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Potential deleterious haemodynamic effects of glyceryl trinitrate on myocardial ischaemia in man

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SUMMARY The potential adverse effects of glyceryl trinitrate on myocardial ischaemia were studied using low and high dose infusions in 10 patients with coronary heart disease. Cardiac venous flow was measured by the thermodilution technique and blood was sampled for metabolic studies. Angina pectoris was provoked by atrial pacing before drug infusion and the same heart rate was regained with low and high doses of glyceryl trinitrate. Both doses reduced myocardial ischaemia equally. The low dose of glyceryl trinitrate reduced mean systolic aortic pressure from 145(23) to 128(23) mm Hg and the high dose further to 103(9) mm Hg. Myocardial oxygen uptake decreased owing to a combined reduction in preload and afterload with the low dose and was substantially more reduced with the high dose owing to a further afterload reduction. Transmural perfusion gradient did not change with the low dose of glyceryl trinitrate but fell significantly with the high dose. This fall in myocardial perfusion probably accounts for the lack of further reduction in ischaemia with the high dose. Thus the adverse effects of glyceryl trinitrate infusion are small and do not increase myocardial ischaemia.

Treatment with vasodilators has become a standard approach for severe heart failure complicating myocardial ischaemia.[1 2] The benefits of vasodilators when used in coronary heart disease may, however, be offset by a drug induced fall in perfusion pressure or by a coronary steal effect owing to its action on resistance vessels.[3–5] Reports on the subject have been conflicting.[6–8] The pathoanatomical heterogeneity of patients with coronary artery disease and the complex action of vasodilators create difficulties in comparing interventions in different groups of patients. These problems are reduced if the patient is used as his own control. The present study was performed to assess the effects on myocardial circulation and pacing induced ischaemia when glyceryl trinitrate was given to induce either a small or a considerable reduction in blood pressure in the same patient.

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Patients and methods

STUDY POPULATION

Ten men undergoing cardiac catheterisation for the evaluation of severe angina pectoris gave their informed consent to participate in the study. The mean age was 54 (range 35–62) years. A bicycle exercise test using six precordial electrocardiographic leads was positive[9] in all. None had signs of valvar heart disease or myocardial insufficiency, and all were in regular sinus rhythm. Table 1 gives the results of coronary angiography, which was performed separately. Significant stenosis (≥75% of the vessel lumen) of the left anterior descending artery was present in all. Treatment with cardioactive drugs had been stopped at least 36 hours before the study, which was performed in the supine position and the fasting condition.

CATHETERISATION TECHNIQUE

A Wilton-Webster double thermistor thermodilution catheter with pacing electrodes was positioned in the proximal part of the coronary sinus, a polyethylene catheter in the thoracic aorta, and a Cournand catheter in the pulmonary artery. All were flushed with saline without heparin. Cardiac venous flow was

Table 1 *Angiographic and electrocardiographic findings*

Case No	Coronary angiography*			Collateral filling to LAD	Left ventricular angiography		ECG
	LAD	LCX	RCA		EF(%)†	Wall motion	
1	90	Normal	Normal	Fair	70	Normal	Normal
2	100	100	75	Good	75	Apical hypokinesia	Normal
3	100	Normal	Normal	Poor	54	Apical hypokinesia	Anterior infarction
4	99	Normal	Normal	Fair	79	Normal	Normal
5	100	Normal	75	Good	75	Anterior hypokinesia	Normal
6	75	90	100	Fair	70	Normal	Normal
7	99	90	90	Good	67	Anterior hypokinesia	Normal
8	75	99	Normal	Fair	79	Normal	Normal
9	75	Normal	Normal	Poor	83	Apical hypokinesia	Normal
10	100	99	100	Good	64	Normal	Normal

*Percentage narrowing of lumen.
†Calculated using a single plane elipsoidal formula.[32]
LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; EF, ejection fraction; ECG, electrocardiogram.

measured by the continuous infusion thermodilution method,[10] which has been found to be reproducible and reliable.[11] Aortic and pulmonary artery pressures were measured by a Siemens Elema transducer 746 and recorded on a Mingograph 82 over a mean of 10 cardiac cycles, and mean pressure was obtained by electrical integration. Diastolic pulmonary artery pressure was taken to represent left ventricular filling pressure.

