Nephrol Dial Transplant (2019) 1–10
doi: 10.1093/ndt/gfz182

ndt
Nephrology Dialysis Transplantation

Sudden cardiac death in dialysis patients: different causes and management strategies

Simonetta Genovesi [1,2], Giuseppe Boriani [3], Adrian Covic[4,5], Robin W.M. Vernooij[6,7], Christian Combe [8,9], Alexandru Burlacu [5,10], Andrew Davenport[11], Mehmet Kanbay[12], Dimitrios Kirmizis[13], Daniel Schneditz[14], Frank van der Sande[15] and Carlo Basile[16,17] on behalf of the EUDIAL Working Group of ERA-EDTA

[1]School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy, [2]Nephrology Unit, San Gerardo Hospital, Monza, Italy, [3]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena University Hospital, Modena, Italy, [4]Nephrology Clinic, Dialysis and Renal Transplant Center - 'C.I. Parhon' University Hospital, Iasi, Romania, [5]'Grigore T. Popa' University of Medicine, Iasi, Romania, [6]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, [7]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, [8]Service de Néphrologie Transplantation Dialyse Aphérèse, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, [9]Unité INSERM 1026, Université de Bordeaux, Bordeaux, France, [10]Department of Interventional Cardiology - Cardiovascular Diseases Institute, Iasi, Romania, [11]UCL Centre for Nephrology, Royal Free Hospital, Division of Medicine, University College London, London, UK, [12]Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey, [13]Department of Nephrology, Colchester General Hospital, Essex, UK, [14]Otto Loewi Research Center, Medical University of Graz, Graz, Austria, [15]Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands, [16]Division of Nephrology, Miulli General Hospital, Acquaviva delle Fonti, Italy and [17]Associazione Nefrologica Gabriella Sebastio, Martina Franca, Italy

Correspondence to: Carlo Basile; E-mail: basile.miulli@libero.it; Twitter handle: @robinvernooij

ABSTRACT

Sudden cardiac death (SCD) represents a major cause of death in end-stage kidney disease (ESKD). The precise estimate of its incidence is difficult to establish because studies on the incidence of SCD in ESKD are often combined with those related to sudden cardiac arrest (SCA) occurring during a haemodialysis (HD) session. The aim of the European Dialysis Working Group of ERA-EDTA was to critically review the current literature examining the causes of extradialysis SCD and intradialysis SCA in ESKD patients and potential management strategies to reduce the incidence of such events. Extradialysis SCD and intradialysis SCA represent different clinical situations and should be kept distinct. Regarding the problem, numerically less relevant, of patients affected by intradialysis SCA, some modifiable risk factors have been identified, such as a low concentration of potassium and calcium in the dialysate, and some advantages linked to the presence of automated external defibrillators in dialysis units have been documented. The problem of extra-dialysis SCD is more complex. A reduced left ventricular ejection fraction associated with SCD is present only in a minority of cases occurring in HD patients. This is the proof that SCD occurring in ESKD has different characteristics compared with SCD occurring in patients with ischaemic heart disease and/or heart failure and not affected by ESKD. Recent evidence suggests that the fatal arrhythmia in this population may be due more frequently to bradyarrhythmias than to tachyarrhythmias. This fact may partly explain why several studies could not demonstrate an advantage of implantable cardioverter defibrillators in preventing SCD in ESKD patients. Electrolyte imbalances, frequently present in HD patients, could explain part of the arrhythmic phenomena, as suggested by the relationship between SCD and timing of the HD session. However, the high incidence of SCD in patients on peritoneal dialysis suggests that other risk factors due to cardiac comorbidities and uraemia per se may contribute to sudden mortality in ESKD patients.

Keywords: dialysate, end-stage kidney disease, implantable cardiac device, sudden cardiac arrest, sudden cardiac death

INTRODUCTION

Sudden cardiac death (SCD) is defined as an unexpected death due to cardiac causes in a person with known or unknown cardiac disease, within 1 h of symptom onset (witnessed SCD) or within 24 h of the last proof of life (unwitnessed SCD). Since cause of death is subject to interobserver variability, there can be misclassification of SCD [1].

