

Relationship between the frequency of paroxysmal episodes of atrial fibrillation and pulmonary venous flow pattern

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Aims Chronic atrial fibrillation causes mechanical remodelling of the atria, but it is uncertain whether self-terminating episodes of paroxysmal atrial fibrillation (PAF) alter atrial mechanical function during normal sinus rhythm. This study was designed to assess the relationship between the frequency of symptomatic arrhythmic episodes and pulmonary venous flow (PVF) pattern among patients with PAF.

Methods and Results The effect of symptomatic arrhythmic episodes on PVF was studied in 85 patients with lone PAF (age 48 ± 8 years, 66 men). PVF was measured with transthoracic echocardiography during sinus rhythm. Adequate recordings of PVF were achieved in 81 (95%) patients. Peak systolic PVF had an inverse correlation ($r = -0.35$, $P = 0.002$) with the frequency of PAF episodes. The peak systolic PVF was 76 ± 14 cm/s vs 62 ± 12 cm/s

($P = 0.008$) among the quartiles with the most and the least frequent episodes of PAF, respectively. There were no significant differences in the other echocardiographic measurements or demographic variables.

Conclusions Frequent arrhythmic episodes significantly diminished systolic PVF among patients with PAF, suggesting that PAF results in gradual mechanical remodelling of the atrium, which may favour recurrence and perpetuation of AF and/or formation of atrial thrombus.

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Key Words: Pulmonary venous flow, paroxysmal atrial fibrillation.

Introduction

Atrial fibrillation (AF) has been shown to cause electrophysiological, haemodynamic and histological changes that render the patient vulnerable to arrhythmia recurrence and thromboembolic complications^[1–4]. The mechanical function of the left atrium is impaired ('stunning') after electrical, medical and spontaneous cardioversion of long-lasting AF including patients with no other cardiac disease^[5–7].

Pulmonary venous flow (PVF) pattern reflects, in part, left atrial mechanical function^[8,9]. Several studies have shown that PVF pattern is different during AF than during normal sinus rhythm^[4,10,11]. In patients with chronic AF, systolic PVF and atrial reverse PVF are diminished due to loss of atrial relaxation and contraction, respectively^[10,11]. Likewise, even in patients without significant mitral valve regurgitation, systolic reverse PVF is common during AF^[12]. However, there is limited information on the effects of paroxysmal atrial fibrillation (PAF) episodes on PVF pattern. In particular, no prior study has evaluated the effects of the frequency of PAF episodes on PVF during normal sinus rhythm. Hence, we evaluated the relationship between the frequency of PAF episodes and transthoracically measured PVF pattern among patients without structural heart disease. It was hypothesized that repeated 'stunning' periods during frequent episodes of PAF cause gradual impairment of atrial mechanical function.

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Table 1 *Clinical characteristics*

	Group A (n=19)	Group B (n=21)	Group C (n=20)	Group D (n=21)
Age (yr)	45 ± 8	50 ± 6	49 ± 9	49 ± 6
Male/Female	15/4	17/4	16/4	15/6
Concomitant hypertension	10 (53%)	9 (43%)	10 (50%)	11 (52%)
Cardiovascular drugs during the study	7 (37%)	4 (19%)	5 (25%)	6 (29%)
Body mass index (kg/m ²)	27 ± 3	27 ± 3	29 ± 6	27 ± 4
Heart rate (bpm)	65 ± 12	65 ± 11	71 ± 14	66 ± 7
Systolic blood pressure (mmHg)	145 ± 22	155 ± 20	146 ± 18	146 ± 19
Diastolic blood pressure (mmHg)	86 ± 12	92 ± 13	87 ± 14	88 ± 11
Duration of PAF (yr)	8 ± 6	9 ± 8	11 ± 8	10 ± 8
Number of symptomatic PAF episodes	2 ± 2	7 ± 8	22 ± 17	64 ± 39
Frequency of PAF (median/yr)	0.25	0.67	2.0	5.0*
Days from the most recent PAF	962 ± 690	305 ± 332	320 ± 529	87 ± 40*
Number of subjects with PAF within 30 days	1 (5%)	4 (19%)	4 (20%)	15 (71%)*
Number of subjects with PAF in Holter	1 (5%)	2 (10%)	0	7 (29%)*

The subjects were grouped by frequency of paroxysmal atrial fibrillation (PAF) episodes. Group A represents the least symptomatic quartile and Group D the most symptomatic quartile. Values are mean ± SD unless otherwise indicated. * $P < 0.05$ by ANOVA or Kruskal–Wallis test.

