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Effect of Nitroglycerin During Hemodynamic Estimation of Valve Orifice in Patients With Mitral Stenosis

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In patients with mitral stenosis, valve orifice calculations using pulmonary capillary wedge pressure as a substitute for left atrial pressure may overestimate the severity of disease. Previous studies have shown that mitral valve area determined from transseptal left atrial pressure measurements exceeds that area derived from pulmonary wedge pressure measurements. This is probably due to pulmonary venoconstriction, which is reversed by nitroglycerin. Nitroglycerin, 0.4 mg, was administered sublingually to 20 patients with mitral valve disease during preoperative cardiac catheterization using the pulmonary capillary wedge pressure as the proximal hydraulic variable. At the time of peak hypotensive effect, 3 to 5 minutes after nitroglycerin administration, the mean pulmonary capillary wedge pressure decreased from 23 ± 2 (mean ± SEM) to 19 ± 2 mm Hg ($p < 0.005$). The mean diastolic transmitral pressure gradient (12.6 ± 1.2 mm Hg before and 11.5 ± 1.0 mm Hg after nitroglycerin; p = NS) and cardiac output (4.0 ± 0.3 to 4.1 ± 0.3 liters/min; p = NS) did not change significantly. Nevertheless, the hemodynamic mitral orifice area, calculated using the Gorlin formula, increased from 0.8 ± 0.1 to 1.1 ± 0.2 cm² ($p < 0.05$). In 12 patients with isolated mitral stenosis, without regurgitation, the mitral valve orifice area after nitroglycerin was 0.4 ± 0.2 cm² larger than it was before drug administration ($p < 0.05$).

Administration of nitroglycerin during evaluation of mitral stenosis eliminates pulmonary venoconstriction, which raises the pulmonary capillary wedge pressure above the left atrial pressure in some patients. Nitroglycerin may add diagnostic accuracy without transseptal catheterization. Whether this response to nitroglycerin has direct therapeutic value in patients with mitral valve obstruction has yet to be determined.

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Application of hydraulic formulas to the determination of the severity of mitral stenosis depends on the faithfulness with which left atrial pressure is reflected in the pulmonary capillary wedge pressure. Under certain circumstances of pulmonary hypertension, pulmonary venoconstriction can increase the pulmonary wedge pressure above left atrial pressure, leading to overestimation of the severity of mitral valve obstruction (1). Discrepancies of this sort have been reported (2) to produce errors ranging up to 27 mm Hg in mitral valve pressure gradient determinations and errors up to 1.5 cm² in mitral orifice area calculations although differences are usually much smaller. To avoid this source of error, direct left atrial catheterization is employed in some laboratories using methods such as the transseptal puncture technique, but these are relatively difficult and sometimes dangerous (3). We have recently demonstrated in postoperative patients (4) that sublingual administration of nitroglycerin produces prompt dilation of the pulmonary veins or microcirculation, reducing the pulmonary venous gradient, which can spuriously separate pulmonary wedge and left atrial pressures. The present study was undertaken to determine whether the improved agreement between pulmonary wedge and left atrial pressures produced by nitroglycerin might have significant hemodynamic impact on effective orifice and flow characteristics during diagnostic cardiac catheterization in patients with a clinical diagnosis of mitral stenosis.

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Methods

Study patients (Table 1). Twenty patients with clinical and echocardiographic features of mitral valve disease were studied during preoperative cardiac catheterization. Informed consent was obtained from each patient in accordance with institutional guidelines. There were 4 men and 16 women, ranging in age from 26 to 74 years (average 50 ± 4). Mitral stenosis was accompanied by cineangiographic evidence of mitral regurgitation in five cases; there was associated aortic valve disease in nine and tricuspid disease in two. In 12 patients, mitral stenosis was not accompanied by a significant regurgitant valvular lesion, and results in these cases were subjected to supplementary analysis. Eight patients had sinus cardiac rhythm and 12 had atrial fibrillation.

Instrumentation and measurements. A transvenous 7F Swan-Ganz catheter was positioned in a pulmonary artery segment in each case and pulmonary capillary wedge pressure was verified by examination of pulse wave configuration and by oximetry of blood sampled through the occluding catheter. A 7F catheter was also positioned in the left ventricular cavity for measurement of systolic and diastolic pressures. Both left and right heart pressures were measured using fluid-filled catheters connected to equisensitive Statham P23Db transducers that were independently calibrated against a mercury column with the zero reference at the level of the midaxillary line. Pressure waveforms and a simultaneous electrocardiographic (ECG) signal were displayed and recorded on an Electronics for Medicine multichannel photographic recorder before and after reversal of the transducers to minimize the systematic error of measurement. The left ventricular catheter was employed for measurement of systolic blood pressure except in Patient 8 (with associated aortic stenosis) in whom direct proximal aortic pressure was measured.

