Effects of propranolol on myocardial oxygen consumption, substrate extraction, and haemodynamics in hypertrophic obstructive cardiomyopathy

D S THOMPSON, N NAQVI, S M JUUL, R H SWANTON, D J COLTART, B S JENKINS, M M WEBB-PEPLOE

From the Departments of Cardiology and Medicine, St. Thomas' Hospital, London

SUMMARY Myocardial substrate extraction, coronary sinus flow, cardiac output, and left ventricular pressure were measured at increasing pacing rates before and after propranolol (0·2 mg/kg) in 13 patients with hypertrophic obstructive cardiomyopathy (HOCM) during diagnostic cardiac catheterisation. At the lowest pacing rate myocardial oxygen consumption varied considerably between patients and very high values were found in several individuals (range 10·1 to 57·5 ml/min). These large differences between patients were not explicable by differences in cardiac work; consequently, cardiac efficiency, estimated from the oxygen cost of external work, varied between patients and was lower than normal in all but two. The pattern of substrate extraction at the lowest pacing rate was similar to results reported for the normal heart, and measured oxygen consumption could be accounted for by complete oxidation of the substrates extracted; thus there was no evidence of a gross abnormality of oxidative metabolism, suggesting that low efficiency lay in the utilisation rather than in the production of energy. Each of the four patients with the highest myocardial oxygen consumption and lowest values of efficiency sustained progressive reductions in lactate and pyruvate extraction as heart rate increased, and at the highest pacing rate had low (<3%) or negative lactate extraction ratios. In three of these four, coronary sinus flow did not increase progressively with each increment in heart rate. One patient with low oxygen consumption and normal efficiency also failed to increase coronary flow with the final increment in heart rate, and produced lactate at the highest pacing rate. Thus the five patients in whom pacing provoked biochemical evidence of ischaemia all had excessive myocardial oxygen demand and/or limited capacity to increase coronary flow. Propranolol did not change lactate extraction significantly at any pacing rate in either the ischaemic or non-ischaemic groups. In only one patient was ischaemia at the highest pacing rate abolished after propranolol, and this was associated with a 30 per cent reduction in oxygen consumption. These results do not demonstrate a direct effect of propranolol upon myocardial metabolism in patients with HOCM, but emphasise the potential value of beta-blockade in protecting these patients from excessive increases in heart rate.

Angina pectoris is a common symptom in patients with hypertrophic obstructive cardiomyopathy (HOCM),[1][2] suggesting that the oxygen demand of the hypertrophied heart may exceed the capacity of the coronary circulation to supply it. The occurrence of angina is not related to the severity of obstruction,[3] implying that high myocardial oxygen demand secondary to increased left ventricular work is not the usual mechanism of ischaemia.

The severity of hypertrophy is out of proportion to the increase in cardiac work that would be needed to overcome obstruction[4]; this inappropriate increase in muscle mass may lead to increased myocardial oxygen demand which is excessive when considered in relation to the external work performed by the heart. In the presence of severe hypertrophy resulting from aortic stenosis, coronary flow is unable to increase when the heart is stressed[5]; thus in addition to increasing oxygen demand,

hypertrophy may limit the ability of the coronary vasculature to increase oxygen delivery.

Propranolol has been used extensively in the treatment of patients with HOCM, and has been shown to improve angina,[6 7] reduce the outflow tract gradient,[8] and increase left ventricular diastolic distensibility.[9] Its beneficial effect upon angina may be because of reduction of heart rate on exercise, but recent studies in patients with coronary artery disease have suggested that beta-blockade may improve myocardial ischaemia even when heart rate is controlled by pacing.[10 11]

In this report we present the results of studies upon myocardial metabolism, coronary flow, and haemodynamics at increasing heart rates in patients with HOCM, with particular reference to the factors contributing to the development of metabolic evidence of ischaemia. In addition, the effects of propranolol administration were studied to determine whether or not this drug has beneficial actions that are independent of heart rate.

Patients and methods

Thirteen patients (age 18 to 62) were studied. All were symptomatic and were undergoing diagnostic cardiac catheterisation for suspected HOCM. The patients gave written consent and the Hospital Ethical Committee approved the study.

Beta-blocking drugs were stopped two days before catheterisation. All studies were performed in the morning after an overnight fast. Atropine 0·3 mg and diazepam 10 mg intramuscularly and heparin 45 units/kg intravenously were given one hour before catheterisation. Pretreatment with heparin has been shown to minimise the effect of a subsequent dose upon arterial free fatty acid concentration.[12] Right and left heart catheterisation were performed via the right femoral vein and artery. A second dose of heparin was given immediately after arterial catheterisation. In four patients transseptal puncture was performed and the outflow gradient demonstrated by simultaneous measurement of left ventricular body pressure via the transseptal catheter and outflow pressure via the arterial catheter. In the other patients gradients were measured by withdrawal of an end-hole catheter from the ventricular apex to the aorta, and then confirmed by a twin lumen catheter. Inhalation of amyl nitrate was used to provoke a gradient when appropriate.

Using the long sheath technique[13] the left heart catheter was replaced by a catheter tip micromanometer (Telco MM52, or Millar) which was positioned in the body of the left ventricle. The right heart catheter was replaced by a Schwarzer

Swan Ganz fibreoptic catheter which was advanced to the pulmonary artery for measurement of cardiac output. Via a left antecubital vein a Ganz pacing and thermistor catheter was advanced into the coronary sinus. Its site was confirmed by injection of contrast medium, and infusion of cold saline into the right atrium.[14] Coronary sinus pacing was established just above basal heart rate. Cardiac output, left ventricular pressure, and coronary sinus flow were measured, and left ventricular and coronary sinus blood sampled simultaneously. The procedure was repeated at three or four pacing rates. Pacing was stopped, and propranolol 0·2 mg/kg given intravenously. Twenty minutes later the outflow gradient was measured at basal heart rate, and then the pacing study repeated. Biplane left ventricular cineangiography was performed at the end of the study. In nine patients the left anterior oblique view with simultaneous hand injection into the right ventricle was used to define septal hypertrophy.[15] Selective coronary arteriography was performed in 12 patients.

