Kidney Medicine

Arrhythmia and Time of Day in Maintenance Hemodialysis: Secondary Analysis of the Monitoring in Dialysis Study

Qandeel H. Soomro, Bruce A. Koplan, Alexandru I. Costea, Prabir Roy-Chaudhury, James A. Tumlin, Vijay Kher, Don E. Williamson, Saurabh Pokhariyal, Candace K. McClure, and David M. Charytan, for the MiD Investigators

Rationale & Objective: The incidence of arrhythmia varies by time of day. How this affects individuals on maintenance dialysis is uncertain. Our objective was to quantify the relationship of arrhythmia with the time of day and timing of dialysis.

Study Design: Secondary analysis of the Monitoring in Dialysis study, a multicenter prospective cohort study.

Settings & Participants: Loop recorders were implanted for continuous cardiac monitoring in 66 participants on maintenance dialysis with a follow up of 6 months.

Exposure: Time of day based on 6-hour intervals.

Outcomes: Event rates of clinically significant arrhythmia.

Analytical Approach: Negative binomial mixed effects regression models for repeated measures were used to evaluate data from the Monitoring in Dialysis study for differences in diurnal patterns of clinically significant arrhythmia among those with end-stage kidney disease with heart failure and end-stage kidney disease alone. We additionally analyzed rates according to presence of heart failure, time of dialysis shift, and dialysis versus nondialysis day.

Results: Rates of clinically significant arrhythmia peaked between 12:00 AM and 5:59 AM and were more than 1.5-fold as frequent during this interval than the rest of the day. In contrast, variations in atrial fibrillation peaked between 6:00 AM and 11:59 AM, but variations across the day were qualitatively small. Clinically significant arrhythmia occurred at numerically higher rate in individuals with end-stage kidney disease and heart failure (5.9 events/mo; 95% CI, 1.3-26.8) than those without heart failure (4.0 events/mo; 95% CI, 0.9-17.9). Although differences in overall rate were not significant, their periodicity was significantly different ($P < 0.001$), with a peak between 12:00 AM and 6:00 AM with kidney failure alone and between 6:00 AM and 11:59 AM in those with heart failure. Although the overall clinically significant arrhythmia rate was similar in morning compared with evening dialysis shifts ($P = 0.43$), their periodicity differed with a peak between 12:00 AM and 5:59 AM in those with AM dialysis and a later peak between 6:00 AM and 11:59 AM in those with PM shifts.

Limitations: Post hoc analysis, unable to account for unmeasured confounders.

Conclusion: Clinically significant arrhythmias showed strong diurnal patterns with a maximal peak between 12:00 AM and 5:59 AM and noon. Although overall arrhythmia rates were similar, the peak rate occurred overnight in individuals without heart failure and during the morning in individuals with heart failure. Further exploration of the influence of circadian rhythm on arrhythmia in the setting of hemodialysis is needed.

Complete author and article information provided before references.

Correspondence to Q.H. Soomro (qandeel.soomro@nyulangone.org)

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The oscillation of the body's circadian clock controls 24-hour rhythmicity and synchronizes it with external time.[1] Circadian rhythms regulate several cardiovascular physiological functions, including myocardial electrical activity. Disruption of external regulators or endogenous oscillators, such as neurohumoral responses can alter

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circadian rhythms and lead to cardiovascular disease.[1] Indeed, several cardiovascular diseases, such as myocardial infarction, stroke, ventricular tachycardia, and sudden cardiac death demonstrate circadian patterns with a peak in the early morning hours after waking,[2,3] and data on cyclic 24-hour periodicity in cardiac conduction, refractoriness, and susceptibility to arrhythmia are particularly robust.[3-7] Although the underlying mechanisms are complex, associations with arrhythmia likely reflect, at least partially, the balance of circadian and autonomic inputs to the sinus and atrioventricular nodes. This has fueled interest in chronotherapy and drugs that directly modify circadian rhythms such as melatonin, which has been shown to have a pleiotropic antiarrhythmic effect.[8,9] Although circadian patterns to arrhythmia have been studied in healthy adults and those with heart disease, less is known about these patterns in patients on chronic dialysis, despite recognition of the high prevalence of autonomic dysfunction and sleep disturbances in this population.[10,11]

Our primary objective in this study was to use data from the Monitoring in Dialysis study (MiD; ClinicalTrials.gov identifier: NCT01779856) to examine differences in diurnal patterns of arrhythmia among those with end-stage

PLAIN-LANGUAGE SUMMARY

Arrhythmias occur with a high frequency in individuals with kidney failure. We sought to understand whether there were diurnal patterns for common types of arrhythmias in individuals with kidney failure. We used continuous rhythm data from 66 individuals on dialysis with implantable loop recorders. We found that clinically significant arrhythmias including bradycardia primarily occur overnight and in the early morning, whereas atrial fibrillation is more evenly distributed during the day.

kidney disease on dialysis and to compare patterns in patients with and without heart failure. Second, we aimed to study whether patterns of diurnal variation in arrhythmia differ on dialysis compared with nondialysis days or according to the time of the dialysis treatments (ie, morning or afternoon).

