Acute Effect of Nitroglycerin on Haemodynamics of Angina Pectoris

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Although nitroglycerin (glyceryltrinitrate) has been used for relief of angina pectoris for a century, the action of the drug is not yet completely understood (Brunton, 1867; Christensson, Karlefors, and Westling, 1965; Bernstein *et al.*, 1966; Hoeschen *et al.*, 1966; Ferrer *et al.*, 1966; Najmi *et al.*, 1967). Nitroglycerin is regarded as a "coronary vasodilator", but it is unlikely that, given sublingually, this drug could widen narrowed and calcific main branches of coronary arteries. Furthermore, no studies to date have shown any significant increase in myocardial blood flow in patients with diseased coronary arteries (Gorlin *et al.*, 1959; Bing *et al.*, 1964; Bernstein *et al.*, 1966).

Nitroglycerin has a decided effect on the arteriolar and venous beds of normal subjects, by reducing systemic arterial blood pressure, lowering vascular resistance, and decreasing venous tone (Mason and Braunwald, 1965). Similar effects have also been demonstrated in patients with coronary heart disease studied during continuous exercise in the sitting position (Christensson *et al.*, 1965). These peripheral effects reduced cardiac output and stroke volume, and angina pectoris disappeared. The authors suggest that nitroglycerin may relieve angina pectoris by reducing the work of the heart.

The present study with intracardiac pressure measurements was carried out on patients in the supine position to allow for calculations of cardiac work and to minimize orthostatic effects.

SUBJECTS AND METHODS

Studies were made of 18 male patients between 42 and 64 years of age; all had a history of classical angina pectoris and electrocardiographic and angiographic evidence of coronary heart disease. The studies were done as part of a thorough evaluation of their cardiac

function before carrying out an operation to improve their myocardial blood supply (Malm, 1962-63). This evaluation included a careful medical history, electrocardiogram, estimation of heart volume (Jonsell, 1939), exercise tolerance test (Malmberg, 1965), and coronary angiography (Paulin, 1964). None of the patients had signs of congestive heart failure or rheumatic heart disease, and all had a sinus rhythm at the time of study. For pertinent clinical data see Table I.

The patients were studied in the morning, while in the post-absorptive basal state. The right heart was catheterized via an antecubital vein with a double lumen catheter. The brachial artery was catheterized using a percutaneous technique (Seldinger, 1953). Cardiac output was measured with the indicator dilution technique (Wassén, 1956). Bromsulphalein (BSP) was injected via the right heart catheter into the pulmonary artery. Pressures were registered by inductance manometers on a four-channel mingograph*. The patients were studied in the supine position and exercise tests

* AB Elema, Stockholm, Sweden.

TABLE I
CLINICAL AND LABORATORY DATA IN 18 MEN
WITH CORONARY HEART DISEASE

Patient No.	Age (yr.)	Functional class I-IV*	Heart volume (ml./m. ²)	No. of myocardial infarctions	Exercise tolerance (kpm./min.)
1	56	III	480	2	300
2	64	II	450	0	300
3	62	III	470	0	300
4	50	III	420	2	100
5	57	III	500	3	100
6	53	III	520	1	300
7	46	III	450	2	450
8	56	III	340	0	300
9	56	I	440	1	450
10	53	II	430	1	600
11	47	II	490	1	300
12	50	III	525	0	450
13	53	II	450	0	450
14	43	III	490	2	300
15	58	II	420	1	300
16	64	II	450	1	300
17	57	II	430	0	800
18	48	II	470	1	600

* New York Heart Association.

