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THE PREVALENCE OF CARDIAC VALVULAR INSUFFICIENCY ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY IN OBESE PATIENTS TREATED WITH APPETITE-SUPPRESSANT DRUGS

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ABSTRACT

Background After case reports of cardiac-valve abnormalities related to the use of appetite suppressants were published, we undertook a study to determine the prevalence of the problem using transthoracic echocardiography.

Methods We examined patients who had taken dexfenfluramine alone, dexfenfluramine and phentermine, or fenfluramine and phentermine for various periods. We enrolled obese patients who had taken or were taking these agents during open-label trials from January 1994 through August 1997. We also recruited subjects who had not taken appetite suppressants and who were matched to the patients for sex, height, and pretreatment age and body-mass index. The presence of cardiac-valve abnormalities, defined by the Food and Drug Administration and Centers for Disease Control and Prevention as at least mild aortic-valve or moderate mitral-valve insufficiency, was determined independently by at least two cardiologists. Multivariate logistic-regression analysis was used to identify factors associated with cardiac-valve abnormalities.

Results Echocardiograms were available for 257 patients and 239 control subjects. The association between the use of any appetite suppressant and cardiac-valve abnormalities was analyzed in a final matched group of 233 pairs of patients and controls. A total of 1.3 percent of the controls (3 of 233) and 22.7 percent of the patients (53 of 233) met the case definition for cardiac-valve abnormalities (odds ratio, 22.6; 95 percent confidence interval, 7.1 to 114.2; $P < 0.001$). The odds ratio for such cardiac-valve abnormalities was 12.7 (95 percent confidence interval, 2.9 to 56.4) with the use of dexfenfluramine alone, 24.5 (5.9 to 102.2) with the use of dexfenfluramine and phentermine, and 26.3 (7.9 to 87.1) with the use of fenfluramine and phentermine.

Conclusions Obese patients who took fenfluramine and phentermine, dexfenfluramine alone, or dexfenfluramine and phentermine had a significantly higher prevalence of cardiac valvular insufficiency than a matched group of control subjects. (N Engl J Med 1998;339:713-8.)

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APPETITE-SUPPRESSANT medications such as fenfluramine and phentermine have been used for several decades for the treatment of obesity, with phentermine approved for use in the United States in 1959 and fenfluramine approved in 1973. These medications were predominantly given as monotherapy for short periods (less than three months), but a change in the pattern of use occurred after the publication of a series of articles in 1992.¹⁻⁹ These articles suggested the potential for the long-term use of fenfluramine in combination with phentermine. In the ensuing years, the use of appetite suppressants, particularly fenfluramine and phentermine in combination, increased exponentially.¹⁰ Dexfenfluramine, the *d*-isomer of fenfluramine, was initially marketed in Europe for the treatment of obesity, where its use was predominantly short term. In 1996, its use was approved in the United States for the long-term treatment of obesity. Since 1995, approximately 14 million prescriptions have been written for fenfluramine or dexfenfluramine, with the greatest product use among women and persons less than 60 years of age.¹¹

On July 8, 1997, the Food and Drug Administration (FDA) issued a public health advisory after researchers found that 33 women who had taken fenfluramine and phentermine in combination (commonly called "fen-phen") had unusual heart-valve morphology and regurgitation. The duration of treatment ranged from 1 to 28 months. The most common condition was multivalvular disease involving the mitral, aortic, and tricuspid valves. A published

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report on 24 of these 33 patients noted valvular insufficiency with unusual morphologic changes.¹² These patients had used fenfluramine and phentermine for an average of 12 months. In five of these patients who had undergone valve replacement, the pathological findings resembled those of carcinoid heart disease or heart disease associated with ergotamine toxicity, both of which are serotonin-related syndromes. Subsequently, the FDA analyzed a series of independent reports from clinicians and investigators and estimated that the prevalence of valvular insufficiency among patients using various appetite suppressants was 20 to 30 percent. In consideration of these data, the manufacturer of fenfluramine and dexfenfluramine stopped marketing these drugs in the United States (a similar action followed in Europe). These data also prompted the Department of Health and Human Services to issue interim recommendations for health care professionals regarding cardiac-valve abnormalities in association with exposure to these drugs.¹¹

A number of questions remained after these initial reports. In particular, it was not clear whether the valvular insufficiency was related to the use of these medications or was simply a consequence of obesity. The exact mechanisms involved in the development of valvular disease were not known. To investigate the effect of appetite suppressants on cardiac valvular insufficiency, we studied obese patients who had taken dexfenfluramine alone, dexfenfluramine in combination with phentermine, or fenfluramine in combination with phentermine as well as a matched group of obese control subjects who had not taken these medications. The purpose of the study was to determine the prevalence and severity of valvular dysfunction in obese patients who had taken appetite suppressants and in those who had not.

