Original Article

Temporal Trends and Temperature-Related Incidence of Electrical Storm

The TEMPEST Study (Temperature-Related Incidence of Electrical Storm)

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Background—The occurrence of ventricular tachyarrhythmias seems to follow circadian, daily, and seasonal distributions. Our aim is to identify potential temporal patterns of electrical storm (ES), in which a cluster of ventricular tachycardias or ventricular fibrillation, negatively affects short- and long-term survival.

Methods and Results—The TEMPEST study (Circannual Pattern and Temperature-Related Incidence of Electrical Storm) is a patient-level, pooled analysis of previously published data sets. Study selection criteria included diagnosis of ES, absence of acute coronary syndrome as the arrhythmic trigger, and ≥10 patients included. At the end of the selection and collection processes, 5 centers had the data set from their article pooled into the present registry. Temperature data and sunrise and sunset hours were retrieved from Weather Underground, the largest weather database available online. Total sample included 246 patients presenting with ES (221 men; age: 65±9 years). Each ES episode included a median of 7 ventricular tachycardia/ventricular fibrillation episodes. Fifty-nine percent of patients experienced ES during daytime hours (P<0.001). The prevalence of ES was significantly higher during workdays, with Saturdays and Sundays registering the lowest rates of ES (10.4% and 7.2%, respectively, versus 16.5% daily mean from Monday to Friday; P<0.001). ES occurrence was significantly associated with increased monthly temperature range when compared with the month before (P=0.003).

Conclusions—ES incidence is not homogenous over time but seems to have a clustered pattern, with a higher incidence during daytime hours and working days. ES is associated with an increase in monthly temperature variation.

Clinical Trial Registration—https://www.crd.york.ac.uk. Unique identifier: CRD42013003744.

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Key Words: arrhythmias, cardiac ■ Brugada syndrome ■ catheter ablation ■ circadian rhythm ■ prevalence ■ tachycardia, ventricular ■ ventricular fibrillation

Electrical storm (ES) is usually defined as the occurrence of ≥3 episodes of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) within 24 hours requiring either antitachycardia pacing or cardioversion/defibrillation.[1] ES represents a true medical emergency that requires a multidisciplinary approach, and its prevalence is steadily rising along with the number of patients bearing an implantable cardioverter-defibrillator (ICD).[2]

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The occurrence of ventricular tachyarrhythmias seems to follow circadian and seasonal distributions.[3] Unfortunately, the temporal patterns described to date vary widely in patients with ischemic and nonischemic heart disease,[4] hypertrophic cardiomyopathy,[5] and Brugada syndrome.[6]

Although some studies have shown potential candidates as ES predictors,[7] there is currently no evidence on the association of this condition with environmental and external factors such as temperature, time of the day, and time of the year.

The aim of the present study was to describe the incidence of ES over time and test the potential association between ES and time of the year, time of the week, time of the day, and short-term temperature variations.

Methods

Study Selection

The TEMPEST study (Circannual Pattern and Temperature-Related Incidence of Electrical Storm) is a patient-level, pooled analysis of previously published data sets. The study was conducted following the current guidelines[8,9] and registered in the PROSPERO International

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WHAT IS KNOWN

- A circadian and seasonal distribution of unclustered ventricular tachyarrhythmias has been described in patients with ischemic and nonischemic heart disease, hypertrophic cardiomyopathy, and Brugada syndrome.
- There is currently no evidence on the association of electrical storms (ES) with environmental and external factors such as temperature, time of the day, and time of the year.

WHAT THE STUDY ADDS

- ES incidence is not homogenous over time but seems to recognize a clustered pattern, alternating low-incidence periods alternating with periods of many ES admitted within a few days from one another.
- A higher incidence of ES can be demonstrated during working hours and working days.
- Although ES does not seem to be associated with absolute temperature values, most ES happen in association with an increase in monthly temperature range.

prospective register of systematic reviews of the University of York, United Kingdom (registration no. CRD42013003744).

