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Heart rate variability in patients with atrial fibrillation and hypertension

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Abstract

Background: Atrial fibrillation (AF) and hypertension are independently associated with impaired autonomic function determined using heart rate variability (HRV). As these conditions frequently co-exist, we sought to determine whether AF would worsen HRV in hypertensive patients.

Design: We studied HRV in AF (and hypertension) (n = 61) and hypertension control group (n = 33). The AF (and hypertension) group was subdivided into permanent AF (n = 30) and paroxysmal AF (n = 31) and re-studied. Time-domain, frequency-domain and nonlinear measures of HRV were determined. Permanent AF group (n = 30) was followed up after 8 weeks following optimisation of their heart rate and blood pressure (BP).

Results: Time-domain and nonlinear indices of HRV were higher in AF (and hypertension) group compared to hypertensive controls ($P \leq .01$). Time-domain and nonlinear indices of HRV were higher in permanent AF group compared to paroxysmal AF ($P \leq .001$). Permanent AF was an independent predictor of HRV on multivariable analysis ($P = .006$). Optimisation of heart rate and BP had no significant impact on HRV in permanent AF.

Conclusions: AF, independent of hypertension, is characterised with marked HRV and is possibly related to vagal tone. HRV is higher in permanent AF compared to paroxysmal AF suggesting evident autonomic influence in the pathophysiology of permanent AF. Modulation of autonomic influence on cardiovascular system should be explored in future studies.

KEYWORDS

atrial fibrillation, autonomic nervous system, heart rate variability, hypertension

Thomas, Fisher, and Lip are joint senior authors.

1 | INTRODUCTION

Atrial fibrillation (AF) is widely recognised as a significant cardiovascular condition associated with poor outcomes.[1] There is increasing evidence that abnormalities of the cardiac autonomic nervous system (ANS) are involved in the pathogenesis of AF.[2] The cardiac ANS has a significant role in the atrial environment, predisposing to the substrate, perpetuators and triggers for AF.[3] This includes direct electrophysiological effects leading to alterations in atrial structure.[3]

In majority of patients with AF, reflex excitation of cardiac myocytes due to AF itself together with involvement of concomitant risk factors such as hypertension, obesity and obstructive sleep apnoea influence cardiac ANS activity.[3] As such, the cardiac ANS plays a central pathophysiological role in the initiation and progression of AF. Additionally, cardiac ANS activation might also determine the presence and severity of AF-related episodes, such as dizziness, presyncope or syncope secondary to impaired baroreflex or carotid sinus sensitivity.[4,5]

Studies have reported that both sympathetic and parasympathetic branches of the cardiac ANS are involved in the pathophysiology of AF.[6-8] Exploring cardiac ANS is possible through heart rate variability (HRV) evaluation. HRV has been studied extensively in patients with normal sinus rhythm and shown to have important prognostic implications for various cardiovascular disorders including hypertension.[9-12] However, there have been limited reports examining HRV in AF.[13-15]

Barauskiene et al have shown that HRV is significantly lower in AF patients compared to controls.[16] Conversely, Freedman and colleagues found HRV to be greater in lone AF than other cardiac disorders.[17] Even then these studies examined HRV in AF patients while they were in sinus rhythm at the time of the study. However, using selective pharmacological blockade of cardiac sympathetic and parasympathetic activity, van den Berg and colleagues determined that HRV is related to vagal tone in AF patients when not in sinus rhythm.[13] Given these findings, and the high propensity of AF and hypertension to co-exist, we hypothesised that HRV will be worsened in patients with AF and hypertension, compared to hypertension alone, and that optimisation of AF and BP therapy would improve HRV.

2 | METHODS

2.1 | Participants

Eligible participants underwent screening against inclusion and exclusion criteria before being invited to take part in the study (see Supplementary Material). Participants were provided with detailed information sheets, and written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki (2013). The study was approved by the Health Research Authority (HRA) and National Research and Ethics Service (NREC) Committee London—Camden & Kings Cross (18/LO/1064). Anonymised data and materials have been made publicly available at the Harvard Dataverse and can be accessed at https://doi.org/10.7910/DVN/ST2UUL. Reporting of the study conforms to broad EQUATOR guidelines.[18]

A total of 94 participants were recruited from the AF and hypertension services at Sandwell and West Birmingham Hospitals NHS Trust between October 2018 and March 2019. No participants were excluded from the study after initial screening. The patients recruited were representative of the typical patients seen in outpatient clinics. We recruited 2 groups of patients: those with AF (and hypertension) ($n = 61$) and hypertensive controls ($n = 33$). Patients with AF were stable on rate control and antithrombotic medication. The AF (and hypertension) group was further subdivided into permanent AF ($n = 30$) and paroxysmal AF (PAF) ($n = 31$). Permanent AF was defined as an episode of AF in which efforts to restore normal sinus rhythm had either failed or been abandoned. PAF was defined as an episode of AF that terminated spontaneously or with intervention in less than seven days. The hypertension control group included patients with hypertension (defined as previous diagnosis of hypertension or clinic BP of >140/90 mmHg) but not AF. These patients had additional cardiovascular risk factors similar to the other two groups and acted as the control group.

Initially, a cross-sectional age/gender-matched comparison of the two main groups (AF (and hypertension) versus hypertension control) was carried out. This was followed by a comparison of the two subgroups of AF (and hypertension) group, that is PAF and permanent AF. Lastly, the patients with permanent AF (and hypertension) ($n = 30$) were studied longitudinally with a single follow-up interval at 8 weeks duration following optimisation of their heart rate and BP medication. The medication optimisation was carried out by a single clinician with experience in managing these conditions and involved either increasing the dosage of existing cardiovascular medication or addition of new medication (for which the prescription was provided) according to participants' needs, allergy status, known contraindications and clinical indication. These patients underwent the same measurements as at their first visit.

