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Unexpected Shift in Circadian and Septadian Variation of Sudden Cardiac Arrest: The Oregon Sudden Unexpected Death Study

Yu-Ming Ni, MD^{#1}, Carmen Rusinaru, MD PhD^{#1}, Kyndaron Reinier, PhD¹, Audrey Uy-Evanado, MD¹, Harpriya Chugh, BS¹, Eric C. Stecker, MD MPH², Jonathan Jui, MD MPH², and Sumeet S. Chugh, MD, FHRS¹

¹The Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles CA, USA

²Oregon Health and Science University, Portland, OR, USA

These authors contributed equally to this work.

Abstract

Background: Earlier studies have reported both early morning and Monday peaks in occurrence of sudden cardiac arrest (SCA) in the community, and appropriate defibrillator shocks in patients with implantable cardioverter defibrillators (ICD). However, a more recent analysis of ICD shocks reported absence of these peaks. Objective: To perform a contemporary evaluation of the circadian and septadian variation of SCA in the general population.

Methods: The analysis was performed from an ongoing, population-based study of SCA in a Northwestern US community of approximately one million residents. To maximize accuracy, we focused on consecutive patients who presented with witnessed SCA and were attended by the emergency medical services (EMS). The specific time of each SCA event was determined based on the time of the 911 call to the EMS.

Results: During 2002–2014, we identified 1535 patients age 18 years who suffered witnessed SCA, with time of first EMS contact recorded. There was no morning (6 am to 12 pm) peak and we observed an early morning (12 am to 6 am) nadir in SCA events, with only 13.9% of events occurring during this 6-h block ($p < 0.0001$). There was no peak on Mondays but a nadir was observed on Sundays that accounted for only 11.3% of SCA events during the week ($p = 0.004$).

Conclusion: In this contemporary community-based study, we failed to observe the expected morning peak or the Monday peak in SCA, duplicating recent findings in primary prevention defibrillator patients. There are significant public health implications of these findings which merit further investigation.

Address correspondence to: Sumeet S. Chugh MD, Smidt Heart Institute, Cedars-Sinai, Advanced Health Sciences Pavilion, Suite A3100, 127 S. Vicente Blvd., Los Angeles, CA 90048, Fax 310-423-3522; Phone 310-423-1206, sumeet.chugh@cshs.org.

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Keywords

sudden cardiac death; circadian; septadian; diurnal; population; epidemiology

INTRODUCTION

Earlier studies of sudden cardiac arrest (SCA) demonstrated a circadian and septadian pattern of incidence. A morning peak, followed by a smaller peak in the afternoon, was initially reported in the Framingham cohort,¹ and subsequently verified in prospective community studies of SCA and in cohorts of patients implanted with ICDs.^{2–7} Regarding the septadian pattern, several community-based studies have consistently demonstrated a Monday peak in SCA occurrence, commonly attributed to the stress of the new workweek.^{8–10} However, a recent study of patients with primary prevention ICDs enrolled in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated an absence of the morning peak¹¹ in ICD therapies, and attributed the finding to changes in drug therapy. However, ICD therapies may not be an effective surrogate for SCA events, and primary prevention ICD patients constitute a selected subgroup of high risk subjects. Therefore, we decided to perform a corresponding, contemporary evaluation of this phenomenon in the community, from the ongoing Oregon Sudden Unexpected Death Study.

METHODS

The Oregon Sudden Unexpected Death Study is an ongoing, prospective community-based study of out-of-hospital SCA in the Portland, Oregon metropolitan area. Detailed methods have been previously described,^{12,13} but in brief, cases of SCA are identified prospectively from among all residents of the region. For this analysis, cases age ≥18 years of age identified between February 1, 2002 and January 31, 2014 were included. SCA was defined as a sudden collapse with loss of pulse, occurring without obvious extra-cardiac cause.¹⁴ Unwitnessed patients were included if their SCA occurred within 24 hours of having been observed alive and without symptoms. Both survivors of SCA and deceased patients were included. Patients were excluded from the study if they had a non-cardiac chronic terminal illness or a known non-cardiac etiology for death (including trauma, violent death, overdose, drowning, and suicide). Time of cardiac arrest was determined by the time of 911 call to emergency medical services (EMS). All potential SCA cases were adjudicated based on the EMS prehospital care report detailing arrest circumstances, available prior medical records, and autopsy results if available. Independent assessment of available data was made by three cardiologists, and a consensus opinion was determined of whether each case of sudden death was likely from a cardiac cause. The clinical profile of cases was assembled from the lifetime medical records, as described in detail previously.^{12,13}

Statistical analysis was conducted using SAS 9.3 (SAS Institute Inc, Cary, NC). Time of SCA was categorized into two-hour increments starting at midnight (0001–0200, etc.), as well as into four 6-hour time groups: early-morning (0001–0600), morning (0601–1200), afternoon (1201–1800), and evening (1801–0000). The main statistical analysis was conducted among witnessed SCA cases and a sensitivity analysis was performed among all

SCA cases, regardless of their witnessed status. The distribution of SCA was tested for differences among the 6-hour, 2-hour, and day of the week groups using chi-square tests. Additional subgroup analyses were performed by age, sex, presence of coronary artery disease or sleep apnea. $P < 0.05$ from a chi-square test for equal proportions was considered as significant. This study was approved by the Institutional Review Boards of participating hospitals and health systems.

