



Cardiac Autonomic Modulation Following a 50 mg Oral Dose of Dimenhydrinate in Healthy Young Adults: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Heart rate variability (HRV) reflects beat-to-beat changes in the cardiac cycle that result from interactions between sinus node cells and the autonomic nervous system. Dimenhydrinate is a first-generation H₁ receptor antihistamine of the monoethanolamine class.

Objectives: This study aimed to evaluate the effects of oral dimenhydrinate on cardiac autonomic activity using heart rate variability (HRV) indices.

Methods: This double-blind crossover study included volunteers who attended two sessions separated by a 2-week interval. In each session, a 5-minute electrocardiogram (ECG; lead II) was recorded at baseline and at multiple time points within 4 hours after oral administration of either placebo or 50 mg dimenhydrinate. Time- and frequency-domain HRV parameters were calculated and statistically analyzed.

Results: Placebo had no significant effects on any HRV indices. Administration of 50 mg dimenhydrinate resulted in a significant increase in mean SDNN (standard deviation of normal-to-normal intervals) at 90 minutes. At 4 hours after administration, both RMSSD (root mean square of successive differences) and PNN50% (percentage of successive NN intervals differing by more than 50 ms) were significantly elevated in the dimenhydrinate group, indicating enhanced parasympathetic modulation.

Conclusions: These findings suggest that oral dimenhydrinate, which crosses the blood-brain barrier, modulates cardiac autonomic balance by enhancing parasympathetic activity and reducing sympathetic dominance via H₁ receptor antagonism.

Keywords: Dimenhydrinate, Heart Rate Variability, Autonomic Nervous System

1. Background

The cardiac autonomic nervous system is central to the regulation of cardiovascular homeostasis and orchestrates the balance between sympathetic and parasympathetic activity (1). This dynamic equilibrium modulates heart

rate, blood pressure, and cardiac responses to internal and external stimuli. Disruptions in autonomic balance, as assessed by heart rate variability (HRV), are associated with increased cardiovascular risk, including arrhythmias, hypertension, and ischemic heart disease (2,3).

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Heart rate variability has emerged as a noninvasive, reliable, and sensitive biomarker for evaluating cardiac autonomic function (4). It reflects the heart's capacity to adapt to physiological and environmental demands and provides insight into sympathovagal balance. Time-domain indices, such as the standard deviation of normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), and the percentage of successive NN intervals differing by more than 50 ms (PNN50%), quantify the magnitude of beat-to-beat variability. Frequency-domain analysis distinguishes contributions from low-frequency (LF) and high-frequency (HF) components, which correspond primarily to sympathetic and parasympathetic activity, respectively (5). The LF/HF ratio is widely used as an indicator of cardiac sympathovagal balance, and alterations in these parameters may reveal shifts in autonomic tone even in otherwise healthy individuals (6).

Pharmacological agents can substantially affect autonomic regulation (7). Dimenhydrinate, a first-generation H₁ histamine receptor antagonist, is commonly administered to alleviate motion sickness, nausea, and vomiting (8). Its primary mechanisms involve central vestibular suppression and modulation of histaminergic pathways; however, its anticholinergic and mild sedative properties may also influence cardiovascular autonomic control (9). Although dimenhydrinate is generally regarded as safe in healthy adults, its acute effects on HRV and cardiac autonomic function remain poorly characterized, particularly in young, healthy populations (10).

Previous research has shown that antihistamines and other agents acting on the central nervous system can modify autonomic indices, including HRV, blood pressure, and baroreflex sensitivity (11). Most studies, however, have focused on patient populations or chronic drug administration, leaving a notable gap regarding the immediate impact of a single oral dose of dimenhydrinate on cardiac autonomic regulation in healthy young adults (10, 12). Investigating this effect is important because even transient alterations in autonomic balance may provide valuable insights into drug safety, physiological adaptation, and potential implications for susceptible individuals (4, 10).

Advances in HRV analysis, including time-domain and frequency-domain metrics, enable precise quantification of autonomic responses following pharmacological challenges (5). Short-term 5-minute ECG recordings provide reliable estimates of LF, HF, and the LF/HF ratio, allowing high-resolution temporal monitoring of autonomic dynamics (6). These methods are particularly useful in crossover clinical trial designs, in which

participants serve as their own controls, thereby minimizing interindividual variability and enhancing statistical power (12).

2. Objectives

Given the widespread use of dimenhydrinate, its well-characterized pharmacokinetics, and the limited number of controlled studies evaluating its autonomic effects in healthy volunteers, this randomized, double-blind, placebo-controlled crossover study was designed to assess the acute effects of 50 mg oral dimenhydrinate on cardiac autonomic responses in healthy young adults, as measured using time-domain and frequency-domain HRV indices.

