Sudden cardiac death (SCD) due to sustained ventricular tachyarrhythmias (VTA) remains a major public health problem because of poor understanding of the mechanisms. Initiation of VTA in animal models and in patients usually requires intense metabolic or electrical stimuli not often observed for spontaneous arrhythmias, suggesting that profound but clinically silent electrophysiological changes are responsible for lethal VTA (1). Studies performed in the 1980s and 1990s showing diurnal variations of SCD and VTA generated excitement because they suggested that time-varying factors participate in the initiation of lethal VTA. For example, in a study of more than 24,000 SCDs, Arnzt et al. (2) observed a nadir of events between 12 AM and 6 AM with a striking increase in events between 6 AM and 12 PM as well as a nadir on Sundays and greater event rate on Mondays. Similar distributions were reported in patients with implantable cardioverter-defibrillators (ICDs), which provide superior temporal precision and arrhythmia accuracy (3).

The mechanisms for the diurnal variations have not been established. Exogenous factors such as physical activity or mental stress that could stimulate sympathetic activity or cause ischemia were suggested to account for the morning peak and increase in events on Mondays. True circadian rhythms are governed by biological clocks driven by a transcription-translation feedback mechanism that takes approximately 24 h. Biological clocks are composed of a hierarchical system that extends to individual cells of many types and are coordinated in the suprachiasmatic nucleus of the hypothalamus and synchronized to the environment by light and other exogenous factors. The many processes affected by biological clock activity result in a vast array of permutations by which diurnal variations in arrhythmias could occur. Most explanations involve indirect effects on tissue electrophysiology related to autonomic activity or ischemia (2,3). Cellular electrophysiological changes that could account for diurnal variability of VTA due to direct regulation of membrane ion channels by biological clocks have been shown. Jeyaraj et al. (4) studied mice placed in constant darkness and confirmed that heart rate, QTc interval, and cardiac expression of the alpha subunit for the transient outward potassium current (Ito), Kv4.2 (encoded by Kcnd2), and the regulatory beta subunit, potassium channel interacting protein 2 (KChIP2) (encoded by Kcnip2), exhibit circadian rhythmicity, as do components of the biological clock in the heart. New was the discovery that the biological clock regulates KChIP2 by the circadian oscillation of Krüppel-like factor 15 (Klf15), a member of the family of Krüppel-like transcription factors (4). KLF15 also influences cardiac remodeling, fibrosis, and myocyte hypertrophy in response to stress (4). Circadian variation of potassium channel density and the associated lengthening and shortening of repolarization duration and refractoriness will alter the propensity for reentrant arrhythmias, particularly when the change increases dispersion of refractoriness. Schroder et al. (5) demonstrated regulation of the sodium channel gene (Scn5a) by the biological clock of the cardiomyocyte in rodents. Mutations of Scn5a are responsible for pathologic cardiac phenotypes such as the congenital long QT syndrome type 3, Brugada syndrome, and progressive cardiac conduction disorders. Oscillation of Scn5a transcription could precipitate arrhythmias in vulnerable tissue due to rhythmic variation of conduction velocity, refractoriness, excitability, or automaticity. Although the relevance of findings in rodents to human disease is a major question, the evidence points to several mechanisms for periodic variation of cardiac electrophysiology that could help explain the temporal distribution of VTA.

Although it is known that not all arrhythmias exhibit the classic diurnal variation, Patton et al. (6) report in this issue of the Journal that a large and important group of patients who receive ICDs do not show the phenotype expected from previous studies (2,3). They examined the timing of appropriate ICD interventions from SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), a primary prevention trial in which patients with heart failure and a low ejection fraction (<36%) were randomized to placebo, amiodarone, or an ICD (6). This analysis was driven by 3 hypotheses. The first was that more than 25% of the VTA episodes would occur between 6 AM and 12 PM (representing 25% of the day), as expected on the basis of previous reports (2,3). A total of 714 appropriate ICD therapies for VTA occurred in 186 subjects. The
proportion of VTA events occurring between 6 AM and 12 PM was only 20.7%. The per-patient analysis, which was adjusted for the variation in the number of episodes of VTA and provided equal weight to each patient, showed a VTA frequency of only 21.3%. Therefore, the hypothesis was rejected. Subgroup analysis of ischemic versus non-ischemic etiology, age older than or younger than 50 years, New York Heart Association (NYHA) functional class, and use of beta-blockers did not identify a subgroup with a significant morning peak of VTA.

