Mode of Action of Nitroglycerin in Angina Pectoris

Correlation Between Haemodynamic Effects During Exercise and Prevention of Pain*

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Nitroglycerin is generally agreed to be the most effective drug available for the treatment of angina pectoris, but its mode of action remains uncertain. Two main explanations have been put forward. The first suggests that it acts by lowering the arterial pressure and so reducing cardiac work; the second that it acts by dilating the coronary arteries and so improving the myocardial blood supply. For many years the coronary dilator action of the drug has been widely accepted as the probable mechanism for its therapeutic effect, and its action in reducing blood pressure has been regarded as of secondary importance, if not actually harmful. Attempts to demonstrate a beneficial effect on coronary flow in patients with ischaemic heart disease, however, have met with no success, and it appears that sublingual nitroglycerin is unable to increase the myocardial blood supply *when the coronary arteries are diseased* (Gorlin *et al.*, 1959; Bernstein *et al.*, 1966). This failure to confirm the coronary dilator theory has led to renewed interest in the possibility that the drug acts by reducing cardiac work, but the evidence to support this view is inconclusive. Most studies of the effect of nitroglycerin on the circulatory response to exercise have shown that the drug reduces arterial pressure both in normal subjects and in patients with ischaemic heart disease (Eldridge *et al.*, 1955; Müller and Rørvik, 1958; Christensson, Karlefors, and Westling, 1965; Najmi *et al.*, 1967). In none of these investigations, however, have the changes in the circulatory response been correlated with the alteration in capacity for exercise. In consequence, though it is generally accepted that nitroglycerin does cause some attenuation of the circulatory response to exercise, it has been impossible to assess the extent

to which this action of the drug could account for its beneficial effect on exercise tolerance. The present investigation was designed to clarify this problem.

SUBJECTS AND METHODS

Nine patients with angina pectoris were investigated: there were eight men and one woman (Table I). Every patient gave a typical history of exertional chest pain, and most were regular users of nitroglycerin. None of the patients had established hypertension, though the arterial pressure exceeded normal levels in several at the time of the investigation. The heart shadow was of normal size on the standard chest radiograph in all except two patients who showed slight to moderate enlargement.

The patients ate breakfast as usual on the morning of the investigation and they received no premedication. The temperature of the laboratory in which they were studied was not controlled, but was usually between 20–23°C. The investigation formed part of a wider study of the circulation in angina and the methods used have been described in detail elsewhere (Robinson, 1967). In brief, a polyethylene catheter was introduced percutaneously into the brachial artery and advanced to the subclavian; arterial pressure was then recorded continuously by means of a Statham 23D transducer and photographic recorder before, during, and after periods of standardized exercise. Eight of the patients exercised in the sitting position on a bicycle ergometer calibrated in watts; the remaining patient was unable to master the technique of cycling and performed a step test instead.

Following a study of the patient's response to varying levels of exertion, a rate of work was selected which could be expected to cause angina in less than 5 minutes. The patient then performed a control period of exercise at this level with continuous recording of arterial pressure; exercise was discontinued when pain developed and the patient was allowed to rest for at least 10 minutes. Nitroglycerin (0.5 mg.) was then given sublingually and arterial pressure was recorded continuously with the subject at rest sitting on the bicycle. Three minutes

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TABLE I
CLINICAL DETAILS OF PATIENTS

Case No.	Age (yr.)	Sex	Previous infarction*	Comments
1	48	M	Yes	Moderate cardiac enlargement on chest radiograph
2	63	M	Yes	
3	49	M	Probable	
4	60	M	Yes	Selective coronary arteriography showed severe disease of all major vessels
5	41	M	No	
6	67	M	Yes	
7	52	M	No	Selective coronary arteriography showed generalized disease of major vessels
8	57	M	Yes	
9	57	F	No	

* Yes = pathological Q waves in electrocardiogram. Probable = episode of chest pain in past which was followed by pathological inversion of T wave.

after the drug had been given, exercise was started again at the same rate as that used in the control study. If the drug proved effective in postponing the onset of pain, the patient was allowed to continue exercise at the control level of work for up to 5 minutes; if pain had still not developed, the rate of work was then increased and the test continued until the patient either developed pain or became limited by dyspnoea and fatigue. Heart rate and arterial pressure were measured at minute intervals at rest and during exercise, and again at the time of onset of angina. The rate was counted over the second half of each minute while the arterial pressure was averaged over a period of 10–15 seconds. The ejection time was measured from the onset of the pulse wave to the incisura.

