SCIENTIFIC LETTER

Role of the autonomic nervous system in vagal atrial fibrillation

M P van den Berg, R J Hassink, C Baljé-Volkers, H J G M Crijns

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Based on the seminal work of Coumel, the autonomic nervous system is considered to play a pathophysiological role in a subset of patients with atrial fibrillation (AF).¹ In particular, Coumel put forward the concept of so-called vagal AF. Yet, the precise role of the autonomic nervous system in vagal AF is unclear. Is vagal AF caused by abnormal autonomic function or abnormal autonomic tone, or is there perhaps an increased sensitivity of the heart to vagal influences? In previous studies,^{2,3} both autonomic function and autonomic tone were shown to be normal in patients with AF, suggesting that increased sensitivity of the heart to vagal influences plays a role. However, these studies were limited by small sample size. In the present study we sought to collect additional data to define the role of the autonomic nervous system in vagal AF.

METHODS

The study group comprised 73 patients with paroxysmal AF. None of the patients had congestive heart failure. On average, patients had a three year history of one paroxysm per week lasting two hours. Patients were considered to have vagal AF if they met the following clinical criteria: (1) most attacks occurred at rest or during sleep, and generally terminated with exercise or in the morning; and (2) if available, typical electrocardiographic findings (preceding sinus bradycardia and a slow ventricular response during AF) were present. Ten patients fulfilled these clinical criteria (vagal AF group); eight men, mean (SD) age 59 (12) years. One patient had hypertension, one patient had mild aortic valve disease, and one patient had angina pectoris, but the other seven patients had lone AF. Mean left atrial dimension was smaller in the vagal AF group than in the other 63 patients (30 (2) mm and 35 (6) mm, respectively; $p = 0.04$), but all other clinical characteristics were comparable in the two groups, including demographics, underlying heart disease, medication, and arrhythmia burden.

Autonomic tone was considered to refer to overall, long term activity of the autonomic nervous system, whereas autonomic function was considered to refer to short term reactivity. Methods have been detailed previously.⁴ Briefly, heart rate variability (HRV) was analysed as a measure of autonomic tone. Using Holter monitoring the following parameters were calculated: the standard deviation of all normal-to-normal RR intervals (SDNN), the root mean square of successive differences between normal RR intervals (RMSSD), the percentage normal RR intervals differing > 50 ms with the preceding interval (pNN50), low frequency power (0.04–0.15 Hz), high frequency power (0.15–0.40 Hz), and total power (0.0033–0.40 Hz). Ectopy was accounted for using standard procedures, including manual editing and substitution of ectopic beats.

A battery of four tests was performed to assess autonomic function (with use of the Finapres system): (1) deep breathing—using a metronome, the mean of six breaths was taken to calculate the ratio between inspiratory and expiratory

heart rate; (2) isometric handgrip—a handgrip was held at 30% of maximum force and the increase in diastolic blood pressure was measured; (3) Valsalva manoeuvre—after blowing into a mouthpiece for 15 seconds at 40 mm Hg, the four phases of the manoeuvre were analysed allowing calculation of the Valsalva ratio as the highest heart rate and the lowest heart rate; and (4) standing up—the 30:15 ratio was calculated as the ratio between the highest heart rate and the lowest heart rate after standing up. In addition, baroreflex sensitivity (BRS) was determined non-invasively according to the method of Robbe and colleagues.⁵ Briefly, by performing cross spectral analysis between blood pressure and heart rate time series (> 4.5 minute) the coherence function and the transfer function modulus were computed. The mean value of the transfer function modulus in the frequency band 0.07–0.14 Hz, considering only those points where coherence was > 0.3 , was taken as the measure of BRS. In order to assess vasovagal reactivity head up tilting was performed, using standard procedures (80° angle, 30 minutes).

Quantitative variables were compared between groups using an unpaired t test for normally distributed variables or a Wilcoxon test for skewedly distributed variables. Qualitative/categorical variables were compared using a Fisher's exact test or a χ^2 test as appropriate.

RESULTS

In 20 Holter recordings $> 5\%$ ectopy was present due to paroxysms of AF, precluding further analysis. Measurements from the other 53 patients are listed in table 1, comparing the vagal AF group with the non-vagal AF group ($n = 7$ and $n = 46$, respectively). The number of atrial premature beats did not differ significantly. RMSSD was significantly higher in the vagal AF group than in the non-vagal AF group. pNN50, total power, and high frequency power were also higher in the vagal AF group, but these differences did not reach significance. Furthermore, there were no differences between the vagal AF group and the non-vagal AF group in any of the autonomic function tests (table 1). BRS was higher in the vagal AF group, but the difference was not significant. Because of AF and one technical failure head up tilting was not feasible in four patients, leaving nine patients in the vagal AF group and 60 patients in the non-vagal AF group. A vasovagal reaction was observed in one patient in the vagal AF group and eight patients in the non-vagal AF group ($p = 1.00$).