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TABLE
HAEMODYNAMIC DATA IN 18 MEN WITH CORONARY HEART DISEASE, DURING ATTACK OF ANGINA AT

Patient No.	Work load	Heart rate (beats/min.)		Stroke vol. (ml.)		Cardiac output Q (l./min.)		Arteriovenous O ₂ diff. (ml./l.)		Pulm. capill. venous pressure (mean) $\bar{P}_{PCV}$ (mm. Hg)		Pulm. artery pressure (mean) $\bar{P}_{PA}$ (mm. Hg)	
		A	B	A	B	A	B	A	B	A	B	A	B
1	0	84	-8	61	+10	5.1	+0.3	47	-3	31	-24	38	-25
2	0	81	+3	68	-12	5.5	-0.8	—	—	16	-10	24	-12
3	50	84	+1	83	—	7.0	—	73	+5	18	-10	24	-11
4	50	68	+4	118	-21	8.0	-1.0	70	-2	18	-6	26	-10
5	100	104	-8	53	+8	5.5	+0.3	90	-8	35	-15	52	-24
6	100	108	+2	46	+2	4.9	+0.4	79	+1	30	-24	38	-22
7	200	108	-2	65	+13	7.1	+1.2	80	-3	20	-7	36	-12
8	250	76	-2	73	+28	5.5	+2.0	—	—	30	-22	39	-20
9	250	104	+8	87	-9	9.0	-0.2	83	+4	19	-18	30	-15
10	300	94	+8	108	-6	10.2	+0.2	65	+6	16	-10	26	-9
11	300	120	+16	79	-6	9.5	+0.5	—	—	24	-21	34	-22
12	300	94	+8	84	-4	7.9	+0.3	98	-12	16	-10	25	-7
13	300	86	+7	115	-18	9.9	-0.9	90	+1	25	-17	33	-17
14	300	110	-4	85	+18	9.4	+1.5	107	-1	27	-12	36	-11
15	300	102	0	59	+23	6.0	+2.4	95	-19	40	-19	44	-13
16	400	108	+6	76	0	8.3	+0.4	96	-5	32	-4	39	-3
17	400	106	+6	116	+2	12.3	+1.5	49	+3	17	-13	30	-16
18	450	144	+16	—	—	—	—	83	-3	23	-9	33	-18
n			18		16		16		15		18		18
d			+3.4		+1.8		+0.5		-2.4		-14		-15
SD			6.9		14.2		1.0		6.7		6.3		6.1
SE			1.6		3.5		0.25		1.7		1.5		1.5
P			>0.05		>0.05		>0.05		>0.05		<0.001		<0.001

were carried out on an electrically braked bicycle ergometer*, with the pedals slightly above heart level. Blood oxygen, carbon-dioxide tensions, and pH were measured with conventional electrodes†, and the arteriovenous oxygen differences were calculated from these values using the Severinghaus nomogram supplied by the manufacturers (Severinghaus and Bradley, 1958). Vascular resistances were calculated according to the formulae:

pulmonary vascular resistance:
$$PVR = \frac{\bar{P}_{PA} - \bar{P}_{PCV}}{Q};$$

systemic vascular resistance:
$$SVR = \frac{\bar{P}_{BA}}{Q}$$

expressed in arbitrary units. Left ventricular stroke work was calculated according to the formula:

$$LVSW = \frac{SV(\bar{P}_{BA} - \bar{P}_{PCV}) \times 13.6}{1000}$$

and expressed in gram metres (g.m.).

The patients were studied at rest and during an exercise test, with a level of work predetermined to provoke supportable angina pectoris. During the attacks of angina new measurements were made, and the patients were given 0.5 mg. nitroglycerin sublingually and instructed to continue the exercise under continuous control of pulmonary capillary venous (PCV), pulmonary arterial (PA), and brachial arterial (BA) pressures. When the discomfort subsided or had completely disappeared, measurements were repeated. This always

occurred within 4 to 6 minutes after the administration of the drug.

RESULTS

Measurements obtained at rest are not included in the present report, but they agree with findings from previous work (Müller and Rørvik, 1958; Malmberg, 1965). In two patients (No. 1 and 2), angina pectoris occurred during preparation for the exercise test, and so that measurements without and with nitroglycerin were obtained while the patients were at rest. In the remaining 16 patients the level of exercise varied between 50 and 450 kpm./min. Angina pectoris was precipitated in all patients and subjective improvement occurred in all cases after the administration of nitroglycerin.

The haemodynamic variables measured during angina pectoris and the changes after nitroglycerin are presented in Table II, together with the mean differences and significance levels.