RESULTS

In 6 patients the control work load was performed on two occasions before the administration of nitroglycerin. When the responses during the two bouts of exercise were compared, it was seen that

the differences between them were, on average, relatively small and did not achieve statistical significance (Table II). In the 3 other patients, the responses during the control study were fully consistent with the responses previously observed at other levels of exertion. There was thus no evidence that repetition of the work load had more than a slight effect upon either the circulatory response or the time taken to induce pain.

Effect of Nitroglycerin. The circulatory changes produced by nitroglycerin would be important in preventing angina only inasmuch as they altered the oxygen requirements of the heart. It is, therefore, necessary to assess the circulatory changes by an index which reflects the work and metabolic requirements of the myocardium rather than the external work of the heart. The index used in this study is the product of heart rate and systolic blood pressure (rate-pressure product) corrected when necessary in direct proportion to changes in ejection time. The rate-pressure product would be expected to correlate with the oxygen requirements of the heart since heart rate, ejection time, and arterial pressure are important determinants of myocardial oxygen consumption (Gerola, Feinberg, and Katz, 1957; Sarnoff *et al.*, 1958; Monroe and French, 1961; Cooper, Braunwald, and Morrow, 1958). Furthermore, it has been shown in a previous study that the rate-pressure product tends to be relatively constant at the onset of pain in any given patient with angina even when there are wide variations in the type and intensity of exercise (Robinson, 1967).

Rest. In all nine patients, nitroglycerin had a distinct effect upon the arterial pressure at rest which started 1½–1¾ minutes after the tablet was given (Fig. 1). By the end of the third minute (Table III), systolic pressure had fallen by an

TABLE II
RESPONSE TO DUPLICATE CONTROL BOUTS OF EXERCISE

Case No.	Work (watts)	Control 1				Control 2			
		Duration (min.)	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)	Duration (min.)	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)
1	40	2.75	112	295/145	0.25	2.25	108	290/135	0.26
2	40	3.5	124	135/78	0.22	4.75	136	130/78	—
3	80	3.5	124	170/87	0.24	3.5	130	162/77	0.22
6	40	2.5	102	180/75	0.25	2.5	108	180/74	0.26
7	40	2.5	114	205/105	0.22	3.75	120	202/100	0.23
8	40	2.5	116	174/72	—	3.5	116	175/72	0.22
Mean		2.88	115	193/94		3.38	120	190/89	
Significance						N.S.	N.S.	N.S.	

N.S. = not significant.

FIG. 1.—Effect of sublingual nitroglycerin (0.5 mg.) on arterial pressure at rest. The drug has no detectable effect for about 1½ minutes; thereafter a progressive fall in systolic pressure is seen, with a smaller fall in diastolic pressure. The scale for arterial pressure is in mm. Hg.

TABLE III
EFFECT OF NITROGLYCERIN AT REST

Case No.	Control				3 min. after nitroglycerin			
	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)	Rate-pressure product†	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)	Corrected rate-pressure product
1	64	190/90	0.28	122	76	170/100	—	—
2	72	128/80	0.22	92	92	105/72	0.21	92
3	80	118/72	0.24	94	94	100/69	0.21	82
4	116	150/95	0.18	174	142	135/90	0.17	182
5	96	130/80	0.20	125	104	125/85	0.20	130
6	76	120/58	0.25	91	90	110/60	0.22	87
7	74	180/90	0.24	133	78	170/92	0.23	127
8	110	154/80	0.21	169	118	115/70	0.20	130
9	66	180/72	0.32	119	70	155/70	—	—
Mean	84	150/80	0.22*	125*	96	132/79	0.21*	119*
Significance					p < 0.01	syst. p < 0.01 diast. N.S.	p < 0.02	N.S.

