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Autonomic influences related to frequent ventricular premature beats in patients without structural heart disease

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Abstract
To study the possible role of autonomic influences on the occurrence of frequent premature ventricular beats (VPBs) in subjects without structural heart disease.

24-hour Holter ECG recordings ($\geq$1500 VPBs/d, sinus rhythm) of 20 symptomatic patients (9 women, 11 men, mean age 58.9 years) without structural heart disease were used for the study. The circadian distribution pattern of VPBs was studied (paired t test) by dividing the day into 3 periods (16:00–22:00–06:00–16:00), and correlations were analyzed between the absolute (ln transformed) and relative (% of total beats) average hourly numbers of VPBs and the hourly mean values of global and vagal time domain parameters of heart rate variability (Pearson correlation).

No significant ($P > .3$ for every comparison) tendency for circadian distribution of VPBs was found. However, VPBs showed a significant correlation with rMSSD ($r = 0.51$ and $P = .02$ for the relative number), which became even stronger if VPBs were > 8000/d ($r = 0.65$ and $P = .04$ for both numbers).

The significant correlation between the number of VPBs and a vagally mediated parameter underlines the triggering/permitting effect of parasympathetic tone on ventricular ectopy. This fact suggests that initiation of beta-blocker therapy could not be recommended routinely in these patients.

Abbreviations: HRV = heart rate variability, VPBs = ventricular premature beats.

Keywords: autonomic nervous system, heart rate variability, premature ventricular beats

1. Introduction

Ventricular premature beats (VPBs) are relatively common in healthy individuals without structural heart disease, representing an entirely benign phenomenon in the vast majority of cases. However, they could be symptomatic (palpitations, feeling of "missed" heart beats), or, very rarely, could trigger episodes of ventricular tachycardia accompanied by dyspnea, chest discomfort, hypotension, and/or syncope.[1]

VPBs can be easily diagnosed and quantified using 24-hour Holter ECG monitoring. The number of VPBs increases with age, and are more common in asymptomatic males. Repetitive and polymorphic forms may also occur in healthy individuals.[2,3]

Autonomic influences are frequently involved in arrhythmogenesis. Autonomic imbalance, both increased vagal tone or hypersympathicotonia, could trigger arrhythmias. Exploration of cardiac autonomic tone and its dynamics is an important part of arrhythmia evaluation. The most frequently used method in this regard, based on Holter ECG recordings, is heart rate variability (HRV) analysis, because spectral, time domain and nonlinear parameters of HRV reflect mainly the autonomic modulation of the heart.[4,5]

A specific subset of healthy individuals presents with very frequent VPBs (>1500/d). These cases are often challenging and always need an individualized approach to follow-up and treatment. The aim of our study was to evaluate if autonomic influences could be identified in these patients, with potential consequences on their management.

2. Methods

To evaluate the possible association between autonomic influences and frequent VPBs in individuals without structural heart disease, we used the cross-sectional type study design.

Twenty recordings were used for the study from the ECG Holter database of the Cardiology Department of the Clinical County Hospital Mures, Targu Mures, Romania. The recordings were selected based on the following criteria: good quality (<5% artifacts), permanent sinus rhythm, and the presence of frequent

Time domain parameters of HRV.

P parameter	Definition	Significance
SDNN (ms)	Standard deviation of NN (normal-to-normal = free from VPBs and artifacts) intervals	A measure of global HRV (both sympathetic and vagal influences)
rMSSD (ms)	The root mean square of the successive differences (of NN intervals)	A measure of vagally mediated beat-to-beat variability
pNN50 (%)	The proportion of consecutive NN intervals that differ by more than 50 ms	A measure of vagally mediated beat-to-beat variability

HRV = heart rate variability, VPBs = ventricular premature beats.

VPBs (at least 1500/d). The patients (11 men, 9 women, mean age 58.9 years) were free of structural heart disease (normal clinical findings, echocardiography and resting ECG), and underwent a routine 24-hour Holter monitoring for palpitations. The study was conducted respecting the International Ethical Guidelines and the Declaration of Helsinki.