METHODS

Study Population

MiD was a multicenter, prospective cohort study. The design, objectives, and primary outcomes have been reported in detail.[12,13] In summary, loop recorders (Medtronic Reveal XT or LINQ) were implanted in 66 individuals on thrice-weekly maintenance in-center hemodialysis (HD). Individuals with existing permanent pacemakers or implantable defibrillators were excluded. Loop recorders were utilized for continuous cardiac rhythm monitoring to detect the occurrence of clinically significant arrhythmia (CSA) for 6 months and were interrogated before each HD session during the 6-month primary outcome as well as after every session with protocol-mandated phlebotomy. Informed consent was obtained from all subjects, and the study was approved by applicable institutional review boards.

Primary Analysis

For the present analysis, the primary exposure of interest was time of day based on 6-hour time intervals, and the primary outcome was the CSA rate. Several secondary analyses were planned as follows: (a) according to the presence or absence of heart failure at baseline; (b) according to dialysis shift (AM or PM); and (c) according to dialysis day versus nondialysis day.

CSA was defined according to the primary definition used in the MiD study and included (a) ventricular tachycardia at a rate of ≥115 beats per minute for at least 30 seconds. The threshold was subsequently changed to ≥130 beats per minute by a protocol amendment while the study was underway. (b) Bradycardia at ≤40 beats per minute lasting at least 6 seconds; (c) Asystole lasting at less ≥3 seconds; (d) Patient-marked (symptomatic) events with electrocardiogram (ECG)-confirmed clinically relevant arrhythmia.[12,13] We additionally examined the occurrence of atrial fibrillation (AF), which was not included in the CSA definition, but was the most frequently detected arrhythmia in MiD.[13]

Statistical Analyses

Baseline demographics, dialysis parameters, and laboratory characteristics are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables and percentage (n/N) for categorical variables. Characteristics between subjects with and without at least one CSA were compared using unpaired *t* tests or Wilcoxon rank sum tests for continuous variables, and Fisher exact tests for categorical variables. Where 3 or more groups were assessed, analysis of variance and Kruskal-Wallis tests were used for continuous variables, and Fisher exact tests were used for categorical variables.

Population-averaged (marginal) repeated measures negative binomial regression models were used to evaluate associations between time of the day and outcomes in the 2 groups. *P* values were adjusted for multiple comparisons using the Tukey-Kramer method. Interaction terms were used to assess the effect of time of the day and presence or absence of heart failure on arrhythmia rates. In a sensitivity analysis, periodicity was captured by applying trigonometric transformations to the data under negative binomial models. All analyses were conducted in SAS version 9.4 (SAS Institute). *P* value of <0.05 was considered significant.

RESULTS

Baseline Characteristics and Events Stratified by Presence of Heart Failure

Of 66 enrolled participants, 17 had both kidney failure and heart failure, and 49 had kidney failure alone (Table 1). The majority of individuals with heart failure had preserved left ventricular ejection fraction median 55% (IQR, 55-60). Only 3% of those with heart failure had ejection fraction <35%. Individuals with kidney failure and heart failure were older than those with kidney failure alone. Overall, slightly more than half of the participants were Black. Hypertension was the most common cause of kidney failure in individuals with heart failure, whereas diabetes was the most common cause of kidney failure in those with kidney failure alone. Those with heart failure were also more likely to have a history of myocardial infarction and arrhythmia and had significantly higher body mass index. Use of β-blocker, calcium channel blocker, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was similar in individuals with and without heart failure. Most participants (86%) were dialyzed in morning shifts rather than afternoon or evening shifts (14%). Overall, bradycardia was the most common CSA arrhythmia type with 1,461 events, and a rate of expected events per month of 3.9 (95% confidence interval [CI], 1.1-13.9). AF was also frequent with 4,419 events and monthly event rate of 11.9 (95% CI, 4.6-30.4)

