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Morphologic Features of Fossa Ovalis Membrane Aneurysm in the Adult and Its Clinical Significance

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Objectives. **This study evaluated morphologic features of fossa ovalis membrane aneurysm and associated cardiac abnormalities that may predispose to systemic embolism.**

Background. **An increasing number of fossa ovalis membrane aneurysms are diagnosed by echocardiography. Higher frequencies of such aneurysms have been reported in patients with embolic stroke.**

Methods. **The hearts of 20 adults with fossa ovalis membrane aneurysms (mean [±SD] age 62 ± 19 years, range 24 to 87; 12 women [60%], 8 men [40%]) were examined. The areas of excised atrial septum, fossa ovalis membrane and fossa ovalis were measured. An aneurysm was defined as the ratio of the fossa ovalis membrane to fossa ovalis area ≥1.5.**

Results. **Compared with a control group of 20 adults (mean age 58 ± 21 years, range 18 to 86; 12 women [60%], 8 men [40%]), the 20 patients with fossa ovalis membrane aneurysm had larger (711 ± 240 vs. 203 ± 105 mm^2, $p < 0.0001$) and thinner fossa ovalis membranes (0.6 ± 0.1 vs. 1.9 ± 0.9 mm^2, $p < 0.0001$). The mean ratio of the fossa ovalis membrane to fossa ovalis area was 2.1 ± 0.4 in patients with and 1.2 ± 0.1 in those without fossa ovalis membrane aneurysm. Patent foramen ovale was seen in 14 (70%) of 20 patients with fossa ovalis membrane aneurysm and in 4 (20%) of 20 control subjects ($p = 0.0005$).**

Conclusions. **Fossa ovalis membrane aneurysm is characterized by thinning and marked redundancy without adherent thrombi or fibrin tags. Mitral valve prolapse, dilated atria, intracardiac thrombi and patent foramen ovale are frequently seen in association with fossa ovalis membrane aneurysm and may explain the increased frequency of embolic stroke in patients with such aneurysms.**

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Since its early description (1,2), an increasing number of fossa ovalis membrane aneurysms have been found at autopsy study (3–5) or during life (6–19). Echocardiography, especially transesophageal, has facilitated the detection of such aneurysmal membranes (6–19). Several studies (6–9) have shown an increased incidence of fossa ovalis membrane aneurysm in adults with systemic embolism. The exact mode of such association, however, remains uncertain. Small tags of fibrin or other thrombotic material in the aneurysmal membrane (4), paradoxic embolism through an interatrial communication (10) and an associated mitral valve prolapse (11–13) have been implicated, but proof of their etiologic role is lacking. This study evaluated the morphologic features of fossa ovalis membrane aneurysm and other associated cardiac structural abnormalities that may be potential sources of systemic embolism in the adult.

Methods

Patients. The files of the Pathology Branch, National Heart, Lung, Blood Institute, were searched for all accessioned adult hearts coded as having aneurysm of the fossa ovalis membrane, atrial septal aneurysm or redundant fossa ovalis membrane. From January 1983 to April 1993, 20 such hearts were located and are the subject of this study. The clinical and autopsy records, photographs of the heart and histologic slides from each patient were reviewed, and all hearts were reexamined. Similarly, 20 hearts of adults without atrial septal abnormalities were examined and served as control hearts.

Examination of hearts. Heart were weighed on an accurate scale after removal of all extraneous tissues and excision of the ascending aorta and pulmonary trunk at ~2 cm cephalad to the sinotubular junction. For each heart the presence or absence of foci of left ventricular fibrosis or necrosis, dilated cavities, mitral valve prolapse, mitral annular calcium, interatrial communications (in the form of valvular-competent or valvular-incompetent patent foramen ovale, atrial septal defect or fossa ovalis membrane fenestrations) or significant (>75% cross-sectional lumen narrowing) in the four major (left main, left anterior descending, left circumflex and right) coronary arteries were recorded. The left and right atria, aorta and both ventricles were then excised close to their attachment to the atrial septum. The atrial septum with the surrounding tissue was placed on a light source to illuminate its margins and guide excision. The fossa ovalis membrane also was excised at its margin of attachment to the atrial septum. The thickness of atrial septa and fossa ovalis membranes was measured by calipers with a revolving adjustable arm and accuracy of 0.1 mm.

