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Structural Remodeling of the Left Atrial Appendage in Patients with Chronic Non-Valvular Atrial Fibrillation: Implications for Thrombus Formation, Systemic Embolism, and Assessment by Transesophageal Echocardiography

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Left atrial appendage (LAA) is frequently the site of thrombus formation in patients with chronic atrial fibrillation (AF). Transesophageal echocardiography and hematologic studies have identified blood flow stasis (spontaneous echogenic contrast) and abnormal coagulation (increased serum fibrinogen) as important predisposing factors to formation of LAA thrombi. However, the third component of the Virchow's triad, i.e., endothelial abnormalities, has not been adequately studied. Accordingly, we studied, at necropsy, the LAA morphology in 46 hearts of patients with ($n = 22$) and without ($n = 24$) chronic AF. Compared to patients without AF, those with AF had significantly larger LAA volumes (1.7% 1.1 vs. 5.4% 3.7 mL, $p = 0.0002$), and larger luminal surface area of the bisected LAA (4.4% 1.8 vs. 7.1% 4.5 cm^2, $p = 0.01$). However, both the absolute and relative surface area of the transected pectinate muscles were reduced in patients with AF (2.6% 1.1 vs. 1.8% 1.0 cm^2, $p = 0.02$ and 38% 15 vs. 21% 14%, $p = 0.0003$). In addition, in most patients (73%) with chronic AF, the LAA showed significant endocardial thickening with fibrous and elastic tissue (endocardial fibroelastosis) compared to those without AF (13%, $p < 0.0001$). Endocardial fibroelastosis resulted in a smooth LAA luminal surface and encased the pectinate muscles. These findings suggest that LAA remodeling (dilation, stretching, and reduction in pectinate muscle volume, as well as endocardial fibroelastosis) occurs frequently in chronic AF and may contribute to the increased risk of thrombus formation and systemic embolism. Additionally, the information may have relevance in interpreting transesophageal echocardiographic images of the LAA in patients with chronic AF. *Cardiovasc Pathol 2000;9:95–101*

Left atrial appendage (LAA) is a geometrically complex structure with prominent muscular bands (pectinate muscles), which divide the lumen into multiple lobes; it is an end-organ and frequently the site of origin of systemic thromboemboli (1). Clinical evaluation of the LAA structure and function and identification of thrombi or predisposing conditions to thrombus formation, such as spontaneous echogenic contrast, is now possible with the use of transesophageal echocardiography (2). In fact, the success of transesophageal echocardiography, in detecting LAA abnormalities, has made this procedure an integral part of the management of patients with systemic embolism (3) or atrial fibrillation (AF) (4). In recent studies, transesophageal echocardiography has been shown to have an excellent sensitivity, in detecting LAA thrombi, when compared to direct visualization at surgery (5,6).

In some patients, exclusion of thrombi by transesophageal echocardiography may not be possible due to the presence of prominent pectinate muscles (5,7) or dense spontaneous echogenic contrast (6). In addition, the structural changes, induced by chronic AF (8), may influence the

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echocardiographic appearance of LAA in the presence or absence of a thrombus. Finally, although two main predisposing factors to thrombogenesis, namely blood flow stasis (9,10) and hypercoagulable state (11), have been well studied in AF, the endocardial components of thrombus formation has not received adequate attention (4). With these considerations in mind, the present study evaluates the LAA structural remodeling, including endocardial changes, in patients with chronic AF and its potential implications for the risk of thrombus formation and systemic embolism as well as its relevance to the assessment of LAA by transesophageal echocardiography.

Materials and Methods

Study Hearts

The study material consisted of 46 hearts of adults [age 18–96 (mean 59 ± 17) years, 32 (70%) men] who either died ($n = 31$) or underwent cardiac transplantation ($n = 15$). Clinical information was obtained from hospital records. The hearts were fixed in 10% buffered formaldehyde before examination.

