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Original Research Article

Graded Loss of Cardiac Autonomic Function across HbA1c Strata in Type 2 Diabetes: A Cross-Sectional Study of Resting Heart Rate, Heart Rate Variability and Orthostatic Blood Pressure Response

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Abstract:

Objectives: We measured resting heart rate, short-term heart rate variability and the orthostatic blood pressure response in patients with type 2 diabetes stratified by glycated haemoglobin, and asked whether autonomic impairment tracks glycaemic exposure in a graded fashion rather than appearing only at the extreme.

Materials and Methods: One hundred adults with type 2 diabetes attending the medicine outpatient department were studied cross-sectionally in three strata by HbA1c: <7.0% (n = 32), 7.0–8.5% (n = 38) and >8.5% (n = 30). After 10 min supine rest, a 5-min lead II electrocardiogram was recorded for time-domain and frequency-domain analysis. Ewing's battery was performed, and blood pressure was measured supine and at 1 and 3 min of standing. Groups were compared by one-way ANOVA with Tukey post hoc testing; independent effects were tested by multiple linear and logistic regression.

Results: Resting heart rate rose across strata (70.2 ± 7.6, 76.3 ± 6.8 and 83.6 ± 8.3 beats/min; $p < 0.001$) while SDNN fell (46.7 ± 10.3, 42.7 ± 9.9 and 27.7 ± 9.5 ms; $p < 0.001$), as did RMSSD and pNN50. The systolic fall on standing widened from +1.1 ± 6.3 to −11.5 ± 6.3 mmHg ($p < 0.001$). Orthostatic hypotension occurred only in the >8.5% stratum (23.3%; $p < 0.001$). HbA1c correlated with RMSSD ($r = −0.715$) and with the systolic orthostatic change ($r = −0.636$). Each 1% rise in HbA1c predicted a 4.23 ms fall in SDNN independent of age, duration and body mass index.

Conclusion: Autonomic impairment was already measurable in the 7.0–8.5% stratum and was not confined to patients with overtly poor control.

Keywords: Cardiac Autonomic Neuropathy; Glycated Haemoglobin; Heart Rate Variability; Orthostatic Hypotension; Type 2 Diabetes Mellitus.

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Introduction

Cardiac autonomic neuropathy carries a mortality risk that most Indian diabetes clinics never quantify, because the tests that detect it sit outside routine follow-up. India now accounts for the largest absolute number of adults living with diabetes worldwide, and the burden is concentrated in exactly the middle-aged working population in whom silent ischaemia and perioperative instability matter most.[1] The American Diabetes Association position statement on diabetic neuropathy places cardiovascular autonomic testing firmly within recommended care, yet uptake at district and teaching hospital level in Gujarat remains patchy.[2]

The physiology is not in dispute. Vagal fibres to the sinoatrial node degenerate before sympathetic fibres, producing an early resting tachycardia, a narrowed beat-to-beat variability and, later, a failure of the vasoconstrictor response that maintains standing blood pressure.[3] What remains less settled is the shape of the relationship with glycaemic exposure. Is there a threshold beyond which autonomic function deteriorates, or does the loss accrue steadily with each increment of HbA1c? The Toronto consensus panel set out the methods but did not resolve the dose-response question.[4] Ewing's original battery, still the reference standard four decades on, was validated against mortality rather than against glycaemia.[5] And the 1996 Task Force standards for heart rate variability were written for cardiology populations, with diabetic cohorts treated as a subgroup.[6]

A meta-analysis of 25 studies found consistent reductions in both time-domain and frequency-domain indices in type 2 diabetes compared with controls, though heterogeneity across recording protocols was substantial.[7] Smaller cross-sectional work has compared well-controlled with poorly controlled patients dichotomously, typically

at a 7% cut-off, and reported lower SDNN and RMSSD in the poorly controlled group.[8] Dichotomising discards information. If the intermediate stratum — the 7.0–8.5% band where a large share of our outpatient population actually sits — already shows measurable impairment, that changes who deserves screening.

