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

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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.

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
arteriographic studies, agreed to participate in this investigation. No patient had congenital, primary myocardial or valvular heart disease, congestive heart failure, unstable angina or recent myocardial infarction. None had diabetes mellitus or was taking digitalis. Twelve patients had angina pectoris and eight had suffered a well documented myocardial infarction. Four patients had type IV hyperlipidemia and six type II hyperlipidemia. After a twelve hour fast, the mean plasma triglyceride concentration was 228 mg/100 ml (range 53 to 680) and the mean blood cholesterol concentration was 250 mg/100 ml (range 168 to 336). Coronary arteriographic studies, done immediately after the investigative procedure, were assessed by two independent observers. All patients had atherosclerotic narrowing of at least 50% in the right, left anterior descending and/or circumflex coronary vessel. Four patients had one coronary vessel disease, three had two vessel disease and eight had three vessel disease. All antianginal drugs were discontinued at least 48 hours before the procedure. All patients had been fasting for at least 10 hours before the procedure except for 10 mg of diazepam given orally with water one to two hours before catheterization.

From a basilic vein a number 7 or 8 pacing catheter was advanced to the midportion of the coronary sinus under fluoroscopic guidance. The position of the catheter, which was verified by a manual injection of contrast medium, did not change during the study. The catheter was connected to a Medtronic 5800 pacing generator. A second catheter was introduced percutaneously into the femoral artery and advanced to the distal portion of the abdominal aorta. No heparin or glucose was infused during these procedures. Aortic pressure was measured with a Statham P23Db pressure transducer. Electrocardiographic (ECG) leads II, III, aVF, and V₆ and aortic pressures were monitored and recorded with an Electronics for Medicine DR-8 recorder. Simultaneous blood samples from aorta and coronary sinus were obtained in duplicate for oxygen, pH, PCO₂, lactate, inorganic phosphate and FFA.

After a 10 minute rest period, heart rate, aortic pressure, ECG and blood samples were obtained. Subsequently, coronary sinus pacing was begun and increased by 10 beats/min until a heart rate of at least 160 beats/min was reached or until the patient complained of angina. At the maximal heart rate, the pacing was maintained for five minutes. During the last two minutes of pacing, hemodynamic, ECG and metabolic observations were made. After pacing had been discontinued, the patients received 3000 units of crystalline heparin intravenously as a bolus and another 3000 units in a slow infusion of 0.155 M NaCl for the remainder of the study. This was followed by a thirty minute rest period, after which identical rest and pacing measurements were repeated. In four patients, atropine sulfate, 0.4 to 0.8 mg, was given during the first pacing to correct an atrioventricular block induced by pacing. No conduction disturbance was observed during the second pacing. After the second pacing, angiographic catheters were introduced percutaneously in the other femoral artery to perform ventriculographic and coronary arteriographic studies.

Oxygen content was analyzed according to the method of Van Slyke and Neill and pH, PCO₂ and PO₂ were measured with a type AME 1 c Astrup Micro Equipment. 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.

\[
\begin{align*}
\text{(Arterial)} \text{FFA} & \quad \text{μmoles/ml} \\
0.5 & \quad 1.0 \\
1.5 & \quad 2.0 \\
2.5 & \quad 3.0 \\
\end{align*}
\]

**Figure 1.** Relationship between arterio-coronary sinus FFA difference and arterial FFA concentration before and during heparin infusion. The two Xs with a negative arterio-coronary sinus FFA difference are from the same patient.
before and during heparin infusion in each of the 15 patients. Before heparin was infused, a slight association \( r = 0.38 \) was observed between oxygen and FFA arterio-coronary sinus difference. This finding is similar to the observations reported by Wahlqvist et al. in normal resting subjects. On the other hand, during heparin infusion, no correlation was observed between the elevated FFA and arterio-coronary sinus difference. This finding is illustrated in more detail in figure 3 for each of the 15 patients at rest and during pacing. It can be seen that although FFA aorto-coronary sinus difference increased, the myocardial oxygen extraction remained unchanged. No change was observed in blood pH, PO\(_2\) or PCO\(_2\).

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

| Table 1. Clinical, Hemodynamic and Electrocardiographic Findings (mean ± SE) |
|-----------------------------------|----------------------|----------------------|
|                                   | Before heparin       | During heparin       |
|                                   | Rest                | Pacing              |
|                                   | Rest                | Pacing              |
| Group A (N = 7)                   |                      |                      |
| Anginal pain                      | 0/7                 | 0/7                 |
| Heart rate (beats/min)            | 74 ± 3              | 161 ± 3             |
| Double product (10-4)*            | 94 ± 5              | 203 ± 6             |
| Triple product (10+5)*            | 249 ± 19            | 373 ± 11            |
| ECG ST depression (mm)‡           | —                   | 0.5 ± 0.2           |
| Group B (N = 8)                   |                      |                      |
| Anginal pain                      | 0/8                 | 8/8                 |
| Heart rate (beats/min)            | 76 ± 4              | 154 ± 4             |
| Double product (10-4)*            | 98 ± 6              | 200 ± 10            |
| Triple product (10+5)*            | 257 ± 12            | 389 ± 12            |
| ECG ST depression (mm)‡           | —                   | 1.3 ± 0.3           |

*Systolic pressure X heart rate.
*Systolic pressure = heart rate X 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 or coronary sinus blood flow in fasting patients. 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 or by adding heparin to an intralipid emulsion infusion in anesthetized dogs. The other approach to increasing FFA in anesthetized dogs has been to infuse catecholamines or nicotine and later on by blocking the induced lipolysis with β-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, Mjøs obtained a mean arterial FFA concentration of 3.5 μmoles/ml with the intralipid/heparin emulsion infusion, which induced a 24% increase in myocardial oxygen extraction. In the present study, even though three of the 15 patients had arterial FFA between 2.6 and 3.1 μmoles/ml,
no increase in myocardial oxygen extraction was observed. Nevertheless the possibility of excessively high FFA increasing myocardial oxygen extraction cannot be totally excluded.6

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. Enhancement 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.4 On the other hand, when the lipolysis induced during norepinephrine,6 isoproterenol6, 11 or dopamine10 infusion was inhibited by ß-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 glycolysis18 and particularly of mitochondrial adenine nucleotide translocase18 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.20, 21 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.23 Similar observations have been obtained in patients with acute myocardial infarction during infusion of glucose–insulin–potassium.24 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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