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Cardiac PET: Microcirculation and substrate transport in normal and diseased human myocardium

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The development and validation of quantitative assay techniques for the noninvasive study of human myocardium has opened up new avenues for the study of the normal and diseased human heart's physiology. Measurements of regional myocardial blood flow, which delineates nutrient rather than coronary blood flow, has enabled the exploration of the coronary microcirculatory physiology under normal and abnormal conditions. It permits the study of pharmacologic effects and of cardiovascular disease on the coronary resistance and capillary perfusion. If combined with metabolic assay techniques, the transcapillary exchange of substrates in oxygen can be quantified and changes imposed by physiologic interventions and substrate metabolism being measured. These study approaches further serve to characterize changes in response to reductions in coronary blood flow as well as altered states of potentially reversible contractile function. It is anticipated that further studies with PET will clarify at the microcirculatory level the changes associated with ischemia, post-ischemic stunning and myocardial hibernation. Further, it offers the possibility to measure potentially beneficial effects of therapeutic interventions or, alternatively, to provide a rationale for novel therapeutic approaches.

Key words: coronary circulation, myocardial blood flow, positron emission tomography, coronary vasodilator capacity, myocardial metabolism

Introduction

Positron Emission Tomography provides a set of tools for the study and, importantly, the noninvasive quantification of regional functional processes in the human myocardium. The number of physiologic compounds that have been or can potentially be labeled with positron emitting isotopes like oxygen-15, carbon-11, nitrogen-13 and fluorine-18 is virtually unlimited. This in turn offers the possibility to probe noninvasively numerous aspects of myocardial function and to dissect various physiologic and pathophysiologic processes. However, each of these assay techniques requires a thorough understanding of the tissue kinetics of the radiotracer, the relationship of the tissue kinetics to the physiologic process to be studied and the configuration and validation of a tracer compartment model that yields a quantitative estimate of a functional process. Accordingly, studies of the normal and diseased human heart in our laboratories have relied only on those tracer techniques that have been firmly established and validated. These assay techniques include the measurement of regional myocardial blood flow with N-13 ammonia, the quantification of regional myocardial utilization of exogenous glucose with F-18 2-fluoro 2-deoxyglucose, the measurement of regional myocardial oxygen consumption with C-11 acetate as a tracer of the myocardial TCA cycle activity and the evaluation of regional myocardial fatty acid oxidation and storage with C-11 palmitate. These probes have permitted the study of the coronary physiology and pathology of the human heart, the evaluation of microcirculatory changes and of transmembranous substrate exchange and transport as well as of normal and abnormal patterns of substrate

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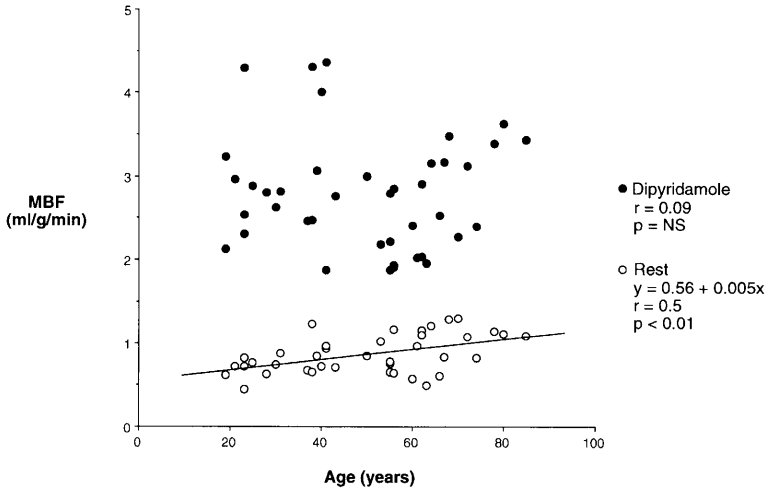

Fig. 1 Relationship between age and myocardial blood flow in normal volunteers. The open circles indicate myocardial blood flow (MBF) at rest, the solid circles indicate the hyperemic blood flows. While there is a tendency of lower hyperemic blood flows in older volunteers, a statistically significant, progressive increase in rest blood flow is observed. (Reproduced with permission of the American Heart Association from Czernin et al.[11])

selection and utilization.

Development of Noninvasive Assay Techniques and Biochemical Probes

Because the quantification of regional of functional processes necessitates the *in vivo* determination of the arterial tracer input function and of the tissue response to it, such measurements are tedious and time consuming which limits their use in the clinical setting or for investigations in larger patient populations. Much of our research efforts in the past several years have focused on simplifying these assay techniques; consequently, computationally efficient and standardized image analysis approaches have been implemented on user friendly Macintosh desktop computer systems. These approaches have allowed processing and analysis of large amounts of patient image data in a relatively short time. Serially acquired transaxial PET images are rapidly reoriented into less partial volume sensitive short axis images of the left ventricular myocardium that can be assembled into polar map displays for comparison to data bases of normal and for generation of blood and myocardial tissue time activity curves for tracer compartment model fitting.[1-3] Graphical analysis approaches have been developed for rapid though accurate quantification of regional functional processes.[4] Again, the three-dimensional distribution of these processes can be displayed in the form of color coded polar maps. Color gradations on these maps reflect discrete values of regional functional processes. These approaches include the now widely used PATLAK graphical analysis of F-18 deoxyglucose tissue kinetics[4, 5] and, more recently, a linear graphical analysis for flow measurements with intravenous N-13 ammonia.[4] Further, we have developed a graphical first tracer transit analytical technique for parametric imaging of regional myocardial oxygen consumption with C-11 acetate.[6]