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Planimetry. The margins of the atrial septum, fossa ovalis and fossa ovalis membrane were traced with a fine-tipped marker pen on a transparent sheet while the specimens were spread on a corkboard without being stretched. The area of the atrial septum, fossa ovalis and fossa ovalis membrane were measured using a Micro Digi-pad and stylus in association with the MacMeasure software program adapted to a Macintosh SE computer. The percent area of the atrial septum occupied by the fossa ovalis was calculated as the area of fossa ovalis divided by that of the atrial septum × 100. The extent of the redundancy of the fossa ovalis membrane was likewise calculated by dividing the area of the fossa ovalis membrane by that of the fossa ovalis. An *aneurysm* was defined as the ratio of fossa ovalis membrane to fossa ovalis area ≥1.5.

Histologic examination. Coronal sections of the excised fossa ovalis membrane were paraffin embedded, sectioned and stained with hematoxylin-eosin and Masson's trichrome.

Statistics. Results for each variable are presented as number, mean value ± SD or percent. The Student *t* test was used to assess the significance of differences between continuous variables, and chi-square analysis was used when the data were noncontinuous; $p < 0.05$ was considered significant.

Results

Patients with fossa ovalis membrane aneurysm. Clinical and cardiac morphologic findings in the 20 patients with fossa ovalis membrane aneurysm are shown in Table 1, and the gross appearance of one such membrane is illustrated in Figure 1. Fossa ovalis membrane aneurysm was the only abnormality found at necropsy in two patients (Patients 1 and 3, Table 1). Patient 1, a 24-year old woman, had complained of intermittent episodes of dyspnea and "anxiety" for ~1 year before her death. There was no diagnosis made and no treatment given. On the day of death she sat on the floor and became unconscious and pulseless while attempting to rise. Patient 3, a 33-year old man with a history of asthma, died suddenly while watching an outdoor soccer game; however, at necropsy, the lungs were normal.

Two patients (Patients 13 and 15, Table 1) had a cerebrovascular accident, of which one was fatal (Patient 13). The latter, a 71-year old man, had a history of systemic hypertension and chronic atrial fibrillation, and necropsy findings showed left ventricular hypertrophy and dilation. The other cardiac chambers were also dilated, and thrombi were seen in the right and left atria and left ventricle. No sources of emboli could be detected at autopsy in Patient 15, the other patient with cerebrovascular accident. In addition to Patient 13, two other patients (Patients 2 and 12, Table 1) had chronic atrial fibrillation, both in association with idiopathic dilated cardiomyopathy.

In patients with fossa ovalis membrane aneurysm, heart weight ranged from 240 to 495 g (mean 380) in women and 370 to 710 g (mean 475) in men and was increased (>350 g in women, >400 g in men) in 12 (60%). Mitral valve prolapse was present in four patients (20%) (Patients 4, 8, 9 and 19). An

