

Effects of nitroglycerin on left ventricular volumes and wall tension in patients with ischaemic heart disease¹

Simon J. K. Lee, Y. K. Sung, and A. J. Zaragoza

From the Department of Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada

Since the dimensions of the ventricles are related to both myocardial tension and myocardial oxygen consumption (MVO₂), the effects of nitroglycerin on the left ventricular volumes and left ventricular haemodynamics were studied in patients with ischaemic heart disease. The ventricular volumes were estimated using the constant infusion technique (indocyanine green) of Shaffer (1964). Sublingual administration of nitroglycerin (0.6 mg.) resulted in a significant reduction in cardiac output (27%), mean systolic pressure (21%), left ventricular end-diastolic pressure (63%), stroke volume (27%), left ventricular end-diastolic volume (26%), and left ventricular work (41%). Both calculated circumferential myocardial force (40%) and the myocardial tension (33%) decreased during systole, while the pressure-time index decreased by 27%. A similar decrease was also found in the contractile element work (42%), and mean circumferential fibre shortening rate (22%). Thus, this study has shown that the major determinants of MVO₂, i.e. myocardial wall tension, the velocity of contraction, and contractile element work, decrease significantly after administration of nitroglycerin.

Despite 100 years of effective use, the mechanism of action of nitroglycerin is not yet firmly established. Since it does not appear to increase myocardial blood flow in patients with ischaemic heart disease (Gorlin *et al.*, 1959; Bernstein *et al.*, 1966), it has been generally accepted that the benefit results from reduced myocardial oxygen consumption (MVO₂) (Winbury, 1964), and it has been suggested that a favourable redistribution of myocardial blood flow may play a role (Fam and McGregor, 1964).

Previous studies have shown that nitroglycerin reduces the systolic pressure-time index and calculated left ventricular work (Gorlin *et al.*, 1959; Parker, West, and Di Giorgi, 1967), which have been cited as the main evidence of reduced MVO₂. Sarnoff *et al.* (1958) showed that the product of arterial pressure and heart rate (tension-time index) has been found to correlate well with MVO₂, presumably without a significant change in the ventricular size. However, many have subsequently pointed out that the calculation

of myocardial tension should include the ventricular radius according to Laplace's law (Burton, 1957; Burch, Ray, and Cronvich, 1952), and increasing evidence has been accumulated indicating that the ventricular volume is an important determinant of MVO₂ (Levine and Wagman, 1962; Monroe and French, 1961; Rolett *et al.*, 1965; Britman and Levine, 1964). Therefore, the purpose of this communication is to report the effects of nitroglycerin on the left ventricular volumes and the myocardial tension, as well as on the fibre shortening rate, as the velocity of contraction is an important determinant of MVO₂ (Sonnenblick *et al.*, 1965).

Subjects

Studies were successful in 9 patients undergoing angiography for the investigation of angina pectoris. The criteria for selection were: (1) a history of anginal pain; (2) electrocardiographic evidence of either old myocardial infarction or ST depression at rest or exercise; (3) angiographic evidence of occlusive coronary artery (50% narrowing of one or more branches); and (4) no evidence of valvular disease, as valvular regurgitation produces error in estimating volumes by the indicator dilution technique (Petrle and Avasthey, 1968). All patients were men, averaging 51 years of age. Four patients had electrocardiographic evidence

Received 16 February 1970.

¹ Supported by grant-in-aid from the Alberta Heart Foundation. This work was carried out during Dr. Lee's tenure of a Senior Research Fellow of the Canadian Heart Foundation.

of old myocardial infarction, and one patient had severe left ventricular failure with obvious cardiac enlargement.