Gross Measurements

Hearts were weighed after removal of all extraneous materials. The cardiac ventricles were then cut transversely from apex to base at ~1 cm intervals and the left ventricular diameter was measured at the mid-cavity level. The atria were also cut transversely and the left atrial circumference was measured ~2 cm above the mitral annulus. The LAA was excised intact at its junction with the left atrium and the luminal volume was measured by filling the cavity with normal saline. The LAA was then coronally bisected along the lateral and medial margins and its luminal surface area and areas of the transected pectinate muscles, on both sides, were measured by planimetry after tracing all margins on a transparent sheet with a pinpoint marker. The volume fraction of pectinate muscles was calculated as the mean percentage of the total LAA surface area (luminal area plus pectinate muscle area) occupied by the transected muscle bands on both halves of the LAA.

Endocardial Fibroelastosis

Thickening of the LAA endocardial surfance by fibrous and elastic tissue (endocardial fibroelastosis) was noted in some hearts and was visually graded as 0 if absent, 1+ if mild, and 2+ if extensive. All appendages were also sectioned and studied microscopically for verification of endocardial fibroelastosis and assessment of other histomorphologic changes.

Statistical Analysis

Results are reported as range and mean ± 1 SD or as percentage of the population size. Differences between various subsets of patients were assessed with unpaired student *t* test for continuous variables and with chi-square analysis for non-continuous variables. A p value <0.05 was considered statistically significant. Correlations were calculated between LAA volume and other necropsy data. The relationship of LAA volume to its luminal area was examined by simple linear regression.

Results

Clinical Information

Certain clinical and cardiac morphologic findings in the 46 patients are summarized in Table 1. By history, 17 (37%) had hypertension, 24 (52%) had congestive heart failure, and 22 (48%) had chronic AF. Of the latter, 3 (7%) had a history of cerebrovascular accident. Fifteen patients had undergone cardiac transplantation for ischemic ($n = 14$) or idiopathic dilated ($n = 1$) cardiomyopathy. The causes of death in the remaining 31 patients were cardiac in 12, vascular in 3, and non-cardiovascular in 16.

Table 1. Comparison of the Clinical and Cardiac Morphologic Findings

	All patients ($n = 46$)	Atrial Fibrillation ($n = 22$)	Sinus Rhythm ($n = 24$)
Clinical			
Age, years	59 ± 17	60 ± 14	58 ± 20
Men	32 (70%)	17 (77%)	15 (63%)
Systemic hypertension	17 (37%)	10 (45%)	7 (29%)
Congestive heart failure	22 (48%)	19 (86%)	5 (21%)*
Cerebrovascular accident	3 (7%)	3 (14%)	0
Cardiac morphologic			
Heart weight, g	440 ± 92	478 ± 76	405 ± 94*
Dilated chamber			
Left ventricle	26 (57%)	19 (86%)	7 (29%)*
Left atrium	29 (63%)	20 (91%)	9 (38%)*
Left ventricular diameter, mm	40 ± 14	49 ± 12	31 ± 8*
Left atrial circumference, cm	14.6 ± 3.4	16.9 ± 2.5	12.5 ± 2.5*
Myocardial infarct			
Acute	3 (7%)	0	3 (13%)
Healed	23 (50%)	16 (73%)	7 (29%)*
Both	2 (4%)	0	2 (8%)
Left atrial appendage			
Volume, mL	3.4 ± 3.2	5.4 ± 3.7	1.7 ± 1.1*
Luminal surface area, cm^2	5.7 ± 3.6	7.1 ± 4.5	4.4 ± 1.8*
Pectinate muscle area, cm^2	2.2 ± 1.1	1.8 ± 1.0	2.6 ± 1.1*
Pectinate muscle area %	30 ± 17	21 ± 14	38 ± 15*
Endocardial fibroelastosis	19 (41%)	16 (73%)	3 (13%)*

*$p < 0.05$ vs. patients with atrial fibrillation.

