
Effect of Increased Free Fatty Acids on Myocardial Oxygen Extraction and Angina Threshold during Atrial Pacing

GILLES R. DAGENAIJ, M.D., AND BERNARD JALBERT, M.D.

SUMMARY To evaluate whether elevated arterial free fatty acids (FFA) increase myocardial oxygen demand and ischemia, 15 fasting patients with coronary artery disease underwent a standardized atrial pacing test before (PT1) and during (PT2) heparin infusion. The patients were monitored for clinical and electrocardiographic (ECG) manifestations of ischemia. Myocardial extraction of lactate, inorganic phosphate, oxygen and FFA was measured before and during each PT. The control arterial FFA was 0.65 ± 0.03 μmole/ml and rose to 1.83 ± 0.16 μmole/ml during heparin infusion. Myocardial oxygen extraction at rest and during PT was not affected by the increase in arterial FFA. Seven patients asymptomatic during PT1 did not develop ischemic manifestations during PT2. In eight patients with angina during both PTs, increased arterial FFA concentration did not modify the severity of anginal pain, the amount of ST-segment depression and the myocardial balance of lactate or inorganic phosphate. Elevation of arterial FFA by heparin neither increased myocardial oxygen extraction at rest or during pacing nor accentuated ischemic manifestations during PT.

MYOCARDIAL OXYGEN EXTRACTION of the isolated rat heart4 and the anesthetized dog heart4-6 is augmented, with no change in mechanical work, when free fatty acid (FFA) delivery to the myocardium is increased. Furthermore, elevated arterial FFA increase myocardial ischemia in anesthetized dogs.4-11 From these observations, it might be expected that pharmacological agents such as heparin or catecholamines, which increase arterial FFA, would prove hazardous in patients with ischemic heart disease. The present study was undertaken to determine whether a heparin induced elevation of arterial FFA increases myocardial oxygen extraction and ischemic manifestations at rest and during a standardized atrial pacing test in patients with angiographically documented coronary artery disease.

Patients and Methods

Fourteen males and one female, aged between 35 and 56 years, hospitalized because of chest pain for coronary...
Myocardial lactate and inorganic phosphate balances were determined as metabolic indicators of myocardial ischemia and measured enzymatically and colorimetrically, respectively, as described previously. FFA were analyzed using a gas chromatographic method with heptadecanoic acid as an internal standard added during the Dole extraction process, as reported previously. Myocardial extraction was expressed in percent and obtained by dividing the arterio-coronary sinus difference by the arterial concentration. Electrocardiographic changes indicative of ischemia during pacing were defined as a flat or downsloping ST-segment depression of at least 1.0 mm for 0.08 sec in comparison with the resting tracing.

**Results**

No complications or dysrhythmias occurred during these procedures. Before heparin infusion the mean (± SE) arterial plasma FFA concentration for the entire group was 0.65 ± 0.03 μmole/ml. It rose to 1.83 ± 0.16 μmole/ml during heparin infusion (P < 0.001). Higher values of arterial FFA after heparin infusion (2.6 to 3.1 μmole/ml) were observed in three patients who had plasma triglycerides above 300 mg/100 ml. In all except one patient, changes in arterial plasma FFA concentration before and during heparin infusion correlated with the FFA arterio-coronary sinus difference (r = 0.70) (fig. 1).

**Effects of Increased FFA on Myocardial Oxygen Extraction**

Figure 2 illustrates the relationship between arterio-coronary sinus concentration differences of oxygen and FFA.
Effects of Increased FFA on Myocardial Ischemic Manifestations

In order to detect whether the elevation of FFA by heparin increased the ischemic manifestation during pacing, the 15 patients were divided into two groups: group A consisted of seven patients who had no angina during the first pacing and group B of eight who sustained angina during the first pacing. Table 1 shows the clinical, hemodynamic and ECG findings in each group at rest and during the two pacing tests. In group A, the second pacing test failed to show any significant change from the first test, regarding heart rate, aortic pressure, double product (product of heart rate and systolic pressure), triple product (product of heart rate, systolic pressure and ejection time) and ECG findings. None of these patients experienced angina. In group B there was also no difference in the hemodynamic and ECG observations in the eight patients after heparin infusion. Furthermore, in this last group the anginal pain which occurred during both pacing tests was not more pronounced when FFA were elevated.

Table 2 summarizes the arterial concentration and the myocardial extraction of FFA, oxygen, lactate and inorganic phosphate at rest and during pacing in both groups. In group

![Figure 2](image)

**Figure 2.** Individual values of arterio-coronary sinus oxygen [(A-CS) O₂] and FFA [(A-CS) FFA] difference relationship before and during heparin infusion. A small association was observed only in absence of heparin.

![Figure 3](image)

**Figure 3.** Relationship between arterio-coronary sinus difference in oxygen and FFA before and during heparin at rest and during pacing in each patient. (A-CS) O₂ was not increased during (A-CS) FFA elevation.

### Table 1. Clinical, Hemodynamic and Electrocardiographic Findings (mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Before heparin</th>
<th>During heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Pacing</td>
</tr>
<tr>
<td><strong>Group A (N = 7)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anginal pain</td>
<td>0/7</td>
<td>0/7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 3</td>
<td>161 ± 3</td>
</tr>
<tr>
<td>Double product (10⁻²)*</td>
<td>94 ± 5</td>
<td>203 ± 6</td>
</tr>
<tr>
<td>Triple product (10⁻²)</td>
<td>249 ± 19</td>
<td>373 ± 11</td>
</tr>
<tr>
<td>ECG ST depression (mm)†</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td><strong>Group B (N = 8)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anginal pain</td>
<td>0/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 4</td>
<td>154 ± 4</td>
</tr>
<tr>
<td>Double product (10⁻²)*</td>
<td>98 ± 6</td>
<td>200 ± 10</td>
</tr>
<tr>
<td>Triple product (10⁻²)</td>
<td>257 ± 12</td>
<td>389 ± 12</td>
</tr>
<tr>
<td>ECG ST depression (mm)†</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
</tbody>
</table>

*Systolic pressure × heart rate.
†Systolic pressure × heart rate × ejection time.
‡Depression measured from resting tracing.
A, the increased FFA induced by heparin did not modify myocardial oxygen, lactate and inorganic phosphate balance. In group B, a significant output of myocardial lactate and to a lesser degree of myocardial inorganic phosphate was observed before heparin infusion. However, the increased FFA induced by heparin failed to modify these metabolic parameters.