3. Methods

3.1. Study Design

This randomized, double-blind, placebo-controlled, crossover phase I clinical trial was designed to investigate the acute effects of a single oral dose of dimenhydrinate on cardiac autonomic function in healthy young adults. Each participant served as their own control and received both interventions (50 mg dimenhydrinate and a visually identical placebo) in 2 separate sessions in randomized order. A 2-week washout period separated the sessions to minimize potential carryover effects.

3.2. Participants

Fifteen healthy volunteers aged 19 to 26 years (mean body mass index [BMI], 22.75 ± 1.62 kg/m²) were recruited from Babol University of Medical Sciences. Inclusion criteria were normal health status, absence of chronic or acute disease, and no use of medications, alcohol, or tobacco. Exclusion criteria included cardiovascular disorders, contraindications to dimenhydrinate, substance abuse, and abnormal ECG findings. Dimenhydrinate tablets and matching placebo were manufactured by Darou Pakhsh Pharmaceutical Manufacturing Co., a major Iranian pharmaceutical company headquartered in Tehran, Iran. Written informed consent was obtained from all participants before the study procedures. The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1402.018) and registered in the Iranian Clinical Trial Registry (IRCT20230606058390N1).

3.3. Experimental Procedure

Participants attended 2 experimental sessions conducted between 8:00 and 12:00 AM after receiving standardized pretest instructions, including abstinence

from caffeine, alcohol, strenuous exercise, and heavy meals. Each session began with a 15-minute rest period in the supine position. Baseline 5-minute ECG recordings were obtained in lead II using a 3-electrode configuration (right wrist $\times$ 2 and left wrist $\times$ 1) connected to an eWave bioamplifier (ScienceBeam, Iran), with a 1 kHz sampling frequency and 24-bit resolution. Participants then ingested either 50 mg dimenhydrinate or placebo. ECG recordings were acquired at 30-minute intervals over a 4-hour period after ingestion. Raw ECG signals were digitized, stored, and processed using eProbe software to extract R-R intervals. The resulting NN interval series were visually inspected to remove artifacts, ectopic beats, and noise.

3.4. Heart Rate Variability Analysis

Heart rate variability was analyzed in both the time and frequency domains. Time-domain indices included SDNN, RMSSD, PNN50%, and the mean NN interval. Frequency-domain analysis was performed using fast Fourier transform to calculate HF power (0.15 - 0.40 Hz) and LF power (0.04 - 0.15 Hz). High-frequency power was interpreted as a marker of parasympathetic activity, LF power reflected combined sympathetic and parasympathetic influences mediated by baroreflex mechanisms, and the LF/HF ratio served as an index of sympathovagal balance. LF and HF powers were calculated in both absolute and normalized units (LFnu and HFnu) for comprehensive assessment.

3.5. Statistical Analysis

Data normality was assessed using the Kolmogorov-Smirnov test. Parametric data were analyzed using repeated-measures analysis of variance to compare HRV indices across time points and conditions. Nonparametric data were evaluated using the Kruskal-Wallis test, followed by post hoc Mann-Whitney comparisons. Statistical significance was set at $P \leq 0.05$. All results are presented as mean $\pm$ standard deviation. Statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA).

4. Results

A total of 15 healthy young adults participated in this study. The mean age of the participants was 23.87 ± 2.16 years (range, 19 - 26 years), and the mean BMI was 22.75 ± 1.62 kg/m² (range, 19.9 - 24.5 kg/m²). The study population included 8 males (53.3%) and 7 females (46.7%). Baseline comparisons of all study variables were performed at time zero on day 1 and day 14 (repeat session) to assess potential carryover effects. No statistically significant differences were observed between baseline measurements across the

2 sessions (all $P > 0.05$), indicating comparability between the 2 study periods.

Repeated-measures analysis of variance showed that the mean RR interval (MRR) did not differ significantly across measurement time points in either the placebo group or the dimenhydrinate group ($P = 0.307$ and $P = 0.921$, respectively). Similarly, comparisons of MRR values between baseline and postadministration time points showed no significant interaction between time and treatment condition ($P = 0.265$), indicating that oral administration of dimenhydrinate did not induce statistically significant alterations in MRR compared with placebo. The mean $\pm$ SD of MRR values for both the dimenhydrinate and placebo conditions at all time points are presented in [Table 1](#). Pairwise comparisons using paired *t* tests showed no statistically significant differences between the 2 groups at any individual time point ($P > 0.05$ for all comparisons). Notably, at 1 hour after administration, a trend toward a greater increase in MRR was observed in the dimenhydrinate group than in the placebo group ($P = 0.068$). Although this difference did not reach statistical significance, the magnitude of change may be clinically relevant. As illustrated in [Figure 1](#), mean MRR values decreased in the dimenhydrinate group at 1.5, 2, and 3 hours after administration, a pattern not evident in the placebo group. However, these changes did not reach statistical significance.