The micromanometer and thermistor signals were displayed on a Cambridge 12 channel recorder and stored on tape. The pressure signal was differentiated, and KV_{max} derived from developed pressure.[16] Mean systolic pressure was estimated by planimetry of the left ventricular pressure trace and used in the calculation of systolic pressure time index and left ventricular minute work. Green dye curves obtained in the pulmonary artery were analysed by an IVH 3 Schwarzer cardiac output computer. Coronary sinus blood flow was measured by constant infusion thermodilution.[17]

Blood samples were added to an aliquot of 10 per cent perchloric acid for deproteinisation and subsequent determination of lactate and pyruvate,[18] hydroxybutyrate and acetoacetate,[19] and glycerol.[20] For measurement of free fatty acids[21] blood was added to sequestrene tubes and centrifuged. All samples were put on ice, and then stored at −20°C. Heparinised samples were taken for determination of oxygen content upon a LEX-0_2 CON-TL.

Extraction of a substrate is defined as the difference in concentration between arterial and coronary sinus blood (A − V), and extraction ratio is that difference as a percentage of arterial concentration (A − V/A%). Oxygen extraction ratio of a substrate is defined as the amount of oxygen required to catabolise completely the amount of that substrate extracted, expressed as a percentage of the total oxygen extracted by the heart. For example, one mole of lactate requires three mole of

oxygen. Thus the amount of oxygen needed to catabolise extracted lactate can be calculated, and expressed as a percentage of the total oxygen extracted by the heart. Myocardial oxygen consumption is calculated as the difference between arterial and coronary sinus oxygen consumption $(A - V)$ multiplied by coronary sinus flow. Myocardial efficiency is estimated by the formula of Bing and Michal[22] where

$$efficiency = \frac{\text{Left ventricular minute work (kg m/min)}}{\text{Myocardial } O_2 \text{ consumption (ml/min)} \times 2{\cdot}059 \times 0{\cdot}806} \%$$

Statistical analysis was performed using Student's t test, paired t test, and linear regression. A value of $p < 0{\cdot}05$ was considered significant. Values are expressed as mean ±standard error of the mean.

Results

The clinical details of the 13 patients are listed in Table 1. Twelve complained of exertional dyspnoea, and eight of angina pectoris. All had physical signs suggestive of HOCM. One patient (case 9) had auscultatory and echocardiographic signs of mitral stenosis found at catheter to be trivial (Gorlin valve area 3·3 cm²); this patient's aortic valve was normal.

At basal heart rate the mean left ventricular outflow gradient was 43·9 mmHg before, and 35·9 mmHg after propranolol (NS). In case 13,

no gradient was present at rest, but inhalation of amyl nitrate provoked an outflow gradient of 13 mmHg.

Angiographic assessment of the severity and distribution of hypertrophy showed it to be limited to the septum in seven patients, with hypertrophy of both septum and free wall in six. The coronary arteries were normal in 12 patients (as judged from coronary arteriography in 11, and aortography in one). Minor irregularities but no critical stenoses were seen in case 4 on coronary arteriography.

METABOLIC RESULTS

Arterial lactate concentration was $0{\cdot}474 \pm 0{\cdot}02$ mmol/l before and $0{\cdot}496 \pm 0{\cdot}02$ mmol/l after propranolol (NS). Fig. 1 shows myocardial lactate extraction ratio at each pacing rate. Before propranolol mean lactate extraction ratio fell from 37·4 per cent ±3·1 at the lowest pacing rate to 9·1 per cent ±7·8 at the highest pacing rate. This fall was largely because of five patients in whom lactate extraction fell progressively as heart rate increased. At the highest pacing rate the mean lactate extraction ratio of these five patients was −11·8 per cent (range 2·7 to −33·4%), and three of them experienced angina. Lactate extraction ratio remained high in the other eight patients at all pacing rates, and the difference between the two groups was significant at the second, third, and fourth pacing rates. After propranolol, lactate extraction did not change significantly at any heart rate in either group of patients. Only one of the five

Table 1 *Clinical and haemodynamic details of patients*

Case no.	Age	Sex	Symptoms				Resting gradient		Distribution of hypertrophy	Mitral ** regurgitation	Myocardial efficiency at first pacing rate (%)	
			Dyspnoea	Angina	Palpitation	Syncope	Control	Propranolol			Control	Propranolol
1	41	M	+	0	+	0	27	13	Septum and moderate generalised	I	22·7	9·1
2	58	M	+	+	+	0	26	47	Septum	0	15·9	20·2
3	42	F	+	0	+	0	65	48	Septum	I	22·3	23·7
4	62	M	+	0	+	+	38	35	Mid septum	0	38·6	33·1
5	24	M	+	0	0	0	70	11	Septum	II	20·3	—
6	42	M	+	+	+	0	49	36	Septum	0	23·4	13·9
7	26	M	+	+	+	0	22	12	Septum	0	22·7	22·1
8	39	M	+	+	+	0	5	0	Septum and moderate generalised	I	24·4	26·2
9*	53	F	+	+	0	0	100	91	Septum	II	40·3	28·3
10*	18	F	+	+	0	0	27	26	Massive septal and severe generalised	II	6·1	6·3
11*	29	F	+	+	+	0	69	36	Septal and moderate generalised	II	10·4	13·0
12*	23	F	+	+	+	0	61	100	Septal and severe generalised	II	12·0	11·9
13*	28	M	0	0	+	+	0	0	Generalised	0	14·4	17·8
							Mean 43 ±9	35 ±9			Mean 21·5 ±2·7	19·7 ±2·2
								NS				NS

*Patients who developed abnormal lactate extraction at the highest pacing rate.
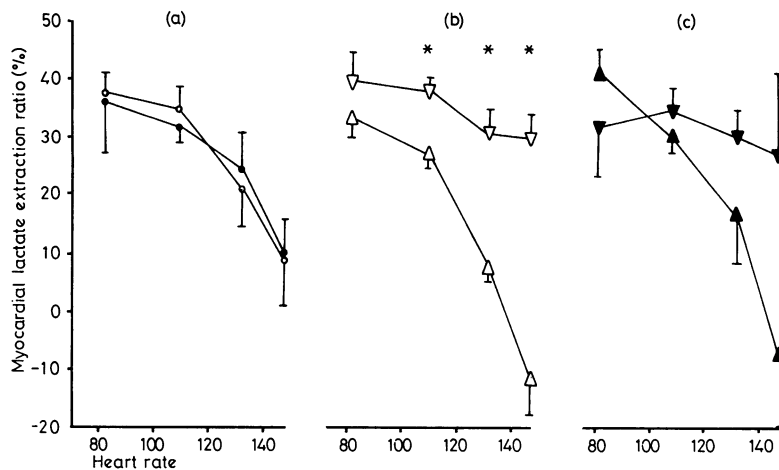**Mitral regurgitation, grade 0 = none, I = mild, II = moderate, III = severe, IV = very severe.

