The Effect of Free Fatty Acids on Myocardial Oxygen Consumption During Atrial Pacing and Catecholamine Infusion in Man

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SUMMARY The effect of myocardial uptake of free fatty acids (FFA,) on myocardial oxygen consumption (MVO,) in relation to increased heart rate and inotropic stimulation was determined in patients with coronary artery disease. Submaximal atrial pacing and isoproterenol stimulation increased MVO, by 66% and 142%, respectively, at similar heart rates. Inhibition of lipolysis with 1-pyrindyl carbinol almost abolished FFA, and reduced MVO, significantly. Increased heart rate contributed 47% and FFA, 50% of the raised MVO, during catecholamine stimulation. During inhibition of lipolysis, the increased MVO, attributed to inotropic stimulation was 30%. Augmentation of FFA, by triglyceride/heparin infusion increased MVO, significantly above control levels, both during pacing and isoproterenol infusion.

We conclude that MVO, is closely correlated to FFA,, catecholamines sensitize the heart to FFA, and increased FFA, account for a major part of the increased MVO, during catecholamine stimulation. The importance of reducing heart rate and lipolysis to reduce myocardial oxygen requirements is emphasized.

THE EVOLUTION OF myocardial infarction is a dynamic process which may be modified by therapy. Therefore, interventions which can reduce infarct size have been intensively investigated. It has been shown that factors which increase myocardial oxygen consumption (MVO,) also increase infarct size. Conversely, interventions which reduce myocardial oxygen requirement, including reduction in heart rate (HR) and myocardial contractility, have a favorable effect on the severity of myocardial damage. Recent studies in dogs have demonstrated that inhibition of lipolysis has a protective effect on the acutely ischemic myocardium. Free fatty acids (FFAs) released by catecholamine stimulation have been shown to augment MVO, in anesthetized dogs over and above the changes induced by the increase in mechanical activity of the heart. Similar studies have not been performed in man. Therapy aimed at reducing ischemic myocardial damage should be evaluated in terms of a quantitative reduction of MVO,

In this study we examined patients with coronary heart disease to assess the quantitative contribution of FFAs on MVO, relative to changes in HR and contractility induced by catecholamines.

Material and Methods

Twelve patients undergoing evaluation for coronary bypass surgery were investigated. Before the study informed consent was obtained from all the participants. All patients had coronary arteriosclerotic disease with stenotic processes of more than 50% demonstrated by coronary angiography before the study. Four had double, and eight triple vessel disease. Left ventricular ejection fraction averaged 65 ± 5% (SEM) and diastolic ventricular pressure was less than 12 mm Hg in all patients. None of the patients had signs of additional valvular or myocardial disease. All studies were performed in the morning with the patients in a fasting state premedicated with 0.1 g allylpropyl. Measurements were made with the patients in the supine position.

Cardiac venous blood flow was measured by the continuous infusion thermodilution technique7 using a constant infusion rate of 36 ml 0.9% saline solution per min for 20–30 sec. The mean of differences between duplicate measurements performed within 1 minute is 3.3% for the coronary sinus ostial flow and 3.5% for the great cardiac vein.8 A 7 F two thermistor catheter (Wilton Webster lab) was passed through the left basilic vein and advanced to the coronary sinus. In nine patients, the sensing thermistor was positioned in the great cardiac vein. In the remaining three patients, the catheter could not be advanced that far and was left to measure total coronary sinus flow. Earlier investigations have demonstrated that relative changes in cardiac venous flow from different myocardial regions parallel each other. As long as relative effects were studied, with the patient serving as his own control, the catheter position inside the coronary sinus was disregarded.

Blood pressure was measured via a polyethylene catheter in the aorta with an EMT 35 Elema Shønander, Stockholm (ES) transducer and recorded on a Mingograph 800 (ES) ink jet recorder. An average of 10 consecutive beats was used. Mean arterial pressure was obtained by electrical integration.

Blood samples for analysis of hemoglobin, hematocrit, oxygen saturation and FFAs were obtained from the aorta and the cardiac vein directly into precooled vials immediately before each flow measurement. Oxygen saturation was measured in duplicate using an ABL 1 Radiometer Copenhagen apparatus. FFAs were assayed according to Dole as modified by Trout.