Analysis of variance within the drug and placebo groups showed no statistically significant differences in mean RMSSD across measurement times ($P = 0.716$ and $P = 0.865$, respectively). Repeated-measures analysis of variance comparing preadministration and postadministration time points showed no significant changes in RMSSD between the 2 groups ($P = 0.236$). The mean $\pm$ SD of RMSSD values in the drug and placebo groups are presented in [Table 2](#). Pairwise comparisons at each time point using the paired *t* test indicated that, at 4 hours, the mean RMSSD in the drug group was significantly higher than that in the placebo group ($P = 0.042$). As illustrated in [Figure 2](#), although differences in RMSSD trends were observed at 1, 2, 3, and 4 hours, the 4-hour measurement corresponded to a statistically significant difference between the 2 groups, as also shown in [Table 2](#).

Analysis of variance within the placebo and drug groups showed no statistically significant differences in mean PNN50% across measurement times ($P = 0.957$ and $P = 0.818$, respectively). Repeated-measures analysis of variance comparing preadministration and postadministration time points showed no significant changes in PNN50% between the 2 groups ($P = 0.228$). The mean $\pm$ SD of PNN50% values in the drug and placebo groups are presented in

Table 1. Comparison of Mean $\pm$ SD SDNN Before and for 4 Hours After Oral Administration of Drug and Placebo ^a

Time Points and Groups	SDNN (ms)	Standard Deviation	P-Value
Baseline			0.284
Dimenhydrinate	74.66	23.33	
Placebo	65.09	24.66	
30 min			0.861
Dimenhydrinate	73.31	28.68	
Placebo	71.06	40.34	
60 min			0.218
Dimenhydrinate	108.50	135.84	
Placebo	63.98	17.34	
90 min			0.038
Dimenhydrinate	73.81	28.39	
Placebo	51.57	27.46	
120 min			0.882
Dimenhydrinate	74.02	33.87	
Placebo	76.20	45.55	
150 min			0.330
Dimenhydrinate	86.72	55.46	
Placebo	71.67	19.57	
180 min			0.216
Dimenhydrinate	75.75	25.53	
Placebo	63.78	26.21	
210 min			0.672
Dimenhydrinate	79.54	32.80	
Placebo	74.99	24.91	
240 min			0.135
Dimenhydrinate	78.90	29.18	
Placebo	63.86	24.10	

^a P-value was calculated using the paired t-test. A P-value < 0.05 was considered statistically significant.

Table 3. Pairwise comparisons at each time point using the paired t test indicated that, at the 4-hour measurement, the mean PNN50% in the drug group was significantly higher than that in the placebo group ($P = 0.027$). As illustrated in **Figure 3**, a marked decline in PNN50% was observed in the placebo group at 4 hours, whereas the drug group exhibited an increasing trend.

For LFnu, both analysis of variance and repeated-measures analyses showed no significant differences between groups ($P \approx 0.99$ and $P \approx 0.68$, respectively). Overall trends were similar, with only minor variations at 4 hours, when the placebo group showed a slight increase and the dimenhydrinate group showed a slight decrease.

High-frequency normalized units similarly showed no significant between-group differences ($P \approx 0.99$ and $P \approx 0.69$). Overall trends were comparable, with small deviations at 0.5 hours, including a slight decrease in the drug group and stable values in the placebo group, and at 4 hours, including an increase in the drug group and a decrease in the placebo group.

The LF/HF ratio also remained unaffected, with no significant differences between groups ($P \approx 0.71$ and $P \approx 0.72$) and only minor fluctuations over time that did not reach statistical significance.

Within-group analysis of SDNN indicated no significant changes across time points in either the placebo group ($P = 0.431$) or the dimenhydrinate group ($P = 0.753$). Between-group repeated-measures analysis revealed no significant

overall group-time interaction ($P = 0.106$), indicating that the temporal pattern of SDNN changes did not differ meaningfully between interventions. Pairwise comparisons showed no significant differences at most time points. Although SDNN in the placebo group showed a slight decrease at 60 minutes and SDNN in the dimenhydrinate group showed a transient increase, these variations were not statistically significant.

