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Exploring the Link between Interoception and Symptom Severity in Premature Ventricular Contractions

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Abstract: Background/Objectives: The physiological basis underlying symptomatic versus asymptomatic premature ventricular contractions (PVC) remains poorly understood. However, symptomatic PVC can significantly impair quality of life. In patients without structural heart disease, symptom intensity is crucial for guiding management strategies and determining the need for medical or surgical intervention. In this study, we aimed for the first time to examine the associations between PVC symptoms and cardiac interoception. **Methods**: The study included 34 participants with PVC (20 women; median age = 42 years; 17 participants had asymptomatic PVC) without concomitant disorders. Interoception was assessed through interoceptive accuracy (IA) probed by two behavioral tests—mental tracking (MT) and heartbeat detection (HBD)—and the neurophysiological marker of cardiac interoception, the heartbeat-evoked potentials (HEPs). Symptom intensity scores reported by patients served as the response variable in the regression analysis, with IA and HEP as predictors. Other factors such as sex, age, percent of body fat, trait anxiety, and alexithymia were added to the models as confounding variables. **Results**: IA_{MT} was significantly higher in patients with symptomatic PVC. IA_{MT} and HEP modulation for the HBD task were associated with symptom intensity. A combined regression model incorporating both metrics showed the highest predictive accuracy for symptom severity. Adding confounding variables improved model quality (lower AIC); however, only the male sex emerged as a significant negative predictor for symptom intensity. **Conclusions**: Our findings confirm a significant association between interoception and PVC symptom severity. Integrating behavioral and neurophysiological interoception measures enhances symptom prediction accuracy, suggesting new ways to develop diagnostic and non-invasive treatment strategies targeting interoception in PVC management.

Keywords: premature ventricular contractions; symptoms; cardiac interoception; interoceptive accuracy; mental tracking task; heartbeat detection task; heartbeat-evoked potentials; electroencephalography

1. Introduction

Interoception refers to the processes of perception, integration, and regulation of internal bodily signals [1]. A common approach to testing an interoceptive process is to assess cardiac interoception (or cardioception). Cardiac interoceptive accuracy (IA) can be probed in behavioral tests, which are various modifications of heartbeat counting/detection tasks. However, these tests have certain

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limitations [2], therefore a neurophysiological measure of interoceptive processing, heartbeat-evoked potentials (HEP), is of particular interest [3]. Interoception is gaining increasing attention in various fields of research, as its dysfunction may be involved in the expression of various disorders [4]. In addition, the role of interoception in symptom experience has recently been discussed. Studies summarized in the systematic review by Locatelli et al. [5] showed conflicting results regarding the relationship between IA and symptom severity. However, data on interoception and cardiac symptom severity are limited. In a recent study by Lee et al. [6], findings indicated that interoceptive awareness, measured using the Multidimensional Assessment of Interoceptive Awareness questionnaire, was linked to improved self-care management of symptoms in patients with cardiovascular diseases. Conversely, tendencies to ignore or distract oneself from discomfort were associated with poorer self-care practices. The authors suggest that interoception could serve as a valuable target for interventions aimed at improving self-care management behaviors in patients with cardiovascular disease. However, IA is only partially related to interoceptive awareness [7]. Further investigations are required to establish the associations between IA and cardiological symptoms.

One of the most common cardiac symptoms is palpitations, and its possible relationship with cardioception has recently been discussed [8]. Premature ventricular contractions (PVCs) are a common cause of palpitations, while in asymptomatic individuals, they could also be detected as an accidental finding. On the one hand, arrhythmias may be asymptomatic [9,10]. On the other hand, the feeling of palpitations may not be caused by actual heart rhythm disturbances with a psychiatric or somatoform disorder being an underlying cause [11–13]. In case of the absence of cardiopulmonary etiology, PVCs are often benign. However, they can cause symptoms that significantly impair the quality of life [Klewer 2022]. Thus, for benign PVCs the clinical decision about treatment strategy depends on the severity of the symptoms. In asymptomatic individuals, no treatment may be required. Nevertheless, for patients who experience palpitations that drastically affect their quality of life, antiarrhythmic drugs or even surgical treatment (ablation) may be used [14]. These treatments, though, only aim to improve quality of life but do not affect the risk of future cardiovascular events and may have side effects. Currently, only a few studies evaluated cardiac interoception in palpitation patients and demonstrated higher IA in behavioral tests in comparison with healthy control subjects [15,16]. We suggest that understanding the mechanisms underlying the experience of symptoms in patients with benign PVCs would pave the way for the development of new therapeutic approaches.

In our study, we proposed that the intensity of symptoms of PVC may be associated with interoception. To test this hypothesis, we have explored interoception in patients with symptomatic and asymptomatic PVCs using two approaches (1) behavioral: we evaluated IA in two commonly used behavioral tasks: mental tracking (MT) [17] and heartbeat detection (HBD) [18]; (2) neurophysiological: we studied the neural marker of cardiac interoceptive processing [19] – the HEP amplitude and its modulation (ΔHEP). Studies have demonstrated that disturbances in interoceptive signaling are linked to the regulation of emotions and stress [20], contributing to the development of various mental health conditions, including anxiety, depression, and somatic symptom disorders [21]. Moreover, interoceptive training has been shown to improve IA, reduce anxiety, and alleviate somatic symptoms. These effects are associated with enhanced neural activity in the anterior insular cortex [22]. The insula cortex is involved in interoceptive [23] and emotional processing [24] and is also a key component of central autonomous system network [25,26]. At the same time, stress and imbalance in autonomic regulation are among predisposing factors for PVC [27]. Considering the research mentioned above, to explore the potential contributions of anxiety and alexithymic traits to symptom severity in patients with PVCs, we administered the State Trait Anxiety Inventory–Trait Inventory [28] and the Toronto Alexithymia Scale [29] questionnaires.

2. Materials and Methods

2.1. Participants.

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We calculated the sample size required to detect a within-group difference between conditions (power of 0.8, significance level of 0.05) using G*Power. An effect size of d = 0.74 was used based on the difference in HEP amplitudes between resting state and perceptual task performance in high symptom reporters as described in the literature [30]. A paired permutation t-test (from the family of t-tests accounting for mean difference) indicated that N = 17 per group is required. A priori analyses of the required sample size for between-group comparisons were not possible due to the novelty of the design for such clinical groups, and articles with similar designs either lack an effect [30] or the required measures of the effect size [15]. Thus, we included 34 participants (20 females; Me [Q1; Q3] = 42 [38.25; 44.75] years old; body mass index (BMI) Me [Q1; Q3] = 24.4 [21.95; 26.65]; 17 participants had asymptomatic PVCs) who were either seeking medical care or undergoing a routine health check-up . All participants provided written informed consent, approved by the local Ethics Committee at the National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russian Federation. The study adhered to the principles outlined in the Declaration of Helsinki.

