# Circadian and Weekly Patterns of Electrical Storm
## A Role for Stress?

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Electrical storm (ES) worsens morbidity, mortality, and quality of life in patients with implantable cardioverter-defibrillators (ICDs). The reported incidence of ES varies widely depending on definition used, underlying cardiac pathology, and device programming but ranges between 2% and 10% per year, ≤20% in patients with ICDs implanted for secondary prevention.[1–3] ES generally portends a poor prognosis, associated with an elevated risk of death that ranges between 2.4- and 7.4-fold increase, with risk during the first 3 months as high as a 17.8-fold.[1,2,4,5] Hospitalization also increases after ES, at a rate 3× that in patients suffering an isolated ventricular tachyarrhythmia.[6] Psychologically, multiple shocks can be devastating. While psychopathology specifically after ES has not been described, in general, receipt of >5 shocks is associated with an increase in both anxiety and depression and a reduction in both physical and mental health.[1,7]

**See Article by Guerra et al**

Despite the deleterious impacts on morbidity, mortality, and quality of life, there are few data evaluating potential triggers for ES, which may lead to mechanistic understanding and ultimately point to novel therapies. The TEMPEST trial (Temperature-Related Incidence of Electrical Storm), reported by Guerra et al[8] in this month's *Circulation: Arrhythmia and Electrophysiology*, examined temporal patterns and potential environmental triggers for ES and demonstrated a heterogeneous incidence of ES with a clustered pattern. They demonstrated the prevalence of ES to be significantly higher during work days and during morning hours. Their findings are highly suggestive of possible autonomic triggering mechanisms for ES, which has significant implications for both current and potential future therapies.

## Potential Mechanisms

The TEMPEST study highlights the important roles that the autonomic nervous system plays in ES. Guerra et al demonstrated that ES follows a circadian variation, with a higher incidence of ES occurring in the morning hours, at the time of peak catecholamine levels and lowest vagal tone. Similar circadian variations of ventricular tachyarrhythmia have been demonstrated[9]; however, the current study excludes acute coronary syndrome as the arrhythmic trigger, which previous studies have not. These finding reinforce the direct relationship between ventricular arrhythmogenesis and circadian variations.

The autonomic nervous system plays a critical role in ventricular arrhythmogenesis, with the left stellate ganglia providing the majority of the sympathetic innervation to the ventricles. The intrinsic cardiac sympathetic innervation lies within the subepicardial layer, following the epicardial coronary vessels as they branch out over the myocardium. Activation of the cardiac sympathetic system is mediated through multiple organs at multiple levels. The major neurotransmitter-mediating sympathetic response in the heart is norepinephrine, having an overall effect of shortening the ventricular action potential duration and refractory period. Increased adrenergic activation is felt to be arrhythmogenic via increasing the frequency and rate of automaticity, as well as by increasing the likelihood of generating early after-depolarizations and delayed after-depolarizations.[10,11]

The TEMPEST study also demonstrated a higher incidence of ES occurring during working hours on weekdays,[8] suggesting a role of stress in precipitating ES. Negative emotion results in changes in autonomic function, which in turn lead to arrhythmia. Prior studies have demonstrated that anger can trigger ventricular arrhythmia in patients with ICDs, and strong emotion has been linked to sudden cardiac death (SCD) as well.[12] Prior studies have reported that ventricular tachycardia occurs more frequently on Mondays in working patients with ICDs.[13,14]

ES presentation in the TEMPEST study had a clustered pattern in which many patients were admitted with ES within a few days of each other. As noted by the authors, the clustering phenomenon seen could potentially be explained by a large-scale population stressor.[8] Population stressors, such as the earthquakes in Athens in 1981, Los Angeles in 1994, Japan in 2004, and China in 2008, were associated with increased cardiovascular events and mortality, as well as SCD.[15,16] More recently, the Great East Japan earthquake and tsunami of 2011 resulted in an increase in SCD seen in areas not directly affected, confirming the impact of mental stress.[17] Acts of war increase arrhythmic events even in those not directly attacked, with an increase in SCD in Israeli civilians during the first Iraq war in 1991 and a 2 to 3 times increase in ICD firings associated with the attack on the World Trade Center in New York on 9/11.[18,19] Even sports events such as the world soccer championships in



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Switzerland in 2002 and Munich in 2006 were associated with increased rates of cardiovascular events and incidence of SCD.[20] The TEMPEST study did not evaluate whether particular population stressors may have underlain the clustering pattern seen. It would be interesting to assess if such events occurred in the respective geographic locations around the time of the ES clustering.

## Treatment Implications

Current treatment options for ES include pharmacological management, including antiarrhythmic drugs, or catheter ablation. However, both of these options are limited, with success rates for antiarrhythmic drugs of <50% and for ablation of ≈72%.[6,21] Ablation also carries risks, particularly in acutely sick patients. There is often a critical need for other therapy options for the patient experiencing ES. One early management strategy focuses on the identification of triggers or exacerbating factors, with an elevated sympathetic tone often playing a role in both. In addition to antiarrhythmic drug therapy and catheter ablation, other treatment options are aimed at inhibiting the effects of sympathetic nervous activation. Modulation and blockade of the sympathetic nervous system can be achieved on multiple levels, and these therapies have been shown to reduce the burden of arrhythmia. Acutely, general anesthesia and sedation can suppress or significantly reduce the burden of ventricular arrhythmias and ICD shocks in ES. Additionally, thoracic epidural anesthesia has been reported to substantially reduce the burden of arrhythmias.[22]

For chronic therapy, left or bilateral sympathetic blockade and denervation offer a feasible and safe option for the treatment of ES, especially when used in conjunction with ablation. This can be achieved temporarily via left stellate ganglion block, a percutaneous injection of local anesthetic just anterior to the longus colli muscle at the C6 level under ultrasound or fluoroscopic guidance. It may also be achieved more permanently via left cardiac sympathetic denervation, a surgical technique that involves ablation of the lower half of the left stellate ganglion and the T2 to T4 thoracic ganglia, severing the sympathetic innervation to the heart. Reduction in the burden of ventricular arrhythmias has been clearly demonstrated with left cardiac sympathetic denervation in patients following myocardial infarctions and in patients with channelopathies.[23,24] Left cardiac sympathetic denervation has been used to treat ES with good efficacy. Vaseghi et al[25] demonstrated that the beneficial effects extend beyond the acute period, with freedom from ICD shocks in 48% of patients and a significant reduction in ICD shocks in 90% of patients on long-term follow-up. Left cardiac sympathetic denervation can be used as an adjunctive therapy during the acute management of ES, and for those who respond, a more definitive surgical denervation can be pursued. It may also help stabilize a patient long enough to perform a catheter ablation of the ventricular arrhythmic substrate.

The TEMPEST study also demonstrates the power of collaboration. The authors were able to create a large and detailed database through the collaborative efforts of authors of previously published studies, allowing analysis of questions no single study may have been large enough to answer. Although not all the investigators these authors contacted were interested in participating, sharing access to data maximally leverages the work behind each study, multiplying the productivity of all.

## Disclosures

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