5. Discussion

In this double-blind crossover study, the effects of a single oral 50 mg dose of dimenhydrinate versus placebo on cardiac autonomic nervous system activity were evaluated (13). Heart rate variability, a widely accepted, noninvasive, and reliable method for estimating autonomic function, was analyzed using time-domain and frequency-domain indices (14). Overall, the findings can be summarized as follows. First, placebo administration had no significant effect on any time-domain or frequency-domain HRV indices during 5-minute short-term ECG recordings over the 4-hour postadministration period (15). Second, repeated-measures analysis of variance showed that, across all time points, 50 mg dimenhydrinate did not induce statistically significant changes in most HRV indices compared with placebo (16). Third, time-specific analyses showed modest but statistically significant increases in SDNN at 90 minutes and in RMSSD and PNN50% at 240 minutes after dimenhydrinate

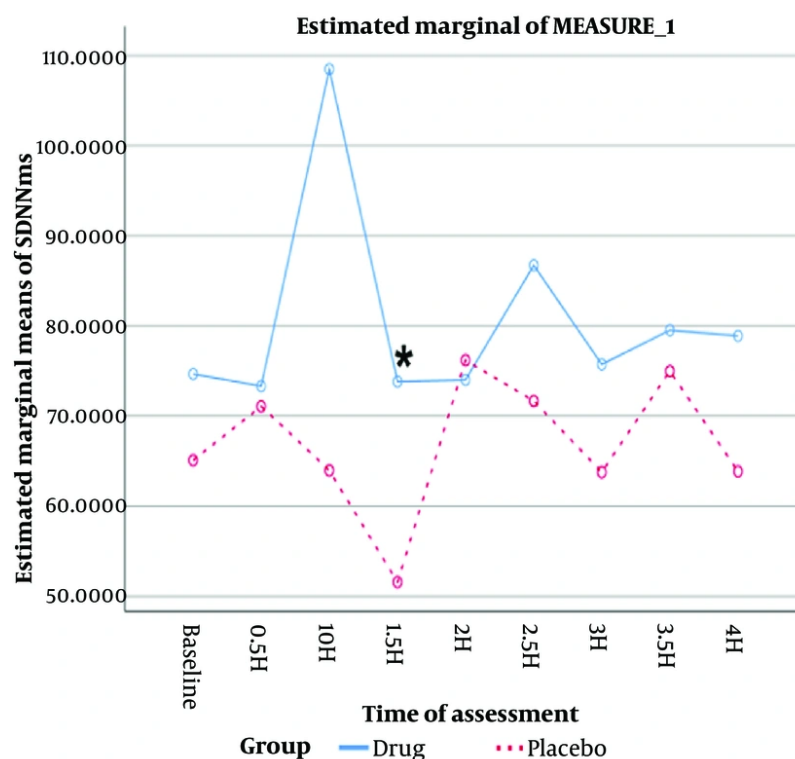


Figure 1. Mean $\pm$ SD of SDNN before and for 4 hours after oral administration of drug and placebo (values presented as mean; $P \leq 0.05$)

administration, indicating a transient enhancement of parasympathetic activity (17).

Inspection of the line plots comparing dimenhydrinate and placebo revealed a notable reduction in LFnu after dimenhydrinate intake (18). Low-frequency power, which primarily reflects sympathetic modulation within the 0.04 - 0.15 Hz frequency range, has been variably interpreted in previous studies; some reports suggest contributions from both sympathetic and vagal activity (19), whereas others emphasize a predominantly sympathetic origin, particularly when expressed in normalized units. SDNN, which represents overall HRV influenced by both sympathetic and parasympathetic activity, remained largely unchanged except at 90 minutes (4). The similarity of SDNN trends between groups supports the notion that the observed reduction in LFnu primarily reflects decreased sympathetic activity (20). This sympatholytic effect of dimenhydrinate is consistent with its H₁ receptor antagonism and the known interactions between the histaminergic and sympathetic systems, likely mediated at both ganglionic and central levels (21). These findings are

