

Haemodynamic and metabolic effects of atenolol in patients with angina pectoris

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SUMMARY Myocardial substrate extraction, coronary sinus flow, left ventricular pressure, and cardiac output were measured in 11 patients with angina pectoris at three pacing rates before and after atenolol (0.2 mg/kg). Left ventricular pressures, and the product of systolic pressure time index and heart rate did not change, but max dP/dt and KV max fell after atenolol. Only at the lowest pacing rate did the drug reduce cardiac output. Coronary sinus blood flow and myocardial oxygen uptake did not change after atenolol. At the highest pacing rate before atenolol four patients developed angina, accompanied by a rise in end-diastolic pressure. After atenolol angina was abolished in three, but the end-diastolic pressure still rose at the highest pacing rate. Myocardial lactate extraction ratio fell as heart rate increased, and was lower in the patients who developed angina. After atenolol, lactate extraction ratio increased significantly at the highest and lowest pacing rates. Myocardial pyruvate extraction rose after the drug. Arterial concentrations of hydroxybutyrate and acetoacetate fell after atenolol, but the decrease in their extraction was not significant. Myocardial extraction of free fatty acids was related to arterial concentration, which fell after atenolol. The changes in lactate and pyruvate extraction after atenolol were related inversely to changes in arterial free fatty acid concentration suggesting that the improvement in myocardial metabolism could have been secondary to reduced peripheral lipolysis. The increase in lactate extraction was associated with relief of angina, but did not abolish the rise in end-diastolic pressure induced by pacing.

The beneficial effect of beta-adrenergic blocking drugs in angina has been attributed to a reduction in myocardial oxygen demand secondary to their haemodynamic actions.¹⁻³ When heart rate is controlled by atrial pacing, beta blockade has little effect upon myocardial oxygen consumption.^{4,5} Studies in which patients with angina have been paced before and after beta-blocking drugs have yielded conflicting results; some have shown no beneficial effect,^{3,6} while others have shown an improvement in anginal threshold or lactate extraction,^{4,7} suggesting that beta blockade may modify myocardial metabolism independently of its haemodynamic actions. The possible direct effects of beta-blocking drugs upon the human myocardium are poorly understood, and though their actions upon peripheral metabolism are well documented⁸ the relevance of these to the heart has not been established.

Atenolol is a cardioselective beta-adrenergic antagonist without intrinsic sympathomimetic ac-

tivity,⁹ and is effective in the treatment of angina.¹⁰ When heart rate is controlled, atenolol does not change myocardial oxygen consumption or coronary blood flow.⁵ This study describes the effects of atenolol upon myocardial substrate extraction, coronary sinus blood flow, and systemic haemodynamics during pacing in 11 patients with angina, and attempts to identify the mechanisms by which it might improve the metabolism of the ischaemic myocardium.

Patients and methods

Eleven men (aged 40 to 59) were studied. All were limited by angina and were undergoing diagnostic cardiac catheterisation and coronary angiography. The patients gave written consent, and the hospital ethical committee approved the study.

Beta-blocking drugs were stopped 48 hours 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. Right and left heart catheterisations were performed via the right femoral vein and artery. Immediately after arterial catheterisation blood was taken for substrate concentration, and a second dose of heparin (45 units/kg) given. Coronary arteriography was performed using the Judkins technique, after which the patient was asked if he wished to continue with the metabolic study. A Ganz thermistor and pacing catheter (7Fr CCS 7U, Wilton Webster Inc) was introduced via a left antecubital vein and positioned in the coronary sinus. Its position was confirmed by injection of contrast medium. Cold saline was injected into the right atrium to ensure that the thermistors were unaffected by reflux of atrial blood.¹¹ A Schwarzer Swan-Ganz catheter was positioned in the pulmonary artery, and a catheter tip micromanometer, either no. 5 Millar or no. 8 Telco (MM52), introduced into the left ventricle. No measurements were made until at least 20 minutes after coronary arteriography. Coronary sinus pacing was established just above basal heart rate. Cardiac output, left ventricular pressure, and coronary sinus blood flow were measured, and left ventricular and coronary sinus blood were sampled simultaneously. The procedure was repeated at three pacing rates. Pacing was stopped and atenolol 0.2 mg/kg was given intravenously. Twenty minutes later, measurements were repeated at the same three pacing rates. Left ventricular cineangiography was performed after the metabolic study.

The pressure and coronary sinus thermistor signals were displayed on a Cambridge 12-channel recorder, and stored on tape. The micromanometer signal was differentiated either electrically or on-line by computer. KV max was derived from the plot of $\log d$ (developed pressure)/dt against pressure¹² by an electronic processor¹³ or by computer. Systolic pressure time index was calculated from planimetric integration of the ventricular pressure trace. Cardiac output was measured by dye dilution. Indocyanine green was injected in the right atrium, and its concentration in the pulmonary artery sampled. The dye curve was analysed by an IVH3 Schwarzer cardiac output computer. Coronary sinus blood flow was measured by constant infusion thermodilution.¹⁴ Left ventricular volume, ejection fraction, and mass were estimated from the right anterior oblique projection of the cineangiogram using a computer-light pen system.¹³

Blood was added to an aliquot of 10 per cent perchloric acid for deproteinisation and subsequent enzymatic photometric determination of lactate and pyruvate,¹⁵ acetoacetate and hydroxybutyrate,¹⁶ and glycerol.¹⁷ For measurement of free fatty acids¹⁸

blood was added to sequestrine tubes, mixed, 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 O₂ Con-TL (Lexington Instrument Corporation).

