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VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE-PHENTERMINE

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ABSTRACT

Background Fenfluramine and phentermine have been individually approved as anorectic agents by the Food and Drug Administration (FDA). When used in combination the drugs may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent and perhaps fewer side effects. Although the combination has not been approved by the FDA, in 1996 the total number of prescriptions in the United States for fenfluramine and phentermine exceeded 18 million.

Methods We identified valvular heart disease in 24 women treated with fenfluramine-phentermine who had no history of cardiac disease. The women presented with cardiovascular symptoms or a heart murmur. As increasing numbers of these patients with similar clinical features were identified, there appeared to be an association between these features and fenfluramine-phentermine therapy.

Results Twenty-four women (mean [±SD] age, 44±8 years) were evaluated 12.3±7.1 months after the initiation of fenfluramine-phentermine therapy. Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients. Both right-sided and left-sided heart valves were involved. Eight women also had newly documented pulmonary hypertension. To date, cardiac surgical intervention has been required in five patients. The heart valves had a glistening white appearance. Histopathological findings included plaque-like encasement of the leaflets and chordal structures with intact valve architecture. The histopathological features were identical to those seen in carcinoid or ergotamine-induced valve disease.

Conclusions These cases arouse concern that fenfluramine-phentermine therapy may be associated with valvular heart disease. Candidates for fenfluramine-phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease. (N Engl J Med 1997;337:581-8.)

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FENFLURAMINE and phentermine are prescription medications that have been individually approved by the Food and Drug Administration (FDA) as appetite suppressants for the treatment of obesity. When used in combination they may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent, fewer side effects, and improved patient tolerance.¹ Even though the FDA has not approved the use of the combination, in 1996 the total number of prescriptions for fenfluramine and phentermine in the United States exceeded 18 million.²

Pulmonary hypertension has been reported in association with treatment with fenfluramine^{3,4} or phentermine⁵ alone. The *d*-isomer of fenfluramine, dexfenfluramine, also increases the risk of pulmonary hypertension,⁶ particularly when patients receive high doses for more than three months. These drugs may cause pulmonary hypertension through the vasoconstrictor action of serotonin or by altering the depolarization of pulmonary vascular smooth-muscle membrane.⁷

Valvular disease has been reported after exposure to serotonin-like drugs such as ergotamine and methysergide⁸ and with increased serotonin levels associated with carcinoid disease.^{9,10} Valvular heart disease has not been reported in patients taking anorectic agents. We report 24 cases of unusual valvular disease in patients taking fenfluramine-phentermine.

METHODS

All the patients (Table 1) were identified during the course of routine evaluation for various clinical problems. No attempt was

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TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS.*

PATIENT NO.	AGE (YR)/SEX	BEFORE APPETITE SUPPRESSANTS					APPETITE SUPPRESSANTS		
		WEIGHT kg	HEIGHT cm	BODY-MASS INDEX†	MEDICATIONS	CARDIO- VASCULAR EXAMINATION	MAXIMAL DOSE OF PHEN- TERMINE mg/day	MAXIMAL DOSE OF FENFLUR- AMINE mg/day	DURATION OF THERAPY mo
1	41/F	108	165	39.7	None	Normal	48	120	25
2	44/F	91	160	35.5	Lisinopril, conjugated estrogens, theophylline	Normal	30	60	12
3	48/F	85	157	34.5	Sertraline, hydrochlorothiazide	Normal	30	60	9
4	52/F	69	158	27.6	Fluoxetine	Normal	15	40	12
5	49/F	96	158	38.5	Nortriptyline, propylthiouracil	Normal	30	60	11
6	51/F	133	153	56.8	Conjugated estrogens, medroxyprogesterone acetate, hydrochlorothiazide-benazepril	Normal	30	60	7
7	44/F	85	167	30.5	None	Normal	60	220	12
8	41/F	100	161	38.6	None	Normal	15	60	6
9	50/F	92	158	36.9	None	Normal	30	40	4
10	50/F	84	152	36.4	None	Normal	15	40	6
11	42/F	67	150	29.8	Bronchodilators	Normal	30	60	1
12	41/F	124	157	50.3	Sertraline	Normal	30	40	6
13	48/F	93	158	37.3	None	Normal	30	20	15
14	34/F	152	163	57.2	None	1/6 SEM	30	60	15
15	35/F	91	157	36.9	None	Normal	30	40	14
16	63/F	68	153	29.0	Fluoxetine	Normal	30	60	8
17	38/F	101	165	37.1	None	Normal	30	40	6
18	43/F	78	150	34.7	None	Normal	30	20	28
19	56/F	62	150	27.6	None	Normal	30	40	17
20	44/F	98	165	36.0	None	Normal	30	40	17
21	41/F	94	162	35.8	Sertraline	1/6 SEM	30	40	7
22	33/F	122	170	42.2	None	Normal	30	40	2
23	30/F	70	165	25.7	None	Normal	30	60	20
24	38/F	NA	NA	NA	None	Normal	30	40	4
Mean ±SD	44±8	96±22.1	159±5.8	37.9±7.9			30.8±8.5	56.5±40.7	11±6.9