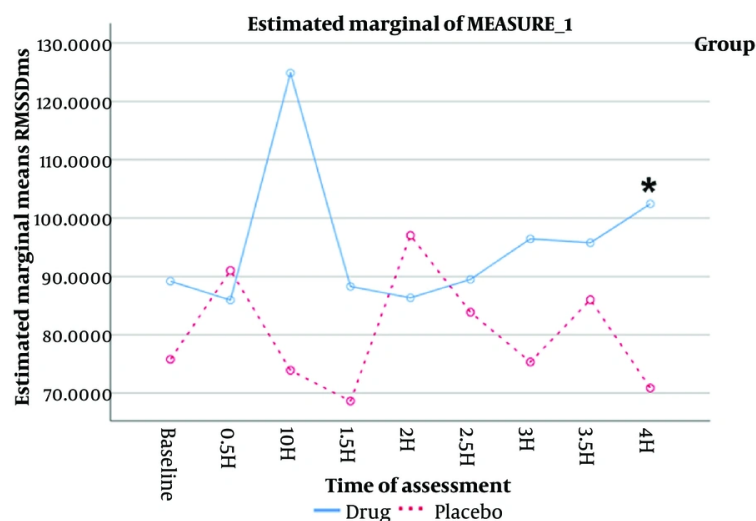
consistent with Rezaeyanzade et al., who reported sympatholytic effects of oral hydroxyzine (13), and with studies of promethazine, another first-generation H₁ antihistamine, which showed reductions in LFnu after oral administration (23). Notably, in the present study, the sympatholytic effect of dimenhydrinate became apparent 4 hours after administration, whereas the effects of hydroxyzine in prior studies emerged earlier, peaked at 30 to 120 minutes, and returned to baseline by 180 to 240 minutes (22, 23).

In addition, dimenhydrinate increased indices associated with cardiac vagal activity (24). RMSSD increased at 1, 3, and 4 hours, HFnu increased at 4 hours, and PNN50% was elevated at 4 hours after administration, indicating enhanced parasympathetic modulation (25). These changes coincide with the expected time to peak plasma concentration (3 - 6 hours) (26), supporting a temporal correlation between pharmacokinetics and vagomimetic effects. Similar effects have been reported by Rezaeyanzade et al. for hydroxyzine (13) and for promethazine (23), although the timing of maximal vagal

Table 2. Comparison of Mean $\pm$ SD RMSSD Before and for 4 Hours After Oral Administration of Drug and Placebo

RMSSD (ms) and Groups	Mean $\pm$ SD	P-value
Baseline		0.324
Drug	18.89 $\pm$ 38.20	
Placebo	75.77 $\pm$ 34.84	
30 min		0.792
Drug	85.92 $\pm$ 44.12	
Placebo	91.02 $\pm$ 59.57	
60 min		0.227
Drug	124.87 $\pm$ 157.13	
Placebo	73.90 $\pm$ 28.28	
90 min		0.261
Drug	88.27 $\pm$ 49.98	
Placebo	68.62 $\pm$ 43.61	
120 min		0.660
Drug	86.31 $\pm$ 51.32	
Placebo	97.03 $\pm$ 77.83	
150 min		0.696
Drug	89.50 $\pm$ 38.48	
Placebo	83.85 $\pm$ 39.88	
180 min		0.163
Drug	96.43 $\pm$ 44.34	
Placebo	75.31 $\pm$ 36.00	
210 min		0.581
Drug	95.75 $\pm$ 55.12	
Placebo	85.99 $\pm$ 39.26	
240 min		0.042 ^a
Drug	102.42 $\pm$ 48.70	
Placebo	70.87 $\pm$ 30.45	

^a P value < 0.05 was considered statistically significant. P-value was calculated using the paired t test.

**Figure 2.** Root mean square of RMSSD before and for 4 hours after oral administration of drug and placebo (values presented as mean; $P \leq 0.05$)

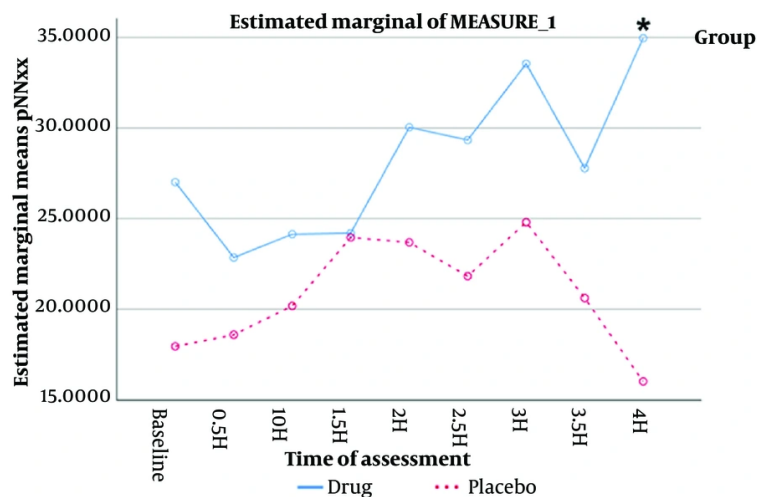
effects differed because of differences in pharmacokinetic profiles (26). Mechanistically, these findings align with animal and in vitro studies showing that H₁ receptor blockade can modulate vagal output centrally through depolarization of neurons in the dorsal motor nucleus and

nucleus tractus solitarius (27) and peripherally through effects on parasympathetic ganglia. Interestingly, despite the known anticholinergic properties of first-generation H₁ antihistamines, dimenhydrinate enhanced vagal indices in the present study, potentially because of its