Two big medical databases (MEDLINE and Embase) were systematically searched to include all available articles. MEDLINE was searched using the following query: electrical storm [Mesh] OR arrhythmic storm [Mesh] OR recurrent ventricular arrhythmias [Mesh] OR ventricular tachycardia clusters [Mesh] OR electrical instability [Mesh]. ISI Web of Science was searched using the following query: title contains electrical storm OR arrhythmic storm OR recurrent ventricular arrhythmia OR ventricular tachycardia clusters OR electric instability. The search was performed up until November 1, 2015, and was limited to English-language literature. Two authors independently screened all the records reviewed full-text articles and determined their eligibility. Reviews and other meta-analyses on the subjects, as well as reference lists of all identified articles, were searched for relevant studies. To be selected, a study had to meet all the following criteria:

1. diagnosis of ES as the occurrence of ≥3 episodes of VT/VF within 24 hours (each episode at least 5 minutes apart) or VT for >12 hours;
2. absence of acute coronary syndrome as the arrhythmic trigger;
3. ≥10 patients included;
4. selection of the most recent publication when the same group reported on the same patients in separate publications.

Interobserver concordance was optimal during the whole selection process (k=0.97). At the end of the selection process, 35 articles were included in the data collection process.

Data Collection

Corresponding authors of the aforementioned papers were contacted by e-mail and asked to participate. Of those, 19 agreed, and the study protocol was provided to them. All authors were asked for additional information on a patient-level basis about clinical characteristics, laboratory exams, ES characteristics, time and zone of ES onset, electric therapies delivered by the ICD (if present), and pharmacological and nonpharmacological management. Nine authors replied back with a complete data set. To ensure optimal data quality, data sets with no data available on ES time and geographical location of each patient were excluded, as were data sets collecting nonconsecutive patients.

Figure 1 shows the study selection flow chart according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). At the end of the selection and collection processes, 5 centers had the data sets from their articles[10–14] merged into the present registry (Table 1).

Temperature Data Collection

Temperature data were retrieved from the historical weather section of Weather Underground (www.wunderground.com), the largest weather database available online. For each patient, average, maximum, and minimum temperatures during the event day were collected, as were average mean, maximum, and minimum temperatures during the week and the month of the ES and the week and the month before the ES. All centers were asked to retrieve information about the geographical whereabouts of each patient at ES onset. This included residence address, for ES that occurred at home, or the area where the ambulance was dispatched in case of an Emergency Medical System intervention. If none of them were available, the location of the first in-hospital medical contact was used instead. If the weather almanac was not available for the geographical location at that time, the nearest forecast station with available data was used instead. Weekly and monthly temperature ranges were defined as the average of maximum temperatures minus the average of minimum temperatures during a week or a month, respectively. The same database was used to retrieve sunrise and sunset hours. If ES started after sunrise and before sunset, it was considered as happened during daytime; if it started after sunset and before sunrise, it was considered as happened during night-time.