The mean pulmonary artery and mean pulmonary capillary wedge pressures were determined by electronic integration of phasic signals. The diastolic transmitral pressure gradient was determined by planimetry of waveform transcriptions throughout the diastolic filling period over 10 consecutive beats during cyclic respiration, after transposing the pressure tracings to correct for phase delay. Transmitral blood flow was estimated by right heart thermodilution technique, using an American Edwards Laboratories model 9520A cardiac output computer, averaging at least three replicate determinations differing by <10%.

Hemodynamic formulas. Mitral valve orifice was calculated according to the formula:

$$MVA = (MVF/38\sqrt{MVG}),$$

where MVA = mitral valve area in cm^2, MVF = mitral flow determined by dividing the diastolic filling period in seconds/min into cardiac output in ml/min and MVG = mean mitral diastolic gradient in mm Hg.

The total pulmonary vascular resistance (TPR) in dynes·s·cm^{-5} was calculated as

$$TPR = (\overline{PA} \times 80/CO),$$

Table 1. Clinical Characteristics of the 20 Patients

Patient No.	Age (yr) & Sex	Diagnosis	Rhythm	MR
1	41F	MS	AF	0
2	55M	MS, TVD	AF	0
3	73M	MS, MR	SR	1+
4	65F	MS, AVD	AF	0
5	74F	MS	AF	0
6	37F	MS, AVD	SR	0
7	48F	MS, AVD	AF	0
8	31F	MS, AVD	SR	0
9	36F	MS, MR	AF	4+
10	44F	MS	AF	0
11	28M	MS, AVD	SR	0
12	50F	MS, MR	SR	2+
13	56M	MS, TVD, AVD	AF	0
14	67F	MS, MR, AVD	AF	3+
15	74F	MS, MR, AVD	AF	2+
16	26F	MS	SR	0
17	58F	MS, AVD	AF	0
18	37F	MS	AF	0
19	61F	MS	SR	0
20	42M	MS	SR	0

AF = atrial fibrillation; AVD = aortic valve disease; F = female; M = male; MR = mitral regurgitation (graded 0 to 4+); MS = mitral stenosis; SR = sinus rhythm; TVD = tricuspid valve disease.

where $\overline{PA}$ = mean pulmonary artery pressure in mm Hg and CO = cardiac output in liters/min.

Pulmonary "arteriolar" resistance (PAR) in dynes·s·cm^{-5} was defined as

$$PAR = [(\overline{PA} - \overline{PW})80/CO],$$

where $\overline{PW}$ = the mean pulmonary capillary wedge pressure in mm Hg (5).

Drug intervention. Cardiovascular medications were withheld in each case for at least 8 hours before hemodynamic study in the laboratory. Stable baseline hemodynamic status was verified by repeated measurements over 20 minutes. Each patient was then given nitroglycerin, 0.4 mg sublingually, and measurements of pressure and flow were repeated within the time of peak systemic hypotensive effect. This dose of nitroglycerin was repeated 5 to 10 minutes later when mean arterial pressure did not decrease at least 5 mm Hg after the first dose.

Statistics. Results were expressed as the mean ± SEM for measured and derived data in all patients and in those with isolated mitral stenosis. Drug-induced changes were evaluated by the Student's *t* test for paired variables. Significance was accepted at a confidence level of 95% ($p \leq 0.05$).

Results

Hemodynamics. Hemodynamic data obtained at baseline and during the peak systemic hypotensive effect of sublingual nitroglycerin are displayed for each patient in Table 2. Systolic left ventricular pressure was normal in most of these cases before intervention, but moderate pulmonary artery hypertension was generally present. The pulmonary capillary wedge pressure was elevated, but the left ventricular end-diastolic pressure was within the normal range in these patients with predominant mitral stenosis. Valvular obstruction was, on average, moderately severe, with valve areas in the range of 0.8 cm^2. This constitutes an essentially minimal estimate in patients with associated valvular regurgitation.

