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Clinical evidence of autonomic dysfunction due to atrial fibrillation: implications for rhythm control strategy

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Abstract

Purpose The role of the autonomic nervous system in the genesis of atrial fibrillation (AF) has been well studied; however, the converse remains poorly understood. Pulmonary veins (PV) contain receptors important in cardiac reflexes. Here, we evaluated reflex responses in patients with paroxysmal AF (PAF) to lower body negative pressure (LBNP).

Methods Thirty-four PAF patients (including 14 PAF patients post successful PV Isolation; PVI) were compared to 14 age and sex-matched controls. Mean arterial pressure (MAP), heart rate (HR), systemic vascular resistance index (SVRI), cardiac index (CI), and stroke volume index (SVI) were measured continuously during − 0, − 20, and − 40 mmHg LBNP. LBNP reduces venous return, deactivating atrial receptors, thereby eliciting a reflex increase in SVRI to maintain MAP.

Results AF patients have higher BMI than the controls ($p = 0.02$). In control subjects, LBNP did not alter MAP as SVRI increased. In PAF patients, LBNP resulted in a reduction in MAP (− 4.8%) with attenuated SVRI response (+ 4.2%) compared to controls ($p < 0.05$). However, in the post-PVI group, SVRI increase was similar to controls ($p = 0.12$) although that was insufficient to maintain MAP. In all patients, both reduction in SVI and CI and increase in HR were similar in response to LBNP.

Conclusions This study provides novel clinical evidence of autonomic dysfunction in PAF patients. Successful PVI results in partial recovery of the cardiac reflex. Therefore, not only does autonomic disturbance predispose to AF but it is also a consequence of AF; potentially contributing to disease progression. This could help explain the dictum "AF begets AF."

Keywords Atrial fibrillation · Autonomic nervous system · Pulmonary vein isolation · Orthostatic reflexes · Lower body negative pressure

Abbreviations

AF	Atrial fibrillation
CI	Cardiac index
HR	Heart rate
MAP	Mean arterial pressure
PVI	Pulmonary vein isolation
SV	Stroke volume
SVRI	Systemic vascular resistance index

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1 Introduction

The autonomic nervous system is implicated in the genesis of atrial fibrillation (AF) with robust experimental [1–4] and clinical evidence [5, 6]. Indeed, cardiac ganglionic plexi are in close proximity to the sites where pulmonary veins enter the left atrium [7]. Experimentally, the stimulation of autonomic nerves has been shown to elicit rapid firing triggered by early afterdepolarizations in pulmonary vein preparations, providing a possible mechanistic explanation for autonomic triggering of AF [4]. While triggering of AF by the autonomic nervous system has received much attention, the converse that AF begets autonomic nervous system dysfunction has not been extensively studied in humans. Animal models of rapid atrial pacing-induced AF has been shown to increase both sympathetic and parasympathetic innervation of the atria [8–10]. In humans, Brignole et al. [11] demonstrated autonomic disturbances in patients with syncopal events associated with onset of AF. Further, there is case evidence that the

restoration of sinus rhythm can abolish incessant orthostatic hypotension in a patient with persistent AF [12].

In normal individuals, lower body negative pressure (LBNP) decreases venous return to the heart, unloads cardiopulmonary receptors, and results in compensatory systemic vasoconstriction [13]. Atrial stretch receptors, particularly cardiopulmonary receptors found in the pulmonary vein-left atrial junctions, are critical mediators of such reflexes [13, 14]. Here, we hypothesize that AF induces autonomic dysfunction with abnormal reflex responses to decreased venous return and that successful pulmonary vein isolation (PVI) may reverse this abnormality. Therefore, we compared reflex cardiovascular responses to LBNP in subjects with frequent episodes of paroxysmal atrial fibrillation (PAF) and those who had undergone successful PVI to age- and sex-matched healthy controls.

2 Methods

All participants provided written informed consent and the study was approved by the institutional human research ethics committees. This study involved three groups. The first group consisted of 20 patients who had symptomatic paroxysmal AF referred for consideration of pulmonary vein isolation (PVI) and were studied prior to PVI. The second group consisted of 14 patients who were studied following successful treatment with PVI (referred to as the post-PVI group). These patients were only studied (i) after the 3-month blanking period post-PVI and (ii) if they remained symptom-free up to 2 years post-PVI. These two groups were compared to 14 age- and sex-matched healthy controls (control group).