Measurements of Myocardial Blood Flow

We have extensively employed the N-13 ammonia tracer technique for the noninvasive quantification of regional myocardial blood flow. Even though the dependence of N-13 ammonia trapping in myocardium on metabolism has been claimed as a potential drawback, we have found that this approach does yield reliable and accurate estimates of myocardial blood flow[2] and, as an advantage over the widely used O-15 water approach, offers high quality images of the relative distribution of myocardial blood flow.[7] Fundamental to this approach is a constant relationship between blood flow and the first pass retention fraction of N-13 ammonia. While extensively verified in canine myocardium,[8] more recent studies in our laboratory with both, the O-15 water and the N-13 ammonia approach, supports the notion that this relationship is not species related and does in fact apply to the human myocardium.[9] Paired O-15 water and N-13 ammonia measurements of blood flow at rest and during adenosine induced hyperemia in normal volunteers did in fact yield nearly identical values. This comparative study on the other hand demonstrated a somewhat higher coefficient of variation for the O-15 water technique. This suggests a greater method related heterogeneity for flow measurements with O-15 water than with N-13 ammonia with a lower confidence in regional measurements of blood flow.

The N-13 ammonia approach, like other techniques with diffusable tracers of blood flow, reflects true nutrient blood flow, e.g. delivery of flow directly to the myocardial tissue. In this respect, the approach differs from the microsphere technique. In normal volunteers, we noted a considerable inter-individual variability in flow esti-

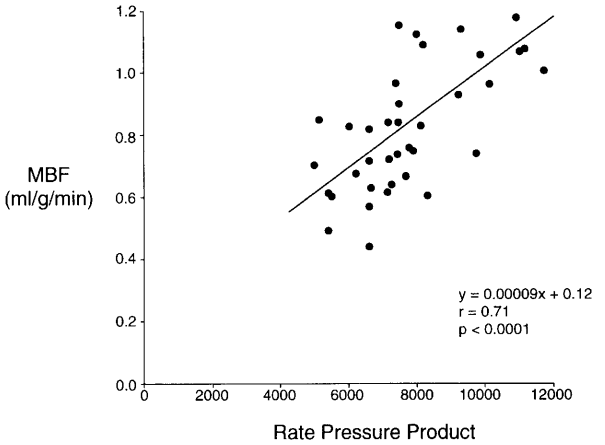

Fig. 2 Relationship between resting myocardial blood flow (MBF) and cardiac work as described by the rate pressure product. Note the statistically significant linear relationship between both parameters. Taken from Czernin et al.[11]

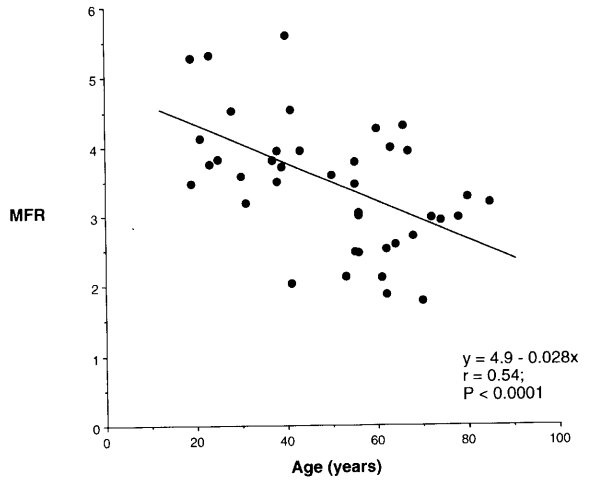

Fig. 3 Myocardial blood flow reserve (MFR) in normal volunteers in relation to age. Note the significant decline in the myocardial flow reserve with age. It is primarily a function of progressively increasing blood flows at rest as shown in Figure 1. (Reproduced with permission of the American Heart Association from Czernin et al.[11])

mates.[10,11] This then raised the question as to whether this variability was method related, was age and/or gender dependent or, more importantly, it raised the question to what specific parameter estimates of myocardial blood flow should be related. Similarly, we noted a considerable inter-individual variability in hyperemic flows as induced with intravenous dipyridamole or adenosine. This again raised questions regarding variations in the pharmacologic effect of vasodilator agents, a dose dependency as well as possible age and gender related factors.

In answering these questions, we observed a progressive increase in resting blood flows with age (Fig. 1).[11] On the other hand, cardiac work as described by the product of systolic arterial blood pressure and heart rate (the rate pressure or the double product) similarly increased progressively with age so that cardiac work or the rate pressure product proved to be the primary determinant of the observed inter-individual variability in myocardial blood flows (Fig. 2). There was no evidence that gender contributed to this variability. The rate pressure product has been found to correlate closely with myocardial oxygen consumption in normal human volunteers and in patients.[11,12] Yet, it remains unclear to what extent it accommodates fully changes in cardiac work effected primarily through changes in the inotropic state.