Statistical Analysis

Quantitative variables were checked for normality by the Kolmogorov–Smirnov test. Normally distributed variables were described as mean±SD. Non-normally distributed variables were described as median and first-to-third interquartile range (1st–3rd IQR). Categorical variables were described as absolute or relative prevalence. ES occurrence was coded as a binary variable. Exact binomial probabilities were used to test the probability of clusters of ES to happen, assuming a completely homogeneous temporal distribution of such episodes. A prespecified analysis was planned to test the association between ES and each of the following variables: hour; day of the week; month; season; average, minimum and maximum daily, weekly, and monthly temperatures; temperature weekly range; temperature monthly range; difference in weekly temperature range between ES week and the week before; and difference in monthly temperature range between ES month and the month before. On the basis of hour of occurrence, ES was assigned to 1 of 8 time intervals: 5:00 AM to 7:00 AM, 8:00 AM to 10:00 AM, 11:00 AM to 1:00 PM, 2:00 PM to 4:00 PM, 5:00 PM to 7:00 PM, 8:00 PM to 10:00 PM, 11:00 PM to 1:00 PM, and 2:00 PM to 4:00 PM. For each 3-hour interval, the proportion of all ES occurring during that interval was calculated and tested using a one-sample *t* test against 0.125 (ie, the expected mean value if each interval, representing one eighth of the 24-hour circle, would account for one eighth of all ES episodes). A similar approach was used to test for each day of the week (expected mean=0.143, ie, one seventh of the week) and each month of the year, where each month's ES proportion was weighted by the ratio between the duration of such month in days and 365.25 (expected mean=0.083, ie, one twelfth of the year). Pooled mean prevalence of ES during working days (Monday to Friday) was also compared with the prevalence of ES during Saturdays and Sundays, respectively. Regarding daytime versus night-time hours, each ES episode occurring during daytime was weighted by the ratio between the hours of day light at each location and for each date and 24, and the weighted proportion tested by one-sample *t* test against an expected mean of 0.5. One-sample *t* test was also used to test the association between ES occurrence and seasons using northern meteorologic seasons: spring (March 1–May 31), summer (June 1–August 31), fall (September 1 –November 31), and winter (December 1–February 28 or 29 in a leap year), using an expected mean of 0.25. Average, minimum, and maximum daily, weekly, and monthly temperatures were all

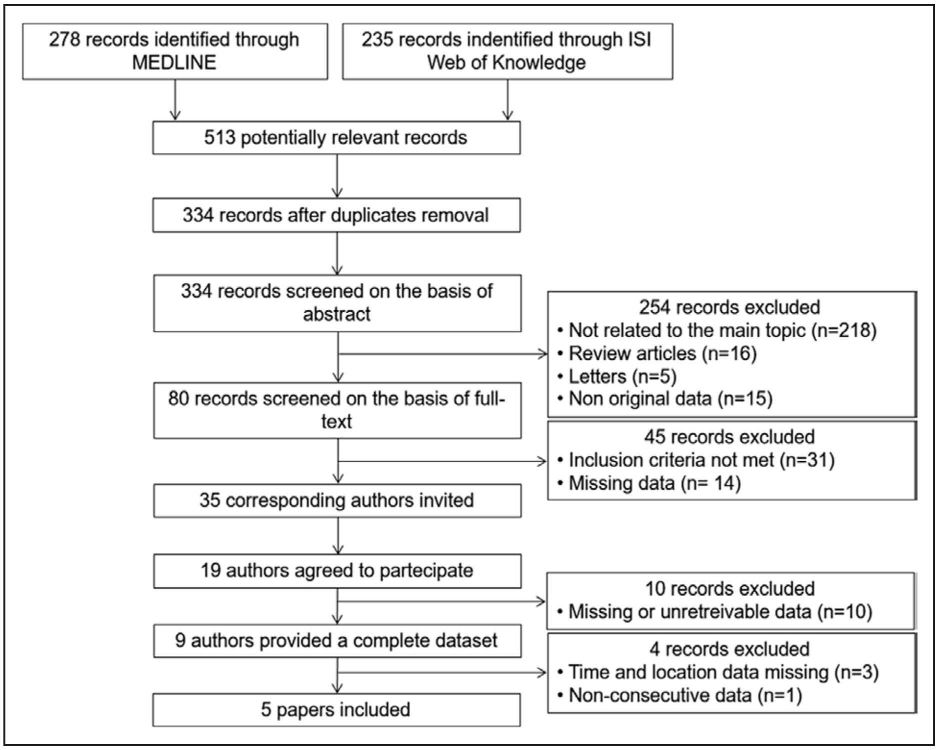

Figure 1. PRISMA study (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) selection chart.

divided into quintiles, and the proportion of ES for each quintile tested against an expected value of 0.2. One-sample *t* test was used to test whether the monthly temperature range variation, defined as the delta between the mean monthly variation when ES occurred and the mean monthly variation in the month preceding the ES was comparable to zero (ie, no difference between the 2 months). A similar approach was used to test the association between ES and weekly temperature range variation. SPSS 21.0 for Windows (SPSS Inc, Chicago, IL) was used for statistical analysis. Values of $P<0.05$ (2-tailed) were taken as statistically significant.