Table 3. Comparison of Mean Percentage of Successive R-R Intervals Differing by PNN50% Before and for 4 Hours After Oral Administration of Drug and Placebo

PNN50% and Groups	Mean $\pm$ SD	P-Value
Baseline		0.171
Drug	27.01 $\pm$ 20.54	
Placebo	17.94 $\pm$ 14.18	
30 min		0.538
Drug	22.84 $\pm$ 20.43	
Placebo	18.58 $\pm$ 16.86	
60 min		0.607
Drug	24.13 $\pm$ 21.64	
Placebo	20.17 $\pm$ 20.02	
90 min		0.979
Drug	24.19 $\pm$ 21.05	
Placebo	23.95 $\pm$ 28.20	
120 min		0.459
Drug	30.03 $\pm$ 24.80	
Placebo	23.68 $\pm$ 21.42	
150 min		0.360
Drug	29.33 $\pm$ 21.67	
Placebo	21.82 $\pm$ 22.53	
180 min		0.268
Drug	33.55 $\pm$ 18.91	
Placebo	24.80 $\pm$ 23.28	
210 min		0.328
Drug	28.78 $\pm$ 21.75	
Placebo	20.61 $\pm$ 17.46	
240 min		0.027 ^a
Drug	34.96 $\pm$ 26.34	
Placebo	16.00 $\pm$ 16.98	

^a P value < 0.05 was considered statistically significant. P value was calculated using the paired t test.

**Figure 3.** PNN50% before and for 4 hours after oral administration of drug and placebo (values are presented as mean) ($P \geq 0.05$)

central penetration and interaction with muscarinic receptors in vagal motor nuclei (28).

Finally, the LF/HF ratio, reflecting sympathovagal balance, decreased at 4 hours after dimenhydrinate

administration, indicating a shift toward reduced sympathetic dominance and enhanced parasympathetic dominance (29). In summary, although repeated-measures analysis of variance did not reveal statistically significant overall effects of dimenhydrinate across all time points,

analyses of temporal trends showed that H₁ receptor-mediated histaminergic modulation exerts a measurable, albeit transient, influence on cardiac autonomic regulation (30). This modulatory effect is likely counterbalanced by other homeostatic mechanisms, which may explain why overall statistical significance was limited (31). Collectively, these findings highlight the nuanced role of histaminergic signaling in the autonomic control of heart rate and provide evidence that oral dimenhydrinate can transiently modulate both sympathetic and parasympathetic cardiac activity (32).

5.1. Limitations

A limitation of the present study is the relatively small sample size (n = 15), which may limit the generalizability of the findings. Although the crossover design reduces interindividual variability and strengthens internal validity, the statistical power to detect subtle effects may still be limited. Therefore, future studies with larger, adequately powered cohorts and more diverse populations are warranted to confirm and extend these findings.

5.2. Conclusions

Overall, these findings indicate that oral administration of dimenhydrinate, a first-generation H₁ receptor antihistamine capable of crossing the blood-brain barrier, stabilizes H₁ histamine receptors in their inactive state, thereby shifting cardiac sympathovagal balance toward reduced sympathetic activity and enhanced vagal activity. This effect is consistent with the peak plasma concentration of dimenhydrinate occurring between 3 and 6 hours after administration.

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Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: S. R. A.: Proposal writing, investigation, and data collection; M. R. A.: Initial study conceptualization and assistance with methodology development; M. T. H. G.: Conceptualization, methodology, supervision, writing-original draft, and critical manuscript review; E. A.: Study implementation support and practical research consultation; H. S.: Formal analysis, data

interpretation, and statistical analysis; R. P.: Study conceptualization, project administration, supervision, validation, manuscript review and editing, and research team coordination. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Clinical Trial Registration Code: The study protocol was registered in the Iranian Clinical Trial Registry (IRCT20230606058390N1).

Conflict of Interests Statement: The authors declare that there are no conflicts of interest related to this study.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethical restrictions and participant confidentiality.

Ethical Approval: The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1402.018).

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Informed Consent: Written informed consent was obtained from all participants after completion of the study procedures.