So we measured resting heart rate, short-term heart rate variability and the orthostatic blood pressure response in 100 patients with type 2 diabetes across three HbA1c strata, using equipment available in any physiology department.

Materials and Methods

Study design and setting: This cross-sectional study was conducted in the Department of Physiology, Shri M. P. Shah Government Medical College, Jamnagar, in collaboration with the Department of Medicine, Guru Gobind Singh Government Hospital, over [ ] months from [month year] to [month year]. Approval was obtained from the Institutional Ethics Committee (approval number [ ], dated [ ]) and written informed consent was taken from every participant in Gujarati or English as preferred.

Participants: Adults aged 30–65 years with type 2 diabetes of at least one year's duration, diagnosed by American Diabetes Association criteria and attending the medicine outpatient department, were recruited by consecutive sampling.

We excluded patients with known ischaemic heart disease, atrial fibrillation or any non-sinus rhythm, heart failure, stage 3 or worse chronic kidney disease, a history of stroke, chronic obstructive pulmonary disease, thyroid dysfunction, pregnancy, and alcohol dependence.

Drugs that confound autonomic testing were an exclusion: beta-blockers, non-dihydropyridine calcium channel blockers, tricyclic antidepressants and anticholinergics. Patients on antihypertensive agents from other classes were retained, since excluding them would have removed roughly [ ]% of the eligible pool and biased the sample towards atypically healthy diabetics.

Sample size was fixed at 100 on the basis of an expected difference in SDNN of 10 ms between the best- and worst-controlled strata with a pooled SD of 12 ms, giving 80% power at $\alpha = 0.05$ with a design allowance for unequal group sizes [confirm with statistician; recalculate if the ethics committee asks for the exact formula used].

Participants were assigned to three strata by their HbA1c on the day of testing: <7.0%, 7.0–8.5% and >8.5%. The middle boundary follows common Indian clinical practice, where 8.5% is often the point at which therapy is escalated rather than titrated.

Preparation and measurements: Participants were asked to avoid caffeine, tobacco and heavy exertion for 12 h before testing, and to take their usual morning medication with a light breakfast. All recordings were made between 09:00 and 12:00 in a quiet room at 24–26 °C to limit circadian and thermal effects on autonomic tone.

Height and weight were measured with a stadiometer and a digital weighing scale, and body mass index calculated as weight in kilograms divided by height in metres squared. Venous samples for fasting plasma glucose and HbA1c were drawn the same morning; HbA1c was estimated by [HPLC / immunoturbidimetric method] on a [instrument name and manufacturer] in the Department of Biochemistry, and the laboratory participates in [external quality assurance scheme].

Electrocardiographic recording and heart rate variability: After 10 min of supine rest, a continuous lead II electrocardiogram was recorded for 5 min on a [make and model] digital ECG machine at a sampling rate of [ ] Hz, with the participant breathing quietly and not speaking. RR intervals were extracted and the tachogram inspected manually; ectopic beats and artefacts were corrected by interpolation, and any record with more than 5% corrected beats was discarded and repeated. Time-domain and frequency-domain analysis followed the Task Force standards, using [software name and version].[6]

We report SDNN, RMSSD and pNN50 from the time domain. Frequency-domain analysis by fast Fourier transform yielded total power (0.003–0.40 Hz), low-frequency power (0.04–0.15 Hz), high-frequency power (0.15–0.40 Hz), the two latter expressed in normalised units, and the LF/HF ratio.

Cardiovascular reflex tests: Ewing's battery was performed in a fixed order with 5 min rest between tests.[5] For the expiration–inspiration ratio, participants breathed at six breaths per minute for one minute, paced by the investigator, and the ratio of the longest RR interval during expiration to the shortest during inspiration was taken as the mean of six cycles.