METHODS

Study Design

This cross-sectional study was approved by the human subjects research committee at Hennepin County Medical Center, an affiliated teaching hospital of the University of Minnesota in Minneapolis, where the work was conducted. All participants provided informed consent before enrollment in the study.

The study was initiated in August 1997 and used echocardiography to estimate the prevalence of valvulopathy in patients who were currently taking or had taken appetite suppressants during open-label trials from January 1994 through August 1997. For comparison, a matched group of obese subjects who had not taken fenfluramine-derived appetite suppressants was recruited after August 1997 from the community at large.

Patients

The sole criterion for inclusion as a patient was participation in one of three appetite-suppressant studies previously conducted at Hennepin County Medical Center. To be eligible for these open-label studies, patients had to be more than 30 percent above their ideal weights. Potential participants were excluded if an assessment of their medical history or a physical examination conducted by one of two physicians revealed clinically significant cardiovascular or psychiatric disorders. All three studies used similar methods

of screening for medical conditions, approaches to diet and behavior modification, and medical follow-up, but different appetite-suppressant regimens. The first study used fenfluramine (Pondimin, A.H. Robins, Richmond, Va.) at a dose of 60 to 120 mg per day in combination with phentermine (several brands) at a dose of 30 mg per day.^{13,14} The second used dexfenfluramine (Redux, Wyeth Laboratories, Philadelphia, under license from Interneuron, Lexington, Mass.) at a dose of 30 mg per day. The third allowed the optional use of phentermine (30 mg per day) for patients who did not lose the targeted amount of weight during dexfenfluramine (30 mg per day) monotherapy.¹⁴ A single team of health care professionals conducted all three studies. Of the 295 patients enrolled in the studies, 257 underwent echocardiography.

Control Subjects

We recruited potential control subjects by advertising in various media in the local metropolitan area. A total of 977 persons (789 women and 188 men) responded. Control subjects were matched to the patients for various pretreatment demographic characteristics: sex, age (within 4 years), height (within 3 in. [7.6 cm]), and body-mass index (within 15 percent). According to self-reports, the control subjects had not taken fenfluramine or its derivatives; one male subject who had taken dexfenfluramine for seven days was included. A total of 239 control subjects were matched to the patients.

Echocardiography

Complete echocardiographic examinations were performed with commercially available ultrasonographs (Sonos model 1000, 1500, or 2500, Hewlett-Packard, Andover, Mass.; Power Vision model SSA 380, Toshiba, Tokyo, Japan; or Sequoia, Acuson, Mountain View, Calif.) with M-mode, two-dimensional, and Doppler echocardiography (pulsed, continuous-wave, and color Doppler). Echocardiograms were obtained in standard parasternal long-axis and short-axis views; apical two-, four-, and five-chamber views; subcostal views; and suprasternal views (parallel to the aortic arch) and were recorded in real time on videotape.

Doppler Imaging

The height (width) of the aortic regurgitant jet at valve level and the width of the left ventricular outflow tract were measured on-line in the parasternal long-axis view.^{15,16} Additional M-mode color Doppler imaging was also performed to measure the width of the aortic regurgitant jet.¹⁷ Continuous-wave Doppler imaging of the aortic regurgitant jet was recorded in the apical five-chamber view for measurement of the pressure half-time, which is an index of severity. Pulsed Doppler measurements of flow in the abdominal aorta were recorded in the subcostal view and in the descending thoracic aorta in the suprasternal view. Pulsed Doppler transmitral diastolic flow velocities were measured at the level of the tips of the mitral-valve leaflets. Peak instantaneous flow rate and the effective area of the mitral regurgitant orifice were measured in subjects with mitral regurgitation,^{18,19} and pulsed Doppler measurement of pulmonary venous flow was performed when technically feasible. For subjects with identifiable tricuspid regurgitation, the right ventricular-right atrial maximal systolic-pressure gradient was estimated with the modified Bernoulli equation: gradient (in millimeters of mercury) = $4v^2$, where v is the maximal velocity of the tricuspid regurgitant jet (in meters per second).²⁰⁻²²

