Expect the Unexpected: Sudden Cardiac Death in Dialysis Patients

Rulan S. Parekh

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Departments of Medicine and Pediatrics, University of Toronto, Toronto, Canada

Correspondence: Dr. Rulan S. Parekh, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. Email: rulan.parekh@sickkids.ca

Over the past decade, a number of clinical trials addressing dialysis dose and frequency and cardiovascular risk have revealed that sudden unexpected deaths are a common occurrence among incident and prevalent dialysis patients (1,2). This high rate of out of hospital deaths has been confirmed in natural history studies, with an incidence as high as 25% over 5 years, and the rate has not substantially changed in the last decade regardless of dialysis modality (3,4). The biologic mechanisms and pathogenesis of sudden cardiac death among the dialysis population are almost certainly different than in the general population, as ESRD is an inflammatory state with regular fluctuations of electrolytes and fluid on an intermittent basis depending on dialysis modality. For the nephrology community to address prevention of sudden cardiac death, we need to answer some key questions to inform and guide our clinical decisions. How do we define sudden cardiac death? What are the potential mechanisms leading to arrhythmias and consequent sudden death among dialysis patients that may differ from the general population? What interventions may improve outcomes? Studying these questions will ultimately lead to preventive strategies to lower mortality risk among dialysis patients.

It may seem inconsequential to have a clear definition of sudden cardiac death; however, it is evident from the large clinical trials in dialysis such as 4D that the classification of sudden cardiac death as an atherosclerotic cardiovascular death perhaps led trials to be underpowered for coronary events. Sudden cardiac death occurs as a result of arrhythmias in a number of vulnerable cardiac states, which include either ischemic heart disease, ventricular hypertrophy, or vascular stiffness. Furthermore, if the risk for sudden cardiac death is overestimated, it may alter referral patterns for unnecessary treatments. Hence, an accurate definition is needed to have consistency among studies and registry data to follow temporal trends, determine risk factors, and evaluate effectiveness of interventions. Definitions of sudden cardiac death have varied widely in the literature but typically include duration of onset of symptoms, witnessed or unwitnessed events, and known prior history of heart disease (Table 1). Sudden cardiac death by definition is a sudden, unexpected event that occurs after <1–24 hours of the onset of symptoms, depending on the definition, and occurs outside of the hospital or on arrival to the emergency room. If the event is witnessed, the ability to refine the classification of sudden cardiac death improves as the symptoms, such as chest pain, can be determined to be cardiovascular in nature. A true arrhythmic cause of death as defined by Hinkle and Thaler (5) depends on a witnessed event where the abrupt loss of consciousness and disappearance of pulse occurs without prior collapse of the circulation. This is almost impossible to define; thus, the most useful definition for dialysis patients is from the Hemodialysis (HEMO) trial where sudden cardiac death is defined as an unexpected death, with a preceding duration of symptoms <24 hours for witnessed deaths and less than the interval since the last dialysis session for unwitnessed deaths.

Among patients on hemodialysis who are seen at least three times per week for treatment, the definition of sudden cardiac death is problematic for a number of reasons. Intermittent fluctuations in the physiologic milieu with changes in BP, electrolytes, and volume status during the dialysis treatment can adversely alter cardiovascular tone, function, and rhythms and ultimately lead to symptoms such as chest pain, shortness of breath, fatigue, weakness, and nausea. The classification of sudden death depends on duration of symptoms, which are extremely variable in presentation and duration among patients on dialysis. Additionally, clinical symptoms can occur at any time surrounding the dialysis treatment, as well as witnessed cardiac arrests within the dialysis unit.

The paper by Pun *et al.* (6) in this issue of *CJASN* highlights the need to carefully classify witnessed sudden deaths in the dialysis unit as these events could be potentially preventable, and the inciting mechanisms could be related to the dialysis treatment *per se*. In the future, adjustments in the dialysis prescription may be necessary as potential interventions. The authors propose a more conservative approach to the definition of sudden cardiac death that classifies sudden death that occurs in the dialysis unit using administrative data and validates the classification to an external source of witnessed events and medical records. The validation of the deaths using the CMS-2746 (death notification form) completed by the attending nephrologist within 30 days of the patient's death is an extremely important exercise as the registry data from the US Renal Data Systems is used to estimate risk of cardiac events, make clinical inferences, and provide data of temporal trends

Table 1. Classification of sudden cardiac death outside of the hospital (exclusions added by Pun et al.)