The PAF patients were highly symptomatic, requiring anti-arrhythmic drug (AAD) therapy and were consecutively enrolled after having been referred to an electrophysiologist for consideration of catheter ablation. Enrolled patients in either group were free from cardiovascular (coronary artery disease, valvular heart disease, or heart failure) and other confounding conditions (autonomic disorders, untreated hypertension, postural hypotension, diabetes mellitus, or renal disease). Patients who had received amiodarone during the last 6 months were also excluded.

The post-PVI group was enrolled from a hospital database of all PVI procedures undertaken for 2 years prior to enrollment. Patients were excluded if they had multiple PVI procedures, were either within the 3-month blanking period at the time of the study or were outside of the two-year window, did not attend regular follow-up with the treating cardiologist, accurate records were not kept in terms of AF recurrence, were not contactable by telephone, or did not consent to presenting for the purposes of this study.

The control group was enrolled last, after analyzing the age and sex of the patient cohorts. Participation was sought from hospital workers between the ages of 30 and 70 years after advertisement through hospital notice boards, flyers, and department presentations. The total number of participants in each 5-year age category, as well as the proportion of males and females, was established for the AF group. Volunteers were consecutively enrolled and assigned to each 5-year age group until similar numbers were achieved in each age-group (Fig. 1a).

2.1 Pulmonary vein isolation

PVI was performed in the fasting state under general anesthesia. Three electrode catheters were introduced percutaneously via the right femoral vein. A 7F quadripolar catheter (Biosense-Webster, Diamond Bar, CA, USA) was placed in the coronary sinus and used for pacing and recording. Variable size of circumferential decapolar mapping catheter (Lasso, Biosense-Webster, Diamond Bar, CA, USA) and an 8F, 3.5 mm irrigated tip ablation catheter (Navistar Thermocool D-F curve, Biosense-Webster, Diamond Bar, CA, USA) were used for mapping and ablation of pulmonary veins (PV). They were introduced to the left atrium via transeptal puncture. The circumferential mapping catheter was positioned as proximal as possible within each of the PV's and was oversized for stability. Systematic isolation of the four PV's was performed at each ostium, guided by the mapping catheter. Entrance block or the presence of dissociation within the pulmonary veins was the ablation endpoint. All veins were rechecked after a 30-min observation and further ablation was performed if acute conduction recovery was detected.

Ablation success was confirmed in all 14 subjects by symptoms and three monthly 24 to 72-h Holter monitoring. No specific attempts were made to locate or ablate areas associated with cardiac autonomic plexus (ganglionated plexi) as per current clinical guidelines [15].

2.2 Experimental protocol

The experimental protocol was performed in the fasting state (4 h) with abstinence from caffeine, alcohol, and strenuous exercise in the preceding 24 h. All AAD (including ß-blockers) were withheld for five half-lives, symptoms allowing, prior to the study protocol. All testing was performed in a climate-controlled laboratory with room temperature of 22 °C. All patients were in sinus rhythm during the testing protocol. Resting brachial blood pressure was checked in the supine position with a standard mercury

sphygmomanometer. Continuous beat-to-beat recordings were obtained using finger photo plethysmography (Nexfin, BMEYE, Amsterdam, The Netherlands) [16] to derive:

1. Mean arterial pressure (MAP, mmHg);
2. Heart rate (HR, bpm);
3. Stroke volume index (SV, mL/m^2);
4. Cardiac index (CI, L/min/m^2); and
5. Systemic vascular resistance index (SVRI, dynes s×m^2/cm^5).

Patients were then subjected to LBNP using a custom-made Perspex chamber placed over the subject's lower limbs with a seal at the iliac crest. A vacuum generator (Model UZ-930; Electrolux, Stockholm, Sweden) was attached to the chamber and connected to a voltage converter, which allowed graduated control of the vacuum intensity (Fig. 1b). Thus, negative pressure could be precisely controlled to 0, − 20 and − 40 mmHg with the aid of an industrial pressure gauge (Ambit Instruments; Wetherill Park, NSW, Australia). All

