

Atrial Enlargement as a Consequence of Atrial Fibrillation

A Prospective Echocardiographic Study

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To test the hypothesis that atrial enlargement can develop as a consequence of atrial fibrillation, left and right atrial dimensions were measured echocardiographically at two different time points in patients with atrial fibrillation. Patients were selected who initially had normal atrial sizes and who had no evidence of significant structural or functional cardiac abnormalities other than atrial fibrillation either by history or two-dimensional and Doppler echocardiography. Fifteen patients were studied (12 men and three women; mean age, 67.3 years). Average time between studies was 20.6 months. Three orthogonal left atrial dimensions and two right atrial dimensions were measured, and all were found to increase significantly between studies. Also, highly significant increases in calculated left atrial volume (from 45.2 to 64.1 cm³, $p < 0.001$) and right atrial volume (from 49.2 to 66.2 cm³, $p < 0.001$) were observed. The relative extents of left and right atrial volume increase did not differ, and left ventricular size did not change significantly between studies. These results indicate that atrial enlargement can occur as a consequence of atrial fibrillation. The maintenance of sinus rhythm, therefore, may prevent atrial enlargement and its adverse clinical effects. (*Circulation* 1990;82:792-797)

Although usually well tolerated by patients, atrial fibrillation has been shown to carry increased risk for cerebral infarction and early mortality.¹⁻⁵ It has also been shown to be associated with left atrial enlargement,⁶⁻⁹ and this chamber dilation is generally considered to contribute, at least in part, to the genesis and persistence of the arrhythmia.

There exists a subset of patients who develop atrial fibrillation in the absence of any identifiable structural cardiac abnormalities but who nonetheless also carry an adverse prognosis.^{1,10-12} Whether such patients subsequently develop enlargement of the left atrium is not clear. Such a finding would serve as evidence that left atrial enlargement can develop as a consequence of atrial fibrillation and would provide a mechanism whereby a self-perpetuating cycle of progressive chamber enlargement and arrhythmia could occur.

Because atrial enlargement may increase refractoriness to medical or electrical conversion of atrial

fibrillation^{8,13} and the likelihood of thrombus formation,¹⁴ its prevention appears to be a worthwhile therapeutic goal in itself. Therefore, demonstration that atrial fibrillation can lead to or perpetuate atrial enlargement may justify a more aggressive clinical approach to the treatment of even asymptomatic patients with this arrhythmia.

This study, therefore, was designed to test the hypothesis that atrial size increases with time in patients with atrial fibrillation, even in the absence of other potential causes of atrial enlargement.

Methods

Patient Selection

Patients were selected from the registry of a large multicenter trial intended to examine the effect of anticoagulation on complications of atrial fibrillation. Entry into the registry was based on the following criteria: 1) documentation of atrial fibrillation by at least two electrocardiograms obtained at least 48 hours apart, 2) no contraindications to anticoagulation, and 3) no echocardiographic evidence of mitral stenosis, intracavitary thrombus, or left ventricular aneurysm. All participants in the registry had undergone a complete two-dimensional echocardiographic examination at entry.

The subgroup for this study was selected on the basis of the following findings at the initial echocar-

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diagram: 1) no significant mitral valve or left ventricular pathology, 2) no significant mitral or tricuspid regurgitation, 3) normal left atrial size, and 4) no evidence of ventricular diastolic dysfunction (i.e., ventricular hypertrophy, abnormal mitral inflow patterns by Doppler, or pericardial abnormalities).

These entry criteria were designed to exclude, as far as possible, any confounding cause of atrial enlargement. Patients in whom these criteria were fulfilled and in whom at least 12 months had elapsed since the initial echocardiographic examination were eligible for study. To maintain consistency in the technical performance of the echocardiographic studies, only those patients who had their initial study performed at our laboratory were considered for inclusion.

There were 246 patients enrolled in the registry at the beginning of this study. Of these, 77 had left atrial size determinations within two standard deviations of normal as determined by previous studies.¹⁵ Forty-six of these 77 patients were excluded because of significant mitral regurgitation (12 patients), depressed left ventricular contractility (two patients), mitral leaflet thickening (six patients), mitral annular calcification (10 patients), or absence of Doppler examination in conjunction with the index imaging study (16 patients). Therefore, 31 patients remained who met eligibility criteria. Fifteen of these who had undergone their initial study at our laboratory and were willing to undergo repeated echocardiographic examination form the study group. These 15 study patients consisted of 12 men and three women whose mean age was 67.3 years (range, 48–78 years). The time between echocardiographic examinations averaged 20.6 months (range, 12–28 months).