Table 1. Baseline Characteristics and Arrhythmia Outcomes

Characteristic	Overall (N = 66)	Kidney and Heart Failure (N = 17)	Kidney Failure Alone (N = 49)
Age (y), mean ± SD	56.3 ± 12.2	61.5 ± 10.7	54.5 ± 12.2
Female % (n/N)	30.3% (20/66)	47.1% (8/17)	24.5% (12/49)
Race % (n/N)			
Asian	34.8% (23/66)	0.0% (0/17)	46.9% (23/49)
Black	53.0% (35/66)	82.4% (14/17)	42.9% (21/49)
Other	1.5% (1/66)	0.0% (0/17)	2.0% (1/49)
White	10.6% (7/66)	17.6% (3/17)	8.2% (4/49)
Hispanic ethnicity	0.0% (0/66)	0.0% (0/17)	0.0% (0/49)
Cause of kidney failure % (n/N)			
Diabetes	42.4% (28/66)	29.4% (5/17)	46.9% (23/49)
Glomerulonephritis	9.1% (6/66)	5.9% (1/17)	10.2% (5/49)
Hypertension	37.9% (25/66)	64.7% (11/17)	28.6% (14/49)
Other	28.6% (14/49)	0.0% (0/17)	14.3% (7/49)
Kidney failure vintage (y)	2.4	2.2	2.5
Median (IQR)	(1.2, 5.3)	(0.9, 4.1)	(1.2, 5.6)
HD access			
AV fistula	69.2% (45/65)	62.5% (10/16)	71.4% (35/49)
AV graft	26.2% (17/65)	37.5% (6/16)	22.4% (11/49)
Catheter	4.6% (3/65)	0.0% (0/16)	6.1% (3/49)
Ischemic heart disease	48.5% (32/66)	52.9% (9/17)	46.9% (23/49)
Arrhythmia	31.8% (21/66)	64.7% (11/17)	20.4% (10/49)
History of MI	9.1% (6/66)	23.5% (4/17)	4.1%% (2/49)
Coronary artery bypass surgery	13.6% (9/66)	23.5% (4/17)	10.2% (5/49)
Hypertension	84.8% (56/66)	94.1% (16/17)	81.6% (40/49)
Hyperlipidemia	60.6% (40/66)	76.5% (13/17)	55.1% (27/49)
Diabetes	63.6% (42/66)	70.6% (12/17)	61.2% (30/49)
Smoking			
Current	7.6% (5/66)	5.9% (1/17)	8.2% (4/49)
Past	22.7% (15/66)	29.4% (5/17)	20.4% (10/49)
Never	69.7% (46/66)	64.7% (11/17)	71.4% (35/49)
BMI (kg/m^2), median (IQR)	27.2 (24.3, 32.5)	27.9 (27.4, 35.4)	26.0 (22.7, 31.6)
Left ventricular ejection fraction, median (IQR)	N = 65 55.0 (55.0, 60.0)	N = 17 55.0 (55.0, 60.0)[a]	N = 48 55.0 (55.0, 60.5)
Medications			
β-blockers	57.6% (38/66)	76.5% (13/17)	51.0% (25/49)
Calcium channel blocker	57.6% (38/66)	64.7% (11/17)	55.1% (27/49)
ACEI or ARB	33.3% (22/66)	47.1% (8/17)	28.6% (14/49)
Dialysis shift % (n/N)			
AM shift	86.4% (57/66)	88.2% (15/17)	85.7% (42/49)
PM shift	13.6% (9/66)	11.8% (2/17)	14.3% (7/49)

Abbreviations: ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; AV, arteriovenous; BMI, body mass index; CI, confidence interval; CSA, clinically significant arrhythmia; HD, hemodialysis; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation.
[a]Out of those (17/66) with heart failure, only 3% of participants had LVEF <35%. Heart failure was ascertained using clinical history.

(Table 2, Table S1). Overall, the rate of CSAs was not significantly different between those with kidney failure and heart failure versus kidney failure alone, whereas AF event rates were higher in the group with kidney failure and heart failure ($P = 0.01$) (Table 3).

Timing and Frequency of Arrhythmia Events Across the Day

CSA events occurred in a distinct temporal pattern (Table 4, Table S2, and Figures S1-S4). Rates of CSAs peaked between 12:00 AM and 5:59 AM and were more than 1.5-fold more frequent during this interval than the rest of the day. This was largely driven by the occurrence of CSA bradycardia, with the lowest rate of events occurring between 12:00 PM and 5:59 PM. In contrast, AF peaked during the 6:00 PM to 11:59 PM period, with significant variation in AF incidence across 6-hour intervals ($P = 0.004$). Sensitivity analyses using periodic regression techniques were qualitatively similar with the primary analyses (Figures S1-S4).

Table 2. Overall Event Rate per Month

Arrhythmia	Overall Rate (N = 66)
CSA overall	4.47 (1.46-13.70)
1) Bradycardia	3.90 (1.09-13.92)
2) Primary asystole	0.04 (0.01-0.10)
3) Primary ventricular tachycardia	0.00 (0.00-0.02)
Non-CSA atrial fibrillation	11.87 (4.63-30.44)

Note: Results from population-averaged (marginal) repeated measures negative binomial regression. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.

Heart Failure and Arrhythmia Periodicity

Overall, CSA events occurred more frequently in the group with kidney failure and heart failure than those with kidney failure alone (Table 3). In terms of the periodicity of the events, in the group with kidney and heart failure, CSAs peaked between 6:00 AM and 11:59 AM, whereas in the kidney failure group, peaked events occurred between 12:00 AM and 5:59 AM. Variation in the timing of arrhythmia event rates was significant ($P < 0.001$ for interaction between time period and presence of heart failure). Qualitatively similar patterns of variation were seen for bradycardia (Table 5). AF events peaked in individuals both with and without heart failure between 6:00 AM and <12:00 AM. However, overall rates of AF in patients without heart failure were much lower, and tests for the interaction between time and presence of heart failure were not significant.