Fig. 1 *Myocardial lactate extraction ratio at each pacing rate.* (a) *Mean* $\pm SEM$ *of all patients. Open circles, before propranolol; closed circles, after propranolol.* (b) *Separation of the two groups on the basis of lactate extraction ratio at the highest pacing rate before propranolol.* △ *mean* $\pm SEM$ *of the five patients who had low or negative extraction ratios at highest pacing rate.* ▽ *mean* $\pm SEM$ *of the remaining patients. Lactate extraction ratio was significantly lower in these five patients than in the others at all but the first pacing rate.* (c) *Comparison of the two groups after propranolol. Differences between the two groups were no longer significant; however, mean extraction ratio did not change significantly in either group at any heart rate* (*$p < 0.5$).

patients with low extraction (case 12) showed distinct improvement after the drug, 43·8 per cent compared with 2·7 per cent at the highest pacing rate, and this was associated with relief of angina.

Arterial pyruvate concentration was 0.036 ± 0.002 mmol/l both before and after propranolol. Considering all pacing rates together, extraction was related to arterial concentration before and after the drug ($r = 0.88$, $p < 0.01$; $r = 0.76$, $p < 0.01$). Before propranolol pyruvate extraction ratio fell from 31·8 per cent ± 5 to 20·6 per cent ± 4.5 between

the highest and lowest pacing rates (Fig. 2). This reduction was the result of the behaviour of the five patients with abnormal lactate extraction. Their pyruvate extraction ratios fell progressively as heart rate increased, while extraction remained high at all heart rates in the other eight patients, and the difference between the two groups was significant at the second, third, and fourth pacing rates. After propranolol, the pyruvate extraction ratio did not change significantly.

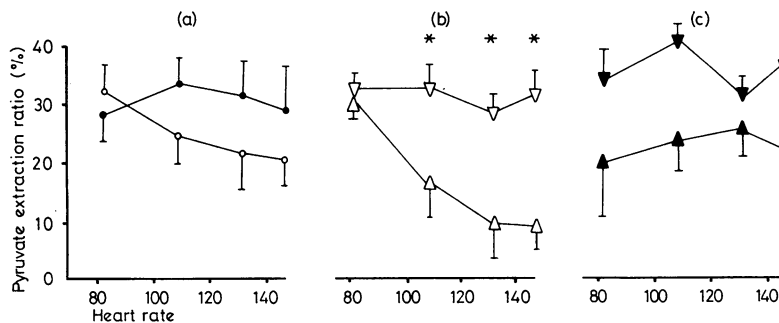Arterial concentration and extraction of hydroxy-

Fig. 2 *Pyruvate extraction ratio at each pacing rate.* (a) *Mean* $\pm SEM$ *of all patients: open circles, before propranolol; closed circles, after propranolol.* (b) *Comparison of the two groups that were separated on the basis of lactate extraction ratios (same symbols as Fig. 1). Before propranolol pyruvate extraction was significantly lower at all but the first pacing rate in the five patients with abnormal lactate extraction* (△) *than in the other patients* (▽).
(c) *Comparison of the two groups after propranolol. The differences between the groups were no longer significant* (*$p < 0.05$).

butyrate, acetoacetate, free fatty acids, and glycerol did not change with heart rate, so the results at each pacing rate are not considered separately.

Arterial concentration of hydroxybutyrate fell from 0.180 ± 0.018 mmol/l to 0.155 ± 0.013 mmol/l after propranolol ($p < 0.05$), but the small decrease in extraction from 0.058 ± 0.008 mmol/l to 0.051 ± 0.008 mmol/l was not significant. Extraction was closely related to arterial concentration before and after the drug ($r = 0.87$, $p < 0.001$; $r = 0.86$, $p < 0.001$).

Arterial concentration of acetoacetate (0.101 ± 0.013 mmol/l and 0.113 ± 0.01 mmol/l) and extraction (0.047 ± 0.005 mmol/l and 0.050 ± 0.005 mmol/l) were similar before and after propranolol, and extraction was related to arterial concentration ($r = 0.93$, $p < 0.001$; $r = 0.96$, $p < 0.001$).

Free fatty acid concentrations were measured in 11 patients. Arterial concentration decreased from 0.739 ± 0.039 mmol/l to 0.584 ± 0.028 mmol/l ($p < 0.01$) after propranolol, but the fall in extraction from 0.131 ± 0.015 to 0.125 ± 0.017 mmol/l was not significant. Extraction was related to arterial concentration only before the drug ($r = 0.49$, $p < 0.01$).

Glycerol concentrations were measured in nine patients. After propranolol arterial concentration fell from 0.058 ± 0.003 to 0.047 ± 0.003 mmol/l ($p < 0.01$), but extraction did not change. Glycerol release was common and extraction was not related to arterial concentration.

Arterial concentration and extraction of free fatty acids, ketone bodies, and glycerol did not differ significantly between the patients who did or who did not develop abnormal lactate extraction.

Oxygen extraction ratios were calculated for the 11 patients in whom fatty acids were measured (Table 2).

