Operation for anorexigen-associated valvular heart disease

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Objectives: Recently, valvular regurgitation has been observed in patients who have taken fenfluramine or dexfenfluramine with or without phentermine. This study describes the clinical, echocardiographic, and pathologic findings of anorexigen-associated valvular heart disease and the surgical interventions required to treat it.

Methods: We reviewed clinical information on 14 patients with severe anorexigen-associated valvular disease who underwent cardiac operations.

Results: Thirteen women (mean age 44.2 ± 5.3 years) received fenfluramine, 58.5 ± 22.3 mg/day, and phentermine, 32.1 ± 11.4 mg/day, for an average of 12.1 ± 7.3 months before presentation. One woman received dexfenfluramine, 30 mg/day for 13 months, and phentermine, 60 mg/day, concomitantly for 6 months. Presenting symptoms included dyspnea (12 cases), palpitations (3), and atypical chest pain (3). Six patients had heart failure, and 4 had a new murmur. Echocardiography demonstrated severe mitral valve regurgitation in all patients. Seven also had aortic regurgitation, and 4 had significant tricuspid regurgitation. Four patients had successful mitral valve repair, 1 with concomitant aortic valve repair. Ten additional patients eventually required mitral valve replacement, 5 with concomitant aortic valve replacement. Excised valves demonstrated a glistening white appearance with plaque-like encasement of leaflets and chordae. Focal surface proliferation and fibrosis with a "stuck-on" appearance was consistently found.

Conclusions: Anorexigen use may lead to severe multivalvular regurgitation with characteristic echocardiographic and pathologic findings. Recognition of drug-induced valvulopathy is important because of widespread use of these medications and the uncertain natural history of the disease. Early surgical experience suggests that valve repair is possible in these young patients.

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Obesity is a medical problem in the United States that affects 58 million people. Despite the estimated 33 billion dollars spent each year by consumers in the United States on diet products and programs,¹ the incidence of obesity rose from 25% in 1980 to 33% in 1991.² Obesity contributes directly to increases in related health complications, such as adult-onset diabetes,³ heart disease, and hypertension, with estimated medical costs of nearly 40 billion dollars a year.⁴

Many weight-loss methods are ineffective, but in prospective trials, prescription anorectics such as fenfluramine and phentermine (Figure 1) produced significantly greater weight loss than did placebo medications.⁵ The combined use of fenfluramine and phentermine was proposed in 1984 by Weintraub and associates.⁶ Dexfenfluramine, the D-isomer of fenfluramine, was approved for use in the United States in April 1996, and in that same year, more than 18 million

Figure 1. Structures of amphetamine, fenfluramine, and phentermine.

monthly prescriptions were written in this country for the three popular anorexigens fenfluramine, dexfenfluramine, and phentermine.⁷

In July 1997, a report called attention to a possible association, in 24 patients, between a unique type of valvular heart disease and the use of diet medications.⁸ By September 1997, more than 100 cases of anorexigen-associated valvular disease had been reported to the Food and Drug Administration (FDA), including those of 21 patients who required cardiac surgery for treatment of their disease. The pathophysiologic mechanism and the natural history of anorexigen-associated valvular disease remain unknown. To define common characteristics among patients with this disease and to suggest a plan for management of patients requiring surgical intervention, we report this review of 14 of the 21 known surgical patients.

Methods

Between May 1996 and April 1997, valvular heart disease was identified in 24 women who had taken the drug combination fenfluramine and phentermine.⁸ In this group, 5 patients required repair or replacement of diseased heart valves. After this initial description, other cases of valvular disease were reported to our institution from physicians nationwide, and a database was established to document identified cases. From a database of 175 patients with suspected anorexigen-associated valvular disease, we found a total of 14 patients (including the original 5) who had cardiac surgery for treatment of severe valvular heart disease; these patients had operations at 9 different institutions. All available diagnostic test reports and patient records were reviewed. In cases missing specific data, patients were contacted directly.