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The patients' angina threshold was tested by atrial pacing, where the heart rate was gradually increased until the patient experienced typical angina pectoris. The patients were then allowed complete rest for 15 minutes before the investigation was continued using atrial pacing 10 beats/min below the angina threshold (submaximal heart rate).

In six patients, measurements were made at rest and at the submaximal heart rate. In order to increase the endogenous release of FFAs, I.V. infusion of isoproterenol was then administered by a constant infusion pump. The infusion rate was slowly increased until the HR equaled the pacing frequency at which measurements already had been performed. The pacemaker was then switched on to assure a constant HR, and measurements were repeated. Myocardial blood flow is adjusted as a response to interventions after a few seconds. During atrial pacing a constant relationship remains between flow, MVO₂ and determinants of myocardial oxygen demand for a time long enough to complete the investigation. Beta-pyridyl carbinol 300–400 mg was then given I.V. and 20 minutes later the procedure was repeated sequentially, at rest, at the same atrial pacing rate and during identical infusion of isoproterenol. In another six patients, the same procedure was followed but instead of beta-pyridyl carbinol, arterial FFAs were elevated by intravenous infusion of a fat emulsion (Intralipid 20%, Vitrium,* 2 ml/min) activated by 5000 U of heparin.

Calculations

Cardiac venous flow was calculated from the formula

$$F_1 \times 1.19 \left(1 - \frac{\Delta T_B \cdot T_1}{T_B \cdot T_M} \right)$$

where $T_B$, $T_1$ and $T_M$ represent the temperature of blood, injectate and mixture of blood and injectate respectively. $F_1$ is the volume of injectate per min and 1.19 is a constant derived from the density and specific heat of saline solution and blood. MVO₂ = (arterial – cardiac venous oxygen content) × cardiac venous flow. Coronary arteriolar resistance = aortic mean pressure / cardiac venous flow. Heart rate pressure index = (HR•BP) = heart rate/min × systolic aortic pressure (mean of 10 beats).

Myocardial uptake of free fatty acids (FFAₜₜ) = (arterial – cardiac venous FFA concentration) × coronary plasma flow. Statistical evaluation was performed using the Student t test for paired analysis. Differences were regarded as significant when $P < 0.05$.

*100 ml contains: Fractionated soya bean oil, 20 g; fractionated egg lecithinase, 1.2 g; glycerol, 2.5 g; water to 100 ml. Main fatty acid components, analyzed by gas-liquid chromatography, were: linolate (40%), oleate (24%), palmitate (10%), and linoleate (7%).

Results

Effects of Beta-Pyridyl Carbinol

The changes in hemodynamics and myocardial metabolism produced by atrial pacing and isoproterenol infusion before and after administration of beta-pyridyl carbinol are summarized in table 1.

Heart Rate and Blood Pressure

After administration of beta-pyridyl carbinol, aortic systolic pressure decreased slightly and HR increased insignificantly at rest. Although not statistically significant, the HR•BP increased slightly. During atrial pacing and isoproterenol infusion, beta-pyridyl carbinol did not alter HR or blood pressure.

FFA Levels and Myocardial Uptake

Basal FFA levels in plasma determined in the resting state were 540 ± 80 μM/l. The arterial concentration remained constant during atrial pacing but was increased to 1165 ± 115 μM/l during isoproterenol infusion. Beta-pyridyl carbinol reduced arterial concentrations of FFA in all the investigated situations. The coronary arteriovenous difference and myocardial uptake of FFA decreased concomitant to the reduction in arterial FFA concentration (figs. 1 and 2). FFAₜₜ after beta-pyridyl carbinol was low during atrial pacing and after isoproterenol was added.

Myocardial Blood Flow and Oxygen Consumption

Atrial pacing from a resting HR of 55 ± 3 (SEM) to 107 ± 6 beats/min (95%) increased myocardial blood flow and oxygen consumption by 61% ($P < 0.01$) and 66% ($P < 0.01$), respectively. When a similar HR was obtained by isoproterenol infusion (1.9 ± 0.3 μg/min), we observed an additional increase in blood flow and oxygen consumption. The values at the end of a 15-minute infusion period were 14% ($P < 0.01$) and 14% ($P < 0.01$) above control values.