2.2 | Experimental protocol

Participants were expected to fast from food, water, caffeine and withhold their cardiovascular medications except anticoagulation for at least 12 hours prior to their appointment. At the study appointment, anthropometric measurements were taken to determine BMI (weight (kg)/height $(m)^2$). An

ECG was performed on all participants to determine baseline heart rhythm (during both visits for longitudinal comparison). Venous samples were taken for full blood count, renal function, liver function, fasting glucose, lipid profile, thyroid function and clotting profile. A full transthoracic echocardiogram study was requested if a participant did not have a recent echocardiogram. Subsequent measurements were performed in a temperature-controlled room under uniform conditions with participants resting quietly in the supine position on a medical examination couch.

2.3 | Measurements

Three serial BP readings were taken over 5 minutes to determine an average. This was followed by assessment of participants' cardiac autonomic function through heart rate variability test. Three ECG leads were attached to the chest which were then connected to a small portable eMotion Faros ECG sensor (eMotion Faros, Bittium Biosignals Ltd). The ECG sensor was connected to a laptop with the Cardioscope software (Cardioscope Analytics, SMART Medical Ltd) via bluetooth to enable real-time ECG rhythm analysis. The ECG is analysed in real time for artefacts and arrhythmia to ensure accurate results are recorded in the HRV data, automatically excluding ectopic beats.

Participants were provided with clear instructions and allowed to practice before readings were taken. Participants remained resting quietly on the couch with the ECG sensor connected to their chest for a period of 5 minutes and ECG data transmitting to the laptop. Following a 5-minute rest period, participants were asked to breath in time to a metronome device set at 12 breaths per minute while lying on the couch for another 5 minutes. The study visit ended and the ECG data were subsequently analysed in line with the European Society of Cardiology (ESC) and the North America Society of Pacing and Electrophysiology standards of measurement of heart rate variability.[9] The ECG data were independently assessed and verified to exclude any artefacts, pauses, ectopics, etc.

The Cardioscope software was unable to provide any reliable frequency-domain indices values for permanent AF group based on the recommended ESC and the North America Society of Pacing and Electrophysiology standards of measurement of HRV. This persisted despite re-analysing data with Kubios HRV software (Kubios, Finland).[9] Therefore, frequency-domain analysis was not carried out to compare differences between the two groups.

2.4 | Statistical analysis

Descriptive statistics are presented as mean ± standard deviation (SD) or median with interquartile range, as appropriate for continuous variables. Categorical variables are expressed as numbers and percentages. Statistical analysis was performed using SPSS software, version 26 (SPSS Inc). Continuous variables were tested for normality using the Shapiro-Wilk test. Non-normally distributed data were logarithmically transformed and distribution rechecked with a Shapiro-Wilk test. If passed, data were analysed using independent Student's *t* test (for cross-sectional comparison) or Student's paired *t* test (for longitudinal comparison). Data that were still not normally distributed were analysed with the Mann-Whitney U test (for cross-sectional comparison) or Wilcoxon signed rank test (for longitudinal comparison). A P value of $< .05$ was considered statistically significant.

Associations between HRV indices and co-variates were assessed before and after adjustment for potential confounders using linear regression analysis. Multivariable regression analysis was carried out with individual independent variables found to have significant regression on univariable analysis adjusted for age, gender, body mass index (BMI), presence of ischaemic heart disease (IHD), presence of type 2 diabetes mellitus (DM) and creatinine clearance (CrCl).

To test specific hypothesis ('Patients with AF and hypertension will have worse parameters of autonomic function compared to hypertension control group'), we recruited 94 patients in total, split between 2 groups (a) AF and hypertension (b) hypertension control. This part of the study was powered based on independent t test, comparing the mean rMSSD values across the two groups. Barauskiene et al reported a mean rMSSD value of 29.44 milliseconds (standard deviation (SD) = 7.458) in AF group.[16] Assuming our SD is similar, the minimum sample size was computed as 9 patients per group at 90% power, 5% alpha and effect size of 1.69.

3 | RESULTS

3.1 | Matched AF (and hypertension) group vs matched hypertension control group

Participants from the AF (and hypertension) and hypertension control groups were well matched (see Table 1). Hypertension control group had more patients with a background of chronic kidney disease (CKD) ($P = .01$). HRV measurements at baseline and with metronome (Table 2) show that there were no significant differences in mean heart rate between the two groups. Time-domain indices of HRV were all significantly higher in the AF (and hypertension) group compared to the hypertension control group. Frequency-domain indices showed no significant differences between the two groups.

Nonlinear indices and cardiac vagal index (CVI) were all significantly higher in AF (and hypertension) group. Cardiac

TABLE 1 Demographics and clinical characteristics of AF (and hypertension) group and hypertension control group