The 30:15 ratio was calculated from the RR interval at beats 30 and 15 after standing from supine. For the Valsalva manoeuvre, participants blew into a mouthpiece against 40 mmHg for 15 s, and the ratio of the longest RR interval after release to the shortest during strain was recorded. Sustained handgrip was performed at 30% of maximum voluntary contraction for up to 5 min, with the rise in diastolic pressure in the contralateral arm taken as the response. Each test was scored 0 (normal), 0.5 (borderline) or 1 (abnormal) against conventional cut-offs, and the summed Ewing score was used to

grade autonomic involvement as normal, early, definite or severe.

Orthostatic blood pressure: Blood pressure was measured with a validated aneroid sphygmomanometer [make and model], calibrated at [interval], using an appropriately sized cuff on the right arm. Three supine readings were taken one minute apart after the rest period, and the mean used. The participant then stood unaided, and readings were taken at 1 and 3 min with the arm supported at heart level.

Orthostatic hypotension was defined by the consensus criteria as a fall of at least 20 mmHg systolic or at least 10 mmHg diastolic within 3 min of standing.[9] The 3-min value is reported throughout.

Statistical Analysis: Analysis was done in [SPSS version 26.0]. Normality was checked by the Shapiro–Wilk test and by inspection of Q–Q plots. Continuous variables are given as mean ± SD and compared across the three strata by one-way ANOVA with Tukey's honestly significant difference for post hoc comparison; skewed variables were also checked by Kruskal–Wallis testing, which did not alter any conclusion. Categorical variables are given as counts with percentages and compared by the chi-square test. Associations between HbA1c as a continuous variable and each autonomic index were examined by Pearson and Spearman coefficients. Multiple linear regression was used to test whether HbA1c predicted SDNN, RMSSD, resting heart rate and the systolic orthostatic change independently of age, duration of diabetes, body mass index and sex. Binary logistic regression was used for orthostatic hypotension. A two-sided $p < 0.05$ was taken as significant.

Results

Baseline Characteristics: The 100 participants had a mean age of 51.4 ± 8.0 years and comprised 53 men and 47 women, with no difference in sex distribution across strata ($p = 0.998$). Age and body mass index did not differ significantly between strata (Table 1), which matters, because both influence heart rate variability and would otherwise confound the comparison. Duration of diabetes did differ, rising from 5.6 ± 3.0 years in the <7.0% stratum to 9.9 ± 4.3 years in the >8.5% stratum ($F = 12.83$, $p < 0.001$), and this was carried forward into the regression models. Fasting plasma glucose separated the strata as expected.

Table 1: Baseline characteristics by HbA1c stratum (mean ± SD unless stated)

Variable	<7.0% (n = 32)	7.0–8.5% (n = 38)	>8.5% (n = 30)	F	p
Age (years)	51.4 ± 7.8	50.7 ± 8.8	52.3 ± 7.3	0.34	0.714
Male, n (%)	17 (53.1)	20 (52.6)	16 (53.3)	χ^2 0.00	0.998
BMI (kg/m²)	25.5 ± 3.8	26.0 ± 3.5	27.1 ± 3.9	1.49	0.231
Duration of diabetes (years)	5.6 ± 3.0	7.0 ± 2.9	9.9 ± 4.3	12.83	<0.001
Fasting plasma glucose (mg/dL)	125.7 ± 19.1	153.3 ± 17.2	203.8 ± 19.0	143.73	<0.001
HbA1c (%)	6.45 ± 0.35	7.75 ± 0.41	9.92 ± 0.75	351.57	<0.001
Supine systolic BP (mmHg)	126.9 ± 10.3	128.7 ± 11.4	131.7 ± 10.4	1.56	0.216
Supine diastolic BP (mmHg)	78.8 ± 6.9	81.2 ± 6.1	80.8 ± 6.4	1.40	0.252