Results

The characteristics of the 14 women (mean age 44.2 ± 5.3 years) and their evaluations, treatments, and findings are

presented in Tables 1 and 2. Preoperatively, 13 women were prescribed fenfluramine (mean dosage 58.5 ± 22.3 mg/day) and phentermine (32.1 ± 11.4 mg/day) for an average duration of 12.1 ± 7.3 months. One woman received dexfenfluramine (30 mg/day) for 13 months with phentermine (60 mg/day) concomitantly for 6 months. The average body mass index (weight in kilograms/height in meters squared) of the surgical patients before initiation of diet drug therapy was 31.6 ± 4.7 kg/m².

Before they began taking diet drugs, 13 of the 14 women had no history of cardiac disease and had normal cardiac findings as part of their general physical examinations. One patient had scarlet fever as a child but with no known cardiac complications and with normal cardiac examinations as an adult. None of the patients had echocardiograms documenting the absence of valvular heart disease before initiation of anorexigen therapy. After diet drug usage, however, all 14 patients had severe valvular disease that could not be attributed to any other cause. The most common symptom, for which 12 patients (85%) saw a physician, was dyspnea. Three patients reported palpitations (21%), and 3 described atypical chest pain. At presentation, 7 patients were noted to be in congestive heart failure on the basis of physical examination and chest x-ray films. In addition, 4 patients had a new, prominent murmur that was identified on their initial physical examination.

Preoperative echocardiography demonstrated severe mitral valve regurgitation in all patients, and 7 (50%) patients also had severe aortic valve regurgitation; 4 had moderate or greater tricuspid valve regurgitation. The characteristic echocardiographic findings included thickened valve leaflets tethered by shortened and thickened chordae.⁸ The valve structure noted by echocardiography was similar to features of chronic rheumatic involvement but without

TABLE I. Patient characteristics

Case	Demographics					Medical history
	Age (y)	Sex	Weight (kg)	Height (cm)	BMI (kg/m ²)	Other medications
1	48	F	85	157	34.5	Sertraline, hydrochlorothiazide
2	44	F	91	160	35.5	Lisinopril, conjugated estrogens, theophylline
3	50	F	96	158	38.5	Nortriptyline, propylthiouracil
4	41	F	108	165	39.7	None
5	52	F	69	158	27.6	Fluoxetine
6	40	F	82	167	29.0	None
7	44	F	89	168	31.7	Ranitidine
8	41	F	71	152	30.7	None
9	51	F	80	158	32.2	Conjugated estrogens
10	44	F	88	160	34.3	Pirbuterol acetate, triamcinolone
11	37	F	74	163	28.0	None
12	46	F	84	162	32.0	Enalapril, lansoprazole, sulfacetamide
13	34	F	63	165	23.5	Prednisone
14	47	F	68	163	25.6	Lisinopril, furosemide, zolpidem
Mean $\pm$ SD	44.2 $\pm$ 5.3		82.0 $\pm$ 12.3	161.1 $\pm$ 4.4	31.6 $\pm$ 4.7	