Hearts at Necropsy (Table 1)

Heart weight ranged from 240 to 660 (mean 440 ± 92) g and was increased in 36 (78%) (12). Left ventricular and left atrial cavities were dilated in 26 (57%) and 29 (63%) patients, respectively. An acute or a healed myocardial infarct was present in 24 (52%). The left ventricular mid-cavity diameter ranged from 17–65 (mean 40 ± 14) mm and the left atrial circumference ranged from 9.4–20.0 (14.6 ± 3.4) cm. In 6 (13%) patients, hearts were judged to be structurally normal. At least 1 of the 4 major epicardial coronary arteries was >75% narrowed in cross-sectional luminal area in 34 (74%) patients.

Left Atrial Appendage (Table 1)

External examination. Externally, the LAA appeared multi-lobulated with extreme variations in the number and sizes of the lobules between patients. The LAA length ranged from 2.0 to 5.9 (mean 3.8 ± 0.8) cm and was longer than its width that ranged from 1.9 to 5.9 (mean 3.0 ± 0.8) cm. In 15 (33%) patients, the LAA had a terminal elongated pouch positioned at right angles to the long axis of the appendage and oriented either laterally ($n = 9$) or medially ($n = 6$).

Measurement of volume and surface area. The LAA volume ranged from 0.4 to 13.0 (mean 3.4 ± 3.2) mL and correlated significantly with the left ventricular diameter ($r = 0.73$, $p < 0.01$), left atrial circumference ($r = 0.69$, $p < 0.01$), and heart weight ($r = 0.42$, $p < 0.01$). When coronally bisected, the LAA ranged from 2.7 to 21.1 (mean 5.7 ± 3.6) cm^2 in luminal surface area. Simple linear regression analysis showed a significant correlation between the LAA volume and luminal area (volume = 0.8 luminal area −1, $r = 0.85$, SEE = 1.7 mL, $p < 0.0001$) (Figure 1).

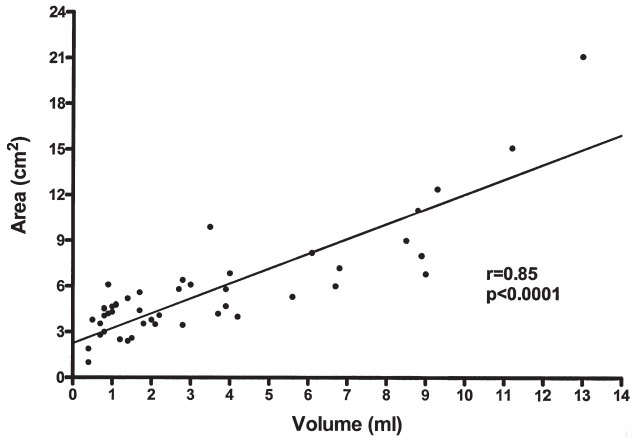

Figure 1. Scatterplot and linear regression graph demonstrating the relationship between the left atrial appendage volume and luminal area at necropsy.

Pectinate muscles. The surface area of the transected pectinate muscles ranged from 0.6–5.5 (mean 2.2 ± 1.1) cm^2 and occupied 7 to 85% (mean 30 ± 17%) of the total LAA surface area. The volume fraction of pectinate muscles correlated inversely with LAA volume ($r = -0.60$, $p < 0.01$), LAA luminal area ($r = -0.91$, $p < 0.01$), left ventricular cavity diameter ($r = -0.50$, $p < 0.01$, and left atrial circumference ($r = -0.51$, $p < 0.01$).

Endocardial fibroelastosis. Endocardial fibroelastosis (Figures 2 and 3) was present in 19 (41%) patients and was judged to be mild (1+) in 5 and extensive (2+) in 14 patients. Compared with those without, patients with LAA endocardial fibroelastosis had significantly larger LAA volume (6.3 ± 3.2 vs. 1.4 ± 0.8, $p < 0.0001$) and luminal surface area (8.2 ± 4.3 vs. 4.0 ± 1.3, $p = 0.0009$). The volume fraction of the transected pectinate muscles, however, was not significantly different in those with and without LAA endocardial fibroelastosis (1.8 ± 1.3 vs. 2.4 ± 0.8, p = NS). Thus, patients with LAA endocardial fibroelastosis had significantly lower volume fraction of pectinate muscles as a percentage of the total LAA surface area (17 ± 9% vs. 40 ± 14%, $p < 0.0001$). In 14 patients with extensive degrees of LAA endocardial fibroelastosis, the pectinate muscles were frequently embedded in the thickened fibrotic endocardium and the LAA lumen appeared smooth (Figure 2 and 3).

