because the aetiology is poorly understood and effective interventions are yet unknown. Improving our knowledge of mechanisms causing sudden cardiac death in haemodialysis patients may help us to design better interventions; and clinical epidemiology of sudden cardiac death could be an important tool to further guide human and animal studies. This review researches the clinical epidemiology of sudden cardiac death to suggest possible mechanisms, although they require further studies. The research shows how traditional cardiovascular risk factors such as age, diabetes and smoking have an impact; non-traditional risk factors such as inflammation, mineral-bone disease and even uraemia itself have higher impact; and how cardiac structural, functional and electrocardiographic markers predict sudden cardiac death in dialysis patients. More in-depth human and animal studies, guided with existing knowledge, are necessary to better understand the mechanisms and design successful interventions.

Keywords: Sudden cardiac death; Haemodialysis; Epidemiology; Mechanism

Introduction

Sudden cardiac death is the most common cause of death in haemodialysis patients; accounting for at least one quarter of lives lost every year. (See Fig. 1).

According to the United States Renal Data System (USRDS), the largest dialysis registry, sudden cardiac death has remained the most common cause of death, as notified by dialysis physicians using "ESRD death notification form 2746" over the last 20 years: 22% of all deaths in 1995 and 24% in 2013 [1,2].

More recent (2015) USRDS reports suggest sudden cardiac death as a cause of 37% of all deaths [3]. The higher figure in the recent USRDS report may be a reflection of improvement in other causes of death or improved coding of deaths: between 2013 and 2015, the sudden cardiac death has increased from 26.9% to 37% and the "all other" causes have decreased from 31.6% to 15%.

Several prospective clinical trials demonstrate sudden death rates similar to these registry reports. In a trial with 1255 diabetic haemodialysis patients, followed for four years, randomised to either Atorvastatin or placebo, the major cause of death was sudden cardiac death, 26.4%. Interestingly, there was no reduction in mortality with the use of Atorvastatin [4].

In the recently completed EVOLVE trial, which investigated the impact of Cinacalcet or placebo on cardiovascular disease outcomes in haemodialysis patients, sudden death was the most frequent cause of death, accounting for 24.5% of all deaths [5]. About 46% of the cardiovascular deaths were due to sudden cardiac death, with only 4% due to myocardial infarction, and 17.4% were due to unknown cardiovascular causes, some of whom may have died due to sudden arrhythmias. The sudden cardiac death rate in the EVOLVE haemodialysis trial was far higher than the statin trials in the general population (24.5% vs 8.6%), whereas atherosclerotic coronary artery disease deaths were much lower (26% vs 10%) of all deaths. Of the 348 sudden cardiac death in EVOLVE trial, 45% were witnessed. It should be noted that even in this relatively young cohort of dialysis patients with a mean age of 54 years and 35–73 years being the 10-90th percentiles, the annualised incidence of sudden cardiac death was 2.7% or 3.2%, including unknown causes.

Impact of age

The incidence of sudden cardiac death in haemodialysis patients may increase with age. However, the relative risk of

☆ Conflict of Interest: None.

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http://dx.doi.org/10.1016/j.jelectrocard.2016.07.016

cardiac arrest is not highest in the oldest patients, as shown in USRDS 2013; being 1.00 in 45 to 64 years (reference range), 1.06 (1.03–1.09) between 65 to 74 years, 0.74(0.72–0.77) between 20 to 44 years, 0.51(0.38–0.69) between 0 to 19 year and 0.99 above 75 (0.97–1.02) [2]. This suggests age-related cardiac changes do not entirely explain sudden cardiac death and that risk factors due to kidney failure may also play a role.

Sudden cardiac death is the commonest cause of death in children on haemodialysis; reported to be as high as 25% of all deaths in the Australia and New Zealand registry; surprisingly high in a cohort of patients who are usually free from the presence and risks of traditional coronary artery disease [6]. This indicates that sudden cardiac death happens in the absence of usual cardiovascular risk factors such as diabetes and hypercholesterolemia, again suggesting uraemia as a cause.