The inclusion criteria were the following: 20-50 years old, with 720-20,000 PVCs during 24-h Holter monitoring. We included only young and middle-aged patients to reduce the risk of comorbidities and cognitive impairment. Patients scoring >11 on the Hospital Anxiety and Depression Scale (HADS, [31]) were excluded, as depression may affect interoception [32–34]. Additionally, participants with >20,000 PVCs during 24-hour Holter monitoring were excluded to preclude the possibility of undiagnosed structural heart pathology. Structural heart pathology in the included participants was ruled out based on their previous medical examinations, including echocardiography, stress testing, and in some cases, cardiac magnetic resonance imaging.

To eliminate potential confounding factors in interoception measurements, stringent exclusion criteria were applied. The exclusion criteria were as follows: uncontrolled arterial hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) based on office, home, or ambulatory monitoring; other arrhythmias observed using ECG or Holter monitoring; organic cardiac pathologies (e.g., heart hypertrophy, prior myocardial infarction, cardiomyopathies of various etiologies, unknown scarring, congenital heart defects); obstructive sleep apnea syndrome; significant atherosclerosis (arterial stenosis ≥50%); neurological or psychiatric disorders; thyroid dysfunction; systemic or autoimmune diseases; significant liver, kidney, or lung pathologies; epilepsy; head trauma in the past year; use of drugs crossing the blood-brain barrier; complications from viral/infectious diseases; endocrine disorders (e.g., diabetes, obesity [>30 kg/m^2]); and pregnancy.

2.2. Data acquisition.

2.2.1. Symptom score

Patients were divided into symptomatic and asymptomatic groups based on the results of a cardiologist consultation and confirmed by Holter ECG monitoring results prior to EEG administration, supplemented by patient diaries documenting their sensations during the monitoring period. Patients in whom PVCs were an incidental finding and not associated with any complaints, were assigned to the asymptomatic group. In case complaints in the diary (such as irregular heartbeat, stopping, jumping, feeling of extra or skipped heartbeats, pounding or vigorous heartbeats) corresponded to PVCs on the ECG, patients were assigned to the symptomatic group. Participants in this group were then asked to rate the intensity of their PVC complaints on a scale of 1 to 10. Patients in the asymptomatic group were assigned a symptom score 0. Patients in the symptomatic group were assigned a symptom score of 1, 2, 3 for the first, second and third tertiles of the reported symptom severity, respectively.

2.2.2. Questionnaires

We used The Toronto Alexithymia Scale (TAS-20) [29] (Russian language adaptation [35] for alexithymia assessment to evaluate difficulties in recognising and expressing emotional experiences and bodily sensations. The scale consists of 20 questions rated from 1 to 5 points, with higher scores

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indicating higher levels of various aspects of alexithymia. The total alexithymia index was calculated as the sum of three subscales: difficulties identifying feelings, difficulties describing feelings, and externally oriented thinking. To assess anxiety, we used the State Trait Anxiety Inventory–Trait Inventory (STAI-T) [[28]](Russian language adaptation by Hanin [36]). We used the trait anxiety subscale, containing 20 statements rated from 1 to 4 points.

2.2.3. Electrophysiological data

Electrophysiological data were collected using the NVX-52 EEG amplifier (Medical Computer Systems, Ltd. [MCS]) with 36 Ag/AgCl electrodes positioned on elastic EEG caps following the international 10-20 system. Channels T3 and T4 served as ipsilateral online references, following the company recommendations. During the recordings, the impedance across all channels was maintained at around 10 kΩ and never exceeded 20 kΩ. Surface electromyography (EMG) was recorded from the first dorsal interosseous muscle using a belly-tendon montage. ECG data were obtained using three pairs of electrodes in a bipolar configuration: one pair was placed on the anterior forearm, another on the chest 2 cm below the clavicles in the infraclavicular fossae [37]. Additionally, two EOG electrodes were placed on the lateral sides of the eyes. Data were sampled at a frequency of 500 Hz and filtered between 0.1 and 70 Hz with a 50 Hz notch filter.

2.2.4. Other variables

Body fat percentage, a more precise indicator of body composition than BMI, was assessed using bioimpedance analysis (Medass, Russia). For the maximum PVC count during 24-hour Holter monitoring, we report the results from the Holter monitoring session that recorded the highest PVC count from the six months before the experiment.

2.3. Experimental procedures

The participants were sitting quietly, with their eyes open. At the onset, five minutes of resting EEG data were recorded, during which participants were instructed to focus on the fixation cross in the middle of the screen in front of them and to avoid moving and excessive blinking. Before each of the behavioral tests, presented in random order, participants had a training session and were instructed to focus on their internal sensations.

The MT task involved counting the heartbeats during six randomly presented time intervals (25, 30, 35, 40, 45, and 50 s) [7]. The participants had to count the number of perceived heartbeats without palpating the pulse anywhere on the body or trying to guess it.

The HBD task [38] required participants to detect the sensation of their heartbeat and indicate it by pressing a button. The test consisted of two conditions: (1) an interoceptive condition where participants had to press the "space" button when they felt a heartbeat, and (2) an exteroceptive condition where participants were required to press the button every time they heard a 1 Hz sound signal with 500 ms duration. Both conditions consisted of a 2.5-minute trial and a 10-second training trial before it. Participants were instructed to report/press only perceived heartbeats, which helps to reduce the influence of estimation and better capture interoceptive ability [39–41], in contrast to earlier studies, where participants were asked to rely on their intuition in case they did not feel heartbeats [42,43].

2.4. Data preprocessing

2.4.1. Behavioral interoceptive accuracy (IA)

IA in the HBD task (IA_{HBD}) was a metric of the mean difference (mean distance, md) between the pressing frequency and heartbeat frequency in the overlapping time windows [44,45] (Equation 1). As it was demonstrated previously [46, personal unpublished data], personal unpublished data] this metric for HBD task was more reliable than the other metrics (modified Schandry index, sensitivity d). Participants who did not make any presses were assigned IA_{HBD} of 0. ECG recording was divided

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into overlapping windows of 10-s duration beginning with the R-peak. The press-to-press intervals (PP intervals) and R-peak intervals (RR intervals) were evaluated in each window. The variation was calculated as the ratio of the standard deviation of PP intervals to their mean in the window. The window was included in the analysis if the variation of PP intervals was <0.5. The formula is:

$$md = 1-1/N\sum |1/PP-1/RR| \quad (1)$$

IA in the MT task (IAMT) was assessed using a modified Schandry index (SI) formula proposed by Garfinkel et al. [7] (Equation 2). SI corrects the IA_{MT} if the number of heartbeats counted by the participant (HBreport) is significantly higher than the actual number of heartbeats recorded by the ECG (HBrecord).

$$IA_{MT} = 1/6\sum(1-(|HBrecord - HBreport|)/((HBrecord + HBreport)/2)) \quad (2)$$

IA_{MT} and IA_{HBD} equal to 1 indicate high interoception.

2.4.2. ECG, EMG processing

The first processing step was to calculate the difference in activity between the left and right electrodes for each pair of ECG electrodes. The ECG data were then filtered between 0.5-45 Hz. The ECG signal from the pair of electrodes below the clavicles was used to calculate R-peaks, as they were the least affected by motor activity. R-peaks and PVCs were determined semi-automatically using the MNE-Python package [47], followed by visual inspection by a cardiologist. Both sinus rhythm peaks and PVC were included in the IA calculation.