All the recordings were performed using the Cardiospy EC-3H Holter system (Labtech Ltd, Debrecen, Hungary). Before analysis, the Holter tracings were manually edited for template verification and for cleaning from artifacts. Then, parameters were calculated by the proprietary computing algorithms of the Holter system software.

To investigate the autonomic influences on the occurrence of VPBs we used 2 methods: the study of circadian distribution and analyzing the correlation with time domain (statistical) parameters of HRV (Table 1.). In our study we used time domain measures of HRV, because in the case of frequent VPBs they are more robust and less sensible to the effect of RR interval eliminations (compulsory for correct HRV analysis) than spectral parameters. At the same time, there exist data supporting strong correlations between spectral and time domain parameters of HRV, especially in the case of the vagally mediated measures.[4]

Circadian profile of the occurrence of VPBs was studied by dividing the day into 3 periods (16:00 to 22:00, 22:00 to 06:00, and 06:00 to 16:00), based on the usual daily activity of an active person. Comparison of the absolute and relative (% of total beats) numbers calculated for these periods was performed using paired t-test.

Correlations between the average hourly numbers (absolute – ln transformed, and relative) of VPBs and the corresponding (measured for the same hour of the day) statistical HRV parameters were studied using Pearson correlation.

For both tests a P value of $< .05$ was considered for statistically significant difference.

In order to strengthen the power of analysis of connections between the absolute and relative numbers of VPBs and HRV parameters, the subgroup of patients with ≥8000 VPBs/d was separately analyzed.

3. Results

Hourly average–absolute and relative–numbers of VPBs are presented in Figs. 1 and 2. Analyzing the circadian profile of the
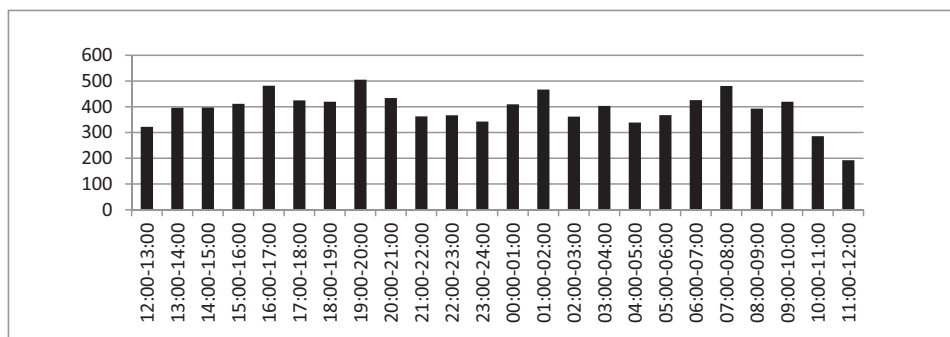

Figure 1. Hourly average absolute numbers of VPBs. VPBs = ventricular premature beats.
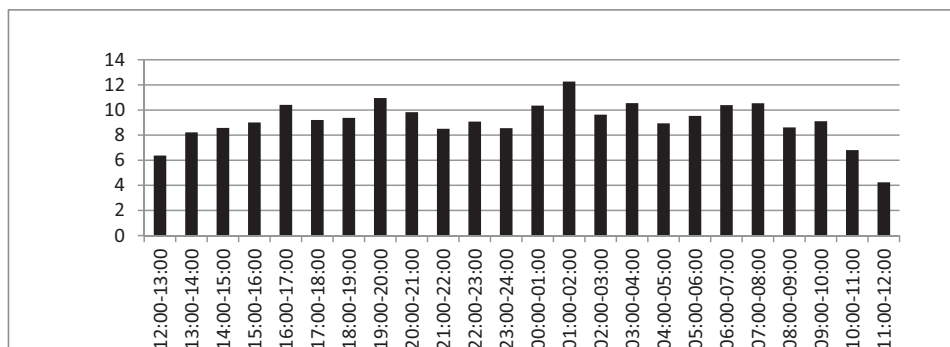