More puzzling remains the observed variability of pharmacologically induced hyperemic blood flows. Because intravenous adenosine and dipyridamole produced comparable hyperemic responses but also comparable degrees of variability[10] this variability did not appear to be agent specific. Although individual differences in the response to pharmacologic vasodilation cannot be ruled out, we were unable to demonstrate dose dependent responses. For example, increasing the standard dose schedule of 0.56 mg/kg of dipyridamole infused over 4 minutes to a total dose of 0.80 mg/kg failed to produce higher flows (Czernin, unpublished data). Furthermore, neither gender or age revealed any statistically significant effect on the magnitude of the hyperemic response despite a tendency of lower hyperemic flows in normal volunteers older than 50 years of age (Fig. 1). However, the myocardial flow reserve as the ratio of hyperemic to resting blood flows declined with age, mainly as a function of the age dependent increase in resting blood flow as a consequence of an age dependent increase in cardiac work (Fig. 3).[11] It is emphasized that characterization of such age dependency on the myocardial flow reserve is important, especially when the myocardial flow reserve in older patients with, for example, coronary artery disease is to be evaluated. A lower flow reserve might simply be attributable to age rather than to angiographically non-detectable coronary artery disease.

Traditionally, the coronary circulation has been thought of as a system of rigid tubes; flow through this system depends on the pressure gradient between aorta and the right atrium and a series of resistances as for example, a fixed resistance in the conductance vessels and the capillaries and a variable for controllable resistance at the pre-arteriolar level (see also Fig. 4). If, in this system, the pre-arteriolar resistance is reduced or minimized by pharmacologic interventions as for example by direct smooth muscle dilators as for example adenosine or, indirectly, dipyridamole, blood flow through the coronary system then depends largely on the coronary driving pressure. The latter can be related to hyperemic blood flows by calculating an estimate of the minimal coronary resistance, e.g., the ratio of the mean arterial blood pressure and hyperemic blood flows.[13] Unlike the observed hyperemic blood flow, the calculated "minimal coronary resistance" reveals a markedly lesser inter-individual variability, suggesting a relatively uniform effect of pharmacologic smooth muscle vasodilators on the human

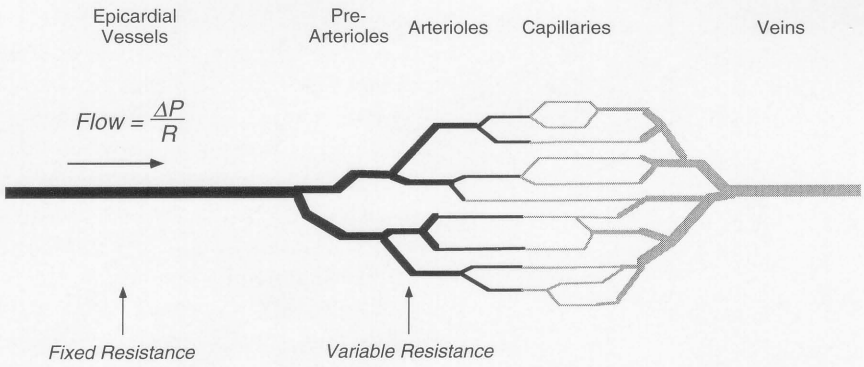

Fig. 4 Schematic representation of the coronary circulation. Flow through the coronary circulation is primarily determined by the pressure gradient between the aorta and the right atrium (coronary driving pressure) and the coronary resistance. Conventionally, the coronary circulation is considered as a system with fixed and with variable resistances. The large epicardial conductance vessels are thought of as part of the fixed resistance while resistance can be variable at the pre-arteriolar and the arteriolar levels. (See text.)

coronary circulation.

While pharmacologic vasodilatory agents can in fact assess the vasodilator capacity of the human coronary circulation, the observed values may not truly reflect the maximum blood flow that can be achieved during physiologic interventions as for example during physical exercise. We had postulated that increases in the mean arterial blood pressure as associated with physical exercise during pharmacologic vasodilation would in fact produce an even higher hyperemic flow because of an augmented coronary driving pressure. Yet, we observed a modest though statistically significant decline in hyperemic blood flows.[14] Resistance estimates during pharmacologic vasodilation plus physical exercise significantly increased. Besides an increase in α_2 stimulation during exercise (while the coronary circulation is already maximally dilated, presumably in excess of the vasodilating effects of β_2 stimulation or of local metabolic factors), a possible explanation for this higher resistance is an augmentation in extravascular resistive forces as for example a consequence of increased contractility and increased intraventricular pressures. Again, this observation is important because pharmacologic manipulations may not fully indicate the true flow reserve or flow responses under physiologic conditions. To exemplify this point, Camici et al. demonstrated a residual, though markedly attenuated flow reserve in patients with hypertrophic cardiomyopathy, using intravenous dipyridamole.[15] In contrast, Nienaber et al.[16] in our laboratory noted that blood flow failed to increase with exercise in patients with hypertrophic cardiomyopathy, presumably as a consequence of excessive extravascular resistive forces due to marked increases in contractility and, even more importantly, intracavitary pressures.