Samples of blood for analysis of haemoglobin concentration, oxygen saturation, and concentrations of lactate and free fatty acids were collected simultaneously from the aorta and coronary sinus immediately after each haemodynamic measurement. Oxygen saturation was measured by OSM 2 Hemoximeter (Radiometer, Copenhagen). Lactate and free fatty acid concentrations were measured by accepted methods.[12 13]

Simultaneously with the blood sampling for lactate analysis, an electrocardiogram was recorded from that precordial lead which showed the deepest ST segment depression during the exercise test. The ST depression was calculated as a mean of 10 consecutive complexes.

ATRIAL PACING AND INFUSION PROCEDURE

Control measurements were performed during sinus rhythm, and atrial pacing was then started. The heart rate was increased stepwise by 10 beats every 20 s until chest pain was reported. The haemodynamic and metabolic measurements were repeated and the pacing stopped. An additional blood sample for lactate determination was collected from the cardiac vein during the first 30 s after pacing.[14] Arterial blood for lactate measurement was not collected during and after pacing as arterial lactate concentrations are unaffected by atrial pacing.[15] An intravenous infusion of glyceryl trinitrate was then started. The rate of infusion was individually adjusted to reduce systolic blood pressure by 10–20 mm Hg and was then kept constant. After 15 min of continuous steady infusion and 20–30 min after the first pacing test the measurements in sinus rhythm and the pacing procedure were repeated. Heart rate was increased precisely as in the preinfusion study to the same frequency, and the same measurements were performed. The rate of the glyceryl trinitrate infusion was then increased to reduce systolic blood pressure to between 100 and 110 mm Hg, and the entire procedure was again repeated exactly as with the lower dose.

CALCULATIONS

Metabolic ischaemia was defined as negative myocardial lactate extraction ratio (lactate production) during pacing or in the immediate period after pacing.[14] The following calculations were performed: myocardial lactate extraction ratio, $(C_a\text{-}C_v)/C_a$; myocardial substrate uptake, $(C_a\text{-}C_v)\times CVF$; triple product, $HR\times SBP\times LVET$; coronary arteriolar resistance, mean aortic $BP\times 80/CVF$; and transmural perfusion gradient, DBP-LVFP, where C_a is arterial and C_v

Table 2 *Individual rates of glyceryl trinitrate infusion needed for reducing the systolic aortic pressure by 10–20 mm Hg (low dose) and to between 100 and 110 mm Hg (high dose)*

Case No	Glyceryl trinitrate	
	Low dose (μg/min)	High dose (μg/min)
1	6	25
2	6	82
3	19	40
4	9	74
5	25	73
6	10	79
7	15	68
8	6	85
9	6	98
10	15	107

Table 3 *Haemodynamic and metabolic effects of low and high dose glyceryl trinitrate infusion during pacing induced angina pectoris (n=10). Values are mean (SD)*