Systolic left ventricular/arterial blood pressure decreased with nitroglycerin administration from 127 ± 5 to 118 ± 5 mm Hg ($p < 0.005$). Cardiac output was preserved (4.0 ± 0.3 liters/min before and 4.1 ± 0.3 liters/min after nitroglycerin (p = NS) and there was a slight increase in heart rate (80 ± 4 to 84 ± 4 beats/min; $p < 0.005$). The stroke volume index, however, did not increase (31 ± 2 to 30 ± 2 ml/beat per m^2; p = NS).

The mean pulmonary capillary wedge pressure decreased from 23 ± 2 to 19 ± 2 mm Hg ($p < 0.005$) after nitroglycerin, whereas the left ventricular end-diastolic pressure decreased from 8 ± 1 to 6 ± 1 mm Hg ($p < 0.005$; Fig. 1). The mean pulmonary artery pressure decreased from 33 ± 3 to 29 ± 3 mm Hg ($p < 0.005$) as a result of drug intervention. The total pulmonary resistance decreased from 685 ± 69 dynes·s·cm^{-5} before to 653 ± 65 dynes·s·cm^{-5} after nitroglycerin ($p < 0.005$), whereas pulmonary "arteriolar" resistance was 262 ± 54 dynes·s·cm^{-5} before and 213 ± 31 dynes·s·cm^{-5} after pharmacologic intervention (p = NS).

Mitral valve pressure gradient and calculated valve area. The mean diastolic transmitral pressure gradient decreased from 12.6 ± 1.2 to 11.5 ± 1.0 mm Hg (p = NS) after nitroglycerin administration. It decreased in 11 of the total group of 20 patients and in 8 of the 12 patients with isolated mitral stenosis. The relation among mitral flow, gradient and area is displayed in Figure 2. Representative hemodynamic recordings from one patient with pure mitral stenosis (Case 10) before and after administration of sublingual nitroglycerin are presented in Figure 3. For the group as a whole the calculated effective mitral orifice area increased from 0.8 ± 0.1 to 1.1 ± 0.2 cm^2 ($p < 0.05$) after nitroglycerin administration, and the average increase was 10%. In patients with mitral stenosis and no mitral regurgitation, the calculated mitral valve area increased an average of 0.4 ± 0.2 cm^2 after nitroglycerin, but in some patients with severe stenosis there was no increase (Fig. 4).

Discussion

Pulmonary wedge-left atrial pressure relation. In the 35 years since Hellems et al. (6) first described human pulmonary capillary wedge pressure, numerous investigators have reported a close correlation between this pressure and directly measured left atrial pressure. As a consequence, pulmonary wedge pressure measurements have become the standard method of estimating left atrial pressure in most cardiac catheterization laboratories. It has long been appreciated, however, that this correlation is occasionally faulty. Luchsinger et al. (7) found pulmonary capillary wedge pressure on average to be 35% higher than mean left atrial pressure. In patients with mitral valve disease, several investigators (8,9) measured pulmonary capillary wedge pressure simultaneously with left atrial pressure and found differences ranging from negligible values to nearly 11 mm Hg, but more often in the range of 5 to 7 mm Hg. When the pulmonary capillary wedge pressure exceeded 10 mm Hg, considerable variation between these values was observed in patients undergoing diagnostic cardiac catheterization (10).

More recently, it has been demonstrated (11) that although mean pulmonary capillary wedge pressure closely approximates mean left atrial pressure over a wide range, important overestimation of the mitral valve gradient may occur in patients with mitral valve disease and this discrepancy has been attributed to the less rapid *y* descent of phasic pulmonary wedge pressure than of left atrial pressure pulse form. Hence, although the pulmonary capillary wedge pres-

