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Triggering of Ventricular Ectopic Beats by Emotional, Physical, and Meteorologic Stress: Role of Age, Sex, Medications, and Chronic Risk Factors

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Aim To investigate the association of a single ventricular ectopic beat with physical, emotional, or meteorologic stress and the role of age, sex, antiarrhythmic and other medicament therapy and participant characteristics.

Methods The study included 457 participants who were consecutively assigned to undergo continuous 24-hour Holter monitoring and who completed a structured questionnaire about their physical activity and mental stress. Multiple regression analysis of data on 11 meteorologic parameters, participants' baseline characteristics, and medications they used was performed for subgroups according to sex and age, with 65 years as age limit.

Results Wind speed, low relative humidity, increasing relative humidity, and emotional stress were independent predictors of ventricular ectopic beat, whereas warm front passage showed a protective effect in all participant subgroups ($P<0.05$ in all cases). Physical activity was an independent predictor of ventricular ectopic beat in women ($P=0.02$) and cold front passage in men $P=0.003$). The circadian variation in frequency of ventricular ectopic beats persisted in all subgroups after adjustments for external triggers ($P<0.001$ in all cases). Among chronic risk factors, familial background and previous myocardial infarction were independent predictors of ventricular ectopic beat in men and younger ($P<0.05$ in all cases). Nitrates ($P<0.03$ in all cases) and angiotensin converting enzyme inhibitors ($P<0.02$ in all cases) exerted protective effect in younger participants as well as did β-blockers in the elderly ($P<0.003$ in all cases).

Conclusion In addition to existence of an endogenous, external triggering-independent circadian pattern, physical, emotional, and meteorologic stress may act as triggers of ventricular ectopic beat in a manner that differs from triggering more complex arrhythmias. Familial background seems to have a significant impact on arrhythmogenesis in men.

The most common substrates for the onset of sudden cardiac events are atherosclerotic plaques, which cause coronary artery occlusion and myocardial ischemia, and myocardial scarring, which is a consequence of myocardial infarction. Certain external conditions and circumstances, such as emotional (1-5), physical (1-3,5-7), and meteorologic stress (1,2) are the "acute risk factors," shown to precipitate the very moment of cardiac events. This moment, multifactorial in nature, results from a complex interplay between these acute and chronic risk factors. In our previous study, we showed that emotional stress and various meteorologic conditions were strong predictors of episodes of ventricular tachycardia, whereas physical activity influenced the occurrence of tachycardia only in men and younger people (1). Furthermore, β-blockers and anxiolytic drugs exhibited a protective effect, especially in men and older people, confirming the role of sympathetic nervous system arousal in ventricular tachyarrhythmias.

Cardiac tachyarrhythmias are a common cause of morbidity and mortality worldwide (8,9). The current hypotheses on the initiation of complex and malignant arrhythmias, e.g., ventricular tachycardia and ventricular fibrillation, admit their complex relationship with single ventricular ectopic beats (9,10). Therefore, the contribution of environmental, behavioral, triggering, and modifying factors in the episodes of ventricular ectopic beats seems to be important, but due to many methodological and practical obstacles, this interdisciplinary area remains understudied.

We performed a prospective observational study to investigate the association of the acute and chronic risk factors with the occurrence of different cardiac arrhythmias, especially ventricular ectopic beats, in patients undergoing continuous 24-hour Holter monitoring. We also wanted to determine if greater frequency of ventricular ectopic beats necessarily meant the greater likelihood of ventricular tachycardia.

Methods

Study Setting

The city of Split, where the study was performed, is located in Dalmatia, a coastal region in the southern Croatia that has a mild Mediterranean climate characterized by frequent and rapid changes in meteorologic conditions, especially during the time of year chosen for the study period. Patients who consecutively underwent continuous 24-hour Holter monitoring at the Diagnostic Units of the Division of Cardiology, Department of Medicine, Split University Hospital, Split, Croatia, between January and April 2001 were eligible for the enrolment into the study. Out of 501 eligible patients, 457 were included (233 men and 224 women). Those who were unable to complete the diary (n = 17) or whose electrocardiographic (ECG) records were inaccurate or had artifacts (n = 27) were excluded.

Interview

The participants were interviewed by the attending cardiologist or specially trained nurses, who filled out the data forms noting patients' demographic characteristics, presence of clinical risk factors, medication used, and information on exact time of exposure to physical activity or emotional upset. In addition to atenolol, bisoprolol, propranolol, metoprolol, and oxprenolol as conventional β-blockers, β-blocker group of medications also included sotalol and carvedilol. Family history of heart disease included the existence of coronary heart disease, cardiomyopathy, arrhythmic disorder, or inherited heart disease verified and treated by a cardiologist. Participants were considered to have been exposed to physical activity during a particular period if they performed activity compatible with level 4 or more on 1-8 scale of metabolic equivalents (1,6,7). Exposure to emotional upset was defined as an emotional state compatible with level 3 or more according to Onset Anger Scale (1,4).

The study protocol was approved by the Hospital Ethics Committee and all participants gave their informed consent.

Holter Monitoring

The participants underwent a continuous 24-hour Holter monitoring for which a Medilog FD4 5-channel recorder (Oxford Instruments, Abingdon, UK) and a PCMCIA flash memory storage card were used. The records were first analyzed by using a devoted software system (Oxford Instruments Medical Ltd, Medilog Cardiology, Information System V1.42) and then manually by an experienced observer (authors). Episodes of ventricular ectopic beats were determined according to the width and prematurity of QRS complexes of at least 30%. The time of the stored episodes was obtained from the time settings of the program set to the local time.