Extraction of a substrate is defined as the difference in concentration between arterial and coronary sinus blood (A-V). Extraction ratio is that difference expressed as a percentage of arterial concentration $[(A-V)/A \ %]$. Myocardial oxygen uptake is calculated as the difference between arterial and coronary sinus blood oxygen content multiplied by coronary sinus flow.

In addition to the 11 patients to whom atenolol was administered, one patient followed the same procedure, but was given saline instead of the drug.

The effect of heparin upon arterial free fatty acid concentration was investigated in a separate group of 21 patients who were undergoing diagnostic left heart catheterisation. In this laboratory all patients are given heparin (45 units/kg) after the introduction of the arterial catheter. Arterial free fatty acid concentration was measured immediately before, and five, 10, and 30 minutes after heparin administration. Of the 21 patients, 11 had received heparin at the time of premedication.

Statistical analysis is by Student's *t* test and linear regression; $p < 0.05$ is considered significant. Values are expressed as mean \pm standard error of the mean.

Results

Ten of the 11 patients had abnormal coronary arteriograms, and the angiographic data are listed in the Table. One patient had angiographically normal coronary arteries, but a history of angina and a lactate extraction ratio of less than 10 per cent at the highest pacing rate.

As basal heart rate differed between individuals, the pacing rates used were not identical in all patients. In each individual the pacing rates before and after atenolol were in close agreement. The mean heart rates measured from the pressure records were 86 ± 2 , 114 ± 3 , and 140 ± 5 beats/min before, and 87 ± 2 , 114 ± 3 , and 139 ± 4 beats/min after atenolol.

The haemodynamic effects of atenolol are summarised in Fig. 1. Left ventricular systolic and end-diastolic pressures did not change significantly after atenolol. Cardiac output was reduced significantly only at the lowest pacing rate: 3.94 ± 0.22 l/min compared to 4.57 ± 0.32 l/min ($p < 0.05$). The maximum rate of pressure rise was lower after atenolol at each pacing rate, falling from 1667 ± 110 mmHg/s to 1501 ± 100 mmHg/s at the first placing

rate ($p < 0.01$), from 1878 ± 107 mmHg/s to 1551 ± 100 mmHg/s at the second ($p < 0.01$), and from 2005 ± 151 to 1567 ± 146 mmHg/s ($p < 0.01$) at the third pacing rate, and KV max fell from 75 ± 4 to $65 \pm 3/s$ ($p < 0.01$), 79 ± 4 to $64 \pm 4/s$ ($p < 0.01$), and from 63 ± 6 to $54 \pm 4/s$ ($p < 0.05$) at the same three pacing rates.

Four patients developed angina at the highest pacing rate before atenolol and, in these patients, between the lowest and highest pacing rates, end-

diastolic pressure rose by a mean of 11 mmHg, whereas in the other seven patients there was a mean fall of 1 mmHg. After atenolol, three of the four did not have pain at the highest pacing rate, but end-diastolic pressure still rose by a mean of 11 mmHg, compared with a rise of 1 mmHg in the other seven.

Coronary sinus flow and myocardial oxygen consumption did not change after atenolol (Fig. 2). Arterial and coronary sinus blood oxygen content

Table Details of coronary arteriography and left ventricular cineangiography

Case no.	Age (y)	RCA	LAD	Cx	Ejection fraction	LV mass (g)
1	52	80%	50%	100%	0.43	217
2	56	100%	80%	80%	0.62	169
3	51	100%	100%	40%	0.56	215
4*	53	70%	90%	40%	0.72	178
5	40	Normal	100%	Normal	0.61	130
6*	48	100%	90%	80%	0.26	157
7	46	Normal	80%	Normal	0.84	246
8*	40	Normal	100%	70%	0.60	176
9*	43	100%	100%	70%	0.44	288
10	59	Normal	Normal	Normal	0.59	112
11	45	Normal	80%	Normal	0.60	132

RCA, right coronary artery; LAD, anterior descending branch of left coronary artery; Cx, circumflex branch of left coronary artery;

* patient developed angina at the highest pacing rate.

The percentage denotes the severity of the major lesion in that coronary artery, or its major branches.

