Coronary and myocardial metabolic effects of combined glyceryl trinitrate and propranolol administration

Observations in patients with and without coronary disease

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SUMMARY Coronary haemodynamic and metabolic effects of propranolol and glyceryl trinitrate were studied in 12 patients with coronary artery disease and 5 without coronary heart disease, at rest and during tachycardia stress. Propranolol-associated reductions in indices of myocardial oxygen demand, left ventricle work, tension time, and left ventricle oxygen utilisation ($LV\dot{V}O_2$) were reversed when heart rate was controlled by atrial pacing. Adding glyceryl trinitrate at rest also restored heart rate but decreased the left ventricular work index and tension time index as coronary resistance declined paradoxically. Tachycardia-related increases in tension time index and $LV\dot{V}O_2$ were unchanged after propranolol, and ischaemia (angina, ST depression, and reduced lactate extraction) was not altered in most of the patients. During tachycardia, the addition of glyceryl trinitrate decreased the tension time index and $LV\dot{V}O_2$; angina recurred in only 4 patients, and ST depression and lactate extraction improved. Similar haemodynamic changes occurred in the patients with normal coronary arteries.

In contrast with propranolol administered alone, propranolol plus glyceryl trinitrate enhances tachycardia tolerance and prevents tachycardia-induced manifestations of ischaemia. This action is attributed to glyceryl trinitrate-associated improvement in the adequacy of myocardial perfusion.

Although nitrates are frequently used in combination with propranolol and have been justified by clinical and haemodynamic rationale (Russek, 1968; Wiener *et al.*, 1969; Aronow, 1972), there is no information on the effect of this combination on the coronary circulation. Propranolol is known to reduce stress-related augmentation of cardiac rate, contractility, and work—all of which have prominent oxygen-sparing effects (Dwyer *et al.*, 1968; Wiener *et al.*, 1969). Some have suggested that this agent also directly affects the coronary circulation and reduces myocardial flow (Parratt, 1965; Wolfson *et al.*, 1966; Naylor *et al.*, 1967, 1968; Stein *et al.*, 1968; Marchetti *et al.*, 1972) and oxygen consumption (Jorgensen *et al.*, 1973; Mueller *et al.*, 1974) while increasing coronary resistance. Since the

effect of propranolol on heart rate also uniformly decreases oxygen requirements, significant direct coronary actions may be obscured. Glyceryl trinitrate, on the other hand, also has oxygen-sparing effects that reduce ventricular pressure (Bernstein *et al.*, 1966), size (William *et al.*, 1965), and work (Robin *et al.*, 1967) determinants of oxygen demand. Though there is angiographic evidence that sublingual glyceryl trinitrate produces coronary dilatation (Likoff *et al.*, 1964), most studies generally have indicated that coronary flow is unchanged or declined in patients with coronary disease (Gorlin *et al.*, 1959; Parker *et al.*, 1971). This presumably is in response to reduced oxygen demand.

Because information describing the effects of glyceryl trinitrate on coronary haemodynamics and metabolism in the presence of beta-blockade was not available, we studied (1) the coronary haemo-

dynamic, metabolic, and antianginal actions of glyceryl trinitrate in patients with angina pectoris after pretreatment with propranolol; (2) the therapeutic efficacy of glyceryl trinitrate in the beta-blocked patient on tachycardia-induced ischaemia; and (3) the importance of chronotropic influences of these agents on these responses. To circumvent propranolol's chronotropic effects, we used atrial pacing to control heart rate and also to evoke angina. Alterations in chest pain and coronary flow, as reflected in the coronary sinus blood flow, and systemic haemodynamic and myocardial metabolic responses occurring during tachycardia were compared before and after administering propranolol and glyceryl trinitrate.

Patients and methods

Twelve patients with clinically stable angina pectoris (New York Heart Association Class II or III) associated with ≥ 75 per cent coronary artery diameter narrowing were studied. Informed consent was obtained to include the procedures outlined subsequently. All antianginal agents were omitted for at least 1 week before study, but use of glyceryl trinitrate was permitted until the study day. Five patients with normal coronary and left ventricular angiography were also studied. None had anatomical or physiological evidence of other forms of heart disease.

