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Original

Heart rate variability in women with migraine: a cross-sectional pilot study

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Abstract

Introduction
Migraine, a neurological disorder highly prevalent among women, affects the autonomic nervous system, which regulates heart rate. Heart rate regulation is assessed through HRV.

Objective
To assess reduced HRV in women with migraine during the interictal period.

Methods
This cross-sectional study included 45 female volunteers aged 20 to 50 years (24 ± 5 SD). Participants were divided into a Migraine Group (MG, n= 35; 25 ± 5 SD) and a Control Group (CG, n = 10; 21 ± 2 SD), according to the ID Migraine Questionnaire criteria. HRV variables analyzed included standard deviation of the average N–N interval (SDNN), square root of the mean squared differences of successive N–N intervals (RMSSD), proportion derived by dividing NN50 by the total number of N–N intervals (pNN50), low frequency (LF), high frequency (HF), and LF/HF. Statistical was performed using Jamovi, applying Student's t-tests and Mann–Whitney tests.

Results
For MG and CG, respectively: SDNN 35.7 ± 11.7 ms vs. 33.0 ± 11.6 ms (P = 0.523); RMSSD 29.9 ± 14.5 ms vs. 28.0±12.8 ms (P = 0.743); pNN50 11.2 ± 12.3% vs. 8.85 ± 10.8% (P = 0.583); LF 730 ± 502 ms^2 vs. 720 ± 454 ms^2 (P = 0.968); HF 547 ± 524 ms^2 vs. 442 ± 357 ms^2 (P = 0.555); LF/HF 2.32 ± 2.48 vs. 2.11 ± 1.23 (P = 0.527).

Conclusion
Both groups exhibited reduced HRV with increased sympathetic activity; however, no statistically significant differences were observed between groups.

Keywords:
Migraine
Autonomic nervous system
Variability
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Introduction

Migraine is a neurological disorder that affects approximately 20% of women between 18 and 50 years of age and 10% of men across the lifespan, substantially impacting quality of life and causing disability due to a wide range of symptoms (1–3). Classified as a primary headache disorder (4), its underlying mechanisms have been extensively investigated, with proposed hypotheses involving alterations in the central nervous system (CNS), autonomic fibers, the trigeminovascular system, and various vasoactive agents (5). The literature describes migraine as a complex condition involving multiple regions of the nervous system, including the brainstem, which also plays a central role in autonomic regulation (6).

Heart rate variability (HRV), a method used to assess the autonomic nervous system (ANS), may show alterations in individuals with migraine. During migraine attacks, patients may exhibit changes in HRV resulting from vasovagal responses triggered by migraine, which may contribute to inflammatory processes associated with insufficient inhibition of pro-inflammatory cytokine release. In this context, inflammatory conditions can alter the ANS, reducing autonomic control of pain, while chronic pain itself is associated with diminished vagal activity (7). However, little is known about HRV during the interictal period, and whether it remains reduced in the absence of migraine episodes (8).

Heart rate variability is a measure derived from the variation in heart rate (9), providing indirect information on autonomic activity and contributing to the detection of ANS and CNS alterations (10). It is associated with the analysis of R–R interval variations, reflecting the interaction between the ANS and the cardiovascular system (11). These intervals represent communication between the sympathetic and parasympathetic divisions of the ANS (12,13). The vagus nerve, the tenth cranial nerve, plays a key role in connecting the CNS and ANS by transmitting sensory and motor information, and is essential for maintaining parasympathetic balance (14,15).

A higher HRV generally indicates better health status, whereas reduced HRV may suggest impaired autonomic regulation, although certain cardiovascular diseases may also present reduced variability (16). Migraine can disrupt ANS balance and consequently alter HRV. Therefore, changes in HRV may serve as indicators of autonomic dysfunction, as HRV is widely used to assess autonomic function. Additionally, HRV is linked to cognitive, affective, and physiological regulatory processes and may help identify conditions such as chronic pain (7).

