Original Article

Autonomic Function Tests in Diabetic Hypertensive and Non-Diabetic Hypertensive Patients: A Case-Control Study

Kafeel Ahmad[1], Eqbal Anwer[2], Abdul Majid Siddiqui[3], Tanya Tripathi[4], Mohd Yaseen[5]

[1]Post Graduate Junior Resident, [2]Professor and Head, [3]Assistant Professor, [4]Assistant Professor, Dept of Pathology, Career Institute of Medical Sciences and Hospital, Lucknow, UP, India, [5]Professor, Dept of Medicine, Career Institute of Medical Sciences and Hospital, Lucknow, UP, India.

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Abstract

Background and Objective: Cardiovascular autonomic dysfunction is common in long-standing hypertension and diabetes, both of which carry elevated cardiovascular risk. Although extensively studied in each condition separately, the comparative assessment between diabetic hypertensive (DH) and non-diabetic hypertensive (NDH) patients is sparse. This study compared cardiovascular autonomic functions in these two groups using standard clinical tests, highlighting the degree and patterns of autonomic impairment in each.

Methods: This study included 260 participants split into two groups: 130 DH patients (cases) and 130 NDH patients (controls), matched for age, sex, and duration of hypertension. Data on baseline clinical characteristics, including body mass index (BMI), duration of hypertension, glycemic control, and comorbidities, were recorded. Standard cardiovascular autonomic function tests were performed, including the heart rate response to deep breathing (HRDB), Valsalva maneuver (Valsalva ratio), orthostatic blood pressure changes, handgrip test, and heart rate variability (HRV) analysis. Statistical comparisons were made using univariate and multivariate analyses to account for covariates such as age, sex, and body mass index.

Results: The DH group showed significantly lower HRDB and HRV indices than the NDH group ($p < 0.05$). Furthermore, the drop in systolic blood pressure upon standing was more pronounced in the DH group, while the Valsalva ratio was decreased to a similar extent in both groups, suggesting a significant parasympathetic impairment in DH participants. Duration of diabetes, poor glycemic control (higher HbA1c), and longer duration of hypertension were significantly correlated with impaired autonomic function.

Conclusion: Diabetic hypertensive patients exhibit more pronounced abnormalities in cardiovascular autonomic control when compared to non-diabetic hypertensive patients. Comprehensive autonomic function testing should be considered in routine clinical assessments for hypertensive patients, especially those with concomitant diabetes, to detect and manage autonomic dysfunction at an early stage.

Keywords: Diabetic hypertension, Non-diabetic hypertension, Autonomic function tests, Cardiovascular autonomic neuropathy, Heart rate variability, Valsalva maneuver, Orthostatic hypotension.

Corresponding Author: Kafeel Ahmad, Post Graduate Junior Resident, Dept of Physiology, Career Institute of Medical Sciences and Hospital, Lucknow, UP, India.

E-mail: dockafeelahmad2025@gmail.com

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Introduction

Cardiovascular diseases (CVDs) are leading causes of morbidity and mortality worldwide, with essential hypertension as a major contributor.[1] Type 2 diabetes mellitus (DM) is also a significant public health concern due to its rising prevalence and complications.[2] When hypertension and diabetes coexist, cardiovascular risk escalates. A critical complication of both is autonomic nervous system (ANS) dysfunction, which regulates cardiac function and vascular tone.[3]

Autonomic dysfunction (or autonomic neuropathy in diabetes) affects both parasympathetic and sympathetic components. Chronic hyperglycemia and metabolic derangements damage nerve fibers, leading to diabetic autonomic neuropathy (DAN).[4] DAN manifests as cardiovascular autonomic dysfunction, characterized by reduced heart rate variability, abnormal blood pressure responses, and impaired autonomic reflexes. Hyperglycemia-induced oxidative stress and advanced glycation end products (AGEs) further contribute to nerve damage.[5]

In hypertension, chronic blood pressure elevations affect vascular and autonomic reflexes. [6] Baroreceptor desensitization impairs blood pressure control, while structural changes in the heart and blood vessels contribute to autonomic imbalance. Over time, hypertension leads to blunted autonomic responses, further disrupting sympathetic-parasympathetic regulation.[7]