Administration of beta-pyridyl carbinol had virtually no effect on MVO₂ at rest. However, due to different directional changes the ratio MVO₂/HR•BP was significantly reduced, suggesting an oxygen-saving effect independent of changes in HR and blood pressure.

Atrial pacing during beta-pyridyl carbinol administration increased MVO₂ by 28% ($P < 0.05$). During isoproterenol infusion, MVO₂ increased by 81% ($P < 0.05$) above resting control values as compared with 142% before beta-pyridyl carbinol was given. MVO₂ and MVO₂/HR•BP was significantly higher ($P < 0.05$) during isoproterenol infusion than during atrial pacing alone before, but not after, administration of beta-pyridyl carbinol.

The relative contribution of increased HR, FFAₜₜ and inotropic stimulation to the increase in MVO₂ during isoproterenol infusion was calculated as shown in table 1. The increase in MVO₂ caused by isoproterenol was used as unity. By raising HR alone with atrial pacing, HR was found to contribute 47% to the increase. The role of FFAs was estimated follow-
Table 1. Hemodynamic and Metabolic Effects on the Myocardium Before and After β-Pyridyl Carbinol (Mean ± SEM.)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Rest</th>
<th>After</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>55</td>
<td>69</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>± 3</td>
<td>± 4</td>
<td>± 6</td>
</tr>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>131</td>
<td>119*</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>± 3</td>
<td>± 4</td>
<td>± 5</td>
</tr>
<tr>
<td>Heart rate pressure index (HR-BP), (mm Hg beats/min)</td>
<td>7290</td>
<td>8160</td>
<td>12001</td>
</tr>
<tr>
<td></td>
<td>± 531</td>
<td>± 664</td>
<td>± 673</td>
</tr>
<tr>
<td>Coronary arteriolar resistance, mm Hg (min/ml)</td>
<td>1.15</td>
<td>1.22</td>
<td>0.75</td>
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<tr>
<td></td>
<td>± 0.11</td>
<td>± 0.13</td>
<td>± 0.08</td>
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<tr>
<td>Myocardial blood flow (ml/min)</td>
<td>84</td>
<td>75</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>± 11</td>
<td>± 7</td>
<td>± 16</td>
</tr>
<tr>
<td>Coronary arteriovenous O₂ difference (ml/l)</td>
<td>109.9</td>
<td>112.2</td>
<td>111.4</td>
</tr>
<tr>
<td></td>
<td>± 6.5</td>
<td>± 4.5</td>
<td>± 4.5</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (MV₂O₂) (ml/min)</td>
<td>8.9</td>
<td>8.4</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>± 0.7</td>
<td>± 0.7</td>
<td>± 1.5</td>
</tr>
<tr>
<td>MV₂O₂/HR-BP · 10⁻⁴ (ml/mm Hg beats)</td>
<td>12.48</td>
<td>10.54</td>
<td>11.28</td>
</tr>
<tr>
<td></td>
<td>± 1.24</td>
<td>± 1.25</td>
<td>± 1.40</td>
</tr>
<tr>
<td>Free fatty acid (FFA), arterial concentration (µM/l)</td>
<td>540</td>
<td>416*</td>
<td>556</td>
</tr>
<tr>
<td></td>
<td>± 80</td>
<td>± 42</td>
<td>± 77</td>
</tr>
<tr>
<td>FFA, coronary arteriovenous difference (µM/l)</td>
<td>133</td>
<td>92</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>± 16</td>
<td>± 20</td>
<td>± 17</td>
</tr>
<tr>
<td>FFA, myocardial uptake (µM/min)</td>
<td>7</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>± 1</td>
<td>± 1</td>
<td>± 1</td>
</tr>
</tbody>
</table>

*P <0.05. †P <0.01.

ing inhibition of lipolysis and furnished 50% of unity. After inhibition of lipolysis the inotropic action of isoproterenol contributed 30% of the increase in MV₂O₂. Systolic arterial pressure during isoproterenol administration did not differ from resting control values and was therefore disregarded in the calculation. Hence, almost similar proportionate effects were obtained for FFA and inotropic stimulation when the ratio MV₂O₂/HR-BP was used. The reduction in myocardial MV₂O₂ induced by β-pyridyl carbinol during atrial pacing or isoproterenol infusion was closely correlated to a reduction in MV₂O₂/HR·BP (r = 0.84) (fig. 3).

