

Searching for triggers of sudden death in hypertrophic cardiomyopathy: Chasing after the wind?

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“No man has power over the wind to contain it; so no one has power over the day of his death.”¹

Sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) is a passionate topic given the age of the victims and the catastrophe that ensues when the diagnosis is made premortem or postmortem.

While the high school basketball player drops dead in the middle of a game and brings a city to a standstill in the midst of the evening news, many young men and women fight to keep their lifestyles, ambitions, and athletic careers alive, even “against medical advice” as in the case of Knapp versus Northwestern University.²

The construct for our understanding of the circadian triggers of SCD has been drawn largely from the general population and from those with ischemic heart disease. Reports as early as the Framingham study suggested an early morning peak with a tight window of 7 to 9 AM presenting a 70% higher chance of SCD than other hours of the day.³ These and other findings, such as the nonuniform occurrence of ventricular arrhythmia even in nocturnal hours,⁴ have suggested a role of autonomic fluctuation or a possible neurohumoral trigger for SCD. Exciting work from the basic laboratory has suggested that impaired circadian clock output genes in the heart as a result of hypertrophy affect the circadian cycle of local gene expression.⁵ It is possible that the hypertrophied heart is less able to adapt to changes in physiologic factors during a day–night cycle as a result of this impairment.

An elegant study by Maron et al⁶ 15 years ago found a morning preponderance of SCD similar to ischemic heart disease in 94 HCM patients in whom time of death could be obtained by clinical records. Last year the Mayo group reported an afternoon peak of implantable cardioverter-defibrillator (ICD) discharges in a cohort of HCM patients, with the highest incidence between the hours of 2 and 4 PM.⁷

In this issue of *Heart Rhythm*, Maron et al⁸ report their findings from the ICD in HCM registry. The authors found a modest increase in appropriate ICD discharges between

the hours of noon to midnight as opposed to midnight to noon. There was no significant correlation of ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes to the day of week, season, sleep, or activity level.

The “traditional” criticism of such a study is that ICD shocks may not represent a surrogate for sudden death in this disease, and that some episodes of ventricular arrhythmia may have terminated spontaneously, as acknowledged by the authors.⁸ In fact, the disparity in circadian variability of SCD in HCM patients reported in the pre-ICD era to these studies describing the timing of ICD shocks remains unreconciled.^{6,7}

However, the findings of a very modest pattern of circadian variability compel a more realistic look at a condition where a heterogeneous substrate exists with a myriad of possible triggers for ventricular arrhythmia, including ischemia, systolic or diastolic dysfunction, hypotension, outflow tract obstruction, and atrial fibrillation, with any or all of these occurring at rest or with intense exertion. Information regarding beat-to-beat/cycle length or other autonomic data just prior to the fatal or near-fatal event were not included in the present report and could be educational. As opposed to defined but poorly understood autonomic states such as sleep, fluctuations of autonomic tone during the day or night could remain a trigger for sudden death.

The clinical implications of this study are valuable. With 30% of the events occurring during sleep and the rest scattered through every hour of the day, a home automatic external defibrillator strategy in these patients would seem inadequate protection.

The issue of activity restriction in these patients remains contentious. The authors themselves have been proponents of restraint from competitive sports.^{2,9,10} The present report found no correlation of VT/VF events to activity level; however, adequate data for analysis was available for only approximately 60% of patients with appropriate ICD activity. Furthermore, the design of the present study was not an attempt to assess risk of severe physical exertion. At this time, it seems reasonable that, pending further investigation, one should adhere to the guidelines in managing these patients and “reason together” with our patients regarding activity level and athletic participation.^{9,11}

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In the final analysis, however, one is left with the uneasy feeling that sudden death in these patients will remain . . . unrestrainable, uncontrollable . . . and sudden.

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