Dialysis Shift and Dialysis Day

The overall rate of CSAs was similar in individuals receiving dialysis in morning and afternoon/evening shifts ($P = 0.43$) (Table 6). However, there was a marked variation in arrhythmia periodicity in those with AM than PM dialysis shifts ($P < 0.001$). CSA events peaked between 12:00 AM and 5:59 AM in those dialyzed in AM shifts compared with 6:00 PM and 11:59 PM in individuals receiving PM dialysis (Table 7). Additionally, AF occurred at similar rates in individuals receiving dialysis in the morning (9.3 events per month; 95% CI, 3.2-27.2) compared with the afternoon/evening shift (28.4; 95% CI, 4.6-176.5) ($P = 0.30$, Table 7). The timing of AF across the day differed significantly between the 2 groups ($P < 0.001$), with a peak in the morning in those with AM dialysis and in the afternoon in those with PM dialysis.

Lastly, we compared event rates on dialysis and nondialysis days. The overall event rates were higher on dialysis days (Table 8). There were significant numerical differences in the distribution of CSAs across the day ($P < 0.001$) on both dialysis and nondialysis days, with peaks between midnight and noon and lower rates in the afternoon and evening (Table 9). Notably, there was a significant interaction between time period and dialysis day ($P < 0.001$). AF rates were higher on dialysis than nondialysis days ($P < 0.001$). There was significant intraday periodicity on dialysis days with a peak between 6:00 PM and 11:59 PM ($P < 0.001$) but not on nondialysis days ($P = 0.30$); the interaction between time period and dialysis day was not significant for AF ($P = 0.18$).

DISCUSSION

In this analysis of the MiD trial, we assessed variation of arrhythmia across the day according to the presence of heart failure, time of dialysis, and dialysis treatment days versus nondialysis days. Several key findings provide initial insights into the periodicity of arrhythmia in the dialysis population. We found that CSAs, including bradycardia demonstrated circadian patterns with peak frequency in the morning and a decline in frequency after midmorning. In contrast, although periodic variations in AF patterns across the course of the day in the HD population were less dramatic than those of the CSAs, there was a significant peak in AF frequency midmorning.

To gain insight into the influence of heart failure in kidney failure, we analyzed patterns of 24-hour arrhythmia periodicity according to the presence of heart failure at baseline. We found that overall CSA rates were similar in individuals with kidney failure with and without heart failure, whereas non-CSA AF events occurred at a higher frequency in those with kidney and heart failure. Similarly, despite similar rates of overall CSAs in individuals receiving dialysis in morning compared with afternoon or evening shifts, there was significant variation

Table 3. Overall Event Rate According to Presence of Heart Failure

Arrhythmia	Overall Rate Adjusted for Heart Failure (N = 66)	Kidney and Heart Failure (N = 17)	Kidney Failure Alone (N = 49)	*P*
CSA overall	4.85 (1.67-14.10)	5.94 (1.32-26.82)	3.96 (0.88-17.92)	0.71
1) Bradycardia	4.15 (1.22-14.13)	4.82 (0.80-28.94)	3.58 (0.67-19.00)	0.81
2) Primary asystole	0.04 (0.02-0.11)	0.06 (0.01-0.25)	0.03 (0.01-0.10)	0.43
3) Primary ventricular tachycardia	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	10.42 (4.05-26.80)	39.83 (14.41-110.05)	2.73 (0.55-13.41)	0.01

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with presence of heart failure included as a fixed covariate. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.

Table 4. Overall Frequency of Arrhythmia Events According to Time of Day

Arrhythmia	Overall Rate (Adjusted for Time of Day)	12:00 AM-5:59 AM	6:00 AM-11:59 AM	12:00 PM-5:59 PM	6:00 PM-11:59 PM	*P*
CSA overall	2.75 (1.15-6.55)	9.66 (2.39-38.99)	6.30 (2.24-17.71)	0.96 (0.47-1.98)	0.97 (0.37-2.56)	<0.001
1) Bradycardia	1.96 (0.69-5.56)	9.28 (2.17-39.72)	5.15 (1.49-17.82)	0.41 (0.15-1.16)	0.75 (0.22-2.56)	<0.001
2) Asystole	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	11.72 (4.51-30.45)	12.25 (4.56-32.88)	13.88 (5.96-32.31)	12.61 (4.54-35.01)	8.79 (3.26-23.68)	0.004

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with time of day (in 6-hour intervals) included as a fixed covariate. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.

in the periodicity of CSA events in individuals receiving dialysis in the morning shift than afternoon/evening shifts. AF occurred at similar rates in individuals receiving dialysis in the morning or evening but also showed significant variation across time periods. Overall, the timing of the dialysis treatment did not appear to have a major effect on the total rate of CSAs, but it did appear to have an association with variation in peak timing of the events. In contrast, the rates of both CSA and non-CSA AF were markedly higher on dialysis days with significant differences in periodicity between dialysis and nondialysis days for CSA but not AF.