SCD is a leading cause of death among the general population, accounting for up to 15% of all deaths [2]. SCD represents

an important cause of death in end-stage kidney disease (ESKD) patients[3], but the precise estimate of its incidence is difficult to establish because studies on the incidence of SCD in ESKD are often combined with those related to sudden cardiac arrest (SCA) occurring during a haemodialysis (HD) session. However, extradialysis SCD and intradialysis SCA represent different clinical situations and should be kept distinct. In fact, the dialysis session may itself favour the onset of life-threatening arrhythmias, beyond the clinical conditions of the patient. Moreover, hypotension and syncope are quite common during HD sessions and highlight a series of risk factors[4,5]. Their occurrence requires immediate interventions of health-care professionals for a prompt diagnosis and for differentiating these events from SCA. The aim of the European Dialysis (EUDIAL) Working Group was to critically review the current literature examining the causes of extradialysis SCD and intradialysis SCA in ESKD patients and potential management strategies to reduce the incidence of such events.

EPIDEMIOLOGY OF SCD AND INTRADIALYSIS SCA IN ESKD PATIENTS

In the US Renal Data System database, arrhythmia and cardiac arrest were the single greatest cause of death, comprising 40% of known causes of death among dialysis patients, constituting nearly 78% of all cardiovascular causes of death[2]. Compared with peritoneal dialysis (PD), the rate of SCD is 50% higher in HD patients 3 months after dialysis initiation, although these rates reach parity by 2 years[3]. Although SCD accounts for a considerable number of deaths in ESKD patients, it is somewhat surprising that the number of such deaths during dialysis sessions is not greater, considering the increased prevalence of left ventricular hypertrophy and coronary atheromatous and arteriosclerotic disease in HD patients and the changes in cardiac perfusion and electrolyte fluxes. Karnik *et al.* [6] reported a rate of intradialysis SCA of 7.0/100 000 HD sessions, while Pun *et al.* [7] described a rate of 4.5 per 100 000 dialysis treatments. The incidence of such events is therefore relatively low, but the prognosis after an intradialysis SCA is very poor. Karnik *et al.* [6] observed that only 40% of patients were successfully resuscitated and were still alive after 2 days. Of the 60% who died within 48 h of the arrest, 13% died in the dialysis unit.

PATHOPHYSIOLOGY OF SCD AND INTRADIALYSIS SCA IN ESKD PATIENTS

When faced with sudden death, presumably of cardiac origin (SCD), it is not easy to determine what arrhythmia led to death. It may happen so that when the first electrocardiogram (ECG) is performed it is impossible to understand whether any recorded asystolic bradyarrhythmia is the cause of the event or is the consequence of an episode of ventricular fibrillation (VF). This doubt can be resolved only if a device [e.g. ECG Holter, intracardiac device or implantable loop recorder (ILR)] was recording the fatal event[8].