* Excluding Cases 1 and 9.

N.S. = not significant.

† The rate-pressure product has been divided by 100 to reduce it to convenient units.

average of 18 mm. Hg (range 5–39 mm. Hg), but in most patients there was little change in the diastolic pressure; heart rate increased by an average of 12 beats/min., and there was a slight reduction in the ejection time; all these changes were statistically significant. The rate-pressure product fell in some patients, but it increased in others, and for the group as a whole there was no significant change.

Exercise. When the circulatory response to exercise after nitroglycerin was compared with that at the same level of exercise in the control study, it was seen that the drug had modified the response in all patients (Table IV). Typically, the systolic pressure was lower, the heart rate higher, and the subclavian ejection time reduced; the diastolic pressure was unchanged or fell only slightly. For the group as a whole, the reduction in systolic pressure averaged 19 mm. Hg (–10%), the rise in heart rate 7 beats/min. (+5%), and the fall in ejection time 0.03 sec. (–13%). The rate-pressure product was reduced on average by 17 per cent ($p < 0.01$). In contrast to these changes in the absolute response to

exercise following nitroglycerin, the general pattern of the increase in heart rate and arterial pressure over the first minute or so of exertion was not greatly changed. The fall in systolic pressure and pulse pressure when exercise was stopped was, however, abnormally rapid, and in some patients large decreases occurred within 5–10 seconds (Fig. 2).

Effect of Nitroglycerin on Work of the Heart in Relation to Effect on Exercise Tolerance. In all of the 8 patients whose exercise tolerance improved after nitroglycerin, the rate-pressure product was reduced when compared with the control study. The solitary patient (Case 8) whose exercise tolerance did not improve was the only one in whom the rate-pressure product was not reduced. The failure to reduce myocardial work in this patient was not due to defective absorption of the drug; systolic pressure fell substantially both at rest and during exercise, but the associated increase in heart rate was so great that the exercising rate-pressure product was not reduced.

Nitroglycerin proved so effective in preventing

TABLE
EFFECT OF NITROGLYCERIN

Case No.	Control						Symptoms
	Work (watts)	Duration (min.)	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)	Rate-pressure product	
1	40	2.25	108	290/135	0.26	313	Pain
2	40	3.5	124	135/78	0.22	167	Pain
3	80	3.5	130	162/77	0.22	211	Pain
4	100	4.25	170	245/100	0.19	417	Pain
5	60	3.75	130	155/80	0.23	202	Pain
6	40	2.5	108	180/74	0.26	194	Pain
7	40	3.75	120	202/100	0.23	242	Pain
8	40	3.5	116	175/72	0.22	203	Pain
9	Step test	1.75	128	208/82	0.27	266	Pain
Mean		3.19	126	195/89	0.23	246	

* Estimates of statistical significance refer to the difference from the mean value in the control study.

angina that it was possible to induce pain after the drug in only 4 patients; in the other 5 tiredness and dyspnoea were the limiting factors. In those patients in whom pain was provoked, the rate-pressure product was always found to have reached a level similar to or slightly above that at which pain had occurred in the control study. The rate-pressure product also reached higher levels after nitroglycerin than before in some patients who did not develop pain; for the group as a whole, however, the maximum rate-pressure product attained after nitroglycerin averaged 2 per cent *less* than in the control study (the difference is not significant). In those subjects who did attain higher rate-pressure products after nitroglycerin, the increases were always relatively small with a maximum of 10 per cent (Case 5) and an average of 5 per cent, and this was so even when the external work which could be achieved had been doubled.

DISCUSSION

The demonstration that nitroglycerin reduces the systolic blood pressure not only at rest but also

during exercise, is in agreement with most previous observations in both normal subjects and in patients with ischaemic heart disease (Eldridge *et al.*, 1955; Müller and Rørvik, 1958; Christensson *et al.*, 1965; Najmi *et al.*, 1967). In addition to the effect on arterial pressure, the present study has also shown that nitroglycerin reduces the ejection time during exercise. These findings are in contrast to those of another recent study of patients with angina (Hoeschen *et al.*, 1966) in which no significant change was found in either systolic pressure or ejection time after nitroglycerin. The explanation for this discrepancy is not clear, but it may reflect differences in the quantity of nitroglycerin absorbed.