Effects of Triglyceride/Heparin Infusion

The changes in hemodynamics and myocardial metabolism produced by atrial pacing and iso-

Figure 1. Relationship between arterial free fatty acid (FFAₐ) concentration and coronary arterio-venous (A-V) FFA difference. Each point represents the mean of six patients.
FIGURE 2. Effect of reducing myocardial free fatty acid uptake (FFA_u) by β-pyridyl carbinol on myocardial oxygen consumption per unit of left ventricular pressure work (MVO_2/HR-BP•10^{-4}) (mean ± SEM). MVO_2/HR-BP is significantly increased (P < 0.05) when isoproterenol is added to atrial pacing while the augmented FFA_u is not. After β-pyridyl carbinol both are significantly reduced.

proterenol infusion before and during administration of lipid emulsion are summarized in table 2.

Heart Rate and Blood Pressure

HR and HR•BP increased after lipid infusion at rest. Otherwise, the hemodynamic state was very stable.

FFA Levels and Myocardial Uptake

Basal FFA levels in plasma in the resting state were 627 ± 69 μM/1. While atrial pacing did not change arterial FFA concentration, isoproterenol infusion increased FFA to 1235 ± 104 μM/1. During lipid and heparin infusion there was a marked increase in arterial concentration in all the investigated situations, with increased coronary arteriovenous

![Graph showing the relationship between changes in free fatty acid uptake (ΔFFA_u) and changes in myocardial oxygen consumption per unit change of left ventricular pressure work (ΔMVO_2/HR-BP). Effect of β-pyridyl carbinol in lower left quadrant (r = 0.64) and heparin-Intralipid in upper right quadrant (r = 0.84). The regression line for all data is ΔMVO_2/HR-BP = 0.18ΔFFA_u + 0.63.]
Table 2. Hemodynamic and Metabolic Effects on the Myocardium Before and During Lipid Administration (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Atrial pacing</th>
<th>+ Isoproterenol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Before</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70</td>
<td>82*</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>± 4</td>
<td>± 2</td>
<td>± 4</td>
</tr>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>125</td>
<td>123</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>± 5</td>
<td>± 5</td>
<td>± 5</td>
</tr>
<tr>
<td>HR-BP (mm Hg beats/min)</td>
<td>868±</td>
<td>1007±*</td>
<td>1307±</td>
</tr>
<tr>
<td></td>
<td>± 517</td>
<td>± 567</td>
<td>± 583</td>
</tr>
<tr>
<td>Coronary arteriolar resistance (mm Hg min/ml)</td>
<td>1.52</td>
<td>1.13</td>
<td>1.20</td>
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<tr>
<td></td>
<td>± 0.36</td>
<td>± 0.20</td>
<td>± 0.34</td>
</tr>
<tr>
<td>Myocardial blood flow (ml/min)</td>
<td>77</td>
<td>102</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>± 18</td>
<td>± 25</td>
<td>± 20</td>
</tr>
<tr>
<td>Coronary arteriovenous O₂ difference (ml/l)</td>
<td>107.9</td>
<td>104.2</td>
<td>112.6</td>
</tr>
<tr>
<td></td>
<td>± 4.4</td>
<td>± 4.8</td>
<td>± 5.3</td>
</tr>
<tr>
<td>MVO₂ (ml/min)</td>
<td>8.2</td>
<td>10.7</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>± 1.6</td>
<td>± 2.6</td>
<td>± 2.0</td>
</tr>
<tr>
<td>MVO₂/HR-BP : 10⁻⁴ (ml/mm Hg beats)</td>
<td>8.80</td>
<td>9.65</td>
<td>7.90</td>
</tr>
<tr>
<td></td>
<td>± 1.80</td>
<td>± 1.77</td>
<td>± 1.58</td>
</tr>
<tr>
<td>FFA arterial concentration (µM/l)</td>
<td>627</td>
<td>1990†</td>
<td>633</td>
</tr>
<tr>
<td></td>
<td>± 69</td>
<td>± 118</td>
<td>± 66</td>
</tr>
<tr>
<td>FFA arterial concentration (µM/l)</td>
<td>189</td>
<td>242</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>± 32</td>
<td>± 56</td>
<td>± 19</td>
</tr>
<tr>
<td>FFA, myocardial uptake, (µM/min)</td>
<td>9</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

*P < 0.05; †P < 0.01.

