Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period

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BACKGROUND Chronic kidney disease (CKD) patients undergoing hemodialysis (HD) have a high risk of sudden cardiac death (SCD). A unique risk factor may be a longer interval between HD sessions (interdialytic period). Inherent in conventional HD (thrice-weekly) are two 48-hour short breaks (SIDP) and one 72-hour long break (LIDP) between HD sessions.

OBJECTIVE We used an implantable cardiac monitor (ICM) to define the incidence and timing of significant arrhythmias in an HD population.

METHODS Fifty CKD patients undergoing HD with left ventricular ejection fraction >35% had an ICM inserted, with intensive follow-up to record SCD events and predefined bradyarrhythmias and tachyarrhythmias.

RESULTS Mean age of the patients was 67 ± 11 years; 72% were male, and the mean follow-up was 18 ± 4 months. There were 8 unexpected SCDs (16%), all during the LIDP. The terminal event was severe bradycardia with asystole in each recorded case. No episodes of polymorphic ventricular tachycardia (VT) occurred. A total of 7686 arrhythmia events were recorded in 43 patients (86%), including bradycardia in 15 patients (30%), sinus arrest in 14 (28%), second-degree atrioventricular block in 4 (8%), nonsustained VT in 10 (20%), and new-onset paroxysmal atrial fibrillation in 14 (28%). The LIDP was the highest-risk period for all arrhythmias ($P < .001$). The arrhythmia event rate per hour was greatest during the first pre-HD period of the week compared with any other peri-HD period ($P < .001$).

CONCLUSION Risk of SCD and significant arrhythmias is greatest during the LIDP. SCD was attributable to severe bradycardia and asystole. Interventions to prevent this type of SCD or shorten the LIDP deserve further evaluation.

CLINICAL TRIAL REGISTRATION INFORMATION URL: https://www.anzctr.org.au (Unique identifier: ACTRN12613001326785).

KEYWORDS Arrhythmia; Bradycardia; Chronic kidney disease; Hemodialysis; Interdialytic; Sudden death

ABBREVIATIONS **AF** = atrial fibrillation; **AV** = atrioventricular; **CKD** = chronic kidney disease; **ECG** = electrocardiogram; **HD** = hemodialysis; **ICM** = implantable cardiac monitor; **LIDP** = long interdialytic period; **LV** = left ventricular; **LVEF** = left ventricular ejection fraction; **SCD** = sudden cardiac death; **SIDP** = short interdialytic period; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Chronic kidney disease (CKD) is a major public health issue, and patients with stage 5 CKD undergoing hemodialysis (HD) experience a high mortality rate of approximately 7% per year.[1,2] One-fourth of all deaths in this population are attributable to sudden cardiac death (SCD).[3–6] Traditional cardiovascular risk factors do not adequately explain the high SCD rate in HD patients.

Thrice-weekly conventional HD is the most widely practiced dialysis regimen worldwide, which invariably consists of two 48-hour breaks (otherwise known as the "short interdialytic period," or SIDP) and one 72-hour break

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between dialysis sessions ("long interdialytic period," or LIDP). The LIDP has increasingly been suggested as a higher-risk period for SCD, but definitive data are lacking.[7] However, the pattern and prevalence of serious bradyarrhythmias and tachyarrhythmias in this group of patients have not been well characterized. Furthermore, the influence of the LIDP on arrhythmia incidence and type is unknown.

We have recently reported on a preliminary observation concerning SCD in stage 5 CKD patients undergoing HD with preserved left ventricular (LV) function.[8] The majority of SCDs appeared to be attributable to bradycardia and asystole. The current study presents long-term follow-up of this prospective cohort study. We postulated that stage 5 CKD patients undergoing HD experience a substantial burden of cardiac arrhythmias often not detected during routine clinical care. The aim of this study was to evaluate the long-term incidence and timing (with specific reference to the LIDP) of arrhythmias in HD patients using an implantable cardiac monitor (ICM).

