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EDITORIAL

Myocardial Blood Flow, Deoxyglucose Uptake, and Myocyte Viability in Ischemia

It has long been supposed that provision of glucose by glycolytic flux should be beneficial to the ischemic myocardium (*1*). The basic logic relies on the benefits of production of ATP independently of oxygen, during the glycolytic process. Even when glycolysis is maximally accelerated in anoxia with maintained coronary flow, glycolytically-produced ATP cannot meet the total energy requirements of the normally contracting heart. ATP produced by glycolysis may, however, play a different role by helping to protect the cell membrane (*2*). Thus, ATP generated by glycolysis preferentially interacts with potassium channels in isolated guinea-pig cardiac myocytes (*3*). Furthermore, it is ATP produced by glycolysis rather than the total ATP level that prevents ischemic contracture in the moderately underperfused myocardium (*4*).

These studies strongly suggest that it is not the overall level nor the concentration of ATP that is critical in the maintenance of ion gradients across the sarcolemma, but rather the rate of provision of ATP derived specifically from glycolysis.

MYOCARDIAL BLOOD FLOW AND GLUCOSE UPTAKE

If glycolysis (both from exogenous glucose uptake and from glycogen) were always increased by ischemia, then the above protective scheme would be relatively straightforward. Rather, in severe ischemia, it is proposed that the accumulation of glycolytic products in the myocardium (e.g., lactate, protons produced from turnover of ATP and from other sources, and increased levels of reduced coenzymes) act to inhibit glycolytic flux at several points and thereby to decrease glucose uptake (*5*). There should accordingly be a "flip-flop" mechanism whereby glucose utilization, initially increased by relatively mild degrees of ischemia, is inhibited by severe degrees of ischemia. Therefore, as the coronary flow rate progressively falls, there will be a critical flow level at which increased uptake of exogenous glucose switches to decreased uptake. A recent hypothesis (*6*) proposes that an increased glucose uptake reflects continued cell viability, whereas a decreased uptake is associated with loss of viability of the ischemic cells which then pass from reversible to irreversible damage.

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On the basis of this proposal, cells threatened by ischemia could be divided into: (a) viable cells with increased values for glucose uptake and (b) nonviable cells with decreased values. It is proposed that in zones of severe ischemia glycolysis is inhibited and fails to exert its proposed protective function on the cell membrane (*6*). Among the consequences would be cytosolic calcium overload, which is a key step in the progression to cell death (*7*).

What is the proposed level of myocardial blood flow for the "flip-flop" in glucose uptake to occur? In the isolated perfused rat heart, during severe ischemia when the coronary flow is reduced to 5%–10% of the pre-ischemic value, then myocardial glucose uptake falls. By contrast, when flow is 15%–20% of the pre-ischemic value, then the glucose uptake increases albeit only modestly (*6*). Thus, in this preparation, the critical flow rate must lie between 5% and 20%. It must be considered that these hearts are perfused without blood, so that the control coronary flow rate is abnormally high, probably 2.5 times that found in the rat in situ (*8*). Suppose, therefore, that at an approximation the critical rate of flow is about 10% of control in the isolated rat heart perfused without blood, then a "correction factor" of about 2.5 would have to be applied to bring it to levels relevant to blood-perfused preparations. Thus, the "guestimated" critical flow in the blood-perfused dog heart would be about 2.5 × 10% or about 25% of the pre-ischemic value. It should be recalled that ischemia is composed of two components, decreased delivery of oxygen and nutrients, and decreased washout of metabolites. Relevant to the glycolytic hypothesis is whether or not glycolytic end-products accumulate in the ischemic tissue, which would reflect the absolute rate of washout. Hence, it is appropriate to make corrections in the calculation for the total coronary flow rate, which reflects the washout rate, rather than the absolute decrease in oxygen delivery.

CHRONIC METABOLIC ISCHEMIA AND HIBERNATION

Consonant with the proposal for a critical level of glucose uptake are the findings that an increased glucose extraction in the presence of decreased coronary flow can indicate the hibernating state in which there is decreased coronary flow; contractility is reduced, yet the viability returns when the blood flow is restored to normal (*9*). Closely related is the entity of "persistent metabolic ischemia," found in patients with unstable angina pectoris at a time when there are no electrocardiographic signs of ischemia (*10*). Studies with PET in patients with coronary artery disease have identified segments of myocardium that are still viable, although contracting poorly (*11*). Hence, it might be supposed that increased uptake of fluorodeoxyglucose (FDG) could reflect tissue viability and possible suitability for operative restitution of coronary flow.

There are, however, certain technical problems. It should be emphasized that what is often measured in man is simply the regional distribution of FDG in the myocardium, which is not the same as the metabolic rate of glucose uptake. To obtain the true metabolic rate of glucose, both the arterial input fraction and the rate of myocardial accumulation of FDG should be known (*12*). In addition, the differences in affinity between glucose and deoxyglucose both for the transmembrane sugar transporter and for hexokinase are not known in human pathophysiological conditions. Thus, considerable extrapolation is still involved.