While autonomic dysfunction in diabetes and hypertension is well-documented separately, fewer studies compare the degree and pattern of dysfunction in diabetic hypertensive (DH) versus non-diabetic hypertensive (NDH) patients. The coexistence of these conditions may accelerate oxidative stress, endothelial dysfunction, and renin-angiotensin-aldosterone system (RAAS) activation, leading to more severe autonomic impairment.[8]

Unrecognized cardiac autonomic dysfunction increases the risk of arrhythmias, silent myocardial ischemia, and sudden cardiac death.[9] In DM, autonomic dysfunction may diminish ischemic pain perception, delaying myocardial infarction diagnosis. Additionally, it impairs blood pressure regulation, leading to dizziness or syncope. [10]These complications reduce quality of life and escalate healthcare costs, underscoring the need for early detection and intervention.[11]

Standard tests of cardiac autonomic function evaluate both parasympathetic and sympathetic function. Some of the most commonly employed clinical tests includeheart rate response to deep breathing (HRDB) evaluating parasympathetic function via heart rate variation during respiration; valsalvamaneuvermeasuring autonomic reactivity through RR interval changes during the maneuver, orthostatic blood pressure changes assessing sympathetic function via blood pressure and heart rate variations upon standing; isometric handgrip test evaluating sympathetic control based on blood pressure response to sustained handgrip; and heart rate variability (HRV) analysis: examining autonomic balance using frequency and time-domain parameters.

Given the high prevalence of hypertension and diabetes, understanding their combined impact on autonomic function is crucial. Identifying specific autonomic impairment patterns can improve risk stratification and guide targeted interventions. This case-control study compares autonomic dysfunction in DH and NDH patients to determine the additive effects of diabetes on hypertensive autonomic impairment. [4] The findings may aid clinicians in assessing autonomic dysfunction severity in DH patients, leading to improved screening and management strategies.[8]

This study evaluates cardiovascular autonomic function in DH and NDH patients using standard non-invasive tests, comparing autonomic parameters between groups. It also examines associations between autonomic dysfunction and clinical variables such as diabetes duration, hypertension duration, glycemic control, and BMI.

Methods

Study Design

This study was a hospital-based, case-control study conducted over 12 months at the Department of Medicine and Physiology of a tertiary care teaching hospital. Ethical clearance was obtained

from the Institutional Ethics Committee vide approval no CIMSH/IEC/MAR/2024/1 dated 11.03.2024 prior to the commencement of the study. Informed written consent was obtained from all participants.

Study Population

Participants were divided into two groups:

1. **Case Group (Diabetic Hypertensive, DH):**
   - o Diagnosed with hypertension (as per Joint National Committee guidelines: systolic blood pressure ≥ 140 mmHg and/ or diastolic blood pressure ≥ 90 mmHg, or on anti-hypertensive medication).
   - o Diagnosed with type 2 diabetes mellitus (fasting plasma glucose ≥126 mg/dL or on glucose-lowering agents).
   - o Age range: 40-55 years.
   - o No history of other causes of autonomic neuropathy (e.g., chronic renal failure, Parkinson's disease, etc.).
2. **Control Group (Non-Diabetic Hypertensive, NDH):**
   - o Matched for age and sex with DH participants.
   - o Diagnosed with hypertension (same criteria as DH).
   - o No diagnosis of diabetes mellitus (fasting plasma glucose <126 mg/dL, HbA1c <6.5%).
   - o Age range: 40-55 years.
   - o No history of other causes of autonomic neuropathy.

Exclusion criteria for both groups included pregnancy, congestive heart failure, advanced kidney or liver disease, significant anemia, and severe musculoskeletal disorders that could interfere with test procedures.

Sample Size

A sample size of 260 participants (130 in each group) was determined based on power calculations from prevalence of 9.3%[17] with a power of 80% and an alpha error of 0.05.

Data Collection

Clinical Evaluation: All participants underwent a detailed clinical history and examination. Demographic data, duration of hypertension, duration of diabetes (where applicable), BMI, and current medications were recorded. A thorough neurological examination was also performed to rule out neurological conditions that might confound the autonomic function results.

Laboratory Investigations:

- o Fasting plasma glucose, postprandial plasma glucose, and glycated hemoglobin (HbA1c) levels for the DH group to assess glycemic control.
- o Lipid profile to assess dyslipidemia.
- o Serum creatinine and estimated glomerular filtration rate (eGFR) to exclude significant renal impairment.

Anthropometric Measurements: Weight and height were measured to calculate BMI.

