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CORRESPONDENCE

Research Correspondence

Chronobiological Patterns of Onset of Tako-Tsubo Cardiomyopathy

A Multicenter Italian Study

To the Editor: Several cardiovascular events, including acute myocardial infarction (AMI), show well-defined temporal patterns in their occurrence throughout the year and the day (1,2). Tako-Tsubo cardiomyopathy (TTC), also called "stress cardiomyopathy" or "transient left ventricular apical ballooning syndrome," is an acquired cardiomyopathy prevalent in elderly women presenting with a history of emotional or physical stress that mimics the clinical scenario of an AMI (3,4). The aim of this study was to verify whether TTC could exhibit significant chronobiological patterns of onset. We analyzed data from 90 consecutive patients with TTC admitted between January 2002 and December 2007 to the coronary care unit of 7 Italian referral cardiac centers. All patients were enrolled according to the Mayo Clinic diagnostic criteria for TTC (4). All patients underwent coronary angiography and left ventriculography. The study was approved by all local ethics committees, and informed consent was obtained by all patients.

Clinical variables were recorded in part retrospectively (January 1, 2002, to December 31, 2004; n = 24 [26%]), and in part prospectively (January 1, 2005, to December 31, 2007; n = 66 [74%]) on a standardized form that included information on patient demographics (sex, age, date and time of onset), signs and symptoms at the event, medical history, trigger events, electrocardiographic ST-segment changes at admission, clinical observations during hospitalization (including major cardiovascular complications), T troponin level peak, and imaging studies (cardiac catheterization and echocardiography). Retrospective data were recorded by searching hospital discharge diagnosis records and coronary care unit and catheterization laboratory databases.

Day of symptom onset was categorized both into 12 1-month intervals and 4 3-month intervals (spring: March 21 to June 20; summer: June 21 to September 22; autumn: September 23 to December 20; and winter: December 21 to March 20) for seasonal analysis. The distribution of symptom onset within the 4 3-month periods was tested for uniformity in the overall population by the chi-square test for goodness of fit. Moreover, a chronobiological analysis of seasonal patterning in TTC was performed by applying a partial Fourier analysis to the monthly data using validated Chronolab software (5). The parameters calculated for the overall 1-year period cosine approximation of the time series data (period of 8,766 h) were the Midline Estimated Statistic of Rhythm (MESOR), which is the rhythm-adjusted mean over the time period analyzed; amplitude (one-half the difference between the absolute maximum and minimum of the fitted curve); and the peak (acrophase), indicating the absolute maximum values during the year. Significance levels were set at $p < 0.05$.

Time of symptom onset was categorized into 4 6-h intervals (night: 12:00 to 5:59 AM; morning: 6:00 to 11:59 AM; afternoon: 12:00 to 5:59 PM; and evening: 6:00 to 11:59 PM) for circadian analysis. The distribution of symptom onset within the 4 6-h periods was tested for uniformity in the overall population by the chi-square test for goodness of fit. Significance levels were set at $p < 0.05$.

From the overall population, 2 and 11 cases were excluded from the seasonal and circadian analysis, respectively (the final group included 88 and 79 cases, respectively) owing to the lack of data on time of occurrence. The mean age of the entire study population was 64.4 ± 11.4 years (range 41 to 85 years). The majority of patients were women (n = 85; 94.4%). The apical form of TTC was markedly prevalent. Presenting symptoms were acute chest pain (64 patients; 71.1%), dyspnea (n = 10; 11.1%), chest pain and dyspnea (n = 5; 5.5%), and other (n = 7; 7.9%). A trigger event (physical and/or emotional stress in the hours immediately before admission) was recorded in 64 (71.1%) patients. Common cardiovascular risk factors included diabetes mellitus in 7 (7.7%) patients, hypertension in 48 (53.3%), hypercholesterolemia in 39 (43.3%), and smoking in 17 (18.8%). The electrocardiogram on admission was characterized by ST-segment elevation in 35 (38.8%) patients; only 10 (11%) patients showed atrial fibrillation. All patients had a mildly elevated troponin (T troponin mean 0.743 ± 0.595 ng/ml; range 0.043 to 2.3 ng/ml [normal value 0.010 to 0.030 ng/ml]). Left ventricular ejection fraction (LVEF), measured by Simpson's method during transthoracic echocardiography, was moderately low (LVEF [mean ± SD]: 37.9 ± 6.08%). Left ventricular outflow tract obstruction was detected in 19 (21%) patients. By visual echocardiographic assessment, right ventricular involvement (dyskinesis or akinesis of the apex and sparing of the base) was documented in 17 (18%) patients.

Coronary angiography showed angiographically normal coronary arteries in 68 (75%) patients and stenosis <50% of 1 vessel in 20 (22%) patients and of 2 vessels in 2 (2%). Apical ballooning defined by ventriculography was predominant (n = 73; 81.1%) compared with the midventricular ballooning. Major in-hospital cardiovascular complications were recorded in 14 (15.4%) patients: cardiogenic shock (n = 6; 6.6%), ventricular tachycardia/fibrillation (n = 4; 4.4%), and pulmonary edema (n = 4; 4.4%). Of note, major complications occurred in 7 of 17 patients with right ventricular involvement. No patients died during hospitalization, and all were uneventfully discharged.