Abbreviations: HP-BP = heart rate pressure index; MVO₂ = myocardial oxygen consumption; FFA = free fatty acid.

FFA difference during atrial pacing and isoproterenol infusion (figs. 2 and 4).

The fractionate myocardial extractions of FFAs decreased when arterial FFA concentrations increased.

Myocardial Blood Flow and Oxygen Consumption

Although there were similar pacing rates in both groups of patients, resting HRs were higher (70 ± 4 beats/min) in this group than in the previous group. Atrial pacing at the submaximal rate (110 ± 4 beats/min) therefore increased the HR by 57% above resting control value. Coronary blood flow increased by 31% (P < 0.01) and MVO₂ by 38% (P < 0.01). The infusion rate of isoproterenol (1.6 ± 0.2 µg/min) was intentionally lower than in the former group because some patients experienced anginal pain during additional administration of lipid emulsion and heparin. Myocardial flow and MVO₂ at the end of a 15-minute isoproterenol infusion period was respectively 81% (P < 0.01) and 67% (P < 0.01) above control values.

Administration of lipid emulsion had no significant effect on MVO₂ at rest; nor was there any effect on the ratio MVO₂/HR-BP. During atrial pacing, however, there was a much larger increase (81%) in MVO₂ than during pacing without lipid administration (38%). Simultaneous infusion of isoproterenol and lipid increased the MVO₂ to 91% above resting control value, compared with 67% during isoproterenol alone.

The ratio MVO₂/HR-BP was also markedly increased, suggesting an oxygen wasting effect independent of changes in HR and blood pressure. The changes in FFA uptake during atrial pacing or isoproterenol infusion was correlated to an increased MVO₂/HR-BP (r = 0.64). There was no significant difference in the relationship between changes in MVO₂/HR-BP and FFA although whether FFA was increased or decreased. The overall correlation coefficient was 0.90 (fig. 3). The increase in MVO₂ during atrial pacing was effected by an increase in blood flow, while during isoproterenol infusion, it was due to an additive effect of increases in arteriovenous oxygen difference and blood flow.

MVO₂ was significantly higher (P < 0.05) during isoproterenol infusion than during atrial pacing alone, but not after lipid administration. Considering left ventricular pressure work, there was significantly increased MVO₂/HR-BP (P < 0.01) after isoproterenol both before and after lipid infusion.

Discussion

This study demonstrated that variations in myocardial uptake of FFAs from exogenous or endogenous supplies are associated with marked directional changes in MVO₂. This pattern conforms with earlier studies in perfused rat hearts,¹¹ and in intact dog hearts with controlled left ventricular function.⁴, ¹² The calorigenic effect of FFAs is observed in other organs as well and is therefore unrelated to mechanical activity. The major increase in total body oxygen consumption induced by catecholamines is due to FFA mobilization and can be abolished by β-
It is unlikely that a reduction in developed wall tension contributed to the lowering of myocardial oxygen requirement, since systolic arterial pressure was not influenced by isoproterenol or β-pyridyl carbinol. Furthermore, all patients had normal end-diastolic pressures measured before ventricular angiography and β-pyridyl carbinol has no effect on left ventricular preload in animal experiments. In addition, a correction for small changes in blood pressure and HR was made by calculating oxygen consumption per unit of left ventricular pressure work (MVO₂/HR·BP). Spurious influence on MVO₂ by changes in hemodynamics induced during infusion of β-pyridyl carbinol or triglyceride/heparin could therefore be ruled out. Thus, a metabolic explanation for the excess oxygen consumption attributable to FFAₜ is likely.