The haemodynamics during angina pectoris are also similar to those observed in previous studies, and usually indicate acute left ventricular failure (Müller and Rørvik, 1958; Malmberg, 1965). The administration of 0.5 mg. nitroglycerin sublingually produced a continuous parallel and highly significant drop of $\bar{P}_{PA}$, $\bar{P}_{PCV}$, and $\bar{P}_{BA}$, which began approximately 1½ to 2 minutes after the drug had been given. No significant changes were noted in heart rate, cardiac output, stroke volume, and arteriovenous oxygen difference when these were measured 4 to 6

* AB Elema, Stockholm, Sweden.

† Instrumentation Laboratories.

II

REST OR INDUCED BY EXERCISE (A), AND CHANGE AFTER NITROGLYCERIN (0.5 mg.) SUBLINGUALLY (B)

Brachial arterial pressures (mm. Hg)						Pulm. vasc. resist.		System. vasc. resist.		Left ventric. stroke work (g.m.)		Arterial O ₂ tension P _a O ₂ (mm. Hg)	
Systolic		Diastolic		Mean $\bar{P}_{PA}$		A	B	A	B	A	B	A	B
A	B	A	B	A	B								
194	-36	100	-18	138	-29	1.4	-0.3	27.1	-6.9	89	+9	78	-12
203	-42	97	-10	145	-35	1.5	-0.2	26.4	-3.0	119	-40	75	—
150	-31	86	-9	118	-18	0.9	—	16.9	—	113	—	73	-9
156	-17	80	-5	109	-9	1.0	-0.4	13.6	+0.7	146	-30	78	-8
155	+5	97	+3	123	-4	3.1	-1.7	22.4	-1.9	63	+19	90	-11
230	-6	145	0	179	-18	1.6	+0.3	36.5	-6.1	93	+8	77	-13
110	-10	73	-3	93	-15	2.2	-0.9	13.1	-3.7	65	+4	87	-6
155	-11	84	-5	110	-2	1.6	-0.1	20.0	-5.6	79	+58	—	—
189	-59	88	-19	127	-30	1.2	+0.5	14.1	-3.1	128	-26	76	-5
186	-28	97	-13	138	-33	1.0	+0.1	13.5	-3.4	179	-42	76	-2
168	-31	94	-13	123	-18	1.1	-0.2	12.9	-2.4	106	-5	—	—
162	-7	84	0	120	-1	1.1	+0.4	15.2	-0.7	119	+4	91	-7
167	-38	93	-28	120	-31	0.8	+0.1	12.1	-2.2	149	-42	74	-4
150	-11	88	-9	118	-12	1.0	-0.1	12.6	-2.9	105	+22	63	-1
—	—	—	—	133	—	0.7	+0.5	22.2	—	75	—	75	+1
—	—	—	—	148	0	0.8	+0.1	17.8	-0.8	120	+4	87	-8
194	-6	106	-3	150	-12	1.1	-0.4	12.2	-2.2	210	+5	82	-6
179	-19	90	0	130	-4	—	—	—	—	—	—	93	-2
—	16	—	16	—	17	—	16	—	15	—	15	—	15
—	-21.7	—	-8.3	—	-15.9	—	-0.1	—	-2.9	—	-3.5	—	-6
—	16.9	—	8.4	—	12.0	—	0.6	—	2.1	—	28	—	4
—	4.2	—	2.1	—	2.9	—	0.1	—	0.5	—	7.2	—	1
—	<0.001	—	<0.001	—	>0.001	—	>0.05	—	<0.001	—	>0.05	—	<0.001

minutes after nitroglycerin and when the patients were relieved of their pain. There was also a highly significant fall in P_aO₂ and the calculated systemic vascular resistance. No change was noted in the calculated PVR or LVSW. The drop in pressure in the majority of cases was greater in the brachial artery than in the pulmonary capillary vein (Fig. 1).

DISCUSSION

The present results show that nitroglycerin given sublingually during an attack of angina pectoris in the supine position and with associated, haemodynamically proven, acute left ventricular failure effectively relieves the pain without reducing the calculated left ventricular stroke work. The myocardial function is improved, as seen by the shift of the work/pressure relation to the left, and, in the majority of cases, upwards (Fig. 2), during unaltered exercise conditions.