TABLE 1. CONTINUED.

PRESENTATION	CARDIOVASCULAR FINDINGS		SURGERY		
	ECHOCARDIOGRAPHY	CARDIAC CATHETERIZATION	PROCEDURE	GROSS PATHOLOGICAL FINDINGS	MICROSCOPICAL PATHOLOGICAL FINDINGS
Murmur, dyspnea	Severe MR, thickened MV	Severe MR, normal coronary arteries	MV repair	Glistening white, thickened, tethered leaflets	NA
CHF, dyspnea, murmur	Severe AR and MR; moderate TR; EF, 40%	Severe AR and MR; PAP, 55/31 mm Hg	AVR, MVR, tricuspid-valve repair	No chordal rupture or flail segment; tri-leaflet aortic valve	"Stuck-on" appearance of plaque on leaflets‡
Dyspnea, edema	Severe MR, moderate AR	Severe MR; normal coronary arteries; PAP, 35/16 mm Hg	MVR	No prolapse or chordal rupture	"Stuck-on" appearance of plaque on leaflets‡
CHF, murmur, dyspnea	RVSP, 75 mm Hg; severe MR	Normal coronary arteries	MV repair	Distinctly unusual; posterior leaflet thickened, tethered	NA
Dyspnea	RVSP, 52 mm Hg; severe MR	Moderate MR; EF, 50%	MVR	Glistening white, thickened leaflets and chordae	"Stuck-on" appearance of plaque on leaflets‡
Murmur, dyspnea, edema	Moderate AR and TR, severe MR	Not done			
Dyspnea	RVSP, 74 mm Hg; moderate AR	PAP, 75/30 mm Hg			
CHF	Severe TR and MR; moderate AR; RVSP, 75 mm Hg; EF, 65%	Not done			
Dyspnea	Moderate MR; RVSP, 60 mm Hg	Not done			
Murmur, palpitations	Moderate AR, mild MR	Not done			
Murmur, edema	Moderate AR; severe MR and TR; RVSP, 72 mm Hg	Not done			
Murmur	Moderate MR; mild AR and TR; RVSP, 23 mm Hg; normal EF	Not done			
Murmur, edema	Moderate MR, TR, and AR; RVSP, 54 mm Hg; normal EF	Not done			
Murmur, edema, dyspnea	Severe MR; moderate AR and TR; RVSP, 93 mm Hg	Not done			
Murmur	Moderate AR; mild MR; EF, 75%	Not done			
Murmur, edema	Moderate AR, TR, and MR; EF, 65%	Not done			
Palpitations	Moderate AR; mild MR; EF, 70%	Not done			
Murmur	Moderate AR, mild MR and TR	Not done			
Supraventricular tachycardia	Mild MR and TR, normal left ventricle	Not done			
Dyspnea	Moderate AR; EF, 66%	Not done			
Murmur	Mild MR, AR, and TR	Not done			
Chest pain	Mild MR, TR, and AR; normal EF	Not done			
Murmur, dyspnea, edema	Severe AR and MR; RVSP, 45 mm Hg	Not done			
Palpitations, chest pain	Mild AR	Not done			

*MR denotes mitral regurgitation, MV mitral valve, NA not available, CHF congestive heart failure, AR aortic regurgitation, TR tricuspid regurgitation, EF ejection fraction, PAP pulmonary-artery pressure, AVR aortic-valve replacement, MVR mitral-valve replacement, RVSP right ventricular systolic pressure, and SEM systolic ejection murmur.