Our findings highlight key temporal patterns such as the predominance of certain arrhythmic events in the morning regardless of their relationship to dialysis and a lack of periodicity in others, which provide preliminary understanding of the circadian influences on dialysis outcomes and point towards novel approaches to the possible variances in dialysis and antiarrhythmic treatment according to time of day. Data on the association of circadian rhythm disruption with arrhythmia in the setting of maintenance dialysis are minimal. One study evaluated autonomic imbalance related to the dialysis procedure using continuous 14-day ECG monitoring and heart rate variability parameters. The authors found that circadian rhythmicity was preserved during the short interdialytic interval as evidenced by a peak in parasympathetic activity at night and peak heart rate during the day. In contrast, circadian rhythmicity was attenuated during the long and ultralong (ie, with missed or delayed dialysis) interdialytic periods with less evident diurnal variation.[14] Although, there are few other studies of these phenomena in the dialysis population, patterns of arrhythmia have been studied in preclinical and clinical studies and in the general

Table 5. Timing and Rates (per Month) of Arrhythmia Events According to the Presence of Heart Failure at Baseline

Arrhythmia		Overall Rate (Adjusted for Time of Day)	12:00 AM-5:59 AM	6:00 AM-11:59 AM	12:00 PM-6:00 PM	6:00 PM-23:59 PM	*P*[a]
CSA	Kidney and heart failure	2.95 (0.82-10.61)	7.57 (1.44-39.72)	13.90 (3.05-63.34)	1.94 (0.54-6.90)	0.37 (0.16-0.87)	<0.001
	Kidney failure alone	2.30 (0.80-6.61)	10.39 (1.89-56.97)	3.66 (0.97-13.75)	0.63 (0.35-1.13)	1.18 (0.40-3.44)	<0.001
	P[b]		1.00	0.89	0.74	0.71	<.0001[c]
1) Bradycardia	Kidney and heart failure	2.07 (0.46-9.25)	6.63 (0.99-44.38)	11.51 (1.90-69.76)	0.84 (0.16-4.40)	0.29 (0.11-0.78)	<0.001
	Kidney failure alone	1.64 (0.46-5.90)	10.19 (1.80-57.81)	2.95 (0.58-14.98)	0.27 (0.08-0.86)	0.91 (0.23-3.54)	<0.001
	P[b]		1.00	0.95	0.95	0.88	<0.001[c]
2) Asystole	Kidney and heart failure	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
		Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	Kidney and heart failure	37.77 (12.62-113.05)	40.70 (14.00-118.37)	44.02 (17.67-109.67)	41.83 (13.61-128.52)	27.16 (8.64-85.37)	0.02
	Kidney failure alone	2.64 (0.53-13.10)	2.38 (0.42-13.34)	3.42 (0.71-16.52)	2.47 (0.55-11.18)	2.42 (0.54-10.86)	<0.001
	P[b]		0.11	0.10	0.06	0.18	0.27[c]

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with time of day (in 6 h intervals) included as a fixed covariate, first in the subset of subjects with kidney and heart failure at baseline, and then in the subset of subjects with kidney failure alone. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.
[a]*P* value for a significant difference across time period (within subset).
[b]Pairwise comparisons for significant difference between kidney and heart failure vs kidney failure alone within time period (adjusted for multiple comparisons [Tukey-Kramer]).
[c]*P* value for interaction between time period and presence of heart failure.

Table 6. Overall Rate of Events According to Timing of Dialysis Shifts

Arrhythmia	Overall rate Adjusted for Dialysis Shift (N = 66)	AM Shift (N = 57)	PM Shift (N = 9)	*P* value (AM versus PM shift)
CSA overall	5.85 (1.88-18.23)	3.73 (0.94-14.83)	9.16 (1.50-55.85)	0.43
1) Bradycardia	5.19 (1.50-17.93)	3.18 (0.63-16.04)	8.47 (1.29-55.44)	0.43
2) Primary asystole	Not estimable	Not estimable	Not estimable	Not estimable
3) Primary ventricular tachycardia	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	16.23 (5.62-46.87)	9.27 (3.15-27.24)	28.43 (4.58-176.54)	0.30

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with dialysis shift included as a fixed covariate. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.

population.[3] In general, bradyarrhythmias appear to peak in healthy individuals at night, which has been linked with a reduction in sympathetic tone and an increase in parasympathetic tone at this time.[15] Similarly a study investigating paroxysmal atrial block showed that AV block peaked between 2:00 AM and 4:00 AM.[16]

Similar to these observations, our data suggest that in the maintenance dialysis population, CSAs, particularly bradyarrhythmias, peaked during the night and very early morning. This could possibly be attributed to a shift in the autonomic modulation towards a parasympathetic activity state at night with a withdrawal of the activity early in the morning. Further studies with detailed data on hourly ECG parameters and information on sleep cycle would be useful to uncover granular patterns of bradycardia and help distinguish between normal physiological modulations during the night versus pathological imbalances of the sympathovagal balance. Such pathological ECG changes can be identified based on their duration, frequency, and severity, with the most extreme scenario being progression to sinus arrest.[17]