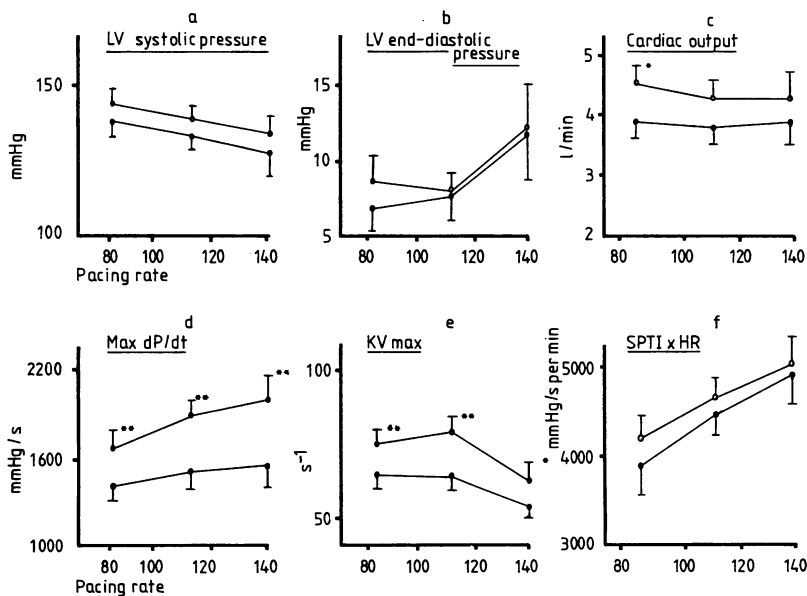


Fig. 1 Haemodynamic observations at each pacing rate. Mean \pm SEM of all 11 patients. Open circles: before atenolol. Closed circles: after atenolol. (a) Left ventricular systolic pressure. (b) Left ventricular end-diastolic pressure. (c) Cardiac output. (d) Maximum rate of rise of left ventricular pressure (max dP/dt). (e) KV max. (f) Product of systolic pressure time index and heart rate. * $p < 0.05$, ** < 0.01 , when pre- and post-atenolol values are compared.

did not change with increasing heart rate or after the drug, so coronary sinus flow closely followed myocardial oxygen uptake. Oxygen uptake/100 g myocardium was related to the product of systolic pressure time index and heart rate before atenolol, $r=0.68$ ($p<0.001$) and after atenolol, $r=0.62$ ($p<0.005$), and the slopes of the two regression lines were similar (Fig. 3). No differences in coronary sinus flow or myocardial oxygen consumption were apparent between the patients who developed angina, and those who did not.

Myocardial lactate extraction ratio fell as pacing rate increased; from 15.4 per cent ± 2.7 at the first, to 0.8 per cent ± 5.4 ($p<0.05$) at the third before atenolol, and from 26.6 per cent ± 3.8 to 18.0 per cent ± 4.2 ($p<0.05$) after atenolol (Fig. 4). The mean lactate extraction ratio of the 11 patients was higher after atenolol at each pacing rate, significantly so at the first, 26.6 per cent ± 3.8 compared with 15.4 per cent ± 2.7 ($p<0.02$), and at the third, 18.0 per cent ± 4.2 compared with 0.8 per cent ± 5.4

($p<0.01$). There was a small increase in arterial lactate concentration from 0.575 ± 0.035 mmol/l to 0.661 ± 0.04 mmol/l ($p<0.01$) after atenolol. At the highest pacing rate before atenolol mean lactate extraction ratio in the four patients with angina was -12.6 per cent ± 8.6 , compared with 9.6 per cent ± 4.2 in the patients without pain.

Arterial concentration and extraction of pyruvate, acetoacetate, hydroxybutyrate, and free fatty acids did not change as heart rate rose, so the results at each pacing rate are not considered separately. After atenolol arterial pyruvate concentration rose from 0.029 ± 0.003 mmol/l to 0.039 ± 0.002 mmol/l ($p<0.01$), and extraction rose from 0.005 ± 0.001 mmol/l to 0.012 ± 0.002 mmol/l ($p<0.01$). The increase in extraction ratio from 17 per cent ± 7.5 to 31 per cent ± 8 was not significant. Extraction was related to arterial concentration before, $r=0.58$

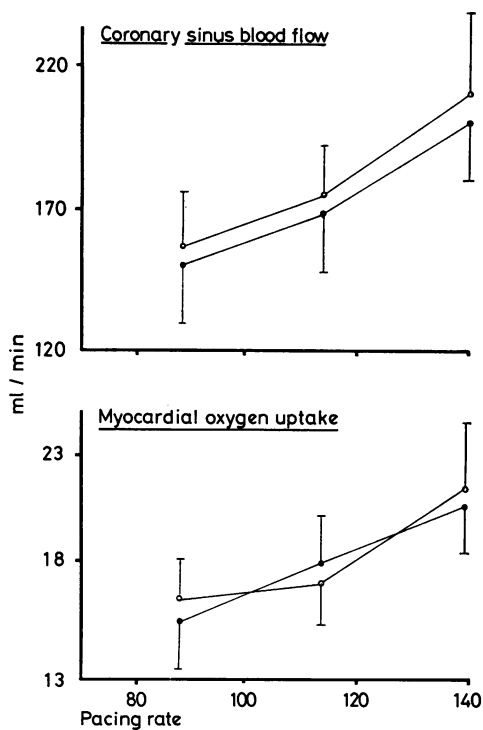


Fig. 2 Upper panel: coronary sinus blood flow, mean \pm SEM at each pacing rate. Lower panel: myocardial oxygen uptake, mean \pm SEM at each pacing rate. Open circles: before atenolol. Closed circles: after atenolol.