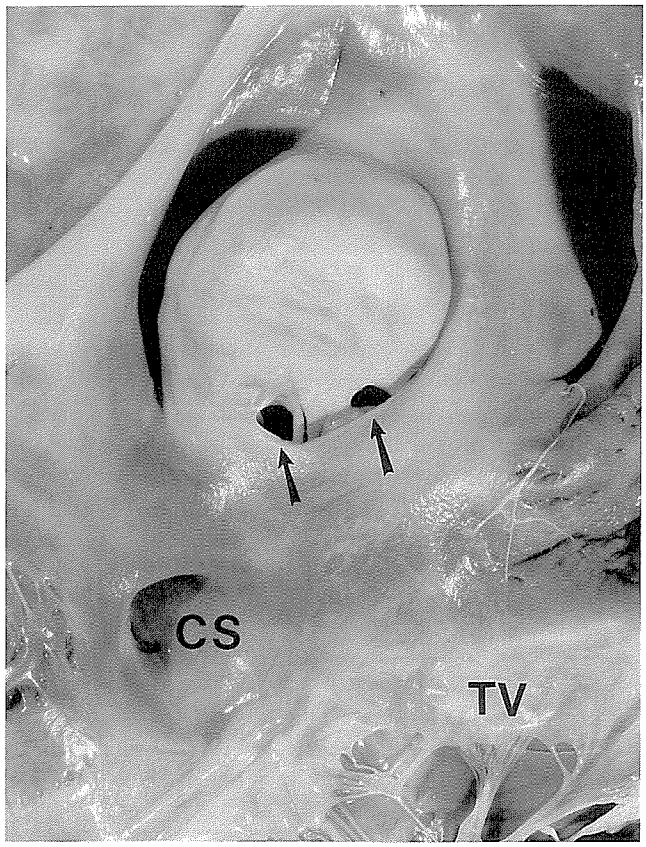

Figure 1. Heart of a 52-year old man who died suddenly while driving a truck. At necropsy, there was no significant internal organ damage. His heart weighed 710 g, and all four cardiac chambers were dilated. Fossa ovalis membrane aneurysm is shown from the right atrial aspect. A valvular-incompetent patent foramen ovale **(arrows)** is also present. CS = coronary sinus; TV = tricuspid valve.

associated patent foramen ovale was found in 14 patients (70%) with fossa ovalis membrane aneurysm and was valvular incompetent in 3. Atrial or ventricular cavities, or both, were dilated in 11 patients (55%). One or more major epicardial coronary arteries were narrowed >75% in cross-sectional area by atherosclerotic plaque in four patients (20%).

The thickness of the atrial septum, cephalad to the fossa ovalis, ranged from 2.6 to 21.0 mm (mean 6.3 ± 3.8). The area of the atrial septum ranged from 1,780 to 3,174 mm^2 (mean 2,334 ± 440); the area of fossa ovalis from 150 to 725 mm^2 (mean 345 ± 138); and that of the fossa ovalis membrane from 347 to 1,190 mm^2 (mean 711 ± 240). The fossa ovalis comprised 15% (range 6% to 29%) of the total area of the atrial septum. On average, the area of the fossa ovalis membrane was 2.1 times (range 1.5 to 2.8) greater than that of the fossa ovalis.

Comparison of patients with and without fossa ovalis membrane aneurysm. There was a higher frequency of congestive heart failure by history (6 [30%] vs. 1 [5%], $p = 0.04$), dilated atria (10 [50%] vs. 2 [10%], $p = 0.03$) and patent foramen ovale (14 [70%] vs. 3 [15%], $p = 0.0005$), and the fossa ovalis membrane was significantly larger (711 ± 240 vs.

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Table 1. Selected Clinical and Cardiac Morphologic Findings in 20 Patients With Fossa Ovalis Membrane Aneurysms Compared With Findings in 20 Control Subjects Without Atrial Septal Abnormalities

