Left atrial enlargement as a predictor of recurrences in lone paroxysmal atrial fibrillation

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BACKGROUND: A mild increase in left atrial (LA) size predicts arrhythmia onset and adverse events in patients with lone paroxysmal atrial fibrillation (LPAF). However, the role of LA size as a predictor of LPAF recurrences is still controversial.

OBJECTIVE: The potential role of LA size in affecting the frequency of recurrent episodes in patients with LPAF was investigated.

METHODS: Fifty-one patients who were admitted for a first episode of LPAF and presenting with one recurrence (group A, n=20), two or three recurrences (group B, n=18), or four or more recurrences (group C, n=13) during an average follow-up period of two years were retrospectively selected. The M-mode LA anteroposterior diameter (LAAPd) was used as an echocardiographic surrogate of LA size.

RESULTS: At baseline, LA size was normal or borderline in the control group, group A and group B, but significantly increased in group C. At two years' follow-up, a significant further LA enlargement from baseline was observed in group B (LAAPd 40 ± 1.1 mm versus 40.7 ± 1.2 mm, $P < 0.01$) and in group C (LAAPd 41.4 ± 1.6 mm versus 42.7 ± 1.7 mm, $P < 0.001$), while LA size remained substantially unchanged in the control group and in group A.

CONCLUSIONS: Observations confirmed the association of increased LA size and LPAF onset, and provide the first evidence for a potential role of LA progressive enlargement as a predictor of arrhythmic recurrences.

Key Words: Arrhythmia; Atrial fibrillation; Echocardiography; Left atrium

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, with a prevalence of 4% in the adult population (1). Lone AF is, by consensus, described as a well-defined, separate and less frequent entity accounting for 10% to 25% of all AF cases (2,3) that occurs in the absence of concomitant cardiovascular diseases or any other known causal factor (4). Previous studies have reported that increased left atrial (LA) size is associated with the occurrence of a first episode of lone AF (5) and predicts cardiovascular adverse events in patients with lone paroxysmal AF (LPAF) (6). The aim of our study was to examine the temporal modification of LA size in a population with recurrences of LPAF over an average follow-up period of two years.

METHODS

Study population

The medical records of the Department of Internal Medicine of the University of Siena General Hospital (Siena, Italy) were reviewed

L'hypertrophie auriculaire gauche comme prédicteur des récurrences de fibrillation auriculaire paroxystique isolée

HISTORIQUE : Une augmentation bénigne de la dimension de l'auriculaire gauche (AG) permet de prédire l'apparition d'arythmies et de réactions indésirables chez les patients atteints de fibrillation auriculaire paroxystique isolée (FAPI). Cependant, le rôle de la dimension AG comme prédicteur des récurrences de FAPI demeure controversé.

OBJECTIF : On a évalué le rôle potentiel de la dimension AG sur la fréquence de récurrences chez les patients atteints de FAPI.

MÉTHODOLOGIE : On a sélectionné 51 patients hospitalisés pour un premier épisode de FAPI et qui avaient consulté à cause d'une récurrence (groupe A, n=20), de deux ou trois récurrences (groupe B, n=18) ou de quatre récurrences ou plus (groupe C, n=13) pendant une période de suivi moyenne de deux ans. On a utilisé l'échocardiographie en mode M pour évaluer le diamètre AG antéropostérieur (dAGAP).

RÉSULTATS : Au départ, la dimension AG était normale ou limite au sein du groupe témoin, du groupe A et du groupe B, mais considérablement accrue au sein du groupe C. Au suivi de deux ans, l'augmentation AG s'était poursuivie de manière significative au sein du groupe B (dAGAP $40 \pm 1,1$ mm par rapport à $40,7 \pm 1,2$ mm, $P < 0,01$) et du groupe C (dAGAP $41,4 \pm 1,6$ mm par rapport à $42,7 \pm 1,7$ mm, $P < 0,001$), tandis que la dimension AG demeurait sensiblement inchangée au sein du groupe témoin et du groupe A.