HAEMODYNAMIC RESULTS
Basal heart rate differed between individuals, so the pacing rates used were not identical in all patients (Fig. 3). The pacing rates before and after propranolol were in close agreement (82 ± 4, 109 ± 3,

132 ± 4, and 147 ± 4 bpm before, and 81 ± 4, 109 ± 3, 131 ± 4, and 147 ± 4 bpm after the drug). Cardiac output was lower after propranolol at all heart rates, significantly so at the second, third, and fourth pacing rates. Left ventricular body systolic pressure tended to fall as heart rate increased, and after propranolol was significantly lower at the third and fourth pacing rates. Left ventricular end-diastolic pressure rose from 11 ±1 mmHg at the lowest pacing rate to 19 ±2 mmHg at the highest pacing rate ($p < 0.01$). After propranolol it was significantly lower at the second (8 ± 1 mmHg compared with 11 ± 1 mmHg: $p < 0.05$) and fourth pacing rates (14 ± 3 compared with 19 ± 1 mmHg). The maximum rate of rise of left ventricular pressure decreased significantly after propranolol at the second, third, and fourth pacing rates and KV_{max} was significantly lower after the drug at the first three pacing rates.

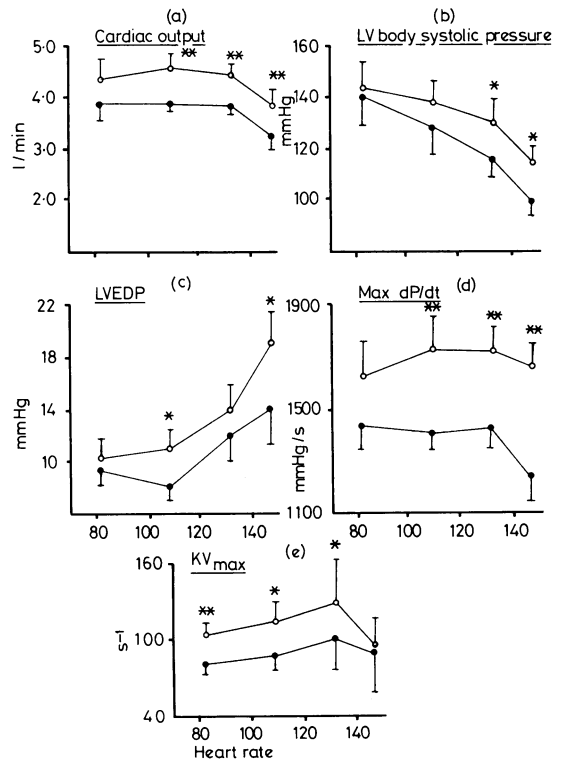Before propranolol coronary sinus blood flow

Fig. 3   *Haemodynamic results. Mean $\pm$ SEM of all patients at each pacing rate. Open circles, before propranolol; closed circles, after propranolol.*
$*p < 0.05$ $**p < 0.01$ *when pre- and postpropranolol values are compared.*

Table 2   *Oxygen extraction ratios at lowest pacing rate*

	Before propranolol	After propranolol
Lactate	14·6% ±2·9	16·5% ±3·1
Pyruvate	1·0% ±0·4	0·8% ±0·2
Hydroxybutyrate	7·8% ±1·6	8·1% ±1·2
Acetoacetate	5·2% ±1·2	7·3% ±1·2
Free fatty acids	86·9% ±14·6	91·7% ±9·7
Total	115·4% ±15	124·9% ±11·7

Pₗ :·· and postpropranolol values do not differ significantly.

(Fig. 4) increased as heart rate was raised, from 216 ± 38 ml/min (range 99 to 604 ml/min) at the lowest pacing rate, to 374 ± 74 ml/min (range 180 to 940 ml/min) at the highest pacing rate. The response of coronary sinus flow to pacing varied between patients. In nine, it rose progressively with each increment in heart rate, in two there were only small increases in flow between the lowest and highest pacing rates (case 12: 443 to 470 ml/min; case 13: 187 to 220 ml/min). In two patients, flow increased with the initial increments in heart rate and then reached a plateau (case 9: 104, 185, 202, and 202 ml/min; case 10: 604, 940, 940, and 940 ml/min). After propranolol, coronary sinus flow in the group as a whole was significantly lower only at the highest pacing rate: 329 ± 62 ml compared with 374 ± 74 ml/min (p < 0·02).

Arterial-coronary sinus oxygen difference did not change with heart rate or propranolol administration, so coronary sinus flow and calculated myocardial oxygen consumption were closely related. At the lowest pacing rate myocardial oxygen uptake was $20·4 \pm 3·8$ ml/min, range 10·1 to 57·7 ml/min. After propranolol it was significantly lower only at the third and fourth pacing rates; $25·4 \pm 6$ compared with $30·8 \pm 7·5$ ml/min (p < 0·005) and $32·6 \pm 7·3$ compared with $37·1 \pm 7·1$ ml/min (p < 0·01).

In this group of patients oxygen uptake bore no relation to the product of either left ventricular body systolic pressure and heart rate or systolic pressure time index and heart rate, and was not related to left ventricular minute work (Fig. 5). Calculated myocardial efficiency (Table 1) showed
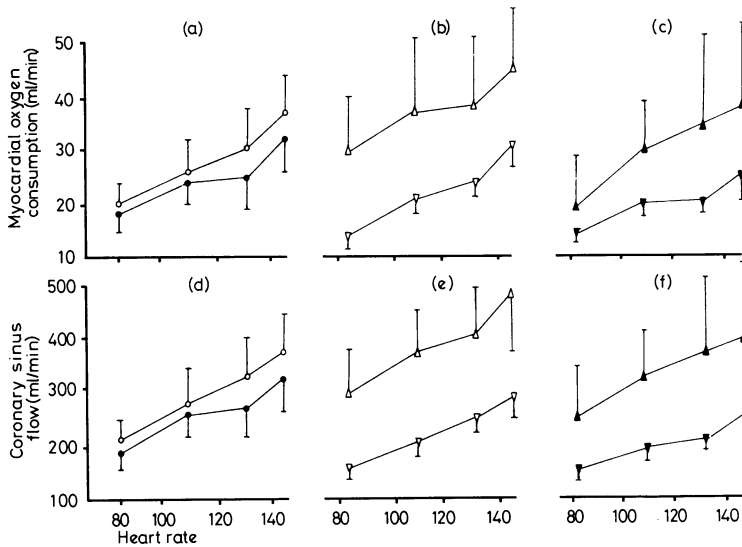