The reduction of systolic blood pressure and the shortening of the ejection time which were observed in the present study would both be expected to reduce the work and oxygen requirements of the myocardium. There is, however, a third mechanism by which the drug could reduce the load on the ischaemic heart. Williams, Glick, and Braunwald (1965) have shown that nitroglycerin produces a decrease in ventricular dimensions at rest in man,

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ON CIRCULATORY RESPONSE TO EXERCISE

Nitroglycerin						
Work (watts)	Duration (min.)	Heart rate /min.	Blood pressure (mm. Hg)	Ejection time (sec.)	Corrected rate-pressure product	Symptoms
40	2.25	100	230/110	0.24	212	No pain
80	5	132	285/135	0.23	333	No pain
40	3.5	128	138/85	0.19	152	No pain
60	5	136	142/85	0.20	175	Pain
80	3.5	146	135/68	0.20	179	No pain
80	5	146	130/67	0.20	173	No pain
100	4.25	174	220/95	0.17	343	No pain
100	5	174	220/90	0.17	343	No pain
60	3.75	134	148/80	0.20	172	No pain
100	5	150	170/85	0.20	222	No pain
40	2.5	122	150/70	0.20	141	No pain
80	5	148	173/75	0.20	199	No pain
40	3.75	112	192/95	0.22	206	No pain
80	5	138	200/92	0.21	252	Pain
40	2.5	144	158/77	0.19	196	Pain
Step test	1.75	134	215/85	0.23	243	No pain
	2.75	140	230/90	0.23	274	Pain
Control work	3.19	133	176/85	0.20	205	—
Significance*		N.S.	syst. $p < 0.05$ diast. N.S.	$p < 0.01$	$p < 0.01$	—
Maximum work	5.75	145	190/88	0.20	241	—
Significance*	$p < 0.01$	$p < 0.01$	N.S.	$p < 0.01$	N.S.	—

and Hoeschen *et al.* (1966) have observed a 9 per cent reduction in the cardiac diameter during upright exercise. A reduction in the size of the ventricle would enable a given systolic pressure to be achieved with a lower tension in the wall and would thus reduce the metabolic needs of the heart. The effect of alterations in ventricular dimensions is not allowed for in the index of myocardial oxygen consumption used in the present study, and it is thus possible that the level of myocardial work after nitroglycerin has been overestimated. However, this would mean that the reduction in myocardial work which followed the drug was underestimated and the demonstration of an error in this direction would only strengthen the conclusions which will be drawn.

In the patients studied, prevention of angina was invariably associated with a reduction in the work of the myocardium as measured by the rate-pressure product. In every patient whose exercise tolerance improved, the ability to repeat the control work load without pain could be accounted for by a reduction in the rate-pressure product. The only

patient who failed to obtain any benefit was also the only one who failed to show any reduction of his exercising rate-pressure product. In those patients in whom the alteration in exercise tolerance could be roughly graded, the degree of improvement was closely related to the reduction in rate-pressure product (Fig. 3). These findings suggest that reduction of myocardial work is one way in which nitroglycerin exerts its therapeutic effect, but they do not exclude an additional effect upon the coronary circulation. Further evidence is available on this point, however, since the investigation included an examination of the circulatory response during relatively intense exercise after nitroglycerin. If an important action of the drug were to improve the myocardial blood supply, it would be expected that the maximum rate-pressure product which could be achieved would be substantially increased. No evidence of this was found. Only small increases in maximum rate-pressure product were observed and it is probable that these changes did not signify a true increase in the working capacity of the myocardium since no allowance was made for the effect

FIG. 2.—Effect of prior administration of sublingual nitroglycerin (0.5 mg.) on the arterial pressure immediately after upright exercise. (A). Control: exercise at 40 watts is stopped at the time shown by the arrow; systolic and diastolic blood pressure fall slowly over the following minute. (B). Nitroglycerin: exercise at 80 watts is stopped at the time shown by the arrow; systolic and diastolic pressure fall very rapidly during the first 10 seconds of recovery. It is clear that measurements of blood pressure made during recovery would be grossly misleading in assessing the circulatory response during exercise. The scale for arterial pressure is in mm. Hg.

of reduced ventricular size. Not all patients developed pain after nitroglycerin, however, and it is possible that some could have achieved slightly higher levels of rate and pressure had they been stressed even harder.

