Hæmodynamic Effects of Angina Pectoris, and of Nitroglycerin in Normal and Anginal Subjects*

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Though the nitrate drugs have been widely used to alleviate or prevent angina pectoris for nearly 100 years, the mechanism of their action remains unknown. The two possibilities that have been most widely considered are (a) that they cause an increase in oxygen supply to the heart through coronary vasodilatation and increase in coronary flow, and (b) that they cause a reduction in energy expenditure of the ventricular muscle.

The evidence in support of these two possible mechanisms is confusing. While there is no doubt that administration of nitrate preparations to experimental animals may well result in increased coronary flow (Wégria *et al.*, 1940; Griggs, Pierson, and Case, 1961), these changes are short lived. They are not demonstrable in human patients suffering from angina pectoris (Gorlin *et al.*, 1959) nor can the administration of such drugs in therapeutic doses be shown to cause any change in coronary sinus oxygen content (Gorlin *et al.*, 1959; Brachfeld, Bozer, and Gorlin, 1959; Rowe *et al.*, 1961). However, the pain and electrocardiographic changes may be prevented when nitroglycerin is administered before the performance of a load normally capable of causing angina (Kinsella, Troup, and McGregor, 1962; Sosa and McGregor, 1963), and this effect is demonstrable as long as 30 minutes from the time the drug is taken (Bunn and Chremos, 1963). The failure to demonstrate consistent increase in coronary flow at this time interval is thus probably more relevant than the transient increments of flow observed in animal experiments.

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The conclusion that nitrates act primarily by causing a reduction in myocardial energy expenditure is based on observations of decreased blood pressure and left ventricular work in anaesthetized dogs (Ganz and Froněk, 1961; Marchetti, Merlo, and Antognetti, 1964) or in resting man (Eldridge *et al.*, 1955; Gorlin *et al.*, 1959; Brachfeld *et al.*, 1959; Rowe *et al.*, 1961) in the supine posture. However, angina pectoris is usually experienced during exercise in the upright posture, when nitroglycerin is still clearly capable of preventing angina pectoris (Sosa and McGregor, 1963; Kinsella *et al.*, 1962; Bunn and Chremos, 1963; Sandler, Ilahi, and Lawson, 1963). The hæmodynamic effects of nitroglycerin, or similar preparations, have not been studied under these conditions.

The investigation described below was designed primarily to supply this information. An additional aim was to determine whether there were hæmodynamic abnormalities which might typify anginal patients at rest and during exercise while experiencing anginal pain.

SUBJECTS AND METHODS

The hæmodynamic effects of nitroglycerin administration were observed in 22 patients with angina pectoris and in 10 normal volunteers. The patients ranged in age from 30 to 69 years (mean 50.6) and were selected on the grounds of clinical history of anginal pain on effort, and absence of cardiac failure or other disability which would prevent adequate performance of the studies. In each patient repeated tests established an appropriate work-load, which would precipitate angina with typical electrocardiographic changes within two to three minutes. The normal subjects were volunteers from the medical staff and ranged in age from 27 to 59 years (mean 35.1).

TABLE I
EFFECTS OF NITROGLYCERIN DURING CONTINUOUS EXERCISE IN 5 NORMAL SUBJECTS:
MEAN $\pm$ SE OF THE MEAN

	$\dot{V}O_2$ (ml./min.)	$\dot{Q}$ (l./min.)	HR (beats/min.)	SV (ml./beat)	Pressure (mm. Hg)				LV minute work (kg. m./min.)
					S	D	M	SM	
Control	920 $\pm$ 21	10.25 $\pm$ 0.55	111 $\pm$ 4	92 $\pm$ 8	124 $\pm$ 4	63 $\pm$ 3	86 $\pm$ 4	98 $\pm$ 3	13.4 $\pm$ 0.8
3 min. after	935 $\pm$ 21	9.97 $\pm$ 0.41	117 $\pm$ 2	85 $\pm$ 5	110 $\pm$ 3†	63 $\pm$ 4	80 $\pm$ 3	89 $\pm$ 2	12.1 $\pm$ 0.8†
6 min. after	942 $\pm$ 22	10.98 $\pm$ 0.46	119 $\pm$ 2*	92 $\pm$ 5	105 $\pm$ 2‡	62 $\pm$ 4	78 $\pm$ 3†	86 $\pm$ 3	12.7 $\pm$ 0.5
9 min. after	957 $\pm$ 36	11.36 $\pm$ 0.17	119 $\pm$ 2	96 $\pm$ 2	105 $\pm$ 6‡	61 $\pm$ 3	77 $\pm$ 3‡	85 $\pm$ 2	13.2 $\pm$ 0.5
12 min. after					118 $\pm$ 4	63 $\pm$ 4	82 $\pm$ 4	92 $\pm$ 1	