RESULTS

During 2002–2014, we identified 2631 adult cases of SCA with the time of the 911 call available, of which 1535 were witnessed by bystanders or EMS personnel. The overall mean age was 66.5 ± 15.7 years and 67% were male. The characteristics of the witnessed SCA group were similar to the entire study case population (Table 1). There was a nadir in SCA occurrence between midnight and 6 am, and no morning peak observed (Figure 1- Witnessed SCA). When unwitnessed SCA was included, this pattern persisted (Figure 1- All SCA). Among the witnessed group, 13.9% of SCA occurred in the early morning, 27.6% occurred in the morning, 31.6% occurred in the afternoon, and 26.9% occurred in the evening ($p < 0.0001$). In subgroup analyses, this pattern of early-morning nadir and lack of any peak persisted when witnessed SCA cases were analyzed by age (< 65 years versus ≥ 65 years), sex, and coronary artery disease (CAD) versus no CAD (Figure 2). However, there was a difference in pattern related to absence or presence of sleep apnea in SCA cases. Among cases with no history of sleep apnea, an early-morning nadir and lack of peak was observed, whereas among cases with history of sleep apnea the circadian differences were not significant, with no nadir observed ($p = 0.39$) (Figure 2).

When looking at SCA cases by day of the week, there was a nadir in cases on Sunday as compared to other days of the week (Figure 3), which was statistically significant for witnessed SCA ($p = 0.004$) and all cases of SCA ($p = 0.02$). When Sunday cases were removed from the analysis, there was no significant difference between days of the week ($p = 0.16$), indicating that the Sunday nadir contributed to the significant differences observed throughout the week.

DISCUSSION

We did not observe a morning peak in SCA in this community-based prospective observational study. Additionally, during the week we did not observe any peak of SCA occurrence on Mondays. Instead, we found a nadir in SCA occurrence on Sundays.

The loss of the morning peak has been reported in smaller observational studies^{15,16} and the more recent SCD-HeFT analysis,¹¹ that evaluated circadian and septadian rhythms of ICD shocks in patients with primary prevention ICDs. Our findings of an absence of a morning peak are in line with these previous findings, even though the Oregon SUDS includes all SCA in the general population, with at least 50% overall having normal EF.¹⁷ An additional contributing factor may be the improved accuracy of determining time of SCA in our study, since this variable was carefully evaluated from each individual's emergency medical response record, and primary analyses were restricted to witnessed SCDs. This could have

affected the overall distribution of time of death compared to earlier studies that did not use this methodology. Unwitnessed events are more likely to have inaccuracy in reporting of time of death, as the exact time of SCA is often extrapolated from family members' or EMS accounting. Previous community-based studies conducted a subgroup analysis for witnessed vs unwitnessed cardiac arrest, and results are mixed, with some showing preservation of the bimodal distribution^{4,18} and others with elimination of the bimodal distribution among witnessed arrest with shockable presenting rhythm.³ In our study, the lack of peaks and early-morning trough were observed in both witnessed SCA cases as well as in overall SCA cases that included unwitnessed events. Another possible explanation for lack of circadian variation is a gradual change in patient factors such as sleep patterns affecting 24-hour patterns of activity. Further contemporaneous studies are needed to elucidate the reasons for these altered patterns of SCA occurrence.

Because of the ability of ICDs to record exact time of cardiac dysrhythmias, ICD-based observational studies were some of the earliest high-quality studies to suggest an early-morning peak and Monday peak. However, ICD shocks may not be an effective surrogate for SCA in the community. Community-based population studies detect at-risk individuals who may not have any warning signs for cardiac death, and may help identify previously undetected patient factors that predispose relatively healthy people to SCA. Determining the circadian distribution of SCA allows medical communities to appropriately distribute emergency response resources to meet the expected demands for treating sudden cardiac death.