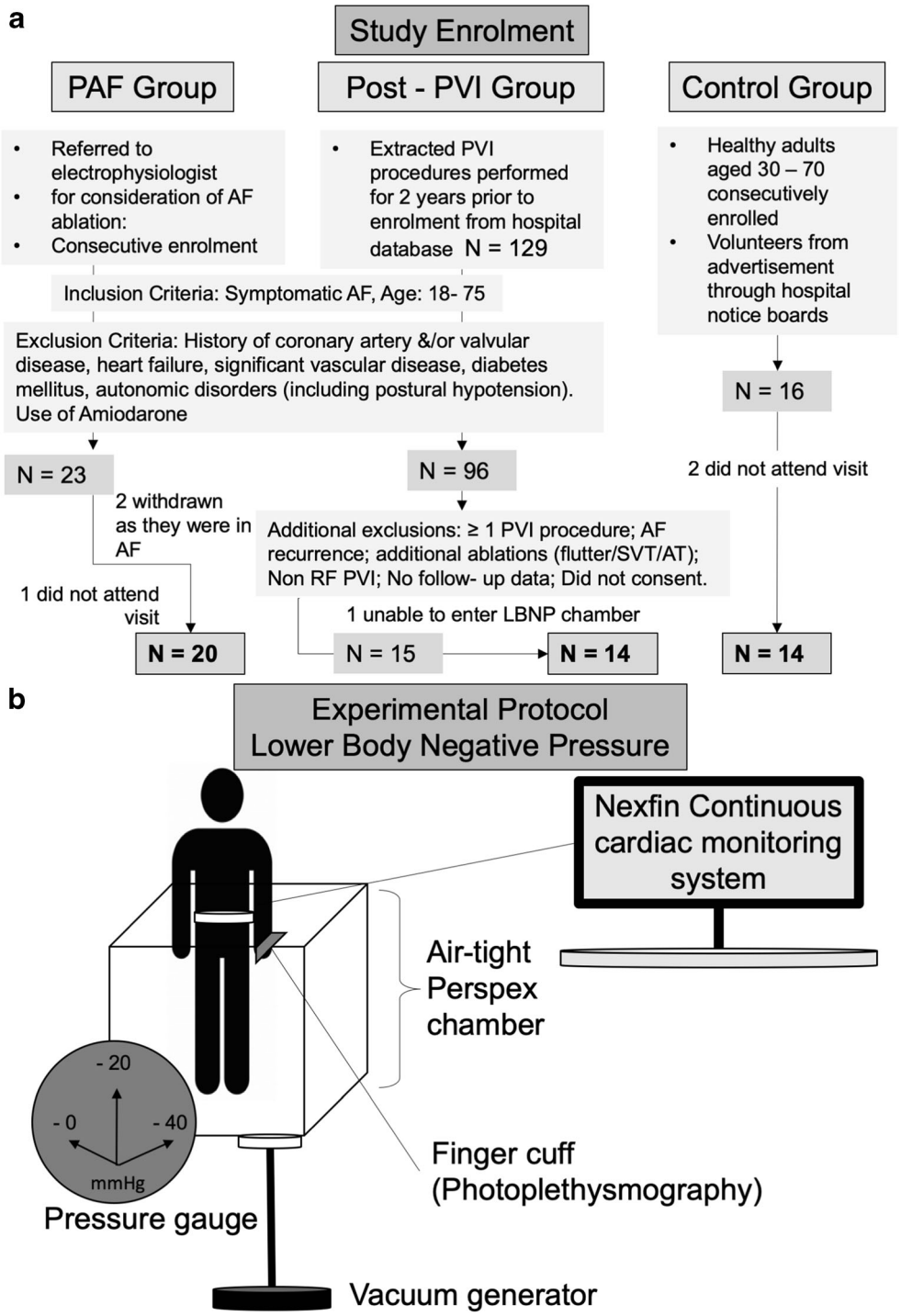

Fig. 1 Study enrollment and experimental protocol. **a** CONSORT diagram. Enrollment flow chart, including patient recruitment, inclusion, and exclusion criteria for each group. **b** Schematic depicting lower body negative pressure (LBNP) technique

patients underwent a short 2-min familiarization period with LBNP application followed by a resting period of 10 min prior to LBNP protocol commencement. The degree of LBNP intensity was randomly applied for each patient for 10 min at each level with a 5 min break in between. Negative pressure was applied slowly over 30 s to minimize patient movement and discomfort.

2.3 Statistical analysis

Continuous patient variables were expressed as mean ± SD. Categorical variables were expressed as frequencies and percentages. The last 2 min of beat-to-beat recorded data for each level of negative pressure (0, − 20 and − 40 mmHg) was extracted and averaged (mean ± SEM). Comparisons within groups were made by repeated measures one-way analysis of variance (ANOVA) with the Dunnett's post-test analysis. Differences across groups were compared with ANOVA and the Bonferroni post-test analysis. Statistical analysis was performed using GraphPad Prism (version 6.0, California, USA). Statistical significance was set at $P < 0.05$.