Table 2. Hemodynamic Data Before and After Nitroglycerin in 20 Cases

Patient No.	Nitroglycerin	PW	LVEDP	PA	SAP	HR	CO	MVG	MVA	SVI	TPR	PAR
1	Before	—	16	—	128	78	4.5	11.4	1.21	29	—	—
	After	—	9	—	123	78	4.7	10.7	1.24	30	—	—
2	Before	25	13	34	147	69	3.7	13.3	0.58	36	604	195
	After	19	6	35	149	72	3.7	13.7	0.64	34	596	350
3	Before	27	9	40	100	72	3.1	17.1	0.41	25	865	335
	After	24	8	34	85	72	3.8	15.9	0.46	30	735	211
4	Before	14	7	18	139	78	3.0	5.4	0.67	27	480	107
	After	11	4	14	116	78	2.3	5.9	0.63	20	487	104
5	Before	19	5	35	123	72	2.4	10.5	0.42	23	1,167	533
	After	18	7	27	106	84	2.1	8.2	0.33	17	1,029	343
6	Before	26	11	35	128	96	6.9	12.5	0.98	38	406	720
	After	22	9	32	123	108	6.3	9.4	1.40	31	406	127
7	Before	33	3	45	160	124	3.2	22.3	0.46	15	1,125	300
	After	24	3	35	136	126	3.1	18.9	0.45	15	903	335
8	Before	23	12	28	140	80	6.0	9.4	2.10	47	373	67
	After	—	5	—	140	84	7.4	11.8	3.90	55	—	—
9	Before	—	8	—	100	78	4.2	13.5	0.95	30	—	—
	After	20	6	—	100	78	5.2	13.7	1.00	38	—	—
10	Before	17	3	—	121	102	4.3	18.0	0.93	30	—	—
	After	10	3	—	132	102	3.9	6.1	3.40	27	—	—
11	Before	—	9	—	100	66	4.5	12.0	0.91	38	—	—
	After	20	9	—	93	60	4.3	14.7	0.71	40	—	—
12	Before	24	14	26	120	71	3.7	11.6	1.08	27	562	43
	After	—	7	—	100	77	3.8	10.1	1.20	26	—	—
13	Before	30	5	38	95	84	3.9	18.7	0.55	26	779	164
	After	28	5	38	104	84	3.9	14.8	0.59	26	779	205
14	Before	10	8	18	114	78	1.9	2.7	0.57	17	758	337
	After	10	9	15	126	72	1.9	2.9	0.59	19	632	211
15	Before	28	9	—	183	78	2.7	10.5	0.43	24	—	—
	After	27	9	—	176	84	2.9	13.3	0.45	24	—	—
16	Before	30	6	36	105	90	5.8	18.4	0.82	41	497	83
	After	21	2	—	108	108	5.8	18.5	0.90	34	—	—
17	Before	—	15	29	142	48	2.7	7.5	0.55	40	859	—
	After	—	13	27	123	54	3.2	10.6	0.42	42	675	—
18	Before	11	9	15	119	54	4.5	4.3	1.70	51	267	71
	After	8	6	14	103	60	4.8	3.4	2.10	49	233	100
19	Before	19	2	32	150	78	3.9	12.9	0.64	29	656	267
	After	17	0	24	126	90	3.8	11.3	1.10	25	505	147
20	Before	32	4	65	117	108	5.9	19.9	1.00	33	881	447
	After	—	1	50	108	114	4.7	15.5	0.82	25	851	—
Mean	Before	23	8	33	127	80	4.0	12.6	0.8	31	685	262
± SEM		± 2	± 1.0	± 3	± 5	± 4	± 0.3	± 1.2	± 0.1	± 2	± 69	± 54
	After	19	6	29	118	84	4.1	11.5	1.1	30	653	213
		± 2	± 1.0	± 3	± 5	± 4	± 0.3	± 1.0	± 0.2	± 2	± 65	± 31
p Value		<0.005	<0.005	<0.005	<0.005	<0.005	NS	NS	<0.05	NS	<0.005	NS

CO = cardiac output (liters/min); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); MVA = mitral valve orifice area (cm^2); MVG = mean diastolic transmitral pressure gradient (mm Hg); PA = mean pulmonary artery pressure (mm Hg); PAR = pulmonary arteriolar resistance ($dynes \cdot s \cdot cm^{-5}$); PW = mean pulmonary capillary wedge pressure (mm Hg); SAP = systolic left ventricular/arterial pressure (mm Hg); SVI = stroke volume index (ml/beat per m^2); TPR = total pulmonary resistance ($dynes \cdot s \cdot cm^{-5}$).

sure has been used as a substitute for left atrial pressure measurement to determine mitral valve orifice area in patients with mitral stenosis, the possible inequality of these readings could be a source of clinically important error.