Given these considerations and recognizing that migraine may influence heart rate through ANS imbalance, this study aimed to investigate whether women with migraine during the interictal period exhibit reduced HRV based on variables that reflect sympathovagal activity.

Methods

This was a pilot observational, cross-sectional, quantitative, and analytical study conducted between June and December 2023. Volunteer recruitment was performed by convenience sampling through social media and in person at the Department of Physical Therapy of the Federal University of Pernambuco (UFPE). Data collection took place at the Motor Learning and Control Laboratory (LACOM) at UFPE, and the study was approved by the Human Research Ethics Committee of the Health Sciences Center (CCS/UFPE) under approval number 6.306.704.

Participants were women aged 20 to 50 years with a diagnosis of migraine, identified using the ID Migraine Questionnaire, which has a sensitivity of 0.87 (95% CI: 0.85–0.89) and specificity of 0.75 (95% CI: 0.72–0.78) for diagnosing migraine (17). In addition, participants completed a questionnaire for migraine characterization. They were assessed during the interictal period.

Eligibility criteria

Inclusion Criteria

In the Migraine Group, female volunteers aged 20 to 50 years were included if they met migraine criteria according to the ID Migraine screening questionnaire and were in the interictal period. In the Control Group, female volunteers aged 20 to 50 years were included if they were healthy, reported no headache complaints, or had experienced fewer than two episodes in the previous year.

Exclusion Criteria

Pregnant women and those with cognitive impairments that could interfere with their understanding or execution of the procedures required for data collection were excluded. Women who were menstruating or in the ictal phase of migraine were asked to return after these periods. Volunteers with other neurological conditions (such as stroke, multiple sclerosis, amyotrophic lateral sclerosis, or peripheral neuropathy) or cardiovascular diseases (such as myocardial infarction or cardiac arrhythmias) were also excluded.

Procedures

The volunteers were assessed in a climate-controlled room (≈ 22°C) at LACOM in the afternoon, as the time-of-day influences HRV results, with increases typically observed in the morning and reductions at night (18). Data collection was conducted individually. Participants were instructed to remain seated in an armchair while the Polar Flow H9 chest strap was placed at the level of the xiphoid process and the Polar Flow watch was positioned on the wrist. HRV was recorded for 15 minutes at rest, and the assessor remained outside the room to avoid interference during data acquisition.

If any discomfort occurred, volunteers were instructed to signal the researcher. Precautions were taken to prevent people from entering the room during the assessment and to avoid noise that could affect the recordings. The data were saved, transferred via USB, and synchronized directly into the Kubios HRV Standard software, version 4.0.2 (2023), where they were subsequently analyzed.

Variables

The primary outcome was the assessment of HRV variables. In the time domain, these included: the standard deviation of normal-to-normal intervals (SDNN), which reflects both sympathetic and parasympathetic activity; the root mean square of successive differences (RMSSD), an index of vagal activity; and the proportion of NN50 divided by the total number of N–N intervals (pNN50), also indicative of vagal modulation. In the frequency domain, the low-frequency component (LF) reflects both sympathetic and parasympathetic influences, though predominantly sympathetic; the high-frequency component (HF) reflects vagal activity; and the LF/HF ratio represents sympathovagal balance (19).

The secondary outcome consisted of characterizing headache features in the migraine group, including intensity (classified as mild, moderate, or severe), duration (< 4 hours, between 4 hours and 3 days, or > 3 days), pain quality (pulsating, tightening, or pressing), laterality (unilateral or bilateral), and pain location (frontal, occipital, vertex, holocranial, temporal, frontotemporal, frontoparietal, or fronto-occipital).

To support the interpretation of HRV results, the reference values proposed by Voss were used, as they provide age- and sex-specific normative ranges for each HRV variable (20). Considering that HRV varies according to these factors, the corresponding normative parameters are presented in Table 1.