	Total		Matched groups		
	AF + hypertension (n = 61)	**Hypertension control (n = 33)**	**AF + hypertension (n = 40)**	**Hypertension control (n = 20)**	**Matched groups *P***
Demographics					
Age, y	71 ± 10	57 ± 12	66 ± 7	65 ± 7	.71
Gender					
Male	42	27	29	15	.84
Female	19	6	11	5	
Ethnicity					
Caucasians, n (%)	53 (86.9%)	13 (39.4%)	34 (85%)	10 (50%)	-
Blacks, n (%)	4 (6.6%)	9 (27.3%)	3 (7.5%)	6 (30%)	
Asians, n (%)	4 (6.6%)	9 (27.3%)	3 (7.5%)	3 (15%)	
Mixed, n (%)	0 (0%)	2 (6%)	0 (0%)	1 (5%)	
Clinical characteristics					
Heart failure, n (%)	3 (4.9%)	1 (3%)	2 (5%)	0 (0%)	.55
IHD, n (%)	10 (16.4%)	7 (21.2%)	5 (12.5%)	5 (25%)	.28
Diabetes Mellitus, n (%)	14 (23%)	11 (33.3%)	10 (25%)	8 (40%)	.23
Previous stroke/TIA, n (%)	7 (11.5%)	5 (15.2%)	5 (12.5%)	5 (25%)	.28
Asthma/COPD, n (%)	13 (21.3%)	3 (9.1%)	5 (12.5%)	2 (10%)	.57
Chronic kidney disease, n (%)	1 (1.6%)	5 (15.2%)	1 (2.5%)	5 (25%)	**.01**
Anaemia, n (%)	2 (3.3%)	4 (12.1%)	0 (0%)	2 (10%)	.11
Thyroid disorder, n (%)	5 (8.2%)	4 (12.1%)	3 (7.5%)	4 (20%)	.21
Hypercholesterolaemia, n (%)	29 (47.5%)	14 (42.4%)	19 (47.5%)	11 (55%)	.58
Arthritis, n (%)	30 (49.2%)	10 (30.3%)	24 (60%)	8 (40%)	.14
CHA_2DS_2-VASc score	3 [2-4]	2 [1-3]	2 [2-4]	3 [1-4]	.74
HAS-BLED score	1 [1-1]	1 [0-2]	1 [1-1]	2 [1-2]	.06
Height (cm)	168.3 ± 9.3	169.9 ± 9.5	170.1 ± 8.9	169.4 ± 11.1	.80
Weight (kg)	88.4 ± 20.3	91.9 ± 13.7	95.5 ± 18.4	92.3 ± 14.7	.50
BMI (kg/m^2)	31.0 ± 5.7	31.8 ± 3.7	32.9 ± 5.2	32.1 ± 4.2	.58
Systolic BP (mm/Hg)	145 ± 23	155 ± 25	142 [133-152]	148 [135-175]	.12
Diastolic BP (mm/Hg)	79 ± 14	90 ± 16	83 ± 14	85 ± 13	.53
Mean Arterial Pressure (MAP) (mm/Hg)	101 ± 14	112 ± 17	103 ± 15	109 ± 16	.23
HbA1c (mmol/mol)	43 ± 9	45 ± 9	41 [39-48]	45 [38-56]	.32
CrCl (mL/min)	84.7 ± 32.2	98 ± 30.2	98.8 ± 29.6	85 ± 28.1	.09
Ejection fraction (%)	58 [55-65]	61 [55-66]	58 ± 11	62 ± 7	.14

Note: Descriptive data are presented as numbers (with percentages). Normally distributed data are expressed as mean ± standard deviation. Non-normally distributed data are displayed as median with interquartile ranges. Normality test was performed using Shapiro-Wilk test. Statistical differences were tested using an independent t test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Categorical data were compared using chi-square test. Where chi-square test was not valid, Fisher's exact test was used. Significance $P \leq .05$. – = unable to calculate p value as sample size too small/statistical test not valid.

Abbreviations: AF, atrial fibrillation; BMI, Body Mass Index; BP, blood pressure; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CrCl, Creatine Clearance (Cockroft-Gault method); HbA1c, haemoglobin A1C; INR, International Normalised Ratio; TIA, transient ischaemic attack; TSH, thyroid-stimulating hormone

sympathetic index (CSI) was noted to be significantly lower in AF (and hypertension) group. Univariable and multivariable analyses of unmatched groups are presented in Table 3. AF ($P = .003$), ejection fraction ($P = .04$) and heart rate ($P = .04$) were independently associated with changes seen on HRV following adjustment for multiple variables.

TABLE 2 Differences in heart rata variability (HRV) between AF (and hypertension) and hypertension control groups—cross-sectional comparison