Fig. 4 Upper panels: *Myocardial oxygen consumption mean $\pm$ SEM of* (a) *all patients at each heart rate. Open circles, before propranolol; closed circles, after propranolol.* (b) *Before propranolol. Comparison of the five patients who developed ischaemia* ($\triangle$) *with the other eight patients* ($\bigtriangledown$). (c) *After propranolol. Comparison of the two groups.*
Lower panels: *Coronary sinus blood flow* (d) *mean $\pm$ SEM of all patients;* (e) *before propranolol: comparison of the two groups;* (f) *after propranolol. Comparison of the two groups.*
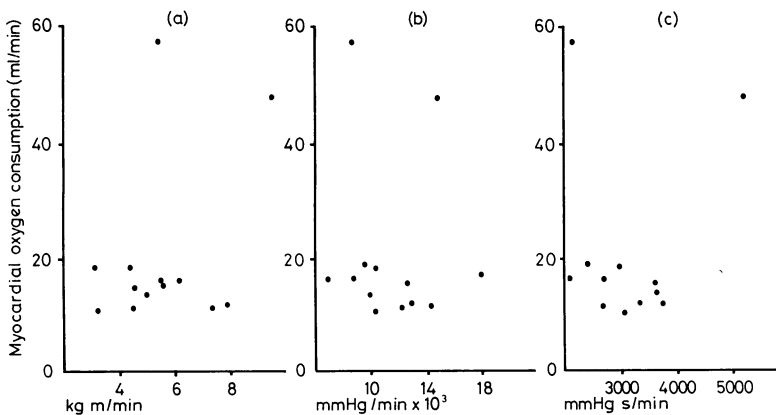

Fig. 5 *Myocardial oxygen consumption at the lowest pacing rate before propranolol plotted against* (a) *left ventricular minute work,* (b) *the product of peak left ventricular body pressure and heart rate,* (c) *the product of systolic pressure time index and heart rate. For the group as a whole myocardial oxygen consumption was not related to any of these indices of left ventricular work.*

a wide range of values at the lowest pacing rate, was normal in only two patients (cases 4 and 9), and did not change after propranolol.

RELATION BETWEEN METABOLIC AND HAEMODYNAMIC RESULTS

The five patients who developed abnormal lactate metabolism on pacing did not differ significantly from the other eight patients in age, severity of obstruction, cardiac output, left ventricular end-diastolic pressure, KV_{max}, or max dP/dt. The changes in these indices induced by pacing were similar in the two groups. Inspection of the left ventricular cineangiograms, however, suggested that the five patients with abnormal lactate metabolism at high heart rates had more severe and extensive hypertrophy (generalised hypertrophy in addition to septal thickening in four, and gross septal hypertrophy in the fifth). At the lowest pacing rate their mean myocardial oxygen uptake was 30.8 ± 9.2 compared with 14.2 ± 1.0 ml/min (p < 0.05). Left ventricular minute work did not differ, so calculated myocardial efficiency tended to be lower in these five patients. On pacing, all eight patients with normal lactate extraction showed progressive increases in coronary sinus flow with each increment in heart rate. Of the five patients who became ischaemic, this pattern was seen in only one (case 11), while in two there was little increase in flow between lowest and highest pacing rates (cases 12 and 13), and in two others, flow reached a plateau (cases 9 and 10).

In the five "ischaemic" patients, at the highest pacing rate propranolol reduced cardiac output, left ventricular body systolic pressure, and hence left ventricular minute work (Table 3). Myocardial oxygen consumption showed little change in two (cases 11 and 13) but fell in the other three patients by 15 per cent (case 10), 25 per cent (case 9), and 30 per cent (case 12). There was a major increase in myocardial lactate extraction after propranolol in only one—the patient (case 12) who sustained the largest fall in oxygen consumption.

Discussion

The normal myocardium derives the majority of its energy supply from the oxidation of free fatty acids, glucose, and lactate, with small contributions from the oxidation of ketone bodies and pyruvate.[23] These substrates are extracted by the heart from arterial blood in proportion to their concentrations. In our patients, at the lowest pacing rate myocardial substrate extraction was broadly similar to results reported in normal subjects[24-26] and the total of the oxygen extraction ratios exceeded 100 per cent; thus myocardial oxygen consumption could be accounted for by the complete oxidation of the substrates extracted. That the total exceeded 100 per cent may have been a result of inaccuracy in calculated free fatty acid oxygen extraction ratio, as complete oxidation is not the invariable fate of extracted free fatty acids.[27]

Lactate by oxidation and glucose by glycolysis are both converted to pyruvate, which the heart can also extract from arterial blood. If pyruvate cannot be oxidised it is converted to lactate, and the production of lactate and its release into coronary venous blood are characteristic findings in ischaemia.[28] At the lowest pacing rate all our patients had high lactate and pyruvate extraction ratios. As heart rate increased extraction ratios remained high in eight patients, but in five fell progressively to levels comparable to those observed during pacing-induced angina in patients with coronary artery disease studied in the laboratory.[12] In normal subjects myocardial extraction of carbohydrates is related inversely to free fatty acid concentration[29] and ketone body extraction.[25] For this reason it is difficult to define a lower limit of lactate extraction below which ischaemia can be diagnosed confidently, and considered in isolation the extraction ratios measured at the middle pacing rates in the five patients who subsequently became ischaemic were not definitely abnormal. However, this decline could not be explained by changes

Table 3 *Effects of propranolol at highest pacing rate upon five patients with low or negative lactate extraction ratios*

Case no.	LVMW (kg m/min)		MVO₂ (ml/min)		Efficiency (%)		CSF (ml/min)		CO (l/min)		CSF/CO%		Lactate extraction ratio (%)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
9	3·6	2·3	22·0	16·4	9·7	7·8	202	174	3·15	2·98	6·4	5·8	−10·5	−34·6
10	4·99	3·49	92·4	77·8	3·3	2·7	948	780	4·99	3·49	19·0	22·4	−18·7	4·3
11	2·38	2·30	43·6	44·1	3·3	3·1	532	519	2·83	2·72	18·8	19·1	2·5	6·6
12	7·95	4·67	47·0	33·0	10·2	8·5	470	331	3·96	3·83	11·9	8·6	2·7	43·8
13	4·7	3·6	22·0	20·0	13·0	10·7	229	229	4·1	2·8	5·9	8·1	−33·4	−46·4