3 Results

3.1 Patient recruitment and baseline characteristics

Figure 1 presents the CONSORT diagram of the patient groups. In the PAF group, 23 patients with symptomatic AF, referred to an electrophysiologist for consideration of PVI were consecutively enrolled after having been assessed for eligibility. Three patients did not undergo autonomic testing and, therefore, 20 patients were included. The post-PVI group ($n = 14$) was derived from a database of 129 PVI procedures, of whom 48 had a single radiofrequency ablation. Fifteen were eligible after review of case notes and contact was made. One patient withdrew as she was unable to participate in the experimental protocol. Fourteen patients (of 16 volunteers) were enrolled in the control group (Fig. 1a). Subjects were age- and sex-matched between groups (all $p > 0.05$). The overall mean age was 57 ± 8.5 years, 70% males. The post-PVI group was studied at an average duration of 8 months post ablation (range 3–22 months). The baseline characteristics of the included patients are presented in Table 1.

3.2 Hemodynamic responses to LBNP

3.2.1 Mean arterial pressure

Baseline MAP was similar across all groups: 97 ± 3 mmHg in the control group, 100 ± 3 mmHg in the PAF group, and 98 ± 3 mmHg in the post-PVI group (Table 2). In control subjects, MAP was maintained at both − 20 and − 40 mmHg LNBP (Fig. 2a, $p = 0.4$). In the PAF group, the decrease in MAP was not significant at − 20 mmHg, however, there was a statistically significant decrease at − 40 mmHg (Fig. 2a, $p < 0.05$). In the post-PVI group, MAP was significantly lower at − 20 mmHg and at − 40 mmHg LNBP (Fig. 2a, both $p < 0.01$). The MAP response to LBNP was different in the PAF group ($p = 0.04$) as well as the post-PVI group ($p = 0.03$) in comparison to control subjects. However, the MAP responses in the post-PVI and the PAF groups were not statistically different ($p > 0.99$).

Table 1 Baseline characteristics

	Controls ($n = 14$)	PAF ($n = 20$)	Post-PVI ($n = 14$)	p value
Age (years)	55 ± 5	58 ± 10	58 ± 8	0.38
Males, n (%)	9 (64)	13 (65)	12 (86)	0.35
Mean body mass index, kg/m^2	25.6 ± 4	30.3 ± 5	31.0 ± 6	0.02*
Hypertension, n (%)	0 (0)	8 (57)	7 (50)	0.99#
Patients not on any AAD, n (%)	14 (100)	4 (20)	9 (64)	0.01*#
ß-blockers (except Sotalol), n (%)	0 (0)	7 (35)	5 (36)	0.99#
Sotalol, n (%)	0 (0)	8 (40)	0 (0)	0.01*#
Amiodarone, n (%)	0 (0)	0 (0)	0 (0)	–
Flecainide, n (%)	0 (0)	6 (30)	0 (0)	0.03*#
Digoxin, n (%)	0 (0)	1 (5)	0 (0)	0.99#
Calcium channel blocker, n (%)	0 (0)	0 (0)	0 (0)	–

One-way ANOVA (Bonferroni post-test) for continuous variables with greater than two groups and students t test for two group comparisons. Categorical variables; X^2 test or Fishers exact test * $p < 0.05$. *AAD*, anti-arrhythmic drugs

*Between group statistical differences, $p < 0.05$

PAF vs post-PVI group statistical comparison only

Table 2 Cardiac index and stroke volume index

	LBNP (mmHg)	Controls ($n = 14$)	PAF ($n = 20$)	p value (vs. controls)	Post-PVI ($n = 14$)	p value (vs. controls)	p value (vs. PAF)
Mean arterial pressure (mmHg)	0	97 ± 3	100 ± 3	0.04†	98 ± 3	0.03†	NS
	− 20	96 ± 3	97 ± 3		93 ± 3**		
	− 40	99 ± 3	96 ± 3*		92 ± 2**		
Heart rate (bpm)	0	61 ± 2	57 ± 2	NS	62 ± 2	NS	NS
	− 20	61 ± 2	58 ± 1		62 ± 4		
	− 40	67 ± 2**	61 ± 2***		67 ± 3*		
Systemic vascular Resistance index (dynes s×m^2/cm^5)	0	2720 ± 132	3131 ± 198	0.04†	2740 ± 135	NS	NS
	− 20	2916 ± 140	3182 ± 166		2793 ± 120		
	− 40	3010 ± 150	3263 ± 167		2910 ± 120		
Cardiac index (L/min/m^2)	0	2.89 ± 0.09	2.70 ± 0.12	NS	2.92 ± 0.10	NS	NS
	− 20	2.69 ± 0.08**	2.51 ± 0.09**		2.69 ± 0.09***		
	− 40	2.62 ± 0.09**	2.43 ± 0.09***		2.55 ± 0.09***		
Stroke volume index (mL/min/m^2)	0	45.3 ± 2.1	47.9 ± 1.6	NS	47.5 ± 1.4	NS	NS
	− 20	41.8 ± 2.1***	43.8 ± 1.5***		43.5 ± 1.5***		
	− 40	37.2 ± 2.5***	39.8 ± 1.5***		38.7 ± 1.6***		