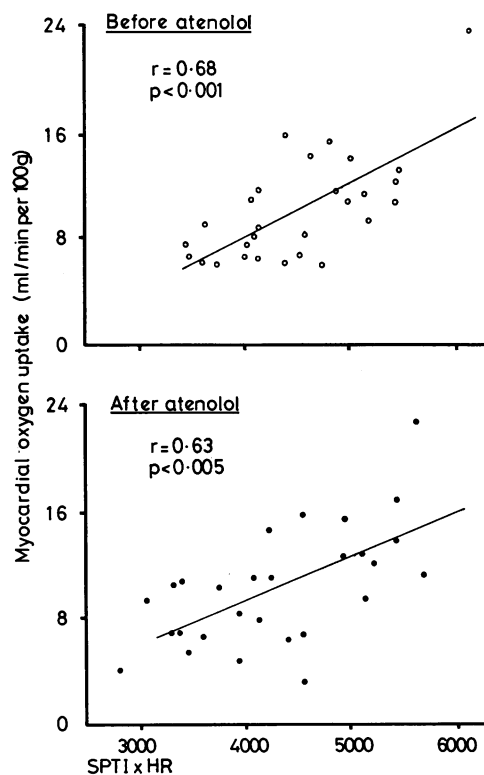
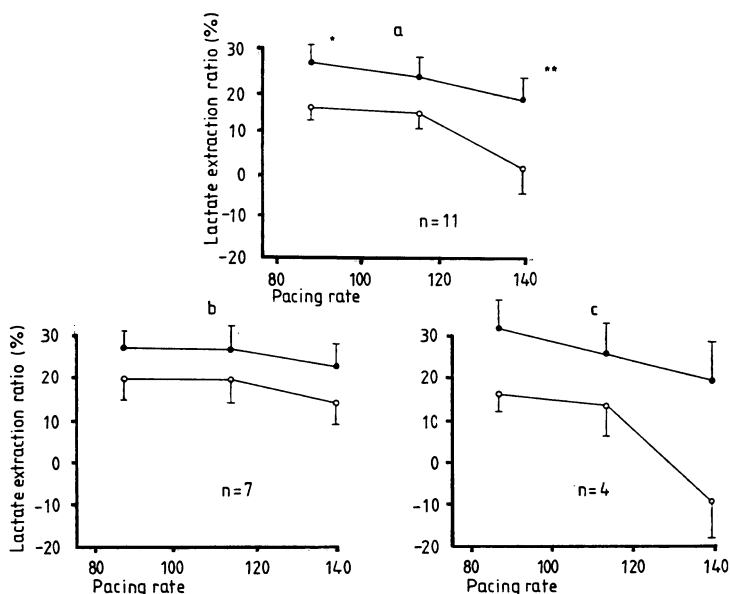


Fig. 3 Relation between oxygen uptake/min per 100 g myocardium and the product of systolic pressure time index and heart rate (mmHg s/min). Upper panel: before atenolol. Oxygen uptake/min per 100 g = 0.0038 ± 0.0008 ($SPTI \times HR$) - 6.78. Lower panel: after atenolol. Oxygen uptake/min per 100 g = 0.0032 ± 0.0008 ($SPTI \times HR$) - 3.63

Fig. 4 Myocardial lactate extraction ratio at each pacing rate. Open circles: before atenolol. Closed circles: after atenolol. (a) Mean \pm SEM of all 11 patients. (b) Mean \pm SEM of seven patients who did not develop angina. (c) Mean \pm SEM of four patients who developed angina at the highest pacing rate before atenolol. * $p < 0.02$, ** $p < 0.01$ when pre- and post-atenolol values are compared.



($p < 0.01$) and after atenolol, $r = 0.74$ ($p < 0.01$) (Fig. 5). Arterial acetoacetate concentration fell from 0.087 ± 0.012 mmol/l to 0.075 ± 0.111 mmol/l, and extraction from 0.039 mmol/l to 0.033 mmol/l after atenolol, but these changes were not significant. Extraction ratios before and after atenolol were 45 per cent ± 5 and 44 per cent ± 6 (NS), and extraction was related to arterial concentration before and after the drug, $r = 0.80$ ($p < 0.001$) and $r = 0.98$ ($p < 0.001$).

After atenolol, arterial hydroxybutyrate concentration fell from 0.153 ± 0.019 mmol/l to $0.111 \pm$

0.018 mmol/l ($p < 0.01$), but the fall in extraction from 0.044 ± 0.006 mmol/l to 0.035 ± 0.007 mmol/l was not significant. Extraction ratios were 29 per cent ± 4 and 32 per cent ± 4 before and after the drug. Extraction was closely related to arterial concentration; $r = 0.88$ ($p < 0.001$) and $r = 0.96$ ($p < 0.001$).

Arterial free fatty acid concentration fell after atenolol from 0.976 ± 0.046 mmol/l to 0.743 ± 0.052 mmol/l ($p < 0.001$). Mean extraction fell from 0.172 ± 0.02 mmol/l to 0.100 ± 0.02 mmol/l ($p < 0.01$), but the decrease in extraction ratio from

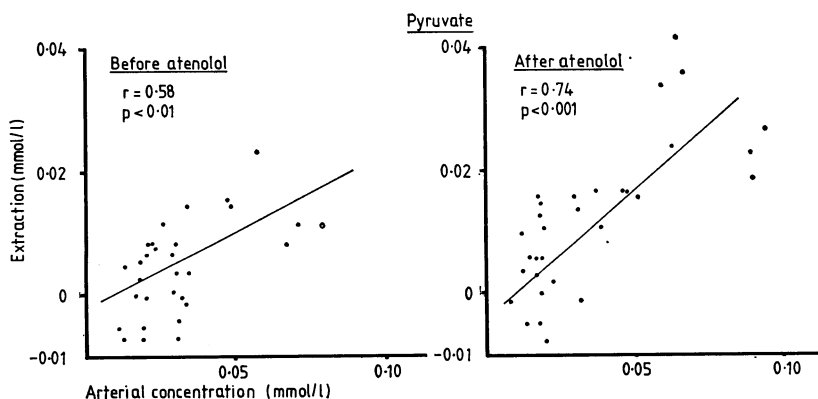


Fig. 5 Relation between myocardial pyruvate extraction and arterial concentration of pyruvate. Left-hand panel: before atenolol. Extraction = 0.255 ± 0.066 (arterial concentration) - 0.002 . Right-hand panel: after atenolol: extraction = 0.415 ± 0.035 (arterial concentration) - 0.004 .