With the patients in a postabsorptive state and without premedication, a No. 18 Teflon catheter was inserted percutaneously into a brachial artery, and systemic pressure was measured (Statham P23Db transducer). Mean arterial pressure was obtained by electric filtering. A specially designed No. 7 pacing catheter (Wilton Webster Co.) was positioned in the midcoronary sinus from a median cubital vein. This catheter was modified to measure coronary sinus blood flow by the continuous thermodilution method (Ganz *et al.*, 1971). The procedures used in our laboratory to determine coronary sinus blood flow, verify catheter position, and simultaneously measure cardiac output and prevent blood volume changes are described elsewhere (Pepine *et al.*, 1974). Electrocardiographic lead V5 was monitored continuously; and the standard limb leads were recorded before, during, and after pacing-induced angina. The ST segment change from control was measured in the 3 to 5 beats after termination of pacing stress to avoid pacing-induced artefacts. Horizontal or down-sloping ST changes of 0.8 s or greater in duration, persisting in 3 consecutive beats, were reported. Recording speed was usually 25 mm per second, but 200 mm per second was used to measure systolic ejection and diastolic filling periods.

Table 1 Outline of study periods

I.	Control measurements
	Rest
	Tachycardia
II.	Propranolol, 10 mg IV
	Propranolol
	Propranolol—heart rate at control rest level
	Propranolol—tachycardia
III.	Glyceryl trinitrate, 0.3 mg SL
	Propranolol + glyceryl trinitrate
	Propranolol + glyceryl trinitrate—heart rate at control rest level
	Propranolol + glyceryl trinitrate—tachycardia

During determinations of cardiac output and coronary sinus blood flow, 10 mm per second was used. Diastolic pressure time index was calculated according to Barnard and co-workers (1973) and the ratio of the diastolic pressure time index to tension time index was determined (Buckberg *et al.*, 1972). Simultaneously obtained coronary sinus and arterial blood samples were analysed in duplicate for oxygen and lactate contents by methods previously described (Pepine *et al.*, 1974).

The experimental design is illustrated in Table 1. After catheters were in position and heart rate and mean arterial pressure stabilised, control resting measurements were made of mean arterial pressure, cardiac output, heart rate, coronary sinus blood flow, and myocardial oxygen and myocardial lactate extractions. Heart rate was then increased by increments of 10 beats per minute until angina occurred, and measurements were repeated before pacing was terminated. After symptoms subsided and ST segment and haemodynamic changes returned to resting levels, propranolol (10 mg) was administered intravenously (1 mg/min). Ten minutes later, measurements were repeated. The heart rate was then controlled by atrial pacing at the same resting heart rate that had been observed before propranolol, and measurements were repeated. Measurements were made as a repeat tachycardia stress test was performed. During this repeat test, heart rate and the duration of increment change duplicated the predrug test. After symptoms subsided and ST segment and haemodynamic changes returned to resting levels, glyceryl trinitrate (0.3 mg sublingually) was given. Measurements were repeated 2 to 3 minutes after the glyceryl trinitrate dissolved and heart rate and mean arterial pressure changes stabilised. When necessary, resting heart rate was again controlled by pacing to resting levels before propranolol administration. Heart rate was then increased as in the previous stress tests to the rate at which angina occurred in the control period. Measurements were repeated with tachycardia stress

Table 2 Summary of clinical findings in the patients with coronary artery disease