Table 1. HRV parameters according to the study by Voss et al.(20)

Variables	Values
SDNN (ms)	44.9 ± 19.2
RMSSD (ms)	36.5 ± 20.1
NN50 (%)	0.17 ± 0.18
LF (ms^2)	159 ± 181
HF (ms^2)	125 ± 147
LF/HF	2.09 ± 2.05

SDNN (standard deviation of the average N-N interval); RMSSD (square root of the mean squared differences of successive N-N interval); pNN50 (proportion derived by dividing NN50 by the total number of N-N intervals); LF (low frequency); HF (high frequency); LF/HF (sympathovagal balance); ms=milisecond.

Statistical analysis

The data analysis was conducted using descriptive and percentage statistical measures, with the data presented as MD±SD and a 5% margin of error applied in statistical test decisions, along with a 95% confidence interval. For statistical analysis, the Shapiro–Wilk test was used, as well as the Mann–Whitney test and t-test. The data were organized in an Excel spreadsheet (2019 version), and the software used to perform the statistical calculations was the open statistical software for desktop and cloud (Jamovi), 2023, version 2.3.

Results

A total of 45 female volunteers were recruited (24.5 ± 5.12 SD years of age), with 35 in the MG (25 ± 5 SD years) and 10 in the CG (21.8 ± 1.75 SD years), as shown in Figure 1.

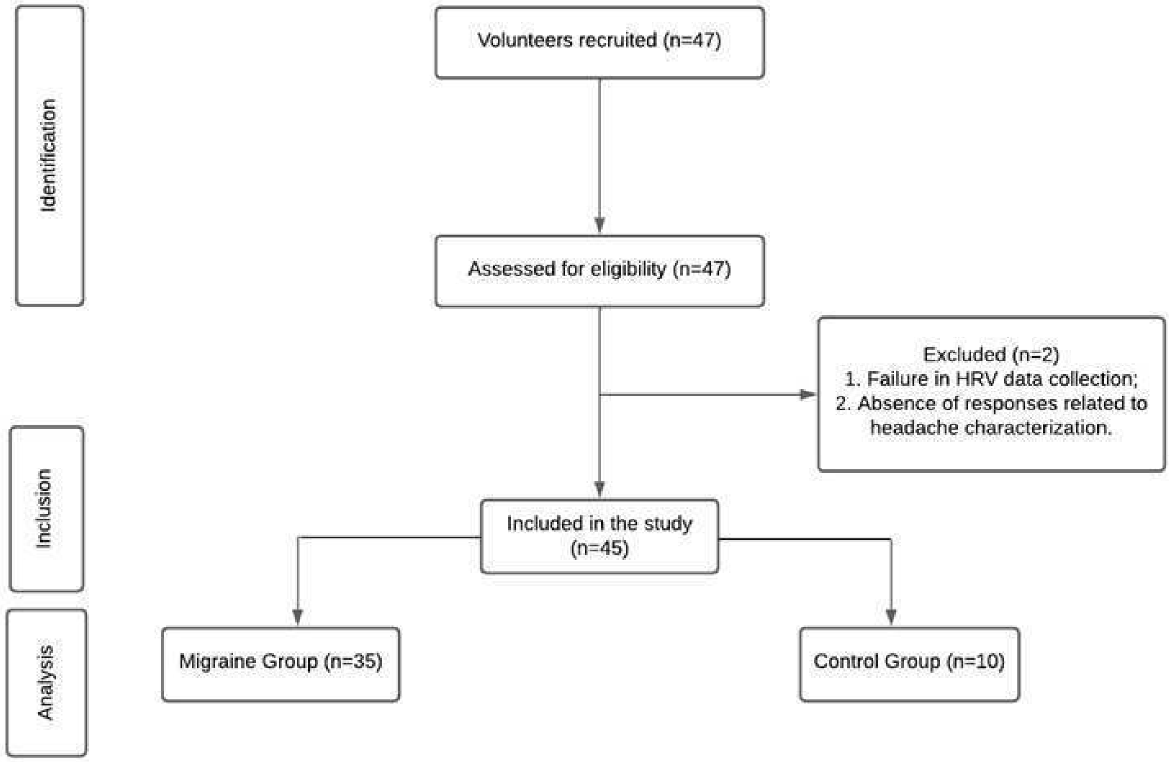

Figure 1. Flowchart of the final sample with 45 volunteers

The clinical characterization of headache in the MG is presented in Table 2. The HRV variables for both groups, time-domain measures (SDNN, RMSSD, pNN50) and frequency-domain measures (LF, HF, and LF/HF), are shown in Table 2.