Pt No./ Gender	Age (yr)	SH	AP	AMI	CHF	SD	CVA	Arrhythmia A	Arrhythmia V	Cause of Death	HW (g)	LV Fi	LV N	MVP
1/F	24	0	0	0	0	+	0	0	0	SD (home)	240	0	0	0
2/F	30	0	0	0	+	+	0	+	+	IDC	395	0	0	0
3M	33	0	0	0	0	+	0	0	0	SD (street)	435	0	0	0
4M	43	+	0	0	0	0	0	0	0	MVP	455	0	0	+
5/F	49	0	0	0	0	0	0	0	0	Cancer	340	0	0	0
6/M	52	+	0	0	0	+	0	0	0	SD (car)	710	+	0	0
7/M	54	0	0	0	0	0	0	0	0	Trauma	395	0	0	0
8/M	57	0	0	0	0	0	0	0	0	Cancer	390	0	0	+
9/F	57	0	0	0	+	0	0	0	0	Rupture SVA	490	0	0	+
10/M	67	+	0	0	0	+	0	0	0	SD (home)	485	0	0	0
11/M	68	0	0	+	0	0	0	0	0	PE	370	+	0	0
12/F	69	0	0	0	+	0	0	+	0	IDC	425	0	0	0
13/M	71	+	0	0	+	0	+	+	+	CVA	575	0	0	0
14/F	72	0	0	0	+	0	0	0	0	Cancer	330	0	0	0
15/F	75	0	0	0	0	0	+	0	0	Cancer	320	0	0	0
16/F	80	0	0	0	0	0	0	0	0	Trauma	390	0	0	0
17/F	82	0	0	0	0	0	0	0	0	Cancer	435	+	0	0
18/F	83	+	+	+	0	0	0	0	0	AMI	495	+	+	0
19/F	85	0	0	0	+	0	0	0	+	Pneumonia	370	0	0	+
20/F	87	0	+	+	0	0	0	0	0	AMI	300	0	+	0
Total*														
12F	24–87	5	2	3	6	5	2	3	3		240–710	4	2	4
(60)	62 ± 19	(25)	(10)	(15)	(30)	(25)	(10)	(15)	(15)		417 ± 104	(20)	(10)	(20)
Control Group Total*														
12F	18–86	4	2	2	1	4	2	0	0		265–485	2	2	0
(60)	58 ± 21	(20)	(10)	(10)	(5)	(20)	(10)				365 ± 65	(10)	(10)	
p value†	NS	NS	NS	NS	NS	NS	<0.05	NS	NS	NS		NS	NS	NS	<0.05

203 ± 105 mm^2, $p < 0.0001$) and thinner (0.6 ± 0.1 vs. 1.9 ± 0.9 mm, $p < 0.0001$) in patients with than without fossa ovalis membrane aneurysm, respectively.

Comparison of patients with fossa ovalis membrane aneurysm with and without atrial dilation. The left or right atrium, or both, was dilated in 10 of patients (50%) with fossa ovalis membrane aneurysm. Although not statistically significant, heart weight (460 vs. 380 g, $p = 0.08$) and number of patent foramen ovale (80% vs. 60%, $p = 0.36$) were greater in patients with than without dilated atria, respectively. Fossa ovalis (404 vs. 286 mm^2, $p = 0.04$) and fossa ovalis membrane area (845 vs. 576 mm^2, $p = 0.008$) were significantly larger, and percent area of the atrial septum occupied by fossa ovalis higher (17% vs. 13%, $p = 0.04$), in patients with than without dilated atria, respectively.

Correlation of fossa ovalis membrane area with other cardiac morphologic findings in patients with fossa ovalis membrane aneurysm. In patients with fossa ovalis membrane aneurysm, the fossa ovalis membrane area correlated with heart weight ($r = 0.60$, $p < 0.01$), presence of atrial dilation ($r = 0.58$, $p < 0.01$), presence of ventricular dilation ($r = 0.67$, $p < 0.01$) and atrial septal area ($r = 0.56$, $p < 0.05$). There was also a negative correlation between the fossa ovalis membrane area and its thickness ($r = -0.47$, $p < 0.05$).

Histologic examination of fossa ovalis membranes. Figure 2 illustrates the histologic features of a nonaneurysmal and several aneurysmal fossa ovalis membranes. The coronal section through the nonaneurysmal membrane (Fig. 2A) shows a relatively thick membrane (2 mm in diameter) with intact muscle cells and collagen and elastic fibers. By contrast, the aneurysmal membranes are thinner (0.4 to 0.8 mm in diameter), the muscle cells are either absent or appear vacuolated (degenerated), and more fat cells and fewer collagen fibers are present (Fig. 2, B to D).