Interpretation of Results

The primary reader reviewed all echocardiograms in a blinded fashion with regard to subjects' drug-exposure status. Results for a subgroup of echocardiograms (60 of the total of 496) from this study were previously reported to the FDA.¹¹ The primary reader interpreted these results before echocardiograms from matched control subjects became available and thus was potentially aware of the appetite-suppressant status of the subjects of these 60 studies. All 496 echocardiograms were also interpreted by one of three secondary readers, using the original real-time videotape record-

ings, who were unaware of the subjects' drug-exposure status. Thus, each of the 496 echocardiograms was interpreted independently by at least two readers. The echocardiographic data, as described above, were available to all readers for the assessment of valvular regurgitation. Acting independently, each reader graded valvular regurgitation for all valves as absent, trace, mild, moderate, or severe. The readers were not shown a reference set of echocardiograms before or during the study. The definition of cardiac-valve abnormalities was that adopted by the FDA and Centers for Disease Control and Prevention: mild aortic-valve insufficiency or more severe disease or moderate mitral-valve insufficiency or more severe disease.¹¹ In the event of disagreement between the primary and secondary readers regarding cardiac-valve abnormalities that met the case definition, a randomly selected third reader provided independent interpretation and served as the tiebreaker. If the two independent readers agreed that cardiac-valve abnormalities were present or absent, then no further attempt was made to reconcile any differences in the grading of valvular insufficiency. The primary reader and all secondary readers were experienced echocardiographers and board-certified cardiologists. According to the Hennepin County Medical Center's computerized echocardiographic data base, the primary reader had interpreted 14,267 echocardiograms from March 1986 to December 1997, including 10,972 Doppler studies.

Collection of Other Data

Medical diagnoses including hypertension and diabetes were verified from the patients' medical records or by control subjects' self-reports. A research assistant administered a questionnaire to the control subjects by telephone regarding their demographic characteristics; personal habits (smoking and alcohol intake); medical history, with emphasis on known cardiopulmonary disorders; and use of appetite suppressants. Height, weight, and blood pressure were documented at the time of echocardiography.

The patients' medical records were used to determine when appetite-suppressant use began and ended during the previous studies at our institution. In approximately 10 percent of the medical records, the date on which treatment was stopped was not given, indicating instances in which the patient had missed the scheduled follow-up visit and had subsequently dropped out of the study. In the case of these patients, the stopping date used was the date 90 days after the patient's last noted medical visit (90 days was the maximal number of days of drug therapy possible through authorized prescription refills).

Statistical Analysis

All statistical analysis was completed with SPSS for Windows (version 7.5). The Spearman correlation coefficient was used to assess concordance of echocardiographic results with respect to the degree of valvular insufficiency. Kappa values were calculated to assess agreement between the primary reader and all secondary readers on cases of cardiac-valve abnormalities that met the case definition. Univariate analyses were used to identify differences in continuous or categorical variables with respect to drug-exposure status and the presence or absence of cardiac-valve abnormalities. Multivariate logistic-regression analysis was used to test continuous or categorical variables obtained from the medical history, demographic characteristics, and measurement factors that might be associated with cardiac-valve abnormalities. Variables were retained in the final analysis only if they were independent risk factors for cardiac-valve abnormalities that met the case definition or if the variables confounded the association between drug use and cardiac-valve abnormalities. All reported P values are two-sided.

RESULTS

Degree of Agreement between Readers of Echocardiograms

Tables 1 and 2 show the concordance between the primary reader and all secondary readers for all 496

cardiac ultrasound studies with respect to aortic-valve and mitral-valve insufficiency. The Spearman correlation coefficients were 0.88 (P<0.001) for the interpretations of aortic-valve insufficiency and 0.63 (P<0.001) for the interpretations of mitral-valve insufficiency. Table 3 shows the concordance between the primary reader and all secondary readers regarding cardiac-valve abnormalities that met the case definition (kappa value, 0.79; P<0.001).