Case	Sex	Age	MI	Coronary angiography*					Tachycardia stress								
									Angina			ST depression (mm)			Abnormal lactate extraction†		
				RCA	MLCA	LAD	LCX	Coll	T	Tp	Tpn	T	Tp	Tpn	T	Tp	Tpn
1	M	61	0	0	0	99	75	+	+	+	0	1.2	1.0	0.5	+	+	0
2	F	59	0	100	0	0	75	0	+	+	0	1.0	1.0	0.0	0	+	0
3	M	35	+	100	0	50	50	+	+	+	0	1.0	1.2	0.3	0	0	0
4	F	55	0	75	0	75	75	+	+	+	0	0.7	0.9	0.0	+	+	0
5	M	52	+	0	0	25	100	0	+	+	+	0.0	0.0	0.0	+	+	0
6	M	49	0	50	50	100	100	0	+	+	0	1.3	1.0	0.5	0	0	0
7	M	53	0	0	0	95	100	0	+	+	+	1.0	0.8	1.0	+	+	+
8	M	55	+	75	0	0	95	0	+	0	0	1.2	1.2	0.7	0	0	0
9	M	55	0	100	0	75	75	+	+	+	+	1.1	1.0	0.5	0	+	0
10	M	44	+	100	0	25	0	+	+	+	0	0.0	0.0	0.0	+	0	0
11	M	46	0	25	0	90	90	+	+	+	+	1.1	1.0	0.8	0	0	+
12	M	50	+	95	10	90	95	+	+	0	0	1.0	1.2	0.3	+	+	0

MI, myocardial infarction; RCA, right coronary artery; MLCA, main left coronary artery; LAD, left anterior descending; LCX, left circumflex coronary arteries, respectively; Coll, coronary collaterals; T, Tp, Tpn refer to tachycardia stress test in control, propranolol, and propranolol + nitroglycerine periods, respectively; 0, No; +, Yes.

*Per cent diameter reduction from 0-100.

†Lactate extraction < 10 per cent.

and glyceryl trinitrate and pacing terminated. In the 5 patients with normal coronary arteries, tachycardia measurements were made at 85 per cent of their maximal predicted heart rate (3 patients) or at peak heart rate achieved before limited by AV block (2 patients).

The following calculations were made: CI = CO/body surface area in m² (litres/m²); MSER = CI/HR per SEP (ml/s per m²); TTI = SPm × SEP × HR (mmHg s/min); LVWI = SPm × CI × 1.36/100 (kg m/min per m²); CRI = SPm/CSBF (resistance units); LVVO₂ = CSBF × arterial-coronary sinus oxygen content ÷ arterial lactate × 100 (%). The ratio of LVWI/LVVO₂ was used as an index of left ventricular mechanical efficiency. Means and standard errors of the mean were calculated and compared by the t test for paired data.

Results

CLINICAL RESPONSES

Pertinent clinical data are summarised in Table 2. Typical angina, occurring during control tachycardia at a mean heart rate of 120 beats per minute in each of the 12 patients with coronary artery disease, recurred after pacing in 10 at the same heart rate. ST depression was not significantly altered. After the administration of glyceryl trinitrate, 6 additional patients did not experience angina. Significant change occurred in average ST segment depression produced by the same tachycardia stress

after administration of glyceryl trinitrate (0.88 ± 0.13 to 0.38 ± 0.1 mm, $P < 0.05$). ST depression was less in 7 of the 8 who did not experience pacing-induced angina. The absence of pacing-induced angina could not be predicted by any other clinical or haemodynamic feature analysed.

SYSTEMIC AND CORONARY HAEMODYNAMIC MEASUREMENTS

Propranolol reduced resting heart rate (73 ± 2 to 67 ± 2 beats/min, mean $\pm$ SEM, $P < 0.01$). This effected proportional reduction of the tension time index (8.5%) and cardiac index (10%) with related decrements in LVVO₂ (7.6%) and coronary sinus blood flow (11%) as the coronary resistance index increased (12%), all $P < 0.05$. When heart rate was returned to control levels, no significant changes were observed (Table 3). The addition of glyceryl trinitrate restored heart rate (67 to 70 ± 3 beats/min), but significant reduction in cardiac, tension time, left ventricular work, and diastolic pressure time indices and ejection rate persisted, though the coronary resistance index was decreased as compared with propranolol resting values. In some patients, heart rate remained several beats slower than resting control rate after glyceryl trinitrate was added. Returning heart rate to control values (atrial pacing) did not influence the reduction noted above (Table 3).