Discussion

Summary of present findings. In 20 patients the fossa ovalis membrane aneurysms were characterized by thin, amus-

PFO		Dilated (0–3+)						MAC	Thickness (mm)		Area (mm^2)			FO/AS	FOM/FO
VC	VI	RA	LA	RV	LV	Thrombus	CAD	(0–3+)	AS	FOM	AS	FO	FOM	Area Ratio	Area Ratio
0	+	0	0	0	0	0	0	0	3.7	0.4	1,780	283	596	0.16	2.1
+	0	++	++	++	++	RAA	0	0	5.5	0.7	2,345	341	849	0.15	2.5
+	0	0	0	0	0	0	0	0	7.1	0.7	2,185	262	400	0.12	1.5
+	0	++	+++	++	+++	0	0	0	3.8	0.4	2,443	442	1,057	0.18	2.4
+	0	+	+	0	0	0	0	0	6.8	0.7	1,811	290	543	0.16	1.9
+	0	+++	+++	+++	+++	0	0	0	4.9	0.4	3,174	577	1,190	0.18	2.1
0	0	0	0	0	0	0	0	0	5.0	0.6	2,146	221	347	0.10	1.6
+	0	0	0	0	0	0	0	0	6.2	0.8	2,092	323	639	0.15	2.0
0	+	+++	0	+++	0	0	0	0	4.1	0.5	2,514	355	794	0.14	2.2
0	+	++	++	+	+	0	+	0	3.6	0.8	1,838	210	535	0.11	2.6
0	0	0	0	0	0	0	+	0	6.9	0.8	3,091	385	815	0.12	2.1
0	0	+++	+++	+++	+++	RAA, LAA	0	0	2.6	0.5	2,525	725	1,115	0.29	1.5
+	0	++	++	++	++	RAA, LAA, LV	0	0	5.3	0.5	2,924	556	1,040	0.19	1.9
0	0	0	+	0	0	0	0	0	6.3	0.7	1,826	233	659	0.13	2.8
0	0	0	0	0	0	0	0	0	5.2	0.6	2,694	150	400	0.06	2.7
+	0	0	0	+	0	0	0	++	5.8	0.7	1,994	331	639	0.17	1.9
+	0	0	0	0	0	0	0	+++	21.0	0.6	2,884	321	614	0.11	1.9
0	0	0	0	0	0	0	+	0	8.7	0.8	2,214	287	713	0.11	2.5
+	0	+	0	0	0	0	0	+	7.3	0.5	2,312	311	672	0.13	2.2
+	0	0	0	0	0	0	+	0	5.9	0.6	1,887	292	596	0.15	2.0
11	4	9	8	7	6	3	4	3	2.6–21	0.4–0.8	1,780–3,174	150–725	347–1,190	0.06–0.29	1.5–2.8
(55)	(20)	(45)	(40)	(35)	(30)	(15)	(20)	(15)	6.3 ± 3.8	0.6 ± 0.1	2334 ± 440	345 ± 138	711 ± 240	0.15 ± 0.05	2.1 ± 0.4
3	0	2	2	2	2	0	4	3	3.0–12	1.0–3.4	650–1,220	85–372	102–521	0.12–0.31	1.1–1.4
(15)		(10)	(10)	(10)	(10)		(20)	(15)	6.5 ± 2.6	1.9 ± 0.9	936 ± 206	161 ± 72	203 ± 105	0.17 ± 0.05	1.2 ± 0.1
<0.01		<0.05		NS		NS	NS	NS	NS	<0.01	<0.01	<0.01	<0.01	NS	<0.01