Meteorologic Variables

Meteorologic data were obtained from the State Hydrometeorological Institute, Marine Meteorological Center in Split. Data included atmospheric temperature (°C), pressure (hPa), relative humidity (%RH), wind speed (m/s) and direction (per 10°), rainfall, and passages of cold or warm atmospheric fronts. The latter two were coded as yes/no categorical variables. The meteorologic data were obtained every 3 hours (at 1, 4, 7, and 10 AM and 1, 4, 7, and 10 PM) for every day of the study period.

Statistical Analysis

The occurrence of episodes of ventricular ectopic beats per hour was expressed as a percentage of total number of ectopic beats recorded during monitoring. This method of adjustment of participant-episodes per hour gave each participant the same weight, independently of absolute number of ventricular ectopic beats during monitoring.

Analyses were performed for 2 sets of data, ie, by 2- and 3-hour intervals. The first set of analyses investigated direct correlations, eg, the occurrence of ventricular ectopic beats in 2-hour intervals for the given values of meteorologic parameters. For that purpose, the percentages of ventricular ectopic beats within an hour before and an hour after the point of measurement of meteorologic parameters were summated and associated with the other triggering and modifying variables. In the second set of analyses, we subtracted values of each successive measurement of atmospheric temperature, atmospheric pressure, and relative humidity from the previous value for every 2 consecutive measurements. The observed differences represented the change in the values of these parameters during each 3-hour interval and were associated to the sum of percentages of ventricular ectopic beats recorded during the respective 3 one-hour intervals between the measurements of meteorologic parameters.

We used linear regression analysis to asses the influence of atmospheric temperature and pressure, relative humidity, wind speed and change in levels of meteorologic variables. The percentage of ventricular ectopic beats was averaged over all observations corresponding to a particular value of an independent variable in question. This included measurements over all participants and each participant could contribute more than once to the value in question. The weight factors, equal to the number of observations corresponding to a particular value of an independent variable, were also used in the regression analyses.

To assess whether the frequencies of ventricular ectopic beats differed according to time of day, we used repeated measures analysis of variance (ANOVA) because a preliminary computed test statistics revealed a symmetric distribution of variables of interest and homogeneity of variances. The general linear model algorithm, representing a two-way ANOVA (time of day × participant characteristic), was run for each baseline characteristic of a participant separately to assess whether the circadian pattern of ventricular ectopic beats occurrence depended on these characteristics. The repeated measures ANOVA was possible only in part of the diurnal rhythm analysis because all external triggers of ectopic beats (meteorologic variables, emotional upset, and physical activity) were uncontrolled and varied both between and within participants, in contrast to time of day and participant baseline characteristics. In other analyses, the repeated sampling per participant allowed for an increase in the sample size, control of confounding variables, and reduction of subject variability, as 8 samples per participant provided more information than 8 samples of 8 different participants.

Multiway ANOVA was used to asses whether the occurrence of ventricular ectopic beats differed during intervals according to physical activity, emotional upset, rainfall, wind direction, and cold, warm or no front passage. Since the diurnal variations in physical activity, emotional stress, and meteorologic parameters varied both within participants (8 measurements a day) and between participants, each measurement was considered as a separate entry. To account for correlations due to repeated measurements on the same participant, the variable consisting of repeated sequences of the numbers 1 to 8 was generated and always used as one of the independent variables in multiway ANOVA. The same test was used to adjust the diurnal and wind direction-dependent variation in frequency of ventricular ectopic beats for other external triggering factors that had shown significant association in final multivariate models in sex and age subgroups. Meteorologic variables were included as independent variables while physical activity and mental stress were included as covariates. In this analysis, the mean percentage of ventricular ectopic beats per 10° were grouped according to winds typical for the region and then further combined according to their origin and type of weather to which they belong to provide comparable classification for analyses.

A stepwise multiple regression analysis was used to estimate the independent predictive significance of a number of acute (external or triggering) and chronic (traditional or modifying) factors on occurrence of ventricular ectopic beats as dependent variable. In the evaluation of confounding chronic factors, such as participants' characteristics and medication used, we also made two preliminary selection models. The variables that in these models showed association at significance level of $P \leq 0.1$ were included together with acute factors in the final models as independendent variables. The final models were separately made for basic (single) meteorologic parameters, passage of atmospheric fronts (complex meteorologic phenomena), and changes in value of meteorologic parameters. Passage of atmospheric front was included as a dummy variable. Separate multivariate analyses were done according to sex and age of participants, and independent predictive values of the variables were expressed by standardized partial regression coefficient β and the corresponding *P* value. For statistical analysis, we used Statistical Package for Social Sciences (SPSS), version 11.0 (SPSS Inc., 2001, Chicago, IL, USA) and Statistica 5.773 (StatSoft Inc., 1998, Tulsa, OK, USA) statistical software.

Results

An equal number of men and women were enrolled in the study (Table 1). The mean age of the participants (±standard deviation) was 59±14 years, and most were outpatients. The average ventricular ectopic beats percentage per 2-hour period was 7.4±7.1 for all participants, and differed significantly between men and women (7.1±6.9 vs 7.7±7.4, respectively, $P=0.033$).

Table 1. Baseline characteristics of study participants (n=457)

Characteristics*	No. (%) of participants
Men	233 (51.0)
Age (years, mean±SD)	59±14
BMI (kg/m^2, mean±SD)	26±3
Out-patients	429 (93.9)
Hypertension	265 (58.0)
Chest symptoms in previous 7 days	244 (53.4)
Hypercholesterolemia	159 (34.8)
Family history of heart disease	154 (33.7)
Smoking	75 (16.4)
Previous myocardial infarction	73 (16.0)
Diabetes mellitus	72 (15.8)
Current medications used:	
aspirin	156 (34.1)
diuretic	143 (31.3)
β-blocker	138 (30.2)
ACE inhibitor	138 (30.2)
anxiolytic	77 (16.8)
hypolipemic	69 (15.1)
nitrate	60 (13.1)
calcium channel blocker	57 (12.5)
digitalis	35 (7.7)
propafenone	27 (5.9)
amiodarone	9 (2.0)

*Abbreviations: SD – standard deviation; BMI – body mass index; ACE – angiotensin converting enzyme.