	Total		Matched		
	AF + hypertension (n = 61)	Hypertension control (n = 33)	AF + hypertension (n = 40)	Hypertension control (n = 20)	Matched groups *P*
Baseline					
Mean heart rate (bpm)	63 [60-67][b]	62 [58-64][b]	63 [60-70][b]	61 [56-64][b]	.09
QTc (ms)	373 [366-380][a]	373 [364-382][a]	372 [362-382][a]	374 [365-383][a]	.76
Time-domain indices					
SDNN (ms)	85 [71-99][a]	47 [37-58][a]	84 [66-101][a]	42 [29-55][a]	**<.001**
rMSSD (ms)	103 [41-114][b]	27 [20-32][b]	106 [30-119][b]	25 [20-32][b]	**.01**
SDSD (ms)	103 [41-114][b]	27 [30-81][b]	106 [30-118][b]	25 [20-32][b]	**.004**
TINN (ms)	440 [360-504][b]	304 [200-344][b]	444 [344-544][a]	272 [205-338][a]	**.02**
pNN50 (%)	63 [20-66][b]	5 [2-10][b]	63 [50-68][b]	3 [1-9][b]	**<.001**
Frequency-domain indices					
VLF (ms^2)	749 [279-1470][b*]	1285 [814-1677][b]	972 [498-1447][a*]	1577 [848-2306][a]	.16
LF (ms^2)	361 [169-627][b*]	567 [247-1048][b]	252 [143-444][a*]	384 [225-654][a]	.26
HF (ms^2)	239 [92-621][b*]	314 [215-527][b]	180 [102-317][a*]	241 [154-377][a]	.39
Total Power (ms^2)	1468 [713-2601][b*]	2552 [1314-3052][b]	1739 [887-2592][a*]	2204 [1617-2791][a]	.34
LF normalised (%)	49 [42-59][b*]	62 [56-69][b]	56 [47-64][a*]	61 [54-67][a]	.34
HF normalised (%)	51 [41-58][b*]	38 [31-44][b]	44 [36-53][a*]	39 [33-46][a]	.34
LF-i/HF-i	0.9 [0.7-1.1][b*]	1.6 [1.3-2.1][b]	1.2 [0.8-1.7][a*]	1.5 [1.1-2.0][a]	.26
Nonlinear indices					
SD1 (ms)	73 [29-80][b]	19 [14-23][b]	75 [21-84][b]	18 [14-22][b]	**.004**
SD2 (ms)	98 [82-114][a]	63 [48-77][a]	97 [76-118][a]	55 [38-71][a]	**.002**
SD1/SD2	0.6 [0.5-0.7][b]	0.4 [0.3-0.5][b]	0.6 [0.5-0.7][a]	0.4 [0.3-0.5][a]	**.001**
CVI	3.5 [3.4-3.7][a]	3.0 [2.8-3.2][a]	3.5 [3.3-3.8][a]	2.9 [2.7-3.2][a]	**.003**
CSI	1.8 [1.6-2.0][a]	2.8 [2.5-3.1][a]	1.8 [1.5-2.1][a]	2.6 [2.2-3.0][a]	**.003**
With metronome					
Mean heart rate (bpm)	67 [63-72][b]	62 [58-68][b]	66 [61-72][a]	60 [56-66][a]	.12
QTc (ms)	372 [363-381][b]	378 [360-384][b]	371 [361-382][a]	375 [366-384][a]	.64
Time-domain indices					
SDNN (ms)	76 [47-89][b]	39 [28-51][b]	62 [48-80][a]	33 [27-41][a]	**<.001**
rMSSD (ms)	86 [35-101][b]	29 [21-37][b]	97 [35-105][b]	26 [20-37][b]	**.002**
SDSD (ms)	90 [41-101][b]	29 [21-37][b]	91 [54-104][b]	26 [20-37][b]	**<.001**
TINN (ms)	392 [328-456][b]	256 [184-320][b]	332 [258-428][a]	230 [181-293][a]	**.047**
pNN50 (%)	58 [25-62][b]	7 [2-20][b]	58 [25-64][b]	5 [1-17][b]	**<.001**
Frequency-domain indices					
VLF (ms^2)	478 [262-986][b*]	578 [314-1099][b]	462 [199-1158][b*]	513 [178-785][b]	.72
LF (ms^2)	265 [133-818][b*]	360 [177-690][b]	289 [127-659][a*]	253 [141-454][a]	.78
HF (ms^2)	385 [165-630][b*]	299 [198-536][b]	339 [169-681][a*]	267 [176-406][a]	.53
Total Power (ms^2)	914 [610-2061][b*]	1507 [800-2414][b]	795 [421-1502][a*]	1103 [726-1675][a]	.35
LF normalised (%)	40 [34-47][a*]	50 [43-57][a]	42 [33-52][a*]	48 [38-58][a]	.39
HF normalised (%)	60 [53-66][a*]	50 [43-57][a]	58 [48-67][a*]	52 [42-62][a]	.39
LF-i/HF-i	0.6 [0.4-0.8][b*]	0.9 [0.6-1.3][b]	0.7 [0.5-1.1][a*]	0.8 [0.6-1.2][a]	.61

(Continues)

TABLE 2 (Continued)

	Total		Matched		
	AF + hypertension (n = 61)	**Hypertension control (n = 33)**	**AF + hypertension (n = 40)**	**Hypertension control (n = 20)**	**Matched groups *P***
Nonlinear indices					
SD1 (ms)	64 [29-71][b]	20 [15-26][b]	65 [38-74][b]	18 [14-26][b]	**<.001**
SD2 (ms)	83 [58-104][b]	45 [34-68][b]	90 [72-108][a]	47 [36-58][a]	**<.001**
SD1/SD2	0.7 [0.5-0.7][b]	0.4 [0.4-0.5][b]	0.7 [0.6-0.7][a]	0.5 [0.4-0.5][a]	**.002**
CVI	3.5 [3.3-3.7][a]	3.0 [2.9-3.2][a]	3.5 [3.3-3.7][a]	2.9 [2.7-3.1][a]	**<.001**
CSI	1.7 [1.5-1.9][a]	2.4 [2.2-2.6][a]	1.7 [1.4-1.9][a]	2.2 [1.9-2.4][a]	**.003**

Note: Bold values indicates significant *P* values.

Normally distributed data are expressed as mean [95% confidence intervals (CI)]. Identified by superscript a. Non-normally distributed data are displayed as median [95% CI]. Identified by superscript b. Normality test was performed using Shapiro-Wilk test. Statistical differences were tested using independent t test (for parametric data) or Mann-Whitney U test (for nonparametric data). Significance $P \leq .05$. * = data presented only for paroxysmal AF patients.

Abbreviations: AF, atrial fibrillation; CSI, cardiac sympathetic index; CVI, cardiac vagal index; HF, high frequency (0.15 - 0.4 Hz); LF, low frequency (0.04 - 0.15 Hz); pNN50, NN50 count divided by the total number of all NN intervals; QTc, corrected QT interval, SDNN, standard deviation of all NN intervals; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SD1, standard deviation of the distance of each point from the y, x axis, specifies the ellipse's width; SD2, standard deviation of each point from the y, x + average R-R interval, specifies the ellipse's length; SDSD, standard deviation of differences between adjacent NN intervals; TINN, triangular interpolation of the NN interval histogram; VLF, very low frequency (≤0.04 Hz).