Final Analysis

Of the 295 patients enrolled in the three appetite-suppressant studies conducted at our institution, 257 (87 percent) agreed to participate in the current study. A matched control subject was found for 239 of the 257 patients (93 percent). We included all 496 study subjects in the analysis of the association between the use of appetite suppressants and cardiac-valve

TABLE 1. EXTENT OF AORTIC-VALVE INSUFFICIENCY ON ECHOCARDIOGRAPHY, ACCORDING TO THE PRIMARY AND SECONDARY READERS.*

PRIMARY READER DEGREE OF AORTIC- VALVE INSUFFICIENCY	SECONDARY READERS DEGREE OF AORTIC-VALVE INSUFFICIENCY				
	None	Trace	Mild	Moderate	Severe
None	364	15			
Trace	9	37	11		
Mild	2	7	29	4	
Moderate			7	7	2
Severe				2	2

*Concordant results are indicated by boldface type (r=0.88 for the correlation between readers, P<0.001 for the comparison across degrees of insufficiency).

TABLE 2. EXTENT OF MITRAL-VALVE INSUFFICIENCY ON ECHOCARDIOGRAPHY, ACCORDING TO THE PRIMARY AND SECONDARY READERS.*

PRIMARY READER DEGREE OF MITRAL- VALVE INSUFFICIENCY	SECONDARY READERS DEGREE OF MITRAL-VALVE INSUFFICIENCY				
	None	Trace	Mild	Moderate	Severe
None	195	58	1		
Trace	49	126	20		
Mild	2	12	25	2	
Moderate			4	2	
Severe					2

*Concordant results are indicated by boldface type (r=0.63 for the correlation between readers, P<0.001 for the comparison across degrees of insufficiency).

TABLE 3. CASES OF CARDIAC-VALVE ABNORMALITIES ON ECHOCARDIOGRAPHY, ACCORDING TO THE PRIMARY AND SECONDARY READERS.*

PRIMARY READER	SECONDARY READERS	
	Cardiac-valve abnormalities absent	Cardiac-valve abnormalities present
Cardiac-valve abnormalities absent	420	12
Cardiac-valve abnormalities present	12	52

*Concordant results are indicated by boldface type ($\kappa=0.79$ for the correlation between readers, $P<0.001$ for the comparison across categories).

abnormalities. The resultant odds ratio was 21.4 (95 percent confidence interval, 6.8 to 108.2).

Of the 257 patients, 6 (5 female and 1 male) were excluded from the final analysis because their use of appetite suppressants exceeded that called for by the treatment protocols. A suitable match could not be found for an additional 18 patients (3 men and 7 women who took fenfluramine in combination with phentermine, 2 men who took dexfenfluramine in combination with phentermine, and 4 men and 2 women who took dexfenfluramine alone). Table 4 shows the demographic characteristics of the remaining 233 patients and their matched controls. The two groups were well matched, with no significant differences in sex, age, body-mass index, or weight. Of the 233 patients, 41 (18 percent) were taking appetite suppressants at the time of echocardiography, 47 (20 percent) underwent echocardiography within 30 days after they stopped taking the medication, 71 (30 percent) underwent echocardiography 1 to 6 months after discontinuing treatment, and 74 (32 percent) underwent echocardiography more than 6 months after discontinuing treatment.

As shown in Table 5, cardiac-valve abnormalities that met the case definition were present in 1.3 percent of the control subjects (3 of 233) and 22.7 percent of the patients (53 of 233) (odds ratio, 22.6; 95 percent confidence interval, 7.1 to 114.2; $P<0.001$).

The results of the multivariate logistic-regression analysis are shown in Table 6. Age, as a continuous variable, was the only covariate that was an independent predictor of cardiac-valve abnormalities that met the case definition. None of the other covariates were independent predictors or confounders of the association between such cardiac-valve abnormalities and the use of appetite suppressants. Consequently, the final model contains only age and type of appetite suppressant as predictors of cardiac-valve abnormalities. Figure 1 shows the overall prevalence of aortic-valve insufficiency among the patients and control subjects.