Meteorologic Variables

The mean percentage of ventricular ectopic beats showed both a positive linear relationship with wind speed (Fig. 1) and a significant variation according to the wind direction before adjusting for other variables and time of day (Fig. 2 and Table 2). Ventricular ectopic beats were significantly less frequent during periods of rainfall (6.4% vs 7.7%, $P=0.041$). More ectopic beats occurred during a cold front (8.2%) than during no front (7.4%) or a warm front (4.8%) passage ($P<0.001$). Static comparison showed an increased frequency of ventricular ectopic beats at lower relative humidity (Fig. 3). Dynamic comparison showed that the frequency of ventricular ectopic beats increased with the magnitude of increment in relative humidity during a given 3-hour period (Fig. 4). The occurrence of ventricular ectopic beats did not vary according to the level or change of atmospheric temperature or pressure.

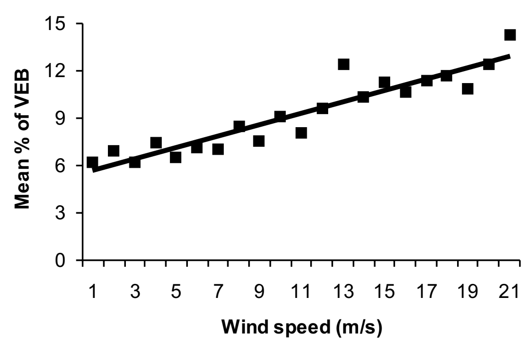

Figure 1. Mean percentage of ventricular ectopic beats (VEB) according to wind speed (m/s). Linear regression analysis, $P<0.001$, r=0.93. Linear regression equation: $y = 5.35+0.36x$.

Table 2. Crude and adjusted values of mean percentage of episodes of ventricular ectopic beats for 4 typical wind directions in all participants and in subgroups by sex and age

	Ventricular ectopic beats (%)								
		men (n=233)		women (n=224)		aged <65 (n=264)		aged>64 (n=193)	
Wind direction	total (n=457)	crude	adjusted	crude	adjusted	crude	adjusted	crude	adjusted
Northeast	6.36	6.24	8.80	6.47	7.90	6.14	8.33	6.65	7.98
East	7.92	7.72	9.80	8.10	8.00	7.87	10.17	7.99	11.04
South-southeast	8.79	8.62	9.55	9.01	9.41	8.77	9.50	8.81	10.59
West	6.16	5.36	5.43	7.88	7.43	6.73	7.31	5.46	7.10
*P**	<0.001	<0.001	0.221	<0.001	0.192	<0.001	0.613	<0.001	0.096

**P* values were derived from analysis of variance (ANOVA) for crude values and multi-way ANOVA when adjusting for meteorologic and other external trigger variables showing significant association in final multivariate model for each subgroup (Tables 7 and 8) and time of day.

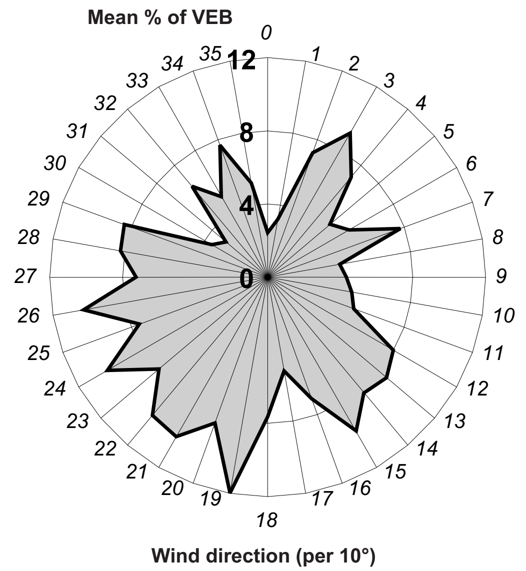

Figure 2. Mean percentage of ventricular ectopic beats (VEB) according to wind direction (degrees). ANOVA, $P<0.001$. Grey area – mean percentage of VEB.

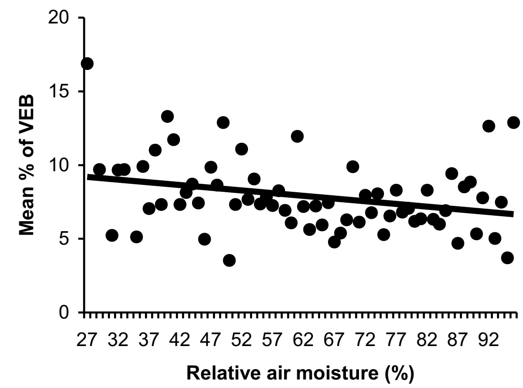

Figure 3. Mean percentage of ventricular ectopic beats (VEB) according to relative humidity (%RH). Linear regression analysis, $P=0.021$, $r=-0.29$. Linear regression equation: $y = 10.19 - 0.04x$.

