Editorial comment
Sleep as an autonomic stress test for the heart

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This excellent article by Stramba-Badiale et al.[1] draws attention to the important, underappreciated problem of sleep-related cardiac risk[2]. Whereas sleep is generally considered to be a relatively tranquil state dominated by the relative autonomic stability of non-rapid-eye-movement (nonREM) sleep, the onset of REM, which occurs 4 to 5 times each night, is associated with marked perturbations in the interplay between the two divisions of the autonomic nervous system. Cardiorespiratory control can also be significantly altered, accounting for marked morbidity and mortality in individuals with coexisting apnea and coronary disease. Apnea has been determined to be a co-morbid factor in 50% of patients with heart failure[3]. Approximately 20% of myocardial infarctions and 15% of sudden cardiac deaths occur in the period between midnight and 6:00 a.m.[4]. Certain infants may not be spared, as a cardiac component in "crib death" has been established and related to prolongation of the QT interval[5]. Because of this intrinsic nocturnal cardiac vulnerability in significant subsets of the population and the degree and reproducibility of heightened autonomic activity, we have proposed that sleep could provide a bona fide autonomic stress test for the heart and thereby aid in identification of individuals at risk for major cardiac events[6].

The intriguing findings provided in the present study by Stramba-Badiale et al. regarding heightened risk during sleep in LQT3 patients lends support to the concept of nighttime neural triggers. The fact that LQT1 patients do not experience elevated propensity to cardiac arrhythmias at night offers significant insights, particularly as the electrophysiologic and genetic bases for the responsible sodium channel gene SCN5A have been studied in detail. The most salient observation in the present study was that the QTc interval was markedly prolonged during nighttime in LQT3 as compared with LQT1 patients. This suggests a nocturnally related disruption in ventricular repolarization among patients with the channel mutation associated with the LQT3 condition. It remains unknown whether these patients' cardiac events emerged during the period of greatest prolongation of the QT interval. This would be anticipated to occur during nonREM sleep, when the cycle length would be the longest, as a result of sinus node restraint by vagus nerve activity. An alternative possibility is that on the background of prolonged repolarization, an abrupt change in cycle length could result during transition to REM sleep, when there is a sudden surge in sympathetic nerve activity. It is well established in humans[7] and in animals that pronounced pauses[8] and surges[9] in heart rate occur during sleep-state transitions and REM sleep in direct consequence of the periodic re-excitation of the brain. It is also well known that pronounced cycle length changes are particularly conducive in the setting of prolonged QT interval to torsade de pointes, the signature arrhythmia in this syndrome. Understanding this process and the potential importance of long-short cycle-length changes could shed light on nocturnal precipitation of arrhythmias in other conditions associated with prolonged QT interval, such as pharmacologic therapy and perhaps in the sudden infant death syndrome.

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As is the case in any groundbreaking study, the present investigation raises more questions than it answers. Among the most enticing is the sleep-state specificity of arrhythmic risk in the LQT3 syndrome. Are the cardiac events triggered primarily during nonREM sleep, as a result of pronounced QT prolongation and concomitant heterogeneity of repolarization? Or, do the life-threatening arrhythmias occur during abrupt cycle-length changes associated with sleep-state transitions and REM sleep? Studies involving heart rate variability and baroreceptor sensitivity measurements will be key to unlocking the autonomic mechanisms involved. Further insights could be provided by analyzing noninvasive markers of vulnerability including T-wave alternans, a hallmark phenomenon of the long QT syndrome[10,11] and a promising measure of cardiac risk[12,13].

In summary, the authors are to be commended on their outstanding article, which has not only advanced our understanding of the pathophysiologic basis for the long QT syndrome but will necessarily focus attention on the topic of sleep-related cardiac risk. Ultimately, future exploration could lead to improved diagnostic and therapeutic strategies aimed at containing the potent triggers which interact with an intrinsically vulnerable myocardium during sleep.

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