matous infiltration of myocardial structures[19] or myocardial abscesses, has been promising. Gd has been used to distinguish neoplasms from nonenhancing infiltrative processes.[20]

In our patient, the homogenous echogenicity of the extracardiac mass, imaged by both precordial and transesophageal approaches, was considered most characteristic of neoplasm. Its origin in the pericardium was suggested, but not definitively identified, by echocardiography. While non-contrast-enhanced MR imaging demonstrated the pericardial origin of the mediastinal mass, Gd enhancement provided the tissue characterization data that suggested that the mass might be composed of fibrotic material. The lack of involvement of the bronchial bed as assessed by thoracic MR imaging, made fibrosing mediastinitis less likely, and fibrosis in association with the patient's previous radiation therapy the more probable diagnosis. MR imaging with nonionic contrast enhancement is a valuable technique for assessing unusual paracardiac masses. This noninvasive modality should be used in the evaluation of any bulky intra-or extracardiac mass for which the differential diagnosis includes non-neoplastic pathology.

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Pulmonary edema with diltiazem in hypertrophic obstructive cardiomyopathy

Deepak Natarajan, MBBS, MD, DM,
Subhash C. Sharma, MBBS, MD, and
Ved P. Sharma, MBBS, MD. *New Delhi, India*

Limited hemodynamic data are available on diltiazem,[1] a benzothiazepin derivative, in patients with hypertrophic obstructive cardiomyopathy. This report describes the development of pulmonary edema in two patients in a study that examines the hemodynamic effects of oral diltiazem in 10 patients with hypertrophic obstructive cardiomyopathy.

Ten patients (9 men and 1 woman); ages 16 to 54 years (34 ± 14 years) with clinical, echocardiographic, and hemodynamic findings that are typical of hypertrophic obstructive cardiomyopathy were studied. All patients had normal sinus rhythm but were functionally limited at the start of study. They were graded according to the New York Heart Association functional classification. The presence

From the Department of Cardiology, Dr. Ram Manohar Lohia Hospital, New Delhi, India.

Reprint requests: Deepak Natarajan, MBBS, MD, DM, Department of Cardiology, Dr. Ram Manohar Lohia Hospital, New Delhi, India.

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Table I. Hemodynamic effects of oral diltiazem in patients with hypertrophic obstructive cardiomyopathy

Patient No.	Age (yr)/sex	HR (beats/min)		MAP (mm Hg)		CI (L/min/m²)		LVSP (mm Hg)		PAWP (mm Hg)		LVEDP (mm Hg)		LVOG (mm Hg)		PLOG (mm Hg)	
		C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
1	16/M	74	68	90	86	2.8	2.8	190	160	15	14	16	15	80	50	150	100
2	54/M	78	74	92	88	2.6	2.6	160	148	18	18	17	17	50	38	90	82
3*	52/F	76	—	94	—	2.6	—	164	—	24	—	21	—	48	—	82	—
4*	18/M	74	82	82	78	2.8	2.8	163	158	22	32	19	28	60	58	108	104
5	22/M	72	68	96	88	3.0	3.1	152	150	16	15	16	16	38	36	70	64
6	48/M	80	68	90	82	2.9	3.2	142	140	15	14	15	15	42	40	80	76
7	26/M	76	70	98	86	2.6	2.7	178	148	12	13	14	14	66	38	108	98
8	44/M	76	72	84	78	2.5	2.6	148	126	14	14	16	15	44	24	82	46
9	30/M	70	68	86	80	2.9	2.9	130	134	14	13	14	14	34	30	92	88
10	28/M	76	68	84	82	3.1	3.2	200	164	12	12	13	12	90	54	170	128
Mean	34	75	71	89	83	2.8	2.9	163	148	16	16	16	16	55	41	103	86
±SD	± 14	± 3	± 7	± 5	± 4	± 0.2	± 0.2	± 2.2	± 12	± 4	± 6	± 2	± 5	± 19	± 11	± 32	± 24

Abbreviations: C, control; CI, cardiac index; D, diltiazem; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; LVOG, left ventricular outflow gradient; LVSP, left ventricular peak systolic pressure; PAWP, mean pulmonary artery wedge pressure; PLOG, provocable left ventricular outflow gradient; MAP, mean arterial pressure; SD, standard deviation.
*Experienced pulmonary edema.