* = $p < 0.05$ † = $p < 0.02$ ‡ = $p < 0.01$

Significance based on "t" test of the absolute change after nitroglycerin (Snedecor, 1956).

Abbreviations for all Tables: $\dot{V}O_2$ =oxygen consumption. $\dot{Q}$ =cardiac output. HR=heart rate. SV=stroke volume. SEP=systolic ejection period. MSER=mean systolic ejection rate. Pressure (S, D, M, SM)=systemic arterial pressure, systolic, diastolic, mean, and mean systolic. PTM=pressure time per minute.

TABLE II
HÆMODYNAMIC EFFECTS OF NITRO

	$\dot{V}O_2$ (ml./min.)	$\dot{Q}$ (l./min.)	HR (beats/min.)	SV (ml./beat)	SEP (sec.)
(a) Normal Subjects					
N	8	8	9	8	9
Pre	289 $\pm$ 18	5.98 $\pm$ 0.29	72 $\pm$ 3.3	84 $\pm$ 5.0	0.30 $\pm$ 0.009
Post	259 $\pm$ 16	6.00 $\pm$ 0.46	80 $\pm$ 4.1	75 $\pm$ 12.2	0.29 $\pm$ 0.01
Mean % Δ^*	-7.1	-0.6	+13.3	-11.7	-3.0
pt†	N.S.	N.S.	N.S.	N.S.	N.S.
(b) Patients in whom Intra-					
N	8	8	9	8	7
Pre	328 $\pm$ 29	6.98 $\pm$ 0.54	73 $\pm$ 2.4	98 $\pm$ 10.8	0.30 $\pm$ 0.01
Post	297 $\pm$ 33	7.04 $\pm$ 0.76	86 $\pm$ 1.6	82 $\pm$ 9.4	0.28 $\pm$ 0.009
Mean % Δ^*	-7.8	-1.3	+18.7	-18.1	-5.5
pt†	N.S.	N.S.	0.01	0.001	N.S.
(c) Patients in whom Intra-arterial Pressures were Not Measured					
N	14	14	14	14	
Pre	264 $\pm$ 17	5.94 $\pm$ 0.44	74 $\pm$ 2.6	80 $\pm$ 5	
Post	265 $\pm$ 13	5.75 $\pm$ 0.43	82 $\pm$ 2.7	70 $\pm$ 5	
Mean % Δ^*	+0.4	-3.2	+10.8	-12.5	
pt†	N.S.	N.S.	< 0.01	< 0.01	

* The mean of the percentage change of individual observations.

TABLE III
HÆMODYNAMIC EFFECTS OF NITROGLYCERIN

	$\dot{V}O_2$ (ml./min.)	$\dot{Q}$ (l./min.)	HR (beats/min.)	SV (ml./beat)	SEP (sec.)
(a) Normal Subjects					
N	10	10	10	10	9
Pre	836 $\pm$ 31	11.32 $\pm$ 0.67	102 $\pm$ 3.0	112 $\pm$ 12.2	0.305 $\pm$ 0.01
Post	815 $\pm$ 25	13.05 $\pm$ 0.77	99 $\pm$ 3.3	133 $\pm$ 9.5	0.30 $\pm$ 0.01
Mean % Δ^*	-1.8	+16.4	-3.0	+20.5	-1.9
pt†	N.S.	< 0.02	N.S.	< 0.02	N.S.
(b) Patients in whom Intra-					
N	9	9	9	9	7
Pre	975 $\pm$ 85	12.05 $\pm$ 1.20	106 $\pm$ 3.3	116 $\pm$ 14.6	0.30 $\pm$ 0.02
Post	919 $\pm$ 70	15.21 $\pm$ 1.69	103 $\pm$ 3.7	151 $\pm$ 19.2	0.29 $\pm$ 0.01
Mean % Δ^*	-4.7	+27.1	-2.8	+31.0	-4.4
pt†	N.S.	< 0.02	N.S.	< 0.01	N.S.
(c) Patients in whom Intra-arterial Pressures were Not Measured					
N	17	17	17	17	
Pre	821 $\pm$ 76	9.86 $\pm$ 0.86	110 $\pm$ 3.7	89 $\pm$ 6.8	
Post	841 $\pm$ 73	11.41 $\pm$ 1.09	106 $\pm$ 4.2	106 $\pm$ 8.3	
Mean % Δ^*	+2.5	+15.7	-3.6	+19.2	
pt†	N.S.	< 0.01	N.S.	< 0.02	