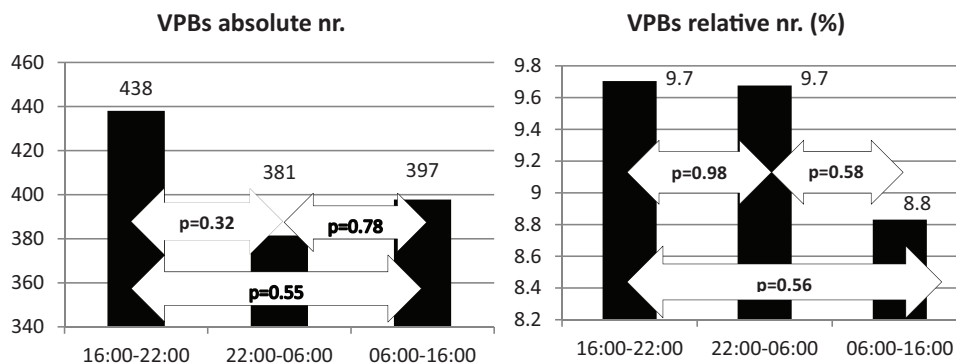**Figure 2.** Hourly average relative numbers of VPBs.

Figure 3. Comparison of the 3 periods of the day for absolute and relative VPBs numbers.

occurrence of VPBs we did not find statistically significant differences between the 3 periods of the day (for every comparison $P > .3$ for absolute numbers, and $P > .5$ for relative numbers, Fig. 3).

Regarding the correlations between the absolute and relative mean hourly numbers of VPBs and parameters of HRV, we found a positive, moderate and a positive, weak correlation between the absolute hourly numbers (ln transformed) and rMSSD (r = 0.34, $P = .13$), and pNN50 (r = 0.24, $P = 0.3$) (Fig. 4). However, in the case of relative hourly numbers, a positive, strong (rMSSD, r = 0.51, $P = .02$) and a positive, moderate (pNN50, r = 0.39, $P = .08$) correlation (Fig. 5) was found. The correlations of absolute and

relative hourly numbers with SDNN proved to be not significant (r < 0.2 and $P > .3$ for both numbers).

In the subgroup of 10 patients with >8000 VPBs/d, we found a positive, strong correlation between the HRV parameters reflecting parasympathetic activity and the absolute and relative mean hourly numbers of VPBs. For rMSSD we found r = 0.65 and $P = .03$ for both the absolute and relative numbers, while in the case of pNN50 we found r = 0.6 and $P = .06$ for the absolute (Fig. 6) and r = 0.6 and $P = .063$ for the relative numbers of VPBs (Fig. 7). Also, we found a negative, moderate correlation between heart rate and relative hourly numbers of VPBs (r = 0.38, $P = .27$) in these patients.

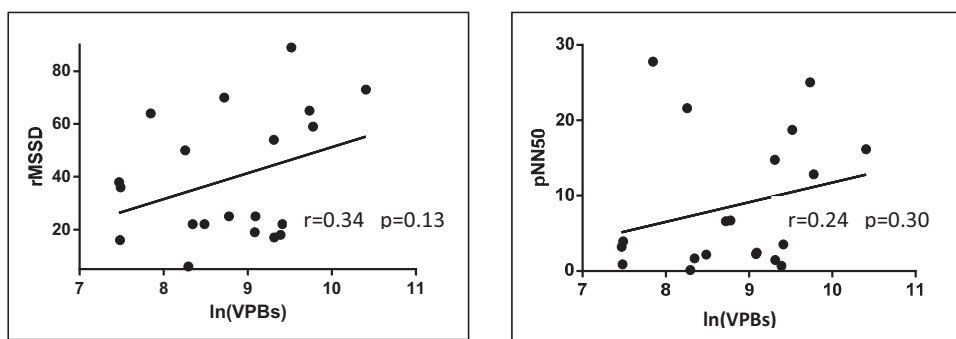**Figure 4.** Correlations between absolute numbers of VPBs (ln transformed) and the parasympathetic HRV parameters rMSSD and pNN50.
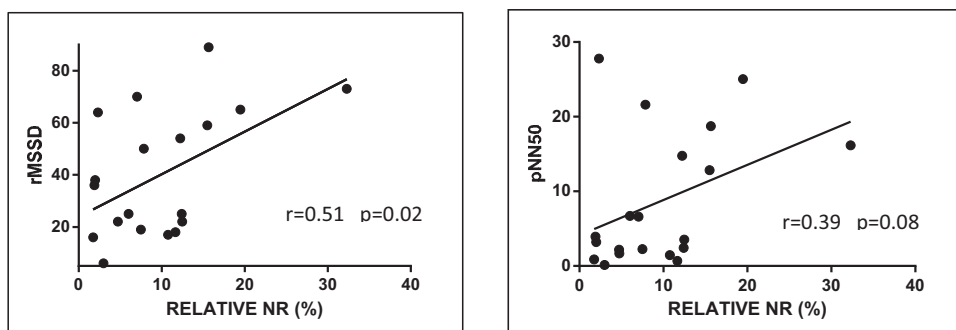