Methods

Study population

A total of 85 patients (66 men and 19 women) with PAF was included in the study. The subjects were selected among 652 consecutive patients aged less than 60 years who were treated in the Oulu University Hospital between January 1995 and July 1999 for AF. Only patients with 'pure' lone PAF or PAF associated with mild hypertension were eligible. That is, subjects with a history of any cardiovascular, pulmonary or metabolic disease except for uncomplicated hypertension or mild asthma were excluded. Other exclusion criteria were electrical or medical cardioversion during the last 30 days before examination, history of thoracic surgery or radiofrequency catheter ablation, permanent pacemaker and any of the following echocardiographic findings: depressed left ventricular systolic function (ejection fraction <50%), abnormal wall motion of left ventricle, septal hypertrophy (>15 mm) and significant valve abnormality. According to the hospital documents 153 patients fulfilled the study criteria and they were invited to participate the study. Ninety-six (63%) patients came to the first study visit and 11 of them were excluded after interview and echocardiography for the following reasons: five subjects for valvular abnormalities, two for history of persistent but not paroxysmal AF, two for diabetes, one for coronary heart disease, one for carotid atherosclerosis. AF was considered to be paroxysmal if the episodes terminated spontaneously and had generally lasted less than 48 h. Forty-two (49%) subjects had uncomplicated hypertension and 12 subjects (14%) had mild asthma. All subjects gave their written informed consent for the study. The study protocol was approved by the local institutional ethics committee.

The total number of symptomatic PAF episodes, the date of the most recent event lasting more than 30 min and the duration of disease were estimated using all available hospital documentation and meticulous interview of the patients. All subjects were interviewed and examined by the same investigator. The frequency of PAF episodes was calculated by dividing the number of symptomatic episodes by the duration of PAF history (i.e., time from first detected PAF episode). To assess the effects of PAF on the echocardiographic measurements, the subjects were divided into quartiles (Groups A–D) according to the frequency of previous PAF episodes. Group A consisted of 19 subjects with the least, and Group D of 21 subjects with the most frequent episodes of PAF. All subjects were asked to stop antiarrhythmic medications, except amiodarone and digoxin, five half-lives before the echocardiographic examination. Antihypertensive medication was allowed during the examination. The characteristics of the patients are presented in Table 1.

Echocardiographic measurements

Transthoracic echocardiography was performed in the left lateral position using a Hewlett–Packard Sonos 5500 echo system with 1.8–4.4 MHz transducer (Andover, Massachusetts, U.S.A.) during sinus rhythm. M-mode measurements were made according to recommendations of the American Society of Echocardiography^[13] and left ventricular ejection fraction was calculated by Teichholz formulae^[14]. Two-dimensional mode was used to identify regional left ventricular wall motion abnormalities and to measure the left atrial area. The area of the left atrium (LA) was traced from apical 4- and 2-chamber views in maximal atrial diastole and systole