NS, non-significant

* $p < 0.05$, within group differences

** $p < 0.01$, within group differences

*** $p < 0.001$, within group differences

† Indicates statistically significant change in response to LBNP between groups ($p < 0.05$).

3.2.2 Heart rate

Baseline HR was similar between groups (61 ± 2 vs. 57 ± 2 vs. 62 ± 2 bpm in the control vs. PAF vs. post-PVI group respectively, $p = 0.4$; Table 2). HR did not change at − 20 mmHg LNBP, however at − 40 mmHg LBNP there was a significant increase in HR consistently in all groups. There was no statistical difference in the HR response to LBNP between groups (Fig. 2b).

3.2.3 Systemic vascular resistance

In controls, there was a significant increase in SVRI at both − 20 and − 40 mmHg LBNP (Fig. 2, both $p < 0.01$). In contrast, there was no SVRI response to LBNP at either − 20 or − 40 mmHg in patients with PAF (both $p > 0.05$). In the post-PVI group, a significant increase in SVRI was only evident at − 40 ($p < 0.01$) but not − 20 mmHg ($p = 0.4$) LNBP. Overall SVRI response to LNBP was different between the PAF and control groups ($p = 0.04$) but not between the post-PVI and control subjects (Fig. 2c, $p = 0.12$).

3.2.4 Cardiac index and stroke volume index

Table 2 shows the CI and SVI at baseline and after application of − 20 and − 40 mmHg LBNP. CI and SVI were similar at baseline and changed similarly in all three groups following application of LBNP at − 20 and − 40 mmHg. Changes induced by LBNP were statistically significant within each group but responses were not different between groups (all $p > 0.05$).

4 Discussion

This study evaluated the effects of AF on the autonomic nervous system by comparing cardiac reflex response to LBNP in patients with symptomatic PAF and after successful PVI to healthy control subjects. Our principal findings are as follows:

- Reflex responses to LBNP were attenuated in patients with PAF, suggesting that autonomic dysfunction in patients with AF persists beyond a bout of the arrhythmia.
- Vasoconstrictor responses to LBNP were absent in PAF patients, whereas no differences were seen between the post-PVI subjects (who were free from the arrhythmia) and healthy controls, indicating partial recovery of autonomic function and, therefore, potentially implicating AF itself as the cause of autonomic dysfunction.
- The above changes were seen in the absence of differences in HR, CI, and SV response to LNBP among the three groups.