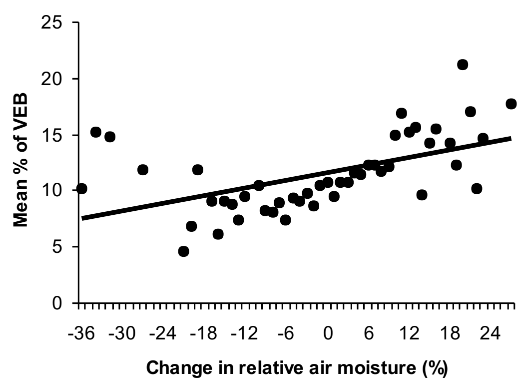

Figure 4. Mean percentage of ventricular ectopic beats (VEB) according to change in relative humidity (Δ %RH). Linear regression analysis, $P=0.0002$, $r=0.52$. Linear regression equation: $y = 11.59 + 0.11x$.

Other External Triggers

Ventricular ectopic beats were more frequent during periods of emotional stress (11.2% vs 7.3%, $P<0.001$), but did not vary significantly in frequency with respect to physical activity (8.1% vs 7.3%, $P=0.109$).

Circadian Pattern

An unequal circadian variation in the frequency of ventricular ectopic beats was observed for the participants as a whole group and in sex and age subgroups. The variation persisted in all subgroups after adjustment for the impact of external triggering factors (Table 3). The influence of baseline characteristics and medicament therapy on daily distribution of ventricular ectopic beats in terms of frequency and interaction effect was also analyzed, as well as circadian pattern of ectopic beats in subgroups with multiple positive fre-

Table 3. Crude and adjusted values of mean percentage of episodes of ventricular ectopic beats for 2-hour daily intervals in all participants and subgroups divided by sex and age

	Percentage of ventricular ectopic beats								
		men (n=233)		women (n=224)		aged <65 (n=264)		aged >64 (n=193)	
Interval (h)	total (n=457)	crude	adjusted	crude	adjusted	crude	adjusted	crude	adjusted
9-11	8.78	7.87	7.83	9.72	9.63	8.54	8.10	9.12	9.81
12-14	8.42	8.38	9.49	8.46	9.46	8.46	10.56	8.35	10.53
15-17	8.88	8.74	9.18	9.04	8.87	9.67	9.52	7.82	9.78
18-20	9.78	8.67	8.86	10.92	11.51	10.25	11.55	9.14	11.39
21-23	6.55	6.89	7.74	6.21	5.78	6.34	6.31	6.84	7.59
0-2	4.00	4.35	4.23	3.65	4.07	3.90	4.43	4.15	5.12
3-5	4.78	4.96	5.49	4.59	4.87	4.76	4.96	4.80	5.26
6-8	8.01	7.29	10.39	8.78	8.56	6.88	8.91	9.54	10.61
*P**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

**P* values were derived from analysis of variance (ANOVA) for crude values and multi-way ANOVA when adjusting for meteorological and other external trigger variables showing significant association in final multivariate model for each subgroup (Tables 7 and 8).

Table 4. Influence of participant characteristics and medication used on circadian distribution of ventricular ectopic beats

	P*	
Variable	variable	interaction
Sex	0.044	0.004
Age group	0.070	0.118
Smoking	0.291	0.453
Hypertension	0.783	0.990
Diabetes mellitus	0.576	0.041
Hypercholesterolemia	0.007	0.982
Previous myocardial infarction	0.119	0.693
Family history of heart disease	0.002	0.214
Chest pain in previous 7 days	0.176	0.815
Aspirin	0.953	0.616
Hypolipemic	0.166	0.888
Diuretic	0.393	0.010
Digitalis	0.559	0.576
β-blocker	0.002	0.002
Calcium channel blocker	0.690	<0.001
Nitrate	0.531	0.099
Angiotensin converting enzyme inhibitor	0.502	0.623
Anxiolytics	0.143	0.357
Amiodarone	0.273	0.312
Propafenone	0.258	0.751
Subgroup analyses:		
men × β-blocker	0.004	<0.001
women × β-blocker	0.099	0.160
men × diuretic	0.510	0.145
women × diuretic	0.561	0.054
men × calcium channel blocker	0.926	0.322
women × calcium channel blocker	0.741	<0.001
men × hypercholesterolemia	0.313	0.307
women × hypercholesterolemia	0.002	0.269
men × family history of heart disease	0.002	0.906
women × family history of heart disease	0.228	0.240

*P values were derived from general linear model analysis (repeated measures analysis of variance). P for variable represents the significance of difference between variable categories; P for interaction represents the significance of difference between the circadian trends (interaction; variable × time of day).

quency and interaction effects (Table 4). Daily frequency of ventricular ectopic beats significantly differed with respect to sex, presence of hypercholesterolemia, family history of heart disease, and β-blocker use. Different circadian trends (interaction) with respect to sex, β-blockers and calcium channel blockers use were also observed. Among men, both the reduction in the overall frequency of ventricular ectopic beats and abolition of the excess occurrence between 9 AM and 8 PM was seen in those using β-blockers (Fig. 5). Among women, there was a prominent morning peak in the frequency of ventricular ectopic beats between 9 and 11 AM in those taking calcium channel blockers (Fig. 5). In women with hypercholesterolemia, the daily frequencies of ventricular ectopic beats were greater than in women without hypercholesterolemia. These differences were not observed for men. Family history of heart disease was associated with a greater occurrence of ventricular ectopic beats throughout the day only in men (Table 4).

Multiple Adjustments

Tables 5 and 6 show the results of stepwise multiple regression analysis of chronic risk factors and current medications used in preliminary selection models for sex and age subgroups. A cut-off value of $P \leq 0.1$ determined the variables that, in addition to external triggering factors, were included into final models according to sex and age.