In all patients, treatment of the arrhythmia was at the discretion of the referring physician. Before entry into the study, five of the 15 patients had undergone unsuccessful attempts at electrical cardioversion. In an additional four patients, chemical conversion was attempted unsuccessfully with type Ia antiarrhythmic agents. In the remaining six patients, no attempts at conversion were made. During the course of the study, 11 of the 15 patients were maintained on digoxin continuously. Three of these also received a type Ia antiarrhythmic agent at various times.

Study Protocol

Two-dimensional and Doppler echocardiography was performed with the patient in the left lateral decubitus position with an ultrasonic instrument (Hewlett-Packard, Arondale, Pa.) equipped with a 2.5-MHz transducer. Images were obtained in the parasternal long-axis, parasternal short-axis, and apical four-chamber planes. Doppler examination for mitral regurgitation was performed by sampling carefully on the left atrial side of the mitral valve. Pulsed wave Doppler was used in all initial studies, and pulsed and color modes were used in the follow-up studies. In eight patients, mitral regurgitation was not

detected. In the remaining seven, minor degrees of mitral regurgitation were detected.

Measurements

An off-line analysis system was used to measure left atrial dimensions (Figure 1). The anteroposterior dimension of the left atrium was measured in the parasternal view, and the mediolateral and superoinferior dimensions of the left atrium were measured in the apical four-chamber view. Left atrial volume was then calculated with the ellipsoid formula indicated on the figure. The apical four-chamber view was similarly used to measure the mediolateral and superoinferior dimensions of the right atrium (Figure 2). Right atrial volume was estimated with the same ellipsoid formula, assuming equivalent anteroposterior and mediolateral dimensions. All measurements were along the line of maximum separation between the chamber walls in the respective planes and were taken at end systole with the inner edge–inner edge convention.

Left ventricular diastolic and systolic dimensions were measured in the parasternal long-axis view in accordance with standard recommendations.¹⁶

Measurements were performed without knowledge of previous results. To assess interobserver variability, the left atrial measurements were repeated by a second person unaware of the findings of the first observer.

Statistical Analysis

Statistical analysis was performed with the Student's *t* test for paired data to determine significant differences between baseline and follow-up studies; a probability of 0.05 was considered significant. For the comparison of relative change between right and left atrial dimensions, the Student's *t* test for unpaired data was used, and a similar probability was considered significant. To assess interobserver variability, the mean difference of the measurements of the two observers was calculated and expressed as a percentage of the cumulative mean of all the observations.

Results

Changes in Left Atrial Size

Left atrial volume determinations for all 15 patients at each study are illustrated in Figure 3. By study design, all patients had normal anteroposterior dimensions at the initial study. In 13 of 15 patients, calculated left atrial volume determination was also within the normal range ($<55 \text{ cm}^3$). In all patients, calculated volume increased to some extent, and mean volume for the group increased from 45.2 to 64.1 cm^3 , a change that was highly significant ($p < 0.001$). Table 1 lists the individual left atrial dimensions measured at each study. The anteroposterior, mediolateral, and superoinferior dimensions all increased significantly during the interval between studies.

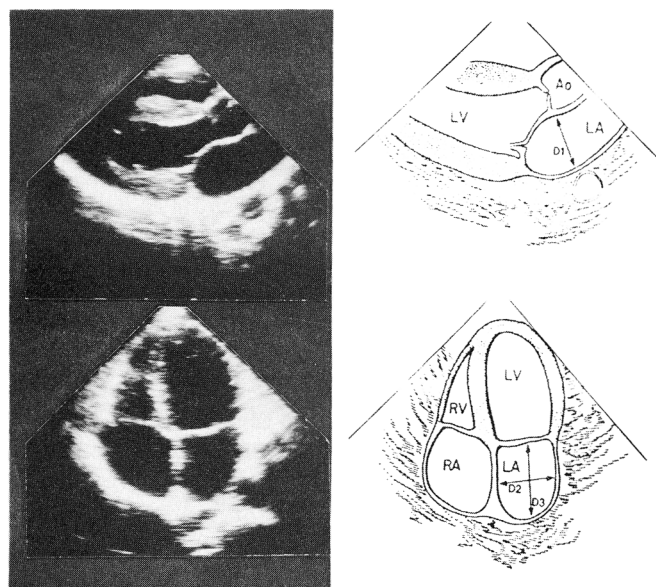
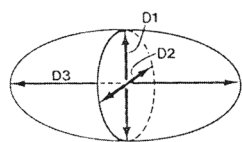