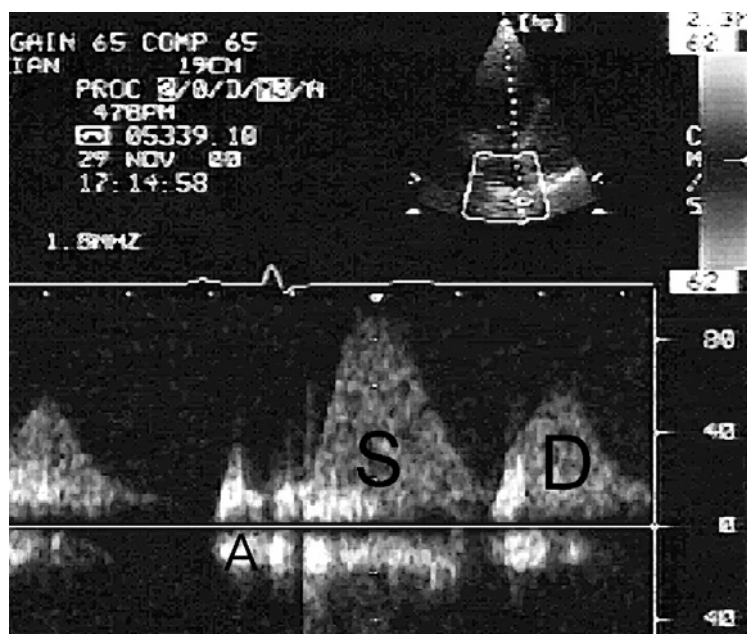


Figure 1 Pulsed Doppler recording of pulmonary venous flow (PVF) measured from right superior pulmonary vein. The components of PVF pattern are systolic (S), diastolic (D) and atrial reverse (A) flow. The measured parameters of PVF were peak velocities, time-velocity integrals of forward PVF flow and durations of atrial reverse flow and diastolic deceleration time (see text).

and total LA reservoir area change (maximum–minimum) was calculated. Left atrial area fractional shortening (%) was calculated using the following formulae: $[(LA_D - LA_S)/LA_D] \times 100\%$, in which LA_D and LA_S were the average of 4- and 2-chamber atrial diastolic and systolic area measurements, respectively. Left atrial volume was calculated by means of the biplane area-length method from both apical chamber views^[15].

Isovolumic relaxation time (IVRT) was measured from the beginning of the aortic valve closure to the onset of transmitral flow with continuous Doppler line in such a position where both the transmitral and aortic flow are simultaneously visualized. Transmitral flow peak E and A wave values, their ratio (E/A), deceleration time of E velocity and time-velocity integrals (TVI) of E and A velocity curves were measured from the 4-chamber view with the pulsed-wave Doppler sample volume between mitral leaflet tips. Colour Doppler imaging was used to quantify valve regurgitation according to jet size and to visualize PVF. The PVF pattern was measured by pulsed-wave Doppler with the sample volume at least 1 cm from the orifice of right superior PV. The horizontal speed of sweep was 100 mm/s. The PVF recordings were considered feasible when forward systolic and diastolic PVF were clearly displayed. The peak flow velocities and flow TVI of systolic and diastolic forward PVF, deceleration time of diastolic PVF and peak flow and duration of atrial reverse PVF (Fig. 1) were measured at the end of the expiration phase of quiet respiration. Systolic reverse PVF and deceleration time of diastolic PVF were

detected as previously described^[12,16,17]. The systolic fraction of PVF flow was obtained from the formulae: $[\text{systolic TVI}/(\text{systolic TVI} + \text{diastolic TVI}) \times 100\%]$. The average of three Doppler measurements was used in further analyses. Heart rate was detected from electrocardiogram (ECG) display during measurement of PVF.

Blood pressure was measured with an automatic oscillometric recorder and 12-lead ECG was recorded with standard filter and amplitude settings at 50 mm/s paper speed before the echocardiographic examination. After clinical examination and echocardiography, subjects had 24-h ambulatory ECG monitoring during their everyday activities outside the hospital.

Data analysis

All data are expressed as mean \pm standard of deviation (SD) unless otherwise indicated. Statistical analyses were performed with the SPSS for Windows software package (SPSS 10.0.1, SPSS Inc., Chicago, Illinois, U.S.A.). Differences between the groups were compared by analysis of variance (ANOVA) with Bonferroni post hoc testing (continuous variables) or Kruskal–Wallis test and chi square test (categorical variables). Correlations between normally distributed and skewed data were analysed using the Pearson correlation coefficient and the Spearman bivariate correlation coefficient, respectively. A *P* value <0.05 was considered statistically significant.