Comparison of Patients with and without AF (Table 1 and Figure 4)

Compared with those in sinus rhythm, the 22 patients with AF had significantly larger left atria and ventricles. In average, the LAA volume was more than 3 times larger in those with AF (5.4 ± 3.7 vs. 1.7 ± 1.1 mL, $p = 0.0002$). The LAA luminal surface area was also larger in atrial fibrillation (7.1 ± 4.5 vs. 4.4 ± 1.8, $p = 0.01$). However, the surface area of the pectinate muscles (1.8 ± 1.0 vs. 2.6 ± 1.1, $p = 0.02$) and the their relative volume (21 ± 14 vs. 38 ± 15, $p = 0.0003$) were significantly lower in AF. Endocardial fibroelastosis was more often seen in patients with AF (73% vs. 13%, $p < 0.0001$). Additionally, endocardial fibroelastosis was more severe in those with than without AF [14 (88%) extensive and 2 (12%) mild versus 3 (100%) mild].

Discussion

Summary of the Findings

This study indicates that the LAA undergoes significant anatomic changes during chronic AF. The main structural alterations observed were a three-fold increase in LAA volume, a significant reduction in the relative volume of the pectinate muscles and marked endocardial thickening. The latter appeared to embed the pectinate muscles, thus, pro-

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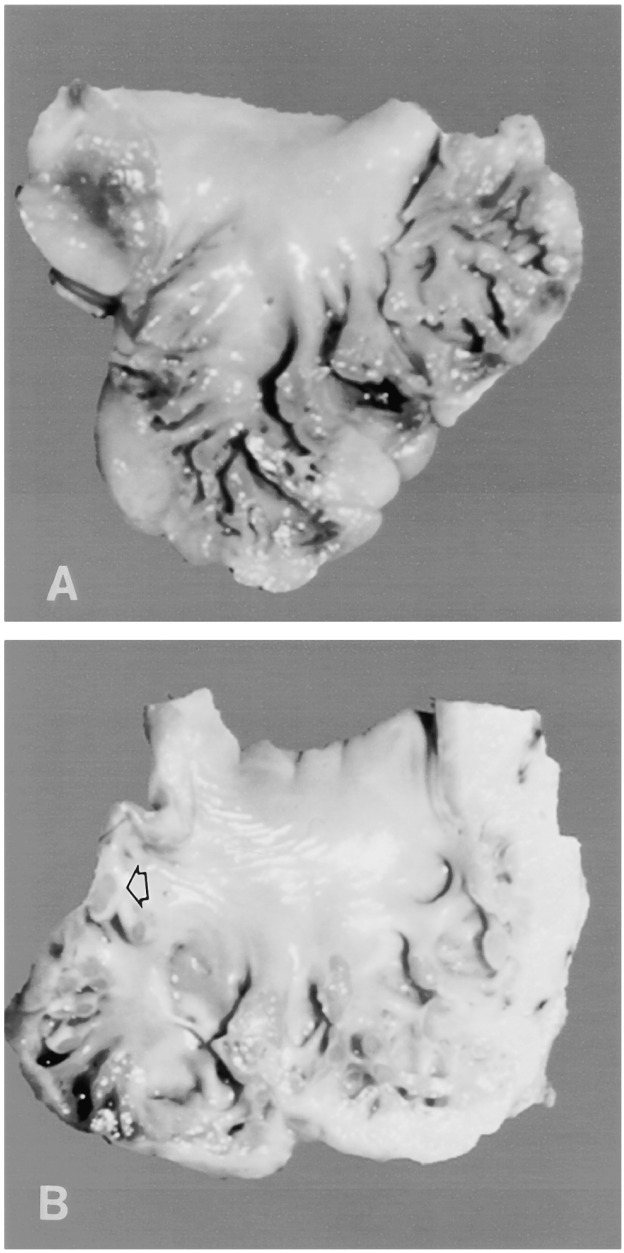