BMI, Body mass index; SD, standard deviation

TABLE 2. Summary of evaluations, treatments, and findings

Case	Presentation	Echocardiography	Catheterization
1	Dyspnea, edema	Severe MR, moderate AR	Severe MR, normal coronaries, PAP 35/16 mm Hg
2	CHF, dyspnea, murmur	Severe AR and MR, moderate TR, EF 40%	Severe AR and MR, PAP 55/31 mm Hg
3	Dyspnea	Severe MR, RVSP 52 mm Hg	Moderate MR, EF 50%
4	Dyspnea, murmur	Severe MR, thickened MV	Severe MR, normal coronaries
5	CHF, murmur, dyspnea	Severe MR, RVSP 75 mm Hg	Normal coronaries
6	Murmur, chest pain, palpitations	Severe MR, thickened ant. and post. MV leaflets, ruptured chordae, dilated LA, EF = 70%	Normal coronaries, severe MR, PCWP 58 mm Hg
7	Dyspnea, chest pain	Moderate MR, AR, valves structurally normal, chamber dimensions normal	Severe MR, AR, normal coronaries, EF 70%, PAP 70/18 mm Hg
8	Dyspnea, CHF	Severe MR, AR, thickened MV leaflets, fixed post. leaflet; PAP 64 mm Hg	Normal coronaries, severe MR
9	Dyspnea, CHF	Severe MR, moderate AR	AR and MR, normal coronaries, normal LV function
10	Dyspnea, chest pain, CHF	Severe MR, mild-moderate TR, AR	Severe MR; mild TR, AR, normal LV function, ostial RCA lesion, PAP 39/15 mm Hg
11	Edema	Severe MR, thickened leaflets	Normal coronaries
12	Hemoptysis, palpitations	Severe MR, thickening of both mitral leaflets with tethering of posterior, dilated LV, PAP 31 mm Hg, EF 60%	Normal coronaries, severe MR, PAP 60/40 mm Hg
13	Dyspnea, palpitations	Severe MR	Severe MR, normal LV function, normal coronaries
14	Dyspnea, CHF	Severe MR, TR; mild AR, thickened mitral, aortic, tricuspid leaflets, tethering of post. mitral leaflet, dilated LV, EF 57%, PAP 41 mm Hg	Normal coronaries

CHF, Congestive heart failure; MR, mitral regurgitation; AR, aortic regurgitation; TR, tricuspid regurgitation; EF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; MV, mitral valve; ant., anterior; post., posterior; LA, left atrium; PAP, pulmonary artery pressure; LV, left ventricle; PCWP, pulmonary capillary wedge pressure; RCA, right coronary artery; MVR, mitral valve replacement; AVR, aortic valve replacement; TV, tricuspid valve; AV, aortic valve; NA, not available.

Medical history		Appetite suppressant use		
Results of previous cardiac examination	Phentermine (mg/d)	Fenfluramine (mg/d)	Duration (mo)	
Normal	30	60	9	
Normal	30	60	12	
Normal	30	60	11	
Normal	48	120	25	
Normal	15	40	12	
Normal	30	60	24	
Normal	15	60	3	
Normal	37	20	6	
Normal	34	40	6	
Normal	30	60	5	
Normal	30	60	12	
Normal (scarlet fever at 1 y), all cardiac exams normal	30	60	7	
Normal	30	60	24	
Normal	60	Dexfenfluramine 30	13 Dex, 6 Phen	
	32.1 ± 11.4	58.5 ± 22.3	12.4 ± 7.5	

Procedure	Operative findings	Pathologic findings
MVR, AVR	No prolapse or chordal rupture	"Stuck-on plaque" on leaflets
MVR, AVR, TV repair	No chordal rupture or flail segment trileaflet AV	"Stuck-on plaque" on leaflets
MVR	Glistening white, thickened leaflets and chordae	"Stuck-on plaque" on leaflets
MV repair	Glistening white, thickened, tethered leaflets	NA
MV repair	Distinctly unusual—post. leaflet, thickened, tethered	NA
Attempted repair, MVR	Avulsion of central cusp of post. leaflet with ruptured chordae, elongated and torn ant. leaflet chordae	White-gray glistening valve cusps, focally thickened chordae, consistent with myxoid valvulopathy
MVR, AVR	Post. leaflet prolapse	Focal myxoid changes
MVR, AVR	Small post. leaflet, fused chordae, fixed ant. leaflet	Thickened chordae
MV and AV repair	Mitral annular dilatation	NA
MVR, AVR	Thickened valve, thickened, tethered chordae	Thickened leaflets and chordae
Attempted repair, MVR	Thickening with retraction and scarring, chordae primarily shortened, primary defect in mid-post. leaflet	Glistening thickening of leaflets and chordae
MV repair	Glistening white, thickened, tethered leaflets	NA
Attempted, repair, MVR	Thickening of chordae, malcoaptation of leaflets	Mitral leaflet biopsy: normal mitral valve leaflet
MVR	Retraction of the post. leaflet with tethering and shortened, fibrosed chordae	Mild focal leaflet and chordal thickening due to focal surface proliferation; "stuck-on" appearance

Figure 2. Representative echocardiographic views of a mitral valve affected by anorexigen use. The *left image* demonstrates the thickened valve leaflets, and the *right* shows severe mitral regurgitation. *LV*, Left ventricle; *MV*, mitral valve.