‡Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡"Stuck-on" refers to the fact that the valve architecture was intact.

made to identify patients by reviewing data bases, conducting cross-index searches of patient files, or soliciting reports of suspected cases from clinical practices. As increasing numbers of patients were identified with similar clinical features, a perceived association between these features and previous or current use of fenfluramine–phentermine evolved. The serendipitous connection between these individual cases was identified as a result of communication among several physicians beginning in May 1996.

May 1996

In May 1996, Patient 1 underwent mitral-valve repair at the Mayo Clinic for the treatment of severe mitral regurgitation. Intraoperatively, the valve was noted to have a glistening white appearance, suggesting ergotamine-induced valvular injury as observed in previous patients,⁸ but the patient had no history of ergotamine ingestion.

July 1996

In July 1996, Patient 1 was evaluated by another physician for severe symptomatic tricuspid regurgitation. Echocardiography confirmed severe tricuspid regurgitation and thickening of the valve leaflets. These findings were similar to those seen in patients with carcinoid or ergotamine-induced valve disease. A history was obtained indicating fenfluramine–phentermine use for 25 months until 1 month before mitral-valve surgery. A 24-hour urinary 5-hydroxyindoleacetic acid value was normal.

January 1997

In January 1997, a woman (Patient 7) with pulmonary hypertension was evaluated at the Mayo Clinic, and echocardiography demonstrated thickened aortic-valve leaflets and aortic regurgitation. An echocardiogram obtained two years previously revealed no abnormalities. The patient had taken fenfluramine–phentermine for one year before the more recent echocardiographic examination.

Also in January 1997, a physician from MeritCare Medical Center (Fargo, N.D.) contacted the Mayo Clinic and inquired whether there was a recognized association between diet medications and valvular heart disease. The inquiry was precipitated by the physician's awareness that his echocardiographic sonographers had identified a cohort of 12 patients (Patients 2, 3, 6, and 10 through 18) with valvular heart disease who had a peculiar valvular mor-

phology. A further review of the patients' records revealed that all 12 patients had taken fenfluramine–phentermine. The patients' records and echocardiograms were sent to the Mayo Clinic. The echocardiograms disclosed valve lesions very similar to those noted in Patients 1 and 7. Excised valve tissue was obtained from two patients (Patients 2 and 3), and slides prepared with elastic–van Gieson stain were reviewed by a cardiac pathologist. Histopathological examination revealed features identical to those of ergotamine-induced and carcinoid valve disease.

March 1997

In March 1997, a surgeon at the Mayo Clinic was contacted by one of his patients (Patient 4) who had undergone mitral-valve repair in 1996. The patient informed him that she had aortic regurgitation and pulmonary hypertension. A review of the surgical records showed that the appearance of the valve was distinctly unusual and not consistent with a history of rheumatic heart disease. Further inquiry revealed that the patient had taken fenfluramine–phentermine for 12 months before mitral-valve surgery.

Also in March 1997, valve tissue from a cardiac surgical patient (Patient 5) operated on at another institution was received by the Mayo Clinic for a pathological opinion. The morphologic features of the explanted valve (Fig. 1) were identical to those of valves from Patients 1 and 4 at the time of surgical inspection. Gross pathological features included thickening of the leaflets and chordae and a glistening white appearance. The histopathological features were identical to those in Patients 2 and 3. Patient 5 had been treated with fenfluramine–phentermine for 11 months.

April 1997

In April 1997, a patient (Patient 8) with a six-month history of fenfluramine–phentermine use was evaluated for dyspnea by a Mayo Clinic cardiologist consulting in another city. Multivalvular heart disease and pulmonary hypertension were identified. The cardiologist, unaware of the previous cases, asked a colleague whether he knew of an association between fenfluramine–phentermine therapy and valvular heart disease. Echocardiography revealed valvular morphology similar to that noted in the other patients.

Seven other patients (Patients 9 and 19 through 24) with similar clinical histories and echocardiographic findings were identified during clinical evaluations at MeritCare Medical Center from January through April 1997.



Figure 1. Explanted Mitral Valve from Patient 5, Demonstrating Glistening White Leaflets and Chordae with Mild-to-Moderate Irregular but Diffuse Thickening.