Previous studies have been criticized because unphysiologically high levels of exogenous FFAs have been used, thus exceeding a physiological FFA/albumin ratio. In our study, isoproterenol, β-pyridyl carbinol and lipid emulsion activated by heparin were all administered in doses relevant for clinical use. In the resting condition MVO₂ was only slightly affected by increases or decreases in arterial FFA concentrations. However, during atrial pacing and isoproterenol infusion the heart became more "sensitized" to the effect of FFA. The change in MVO₂ was proportionate to variations in myocardial uptake of FFAs, both during inhibition of lipolysis and during infusion of triglyceride/heparin, but more so during the former procedure, despite a much lower FFA concentration. The extraction fraction decreased with increasing FFA concentrations when induced by exogenous triglyceride/heparin and/or isoproterenol infusion (fig. 2). Although increased catecholamine stimulation seems to sensitize the heart to the effect of circulating FFA, the extraction of FFA was not increased. The actual FFA concentration, therefore, does not appear to be of primary importance in determining the MVO₂ in the range investigated.

Most et al. did not find any effect of exogenous supply of FFAs on MVO₂. More recently, Rogers et al. found similar results in man at rest, which correlate with our findings in the nonstimulated condition. Although atrial pacing did not increase coronary oxygen extraction in the present and previous studies, coronary flow increased more when FFA uptake was augmented by exogenous supply than during pacing alone without lipid administration. In our investigation changes in arterial FFAs induced the largest changes in MVO₂/HR·BP during administration of isoproterenol and during atrial pacing, when the endogenous release of catecholamines was supposedly increased.

Myocardial FFA uptake influences the proportions of lipids and carbohydrates available for oxidation by the myocardium. Elevation of FFAs results in FFAs as the sole substrate utilized by the heart, while inhibition of lipolysis renders glucose as the sole substrate. In contrast to glucose, which can be metabolized anaerobically, oxygen is obligatory for the oxidation of FFAs. It can also be calculated that the oxygen consumption should be about 10-15% higher in hearts oxidizing fatty acids rather than carbohydrates. This is due to the production of FADH in β-oxidation, which produces only two ATP molecules per molecule of oxygen in contrast to three ATP molecules when NADH is oxidized; but this finding alone cannot explain the increase in MVO₂ because the FFA-induced change in MVO₂ during adrenergic stimulation was larger — close to 40%. This corresponds to observations made in dogs and perfused rat hearts.

The energy in MVO₂ may reflect energy used to increase the cycling rate of FFAs into and out of the

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**Figure 4.** Effect of increasing myocardial free fatty acid uptake (FFAₜ) by heparin-Intralipid on myocardial oxygen consumption per unit of left ventricular pressure work (MVO₂/HR·BP) (mean ± SEM). Both FFAₜ and MVO₂/HR·BP are significantly increased (P < 0.01) from atrial pacing to isoproterenol, with a further increase (P < 0.01) when heparin-Intralipid is added.
triglyceride pool, effected by catecholamine stimulation. Furthermore, in both in vitro and in vivo experiments, FFA's have been shown to reduce the coupling of the oxidative phosphorylation, which might contribute to a rise in oxygen consumption, where the energy is dissipated as heat.

In animal preparations which are made ischemic, an increase in arterial FFAs results in a deterioration of the ventricular function, despite unchanged MVO₂ and extension of myocardial ischemic injury. This suggests an increased imbalance between the oxygen supply and requirement in the ischemic myocardium. The patients in our study had clinically and angiographically proven coronary heart disease, and half of them experienced angina during combined infusion of isoproterenol and lipid solution, suggesting a synergistic effect, as no pain appeared when administered separately.

L rout et al. have reported that reduction of arterial FFAs during exercise testing reduces ST segment depression at a given workload in patients with coronary heart disease. Thus, the myocardial uptake of FFAs may contribute to the ischemic injury during increased workload because of augmented oxygen requirement.

Although a subanginal pacing rate was used in our study, an exogenous supply of FFAs did not provoke angina except in combination with catecholamine stimulation. The present and previous studies support the idea that FFAs contribute relatively more to MVO₂ during catecholamine stimulation in man.