EMG data were used to assess the precise timing of the button press. Teager Kaiser Energy operator was applied to EMG to detect movement onset.

2.4.3. EEG processing

EEG was processed using the MNE-Python package [47]. EEG was notch-filtered at 50 Hz, and then bandpass filtered from 0.5 to 45 Hz using a zero-phase FIR filter with a Hamming window. EEG data were cleaned from the eye movement and cardiac field artifacts (CFA). The independent component analysis (fastica algorithm) was used on the top of PCA components explaining 99% of the variance. We selected no more than three eye movement-related components and no more than two CFA components. EEG data were then filtered between 0.5-20 Hz. Channels affected by motor and technical artifacts were removed and then interpolated.

2.4.4. Heartbeat-evoked potentials (HEPs)

EEG data were segmented into epochs 200 ms before and 600 ms after the R-peaks in the ECG, and the average amplitude over the interval from 200 to 100 ms before the R-peak was subtracted for baseline correction. HEP amplitudes for each channel were obtained from epoch-wise averaging. We excluded epochs time-locked to PVC (two epochs before and one after), and epochs with R-peak intervals shorter than 600 ms. The AutoReject algorithm was applied to remove or interpolate noisy epochs. After automatic artifact removal, additional visual inspection of the epochs was performed. Recordings with more than 20% of epochs removed were excluded from the analysis. Thus, out of 37 subjects, 2 were excluded from the analysis (more than 20% were removed due to frequent (838 and 820 PVCs) PVCs during recordings), and data from 1 subject were missing due to technical problems during the recording. Channels were combined into spatial ROIs as previously described [43,48]: left frontal - LF (LF: Fp1, F3, FC3, C3, F7, FT7), central frontal -CF (Fpz, Fz, FCz, Cz), right frontal - RF (Fp2, F4, FC4, C4, F8, FT8), left temporal - LT (TP7, CP3, P3, T5, P5, PO7), central occipital - CO (CPz, Pz, POz, Oz, PO3, O1, PO4, O2), and right temporal - RT (TP8, CP4, P4, T6, P6, PO8). HEP amplitudes among ROIs were obtained from the within-ROI epoch-wise averaging of the HEP amplitude in the range of 200-600 ms after the R peak.

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2.5. Statistical analyses

2.5.1. Between-group analysis of behavioral data

The analysis was performed using the open-source R 4.3.1 environment. $P < .05$ was considered statistically significant. Data were tested for normal distribution using the Shapiro-Wilk criterion before analysis. The Wilcoxon rank sum test for independent samples with Bonferroni correction was used to compare IA between groups. Two-sided Spearman's rank correlation coefficient was used to investigate the relationships between IA within groups.

2.5.2. HEP statistical analyses

HEP amplitudes were compared using a nonparametric spatiotemporal permutation test based on the Monte Carlo method. The test was performed using Python 3.11 and the MNE-Python [47]. First, HEP amplitudes were randomly assigned to groups, and t-values were calculated at each time point across channels. Next, the cluster with the largest sum of t-values was selected from the points where t-values exceeded a threshold. These steps were repeated 1000 times to form a distribution of t-values and test the null hypothesis. Based on the statistics, areas in the original data where t-values exceeded the threshold by more than 5% were selected and grouped into clusters, considering the spatial connectivity of the channels. HEP amplitude between groups were compared for six conditions (summarized in Table 1). Within-group comparison were performed for 1) HEP_{HBD} compared to HEP_{REST}, 2) HEP_{MT} compared to HEP_{REST} and 3) HEP_{HBD} compared to exteroceptive conditions in the HBD task. The window of examination was from -200 to 600 ms.

Table 1. Conditions for HEP amplitude comparison between groups.

Condition	Description
1	at rest (HEP_{REST})
2	during the HBD task (HEP_{HBD})
3	during the MT task (HEP_{MT})
4	HEP modulation (ΔHEP) in the HBD task compared to rest ($\Delta HEP_{HBD\text{-}REST}$)
5	ΔHEP in the MT task compared to rest ($\Delta HEP_{MT\text{-}REST}$)
6	ΔHEP between the HEP_{HBD} and exteroceptive conditions in the HBD task ($\Delta HEP_{HBD\text{-}EX}$)

Individually, for all 6 conditions, a binary logistic regression model was fitted to predict symptoms - 1 for symptoms` presence and 0 for symptoms` absence - on the basis of the 6 averaged HEP amplitudes registered in the given condition in ROIs over a window of 200-600 ms. The significance of the models was tested by likelihood ratio test (LRT).

A nonparametric Wilcoxon test for dependent samples was used to compare HEP_{REST} and HEP_{HBD}, HEP_{REST} and HEP_{MT}, and the interoceptive and exteroceptive conditions in the HBD task in ROI ∈ {LF, CF, RF, LT, RT, CO} (Section 4.3) within groups. The Benjamini-Hochberg (BH) correction was applied to the p values obtained for ROI within each of the three conditions.

2.5.3. Correlation between HEP amplitude and IA

We assessed the link between the behaviorally assessed IA and the neurophysiologic measure of interoception - the HEP amplitudes in these tasks (IA_{HBD} and HEP_{HBD}, IA_{MT} and HEP_{MT}, IA_{HBD} and $\Delta HEP_{HBD\text{-}REST}$, IA_{MT} and $\Delta HEP_{MT\text{-}REST}$, IA_{HBD}, and $\Delta HEP_{HBD\text{-}EX}$). The previously described permutation test was applied with some modifications in Matlab using the Fieldtrip library [49]. First, IA were shuffled between participants rather than HEP amplitudes. Second, t-statistics were calculated in steps. Initially, a two-sided Spearman's rank correlation coefficient between HEP amplitude and IA was calculated in the randomized data from each permutation and the observed data. The coefficient was then converted to a t-statistic.

2.5.4. Exploratory regression analysis

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The analysis was performed using the open-source R 4.3.1 environment. Firstly, to explore how confounding variables (sex, age, percent body fat, STAI-T score, TAS-20 total score) influenced symptom score, we implemented Poisson Generalized Linear Models (GLM) (Model A0). Secondly, we explored how symptom score was predicted in GLM separately by behavioral and electrophysiological metrics (IA in tasks, HEP amplitude in ROI ∈ {LF, CF, RF, LT, CO, RT} (simple Models A1-A5):

A1. Symptom score ~ IA_{HBD}
A2. Symptom score ~ IA_{MT}
A3. Symptom score ~ $\Delta HEP_{MT\text{-}REST}$ in ROI ∈ {LF, CF, RF, LT, CO, RT}
A4. Symptom score ~ $\Delta HEP_{HBD\text{-}REST}$ in ROI ∈ {LF, CF, RF, LT, CO, RT}
A5. Symptom score ~ $\Delta HEP_{HBD\text{-}EX}$ in ROI ∈ {LF, CF, RF, LT, CO, RT}

Then, to explore how confounding variables influenced the predictions, for models 1-5, we implemented multiple models adding confounding variables (Models B1-B5). Covariates in each model were tested for the lack of multicollinearity (variance inflation factor (VIF) did not exceed the threshold of 5). For simple and multiple models 3-5, we used BH correction on the p-values obtained for ROI within each of the three conditions.

