Response of the left ventricle to nitroglycerin in patients with and without mitral regurgitation¹

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Left ventricular cineangiographic volumes and haemodynamics were measured before and after nitroglycerin in 17 patients. The average end-diastolic volume was reduced by nitroglycerin from 82 to 69 ml/m² ($P < 0.001$) in 8 patients without mitral regurgitation and from 159 to 116 ml/m² ($P < 0.005$) in 9 patients with mitral regurgitation. The haemodynamic response, however, differed in the two circumstances. Whereas nitroglycerin increased the average ejection fraction from 0.53 to 0.64 ($P < 0.01$) in the patients without mitral regurgitation, the ejection fraction was decreased by the drug from 0.65 to 0.52 ($P < 0.005$) in the mitral regurgitation patients. However, the forward cardiac output was not changed by nitroglycerin; the reduction in ejection fraction in the patients with mitral regurgitation must therefore have been due to a reduction in backflow into the left atrium. This indicates that nitroglycerin reduced the severity of mitral regurgitation in association with (and probably as a result of) a reduction in heart size.

Mean circumferential fibre shortening rate was reduced ($P < 0.05$) by nitroglycerin in 5 of the patients with mitral regurgitation who also had coronary artery disease but not for this group of patients as a whole, nor for the group without mitral regurgitation (all with coronary artery disease). Average left ventricular end-diastolic pressure was reduced by nitroglycerin in the patients without mitral regurgitation ($P < 0.01$) but not in the patients with mitral regurgitation.

Although nitroglycerin has been used clinically since 1879, its haemodynamic consequences remain incompletely defined. The beneficial effect of nitroglycerin in angina has been ascribed to mechanisms which either reduce myocardial oxygen consumption by decreasing preload or afterload (Gorlin *et al.*, 1959; Marchetti, Merlo, and Antognetti, 1964; Perloff, Ronan, and de Leon, 1965) or improve the manner in which oxygen supply reaches the myocardium (Fam and McGregor, 1964).

Energy requirements in the intact heart are determined to a significant degree by ventricular size (Braunwald, 1969). Although two studies have shown a reduction in ventricular dimensions with nitrates (Lee, Sung, and Zaragoza, 1970; Williams, Glick, and Braunwald, 1965), no angiographic estimation of left ventricular volumes has been performed in the presence of nitroglycerin. In addition, since many patients taking nitroglycerin may have papillary muscle dysfunction or mitral regurgitation from other causes, it seemed pertinent to inquire

whether the effect of the nitrate on ventricular performance could be influenced by such preloaded states.

The present study was designed therefore to determine: (a) the effect of nitroglycerin on left ventricular volumes obtained by cineangiography and (b) the influence nitroglycerin may have on ventricular dimensions and haemodynamics in patients with and without mitral regurgitation.

Subjects and methods

Seventeen patients studied at the time of diagnostic cardiac catheterization were divided into two groups. Group 1 consisted of 8 patients without demonstrable mitral regurgitation, all of whom were suffering from angina and displayed angiographic evidence of coronary artery disease. Group 2 consisted of 9 patients with clinically and angiographically documented mitral regurgitation: 4 of these patients had coronary artery disease with papillary muscle dysfunction and 4 had isolated mitral regurgitation secondary to rheumatic heart disease; the remaining patient in this group (Case 13, Table) had both rheumatic mitral regurgitation and severe stenosis of the left anterior descending coronary artery.

All patients were studied in the resting post-absorptive

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state after premedication with intramuscular pethidine, 50 mg, and oral diazepam, 10 mg. Catheterization of the left heart was performed via the transfemoral approach using a 100 cm multiple hole catheter. Left ventricular pressures were obtained with a Statham P23Db strain gauge transducer and recorded on a DR-8 Electronics for Medicine photographic recorder. Cine ventriculography was performed in the 30° right anterior oblique position. Each powered injection of contrast material consisted of 50–60 ml meglumine diatrizoate delivered over 4 seconds directly into the left ventricular cavity. After a recovery period of 15 minutes, 0.6 mg nitroglycerin was administered sublingually. Five minutes after complete absorption of the pill, the left ventricular cineangiogram was repeated in the same obliquity and with an identical amount of contrast material. Left ventricular systolic and end-diastolic pressures and heart rates were recorded immediately before each injection. All cineangiograms were taken during inspiration using a 23 cm Philips image intensifier tube and recorded on 35 mm film at 80 frames per second.

The vertical image-tube to table-top distance was carefully measured and recorded in each study. Ventricular volumes were determined from the single plane cineangiograms using the area-length method (Greene *et al.*, 1967) and corrected for image magnification. In each state, a corresponding sinus conducted beat within the first four cycles after injection was analysed. All dimensional values were corrected for body surface area.