	Data Sources	Definition of SCD	Exclusions
Classification in Registries	National Death Index: ICD-9: 798 ICD-10: I46.1	Out of the hospital or in the emergency room or "dead on arrival" -sudden death	
	CMS Death Notification Form: #29	Cardiac arrest, cause unknown or cardiac arrhythmia	Withdrawal of dialysis, hospice care, primary or secondary cause of death reported as hyperkalemia, septicemia or malignant disease
	CDC	Sudden unexpected death from a cardiac cause (<1 hr) or death from a cardiac cause occurring outside of a hospital, or in an emergency room or on arrival to the hospital	
Observational Studies	ARIC, NHS, BRHS, Framingham	≤1 hr since onset of symptoms and no other known non-cardiac cause present	
Trials	Hemodialysis (HEMO) Study	Witnessed death:<24 hr; unwitnessed death: less than the interval since the last dialysis session	
	MADIT I/CAPS	Witnessed death:≤1 hr; unwitnessed death: no other cause identified	
	MADIT II	≤1 hr of cardiac symptoms in absence of cardiac deterioration; died in bed during sleep; within 24 hr after last being seen alive	
Guidelines	Task Force on Sudden Cardiac Death of the European Society of Cardiology[a]	Natural unexpected death due to cardiac causes, abrupt loss of consciousness ≤1 hr since onset of acute symptoms and preexisting cardiac disease may have been present	

SCD, sudden cardiac death; ICD, International Classification of Diseases; CMS, Center for Medicare and Medicaid Services; CDC, Center for Disease Control; ARIC, Atherosclerosis Risk in Communities; NHS, Nurse's Health Study; BRHS, British Regional Heart Study; MADIT, Multicenter Automatic Defibrillator Implantation Trial.

[a]Preexisting cardiac disease, ischemic heart disease; arrhythmias, or other pre-existing heart disease may be present.

for the entire US dialysis population. The addition of exclusion criteria to the CMS-2746 data will aid in classifying out of hospital deaths (Table 1) and the further addition of ICD-9 codes will help classify inpatient hospital deaths. The new criteria improve classification with only modest agreement compared to witnessed events; however, it is an important first step. In an observational cohort study, comparison of the causes of death from the death notification form to the National Death Index data derived from death certificates demonstrated that physicians often assign sudden death events as cardiac arrest or unknown (3). Perfecting the use of administrative data will require education of the attending nephrologists to be more precise in choosing causes of death. Improving the reporting of witnessed sudden cardiac deaths in the dialysis unit will also impact how the nephrology community addresses care in the dialysis units. Ultimately, studies are needed to identify specific factors leading to in-center cardiac arrests. Previous studies have suggested that low dialysate potassium concentration may adversely affect outcomes by lowering serum potassium, and in the study by Pun *et al.*, elevated serum potassium, if associated with electrocardiogram changes, was excluded from the analyses because the potassium level could have led to sudden death. We have further work to understand potassium metabolism and arrhythmic risk within the extreme ranges of serum potassium seen among dialysis patients.

Current recommendations in the general population to reduce arrhythmic risk of death suggest that implantable cardiac defibrillators be used. Among dialysis patients, there is no significant benefit seen among US dialysis patients who had received an implantable defibrillator even after a myocardial infarction (7,8). Many dialysis patients could meet criteria for defibrillators and may potentially be referred despite ongoing clinical equipoise and potentially increasing financial burden to Medicare. Moreover, with the high sudden death rates and lack of treatment benefit using proven methods, it is important to understand the pathogenesis of sudden cardiac death among dialysis patients and determine whether there are any modifiable factors. Many dialysis patients already have an underlying burden of cardiovascular disease with atherosclerotic disease, increased ventricular mass, or vascular stiffness that place them at high risk for arrhythmic events, and this is only further exaggerated with intermittent dialysis. To improve our understanding of the causal mechanisms of disease, it is imperative that research address modifiable risk factors and triggers for sudden cardiac death.

The study by Shastri *et al.* (9) in this issue of *CJASN* studies the predictors of sudden cardiac death and the best predictive model of sudden death. The investigators focus on clinical characteristics that are routinely collected and determined the best predictive model associated with sudden cardiac death among prevalent hemodialysis participants in the HEMO study. The study has significant strengths including the standard definition of adjudicated outcomes, use of clinical factors available at baseline, and also competing risk analyses for a more conservative estimate of risk. The most predictive model was able to discriminate sudden cardiac death events across the range of risk and included age, diabetes, ischemic heart disease, peripheral vascular disease, serum creatinine, and alkaline phosphatase in the most parsimonious model. Similar to other observational studies, traditional risk factors such as BP and obesity were not associated with sudden cardiac death (3). It is not surprising that age, diabetes, and preexisting heart and peripheral vascular disease were predictive of sudden cardiac death given the pathogenesis of sudden cardiac death and the underling burden of cardiovascular disease. In contrast, serum creatinine and alkaline phosphatase were selected using an unbiased algorithm but do not have a clear association with sudden cardiac death. The participants of the HEMO trial were predominantly prevalent patients on dialysis for an average of 3 years, where weight loss and bone disease are more common as dialysis duration increases. Creatinine could reflect muscle mass, which may also be associated with additional sarcopenic changes in the myocardium (10). Elevated alkaline phosphatase could also indicate the burden of bone disease in dialysis patients; however, neither serum alkaline phosphatase nor creatinine measures have been systematically studied. Understanding the potential mechanisms of creatinine and alkaline phosphatase with sudden cardiac death is merely circumstantial until the predictive model is validated and tested in other cohorts. Without external validation, clinical prediction models are only a half-tested hypothesis and may result in type 1 errors.