We had mentioned earlier the age dependent decline in the myocardial flow reserve as a function of an age dependent increase in cardiac work and, consequently, in resting myocardial blood flow. Because exercise training and cardiovascular conditioning can reduce both heart rate and blood pressures, we asked therefore whether an age dependent reduction in flow reserve could in fact be improved or be normalized by exercise training. Accordingly, we examined a series of normal volunteers and coronary artery disease patients before and after a six week program of cardiovascular conditioning including lifestyle and dietary changes.[17] As anticipated, both, heart rate and blood pressures at rest declined associated with a proportionate decline in resting myocardial blood flows. Consequently, pharmacologic vasodilation demonstrated a marked increase in the myocardial flow reserve. Unanticipated was however an increase in the maximum hyperemic blood flows and a concomitant decline in the "minimal coronary resistance." The reason for this latter observation are less certain and clearly await further clarification. At the same time, the results question the model of a fixed system of rigid tubes for the human coronary circulation.

Possible explanations for this decrease in minimal coronary resistance include an exercise related increase in the number of capillaries as demonstrated previously in rats.[18] Additional possibilities exist. For example, exercise training may result in an increase in the diameter of the large conductance vessels and lower resistance.[19] It is also possible that the vasodilatory response to smooth muscle agents is potentiated through endothelial dependent factors mediated through shear forces.[20] This endothelial dependent vasodilation may be attenuated by cholesterol and LDL at the level of the pertussis toxin sensitive G-protein or its transduction system.[21] The significant decline in cholesterol and LDL as observed in the participants of the cardiovascular conditioning program may thus have facilitated the endothelial dependent augmentation of hyperemia. Other factors such as lower blood viscosity or lower intracavitary pressures with an associated reduction in extravascular resistive forces may have been additional contributors to the augmented

hyperemic response and the improved vasodilator capacity.

Lastly, it should be mentioned that cardiac disease may in fact alter the relationship between the rate pressure product and myocardial blood flow at rest. For example, in a study in cardiac transplant patients, we observed that myocardial blood flow during an acute rejection period was increased relative to cardiac work.[22] This "inflammatory-like hyperemia" most likely is mediated through cytokines as an integral part of the rejection process and resolves with appropriate immunosuppressive therapy.

Substrate Delivery and Substrate Utilization

Free fatty acid has been considered the myocardium's major substrate fuel. Indeed, early investigations have demonstrated that as much as 70–90%, of the myocardium's oxygen consumption can be accounted for by oxidation of free fatty acid.[23] It is therefore not surprising that C-11 labeled palmitate as a tracer of myocardial fatty acid served as one of the earliest agents for the noninvasive study of myocardial substrate metabolism.[24,25] Although specific patterns of the myocardial clearance curve morphology of C-11 palmitate in both, animal and human myocardium provided unique information on myocardial substrate selection and fatty acid oxidation and demonstrated specific abnormalities in myocardial ischemia, work in this particular area has largely been abandoned in favor of techniques for quantifying the rates of exogenous glucose utilization and of oxidative metabolism.

Research in our laboratory has focused on manipulating glucose utilization in normal as well as in dysfunctional myocardium and on identifying factors that account for changes in glucose utilization.[26] We studied normal volunteers after periods of fasting from 4 to 19 hours and again after an oral glucose load of 100 g. In the fasted state, glucose and lactate plasma levels were low though variable while insulin levels were consistently below 20 μU/m*l*. Rates of exogenous glucose utilization as determined by the PATLAK graphical analysis approach averaged 0.24 ± 0.7 $\mu mol \cdot min^{-1} \cdot g^{-1}$. Of interest, these values did not differ between volunteers who fasted 6 ± 2 hours and those fasted for an average of 16 ± 2 hours. These data suggest that similar glucose metabolic rates can be achieved by fasting periods of only 6 hours instead of the previously advocated overnight fast.

Glucose loading dramatically altered plasma substrate concentrations and, in response, myocardial substrate selection. Plasma glucose and lactate levels rose from 87 ± 6 to 154 ± 32 mg/d*l* and from 8 ± 3 to 42 ± 18 μU/m*l* while free fatty acid levels declined from 0.30 ± 0.25 to 0.19 ± 0.14 mEq/*l* (even though this change failed to attain statistical significance) and glucose utilization rates rose to 0.69 ± 0.10 $\mu mol \cdot min^{-1} \cdot g^{-1}$. Metabolic rates of glucose were, as observed previously, distributed heterogeneously throughout the left ventricular myocardium. This heterogeneity was most prominent in the fasted state where metabolic rates of glucose in the posterolateral wall were 33% higher than in the septum and anterior wall of the left ventricular myocardium. In percentages, the difference declined with glucose loading yet, in absolute terms ($\mu mol \cdot min^{-1} \cdot g^{-1}$), the differences remained similar between the fasted and the glucose loaded state. While hormones like human growth hormone and cortisol revealed no significant effects on glucose utilization rates (or at least within the range occurring in these normal volunteers), insulin and especially the ratio of insulin to glucagon appeared to correlate directly with glucose utilization rates once a certain threshold level of glucose utilization had been exceeded. It is also worthwhile mentioning that our studies failed to detect any significant correlation between plasma catecholamine levels and metabolic rates of glucose. However, the range of observed catecholamine levels was found to be relatively narrow so that it is possible that excessively high catecholamine concentrations may in fact modify glucose utilization rates, either directly or indirectly via their effects on plasma fatty acid levels. Such effects have been demonstrated previously in canine myocardium.[27]