3.2 | Permanent AF (and hypertension) group vs PAF (and hypertension) group

Participants in the permanent AF and PAF groups were also well matched (Table 4). Participants in PAF group had significantly greater prevalence of ischaemic heart disease (IHD) ($P = .01$). There were no significant differences in mean heart rate, or mean corrected QT interval between the two groups (Table 5). All time-domain HRV indices were significantly higher in permanent AF group compared to paroxysmal AF group at baseline and with metronome. Similarly, all nonlinear indices were found to be significantly higher in permanent AF group compared to paroxysmal AF group except for CSI which was significantly lower in the permanent AF group. Permanent AF was the only independent predictor of HRV on multivariable analysis in this cohort of patients ($P = .006$) (Table 3).

3.3 | Permanent AF (and hypertension) group—longitudinal comparison

Following optimisation of BP and heart rate medication, patients with permanent AF (and hypertension) were followed up after 8 weeks and HRV repeated. There were significant reductions in mean heart rate (77 beats per minute (bpm) ± 18 (baseline) vs 72 bpm ± 17 (follow-up), $P = .01$), systolic BP (141 mmHg ± 20 (baseline) vs 134 mmHg ± 17 (follow-up), $P = .01$), diastolic BP (81 mmHg ± 13 (baseline) vs 77 mmHg ± 12 (follow-up), $P = .009$) and mean arterial pressure (MAP) (101 mmHg ± 12 (baseline) vs 96 mmHg ± 10 (follow-up), $P = .005$). HRV measurements at baseline and with metronome showed no significant differences in time-domain and nonlinear indices (Table 6).

4 | DISCUSSION

Our findings show for the first time that HRV is higher in patients with AF (and hypertension) compared to hypertension alone. Second, we observed that HRV is higher in permanent AF compared to paroxysmal AF. Finally, optimisation of AF or BP control medications was found not to improve HRV. HRV has been studied extensively in patients with normal sinus rhythm and shown to have important prognostic implications for various cardiovascular disorders.[9-12] However, there have been relatively few published reports dealing with the phenomenon in AF and none looking at AF and hypertension together.[13-15] Even when studies have looked at AF, they have typically measured HRV when patients were in sinus rhythm.[13-15]

van den Berg et al, however, did assess HRV in patients in AF.[13] They hypothesised that patterning of ventricular rhythm is possible in patients with AF given the function of the atrioventricular (AV) node in AF and its susceptibility to cardiac autonomic influences.[13] Compared to controls, HRV was higher in patients with AF, while intravenous administration of the beta-adrenergic antagonist propranolol (0.2 mg/kg) increased HRV in both groups. HRV was subsequently reduced by intravenous administration of the muscarinic antagonist methylatropine (0.02 mg/kg), and the

TABLE 3 Univariable and multivariable regression analyses

	Univariable			Multivariable[a]		
Variable	R^2	F	P	R^2	F	P
AF (and hypertension) vs hypertension control						
Dependent variable: Baseline rMSSD						
AF	0.206	23.160	<.001	0.222	3.387	**.003**
Age	0.083	8.016	.006	0.123	1.971	.08
EF	0.056	5.065	.03	0.170	2.309	**.03**
Ethnicity	0.054	5.068	.03	0.129	1.760	.11
CKD	0.044	4.054	.05	0.144	1.991	.07
Dependent variable: Baseline SD1						
AF	0.210	23.904	<.001	0.224	3.456	**.003**
Age	0.073	7.131	.009	0.115	1.836	.10
EF	0.058	5.326	.02	0.163	2.226	**.04**
Ethnicity	0.055	5.283	.02	0.123	1.688	.12
CKD	0.044	4.150	.05	0.135	1.878	.08
Dependent variable: Metronome pNN50						
AF	0.236	26.546	<.001	0.260	4.020	**.001**
CKD	0.059	5.367	.02	0.151	2.034	.06
Heart rate	0.054	4.876	.03	0.162	2.210	**.04**
Ethnicity	0.053	4.825	.03	0.118	1.526	.17
Age	0.051	4.663	.03	0.110	1.673	.14
Dependent variable: Metronome SD1						
AF	0.199	21.800	<.001	0.219	3.283	**.004**
Age	0.065	6.152	.02	0.108	1.677	.14
Permanent AF (and hypertension) vs paroxysmal AF (and hypertension)						
Dependent variable: Baseline pNN50						
AF	0.535	61.067	<.001	0.546	8.088	**<.001**
IHD	0.109	6.510	.01	0.128	1.170	.34
Diastolic BP	0.102	6.045	.02	0.225	1.952	.08
EF	0.099	5.616	.02	0.210	1.706	.13
Dependent variable: Baseline SD2						
AF	0.232	17.208	<.001	0.310	3.281	**.006**
IHD	0.072	4.414	.04	0.123	1.210	.32
Dependent variable: Metronome rMSSD						
AF	0.096	5.392	.02	0.201	1.620	.15
Dependent variable: Metronome SD2						
AF	0.235	16.916	<.001	0.358	3.906	**.002**

Note: Bold values indicates significant *P* values.

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; EF, ejection fraction; IHD, ischaemic heart disease

[a]Adjusted for age, sex, BMI, presence of ischaemic heart disease (IHD), presence of type 2 diabetes mellitus (DM) and creatinine clearance (CrCl).

magnitude of this reduction in HRV significantly correlated with the decrease in mean RR interval (used by the authors as an index of 'cardiac vagal control'). In light of these findings, it was concluded that HRV during AF is related to vagal tone.