Table 2 *Baseline echocardiographic measurements*

	Group A (n=19)	Group B (n=21)	Group C (n=20)	Group D (n=21)
EF (%)	66 ± 10	69 ± 7	65 ± 8	66 ± 8
LAD (mm)	40 ± 4	40 ± 4	39 ± 4	40 ± 5
LVEDD (mm)	52 ± 6	50 ± 5	51 ± 4	49 ± 11
IVS (mm)	12 ± 2	12 ± 2	11 ± 1	11 ± 3
LA max area (cm ²)	21 ± 5	21 ± 4	20 ± 4	21 ± 5
LA area FS (%)	37 ± 9	32 ± 7	37 ± 6	34 ± 7
IVRT (ms)	77 ± 18	85 ± 15	86 ± 20	83 ± 15
E peak (cm/s)	73 ± 13	76 ± 16	68 ± 20	68 ± 18
A peak (cm/s)	62 ± 15	64 ± 9	64 ± 16	56 ± 13
E/A ratio	1.2 ± 0.2	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.4

Values are mean ± SD unless otherwise indicated. There were no significant differences between the groups. Abbreviations: EF=M-mode ejection fraction, LAD=left atrial antero-posterior diameter, LVEDD=left ventricular end-diastolic diameter, IVS=interventricular septum diameter in diastole, LA=left atrium, FS=fractional shortening, IVRT=isovolumic relaxation time, E=early transmitral flow, TVI=time-velocity integral, DT=deceleration time, A=atrial transmitral flow.

Results

Patient characteristics and electrocardiographic findings

The underlying clinical characteristics of the patients divided into quartiles according to the frequency of PAF episodes are shown in Table 1. There were no significant differences between the groups in demographic variables such as sex, age, concomitant hypertension, measured blood pressure, body mass index and heart rate. None of the subjects had any signs of ischaemic heart disease in the 12-lead ECGs or during Holter recording. No subject had a history of thromboembolic complications. Nineteen (23%) subjects were not able to discontinue antiarrhythmic medication and three (4%) were on anti-hypertensive medication. The number of subjects with cardiovascular medication was not significantly different between the groups.

The median number of PAF episodes/year in the quartiles are shown in Table 1. There was no difference between groups in the time from the first symptomatic episode of PAF. The time from the most recent symptomatic PAF episode was significantly longer in Group A than Groups B, C and D ($P < 0.001$). None of the subjects had had electrical or medical cardioversion during the last 30 days before the examination, but spontaneously terminated PAF was reported in 24 subjects (30%) and relapses occurred significantly ($P < 0.01$) more often in Group D (71%) than in the other Groups (5–20%). Seven (33%) subjects in Group D and S (0–10%) subjects in the other three Groups had spontaneously terminated PAF episodes during the ambulatory ECG monitoring.

Basic echocardiographic measurements

Transmitral flow, IVRT and M-mode dimensions were measured in all subjects. Because of partial 'drop out' of

the left atrial wall in diastole, acceptable 2-chamber recordings were obtained in only 56 (66%) subjects. Therefore, left atrial areas were measured only from the biplane 4-chamber view and left atrial volumes derived from a single biplane measurement were not taken to further analysis. In these measurements, there were no significant differences between the groups (Table 2). No correlation between the frequency of PAF episodes and any baseline echo measurements was observed.

Pulmonary venous flow pattern

Forward PVF could be satisfactorily measured in 81 subjects (95%). Systolic PVF was biphasic in 41 subjects (51%). None of the subjects had reverse systolic PVF. The frequency of PAF episodes correlated inversely with the peak systolic PVF ($r = -0.35$, $P = 0.002$), the TVI of systolic PVF ($r = -0.32$, $P = 0.004$), systolic-to-diastolic (S/D) ratio of the peak velocities ($r = -0.25$, $P = 0.022$) and the systolic fraction of TVI of PVF ($r = -0.30$, $P = 0.006$). In the quartile analysis, there was a linear relationship between the peak systolic PVF and the frequency of PAF episodes. That is, the subjects with the fewest PAF episodes had the highest and those with the most frequent arrhythmic episodes had the lowest systolic PVF, respectively (Fig. 1). There was also a statistically significant difference in the TVI of systolic PVF between the groups ($P = 0.045$), whereas the diastolic PVF and atrial reverse PVF did not differ between the groups. Data of PVF measurements are shown in Table 3.