With tachycardia stress, propranolol reduced the cardiac and left ventricular work indices and mean systolic ejection rate. Coronary sinus blood flow and coronary resistance index were not appreciably altered, as compared with control tachycardia. In

Table 3 Summary of systemic and coronary haemodynamic effects at the same heart rate in patients with coronary artery disease ($N = 12$)

	Rest (heart rate 72 ± 2 beats/min)			Tachycardia (heart rate 120 ± 5 beats/min)		
	Control	Propranolol	Propranolol + glyceryl trinitrate	Control	Propranolol	Propranolol + glyceryl trinitrate
CI						
(l/min per m ²)	3.4 ± 0.2	3.3 ± 0.2	2.9 ± 0.3	3.8 ± 0.2	3.3 ± 0.3	3.1 ± 0.3
TTI						
(mmHg s/min)	2002 ± 135	2110 ± 144	1815 ± 112	2887 ± 201	3048 ± 250	2714 ± 205
LVWI						
(kg m/min per m ²)	4.3 ± 0.2	4.4 ± 0.3	3.4 ± 0.3	5.2 ± 0.4	4.7 ± 0.3	4.0 ± 0.4
MSER						
(ml/s per m ²)	155 ± 8	152 ± 10	135 ± 10	133 ± 6	117 ± 8	115 ± 10
DPTI						
(mmHg s/min)	3146 ± 171	3456 ± 188	2952 ± 156	2852 ± 192	3002 ± 200	2837 ± 180
DPTI/TTI	1.57 ± 0.1	1.64 ± 0.07	1.62 ± 0.1	1.03 ± 0.09	0.99 ± 0.08	1.06 ± 0.1
CSBF						
(ml/min)	123 ± 10	129 ± 12	122 ± 10	164 ± 13	160 ± 15	137 ± 11
CR						
(mmHg/ml per min)	0.8 ± 0.07	0.91 ± 0.1	0.7 ± 0.05	0.67 ± 0.09	0.7 ± 0.09	0.7 ± 0.08

Abbreviations: CI, cardiac index; CR, coronary resistance index; CSBF, coronary sinus blood flow; DPTI, diastolic pressure time index; LVWI, left ventricular work index; MSER, mean systolic ejection rate; TTI, tension time index.

* $P < 0.01$, † $P < 0.05$ —the only significant comparisons.

contrast, the addition of glyceryl trinitrate reduced the tension time, diastolic pressure time, and left ventricular work indices and coronary sinus flow during tachycardia stress, compared with values after propranolol (Table 3). When compared with control, tachycardia, cardiac index, left ventricular work index, mean systolic ejection rate, and coronary sinus blood flow declined.

INDICES OF MYOCARDIAL METABOLISM AND EFFICIENCY

Analysis of the effects of propranolol on myocardial metabolism revealed that $LV\dot{V}O_2$ declined (12%, $P < 0.05$), whereas lactate extraction and $LVWI/LV\dot{V}O_2$ were not significantly influenced. When heart rate was controlled, $LV\dot{V}O_2$, lactate extraction, and $LVWI/LV\dot{V}O_2$ were not significantly different from control values (Table 4). The addition of glyceryl trinitrate, however, lowered the left ventricular work index disproportionately, so that $LVWI/LV\dot{V}O_2$ decreased significantly (25%, $P < 0.01$) from levels after propranolol alone. Though lactate extraction decreased, the values were not significant ($P = 0.05$).

With tachycardia stress, propranolol decreased $LVWI/LV\dot{V}O_2$ (0.36 to 0.28, $P < 0.01$), compared with values observed after propranolol administration with the subject at rest, through a disproportionate decline in left ventricular work index. The decline in lactate extraction became significant after propranolol (29 to 9%, $P < 0.05$). After glyceryl trinitrate was added, $LV\dot{V}O_2$ declined as compared with propranolol values (17.9 to 15.0). Abnormal decrements in $LVWI/LV\dot{V}O_2$ and lactate extraction did not occur. Lactate extraction was reversed 9.0 to 27%.