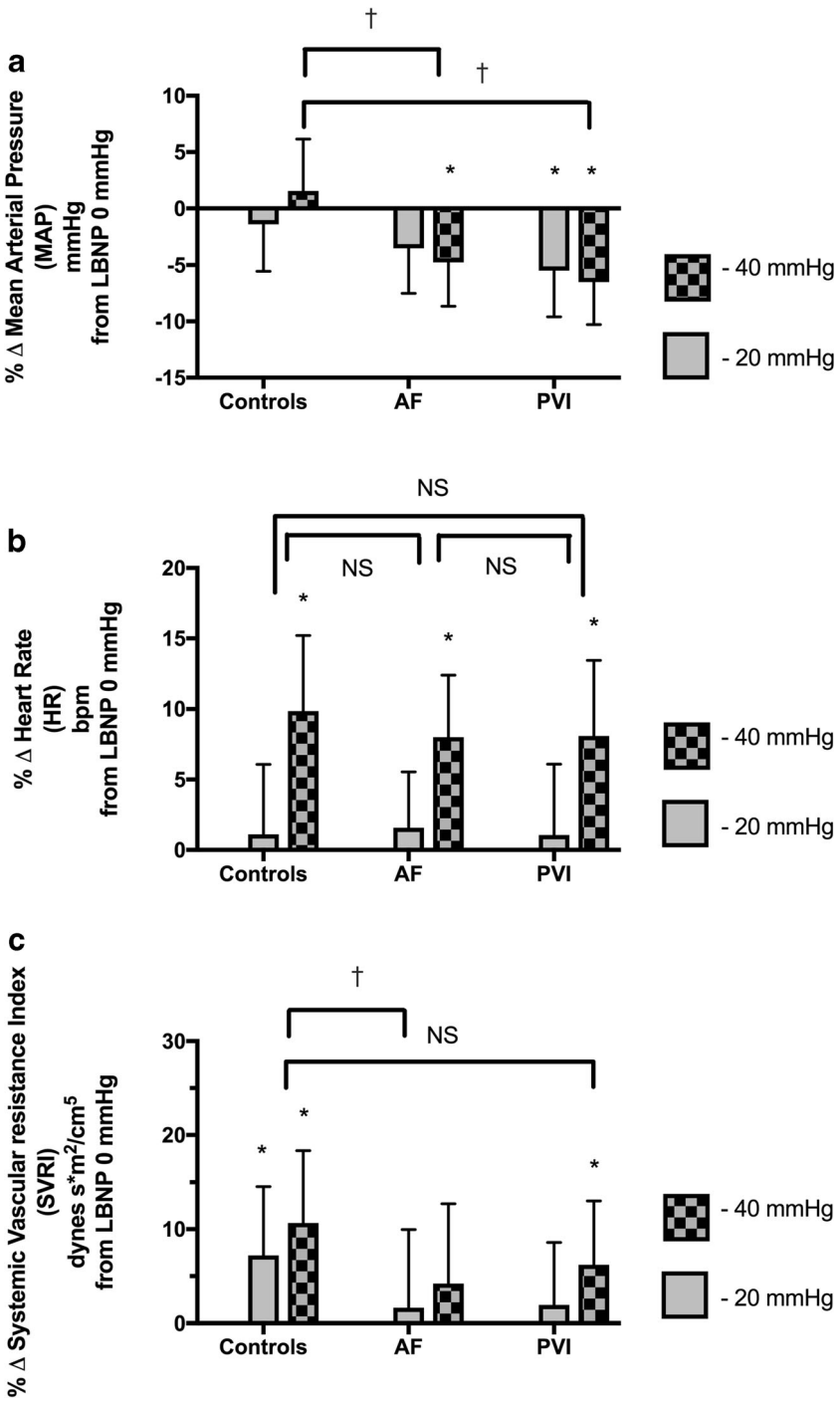

Fig. 2 Hemodynamic responses to LBNP. **a** Mean arterial pressure percentage change in MAP with LBNP (− 20 and − 40 mmHg) for each group expressed as mean ± SEM. **b** Heart rate percentage change in mean HR with LBNP (− 20 and − 40 mmHg) for each group expressed as mean ± SEM. **c** Systemic vascular resistance index percentage change in mean SVRI with LBNP (− 20 and − 40 mmHg) for each group expressed as mean ± SEM. *Statistical difference in comparison to baseline at 0 mmHg LBNP ($p < 0.05$). †Indicates statistically significant change in response to LBNP between groups ($p < 0.05$). *NS*, non-significant

4.1 Abnormal cardiac reflex responses to LBNP due to AF

LBNP is an established technique used to study reflex responses to decreased blood volume. LBNP simulates mild to moderate hypovolemia by displacing 400–550 to 500–1000 mL of volume at − 20 and − 40 mmHg respectively [17]. The application of LBNP at these pressures produces a progressive decrease in venous return and consequent changes in cardiac output in keeping with the Frank-Starling effect [18]. The efferent response to LBNP is primarily a sympathetically mediated peripheral vasoconstriction in order to maintain MAP [13, 14]. Receptors at veno-atrial junctions are thought to be critical in mediating this homeostatic reflex. Arterial receptors are not engaged unless blood pressure falls. HR changes from LBNP are generally the result of interference from other reflexes and, therefore, not helpful in the evaluation of the reflex response to LBNP [19].