Figure 5. Correlations between relative numbers of VPBs and the parasympathetic HRV parameters rMSSD and pNN50.
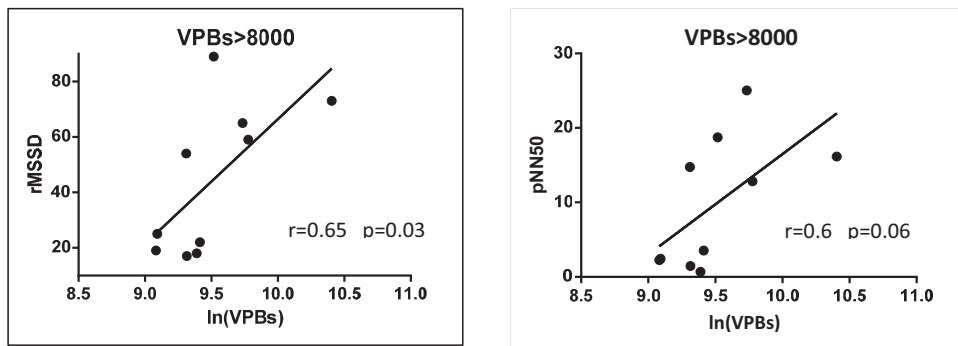
Figure 6. Correlations between absolute numbers of VPBs (ln transformed) and the parasympathetic HRV parameters rMSSD and pNN50 in patients with >8000 VPBs/d.

4. Discussion

VPBs in healthy individuals, without structural heart disease, are relatively frequent. One study, which analyzed 1273 drug-free ambulatory ECG recordings from healthy normal volunteers, has shown that in healthy individuals ventricular arrhythmias occur frequently: VPBs in 43.4%, >200 VPBs/d in 3.3%, multifocal VPBs in 5.3%, nonsustained ventricular tachycardia in 0.7%, and accelerated idioventricular rhythm in 0.3% of cases.[6]

Trigger factors of VPBs in healthy persons are multiple—accidental events (postprandial state, alcohol, caffeine containing beverages, energy drinks, exercise, stress, anxiety), dyselectrolytemia, drugs, thyroid dysfunction, sleep apnea, etc. Autonomic imbalance is a common pathophysiological pathway of many of these triggers. Both sympathetic overactivity and enhanced vagal control could contribute to ventricular arrhythmogenesis by complex electrophysiological mechanisms.[7]

In our patients, the lack of a specific circadian distribution pattern of VPBs does not support the role of autonomic influences in ventricular arrhythmogenesis. This result, however, does not correlate with most studies, which underline the fact that significant and reproducible temporal patterning of VPBs is common in ischemic heart disease, being up to 50% greater in number during diurnal activity than nocturnal sleep. Moreover, it is also reported that the highest prevalence of complex or frequent ventricular arrhythmias, as well as a higher mean number of VPBs/h, are observed between 06:00 AM and noon. It is also reported that the frequency of VPBs, primarily based on studies conducted on patients affected by ischemic heart disease,

appears to be decreased during nighttime sleep by as much as 50%, with the minimum number recorded between midnight and 02:00 AM However, there are studies that did not report this nocturnal decrease of VPBs.[8–10]