Figure 2. Gross photograph of coronally bisected left atrial appendages in a patient in sinus rhythm **(A)** and another patient in chronic atrial fibrillation **(B)**. Marked endocardial fibroelastosis is seen in the patient with atrial fibrillation **(B)** as manifested by a glistening, relatively smooth surface, encasement of pectinate muscles (*arrowhead*) and reduced relative volume of the trabeculations.

ducing a smooth luminal surface compared to the highly trabeculated LAA surface in those without AF. The correlation of the LAA volume with left ventricular size, left atrial diameter, and heart weight indicates that the structural alterations in LAA are at least partly related to chronic elevation in left atrial pressure.

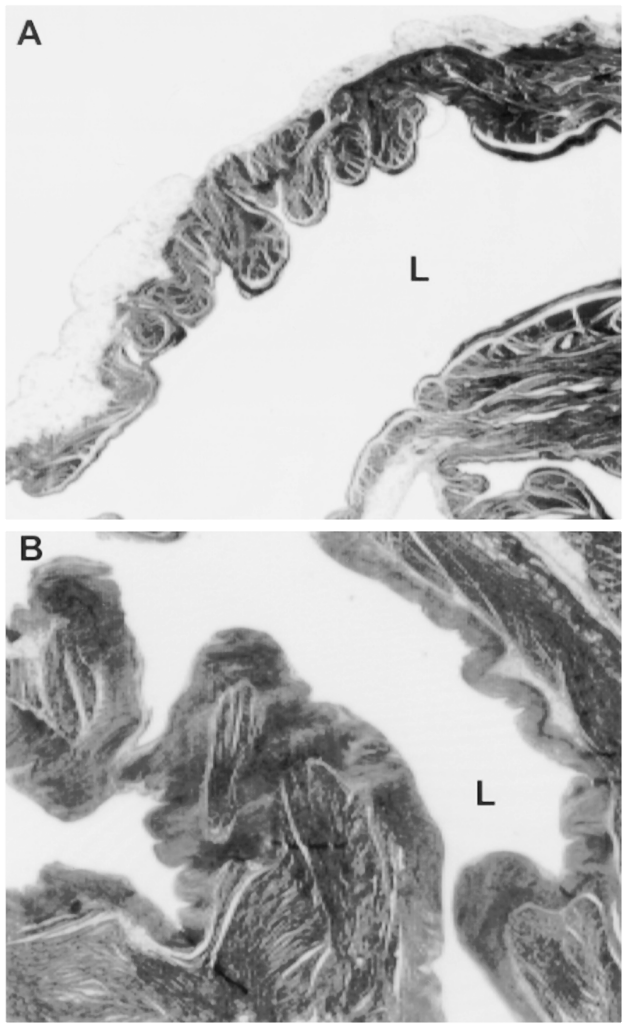

Figure 3. Photomicrographs of histologic sections of left atrial appendage in a patient in sinus rhythm **(A)** and in another patient in chronic atrial fibrillation **(B)**. Marked fibrous thickening of the endocardium is seen in the patient with atrial fibrillation with encasement of the pectinate muscles. L = lumen. Masson's trichrome stain. Both specimens scanned without magnification and enlarged equally at ×120.

Previous Studies

Both necropsy (1) and transesophageal echocardiographic studies (2,13–15) have shown a significant variation in LAA shape and size among individuals. In general, the LAA diameter, length, and surface area by two-dimensional transesophageal echocardiography are significantly larger in patients with AF compared with those in sinus rhythm (16–19). In a previous necropsy study, Ernst et al. made synthetic resin casts of 220 LAAs (8). Among 198 patients with an electrocardiogram available, 55 (28%) had AF. Compared to the 143 patients in sinus rhythm, the 55 in AF had larger LAA cast volumes (7.1 vs. 4.7 mL, $p < 0.01$) and significantly less trabeculations as determined by the num-