Sex. In final multivariate models, wind speed, lower relative humidity, high atmospheric temperature throughout the day, and increasing relative humidity were independent predictors of ventricular ectopic beats in both men and women (Table 7). The passage of a warm front reduced, whereas a passage of a cold front increased the

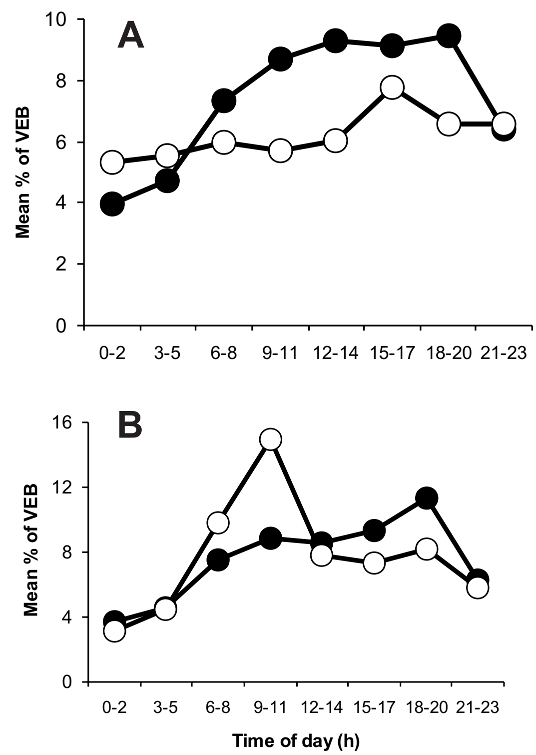

Figure 5. Mean percentage of ventricular ectopic beats (VEB) by 2-hour periods in participants according to use of β-blocker in men (top) and calcium channel blocker in women (bottom). Open circles show the occurrence of ventricular ectopic beats among those who took the medication and closed circles among those who did not. The P values were obtained from the general linear model analysis (repeated measures analysis of variance). While β-blockers reduced the overall occurrence of ventricular ectopic beats (P=0.004) and abolished the circadian variation (P<0.001), calcium channel blocker did not influence the circadian pattern (P=0.739) and predisposed to morning peak of ventricular ectopic beats (P<0.001) in respective participant subgroup.

Table 5. Preliminary selection multivariate analysis models of independent predictors of ventricular ectopic beats according to participants' sex*

Predictors					
Men	β	*P*	Women	β	*P*
Family history of heart disease	0.082	<0.001	Hypercholesterolemia	0.067	0.008
Previous myocardial infarction	0.066	0.008	Body mass index	-0.035	0.175
Current smoking	-0.037	0.134	Family history of heart disease	0.020	0.413
Chest pain in previous 7 days	0.032	0.194	Age	-0.019	0.475
Hypercholesterolemia	0.011	0.639	Diabetes mellitus	0.016	0.559
			Previous myocardial infarction	0.012	0.666
Current medication:			Current medication:		
β-blocker	-0.071	0.006	angiotensin converting enzyme inhibitor	0.063	0.019
amiodarone	0.049	0.045	β-blocker	-0.037	0.138
angiotensin converting enzyme inhibitor	-0.046	0.073	hypolipemic	0.037	0.146
aspirin	0.039	0.169	anxiolytic	-0.019	0.433
anxiolytic	-0.029	0.233	amiodarone	-0.019	0.437
calcium channel blocker	-0.024	0.349	propafenone	0.014	0.581
propafenone	0.019	0.431	diuretic	-0.013	0.636
digitalis	0.015	0.543			

*β and *P* values were obtained from the stepwise multiple regression analysis.

Table 6. Preliminary selection multivariate analysis models of independent predictors of ventricular ectopic beats according to participants' age*

Predictors					
Aged <65 years:	β	*P*	Aged >64 years:	β	*P*
Female sex	0.068	0.003	Family history of heart disease	0.054	0.041
Family history of heart disease	0.053	0.016	Previous myocardial infarction	0.039	0.173
Previous myocardial infarction	0.049	0.034	Hypercholesterolemia	0.036	0.169
Hypercholesterolemia	0.042	0.082	Chest pain in previous 7 days	0.033	0.227
Body mass index	-0.036	0.131	Current smoking	-0.026	0.331
Diabetes mellitus	0.020	0.396	Diabetes mellitus	-0.022	0.425
Current smoking	-0.016	0.472			
Current medication:			Current medication:		
nitrate	-0.060	0.013	β-blocker	-0.096	<0.001
angiotensin converting enzyme inhibitor	-0.056	0.024	propafenone	-0.078	0.005
calcium channel blocker	-0.053	0.028	angiotensin converting enzyme inhibitor	0.059	0.030
propafenone	0.048	0.046	calcium channel blocker	0.055	0.042
hypolipemic	0.044	0.064	anxiolytic	-0.056	0.052
aspirin	0.029	0.245	amiodarone	0.043	0.105
anxiolytic	-0.025	0.275	hypolipemic	0.027	0.314
β-blocker	-0.014	0.569	nitrate	0.026	0.315

*β and *P* values were obtained from the stepwise multiple regression analysis.

likelihood of ventricular ectopic beats in men. Emotional stress was a modest predictor of ectopic beats in men, but a strong one in women. Physical activity was an independent predictor of ventricular ectopic beats only in women. Among chronic risk factors, family history of heart disease and previous myocardial infarction were independent predictors of ventricular ectopic beats in men. In women, these predictors were hypercholesterolemia and taking of ACE inhibitors. Use of β-blockers negatively correlated with ventricular ectopic beats in men (Table 7). Variation in ectopic beats occurrence according to wind directions did not persist in either men or women after adjustment for external triggers and time of day (Table 2).