CASE REPORTS

Patient 1

Patient 1 was a 41-year-old woman (body-mass index [the weight in kilograms divided by the square of the height in meters] before treatment with appetite suppressants, 39.7) who was referred to the Mayo Clinic for mitral-valve surgery three months after a systolic murmur was first noted. She had taken fenfluramine-phentermine (fenfluramine, 40 mg three times per day, and phentermine hydrochloride, 16 mg three times per day) for 25 months. Therapy had been discontinued one month before cardiac surgery because of the reported potentially catastrophic catecholamine-depleting effect of fenfluramine.¹¹ Echocardiography and cardiac catheterization confirmed the presence of severe mitral regurgitation.

During mitral-valve repair, unusual morphologic features were noted: the posterior and anterior leaflets were tethered, and the chordae were shortened. The valve was glistening white, had no rheumatic calcification or yellowish discoloration, and resembled valves affected by ergot alkaloid derivatives.⁸ The patient had not used ergot preparations. Intraoperative transesophageal echocardiography demonstrated severe mitral regurgitation (Fig. 2) and mild tricuspid regurgitation.

After hospital discharge, symptomatic tricuspid valve regurgitation developed. Echocardiography demonstrated that the mitral-valve repair was intact without regurgitation. The tricuspid valve was thickened and failed to coapt; tricuspid regurgitation was severe. With medical management, symptoms of right ventricular failure improved despite the persistence of severe tricuspid regurgitation.

Patient 2

Patient 2 was a 44-year-old woman (pretreatment body-mass index, 35.5) who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for one year before dyspnea and a heart murmur were noted. Echocardiography demonstrated thickened aortic, mitral, and tricuspid valves with regurgitation. Because of progressive symptoms, mitral-valve and aortic-valve replacement and tricuspid-valve repair were performed at MeritCare Medical Center six months after fenfluramine-phentermine therapy was stopped. Histopathological examination of the resected mitral valve dem-

onstrated intact valve architecture, with a plaque-like process that extended along the leaflet surfaces and encased the chordae tendineae (Fig. 3). Lesions on the aortic valve were similar but less extensive.

Patient 3

Patient 3 was a 48-year-old woman (pretreatment body-mass index, 34.5) with no previous cardiac disease who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for nine months. Therapy was discontinued when a murmur was noted, and symptoms of edema and breathlessness were reported. At echocardiography, the mitral valve was thickened and severely regurgitant. Three months later, the patient underwent mitral-valve replacement at MeritCare Medical Center for symptomatic mitral regurgitation. Histopathological examination demonstrated intact valve architecture and plaque-like lesions of apparent myofibroblasts in an abundant extracellular matrix of glycosaminoglycans and collagen (Fig. 4).

Patient 6

Patient 6 was a 51-year-old woman (pretreatment body-mass index, 56.8) with normal findings on cardiac examination who was treated with fenfluramine-phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day in divided doses). Seven months after this treatment was initiated, dyspnea and edema developed and a new murmur was noted. Transthoracic and transesophageal echocardiography at MeritCare Medical Center demonstrated thickened valves with severe mitral regurgitation and moderate aortic-valve and tricuspid-valve regurgitation. Fenfluramine-phentermine therapy was discontinued, and medical therapy for heart failure was instituted. Echocardiography performed three months later demonstrated minimal improvement in the valvular disease. The patient continues to be observed medically and has persistent symptoms of dyspnea.

Patient 7

Patient 7 was a 44-year-old woman who began receiving fenfluramine-phentermine for a pretreatment body-mass index of 30.5. Two years earlier, echocardiography had revealed normal valves. The initial dose was 60 mg of fenfluramine per day in divided doses and 30 mg of phentermine per day. Under medical