17.6 per cent ± 1.6 to 13.5 per cent ± 2.6 was not significant. Extraction was related to arterial concentration before and after the drug; $r=0.57$ ($p < 0.001$), and $r=0.44$ ($p < 0.02$) (Fig. 6).

In Fig. 7 the change in myocardial lactate extraction observed in each patient at each pacing rate after atenolol has been plotted against the corresponding change in arterial free fatty acid concentration. The changes in lactate extraction were related inversely to the changes in arterial free fatty acid concentration; $r = -0.603$ ($p < 0.001$). A similar relation was found between changes in pyruvate extraction and changes in free fatty acid concentration; $r = -0.607$ ($p < 0.001$).

Arterial glycerol concentration decreased after atenolol from 0.060 ± 0.003 mmol/l to 0.045 ± 0.003 mmol/l ($p < 0.001$). Extraction was not related to arterial concentration, and glycerol release from the heart was common. At the lowest pacing rate after atenolol extraction was 0.008 ± 0.003 mmol/l, compared with -0.007 ± 0.002 mmol/l ($p < 0.01$) before the drug. At the higher pacing rates there was no significant change after the drug.

In 10 of the 11 patients arterial substrate concentrations were measured immediately before the second dose of heparin, approximately one hour before the metabolic study. Concentrations of hydroxybutyrate, acetoacetate, and free fatty acids

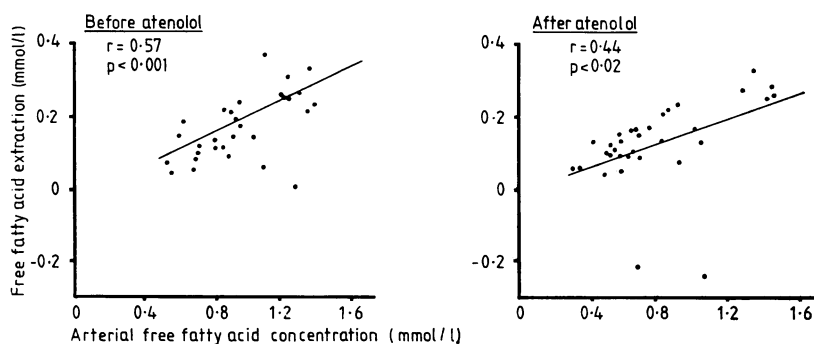


Fig. 6 Relation between myocardial extraction and arterial concentration of free fatty acids. Left-hand panel: before atenolol. Extraction = 0.225 ± 0.069 (arterial concentration) - 0.025 . Right-hand panel: after atenolol. Extraction = 0.17 ± 0.061 (arterial concentration) - 0.01 .

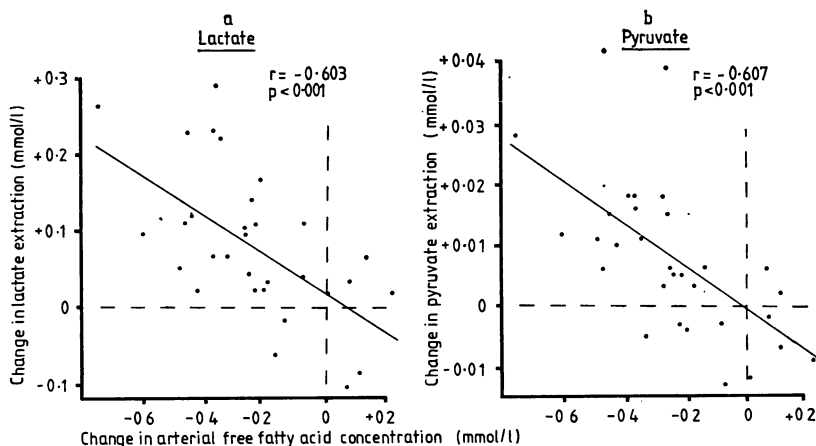
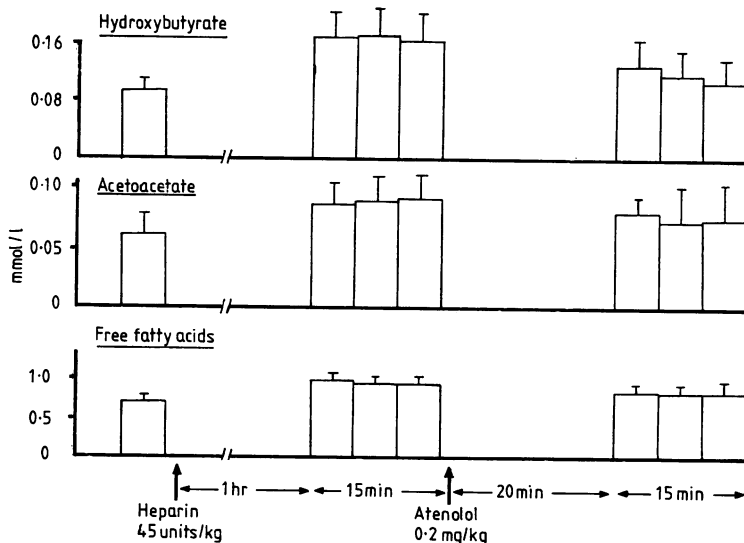


Fig. 7 Left-hand panel: relation between the change in myocardial lactate extraction seen in each patient at each pacing rate after atenolol, and the change in arterial free fatty acid concentration. Change in lactate extraction = -0.252 ± 0.043 (change in arterial free fatty acid concentration) + 0.016 . Right-hand panel: relation between the change in myocardial pyruvate extraction seen in each patient at each pacing rate after atenolol, and the change in arterial free fatty acid concentration. Change in pyruvate extraction = -0.034 ± 0.007 (change in arterial free fatty acid concentration) - 0.0005 .