FIGURE 1. Left atrial size was assessed by measuring three orthogonal dimensions. Anteroposterior dimension (D1) was measured with the parasternal long-axis imaging plane and the mediolateral (D2) and superoinferior (D3) dimensions with the apical long-axis plane. Left atrial volume was then estimated with the formula indicated that models the shape of the atrium to that of a prolate ellipsoid. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

PROLATE ELLIPSOID - BIPLANE
Length-Diameter



$$\text{Left Atrial Volume} = \frac{4\pi}{3} \cdot \frac{D1}{2} \cdot \frac{D2}{2} \cdot \frac{D3}{2}$$

Changes in Right Atrial Size

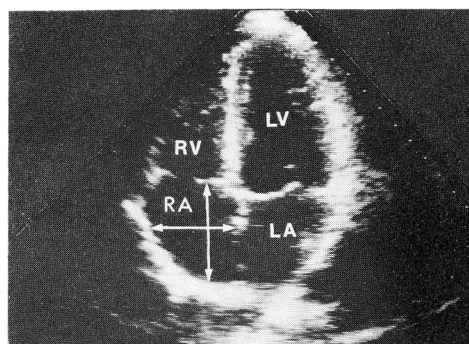
Right atrial volume also increased in all patients studied (Figure 4). In addition, mean volume for the group increased from 49.2 to 66.2 cm³, a change that was also highly significant ($p < 0.001$). Each of the individual dimensions also increased significantly during the interval between studies as Table 1 indicates.

Comparison of Changes in Left and Right Atrial Sizes

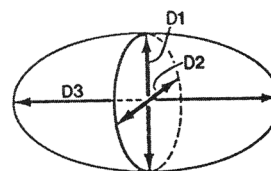
The relative changes in left and right atrial volumes, as well as in mediolateral and superoinferior dimensions, are contrasted in Table 2. In each case, the change in the parameter was assessed both as an absolute change and as a percent change from the initial measurement. In no case was any significant difference detected in the relative extent of right and left atrial changes.

Influence of Minor Mitral Regurgitation

To rule out any possible influence of the minor degrees of mitral regurgitation detected by Doppler in some of the patients, the change in atrial dimensions is contrasted in Table 3 for those patients with and without mitral regurgitation at their follow-up study. The degree of increase in each atrial volume was statistically similar in patients with and without trivial mitral regurgitation.



ELLIPSOID
Length-Diameter



$$\text{Atrial Volume} = \frac{4\pi}{3} \cdot \frac{D1}{2} \cdot \frac{D2}{2} \cdot \frac{D3}{2}$$

FIGURE 2. Mediolateral (D2) and superoinferior (D3) right atrial dimensions were measured in the apical four-chamber imaging plane. Anteroposterior (D1) dimension was assumed equal to mediolateral dimension, and right atrial volumes were then approximated with the same prolate ellipsoid formula used for calculation of left atrial volume. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

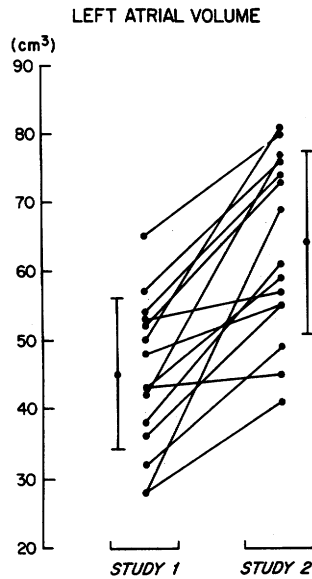


FIGURE 3. Plot of individual left atrial volume determinations.