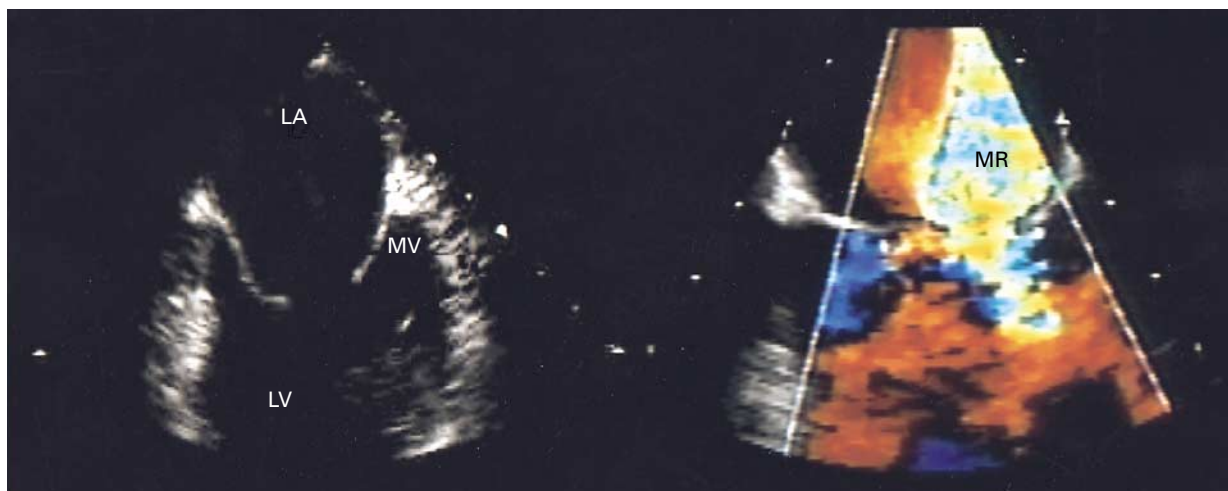


Figure 2. Intraoperative Transesophageal Echocardiograms in Patient 1.

The image on the left shows a thickened mitral valve (MV) during diastole. With the addition of color flow, the image on the right demonstrates severe mitral regurgitation (MR) during systole. LA denotes left atrium, and LV left ventricle.

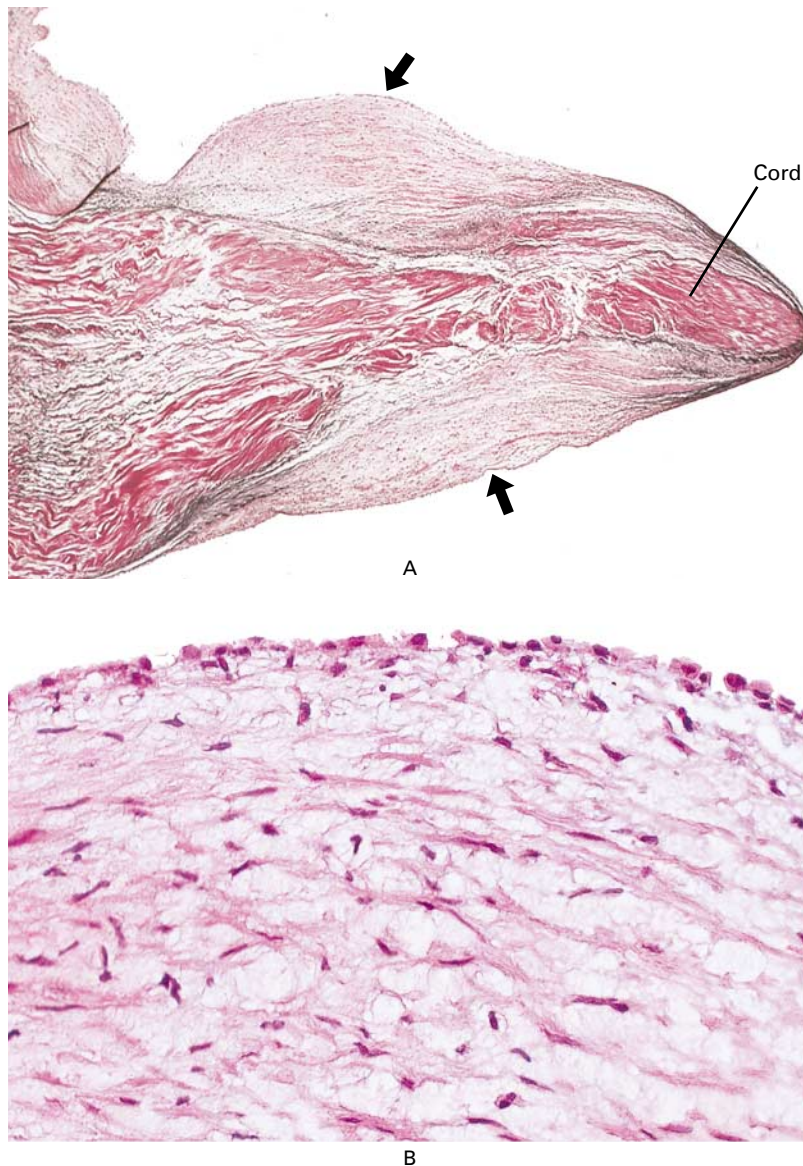


Figure 3. Photomicrographs of Resected Mitral Valve from Patient 2.