Resting heart rate and heart rate variability: Resting heart rate climbed by roughly 13 beats/min across the three strata, from 70.2 ± 7.6 to 83.6 ± 8.3 beats/min ($F = 24.77$, $p < 0.001$), and every pairwise comparison was significant on Tukey testing (Table 2). No participant met the conventional definition of resting tachycardia above 100 beats/min, which is worth stating plainly — the shift was a distributional one, not a matter of a few outliers dragging the mean. RMSSD showed the steepest gradient, falling from 41.9 ± 6.8 ms to 21.6 ± 7.3 ms ($F = 50.99$, $p < 0.001$), with all three pairwise differences significant. SDNN fell from 46.7 ± 10.3 to 27.7 ± 9.5 ms, but here the difference between the first two strata did not reach significance on post hoc testing ($p = 0.228$) while both comparisons against the >8.5% stratum did ($p < 0.001$). Total power dropped from 2005 ± 634 to 1213 ± 518 ms². The normalised low-frequency component rose and the high-frequency component fell only in the worst-controlled stratum, with no separation between the first two, so the LF/HF ratio rose from 1.14 ± 0.33 to 1.64 ± 0.51 largely on the strength of that third group.

The distribution of these indices across strata is shown in Figure 1.

Table 2: Resting heart rate and heart rate variability by HbA1c stratum

Variable	<7.0% (n = 32)	7.0–8.5% (n = 38)	>8.5% (n = 30)	F	p	Tukey p (1v2, 1v3, 2v3)
Resting heart rate (beats/min)	70.2 ± 7.6	76.3 ± 6.8	83.6 ± 8.3	24.77	<0.001	0.003, <0.001, <0.001
SDNN (ms)	46.7 ± 10.3	42.7 ± 9.9	27.7 ± 9.5	31.59	<0.001	0.228, <0.001, <0.001
RMSSD (ms)	41.9 ± 6.8	31.8 ± 9.2	21.6 ± 7.3	50.99	<0.001	<0.001, <0.001, <0.001
pNN50 (%)	17.3 ± 3.6	11.7 ± 4.9	7.1 ± 4.4	42.85	<0.001	<0.001, <0.001, <0.001
Total power (ms²)	2005 ± 634	1576 ± 481	1213 ± 518	16.42	<0.001	0.004, <0.001, 0.021
LF (n.u.)	52.0 ± 7.8	52.9 ± 7.4	60.7 ± 7.9	12.14	<0.001	0.868, <0.001, <0.001
HF (n.u.)	47.9 ± 7.7	46.9 ± 7.5	39.4 ± 7.9	11.44	<0.001	0.840, <0.001, <0.001
LF/HF ratio	1.14 ± 0.33	1.18 ± 0.36	1.64 ± 0.51	14.75	<0.001	0.879, <0.001, <0.001

Cardiovascular reflex tests and orthostatic response: All five Ewing tests deteriorated across strata (Table 3). The expiration–inspiration ratio fell from 1.38 ± 0.11 to 1.20 ± 0.09 and separated all three groups. The systolic pressure change on standing moved from a small rise of 1.1 ± 6.3 mmHg in the best-controlled stratum to a fall of 11.5 ± 6.3 mmHg in the worst ($F = 27.68$, $p < 0.001$). The diastolic change followed the same direction but discriminated only the >8.5% stratum.

Sustained handgrip produced a diastolic rise of 21.0 ± 4.8 mmHg in the first stratum and 13.4 ± 6.3 mmHg in the third, which suggests the efferent sympathetic limb was affected as well as the vagal one.

Table 3: Cardiovascular reflex tests and orthostatic blood pressure response

Variable	<7.0% (n = 32)	7.0–8.5% (n = 38)	>8.5% (n = 30)	F	p
E:I ratio	1.38 ± 0.11	1.28 ± 0.11	1.20 ± 0.09	24.22	<0.001
30:15 ratio	1.26 ± 0.10	1.20 ± 0.11	1.12 ± 0.10	13.96	<0.001
Valsalva ratio	1.47 ± 0.13	1.40 ± 0.11	1.31 ± 0.11	13.25	<0.001
Δ Systolic BP on standing (mmHg)	+1.1 ± 6.3	−3.4 ± 7.5	−11.5 ± 6.3	27.68	<0.001
Δ Diastolic BP on standing (mmHg)	+1.2 ± 4.3	−0.2 ± 3.8	−5.3 ± 4.7	20.44	<0.001
Handgrip Δ diastolic BP (mmHg)	21.0 ± 4.8	17.6 ± 4.9	13.4 ± 6.3	15.58	<0.001

Orthostatic hypotension by consensus criteria was found in 7 patients overall, all of them in the >8.5% stratum, giving a within-stratum prevalence of 23.3% ($\chi^2 = 17.56$, $p < 0.001$).

