Effect of sublingual nitroglycerin on cardiac performance in patients with coronary artery disease and non-dyskinetic left ventricular contraction

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In 8 patients with coronary artery disease and symmetrical left ventricular contraction, an echocardiographic study of left ventricular function was performed before and 3 minutes after the administration of 0.6 mg nitroglycerin sublingually. The left ventricular end-diastolic diameter decreased from 5.2 ± 0.2 to 4.9 ± 0.2 cm ($P < 0.05$) and the end-systolic diameter from 4.2 ± 0.2 to 3.7 ± 0.2 cm ($P < 0.001$). The estimated stroke volume did not change significantly, while the cardiac output increased, 5.8 ± 0.6 to 7.7 ± 0.6 l min⁻¹ ($P < 0.001$) and the heart rate increased from 72 ± 5 to 90 ± 6 ($P < 0.001$). The mean arterial blood pressure decreased from 105 ± 4 to 88 ± 3 mmHg ($P < 0.001$). The ejection fraction increased from 53 ± 3 per cent to 65 ± 6 per cent ($P < 0.001$) and the mean velocity of circumferential fibre shortening (V_{CF}) from 0.81 ± 0.05 to 1.15 ± 0.10 circumferences per second ($P < 0.001$). The estimated midsystolic midwall stress decreased from 155 ± 14 g cm⁻² to 102 ± 12 g cm⁻² after nitroglycerin ($P < 0.001$).

The administration of nitroglycerin was associated with a significant decrease in left ventricular preload and afterload. A vasodilating effect is suggested by the fall in peripheral resistance. The overall improvement in ejection fraction and V_{CF} may not reflect a true increase in contractility, because of the concomitant fall in wall stress.

Although nitrites have been used for more than a century for the relief of angina pectoris (Brunton, 1867), there is still considerable controversy surrounding their exact mode of action. It is uncertain whether nitroglycerin acts chiefly by coronary vasodilatation (Fam and McGregor, 1964; Becker, Fortuin, and Pitt, 1971; Cohen *et al.*, 1973; Goldstein, Stinson, and Epstein, 1973), or by the reduction of myocardial oxygen demands (Mason and Braunwald, 1965; Frick *et al.*, 1968; Ganz and Marcus, 1972). The myocardial oxygen consumption is principally dependent on three variables, the left ventricular wall stress, the heart rate, and the contractile state of the heart (Braunwald, 1971). The left ventricular systolic wall stress, or afterload, is in turn determined by the intracavitary systolic blood pressure, chamber size, and wall thickness.

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estimating left ventricular minor axis, particularly in serial studies, using a patient as his own control (Pombo, Troy, and Russell, 1971; Fortuin *et al.*, 1971; Gibson, 1973; Redwood, Henry, and Epstein, 1974). Though two recent investigations have shown a decrease in the echographic left ventricular dimension after nitroglycerin administration (DeMaria *et al.*, 1974; Burggraf and Parker, 1974), no reports have been published about its effects on estimated wall stress in man. In the present study, changes in left ventricular afterload after nitroglycerin were estimated, using calculations based on a thick-wall spherical model of the chamber. This method probably allows a closer assessment of changes in myocardial oxygen demand than pressure and volume measurements alone. Changes in afterload can then be correlated with concurrent changes in heart rate and in the mean velocity of internal dimension shortening, used as an index of contractility, thus providing an estimate of all three major determinants of myocardial oxygen consumption.

TABLE

Case No.	Age (y)	BSA (m ²)	Cardiac output* (l min ⁻¹)	Pressures (mmHg)		PA	Coronary arteries†		RCA%
				LV	Aorta		LAD%	LC%	
1	53	0.02	4.7	200/25	200/100	21/9	75	75	95
2	50	1.94	4.6	125/19	125/65	20/5	75	100	75
3	65	1.76	3.6	175/15	175/90	18/5	25	100	95
4	64	1.78	4.6	170/16	170/80	25/8	50	95	100
5	55	2.07	5.5	165/10	165/93	17/4	95	75	100
6	53	2.06	3.5	120/4	120/65	25/8	50	100	100
7	45	2.05	4.4	160/15	160/90	40/10	0	0	50
8	59	2.08	7.0	200/25	200/90	22/8	0	0	75

BSA, body surface area; LV, left ventricle; PA, pulmonary artery.