CONCLUSIONS : Ces observations ont confirmé l'association entre la dimension AG accrue et l'apparition de la FAPI et fournissent les premières données probantes quant au rôle potentiel de l'hypertrophie AG progressive pour prédire les récurrences d'arythmie.

to identify subjects who were admitted for a first episode of recent-onset AF (less than 48 h) between January 1, 2001, and December 31, 2003. The criteria for the diagnosis of lone AF included those indicated by the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines (4). Criteria considered mandatory for enrolment in the study included the availability of each patient to have had both an echocardiogram recorded in sinus rhythm at the time of the first episode and an echocardiogram recorded in sinus rhythm after a mean follow-up period of two years from the first episode. Any recurrence of an electrocardiogram-documented episode of AF recorded during the follow-up period was considered (these data were obtained from patient personal medical records in case of a reported admission at another hospital). Patients receiving concomitant prophylactic antiarrhythmic therapy during the two-year follow-up were excluded. Conversion was defined as spontaneous if it occurred before or after administration of only rate-controlling

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TABLE 1
Main baseline clinical characteristics of the study population

	Control group (n=20)	Group A (n=20)	Group B (n=18)	Group C (n=13)
Sex (male/female)	16/4	15/5	13/5	10/3
Age, years	65±6	62±5	64±7	59±4
Heart rate, beats/min	82±4	79±2	80±5	78±6
Systolic BP, mmHg	124±6	118±4	120±8	122±7
Diastolic BP, mmHg	81±5	80±8	83±6	80±4
BMI, kg/m ²	25.9±1.3	25.8±1.6	26.2±1.3	26.4±1.5

Patients were grouped according to the number recurrences of lone paroxysmal atrial fibrillation (group A: one recurrence, group B: two or three recurrences, group C: four or more recurrences). BMI Body mass index; BP Blood pressure

TABLE 2
Baseline echocardiographic measurements in all study groups

	Control group (n=20)	Group A (n=20)	Group B (n=18)	Group C (n=13)
LVEDd, mm	46.7±2.6	47.2±2.8	49.6±3.3	49.9±2.1
LVESd, mm	33.8±3.7	33.6±3.1	32.9±4.1	34±2.9
FS, %	31.8±3.6	29.1±5.2	31.2±3.4	32.6±5.8
LAAPd, mm	38.9±2.5	39.3±1.4	40±1.1	41.4±1.6***

Patients were grouped according to the number recurrences of lone paroxysmal atrial fibrillation (group A: one recurrence, group B: two or three recurrences, group C: four or more recurrences). * $P<0.05$ group C versus group B; ** $P<0.001$ group C versus group A; *** $P<0.001$ group C versus the control group. FS Fractional shortening; LAAPd Left atrial anteroposterior diameter; LVEDd Left ventricular end-diastolic diameter, LVESd Left ventricular end-systolic diameter

medications (2). According to the number of recurrences registered during the two-year follow-up, LPAF patients were divided into group A (one recurrence), group B (two or three recurrences) and group C (four or more recurrences). Twenty healthy age- and sex-matched subjects who were referred to our outpatient echocardiography laboratory for routine evaluation constituted the control group.

Echocardiography

All echocardiographic data were obtained from examinations performed at the inpatient or outpatient echocardiography laboratory of the hospital during initial patient assessments, at the time of the diagnosis and during the course of the hospital's standard follow-up program for AF patients. Transthoracic Doppler echocardiographic examinations were performed in sinus rhythm, at least seven days after cardioversion, with the patient in the partial left decubitus position using a SIM 7000 ultrasound system (Esaote Biomedica, Italy) equipped with a 2.5 MHz to 3.5 MHz transducer, and recorded on super VHS videotapes for offline analysis. Two-dimensional guided M-mode images were obtained from parasternal long- and short-axis views, according to the standards of American Society of Echocardiography (7). LA anteroposterior diameter (LAAPd) was measured at left ventricular end-systole as its largest diameter, and the exact location of the posterior wall was confirmed by two-dimensional echocardiography (5). Two experienced investigators calculated all the measures by considering the average of three or more cardiac cycles. Intra- and interobserver agreements were determined with the analysis of a random sample of 15 subjects from the study population; the resultant intra- and interclass relation coefficients were highly significant (intraobserver $r=0.99$ and $r=0.98$ respectively, and interobserver $r=0.97$, all

TABLE 3
Two-year follow-up echocardiographic measurements in all study groups

	Control group (n=20)	Group A (n=20)	Group B (n=18)	Group C (n=13)
LVEDd, mm	49.4±3.7	47.8±3.8	50.1±2.2	48.7±3.3
LVESd, mm	34.3±2.3	34±2.9	32.4±3.8	35±3
FS, %	33.4±4.1	31.7±3.3	28.8±2.3	30.1±3.8
LAAPd, mm	39±2.6	39.4±1.4	40.7±1.2***	42.7±1.7*** ****

Patients were grouped according to the number recurrences of lone paroxysmal atrial fibrillation (group A: one recurrence, group B: two or three recurrences, group C: four or more recurrences). * $P<0.05$ group B versus the control group; ** $P<0.05$ group C versus group B; *** $P<0.01$ group B versus group A; **** $P<0.001$ group C versus the control group; ***** $P<0.00001$ group C versus group A. FS Fractional shortening; LAAPd Left atrial anteroposterior diameter; LVEDd Left ventricular end-diastolic diameter; LVESd Left ventricular end-systolic diameter

$P<0.00001$), as well as the coefficients of variation (intraobserver 10.7% and 10.8%, respectively, and interobserver 10.9%).