Our study has shown for the first time that all time-domain metrics of HRV were significantly higher in AF (and hypertension) group compared to hypertension control group. Time-domain indices of HRV quantify the amount of variability in measurements of the interbeat interval (IBI),

TABLE 4 Demographics and clinical characteristics of permanent AF (and hypertension) group and paroxysmal AF (and hypertension) group

	Permanent AF + hypertension (n = 30)	Paroxysmal AF + hypertension (n = 31)	*P*
Demographics			
Age, years	70 ± 8	72 ± 11	.64
Gender			
Males	22	20	.46
Females	8	11	
Ethnicity			
Caucasians, n (%)	28 (93.3%)	25 (80.6%)	-
Blacks, n (%)	1 (3.3%)	3 (9.7%)	
Asians, n (%)	1 (3.3%)	3 (9.7%)	
Mixed, n (%)	0 (0%)	0 (0%)	
Clinical characteristics			
Heart failure, n (%)	3 (10%)	0 (0%)	.11
IHD, n (%)	0 (0%)	10 (32.3%)	**<.001**
Diabetes Mellitus, n (%)	7 (23.3%)	7 (22.6%)	.81
Previous stroke/TIA, n (%)	5 (16.7%)	2 (6.5%)	.26
Asthma/COPD, n (%)	9 (30%)	4 (12.9%)	.10
Chronic kidney disease, n (%)	0 (0%)	1 (3.2%)	1.00
Anaemia, n (%)	1 (3.3%)	1 (3.2%)	1.00
Thyroid disorder, n (%)	1 (3.3%)	4 (12.9%)	.35
Hypercholesterolaemia, n (%)	14 (46.7%)	15 (48.4%)	.89
Arthritis, n (%)	14 (46.7%)	16 (51.6%)	.70
CHA_2DS_2-VASc score	3 [2-4]	3 [2-4]	.56
HAS-BLED score	1 [1-1]	1 [1-1]	.18
Height (cm)	169.3 ±± 8.4	167.3 ± 10.1	.40
Weight (kg)	89.6 ± 19.1	87.2 ± 21.7	.66
BMI (kg/m^2)	31.1 ± 5.1	31.0 ± 6.3	.95
Systolic BP (mm/Hg)	140 [128-148]	144 [134-153]	.24
Diastolic BP (mm/Hg)	81 ± 13	76 ± 15	.16
Mean Arterial Pressure (MAP) (mm/Hg)	101 ± 12	101 ± 16	.87
HbA1c (mmol/mol)	41 [38-46]	41 [40-51]	.94
CrCl (mL/min)	86.2 ± 30.8	75.9 ± 38.1	.72
Ejection fraction (%)	55 [55-62]	62 [55-68]	.22

Note: Bold values indicates significant *P* values.

Descriptive data are presented as numbers (with percentages). Normally distributed data are expressed as mean ± standard deviation. Non-normally distributed data are displayed as median with interquartile ranges. Normality test was performed using Shapiro-Wilk test. Statistical differences were tested using an independent t test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Categorical data were compared using chi-square test. Where chi-square test was not valid, Fisher's exact test was used. Significance $P \leq .05$. – = unable to calculate p value as sample size too small/statistical test not valid.

Abbreviations: AF, atrial fibrillation; BMI, Body Mass Index; BP, blood pressure; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CrCl, Creatine Clearance (Cockroft-Gault method); HbA1c, haemoglobin A1C; INR, International Normalised Ratio; TIA, transient ischaemic attack; TSH, thyroid-stimulating hormone.

which is the time period between successive heartbeats.[19] Put simply, participants in our AF (and hypertension) group were found to have higher HRV, beyond that seen in non-AF hypertensives. Indeed, AF is characterised by marked HRV.[13,17] Compared to previous studies, our study included more patients, did not require administration of intravenous rate limiting medication such as propranolol, which could be an important confounder and was performed prospectively with study data recorded in real time as oppose to retrospective analysis of 24-hour ambulatory electrocardiographic recordings.[13,17] Furthermore, we controlled our participants' breathing rate using a metronome to reduce its confounding

TABLE 5 Differences in heart rata variability (HRV) between permanent AF and paroxysmal AF groups—cross-sectional comparison

	Permanent AF + hypertension group (n = 30)	Paroxysmal AF + hypertension group (n = 31)	*P*
Baseline			
Mean heart rate (bpm)	71 [65-76][a]	65 [58-72][a]	.19
QTc (ms)	372 [361-384][a]	374 [364-383][a]	.86
Time-domain indices			
SDNN (ms)	111 [101-122][a]	61 [39-83][a]	**<.001**
rMSSD (ms)	115 [107-132][b]	28 [21-41][b]	**<.001**
SDSD (ms)	115 [106-130][b]	28 [21-41][b]	**<.001**
TINN (ms)	574 [496-653][a]	379 [268-489][a]	**.006**
pNN50 (%)	68 [63-70][b]	7 [2-20][b]	**<.001**
Nonlinear indices			
SD1 (ms)	82 [75-92][b]	20 [15-29][b]	**<.001**
SD2 (ms)	129 [114-143][a]	70 [47-94][a]	**<.001**
SD1/SD2	0.7 [0.6-0.8][a]	0.5 [0.4-0.6][a]	**.006**
CVI	4.0 [4.0-4.1][a]	3.1 [2.8-3.4][a]	**<.001**
CSI	1.5 [1.3-1.6][a]	2.1 [1.8-2.5][a]	**.001**
With metronome			
Sinus rhythm (%)	14 [4-24][b]	99 [98-100][b]	**<.001**
Mean heart rate (bpm)	75 [68-82][a]	66 [60-71][a]	**.03**
QTc (ms)	371 [360-383][a]	375 [365-386][a]	.60
Time-domain indices			
SDNN (ms)	90 [82-113][b]	39 [28-59][b]	**<.001**
rMSSD (ms)	103 [97-118][b]	33 [23-54][b]	**.002**
SDSD (ms)	101 [97-114][b]	33 [23-54][b]	**<.001**
TINN (ms)	496 [432-560][a]	365 [281-449][a]	**.03**
pNN50 (%)	64 [61-70][b]	11 [4-28][b]	**<.001**
Nonlinear indices			
SD1 (ms)	72 [69-80][b]	23 [17-38][b]	**<.001**
SD2 (ms)	104 [96-137][b]	51 [35-65][b]	**<.001**
SD1/SD2	0.7 [0.6-0.8][a]	0.6 [0.5-0.7][a]	.15
CVI	3.9 [3.8-4.0][b]	3.0 [2.8-3.3][b]	**<.001**
CSI	1.5 [1.3-1.6][a]	1.7 [1.4-2.0][a]	.15