Although there were no significant differences in cardiovascular medication between the groups, the data were also analysed after eliminating all patients with antiarrhythmic or antihypertensive medication. In these 59 patients the results were principally the same as described above. That is, the peak systolic PVF (76 ± 10 vs 60 ± 9) and TVI of systolic PVF (22 ± 3 vs 17 ± 5)

Table 3 Pulmonary venous flow

	Group A (n=19)	Group B (n=21)	Group C (n=20)	Group D (n=21)
Peak systolic flow (cm/s)	76 ± 14	72 ± 12	70 ± 13	62 ± 12*
TVI of systolic flow (cm)	21 ± 3	20 ± 4	18 ± 4	17 ± 5*
Biphasic systolic flow	4 (21%)	12 (57%)	13 (65%)	9 (42%)
Peak diastolic flow (cm/s)	53 ± 11	54 ± 8	51 ± 12	53 ± 13
TVI of diastolic flow (cm)	11 ± 4	11 ± 3	11 ± 5	11 ± 3
DT of diastolic flow (ms)	225 ± 45	227 ± 33	225 ± 45	211 ± 38
S/D	1.5 ± 0.5	1.4 ± 0.3	1.4 ± 0.2	1.2 ± 0.3
Systolic fraction of PVF (%)	66 ± 6	63 ± 7	62 ± 8	61 ± 9
Peak AR flow (cm/s)	31 ± 6	31 ± 6	34 ± 12	31 ± 10
ARd-Ad (ms)	-20 ± 24	-16 ± 30	-20 ± 30	-16 ± 22

The subjects were grouped by frequency of PAF episodes. Group A represents the least symptomatic quartile and Group D the most symptomatic quartile. Values are mean ± SD unless otherwise indicated. Abbreviations: PAF=paroxysmal atrial fibrillation, TVI=time-velocity integral, DT=deceleration time, S/D=ratio of peak systolic and diastolic PVF, PVF=pulmonary venous flow, AR=atrial reverse, ARd-Ad=time difference between pulmonary venous and transmitral flow at atrial contraction. * $P<0.05$ by ANOVA.

were significantly ($P=0.003$ and 0.013 , respectively) lower in Group D than Group A (data not shown). Both the peak systolic PVF ($r=-0.43$, $P<0.001$) and TVI of systolic PVF ($r=-0.44$, $P<0.001$) had a linear relationship with the frequency of PAF episodes.

The peak systolic PVF or TVI of systolic PVF were not related to age, gender, blood pressure, body mass index, markers of left ventricular systolic or diastolic function, left atrial size, left atrial area change, left atrial area fractional shortening or atrial reverse PVF. However, transmitral peak A-wave ($r=0.41$, $P<0.001$), TVI of A-wave ($r=0.38$, $P<0.001$) and transmitral peak E-wave ($r=0.24$, $P=0.03$) were related to peak systolic PVF.

Discussion

The main finding of the present study was that patients with frequent episodes of symptomatic PAF had reduced systolic PVF during normal sinus rhythm compared with those with only occasional episodes of PAF. These findings suggest that frequently recurring but spontaneously terminating PAF episodes will influence atrial mechanical function in a similar way to persistent or chronic AF. Furthermore, our results indicate that it is possible to record PVF pattern by means of transthoracic echocardiography in the majority of the patients with PAF.

Effects of paroxysmal atrial fibrillation on pulmonary venous flow and transmitral flow patterns

The frequency of symptomatic PAF episodes modulated PVF pattern by predominantly diminishing the systolic

flow. These findings are in agreement with the results of several previous studies that have shown a significant reduction of systolic PVF during chronic AF^[10,11] leads to 'diastolic dominant' pattern of forward PVF. In the present study the PVF pattern of the subjects was typically 'systolic dominant' which suggests that the effect of frequent PAFs on PVF is not so evident as in chronic AF.