In contrast to our data on bradycardia, the observed patterns of AF in MiD differed considerably from what has been reported in studies of individuals with preserved kidney function. In particular, paroxysmal AF has primarily been shown to exhibit distinct diurnal pattern with a nighttime peak and a daytime trough irrespective of presence of structural heart disease or β-blocker use.[18] In contrast, we found that AF events were more equally distributed throughout the 24-hour period, although there was still a small peak in the midmorning. This might be related to the underlying differences in autonomic function in individuals on dialysis. Prior literature has described 3 distinct variations of AF: "vagally" triggered,

Table 7. Arrhythmia Rate by Time of Day and Time of Dialysis Shift

Arrhythmia		Overall Rate (Adjusted for Time of Day)	12:00 AM-5:59 AM	6:00 AM-11:59 AM	12:00 PM-6:00 PM	6:00 PM-11:59 PM	*P*[a]
CSA	AM	2.22 (0.84-5.85)	9.25 (1.79-47.87)	4.03 (1.42-11.40)	0.64 (0.34-1.22)	1.01 (0.35-2.96)	<0.001
	PM	4.80 (0.97-23.72)	12.30 (1.78-84.93)	20.66 (2.95-144.57)	2.98 (0.70-12.73)	0.70 (0.24-2.01)	<0.001
	P[b]		1.00	0.80	0.50	1.00	<0.001[c]
1) Bradycardia	AM	1.54 (0.47-5.07)	8.80 (1.56-49.60)	2.78 (0.63-12.27)	0.27 (0.10-0.74)	0.85 (0.25-2.97)	<0.001
	PM	2.25 (0.24-20.87)	12.00 (1.65-87.22)	19.65 (2.67-144.92)	1.32 (0.18-9.70)	0.08 (0.01-0.61)	<0.001
	P[b]		1.00	0.72	0.80	0.46	<0.001[c]
2) Asystole	AM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
	PM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	AM	9.08 (3.02-27.30)	8.74 (2.97-25.78)	12.47 (4.78-32.53)	8.66 (2.79-26.83)	7.20 (2.16-23.98)	0.02
	PM	27.32 (3.38-220.89)	34.46 (5.00-237.65)	22.77 (3.55-145.94)	37.65 (5.53-256.43)	18.85 (3.19-111.55)	<0.001
	P[b]		0.91	1.00	0.88	0.98	<0.001[c]

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with time of day (in 6 h intervals) included as a fixed covariate, first in the subset of subjects with AM dialysis, and then in the subset of subjects with PM dialysis.
Abbreviation: CSA, clinically significant arrhythmia.
[a]*P* value for a significant difference across time period (within subset).
[b]Pairwise comparisons for significant difference between AM vs PM within time period (adjusted for multiple comparisons [Tukey-Kramer]).
[c]*P* value for interaction between time period and dialysis shift (AM/PM).

Table 8. Arrhythmia Rate on Dialysis Days versus Nondialysis Days.

Arrhythmia	Overall Rate Adjusted for Dialysis Day (N = 66)	Dialysis Day	No Dialysis Day	*P* (Dialysis Day versus No Dialysis Day)
CSA overall	9.10 (2.96-27.96)	10.85 (3.46-34.06)	7.63 (2.53-22.99)	<0.001
1) Bradycardia	7.93 (2.21-28.43)	9.50 (2.60-34.74)	6.63 (1.88-23.31)	<0.001
2) Primary asystole	0.08 (0.03-0.19)	0.09 (0.03-0.24)	0.06 (0.02-0.16)	<0.001
3) Primary ventricular tachycardia	0.01 (0.00-0.04)	0.01 (0.00-0.04)	0.00 (0.00-0.03)	<0.001
Non-CSA atrial fibrillation	22.10 (8.61-56.77)	25.62 (10.05-65.35)	19.07 (7.37-49.33)	<0.001

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with dialysis day included as a fixed time-varying covariate. Results are presented as least-squares mean estimate and 95% confidence interval.
Abbreviation: CSA, clinically significant arrhythmia.

"adrenergic" triggered, or a more frequent "mixed or random" pattern depending on the type of triggers and circadian pattern.[19,20] Vagally triggered paroxysmal AF with nighttime peak is more often seen in younger individuals without underlying heart disease and is also frequently observed in females, while in the adrenergic triggered pattern of AF, the peak is during the daytime correlating with sympathetic surge and stress.[19,21] Despite a very high burden of AF and some daily periodicity, variation between midnight to approximately 6:00 PM was quantitatively marginal, and the difference between the peak rate (between 6:00 AM and 12:00 AM) and the nadir (between 6:00 PM and 11:59 PM) was modest. This suggests that underlying triggers in patients on dialysis are complex and reflect a unique relationship with underlying autonomic tone compared with that of the general population. In this context, it is interesting to note the complex relationship we observed between the timing of the dialysis treatment and arrhythmia with a change in the temporal pattern of arrhythmia but not the overall rate based on the timing of the dialysis shift.