Data from the patients with normal coronary arteries are summarised in a similar manner in Tables 5 and 6. Propranolol also reduced the resting heart rate (72 ± 4 to 67 ± 3 beats/min) in these patients as coronary sinus blood flow (8.3%), tension time index (10%), and cardiac index (8%) declined and coronary resistance increased (11%). Again at the same heart rate and after glyceryl trinitrate, no significant systemic or coronary haemodynamic differences occurred (Tables 3 and 5). As expected, because more tachycardia stress was tolerated by these normal patients (137 vs. 120

Table 4 Summary of metabolic effects of glyceryl trinitrate after propranolol at same heart rate in patients with coronary artery disease ($N = 12$)

	Rest (heart rate = 72 ± 2 beats/min)			Tachycardia (heart rate = 120 ± 5 beats/min)		
	Control	Propranolol	Propranolol + glyceryl trinitrate	Control	Propranolol	Propranolol + glyceryl trinitrate
LV O_2 utilisation (ml/min)	13.5 ± 0.97	12.8 ± 1.3	12.9 ± 1.0	18.5 ± 1.6	17.9 ± 1.9	15.0 ± 1.3
LV O_2 extraction (%)	65 ± 2	64 ± 2	63 ± 2	65 ± 1.2	63 ± 2	64 ± 2
Lactate extraction (%)	27 ± 8	29 ± 9	17 ± 4	18 ± 5	9 ± 5	27 ± 1
LVWI/LVVO ₂	0.33 ± 0.02	0.36 ± 0.03	0.27 ± 0.03	0.30 ± 0.03	0.28 ± 0.03	0.27 ± 0.02

Abbreviations: LV, left ventricle; LV O_2 , left ventricle oxygen; LVWI, left ventricle work index; LVVO₂, left ventricle oxygen utilisation index; LVWI/LVVO₂, mechanical efficiency index; * $P < 0.01$ —the only significant comparison.

beats/min), coronary sinus blood flow and related values were considerably higher. Except for an increase in lactate extraction with tachycardia before (16 to 22, $P = 0.1$) and after (20 to 29, $P < 0.05$) propranolol, no differences in metabolism or efficiency indices resulted (Tables 4 and 6).

Table 5 Summary of systemic and coronary haemodynamic effects at same heart rate in patients with normal coronary arteries ($N = 5$)

	Rest (heart rate = 72 ± 4 beats/min)			Tachycardia (heart rate = 137 ± 6 beats/min)		
	Control	Propranolol	Propranolol + glyceryl trinitrate	Control	Propranolol	Propranolol + glyceryl trinitrate
CI (litres/min per m ²)	3.7 ± 0.4	3.0 ± 0.2	2.6 ± 0.2	4.2 ± 0.4	3.4 ± 0.3	2.8 ± 0.2
TTI (mmHg s/min)	2150 ± 143	2140 ± 156	1789 ± 131	3229 ± 199	3235 ± 164	2700 ± 94
LVWI (kg m/min per m ²)	5.0 ± 0.6	4.1 ± 0.4	3.1 ± 0.3	5.7 ± 0.6	4.8 ± 0.5	3.4 ± 0.3
MSER (ml/s per m ²)	168 ± 10	140 ± 9	121 ± 10	139 ± 8	115 ± 9	112 ± 9
DPTI (mmHg s/min)	3182 ± 201	3210 ± 213	2505 ± 187	2519 ± 160	2588 ± 192	2214 ± 158
DPTI/TTI	1.48 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	0.78 ± 0.09	0.80 ± 0.08	0.82 ± 0.1
CSBF (ml/min)	99 ± 7	102 ± 6	76 ± 6	143 ± 15	151 ± 17	104 ± 8
CR (mmHg/ml per min)	1.0 ± 0.05	0.99 ± 0.08	1.2 ± 0.07	0.73 ± 0.07	0.72 ± 0.07	0.80 ± 0.07

Abbreviations: CI, cardiac index; TTI, tension time index; LVWI, ventricular work index; MSER, mean systolic ejection rate; DPTI, diastolic pressure time index; CSBF, coronary sinus blood flow; CR, coronary resistance index.

* $P < 0.01$, † $P < 0.05$ —the only significant comparisons.