Finally, we performed a data-driven analysis using behavioral and electrophysiological interoception metrics that yielded significant associations with the symptom scores (Models A6-A7, B6-B7). We used the akaike information criterion (AIC) to estimate the relative quality of GLM models.

3. Results

3.1. Sample characteristics

Table 2 presents the clinical parameters of the study groups. The groups were comparable in age, but the asymptomatic group had significantly more males, significantly higher BMI (but within the normal range for both groups), and the number of PVCs during 24-hour Holter. The groups did not differ in anxiety and alexithymia. 7 (41%) participants from the symptom group had symptom severity <6 and were assigned a symptom score of 1, 4 (24%) participants had a severity between 6 and 7.83 and, respectively, a symptom score of 2, and 6 (35%) participants had a severity >7.83 and a symptom score of 3.

Table 2. Clinical parameters of the groups.

	Symptomatic group, n = 17[1]	**Asymptomatic group, n = 17[1]**	**W/t/χ^2**	**p**
Age, years old	43.0 [39.0; 46.0]	41.0 [38.0; 42.0]	119	.39[a)]
Sex, males	3 (18%)	11 (65%)	5.95	.015[b)]
BMI, kg/m²	22.5 [20.2; 25.5]	24.6 [23.9; 27]	2.36	.025[c)]
Percent of body fat (%)	26 (24; 31)	25 (19; 32)	-1.02	.31[c)]
Smoking	1 (5.9%)	4 (23.5%)	0.94	.33[b)]
Pharmacological treatment: Beta-blockers Class 1C antiarrhythmics Beta-blockers + Angiotensin II receptor blockers+Calcium channel blockers	5 (29.4%) 3 0 0	3 (17.7%) 0 1 1	0.16	.69[b)]

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Beta-blockers + Angiotensin II receptor blockers+Class 1C antiarrhythmics		1		
Beta-blockers + Class 1C antiarrhythmics	0			
Angiotensin II receptor blockers+Class 1C antiarrhythmics		0		
	1	0		
	1			
DBP, mmHg.	74 [70; 80]	75.3 [72; 82]	175.5	.29[a)]
SBP, mmHg.	106 [102; 116]	110 [105; 118]	0.82	.42[c)]
HR, bpm:				
Rest	68.4 [61.8, 74.04]	65.56 [63.3; 72.76]	-0.39	.6[c)]
HBD task, interoceptive condition	69.3 [57.5; 73.6]	67.2 [62.1; 73.1]	0.2	.84[c)]
HBD task, exteroceptive condition	69.5 [62.4; 75.5]	67.4 [61.8; 72.2]	-0.55	.59[c)]
Number of PVC during experiment:				
Rest	0	10 [0; 20]	202	.029[a)]
HBD task, interoceptive condition	0	3 [0; 7]	196	.047[a)]
HBD task, exteroceptive condition	0	1 [0; 7]	191.5	.059[a)]
MT task	0	6 [0; 11]	203.5	.015[a)]
24-hour Holter PVC	3672 [920; 5485]	10173 [1902; 14536]	213	.018[a)]
STAI-T (trait scale score)	45 [39; 50]	37 [31; 48]	-1.87	.07[c)]
TAS-20-R (total alexithymia index)	43 [36; 48]	35 [29; 39]	-1.57	.14[c)]

[1] Median and 25th and 75th percentiles - Me [Q1; Q3], n(%). [a)] Wilcoxon nonparametric test for independent samples; [b)] $\chi 2$ test; [c)] Student's t-test. BMI - body mass index, DBP - diastolic blood pressure, CBP - systolic blood pressure, HR – heart rate. Significant p-values are in bold.

Interoceptive accuracy (IA)

IA_{HBD} did not differ between groups (W = 138.5, p = .84). IA_{MT} in the symptomatic group (n = 17, Me [Q1; Q3]) = 0.77 [0.21; 0.89]) was significantly higher (W = 78, p = .021, after applying the Bonferroni correction $p_{corrected}$ = .042) than in the asymptomatic group (n = 17, Me [Q1; Q3]) = 0.22 [0; 0.35]) (Figure 1).

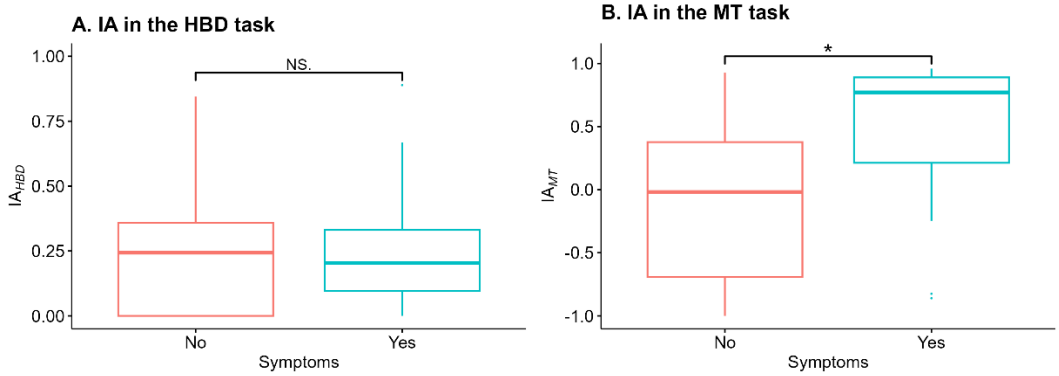

Figure 1. IA_{HBD} (A) and IA_{MT} (B) in the asymptomatic and symptomatic groups (NS - not significant, *$p_{corrected}$ = .042).

The Spearman correlation between IA_{HBD} and IA_{MT} was significant for the symptomatic group (r = .76, p < .001) in contrast to the asymptomatic group (r = .42, p = .09) (Figure 2).

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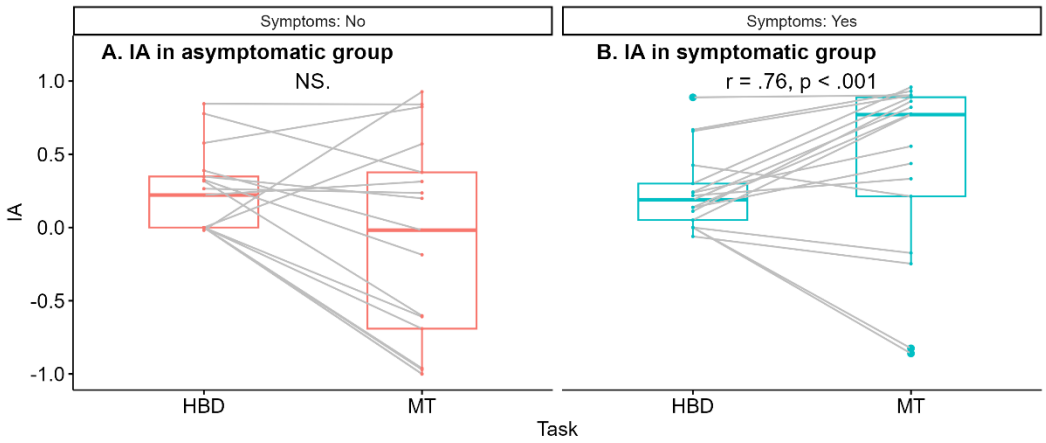

Figure 2. IA_{HBD} and IA_{MT} for asymptomatic (A) and symptomatic (B) groups. NS - not significant.