It is indeed possible that higher catecholamine levels accounted for the lower glucose utilization rates in apparently normal myocardium of patients with severely depressed left ventricular function and ischemic heart disease.[28] After fasting, these rates averaged 0.14 ± 0.8 $\mu mol \cdot min^{-1} \cdot g^{-1}$ and thus were 42% lower than in the normal volunteers studied under similar fasting conditions. Oral glucose loading raised glucose utilization rates in the same myocardial regions to 0.58 ± 0.16 $\mu mol \cdot min^{-1} \cdot g^{-1}$ which again tended to be lower than in normal volunteers. The purpose of this latter study was to determine whether local mechanisms of glucose and substrate regulation are operational in hypoperfused and dysfunctional myocardium and override systemic regulatory mechanisms. The results did in fact confirm this notion. In myocardial segments with blood flow metabolism mismatches, glucose utilization rates declined from the glucose loaded state to fasting by only 70% as compared to 80% in apparently normal myocardium. A similar attenuated response in glucose utilization rates was noted in regions with blood flow metabolism matches. Furthermore, evaluation of regional glucose utilization rates in the fasted state as compared to the glucose loaded state uncovered a substantial number of new blood flow metabolism mismatches. Such "converting" matches were independent of the degree of contractile dysfunction or the severity of resting flow reductions. They are most likely due to sub-populations of cells that preferentially utilize glucose governed primarily through local mechanisms. These observations have several implications. The blood flow metabolism mismatch pattern may depend on the conditions under which patients are evaluated. Mismatches observed only in the fasted state but not in the glucose loaded state may represent small islands of

reversibly dysfunctional cells. However, their number is too small to be of any consequence for an improvement in contractile function after revascularization.

As these studies were combined with measurements of regional myocardial blood flow, they offered the possibility to determine substrate delivery, substrate extraction and glucose utilization per unit blood supply. For example, plasma blood flow can be calculated by total blood flow times (1 – Hematocrit); delivery of glucose to myocardium can then be estimated from the product of the arterial plasma glucose concentrations and plasma flow. From the rate of glucose utilization and the rate of glucose supply, the transmembranous glucose transport or the steady state extraction fraction E can be calculated by:

$$E_{Glc} = \frac{MRGlc}{MBF \cdot (1 - Hct) \cdot [Glc]_{art}} \quad (1)$$

where MBF is myocardial blood flow, $[Glc]_{art}$ the arterial plasma glucose concentration and MRGlc the metabolic rate of glucose.

In normal myocardium, E_{Glc} averaged 14.2% in the glucose loaded state and declined to 4.9% in the fasted state. Compared to normal myocardium, E_{Glc} in mismatch regions was about 10% higher after glucose loading and as much as 63% higher in the fasted state. Again, these calculations confirm the enhanced glucose extraction and transmembranous transport of glucose in reversibly compromised myocardium. There was also a modest increase in glucose extraction in matched regions which might signal the presence of some reversibly compromised cells even though the major fraction of tissue in such regions might represent either normal and scar tissue or mostly scar tissue alone. At the same time, these observations suggest the possibility to evaluate and quantify the fractional distribution of different cell populations with different degrees of ischemic injury or compromise in a given myocardial segment.

Myocardial Oxidative Metabolism

It is of course possible to apply similar calculations to oxygen consumption and to oxygen extraction ratios. This can be accomplished most directly through the use of molecular oxygen-15 labeled oxygen[29,30] but is also possible with C-11 acetate as a tracer of TCA cycle activity and, consequently, of oxygen metabolism. Tissue clearance rate of C-11 acetate correlate directly in canine myocardium with myocardial oxygen consumption[31] by

$$k = 0.0189 + 0.0089\,MVO_2\,(ml O_2 \cdot min^{-1} \cdot 100\,g^{-1}) \quad (2)$$

In our normal volunteers, k averaged 0.048 ± 0.004 min^{-1} at an average rate pressure product of $6{,}516 \pm 1{,}553$ mmHg·beats·min^{-1} which according to equation 2 translates into an oxygen consumption of 3.3 $ml O_2 \cdot min^{-1} \cdot 100$ g^{-1}.[32] Supine bicycle exercise increased the rate pressure product to $17{,}198 \pm 4{,}121$ and k to 0.121 ± 0.25 min^{-1}. The latter translates into an oxygen consumption of 11.5 $ml O_2 \cdot min^{-1} \cdot 100\ g^{-1}$. Both estimates of oxygen consumption appear to be rather low when compared to measurements obtained through the coronary sinus catheter technique and the Fick principle. If one uses the correlation between the rate pressure product and myocardial oxygen consumption as observed by Holmberg et al.,[12] MVO_2 for the two different levels of cardiac work would amount to 7.6 and 17.6 $ml O_2 \cdot min^{-1} \cdot g^{-1}$. Conversion of C-11 acetate clearance rates into units of oxygen consumed from canine studies therefore appears to markedly underestimate the true oxygen consumption in the human myocardium. One possible explanation is a species dependent difference in the size of the TCA cycle metabolite pools which in turn would affect the clearance rates.