* The mean of the percentage change of individual observations.

All subjects were seated in a chair. Exercise was performed on a constant work bicycle ergometer (Elema) at 60 to 70 r.p.m. Observations consisted of oxygen consumption ($\dot{V}O_2$), cardiac output ($\dot{Q}$), blood pressure (BP), heart rate (HR), and electrocardiogram. Cardiac output was measured by the dye dilution technique. Coomassie blue dye (0.4 mg./kg. body weight) was injected into an antecubital vein and immediately flushed in with 10 ml. normal saline. The concentration of the dye was detected by a pre-calibrated ear oximeter (McGregor, Sekelj, and Adam, 1961; Sekelj and McGregor, 1961). Systolic and diastolic arterial pressure was recorded in 16 studies (Tables I, II(a), II(b), III(a), III(b)) by insertion of a brachial arterial needle connected to a Statham P23D strain gauge by 66.2 cm. rigid polyvinyl pressure tubing (internal diameter=2.67 mm.) and multichannel oscillographs (Sanborn No. 550M or

Elema-Schönander Mingograf 428). The complete system had a natural frequency of 17.5 c/sec. and a damping ratio of 0.26. Mean arterial pressure (BPM) was obtained by electrical or planimetric integration, and mean systolic pressure (BP_{sm}) was measured by planimetric integration. In the remaining 14 studies (Tables II(c), III(c)) blood pressure was measured by a sphygmomanometer cuff, but these values were not considered sufficiently accurate for inclusion in the data. Systolic ejection period (SEP) in seconds was measured from the pressure records as the time interval between the onset of the brachial arterial pulse and the dicrotic notch, and was expressed as the average figure from analysis of at least four beats chosen at the extremes of respiratory fluctuation. Heart rate was measured from a simultaneously recorded electrocardiogram which also served to monitor ST segment and T wave changes during exer-

GLYCERIN AT REST: MEAN $\pm$ SE OF THE MEAN

MSER (ml./sec.)	Pressure (mm. Hg)				PTM mm. Hg (sec./min.)	LV work (kg.m./min.)
	S	D	M	SM		
8 280 $\pm$ 15 256 $\pm$ 23 - 8.6	9 115 $\pm$ 6 110 $\pm$ 9 - 4.6	9 63 $\pm$ 4 65 $\pm$ 5 + 2.7	9 81 $\pm$ 5 78 $\pm$ 6 - 3.7	9 95 $\pm$ 6 91 $\pm$ 7 - 3.8	9 1994 $\pm$ 147 2083 $\pm$ 124 + 5.8	8 7.6 $\pm$ 0.5 6.9 $\pm$ 0.6 - 3.6
N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
arterial Pressures were Measured						
6 331 $\pm$ 40 280 $\pm$ 36 - 15.4 < 0.01	7 134 $\pm$ 7 115 $\pm$ 5 - 13.3 < 0.01	7 78 $\pm$ 5 76 $\pm$ 4 - 1.1 N.S.	7 98 $\pm$ 4 88 $\pm$ 3 9.6 < 0.01	7 111 $\pm$ 5 97 $\pm$ 3 - 11.8 0.05	7 2426 $\pm$ 158 2345 $\pm$ 172 1 - 2.2 N.S.	6 10.6 $\pm$ 1.0 9.3 $\pm$ 1.4 - 19.3 < 0.05

† Significance based on "t" test of the absolute change after nitroglycerin (Snedecor, 1956).