These findings indicate that the pain-relieving effect of the drug in the supine position could not be due to a reduction of the work of the heart, as suggested by Christensson *et al.* (1965), at least not the "external" work of the heart that can be estimated from parameters that are measurable in man without undue risks.

What other mechanisms can be postulated? Active vasodilatation of the coronary arteries with increases in myocardial blood flow is not very likely, judging from previous reports (Gorlin *et al.*,

1959; Bing *et al.*, 1964; Bernstein *et al.*, 1966), and bearing in mind that vasodilatation already ought to be maximal as a result of the ischaemia. In the present study there was a highly significant reduction of the systemic vascular resistance but no attempts were made to study changes on the venous side.

Dilatation of the peripheral vascular bed, either arteriolar or venous, would lead to a redistribution

FIG. 1. The relation between pressure changes in pulmonary capillaries ($\Delta\bar{P}_{PCV}$) and the brachial arteries ($\Delta\bar{P}_{BA}$) in 16 men with coronary heart disease induced by 0.5 mg. nitroglycerin given sublingually during attacks of angina pectoris. Line of identity drawn to facilitate comparison.

FIG. 2. Left ventricular stroke work (LVSF) in relation to pulmonary capillary venous mean pressure (P_{PCV}) before and after 0.5 mg. nitroglycerin given sublingually during angina pectoris in 15 men with coronary heart disease.

of the blood volume away from the central circulation, with reduction of the residual volume in the left ventricle. This will also lead to a lowered filling pressure for the left ventricle. Decreased volume of the ventricular cavity will lead to reduced myocardial tension and myocardial oxygen requirements (Burch, 1955; Burton, 1957; Sarnoff *et al.*, 1958; Rodbard, Williams, and Williams, 1959; Rodbard *et al.*, 1964). Furthermore, the lowered filling pressure of the left ventricle, as evidenced by the pulmonary capillary venous pressure, will result in a diminished transmural pressure gradient during diastole. This will allow for improved perfusion of the myocardium, especially the subendocardial layers of the left ventricle (Salisbury, Cross, and Rieben, 1963). Such a mechanism can explain the favourable effect of the drug.

Ferrer *et al.* (1966) measured pulmonary blood volume changes after the administration of nitroglycerin in one patient. An increase was noted together with a decrease in right ventricular diastolic and residual volumes, suggesting vasodilatation of the precapillary and venous pulmonary vascular bed. In the present study the highly significant though small fall in P_{aO_2} could be explained by this action of the drug, resulting in perfusion of unventilated parts of the lungs, i.e. small functional right-to-left shunts. The existence of such mechanisms is suggested by the fact that blood flow normally is

directed away from a hypoventilated to a normo-ventilated lung (Arborelius, 1966).

The results from studies in the sitting position and the present results suggest that the action of nitroglycerin varies with body position at least quantitatively. Schematically, it could be said that in the upright or sitting position nitroglycerin will take volume load away from the heart, whereas in the supine position there is a decrease in pressure load. There are thus at least two different effects of the drug, which decrease oxygen demand and also increase the oxygen supply to the myocardium, giving good experimental support for the effectiveness of the best drug for the relief of angina pectoris at rest and on exercise.

SUMMARY

Eighteen patients with coronary heart disease have been studied using right heart catheterization. Angina pectoris was precipitated at rest in 2 patients and by mild exercise in 16. Haemodynamic measurements were made during the attacks of angina and after sublingual administration of nitroglycerin. During the anginal attack there were haemodynamic signs of left ventricular failure. The subjective improvement after nitroglycerin was associated with improved myocardial function without reduction of cardiac work. This can be explained by peripheral arteriolar vasodilatation resulting in a smaller left ventricular residual volume and lower filling pressure ($\bar{P}_{PCV}$). These changes will result in lower myocardial oxygen requirements and a lower transmural pressure gradient during diastole.

The administration of nitroglycerin also caused a small but highly significant fall in P_{aO_2} , probably as a result of changes in the perfusion of the lungs.

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