TABLE 3. Comparison of valvulopathies

	Common positions	Echocardiography
Rheumatic	Mitral, aortic	Thickened, hypomobile leaflets, MR, AR, AS
Ergot ³⁵	Mitral, aortic	Thickened, hypomobile to nonmobile leaflets with variable stenosis and regurgitation
Methysergide ^{36,37}	Aortic, mitral	Thickened leaflets, MR
Carcinoid ³⁸	Tricuspid, pulmonary	Thickened leaflets with valvular stenosis and regurgitation, hypomobile or nonmobile leaflets with shortening of chordae
Diet drug	Mitral, aortic, tricuspid	Atypical for rheumatic, congenital, or degenerative lesions, thickening of leaflets and chordae, fixation of posterior MV leaflets, no obstruction

MR, Mitral regurgitation; *AR*, aortic regurgitation; *AS*, aortic stenosis; *MV*, mitral valve.

commissural fusion and stenosis. The anterior mitral leaflet appeared thickened, with diastolic doming and retained mobility. The posterior mitral leaflet tended to be thickened with decreased mobility. The chordae tendineae were also thickened and shortened and caused tethering of the posterior leaflet; 1 patient also had chordal rupture. Echocardiographic features of aortic valve involvement included thickened and retracted valve cusps. Involved tricuspid valves also demonstrated thickening with variable fixation of the septal leaflet and decreased mobility of the anterior leaflet (Figure 2). Left ventricular function was decreased in only 1 patient (ejection fraction 40%).

All 14 patients underwent preoperative cardiac catheterization. Results of coronary angiography were normal in 13 patients; 1 patient (40 years old) had 60% narrowing of the

ostium of the right coronary artery. Pulmonary hypertension was found at cardiac catheterization in 6 patients (mean pulmonary artery pressure 35.3 ± 10.6 mm Hg). Five of the 14 patients initially underwent a mitral valve repair, and of these, 1 had concomitant aortic valve repair. At the time of the initial operation in 2 patients, repair of the mitral valve was attempted and then abandoned for prosthetic replacement. Seven patients underwent mitral valve replacement as an initial procedure, 5 with concomitant aortic valve replacement. At operation, diseased valves were described as having a glistening white appearance without the yellowish discoloration or calcification that is often seen in rheumatic heart disease (Figure 3). Valve leaflets and chordae with the glistening white coating tended to have decreased mobility because of both leaflet thickening and

Figure 3. Photographs of valve excised from a patient exposed to fenfluramine and phentermine. Of note is the glistening, pure-white appearance and thickening of the valve leaflets and chordae. *Left*, Viewed from the left atrium. *Right*, Viewed from the left ventricle.

Gross appearance	Histology
White, thickened fibrotic valve leaflets, nodules, calcifications, fused commissures	Dense fibrovascular, postinflammatory tissue, Aschoff nodules, calcifications
White thickening and encasement of valve leaflets and chordae	Proliferation of smooth-muscle cells and fibroblasts, avascular collagen matrix encasing leaflets and chordae, little destruction of normal underlying structures
Uniform glistening white thickening of leaflets and chordae, fusion of commissures and chordae	Avascular, poorly cellular fibrous tissue without elastic fibers, myocardial fibrosis
"Pearly white" thickening of leaflets and chordae sometimes involving chambers	Smooth-muscle cell proliferation without elastic fibers, plaques adherent to normal-appearing underlying structures
Glistening white leaflets and chordae with diffuse thickening, no calcifications, shortening of chordae with tethering of posterior MV leaflet	"Stuck-on" plaques, proliferative myelofibroblasts in an abundant extracellular matrix

tethering by shortened chordae. As noted on the echocardiogram, 1 patient had chordal rupture. Microscopy demonstrated characteristic plaque-like encasement of the leaflets and chordal structures. The elastic–van Gieson stain demonstrated smooth muscle cell hyperplasia in an abundant extracellular matrix. This focal surface proliferation and fibrosis was seen without evidence of inflammation or damage to the underlying valve structure, giving the lesions a "stuck-on" appearance (Figure 4).