Autonomic Function Tests

All tests were performed in a temperature-controlled, quiet environment. Patients were instructed to refrain from smoking, caffeine, and alcohol for at least 12 hours and to abstain from strenuous exercise for 24 hours before testing.

1. **Heart Rate Response to Deep Breathing (HRDB)[12]:** Participants were instructed to lie supine and breathe at a rate of six breaths per minute (5 seconds of inspiration, 5 seconds of expiration). The difference between the maximum and minimum heart rates during each respiratory cycle was calculated. Three cycles were recorded, and the mean value was taken.
2. **Valsalva Maneuver[13]:** Participants blew into a mouthpiece connected to a mercury manometer and maintained a pressure of 40 mmHg for 15 seconds while ECG was continuously recorded. The Valsalva ratio was computed as the ratio of the longest RR interval shortly after the maneuver to the shortest RR interval during the strain phase.
3. **Orthostatic Blood Pressure Measurement[14]:** Blood pressure was measured after 5 minutes of supine rest and then 1 minute

and 3 minutes after standing. The change in systolic and diastolic blood pressure upon standing was recorded. A drop of ≥20 mmHg systolic or ≥10 mmHg diastolic was considered orthostatic hypotension.

4. **Handgrip Test (Isometric Exercise)[15]:** Participants were asked to maintain one-third of their maximum voluntary contraction for 3 minutes using a handgrip dynamometer. Blood pressure was recorded at rest and at 1 minute and 3 minutes of sustained handgrip. The rise in diastolic blood pressure was taken as the measure of sympathetic responsiveness.

5. **Heart Rate Variability (HRV) Analysis[16]:** A 5-minute ECG recording in the supine position under resting conditions was collected. Time-domain measures (SDNN, RMSSD) and frequency-domain parameters (LF, HF, LF/HF ratio) were computed using standard HRV analysis software.

Statistical Analysis

Data were entered and analyzed using SPSS version 26.0. Mean ± standard deviation (SD) was used for continuous variables, and frequencies/percentages for categorical variables. Group comparisons were done with the Student's t-test or Mann-Whitney U test for continuous variables, and chi-square test for categorical variables. Multivariable linear regression was used to explore the relationship between potential predictors (duration of diabetes, HbA1c, duration of hypertension, BMI) and autonomic parameters. A p-value <0.05 was considered statistically significant.

Results

1. Baseline Characteristics

A total of 260 participants were included in this study, with 130 diabetic hypertensive (DH) patients serving as cases and 130 non-diabetic hypertensive (NDH) patients serving as controls. Table 1 summarizes the demographic and clinical parameters for both groups.

Table 1. Baseline Characteristics of the Study Population

Parameter	DH (n=130)	NDH (n=130)	p-value
Age (years), mean ± SD	53.49 ± 1.25	53.14 ± 1.77	0.049
Male/Female, n (%)	66 (51) / 64 (49)	61 (47) / 69 (53)	0.62
BMI (kg/m^2), mean ± SD	29.75 ± 1.33	29.43 ± 1.50	0.129
Duration of Hypertension (years)	7.61 ± 1.4	7.27 ± 1.9	0.106
Duration of Diabetes (years)	6.6 ± 1.20	-	-
HbA1c (%), mean ± SD	8.3 ± 0.24	5.47 ± 0.12	<0.001*
Systolic BP (mmHg)	148.50 ± 2.16	145.41 ± 1.93	<0.001*
Diastolic BP (mmHg)	92.60 ± 1.91	90.16 ± 1.71	<0.001*
Fasting Plasma Glucose (mg/dL)	155.90 ± 6.42	101.40 ± 3.76	<0.001*

** p < 0.05 denotes statistical significance.*

Both groups were well matched for age, sex distribution, BMI, and duration of hypertension. As expected, fasting plasma glucose and HbA1c levels were significantly higher in the DH group.

2. Heart Rate Response to Deep Breathing (HRDB)

In the DH group, HRDB was markedly reduced compared to the NDH group (p < 0.001), indicating significant parasympathetic dysfunction. The mean HRDB in DH patients was 10.90 ± 1.14 beats per minute (bpm), whereas in NDH patients, it was 17.40 ± 1.43 bpm.

3. Valsalva Maneuver

The Valsalva ratio was significantly reduced in DH compared to NDH (1.23 ± 0.03 vs. 1.30 ± 0.03; p = 0.000). While both values were borderline-low compared to a healthy population reference (commonly >1.2 is regarded as normal), the difference suggests an increased burden of autonomic dysfunction in DH.