Impact of dialysis modality

The incidence of sudden cardiac death in peritoneal dialysis is lower than haemodialysis in the first year (2% versus 7%, as reported in USRDS 2013) [2]. The registry data itself suggests somewhat lower rates in prevalent peritoneal dialysis patients [2]. However, in one prospective clinical study of 230 peritoneal dialysis patients followed for 5 years, 28 patients suffered sudden death, 24% of all mortality, and at a rate as high as 5.6% per year, which is similar to that of haemodialysis patients. We can perhaps conclude that at the initiation of renal replacement therapy, intermittent haemodialysis-related sudden changes in physiology, may be an additional factor causing sudden cardiac death. Possible mechanisms of such observations may be the rapid correction of fluid and electrolyte imbalances or the strain on the cardiac tissue with haemodialysis; a phenomenon called “cardiac stunning” demonstrated with echocardiography during dialysis [7].

Moreover, peritoneal dialysis does not cause the electrical and biochemical change characteristic of haemodialysis. Infusions of peritoneal dialysis fluid were shown to have no effect on QT dispersion, serum NTpro-BNP or troponin levels [8]. Peritoneal dialysis is associated with shorter QT dispersion, despite patients having higher left ventricular mass, higher calcium and lower potassium levels compared to haemodialysis patients with left ventricular hypertrophy who had longer QT dispersion [9].

Impact of race

The relationship of race with sudden cardiac death in haemodialysis patients is far from clear and rarely investigated. However, Caucasians seem to have a marginally higher rate of sudden cardiac death as reported in registry data [2].

Impact of time on and away from dialysis

Sudden cardiac deaths are not common during haemodialysis session. The highest incidence of sudden cardiac death is on the day after a long intradialytic interval (1.3 versus 1.0 per 100 patient years; $p < 0.005$), which happens every week for in-centre dialysis patients, around the weekend because the centres are closed on Sunday, as shown in 32,065 US haemodialysis patients [10]. The rates of dysrhythmia related hospital admissions was 3 times more likely on the days after long interdialytic interval. In another study, the incidence of sudden deaths were homogenous during the week in peritoneal dialysis patients but disproportionately higher after the long interdialytic interval, compared to other days in haemodialysis patients [11]. In a detailed study with 228 patients the sudden death was higher in the first 12 h from the beginning of dialysis, and highest in the last 12 h of the long interdialytic interval. More than half the patients who suffered sudden death had coronary artery disease and a quarter had ejection fraction less than 35% [12]. These studies suggest that the accumulation of toxins (electrolytes) and fluids over a long interdialytic interval and rapid changes with haemodialysis may cause cardiac stress and sudden cardiac deaths particularly in the presence of coronary artery disease or heart failure.

Impact of haemodialysis procedure

Electrolyte and acid base changes during renal replacement are common and particularly rapid during haemodialysis. Such changes with peritoneal dialysis are however less rapid. The changes in blood cation concentration, particularly potassium and calcium are almost inevitable during haemodialysis sessions. Generally, the patients start haemodialysis sessions with high serum potassium, which is rapidly corrected over the next 3–4 h. The correction depends on the dialysate potassium, which is usually 2 to 3 mmol/L lower than the serum potassium, but the difference can be larger. The difference in ionised calcium concentration between serum and dialysate is lower than that of potassium, but this does vary in different dialysis practices. The gradients of these cation concentrations across the cardiac conduction and muscle cells are important regulators of electrical conductance and can potentially induce automaticity or re-entry abnormalities, causing arrythmias.

The changes in the potassium and calcium levels during dialysis are the most well studied out of all the electrolyte shifts that happen during dialysis, rather than magnesium, chloride or bicarbonate. Reduction of serum potassium has been shown to cause QT prolongation. The rapid fall in serum calcium also can cause QT prolongation. Abnormalities in levels of potassium and calcium are known to cause after-depolarisation currents. However, studies are inconsistent in predicting ECG changes with dialysis. Retrospective analysis shows that exposure to low dialysate potassium and higher ultrafiltration during haemodialysis is associated with sudden cardiac deaths, yet no prospective study has successfully reduced sudden cardiac death by altering dialysate potassium or calcium [13].

Most of the ECG changes happen during dialysis, yet the majority of sudden cardiac death happens when patients are off dialysis. Cardiac arrest incidence on dialysis is 7 per