*Data presented are range, mean value ± SD or number (%) of patients. †Patients versus control subjects. A = atrial; AMI = acute myocardial infarction; AP = angina pectoris; AS = atrial septum; CAD = atherosclerotic coronary artery disease (one or more major epicardial coronary arteries; >75% in cross-sectional area); CHF = congestive heart failure; CVA = cerebrovascular accident; F = female; Fi = fibrosis; FO = fossa ovalis; FOM = fossa ovalis membrane; HW = heart weight; IDC = idiopathic dilated cardiomyopathy; LA = left atrium; LAA = left atrial appendage; LV = left ventricle; M = male; MAC = mitral annular calcium; MVP = mitral valve prolapse; N = necrosis; PE = pulmonary embolism; PFO = patent foramen ovale; Pt = patient; RA = right atrium; RAA = right atrial appendage; RV = right ventricle; SD = sudden death; SH = systemic hypertension; SVA = sinus of Valsalva aneurysm; V = ventricular; VC = valvular competent; VI = valvular incompetent; 0 = absent or none; + = present or mild; ++ = moderate; +++ = severe.

cular, redundant membranes with a surface area that exceeded that of the fossa ovalis by 2.1 ± 0.4 times. Other cardiac morphologic abnormalities were frequently found in patients with fossa ovalis membrane aneurysm, including patent foramen ovale (14 patients); cardiomegaly (12 patients); dilated atrial or ventricular cavity (11 patients), or both; mitral valve prolapse (4 patients); atherosclerotic coronary artery disease (4 patients); and intracardiac thrombi (3 patients). At least one of these associated cardiac abnormalities was present in 18 of these 20 patients (90%).

Previous necropsy studies of adults with fossa ovalis membrane aneurysm. Silver and Dorsey (4) described 16 adults with fossa ovalis membrane aneurysm (43 to 81 years old, mean 60; 7 women [44%] who constituted 1% of 1,578 adults examined at necropsy in their hospital over a period of 4.5 years. The aneurysmal membrane protruded into an atrial cavity (usually the right) by 1.1 to 2.4 cm, and the diameter of fossa ovalis ranged from 1.5 to 2.5 cm. Interatrial communications and dilated atrial cavities were each present in 8 patients (50%). The aneurysmal membrane was defined histologically as an "attenuated wall composed of connective tissue lined on both aspects by endothelial cells" (4). In addition, Silver and Dorsey (4) described "tiny fibrin-thrombus tags" attached to the convex surface of some aneurysmal membranes, and in one patient thrombus was found "at the base of one aneurysm in the circumferential pit between its wall and adjacent limbus."