4. Orthostatic Hypotension

Orthostatic changes in systolic blood pressure (SBP) were evaluated. In the DH group, 26 (20%) participants exhibited a drop in SBP ≥20 mmHg upon standing, while 11 (8.46%) participants in the NDH group showed this level of drop (p = 0.012). The mean decrease in SBP was 15.50 ± 1.29 mmHg in DH and 9.70 ± 1.62 mmHg in NDH (p = 0.000). This indicates a more pronounced sympathetic impairment in the diabetic cohort.

5. Handgrip Test

The isometric handgrip test results revealed that the mean rise in diastolic blood pressure (DBP) during sustained handgrip was significantly lower in the DH group (13.80 ± 0.98 mmHg) compared to the NDH group (18.80 ± 1.25 mmHg), p < 0.001. This further supports the presence of sympathetic dysfunction in DH patients.

6. Heart Rate Variability (HRV) Analysis

A 5-minute ECG recording was used to compute both time- and frequency-domain parameters.

- **Time-Domain Parameters:**
  - SDNN (ms): 69.50 ± 2.51 in DH vs. 85.80 ± 3.55 in NDH (p < 0.001).
  - RMSSD (ms): 20.80 ± 1.73 in DH vs. 29.10 ± 2.63 in NDH (p < 0.001).
- **Frequency-Domain Parameters (ms^2):**
  - Low Frequency (LF): 384.50 ± 14.62 in DH vs. 466.00 ± 17.65 in NDH (p = 0.01).
  - High Frequency (HF): 158.00 ± 9.03 in DH vs. 228.70 ± 11.09 in NDH (p < 0.001).
  - LF/HF Ratio: 2.44 ± 0.18 in DH vs. 2.04 ± 0.10 in NDH (p = 0.01).

Overall, HRV measures were significantly decreased in the DH group, indicating impaired autonomic modulation, especially in the parasympathetic domain (low HF), but also an increased sympathetic dominance (higher LF/HF ratio).

Table 2. Summary of Autonomic Function Tests

Parameter	DH (n=130)	NDH (n=130)	p-value
HRDB (bpm)	10.90 ± 1.14	17.40 ± 1.43	< 0.001*
Valsalva Ratio	1.23 ± 0.03	1.30 ± 0.03	< 0.001*
Δ SBP on Standing (mmHg)	15.50 ± 1.29	9.70 ± 1.62	< 0.001*
Orthostatic Hypotension [n (%)]	26 (20%)	11 (8.46%)	0.012
Handgrip Test (Rise in DBP, mmHg)	13.80 ± 0.98	18.80 ± 1.25	< 0.001*
SDNN (ms)	69.50 ± 2.51	85.80 ± 3.55	< 0.001*
RMSSD (ms)	20.80 ± 1.73	29.10 ± 2.63	< 0.001*
LF (ms^2)	384.50 ± 14.62	466.00 ± 17.65	< 0.001*
HF (ms^2)	158.00 ± 9.03	228.70 ± 11.09	< 0.001*
LF/HF Ratio	2.44 ± 0.18	2.04 ± 0.10	< 0.001*

** p < 0.05 denotes statistical significance.*

7. Correlational Analyses

Pearson's correlation was used to assess the relationship between key clinical variables (duration of diabetes, HbA1c, duration of hypertension, and BMI) and autonomic parameters. Multiple linear regression analyses were subsequently performed for parameters with significant correlations.

Duration of Diabetes: Negatively correlated with HRDB (r = -0.47, p < 0.001), Valsalva ratio (r = -0.48, p < 0.001), handgrip test (r= -0.408, p < 0.001), SDNN (r=-0.933, p < 0.001), RMSSD (r=-0.378, p < 0.001). Positively correlated with delta SBP on standing (r=0.324, p < 0.001) and LF/HF ratio (r=0.361, p < 0.001). Longer duration of diabetes significantly predicted lower parasympathetic indices.

HbA1c: Showed a significant negative correlation with Valsalva ratio (r = -0.619, p < 0.001), handgrip test (r= -0.208, p =0.017), SDNN (r=-0.555,

p < 0.001), RMSSD (r=-0.380, p < 0.001), delta SBP on standing (r=0.318, p < 0.001) Elevated HbA1c was an independent predictor of reduced parasympathetic function in multivariate analysis (β = -0.29, p = 0.003).