*The cardiac output was measured by the Fick method.

†The maximum percentage narrowings of the left anterior descending (LAD), left circumflex (LC), and right coronary arteries (RCA) are given.

Patients and methods

Eight men with ischaemic heart disease were selected for the study. Their ages ranged from 45 to 65 (Table). All had had cardiac catheterization less than a week before the non-invasive study. All the patients had symmetrical left ventricular contraction without dyskinetic areas. The relevant haemodynamic and angiographic data are presented in the Table. All the patients had previously used nitroglycerin successfully for angina pectoris. None was on digitalis or beta-adrenergic blocking agents at the time of the study.

For the echographic study, a Unirad 100 Series Diagnostic Echoscope was used with a Tektronix

174 strip-chart recorder. Standard procedures (Feigenbaum, 1973) were used for the identification and recording of the left ventricular dimension and posterior wall thickness. Simultaneously, an electrocardiographic lead showing clearly the onset of the QRS complex, an indirect carotid displacement curve, and a phonocardiogram, were recorded at a paper speed of 75 mm s⁻¹ (Fig. 1). The phonotransducer was placed over the third intercostal space at the left sternal edge. The low cut-off phonofilter was set at 100 Hz. The following systolic time intervals (STI) were calculated as described by Weissler, Harris, and Schoenfeld (1968): total electromechanical systole (QA2), left ventricular

FIG. 1 Echocardiographic recordings of left ventricular dimension before and after the administration of sublingual nitroglycerin (GTN). ECG, electrocardiogram; IVS, interventricular septum; CP, carotid pulse; PLVW, posterior left ventricular wall.

ejection time (LVET), and pre-ejection period (PEP). All the intervals were measured to the nearest 5 ms and the means of at least 5 cardiac cycles calculated.

Three control recordings were obtained during normal respiration, with the patients tilted at 20 degrees from the horizontal. The arterial blood pressure was measured twice with a sphygmomanometer. One nitroglycerin tablet (0.6 mg) was given sublingually. Recordings were obtained at 10-second intervals for 5 minutes and the blood pressure was measured at 30 s intervals. Care was taken to keep the position of the echotransducer constant during the study. The left ventricular end-diastolic dimension was measured 40 ms after the onset of the QRS complex and the end-systolic dimension at the time of minimum distance between the two endocardial surfaces. All the patients had normal septal motion.

The mean velocity of circumferential fibre shortening (V_{CF}) was estimated as:

$$V_{CF} = \frac{LVDD - LVSD}{LVDD \times LVET} \text{ (circumferences s}^{-1}\text{)}$$

where LVDD and LVSD represent the left ventricular end-diastolic and end-systolic dimensions. The left ventricular volume, stroke volume, and cardiac output were calculated as described by Fortuin *et al.* (1971). The mean arterial blood pressure was calculated as the diastolic blood pressure plus one-third of the pulse pressure. The total peripheral resistance was obtained by dividing the mean arterial blood pressure by the echographically estimated cardiac output. The left ventricular wall stress (σ) was estimated during mid-ejection from the equation:

$$\sigma = \frac{1 + b^3/2r^3}{b^3 - a^3} Pa^3$$

where P is the left ventricular systolic blood pressure, 'a' the inner radius of the left ventricle, and 'b' the outer radius, i.e. 'a' plus posterior wall thickness. The geometrical shape of the ventricle was thus assumed to be a thick-walled sphere (Mirsky, 1974). Mid-ejection was timed at LVET/2 before the aortic closure sound. The wall stress was calculated for the midwall of the left ventricle, substituting $(a+b)/2$ for r.

