Kidney Medicine

Listening to the Rhythm of Arrhythmias Among Patients Maintained on Hemodialysis

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It is increasingly recognized that patients with end-stage kidney disease receiving intermittent thrice-weekly hemodialysis are among the highest risk populations for cardiac arrhythmias and sudden cardiac death (SCD). The

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~5% annual SCD rate in patients receiving hemodialysis exceeds the general population risk by 20-fold and even exceeds the rate among patients with heart failure with reduced ejection fraction, the most well-recognized high-risk population.[1] Since seminal observations made by Bleyer et al[2] more than 30 years ago, multiple studies have confirmed a temporal pattern of cardiac events in patients receiving hemodialysis according to the day of the week and the timing of hemodialysis treatments. Cardiac arrest is most likely to occur on hemodialysis treatment days, most frequently on the first treatment day after the long dialysis-free weekend (ie Monday or Tuesday).[3] More granular observations identify the early morning hours preceding the first hemodialysis treatment of the week as the highest risk period, followed by the next 12 hours following the start of treatment. These observations suggest that the nonphysiologic periodic accumulation and removal of uremic toxins, electrolytes, and fluids occurring most profoundly on the first dialysis treatment day of the week may be responsible for the temporal patterns observed.[4]

The Monitoring in Dialysis (MiD) study was one of the first studies to prospectively characterize the types and timing of cardiac arrhythmias in patients receiving intermittent hemodialysis. Using implantable loop recorders capable of capturing all significant arrhythmias according to set detection limits, they monitored 66 patients receiving hemodialysis from the United States and India continuously over 6 months. The study provided a trove of information about the types of arrhythmias experienced by patients and the relationships between arrhythmias and dialytic parameters. Previous publications from MiD have confirmed the dual high-risk shoulder periods for arrhythmias surrounding the first hemodialysis treatment of the week. In addition, MiD further delineated bradyarrhythmias and asystolic pauses as predominant arrhythmias in the predialytic period, whereas paroxysmal atrial fibrillation and supraventricular tachycardias were more likely in the intradialytic and intra- and postdialytic period (ventricular arrhythmias were exceedingly rare).[5] Although yet to be proven, these temporal patterns are consistent with probable mechanistic explanations; asystole or bradyarrhythmia may be more likely to be provoked by hyperkalemia and volume overload in the predialytic period, whereas intradialytic and intra- and postdialytic hypokalemia and ischemia-inducing fluid shifts might precipitate atrial arrhythmias.

The present secondary analysis of the MiD study in this issue of Kidney Medicine by Soomro et al[6] introduces another possible layer to the temporal story of cardiac arrhythmias in patients receiving intermittent hemodialysis—the possible contribution of circadian biology. In healthy populations and among those with heart disease, SCD is more likely to occur in the morning after waking, whereas bradyarrhythmias and paroxysmal atrial fibrillation are much more common at night.[7] Central and local circadian clocks in the heart may drive diurnal patterns through a variety of mechanisms, such as hormonal levels, autonomic nervous activity, and ion channel expression.[7] These circadian rhythms have provided therapeutic targets to reduce SCD, such as targeted use of β-blockers at night,[8] and recent interest in the antiarrhythmic properties of melatonin.[9] Given the paucity of evidence regarding the influence of circadian rhythms on arrhythmias in the population receiving hemodialysis, Soomro et al[6] aim to provide this while disentangling complex relationships with the timing of dialysis treatments and the presence or absence of heart failure.

To do this, they examined the rates of clinically significant arrhythmias (CSAs), defined as ventricular tachycardia ≥115 BPM for ≥30 seconds, bradycardia at ≤40 BPM lasting at least 6 seconds, asystole lasting at less ≥3 seconds, and any patient-marked (symptomatic) events with an ECG-confirmed clinically relevant arrhythmia. Atrial fibrillation events were analyzed separately. To examine circadian patterns, arrhythmias were grouped into 6-hour time intervals within 24-hour days. They stratified analyses according to dialysis versus nondialysis days and the presence or absence of heart failure to look for independent effects.

In summary, out of 66 enrolled participants, only 44 had any CSA events and contributed to the primary analysis. Of the 44 participants with CSA, fewer than half had any of the predefined arrhythmias (bradycardia/asystole/ventricular tachycardia); the rest had CSA because of a patient-marked event with an unspecified arrhythmia type.[5] Only 27 participants experienced any atrial fibrillation events during the follow-up. Despite the small sample size, temporal patterns emerged. CSA events were more frequent in the early morning, driven primarily by bradycardia between midnight and 6 AM, but event rates were still markedly high between 6 AM and noon. Atrial fibrillation was predominantly seen among participants with heart failure at baseline, and the timing of events was

much more evenly distributed throughout the day, with only a slight tendency to occur between 6 AM and noon. Comparing CSA events between dialysis and nondialysis days did not change the temporal patterns, with a continued strong tendency toward early AM events; however, adjusted CSA rates were nearly 4 times higher on dialysis days. Of importance, comparing the timing of CSA events between patients undergoing morning versus afternoon dialysis treatments significantly shifted the peak event period from midnight to 6 AM for morning shift patients to 6 AM to noon for afternoon shift patients. Conversely, the difference in the rate of atrial fibrillation events between dialysis and nondialysis days was muted, and the circadian patterns were only minimally present.

What can we learn from these results? First of all, this study confirms the substantial influence that the timing of dialysis treatments exerts on arrhythmia risk. Arrhythmia rates were higher for both CSA and atrial fibrillation on dialysis days, and the highest risk period shifted accordingly among patients who dialyzed later in the day. Therefore, this author does not agree with the authors' conclusion that the timing of dialysis treatment does not appear to exert a major effect on CSA rates or timing. The consistent proximity of significant arrhythmias to the timing of dialysis, whether in the pre- or intra/postdialytic period, is evident through these detailed comparisons.

However, if the timing of arrhythmic events was only influenced by imbalances in homeostasis due to the dialytic cycles, we would not expect to see diurnal patterns emerge on nondialysis days; in fact, one might expect the morning hours on nondialysis days to be a low-risk period where levels of uremic solutes, electrolytes, and fluids are the most normal after postdialysis equilibration has occurred. Without the noise of concurrent dialysis treatment on these days, the observation of persistent diurnal patterns supports the hypothesis that circadian biology may also play a role in arrhythmia risk.

An important caveat, as discussed above, is that the number of patients contributing events was small; stratification according to heart failure, dialysis day, and shift further limited these analytic subgroups to only a handful of patients, thus significantly limiting generalizability. Furthermore, the true clinical significance of investigator-defined CSAs is uncertain and is further limited by the lack of knowledge about the types of arrhythmias that were detected during patient-marked CSAs. However, this study represents the most detailed analysis of arrhythmia timing to date. It further reinforces the importance of reducing the unphysiology of the thrice-weekly hemodialytic cycle as a primary target to mitigate arrhythmia risk, while introducing the possibility of internal circadian rhythms and disordered sleep patterns as additional targets for therapy to combat the epidemic of SCD in patients receiving hemodialysis.

ARTICLE INFORMATION

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