Procedures and methods

Approximately one hour after the intramuscular administration of 50 mg. pethidine, a Teflon catheter was introduced into the left brachial artery using a percutaneous technique and positioned in the ascending aorta under fluoroscopic control. A No. 6 Cournand catheter was then positioned in the pulmonary artery and a Sones catheter introduced into the left ventricle. Selective coronary angiography was then carried out, and 20 minutes after the procedure the patient was studied in a semi-Fowler's position (about 25°) in order to increase the effects of nitroglycerin on the circulation (venous pooling). Pressure recordings were made simultaneously from the left ventricle and aorta, using P23Db Statham transducers and a photographic recorder (Electronics for Medicine). The mean arterial pressure was obtained by the electronic damping, whereas the mean systolic pressure was obtained by the planimetric integration of the systolic pressure curve. The left ventricular end-systolic volume and cardiac output were measured, at least in duplicate, by the method of Shaffer (1964). Indocyanine green was infused into the left ventricle at a constant rate of 5.82 ml./min. (0.5 mg./ml.) using a Harvard pump. Arterial blood was sampled from the aortic root at a constant rate of 14.8 ml./min., and indicator dilution curves were recorded, using a Water Cuvette-Densitometer (300-X), simultaneously with the electrocardiogram. When plateau concentrations had not been obtained before the appearance of recirculation, the procedures were repeated. In 5 patients, cardiac outputs were also estimated by the Stewart-Hamilton principle with an injection of a single bolus of indocyanine green (0.5 mg.) into the pulmonary artery, and the result was compared with the constant infusion technique.

Following basal measurements, the patients were given nitroglycerin (0.6 mg.) sublingually, and measurements were repeated at 2-minute intervals for 8 minutes after the nitroglycerin had completely dissolved.

The cardiac output (CO) was calculated as follows:

$$CO = \frac{I(\text{mg.})/\text{min.}}{C \text{ max. (mg./l.)}}$$

where I is the amount of dye injected and C max. is the concentration of the indicator in the plateau before the appearance of recirculating dye. The end-systolic volume (ESV) was calculated as

$$ESV = \frac{SV}{C \text{ max.}} \left[nC \text{ max.} - \sum_{i=1}^n C(i) \right]$$

where n is the number of heart beats required to reach the plateau concentration (C max.) and C (i) is the concentration at each cardiac cycle. Left ventricular end-diastolic volume was calculated by addition of stroke volume and end-systolic volume.

The circumferential myocardial force was calculated as the product of $P\pi r^2$ assuming the left ventricle to be a sphere (Burch *et al.*, 1952; Levine and Wagman, 1962). Thus, the systolic circumferential force-time index (CFTI) was calculated

$$CFTI = P_{sm} \times \pi r^2 \times SEP,$$

where r is the radius of mean systolic volume (EDV-1/2 SV), P_{sm} the mean systolic pressure, and SEP the systolic ejection period per minute. The tangential myocardial tension-time index (TTTI) was also calculated using the formula $Pr \ 1/2$ (Burton, 1957), ignoring the wall thickness:

$$TTTI = 1/2 \times P_{sm} \times r \times SEP.$$

Again taking the assumption that the left ventricle is spherical, the mean circumferential shortening ratio (MCSR) was calculated using the formula:

$$MCSR = 2\pi \frac{\text{red-res}}{\text{sep}}$$

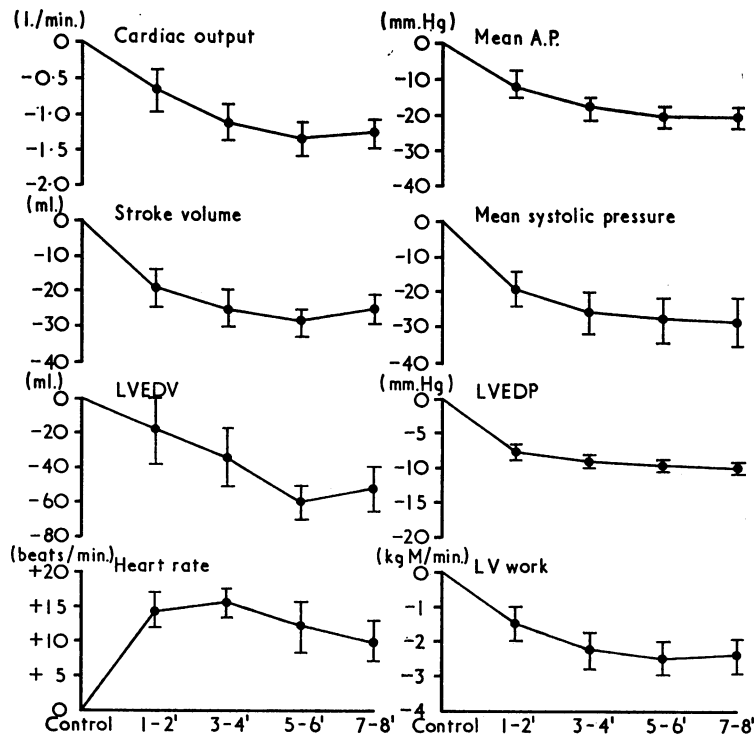
where red is the end-diastolic radius and res is the end-systolic radius (Klein, Herman, and Gorlin, 1967). The contractile element work (CEW) was calculated as was suggested by Britman and Levine (1964):

$$CEW = HR \times P_{sm} \times [SV + (EDV - 1/2 SV)1/9.6].$$

The left ventricular work (LVW) was calculated as follows:

$$LVW(\text{kg. m./min.}) = 13.6 \times [P_{sm} - LVEDP (\text{mm. Hg})] \times CO (\text{l./min.}).$$

FIG. Haemodynamic data before (control) and after nitroglycerin administration.



Results

The haemodynamic data obtained before and after nitroglycerin are listed in Tables 1 and 2. After control measurements, it was repeated after nitroglycerin 4 times at 2-minute intervals. The changes in these parameters are depicted in the Fig.

The mean arterial pressure (AP) was 102 mm. Hg in the control state and decreased to 81 mm. Hg within 5 to 6 minutes (21% decrease) after nitroglycerin administration. The decrease in mean systolic arterial pressure (Psm) obtained by a planimeter was of similar magnitude (from 119 to 91 mm. Hg).

Cardiac output, stroke volumes, heart rate, and SEP: The cardiac output decreased from 4.77 l./min. to 3.44 l./min. after nitroglycerin, a change of 27 per cent. This was entirely as a result of the change in stroke volume (69 ml. to 42 ml.) since the heart rate increased from 70 to 82 beats/min. The systolic ejection

period per heart beat decreased 16 per cent from the control values while peripheral resistance increased slightly (12%) after administration of nitroglycerin.

Left ventricular end-diastolic pressure was increased to 17 mm. Hg in the control state, reflecting impaired left ventricular function in these patients. Nitroglycerin caused a decrease to 6.8 mm. Hg in about 7 minutes, whereas the mean left ventricular end-diastolic volume decreased from 238 ml. to 178 ml., a reduction of 26 per cent. Left ventricular end-systolic volume also decreased from 169 ml. to 136 ml. after the drug. Left ventricular external work decreased 41 per cent, from 6.6 kg. m./min to 3.9 kg. m./min., after administration of nitroglycerin.

Systolic circumferential force-time index (mm. Hg cm.² sec./min./1000) decreased from 117.2 in the control state to 70.6 five to six minutes

TABLE 1 Summary of haemodynamic changes after nitroglycerin in 9 patients (mean and standard error)