LVMW, left ventricular minute work; MVO₂, myocardial oxygen consumption; CSF, coronary sinus blood flow; CO, cardiac output.
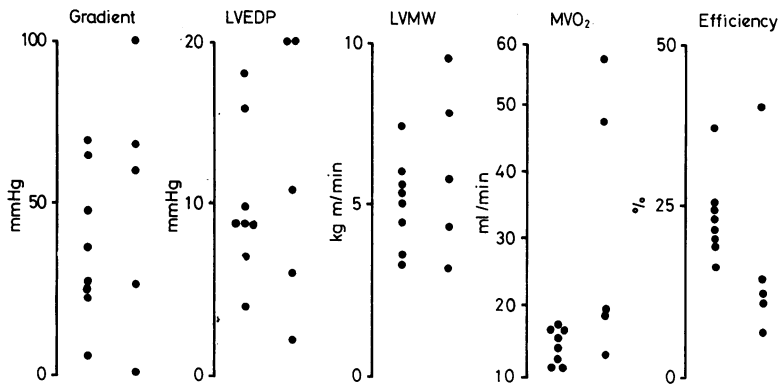
Fig. 6 *Resting gradient, left ventricular end-diastolic pressure, left ventricular minute work, myocardial oxygen consumption, and estimated efficiency at the lowest pacing rate in the eight patients with normal lactate extraction (on the left) and the five patients who became ischaemic on pacing (on the right).*

in free fatty acid or ketone body extractions. Thus we identified a group of patients with HOCM and angiographically normal coronary arteries in whom pacing provoked a progressive decline in aerobic carbohydrate metabolism and frank ischaemia at the highest pacing rate, suggesting that myocardial oxygen demand began to exceed supply even after a small increase in heart rate.

Four patients who had a history of angina of effort had normal myocardial lactate extraction on pacing. In patients with coronary artery disease pacing is less effective than exercise as a means of provoking evidence of ischaemia.[30] This may be particularly true in HOCM, as exercise may increase outflow obstruction,[3] and hence ventricular systolic pressure, whereas in this study ventricular pressure tended to fall as pacing rate increased.

Although we were able to separate our patients into two groups on the basis of pacing-induced changes in lactate and pyruvate extraction, this does not imply the existence of two distinct varieties of HOCM. There were no consistent haemodynamic differences between the two groups. The abnormal geometry and regional variation of wall thickness preclude the estimation of left ventricular mass, so a formal comparison of severity of hypertrophy could not be made. In only one of the patients with abnormal lactate extraction, however, was hypertrophy confined to the interventricular septum, and none of the patients with normal lactate metabolism had the massive hypertrophy seen in cases 10 and 12.

Before discussing coronary sinus blood flow and myocardial oxygen consumption, the method of their estimation should be considered. Coronary sinus flow approximates to the blood supply of the left ventricle,[31] though this has not been substantiated in HOCM. If the Ganz catheter is sited too proximally in the coronary sinus, then flow is

overestimated because of reflux of atrial blood; this error can be excluded by injecting cold saline into the right atrium.[14] Flow is underestimated by about 30 per cent if the catheter is advanced beyond the entry of the posterior interventricular vein.[17] The accuracy of constant infusion thermodilution has been established for flows up to 500 ml/min[17];
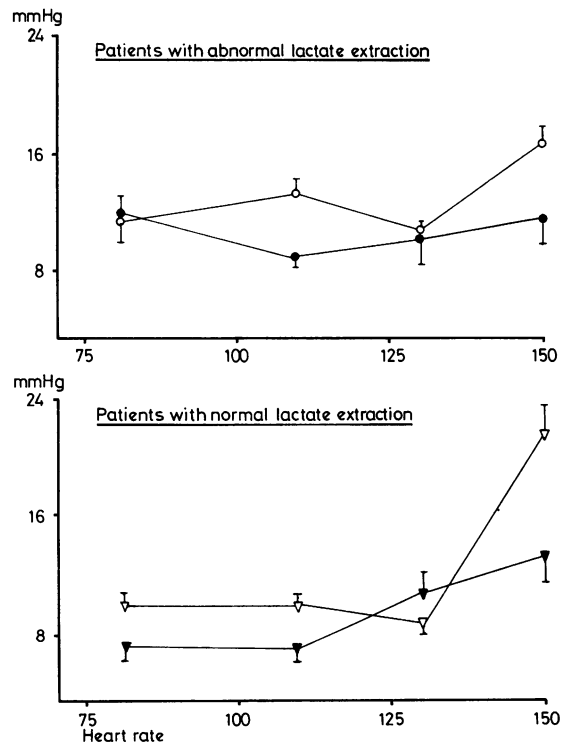

Fig. 7 *Left ventricular end-diastolic pressure at each pacing rate in the ischaemic and non-ischaemic patients. Open symbols, before propranolol; closed symbols, after propranolol.*

one of our patients had flows in excess of this value. Under these circumstances small changes in temperature have a large effect upon calculated flow, so the absolute values of flow and hence myocardial oxygen consumption are liable to be inaccurate. Despite these limitations it is unlikely that the large differences observed between patients were solely the result of methodological error.

When the results for all 13 patients were considered together, myocardial oxygen consumption could not be related to gradient, or to any index of ventricular work. As oxygen consumption was not normalised for ventricular mass, the range of values may reflect large differences in severity of hypertrophy, as in other causes of hypertrophy oxygen consumption is related to ventricular mass.[32] If this were the explanation then it would follow that hypertrophy was not related to work or obstruction, and this lack of correlation is well documented in HOCM.[3 4]

The disparity between external work and myocardial oxygen consumption can be examined by estimating myocardial efficiency.[22] Only two of the patients studied had normal efficiency (approximately 40%), and it is of interest that in both cases hypertrophy was limited to the septum. Low efficiency in the other patients was not a result of dissipation of energy by outflow obstruction, as left ventricular body systolic pressure was used to calculate minute work, but might have been the result either of reduced efficiency in the production of energy from the oxygen consumed, or in the conversion of this energy into measurable external work. The former possibility is unlikely, as oxidation of the substrates extracted would account for measured oxygen consumption. The oxygen cost of external work is increased by ventricular dilatation,[33] but, as is usual in HOCM, our patients had small or normal sized ventricular cavities. Recent studies upon the shape of the septum[34] and fibre disarray in HOCM[35 36] have suggested that areas of the myocardium may contract isometrically during systole, and as a consequence of the shape of the septum isometric contraction would not increase intraventricular pressure. Under these circumstances the oxygen consumed by some areas of the myocardium would not produce measurable external work, resulting in low myocardial efficiency.