Age. Multivariable analysis confirmed that the occurrence of ventricular ectopic beats remained positively associated with wind speed, periods of lower and of rising relative humidity, and emotional stress in both age subgroups (Table 8). The passage of a warm front was associated with a significantly lower ectopic beats occurrence irrespective of participant's age. Of external triggers, higher atmospheric temperature, lower atmospheric pressure, cold front passage, and physical activity were independent predictors of ventricular ectopic beats in those younger than 65 years. In this age group, female sex, family history of heart disease, and previous myocardial infarction were independently associated with ventricular ectopic beats frequency, whereas ACE inhibitor or nitrate use showed an inverse relationship. Among participants older than 64 years, β-blockers showed a strong inverse relationship with ventricular ecto-

Table 7. Final multivariate analysis models of factors influencing the incidence of ventricular ectopic beats according to meteorologic variables by sex*

Men			Women		
Variables	β	*P*	Variables	β	*P*
Single meteorologic parameters:			Single meteorologic parameters:		
wind speed	0.219	<0.001	emotional upset	0.110	<0.001
relative humidity	-0.104	<0.001	relative humidity	-0.108	<0.001
family history of heart disease	0.084	<0.001	wind speed	0.081	<0.001
β-blocker	-0.072	0.002	atmospheric temperature	0.075	0.004
previous myocardial infarction	0.069	0.003	hypercholesterolemia	0.070	0.004
angiotensin converting enzyme inhibitor	-0.055	0.018	angiotensin converting enzyme inhibitor	0.058	0.022
atmospheric temperature	0.055	0.026	atmospheric pressure	-0.047	0.079
atmospheric pressure	-0.049	0.058	physical activity	0.035	0.141
emotional upset	0.043	0.060	rainfall	0.026	0.287
amiodarone	0.043	0.063			
physical activity	0.026	0.259			
Passage of atmospheric front:			Passage of atmospheric front:		
warm front	-0.118	<0.001	emotional upset	0.119	<0.001
family history of heart disease	0.095	<0.001	warm front	-0.112	<0.001
previous myocardial infarction	0.077	0.002	physical activity	0.064	0.023
cold front	0.075	0.003	angiotensin converting enzyme inhibitor	0.051	0.076
β-blocker	-0.068	0.006	hypercholesterolemia	0.046	0.115
emotional upset	0.063	0.011	cold front	0.025	0.310
amiodarone	0.043	0.081			
angiotensin converting enzyme inhibitor	-0.038	0.127			
physical activity	0.021	0.393			
Change in the level of meteorologic parameters:			Change in the level of meteorologic parameters:		
relative humidity	0.198	<0.001	relative humidity	0.160	<0.001
family history of heart disease	0.102	<0.001	emotional upset	0.116	<0.001
emotional upset	0.091	<0.001	hypercholesterolemia	0.058	0.020
previous myocardial infarction	0.082	<0.001	physical activity	0.057	0.020
angiotensin converting enzyme inhibitor	-0.058	0.016	angiotensin converting enzyme inhibitor	0.056	0.024
β-blocker	-0.057	0.017	atmospheric temperature	0.035	0.178
amiodarone	0.045	0.061			
atmospheric pressure	-0.029	0.242			
physical activity	0.021	0.386			

*β and *P* values were obtained from the stepwise multiple regression analysis. Independent variables included meteorologic parameters, physical activity, emotional stress, and factors that showed association of $p \leq 0.1$ in preliminary selection models (Tables 5 and 6).

pic beats in all analyses according to meteorologic variables, as well as propafenone in case of a change in meteorologic parameters. In the same age group, use of ACE inhibitor or calcium channel blockers exhibited a borderline positive association (Table 8). In both age subgroups, adjustment for other acute risk factors revealed that wind direction was not associated with occurrence of ventricular ectopic beats (Table 2).

Discussion

Previously, we have reported our findings on the ventricular tachycardia from the same population (1). This report contributes to the understanding of exogenous and endogenous factors associated with the occurrence of ventricular arrhythmias, revealing differences in influence on ventricular ectopic beats and ventricular tachycardia. The second important finding is the further corroboration of family history of heart disease as an independent predictor of ventricular arrhythmia in male individuals.

We found that wind speed may be involved in triggering ventricular arrhythmias. In contrast to our previous findings of a U-shaped association for ventricular tachycardia (1), the relationship between wind speed and ventricular ectopic beats in this study seemed to be linear. However, it is difficult to speculate on potential reasons and underlying pathophysiological mechanisms for that difference. Unfavorable consequences of a strong wind may be mediated or partly caused by biological effects of rapid atmospheric pressure perturbations created by wind-induced turbulence (11). The variation of occurrence of ventricular ectopic beats according to the four wind directions was abolished by other acute risk factors. This may suggest that south-southeast winds bring some additional risk, especially when coupled with more powerful external stressors, such as physical activity, emotional stress, and several meteorologic variables. However, compared with these stressors, the effect of south-southeast winds is not as strong or as independent. Nev-

Table 8. Final multivariate analysis models of factors influencing the incidence of ventricular ectopic beats according to meteorologic variables by age*