Until the relationship between k_{mono} and MVO_2 has been directly measured and established in the human myocardium, more realistic estimates can be obtained by combining the correlations between MVO_2, k_{mono} and the rate pressure product as described by Holmberg et al.[12] and by Armbrecht et al.[32] According to Armbrecht et al.,

$$k_{mono} = -0.014 + 0.00000589\ RPP \quad (3)$$

while Holmberg et al. found a correlation of MVO_2 to the rate pressure product of

$$MVO_2\ (ml \cdot min^{-1} \cdot 100\ g^{-1}) = -0.664 + 0.00106\ RPP \quad (4)$$

Combining equations 3 and 4 results in

$$MVO_2\ (ml O_2 \cdot min^{-1} \cdot 100\ g^{-1}) = -0.664 + 0.00106 \left(\frac{k_{mono} + 0.014}{0.00000589} \right) \quad (5)$$

Equation 5 predicts estimates of the oxygen consumption of 10.5 and of 23.6 $ml O_2 \cdot min^{-1} \cdot 100\ g^{-1}$ for the above described rest and the supine exercise studies.

It is also possible to estimate the O_2 extraction by combining measurements of blood flow with those of oxidative metabolism. Supply of oxygen represents the product of the arterial O_2 concentration $[O_2]_{art}$ and of myocardial blood flow. The steady state extraction of O_2 (E_{O_2}) can then be estimated by

$$E_{O_2} = \frac{MVO_2}{MBF \cdot [O_2]_{art}} \quad (6)$$

In normal volunteers, we measured blood flow and oxidative metabolism at baseline and during intravenous dobutamine (40 $\mu g \cdot min^{-1} \cdot kg^{-1}$ body weight).[33] At baseline, myocardial blood flow averaged 0.79 ± 0.17 $ml \cdot min^{-1} \cdot g^{-1}$ and MVO_2 (estimated from k_{mono} using equation 5) 10.85 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. The arterial O_2 concentrations were not measured in this study. However, taking an average O_2 content of 19.2 $ml O_2 \cdot 100\ ml^{-1}$ whole blood as observed by Holmberg et al.[12] this amounts to an E_{O_2} of

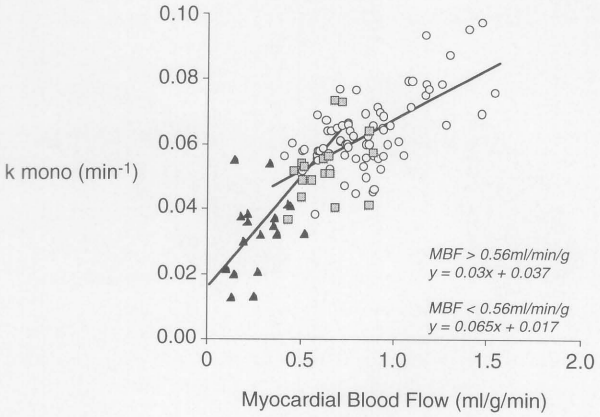

Fig. 5 Relationship between myocardial oxidative metabolism and myocardial blood flow in early post-infarction patients. Oxidative metabolism was estimated from the clearance rate of C-11 acetate from myocardium (k_{mono}) while blood flow was measured with N-13 ammonia. The open circles indicate measurements in apparently normal myocardium, the squares reflect measurements in "mismatched myocardium" and the triangles reflect measurements in "hypoperfused, matched" segments. Note the piecewise relationship. (Reproduced with permission of the American Heart Association from Czernin et al.[34])

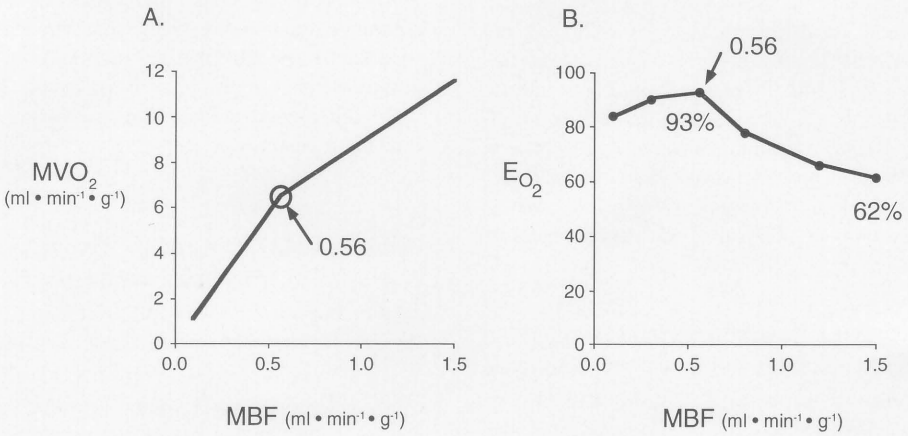

Fig. 6 Relationship between myocardial blood flow, oxygen consumption and myocardial oxygen extraction. The piecewise relationship between myocardial blood flow and oxygen consumption as depicted in Panel A was derived from the data presented in Figure 5. The corresponding oxygen extraction (E_{O_2}), as shown in Panel B, was calculated from the relationship between flow and oxygen consumption as shown in Panel A. Note the increase in the oxygen extraction up to 93%, at a flow of 0.56 $ml \cdot min^{-1} \cdot g^{-1}$.