Three of these had a systolic fall of 20 mmHg or more; the remainder qualified on the diastolic criterion. Only two reported symptoms on standing, which is consistent with the usual clinical experience that the finding is picked up on measurement rather than on history. Some autonomic abnormality — an Ewing score above zero — was present in 59 of 100 patients, rising from 25.0% in the <7.0% stratum to 63.2% and then 90.0% (Table 4).

Definite cardiac autonomic neuropathy, meaning two or more abnormal tests, was found in 10 patients of the >8.5% stratum and in one patient of the middle stratum. None reached the severe category, probably because we excluded patients with established cardiac and renal disease, in whom the worst scores tend to cluster.

Table 4: Ewing score and grade of cardiac autonomic neuropathy

Category	<7.0% (n = 32)	7.0–8.5% (n = 38)	>8.5% (n = 30)	p
Ewing score (mean ± SD)	0.12 ± 0.22	0.41 ± 0.38	1.02 ± 0.64	<0.001
Normal, n (%)	24 (75.0)	14 (36.8)	3 (10.0)	<0.001
Early CAN, n (%)	8 (25.0)	23 (60.5)	17 (56.7)	
Definite CAN, n (%)	0 (0)	1 (2.6)	10 (33.3)	
SDNN <20 ms, n (%)	0 (0)	0 (0)	7 (23.3)	<0.001
E:I ratio <1.11, n (%)	0 (0)	2 (5.3)	5 (16.7)	0.032
30:15 ratio <1.04, n (%)	0 (0)	4 (10.5)	6 (20.0)	0.032
Handgrip Δ DBP <10 mmHg, n (%)	0 (0)	1 (2.6)	9 (30.0)	<0.001
Orthostatic hypotension, n (%)	0 (0)	0 (0)	7 (23.3)	<0.001

Correlation and regression: Treated as a continuous variable, HbA1c correlated with every autonomic index tested.

The strongest associations were with RMSSD ($r = −0.715$, $p < 0.001$) and pNN50 ($r = −0.699$, $p < 0.001$), followed by SDNN ($r = −0.659$), the systolic orthostatic change ($r = −0.636$), the E:I ratio ($r = −0.612$) and resting heart rate ($r = +0.595$). Spearman coefficients were close to the Pearson values throughout, so the relationships were not being

driven by a monotonic non-linearity or by a handful of extreme values. Figure 2 shows the scatter for SDNN and for the systolic orthostatic change against HbA1c. In multiple linear regression adjusting for age, duration of diabetes, body mass index and sex, each 1% increment of HbA1c predicted a 4.23 ms fall in SDNN (95% CI −5.59 to −2.88; p < 0.001) and a 5.13 ms fall in RMSSD (95% CI −6.33 to −3.92; p < 0.001), with the models accounting for 54.9% of the variance in each (Table 5). Resting heart rate rose by 3.53 beats/min per 1% of HbA1c (95% CI 2.36 to 4.69; p < 0.001), and the systolic orthostatic change worsened by 3.23 mmHg (95% CI −4.23 to −2.22; p < 0.001). Age and duration of diabetes retained independent effects on SDNN but not on resting heart rate. Body mass index and sex did not contribute significantly to any model, though the study was not powered to detect small effects of either. Logistic regression gave an odds ratio for orthostatic hypotension of 2.37 per 1% of HbA1c (95% CI 1.12 to 5.01; p = 0.024) after adjusting for age and duration. The confidence interval is wide, as it must be with seven events, and this estimate should be read as directional rather than precise.