Note: Bold values indicates significant *P* values.

Normally distributed data are expressed as mean [95% confidence intervals (CI)]. Identified by superscript a. Non-normally distributed data are displayed as median [95% CI]. Identified by superscript b. Normality test was performed using Shapiro-Wilk test. Statistical differences were tested using independent t test (for parametric data) or Mann-Whitney U test (for nonparametric data). Significance $P \leq .05$. – = unable to calculate p value as sample size too small/statistical test not valid.

Abbreviations: AF, atrial fibrillation; CSI, cardiac sympathetic index; CVI, cardiac vagal index; pNN50, NN50 count divided by the total number of all NN intervals; QTc, corrected QT interval, SDNN, standard deviation of all NN intervals; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDSD, standard deviation of differences between adjacent NN intervals; TINN, triangular interpolation of the NN interval histogram.

influence. It is well established that variation in respiratory rate affects HRV analysis.[20-22]

SDNN (standard deviation of all NN intervals) which reflect the sum contribution of both the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) was found to be significantly higher in the AF group compared to hypertension control group in our study which suggests that perhaps both limbs of cardiac ANS are invested in the pathophysiology of development and propagation of AF. Certainly, this supports data observed in previous studies.[6,7] The rMSSD (square root of the mean of the sum of the squares of differences between adjacent NN intervals) and pNN50% (the percentage of adjacent RR intervals that differed by more than 50 ms) are more

TABLE 6 Differences in heart rata variability (HRV) in permanent AF group—longitudinal comparison

	Permanent AF + hypertension (Baseline)	Permanent AF + hypertension (Follow-up)	*P*
Baseline			
Mean heart rate (bpm)	71 [65-76][a]	69 [63-76][a]	.74
QTc (ms)	369 [355-381][b]	377 [362-384][b]	.92
Time-domain indices			
SDNN (ms)	100 [95-122][b]	105 [82-129][b]	.67
rMSSD (ms)	123 [114-134][a]	115 [101-132][a]	.23
SDSD	123 [114-133][a]	121 [106-137][a]	.56
TINN (ms)	504 [472-584][b]	508 [432-528][b]	.96
pNN50%	68 [63-70][b]	71 [62-86][b]	.18
Nonlinear indices			
SD1 (ms)	87 [80-94][a]	85 [75-97][a]	.56
SD2 (ms)	120 [106-151][b]	121 [95-144][b]	.84
SD1/SD2	0.7 [0.6-0.8][b]	0.7 [0.6-0.8][b]	1.00
CVI	4.0 [3.9-4.1][b]	4.0 [3.8-4.1][b]	.09
CSI	1.5 [1.3-1.6][a]	1.4 [1.3-1.6][a]	.85
With metronome			
Mean heart rate (bpm)	75 [68-82][a]	72 [65-79][a]	.39
QTc (ms)	372 [360-384][a]	371 [362-379][a]	.56
Time-domain indices			
SDNN (ms)	97 [86-109][a]	101 [82-125][a]	.92
rMSSD (ms)	104 [98-118][b]	111 [92-133][b]	.47
SDSD	108 [98-120][a]	108 [96-122][a]	.97
TINN (ms)	496 [432-560][a]	500 [431-570][a]	.23
pNN50%	64 [61-70][b]	66 [59-71][b]	.87
Nonlinear indices			
SD1 (ms)	77 [69-85][a]	76 [68-86][a]	.97
SD2 (ms)	104 [96-137][b]	116 [89-158][b]	.78
SD1/SD2	0.7 [0.6-0.7][b]	0.6 [0.6-0.9][b]	.76
CVI	3.9 [3.8-4.0][b]	3.9 [3.8-4.1][b]	.88
CSI	1.5 [1.3-1.7][b]	1.6 [1.2-1.8][b]	.90

Note: Normally distributed data are expressed as mean [95% confidence intervals (CI)]. Identified by superscript a. Non-normally distributed data are displayed as median [95% CI]. Identified by superscript b. Normality test was performed using Shapiro-Wilk test. Statistical differences were tested using paired t test (if passed) or Wilcoxon signed rank test (if failed). Significance $P \leq .05$.

Abbreviations: AF, atrial fibrillation; CSI, cardiac sympathetic index**;** CVI, cardiac vagal index; pNN50, NN50 count divided by the total number of all NN intervals; QTc, corrected QT interval; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of all NN intervals; SDSD, standard deviation of differences between adjacent NN intervals; TINN, triangular interpolation of the NN interval histogram.

influenced by the PNS than SDNN. In our study, we found that rMSSD and pNN50% were significantly higher in AF (and hypertension) group. This suggests a high vagal tone in these patients.