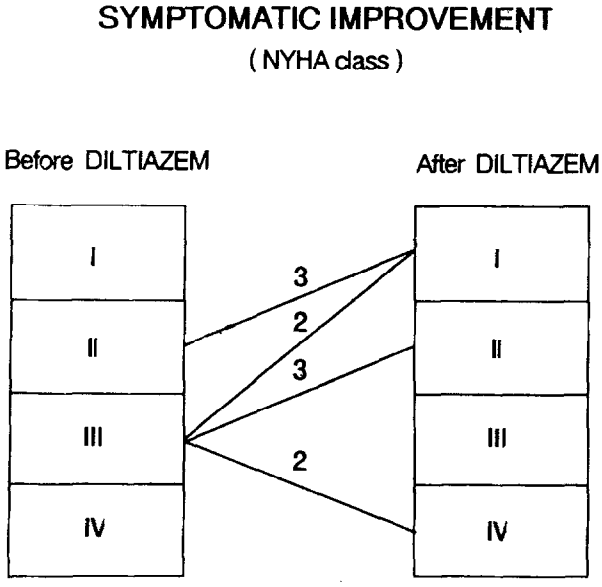

Fig. 1. Functional status after 3 weeks of treatment with diltiazem in a patient with hypertrophic obstructive cardiomyopathy.

Table II. Hemodynamic effects of diltiazem in cases 1, 2, 7, 8, and 10

	Control (n = 5)	Diltiazem (n = 5)	p Value
Heart rate (beat/min)	76 ± 1	70 ± 3	<0.05
Mean arterial pressure (mm Hg)	90 ± 6	84 ± 4	<0.05
Cardiac index (L/min/m²)	2.7 ± 0.2	2.8 ± 0.2	NS
Mean pulmonary artery wedge pressure (mm Hg)	14 ± 3	14 ± 2	NS
Left ventricular outflow gradient (mm Hg)	65 ± 19	41 ± 12	<0.05
Provocable outflow gradient (mm Hg)	120 ± 38	89 ± 30	<0.01
Left ventricular peak systolic pressure (mm Hg)	175 ± 21	149 ± 5	<0.05

or absence of chest pain or presyncope was documented. Seven patients were in functional class III, and the remainder were in class II. Three patients in the class III group also complained of effort presyncope and chest pain. No patient had received any, β-blocker or calcium antagonist before the study. No patient had a basal outflow gradient of less than 30 mm Hg.

Left ventricular pressure was obtained through a fluid-filled catheter system by the retrograde femoral technique. Catheter entrapment was excluded in all cases. The left ventricular outflow tract gradient was measured at rest and after provocation with the Valsalva maneuver, ventricular ectopics and isoproterenol infusion to a heart rate of 120 beats per minute. Cross-sectional echocardiographic studies were performed on a Diasonics Cardiovue 3400 R echocardiograph (Diasonics, Inc., San Francisco, Calif.) with a 2.5 MHz 80 degree wide angle transducer. Phonocardiogram was recorded to define aortic valve closure. All patients were examined in the left lateral decubitus position. The left ventricular isovolumic relaxation time was calculated as the interval between aortic valve closure and opening of the mitral valve. After the various hemodynamic and echocardiographic indices were recorded, each patient received 60 mg oral diltiazem three times a day. After 3 weeks, the patients were re-evaluated by catheterization and echocardiography with the same protocol as used in the

Table III. Effect of diltiazem on isovolumic relaxation time (msec)

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean ± SD*
Control	88	100	92	86	94	102	96	85	102	84	92 ± 7
Diltiazem	64	66	—	86	66	76	68	52	58	68	67 ± 10

$p < 0.01$.

first study. Data were analyzed statistically with a Student's t test.

Two patients with hypertrophic obstructive cardiomyopathy experienced pulmonary edema while being treated with diltiazem. These were patients Nos. 3 and 4 (a 52-year-old woman and an 18-year-old man) (Table I and Fig. 1). Repeat catheterization in the young male patient (the woman refused repeat investigation) revealed a rise in pulmonary artery wedge pressure and left ventricular end-diastolic pressure from 22 to 32 mm Hg and from 19 to 28 mm Hg respectively, without any significant change in the left ventricular outflow gradient or the isovolumic relaxation time. The catheterization was performed without intervention for pulmonary edema. The basal and inducible gradients were significantly reduced in five patients (Table II) with little change in the remaining three. Improvement in outflow obstruction was accompanied by a fall in left ventricular systolic pressure. There was, however, no significant change in cardiac index and mean pulmonary artery wedge pressure. Isovolumic relaxation time decreased significantly in patients with symptomatic improvement from 92 ± 7 msec to 67 ± 10 msec ($p < 0.01$) Table III.