On the other hand, the positive correlations (which were stronger in the case of patients with >8000 VPBs/d) with parasympathetic parameters of HRV underscore the possible role of increased vagal control in enhancing ventricular ectopic activity. This finding is not in line with previous data reporting that the frequency of VPBs is positively associated with the increase in sympathetic and decrease in parasympathetic activity. Other studies underline the fact that, generally, sympathetic nerve activation could trigger or aggravate ventricular arrhythmias. Moreover, it is reported that vagal activity is augmented in response to sympathetic hyperactivity and has a protective effect against ventricular arrhythmias.[11,12]

However, it is also reported that increased vagal activity is associated with the genesis of idiopathic ventricular fibrillation, and vagal activation could facilitate the occurrence of idiopathic ventricular tachycardias in some patients. Furthermore, sympathetic blockers are effective only in part of idiopathic VPBs patients, raising questions about what exact role autonomic control might play on idiopathic ventricular arrhythmias.[7]

We consider that the ectopy permitting effect of relative bradicardia and the direct electrophysiological effects of vagal modulation on the activity of ventricular foci could be the explanations for our findings.
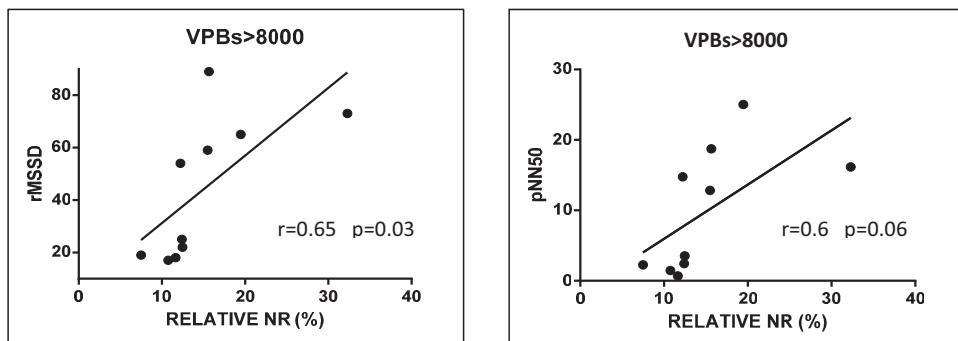

Figure 7. Correlations between relative numbers of VPBs and the parasympathetic HRV parameters rMSSD and pNN50 in patients with >8000 VPBs/d.

Treatment of frequent VPBs in healthy subjects includes the identification and management of trigger factors, and, in selected cases, pharmacological and interventional treatment. The latter are applied mainly in highly symptomatic cases and/or in the presence of progressive left ventricular dysfunction. The most utilized drugs in this regard are the beta-blockers, which are initiated empirically in the majority of cases.[1,7] However, our data do not support this routine approach. Beta-blocker treatment in the management of frequent VPBs has to be recommended when trigger factors involving sympathetic overactivity are present (e.g., stress, anxiety, exercise), or on Holter recordings there are overt signs of relationship between VPBs and hypersympathicotony—a clear diurnal pattern of occurrence, background sinus tachycardia and/or low HRV.

Our results, although having a reasonable pathophysiological explanation, have to be interpreted with caution because of the sample size, and further studies, using higher number of recordings, are required to confirm them.

5. Conclusions

Our data suggest that in patients with frequent VPBs and absence of structural heart disease enhanced vagal control is involved and could play a role in the increase of ventricular ectopic activity. On this basis, we recommend against routine use of beta-blocker therapy in these patients.

Generally, the effects of autonomic modulation on ventricular arrhythmias remain controversial, and both sympathetic and parasympathetic over-regulation might be involved in the appearance of frequent VPBs.

Author contributions

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