The rhythm most easily recorded in cardiopathic patients at the time of SCD appears to be VF[9,10]. However, Cobb *et al.* [11] suggested that the episodes of VF represent the cause of SCD in a smaller proportion than previously thought. It is not clear what fatal arrhythmia is occurring in dialysis patients who undergo SCD. Wan *et al.* [12] showed that 78.6% of the SCAs occurring in 75 HD patients bearing a wearable cardioverter defibrillator were due to ventricular tachycardia (VT) or VF and only 21.4% were due to asystole. The average left ventricular ejection fraction (LVEF) of the study population was 27.4%, with < 19% of patients having an LVEF ≥ 35%. A subsequent study performed in HD patients with an implanted cardiac monitor recorded eight unexpected SCDs due to severe bradycardia with asystole. In this population, one of the exclusion criteria was the presence of LVEF ≤ 35% [13]. The idea that SCDs may be due mainly to bradyarrhythmias has been strengthened by two recent studies in HD patients with ILRs. Sacher *et al.* [14] studied 71 HD patients (follow-up 21 months), documenting four SCDs in diabetic patients due to progressive bradycardia followed by asystole. Three of the four subjects had an LVEF > 50% (for one of them, LVEF was not known). Furthermore, Roy-Chaudhury *et al.* [15] documented 14 episodes of asystole and only one of sustained VT in a population of 66 younger HD patients implanted with an ILR and followed for 6 months. None of these arrhythmias were fatal. Eighty-six percent of patients with clinically significant arrhythmia were diabetic and their mean LVEF was 55%. Several authors have suggested that there is a relationship between the timing of SCDs and the dialysis session in HD patients, showing two frequency peaks, one at the end of the longer interdialytic interval (LIDI) and the second immediately after the first dialysis session of the week[16, 17]. The study by Wong *et al.* [13] confirmed that the risk of SCD was greater during the LIDI. Furthermore, all the events recorded by Sacher *et al.* [14] occurred during the LIDI and the clinically significant arrhythmias described by Roy-Chaudhury *et al.* [15] had the highest frequency during the last 12 h of the LIDI. None of the described studies could provide evidence of an association between plasma electrolyte levels and fatal events. However, the study by Sacher *et al.* [14] showed that a higher risk for cardiac conduction disorders was related to plasma potassium (K^+) concentration > 5.0 mmol/L and a higher risk for ventricular arrhythmia to a plasma K^+ concentration < 4.0 mmol/L. Epidemiological studies suggested a significant association between the values of pre-dialysis hyperkalaemia and SCD [17, 18]. Combining all this evidence, we hypothesize that during the first short interdialysis period of the week HD patients suffer from a sudden decrease in plasma K^+ concentration, whereas at the end of the LIDI they may present with marked hyperkalaemia and acidosis. Both conditions can lead to cardiac electrical instability, which could potentially result in life-threatening arrhythmias (i.e. VF or bradyarrhythmia with asystole). However, it is possible that other risk factors due to cardiac comorbidities and uraemia per se may contribute to sudden mortality in ESKD patients. In fact, PD patients, who do not undergo rapid changes in electrolyte concentrations, also show a high rate of SCD[19]. PD is less intense than HD: the treatment is more or less continuous with slight variations related to different modes of PD. Therefore it is also more

and led to prolongation of QT intervals in many patients. No mortality or cardiovascular outcomes were reported [77].

Amiodarone

Amiodarone exerts many electrophysiological effects and is widely used for both atrial and ventricular tachyarrhythmias, despite the risk of adverse effects (on the thyroid gland, lungs and liver). However, there have been no consistent findings regarding its effectiveness in preventing SCD in HD patients. In an analysis of Dialysis Outcomes and Practice Patterns Study (DOPPS) amiodarone was associated with a higher risk for SCD in HD patients [HR 1.44 (95% CI 1.16–1.81)] [18], however, as for any observational study, no conclusion on causality can be drawn. In a Cochrane systematic review [78] including 24 studies, amiodarone was associated with a significant reduction in the risk of SCD, cardiac and all-cause mortality for persons at high risk (primary prevention) or who have recovered from an SCA (secondary prevention), however, no specific subgroups of ESKD or HD patients were included in these studies.

Digoxin

In a retrospective observational cohort study including 120 864 incident HD patients, digoxin use was associated with a 28% increased risk of death and the increase in mortality risk was most pronounced in patients with lower pre-dialysis serum K^+ levels [79].

In conclusion, contradicting and limited evidence have been found on the efficacy and safety of anti-arrhythmic drugs for HD patients in terms of SCD or fatal cardiovascular events. In addition, poor long-term adherence to drug therapy is found in dialysis patients [80, 81], which might limit the validity of the findings to daily clinical practice. Therefore no strong recommendations in favour of any specific medication or type of medication can be made and large high-quality RCTs in HD patients are needed.