Changes in Left Ventricular Size

To rule out alterations in left ventricular size or function as a precipitant of the observed left atrial enlargement, left ventricular dimensions were measured at each study. As Table 4 indicates, left ventricular diastolic and systolic dimensions did not change significantly during the interval between studies.

Interobserver Variability

Interobserver variability for measurement of the anteroposterior, mediolateral, and superoinferior left atrial dimensions was 0.2%, 0.8%, and 2.3%, respectively. The respective correlation coefficients were 0.80, 0.88, and 0.83. Variability in the calculated left atrial volume was 1.2%.

Discussion

Perhaps as a result of its common association with rheumatic mitral valve disease, atrial fibrillation is generally believed to occur secondary to enlargement of the atria. In this context, it has been postulated that the valvular obstruction results in elevated atrial

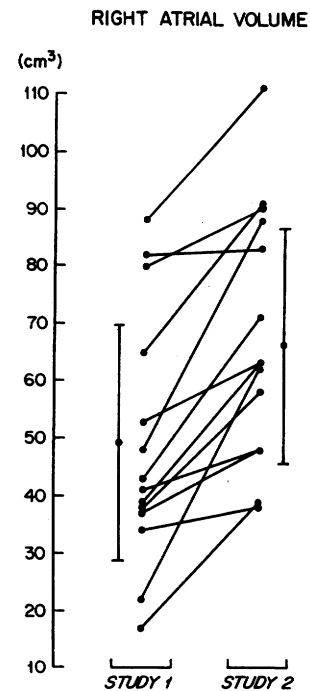


FIGURE 4. Plot of individual right atrial volume determinations.

pressures and subsequent chamber enlargement. This dilation is believed to lead to the thinning and fibrosis of myocardial and conducting fibers that have been demonstrated in pathological¹⁷ and histological¹⁸ studies and thereby result in disordered electrical activation and contractility. Such a mechanism is compatible with the other conditions commonly encountered in association with atrial fibrillation, namely ischemic heart disease and cardiomyopathy. It does not, however, explain the occurrence of fibrillation in patients with structurally normal hearts, which have been shown to constitute between 3% and 11% of the atrial fibrillation population in large epidemiological studies.^{10,11} This observation and the evidence relating the duration of fibrillation with left atrial size^{6,7,9} have led to the suggestion that atrial fibrillation per se leads to chamber enlargement.⁶

This study provides evidence supporting this contention. Because the patients selected were free of any clinically or echocardiographically detectable cardiac abnormality other than atrial fibrillation, the

TABLE 1. Change in Atrial Dimensions Between Initial and Follow-up Studies

	Study 1	Study 2	<i>p</i>
LA measurements			
Anteroposterior (mm)	38.6±4.9	42.4±4.6	0.0078
Mediolateral (mm)	40.6±3.7	46.1±5.2	0.0051
Superoinferior (mm)	54.6±7.8	62.4±6.2	0.0013
Volume (cm ³)	45.2±11.0	64.1±13.5	0.0001
RA measurements			
Mediolateral (mm)	40.7±7.1	46.0±5.7	0.0002
Superoinferior (mm)	53.5±7.2	58.0±7.1	0.0069
Volume (cm ³)	49.2±22.0	66.2±22.1	0.0001

Values are mean±SD.

LA, left atrium; RA, right atrium.

TABLE 2. Relative Mean Changes in Atrial Dimensions

	Left atrium	Right atrium	<i>p</i>
Mediolateral dimension			
mm	5.5	6.0	0.71
%	13.7	16.5	0.61
Superoinferior dimension			
mm	7.5	4.6	0.22
%	15.0	9.2	0.26
Volume			
cm ³	19.0	18.9	0.99
%	46.9	52.2	0.74

TABLE 3. Change in Atrial Measurements in Patients With and Without Mitral Regurgitation

	Without MR	With MR	<i>p</i>
Patients (<i>n</i>)	8	7	
Δ LA volume (cm ³)	20.7	19.3	0.80
Δ RA volume (cm ³)	20.6	16.7	0.62
Follow-up time (mo)	21.0	20.0	0.75

MR, mitral regurgitation; LA, left atrial; RA, right atrial.

observed increase in all left atrial dimensions can be attributed to the presence of the arrhythmia. The symmetrical increase observed in right and left atrial sizes provides further support that the arrhythmia is the primary factor in the genesis of the chamber enlargement, because it would be expected to affect both atria equally, in contrast to valvular regurgitation or alterations in left ventricular compliance. A recent study¹⁹ showed that atrial size decreases after successful electrical conversion but not if atrial fibrillation recurs after conversion, thus further supporting a primary role for arrhythmia in the genesis of chamber enlargement.