	Pressures (mm. Hg)			Cardiac output (l./min.)	Stroke volume (ml.)	Heart rate (beats/min.)	Lt. ventric. end-diast. vol. (ml.)	Syst. ejection period (sec./beat)
	Mean arterial	Mean syst. arterial	Lt. ventric. end-diast.					
Control	102 ± 5	119 ± 7	17 ± 2	4.77 ± 0.51	69 ± 6	70 ± 4	238 ± 23	0.33 ± 0.02
1-2 min.	90 ± 3 (b)	100 ± 4 (b)	8.3 ± 2 (a)	4.18 ± 0.45 N.S.	50 ± 5 (a)	84 ± 4 (b)	226 ± 30* N.S.	0.28 ± 0.01 (a)
3-4 min.	83 ± 3 (a)	92 ± 3 (a)	7.8 ± 2 (a)	3.66 ± 0.36 (a)	40 ± 3 (a)	85 ± 4 (a)	201 ± 26 (c)	0.27 ± 0.01 (a)
5-6 min.	81 ± 3 (a)	91 ± 3 (a)	7.3 ± 2 (a)	3.44 ± 0.37 (a)	42 ± 4 (a)	82 ± 7 (a)	178 ± 20 (a)	0.27 ± 0.01 (a)
7-8 min.	81 ± 3 (a)	92 ± 3 (a)	6.8 ± 2 (a)	3.5 ± 0.39 (a)	44 ± 5 (a)	80 ± 5 (a)	184 ± 24 (a)	0.28 ± 0.01 (a)

* Based on 8 observations only.

(a)— $p < 0.001$; (b)— $0.001 < p < 0.01$; (c)— $0.01 < p < 0.05$; NS—not significant.

TABLE 2 Changes in left ventricular dynamics after nitroglycerin

	Control	1-2 min.	3-4 min.	5-6 min.	7-8 min.
Left ventric. end-diast. ratio (cm.)	3.84	3.78	3.63	3.49	3.53
Left ventric. end-syst. ratio (cm.)	3.43	3.48	3.37	3.19	3.22
Pressure-time index (mm. Hg sec./min./1000)	2.75	2.35	2.11	2.01	2.06
Tangential tension time index (mm. Hg cm. sec./min./1000)	4.99	4.30	3.69	3.37	3.47
Circumferential force-time index (mm. Hg cm. ² sec./min./1000)	117.2	97.3	81.2	70.6	73.7
Contractile element work (mm. Hg cm. ³ /min./1000)	751	595	460	435	448
Mean circumferential time shortening rate (cm./sec.)	7.80	6.95	6.05	6.98	6.95

after nitroglycerin, while *myocardial tension-time index* decreased from 4.99 to 3.37 (mm. Hg cm. sec./min./1000). As the systolic ejection period per heart beat did not change, these were entirely due to the change in the calculated myocardial force or tension. The pressure-time index also decreased after nitroglycerin. *The contractile element work index* was 751 at rest, and decreased by a maximum of 42 per cent (5 to 6 min.). *The mean circumferential fibre shortening rate* decreased from 7.8 cm./sec. to 6.05 cm./sec. three to four minutes after nitroglycerin.

Discussion

Shaffer (1964) was the first to use the constant infusion technique to measure the left ventricular volumes in dogs, and argued on theoretical grounds that the accuracy of his method did not depend on complete mixing with each diastole. Petrie and Avasthey (1968) tested the accuracy of the method using a model heart and found a 15 to 20 per cent overestimation when sampling was done in the ascending aorta, and attributed this to secondary mixing in the aorta. However, the magnitude of the difference was similar at different ventricular volumes; therefore, the relative change in ventricular volumes studied in this way should be meaningful. To validate the accuracy of cardiac output estimation using this constant infusion method, cardiac output was also estimated using a single bolus injection of indocyanine green into the pulmonary artery (Stewart-Hamilton technique). Nine comparisons in five subjects were obtained, which showed little difference in the mean values, with a correlation coefficient of 0.97.

The changes in haemodynamic parameters are depicted in the Fig. Most of the parameters, i.e. cardiac output, stroke volume, arterial pressure, left ventricular end-diastolic volume, and left ventricular work, decreased maximally 5 to 6 minutes after nitroglycerin, and showed a tendency for recovery during the 7 to 8 minute period. Both mean arterial and mean systolic pressure decreased by a maximum value of 21 per cent after the drug. Though the systolic ejection period per beat decreased by a maximum of 16 per cent, the total systolic ejection time did not change due to a concomitant increase in the heart rate. The most conspicuous change was found in the left ventricular end-diastolic pressure which decreased by 63 per cent. This agrees with the previous study (Parker *et al.*, 1967).