Methods

Study population and protocol

Fifty HD patients were enrolled from a population of clinically stable ambulatory HD patients undergoing dialysis in satellite units of Melbourne Health and Western Health (Figure 1) from August 2012 to December 2013. Only stage 5 CKD patients undergoing conventional HD who had been receiving stable medical therapy for at least 1 month were considered eligible for inclusion. Exclusion criteria were (1) severe LV dysfunction (LV ejection fraction [LVEF] $<35\%$), (2) New York Heart Association class IV symptoms, (3) preexisting pacemaker or implantable cardioverter-defibrillator in situ, (4) prior history of clinical ventricular tachyarrhythmias (including ventricular fibrillation [VF] or cardiac arrest) or syncope, (5) unstable angina pectoris or uncontrolled hypertension, (6) bleeding diathesis, (7) inability to provide informed consent, and (8) pregnancy.

All patients provided written informed consent to the study protocol, which was approved by the Melbourne Health Human Research Ethics Committee.

Arrhythmia monitoring, documentation, and follow-up

All patients had an ICM implanted at baseline for continuous electrocardiographic (ECG) monitoring. Each patient underwent insertion of the Confirm (St. Jude Medical, St. Paul, Minnesota) implantable loop recorder, which is a 6.5-cc (56.3 mm × 18.5 mm × 8 mm), 12-g, subcutaneously implantable device designed to continuously monitor cardiac rhythm for up to 3 years. Storage of the ECG is triggered automatically when arrhythmic events fulfill preprogrammed cutoff criteria (as specified below). Subcutaneous insertion of the ICM in the left parasternal region of the chest wall via a small 1-cm horizontal incision was performed under local anesthetic. Surface ECG mapping was performed before each procedure to ensure adequate R-wave amplitude measurement and minimize T-wave oversensing. The ICM uses an automatic detection algorithm that monitors for R-R interval irregularity plus additional rhythm discrimination criteria to reduce the frequency of false-positive atrial fibrillation (AF) detections. Each atrial tachycardia/AF episode was analyzed manually and considered true AF if presence of R-R irregularity and absence of P waves were evident from the ECG mapping. The AF algorithm has a predefined duration parameter of 2 minutes, and therefore, only episodes of at least 2 minutes were included in the analysis. The device memory can store up to 48 minutes of recordings (147 episodes), inclusive of all automatically detected arrhythmias and patient-activated episodes.

Prespecified arrhythmia definitions

Significant arrhythmia events (potential causes of syncope or SCD) consisted of the following: (1) sinus bradycardia ≤ 40 bpm for ≥ 4 beats; (2) sinus arrest with pauses or asystole ≥ 3 seconds; (3) high-degree atrioventricular (AV) block (second- to third-degree AV block) ≤ 40 bpm lasting ≥ 3 seconds; (4) nonsustained ventricular tachycardia (VT), defined as ≥ 125 bpm and >16 beats lasting <30 seconds; (5) sustained VT ≥ 125 bpm lasting ≥ 30 seconds; and (6) VF. Other recorded arrhythmia events consisted of the following: (1) AF, if there was an absence of p waves and the presence of R-R irregularity for ≥ 2 minutes, and (2) supraventricular tachycardia, consisting of ≥ 10 beats of narrow-complex tachycardia.

Arrhythmia event timing definitions

The LIDP was defined as the 72-hour break between HD sessions, whereas the other two 48-hour interdialytic periods were each defined as SIDP. Arrhythmia event timing was analyzed according to the day of the dialysis week and relationship to LIDP or SIDP.

Events that occurred in any of the thrice-weekly peri-HD periods were further defined according to predefined event time periods as follows: (1) the 8 hours before an HD session, or the pre-HD period; (2) the 4 hours of HD, or the intra-HD period; and (3) the 12 hours after an HD session, or the post-HD period.

Follow-up

Patients underwent intensive follow-up beginning on day 7 after implantation for wound review and then every 2 weeks at their regular dialysis session for device data download, which ensured that adequate device memory storage was present. Sensitivity of arrhythmia detection was adjusted individually if undersensing or oversensing was observed. Stored episodes were interpreted and manually verified by study investigators blinded to the patient's clinical details. Patients who experienced SCD had their ICM retrieved for device interrogation (with the consent of the next of kin) to record outcome data.