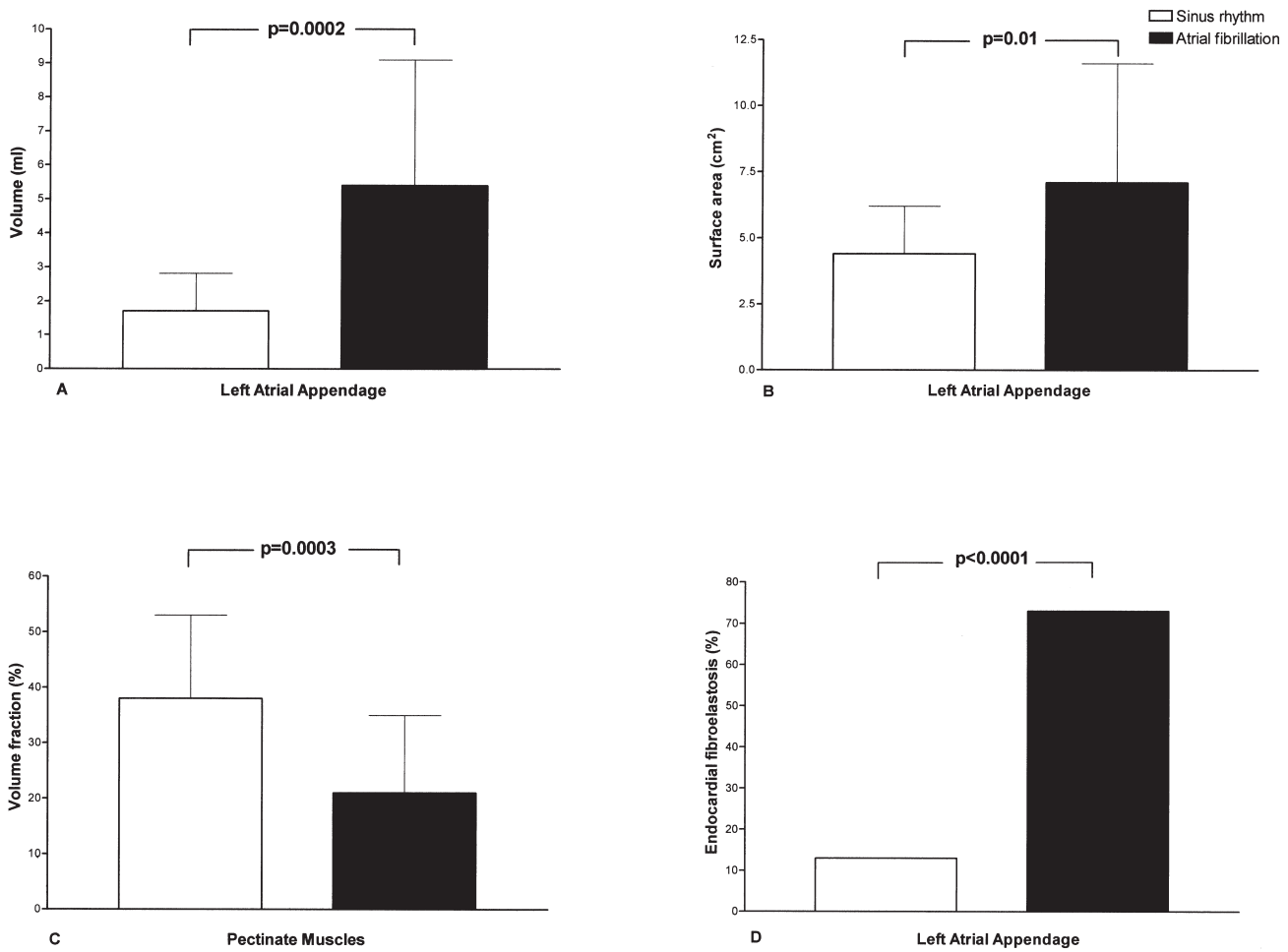

Figure 4. Bar graphs demonstrating significant differences in left atrial appendage volume **(A)**, surface area of coronally bisected left atrial appendages **(B)**, volume fraction of pectinate muscles **(C)**, as well as the presence of endocardial fibroelastosis **(D)** in patients without (*open bars*) and with (*solid bars*) chronic atrial fibrillation.

ber of branches on the cast (8). These findings are similar to the findings of the present study in so far as they indicate an increase in LAA volume and a decrease in the volume of pectinate muscles in chronic AF.