There was no early or late mortality among the 14 patients in this series who underwent surgery. One patient who initially underwent valve replacement elsewhere required early reoperation for bleeding. Additionally, 2 years after valve repair, that same patient required valve replacement for recurrent severe mitral regurgitation

(patient 13, Table 1). The 4 other patients who underwent mitral valve repair are well 24 to 38 months after repair, with no evidence of progression of valvular disease. All patients who underwent valve replacement are well, now 12 to 36 months postoperatively.

Discussion

Fenfluramine was developed in 1962 by Beregi and associates,⁹ through a trifluoromethyl substitution of amphetamine, in an effort to produce a drug with the same anorectic effects but with fewer stimulatory side effects than the parent compound. In the central nervous system, fenfluramine causes the release of serotonin¹⁰; however, it also has direct effects on metabolism by increasing muscle glucose uptake¹¹ and inhibiting lipogenesis.¹² The primary complication associated with the

Figure 4. Photomicrographs of an excised valve from a patient with anorexigen-associated valvular disease. *Left*, Mitral leaflet (hematoxylin and eosin stain; $\times 360$). *Right*, High-power view of plaque (elastic-van Gieson stain; $\times 36$). There is smooth muscle cell hyperplasia in an abundant extracellular matrix, without evidence of inflammation or structural damage to the underlying structures. The plaques appear “stuck on.”

use of fenfluramine has been pulmonary hypertension,¹³⁻¹⁵ although additional studies have also demonstrated that it may be neurotoxic in monkeys.^{16,17} Fenfluramine was approved for short-term treatment of obesity by the FDA in 1973 and has since been prescribed for an estimated 70 million patients worldwide for weight loss, with significant benefit compared with placebo.¹⁸⁻²³ The D-isomer of fenfluramine, dexfenfluramine, has many of the same anorectic properties as racemic fenfluramine²⁴⁻²⁶; it too is associated with pulmonary hypertension^{27,28} and neuronal toxicity.¹⁷

Phentermine is a sympathomimetic amine that acts by interfering with central monoamine pathways through stimulation of dopamine release and has an inhibitory role in the metabolism of serotonin.²⁹ It was approved for use in the treatment of obesity by the FDA in 1959 and has been used since as a single agent in the treatment of obesity.^{30,31} Phentermine, like other anorectics, has also been linked to development of pulmonary hypertension.³²

In 1984, Weintraub and associates⁶ found that the same anorectic effects of fenfluramine and phentermine could be achieved with half doses of each drug used in combination. After this initial report, a clinical trial including 121 patients, who used the drugs for up to 3.5 years, confirmed the efficacy of combination therapy.³³ Prescribing fenfluramine and phentermine in combination for weight loss became a common practice despite warnings such as that of Atkinson and coauthors,³⁴ who wrote, “With such a sparse body of data in the literature, it is very hazardous to condone the growing practice by private practitioners in the United States of long term use of phentermine and fenfluramine.”

Anorexigen-associated valvular disease is similar pathologically to the valvulopathy seen with carcinoid syndrome. This is not unexpected, however, since serotonin metabo-

lism is implicated in the pathophysiology of each condition. Both carcinoid heart disease and anorexigen-associated valvular disease share many similarities with ergot and methysergide-induced valvulopathy. As seen in Table 3, the features of drug-induced valvulopathy overlap but are easily distinguished from those of rheumatic heart disease. In each of these conditions, patients may have symptoms of dyspnea, palpitations, or heart failure related to severe valvular regurgitation. Echocardiographic findings of leaflet thickening and tethering by shortened chordae can suggest a cause, but a detailed clinical history of diet drug use remains the most important element in the diagnosis of anorexigen-associated valvular disease.