DISCUSSION

Cardiac valvular disease has multiple causes, including congenital disorders, such as bicuspid aortic valve, and acquired conditions, such as infection, trauma, and (less commonly) carcinoid syndrome.^{23,24} Ergot alkaloids such as methysergide have been implicated as causes of valvular disease.²⁵ Recent case reports have suggested an association between cardiac-valve abnormalities and the use of serotonergic appetite suppressants, but the mechanism of drug-related valvular dysfunction is unknown.^{11,12}

The initial published reports of valvular disease associated with the use of appetite suppressants described a severe multivalvular condition.^{11,12} We as well as others subsequently reported additional cases of valvular dysfunction, most commonly aortic-valve insufficiency.¹¹ Aortic-valve insufficiency is uncommon in the general population, especially in people under the age of 50 years. Available estimates suggest a prevalence of 1 to 2 percent in this age group.²⁶⁻³¹ The interpretation of both the initial and

TABLE 4. DEMOGRAPHIC CHARACTERISTICS OF 233 PATIENTS AND THEIR MATCHED CONTROLS.*

CHARACTERISTIC	CONTROL SUBJECTS (N=233)	ALL PATIENTS (N=233)	PATIENTS GIVEN DEXFENFLURAMINE (N=39)	PATIENTS GIVEN DEXFENFLURAMINE AND PHENTERMINE (N=31)	PATIENTS GIVEN FENFLURAMINE AND PHENTERMINE (N=163)
Sex (M/F)	30/203	30/203	5/34	3/28	22/141
Age (yr)	45.3±9.5	45.3±9.1	43.0±10.3	44.7±7.7	46.0±9.0
Weight (lb)†	247.9±49.8	247.1±54.3	251.0±63.7	235.6±47.5	248.5±53.2
Body-mass index‡	40.6±7.3	40.4±7.3	40.0±8.2	39.2±7.3	40.7±7.1
Duration of treatment (mo)		20.5±12.0	4.9±3.2§	9.0±2.2§	26.5±9.1§

*Plus-minus values are means ±SD.

†To convert values to kilograms, divide by 2.2.

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

§ $P<0.001$ for the comparison with the other two subgroups.

TABLE 5. CASES OF CARDIAC-VALVE ABNORMALITIES MEETING THE CASE DEFINITION.

GROUP	NO. OF SUBJECTS	CARDIAC-VALVE ABNORMALITIES
		no. of cases (%)
Unexposed control subjects	233	3 (1.3)
Patients	233	53 (22.7)
Patients given dexfenfluramine	39	5 (12.8)
Patients given dexfenfluramine and phentermine	31	7 (22.6)
Patients given fenfluramine and phentermine	163	41 (25.2)

TABLE 6. MULTIVARIATE LOGISTIC-REGRESSION ANALYSIS OF PREDICTORS OF CARDIAC-VALVE ABNORMALITIES THAT MET THE CASE DEFINITION BY CARDIAC ECHOCARDIOGRAPHY.*

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Initial model		
Age	1.1 (1.0–1.1)	0.02
Sex	0.9 (0.3–2.8)	0.80
Body-mass index	1.0 (0.9–1.2)	0.44
Weight	0.99 (0.97–1.0)	0.14
Systolic blood pressure	1.0 (0.99–1.1)	0.14
Diastolic blood pressure	1.0 (0.9–1.0)	0.09
Presence of hypertension	0.6 (0.3–1.3)	0.22
Presence of diabetes mellitus	0.4 (0.1–1.5)	0.17
Dexfenfluramine use	15.4 (3.3–72.4)	<0.001
Dexfenfluramine and phentermine use	24.9 (5.5–111.8)	<0.001
Fenfluramine and phentermine use	31.9 (9.2–110.5)	<0.001
Final model		
Age	1.1 (1.0–1.1)	0.007
Dexfenfluramine use	12.7 (2.9–56.4)	<0.001
Dexfenfluramine and phentermine use	24.5 (5.9–102.2)	<0.001
Fenfluramine and phentermine use	26.3 (7.9–87.1)	<0.001

*The reference category is the control subjects. The values for age, body-mass index, and weight are those before treatment with appetite suppressants for the patients and those at the time of echocardiography for the control subjects. Values for blood pressure were obtained at the time of echocardiography in both groups. Age, body-mass index, blood pressure, and weight are continuous variables. The other variables are categorical. CI denotes confidence interval.

the subsequent case reports was necessarily limited by the absence of an appropriate comparison group — that is, a matched group of similarly obese subjects who had not used appetite suppressants.