Table 6 Summary of metabolic effects at same heart rate in patients with normal coronary arteries (N = 5)

	Rest (heart rate = 72 ± 4 beats/min)			Tachycardia (heart rate = 137 ± 6 beats/min)		
	Control	Propranolol	Propranolol + glyceryl trinitrate	Control	Propranolol	Propranolol + glyceryl trinitrate
LV $\dot{V}O_2$ (ml/min)	10.8 $\pm$ 1.1	11.0 $\pm$ 1.3	8.6 $\pm$ 1.2	16.4 $\pm$ 2.7	15.5 $\pm$ 2.5	10.9 $\pm$ 1.5
LV O_2 extraction (%)	67 $\pm$ 4	68 $\pm$ 4.1	70 $\pm$ 4.2	71 $\pm$ 4.3	70 $\pm$ 4.2	72 $\pm$ 4.5
Lactate extraction (%)	16 $\pm$ 7	20 $\pm$ 8	27 $\pm$ 12	22 $\pm$ 7	29 $\pm$ 11	30 $\pm$ 12
LVWI/LV $\dot{V}O_2$	0.44 $\pm$ 0.08	0.41 $\pm$ 0.1	0.38 $\pm$ 0.09	0.45 $\pm$ 0.11	0.36 $\pm$ 0.08	0.35 $\pm$ 0.06

Abbreviations: LV $\dot{V}O_2$, left ventricular oxygen utilisation; LVWI/LV $\dot{V}O_2$, mechanical efficiency index.

*P < 0.01, †P < 0.05—the only significant comparisons.

Discussion

Glyceryl trinitrate is widely used in combination with propranolol for the treatment of angina pectoris. The therapeutic benefit of this drug combination results from a complex interaction of multiple cardiovascular responses (Goldstein and Epstein, 1972). Propranolol-related actions contributing to this response include negative chronotropic and inotropic effects (Dwyer *et al.*, 1968; Wiener *et al.*, 1969). Counteracting these salutary responses, there is evidence implying that this agent may also increase ventricular size and the duration of systole (Goldstein and Epstein, 1972). The latter effects would tend to augment oxygen consumption by increasing wall tension. Additionally, the possibility of a coronary vasoconstricting action has been suggested (Marchetti *et al.*, 1972). Glyceryl trinitrate, on the other hand, reduces coronary perfusion pressure but may increase coronary flow at least transiently in some patients (Goldstein and Epstein, 1972). However, its major beneficial effect is thought to relate to reduced ventricular size and pressure. These actions decrease tension and shorten the duration of systole, thereby reducing oxygen consumption. Glyceryl trinitrate baroreceptor-mediated effects, however, increase heart rate and contractility. In the light of the foregoing, others have postulated that the negative chronotropic and inotropic actions of propranolol tend to offset potentially deleterious reflex effects of glyceryl trinitrate (Wiener *et al.*, 1969; Goldstein and Epstein, 1972), and its ability to decrease ventricular size and the duration of systole counterbalances the possible disadvantageous actions of propranolol. Thus, though the

net contributions of these responses alone and the role of direct coronary actions have not yet been completely defined, this drug combination appears to be clinically beneficial.

The present study indicates that the antianginal action of propranolol, shown in previous investigations using exercise-evoked angina, is not prominent when heart rate is controlled. Supporting this subjective response was the absence of significant electrocardiographic, haemodynamic, or metabolic data to suggest improvement in the oxygen demand-supply relation. Some evidence also suggested that depression of haemodynamic function persists at the same heart rate. No findings to support a direct coronary action of propranolol were observed when the heart rate was controlled. The addition of glyceryl trinitrate after propranolol favourably influenced the tachycardia/angina threshold and demonstrated that heart rate changes are not of major importance in the anti-ischaemic action of this drug combination. The latter apparently derives from reduced oxygen consumption at a given level of tachycardia stress. Though this response results in reduced tachycardia coronary flow, the flow level appears adequate for the reduced oxygen demands because the clinical, electrocardiographic, and metabolic ischaemic indices improved.

