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Myocardial substrate utilization and hemodynamics following repeated coronary flow reduction in pigs*)

Myokardialer Substratverbrauch und Hämodynamik während wiederholter Reduktion der Koronardurchströmung in Schweinen

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With 7 figures and 2 tables

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Summary

The effect of repeated local ischemia and reperfusion on myocardial metabolism and ventricular performance was studied in 12 open-chested pigs fasted overnight. Myocardial ischemia was induced by reduction of the flow in the left anterior descending coronary artery to 40% of control during 30 min. After 35 min of reperfusion a second 30-min occlusion period was started, again followed by a 35-min reperfusion period. At the end of both reperfusion periods coronary flow and coronary resistance had returned to control values. During control there was lactate uptake, but no significant uptake of glucose, free fatty acids (FFA), triglycerides, glycerol and inosine. During the first occlusion period the heart released lactate and inosine, and used glucose and FFA. At the end of the first reperfusion period lactate uptake approached control values, but inosine was still released by 10 of the 12 animals. In the second ischemic period, glucose and FFA were again taken up. Lactate and inosine were released, but the production was much smaller than during the first occlusion period. Depletion of myocardial glycogen and high-energy phosphates could be responsible for this quantitatively different response. Necrosis may have played a role, although enzyme release was minimal and only observed after the second occlusion period.

Heart rate, peripheral resistance and ventricular filling pressure were virtually unchanged throughout the course of the experiments. Maximum rate of fall of left ventricular pressure (min LV\(\frac{dP}{dt}\)) decreased during ischemia and did not recover during reperfusion. Changes in min LV\(\frac{dP}{dt}\) and cardiac output were more closely related than changes in max LV\(\frac{dP}{dt}\) and cardiac output.

This model cannot be used for the study of interventions during myocardial ischemia in which the animal serves as its own control.

A large number of experimental studies dealing with the consequences of acute myocardial ischemia or infarction have been carried out in the dog. However, the coronary vasculature and the collateral circulation of

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the dog is quite different from that found in man (14). The pig may be more suitable for these studies, since striking similarities exist between the hearts of man and pig (4, 7, 13, 28 and 29). Consequently different aspects of myocardial ischemia have been studied in the pig heart (1, 7, 8, 11, 18, 23, 31, 34 and 36). In an earlier report from our laboratory (10), we compared myocardial lactate release with the release of the ATP-catabolites inosine and hypoxanthine, during severe ischemia and reperfusion. In a large number of investigations multiple occlusions are carried out in order to evaluate the capability of drugs to modify the degree of ischemia. ST-segment changes are frequently used as an indicator of the degree of ischemia in such studies. However, little attention has been paid to myocardial metabolism, although alterations in the oxygen demand/supply ratio is often the prime target of such interventions. We therefore studied myocardial metabolism during two periods in which the flow in the left anterior descending coronary artery (LAD) was reduced to 40% of its control value for 30 minutes. After the first partial occlusion period the LAD was reperfused until flow and coronary vascular resistance resumed control values. Subsequently the second occlusion period was started. In our previous communication (10) nucleoside and carbohydrate metabolism were evaluated. In this study considerable attention has been paid to the role of free fatty acids.

Materials and methods

The experiments were performed on 12 Yorkshire pigs fasted overnight. The animals were sedated with 120 mg azaperone i.m. (Stresnil®, Janssen Pharmaceutica, Beerse, Belgium). Subsequently 150 mg metomidate (Hypnodil®, Janssen Pharmaceutica, Beerse, Belgium) was administered via a vein on the dorsal surface of the ear. The animals were intubated and connected to a Bird Mark 4 respirator for assisted ventilation with a mixture of 33% oxygen and 67% nitrous oxide. Ventilation was controlled by intermittent measurement of arterial blood gases (ABL1, Radiometer, Copenhagen, Denmark). The temperature of the animals was kept between 36.5 and 37.5 °C with a heating pad. ECG leads I, II and III were monitored throughout the experiment. The animals were kept anesthetized with a mixture of 2 mg·kg⁻¹·hour⁻¹ azaperone and 8 mg·kg⁻¹·hour⁻¹ metomidate, administered through the lumen of an 8 F Cournand catheter placed in the right atrium from the right jugular vein. A single 8 F Cournand catheter with its tip positioned in the thoracic aorta, was used for central aortic pressure measurements and for the collection of blood samples for the determination of blood gases and biochemical parameters. Through the left carotid artery a high fidelity 8 MMC Telco tipmanometer catheter (Thomson, Paris, France) was placed in the left ventricle for pressure measurements. Cardiac output was measured using the thermodilution technique. To this end a 7 F triple lumen balloon-tipped catheter was inserted in a femoral vein and its tip was positioned in the pulmonary artery. A 7 F Cournand catheter was positioned in the vena cava inferior for infusion purposes.

Surgical procedure

The left anterior descending coronary artery (LAD) was exposed by means of a midsternal thoracotomy. Parts of the fourth and fifth ribs were removed to get easy access to the LAD and its accompanying vein. The LAD was prepared free from its origin to its first branch and an electromagnetic flow probe (Skalar, Delft, The Netherlands, 20–25 mm in diameter) and a screw clamp were placed around the artery.