Nitroglycerin has been reported either to cause no change (Hoeschen *et al.*, 1966; Brach-

feld, Bozer, and Gorlin, 1959), or to decrease cardiac output (Gorlin *et al.*, 1959; Parker *et al.*, 1967). Williams, Glick, and Braunwald (1965) also reported a decrease of 10 per cent in normal subjects while Parker *et al.* (1967) found a decrease of 20 per cent in subjects with angina. The reason for the greater reduction in this study (-27%) is probably due to the large dose of nitroglycerin (0.6 mg.) and multiple determinations which perhaps delineated the truly maximal change.

Our most significant finding was a reduction in both left ventricular end-diastolic volume (26%) and end-systolic volume (20%) after nitroglycerin administration. Making the assumption that the left ventricle is spherical, the ventricular radius at the end of diastole was decreased by 9 per cent, and at the end of systole by 7 per cent (Table 2). This is similar to the reduction of 6.2 and 5.9 per cent, respectively, found by Williams *et al.* (1965), using myocardial clips and cine-radiography. This does suggest that the relative changes in ventricular volumes obtained by this method are reliable.

The left ventricular myocardial tensions and force have been calculated by using the formula of $Pr^{1/2}$ (Burton, 1957; Badeer, 1963) or $p\pi r^2$ (Burch *et al.*, 1952; Levine and Wagman, 1962). The circumferential force-time index, using the latter formula, decreased by a maximum of 40 per cent 5 to 6 minutes after nitroglycerin (Table 2), while the tangential tension-time index, using the former formula, decreased to the maximum of 33 per cent (Table 2). The pressure-time index also decreased after nitroglycerin, but the magnitude of change was less than the two previous calculations, being only a 27 per cent decrease at the maximum.

The contractile element work as calculated (Britman and Levine, 1964) represents the approximate work done by the ventricle in ejecting blood and in stretching the series elastic component, and it has shown that MVO_2 is more closely related to the contractile element work than the left ventricular work. A maximum decrease of 42 per cent in contractile element work (5 to 6 min.) was found after the drug. These findings suggest that the previous studies on the pressure-time index may underestimate the changes of myocardial oxygen consumption after nitroglycerin.

The velocity of contraction is recognized as an important determinant of myocardial oxygen consumption (Sonnenblick *et al.*, 1965; Sonnenblick, Ross, and Braunwald, 1968), but the effects of nitroglycerin on the velocity of contraction have not been reported. The

calculated mean circumferential fibre shortening rate decreased by 22 per cent after nitroglycerin. In the isolated papillary muscle, the velocity of contraction accelerates with decreasing after-load (arterial pressure) while a reduction in pre-load (end-diastolic pressure) or end-diastolic fibre length has an opposite effect (Sonnenblick, 1962). Therefore, the reduced velocity of contraction shown by us suggests that the effects of reduced left ventricular end-diastolic pressure and volume on the velocity have overshadowed the accelerating effect which should have occurred from the lower arterial pressure. While the finding of reduced mean fibre shortening rate should be confirmed using a more reliable method, our finding suggests that the reduced velocity may play an additional role to the myocardial tension and the contractile element work in reducing myocardial oxygen consumption.

Taking the contractile element work or myocardial tension-time indexes as an indication of myocardial oxygen consumption, it is postulated that nitroglycerin may reduce oxygen requirement by 33 to 42 per cent, which should increase the oxygen supply-demand ratio of the myocardium, as this drug does not reduce (Knoebel *et al.*, 1968) or even increase the total myocardial blood flow (Cowan *et al.*, 1969).