References

- Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. 2017;5: 258. [PubMed ID: 29034226]. [PubMed Central ID: PMC5624990]. <https://doi.org/10.3389/fpubh.2017.00258>.
- Billman GE. Heart rate variability-a historical perspective. *Front Physiol*. 2011;2:86. [PubMed ID: 22144961]. [PubMed Central ID: PMC3225923]. <https://doi.org/10.3389/fphys.2011.00086>.
- Lamendola P, Lanza GA, Spinelli A, Sgueglia GA, Di Monaco A, Barone L, et al. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol*. 2010;141(2):122-31. <https://doi.org/10.1016/j.ijcard.2008.11.026>.
- Electrophysiology TFOTESOCTNA. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93(5):1043-65. <https://doi.org/10.1161/01.CIR.93.5.1043>.
- Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research-recommendations. *Front Psychol*. 2017;8:213. [PubMed ID: 28265249]. [PubMed Central ID: PMC5316555]. <https://doi.org/10.3389/fpsyg.2017.00213>.
- Porta A, Tobaldini E, Guzzetti S, Furlan R, Montano N, Gneccchi-Ruscone T. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. *Am J Physiol Heart Circ Physiol*. 2007;293(1):H702-8. [PubMed ID: 17308016]. <https://doi.org/10.1152/ajpheart.00006.2007>.
- Xu X, Ding Z, Wang Z, Song Z, Chen X, Ke M. The alteration of multi-channel electrogastrography and autonomic nervous system