Schoenfeld et al. (12) compared estimates of mitral hemodynamics using pulmonary capillary wedge pressure and direct transseptal catheterization of the left atrium in patients with a prosthetic mitral valve and symptoms of congestive heart failure. The diastolic gradient across the prosthetic valve was overestimated when pulmonary wedge rather than direct left atrial pressure measurement was used, and the calculated mitral valve prosthetic orifice area was underestimated by the pulmonary wedge determination. These findings were attributed either to the phase delay of the

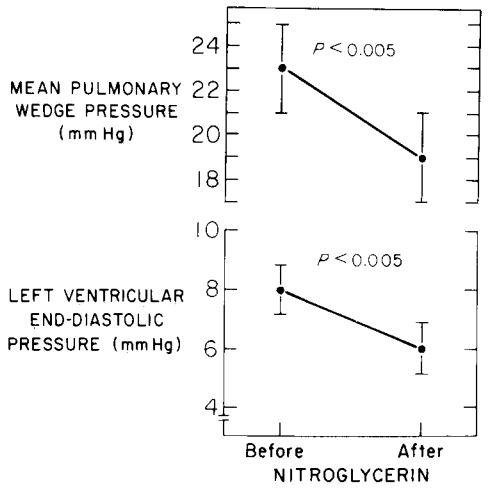


Figure 1. Mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure in 20 patients with mitral valve disease at cardiac catheterization, before and after administration of sublingual nitroglycerin (mean ± SEM).

pulmonary wedge *V* waves relative to the atrial *V* waves, resulting in higher indirect estimates of mean diastolic left atrial pressure, or to faulty wedge determinations in the setting of pulmonary hypertension. In our study, left atrial pressure was not measured directly, and comparison with results obtained by transseptal, transbronchial or retrograde transmitral catheterization of the atrium must be made cautiously. The results of both studies (the present one and that

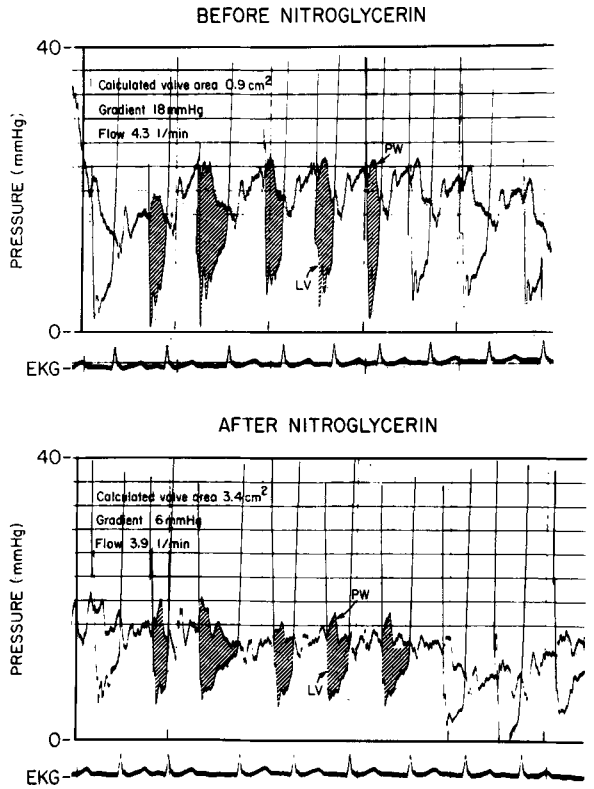


Figure 3. Simultaneous pulmonary wedge (PW) and left ventricular (LV) pressure waveform recordings obtained from one patient before and after nitroglycerin administration. Despite the modest decline in mitral flow in this case, the effective valve area increased from 0.9 to 3.4 cm^2. EKG = electrocardiogram.

Figure 2. Calculated effective mitral valve area, mean diastolic pulmonary wedge-left ventricular pressure gradient (determined by graphic planimetry) and cardiac output before and after nitroglycerin in 20 patients with mitral valve disease (mean ± SEM).

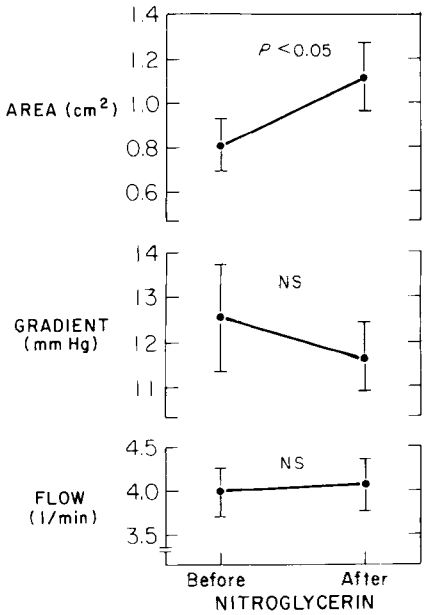
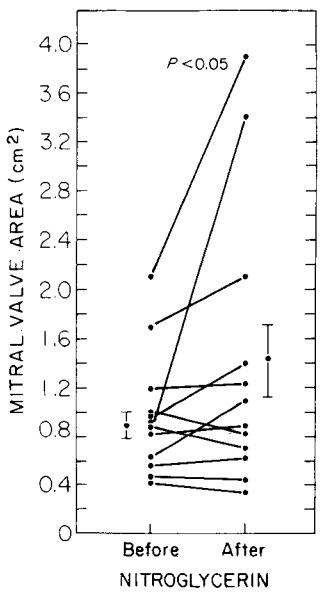


