《招待講演5》

Cardiac PET: Microcirculation and Substrate Transport in Normal and Diseased Human Myocardium

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Given the large number of tracer compounds, the quantitative imaging capability and the development of appropriate tracer kinetic models, Positron Emission Tomography now permits the noninvasive quantification of different components of the human heart's physiology and pathophysiology. Processes that can be quantified range from blood flow, substrate utilization and oxidation to neuronal control and receptor density and occupancy. Work in our laboratory has utilized quantitative techniques to explore blood flow, substrate delivery, transmembranous substrate exchange and substrate consumption in normal and in ischemically injured myocardium. With these studies it became possible to study microcirculatory control and substrate exchanges.

Initial studies determined normal values of blood flow in human myocardium. The inter-individual variability in flow values was accounted for by inter subject differences in cardiac work as individual flow values were found to closely correlate with the rate pressure product. Changes in cardiac work induced pharmacologically by dobutamine were associated with proportionate changes in myocardial flow. Similarly, as cardiac work increased with age, resting blood flows were also found to be dependent upon age, at least in mostly sedentary subjects. The same studies also observed an age dependent decline in myocardial flow reserve, elicited by pharmacologic vasodilation. The age dependent increase in resting blood flow mostly accounted for this decline; however, estimates of coronary resistance as a means of relating coronary perfusion pressure to hyperemic flows demonstrated a modest though statistically significant age dependent decline in the microcirculatory vasodilator capacity. Maximum vasodilatory flow appeared to be largely independent of heart rate but not of cardiac work or the inotropic state. For example, an increase in arterial pressures induced by supine bicycle exercise during adenosine infusion induced vasodilation resulted in a decline, though modest, rather than an anticipated increase in hyperemic flow. While possible alpha-stimulatory effects on the coronary circulation during exercise might account for such decline, extravascular compressive forces as a consequence of increased contractility are a more likely explanation. Equally intriguing are more recent observations in normal volunteers submitted to cardiovascular conditioning and lipid lowering diet. Cardiovascular conditioning resulted in a significant reduction in resting cardiac work and, in turn, resting myocardial blood flow. Consequently, for a given age, myocardial flow reserve markedly increased. Importantly however, maximum hyperemic flows were higher or, when related to coronary perfusion pressure, coronary resistance was lower, indicating an improved vasodilator capacity after cardiovascular conditioning. While capillary recruitment may serve as one explanation, the observed decrease in serum cholesterol with greater endothelial dependent vasodilation may serve as another one. If cardiovascular conditioning produces similar microcirculatory changes in coronary artery disease, it may prove to be protective and may serve as an additional explanation for previously reported reductions in exercise induced perfusion defects after drastic dietary and lifestyle changes.

Estimates of substrate delivery can be calculated from blood flow and the arterial plasma concentrations as for example glucose or oxygen. Transmembranous substrate exchange can then be calculated from the rate of substrate delivery and the rate of substrate consumption. The latter can, for example, be derived for exogenous glucose utilization with F-18 deoxyglucose or for oxygen consumption with C-11 acetate. Transmembranous substrate exchange and consumption may be heterogeneous in normal myocardium. This has been observed for glucose. Initially demonstrated in the

fasted state, more recent studies in our laboratory have indicated that this heterogeneity is independent of the dietary state although in relative terms it becomes less apparent after glucose loading. This normal pattern of glucose extraction persists in myocardium afflicted by post-ischemic necrosis and scar tissue formation. Glucose utilization may change in proportion to blood flow so that the regional glucose extraction remains constant.

However, in reversibly dysfunctional myocardium as a consequence of "stunning" or "hibernation," glucose extraction increases. F-18 deoxyglucose uptake usually exceeds blood flow resulting in the well known blood flow-glucose metabolism mismatch pattern. While the reasons for the selective increase in glucose extraction and consumption have remained uncertain, studies in our laboratory have demonstrated that glucose utilization in reversibly dysfunctional myocardium does not fully participate in normal substrate regulatory mechanisms. Accordingly, local regulatory mechanisms prevail. Therefore, normal responses to changes in plasma substrate levels are attenuated in reversibly dysfunctional myocardium. Two major causes of reversible dysfunction have been identified—stunning and hibernation. If hibernation represents a down regulation of contractile function in response to a chronic reduction in blood flow, then myocardial flow reserve should be absent. This is because vasodilation distal to the stenosis as a compensatory mechanism to increase a transstenotic pressure gradient and thus to maintain blood flow. Findings of an absent vasodilatory response in our laboratory are consistent with this notion. On the other hand, as only transmural flow can be quantified with Positron Emission Tomography, a possible vasodilatory increase in flow may have been offset by a coronary steal in the same myocardial region. This possibility may explain the modest though statistically significant increase in blood flow in reversibly dysfunctional myocardium in response to low dose dobutamine infusion which is also associated with an increase in contractile function.

The same quantitative assay techniques allowed a more comprehensive characterization of ischemic and post-ischemic dysfunctional myocardium in early post-infarction patients. Both, blood flow and oxidative metabolism in non-affected myocardium continued to correlate to the rate pressure product as an index of overall cardiac work. Such correlations did however not exist in hypoperfused myocardium. Reductions in regional blood flow were associated with reductions in regional oxidative metabolism. As an observation that was unexpected, oxidative metabolism did not decline in strict proportion to blood flow but rather in a piecewise relationship. For example, oxidative metabolism declined only modestly down to flows of about 0.5 ml/min/g. Further flow reductions below this apparent threshold were followed by a more precipitous decline in oxygen consumption. While inconsistent with the classic concept of a linear relationship between blood flow and oxygen consumption, these observations are in agreement with more recent findings in experimental animals. They possibly reflect an adaptative or compensatory response. Modest reductions in flow are associated with a progressive increase in the extraction of oxygen in order to maintain adequate tissue oxygenation. Once this compensatory increase has reached a maximum, which is believed to occur at an about 50% flow reduction, further decreases in flow are associated with disproportionately greater decreases in oxygen supply with possible deleterious consequences on cell survival. The regional shift in substrate selection to the more oxygen efficient glucose may represent an additional compensatory mechanism. As a result, the regional extraction of glucose markedly increases. This increase was found to be maintained even for very low flows when myocytes possibly rely mostly on glycolysis as the sole source of high energy phosphate production. The same studies further pointed out the limited value of quantitative estimates of regional glucose utilization rates. This was because the considerable inter-patient variability in glucose utilization rates in normal myocardium which necessitated the use of relative rather than absolute estimates of glucose metabolism. Ongoing research seeks to identify the significance of these compensatory mechanisms for tissue survival or recovery of contractile function. Further, these studies seek to explore whether these altered interrelationships between blood flow, oxidative metabolism and glucose utilization return to normal once coronary flow has been restored.

In summary, it is clear that appropriate use of these new tracer techniques permit the noninvasive exploration and characterization of the human heart's microcirculatory function. As many novel observations raise new questions and result in formulation of new hypotheses, it is also clear that these hypotheses can now be tested. This is especially true as new quantitative techniques for probing different aspects of myocardial tissue function continue to evolve and become available for use in humans.