Initial reports estimated that as many as one third of patients who have used these diet medications may acquire valvular disease; 2 recent studies suggest a lower incidence. Khan and associates³⁹ found that 22.7% of patients treated with diet medications had valve abnormalities noted by echocardiography, compared with 1.3% among controls. Jick and coauthors⁴⁰ found in their prospective case-controlled study that the incidence of clinically detected valve disease was only 35 per 10,000 patients who received fenfluramine or dexfenfluramine for more than 4 months.

On the basis of this experience, several points regarding surgical patients should be emphasized. First, even though we recognize that many other patients having anorexigen-induced valvulopathy have undergone surgery but were not reported to us or the FDA, it is clear that severe valvular regurgitation necessitating valve repair or replacement is rare; millions of patients have been exposed to diet drugs, but only a few will acquire valvular disease severe enough to require surgery.

Second, the patient history is the most important feature

leading to diagnosis. Patients with unexplained valvular regurgitation should be queried regarding diet drug use, ergot use for migraine headache, rheumatic fever, or symptoms of carcinoid disease. The clinician should have a high index of suspicion in a previously healthy patient who presents with new symptoms of valve dysfunction and characteristic echocardiographic features.

Third, patients exposed to anorexigens may have associated pulmonary hypertension that seems out of proportion to the duration and severity of the mitral and aortic valvular regurgitation. In this series, pulmonary hypertension did not appear to affect early or late results of valve repair or replacement, and pulmonary hypertension may improve with discontinuation of medications and the repair or replacement of diseased valves.

Fourth, at operation, the gross morphologic characteristics of the valve may lead the surgeon to the correct diagnosis; the valves have a characteristic appearance and one that can be distinguished from that in rheumatic heart disease. In each of the included cases, the operative findings were similar, with thickening of the valves and chordae, which had a brilliant glistening white appearance. Histologic evaluation of excised valves also demonstrated a consistent picture, with smooth muscle proliferation in an abundant extracellular matrix, creating a "stuck on" appearance.

Fifth, in contrast to management of patients with carcinoid heart disease, in which the involved tricuspid valve exhibits variable degrees of stenosis mandating prosthetic replacement, valve repair is an option for patients with anorexigen-induced valvulopathy. In this study, patients who underwent repair had the same characteristic tethering of their posterior mitral leaflet and shortened chordae as did patients who required valve replacement. However, in the 4 patients who had a successful repair, the anterior mitral leaflets were still quite mobile. Placement of a posterior annuloplasty ring was sufficient to restore coaptation of the leaflet in 3 patients. In 1 patient, incision of the posterior medial papillary muscle, in addition to placement of a posterior annuloplasty ring, allowed a greater excursion of the posterior leaflet and restored coaptation. One patient who initially underwent mitral valve repair with the placement of an annuloplasty ring later required valve replacement, but we do not know with certainty whether this patient discontinued use of anorexigens or whether the initial repair was completely satisfactory. Because patients affected by this disease are primarily young women, valve repair in this fashion, when possible, seems preferable to valve replacement. Although valve repair is advocated in select patients with preserved mobility of leaflets, the severity of valvular disease in this group required valve replacement in the majority of patients (10/14). In only 4 patients was the degree of valve thickening and chordal shortening limited enough to

allow repair. Although preservation of anterior leaflet mobility was not the most common finding, in the situation in which it is preserved, valve repair has worked well.

Finally, although the natural history of this disease is not completely known, early anecdotal reports give no indication that valvulopathy progresses once use of the medications has been stopped; indeed, there may be improvement in mild regurgitation over time.⁴¹ Additionally, we have had good results with mitral valve repair performed for anorexigen-associated valvular disease at our institution, and we have not seen progression of mitral valvulopathy on follow-up echocardiography.

In conclusion, it remains unclear how many patients will eventually acquire severe valvulopathy from exposure to anorexigens, but it is important for the cardiac surgeon to be aware of this unique disease and to understand that valve repair is a viable option for these young patients.

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