Student's t-test was used for the comparison of paired data.

Results

The results given are those for the control period and for 3 minutes after the administration of nitroglycerin, when the maximal changes in heart rate,

FIG. 2 Changes in heart rate, stroke volume, and cardiac output, after nitroglycerin.

arterial blood pressure, and left ventricular dimension occurred.

The systolic blood pressure decreased from 142 ± 7 (SEM) mmHg in the control period to 116 ± 7 mmHg ($P < 0.001$) and the diastolic pressure from 84 ± 3 to 74 ± 2 mmHg ($P < 0.001$). The calculated mean blood pressure also decreased significantly, from 105 ± 4 to 88 ± 3 mmHg ($P < 0.001$). The end-diastolic and end-systolic dimensions of the left ventricle both decreased significantly, from 5.2 ± 0.2 cm to 4.9 ± 0.2 cm ($P < 0.05$), and from 4.2 ± 0.2 cm to 3.7 ± 0.2 cm ($P < 0.001$), respectively. Corresponding changes were seen in the calculated left ventricular end-diastolic and end-systolic volumes, from 155 ± 15 ml to 139 ± 13 ml ($P < 0.05$) and from 75 ± 10 to 53 ± 11 ml ($P < 0.001$), respectively. The end-diastolic posterior wall thickness did not change significantly after nitroglycerin. The cardiac output, as estimated from the left ventricular volumes and the heart rate, was increased from 5.8 ± 0.6 l min⁻¹ to 7.7 ± 0.6 l min⁻¹ ($P < 0.001$). However, with one exception, this was the result of an increase in heart rate from 72 ± 5 to 90 ± 6 beats per minute ($P < 0.001$), while the stroke volume did not change significantly from the resting value of 80 ml (Fig. 2). The total peripheral resistance, however, decreased from 18 ± 4 to 11 ± 1 units ($P < 0.001$).

The ejection fraction increased after nitroglycerin administration from 53 ± 3 per cent to 65 ± 6 per cent ($P < 0.001$) and the V_{CF} increased from 0.81 ± 0.05 to 1.15 ± 0.10 circ s⁻¹ ($P < 0.001$). The calculated midsystolic midwall stress decreased from 155 ± 14 to 102 ± 11 g cm⁻² ($P < 0.001$). No significant changes were seen in the rate corrected systolic time intervals: LVETI was 400 ± 9 before and 390 ± 6 at 3 minutes after nitroglycerin; PEPI

was 141 ± 3 and 143 ± 3 and QA2I was 542 ± 8 and 531 ± 6 before and after nitroglycerin.

Discussion

Recently, interest has been growing in the use of agents which decrease left ventricular afterload for the treatment of patients with myocardial infarction (Franciosa *et al.*, 1974; Hirshfeld *et al.*, 1974) or contraction abnormalities in chronic ischaemic heart disease (Helfant *et al.*, 1974; Dove, Shah, and Schreiner, 1974). In the present study, echocardiographic techniques were used for the estimation of afterload as expressed by the left ventricular wall stress, before and after the administration of nitroglycerin. These changes in afterload can be related to the attendant variations in V_{CF} (Fig. 3). Since the long axis of the left ventricle cannot be measured echocardiographically, a thick-wall spherical model is assumed, and the formula used allows estimations of wall stress to be made at any given level through the wall thickness. This model can, however, only be applied to symmetrically contracting ventricles. Ratshin, Rackley, and Russell (1974) have shown that when left ventricular wall stress is calculated, using intracavitary pressure recordings with measurements of left ventricular dimension by echocardiography and by simultaneous angiography, similar results are obtained by both techniques. When intracardiac pressure recordings are not available, only the peak systolic blood pressure,

measured sphygmomanometrically, can be used. The peak systolic pressure is assumed to occur at mid-ejection and the left ventricular dimension can be estimated at this moment as described above.