Whether or not nitroglycerin is sometimes able to produce a marginal increase in coronary blood flow and so raise the capacity for myocardial work, it is clear that, in the patients studied, reduction of the circulatory response to exercise was a much more important factor in improving exercise tolerance. For example, in the three patients who showed the greatest increase in exercise tolerance (Cases 1, 6, and 7), the average reduction of rate-pressure product during exercise was 20 per cent, but the average increase in maximum rate-pressure product was only 4 per cent. The results thus suggest that the main action of nitroglycerin is to alter the gearing between external stress and myocardial work so that the patient is able to achieve

higher levels of exercise before the load on his heart is raised to the point at which pain develops. It must be noted that a small reduction in myocardial work might sometimes result in a large increase in the time for which exercise could be continued without pain. If a patient subjected to a particular stress develops angina only as his circulatory response is approaching the steady state, a very small reduction in the response might suffice to keep the load on the myocardium below the critical level and so enable him to continue indefinitely without pain.

The failure to demonstrate an increase in the capacity for myocardial work after nitroglycerin is consistent with the results of studies in which coronary flow has been measured. Brachfeld, Bozer, and Gorlin (1959) observed an increase in myocardial blood flow after sublingual nitroglycerin in subjects with normal coronary arteries, but the same group was unable to demonstrate any increase in flow when the coronary arteries were diseased

FIG. 3.—Relation between the action of nitroglycerin in reducing rate-pressure product at control work load and its effect in preventing the development of angina. I: no improvement in exercise tolerance (Case 8); II: small improvement in exercise tolerance (Cases 2 and 9); III: large improvement in exercise tolerance (Cases 1, 5, 6, and 7). There is a distinct relation between the percentage reduction of the rate-pressure product and the degree of improvement in exercise tolerance.

(Gorlin *et al.*, 1959). Other investigators using different techniques have also found that sublingual nitroglycerin is ineffective in increasing the myocardial blood supply in patients with ischaemic heart disease (Hollander, Madoff, and Chobanian, 1963; Bernstein *et al.*, 1966). An increase in the calibre of the coronary arteries in response to nitroglycerin has been clearly demonstrated by coronary arteriography (Likoff *et al.*, 1964), but this finding cannot be taken to imply that there is any increase in flow. The dilatation presumably involves the less severely diseased parts of the vessels, and there is no evidence that the drug can reduce the resistance offered by the rigid obstructions which limit blood flow.

SUMMARY

The effect of nitroglycerin on the response to exercise was studied in nine patients with angina pectoris. Arterial pressure was recorded directly and continuously at rest and during a control bout of exercise which was continued until the onset of pain. Nitroglycerin (0.5 mg.) was then given sublingually and the study was repeated; exercise began 3 minutes after the drug had been given and was

continued, with an increase in the rate of work if necessary, until either pain was provoked or dyspnoea and fatigue prevented further effort.

The typical response to nitroglycerin was a reduction in systolic pressure and ejection time during exercise with an increase in heart rate. The product of heart rate and systolic pressure corrected for changes in ejection time (rate-pressure product), which is an index of the work and metabolic needs of the myocardium, was reduced on average by 17 per cent ($p < 0.01$). The ability to repeat the control work load without provoking pain was always associated with a reduction in the exercising rate-pressure product. The maximum rate-pressure product which could be achieved, however, showed little or no increase (average change -2% ; maximum increase $+10\%$), and this was so even in patients who were able to exercise at double the control work load without pain. There was thus no evidence to suggest that the drug produced a significant improvement in the capacity for myocardial work in any of the patients studied. It was concluded that the beneficial effect of nitroglycerin in angina pectoris could be accounted for largely, if not entirely, by its effect in attenuating the circulatory response to exercise.

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