Statistical analysis

All the data are presented as the mean $\pm$ SD. ANOVA with Bonferroni correction for multiple comparison was used to estimate intergroup differences, while intragroup differences were calculated by t test for paired data. Linear regression analysis and partial correlation test using Pearson's method were used to assess univariate relations. The null hypothesis was rejected at $P<0.05$.

RESULTS

Three hundred twenty-one patients were admitted with a primary diagnosis of AF between January 1, 2001, and December 31, 2003. Of these, 61 had lone AF and 51 fulfilled the criteria for study entry (six had inadequate follow-up testing and four were prescribed antiarrhythmic drugs at some point during follow-up period). Fifty-one LPAF patients (38 men, age 62 ± 6 years) and 20 healthy subjects (16 men, age 65 ± 6 years) comprised the final study population; the mean follow-up period was 23.7 ± 2.8 months. Among the LPAF patients, 20 constituted group A, 18 constituted group B and the remaining 13 constituted group C. Main baseline clinical characteristics of the study population are shown in Table 1. All four groups were similar in sex distribution, age, heart rate, systolic and diastolic blood pressure, as well as body mass index. Echocardiographic M-mode quantitative analysis at baseline and at two-year follow-up are reported in Tables 2 and 3, respectively. No significant intergroup differences in left ventricular diameters or fractional shortening were observed at baseline or at two-year follow-up. Baseline LA diameters were normal (or borderline) in the control group (38.9 ± 2.5 mm), group A (39.3 ± 1.4 mm) and group B (40 ± 1.1 mm); LA size was significantly enlarged in group C (41.4 ± 1.1 mm) compared with the other groups ($P<0.001$ versus the control group, $P<0.001$ versus group A and $P<0.05$ versus group B). At follow-up analysis, the LA was enlarged both in group B (40.7 ± 1.2 mm) and group C (42.7 ± 1.7 mm), but was still within normal range in group A (39.4 ± 1.4 mm) and in the control group (39 ± 2.6 mm). The LAAPd was increased significantly in group B compared with the control group (40.7 ± 1.2 mm versus 39 ± 2.6 mm, $P<0.05$) and group A (40.7 ± 1.2 mm versus 39.4 ± 1.4 mm, $P<0.01$), and in group C compared with all the other groups ($P<0.001$ versus the control group, $P<0.00001$ versus group A and $P<0.05$ versus group B, respectively). The intragroup comparisons of LAAPd change between baseline and the two-year follow-up (Table 4) showed progressive LA dilation in group B (40 ± 1.1 mm versus 40.7 ± 1.2 mm, $P<0.01$) and in group C

(LAAPd 41.4 ± 1.6 mm versus 42.7 ± 1.7 mm, $P < 0.001$), while LAAPd was, for the most part, unchanged in group A (39.3 ± 1.4 mm versus 39.4 ± 1.4 mm) and the control group (38.9 ± 2.5 mm versus 39.0 ± 2.6 mm). No thromboembolic events were recorded during the follow-up period in the study population. Among the overall 20 LPAF recurrences that occurred in group A, spontaneous restoration of sinus rhythm was observed in 14 cases (70%); this reversion rate was reduced to 22% of cases in group B and 15.4% in group C. The univariate analysis showed a direct correlation between the number of LPAF recurrences and LA size both at baseline ($r = 0.51$, $P < 0.001$) and at the two-year follow-up ($r = 0.70$, $P < 0.00001$).