Figure 4. Effective mitral valve area in each of 12 patients with mitral stenosis and no mitral regurgitation, before and after nitroglycerin. In several patients with severe stenosis there was no change in calculated valve orifice, but substantial changes occurred in patients with less severe disease.



of Schoenfeld et al. [12]) nevertheless support the contention that mitral area calculations based on pulmonary capillary wedge pressure readings in the absence of nitroglycerin may underestimate the hemodynamic area. The actual mechanical valve orifice, however, has eluded precise direct measurement even in surgical cases of rheumatic mitral stenosis.

Pulmonary venous hemodynamics. We have previously demonstrated (4), in patients after mitral valve replacement surgery, that the pulmonary capillary wedge pressure may exceed left atrial pressure and that this discrepancy is due to reversible constriction of the pulmonary veins or microcirculation, which is reversed by nitroglycerin. In animal studies conducted over two decades ago (13), the decrease in pressure between the pulmonary venules and left atrium was shown to account for up to half the total gradient between the pulmonary artery and left atrium. In our previous work (4), nitroglycerin administered sublingually produced prompt pulmonary venodilation, reduced the pulmonary venous gradient and brought the pulmonary capillary wedge pressure into closer agreement with left atrial pressure. It was this observation that formed the basis for the present investigation.

Action of nitroglycerin. The vasodilator effects of nitroglycerin, although more pronounced on peripheral veins, nevertheless result in lowering of left ventricular filling pressure by reducing both venous return and peripheral resistance. However, Mookherjee et al. (14) noted that nitroglycerin produces pulmonary vasodilation even when cardiac output and systemic vascular resistance are unchanged. Hence, pulmonary artery pressure and pulmonary capillary wedge pressure decrease after administration of nitroglycerin in patients with congestive heart failure as a result of a decrease in both left atrial pressure and aortic impedance to left ventricular ejection. Direct pulmonary arteriolar dilation may also be contributory, and the use of nitroglycerin has been advocated in patients with severe pulmonary hypertension (15).

Clinical implications. Clinical application of hydraulic formulas, such as that devised by Gorlin and Gorlin (16), to the determination of the severity of mitral stenosis depends in large part on the faithfulness with which left atrial pressure is reflected in the pulmonary capillary wedge pressure. Pulmonary venoconstriction in cases of pulmonary hypertension could increase the regional resistance to blood flow independent of arteriolar or atrial tone, leading to overestimation of the severity of mitral stenosis as reported by several investigators. This method presumes a single level of stenosis, namely, that at the mitral orifice. Because available data suggest an additional level of disequilibrium between pulmonary capillary wedge pressure and left heart diastolic pressure at the level of the pulmonary veins or microcirculation, calculations based on pulmonary capillary wedge pressure measurements may give rise to potentially large errors in mitral gradient estimations and underestimation of mitral valve areas by as much as 1.5 cm^2.

The results of this study suggest that the administration of nitroglycerin during the evaluation of mitral stenosis lessens the pulmonary venoconstriction which raises pulmonary wedge pressure above left atrial pressure in some patients. Nitroglycerin produces changes in estimated proximal (pulmonary wedge/left atrial) pressure, diastolic gradient and effective valve area, which are analogous to those obtained during direct left atrial catheterization using transseptal technique. It might be argued, therefore, that administration of sublingual nitroglycerin should be incorporated in the routine hemodynamic evaluation of patients with suspected mitral valve disease, and might avoid the occasional need for transseptal puncture, because the latter technique carries the risk of aortic perforation and intrathoracic hemorrhage (17). Lowering of pulmonary artery and pulmonary capillary wedge pressures while preserving cardiac output may also have direct therapeutic value in some patients with this form of valvular heart disease. Whether clinical benefit accrues from such intervention, however, remains to be determined from placebo-controlled trials.

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