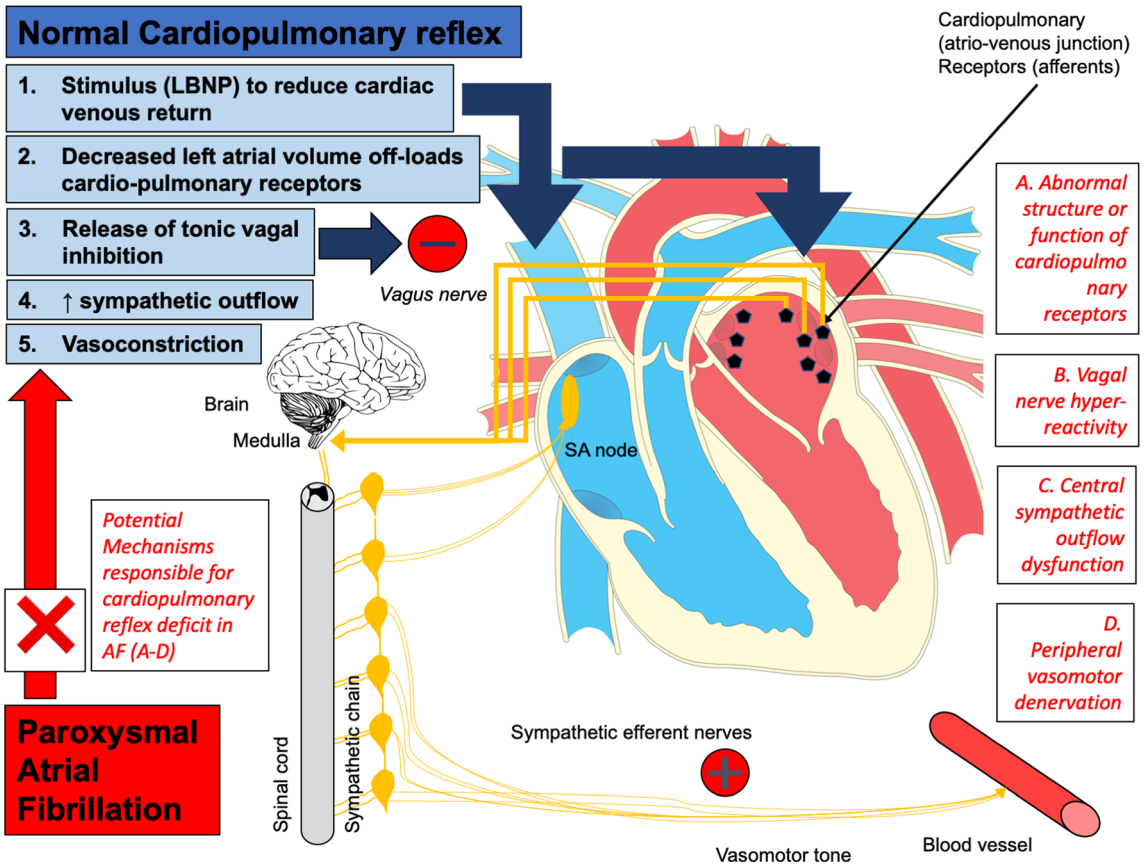

Fig. 3 Central diagram. A schematic of the neural components responsible for normal reflex control of blood pressure and heart rate in responses to LBNP. PAF results in a reflex deficit (attenuation of vasomotor response to LBNP). This diagram incorporates a sketch of the heart and the brain that have been modified from clipart provided by www.openclipart.org and www.pixabay.com, respectively. These images have been placed in the public domain, have had their copyright waived as part of the creative commons zero 1.0 public domains license, and can be modified and reproduced without permission (https://creativecommons.org/publicdomain/zero/1.0). No other components of this diagram have been copied or modified from other sources

In this study, LBNP lowered both SVI and CI to a similar extent in all the three groups, indicating that an equivalent stimulus was applied in each group. Blood pressure was maintained at both levels of LBNP in the control subjects but not in the AF or post-PVI groups whereby MAP fell progressively. This indicates a clear reflex deficit in subjects with PAF that was not rectified by successful ablative treatment of PAF in the post-PVI group. While no differences were seen in HR response, clear differences were observed between groups in the reflex vasoconstrictor responses elicited by LBNP. Specifically, no significant vasoconstrictor response was seen in PAF subjects at either level of LNBP. In contrast, significant vasoconstriction was observed at −40 mmHg LNBP in the post-PVI subjects with no overall differences seen in the SVRI responses between the post-PVI and control groups. The recovery in vasoconstrictor responses in the post-PVI group raises the hypothesis that the impaired vasoconstrictor response observed in PAF is a consequence of AF rather than a pre-existing abnormality that predisposes the subjects to the development of the arrhythmia.

Our finding of impaired cardiac reflex response due to AF affirmed previous findings by Brignole et al. [11] whereby disturbances of the autonomic nervous system was thought to be responsible for syncope in patients with PAF. Further, our results may also explain the enhanced susceptibility to autonomic provocation seen in patients with lone PAF [20]. Persisting autonomic changes as a result of AF have not previously been described. Thus, our study adds to prior observations by demonstrating reflex changes that are not the immediate response to AF but rather changes in reflex function that persist beyond a bout of PAF.