Table 2. Results of HRV variables in the Migraine Group (n = 35) and Control Group (n=10), statistical analysis and characterization of headache in the Migraine Group

Variables	GM (n = 35) MD ± DP	GC (n = 10) MD ± DP	P-value*	Normality parameters
Age (years)	25.3 ± 5.51	21.8 ± 1.75	0.010	
SDNN (ms)	35.7 ± 11.7	33.0 ± 11.6	0.523	44.9 ± 19.2
RMSSD (ms)	29.9 ± 14.5	28 ± 12.8	0.743	36.5 ± 20.1
pNN50 (%)	11.2 ± 12.3	8.85 ± 10.8	0.586	0.17 ± 0.18
LF (ms^2)	730 ± 502	720 ± 454	0.968	159 ± 181
HF (ms^2)	547 ± 524	442 ± 357	0.555	125 ± 147
LF/HF	2.32 ± 2.48	2.11 ± 1.23	0.527	2.09 ± 2.05
Characteristics of Migraine	**n (%)**			
Intensity				
Mild	3 (8.6)	-	-	-
Moderate	26 (74.3)	-	-	-
Intense	6 (17)	-	-	-
Duration (h)				
<4	10 (28.6)	-	-	-
4 - 72	19 (54.3)	-	-	-
>72	6 (17)	-	-	-
Laterality				
Unilateral	13 (37)	-	-	-
Bilateral	22 (62.8)	-	-	-
Type of pain				
Pulsatile	29 (82.9)	-	-	-
Tighten/Pressure	6 (17)	-	-	-
Location				
Frontal	12 (34.3)	-	-	-
Temporal	4 (11.4)	-	-	-
Occipital	1 (2.9)	-	-	-
Holocranial	6 (17)	-	-	-
Frontotemporal	2 (5.7)	-	-	-
Frontoparietal	6 (17)	-	-	-
Fronto occipital	4 (11.4)	-	-	-

SDNN (standard deviation of the average N-N interval); RMSSD (square root of the mean squared differences of successive N-N interval); pNN50 (proportion derived by dividing NN50 by the total number of N-N intervals); LF (low frequency); HF (high frequency); LF/HF (sympathovagal balance); ms=milisecond; MD (mean); DP (Standard Deviation); *Mann Whitney, t-test.

In both groups, SDNN and RMSSD values were lower than the established reference ranges, although no differences were observed between groups. Conversely, pNN50, LF, HF, and LF/HF values were higher than expected according to normative parameters, but again with no significant differences between the groups.

Discussion

The aim of this study was to assess HRV alterations in women with migraine during the interictal period by measuring time and frequency domain parameters. The variables SDNN and RMSSD showed reductions, indicating lower variability due to decreased vagal activity, whereas pNN50, LF, HF, and LF/HF were higher than expected, suggesting HRV dysregulation.

The ANS performs several functions, including the regulation of HR, thereby maintaining bodily equilibrium in response to internal or external stimuli that may destabilize hemodynamic homeostasis (21). Multiple approaches are available to assess ANS function in patients with migraine, one of which is HRV analysis (22).

HR can be assessed through HRV, which reflects its association with the ANS and its subsystems, potentially resulting in increased parasympathetic activity and reduced sympathetic activity (23). HRV can be evaluated using simple or computerized tests, as well as electrocardiography (ECG), focusing on frequency- and time-domain parameters (10). HRV encompasses both linear and nonlinear measures that are essential for interpreting its findings (20).