There are several potential explanations for these observations. According to previous studies, the main

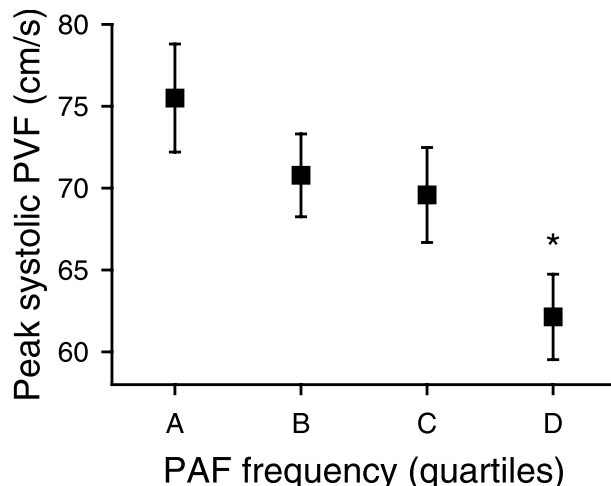


Figure 2 Effects of the frequency of paroxysmal atrial fibrillation (PAF) episodes on peak systolic pulmonary venous flow (PVF) velocities. Data are represented as mean ± standard error of the mean (SEM). The subjects were grouped by the frequency of symptomatic PAF episodes. Subjects in Group A had the least frequent and those in Group D the most frequent relapses of PAF. ANOVA followed by Bonferroni post hoc test gave * $P<0.01$ for the difference between Group A and Group D.

determinants of total systolic PVF are left ventricular performance, left atrial pressure and relaxation^[18], and possibly right ventricular function^[19]. In the present study, there were no significant differences in left ventricular size and ejection fraction. Concurrent with the results of a prior study^[18], there was no correlation between left atrial area change and total TVI of systolic PVF. Furthermore, we found no significant differences in the noninvasive markers of left atrial pressure (i.e., deceleration time of diastolic PVF^[17,20]) or left atrial size measurements between the groups. These data argue against the concept of impaired left ventricular function and elevated left atrial pressure as the primary cause of the observed systolic PVF reduction. Because of the lack of correlation between the above parameters and systolic PVF, we consider that an abnormality in atrial function, mainly relaxation^[9], caused by repeated ‘stunning’ periods may be the major reason for diminished systolic PVF among patients with frequent episodes of PAF. However, subtle diastolic ventricular dysfunction or dilatation of the arrhythmogenic pulmonary veins cannot be completely excluded. It has been recently demonstrated that despite the lack of evidence of echocardiographic diastolic dysfunction, invasively measured end-diastolic left ventricular pressure and early diastolic pressure are commonly elevated in highly symptomatic patients with drug-resistant lone PAF^[3]. It is also possible that pulmonary veins are wider in patients with highly symptomatic PAF^[21] than in subjects with no history of AF.

Measurement of pulmonary venous flow pattern

The normal PVF values in healthy subjects have a wide range^[22]. PVF pattern depends on age^[22,23], left ventricular function, degree of mitral valve regurgitation^[24,25], respiration and heart rate^[26]. In the absence of cardiovascular disease, the main determinant of forward PVF is age, and the influence of other factors is minor^[22]. In our study, no subject had depressed left ventricular function or wall motion abnormalities or valvular abnormality. There were no significant differences between the groups in demographic variables, such as sex, age, concomitant hypertension, measured blood pressure and body mass index. Measurement of PVF pattern was timed by respiration cycle and heart rate was not different between the groups. Hence, it is unlikely that any of the above variables could have affected our results. Much less information exists on the effects of antiarrhythmic drugs on PVF pattern. In the current study, the subgroup analysis of the patients without any cardiovascular medication did not alter our principal findings. In addition, there were no significant differences in PVF values between the patients with ‘pure’ lone AF and those with mild hypertension.

Most investigators who have evaluated PVF pattern in AF patients^[4–12] and determinants of PVF pattern in

other patient groups^[17,19,24,25] have used the transoesophageal approach. Our data confirmed that PVF can be measured in the vast majority of ambulatory patients by the means of transthoracic echocardiography. One may argue that the transoesophageal approach might have given slightly different values, especially in cases with low velocity Doppler measurements, such as atrial flow reversal^[26] and detection of systolic flow reversal. However, the transthoracic approach has not been shown to cause any systematic tendency to over- or underestimate flow velocities, and there have not been any significant differences between the transthoracic and transoesophageal measurements of systolic and diastolic forward PVF values^[23]. Moreover, because transthoracic echocardiography is easier to perform and more convenient for the patients than transoesophageal echocardiography, it is more suitable for examinations of large consecutive series of patients.