It is interesting to speculate on the mechanism of atrial enlargement as a consequence of atrial fibrillation. Previous studies demonstrated that the acute induction of atrial fibrillation in animal preparations results in immediate increases in left atrial pressure^{20,21} and wall stress²¹ and decreases chamber distensibility.²¹ Conversely, hemodynamic studies in humans have demonstrated acute increases in cardiac output and decreases in pulmonary capillary wedge pressure after electrical conversion of atrial fibrillation.²² In contrast, hemodynamic studies of patients with chronic rheumatic atrial fibrillation have shown that, in this setting, left atrial pressure returns to normal.^{6,9} It appears, therefore, that the initial elevation in left atrial pressure results in a gradual increase in atrial volume until pressure is normalized. Another potential mechanism may relate to loss of the active atrial component of ventricular filling that is known to be approximately 20%. If venous return to the atrium remains constant, mean atrial pressure must increase to maintain the same level of ventricular filling, thus further contributing to atrial enlargement.

Such mechanisms by no means rule out other potential contributions to chamber enlargement in patients with fibrillation. In rheumatic mitral valvular disease, for instance, atrial dilatation may occur as a

result of the combined influences of increased resistance to outflow, volume overload resulting from valvular regurgitation, and the fibrillation itself. This study, however, provides a potential explanation for the observed occurrence of left atrial enlargement in patients with "lone" atrial fibrillation.

These findings are of more than theoretical interest in view of potential adverse effects of left atrial enlargement. Early radiographic studies linked the size of the left atrial shadow to the occurrence of systemic embolization^{23,24} and led to the recommendation for amputation of the left atrial appendage at valvotomy.²⁵ Since the advent of echocardiography, which allows more accurate assessment of left atrial size in multiple dimensions, this relation has been confirmed by one study²⁶ but not by others.²⁷⁻²⁹ Enlargement of the left atrium has also been reported to increase refractoriness to conversion to sinus rhythm,^{8,13} although this conclusion was recently challenged.³⁰ Last, thrombus formation is more likely to occur in larger atria.¹⁴ Taking these factors into consideration, left atrial enlargement appears to carry a certain degree of risk in itself, and its prevention should be considered a worthwhile therapeutic goal. The results of this study suggest that the maintenance of sinus rhythm prevents the progression of left atrial enlargement and, therefore, prevents these adverse effects.

Although the treatment of atrial fibrillation must be individualized based on the relative benefits and risks for each patient, these findings provide some support for more aggressive attempts to maintain sinus rhythm and, therefore, should enter into the decision-making process.

Limitations of This Study

Although these results demonstrate that atrial dimensions increase in the setting of atrial fibrillation, they do not allow us to examine subgroups in whom the degree of change may vary. By design, the study excluded patients with pathologies known to influence atrial size, such as mitral regurgitation and left ventricular hypertrophy; therefore, we could not determine how these factors affect the degree or time course of morphological change. Also, all patients were presumed to be in sustained atrial fibrillation at the outset of the study, and most had several confirmatory electrocardiograms during the course of the study. However, there was no mechanism for regular, continuous monitoring, so the question of whether the morphological changes vary in patients with paroxysmal atrial fibrillation cannot be addressed. These issues are of great interest and should be addressed prospectively in studies involving larger numbers of patients.

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TABLE 4. Left Ventricular Dimensions at Initial and Follow-up Studies

	Study 1	Study 2	<i>p</i>
LVDD (mm)	48.5±3.8	49.0±4.1	0.56
LVSD (mm)	33.3±3.6	33.8±3.3	0.51
Fractional shortening (%)	31.3±6.4	31.1±3.8	0.91

Values are mean±SD.

LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension.

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