4.2 Potential mechanisms and clinical implications

Changes in efferent innervation of the atria have been reported after the induction of AF in dogs [8–10]. Both structural and functional changes in atrial autonomic innervation may be mechanistically responsible for the abnormal reflex changes we have observed in our PAF patients. The normal reflex response to LBNP is a complex reflex arc that relies on intact afferent receptors, vagus nerve traffic, inputs to the medulla, and the sympathetic outflow from the spinal cord, which together mediates peripheral vasoconstriction in response to

decreased venous return to the heart (Fig. 3, central diagram). Our findings may result from an abnormality of any one of these; however, given the changes we have demonstrated partially reverse after PVI, we hypothesize that aberrations within the left atrium are principally responsible for our findings and we, therefore, postulate atrial deafferentation as a possible explanation for our findings. Our observations may have important clinical implications. Autonomic dysfunction may be associated with orthostatic intolerance in those with AF, particularly in the elderly. In addition, autonomic dysfunction caused by AF could compound the neuro-hormonal dysregulation seen in heart failure, a common coexisting morbidity in AF individuals.

The progression of intermittent AF through to a more permanent form (AF begets AF) occurs through atrial remodeling; a process which relies on a number of both anatomical (structural) and physiological (functional) components, of which autonomic dysfunction may be one. Our data implies that rhythm control of AF with PVI may modulate its autonomic substrate and, therefore, may potentially impede this self-perpetuating process. Taken together, the presence of these clinical conditions in individuals with AF may warrant a more aggressive rhythm control strategy to improve outcomes.

4.3 Study limitations

There were limitations to our study. Our patients were highly symptomatic from AF, requiring rate slowing and anti-arrhythmic drugs therapy that might interfere with the HR component of the response, not attributed to atrial cardiopulmonary receptor unloading from LBNP [19]. However, β-blockade has been shown to not have any impact on vasoconstrictor responses to LBNP [21], which are mediated by α-adrenergic receptors. These medications may also decrease resting blood pressure, however, there were no differences seen in resting MAP between the groups. Further, we did not see any differences in the resting HR and HR increase induced by LBNP among the three groups studied.

While the use of post-PVI subjects who were free of clinical AF implicates AF itself as the cause of the persisting autonomic changes we have observed, it remains possible that PVI itself can modulate these changes, although the expected effect of PVI is to damage the autonomic tissue. The PAF and PVI groups were both heavier than control subjects and, therefore, obesity may represent a potential confounder. The presence of hypertension, which, itself is a risk factor for AF, may influence responses to LBNP, although this occurs only in the context of untreated hypertension with severe left ventricular hypertrophy [22]. There were no patients with either untreated hypertension or severe left ventricular hypertrophy and there was no statistical difference in the prevalence of hypertension in the PAF group compared to the PVI group, suggesting that hypertension was not the cause of the reflex deficit that we have identified. Last, we did not measure MAP invasively as the protocol was conducted in all subjects in the ambulatory setting.

5 Conclusions

The abnormal vasoconstrictor response to LBNP seen in PAF patients provides novel clinical evidence of autonomic dysfunction that persists during sinus rhythm. Rhythm control with PVI results in partial recovery of autonomic function, raising the hypothesis that the autonomic dysfunction we have observed occurs, at least partly due to the arrhythmia itself. Therefore, not only does autonomic disturbance predisposes to AF but it may also be a consequence of AF, leading to a feedback loop that could partially contribute to the well-known dictum of "AF begets AF."

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Compliance with ethical standards

Disclosure of potential conflicts of interest The University of Adelaide reports receiving on behalf of Dr. Lau lecture and/or consulting fees from Boehlringer Ingelheim, Pfizer, and St Jude Medical. The University of Adelaide reports receiving, on behalf of Dr. Lau, research funding from St Jude Medical. Dr. Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, Abbott, Boston Scientific and CathRx. The University of Adelaide reports receiving on behalf of Dr. Sanders lecture and/or consulting fees from Biosense-Webster, Medtronic, Abbott, and Boston Scientific. The University of Adelaide reports receiving on behalf of Dr. Sanders research funding from Medtronic, Abbott, Boston Scientific, Biotronik and Liva Nova.

Research involving human participants This study was approved by the institutional human research ethics committees where the work was carried out.

Informed consent All participants provided written informed consent.

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