The total ejection fraction (EF) was calculated as

$$EF = \frac{EDV - ESV}{EDV}$$

where EDV is end-diastolic volume and ESV end-systolic volume determined angiographically. In cases with mitral regurgitation the forward stroke volume was determined independently by the Fick method before and after nitroglycerin.

The mean rate of circumferential fibre shortening was defined as the extent of shortening of the calculated minor internal circumference between end-diastole and end-systole divided by the period of systolic ejection. Since this period includes part of the isovolumic phase, 50 msec was subtracted from the total systolic period in all cases without mitral regurgitation (Karliner *et al.*, 1971).

All statistical comparisons were performed with Student's paired *t* test.

Results

The Table summarizes the dimensional and haemodynamic effects of nitroglycerin in patients with and without mitral regurgitation.

Effect on ventricular volume

The most consistent feature associated with nitroglycerin was the reduction in left ventricular end-diastolic volume in all patients studied (Fig. 1). This occurred in both groups despite the significant difference in average resting end-diastolic volumes; 82 ml/m² for group 1 and 159 ml/m² for group 2. In patients without mitral regurgitation, there was a corresponding reduction in the average end-systolic

TABLE I Effect of nitroglycerin on left ventricular volumes and haemodynamics

Case No.	Age	Sex	Diagnosis	Heart rate (beats/min)		Peak LV systolic pressure (mmHg)		LV end-diastolic pressure (mmHg)	
				Control	Nitroglycerin	Control	Nitroglycerin	Control	Nitroglycerin
Group 1: Without mitral regurgitation									
1	60	F	CAD†	83	69	170	150	14	4
2	48	M	CAD	81	69	122	115	10	4
3	44	M	CAD	82	94	125	115	8	3
4	64	F	CAD	62	66	112	89	8	8
5	48	M	CAD	80	95	188	180	16	10
6	48	M	CAD	71	79	124	129	18	16
7	58	M	CAD	65	65	105	110	24	20
8	60	F	CAD	88	86	158	145	8	8
Mean				77	78	138	129	13	9
				NS		P < 0.05		P < 0.01	
Group 2: With mitral regurgitation									
9	61	M	CAD	65	71	90	90	20	25
10	46	M	CAD	88	79	142	128	4	11
11	59	M	CAD	79	79	135	120	20	19
12	53	M	CAD	68	94	140	130	12	8
13	40	M	CAD	60	66	102	110	4	6
14	39	F	RHD‡	79	71	105	110	21	16
15	60	M	RHD	96	96	113	105	14	10
16	46	F	RHD	100	105	119	115	10	10
17	28	F	RHD	60	66	105	105	12	12
Mean				77	81	117	113	13	13
				NS		NS		NS	

Abbreviations: *Vcf = circumferential fibre shortening rate. †CAD = coronary artery disease. ‡RHD = rheumatic heart disease; NS = significance (*P* > 0.05).

volume from 38 to 26 ml/m², accounting for a significant increase in the mean ejection fraction from 0.53 to 0.64. Conversely, in patients with mitral regurgitation, the average end-systolic volume did

not change appreciably with nitroglycerin (64 to 65 ml/m²), whereas the total mean ejection fraction fell significantly from 0.65 to 0.52 (Fig. 1).

The initial size of the ventricular cavity did not appear to influence the results since the ejection fraction fell in those patients with mitral regurgitation in whom the end-diastolic volume was within normal limits.

Effect on regurgitant flow

The effect of nitroglycerin on the distribution of the total ejectate was determined in 4 patients with mitral regurgitation in whom Fick cardiac outputs were obtained in both states. Nitroglycerin produced only a slight and insignificant decrease in the effective cardiac index in patients without mitral regurgitation (3.2 to 3.0 l./m²). Similarly, the measured effective cardiac index in 4 patients with mitral regurgitation was unchanged with nitroglycerin (3.4 to 3.3 l./m²). However, since the ejection fraction in these cases fell with a concomitant decrease in end-diastolic volume (findings indicating a decreased stroke volume from the left ventricle) and since forward stroke volume through the aortic valve (as measured by the Fick method) was unchanged, the regurgitant volume must be considerably diminished after nitroglycerin. Indeed, in one patient after nitroglycerin, mitral regurgitation could not be de-

FIG 1 Effect of nitroglycerin on left ventricular end-diastolic volume and ejection fraction in patients without mitral regurgitation (solid circles) and patients with mitral regurgitation (open circles). Vertical bars represent standard error of the mean.