Heartbeat-evoked potential (HEPs).

We found no significant difference in the HEP amplitude during all 6 conditions between symptomatic and asymptomatic groups. A significant effect of condition was observed in the symptomatic group when comparing the HEP amplitudes recorded during the interoceptive and exteroceptive conditions in the HBD task (Monte Carlo p = .029) (Figure. 3). A significant cluster, spanned from 136 to 244 ms, included the following channels: Fp1, Fpz, F7, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, TP7, CP3, CPz, CP4, T5, P3, Pz, P4, P5, PO3, POz, PO4 and PO7. Cluster-averaged HEP amplitudes for the interoception (M = -0.39, SD = 0.4) were significantly less than for exteroception (M = 0.03, SD = 0.54). After restricting the time window from 200 to 600 ms, this result became nonsignificant.

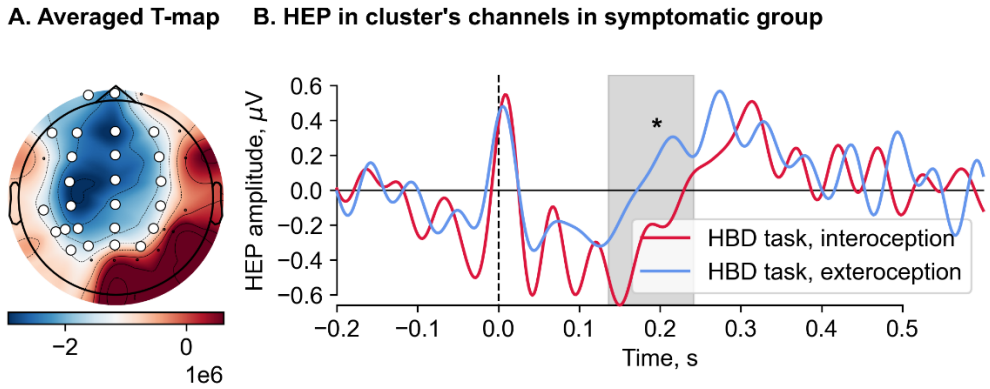

Figure 3. HEP amplitude comparison between the interoceptive and exteroceptive conditions in the HBD task in the symptomatic group (nonparametric permutation paired t-test). (A) Averaged T-map (significant cluster channels are highlighted). (B) Grand averages of HEP amplitude during the interoceptive and exteroceptive conditions in the HBD task within the channels comprising the significant cluster (the significant time range is highlighted in gray).

The amplitude of HEP in ROIs did not differ between conditions in the asymptomatic group. HEP_{REST} in CF ROI (M = 0.17, SD = 0.37) was higher (W = 33, p = .04) than HEP_{HBD} (M = -0.07, SD = 0.55) in the symptomatic group; however, the result did not survive BH correction (p_{BH} = .12) (Figure. 4).

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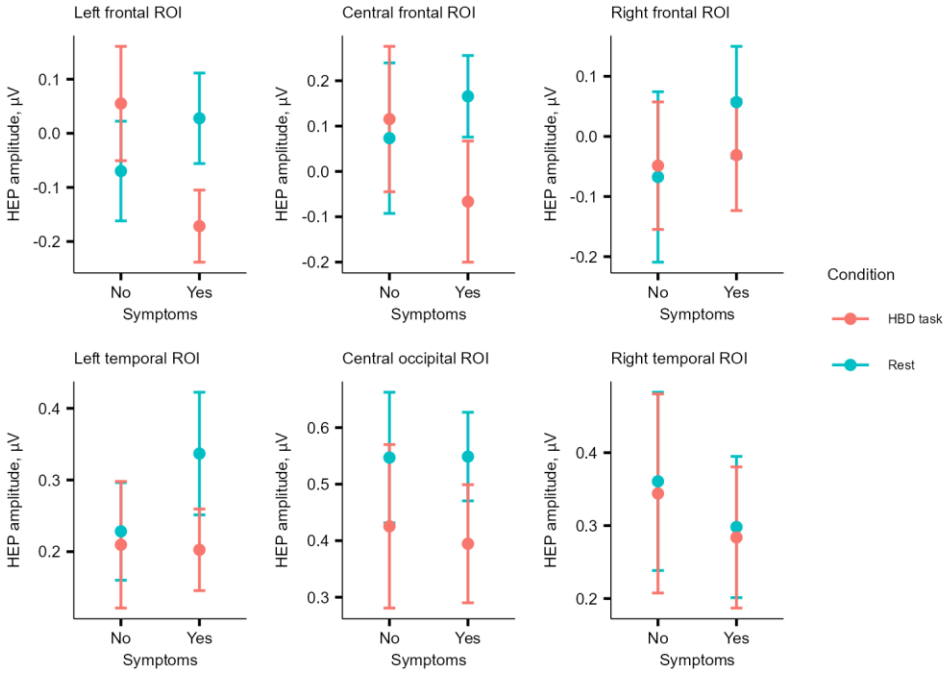

Figure 4. S.E.M error bars HEP_{HBD} and HEP_{REST} for asymptomatic and symptomatic groups for ROIs.

$\Delta HEP_{MT\text{-}REST}$ averaged within channels and over cluster time was significantly correlated with IA_{MT} (r = .47, p = .005) within one cluster (Monte Carlo cluster p = .005 (Figure. 5)). The cluster spanning channels Fpz, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, C3, Cz, C4, CPz, CP4, Pz, P4, T6, PO4, P6, O1, Oz, O2 and PO8 and a time period ranging from 198 to 398 ms. $\Delta HEP_{MT\text{-}REST}$ was significantly correlated with IA_{MT}. HEP_{HBD}, HEP_{MT}, $\Delta HEP_{HBD\text{-}REST}$, $\Delta HEP_{HBD\text{-}EX}$ did not correlate with IA for corresponding task.