References

- Badeer, H. S. (1963). Contractile tension in the myocardium. *American Heart Journal*, **66**, 432.
- Bernstein, L., Friesinger, G. C., Lichtlen, P. R., and Ross, R. S. (1966). The effect of nitroglycerin on coronary circulation in man and dogs. Myocardial blood flow measured with Xenon¹³³. *Circulation*, **33**, 107.
- Brachfeld, N., Bozer, J., and Gorlin, R. (1959). Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects. *Circulation*, **19**, 697.
- Britman, N. A., and Levine, H. J. (1964). Contractile element work: a major determinant of myocardial oxygen consumption. *Journal of Clinical Investigation*, **43**, 1397.
- Burch, G. E., Ray, C. T., and Cronvich, J. A. (1952). The George Fahr Lecture - Certain mechanical peculiarities of the human cardiac pump in normal and diseased states. *Circulation*, **5**, 504.
- Burton, A. C. (1957). The importance of the shape and size of the heart. *American Heart Journal*, **54**, 801.
- Cowan, C., Duran, P. V. M., Corsini, G., Goldschlager, N., and Bing, R. J. (1969). The effects of nitroglycerin on myocardial blood flow in man; measured by coincidence counting and bolus injections of 84 rubidium. *American Journal of Cardiology*, **24**, 154.
- Fam, W. M., and McGregor, M. (1964). Effects of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circulation Research*, **15**, 355.
- Gorlin, R., Brachfeld, N., MacLeod, C., and Bopp, P. (1959). Effects of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation*, **19**, 705.
- Hoeschen, R. J., Bousvaros, G. A., Klassen, G. A., Fam, W. M., and McGregor, M. (1966). Haemodynamic effects of angina pectoris, and nitroglycerin in normal and anginal subjects. *British Heart Journal*, **28**, 221.
- Klein, M. D., Herman, M. V., and Gorlin, R. (1967). A hemodynamic study of left ventricular aneurysm. *Circulation*, **35**, 614.
- Knoebel, S. B., McHenry, P. L., Roberts, D., and Stein, L. (1968). Myocardial blood flow in man measured by a coincidence counting system and a single bolus of 84 rubidium chloride; effect of nitroglycerin. *Circulation*, **37**, 932.
- Levine, H. J., and Wagman, R. J. (1962). Energetics of the human heart. *American Journal of Cardiology*, **9**, 372.
- Monroe, R. G., and French, G. N. (1961). Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. *Circulation Research*, **9**, 362.
- Parker, J. O., West, R. O., and Di Giorgi, S. (1967). The hemodynamic response to exercise in patients with healed myocardial infarction without angina, with observations on the effects of nitroglycerin. *Circulation*, **36**, 734.
- Petle, M., and Avasthey, P. (1968). Some problems in the estimations of the end-diastolic volume of the ventricle by dye dilution techniques. *Cardiovascular Research*, **2**, 193.
- Rolett, E. L., Yurchak, P. M., Hood, W. B., and Gorlin, R. (1965). Pressure-volume correlates of left ventricular oxygen consumption in the hypervolemic dog. *Circulation Research*, **17**, 499.
- Sarnoff, S. J., Braunwald, E., Welch, G. H., Case, R. B., Stainsby, W. N., and Macruz, R. (1958). Hemodynamic determinants oxygen consumption of the heart with special reference to the tension-time index. *American Journal of Physiology*, **192**, 148.
- Shaffer, A. B. (1964). Estimation of ventricular volumes by a constant infusion indicator dilution technique. *Circulation Research*, **15**, 168.
- Sonnenblick, E. H. (1962). Force-velocity relations in mammalian heart muscle. *American Journal of Physiology*, **202**, 931.
- , Ross, J., Jr., and Braunwald, E. (1968). Oxygen consumption of the heart. New concepts of its multifactorial determinations. *American Journal of Cardiology*, **22**, 328.
- , —, Covell, J. W., Kaiser, G. A., and Braunwald, E. (1965). Velocity of contraction as a determinant of myocardial oxygen consumption. *American Journal of Physiology*, **209**, 919.
- Williams, J. F., Glick, G., and Braunwald, E. (1965). Studies on cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin. *Circulation*, **32**, 767.
- Winbury, M. M. (1964). Experimental approaches to the development of anti-anginal drugs. *Advances in Pharmacology*, **3**, 1.