The patients with the four highest values of myocardial oxygen consumption had the four lowest values of efficiency, and all developed ischaemia on pacing. The other patient who became ischaemic had relatively low myocardial oxygen consumption and normal efficiency, but as the heart rate increased, coronary sinus flow reached a plateau, failing to rise with the final increment in heart rate. Of the five patients who became ischaemic on pacing, only one showed progressive rises in coronary sinus flow with each increment in heart rate, whereas this pattern was seen in each of the other eight. In severe hypertrophy caused by tight aortic stenosis there is evidence to suggest that the coronary vasculature is near maximal dilatation at rest.[5] Aortic diastolic pressure was not measured in all patients at all pacing rates, so coronary vascular resistance has not been calculated, but in the two patients whose coronary sinus flow barely changed with pacing (cases 12 and 13) aortic pressure did not fall as heart rate increased, implying that the coronary vasculature failed to dilate sufficiently in response to pacing.

No single factor predicted which patients became ischaemic on pacing, but each of the five that did had at least one of the following features, none of which was seen in the other eight patients: high myocardial oxygen consumption ($> 18 \cdot 7$ ml/min) and low efficiency ($< 15\%$) at the lowest pacing rate, or a failure of coronary sinus flow to increase with each increment in heart rate.

The beneficial effect of beta-blocking drugs upon angina may result from reduction of myocardial oxygen demand secondary to their haemodynamic actions.[37–39] When heart rate is controlled by pacing, beta-blockade has little effect upon myocardial oxygen consumption,[11 40] but may still improve lactate extraction or anginal threshold[10 11] in patients with coronary artery disease, suggesting that it modifies the metabolism of ischaemic myocardium independently of haemodynamic effects. This might be a result in part of reduction of arterial free fatty acid concentration.[12]

In this study propranolol did not change myocardial lactate extraction. Its lack of effect upon the non-ischaemic patients was not surprising, as their consistently high lactate and pyruvate extraction ratios suggest that aerobic carbohydrate metabolism before the drug was not limited by lack of oxygen or high rates of free fatty acid catabolism. In two ischaemic patients (cases 11 and 13) propranolol had little effect upon oxygen consumption, coronary sinus flow, or lactate extraction. Thus in these patients there was no evidence that propranolol had a direct effect upon the metabolism of ischaemic myocardium. Reduction of 15 and 25 per cent in myocardial oxygen uptake after propranolol (cases 9 and 10) was not accompanied by a major change in lactate extraction; the decrease in oxygen demand was balanced by a commensurate decrease in supply. If the coronary vasculature were maximally dilated, and the length of diastole fixed by pacing, then after propranolol coronary flow would fall in proportion

to cardiac output. In these two patients coronary sinus flow expressed as a percentage of cardiac output was similar before and after the drug. While the reduction of myocardial oxygen consumption by propranolol was probably a result of decreased pressure-work and contractility, the accompanying fall in cardiac output may have been the reason for the failure of decreased oxygen demand to abolish ischaemia. The only patient in whom propranolol had a distinct beneficial effect upon lactate extraction (case 12) sustained a large fall in myocardial oxygen consumption but only a minor reduction in cardiac output after the drug.

Pacing of the normal heart reduces left ventricular end-diastolic pressure[41][42] whereas in our patients it rose between the lowest and highest pacing rates. In patients with coronary artery disease pacing-induced ischaemia may be associated with an increase in end-diastolic pressure,[43] but in this study pressure rose both in ischaemic and non-ischaemic patients. After propranolol, end-diastolic pressure was lower at the highest pacing rate, and this reduction could not be explained by relief of ischaemia. Propranolol increases diastolic ventricular compliance in HOCM,[9] and the fall in end-diastolic pressure reported here may have been a result of this effect. The mechanism by which propranolol improves compliance in HOCM is not known; our results suggest that it is not related to relief of ischaemia.

We conclude that ischaemia in HOCM is a consequence either of high myocardial oxygen demand, which is excessive for the external work performed, or the inability of coronary flow to increase appropriately with heart rate. When heart rate is controlled by pacing propranolol does not influence either of these problems; nor does it appear to have a direct beneficial effect upon myocardial metabolism. These results emphasise, however, the possible deleterious effects of tachycardia in HOCM, and stress the value of using beta-blockade to reduce heart rate and prevent tachyarrhythmias.

References

1 Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 1960; **22**: 403–14.

2 Braunwald E, Morrow AG, Cornell WP, Aygen MM, Hilbish TF. Idiopathic hypertrophic subaortic stenosis: clinical, hemodynamic and angiographic manifestations. *Am J Med* 1960; **29**: 924–45.

3 Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AC. Idiopathic hypertrophic subaortic stenosis: 1. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964; **30/31**, suppl IV: 3–119.

4 Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972; **34**: 545–52.

5 Fallen EL, Elliot WC, Gorlin R. Mechanisms of angina in aortic stenosis. *Circulation* 1967; **36**: 480–8.

6 Cohen LS, Braunwald E. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* 1967; **35**: 847–51.

7 Sloman G. Propranolol in management of muscular subaortic stenosis. *Br Heart J* 1967; **29**: 783–7.

8 Flamm MD, Harrison DC, Hancock EW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. *Circulation* 1968; **38**: 846–58.

9 Swanton RH, Brooksby IAB, Jenkins BS, Webb-Peploe MM. Haemodynamic studies of beta blockade in patients with hypertrophic obstructive cardiomyopathy. *Eur J Cardiol* 1977; **5/4**: 327–41.