DURING EXERCISE: MEAN $\pm$ SE OF THE MEAN

MSER (ml./sec.)	Pressure (mm. Hg)				PTM mm. Hg (sec./min.)	LV work (kg. m./min.)
	S	D	M	SM		
9 358 $\pm$ 14 450 $\pm$ 25 + 25.8 < 0.01	9 131 $\pm$ 7 124 $\pm$ 8 - 5.7 N.S.	9 63 $\pm$ 6 64 $\pm$ 3 + 3.3 N.S.	9 87 $\pm$ 6 82 $\pm$ 5 - 5.8 N.S.	9 101 $\pm$ 6 95 $\pm$ 6 - 6.2 < 0.02	9 3075 $\pm$ 172 2760 $\pm$ 213 - 10.8 < 0.01	9 15.1 $\pm$ 1.2 16.6 $\pm$ 1.1 + 11.5 < 0.05
arterial Pressures were Measured						
7 382 $\pm$ 53 489 $\pm$ 69 + 28.0 < 0.05	7 157 $\pm$ 13 155 $\pm$ 13 - 0.8 N.S.	7 83 $\pm$ 4 82 $\pm$ 5 - 1.4 N.S.	7 108 $\pm$ 6 107 $\pm$ 6 - 0.1 N.S.	7 129 $\pm$ 9 120 $\pm$ 6 - 5.5 N.S.	7 4049 $\pm$ 296 3578 $\pm$ 281 - 11.3 N.S.	7 20.9 $\pm$ 3.5 23.6 $\pm$ 4.1 + 13.5 N.S.

† Significance based on "t" test of the absolute change after nitroglycerin (Snedecor, 1956).

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cise. Oxygen consumption was determined by collection of expired gas in meteorological balloons for two minutes at rest and one minute during exercise.

The following parameters were derived from the observed data.

A) Stroke volume (SV), ml./beat.

B) Mean systolic ejection rate (MSER), ml./sec. =

$$\frac{SV}{SEP}$$

C) Pressure time per minute (PTM), mm. Hg sec./min. = $BP_{sm} \times SEP \times HR$.

D) Left ventricular minute work (LV_w), kg. m./min. =

$$\frac{13.6 \times BP_{sm} \times Q}{1,000}$$

Study I. The first study was designed to show the time relationship of the changes induced by nitroglycerin in continuously exercising normal subjects. In 5 volunteers control observations were made at the fifth minute of continuous exercise at a rate of 300 kg. m./min. While continuing to exercise, 0.6 mg. nitroglycerin was administered sublingually and the observations repeated at 3, 6, 9, and 12 minutes thereafter.

Study II. It is not possible to maintain steady exercise for long periods in patients with angina pectoris. In order to observe the influence of nitroglycerin in such subjects, a different experimental design was employed. After the initial resting measurement, exercise was performed at a previously determined load which would cause anginal pain within 2-3 minutes. This varied between 200 and 300 kg. m./min. in 9 studies (Table II(b)) and between 50 and 400 kg. m./min. in the remaining studies (Table II(c)). Observations were made when pain commenced. After a 15-minute period of rest, measurements were repeated at rest before and 3 minutes after nitroglycerin administration. Exercise was then recommenced at exactly the same work-load; observations were repeated after exactly the same period of exercise. Thus in each study exercise comparisons were made at identical loads before and 8-10 minutes after nitroglycerin administration.

A comparable study was performed in 10 normal volunteers, the only difference being that the exercise load could be standardized at 300 kg. m./min. in each. Exercise was continued for 3-3½ minutes, exactly the same period of exercise being employed in each subject before and after nitroglycerin administration.

FIG. 1.—The hemodynamic effects of nitroglycerin during continuous exercise in 5 normal subjects. For abbreviations see Table I. Open circles represent the means of observations made after 5 minutes of exercise and one minute before administration of nitroglycerin. Closed circles represent mean values 3, 6, 9, and 12 minutes after nitroglycerin. Standard errors are represented by vertical bars.

FIG. 2.—The haemodynamic effects of exercise in normal subjects and in patients with angina pectoris (mean values). Solid lines: normal volunteers. Interrupted lines: patients with intra-arterial pressure measurements. Dotted lines: patients with cuff pressure measurements (blood pressure and derived parameters not included).