This depression of left ventricular oxygen utilisation by the addition of glyceryl trinitrate, independent of heart rate, suggests that reduction of tension was of primary importance. Evidence for a coronary circulatory effect is suggested by the reduced coronary resistance index observed after glyceryl trinitrate was added. Because heart rate was controlled and other factors relating to oxygen

requirements declined with the addition of glyceryl trinitrate, the decline in coronary resistance cannot be attributed to increases in myocardial oxygen demand. It is possible for an agent to reduce coronary resistance by augmenting oxygen consumption and not be reflected in these indices through increases in cardiac size or contractility. The former is at variance to the known action of glyceryl trinitrate on ventricular size. The latter is unlikely, since changes in contractility caused by reflex or general release of catecholamines should have been blocked by the propranolol. Furthermore, because a decline in tension and work indices would be expected to cause coronary vasoconstriction, the observed reduction in resistance may underestimate the degree of vasodilatation influence.

The magnitude of the coronary resistance decline at rest after administration of glyceryl trinitrate was quantitatively similar to that observed during tachycardia-induced angina before treatment. When LVVO_2 was again increased in response to the demands imposed by tachycardia stress after glyceryl trinitrate, no further decline in coronary resistance accompanied this usually potent stimulus to vasodilatation. These findings suggest that either maximum dilatation of the diseased coronary bed had already occurred or that reduction of diastolic pressure time by glyceryl trinitrate abbreviated potential flow responses to augmented oxygen demands. Possibly a combination of these effects occurred. This could explain the finding that several patients still experienced angina after this usually potent combination, and it warrants more detailed investigation.

Several limitations to the coronary sinus sampling techniques have been reviewed elsewhere but should be re-emphasised (Klocke, 1975). In a segmental disease, such as coronary artery disease, regional alteration in perfusion and metabolism may not necessarily be reflected in the total coronary sinus effluent. Findings of a relatively high coronary sinus oxygen concentration in some patients with coronary artery disease support this assumption and suggest that midcoronary sinus sampling may actually be weighed in favour of relatively normally perfused areas of myocardium. Because of this limitation, we felt that considerable additional insight into the mechanism responsible for the coronary actions observed could be obtained by extending these observations to patients with normal coronary arteries. Interestingly, with the exception of the lactate changes, these normal subjects responded similarly to propranolol. After administration of glyceryl trinitrate, however, pronounced tachycardia-induced changes in coronary blood flow and resistance persisted. Though not conclusive, this

finding supports the suggestion that the maximum dilatory capacity of the patient with coronary disease is very limited.

These findings are of clinical interest in treating patients with coronary heart disease. For example, patients with acute myocardial ischaemia who develop tachyarrhythmias that persist after propranolol therapy may be at a distinct disadvantage. The evidence presented indicates that adding glyceryl trinitrate under these circumstances is particularly advantageous. Its use should not be delayed pending the evaluation of other therapeutic interventions.

In conclusion, glyceryl trinitrate appears to retain its potentially beneficial coronary haemodynamic and metabolic actions in the presence of beta-blockade. The oxygen cost of a given tachycardia stress is reduced, and evidence for resting coronary vasodilatation is present. Because deterioration of myocardial lactate metabolism and efficiency during tachycardia is prevented, the adequacy of myocardial perfusion is improved. These data indicate that an important advantage relative to the coronary circulation ensues when glyceryl trinitrate is used in the presence of propranolol.