This study demonstrates significant reduction in the basal left ventricular outflow obstruction in five of 10 patients with hypertrophic obstructive cardiomyopathy who were being treated with oral diltiazem. Isovolumic relaxation time in hypertrophic cardiomyopathy depends on both rate and magnitude of pressure drop from aortic valve closure to mitral valve opening. In the presence of a markedly delayed aortic closure sound or reverse splitting of the second heart sound, the isovolumic relaxation time may be short or actually zero, and consequently, unreliable.[2] In this study, however, all patients demonstrated prolonged basal relaxation periods before the administration of diltiazem.

However, two patients experienced pulmonary edema, and both had a pulmonary artery wedge pressure >20 mm Hg. Although diltiazem reduced isovolumic relaxation, there was no evidence of any clinically important effect on pulmonary wedge pressure or cardiac index in any patient in the study, and it was actually deleterious in the two patients with the highest filling pressures. But because both of these patients started with the highest filling pressures, it is difficult to conclude that their conditions worsened because of diltiazem. However, both patients felt better on withdrawal of diltiazem, and the patient who consented to repeat catheterization deteriorated once again when diltiazem was readministered after a span of 10 days. Hence there is a strong suggestion that pulmonary edema may occur in association with diltiazem in certain patients with hypertrophic obstructive cardiomyopathy.

The only hemodynamic variable that was predictive of pulmonary edema was the raised pulmonary artery wedge pressure. Neither the basal outflow gradient nor the isovolumic relaxation time differ significantly from those in the other patients under control conditions. The patients who tolerated diltiazem in the study were those with the lowest left ventricular filling pressures. The pulmonary edema in these two patients was not precipitated by an increase in left ventricular outflow obstruction or a fall in systemic pressure as has been noted with the use of verapamil.[3] The most likely explanation is a direct negative inotropic effect of diltiazem on the myocardium. There are anecdotal reports of pulmonary edema developing after administration of both verapamil and nifedipine due to negative inotropic potential in patients with nonobstructive hypertrophic cardiomyopathy.[3] These reports help to remind us that although some patients with hypertrophic cardiomyopathy have normal to supernormal indexes of global left ventricular systolic function, they may paradoxically have diminished myocardial contractility due to reduced end-systolic stress.[4]

Pulmonary edema with diltiazem in hypertrophic cardiomyopathy has not been previously reported. A double-blind comparative study[5] has indicated that the use of diltiazem may be preferable to verapamil in the management of patients with hypertrophic cardiomyopathy because, besides being equally effective, it produced fewer side effects. However, no patient in the study began with a markedly elevated left ventricular end-diastolic pressure. Intravenous diltiazem has been shown to prevent exercise-induced increase in pulmonary artery diastolic pressure in patients with hypertrophic cardiomyopathy.[6] However, in this Japanese study, there was one patient (age, sex, and type of hypertrophic cardiomyopathy not elaborated) whose pulmonary diastolic pressure increased more on exercise with diltiazem than on exercise without diltiazem. The basal pulmonary diastolic pressure was almost 30 mm Hg.[6] Suwa, Hirota, and Kewamusa[7] demonstrated improved left ventricular diastolic function, whereas lessening of diastolic abnormality on mild exercise with oral diltiazem has been detected with pulsed Doppler echocardiography.[8] These studies have been short-term, involving only a few patients, and did not include left heart catheterization. This study, though describing a reduction in left ventricular outflow gradient in some patients and improvement in isovolumic relaxation in most, highlights the potential danger of administering diltiazem to patients with left ventricular filling pressures greater than 20 mm Hg. There was no instance of sinus node suppression or atrioventricular nodal defect. It is still unclear as to which clinical parameter or echocardiographic variable best iden-

tifies patients most likely to experience pulmonary edema. Moreover, clinical symptoms are notoriously subjective and may not correlate with left ventricular filling pressures. Hence, until further data are acquired, diltiazem should be used with extreme caution in patients who have hypertrophic obstructive cardiomyopathy with markedly raised pulmonary artery wedge pressures.

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