	Control		*Low dose*		*High dose*	
	Sinus rhythm	*Pacing*	*Sinus rhythm*	*Pacing*	*Sinus rhythm*	*Pacing*
			Haemodynamic effects			
Heart rate (beats/min)	67(8)	134(14)	68(9)	134(14)	71(14)	134(14)
Blood pressure (mm Hg)						
Systolic	147(18)	145(23)	137(21)†	128(23)**	107(13)**	103(9)**
Diastolic	80(10)	99(14)	81(9)	90(12)**	70(11)**	76(6)**
Mean	105(11)	117(17)	103(12)	105(16)**	83(12)**	85(9)**
Triple product (mm Hg beats s/min)	3075(195)	4405(274)	2822(194)	3714(274)**	2086(140)**	2788(107)**
Left ventricular filling pressure (mm Hg) (n=9)	9(3)	15(5)	7(3)*	8(3)**	5(3)**	6(3)**
Transmural perfusion gradient (mm Hg) (n=9)	71(10)	84(14)	74(9)	81(12)	65(11)	70(6)**
Cardiac venous flow (ml/min)	80(29)	156(65)	80(19)	125(48)†	70(18)	107(38)**
Coronary arteriolar resistance (dyn s cm^{-5})	114(30)	69(26)	106(22)	76(27)	100(22)	71(24)
			Metabolic effects			
Myocardial oxygen consumption (ml/min)	9·5(3·8)	17·3(7·6)	9·3(2·5)	13·6(5·5)†	7·8(2·3)†	10·7(3·4)**
Arteriovenous difference in oxygen saturation (%)	66(6)	63(5)	65(4)	62(4)	63(4)	61(6)
Lactate (arterial) (mmol/l)	0·81(0·26)		0·81(0·29)		0·84(0·25)	
Lactate extraction ratio	0·16(0·11)	−0·15(0·22) −0·54(0·43) (PP)	0·11(0·12)	−0·09(0·28) −0·33(0·53) (PP)	0·10(0·14)	−0·09(0·23) −0·23(0·36)† (PP)
Lactate uptake (μmol/min)	11·4(9·3)	−15·3(27·0)	8·3(10·4)	−2·7(18·0)	6·7(9·1)	−4·6(18·9)
Free fatty acids (arterial) (μmol/l) (n=8)	682(203)	695(197)	726(201)	733(161)	627(150)	635(184)
Free fatty acids uptake (μmol/min) (n=8)	9·3(3·5)	12·0(5·9)	10·0(5·0)	13·2(8·6)	7·7(3·7)	9·4(4·1)†
ST segment depression (mm)	0	1·8(0·2)	0	0·8(0·1)**	0	0·6(0·2)**

PP, post-pacing period; †$p<0.05$ *v* control; *$p<0.02$ *v* control; **$p<0.01$ *v* control.

cardiac venous substrate concentration, CVF cardiac venous flow (plasma flow for free fatty acids), HR heart rate, SBP systolic blood pressure, DBP diastolic blood pressure, BP blood pressure, LVET left ventricular ejection time (onset of rise of aortic pressure pulse to the incisure, in seconds), and LVFP left ventricular filling pressure.

STATISTICAL ANALYSIS

Statistical analysis was performed with Wilcoxon's rank sum test on paired data and linear regression analysis. All values are given as mean (1SD). A p value <0.05 was regarded as statistically significant.

Results

SYSTEMIC HAEMODYNAMIC EFFECTS

Angina pectoris was reported at a mean paced heart rate of 134(14) beats/min. The intended blood pressure reductions were achieved at infusion rates of glyceryl trinitrate which varied widely in the different patients (Table 2). The mean low dose of the drug was 12(7) μg/min and the high dose 73(25) μg/min leading to the haemodynamic effects summarised in Table 3. Small changes occurred during the low dose infusion in sinus rhythm; only systolic aortic pressure and left ventricular filling pressure decreased significantly. During pacing, however, both systolic and diastolic aortic pressure fell considerably, and the ventricular filling pressure fell from 15(5) to 8(3) mm Hg. The high dose of glyceryl trinitrate reduced all pressures appreciably both in sinus rhythm and during pacing. During pacing the systolic aortic pressure fell 25 mm Hg from the value during the low dose whereas the ventricular filling pressure was not significantly different from that obtained with the lower dose. No significant increase in resting heart rate occurred during the drug infusions despite falling blood pressures. Cardiac work, as measured by the triple product, decreased with the low and high dose during pacing by 16% and 37% respectively.