In addition to the morphologic changes described above, transesophageal echocardiographic studies in AF have demonstrated LAA contractile dysfunction and blood stasis as evidenced by diminished Doppler flow velocities (13,14,20) and the presence of spontaneous echogenic contrast (9,11). Longstanding LAA functional abnormalities in chronic AF are associated with an increased risk of thrombus formation and systemic embolism (21,22). The present study extends these observations to include the presence of endocardial abnormality as a potential predisposing factor to thrombus formation in chronic AF. Whether or not the decreased volume fraction of pectinate muscles would contribute to the likelihood of thrombus dislodgment in chronic AF remains speculative.

Exclusion of LAA thrombi by transesophageal echocardiography may be difficult in some patients at risk of systemic embolism. This is generally due to the presence of prominent pectinate muscles or dense spontaneous echogenic contrast (5,6). Our study indicates that the volume fraction of pectinate muscles is significantly lower and the surface area of LAA much smoother in the dilated appendages of patients with chronic AF (Figure 5). Consequently, presence of LAA luminal irregularities on transesophageal echocardiogram in patients with chronic AF should not be easily dismissed as trabeculations.

Limitations

The major limitation of our study is that it evaluates gross and histomorphologic features of LAA at necropsy. Although this may have changed the dimensions of the LAA cavity and its relation to the pectinate muscles, the data appears concordant with previous transesophageal echocardiographic studies. Furthermore, although, the number of structurally normal hearts were small in our study

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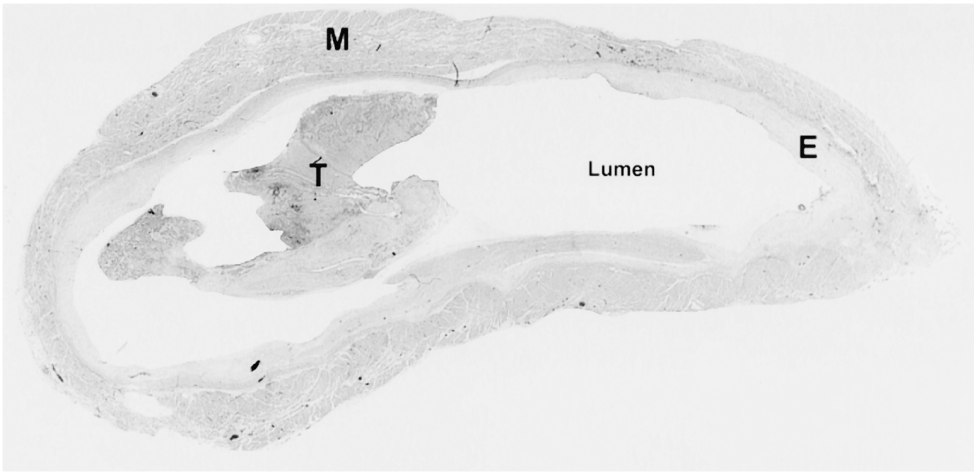

Figure 5. Photomicrograph of the transversely cut left atrial appendage in a patient with chronic atrial fibrillation and systemic embolism showing the presence of a thrombus (T), and a markedly thickened and smooth endocardium (E). M = muscle. Hematoxylin and eosin stain.

(n = 6, 13%), the purpose of the study was not to compare normal and abnormal hearts.

Conclusion

The findings of this study suggest that LAA remodeling (dilation, stretching and reduction in pectinate muscle volume, as well as endocardial fibroelastosis) occurs frequently in chronic AF. Such pathologic remodeling of the endocardium, when combined with the flow stasis and hematologic abnormalities already shown in AF, would probably explain the increased risk of thrombus formation and systemic embolism. Additionally, the information may have relevance in interpreting transesophageal echocardiographic images of the LAA in patients with chronic AF.

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