Limitations and implications of the study

Estimation of the exact number of previous PAF episodes is difficult. In the current study, only symptomatic PAF episodes were taken into account. According to recent data it is apparent that many PAF relapses are asymptomatic^[27]. Although some overlapping in the frequency of PAF episodes between the quartiles may have existed, it is unlikely that this caused a major bias in our results. This is supported by the observation that PAF episodes were significantly more common in Group D (i.e., the quartile with most frequent episodes of PAF) than in the other Groups during 24-h Holter recording. The main goal of the current study was to estimate the influence of the frequency of arrhythmic episodes on PVF patterns in patients with lone PAF. Although the patients with the least frequent PAF episodes may well represent the population without any AF burden, additional studies with a well-matched control population are needed to determine whether the reduction of systolic PVF is a cause or a result of PAF. Atrial remodelling may not be only be related to the total AF burden, but also to the time elapsed since the last AF episode. Therefore, it is possible that the present results may partly be explained by the time period from the last AF episode to the ultrasound examination. These data may not be directly extrapolated to patients with structural heart disease that predisposes to PAF.

Reduction of systolic PVF among patients with a history of frequent arrhythmic episodes indicates that not only persistent or chronic AF but also recurrent self-terminating PAF episodes may cause mechanical remodelling of the atria. Systolic PVF variables are known to correlate with the left atrial appendage flow velocity^[9,28] and decrease of left atrial appendage flow is associated with thrombus formation, thromboembolic complications and early recurrence of AF after cardioversion^[29]. Therefore, it is tempting to speculate that the reduction of systolic PVF in patients with frequent

episodes of PAF is a warning of subtle left atrial dysfunction that may predispose the patients to formation of atrial thrombus and favour reinitiation and perpetuation of AF. Further studies are needed to confirm this hypothesis.