The second hypothesis, that the proportion of ICD therapies occurring between 12 AM and 6 AM would be significantly below the 25% threshold, was supported by the finding that the mean weighted frequency was 21%; however, the significance of the difference was marginal \((p = 0.048\), one-sided test\). Subgroup analysis showed that patients with ischemic cardiomyopathy, NYHA functional class II, older than 50 years, or on beta-blocker therapy had events occurring during this interval that were also significantly less than 25%, with a weighted frequency range of 17% to 19%. Conversely, patients with non-ischemic cardiomyopathy, NYHA functional class III, younger than 50 years, or on beta-blocker therapy at baseline had weighted frequencies that were not significantly less than 25%, with adjusted event frequencies of 22.6% to 29.0%. Furthermore, instead of the marked increase in event rate seen in the transition from the 12 AM to 6 AM period to the 6 AM to 12 PM period in previous studies, Patton et al. (6) observed that the event rate remained low until 12 PM (2,3).

The hypothesis that the proportion of therapies on Mondays would be greater than one-seventh (14.3%) was also not supported. The only subgroup with a significantly higher event rate on Mondays was patients not on beta-blocker therapy at baseline (mean weighted frequency of 22%; \(p = 0.029\), one-sided test). Although the investigators did not test for a nadir in Sunday events, examination of the data provided show that event rates on Sundays were lower than that on Mondays but similarly low on Thursdays.

The analysis of Patton et al. (6) was not a prespecified analysis of the original SCD-HeFT and therefore might be considered hypothesis generating rather than hypothesis testing. On the other hand, several features of the study enhance the reliability of the observations. The rigorous enrollment criteria of SCD-HeFT ensured relative homogeneity with respect to severity of structural heart disease and depressed heart function as well as absence of a history of sustained VTA or cardiac arrest. In addition, there was prospective data collection, uniform ICD programming, and independent tachyarrhythmia event adjudication. It was appropriate for the authors to use one-sided statistical testing because this increases the sensitivity of agreement with previous studies. However, with respect to the failure to reject the null hypothesis for a nocturnal nadir in VTA events and a higher Monday event rate in a single subgroup, it should be recognized that one-sided testing increases the probability of a type I error.

Many explanations could be posited for the absence of a circadian distribution of VTA in the SCD-HeFT ICD patients. Potential influences include underlying cardiac disease, past and current therapy, and lifestyle factors. The severity of heart disease was likely greater (mean left ventricular ejection fraction of 20%; 36% were NYHA functional class III) in SCD-HeFT patients because previous studies did not exclude patients with minimal structural heart disease (2,3,6). The use of neuroendocrine antagonists and lipid-lowering drugs was likely greater in SCD-HeFT (56% on beta-blockers, 94% on renin angiotensin system inhibitors, and 34% on statins). No information is available for comparison of work and lifestyle variables. If it is argued that adrenergic and renin-angiotensin system antagonist therapy reduced the diurnal influence of sympathetic activity and that aggressive revascularization and anti-ischemic and antiplatelet therapy reduced diurnal variation due to ischemia, an alternative explanation for persistent VTA is necessary.

Disruption of the biological clock could plausibly link cardiomyopathy, arrhythmias, and loss of diurnal variation of arrhythmias. A germline knockout mouse of the core clock gene, brain and muscle Amt-like protein 1 (Bmal1), was associated with stretch-induced arrhythmias and development of dilated cardiomyopathy (5). Cardiomyocyte-specific deletion of Bmal1 was associated with loss of circadian variation of the sodium channel gene \((\text{Scn5a})\), reduced functional expression of Scn5a, and arrhythmia susceptibility (5). Deficiency or excess of the clock-dependent oscillator Klf15 caused abnormal repolarization and enhanced susceptibility to ventricular arrhythmias and loss of the circadian variation of QTc interval (4). It is notable that KLF15 is also a transcriptional inhibitor of cardiac hypertrophy, fibrosis, and structural remodeling. Although these findings in animal models are of uncertain relevance to human disorders, they indicate a potential mechanistic link between persistent VTA, loss of circadian variation in arrhythmia events, and possible inhibition of reverse remodeling in patients enrolled in SCD-HeFT. It might be fruitful to examine other signs of altered biological clock function in patients with SCD-HeFT characteristics and determine if reverse remodeling of clock functions can be shown. Better understanding of the links between biological clocks and VTA may open new avenues for identifying and treating patients at risk for SCD.

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