Variables					
Age <65 years	β	*P*	Age >64 years	β	*P*
Single meteorologic parameters:			Single meteorologic parameters:		
wind speed	0.159	<0.001	wind speed	0.214	<0.001
relative humidity	-0.141	<0.001	β-blocker	-0.109	<0.001
atmospheric temperature	0.083	<0.001	emotional upset	0.093	<0.001
atmospheric pressure	-0.069	0.005	relative humidity	-0.066	0.021
women	0.064	0.004	calcium channel blocker	0.052	0.040
emotional upset	0.061	0.004	angiotensin converting enzyme inhibitor	0.052	0.047
nitrate	-0.052	0.026	family history of heart disease	0.046	0.070
angiotensin converting enzyme inhibitor	-0.050	0.025	atmospheric temperature	0.022	0.411
previous myocardial infarction	0.049	0.039			
physical activity	0.047	0.029			
family history of heart disease	0.043	0.049			
hypercholesterolemia	0.047	0.072			
rainfall	0.038	0.085			
Passage of atmospheric front:			Passage of atmospheric front:		
warm front	-0.112	<0.001	warm front	-0.112	<0.001
emotional upset	0.081	<0.001	emotional upset	0.109	<0.001
cold front	0.080	<0.001	β-blocker	-0.092	0.003
angiotensin converting enzyme inhibitor	-0.076	0.005	calcium channel blocker	0.064	0.037
physical activity	0.063	0.015	family history of heart disease	0.046	0.141
family history of heart disease	0.057	0.015	cold front	0.028	0.296
previous myocardial infarction	0.055	0.031			
women	0.054	0.021			
hypercholesterolemia	0.049	0.071			
calcium channel blocker	-0.044	0.060			
Change in meteorologic parameters:			Change in meteorologic parameters:		
relative humidity	0.170	<0.001	relative humidity	0.195	<0.001
emotional upset	0.086	<0.001	emotional upset	0.131	<0.001
physical activity	0.073	0.001	β-blocker	-0.115	<0.001
nitrate	-0.068	0.006	propafenone	-0.089	<0.001
women	0.062	0.007	angiotensin converting enzyme inhibitor	0.055	0.040
previous myocardial infarction	0.058	0.018	anxiolytic	-0.053	0.055
angiotensin converting enzyme inhibitor	0.057	0.014	calcium channel blocker	0.046	0.080
family history of heart disease	0.048	0.034			
atmospheric pressure	-0.037	0.115			

*β and *P* values were obtained from the stepwise multiple regression analysis. Independent variables included meteorologic parameters, physical activity, emotional stress, and factors that showed association of $P \leq 0.1$ in preliminary selection models (Tables 5 and 6).

ertheless, as shown previously, south-southeasterly winds did have an independent triggering potential for ventricular tachycardia in women (1).

We observed an adverse effect of higher temperatures on ventricular ectopic beats. In animal studies, increased cardiac output and blood viscosity, arterial hypotension, dehydration, endothelial damage, and intracranial hypertension and ischemia were observed during the high temperature exposure (12). It seems that high temperature may drastically disturb overall cardiovascular and nervous system homeostasis, providing a link with arrhythmogenesis.

In our previous study, a stable relative humidity showed no influence, whereas increasing humidity was a predictor of ventricular tachycardia (1). In present study, the periods of lower humidity and periods of increasing humidity were associated with greater frequency of ventricular ectopic beats. This may indicate that periods of changing weather conditions represent a greater burden for compensatory response of the cardiovascular system than the stable meteorologic conditions. Recently, Shusterman et al (13) suggested that a change in the dynamics of heart rate variability itself rather than the direction of such a change facilitates arrhythmogenesis. Since our findings in terms of meteorologic factors influence were similar, it seems likely that any divergence from compensated homeostasis increases the risk of arrhythmia, while that risk correlates with the magnitude of change and is inversely related to the capacity of the cardiovascular system.

In the present study, younger participants were more susceptible to meteorologic factors. Such an increased number of ventricular ectopic beats may represent a benign compensatory response of normal adaptive processes, which are well tolerated by a healthy organism. In contrast, meteorologic environment had more impact on triggering ventricular tachycardia among the older participants (1). Their milder or more inert response to external stimuli may result from poorer cardiovascular ability and preexisting increased sympathetic activity. Another explanation may be that this is a natural protection against the steady-state changes and greater numbers of ventricular ectopic beats that may precipitate malignant arrhythmia in damaged myocardium under the already increased sympathetic tone. This may also be a reason why β-blockers exerted a protective effect in older participants, whereas ACE inhibitors, the use of which implies a functionally weaker heart, were associated with greater occurrence of ventricular ectopic beats.

Our results confirmed beneficial effect of warm fronts and adverse effect of cold fronts on occurrence of ventricular ectopic beats in susceptible subgroups. We did not find any relationship between ventricular ectopic beats and increased or decreasing atmospheric pressure, which were independent predictors of ventricular tachycardia in some population subgroups (1).

Particular pathophysiological mechanisms have different importance for triggering myocardial infarction in different population subgroups (2,14,15). The present study corroborates the view that men and women should be analyzed separately in cardiovascular or autonomic nervous system studies. The existence of pathophysiological diversity could be the reason for differences observed in the effects of physical activity and emotional stress on ventricular arrhythmia. On the other hand, although both of these triggers increase sympathetic activation (2,4,7), they may produce different cardiovascular responses. Studies using case-crossover methodology in patients with implantable cardioverter defibrillators provided evidence that emotional stress and physical activity could trigger ventricular arrhythmias (16,17). However, our participants were much younger and presumably healthier. The role of emotional stress in causing ventricular tachyarrhythmias has been most clearly defined (16-18), and our findings show it to be the case in all population subgroups.

The association of physical activity and ventricular tachycardia in men significantly depended on the meteorologic environment, from positive when considering stable levels of meteorologic variables, to negative when considering meteorologic changes (1). In the present study, we found a strong positive association between physical activity and ventricular ectopic beats in women younger than 65 years and lack of any such association in men and those over 64 years of age. This nonlinear relation between the number of ventricular ectopic beats and occurrence of tachycardia further supports the concept of the multifactorial nature of malignant arrhythmia. Therefore, the place of physical activity, apparently more than other acute risk factors, should be judged within a complex situational frame combined with an individual risk status.