References

- [1] Schotten U, Ausma J, Stellbrink C, *et al.* Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. *Circulation* 2001; 103: 691–8.
- [2] Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; 96: 1180–4.
- [3] Jais P, Peng JT, Shah DC, *et al.* Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation. *J Cardiovasc Electrophysiol* 2000; 11: 623–5.
- [4] Kato H, Yoshida M, Takata K, *et al.* Hemodynamic abnormalities in the left atrial appendage in patients with paroxysmal atrial fibrillation, with special reference to albumin-contrast echocardiographic aspects. *Cardiology* 1999; 92: 135–43.
- [5] Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for 'atrial stunning' as a mechanism of thromboembolic complications. *J Am Coll Cardiol* 1994; 23: 307–16.
- [6] Antonielli E, Pizzuti A, Bassignana A, *et al.* Transesophageal echocardiographic evidence of more pronounced left atrial stunning after chemical (propafenone) rather than electrical attempts at cardioversion from atrial fibrillation. *Am J Cardiol* 1999; 84: 1092–100.
- [7] Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. *Am J Cardiol* 1996; 78: 435–9.
- [8] Chen YT, Kan MN, Lee AY, Chen JS, Chiang BN. Pulmonary venous flow: its relationship to left atrial and mitral valve motion. *J Am Soc Echocardiogr* 1993; 6: 387–94.
- [9] Bollmann A, Binias K, Grothues F, *et al.* Left atrial appendage flow in nonrheumatic atrial fibrillation: relationship with pulmonary venous flow and ECG fibrillatory wave amplitude. *Chest* 2001; 119: 485–92.
- [10] Ren WD, Visentin P, Nicolosi GL, *et al.* Effect of atrial fibrillation on pulmonary venous flow patterns: transesophageal pulsed Doppler echocardiographic study. *Eur Heart J* 1993; 14: 1320–7.
- [11] Chao T-H, Tsai L-M, Tsai W-C, Li Y-H, Lin L-J, Chen J-H. Effect of atrial fibrillation on pulmonary venous flow patterns assessed by Doppler transesophageal echocardiography. *Chest* 2000; 117: 1546–50.
- [12] Paraskevaidis IA, Kremastinos DT, Matsakas EP, *et al.* Transesophageal detection of early systolic reverse pulmonary venous flow in atrial fibrillation. *Am J Cardiol* 1994; 73: 392–6.
- [13] Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072–83.
- [14] Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 1976; 37: 7–11.
- [15] Pitsavos C, Aggeli C, Stefanadis C, Toutouzas P. Non-invasive assessment of left atrial performance by echocardiographic modalities. *Eur Heart J* 2000; 2: K26–K33.
- [16] Chirillo F, Brunazzi MC, Barbiero M, *et al.* Estimating mean pulmonary wedge pressure in patients with chronic atrial fibrillation from transthoracic Doppler indexes of mitral and pulmonary venous flow velocity. *J Am Coll Cardiol* 1997; 30: 19–26.
- [17] Kinnaird TD, Thompson CR, Munt BI. The deceleration time of pulmonary venous diastolic flow is more accurate than the pulmonary artery occlusion pressure in predicting left atrial pressure. *J Am Coll Cardiol* 2001; 37: 2025–30.
- [18] Barbier P, Solomon S, Schiller NB, Glantz SA. Determinants of forward pulmonary vein flow. An open pericardium pig model. *J Am Coll Cardiol* 2000; 35: 1947–59.
- [19] Smiseth OA, Thompson CR, Lohavanichbutr K, *et al.* The pulmonary venous systolic flow pulse – its origin and relationship to left atrial pressure. *J Am Coll Cardiol* 1999; 34: 802–9.
- [20] Yamamuro A, Yoshida K, Hozumi T, *et al.* Noninvasive evaluation of pulmonary capillary wedge pressure in patients with acute myocardial infarction by deceleration time of pulmonary venous flow velocity in diastole. *J Am Coll Cardiol* 1999; 34: 90–4.
- [21] Lin WS, Prakash VS, Tai C-T, *et al.* Pulmonary vein morphology in patients with paroxysmal atrial fibrillation initiated by ectopic beats originating from the pulmonary veins implications for catheter ablation. *Circulation* 2000; 101: 1274–81.
- [22] Gentile F, Mantero A, Lippolis A, *et al.* Pulmonary venous flow velocity patterns in 143 normal subjects aged 20 to 80 years old. An echo 2D colour Doppler cooperative study. *Eur Heart J* 1997; 18: 148–64.
- [23] de Marchi SF, Bodenmüller M, Lai DL, Seiler C. Pulmonary venous flow velocity patterns in 404 individuals without cardiovascular disease. *Heart* 2001; 85: 23–9.
- [24] Castello R, Pearson AC, Lenzen P, Labovitz AJ. Effect of mitral regurgitation on pulmonary venous velocities derived from transesophageal echocardiography color-guided pulsed Doppler imaging. *J Am Coll Cardiol* 1991; 17: 1499–1506.
- [25] Klein AL, Stewart WJ, Bartlett J, *et al.* Effects of mitral regurgitation on pulmonary venous flow and left atrial pressure: an intraoperative transesophageal echocardiographic study. *J Am Coll Cardiol* 1992; 20: 1345–52.
- [26] Meijburg HW, Visser CA, Westerhof PW, *et al.* Normal pulmonary venous flow characteristics as assessed by transesophageal pulsed Doppler echocardiography. *J Am Soc Echocardiogr* 1992; 5: 588–97.
- [27] Frykman V, Frick M, Jensen-Urstad M, Östergren J, Rosenqvist M. Asymptomatic versus symptomatic atrial fibrillation: clinical and noninvasive characteristics. *J Int Med* 2001; 250: 390–3.
- [28] Tukek T, Atilgan D, Akkaya V, *et al.* Assessment of left atrial appendage function and its relationship to pulmonary venous flow pattern by transesophageal echocardiography. *Int J Cardiol* 2001; 78: 121–6.
- [29] Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994; 23: 961–9.