Nonetheless, first principles would suggest that an increase of FDG uptake occurring in zones of mild ischemia shows the long-term potential for tissue viability, whereas in zones of severe ischemia the depressed uptake of deoxyglucose indicates a high risk of necrosis. Thus, according to the hypothesis linking glucose uptake and ischemia (*6*), it should be possible to predict which myocardial zones will have reversible ischemia and which will undergo necrosis according to the pattern of extraction of fluorodeoxyglucose. Studies relevant to this hypothesis in man have been summarized elsewhere (*10*). The crucial data linking glucose extraction and myocardial blood flow, however, have been missing.

FINDINGS WITH FDG AND MYOCARDIAL BLOOD FLOW IN DOGS

In this issue of the *Journal*, Kalff et al. show that the uptake of FDG measured per unit of tissue after coronary ligation in open-chest dogs increases relative to that of the myocardial blood flow as the latter falls (*13*). In other words, ischemia induces a relative rise in the glucose extraction, so that the absolute level of uptake (extraction × blood flow) remains at normal or near-normal levels (*13*). The crucial observations are that in samples with severe ischemia, FDG uptake decreased precipitiously. These data confirm a threshold myocardial blood flow value for maintenance of glycolytic flux during ischemia. Since it is known that such low flows are often associated with irreversible ischemia (*14*), it is tempting to propose that the Kalff data lend strong support to the proposed hypothesis that a crucial factor in precipitating myocardial cell necrosis is reduction of glycolytic flux when the myocardial flow falls beyond a critical value (*6*). In the dog, this critical reduction of flow is in rates about 20% of control levels, remarkably close to the 25% predicted from the rat heart data. The Kalff paper does not directly prove that it is the fall in glycolytic flux that is the cause of the cell necrosis; these crucial data must still be collected. Kalff et al. (*13*) measured neither glycolytic flux nor cell necrosis. Although there is a direct relation between a decreased glycolytic flux and ischemic contracture (*4*) and the latter is often taken as an irreversible end-point of ischemia, further work is required before it can be ascertained that it is the fall in glycolytic flux which is the crucial factor in precipitating cell death.

FURTHER POSSIBILITIES FOR PET IMAGING OF GLUCOSE METABOLISM

Carbon-11-glucose is an infrequently used tracer (*15*). It is a marker of glucose carbon and therefore its early expected fate is the formation of CO_2. In the normally oxygenated myocardium, the most important cellular metabolic fate of glucose is glycogen rather than rapid oxidation (*16*). When ^{11}C-glucose can be imaged in the myocardium late after its administration, a nonoxidative fate of glucose is detected. Therefore, a comparison of the images achieved with ^{11}C-glucose and ^{18}FDG should show a difference. For example, in the data of Lammertsma et al. (*15*), the relative values for uptake of FDG and ^{11}C-glucose were 0.019 versus 0.0044 ml/g/min ($p < 0.05$) in normal subjects. Thus, it is possible by using both FDG and ^{11}C-glucose to determine: (1) the uptake of glucose by the myocardium (FDG), (2) the incorporation of glucose into glycogen (^{11}C-glucose) and (3) the flow of glucose along glycolysis (FDG uptake less late tissue recovery of ^{11}C-glucose). It can be predicted that the greater the glycolytic flux in the tissue suspected to be ischemic, the better the chances of survival, a proposal that could be applied to the hibernating heart.

Postanginal Carbohydrate Metabolism. In patients with stable exercise-induced angina, in the early recovery phase, the regional uptake of both FDG and ^{11}C-glucose is increased in the postischemic myocardium with close correspondence of the image densities and distribution (Fig. 1), suggesting that a greater part of glucose uptake is being incorporated into glycogen where the ^{11}C-glucose is probably trapped. This concept is in agreement with the previously reported replenishment of glycogen in the postischemic rat heart (*17*) and with data from patients, including the chemical determination of carbohydrate oxidation (*11,18*).

Glucose Extraction Versus Fate. It should be possible to further subdivide myocardial segments on the basis of ^{18}FDG and ^{11}C-glucose patterns into those that are taking up glucose, those that are storing glycogen and those with active glycolytic flux.

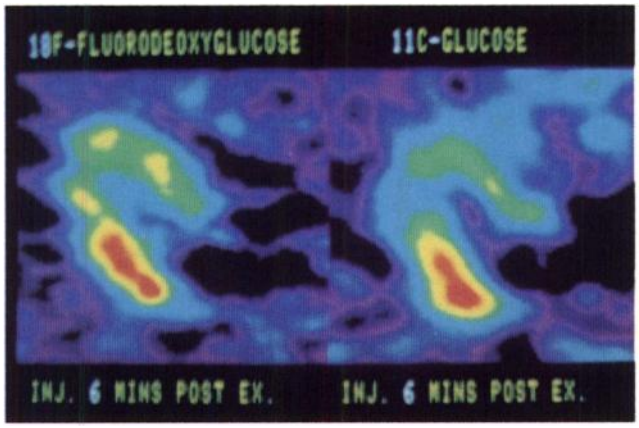

FIGURE 1. Tomograms showing transaxial slice of heart at mid-ventricular level. The septum is in the position from 1 p.m. to 3 p.m., and the free wall of the left ventricle is from 6 p.m. to 10 p.m.; the anterior wall is from 10 p.m. to midnight. The left panel shows myocardial uptake of ^{18}F-deoxyglucose in the postischemic myocardium (free wall) after an episode of exercise-induced angina pectoris. The right panel shows distribution of ^{11}C-labeled glucose in the myocardium of the same patient after a different episode of angina. Note the close correspondence of patterns of the two tracer images. The proposal is that the enhanced post-ischemic uptake of deoxyglucose reflects an increased uptake of glucose that is converted significantly to myocardial glycogen, the latter being imaged by ^{11}C-glucose.