In the HEMO study, there was an obvious lack of data on dialysis prescription, dialysis bath, and dysrhythmias as some prime examples of factors that increase risk for sudden cardiac death. None of these risk factors were readily available in the HEMO trial; however, they do need to be considered for future studies and are clinically relevant for any predictive model. Dysrhythmias lead to sudden cardiac death often as a result of abnormal heart rate regulation or altered conduction and repolarization of ventricular conduction. This is also exacerbated by biochemical alterations such as changes in calcium, magnesium, and potassium. It is especially important to study because the clinical trial of frequent dialysis and recent observational studies demonstrate that intermittent dialysis or 2 days off dialysis increases the risk of mortality (11–13) and likely potentiates arrhythmic triggers such as low calcium and potassium dialysate, increased volume removal, vascular stiffness, hypo/hypertension, electrolyte changes, and inflammation. The two studies in this issue of *CJASN* illustrate the importance of sudden cardiac death in dialysis patients, but we have a long way to go to better understand the mechanisms leading to sudden death.

As nephrologists, we need to expect the unexpected and anticipate that sudden death occurs commonly among our patients on dialysis. We do not have definitive answers yet on the modifiable risk factors leading to sudden cardiac death or prevention strategies to mitigate risk. We can, however, address simple practices ensuring education of dialysis staff on the frequency of sudden death and education of nephrologists on the classification of causes of death. Training of cardiopulmonary resuscitation and use of external defibrillators in the dialysis units is standard, but it has not been shown to decrease risk of in center deaths. How we address sudden cardiac death prevention in the future will be based on ongoing clinical studies and ultimately clinical trials to test interventions to reduce the risk of death.

Disclosures

None.

References

1. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, Lewis J, Rocco M, Toto R, Windus D, Ornt D, Levey AS; HEMO Study Group: Cardiac diseases in maintenance hemodialysis patients: Results of the HEMO Study. *Kidney Int* 65: 2380–2389, 2004
2. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353: 238–248, 2005
3. Parekh RS, Plantinga LC, Kao WH, Meoni LA, Jaar BG, Fink NE, Powe NR, Coresh J, Klag MJ: The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney Int* 74: 1335–1342, 2008
4. Wang AY, Lam CW, Chan IH, Wang M, Lui SF, Sanderson JE: Sudden cardiac death in end-stage renal disease patients: A 5-year prospective analysis. *Hypertension* 56: 210–216, 2010
5. Hinkle LE Jr, Thaler HT: Clinical classification of cardiac deaths. *Circulation* 65: 457–464, 1982
6. Pun PH, Herzog CA, Middleton JP: Improving ascertainment of sudden cardiac death in patients with end stage renal disease. *Clin J Am Soc Nephrol* 7: 116–122, 2012
7. Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT: Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int* 68: 818–825, 2005
8. Sakhuja R, Keebler M, Lai T-S, McLaughlin Gavin C, Thakur R, Bhatt DL: Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. *Am J Cardiol* 103: 735–741, 2009
9. Shastri S, Tangri N, Tighiouart H, Beck GJ, Vlagopoulos P, Ornt D, Eknoyan G, Kusek JW, Herzog C, Cheung AK, Sarnak MJ: Predictors of sudden cardiac death: A competing risk approach in the Hemodialysis Study. *Clin J Am Soc Nephrol* 7: 123–130, 2012
10. Drechsler C, Grootendorst DC, Pilz S, Tomaschitz A, Krane V, Dekker F, Marz W, Ritz E, Wanner C: Wasting and sudden cardiac death in hemodialysis patients: A post hoc analysis of 4D (Die Deutsche Diabetes Dialyse Studie). *Am J Kidney Dis* 58: 599–607, 2011
11. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS: In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 363: 2287–2300, 2010
12. Foley RN, Gilbertson DT, Murray T, Collins AJ: Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med* 365: 1099–1107, 2011
13. Bleyer AJ, Russell GB, Satko SG: Sudden and cardiac death rates in hemodialysis patients. *Kidney Int* 55: 1553–1559, 1999

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See related articles, "Improving Ascertainment of Sudden Cardiac Death in Patients with End Stage Renal Disease" and "Predictors of Sudden Cardiac Death: A Competing Risk Approach in the Hemodialysis Study," on pages 116–122 and 123–130.