Several factors, whether environmental or physiological, can influence HRV, which may have contributed to the control group values falling outside the reference range. Stress can decrease HRV, as activation of the SNS triggers cortisol release, increasing cardiac output and reducing HRV (19). Age is an important determinant of HRV: younger individuals generally show higher HRV, whereas increasing age is associated with lower HRV. In addition to age, respiratory excursions may also influence HRV, either increasing or decreasing its values (20).

Some studies have reported differences between these periods, with a reduction in HRV observed during the ictal phase (15), It is important to verify whether HRV decreases during the interictal period.

For the SDNN variable, both groups showed values below the expected range, indicating concurrent alterations in sympathetic and parasympathetic activity. SDNN is a robust marker associated with morbidity and mortality, and the literature shows that individuals with migraine with aura in the interictal period tend to exhibit lower SDNN values, reflecting increased sympathetic predominance (9).

SDNN and RMSSD are considered gold-standard variables for assessing autonomic function, as both are correlated with parasympathetic activity. In the present analysis, both measures were reduced, and although no statistically significant differences were found between groups, the results indicate decreased vagal activity in both. Individuals experiencing pain may exhibit reduced RMSSD (8), as observed in our findings, which is consistent with the reduction observed in the migraine group. However, the control group also showed reduced values, which may be explained by underlying conditions that were not identified during the screening process. Additionally, both groups demonstrated pNN50 values above the established reference range, indicating alterations in vagal activity.

The LF and HF variables showed values above the established reference ranges in both groups. When examining the LF/HF ratio, which reflects the balance between sympathetic and parasympathetic activity, both groups demonstrated a predominance of sympathetic activity. This higher LF/HF ratio is associated with reduced variability in the migraine group, likely influenced by the inflammatory processes characteristic of the condition, which can alter autonomic function. In the control group, elevated values may be explained by underlying inflammatory conditions or chronic pain not detected during screening. In general, a higher LF/HF ratio indicates lower vagal activity, whereas a lower ratio reflects greater parasympathetic activity (24). Furthermore, the small sample size in the control group is an important factor that may have influenced these findings.

HRV assessments can be performed in the supine, standing, or seated position, and it is essential to report the position in which the measurement was obtained (16). Because the reference parameters used in this study were collected from volunteers in the supine position, the values observed here may differ due to postural variations, which could have influenced the results. Trunk position changes can alter sympathetic activity and consequently affect autonomic modulation (25). For more accurate heart rate acquisition, the seated position is generally recommended (18).

In addition to the HRV findings, headache characteristics were analyzed in the migraine group, an essential component for accurate classification and diagnosis, as it distinguishes migraine from other headache types (4). This characterization included assessments of pain intensity, duration, quality, laterality, and location. The results were consistent with the criteria established by the ICHD-3 and supported the findings from the screening conducted using the ID-Migraine questionnaire.

Cardiovascular diseases (CVD) and stroke are known to be associated with migraine (26), as widely reported in the literature, and identifying HRV alterations may help reduce future risks, thereby contributing to decreased morbidity and mortality.

Identifying reduced HRV in women with migraine will help clarify the functioning of vagal and sympathetic activity within the ANS and may indicate pathways to lessen the burden of the disease, guiding strategies that can support patients and improve their quality of life. Therefore, expanding research on HRV and migraine during the interictal period is essential.

Study limitations

The diagnoses established in this study were based on the ID-Migraine questionnaire and were not confirmed by neurological evaluation. Moreover, the small sample size and the imbalance between the evaluated groups represent important limitations of the research. Therefore, studies with a larger number of participants in the interictal period are needed to enable the generalization of the findings.

Conclusion

Based on the results obtained, a reduction in HRV was observed in both the migraine and control groups, even though no significant differences were observed between them. Both groups demonstrated decreased vagal activity, primarily evidenced by the reduction in RMSSD. Considering that this is a pilot study, the small sample size may have influenced these findings, and caution is warranted when interpreting the results.

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