Results

Population Characteristics

Total sample included 246 patients presenting with ES (221 men; age: 65±9 years). Clinical characteristics of the sample and pharmacological therapy used to terminate ES are shown in Table 2.

Although mean serum potassium levels were within the normal ranges (4.3±0.6 mEq/L), 23 patients (9.3%) had hypokalemia, and 6 patients (2.4%) had hyperkalemia on presentation. Mean creatinine levels were 1.3±0.5 mg/dL, and 22 patients (8.9%) were admitted with creatinine serum levels ≥2 mg/dL.

Each ES episode was made up by a median of 7 VT/VF episodes (1st–3rd IQR 4–16). On average, each patient with an ICD already implanted experienced a median of 8 antitachycardia pacing therapies (1st–3rd IQR 3–10) and 5 shocks (1st–3rd IQR 3–6) before ES termination.

Electrical Storm Incidence Over Time

ES occurrence over time followed a nonhomogeneous distribution in all participating centers (Figure 2), with low-incidence periods alternating with clusters of many ES within a

Table 1. Baseline Characteristics of the Electrical Storms of the Included Articles

			Men, n (%)		Underlying Heart Disease, n (%)				Triggering Arrhythmia, n (%)			ICD, n (%)
Study	Sample Size	Main Intervention		Age	IHD	NIDCM	Other	EF	mVT	pVT	VF	
Carbucicchio et al[10]	95	VT ablation	85 (89.5)	64±13	72 (75.8)	10 (10.5)	13 (13.7)	36±11	68 (71.6)	6 (6.3)	21 (22.1)	95 (100)
Koźluk et al[11]	24	VT ablation	21 (87.5)	62±8	16 (66.7)	2 (8.3)	6 (25.0)	27±7	11 (45.8)	7 (29.2)	6 (25.0)	23 (95.8)
Izquierdo et al[12]	52	VT ablation	48 (92.3)	70±9	38 (73.1)	9 (17.3)	5 (9.6)	34±10	50 (96.2)	0 (0.0)	1 (3.8)	38 (75.0)
Vaseghi et al[13]	41	CSD	35 (85.4)	59±13	9 (21.9)	22 (53.6)	10 (24.3)	31±13	33 (80.5)	3 (7.3)	5 (12.2)	41 (100)
Guerra et al[7]	34	Medical therapy	32 (94.1)	71±9	20 (58.8)	8 (23.6)	6 (17.6)	30±8	30 (88.2)	1 (2.9)	3 (8.9)	34 (100)

CSD indicates cardiac sympathetic denervation; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; mVT, monomorphic ventricular tachycardia; NIDCM, nonischemic dilated cardiomyopathy; pVT, polymorphic ventricular tachycardia; and VF, ventricular fibrillation.