Table 5: Multiple linear regression with HbA1c as predictor, adjusted for age, duration, BMI and sex

Dependent variable	B for HbA1c (per 1%)	95% CI	p	Model R^2
SDNN (ms)	−4.23	−5.59 to −2.88	<0.001	0.549
RMSSD (ms)	−5.13	−6.33 to −3.92	<0.001	0.549
Resting heart rate (beats/min)	+3.53	+2.36 to +4.69	<0.001	0.365
Δ Systolic BP on standing (mmHg)	−3.23	−4.23 to −2.22	<0.001	0.445

A longitudinal follow-up of the same cohort, repeating the battery at [12 or 24] months alongside serial HbA1c, would answer the question this design cannot.

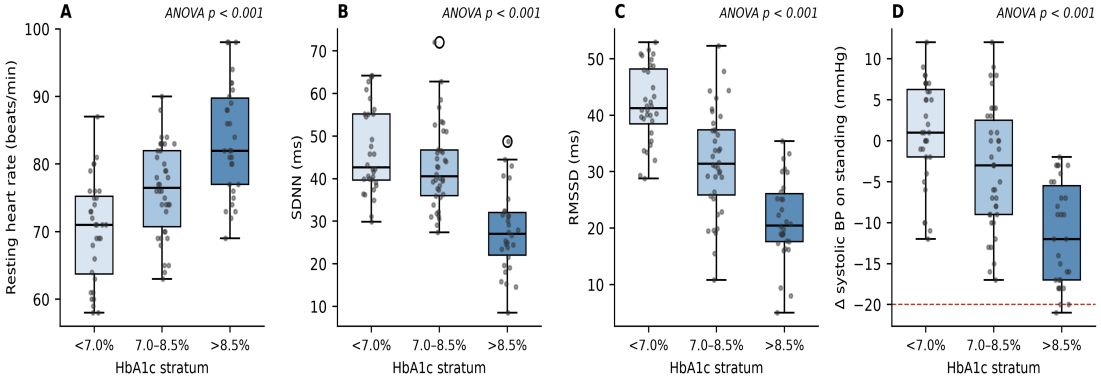


Figure 1: Distribution of resting heart rate (A), SDNN (B), RMSSD (C) and the change in systolic blood pressure at 3 min of standing (D) across the three HbA1c strata. Boxes show median and interquartile range, whiskers 1.5 × IQR, with individual observations overlaid. The dashed line in panel D marks the −20 mmHg threshold for orthostatic hypotension. One-way ANOVA p < 0.001 for each panel.

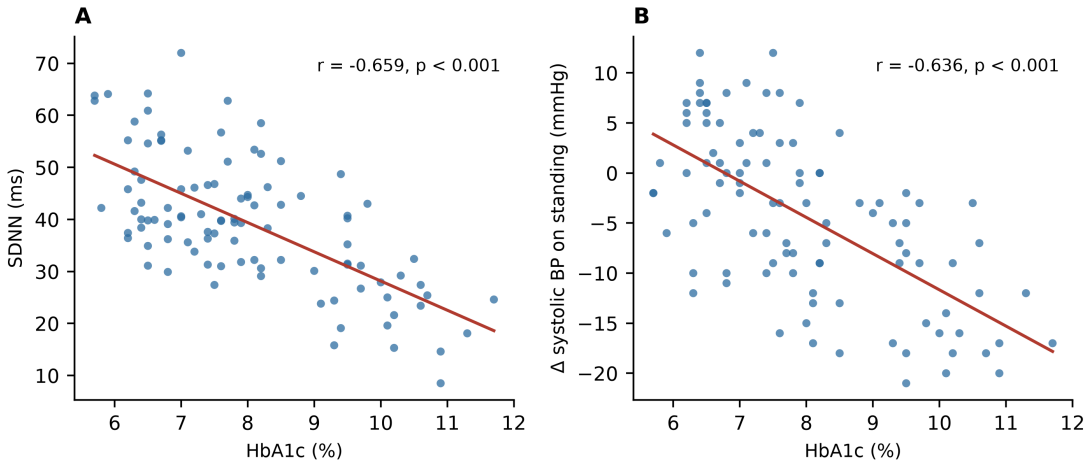


Figure 2: Scatter plots of HbA1c against SDNN (A) and against the change in systolic blood pressure at 3

min of standing (B), with least-squares regression lines. Pearson coefficients are shown; n = 100.