RESULTS

Study I. The effects of nitroglycerin on mean values in 5 normal subjects, while performing continuous light exercise, are shown in Fig. 1 and Table I. At no time after administration of nitroglycerin was there any significant change in stroke volume, total body oxygen consumption, diastolic pressure, or cardiac output. The latter fell initially, but by 9 minutes it exceeded the control value by 10 per cent. At this time, systolic and mean blood pressures were decreased by 15 per cent ($p < 0.01$) and 10 per cent ($p < 0.01$), respectively, but by 12 minutes these too had largely returned to control values. Left ventricular minute work, which

initially fell (10%) ($p < 0.02$), had returned to control levels by the ninth minute.

Study II. Exercise Response Without Nitroglycerin. During exercise the load imposed on normal subjects and patients was not always identical. However, in some patients the load imposed and the oxygen consumption were very comparable to the normal subjects, and it was thus possible to compare the response to exercise of these two groups (Tables III(a), III(b), Fig. 2). In spite of the fact that exercise observations in the patients were made in the presence of angina pectoris, there was no statistically significant difference between the haemodynamic responses of the two groups.

FIG. 3.—Resting mean values before and 3 minutes after nitroglycerin. Code as in Fig. 2.

Hæmodynamic Effects of Nitroglycerin at Rest. (Table II, Fig. 3). Three minutes after administration of nitroglycerin there was a significant decrease in systolic, mean arterial, and mean systolic pressure, and in left ventricular minute work in the patient group. Heart rate was significantly increased, and stroke volume and mean systolic ejection rate were reduced. Similar directional changes were observed in the normal subjects but were not statistically significant. There was no significant change in cardiac output, diastolic pressure, or pressure time per minute in either group. It should be noted that the tables do not reflect the maximal fall of blood pressure in most subjects. In 6 of the normal subjects in whom blood pressure was recorded continuously, the average time of

maximum change was 2.2 minutes following nitroglycerin, and in the 7 patients the average time of maximum change was 2.4 minutes. Thus the values at 3 minutes recorded in the table represent partial recovery.

Hæmodynamic Effects of Nitroglycerin During Exercise. Exercise values before and 8–10 minutes after taking nitroglycerin are shown in Table III and Fig. 4. All anginal patients experienced pain before administration of nitroglycerin; none did so after its administration. However, the hæmodynamic changes after nitroglycerin were comparable with those of the normal subjects. They consisted of an increase of cardiac output due to an increase in stroke volume without change in heart rate.

FIG. 4.—Mean values during exercise, before and 8 to 10 minutes after nitroglycerin. Code as in Fig. 2.

There was no change in diastolic pressure, a small reduction in systolic mean pressure which was significant in the normal subjects and a corresponding fall in pressure time per minute.

DISCUSSION

Experimental Methods. Before considering the significance of these observations, the validity of the methods employed must first be reviewed. (a) Measurement of cardiac output by these methods has been validated previously. First, use of the peripheral venous injection site is not a source of significant error if dye is rapidly flushed into the vein with normal saline (Bousvaros *et al.*, 1963). The ear oximetric method involved (Sekelj and McGregor, 1961) gives values of comparable repeatability

(Bousvaros *et al.*, 1963) and accuracy to conventional whole blood cuvette technique (McGregor *et al.*, 1961). Accuracy is greatest in the estimation of changes in cardiac output. Further, the possibility was considered that vasomotor changes in the ear resulting from nitroglycerin administration might prove a source of error. Consequently in 25 injections (14 rest, 11 exercise, of which 6 resting and 6 exercise injections followed nitroglycerin administration) the dilution curves were recorded simultaneously by ear oximetric and whole-blood cuvette methods described elsewhere (McGregor *et al.*, 1961). Average values for cardiac index were not significantly different (mean ear = 4.80, SE $\pm$ 0.37; mean cuvette = 4.77, SE $\pm$ 0.4 l./min. m.² BSA) and the standard deviation of paired observations was 0.75 l./min. m.² The absence of

systematic differences suggests that use of the ear oximetric method does not produce systematic error under the conditions of use in this study.

(b) The possibility was considered that the performance of successive work-loads with an intervening rest period of 15 minutes (as in Study II) might be the source of systematic changes in cardiac output. In 9 of the normal subjects, cardiac output was measured after exercise for 3 minutes at a rate of 300 kg.m./min. on successive occasions with intervening rest periods of 15 minutes. Methods were the same as in Study II above. In 13 pairs of measurements, the second observation was on the average 2 per cent lower than the first ($p > 0.4$). The standard deviation of the differences between pairs of observations was 1.06 l./min. or 9 per cent of the average initial cardiac output. The latter figure reflects the over-all repeatability under these circumstances and includes both variations in technique and variations in physiological response to exercise.