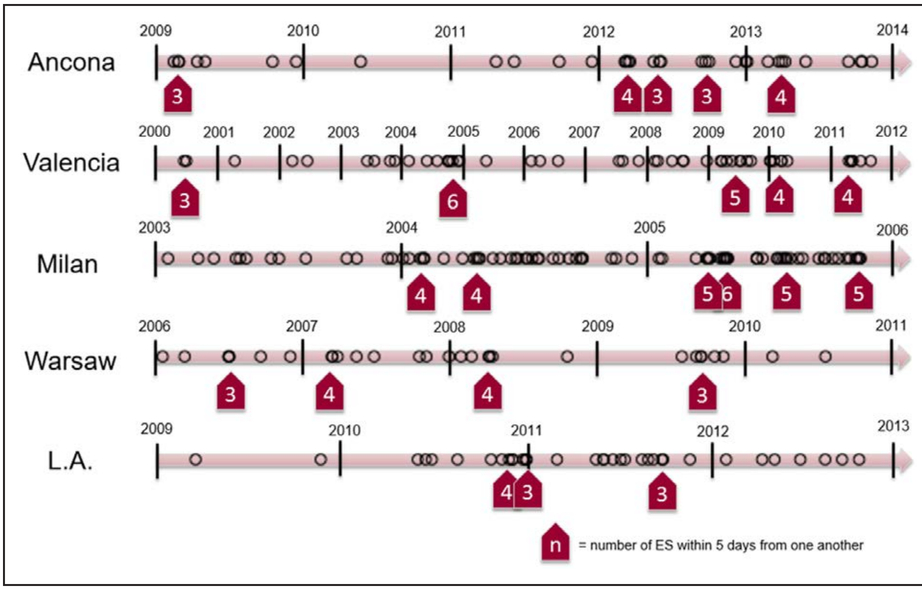

Figure 2. Distribution of electrical storm incidence over time in each participating center showing a cluster presentation.

few days from one another. A random distribution of ES episodes is unlikely as, according to the reported prevalence of each participating center, there was a low chance to expect ≥3 (P=2.4×10^{-4}), ≥4 (P=2.2×10^{-5}), or even ≥ ES within a 5-day period (P=1.9×10^{-6}) if a completely homogeneous distribution over time is assumed.

Regarding ES distribution over the day, a significantly higher number of ES happened during daytime hours rather than during night-time hours (58.7% versus 41.3%; adjusted P<0.001). Plotting ES episodes over time shows a significantly higher incidence of ES in the morning, with 29% of all ES starting from 8:00 AM to 10:00 AM (P=0.04) and a reduction during the following hours (Figure 3). Weekly occurrence of ES was similar from Monday to Friday, whereas both Saturday and Sunday showed lower rates of ES (all P<0.05; Figure 4).

ES distribution over the year was homogeneous with no month significantly associated with a higher prevalence of ES (Figure 5). Similar rates of ES were found between winter, spring, summer, and fall.

Temperature and Electrical Storm

No association was found between ES occurrence and average, minimum, and maximum daily, weekly, or monthly temperatures. However, ES occurrence was significantly associated with an increase in monthly temperature range when compared with the month before, with 68.9% of ES happening after an increase in monthly temperature range (P=0.003; Figure 6).

Table 2. General Characteristics of the Population

Variable	Patients (n=246)
Male sex, n (%)	221 (89.8)
Age, y	65±9
Type of heart disease	
Ischemic cardiomyopathy, n (%)	155 (63.0)
Nonischemic cardiomyopathy, n (%)	51 (20.7)
Other, n (%)	40 (16.3)
Left ventricular ejection fraction (%)	31.6±10.4
Serum potassium, mEq/L	4.3±0.6
Serum creatinine, mg/dL	1.3±0.5
Previous ICD implant, n (%)	232 (94.3)
Triggering arrhythmia	
Monomorphic ventricular tachycardia, n (%)	192 (78.0)
Polymorphic ventricular tachycardia, n (%)	17 (6.9)
Ventricular fibrillation, n (%)	37 (15.1)
Acute pharmacological treatment	
Amiodarone, n (%)	172 (69.9)
β-Blocker, n (%)	187 (76.0)
D-Sotalol, n (%)	10 (4.1)
Lidocaine, n (%)	58 (23.6)
Magnesium sulfate, n (%)	39 (15.9)
Procainamide, n (%)	65 (26.4)
Propafenone, n (%)	40 (16.2)
Sedation, n (%)	25 (10.2)

ICD indicates implantable cardioverter-defibrillator.

Discussion

Temperature-Related Variations

From our data, ES presentation is not homogenous over time but seems to recognize a clustered pattern, alternating low-incidence periods and high-intensity clusters, when many patients are admitted with ES within a few days. This pattern, although not superimposable for each center because of the different timeframes and geographical coordinates considered, was evident for all of the 5 participating hospitals (Figure 2). The pattern described was not related to a specific circannual pattern neither to absolute temperatures, as centers varied widely in terms of latitude, longitude, and temperatures