DISCUSSION

Vagal AF is an enigmatic entity. Our main finding is that the patients with presumed vagal AF in the present study were

Abbreviations: AF, atrial fibrillation; BRS, baroreflex sensitivity; HRV, heart rate variability; pNN50, percentage normal RR intervals differing > 50 ms with the preceding interval; RMSSD, root mean square of successive differences between normal RR intervals; SDNN, standard deviation of all normal-to-normal RR intervals

Table 1 Holter monitoring and autonomic function testing

	Vagal AF	Non-vagal AF	p Value
Heart rate (beats/minute)	69 (10)*	69 (9)*	0.95
Atrial premature beats	62 (21–1654)	37 (8–113)	0.12
SDNN (ms)	126 (49)*	127 (31)*	0.98
RMSSD (ms)	41 (32–45)	24.5 (18–34)	0.006
PNN50 (%)	7.8 (3.8–16.8)	4.0 (1.3–8.1)	0.064
Total power (ms)	36 (15)*	28 (10)*	0.067
Low frequency power (ms)	24 (12–35)	17.5 (12–21)	0.11
High frequency power (ms)	13 (8–15)	8 (6–12)	0.079
Deep breathing (beats/min)	10 (9–18)	12 (7–20)	0.97
Isometric handgrip (mmHg)	20 (15–27)	19 (14–27.5)	0.90
Valsalva manoeuvre	1.30 (1.22–1.50)	1.37 (1.22–1.49)	0.76
Standing up, 30:15 ratio	1.25 (1.19–1.32)	1.15 (1.07–1.29)	0.19
BRS (ms/mm Hg)	10.3 (7.5–14.5)	6.3 (3.8–9.0)	0.12

*Mean (SD)

characterised by increased vagal tone but not vagal reactivity as compared to the patients with non-vagal AF.

Murgatroyd and Camm³ studied 28 patients who participated in CRAFT (controlled randomized atrial fibrillation trials). Using a questionnaire regarding the onset of AF (triggers), patients were assigned a “vagal” score. There turned out to be no correlation between vagal score and BRS. Lok and Lau² studied a group of 28 patients with paroxysmal AF, nine of whom had “autonomic mediated” AF, which in fact was vagal AF in eight cases and adrenergic AF in one case. In addition to BRS, a battery of autonomic function tests was performed and HRV was analysed. In summary, patients with “autonomic mediated” AF did not differ from the remaining AF patients nor the controls in any of these tests. Our “negative” finding regarding BRS confirms the above studies, and it thus seems fair to conclude that BRS in patients with vagal AF is normal. The same holds true for the other tests of autonomic function. In particular, the vagal tests (deep breathing, Valsalva manoeuvre) were normal both in our study and in the study by Lok and Lau.² In contrast, our findings regarding vagal tone are at variance with the findings by Lok and Lau.² In our study, RMSSD was significantly higher in the vagal AF group than in the non-vagal AF group. A similar trend was observed for pNN50 and high frequency power. The explanation for this discrepancy is speculative, but may relate to differences in patient characteristics. In particular, the concept of “autonomic mediated” AF in the study by Lok and Lau² is confusing since they grouped together vagal AF and sympathetic AF, which may have diluted their results.

It is well established that because of the inherent potent vagal stimulus, vasovagal syncope occasionally elicits a paroxysm of AF.⁶ This observation suggests a possible role for increased susceptibility to vasovagal reactions in the genesis of vagal AF. We therefore performed head up tilt testing comparing vagal and non-vagal AF patients. Nine patients developed a vasovagal reaction, but no more often in the vagal AF

patients than in the non-vagal AF patients. It therefore appears that increased susceptibility to vasovagal reactions does not play a major role in vagal AF.

We conclude that vagal AF is not caused by increased vagal reactivity. Also, vasovagal reactivity appears not to play a role. Increased susceptibility of the heart to vagal influences is difficult to determine in the clinical setting and cannot be ruled out, but at present there is no direct evidence. Instead, the present study suggests that increased vagal tone is implicated in the genesis of vagal AF.

Authors' affiliations

M P van den Berg, R J Hassink, Department of Cardiology, Thorax Centre, University Hospital Groningen, Groningen, The Netherlands
C Baljé-Volkers, Trial Coordination Center, University Hospital Groningen
H J G M Crijns, Department of Cardiology, University Hospital Maastricht, The Netherlands

Correspondence to: Dr MP van den Berg, Department of Cardiology, Thorax Centre, University Hospital Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands; m.p.van.den.berg@thorax.azg.nl

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REFERENCES

- Coumel P**. Neural aspects of paroxysmal atrial fibrillation. In: RH Falk, PJ Podrid, eds. *Atrial fibrillation. Mechanisms and management*. New York: Raven Press, 1992:109–25.
- Lok NS**, Lau CP. Abnormal vasaovagal reaction, autonomic function, and heart rate variability in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 1998;**21**:386–95.
- Murgatroyd FD**, Camm AJ. Sinus rhythm, the autonomic nervous system, and quality of life. In: JH Kingma, NM van Hemel KI Lie, eds. *Atrial fibrillation, a treatable disease?* Dordrecht: Kluwer Academic Publishers, 1992:195–210.
- van den Berg MP**, Hassink RJ, Tuinenburg AE, et al. Quality of life in patients with atrial fibrillation and its predictors: importance of the autonomic nervous system. *Eur Heart J* 2001;**22**:247–53.
- Robbe HWJ**, Mulder LJM, Rüddel H, et al. Assessment of baroreflex sensitivity by means of spectral analysis. *Hypertension* 1987;**10**:538–43.
- Leitch J**, Klein G, Yee R, et al. Neurally mediated syncope and atrial fibrillation. *N Engl J Med* 1991;**324**:495–6.