In Panel A, a low-power view (elastic-van Gieson stain, $\times 36$) shows intact valve architecture with "stuck-on" plaques (arrows). In Panel B, a high-power view (hematoxylin and eosin, $\times 360$) shows proliferative myofibroblasts in an abundant extracellular matrix.

direction, the daily doses were gradually increased to 220 mg of fenfluramine and 60 mg of phentermine.

Twelve months after fenfluramine-phentermine treatment was initiated, dyspnea developed on exertion. Echocardiography demonstrated a thickened trileaflet aortic valve with moderate regurgitation. Pulmonary-artery systolic pressure measured by cardiac catheterization was 75 mm Hg. Treatment with fenfluramine-phentermine was discontinued.

RESULTS

Table 1 summarizes the clinical features of the patients. Except for systemic hypertension, all of the

patients were thought to be free of cardiovascular disease at the onset of weight-reduction therapy. The physicians who prescribed the anorectic agents for the patients were not the ones who evaluated the cardiovascular changes. The patients were evaluated a mean (\pm SD) of 12.3 ± 7.1 months after the initiation of fenfluramine-phentermine treatment. The actual durations of drug therapy are shown in Table 1. Twenty patients presented with cardiovascular symptoms, and four patients had only a new murmur.

All patients underwent comprehensive two-dimen-

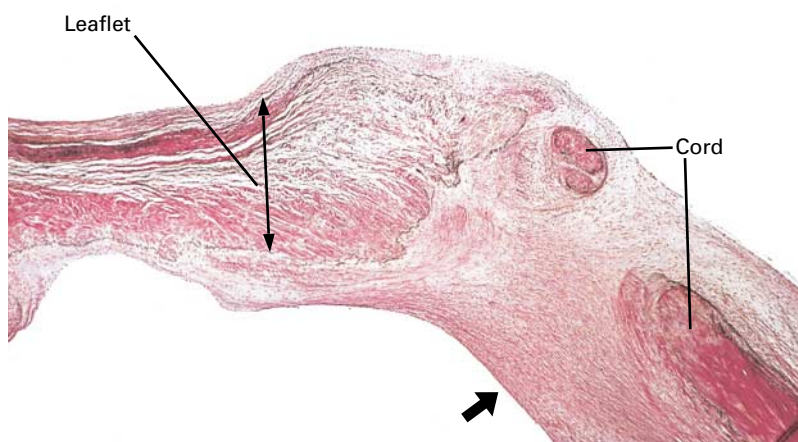


Figure 4. Photomicrograph of Resected Mitral Valve from Patient 3. A low-power view (elastic-van Gieson stain, $\times 36$) shows intact leaflet and tendinous cord, with encasement by proliferative plaque (arrow).

sional echocardiography, pulsed- and continuous-wave Doppler imaging, and color-flow examination according to previously described techniques.^{12,13} Valve morphology was noted by two examiners to be atypical for rheumatic, congenital, or degenerative lesions. The mitral and aortic valves exhibited echocardiographic features similar to those seen in patients with chronic rheumatic involvement; however, there was no evidence of valve obstruction. Thickening and diastolic doming of the anterior mitral leaflet, with preserved mobility and thickening, and immobility of the posterior leaflet were typical findings (Fig. 2). Subvalvular involvement was characterized by thickening and shortening of the chordae tendineae, causing tethering of the posterior leaflet. The combination of abnormalities resulted in malcoaptation and central regurgitation. The aortic valve was characterized by thickening and mild retraction of the leaflets. With tricuspid-valve involvement, the septal leaflet was thickened and variably fixed to the septum. The anterior leaflet appeared thickened and exhibited decreased mobility, diastolic doming, and loss of coaptation visible on two-dimensional imaging. Color-flow imaging demonstrated variable degrees of regurgitation in all patients. The echocardiographic appearance of the valves was similar in the medically treated and the surgically treated patients.