72%. With dobutamine, blood flow rose to 2.27 ± 0.25 $ml \cdot min^{-1} \cdot g^{-1}$ and MVO_2 to 30.2 $ml \cdot min^{-1} \cdot 100\, g^{-1}$ while E_{O_2} was estimated to be 69%.

In a study in early post infarction patients with near simultaneous measurements of myocardial blood flow and oxidative metabolism,[34] k for a blood flow of 0.83 ± 0.20 $ml \cdot min^{-1} \cdot g^{-1}$ in normal remote myocardium averaged 0.063 ± 0.012 min^{-1} which corresponds to an oxygen consumption of about 13.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. Assuming again an arterial oxygen content of 19.2 $mlO_2 \cdot 100\ ml^{-1}$ whole blood, the oxygen extraction is calculated to be 83%. This value is somewhat higher than those reported with invasive techniques but similar to that as recently reported with the O-15 water and oxygen 15 approach.[30] In the same study, we characterized the relationships between blood flow and oxygen and glucose utilization and consumption as a function of progressively declining blood flows. Different from the conventionally established linear relationship between blood flow and oxygen consumption, our studies revealed a piecewise relationship.[34] As shown in Figure 5, MVO_2 declines initially less than blood flow. However, the relationship changes when flows fall below 0.56 $ml \cdot min^{-1} \cdot g^{-1}$ when further flow reductions produce striking decreases in oxygen consumption.

Method related limitations have been considered as an explanation for this piecewise relationship. However, more likely are compensatory mechanisms. They would also be consistent with more recent animal experimental findings and a similar piecewise relationship as predicted by a model approach that included coronary flow, coronary pressure, autoregulatory mechanisms, oxygen content and extraction.[35] Reductions in blood flow produce reductions in contractile work. At the same time, the decrease in oxygen delivery is compensated for by an increase in the oxygen extraction. If for example, as estimated above, the extraction fraction for a flow of about 1.4 $ml \cdot min^{-1} \cdot g^{-1}$ amounts to 62%,[12] then the piecewise relationship as described in Figure 6 indicates a progressive increase in the oxygen extraction up to a value of 93% for a flow reduction down to 0.56 $ml \cdot min^{-1} \cdot g^{-1}$. Once the oxygen extraction has achieved a maximum, further decreases in flow are associated with a precipitous decline in oxygen consumption.

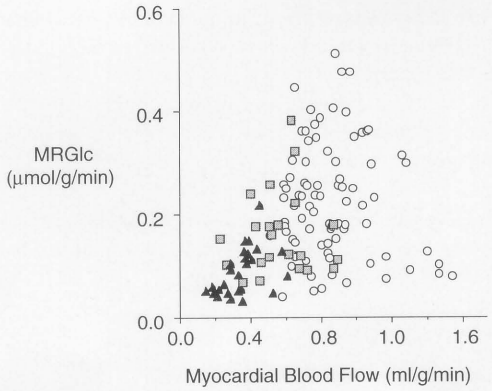

Fig. 7 Relationship between regional rates of myocardial glucose utilization (MRGlc) and myocardial blood flow in early post-infarction patients. As in Figure 5, the open circles indicate measurements in normal myocardium, the squares measurements in blood flow metabolism mismatch segments and the solid triangles measurements in blood flow metabolism match segments. Note the absence of a significant correlation between rates of glucose utilization and myocardial blood flow. Nevertheless, metabolic rates of glucose appear to peak at intermediate flows. (Reproduced with permission of the American Heart Association from Czernin et al.[34])

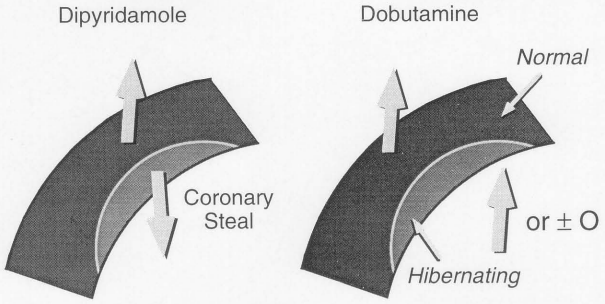

Fig. 8 Different mechanisms of flow responses to pharmacologic stress. A segment of the left ventricular wall is depicted schematically. The inner layer consists of "hibernating" and the outer layer of normal myocardium. In response to dipyridamole stress, blood flow increases in normal myocardium but might decrease in hibernating myocardium because of "coronary steel." Dobutamine also increases flow in the normal myocardium. Different from dipyridamole, the occurrence of a steel phenomenon in hibernating myocardium is unlikely. Blood flow might increase or, given a fixed reduction in flow, remain unchanged, resulting in a net increase in transmural blood flow.