10 Jackson G, Atkinson L, Oram S. Improvement of myocardial metabolism in coronary artery disease by beta-blockade. *Br Heart J* 1977; **39**: 829–33.

11 Armstrong PW, Chiong MA, Parker JO. Effects of propranolol on the hemodynamic, coronary sinus blood flow and myocardial metabolic response to atrial pacing. *Am J Cardiol* 1977; **40**: 83–9.

12 Thompson DS, Naqvi N, Juul SM, Coltart DJ, Jenkins BS, Webb-Peploe MM. Haemodynamic and metabolic effects of atenolol in patients with angina pectoris. *Br Heart J* 1980; **43**: 668–79.

13 Brooksby IAB, Swanton RH, Jenkins BS, Webb-Peploe MM. Long sheath technique for introduction of catheter tip micromanometer or endomyocardial bioptome into left or right heart. *Br Heart J* 1974; **36**: 908–12.

14 Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. *Circulation* 1978; **57**: 778–86.

15 Redwood DR, Scherer JL, Epstein SE. Biventricular cineangiography in the evaluation of patients with asymmetric septal hypertrophy. *Circulation* 1974; **49**: 1116–21.

16 Kolettis M, Jenkins BS, Webb-Peploe MM. Assessment of left ventricular function by indices derived from aortic flow velocity. *Br Heart J* 1976; **38**: 18–31.

17 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow in man by constant thermodilution in man. *Circulation* 1971; **44**: 181–95.

18 Hohorst HJ, Kreutz FH, Bücher T. Über Metabolitgehalte und Metabolit-konzentrationen in der Leber der Ratte. *Biochemische Zeitschrift* 1959; **332**: 18–46.

19 Williamson DH, Mellanby J, Krebs HA. Enzymatic determination of D(—) B-Hydroxybutyric acid and acetoacetic acid in blood. *Biochem J* 1962; **82**: 90–6.

20 Kreutz FH. Enzymatische Glycerinbestimmung. *Klin Wochenschr* 1962; **40**: 362–3.

21 Carruthers M, Young DAB. Free fatty acid esti-
   mation by a semi-automated fluorimetric method.
   Clin Chim Acta 1973; **49:** 341–8.
22 Bing RJ, Michal G. Myocardial efficiency. *Ann NY
   Acad Sci* 1959; **72:** 555–8.
23 Bing R. Cardiac metabolism. *Physiol Rev* 1965; **45:**
   171–213.
24 Bing RJ, Siegel A, Vitale A, *et al.* Metabolic studies
   on the human heart in vivo. I. Studies in carbo-
   hydrate metabolism of the human heart. *Am J Med*
   1953; **15:** 284–96.
25 Bing RJ, Siegel A, Ungar I, Gilbert M. Metabolism
   of the human heart. II. Studies on fat, ketone and
   amino acid metabolism. *Am J Med* 1954; **16:** 504–15.
26 Goodale WT, Olson RE, Hackel DB. The effects of
   fasting and diabetes mellitus on myocardial meta-
   bolism in man. *Am J Med* 1959; **27:** 212–20.
27 Zierler KL. Fatty acids as substrates for heart and
   skeletal muscle. *Circ Res* 1976; **38:** 459–63.
28 Gorlin R. Evaluation of myocardial metabolism in
   ischemic heart disease. *Circulation* 1969; **39–40,**
   suppl IV: 155–63.
29 Lassers BW, Wahlqvist ML, Kaijser L, Carlson LA.
   Relationship in man between plasma free fatty acids
   and myocardial metabolism of carbohydrate sub-
   strates. *Lancet* 1971; **ii:** 448–50.
30 O'Brien KP, Higgs LM, Glancy DL, Epstein SE.
   Hemodynamic accompaniments of angina. A com-
   parison during angina induced by exercise and by
   atrial pacing. *Circulation* 1969; **39:** 735–43.
31 Hood WB Jr. Regional venous drainage of the human
   heart *Br Heart J* 1968; **30:** 105–9.
32 Dodge HT, Baxley WA. Hemodynamic aspects of
   heart failure. *Am J Cardiol* 1968; **22:** 24–34.
33 Rodbard S, Williams CB, Rodbard D, Berglund E.
   Myocardial tension and oxygen uptake. *Circ Res*
   1964; **14:** 139–49.
34 Hutchins GM, Bulkley BH. Catenoid shape of the
   interventricular septum: possible cause of idiopathic

35 Bulkey BH, Weisfeldt ML, Hutchins GM. Isometric
   cardiac contraction. A possible cause of the dis-
   organized   myocardial   pattern   of   idiopathic
   hypertrophic subaortic stenosis. *N Engl J Med* 1977;
   296: 135–9.
36 Wigle ED, Silver MD. Myocardial fibre disarray
   and ventricular septal hypertrophy in asymmetrical
   hypertrophy of the heart. *Circulation* 1978; **58:**
   398–402.
37 Wolfson S, Heinle RA, Herman MV, Kemp HG,
   Sullivan JM, Gorlin R. Propranolol and angina
   pectoris. *Am J Cardiol* 1966; **18:** 345–53.
38 Robinson BF. The mode of action of beta-antagonists
   in angina pectoris. *Postgrad Med J* 1971; **47,** suppl:
   41–3.
39 Schang SJ, Pepine CJ. Effects of propranolol on
   coronary hemodynamic and metabolic responses to
   tachycardia stress in patients with and without
   coronary disease. *Cathet Cardiovasc Diagn* 1977; **3:**
   47–57.
40 Simonsen S. Effects of atenolol (ICI 66 082) on
   coronary haemodynamics in man. *Br Heart J* 1977;
   39: 1210–6.
41 Linhart JW. Pacing-induced changes in stroke
   volume in the evaluation of myocardial function.
   Circulation 1971; **43:** 253–61.
42 Parker JO, Khaja F, Case RB. Analysis of left
   ventricular function by atrial pacing. *Circulation*
   1971; **43:** 241–52.
43 Linhart JW, Hildner FJ, Barold SS, Lister JW,
   Samet P. Left heart hemodynamics during angina
   pectoris induced by atrial pacing. *Circulation* 1969;
   40: 483–92.