CORONARY HAEMODYNAMIC EFFECTS

Cardiac venous flow was unchanged by low and high dose treatment in sinus rhythm but fell during pacing by 20% and 31% respectively. Since the blood pressure also fell the calculated coronary vascular resistance did not change. No alteration in transmural perfusion gradient occurred during the low dose infusion since ventricular filling pressure and diastolic aortic

Table 4 *Individual values of myocardial ischaemia indices during pacing induced angina pectoris before and after low and high dose glyceryl trinitrate infusions*

Case No	*Myocardial lactate extraction ratio*						*ST segment depression (mm)*		
	During pacing			*Post pacing*					
	Control	*Low dose*	*High dose*	*Control*	*Low dose*	*High dose*	*Control*	*Low dose*	*High dose*
1	−0·09	0·12	0·32	−0·37	−0·09	0·22	3·3	0·9	0
2	−0·20	−0·22	−0·39	−0·72	−0·56	−0·56	1·7	1·0	0·8
3	0·08	0·01	0·03	−0·08	0·06	0·09	1·2	0·5	1·6
4	−0·04	−0·12	−0·18	−0·06	−0·25	−0·32	0·9	1·3	0·8
5	−0·68	−0·82	−0·48	−1·42	−1·73	−1·00	2·4	0·8	0·5
6	−0·19	−0·02	−0·08	−1·04	−0·20	−0·10	1·7	0	0
7	−0·02	0·03	0·05	−0·24	−0·19	0·01	2·3	1·6	1·4
8	−0·25	−0·06	−0·16	−0·68	−0·30	−0·40	1·7	0·8	0·3
9	−0·10	0·02	−0·01	−0·42	−0·10	−0·20	1·5	0·7	0
10	0·04	0·18	0·05	−0·34	0·08	0	1·6	0·5	0·3

pressure were equally reduced. When the higher dose was given, however, only the aortic pressure decreased, and this caused a 13% fall in the perfusion gradient.

MYOCARDIAL METABOLIC EFFECTS

Tables 3 and 4 give the mean and individual metabolic indices respectively during glyceryl trinitrate treatment. After the low dose of the drug myocardial oxygen uptake did not fall in sinus rhythm, whereas it fell by 21% during pacing. This reduction during pacing increased to 38% with the high dose. These changes in oxygen uptake paralleled the changes in the triple product. Arteriovenous oxygen difference, arterial free fatty acid concentrations, and myocardial uptake of free fatty acids were all unchanged by the drug infusion, except at the higher dose when the uptake of free fatty acids was reduced by 22% during pacing.

All patients included in the study fulfilled the metabolic criteria for ischaemia. Glyceryl trinitrate did not affect arterial lactate concentrations, whereas lactate extraction ratio and lactate uptake fell slightly with both dosages, but statistical significance was achieved only at the highest dose in the period after pacing. Lactate production occurred during pacing in eight patients during the control measurements, in five patients with the low dose, and in six patients with the high dose. In the period after pacing the corresponding numbers of patients showing lactate production were 10, eight, and six respectively.

ELECTROCARDIOGRAPHY

Mean ST segment depression during control pacing was 1·8(0·2) mm. It fell to 0·8(0·1) and 0·6(0·2) mm during the low dose and high dose infusions respectively. Increased ischaemia was found in one patient at the low dose (case 4) and in one at the high dose (case 3). There was no significant difference between the ST segment depression with the two infusion doses.

Discussion

Although relief of angina pectoris by amyl nitrite was reported more than 100 years ago,[16] the mechanisms of nitrate action is still a subject of controversy.[17] The major mechanism may be a reduction in cardiac work,[18 19] but direct effects on the coronary circulation are also possible.[20–22] This study was designed to determine the potential adverse effects of these mechanisms on myocardial ischaemia. Standard doses of glyceryl trinitrate could not be used because of the great variation in individual sensitivity to the drug. This was not a problem, however, since in this study the terms low dose and high dose of glyceryl trinitrate were based on the individual systolic blood pressure response. An interval of 20 min between the two pacing tests is sufficient to ensure reproducible results if no intervention is performed.[14 15]

The low dose of glyceryl trinitrate reduced myocardial ischaemia without additional adverse effects when the dose was increased. These conclusions are based on the changes in the electrocardiogram and lactate metabolism but not on chest pain since it is a relative non-specific marker of ischaemia and difficult to quantify.[23] Reduced myocardial ischaemia may be achieved by either a reduced oxygen demand or an increased oxygen supply. Cardiac work and oxygen consumption were reduced during the low dose infusion. The high dose infusion reduced cardiac work and oxygen consumption further, but ischaemia was unchanged. Different mechanisms may explain this discrepancy.