Discussion

The gradient was continuous, not stepped. Patients in the 7.0–8.5% band already had a resting heart rate 6 beats/min higher and an RMSSD 10 ms lower than the well-controlled group, and 63% of them had at least one abnormal reflex test. That is the finding with practical consequence, because these are patients a physician would ordinarily describe as reasonably controlled and would not think to send for autonomic testing.

Our resting heart rate gradient sits close to what has been reported elsewhere. A large cohort from eastern China found HbA1c positively correlated with resting heart rate in type 2 diabetes, though with a much weaker coefficient than ours ($\rho = 0.15$ against our 0.56), which is what one expects when a broad community sample is compared with a stratified hospital sample selected to spread the exposure.[10] The heart rate variability findings agree in direction with the meta-analytic estimate of reduced SDNN and RMSSD in type 2 diabetes.[7] The MIDUS analysis reported that HbA1c predicted adverse differences in high-frequency and low-frequency variability among participants with diabetes but not among those without, which fits our observation that the frequency-domain shift appeared mainly in the >8.5% stratum.[11]

The orthostatic findings deserve a more careful reading. Our overall prevalence of orthostatic hypotension was 7%, well below the pooled estimate of 24% from a meta-analysis of diabetic cohorts.[12]

Three things probably explain the gap. We excluded patients on beta-blockers and those with established cardiac or renal disease, our participants were younger than most published cohorts, and we used the 3-min standing value rather than a tilt protocol. Studies using head-up tilt consistently report higher figures. What our data do show, and what matters more than the absolute prevalence, is that the systolic response shifted progressively even in patients who never crossed the diagnostic threshold — a mean fall of 3.4 mmHg in the middle stratum is subclinical, but it is not nothing.

An Indian study from a tertiary centre found heart rate variability reduced in type 2 diabetes within the first five years of diagnosis, before any clinical sign of neuropathy.[13] Work from Iraq using Ewing's battery reported that HbA1c and duration correlated with the severity of cardiovascular autonomic neuropathy, with age and waist–hip ratio contributing.[14] A study from Odisha found autonomic neuropathy in 83% of patients with type 2 diabetes and an odds ratio above 10 for an HbA1c of 6.5% or more, considerably higher than our figures.[15] Their cohort was older and included patients with longer disease duration, and they did not exclude those with cardiac comorbidity, so the difference in prevalence is unsurprising. The direction of association is the same in all of these. Whether the association is causal cannot be settled by a cross-sectional design. Chronic hyperglycaemia damages autonomic fibres through polyol flux, advanced glycation end-product accumulation and microvascular ischaemia of the vasa nervorum, and the vagus is affected first because it is the longest autonomic nerve.[3] But reduced parasympathetic tone also raises resting heart rate, which in turn associates with insulin resistance, and the arrow could point both ways. Duration of diabetes was longer in our worst-controlled stratum and retained an independent effect on SDNN, so cumulative exposure and current control are not fully separable here.

The practical suggestion is a modest one. A 5-min supine electrocardiogram and a standing blood pressure measurement take under fifteen minutes and need no equipment beyond what a physiology department already owns. Applying that to patients above 7.0% rather than waiting for symptoms or for an HbA1c above 9% would identify a group in whom silent ischaemia and intraoperative hypotension are more likely, and in whom the anaesthetist would want to know before an elective procedure.