Although the peak left ventricular wall stress usually occurs early in systole, the wall stress at mid-ejection is probably comparable in any individual patient before and after acute interventions. If the wall stress falls nearly linearly from an early systolic peak (Mirsky, 1968), the midsystolic measurement can be used as an approximate measure of the mean systolic stress and therefore correlated with the mean velocity of circumferential fibre shortening.

In spite of the usually reported good correlations between echocardiographic and angiographic left ventricular dimensions, there is considerable scatter at all levels (Fortuin *et al.*, 1971; Gibson, 1973). The wide confidence margins are reflected in the absolute values for wall stress. However, recent studies (Redwood *et al.*, 1974) have supported the use of echocardiographic left ventricular dimensions in the study of the effects of haemodynamic interventions. In the present context, directional changes in wall stress are emphasized.

Fig. 3 shows that in all the patients, a decrease in left ventricular afterload was accompanied by an increase in V_{CF} , thus illustrating a modified force-velocity relation. With decreased afterload and total peripheral resistance, the increased V_{CF} cannot be attributed to increased left ventricular contractility, even though the left ventricular end-diastolic volume was decreased. Isolated muscle studies (Zelis *et al.*, 1970a, b) have failed to show any alteration in contractility after moderate doses of nitroglycerin. However, in man, nitroglycerin may elicit reflex sympathetic activity as a result of its vasodilator action (Zelis *et al.*, 1970a, b). In a recent study, DeMaria *et al.* (1974), reported a small decrease in V_{CF} after nitroglycerin. In that study, however, left ventricular ejection time was measured from the beginning of the QRS complex to the time of maximal anterior position of the posterior left ventricular wall, assuming a pre-ejection period of 50 ms. This method is probably less reliable than that using the indirect carotid tracing; the implied prolongation of left ventricular ejection time after nitroglycerin is also at variance with results of this and previous studies (Sawayama *et al.*, 1973). Redwood *et al.* (1974) found an increase in V_{CF} from 1.3 to 1.7 circ s⁻¹ in their normal subjects, a change similar to that observed in our patients. The increase in cardiac output found in the present study exceeds the insignificant increases observed by DeMaria *et al.* (1974), and Burggraf and Parker

FIG. 3 Changes in the velocity of circumferential fibre shortening (V_{CF}) and midsystolic midwall stress after nitroglycerin.

(1974). The changes in cardiac output are probably largely determined by the relative predominance of venous or arteriolar dilatation (Mason and Braunwald, 1965). A dominant arteriolar depressant effect is likely in our group of patients.

Opinion is still divided as to whether nitroglycerin relieves angina pectoris mainly by its effect on left ventricular pump function or by coronary vasodilatation (Cohn and Gorlin, 1974). In 1867, Brunton reported after Gamgee that amyl nitrite 'greatly lessens the arterial tension both in animals and man . . . which led me to try it in angina pectoris'. The present study confirms earlier reports (Brachfeld, Bozer, and Gorlin, 1959; DeMaria *et al.*, 1974; Burggraf and Parker, 1974) that arterial pressure and left ventricular dimensions are decreased after nitroglycerin, both effects combining to produce a sharp decrease in afterload or wall stress. Preload, as reflected by the left ventricular end-diastolic dimension, is also significantly reduced. Directional changes in myocardial oxygen consumption cannot be predicted from these data, since its main determinants are changed in opposite directions. It is likely, nevertheless, that the abrupt fall in wall tension would override changes having a contrary effect, producing a net decrease in myocardial oxygen requirements. This effect alone, regardless of possible increases in coronary blood flow, might successfully relieve angina pectoris in many patients. However, there is some evidence (Kjekshus, 1973) that a reduction of left ventricular preload may by itself improve coronary blood flow to underperfused subendocardial areas. Both the postulated mechanisms of action of nitroglycerin may, therefore, be operating.

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