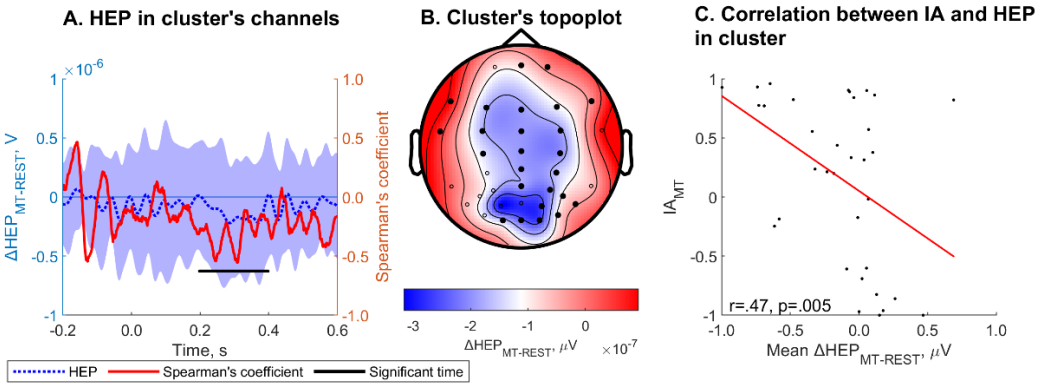

Figure 5. Spearman's rank correlation coefficient between $\Delta HEP_{MT\text{-}REST}$ and IA_{MT} (permutation t-test on correlation). (A) The dotted blue line represents the $\Delta HEP_{MT\text{-}REST}$ averaged over the significant cluster channels, and the shaded blue area represents the standard deviation. The black line indicates a significant cluster period. (B) Topoplot of $\Delta HEP_{MT\text{-}REST}$, averaged over the significant cluster period, channels comprising the cluster are highlighted in black. (C) Scatter plot for IA_{MT} and $\Delta HEP_{MT\text{-}REST}$ averaged over the significant cluster channels and over the significant cluster period.

HEP_{HBD} in LF ROI was a significant negative predictor of symptoms presence (n = 34, β = -7.35, p = .022), LRT in logistic regression model showed a significance (p = .047) (Fig. 4). HEP_{MT} in RT ROI was a significant negative predictor of symptoms presence (β = -7.2, p = .035), but LRT in logistic regression model showed a non-significance (p = .21). HEP_{REST}, $\Delta HEP_{HBD\text{-}REST}$, $\Delta HEP_{MT\text{-}REST}$ and $\Delta HEP_{HBD\text{-}EX}$ were not significant predictors of symptoms presence.

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Regression analyses.

Male sex in Model A0 emerged as a significant factor for lower symptom scores (β = -1.22, p = .028). IA_{MT}, but not IA_{HBD}, showed a significant positive effect on the symptom score (β = .82, p = .01) in a simple model, which was sustained when adding clinical parameters (β = .77, p = .025) in a multiple model.

$\Delta HEP_{HBD\text{-}REST}$ in LF (p = .017, p_{BH} = .037), CF (p = .016, p_{BH} = .033) ROIs and $\Delta HEP_{HBD\text{-}EX}$ in LF (p = .025, p_{BH} = .037), CF (p = .022, p_{BH} = .033) ROIs were significant negative predictors of symptom score in a simple model. The result for $\Delta HEP_{HBD\text{-}REST}$ in LT (p = .037, p_{BH} = .112) ROI did not survive BH correction. Adding clinical parameters to the model made nonsignificant the effect of $\Delta HEP_{HBD\text{-}EX}$ on the symptom score in LF and CF ROIs, and reduced to tendency the effect of $\Delta HEP_{HBD\text{-}REST}$ in CF (p = .019, p_{BH} = .058) ROI. A trend toward a significant association for $\Delta HEP_{HBD\text{-}REST}$ in LT (p = .019, p_{BH} = .058) and CO (p = .018, p_{BH} = .055) was observed only in the multiple models. ΔHEP_{MT} was not associated with the symptom score (Table 3).

Table 3. Simple (model A) and multiple (model B) models regression models 3-5.

Model	$\Delta HEP_{CONDITION}$ in predictors	ROI					
		LF	**CF**	**RF**	**LT**	**CO**	**RT**
A3	$\Delta HEP_{MT\text{-}REST}$	.503	.766	.919	.209	.124	.095
B3		.271	.340	.904	.221	.115	.124
A4	$\Delta HEP_{HBD\text{-}REST}$	**.017**** β = -0.84, SE = 0.35 AIC = 93.92	**.016**** β = -0.84, SE = 0.35 AIC = 93.13	.082	**.037**	.095	.103
B4		**.035**	**.019*** β = -0.98, SE = 0.42 AIC =87.63	.094	**.019*** β= -1.05, SE =0.45 AIC =88.12	**.018*** β = -0.99 SE =0.42 AIC = 87.41	**.033**
A5	$\Delta HEP_{HBD\text{-}EX}$	**.025**** β = -0.78, SE = 0.35 AIC = 93.78	**.022**** β = -.62, SE = .27 AIC = 93.87	.234	.153	.182	.206
B5		.131	.181	.305	.466	.537	.741

Model A - Symptom score ~ Predictor, Model B - Symptom score ~ Predictor + clinical parameters (sex, age, percent body fat, STAI trait scale score, TAS total alexithymia index). Significant p-values are in bold. SE - standard error. ** stands for p values which survived BH correction , * stands for p in range 0,05-0,06 after BH correction/.

The final models included $\Delta HEP_{HBD\text{-}REST}$ in ROI ∈ {LF, CF, LT} and IA_{MT}, $\Delta HEP_{HBD\text{-}EX}$ in ROI ∈ {LF, CF} and IA_{MT} as predictors on the interoception aspect. The best model based on AIC was model B6 where $\Delta HEP_{CONDITION}$ is $\Delta HEP_{HBD\text{-}REST}$ in LT ROI (Table 4).

Table 4. Final model selection.

Model	$\Delta HEP_{CONDITION}$ in predictors	ROI	Predictors	β	SE	p	AIC
A6	$\Delta HEP_{HBD\text{-}REST}$	LF	IA_{MT}	0.93	0.32	**.004**	86.05
			$\Delta HEP_{CONDITION}$	-1.03	0.38	**.006**	
B6			IA_{MT}	0.9	0.37	**.015**	83.72
			$\Delta HEP_{CONDITION}$	-1.12	0.47	**.016**	
			clinical parameters (male sex)	-2.04	0.77	**.008**	
A6		CF	IA_{MT}	0.92	0.32	**.004**	85.14
			$\Delta HEP_{CONDITION}$	-0.99	0.36	**.005**	
B6			IA_{MT}	0.77	0.34	**.025**	83.79
			$\Delta HEP_{CONDITION}$	-1.04	0.45	**.022**	
			clinical parameters (male sex)	-2.16	0.79	**.006**	
A6		LT	IA_{MT}	1.28	0.39	**.001**	82.49
			$\Delta HEP_{CONDITION}$	-1.69	0.52	**.001**	