The mechanisms by which circadian rhythm disruptions trigger arrhythmias in the dialysis population remain unclear. In one study, circadian rhythm disruption in individuals on dialysis was associated with reduced nocturnal concentration of melatonin, cortisol rhythmicity, and lower nighttime sleep quality.[22] Based on initial studies, circadian disruption appears to affect different levels of control, such as the suprachiasmatic nucleus in the hypothalamus, which is the central circadian clock and is synchronized by external clues. In addition, this nucleus entrains peripheral clocks via neurohumoral, autonomic, and glucocorticoid signals, and the resulting alterations in the circadian clock genes in the heart can lead to remodeling in cardiac channels and electrophysiological properties.[3-5,23] Sleep deprivation and disruption are common in the dialysis population and are known to disrupt circadian rhythm.[24] It has been demonstrated to be an

Table 9. Arrhythmias (Rates per Month) by Time of Day and Dialysis Day

Arrhythmia		Overall rate (adjusted for time of day)	12:00 AM-5:59 AM	6:00 AM-11:59 AM	12:00 PM-6:00 PM	6:00 PM-11:59 PM	*P*[a]
CSA	No dialysis	1.34 (0.57-3.14)	2.19 (0.60-8.03)	3.78 (1.15-12.48)	0.34 (0.16-0.75)	1.12 (0.32-3.96)	<0.001
	Dialysis day	4.02 (1.86-8.69)	20.90 (4.39-99.55)	9.79 (3.74-25.62)	1.76 (0.75-4.16)	0.72 (0.27-1.92)	<0.001
	P[b]		<0.001	<0.001	<0.001	<0.001	<0.001[c]
1) Bradycardia	No dialysis	1.12 (0.43-2.92)	2.06 (0.52-8.20)	3.62 (1.04-12.61)	0.23 (0.09-0.63)	0.90 (0.19-4.30)	<0.001
	Dialysis day	2.60 (0.96-7.07)	20.17 (4.00-101.76)	7.32 (2.11-25.45)	0.64 (0.16-2.51)	0.49 (0.13-1.92)	<0.001
	P[b]		<0.001	<0.001	<0.001	<0.001	<0.001[c]
2) Asystole	No dialysis	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
	Dialysis day	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Non-CSA atrial fibrillation	No dialysis	9.64 (3.70-25.12)	9.83 (3.11-31.10)	9.00 (3.58-22.62)	9.61 (3.58-25.83)	10.15 (3.65-28.22)	0.30
	Dialysis day	13.75 (5.22-36.23)	15.26 (5.30-43.99)	20.31 (8.93-46.21)	16.53 (5.56-49.20)	6.96 (2.40-20.23)	<0.001
	P[b]		<0.001	<0.001	<0.001	<0.001	0.18

Note: Results from population-averaged (marginal) repeated measures negative binomial regression with time of day (in 6 h intervals) included as a fixed covariate, first in the subset of dialysis days and then nondialysis days. (Note that subjects can be included on both dialysis and nondialysis days.)
[a]*P* value for a significant difference across time period (within subset).
[b]Pairwise comparisons for significant difference between Dialysis Day and No Dialysis Day within time period (adjusted for multiple comparisons [Tukey-Kramer]).
[c]*P* value for interaction between time period and dialysis day.

independent predictor of all-cause mortality and day–night dyssynchrony, which increases the risk of myocardial infarction, stroke, hypertension, and dyslipidemia.[25,26] More recently, interest in the association of sleep disruption with risk of arrhythmia and sudden cardiac death has increased.[27,28] The consequences of sleep disruption and dialysis shifts present an area that might be targeted in the dialysis population to better understand the high burden of arrhythmia and sudden cardiac death.

There are some limitations of our analysis that stem from its post hoc nature. The majority of the patients had heart failure with preserved ejection fraction, and our analysis of the associations with heart failure should be generalized cautiously to those with heart failure with reduced ejection fraction. Sleep–wake cycles, sleep disordered breathing, daily activities such as eating and exercise, and body temperature have important influences on the circadian rhythm, but our study design did not allow us to assess their influence. In addition, analyzing the data in 6-hour intervals might have prevented us from more granular information regarding arrhythmia timing in relation to the dialysis treatment, although results of periodic regression provided qualitatively similar results. Although patients with significant adherence issues were typically not viewed as suitable candidates for this study, we were unable to adjust our results for adherence with the HD schedule as data on adherence was not readily available. We also lacked comparative data on a population with preserved kidney function. We cannot rule out the possibility that study design or factors other than kidney dysfunction and the dialysis procedure account for differences in patterns we observed and those previously described in studies of individuals with preserved kidney function. Apparent differences should be interpreted in this context and confirmed with additional studies where possible. Lastly, the sample size was modest, which may have limited power to detect small differences in rates. Nevertheless, this analysis addresses an area of growing concern and interest. It provides hypothesis-generating evidence on the patterns in arrhythmia by the time of day, in relation to the dialysis treatment, and in those with and without heart failure. Future prospective studies with larger sample sizes can be designed to specifically collect information on important covariates that might contribute to the changes in circadian rhythm to gain a comprehensive understanding.