(c) The recording system used in most studies was somewhat under-damped (see methods). In Study I, during continuous exercise a smaller (20 gauge) arterial needle was employed, and it was considered that the degree of damping thus introduced invalidated the records for accurate measurement of systolic duration. These data have been omitted. Even with a perfect recording system, however, estimation of ventricular systolic duration from a brachial artery record is a probable source of inaccuracy, though there is some evidence that the interval measured in this way may not differ from central aortic measurements (Levine *et al.*, 1962). Though somewhat greater than the values reported by Levine *et al.* (1962) using the brachial pulse, the values for the systolic ejection period observed in this study are of the same order as those measured from the central aorta by Jones and Foster (1964) for comparable levels of heart rate, diastolic pressure, and stroke volume. Values for systolic ejection period and indices derived therefrom should, however, be interpreted with caution when measured on brachial pulse records.

Resting Values. Apart from the higher blood pressure in the patient group, all values in normal and anginal subjects were comparable. Messer *et al.* (1963) found lower values for resting cardiac output, left ventricular work, and mean systolic ejection rate in anginal patients. This discrepancy may well be due to selection of patients with a greater element of myocardial failure.

Exercise Response Without Nitroglycerin. It is surprising that the exercise response of the patients

was indistinguishable from normal in all parameters, even though the patients were experiencing anginal pain at the time of measurement (Fig. 2). Comparable observations in 2 patients are reported by Müller and Rørvik (1958). Reports of a less-than-normal increase in mean systolic ejection rate (Foster and Reeves, 1964; Messer *et al.*, 1963; Cohen *et al.*, 1965) may have been due to differences in case material. From our data it seems that the exercise response with respect to the parameters measured may be within normal limits in such subjects when they are experiencing anginal pain.

Hæmodynamic Effects of Nitroglycerin at Rest. The hæmodynamic effects of nitrate and nitrite preparations have been the subject of numerous studies in the anesthetized dog and in supine resting man. Most workers have reported a reduction (Eldridge *et al.*, 1955; Gorlin *et al.*, 1959; Rowe *et al.*, 1961) or no change (Brachfeld *et al.*, 1959; Johnson, Fairley, and Carter, 1959) in cardiac output. In dog studies, Honig, Tenney, and Gabel (1960) concluded that cardiac output would fall unless venous return were augmented in some way, and we had anticipated this result in resting man in the sitting posture. However, there was no significant change in cardiac output in either our normal subjects or our anginal patients 3 minutes after taking nitroglycerin, in spite of a fall in systolic pressure and a rise in heart rate.

Observations in dogs (Ganz and Froněk, 1961; Marchetti *et al.*, 1964) and in resting supine man with (Gorlin *et al.*, 1959; Rowe *et al.*, 1961) and without (Eldridge *et al.*, 1955; Brachfeld *et al.*, 1959) coronary vascular disease, indicate that these drugs may be expected to cause a reduction in left ventricular minute work, and it has been commonly concluded that this is the chief cause of the therapeutic effect of these substances (Darby and Aldinger, 1960; Eldridge *et al.*, 1955; Ganz and Froněk, 1961; Gorlin *et al.*, 1959; Marchetti *et al.*, 1964; Rowe *et al.*, 1961).

In our resting subjects the reduction in LV work at 3 minutes was small, and pressure time per minute, an index that may be expected to give a better indication of ventricular oxygen consumption (Sarnoff *et al.*, 1958), was not significantly changed after nitroglycerin.

Hæmodynamic Effects of Nitroglycerin During Exercise. In normal subjects performing steady exercise in the sitting posture (Fig. 1), nitroglycerin caused a rapid reduction in systolic pressure (3rd to 9th minute). Diastolic pressure did not change and cardiac output only increased slightly at

9 minutes. As the therapeutic effect of nitroglycerin is known to be present at this time, the period of 8–10 minutes was selected for further study in the normal and anginal subjects.