Studies along the above lines with PET techniques and new tracers should considerably advance our knowledge of glucose metabolism in the ischemic or hibernating myocardium and help to assess the validity of the hypothesis linking continuing glucose metabolism and glycolysis to myocardial cell viability in ischemia.

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SELF-STUDY TEST
Pulmonary Nuclear Medicine

True statements concerning hemoptysis include:

40. The major cause is bronchial inflammatory disease (chronic bronchitis or bronchiectasis).
41. It is rarely caused by carcinoma metastatic to lung.
42. The site of bleeding can be detected noninvasively by scintigraphy with either ^{99m}Tc sulfur colloid or ^{99m}Tc-labeled red blood cells.
43. Scintigrams in patients with hemoptysis usually show abnormal pulmonary activity within the first hour after injection of the radiopharmaceutical.
44. A bleeding rate of at least 100 ml/day is needed for localization of bleeding sites by scintigraphy.

SELF-STUDY TEST
Pulmonary Nuclear Medicine

ANSWERS

ITEMS 1-4: Pulmonary Lymphangitic Carcinomatosis

ANSWERS: 1, T; 2, F; 3, F; 4, T

The ventilation images in Figure 10 are normal; the perfusion images show many small and medium-size defects scattered throughout both lungs. Many of the defects appear to outline bronchopulmonary segments. This scintigraphic pattern is unusual for acute pulmonary embolism and has been described in patients with cancer who have autopsy evidence of tumor microembolism and lymphangitic carcinomatosis. The patient shown here had a history of metastatic rectal carcinoma with diffuse interstitial infiltrates. No pulmonary emboli were found at angiography.

Pulmonary lymphangitic carcinomatosis is usually caused by tumor microemboli with subsequent spread of tumor to the pulmonary parenchyma and lymphatics. The cause of the characteristic pattern of perfusion defects in which the perfusion abnormalities appear to outline the segments ("contour mapping") is controversial. Some investigators believe the findings are due entirely to small tumor microemboli that lodge in the smaller peripheral vessels with sparing of the larger, more central segmental and subsegmental arteries. Others hold that there must be interstitial or parenchymal disease in addition to the pulmonary microemboli.

A normal chest radiograph is seen in approximately 20% of patients with lymphangitic carcinomatosis. Other causes of similar perfusion abnormalities include pulmonary vasculitis, primary pulmonary hypertension, and nonthrombotic emboli (fat, oil, or septic).

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ITEMS 5-9: Distribution of Pulmonary Ventilation and Perfusion

ANSWERS: 5, T; 6, F; 7, T; 8, F; 9, F

In upright subjects, there is increasing ventilation from the apex to the base of the lung. Similarly, dependent lung regions ventilate best in supine patients. This dependence on gravity is mediated by the effect of lung weight on the size of alveoli at end-expiration. The smaller distending intrapleural pressure in the dependent lung zones results in smaller alveoli at end-expiration and a larger change in alveolar volume with inspiration. Thus, airflow is lowest in the apical portion of an upright patient's lung. Gravity causes increasing air and blood flow from apex to base in upright individuals, but because the bloodflow gradient is steeper than the airflow gradient, the ratio of ventilation to perfusion decreases. The effects of gravity are modified by the local influences of airways resistance and alveolar compliance. More compliant alveoli generate a smaller recoil force to empty the alveolus of gas and, hence, are slower to clear their content of xenon during washout. Optimum gas exchange takes place when the flow of air and blood is matched. In obstructive pulmonary disease, alveolar hypoxia causes precapillary vasoconstriction to reduce blood flow to poorly ventilated lung regions. This is a protective mechanism, which tends to compensate for reduced airflow by reducing blood flow, thereby improving regional gas exchange.

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ITEMS 10-14: Pathologic Conditions Affecting Pulmonary Function

ANSWERS: 10, T; 11, F; 12, T; 13, F; 14, F

Three significant respiratory events follow embolic obstruction of pulmonary arteries: (1) addition of a large alveolar dead space; (2) pneumoconstriction; and (3) loss of alveolar surfactant. Pneumoconstriction involves the terminal airways and is caused by several factors. Reduction in the carbon dioxide tension in the embolized lung causes constriction that can be overcome by deep inhalation. In addition, humoral agents, such as serotonin and histamine, which presumably are released from platelets adhering to the embolus may also promote pneumo-

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