In summary, circadian rhythm disruption is an untapped, potentially modifiable contributor to the elevated risk of arrhythmia in the dialysis population. Our analysis suggests modest differences in arrhythmia based on the time of day in individuals on maintenance HD than in those not requiring HD, particularly with respect to the timing of bradyarrhythmia with a later peak in the dialysis population and a distinct pattern of AF in individuals undergoing maintenance HD with and without heart failure. These data suggest that strategies targeting autonomic function to prevent arrhythmia may need to be modified for individuals on maintenance HD or that personalized targeting of circadian rhythmicity may be needed to reduce the risk of arrhythmia in the HD population.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Figure S1: Clinically Significant Arrhythmia (CSA) According to Time of Day (Fitted Curve)

Figure S2: Primary Bradycardia (Fitted Curve)

Figure S3: Primary Asystole (Fitted Curve)

Figure S4: Reveal Detected Atrial Fibrillation (Fitted Curve)

Table S1: Rate of Arrhythmia Events by Time of the Day Using Periodic Regression Model (Analyses Do Not Account for Repeated Measures Per Subject.)

Table S2: Number of Events and Number of Patients With Events

ARTICLE INFORMATION

MiD Investigators and Committee Members: Nephrology investigators: Don Williamson, USA; Prabir Roy-Chaudhury, USA; James Tumlin, USA; Vijay Kher, India; Vikranth Reddy, India; Kowdle Chandrasekhar Prakash, India; David Charytan, USA; Suresh Chandra Tiwari, India; Saurabh Pokhariyal, India; Amber Podoll, USA; Sanjeev Jasuja, India

Cardiology investigators: G. Leslie Walters, USA; Kraig Wangsnes, USA; Alexandru Costea, USA; Selcuk Tombul, USA; Balbir Singh, India; Brajesh Mishra, India; Sachin Yalagudri, India; Abhijeet Shelke, India; Calambur Narasimhan, India; A.M. Karthigesan, India; Abraham Oomman, India; K.P. Pramod Kumar, India; Bruce Koplan, USA; Upendra Kaul, India; Tapan Ghose, India; Ripen Gupta, India; Arvind Sethi, India; Nikhil Kumar, India; Ramesh Hariharan, USA; Rajnish Sardana, India; Arif Wahab, India; N.N. Khanna, India

Nephrology co-investigators: Mark Smith, USA; Suresh Kamath, USA; Claude Galphin, USA; Puneet Sodhi, India; Rajsekara Chakravarthy, India; Subba Rao Budithi, India; Finnian McCausland, USA; Sanjeev Gulati, India; Munawer Dijoo, India; Upendra Singh, India; Salil Jain, India; Vishal Saxena, India; Gaurav Sagar, India

Advisory committee: David Charytan, USA; Rachel Fissell, USA; Robert Foley, USA; Charles A. Herzog, USA; Peter McCullough, USA; John D. Rogers, USA; James A. Tumlin, USA; Peter Zimetbaum, USA

Adverse events committee: Manish Assar, USA; Mark Kremers, USA; Wolfgang C. Winkelmayer, USA

Authors' Full Names and Academic Degrees: Qandeel H. Soomro, MD, MS, Bruce A. Koplan, MD, Alexandru I. Costea, MD, Prabir Roy-Chaudhury, MD, PhD, James A. Tumlin, MD, Vijay Kher, MD, Don E. Williamson, MD, Saurabh Pokhariyal, MD, Candace K. McClure, PhD, and David M. Charytan, MD, MSc, for the MiD Investigators

Authors' Affiliations: Nephrology Division, Department of Medicine, NYU Langone Medical Center, New York, New York (QHS, DMC); Brigham & Women's Hospital, Boston, Massachusetts (BAK); University of Cincinnati School of Medicine, Cincinnati, Ohio (AIC); University of North Carolina Kidney Center, Chapel Hill, North Carolina (PRC); WG (Bill) Hefner VA Medical Center, Salisbury, North Carolina (PRC); Georgia Nephrology Clinical Research Institute, Atlanta, Georgia (JAT); Fortis Escorts Kidney & Urology Institute, Fortis Escorts Hospital, New Delhi, India (VK); Southeastern Clinical Research Institute, Augusta, Georgia (DEW); Manipal Hospital, Dwarka, New Delhi, India (SP); and NAMSA, Minneapolis, MN (CKM).

Address for Correspondence: Qandeel H. Soomro, MD, MS, Nephrology Division, Department of Medicine, NYU Langone Medical Center, 550 First Ave, New York, NY 10016. Email: qandeel.soomro@nyulangone.org

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