SCIENTIFIC LETTER

Atrial extrasystoles after exercise predict atrial fibrillation in patients with left ventricular hypertrophy

R J Folkerlinga, J Hartgers, R G Tieleman, A P Gorgels, W R M Dassen, H J G M Crijns

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Prediction of atrial fibrillation (AF) is usually based on anatomical and functional characterisation of the atrial substrate, such as left atrial diameter, ejection fraction, and P wave duration.¹ In this respect, triggers such as atrial extrasystoles are often neglected.² Atrial extrasystoles may occur during or shortly after exercise as a result of acute atrial stretch, especially in patients with left ventricular hypertrophy (LVH) and diastolic dysfunction. As LVH may induce the atrial substrate and atrial extrasystoles are the trigger for AF, we reasoned that these exercise induced atrial extrasystoles may predict AF in patients with LVH.

METHODS

Patients with LVH (interventricular septal diameter ≥ 11 mm) and ejection fraction $\geq 55\%$ who underwent an exercise test between 1994 and 2004 were studied. Patients with prior AF or flutter or pacemaker rhythm, patients without at least one follow up ECG, and those with an incomplete exercise test were excluded. Of 864 screened patients 258 were selected.

The exercise tests (Case Exercise Testing System; GE Medical Systems, Milwaukee, USA) were performed according to standard protocols.³ Each test was manually reviewed for atrial extrasystoles and supraventricular tachycardia (SVT; three or more consecutive supraventricular extrasystoles).

Follow up ECG data were retrieved from an electronic storage system containing all ECGs recorded in our institution since 1994. The follow up period lasted from the date of the exercise test until the date of the last ECG or when AF was documented.

Data for patients with LVH were compared between those with permanent sinus rhythm and those who developed AF. All continuous variables are expressed as mean (SD). Student's *t* test was used for continuous variables and the χ^2 test for dichotomous variables. Mann-Whitney U test was used to compare the non-homogeneous distribution of the total number of atrial extrasystoles. Pearson's correlation coefficient was used to test whether a higher number of atrial extrasystoles increases the risk of AF. A receiver operating characteristic (ROC) curve was constructed to define sensitivity. Multivariate logistic regression forward analysis considered all univariate variables with a $p < 0.2$.

RESULTS

Seventeen per cent of patients developed AF. Mean follow up of the AF and sinus rhythm groups was 44 months and 45 months, respectively. Patients who developed AF had a larger left atrial diameter, a higher left ventricular mass index, and longer PR interval and P wave duration (table 1).

Atrial extrasystoles and SVT during exercise occurred equally in both groups. In the recovery phase, however, atrial extrasystoles and SVT occurred more often in the AF group. Pearson's correlation coefficient with atrial extrasystoles as the continuous variable without SVT showed a small but significant correlation between the number of atrial extrasystoles during recovery and AF ($p = 0.006$,

$r = 0.171$). There was no relation between atrial extrasystoles during exercise and AF ($p = 0.410$).

For ROC curve analysis, an SVT was set equal to the highest number of atrial extrasystoles. For atrial extrasystoles during exercise the area under the ROC curve was 0.523 ($p = 0.641$, asymptotic 95% confidence interval (CI) 0.428 to 0.617). For atrial extrasystoles during recovery the area under the curve was 0.638 ($p = 0.004$, asymptotic 95% CI 0.539 to 0.737). On the basis of the ROC curves the sensitivity at ≥ 1 atrial extrasystole/min during recovery was 33%.

The incidence of AF increased from 12% (19 of 158) if no atrial extrasystoles occurred to 15% (9 of 59) with 0–1 atrial extrasystole/min, and further to 37% (15 of 41) if ≥ 1 atrial extrasystole/min or an SVT was seen ($p = 0.001$). The positive and negative predictive values were 37% and 87%, respectively.

Multivariate analysis was performed with frequent atrial extrasystoles during recovery as a categorical variable. Atrial extrasystoles during recovery remained a predictor of AF ($p = 0.010$, 95% CI 0.139 to 0.975), independent of left atrial size ($p = 0.022$, 95% CI 1.01 to 1.16), PR interval, and P wave duration (both not significant).

DISCUSSION

This study shows that frequent atrial extrasystoles after exercise convey a high risk of future AF in patients with LVH. It is intriguing that supraventricular arrhythmias during recovery may predict AF in the long term, as the mean time to AF was 3.5 years.

Our finding that patients with LVH with high frequency atrial extrasystoles during recovery rather than during the active exercise phase develop AF is difficult to explain. AF did not necessarily present as exercise induced AF in our population. Therefore, post-exercise extrasystoles should be considered a marker of future AF rather than the mechanism. Patients with and without future AF differ with respect to the incidence of post-exercise atrial extrasystoles. After exercise vagal activity recurs and this may be associated with vagally mediated AF.⁴ In this context it is tempting to speculate that the patients who will eventually have AF are from time to time prone to vagal predominance producing short refractory periods. Additionally, their autonomic configuration may promote AF by increasing automaticity and heterogeneity of repolarisation. Thus, post-exercise extrasystoles predicting future AF may simply result from a higher extrasystolic burden presumably facilitated by the autonomic nervous system.