References

- Aronow, J. (1972). Medical treatment of angina pectoris. III. Pharmacology of sublingual nitrites as antianginal drugs. *American Heart Journal*, **84**, 273-275.
- Barnard, R. J., MacAlpin, R., Kattus, A. A., and Buckberg, G. D. (1973). Ischemic response to sudden strenuous exercise in healthy men. *Circulation*, **48**, 936-942.
- Bernstein, L., Friesinger, G. C., Lichtlen, P. R., and Ross, R. S. (1966). The effect of nitroglycerin on the systemic and coronary circulation in man and dogs. *Circulation*, **33**, 107-116.
- Buckberg, G. D., Fixler, D. E., Archie, J. P., and Hoffman, J. I. E. (1972). Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circulation Research*, **30**, 67-81.
- Dwyer, E. M., Jr., Wiener, L., and Cox, J. W. (1968). Effects of beta-adrenergic blockade (propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise-induced angina pectoris. *Circulation*, **38**, 250-260.
- Ganz, W., Tamura, K., Marcus, H. S., Donoso, R., Yoshida, S., and Swan, H. J. C. (1971). Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation*, **44**, 181-195.
- Goldstein, R. E., and Epstein, S. E. (1972). Medical management of patients with angina pectoris. *Progress in Cardiovascular Diseases*, **14**, 360-398.
- Gorlin, R., Brachfield, N., MacLeod, C., and Bopp, P. (1959). Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation*, **19**, 705-718.
- Jorgensen, C. R., Wang, K., Wang, Y., Gobel, F. L., Nelson, R. R., and Taylor, H. (1973). Effect of propranolol on myocardial oxygen consumption and its hemodynamic correlates during upright exercise. *Circulation*, **48**, 1173-1182.
- Klocke, F. J. (1975). Quantitative evaluation of coronary perfusion in man. *Catheterization and Cardiovascular Diagnosis*, **1**, 349-360.

- Likoff, W., Kasparian, H., Lehman, J. S., and Segal, B. L. (1964). Evaluation of 'coronary vasodilators' by coronary arteriography. *American Journal of Cardiology*, **13**, 7-9.
- Marchetti, G., Merlow, L., and Nosedà, V. (1972). Mechanism of the decrease in coronary blood flow after beta-blockade in conscious dogs. *Cardiovascular Research*, **6**, 532-540.
- Mueller, H. S., Ayres, S. M., Religa, A., and Evans, R. G. (1974). Propranolol in the treatment of acute myocardial infarction. Effect on myocardial oxygenation and hemodynamics. *Circulation*, **49**, 1078-1087.
- Nayler, W. G., McInnes, I., Swann, J. B., Carson, V., and Lowe, T. E. (1967). Effect of propranolol, a beta-adrenergic antagonist, on blood flow in the coronary and other vascular fields. *American Heart Journal*, **73**, 207-216.
- Nayler, W. G., McInnes, I., Swann, J. B., Race, D., and Lowe, T. E. (1968). Effect of adrenergic beta-receptor blocking drugs on blood flow in the coronary and other vascular fields. *Cardiovascular Research*, **2**, 371-378.
- Parker, J. O., West, R. O., and Di Giorgi, S. (1971). The effect of nitroglycerin on coronary blood flow and the hemodynamic response to exercise in coronary artery disease. *American Journal of Cardiology*, **27**, 59-65.
- Parratt, J. R. (1965). Blockade of sympathetic beta-receptors in the myocardial circulation. *British Journal of Pharmacology and Chemotherapy*, **24**, 601-611.
- Pepine, C. J., Schang, S. J., and Bemiller, C. R. (1974). Effects of perhexiline on coronary hemodynamic and myocardial metabolic responses to tachycardia. *Circulation*, **49**, 887-893.
- Robin, E., Cowan, C., Puri, P., Ganguly, S., DeBoyrie, E., Martinez, M., Stock, T., and Bing, R. J. (1967). A comparative study of nitroglycerin and propranolol. *Circulation*, **36**, 175-186.
- Russek, H. I. (1968). Propranolol and isosorbide dinitrate synergism in angina pectoris. *American Journal of Cardiology*, **21**, 44-54.
- Stein, P. D., Brooks, H. L., Matson, J. L., and Hyland, J. W. (1968). Effect of beta-adrenergic blockade on coronary blood flow. *Cardiovascular Research*, **2**, 63-67.
- Wiener, L., Dwyer, E. A., Jr., and Cox, J. W. (1969). Hemodynamic effects of nitroglycerin, propranolol and their combination in coronary heart disease. *Circulation*, **39**, 623-632.
- William, J. F., Jr., Glick, G., and Braunwald, E. (1965). Studies on cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin. *Circulation*, **32**, 767-771.
- Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R. (1966). Propranolol and angina pectoris. *American Journal of Cardiology*, **18**, 345-353.

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