Fig. 8 Arterial concentration (mean \pm SEM) of hydroxybutyrate, acetoacetate, and free fatty acid before the second dose of heparin, at the three pacing rates before atenolol, and the three pacing rates after atenolol.

The times at which these samples were taken in relation to heparin and atenolol administration are shown on the abscissa.



were higher at the beginning of the metabolic study than before the second dose of heparin (Fig. 8). Their concentrations at the three pacing rates before atenolol showed little variation. Similarly, after atenolol concentrations were stable over the three pacing rates, though lower than pre-drug levels. Arterial concentration of lactate, pyruvate, and glycerol at the beginning of the metabolic study did not differ significantly from levels before the second dose of heparin.

The patient who followed the same procedure, but received saline instead of atenolol, proved to have only minor irregularities in the coronary arteries, and pacing did not precipitate pain. At the three pacing rates before saline myocardial lactate extraction ratios were 26, 30, and 32 per cent, and after saline, 24, 22, and 30 per cent. Arterial free fatty acid concentrations were 0.57, 0.63, and 0.56 mmol/l before, and 0.64, 0.53, and 0.56 mmol/l after saline.

Fig. 9 summarises the effects of heparin upon arterial free fatty acid concentration in the 21 patients undergoing routine catheterisation. The initial arterial free fatty acid concentrations were similar in both groups. In the 10 patients who had not been pretreated with heparin mean concentration rose from 0.69 ± 0.048 mmol/l to 1.244 ± 0.186 mmol/l ($p < 0.01$) five minutes after heparin, and was still significantly raised at 10 minutes, 1.163 ± 0.16 mmol/l ($p < 0.01$), though at 30 minutes, 0.982 ± 0.157 mmol/l, was not significantly different from the pre-heparin level. In contrast, in the patients who had received heparin at the time of premedication, arterial concentration did not rise

significantly after the second dose of heparin, and mean concentration was similar before, 0.747 ± 0.067 mmol/l, and 30 minutes after heparin, 0.762 ± 0.122 mmol/l.

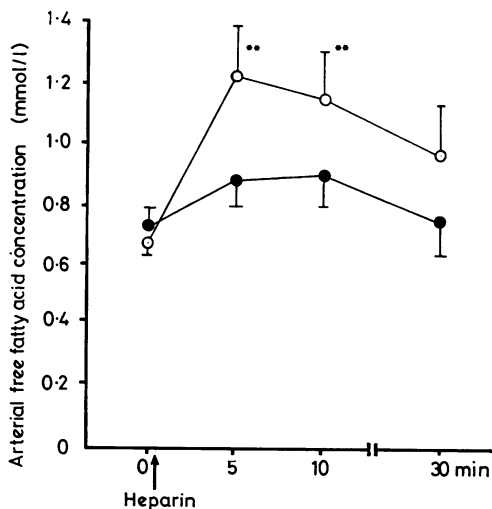


Fig. 9 Effects of heparin on arterial free fatty acid concentration in 21 patients undergoing cardiac catheterisation. Open circles: mean \pm SEM of 10 patients given a single dose. Closed circles: mean \pm SEM of 11 patients who received heparin at the time of premedication in addition to the dose given after arterial catheterisation. $^{***}p < 0.01$ compared to pre-heparin levels.

Discussion

In this study we used coronary sinus pacing to investigate the effects of atenolol upon myocardial metabolism and haemodynamics at progressively increasing levels of myocardial oxygen demand. We did not deliberately seek to induce angina, so the pacing rates employed were comparatively low. In a study using a similar procedure, pacing-induced changes in myocardial lactate extraction in both normal subjects and patients with coronary artery disease have been shown to return to normal within 15 minutes of stopping pacing.⁴ To confirm this, one patient was given saline instead of atenolol, and it was found that both lactate extraction ratio and arterial free fatty acid concentration were comparable in the two periods of pacing.

All our patients were studied after coronary arteriography.

Injection of contrast media into the coronary circulation may increase myocardial blood flow (though oxygen consumption does not change¹⁹), depress myocardial contractility,²⁰ and produce a small rise in left ventricular end-diastolic pressure.²¹ These effects are short lived and, as arteriography did not precipitate angina in any of our patients, it is likely that the interval of at least 20 minutes between arteriography and the first metabolic measurements was adequate to allow recovery.