PREVENTION TOOLS—IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDs)

Guidelines for sudden death prevention published by the main cardiology associations recommend implanting an implantable cardioverter defibrillator (ICD) in primary prevention in patients with LVEF <35% and with a life expectancy of at least 1 year and, in the setting of secondary prevention, in patients with documented VF or haemodynamically not tolerated VT in the absence of reversible causes [82]. However, the presence of ESKD was an exclusion criterion in the RCTs that demonstrated that the ICD confers a survival benefit in populations with a high risk of SCD [83–85]. Several observational studies have shown that, in patients implanted with an ICD in primary prevention, the presence of ESKD constitutes a negative prognostic factor in terms of mortality [86–88]. However, when populations of dialysis patients with indication for ICD implantation are compared, data are not consistent. Hiremath *et al.* [89], in an observational study collecting data from two registries, showed that an ICD implant is associated with better survival in ESKD patients with ventricular dysfunction (LVEF <35%) when compared with patients not implanted with the device [HR 0.40 (95% CI 0.19–0.82)] [89]. The risk of bias and unmeasured confounding obviously constitutes an important limitation and propensity score matching can be employed for reducing this risk. Indeed, Pun *et al.* [90], comparing two propensity-matched cohorts of ESKD patients, one that received an ICD in primary prevention and the other without ICD, did not observe differences in mortality in the two groups (43.4% in the ICD cohort versus 39.7% in the control group). The uncertainty about evidence leads to the fact that only a minority of ESKD patients with an indication for ICD implantation actually receive the device. In an Italian population of 2072 ESKD patients (154 of them having an LVEF <35%), only 52 (33%) were implanted with an ICD. As expected, mortality was higher in patients with an ICD indication than in those without [HR 1.59 (95% CI 1.06–2.38)], but subjects with ventricular dysfunction and without an ICD implant had the worst prognosis [HR 2.67 (95% CI 2.09–3.39)]. The rate of SCD was higher not only in patients with an ICD indication, but also patients without an ICD indication had a high incidence of SCD [91]. The high incidence of SCD in dialysis patients with preserved LVEF is the rationale of the only RCT so far performed in this population, the ICD2 trial [92]. This very recent study is particularly interesting because the presence of LVEF <35% was an exclusion criterion, thus leading to an RCT exploring a new indication for ICD implantation in the specific setting of dialysis patients. The study tried to answer the question whether ESKD per se is a risk factor for SCD, independent of a low ejection fraction, and if this risk can be minimized by ICD implantation. Indeed, patients who, according to the guidelines, would have a classical indication for ICD implantation for primary prevention of SCD, on the basis of a depressed ejection fraction, were not recruited. The trial was stopped, as per the recommendation of the data and safety monitoring board, for futility reasons (i.e. inability of the RCT to achieve its original objectives) after inclusion of 188 patients of the 200 planned, 97 in the ICD group and 91 in the control group. The median duration of follow-up was 6.8 years. The 5-year mortality rate was high and similar in the two groups (50.6% in the ICD group versus 54.5% in the control group). The cumulative incidence of SCD was 9.7% in the ICD group versus 7.9% in the control group [HR 1.32 (95% CI 0.53–3.29)] [92]. The reasons for the failure of the ICD strategy to reduce total and sudden mortality may be several: first of all, we must consider the possibility of a failure of the device linked to the presence of non-shockable rhythms (asystole/pulseless electrical activity) or of an arrhythmia arising in a setting of hyperkalaemia and/or severe disorders of the acid–base balance [13, 93], leading to ineffective termination by ICD shocks or immediate reinitiation after shock delivery. Only post-mortem analysis of the intracardiac ECGs (actually planned in the design of the ICD2 trial) was able to clarify what arrhythmia was associated with SCD. It is important to underline that the rate of device-related adverse events was very high (27.5%) [92]. They were directly related to the ICD implantation procedure (haematoma or infection) or were due to lead dysfunction. ICD explantation was necessary in 7.5% of cases, mostly because of bacteraemia [92]. The outcome of patients implanted with an ICD appears more

HD session. However, the high incidence of SCD in PD patients suggests that other factors are also involved in determining sudden mortality in the uraemic patient.

CONFLICT OF INTEREST STATEMENT

S.G. declares speaker's fees of a small amount from AstraZeneca and Pfizer. G.B. declares speaker's fees of a small amount from Medtronic, Boston Scientific and Biotronik. D.S. is consulting for American Renal Clinical Research Services and CHF Solutions. All other authors declare no conflicts of interest.

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Received: 12.7.2019; Editorial decision: 1.8.2019