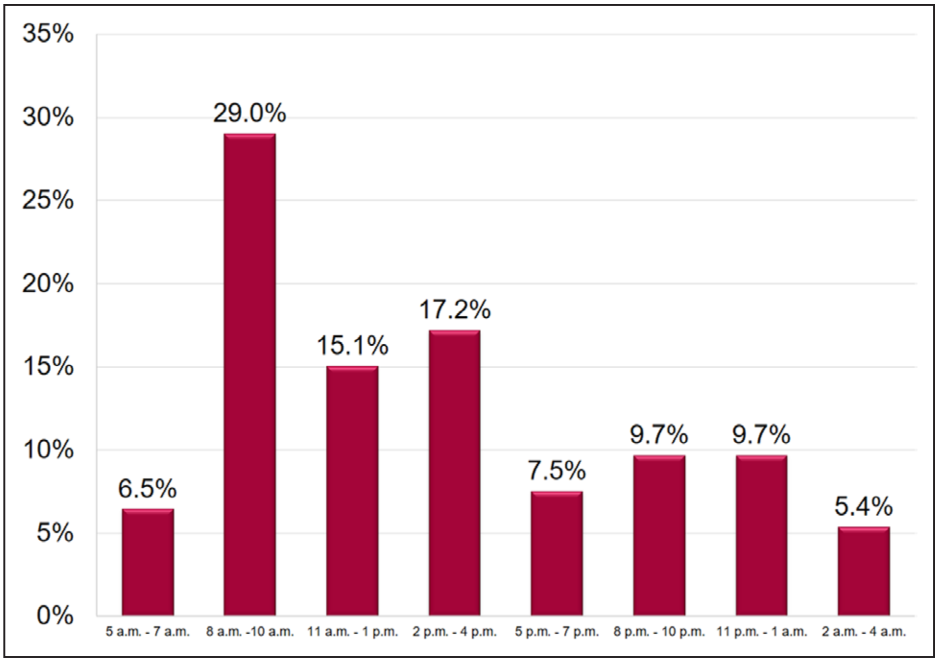

Figure 3. Circadian pattern of electrical storm triggering arrhythmia.

(these latter ranging from a yearly average of 10°C in Warsaw to 21°C in Los Angeles). On the contrary, we found a significant association between ES incidence and variations in the temperature range (Figure 6), with ≈70% of all ES happening after an increase in monthly temperature range. The mechanisms underlying the connection between ES and environmental triggers are unknown, but some hypothesis can be made. In favor of a direct causal relationship, we have many available data underlying an increased risk of ventricular arrhythmias in patients undergoing fast body temperature cooling and rewarming, as commonly experienced in therapeutic hypothermia.[15] Animal models demonstrated that inducing hypothermia amplifies dispersion of repolarization[16] and increases myocardial vulnerability to VF,[17] thus potentially eliciting multiple arrhythmic events in predisposed patients. Of course, our patients experienced a variation in external rather than body temperature, which was neither as big in magnitude nor so concentrated in time. Therefore, other hypotheses must be sought. Recently, it has been suggested that the increased mortality and morbidity caused by hot and cold temperatures could not be strictly related to hypothermia/hyperthermia but by other causes triggered by the human organism's attempts to adapt to the external temperature.[18] In this regard, increased mortality and hospitalization rates for cardiovascular diseases have been reported after both cold spells and heat waves in many different geographical locations.[19] Hospitalization rates from a large population-based study showed a J-shaped association between hospitalization for blood pressure, diabetes mellitus, and, with a minor extent, arrhythmias over a lag of 21 days, with higher risks at both temperatures extremes.[20]