Frequency-domain measurements employ autoregressive modelling to separate HRV into its components, such as ultra-low frequency (ULF), very low frequency (VLF), low frequency (LF) and high frequency (HF) rhythms that operate within different frequency ranges.[8] We hypothesise that the erratic ventricular response to random atrial impulses seen in permanent AF would have led to generation of 'noise' which would have prevented the HRV software from

interpreting the data consistently, a notion supported by Frey et al[15] Another possible explanation could be that the peak variability in these patients was perhaps occurring beyond the high-frequency range in AF, and therefore, our HRV software was unable to capture this.

Possible reasons for not seeing any significant differences in frequency-domain indices between the AF (and hypertension) and hypertensive control groups could be that patients had similar demographic profiles (age, gender and ethnicity), similar clinical characteristics and baseline heart rate. It is well established that age, gender, clinical characteristics, heart rate and blood pressure can all affect HRV.[23-27] Another reason could be the shorter length of HRV recording (5 minutes as oppose to the gold standard 24 hours), which may have masked any differences.[28]

Similar to time-domain metrics, nonlinear indices of HRV were found to be significantly higher in AF (and hypertension) group compared to hypertension control group. One of the key markers in the nonlinear metrics is the cardiac vagal index (CVI), which represents the contribution of the PNS to cardiac regulation and is found to be a more reliable metric.[29,30] CVI sets the parameters SD1 and SD2 into a direct relationship and therefore serves to capture the parasympathetic (vagal) activity. In our study, it was found to be significantly higher in patients with AF. Conversely, the cardiac sympathetic index (CSI) representing the contribution of SNS to cardiac regulation was noted to be significantly lower in the AF group.[30,31] Higher CSI is associated with lower variability.[31] This further supports our previous findings.

It is well known that vagal stimulation contributes to the development of AF by heterogenous shortening of action potential duration and refractory period through actions of acetylcholine (ACh) on the muscarinic receptors found in the heart.[2] Additionally, recent studies have shown evidence of noncholinergic vagal effects that may also contribute to the pathogenesis of vagally induced AF.[32,33] Lastly, there is a pronounced vagal innervation of the atrial muscle sleeves extending into the pulmonary veins, a site well known for AF origin.[34] All of this combined can help explain the HRV findings in our study.

It is well known that HRV is strongly influenced by respiratory rate.[19,20,22] Respiratory rate changes can produce large-scale shifts in respiratory sinus arrhythmia magnitude without affecting vagal tone.[35] Therefore, we attempted to control the respiratory rate by asking our participants to control their breathing with help of a metronome to reduce this bias and repeated HRV measurements over 5 minutes. Overall, there were no significant differences in the data obtained with and without metronome and the conclusions from the data were similar, which was reassuring.

The second part of the study compared permanent AF with paroxysmal AF and found significantly higher time-domain and nonlinear indices of HRV in permanent AF, which may suggest pronounced cardiac autonomic influence in the pathophysiology of permanent AF. Similar to first part of the study, using a metronome did not change the data significantly when compared with baseline data except for SD1/SD2 ratio and CSI, which now showed no significant differences between the two AF groups. SD1/SD2 ratio and CSI are both markers of sympathetic activity. It is previously understood that controlled breathing can influence sympathetic activity, as seen in our study.[19] For the last part of our study, although there are interventions that modulate cardiac autonomic activity and thus reduce the incidence of spontaneous or induced atrial arrhythmias, this was not observed in our study.[36-40]

4.1 | Strengths and limitations

As far as we are aware, this is the first study to look at HRV in patients with AF and hypertension. Participants in our groups were well matched for age, gender and comorbidities. Our study does have several limitations, such as modest sample sizes, raising the potential for a type II error, which may contribute to the small number of independent associations in our univariable and multivariable analyses. The cross-sectional design is another limitation of our study. We also acknowledge the redundancy between rMSSD and SD1.[19] The erratic nature of permanent AF rhythm prevented the HRV software to produce any frequency-domain information. The follow-up period of 8 weeks in the longitudinal study may not be enough to observe any changes in HRV and may explain no differences observed in HRV.

It is perceived that antihypertensives and other medications affect cardiac autonomic function. The use of cardiovascular medications including rate control, antihypertensives and anticoagulants at baseline in our participants was according to clinical indication, and therefore, we cannot exclude their possible influence on HRV. Furthermore, it is possible that patients in one group were more adherent to cardiovascular medications, and this may have affected our results. Lastly, ANS function is known to be confounded by a large number of lifestyle-related and cardiometabolic factors, including sleep, sitting time, physical activity, fitness parameters and socioeconomics. While we have included in our regression analysis some of these factors, such as smoking, alcohol intake, biomarkers (HbA1c, creatinine clearance), we cannot completely exclude the possibility of other lifestyle factors that may have affected our results.

In summary, we have shown that AF independent of hypertension is characterised with marked HRV and is predominantly related to vagal tone. Second, HRV is more

pronounced in permanent AF as oppose to paroxysmal AF, with AF being an independent predictor of HRV on univariable and multivariable analyses. Further studies should attempt to look at the role of HRV in the pathogenesis of permanent AF, how HRV can be modulated through various interventions and assess its long-term implications. In patients with difficult to manage AF, autonomic influences should be considered as a contributory factor and investigated further to see whether neuromodulation through drugs may be helpful.

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CONFLICTS OF INTEREST

No conflicts of interest, financial or otherwise, are declared by the authors. GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo; and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No personal fees received.

AUTHOR CONTRIBUTIONS

AAK, JPF and GYHL conceived and designed research; AAK performed experiments; AAK analysed data; AAK, RTJ, GNT, JPF and GYHL interpreted results of experiments; AAK drafted manuscript; AAK, RTJ, GNT and JPF edited and revised manuscript; AAK, RTJ, GNT, JPF and GYHL approved final version of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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