Effective index (ml/beat/m ²)	Mean Vcf* (circ/sec)		End-diastolic vol. (ml/m ²)		End-systolic vol. (ml/m ²)		Ejection fraction	
	Control	Nitroglycerin	Control	Nitroglycerin	Control	Nitroglycerin	Control	Nitroglycerin
40	1.41	1.97	69	58	25	18	0.64	0.69
45	1.52	1.08	94	69	44	24	0.53	0.65
43	1.38	1.38	86	70	44	27	0.49	0.61
44	0.92	1.18	81	69	40	25	0.51	0.64
24	1.33	1.43	42	35	24	11	0.43	0.69
47	0.70	1.35	98	89	49	42	0.50	0.53
48	0.39	0.64	94	83	52	35	0.45	0.58
54	1.62	1.50	93	77	28	23	0.70	0.70
43	1.16	1.32	82	69	38	26	0.53	0.64
NS	NS		P < 0.001		P < 0.001		P < 0.01	
34	0.60	0.35	306	210	211	176	0.31	0.16
37	3.46	1.90	70	43	7	6	0.90	0.86
32	0.91	0.37	173	141	110	109	0.36	0.23
54	1.95	0.82	140	100	54	46	0.61	0.54
60	2.01	1.68	194	120	31	60	0.84	0.50
53	0.74	0.84	147	102	49	49	0.67	0.52
74	1.95	1.88	155	140	48	66	0.69	0.53
47	0.88	1.30	82	70	25	23	0.70	0.67
95	1.14	1.16	162	147	43	52	0.74	0.65
54	1.52	1.14	159	116	64	65	0.65	0.52
< 0.005	NS		P < 0.005		NS		P < 0.005	

tected angiographically. While it is unfortunate that reduction of mitral regurgitation was not quantitated in all cases, we note that the directional changes induced by nitroglycerin in the end-diastolic volume and ejection fraction were uniform in all patients studied.

Effects on haemodynamics

In patients without mitral regurgitation, there were no significant alterations in heart rate, mean rate of circumferential fibre shortening, or stroke index (Table) with nitroglycerin. The peak left ventricular systolic pressure was reduced significantly.

In patients with mitral regurgitation, no significant change in heart rate or peak systolic left ventricular pressure with nitroglycerin was present at the time the angiograms were performed. Though the mean circumferential fibre shortening rate was only reduced from 1.18 to 1.14 circ/sec for the group, it was of interest that in all 5 patients with mitral regurgitation and coronary artery disease the mean circumferential fibre shortening rate decreased by 43 per cent from 1.79 to 1.02 cm/sec (Fig. 2) ($P < 0.05$).

FIG 2 Effect of nitroglycerin on the mean fibre shortening rate in patients without mitral regurgitation (solid circles), patients with mitral regurgitation secondary to coronary artery disease (open circles with central dot), and patients with rheumatic mitral regurgitation (open circles). Vertical bars are the standard error of the mean.

Discussion

In this study, administration of nitroglycerin to patients without mitral regurgitation resulted in reduction of ventricular dimensions, both at end-systole and end-diastole. Earlier studies by Mason

and Braunwald (1965) have shown that nitroglycerin causes venous vasodilatation, peripheral venous pooling, and reduction of external cardiac dimensions (Williams *et al.*, 1965). Lee *et al.* (1970) measured this effect by indicator dilution studies, and noted that in 9 patients end-diastolic volume and stroke volume were reduced by 26 and 27 per cent, respectively.

The present study using angiocardiology differs in design from those previously in that the effect of nitroglycerin is studied after the subsidence of tachycardia. It is noteworthy that ventricular volume remains reduced and that stroke volume is maintained by an increased ejection fraction. While not establishing the mechanism of action of nitroglycerin, these results confirm the previous observations and indicate further that reduction of ventricular volume (and presumably of oxygen consumption) persists beyond the phase of tachycardia.

However, the patients with mitral regurgitation responded differently. Nitroglycerin in all these patients did decrease end-diastolic volume, but the ejection fraction was now reduced. In 4 patients, forward cardiac output measured directly was unchanged and thus the degree of mitral regurgitation was reduced. One possible explanation is the opportunity for better coaptation of the mitral leaflets in the less dilated ventricle. Alternatively, with the reduced volume, normal segmental wall kinetics may be restored in patients with papillary muscle dysfunction.

Finally, we are unable to explain fully the apparent deterioration in ventricular haemodynamics in patients with ischaemia and mitral regurgitation after nitroglycerin. If the mitral valve is incompetent, the volume of the left ventricle diminishes rapidly with the onset of systolic contraction. According to Eckberg *et al.* (1973) almost 50 per cent of the regurgitant volume is delivered to the left atrium before aortic valve opening. But the energy cost of ventricular function is in part dependent on peak developed stress which occurs at or coincident with aortic valve opening (Mirsky, 1969; Burns *et al.*, 1971). Though end-diastolic volume was reduced after nitroglycerin, ventricular volume at aortic valve opening is not known and is perhaps unchanged or increased. Studies are in progress to test this hypothesis, since it may in part explain an unfavourable response to mitral valve replacement seen in some patients with ischaemic heart disease and mitral regurgitation.

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