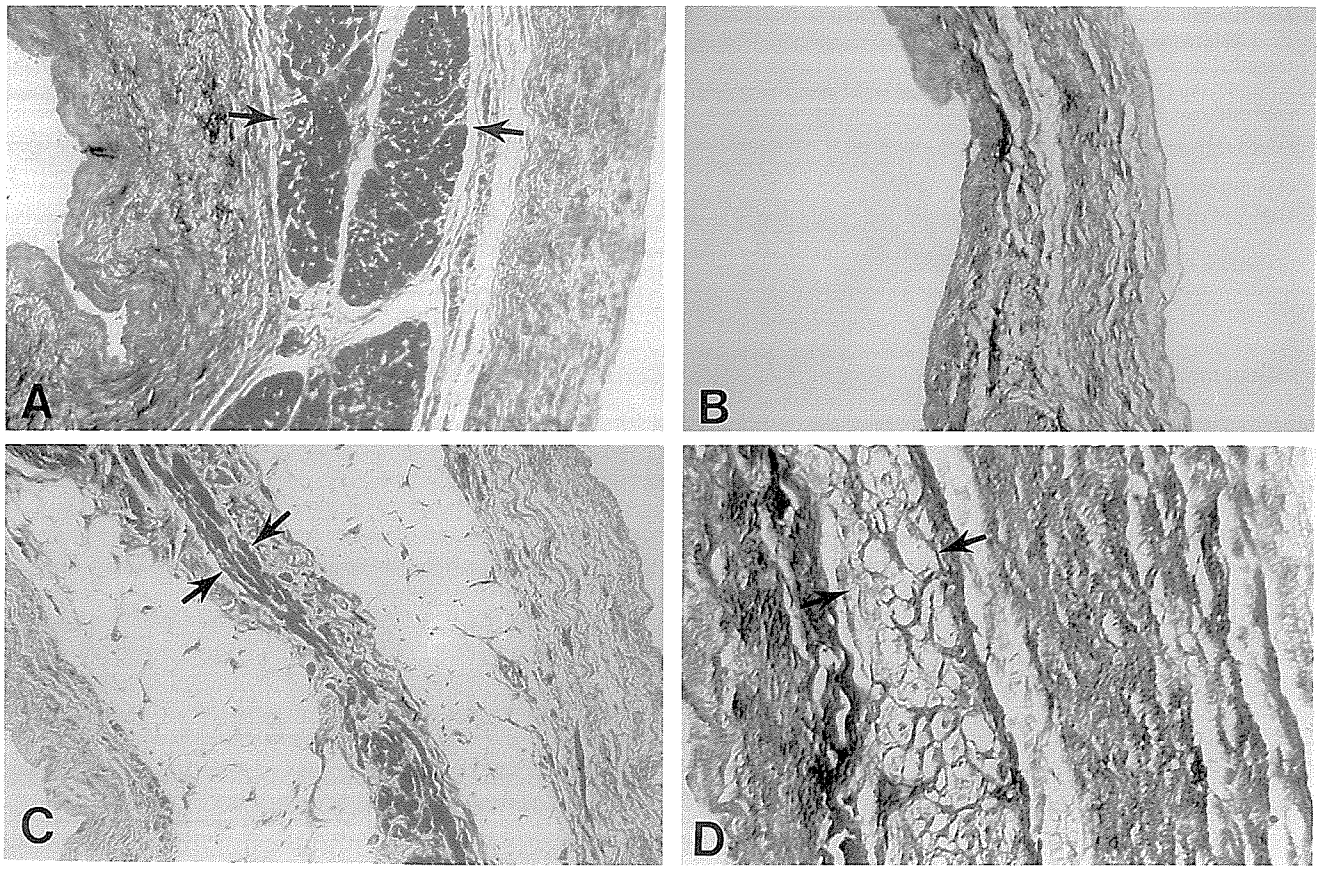

Figure 2. Coronal sections of fossa ovalis membrane in one patient without **(A)** and three patients with **(B to D)** fossa ovalis membrane aneurysm. **A,** The fossa ovalis membrane contains relatively large, normal-appearing muscle cells (enclosed by the **arrows**). **B,** The fossa ovalis membrane is thinned and devoid of muscle cells. **C,** Thin muscle layer is seen at the center of the fossa ovalis membrane and is surrounded by fat. **D,** Degenerated muscle cells are seen in the central portion of the fossa ovalis membrane. Masson's trichrome. Original magnification **A** and **B** ×50, **C** and **D** ×100, all reduced by 20%.

Although our findings agree for the most part with those of Silver and Dorsey (4), we did not find any thrombi in association with aneurysmal aneurysms.

Implications for management of patients with fossa ovalis membrane aneurysm and stroke. Our findings indicate that in most adults with fossa ovalis membrane aneurysm, known predisposing factors for cerebrovascular accidents can be found. A diligent search for these associated cardiac abnormalities, using combined transesophageal (8,9,18,19) and contrast echocardiography with Valsalva maneuver (10), is essential in formulating a management strategy. The degree of redundancy of the aneurysmal membrane is relevant only in that the prevalence of interatrial communication and atrial enlargement is probably higher in those patients with more redundant membranes. Thus, at the present time, echocardiographic definitions that are based on the size of the fossa ovalis and degree of redundancy of the fossa ovalis membrane, may not be useful.

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