It is apparent (Fig. 4) that at this time after taking the drug there was a significant increase in cardiac output and stroke volume, and left ventricular minute work was, if anything, increased rather than reduced. These changes could not have been the consequence of increasing coronary flow to ischæmic areas of the myocardium, as they were observed equally in the normal subjects in whom there was presumably no myocardial ischæmia. They were more likely to be a consequence of the effects of the drug on peripheral vasculature.

The changes in cardiac output observed after nitroglycerin in the exercising subject will depend on the time at which measurements are made (Fig. 1). Thus up to 6 minutes after drug administration there may be no change, and after 9 minutes an increase, and it is possible that observations from 1–3 minutes might have shown a reduction in cardiac output. These measurements are, however, of secondary importance in estimating the myocardial oxygen consumption.

Of greater significance in this respect are the effects of nitroglycerin on blood pressure. In the absence of change in heart rate a reduction in systolic pressure would suggest a reduction in myocardial oxygen consumption (Sarnoff *et al.*, 1958; Katz, 1963). The data (Table III) do reflect small reductions in these values which were statistically significant, however, only in the case of the systolic mean pressure of the normal volunteers. Before rejecting the possibility that the therapeutic effects of the drug were a consequence of reduced energy expenditure by the myocardium, however, two other possibilities should be considered. There may well have been greater reduction of systolic pressure in the period before the time of measurement at 9 minutes, as suggested by the data reported in Fig. 1. In addition nitroglycerin has been shown to cause venodilatation (Sharpey-Schafer and Ginsburg, 1962) with a reduction in central filling pressure (Müller and Rørvik, 1958; Johnson *et al.*, 1959) and a reduction in cardiac size (Brandt, Caccese, and Dock, 1952). We have confirmed this and have found an average 9 per cent reduction of cardiac diameter even during exercise on a bicycle ergometer in both normal and anginal subjects. According to the Laplace relationship, this would result in development of the same luminal pressure at a lower wall tension with consequent reduction in oxygen usage (Levine and Wagman, 1962; Williams and Glick, 1964), changes that have already been invoked to explain the

therapeutic action of this drug (Klensch and Južnič, 1964).

Thus it must be concluded that the hæmodynamic changes observed after nitroglycerin tend to reduce energy expenditure of ventricular muscle. These changes are small and other possible therapeutic actions should be considered. Although the increase of total coronary flow following nitroglycerin appears too small and too short-lived to produce a therapeutic effect, the retrograde flow in an area of long-standing ischæmia is considerably increased for at least 20 minutes following the administration of this drug to dogs (Fam and McGregor, 1964; Fam, Sekelj, and McGregor, 1965). Thus, in addition to the effects outlined in this study, nitroglycerin appears to cause a specific form of coronary vasodilatation which may result in redistribution of blood to chronically ischæmic areas of myocardium. It may well be, therefore, that the therapeutic effects of this drug are attributable to more than one pharmacological action.

SUMMARY

Observations were made of total body oxygen consumption, heart rate, cardiac output, stroke volume, and blood pressure in 10 normal subjects and in 22 patients with angina pectoris, at rest and during exercise in the sitting posture, before and then after the administration of nitroglycerin.

In the absence of nitroglycerin, resting values and hæmodynamic response to exercise were comparable in normal subjects and patients with angina pectoris, in spite of the presence of anginal pain in all the patients during exercise observations.

Changes observed 3 minutes after nitroglycerin taken at rest were again comparable in normal subjects and patients. While cardiac output, diastolic pressure, and pressure time per minute were unchanged, there was a small increase in heart rate and a fall in stroke volume and systolic pressure.

In 5 normal subjects performing steady exercise for 12 minutes nitroglycerin caused a fall in systolic pressure which was significant from 3 minutes to 9 minutes. Diastolic pressure was unchanged. Cardiac output appeared first to fall, but by 9 minutes had exceeded control values. These changes were small and not statistically significant.

When exercise performance was studied before and 8–10 minutes after nitroglycerin in 10 normal subjects and in 17 patients with angina pectoris, there was a significant increase in cardiac output and stroke volume. There was a small reduction in systolic mean pressure and pressure time per minute,

which was significant only in the normal subjects. Heart rate and diastolic pressure were unchanged.

These changes, together with a reduction of ventricular dimensions, would tend to reduce energy expenditure of ventricular muscle. They are, however, small and the therapeutic action of this drug in angina pectoris may well result also from its direct effect on coronary arteries.

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