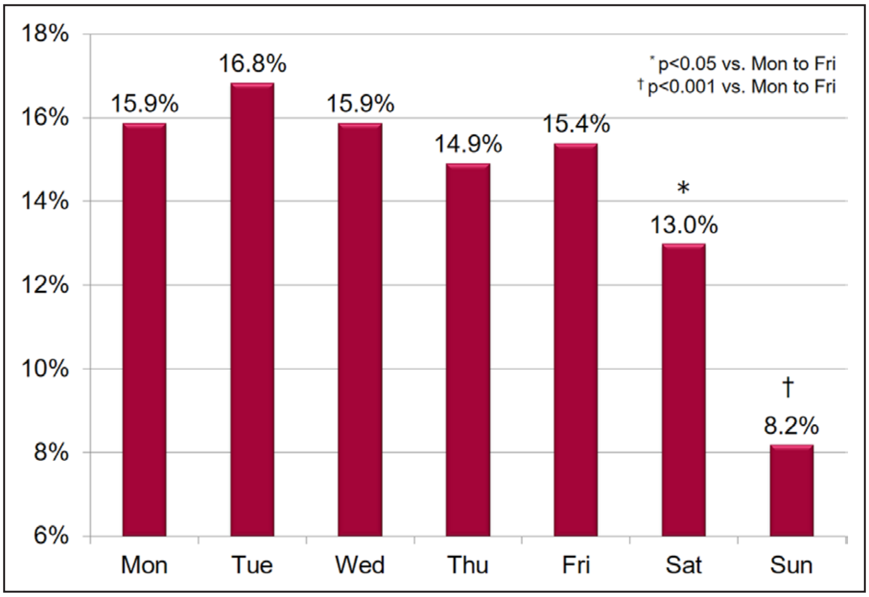

Figure 4. Electrical storm incidence over the week.

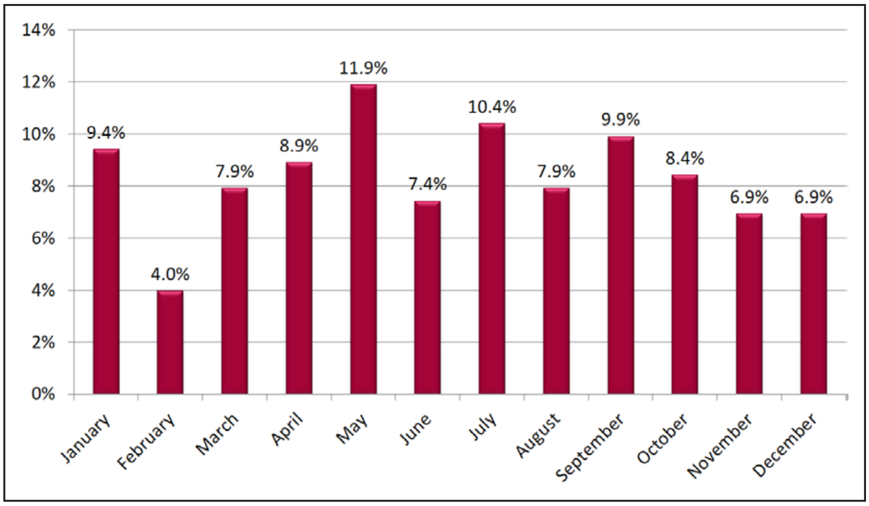

Figure 5. Electrical storm incidence over the year.

Thermoregulation-mediated vasoreactivity,[21] sympathetic nervous system activation,[21] and sodium and volume retention through the renin–angiotensin–aldosterone system[22] could all be involved as underlying pathophysiological mechanisms. On a note, the changes in atmospheric pressure related to weather and temperature variations are also associated with the concentration of particulate and gaseous air pollutants, both of which have been related to an increased risk of arrhythmia-related hospitalization or mortality.[23]

Weekly and Daily Variations

The higher incidence of ES during working days in our population was not totally unexpected, as was already underlined on unclustered VT/VF.[24] This behavior could highlight a predominant role of autonomic regulation in triggering the ES, similar to the well-known circadian pattern in acute myocardial infarction.[24] This hypothesis is supported by a recent subanalysis of the SCD-HeFT trial, which demonstrated a significant weekly variation with an increase in VT/VF incidence on Mondays only in patients not treated with β-blockers.[3]