Our data suggest that post-exercise atrial extrasystoles predict future AF. The finding that ≥ 1 atrial extrasystole/min results in a sensitivity of 33% is rather modest and may reflect the multifactorial causality of AF, of which the autonomic function is only one component. However, in our opinion, it is an important clinical finding providing a

Abbreviations: AF, atrial fibrillation; CI, confidence interval; LVH, left ventricular hypertrophy; ROC, receiver operating characteristic; SVT, supraventricular tachycardia

Table 1 Baseline characteristics and comparison of patients who remained in sinus rhythm (SR) with those who developed atrial fibrillation (AF)

	All (n = 258)	SR (n = 215)	AF (n = 43)	p Value
Age (years)	65 (11)	65 (12)	67 (10)	0.157
Men	155 (60%)	128 (60%)	27 (63%)	0.691
Hypertension	200 (78%)	169 (79%)	31 (72%)	0.350
Hyperthyroidism	2 (1%)	1 (1%)	1 (2%)	0.204
Heart rate (beats/min)	77 (13)	78 (13)	75 (14)	0.262
Systolic BP (mm Hg)	149 (21)	149 (20)	151 (24)	0.433
Diastolic BP (mm Hg)	87 (12)	88 (12)	85 (13)	0.122
Ejection fraction (%)	66 (6)	66 (6)	66 (6)	0.754
Left ventricle mass index (g/m ²)*	137 (30)	135 (30)	145 (31)	0.044
Left atrial size (mm)	46 (5)	45 (5)	48 (6)	0.007
PR interval (ms)	172 (30)	170 (27)	182 (40)	0.011
P wave duration (ms)	102 (21)	101 (21)	109 (21)	0.026
Total ECGs (range)	12 (1–74)	11 (1–74)	15 (1–49)	0.016
Reason for exercise test				
Ischaemia	191 (74%)	163 (76%)	28 (65%)	0.219
Rhythm disturbances	25 (10%)	18 (8%)	7 (16%)	
Other	42 (16%)	34 (16%)	8 (19%)	
During exercise				
Bruce protocol	242 (92%)	201 (94%)	41 (95%)	0.644
Peak heart rate (beats/min)	138 (24)	139 (24)	131 (24)	0.059
Peak systolic BP (mm Hg)	190 (32)	190 (33)	187 (31)	0.592
Peak diastolic BP (mm Hg)	86 (14)	86 (14)	85 (13)	0.851
Exercise capacity (METs)	7.8 (3.0)	7.9 (3.0)	7.3 (3.1)	0.197
Exercise induced ST depression	64 (25%)	51 (24%)	13 (30%)	0.367
Number of AEs/min (range)	0.5 (0–22)	1.8 (0–22)	2.0 (0–12)	0.539†
SVT	13 (5%)	10 (5%)	3 (7%)	0.529
During recovery				
Disturbed vagal recovery‡	40 (16%)	34 (16%)	6 (14%)	0.794
Number of AEs/min (range)	0.6 (0–14)	0.5 (0–14)	1.3 (0–12)	0.001†
SVT	6 (2%)	3 (1%)	3 (7%)	0.028
Recovery duration (min)	5.7 (3.1)	5.7 (3.2)	5.8 (2.6)	0.795

Data are mean (SD), number (range), or number (%).

*10 missing values; †Mann-Whitney U results; ‡percentage of patients with a <12 beat decrease in the first minute of recovery.

AE, atrial extrasystoles; BP, blood pressure; METs, metabolic equivalents; SVT, supraventricular tachycardia (defined as three or more consecutive supraventricular extrasystoles).

potential basis for primary prevention of AF. The presence of post-exercise atrial extrasystoles may prompt a more intensive follow up or even initiation of anti-remodelling treatment to prevent further atrial dilatation and fibrosis.

This is the first study that addressed the value of atrial extrasystoles during exercise testing in the prediction of AF. As this was an observational study, we cannot exclude the possibility that some patients may have had asymptomatic AF. In addition, these findings cannot be extrapolated to populations other than patients with uncomplicated LVH.

We were not able to measure reliably coupling intervals or the site of origin of the atrial extrasystoles, which might have shed light on arrhythmogenic mechanisms. Nevertheless, we feel that our findings are important for doctors who see similar patients in their clinical practice. Our study supports the notion that frequent supraventricular extrasystoles after exercise may predict AF in patients with LVH.

Authors' affiliations

R J Folkeringa, J Hartgers, R G Tieleman, A P Gorgels, W R M Dassen, H J G M Crijns, Department of Cardiology, University Hospital Maastricht, Maastricht, the Netherlands

Competing interest statement: We declare that we have used only original data and that these data are not under review elsewhere or published before. In addition, none of the authors have competing interests.

Ethical statement: Since the exercise tests were analysed in retrospect for the purpose of this observational study, the need for ethical approval was waived.

Correspondence to: Dr Richard J Folkeringa, P Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, Netherlands; rfol@cardio.azm.nl

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