Eight patients had Doppler echocardiographic or catheter evidence of pulmonary hypertension (right ventricular systolic pressure, >50 mm Hg; range, 52 to 93) that had not been documented previously. Tricuspid regurgitation of moderate or greater severity was present in five of the eight patients with pulmonary hypertension.

DISCUSSION

Fenfluramine is a sympathomimetic amine that has an anorectic action mediated through the activation of serotonergic pathways in the brain. Fenfluramine promotes the rapid release of serotonin, inhibits its reuptake, and may have receptor-agonist activity,¹⁴ thus making serotonin more susceptible to metabolism and breakdown. The *d*-isomer of fenfluramine, dexfenfluramine, appears to be relatively selective for the central serotonergic system. Phentermine is a noradrenergic agent. Commonly used doses of these medications are 20 to 120 mg of fenfluramine per day and 18.75 to 37.5 mg of phentermine resin per day or 15 to 30 mg of phentermine hydrochloride per day.

Patients with malignant carcinoid syndrome have high levels of circulating serotonin. Associated cardiac disease is characterized by fibroplasia that involves primarily the valvular endocardium on the right side of the heart.^{10,15} The mechanism of valve injury in patients with carcinoid syndrome has not been determined but is believed to be serotonin-mediated, because such patients have higher circulating levels of serotonin than do their counterparts without cardiac involvement.¹⁰ The predilection for right-sided valve disease in carcinoid syndrome is most likely related to the serotonin-rich blood that enters the right atrium directly from the liver and the subsequent partial pulmonary degradation of serotonin. In our patients both left-sided and right-sided valvular lesions were seen, and multiple valves were often involved in individual patients.

The pathophysiologic mechanism in patients with ergot-alkaloid-induced valve disease has not been established, but the similar chemical structures of se-

rotonin, methysergide, and ergotamine may provide a clue.¹⁶ Ergotamine-induced and carcinoid valve disease are microscopically identical, with fibrotic endocardial changes.⁸ The pathological, surgical, and echocardiographic features of carcinoid and ergotamine-induced valve disease are indistinguishable from the features noted in our patients.

Fenfluramine alters serotonin metabolism in the brain.¹⁴ Phentermine interferes with the pulmonary clearance of serotonin, which may explain its association with primary pulmonary hypertension.¹⁷ Although serotonin levels were not measured in our patients, we postulate that the combination of fenfluramine and phentermine may potentiate the effect or concentration of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome or in those taking ergot preparations. However, the precise process by which this might occur is not known. No studies examining the effect of the combination of fenfluramine and phentermine in animals have been reported. Five of the 24 patients included in this series were taking either sertraline or fluoxetine while receiving fenfluramine–phentermine.

This description of patients is limited by the absence of pathological confirmation in the majority of cases. Many of the patients continue to be treated medically and have not undergone invasive or interventional procedures. Consequently, neither direct inspection nor histopathological evaluation has been carried out in most of the patients. Because no patient had symptomatic or clinical evidence of cardiovascular disease before the initiation of therapy with appetite suppressants, no routine pretreatment echocardiographic base-line studies were obtained. Only one patient had had an incidental echocardiographic study two years before treatment, and it showed no abnormalities. In the aggregate, however, these patients and those who underwent operative intervention had similar clinical and echocardiographic features. The mean age at the initiation of treatment, body-mass index, and duration of treatment before symptoms developed were similar in the medically and surgically treated groups.

In the absence of a control group or a case–control study, definitive statements about a true association of valvular disease with fenfluramine–phentermine therapy cannot be made. However, the appearance of clinically significant left-sided regurgitant valvular heart disease in a population less than 50 years old is rare.¹⁸ Thus, the association of valvular regurgitation with fenfluramine–phentermine treatment is not likely to be due to chance. Moreover, the unusual echocardiographic morphology of the lesions further diminishes the likelihood of a coincidental observation.

These cases should arouse concern that this combination of appetite suppressants has important implications regarding valvular heart disease. Prospective studies of this association will be required to validate the possibility that this combination of medications may cause valvular heart disease. The mechanism of valve injury and the frequency of the association have yet to be determined. Candidates for fenfluramine–phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease.

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