The onset of TTC differed as a function of season ($p < 0.001$), with the peak in July and the nadir in March (Fig. 1, upper panel). Events were most frequent in summer (n = 51; 57.9%) and least so in autumn (n = 10; 11.4%; chi-square = 20.113; $p < 0.001$) (Fig. 1, middle panel). Chronobiological analysis identified a significant annual rhythmic pattern in TTC, with the peak in late July, and 95% confidence limits in July and August (MESOR 7.36 ± 1.17; amplitude 6.12 ± 1.66; p = 0.016). TTC was most frequent in the morning (n = 32; 40.5%) and least so at night (n = 8; 10.2%; chi-square = 10.303; p = 0.021) (Fig. 1, lower panel).

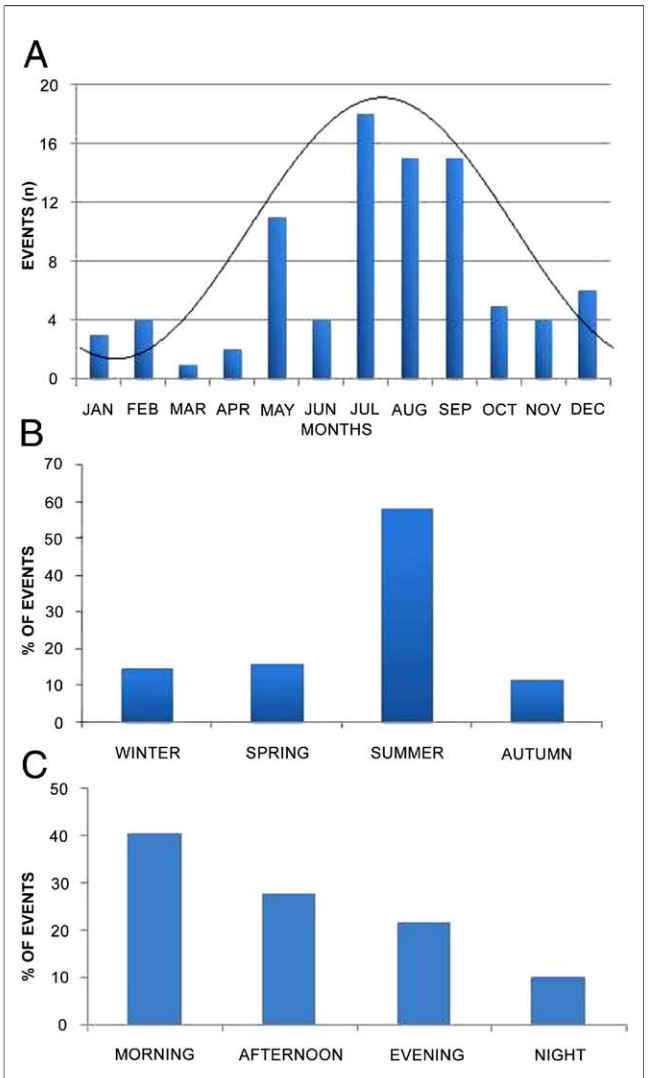

Figure 1 **Temporal Distribution of TTC Events**

Temporal distribution of Tako-Tsubo cardiomyopathy (TTC) events: **(A)** monthly distribution (cosinor fit is superimposed on the graph), **(B)** seasonal distribution, and **(C)** circadian distribution.

This is the first report of significant chronobiological variation in TTC occurrence, characterized by summer and morning preference in a large cohort of Caucasian patients. Regarding seasonal variation, TTC shows an opposite pattern compared with the major acute cardiovascular diseases, especially AMI, which is characterized by peaks in winter and troughs in summer (1). Furthermore, our findings represent new distinctive features that, once again, distinguish TTC from acute coronary syndrome.

Additional studies are needed to investigate the potential link between seasonal and diurnal TTC onset and the underlying pathophysiologic mechanisms.

***Rodolfo Citro, MD**

*Via Matteo Rossi, 7
Salerno 84127
Italy
E-mail: rodolfocitro@tele2.it

Mario Previtali, MD
Daniella Bovelli, MD
Olga Vriz, MD
Costantino Astarita, MD
Marco Mariano Patella, MD
Gennaro Provenza, MD
Corinna Armentano, MD
Quirino Ciampi, MD
Giovanni Gregorio, MD
Massimo Piepoli, MD
Eduardo Bossone, MD, PhD
Roberto Manfredini, MD

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Key Words: Tako-Tsubo cardiomyopathy ■ transient left ventricular apical ballooning ■ cardiomyopathy ■ heart failure ■ chronobiology.

Letter to the Editor

Serendipity

During this time of political change, we have been reading numerous editorials outlining current ideas about how medicine should be reorganized. This letter was stimulated by some of those recently published.

I have especially appreciated comments about the need for research, the impending manpower shortage, and the financial