- function in patients with gastroesophageal reflux disease with test meal. *Neurogastroenterol Motil*. 2006;**18**(6):488-9.
8. Scharman EJ, Erdman AR, Wax PM, Chyka PA, Martin Caravati E, Nelson LS, et al. Diphenhydramine and dimenhydrinate poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol*. 2006;**44**(3):205-23. [PubMed ID: 16749537]. <https://doi.org/10.1080/15563650600585920>.
 9. Moss AJ, Chaikin P, Garcia JD, Gillen M, Roberts DJ, Morganroth J. A review of the cardiac systemic side-effects of antihistamines: Ebastine. *Clin Exp Allergy*. 1999;**29**(S3):200-5. [PubMed ID: 10444238]. <https://doi.org/10.1046/j.1365-2222.1999.0290s3200.x>.
 10. Ghanbarpour MH, Dabbagh A, Jahangirifard A, Shafigh N, Fani M, Fani K. The effect of intraoperative dexmedetomidine on postoperative delirium sedation agitation score in cardiac surgery. *Anesth Pain Med*. 2025;**15**(2). e156544. [PubMed ID: 40454256]. [PubMed Central ID: PMC12125664]. <https://doi.org/10.5812/aapm-156544>.
 11. Elghozi J, Julien C. Sympathetic control of short-term heart rate variability and its pharmacological modulation. *Fundam Clin Pharmacol*. 2007;**21**(4):337-47. [PubMed ID: 17635171]. <https://doi.org/10.1111/j.1472-8206.2007.00502.x>.
 12. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome. *Front Psychol*. 2014;**5**:1040. [PubMed ID: 25324790]. [PubMed Central ID: PMC4179748]. <https://doi.org/10.3389/fpsyg.2014.01040>.
 13. Rezaeyanzade F, Ahangar N, Alipour A, Ghaemian A, Akbari E. Transient modulation of hydroxyzine, an antihistamine and anxiolytic agent, on the cardiac autonomic activity in healthy subjects. *Physiol Pharmacol*. 2019;**23**(1):59-69.
 14. Plaza-Florido A, Sacha J, Alcantara JM. Short-term heart rate variability in resting conditions: Methodological considerations. *Kardiol Pol*. 2021;**79**(7 - 8):745-55. [PubMed ID: 34227676]. <https://doi.org/10.33963/kp.a2021.0054>.
 15. Driscoll D, DiCicco G. The effects of metronome breathing on the variability of autonomic activity measurements. *J Manipulative Physiol Ther*. 2000;**23**(9):610-4. [PubMed ID: 11145801]. <https://doi.org/10.1067/jmmt.2000.110944>.
 16. Carter JR. Microneurography and sympathetic nerve activity: A decade-by-decade journey across 50 years. *J Neurophysiol*. 2019;**121**(4):1183-94. [PubMed ID: 30673363]. [PubMed Central ID: PMC6485724]. <https://doi.org/10.1152/jn.00570.2018>.
 17. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: Meta-analysis. *Psychiatry Investig*. 2018;**15**(3):235-45. [PubMed ID: 29486547]. [PubMed Central ID: PMC5900369]. <https://doi.org/10.30773/pi.2017.08.17>.
 18. Wang HM, Huang SC. SDNN/RMSSD as a surrogate for LF/HF: A revised investigation. *Model Simul Eng*. 2012;**2012**(1):931943-8. <https://doi.org/10.1155/2012/931943>.
 19. von Rosenberg W, Chanwimalueang T, Adjei T, Jaffer U, Goverdovsky V, Mandic DP. Resolving ambiguities in the LF/HF ratio: LF-HF scatter plots for the categorization of mental and physical stress from HRV. *Front Physiol*. 2017;**8**: 360. [PubMed ID: 28659811]. [PubMed Central ID: PMC5469891]. <https://doi.org/10.3389/fphys.2017.00360>.
 20. Khan WN, Tobias JD. Diphenhydramine: A review of its clinical applications and potential adverse effect profile. *J Pediatr Pharmacol Ther*. 2025;**30**(2):182-90. [PubMed ID: 40717751]. [PubMed Central ID: PMC12288571]. <https://doi.org/10.5863/1551-6776-30.2.182>.
 21. Manzo Atencio AS, Pérez de Manzo FA, Velasco M. Blood levels of histamine and norepinephrine in humans with sympathetic hyperactivity. *Gaceta Médica de Caracas*. 2020;**128**(4):512-524. <https://doi.org/10.47307/gmc.2020.128.4.7>.
 22. Sanchez A, Valverde A, Sinclair M, Mosley C, Singh A, Mutsaers AJ, et al. Antihistaminic and cardiorespiratory effects of diphenhydramine hydrochloride in anesthetized dogs undergoing excision of mast cell tumors. *J Am Vet Med Assoc*. 2017;**251**(7):804-13. [PubMed ID: 28967819]. <https://doi.org/10.2460/javma.251.7.804>.
 23. Brown TE, Eckberg DL. Promethazine affects autonomic cardiovascular mechanisms minimally. *J Pharmacol Exp Ther*. 1997;**282**(2):839-44. [PubMed ID: 9262349]. [https://doi.org/10.1016/s0022-3565\(24\)36852-1](https://doi.org/10.1016/s0022-3565(24)36852-1).
 24. Laborde S, Allen MS, Borges U, Iskra M, Zammit N, You M, et al. Psychophysiological effects of slow-paced breathing at six cycles per minute with or without heart rate variability biofeedback. *Psychophysiology*. 2022;**59**(1). e13952. [PubMed ID: 34633670]. <https://doi.org/10.1111/psyp.13952>.
 25. Flores-Monroy J, Ramírez-Hernández D, Lezama-Martínez D, Velasco-Bejarano B. Effects of dimenhydrinate on motor behavior and vascular function: Possible implications for the field of sports. *Drug Test Anal*. 2025;**17**(9):1750-8. [PubMed ID: 40049629]. [PubMed Central ID: PMC12401633]. <https://doi.org/10.1002/dta.3875>.
 26. Szabadi E, Hou RH, Langley RW, Bradshaw CM. Comparison of the effects of modafinil and diphenhydramine on arousal and autonomic functions in healthy volunteers. *Br J Clin Pharmacol*. 2006;**61**(5):619-20.
 27. Hey JA, Del Prado M, Cuss FM, Egan RW, Sherwood J, Lin CC, et al. Antihistamine activity, central nervous system and cardiovascular profiles of histamine H1 antagonists: Comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. *Clin Exp Allergy*. 1995;**25**(10):974-84. [PubMed ID: 8556569]. <https://doi.org/10.1111/j.1365-2222.1995.tb00400.x>.
 28. Labarinas S, Meulmester K, Greene S, Thomas J, Virk M, Erkonen G. Extracorporeal cardiopulmonary resuscitation after diphenhydramine ingestion. *J Med Toxicol*. 2018;**14**(3):253-6. [PubMed ID: 29956117]. [PubMed Central ID: PMC6097973]. <https://doi.org/10.1007/s13181-018-0672-6>.
 29. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, et al. Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. *J Am Coll Cardiol*. 2008;**52**(17):1353-65. [PubMed ID: 18940523]. <https://doi.org/10.1016/j.jacc.2008.07.041>.
 30. Brenner IK, Thomas S, Shephard RJ. Autonomic regulation of the circulation during exercise and heat exposure: Inferences from heart rate variability. *Sports Med*. 1998;**26**(2):85-99. [PubMed ID: 9777682]. <https://doi.org/10.2165/00007256-199826020-00003>.
 31. Turrigiano G. Homeostatic synaptic plasticity: Local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb Perspect Biol*. 2012;**4**(1):a005736-a005736. [PubMed ID: 22086977]. [PubMed Central ID: PMC3249629]. <https://doi.org/10.1101/cshperspect.a005736>.
 32. Levick SP. Histamine receptors in heart failure. *Heart Fail Rev*. 2022;**27**(4):1355-72. [PubMed ID: 34622365]. <https://doi.org/10.1007/s10741-021-10166-x>.