Duration of Hypertension: Moderately but significantly correlated with reduced Valsalva ratio (r = 0.383, p < 0.001), delta SBP on standing (r=0.320, p < 0.001), SDNN (r = -0.24, p = 0.005), RMSSD (r=0.237, p=0.007) and LF/HF ratio (r=-0.413, p < 0.001). In the combined multivariate model, duration of hypertension retained significance in predicting overall autonomic dysfunction (β = -0.24, p = 0.01).

BMI: BMI was significantly correlated with HRDB (r=0.243, p=0.005), Valsalva ratio (r=0.192, p=0.029), delta SBP (r=-0.462, p<0.001), handgrip test (r=-0.208, p=0.017), SDNN (r=0.316, p=0.000) and RMSSD (r=-0.400, p<0.001).

Discussion

The present study demonstrates that individuals with coexistent hypertension and type 2 diabetes have significantly greater cardiovascular autonomic dysfunction compared to those with hypertension alone. As measured by HRDB, Valsalva ratio, and HF power, the DH group displayed more severe parasympathetic dysfunction compared to NDH. Sympathetic dysfunction was also greater in DH, as evident from a higher incidence of orthostatic hypotension and a blunted handgrip response. Both time and frequency domain indices supported a shift toward sympathetic dominance in DH patients. Longer duration of diabetes, poorer glycemic control, and to a lesser degree, longer duration of hypertension were associated with more severe autonomic dysfunction. The results underscore the additive or synergistic adverse effects of chronic hyperglycemia on top of the vascular and autonomic consequences of hypertension. Several specific findings warrant detailed discussion in the context of existing literature.

A clear trend emerged indicating marked reductions in parasympathetic function in the diabetic hypertensive (DH) group, evidenced by lower HRDB, lower Valsalva ratio, reduced RMSSD, and reduced HF power in HRV analysis. These findings align with prior studies which noted that parasympathetic fibers are often affected earliest and most prominently in diabetic autonomic neuropathy. [18, 19] The chronic hyperglycemic environment leads to microvascular damage in the vasa nervorum, reduced nerve conduction velocity, and direct neurotoxic effects of advanced glycation end-products. Hence, the presence of diabetes, even when relatively well controlled, can exacerbate the autonomic dysfunction already present in hypertensive individuals.[20, 21]

In non-diabetic hypertensive (NDH) individuals, heightened sympathetic drive and decreased baroreflex sensitivity partially explain the observed mild reductions in parasympathetic markers such as HRDB. However, our findings suggest that superimposition of type 2 diabetes significantly amplifies these changes, possibly by direct neuronal injury, the generation of reactive oxygen species (ROS), and endothelial dysfunction that further impairs neural control.[22, 23]

Although traditional teaching holds that sympathetic fibers tend to be spared until later stages of diabetic neuropathy, our study revealed significant impairments in sympathetic function in DH patients. Notably, 20% of DH participants met the criteria for orthostatic hypotension, more than double the prevalence in the NDH group. A plausible explanation is that hypertension itself exerts chronic stress on the baroreceptors and vascular smooth muscle, contributing to a diminished capacity to respond to postural changes. The concurrent metabolic and vascular insults from diabetes further compromise neuronal function.[24]

Multiple studies corroborate these findings, indicating that diabetic neuropathy eventually involves both parasympathetic and sympathetic fibers, particularly in patients with longer disease durations or poor glycemic control.[8]Our correlational analyses, showing significant links between autonomic test abnormalities and both diabetes duration and HbA1c, reinforce the concept that prolonged exposure to hyperglycemia accelerates neuronal injury.

HRV analysis provides a more nuanced perspective on autonomic control, often detecting early subclinical dysfunction. We found that both time-domain (SDNN, RMSSD) and frequency-domain (HF

power, LF/HF ratio) parameters were significantly altered in DH. The combination of decreased HF (parasympathetic) and comparatively normal or even slightly elevated LF (sympathetic) results in an increased LF/HF ratio, reflecting autonomic imbalance. This result parallels prior literature in which type 2 diabetes is a well-documented risk factor for reduced HRV. [8] Concomitant hypertension accentuates these changes via reduced arterial compliance and amplified sympathetic outflow.