Atrial pacing of the normal heart has little effect upon cardiac output, reduces stroke volume and end-diastolic pressure,²²⁻²³ and increases max dP/dt and KV max.²⁴ In some patients with coronary artery disease pacing may fail to induce angina because the pacing rate required to produce pain is higher than the heart rate at which angina occurs during exercise; under these circumstances the haemodynamic response to pacing may be normal.²⁵ If angina does occur during pacing there is often an associated rise in left ventricular end-diastolic pressure²⁶⁻²⁷ and a fall in V max,²⁸ though augmentation of max dP/dt by heart rate may be preserved. The rise in end-diastolic pressure has been attributed to acute failure,²⁷ or reduced diastolic compliance.²⁹ In our study the four patients who developed angina at the highest pacing rate before atenolol showed a rise in end-diastolic pressure, whereas in the other seven patients end-diastolic pressure fell as heart rate increased. The small number of patients does not allow a formal statistical comparison of the patients with and without angina, but it is of interest that after atenolol end-diastolic pressure still rose on pacing in the four patients who had experienced angina before the drug, despite relief of angina in three, and increased lactate extraction in all four. It might be

argued that whereas the increase in end-diastolic pressure before atenolol was a result of reduced diastolic compliance secondary to ischaemia, the rise after the drug was the result of ventricular dilatation and failure caused by beta blockade. This explanation is unlikely because end-diastolic pressure did not rise after atenolol in the other seven patients. These observations raise the possibility that when myocardial oxygen consumption is controlled by pacing, atenolol may have a more favourable effect upon lactate extraction than upon the mechanical properties of the ischaemic myocardium.

One mechanism by which beta-blocking drugs relieve angina is reduction of myocardial oxygen demand secondary to their haemodynamic actions.² The major determinants of myocardial oxygen demand are heart rate, contractility, and left ventricular wall tension.³⁰ As calculation of wall tension requires complex simultaneous measurement of ventricular volume and pressure, the product of systolic pressure time index and heart rate has been used to predict myocardial oxygen demand,³¹ but suffers the disadvantage of being insensitive to changes in ventricular volume and contractility.³² The haemodynamic effects of atenolol shown in this study are similar to those reported by Robinson *et al.*³³ Cardiac output fell at the lowest pacing rate; left ventricular systolic and end-diastolic pressures did not change. Max dP/dt and KV max were consistently lower at all pacing rates after the drug, suggesting that myocardial contractility was reduced, though conclusions drawn from indices derived from isovolumic pressure rise are open to criticism in the presence of ventricular asynergy.³⁴ Indices of contractility derived from quantitative angiography also fall after atenolol,³⁵ but end-diastolic volume rises, so that reduction in myocardial oxygen demand resulting from a decrease in contractility may be offset by an increase resulting from higher wall tension caused by ventricular dilatation. In agreement with other work⁵ myocardial oxygen uptake did not change after atenolol when heart rate was controlled, and was still related to the product of systolic pressure time index and heart rate. Reduced contractility did not cause a fall in myocardial oxygen consumption, possibly because of the counterbalancing effect of increased wall tension caused by ventricular dilatation. The significant improvement in myocardial lactate extraction in our patients after atenolol occurred without reduction in oxygen uptake, or systolic pressure time index, and cannot be attributed to any haemodynamic change caused by the drug.

Coronary sinus blood flow did not change after atenolol and remained closely related to myocardial

oxygen uptake. Redistribution of myocardial blood flow in favour of ischaemic areas has been suggested as a mechanism by which beta blockade relieves angina.³⁶ Atenolol does not increase venous drainage from the territory of a stenosed coronary artery,⁵ nor does it increase perfusion in dyskinetic segments of left ventricular myocardium.³⁵ The metabolic effects of the drug are thus unlikely to have been the results of a direct action upon the diseased coronary circulation.

The energy requirements of the normal heart are met primarily by oxidation of free fatty acids, glucose, and lactate.³⁷ The citric acid cycle is the final common path for complete oxidation of all these substrates. Lactate by oxidation, and glucose by glycolysis, are both converted to pyruvate, which the heart can also extract from arterial blood. The entry of pyruvate into the citric acid cycle is controlled by pyruvate dehydrogenase, which is inhibited by high ratios of acetyl CoA : CoA and NADH : NAD.³⁸ High rates of fatty acid catabolism cause accumulation of acetyl CoA and NADH and inhibit pyruvate dehydrogenase, thus slowing the entry of pyruvate into the citric acid cycle. Ischaemia impairs the regeneration of CoA and NAD and may further inhibit pyruvate dehydrogenase. If pyruvate cannot be oxidised it is converted to lactate, and production of lactate and its release into coronary venous blood are characteristic findings in myocardial ischaemia.³⁹

In normal subjects there is wide individual variation in myocardial lactate extraction.⁴⁰ As might be expected from the competition between pyruvate and free fatty acid metabolites for entry into the citric acid cycle, in a group of normal subjects myocardial lactate and pyruvate extraction are related inversely to arterial free fatty acid concentration ($r = -0.62$),⁴⁰ and increase when free fatty acid concentration is reduced.⁴⁰ Thus, approximately 40 per cent of the variation in lactate extraction between normal individuals can be related to differences in arterial free fatty acid concentration, and lactate extraction in individual subjects can be changed by altering free fatty acid concentration. In a group of patients with coronary artery disease differences in severity of ischaemia lead to even wider individual variation of lactate extraction and/or production which may obscure the relation between lactate extraction and free fatty acid concentration. It is not surprising, therefore, that we found no relation between myocardial lactate extraction and free fatty acid concentration in our patients. But even in the presence of ischaemia, changes in arterial free fatty acid concentration might still affect lactate metabolism; lactate production by the ischaemic canine myocardium is

increased when arterial free fatty acid concentration is raised,⁴¹ suggesting an additive inhibitory effect of ischaemia and high rates of free fatty acid catabolism upon aerobic carbohydrate metabolism. In our patients the change in lactate extraction after atenolol bore a significant inverse relation to the change in arterial free fatty acid concentration. After atenolol mean free fatty acid concentration fell from 0.976 to 0.743 mmol/l, from which the published regression equation [lactate extraction = $0.37 - (\text{FFA}) \text{ART} \times 0.31$; $r = -0.62$],⁴⁰ predicts an increase in lactate extraction of 0.073 mmol/l, compared with the observed mean increase of 0.081 mmol/l. Thus, the correlation coefficient and the slope of the regression line of the relation, which we found between change in lactate extraction and change in free fatty acid concentration, are similar to those described for the relation between lactate extraction and arterial free fatty acid concentration in normal subjects.