Enhanced glucose extraction represents similarly a compensatory mechanism. However, values of glucose extraction vary considerably more, presumably as a result of the severity of the ischemic compromise of the transmural fraction that has been injured ischemically and, as described earlier, as a function of differences in the preferential substrate usage by remote and presumably normal myocardium. As indicated in Figure 7, there is almost no correlation between the reduction in blood flow and regional rates of glucose utilization. Nevertheless, values for glucose utilization rates peak at intermediate blood flows. Although we had attempted to standardize and, thus, control glucose utilization in remote myocardium in these early post infarction patients, this was of limited success presumably because other factors modified glucose utilization as for example elevated plasma catecholamine levels in early post infarction patients. Nevertheless, the mean glucose extraction in segments with reduced blood flow (average 0.57 ± 0.20 $ml \cdot min^{-1} \cdot g^{-1}$) was 12.3% as compared to 8.7% in apparently normal myocardium. It is also possible to estimate the oxygen extraction ratios from these values. Such stochiometric calculations assume that glucose is oxidized completely. According to

$$1 \text{ mmol glucose} = 6 \text{ mmol}O_2 = 134.48 \text{ m}l O_2 \qquad (7)$$

glucose oxidation in normal myocardium accounted for 69%, and in hypoperfused myocardium for 82% of the total oxygen consumption.

One possibility to compensate for the observed variability in glucose utilization rates in normal myocardium is to normalize the glucose utilization in hypoperfused to that in normal myocardium. Two patterns emerge. One demonstrates a marked increase in relative glucose utilization rates and glucose extraction and is consistent with the disproportionate enhancement of glucose utilization as observed previously in reversibly dysfunctional myocardium. This pattern appears to reflect either transmurally compromised or injured myocardium or the coexistence of normal and injured myocardium. A second pattern is associated with a decline in glucose utilization rates and constant glucose extraction values, presumably as a reflection of complete transmural necrosis or the coexistence of normal and necrotic myocardium in the same myocardial segment. Equally interesting is the lack of a statistically significant increase in glucose extraction in regions with severely reduced blood flow. This might indicate the absence of reversibly injured or ischemic myocardium. Thus, severe flow reductions produce severe ischemia that probably has already or will progress to necrosis and formation of scar tissue.

As mentioned earlier, the above observations were made in early post infarction periods. It is therefore likely that the observed metabolic patterns relative to blood flow represent different types of tissue injury with different degrees of severity. Some of these abnormal patterns may have reflected post-ischemically stunned myocardium; other persistently ischemic segments that ultimately will progress to necrosis while others again might be consistent with a chronic reduction in blood flow matched by a proportionate reduction in contractile function. As an additional possible altered state, some segments may have been severely injured. Although reperfused, metabolism remains initially depressed in proportion to blood flow but, as demonstrated by repeat examinations two to three months later, recovered metabolic activity with a long term gain or improvement in regional contrac-

tile function.

One of the challenges ahead will be the characterization of hibernating versus reperfused or stunned myocardium. While by definition blood flow should be normal in stunned myocardium, this is frequently not the case probably as a result of the impaired systolic thickening and a segmentally enhanced partial volume effect. Other possibilities for the reduced blood flow may include the admixture of scar tissue or hibernating myocardium. On the other hand, different from hibernating myocardium, myocardial flow reserve may be preserved, at least to some extent. In contrast, one would hypothesize that hibernating myocardium results from a fixed reduction of myocardial blood flow matched by a down regulation in contractile function in order to match the diminished supply by a diminished demand. Accordingly, myocardial flow reserve should have been lost in stunned myocardium. In fact, studies in our laboratory have demonstrated that blood flow in mismatched myocardium does not increase in response to pharmacologic vasodilation.[36] If blood flow cannot increase, this then raises the question how glucose metabolism responds to increases in contractile function as evoked with low does dobutamine infusions. Preliminary data to answer these questions have been obtained in our laboratory.

These studies indicate that dobutamine stimulation (5–10 $\mu g \cdot min^{-1} \cdot kg^{-1}$ body weight) does in fact increase myocardial blood flow even though this increase is significantly less than that in normal myocardium.[37] Blood flow increased in mismatch regions from 0.54 ± 0.22 to 0.78 ± 0.33 to $ml \cdot min^{-1} \cdot g^{-1}$ (44%) as compared to a 71% increase in remote myocardium. Further, while glucose utilization rates declined in normal myocardium, presumably because of a dobutamine mediated increase in plasma fatty acid concentrations, it increased in mismatched regions from 0.46 ± 0.12 to 0.63 ± 0.18 $\mu mol \cdot min^{-1} \cdot g^{-1}$. These preliminary findings suggest that increases in contractile function and, consequently, in substrate demand in "hibernating myocardium" are preferentially met by increased glucose uptake. These findings further implicate different mechanisms and flow responses to purely vasodilating and to positive inotropic agents with secondary increases in myocardial blood flow. A pure vasodilator agent may induce an increase in flow in a given transmural segment which may be offset by a "steal" in an adjacent transmural portion of the same myocardial segment, resulting in a net effect on blood flow of zero (Fig. 8). Such a "steal phenomenon" may not exist with positive inotropic stimulation. Flow might actually increase or, as postulated above, remain constant. Nevertheless, there will be a net increase in transmural myocardial blood flow. At the same time, it is possible that the increase in exogenous glucose utilization represents an "ischemia-like" response in transmural segments which are unable to adequately increase myocardial blood flow.

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