DISCUSSION

Atrial chamber enlargement is a common finding in patients with chronic AF (8-10), and although the link between increased LA size and AF is widely recognized, it is not clear whether LA enlargement is the consequence or the cause of this arrhythmia (11-13). The relationship between LA enlargement and AF is somehow 'weaker' in LPAF patients. Previous studies have failed to demonstrate an association between baseline and follow-up LA size, and arrhythmia onset and paroxysmal episodes, supporting the hypothesis that LA enlargement occurs only if AF becomes chronic (14,15). However, Phang et al (16) recently reported that even in a highly selected cohort of young LPAF patients with a classically 'normal' LA (ie, LAAPd smaller than 40 mm), subtle structural alterations may be present as suggested by the increased LA area and volume. Our data confirm the association between increased LA size and LPAF onset, and the findings of normal LA size in group A (LAAPd 39.3 ± 1.4 mm) may be an underestimation of the actual LA three-dimensional geometry. Moreover, the results of the univariate analysis in our LPAF population establish a direct correlation between increased LA size at baseline and progressive LA enlargement during follow-up, as well as the number of arrhythmic recurrences, thus suggesting an association between intrinsic LA structural modifications and the natural history of LPAF. The major degree of progressive LA enlargement observed in patients with the highest number of arrhythmic episodes is in agreement with previous observations of LPAF-induced LA remodelling (5,13). Indeed, Suarez et al (5) reported that LPAF may determine slowly progressive LA enlargement, although this may be less evident than in chronic AF, the extent of the increase in LA size being related to follow-up duration.

The spontaneous conversion to sinus rhythm is common in the natural history of AF (17), being observed in more than 50% of cases (2,3,18). In our study, we observed a higher likelihood of spontaneous conversion (70%) in LPAF patients with a smaller LA size (group A). A shorter duration of AF at presentation (less than 12 h [18] or less than 24 h [19]) and a younger age have been identified as powerful clinical predictors of spontaneous conversion in the general AF population (18,19), while the role of LA size remains controversial. In accordance with our findings, Galve et al (19) reported that a smaller LA size is predictive of pharmacological and spontaneous conversion, but our data are unique because they refer exclusively to a LPAF population.

The potential clinical value of our observations is that LA size can be used to stratify LPAF patients into subgroups that require differentiated acute and prophylactic therapeutic approaches according to the presence and degree of LA enlargement.

Limitations

Our study contains several potential limitations and sources of bias that should be taken into consideration. The major limitations of

TABLE 4
Intragroup comparisons of left atrial anteroposterior diameter (LAAPd) at baseline and two-year follow-up

	Baseline LAAPd, mm	Follow-up LAAPd, mm	P
Control	38.9 ± 2.5	39 ± 2.6	NS
Group A	39.3 ± 1.4	39.4 ± 1.4	NS
Group B	40 ± 1.1	40.7 ± 1.2	< 0.01
Group C	41.4 ± 1.6	42.7 ± 1.7	< 0.001

Patients were grouped according to the number recurrences of lone paroxysmal atrial fibrillation (group A: one recurrence, group B: two or three recurrences, group C: four or more recurrences). NS Not significant

the study are its small population size and its retrospective nature. In addition, the M-mode LAAPd, although routinely used and accepted as a surrogate of LA size, may underestimate the actual LA dimension compared with the determination of LA area or volume (20). However, this measure was shown to strongly correlate with two-dimensional values in both parasternal and apical views in a population free from valvular heart disease (21). This observation may lead to the assumption that M-mode LAAPd also provides a good level of accuracy in the estimation of LA size in LPAF patients. The timing of the echocardiographic examination after conversion of AF to sinus rhythm is crucial, given the temporary course of the recovery of atrial functional impairment and dilation (22,23); however, this may not apply to patients with lone AF. In fact, previous observations (24,25) showed that LA size, namely, LAAPd, assessed in serial echocardiograms performed 12 h to 30 days after cardioversion does not undergo significant, if any, change. Despite this evidence, to avoid any potential bias, we preferred to systematically collect data only obtained from echocardiograms performed at least seven days after sinus rhythm restoration, because no further significant changes in LA size are usually observed between one week and one month after conversion, even in non-LPAF patients with borderline LA dimensions (23). An accurate assessment of the number of arrhythmic events in an AF population is usually challenging, and the global burden of episodes is, in general, underestimated because asymptomatic episodes are common and go unrecognized unless a continuous monitoring system is available (26,27). In our study, a further underestimation of the number of paroxysmal episodes may derive from the fact that, by design, we counted only episodes with ECG documentation of AF as recurrences. However, the correlation between self-reported AF-like episodes and confirmed ECG diagnosis is rather variable and inaccurate (27); therefore, including self-reported events in our count might have provided an additional source of bias.

CONCLUSIONS

Our study confirms the association between increased LA size and LPAF onset, and provides the first evidence for a novel role of LA progressive enlargement as a predictor of arrhythmic recurrences. Further investigations are needed to confirm our findings.

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