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B6			IA_{MT}	1.11	0.42	**.008**	80.86
			$\Delta HEP_{CONDITION}$	-1.61	0.56	**.004**	
			clinical parameters (male sex)	-1.97	0.81	**.016**	
A7	ΔHEP_{HBD-EX}	LF	IA_{MT}	0.77	0.32	**.015**	88.71
			$\Delta HEP_{CONDITION}$	-0.67	0.33	**.044**	
B7			IA_{MT}	0.71	0.35	**.039**	
			$\Delta HEP_{CONDITION}$	-0.50	0.44	.265	87.95
			clinical parameters (male sex)	-1.78	0.72	**.014**	
A7		CF	IA_{MT}	0.80	0.32	**.012**	88.28
			$\Delta HEP_{CONDITION}$	-0.55	0.25	**.029**	
B7			IA_{MT}	0.74	0.34	**.031**	
			$\Delta HEP_{CONDITION}$	-0.40	0.36	.267	87.95
			clinical parameters (male sex)	-1.80	0.73	**.014**	

4. Discussion

We hypothesized that the intensity of symptoms in PVC may be associated with interoception. To test this hypothesis, we compared IA in two behavioral tests (MT and HBD) and a neurophysiological marker of cardiac interoceptive processing - the HEP - between symptomatic and asymptomatic individuals with PVC. Interestingly, patients in the asymptomatic group had significantly higher PVC both during the experimental procedure and 24-hour Holter monitoring. This precludes discussing the results regarding symptom severity just in the context of the total number of PVC. An important methodological aspect of the HEP analysis we used is the exclusion of epochs with PVC and epochs time-locked to PVC (two before and one after the PVC) to avoid the influence of PVC on HEP and evaluated only basal HEP, which can be considered as a marker of interoception as a personal trait.

Currently, there are no broadly accepted theories that explain symptom intensity in cardiac diseases. However, some models address medically unexplained symptoms. One of these models is a perception-filter model [50]. Schulz et al. [30] tested the assumptions of this model to investigate alterations in the neurophysiological processing of the interoceptive signals in individuals with medically unexplained symptoms (not exteroceptive, as in previous studies [51,52], on which the perception-filter model was mainly based). The authors tested all three levels of this model: afferent bodily signals (evaluated via heart rate and heart rate variability), filter system activity (evaluated via ΔHEP), and perception (evaluated via IA in the behavioral tests - the MT and heartbeat discrimination tasks). The authors hypothesized that high symptom reporters would have 1) higher heart rate and relative sympathetic tone, 2) higher IA than low symptom reporters, and 3) lower filter activity, indicated by lower ΔHEP. Our results are in accordance with their hypothesis.

Interoceptive accuracy (IA) and symptoms

Hypervigilance models predict higher IA, which aligns with our findings of greater IA_{MT} in symptomatic patients [53]. It could be argued, however, that the higher IA_{MT} in symptomatic individuals does not necessarily reflect true heartbeat perception. Instead, it may stem from symptomatic individuals' belief that they perceive their heartbeats, leading them to report a higher number, which incidentally matches the actual heartbeat count. Indeed, one of the limitations of the MT task is its inability to distinguish between true sensitivity and response bias [54]. To explore this further, we calculated the modified Schandry index for HBD [44–46], where a higher score indicates more frequent tapping during HBD. No difference in this index was found between groups. This result could be extrapolated to some extent to the results of MT in the sense, that patients from symptomatic group are not characterized by reporting higher numbers independent of actual perception. Additionally, IA_{MT} and IA_{HBD} correlated only in the group of symptomatic individuals, consistent with findings by Kormendi et al. [55]. Furthermore, in contrast to the findings of Schulz et al. 2020 [30], our results demonstrated a correlation between IA and ΔHEP, but only for MT, not HBD task. This suggests that increased attentional resources directed towards bodily sensations may enhance perceptual accuracy. These findings further support the fact that the difference in

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IA_{MT} between symptomatic and asymptomatic patients with PVC reflects actual differences in interoception. Our results of higher perception are in line with a previous study by Petersen et al. [56], who found that individuals reporting more frequent symptoms and higher levels of negative affect also showed greater accuracy in an interoceptive classification task, where they were asked to discriminate between various respiratory stimuli.

Heartbeat-evoked potential (HEPs) and symptoms.

Attention to heartbeats has previously been shown to modulate HEP amplitude [57–59]. We initially hypothesized that symptomatic individuals would have a higher HEP_{REST}, an indicator of hypervigilance to internal signals, consistent with cognitive-behavioral models (for review, see [53,60]). In this case, due to this permanent heightened attention to the body, ΔHEP during the interoceptive test should be lower than in asymptomatic individuals. However, we found no differences in HEP_{REST} between the two groups. This may be due to the small sample size, as the regression analysis did capture the association between ΔHEP and symptom severity.

Within-group analyses of ΔHEP showed a significant difference between exteroceptive and interoceptive tasks in the time window from 136 ms to 244 ms for the symptomatic group, with more negative HEP observed in the interoceptive condition. However, when the analyses were restricted to the 200-600 ms time window, this result was no longer significant. While some studies selected a time window of 200 ms or more after the R-peak to avoid contamination of the HEP with cardiac artifacts [20,38,57], other studies did not impose such limitations after removing cardiac field artifacts [42,58,61]. These studies demonstrated HEP differences beginning before 200 ms, which aligns with our findings.

Results regarding the direction (positive or negative) of HEP deflection during cardiac interoceptive tasks vary across studies. Our results indicated that a lower ΔHEP in HBD task (both $\Delta HEP_{HBD\text{-}REST}$ and $\Delta HEP_{HBD\text{-}EX}$) was associated with higher symptom intensity. In the study by Couto et al. [42], a positive deflection of $\Delta HEP_{HBD\text{-}REST}$,but not of $\Delta HEP_{HBD\text{-}EX}$, was observed in control subjects. In contrast, other studies demonstrated both negative $\Delta HEP_{HBD\text{-}REST}$ [61] and $\Delta HEP_{HBD\text{-}EX}$ deflection [61,62] in control subjects as well as in patients with hypertension [38] and obsessive–compulsive disorder [61], but not in patients with panic disorder [61]. Additionally, the study by Leopold et al. [63] showed no difference in HEP_{HBD} compared to the exteroceptive condition. For the MT task, higher HEP_{MT} were observed compared to both the exteroceptive condition [59] and the HEP_{REST} in control subjects [20], although this was not the case for patients with depersonalization disorders [20]. Furthermore, higher HEP_{MT} were reported in high symptom reporters, but not in low symptom reporters [30]. In another study, participants did not perform any cardiac interoceptive tasks but were instructed to focus their attention either on their own heartbeat or on white noise emitted through headphones. HEP was significantly higher during attention to the heartbeat [57].

The insular cortex, prefrontal cortex and left somatosensory cortex [23,64] as well as the frontal-temporal cortex [65] were described as one of the sources of HEP generation. Previous studies in the sensor domain showed that there is an effect of attention to heartbeat pronounced in the modulation of HEP in frontal-central regions [3], as well as an effect of AF presence in patients characterized by modulation of HEP in the frontal-temporal regions [66]. The left lateralization of insular involvement during HBD task was demonstrated by Fittiapldi et.al [46]. We found modulation in left-frontal, fronto-central and left temporal regions, which is in line with previous studies. We hypothesize that HEP modulation in these regions may indicate a role of interoception in the formation of symptoms associated with cardiovascular pathology.