Discussion

The failure of elevated arterial FFA to increase myocardial oxygen extraction and ischemia in the present investigation is at variance with previously reported studies in animals. The discrepancy may be due to difference in species and different methodological approaches.

Effects of Increased FFA on Myocardial Oxygen Extraction

In the present study, myocardial oxygen extraction was not increased by elevated FFA. In the animal studies, myocardial oxygen uptake was augmented by increased oxygen extraction rather than by increased coronary blood flow. In humans, myocardial oxygen uptake is usually increased by augmenting coronary blood flow. Although in the present investigation coronary blood flow was not measured, there is evidence that heparin which increases plasma FFA in humans, does not increase coronary blood flow in “lipemic” subjects\(^\text{14}\) or coronary sinus blood flow in fasting patients.\(^\text{15}\)

Furthermore, the correlation obtained in the present study between simultaneous myocardial extraction of FFA and oxygen would not be affected by changes in blood flow since these substances were measured at the same time and are thus dependent on the same blood flow. So the discrepancy between the animal studies and the present investigation cannot be explained on the basis of different coronary blood flow response to increased FFA.

The failure to produce increased myocardial oxygen extraction by elevated FFA may be due to the method used in augmenting arterial FFA. Arterial FFA in anesthetized mongrel dogs, in contrast to humans, do not increase during infusion of heparin alone. Increased FFA delivery to the myocardium has been achieved by augmenting their concentration in the perfusion solution of the isolated rat heart\(^\text{1}\) or by adding heparin to an intralipid emulsion infusion in anesthetized dogs.\(^\text{3,4}\) The other approach to increasing FFA in anesthetized dogs has been to infuse catecholamines\(^\text{4,5}\) or nicotine\(^\text{6}\) and later on by blocking the induced lipolysis with \(\beta\)-pyridilcarbinol which does not affect the hemodynamic effects of these agents. By comparing the effects of catecholamines in the presence and absence of elevated FFA, it was observed that up to 30% of myocardial oxygen extraction was attributed to the increased FFA delivery to the myocardium. Not only the mode but the degree of FFA elevation could contribute to the discrepancy. For example, Mjöös obtained a mean arterial FFA concentration of 3.5 \(\mu\)moles/ml with the intralipid/heparin emulsion infusion, which induced a 24% increase in myocardial oxygen extraction.\(^\text{9}\) In the present study, even though three of the 15 patients had arterial FFA between 2.6 and 3.1 \(\mu\)moles/ml,
no increase in myocardial oxygen extraction was observed. Nevertheless the possibility of excessively high FFA increasing myocardial oxygen extraction cannot be totally excluded.

Effects of Increased FFA on Myocardial Ischemia

In anesthetized dogs, increased delivery of FFA to the ischemic myocardium has been shown to have deleterious effects by accentuating the ischemic process. Elevation of FFA by infusion of intralipid/heparin emulsion produced increased lactate release from the ischemic myocardium. The accentuated ischemia resulted from increased myocardial oxygen requirements due to an augmented ventricular size. On the other hand, when the lipolysis induced during norepinephrine, isoproterenol, or dopamine infusion was inhibited by \( \beta \)-pyridilcarbinol or p-chlorophenoxyisobutyrate, the mechanical performance remained unchanged but the ischemic injury, as assessed by epicardial ECG alone or in conjunction with myocardial lactate balance, decreased. The mechanisms responsible for the augmentation in myocardial oxygen extraction and ischemia due to the increased myocardial FFA uptake have not been defined. Inhibition of myocardial glycolysis and particularly of mitochondrial adenine nucleotide translocase due to increased intracellular concentration of long-chain acyl-CoA esters, have been entertained as hypotheses to explain this increased energy requirement.

In the present study, heparin-induced FFA elevation did not increase myocardial oxygen extraction in the 15 patients at rest. In the seven patients of group A, the heparin-increased arterial FFA failed to produce ischemic events during pacing. The eight patients of group B did not have earlier or more pronounced anginal pain, ECG or metabolic evidence of ischemia during pacing when FFA were elevated. The possibility that heparin by itself may prevent worsening of ischemia cannot be totally excluded. Such an effect could explain the discrepancy between the present study and the findings reported in dogs. However it remains to be determined whether excessively high plasma FFA either alone or in association with other critical factors such as increased catecholamine levels, would have deleterious effects in more extensive and prolonged ischemia in humans. A preliminary report indicates that a nicotinic acid analog which reduces exercise-induced FFA elevation without affecting the pressure rate product, decreases the amount of ST-segment depression during and following exercise in patients with angina pectoris. Similar observations have been obtained in patients with acute myocardial infarction during infusion of glucose-insulin-potassium. Further research is required to determine whether these results are caused by the changes in FFA concentration. Nevertheless, the results of the present study reveal that FFA elevated by heparin neither increased myocardial oxygen extraction at rest and during pacing nor accentuated ischemic manifestations during pacing in patients with coronary artery disease.

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References

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