Our data show that the prevalence of valvular insufficiency is significantly higher among patients who have taken appetite suppressants than among subjects matched for age, sex, and body-mass index who have not taken such drugs. The most common — and often the only — abnormality that met the case definition in our study was aortic-valve insufficiency. Using univariate analysis, we found a significant relation between the use of appetite suppres-

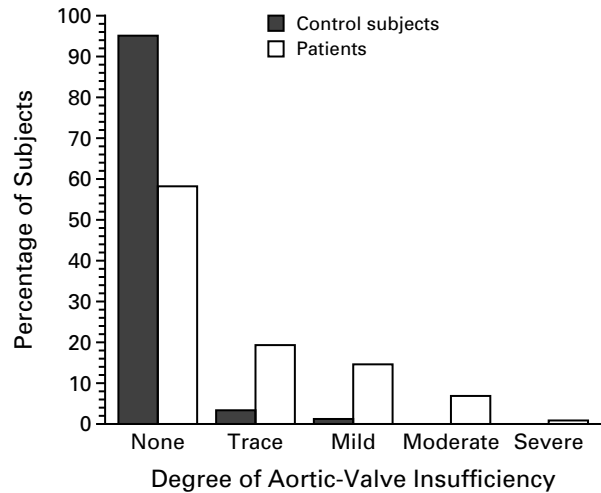


Figure 1. Degree of Aortic-Valve Insufficiency in 233 Patients and Their Matched Controls.

The interpretations are those of the primary reader except in instances in which there was disagreement between readers with respect to abnormalities that met the case definition, in which case the tie-breaking interpretation of the third reader is shown.

sants and the presence of cardiac-valve abnormalities that met the case definition. Multiple logistic-regression models clearly showed significant increases in the risk of valve disease with the use of appetite suppressants, regardless of the drug regimen. Although the odds ratios for such cardiac-valve abnormalities with the use of a combination of dexfenfluramine and phentermine (24.5) and fenfluramine and phentermine (26.3) were twice the odds ratio with dexfenfluramine alone (12.7), these data are confounded by the duration of treatment. The duration of treatment differed among the three subgroups, and the effect of this variable on the relative prevalence of valvular insufficiency requires further study.

A higher percentage of patients than controls had trace aortic-valve insufficiency. This finding suggests that the case-definition threshold for cardiac-valve abnormalities in association with appetite suppressants set by the FDA and Centers for Disease Control and Prevention may be too high.

We analyzed our data to determine which factors might predispose patients to valvular insufficiency. As shown in Table 6, only age at the time drug therapy was initiated and the use of dexfenfluramine or combinations of dexfenfluramine and phentermine or fenfluramine and phentermine were statistically significant. The natural history and therefore the clinical significance of appetite-suppressant-associated valvular insufficiency are not known. Follow-up studies of patients with valvular dysfunction and those without it, as well as of matched control subjects are needed to help define the natural history of valvular insufficiency.

Until such research has been conducted, the Department of Health and Human Services has issued interim guidelines for the evaluation and care of patients who have taken appetite suppressants that include prophylaxis against bacterial endocarditis.¹¹

When used to diagnose valvular insufficiency, echocardiography requires both objective criteria and the subjective interpretation of images. To minimize bias in the diagnosis of valvular dysfunction in the present study, secondary readers were not told which subjects had taken appetite suppressants. The primary reader was unaware of the subjects' history of appetite-suppressant use in the case of 436 of 496 echocardiograms. Furthermore, the secondary readers did not know how the primary reader had interpreted the echocardiograms. As shown in Table 1, the concordance among readers was excellent, despite the absence of any reference set or attempts to improve concordance.

In conclusion, our data show that patients who took fenfluramine and phentermine, dexfenfluramine alone, or dexfenfluramine and phentermine had a significantly higher prevalence of cardiac valvular insufficiency than matched control subjects. In experienced hands, echocardiography is a reproducible and objective means of assessing the presence of drug-related valvular insufficiency. The clinical significance and natural history of this type of valvular disease are currently unknown.

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