Studies upon human myocardial metabolism may be complicated by changes in arterial substrate concentration. Free fatty acid concentration may increase because of prolonged fasting, the stress of the procedure, or the use of heparin. We believe that adequate anticoagulation is mandatory for left heart catheterisation, and all the patients in this study were given heparin. Heparin raises free fatty acid concentration by activating lipoprotein lipase,⁴² and its maximum effect is within about 10 minutes of administration.⁴³ The first dose of heparin, at the time of premedication, was given in an attempt to reduce circulating triglycerides, and thus reduce the effect of the second dose of heparin. The results of our study upon the 21 patients undergoing routine catheterisation show that heparin administration at the time of premedication is effective in blunting the rise in free fatty acid concentration that follows a second dose, and that in 30 minutes levels have returned to control values. The metabolic studies were made approximately one hour after the second dose of heparin, and it is unlikely, therefore, that arterial free fatty acid concentration measured then was influenced by the prior administration of heparin. That levels were higher at the beginning of the metabolic study than before the second dose of heparin may have been the result of stress. Arterial concentration was stable over the three pacing rates before atenolol administration; after the drug, arterial concentration was lower, but again similar at each pacing rate. In the patient who did not receive atenolol, free fatty acid concentration was comparable during both pacing runs. All these factors suggest strongly that the reduction in free fatty acid concentration observed after atenolol administration was the result of a

direct action of the drug rather than a progressive decline in the action of heparin. These results are in agreement with the known peripheral antilipolytic action of atenolol.⁴⁴

Although we were able to relate changes in lactate and pyruvate extraction to changes in arterial free fatty acid concentration, this statistical association may not be causal, even though a physiological basis exists for such a relation. Alternative mechanisms should be considered by which atenolol might increase myocardial lactate extraction without reducing myocardial oxygen consumption.

Experiments with labelled palmitate have demonstrated myocardial lipolysis,⁴⁵ which may provide an important source of free fatty acids for consumption by the myocardium.⁴⁶ Free fatty acids derived from this source might influence lactate and pyruvate metabolism by competition for entry into the citric acid cycle, or, particularly in the presence of ischaemia, by accumulation of long-chain fatty acyl CoA esters which inhibit oxidative metabolism.⁴⁷ Myocardial lipolysis is increased by catecholamines, and inhibited by propranolol.⁴⁸ In this study the moderate correlation between free fatty acid extraction and arterial concentration, the occasional negative extraction values, and the frequent finding of glycerol release all suggest that myocardial lipolysis was taking place. Atenolol increased glycerol extraction only at the lowest pacing rate, but did not appear to have any consistent effect at higher heart rates. Reduction in peripheral lipolysis was not, therefore, accompanied by an obvious reduction in myocardial lipolysis.

Adrenaline reduces the activity of pyruvate dehydrogenase, and this can be prevented by propranolol.⁴⁹ In the present study the fall in arterial free fatty acid concentration, and its likely effect upon lactate and pyruvate extraction, made it impossible to distinguish any similar direct action of atenolol upon pyruvate dehydrogenase. High ketone body consumption has been reported to reduce lactate extraction by the canine heart,⁵⁰ but in this study there was only a modest reduction in arterial concentration of hydroxybutyrate and acetoacetate after atenolol.

Coronary sinus blood contains venous effluent from both ischaemic and normal areas of myocardium. An increase in global lactate extraction could therefore be the result either of reduced lactate production by severely ischaemic areas, or of increased extraction by moderately ischaemic and normal areas, and these two mechanisms cannot be readily distinguished. The improvement in pain in three of the four patients with pacing-induced angina suggests that lactate production in ischaemic areas was reduced after atenolol, but the lack of

effect upon end-diastolic pressure argues for the persistence of some ischaemia. The increase in lactate extraction after atenolol was greater in the patients in whom pacing had produced angina than in the other seven patients, but they also sustained a greater fall in arterial free fatty acid concentration after the drug. Thus, the effects of atenolol were qualitatively similar irrespective of the severity of ischaemia. The reason for the greater fall in free fatty acid concentration in these patients is not clear, but it is possible that they had greater sympathetic drive, or higher levels of circulating catecholamines, and therefore showed greater changes after beta blockade.

When heart rate is controlled by pacing the acute administration of atenolol increases myocardial lactate extraction without reduction of myocardial oxygen consumption or the product of systolic pressure time index and heart rate. This effect may be the result of a reduction of arterial free fatty acid concentration rather than of a direct action upon the myocardium. Inhibition of peripheral lipolysis may therefore contribute to the efficacy of atenolol in the relief of angina. These results emphasise the importance of measuring arterial free fatty acid concentration during studies upon myocardial lactate and pyruvate extraction, particularly in the investigation of antianginal drugs that may influence peripheral lipolysis.

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