Undoubtedly, the exogenous and endogenous triggering mechanisms of acute cardiovascular events are closely interrelated. This is particularly important in assessing the independence of circadian rhythm. Circadian pattern of ventricular tachycardia was abolished by external triggers in men and the older participants (1). The pattern of ventricular ectopic beats was not altered by external triggers in any subgroup, possibly reflecting the independent baseline rhythm of sympathetic activity and benign ectopy. On the other hand, more complex arrhythmias seem to be a result of superposition of triggering circumstances on pathomorphological substrates in susceptible individuals.

Although somewhat limited by the fact that we did not distinguish between types of heart diseases, our results emphasized the importance of familial background for propensity to ventricular arrhythmias in men. Recent understanding of the diversity in ion channels and gap junction proteins, the key components in cardiac electrophysiology, brought out a concept that genetic variations might modify arrhythmia susceptibility. The mutations that cause the phenotype susceptible to arrhythmia have been linked to congenital disorders such as long QT, Brugada, Andersen and sudden infant death syndrome, and cardiac conduction disease (19-22), with sex-dependent differences in propensity to arrhythmic syndromes (22,23) or arrhythmia triggering (24). The role of genetic component in modification of risk of acute myocardial infarction due to external factor, such as extremely low frequency magnetic fields, has also been described (25). We found the association between familial background and ventricular tachycardia among men and the elderly, and an association with ventricular ectopic beats among men and those under the age of 65 years. Arrhythmia propensity at younger ages may be expressed through benign forms like ectopic beats, but increasing age and associated comorbidities may precipitate more dangerous arrhythmia. Another hypothesis is that those with adverse genetic background had already died before the age of 65, so that less lethal genetic variations become important for genesis of ventricular arrhythmia in those over the age of 65. Most people who die of sudden arrhythmic death syndrome are male and young, and die during sleep or rest. Of sudden cardiac deaths in "healthy" people aged 16-64 years, 4.1% were unexplained, and heritable cardiac disease was diagnosed in 22% of families of their first-degree relatives (26,27). It seems that gene polymorphism and complex interaction of several genes determine individual risk status and arrhythmia susceptibility, but this data are not yet conclusive. Although both our previous and the present report suggest the importance of familial background in men, the more detailed research of this field is needed.

Similar to ventricular tachycardia, the protective effect of β-blockers against ventricular ectopic beats was seen in men and the older participants. Calcium channel blockers did not influence the circadian pattern of ventricular tachycardia (1), but they predispose to morning excess in frequency of ventricular ectopic beats. This may be due to the lack of suppression of sympathetic arousal in the morning, which could be reactive to or even more pronounced because of coupling of nighttime parasympathetic predomination and calcium channel blocker-related decrease in heart rate and blood pressure.

In contrast to our finding regarding ventricular tachycardia (1), the anxiolytic drugs had no effect on the occurrence of ventricular ectopic beats. Perhaps more complex processes including both central and peripheral nervous systems provide a better balance of autonomic control and suppression of arrhythmogenic heterogeneous sympathetic activity.

The limitation of the present investigation is the lack of methodology for studying such phenomena. Since meteorologic parameters, emotional stress, and physical activity varied both between patients and 8 successive measurements in each patients, we analyzed the influence of these variables through framework of multiple regression analysis, enabling the parallel control for chronic risk factors. In comparison to our study, the case-crossover studies (16,17) have greater strength in proving the causal relationship between triggering factors and event. However, case-crossover studies lack a control for environmental factors that have been correlated with arrhythmia occurrence in our and other studies such as the level of air pollution (28) and meteorologic factors (1). The methodology used in the present study simultaneously compared and weighted the impact of emotional and physical stress on arrhythmic episodes. Obviously, these approaches are complementary as both found a clear association between ventricular arrhythmias and physical activity and emotional stress, implying that such conditions should be considered triggers of arrhythmic events.

Misclassification bias may result from difficulty in precise definition of timing of atmospheric front passage. We did not control for the levels of air pollutants, which could be associated with ventricular arrhythmias (28) and for micturition, defecation, coffee and alcohol consumption, which have also been related to the sudden cardiac events (29-31). Furthermore, we did not account for the time spent indoors and outdoors, but significant difference in influence of environmental factors is not likely (11,32,33).

Our definition of family history of heart disease was not confined only to arrhythmic disorders, but also included a wider scale of cardiac conditions. Also, iInfluences of specific cardiac disorders in our participants could not be investigated because most of them were undergoing diagnostic procedure aiming to determine existence of such disorders. Calcium channel blockers, as heterogeneous groups of drugs, may have a different influence on ventricular ectopic beats, but we were not able to research this issue further due to lack of data on the drug subgroup.

We did not have data about magnesium or potassium serum levels, whose lower levels may precipitate the occurrence of ventricular ectopic beats. Sleeping regimen and other psychotropic medication might also influence the ventricular ectopic activity, as was observed for anxiolytic medications. Especially interesting are observations of a borderline significance of adverse effect of amiodarone in men and a protective effect of propafenone only when considering the impact of meteorologic changes among older participants. It is likely that in both cases, however, these results cannot be conclusive because of a small number of patients who used these drugs (amiodarone 2%, propafenone 6%) and inappropriate subgroups for meaningful comparisons.

Future investigations should include a detection of people with an inherited propensity to arrhythmic events or with a greater propensity to external triggering of such events, detection of yet unidentified external triggers of cardiac arrhythmia, and assessment of therapies and methods targeted at blocking the adverse effects of response to such triggers. Mechanisms and circumstances involved in triggering of arrhythmias as well as individual response or susceptibility remain to be further elucidated. An important breakthrough would be achieved by gaining insight into the potential scope of heritable cardiac disorders and developing of screening, assessment and care standards for the people at risk.

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