Because catecholamines increase myocardial oxygen utilization in several ways — by chronotropic, inotropic and lipolytic augmentation — we attempted to analyze the contribution of the different factors. This has important relevance to the subject of reducing infarct size because effective protection is possible only in terms of a quantitative reduction in myocardial oxygen requirement. Pacing-induced increases in HR to a level similar to that obtained with isoproterenol resulted in a significant increase in MVO₂ but a small and inconsistent increase in myocardial uptake of FFAs. When changes in heart rate were accounted for, the inhibition of lipolysis almost abolished the effect of isoproterenol on myocardial oxygen utilization. This does not rule out the inotropic effect as a powerful determinant of MVO₂ but does indicate that the marked reduction in FFₐ below control values after β-pyridyl carbinol balances the increase in MVO₂ induced by the inotropic stimulation. Myocardial FFₐ, therefore, is a major determinant of myocardial oxygen requirement during concomitant catecholamine stimulation. Administration of isoproterenol in doses above the therapeutic range might result in a relatively larger inotropic than lipolytic contribution to myocardial oxygen requirement, because the increase in oxygen utilization tends to level off when FFₐ is increased. Since marked catecholamine release takes place in the acute phase of myocardial infarction, our study demonstrates the primary importance of a reduction in HR and inhibition of lipolytic stimulation in order to accomplish a reduction in myocardial oxygen requirement. Reduction of arterial FFA alone by β-pyridyl carbinol or by glucose insulin in patients with acute myocardial infarction has decreased ischemic injury and improved the hospital survival rate. The present study suggests that this is due to improved oxygen balance in the ischemic myocardium.

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WALL DYNAMICS IN CORONARY ARTERY DISEASE/St. John Sutton et al.


Relation Between Left Coronary Artery Stenosis and Regional Left Ventricular Function

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SUMMARY The effect of stenosis of the left main and proximal anterior descending coronary arteries on anterior left ventricular wall dynamics was investigated in 70 patients with ischemic heart disease by the use of roentgen videometric analysis of left ventricular angiograms. In all patients with ischemic heart disease, mean values for peak rate of systolic wall thickening and diastolic wall thinning were significantly smaller than normal (P < 0.01). In patients without infarction, there was no correlation between peak rate of systolic anterior wall thickening and stenosis of the coronary artery supplying it, but there was a significant reduction in peak rate of diastolic wall thinning (P < 0.01) in patients with stenosis greater than 90%; this difference was not apparent at any lower degree of stenosis. This population could not be recognized by any other parameter of global or regional ventricular function; thus, diastole is more sensitive to regional left ventricular dysfunction than systole.

THE SIGNIFICANCE OF REDUCTION of coronary blood flow and its relation to the severity of coronary artery stenosis in ischemic heart disease has been difficult to assess, partly because of the inability to quantitate collateral coronary flow, and because the capacity of the coronary flow is generally adequate to maintain normal resting demands in the presence of stenoses up to 85%. Techniques using isotope indicator washout and catheter flow probes provide no information regarding anatomic definition of the coronary artery stenoses or the functional state of the myocardium supplied by stenotic coronary arteries.

The relationship between resting coronary blood flow and regional systolic left ventricular function has been established in animals but not in man. Since left ventricular dysfunction may be recognized in diastole before systole, we investigated the effects of stenosis of the left main and proximal left anterior descending (LAD) coronary arteries on global function and on regional systolic thickening and diastolic thinning of the anterior left ventricular wall (LVW). Left ventricular angiograms were analyzed by roentgen videometry in 70 patients with ischemic heart disease (pre-angiographic diagnosis) and in 20 normal patients (post-angiographic diagnosis of normal coronary vessels).

Methods

The left ventricular angiograms of patients who underwent clinically indicated left heart catheterization, biplane left ventricular angiography, and coronary arteriography were analyzed. The patients were divided into two groups. One group consisted of 20 patients investigated for atypical chest pain with normal electrocardiograms, negative treadmill exercise electrocardiograms, and completely normal coronary angiograms. Twelve were male and eight were female. They ranged in age from 29–64 years, with a mean age of 48 years.

The second group consisted of 70 patients with ischemic heart disease with grade 2–4 angina (Canadian Heart Association classification) and abnormal electrocardiograms during treadmill exercise. Thirteen patients were female and 57 were male. They ranged in age from 37–70 years, with a mean age of 54 years. Twenty-three patients had electrocardiographic
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