In terms of the septadian pattern of SCA, these findings are the first instance of combined significant Sunday nadir and lack of Monday peak in a community study, similar to the findings of the SCD-HeFT analysis. A broader pattern of major cardiovascular events on Mondays has been previously described, and increased incidence of SCA on Mondays has been previously seen in community and ICD studies. Some of these studies described a weekend or Sunday nadir. More recently, a few reports have emerged, describing the loss of Monday peak, including two community studies in Tunisia¹⁶ and Spain,¹⁹ and the SCD-HeFT analysis.¹¹ Absence of the Monday peak in acute myocardial infarction was also reported in two studies from Asia,^{20,21} but these studies did not evaluate SCA. In the past the proposed mechanism for the Monday peak was the stress of the upcoming work-week contributing to development of life-threatening cardiac dysrhythmias. There is a body of evidence suggesting that psychosocial stress increases the risk of SCA and ventricular arrhythmias²²; along with animal data showing that chronic mental stress increases coronary stenosis and perivascular fibrosis.²³ However, with the loss of the Monday peak, there appears to be some re-distribution of these psycho-social stressors. While the exact mechanisms need further investigation, it is tempting to speculate a potential role for the advent of the internet and smart phones, allowing for access to entertainment, social life, and even work activities 24 hours a day, 7 days a week.

In the group with sleep apnea, the overnight nadir was not observed. This suggests that, compared to those without sleep apnea, a higher proportion of SCAs occurred at night. While our study was not designed to examine risk associated with any specific factor, a link between sleep disordered breathing and SCA has been suggested in smaller studies.²⁴ The

proposed mechanism has been intermittent nocturnal hypoxia and associated increased sympathetic activity contributing to increased risk of lethal cardiac dysrhythmias.²⁵

Some limitations of our study include the observational nature of community-based prospective studies, limiting complete understanding of the time course of SCA. In unwitnessed cases, the actual time of SCA is often unknown; some of these cases occurring overnight or on Sunday could have been recorded as having occurred in the morning or on Monday when discovered. However, we did not identify any clear association between our reported circadian and septadian rhythms in SCA occurrence and the likelihood of witnessed arrests by time of day or day of week (data not shown). In addition, we did not have detailed information regarding the cause of SCA in all cases. With detailed autopsies in 8.2% of SCAs plus post-SCA investigation data in the 10.4% who survived to hospital discharge, detailed information regarding the cause of SCA was limited to approximately one-fifth of subjects. However, as a routine we obtain lifetime, detailed pre-SCA medical records in all cases, and are successful in determining the clinical profile in at least 90%, providing possible attributable etiologies in the majority of subjects. Because of the observational nature of our study, we did not have access to comprehensive data on chronic or acute stress, sleep-work schedule, work hours, or weekend activities. These limitations of the observational community-based design are balanced by the mitigation of the SCA rate overestimation typically observed in retrospective death-certificate and physician survey-based studies.^{12,26}

CONCLUSIONS:

In conclusion, our community-based prospective observational study demonstrated a notable deviation in the timing of SCA during the day, with a loss of the morning peak. During the week, we did not observe the expected Monday peak, but instead identified a new nadir in SCA occurrence on Sundays. These findings have health care utilization and public health implications, and warrant further investigation.

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Figure 1.

Circadian patterns in SCA as evaluated by proportions of events occurring during 2-hour intervals. The expected SCA peak during the morning hours was absent. There were no significant differences in the subgroup of SCA events witnessed by bystanders or emergency medical response personnel, compared to the overall SCA events.

Figure 2.

Proportions of SCA occurrence in specific subgroups of individuals based on time of day.

Figure 3. Septadian variation in SCA evaluated as proportions of events occurring on each day of the week. The expected Monday peak was absent, and a new nadir was seen on Sunday.

Table 1.

Demographics, initial rhythm, and clinical characteristics of SCA cases

Categories	All SCA (n = 2631)	Witnessed SCA (n = 1535)
Mean age	66.5 ± 15.7	66.8 ± 15.3
Age <65 years	1194 (45.4%)	680 (44.3%)
Male	1773 (67.4%)	1059 (69.0%)
Initial rhythm *		
VF/VT	963 (41.9%)	750 (51.0%)
PEA	574 (25.0%)	410 (27.9%)
Asystole	707 (30.8%)	272 (18.5%)
Other	52 (2.3%)	38 (2.6%)
Missing	335	65
Hypertension †	1472 (59.5%)	874 (60.5%)
Hyperlipidemia †	1037 (41.9%)	639 (44.2%)
Diabetes †	847 (34.2%)	502 (34.7%)
CAD	1151 (43.8%)	740 (48.2%)
Heart failure	730 (27.7%)	448 (29.2%)
2 Cardiovascular risk factors with no heart disease	330 (13.3%)	176 (12.2%)
Sleep apnea †	187 (7.7%)	103 (7.1%)

* Information available for 2296 subjects in the all SCA group and 1470 subjects in the witnessed SCA subgroup.

† Information available for 2474 subjects in the all SCA group and for 1445 subjects in the witnessed SCA subgroup.

CAD, coronary artery disease; PEA, pulseless electrical activity; SCA, sudden cardiac arrest; VF/VT, ventricular fibrillation/ventricular tachycardia.