Interestingly, while NDH patients also displayed some reduction in HRV compared to healthy reference values reported in prior studies, the degree of decline was milder than in the DH group. This demonstrates that while hypertension alone compromises autonomic function, the superimposed diabetic state causes an appreciably greater insult.

Several earlier investigations have independently analyzed diabetic and hypertensive populations, but fewer have directly contrasted these two groups as we have. In one study by Ewing and Clarke[25], among patients with diabetes, abnormal HRDB and Valsalva ratios were frequently observed, indicating an early parasympathetic deficit. Studies also emphasizes that poor glycemic control is a prime driver of autonomic dysfunction in diabetes. [26] While these studies did not include a comparative hypertensive-only control group, their findings echo our results regarding the strong association between hyperglycemia and autonomic impairment.

On the hypertension side, studies have shown decreased baroreflex sensitivity and lower HRV in hypertensive patients compared to normotensives, pointing to an imbalance favoring sympathetic dominance. [27] However, the effect magnitude described in these papers is less pronounced than that observed in diabetic cohorts, underscoring that diabetes is likely the stronger determinant of autonomic neuropathy.

In a case-control analysis closer to our design, study by Low PA et al [28] investigated autonomic function in hypertensive diabetics versus normotensive diabetics. They found that hypertensive diabetics had worse autonomic indices than those with diabetes alone, highlighting the detrimental synergy of combined diseases. Our study expands on this perspective by comparing diabetic hypertensives with non-diabetic hypertensives, adding new clarity to the role of hyperglycemia.

The results of this study have immediate clinical relevance. Autonomic dysfunction increases the risk of arrhythmias, silent myocardial infarction, and sudden death in both diabetic and hypertensive populations. This risk is likely compounded when both conditions coexist, indicating an urgent need for vigilance. Study by Kaze et al [9] analyzing a large cohort of 4842 participants found that CAN was significantly associated with an increased risk of incident silent myocardial infarction. Standard screening tests such as HRDB, orthostatic blood pressure measurements, or short-term HRV could be implemented in routine clinical practice to identify at-risk individuals early. Our analysis suggests that good glycemic control (lower HbA1c) may offer some protection against severe autonomic dysfunction. Clinicians should therefore prioritize optimizing metabolic parameters in DH patients. Aggressive but safe control of blood pressure might mitigate further autonomic deterioration, as improved baroreflex sensitivity is documented after successful antihypertensive therapy in some studies. However, caution is essential when initiating therapy in a patient with significant autonomic dysfunction since orthostatic hypotension could be exacerbated. Beyond glucose and blood pressure, addressing lifestyle factors such as obesity, physical inactivity, and smoking cessation is vital. Pharmacological strategies that may exert beneficial effects on autonomic function (e.g., ACE inhibitors, ARBs, or beta-blockers) should be considered, although their specific impact on autonomic neuropathy remains an area of ongoing research.

This study has its strength in a direct head-to-head comparison of DH and NDH groups, which allowed for a clearer delineation of diabetes-specific contributions to autonomic dysfunction. Comprehensive autonomic testing, including both traditional bedside tests (HRDB, Valsalva, orthostatic BP) and HRV analysis, provides a robust assessment of autonomic function. Also, statistical controls for confounders like age, BMI, and duration of hypertension were beneficial.

However, limitations do exist. This was a single-center study with a moderate sample size, which may limit the generalizability of findings. Potential confounders such as medication types (e.g., beta-blockers, ACE inhibitors) could influence autonomic indices, although medication use was relatively well balanced between groups and accounted for in some analyses. The cross-sectional design precludes inferences about causality. Prospective longitudinal data would be ideal to confirm the progression of autonomic dysfunction over time.

Conclusion

Diabetic hypertensive patients show significantly worse autonomic dysfunction than their non-diabetic counterparts, with marked reductions in parasympathetic indicators (e.g., HRDB, Valsalva ratio, HF-HRV) and higher rates of orthostatic hypotension, suggesting impaired sympathetic control as well. Poor glycemic control and longer diabetes duration strongly correlate with this dysfunction. Clinically, unrecognized or uncontrolled autonomic impairment can precipitate serious cardiovascular events, highlighting the need for regular autonomic assessments in this population. Future studies should investigate whether better glycemic and blood pressure control can reverse or attenuate these deficits, ultimately improving cardiovascular outcomes for patients bearing the dual burden of diabetes and hypertension.

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