Available analyses of VT/VF daily patterns report a higher incidence of ICD therapies in the early morning both in ischemic and in nonischemic cardiomyopathy,[4] whereas patients with hypertrophic cardiomyopathy and Brugada syndrome experience ICD therapy more often during the afternoon[5] and late night,[6] respectively. In our population, mainly composed of ischemic (63.0%) and idiopathic dilated cardiomyopathy (20.7%), ES starting hour distribution is similar to the circadian distribution of VT/VF described by Anand et al,[24] although the late rise described during the afternoon hours is much less evident in our population (Figure 3). So, although it is feasible to hypothesize that the first VT/VF triggering the ES follows the same circadian pattern already described, some other factors must be held responsible for the coalescence of many VT/VF into an ES. Given the high prevalence of structural heart disease and severe left ventricular dysfunction in our population, it is feasible to identify heart failure as a major potential actor. A recent observational study on a 5-year follow-up showed that ES patients share some striking similarities with patients admitted for heart failure exacerbation.[14] In this setting, ES could be seen as a warning sign of impending pump failure rather than an independent event, and the many dysregulated biochemical pathways typical of heart failure could help in creating a substrate for arrhythmia recurrence, with ES as an epiphenomenon.[25] Another potential candidate is sleep-disordered breathing, which is often described as an arrhythmic risk factor in heart failure patients.[26] Although recent observational data have shown that sleep-disordered breathing is an independent predictor of appropriate therapy in ICD patients,[27] the increased risk of ventricular arrhythmias because of sleep-disordered breathing seems concentrated in

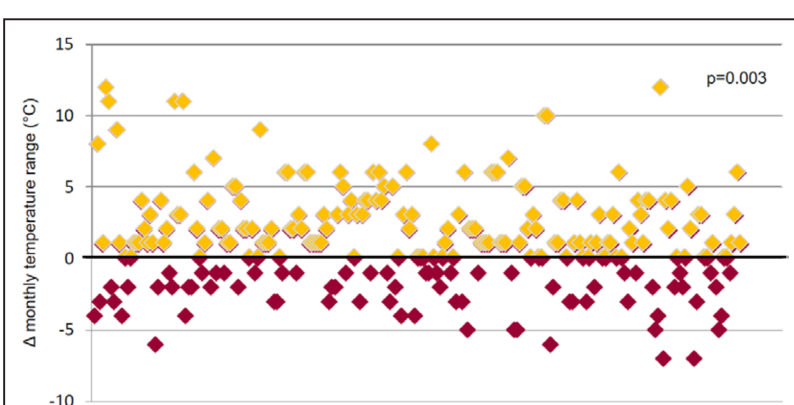

Figure 6. Difference in monthly temperature range for each patient with electrical storm.

the sleep hours,[28] in steep contrast with our reported peak of ES incidence from 8:00 AM to 10:00 AM.

Limitations

The present article shares all the limitation intrinsic to a retrospective, patient-level pooled analysis. In addition, a referral bias should be taken into account as all participating centers are highly-specialized, hub centers covering a large area. Therefore, it is highly likely that patients referred in the participating centers are not representative of all patients with ES.

Regarding collected data, average temperatures were extracted from a web-based forecasting service, thus limiting the real assessment of external temperature to a wide geographical area. Moreover, baseline medications were not routinely collected, as the selected papers focused on the acute treatment of ES. Therefore, it is not cautious to extend the present findings to specific subpopulations (ie, patients previously treated with β-blockers or other antiarrhythmic drugs), and the presented data should be taken as hypothesis generating rather than conclusive. In fact, a plethora of other environmental triggers, such as (but not limited to) heavy precipitations, snowing, natural disasters, blackouts, sport events, political elections, and holidays, could contribute to the clustering of ES as reported in the present article.

We were also not able to recover data on ICD programming, which has been shown as an important risk factor for ES and therefore a potential confounder.[29]

Conclusions

ES incidence is not homogenous over time but seems to recognize a clustered pattern. Although ES does not seem to be associated with absolute temperature values, most ES happened in association with an increase in monthly temperature range. Although a higher incidence of ES can be demonstrated also during working hours and working days, the present findings are observational in nature, and new hypotheses must be tested to explain this peculiar behavior.

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Disclosures

None.

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