The afterload reduction obtained by falling blood pressure improved the oxygen demand-supply balance only when preload was also reduced. Since the resistance vessels are maximally dilated in an

ischaemic area flow to this region is entirely dependent on diastolic perfusion pressure and subendocardial tension in diastole.[24] A fall in left ventricular filling pressure may therefore improve subendocardial flow by reducing subendocardial tension.[25,26] The low dose of glyceryl trinitrate did not change the transmural perfusion gradient because diastolic aortic pressure and left ventricular filling pressure were equally reduced. The perfusion of the ischaemic area may thus have been only moderately reduced even though our coronary sinus measurements did not allow direct estimation of ischaemic tissue flow. On the other hand, the perfusion gradient was substantially reduced by the high dose of glyceryl trinitrate as a result of a reduction in aortic blood pressure, and diminished coronary flow might counteract the beneficial effect of afterload reduction on oxygen demand. Direct evidence for this adverse action of the drug has recently been provided in dogs[27] and now also in man. Whereas the effect on infarct size was abolished in dogs, there was still a significant effect on ischaemia in man. Our results indicate that preload reduction plays an important part when cardiac work is reduced by vasodilatation because myocardial perfusion is less affected. This finding was seen in patients who were mildly hypertensive and in whom afterload reduction should be even more important.[3]

Glyceryl trinitrate acted differently on the coronary circulation in sinus rhythm and during atrial pacing. Myocardial blood flow was reduced during atrial pacing, which is consistent with earlier reports.[18,19] This has been attributed to a reduced perfusion gradient and autoregulatory adjustments of arteriolar tone in response to reduced oxygen demand, which offset the vasodilating effects of glyceryl trinitrate on the coronary circulation. In sinus rhythm, however, myocardial blood flow did not fall significantly at the highest infusion rate despite reduced triple product and oxygen consumption. A similar observation was recently reported in patients with occluded anterior descending coronary artery,[28] and increased collateral flow was suggested. Our patients had severe stenosis of this artery with collaterals to the poststenotic segment. Since proximal coronary sinus measurements determine mainly the drainage from the anterior descending artery area[14] increased collateral flow may explain maintained flow. A drug induced dilatation of the stenotic arterial segment is also possible.[29] These contributions to regional myocardial flow are, however, limited[30]; the alterations in metabolic demand dominate the flow measurements during atrial pacing.

Thus the flow measurements suggested redistribution of blood flow by increased collaterals at the high dose of glyceryl trinitrate. Blood flow may be redistributed also by changes in arteriolar tone. Arteriolar dilative drugs decrease vascular resistance in non-ischaemic myocardium but cause little change in ischaemic zones. This reduces the pressure gradient between vessels in non-ischaemic and ischaemic tissue, which might produce a coronary steal effect.[17,31] The unchanged coronary resistance and the arteriovenous oxygen difference in our study suggest indirectly that the coronary steal effect is a minor problem during glyceryl trinitrate treatment. These measurements, however, apply to the entire coronary circulation and have to be interpretated with caution. Other potential dangers associated with vasodilator treatment are reflex tachycardia and catecholamine stimulation, which increase oxygen demand.[2] Unchanged heart rate and arterial free fatty acid concentrations strongly suggest that these mechanisms are of minor importance during glyceryl trinitrate infusion.

We have shown that the potential adverse effects of vasodilatation during myocardial ischaemia are not of major importance when glyceryl trinitrate infusions are used. The oxygen demand-supply balance is maintained during afterload reduction because the effect of decreased myocardial perfusion is offset by falling oxygen consumption. Nevertheless, moderately reduced arterial blood pressure should be the target as higher doses do not produce an additional beneficial effect on ischaemia and may adversely affect other vascular beds, especially the brain in hypertensive patients.

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