Several limitations qualify all of this. The sample of 100 is adequate for the group comparisons but thin for the logistic model, where seven events cannot support a precise odds ratio. A single HbA1c measurement stands in for years of glycaemic exposure, and a time-weighted average would have been better if the records allowed it. We had no non-diabetic control group, so the values in our <7.0% stratum cannot be assumed normal — they are simply the best-controlled diabetics in the sample, and Indian reference data for short-term heart rate variability remain scarce. Short 5-min recordings capture vagal indices well but estimate SDNN and total power less reliably than 24-h Holter monitoring.

Respiratory rate was paced only during the E:I test and not during the 5-min resting recording, which introduces variance into the high-frequency band that we could not control. And we did not test for distal symmetric polyneuropathy or retinopathy, so we cannot say whether cardiac autonomic involvement preceded or followed other microvascular complications in these patients.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels: International Diabetes Federation; 2025. Available from:

https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/ [Last accessed on 2026 Aug 14].
2. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic neuropathy: A position statement by the American Diabetes Association. Diabetes Care 2017;40:136-54. doi:10.2337/dc16-2042. PMID: 27999003.
3. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-79. doi:10.2337/diacare.26.5.1553. PMID: 12716821.
4. Bernardi L, Spallone V, Stevens M, Hilsted J, Frontoni S, Pop-Busui R, Ziegler D, Kempler P, Freeman R, Low P, Tesfaye S, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy. Methods of investigation for cardiac autonomic dysfunction in human research studies. Diabetes Metab Res Rev 2011;27:654-64. doi:10.1002/dmrr.1224. PMID: 21695761.
5. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8:491-8. doi:10.2337/diacare.8.5.491. PMID: 4053936.
6. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-65. PMID: 8598068.
7. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, Dutheil F. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. PLoS One 2018;13:e0195166. doi:10.1371/journal.pone.0195166. PMID: 29608603.
8. Nganou-Gnindjio CN, Mba CM, Azabji-Kenfack M, Dehayem MY, Mfeukeu-Kuate L, Mbanya JC, Sobngwi E. Poor glycemic control impacts heart rate variability in patients with type 2 diabetes mellitus: A cross sectional study. BMC Res Notes 2018;11:599. doi:10.1186/s13104-018-3692-z. PMID: 30126442.
9. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21:69-72. doi:10.1007/s10286-011-0119-5. PMID: 21431947.
10. Chen X, Lu F, Zhang J, Du X, Xu C, Liang M, Chen L, Zhong J. The association between resting heart rate and HbA1c-assessed glycemic control in patients with type 2 diabetes in Eastern China. Front Endocrinol (Lausanne) 2025;16:1478575. doi:10.3389/fendo.2025.1478575. PMID: 40589519.
11. Huang Y, Chen H, Hu D, Wan R. Blood hemoglobin A1c might predict adverse differences in heart rate variability in a diabetic population: Evidence from the Midlife in the United States (MIDUS) study. Front Endocrinol (Lausanne) 2022;13:921287. doi:10.3389/fendo.2022.921287.
12. Zhou Y, Ke SJ, Qiu XP, Liu LB. Prevalence, risk factors, and prognosis of orthostatic hypotension in diabetic patients: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e8004.doi:10.1097/MD.0000000000008004. PMID: 28885363.
13. John APP, Udupa K, Avangapur S, Sujan MU, Inbaraj G, Vasuki PP, Mahadevan A, Anilkumar R, Shekar MA, Sathyaprabha TN. Cardiac autonomic dysfunctions in type 2 diabetes mellitus: An investigative study with heart rate variability measures. Am J Cardiovasc Dis 2022;12:224-32. PMID: 36147784.
14. Dhumad MM, Hamdan FB, Khudhair MS, Al-Matubsi HY. Correlation of staging and risk factors with cardiovascular autonomic neuropathy in patients with type II diabetes mellitus. Sci Rep 2021;11:3576. doi:10.1038/s41598-021-80962-w. PMID: 33574349.
15. Meher M, Panda JK. Impact of glycemic control over cardiac autonomic neuropathy. J Diabetes Metab Disord 2020;19:1339-44. doi:10.1007/s40200-020-00653-7. PMID: 33520839.