Multimodality of symptom intensity

The multimodal nature of interoception is known to be influenced by factors such as sex and age [67,68]. Studies on the contribution of clinical factors to cardiac disease symptomatology have mainly focused on patients with atrial fibrillation . According to them it can be concluded that female sex, young age were associated with symptomatic AF [69–71], while male sex and older age were associated with asymptomatic atrial fibrillation [72,73]. In studies with gut interoception, female sex

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was also associated with gastrointestinal symptom severity [74]. Similarly, patients with palpitation caused by awareness of sinus rhythm were significantly more likely to be women than those with palpitation due to arrhythmias [75]. The distribution of sex in our groups is consistent with this (with female preponderance in symptomatic group), and regression analyses showed that male sex predicted a low symptom score. However, there is a study showing that patients who under-estimated the length and frequency of atrial fibrillation episodes could be predicted by female sex [76], and a study where older patients had better matching of symptoms with ECG activity [10]. The lack of influence of age on the symptom score in our work is consistent with a study in which asymptomatic patients with atrial fibrillation/atrial flutter/atrial tachycardia after ablation were not predicted by age [9].

Rouse et al. (1988) showed a negative relationship between IA and BMI and percentage of fat mass in healthy individuals. Patients with higher BMI also demonstrated interoceptive deficits [77]. Studies on other clinical groups with comorbid overweight and obesity have shown a direct association between increased BMI and greater symptom severity. For instance, higher BMI was linked to more severe symptoms in women with fibromyalgia syndrome, as measured by the Fibromyalgia Impact Questionnaire (FIQ-R) [78]. Similarly, in patients with atrial fibrillation, elevated BMI was associated with higher symptom burden scores, assessed using the Toronto Atrial Fibrillation Severity Scale (AFSS) [79]. Additionally, in patients with metabolic syndrome, body fat percentage was correlated with increased severity of anxiety and depressive symptoms [80]. In our study, the lack of influence of body composition on symptom scores can be explained by the fact that (1) there was no variability in body fat percentage in the non-obese sample, which did not allow testing associations; (2) body composition is not involved in the formation of PVC symptomatology.

Alexithymia, defined as difficulties in identifying and describing one's own feelings, is characterised by impaired interoception [81], which, in its turn, is related to emotional processing [82]. Previous research has demonstrated a higher prevalence of alexithymia in patients with medically unexplained symptoms, with a correlation between alexithymia and symptom severity [83]. Therefore, we hypothesized that the presence or absence of symptoms of PVC may be associated with alexithymia. However, multiple regression models identified no associations of alexithymia and symptom intensity as the response variable. Although inverse associations between IA_{MT} and alexithymic traits in a group of healthy subjects have been demonstrated [81,84], recent meta-analyses by Desmedt [67] have revealed no significant associations between IA_{MT} and trait anxiety or alexithymia. The authors hypothesized that this may be due to the inability of the IA_{MT} to adequately capture individual differences in interoception. Indeed, the existing literature on the relationship between interoception and alexithymia is inconclusive, with findings varying depending on the methodological approach employed. In the study by Flasbeck et al. [85], there was a positive correlation between HEP amplitudes over frontal electrodes and alexithymia for the entire study sample (control subjects and patients with borderline personality disorder), but not within the aforementioned groups. This may explain the absence of associations between alexithymia and symptom severity in our study, because participants did not have any psychological or psychiatric disorders and exhibited low alexithymia. Consequently, the TAS-20 score may not have been sufficiently sensitive to detect subtle differences in emotional processing.

Palser et al. [86] demonstrated that the combination of altered interoceptive processing and alexithymia is linked to a higher risk of developing anxiety disorders compared to altered interoception alone. Notably, palpitations are among the common symptoms reported by patients with anxiety disorders [13]. Conversely, the presence of an actual arrhythmia may be associated with anxiety, resulting in misdiagnosis as anxiety or panic disorder [87–89]. The study by Rutledge et al. demonstrated that women's perceptions of their risk for coronary artery disease were more closely linked to symptoms of anxiety than to their actual coronary artery disease status [90]. Moreover, studies have shown an association between anxiety and the severity of symptoms in chronic gastrointestinal diseases [91,92] as well as in functional somatic syndromes [93]. Based on these findings, we hypothesized that the inclusion of trait anxiety into the regression models would contribute to an improvement in their quality. However, no association with symptom intensity was

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identified. Our negative results may be attributed to the non-uniform relationship between anxiety and symptom perception, as previously demonstrated by Chen et al. [94].

Interoceptive metrics for predicting symptom score

One of the aims of the current study was to evaluate which of the interoceptive metrics discussed above would result in a better model for predicting symptom scores. Results from simple GLM models showed that 1) the behavioral interoceptive metric IA_{MT}, but not IA_{HBD}, and 2) the electrophysiological metric $\Delta HEP_{HBD\text{-}REST}$, but not $\Delta HEP_{MT\text{-}REST}$, showed associations with symptom score. Association for $\Delta HEP_{HBD\text{-}EX}$ became not significant after inclusion of clinical parameters in the model. Despite the correlation between IA_{MT} and $\Delta HEP_{MT\text{-}REST}$, models including $\Delta HEP_{MT\text{-}REST}$ showed no associations with symptom score. This may indicate complex interactions between symptom perception, IA and HEP amplitude. Probably, ΔHEP represents individual perceptive ability, and IA may be just an indicator of this ability. As IA_{MT} did not correlate with $\Delta HEP_{HBD\text{-}REST}$ we performed data-driven multivariate regression including these metrics as predictors in a joint regression model, which yielded the best result for predicting symptom score. It was quite unexpected that in binary logistic regression models HEP_{HBD}, but not $\Delta HEP_{HBD\text{-}REST}$ (as in GLM models), was a significant negative predictor of symptom presence. It can be suggested that for robust prediction (presence or absence of symptoms) the absolute HEP value during the HBD task is sufficient, but for more accurate prediction (the intensity of symptoms) the HEP modulation (difference between resting state and interoceptive task) should be used.

A limitation of this study is that the sample size may have been insufficient to detect differences in HEP amplitudes (rather than modulation) across different conditions between groups.

5. Conclusions

To our knowledge, this is the first study to examine the relationship between interoception and symptom severity in PVC. By applying strict exclusion criteria and selecting only young patients without comorbidities, we aimed to minimize confounding effects, allowing a clearer analysis of the association between interoception and symptom intensity. Our findings confirm that interoception is significantly associated with PVC symptom severity, supporting our initial hypothesis. The results suggest that integrating both approaches (behavioral and neurophysiological) to assess interoception improves the accuracy of predicting symptom intensity. This insight opens promising avenues for the development of novel diagnostic strategies for PVC, with interoception emerging as a potential target for non-invasive and non-pharmacological treatment approaches.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the local Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine (protocol code 02-02/21, date of approval 25.02.2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent for publication must be obtained from participating patients who can be identified - not applicable (patients` data can not be identified).

Data Availability Statement: The datasets generated and analyzed during the current study and code we used are openly available in the OSF repository at https://doi.org/10.17605/OSF.IO/BF6P5

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