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Blood flow, flow reserve, and glucose utilization in viable and nonviable myocardium in patients with ischemic cardiomyopathy

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Abstract

Purpose—The aim of the study was to determine whether glucose uptake in viable myocardium of ischemic cardiomyopathy patients depends on rest myocardial blood flow (MBF) and the residual myocardial flow reserve (MFR).

Methods—Thirty-six patients with ischemic cardiomyopathy (left ventricular ejection fraction $25 \pm 10\%$) were studied with ^{13}N -ammonia and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET). Twenty age-matched normals served as controls. Regional MBF was determined at rest and during dipyridamole hyperemia and regional FDG extraction was estimated from regional FDG to ^{13}N -ammonia activity ratios.

Results—Rest MBF was reduced in viable (0.42 ± 0.18 ml/min per g) and nonviable regions (0.32 ± 0.09 ml/min per g) relative to remote regions (0.68 ± 0.23 ml/min per g, $p < 0.001$) and to normals (0.63 ± 0.13 ml/min per g). Dipyridamole raised MBFs in controls, remote, viable, and nonviable regions. MBFs at rest ($p < 0.05$) and stress ($p < 0.05$) in viable regions were significantly higher than that in nonviable regions, while MFRs did not differ significantly ($p > 0.05$). Compared to MFR in remote myocardium, MFRs in viable regions were similar (1.39 ± 0.56 vs 1.70 ± 0.45 , $p > 0.05$) but were significantly lower in nonviable regions (1.23 ± 0.43 , $p < 0.001$). Moreover, the FDG and thus glucose extraction was higher in viable than in remote (1.40 ± 0.14 vs 0.90 ± 0.20 , $p < 0.001$) and in nonviable regions (1.13 ± 0.21 , $p < 0.001$). The extraction of FDG in viable regions was independent of rest MBF but correlated inversely with MFRs ($r = -0.424$, $p < 0.05$). No correlation between the FDG extraction and MFR was observed in nonviable regions.

Conclusion—As in the animal model, decreasing MFRs in viable myocardium are associated with increasing glucose extraction that likely reflects a metabolic adaptation of remodeling hibernating myocytes.

Keywords

Ischemic cardiomyopathy; Myocardial flow reserve; Myocardial viability; Glucose metabolism

Introduction

Sustained or increased glucose utilization in hypoperfused dysfunctional myocardial regions has been referred to as “myocardial viability,” a condition where contractile function may recover if myocardial blood flow (MBF) is restored [1]. Also called “myocardial hibernation,” the reduction or loss of contractile function is viewed as a downregulatory adaptation of myocardial energy expenditures so that together with the more oxygen efficient glycolytic ATP production a new steady state between supply and demand is reached. Clinical evidence however suggests that such new steady state may not persist indefinitely. For example, delays in revascularization of viable myocardium may lead to loss of functional reversibility [2] so that such downregulation in myocardial energy expenditures has also been considered an “incomplete adaptation to ischemia” [3]. Findings in chronic animal models of myocardial hibernation or of potential reversibility of contractile dysfunction suggest a similarly progressive change in reversibly dysfunctional myocardium, where downstream of an experimentally induced coronary stenosis with normal flow at rest but an impaired flow reserve myocardium becomes initially chronically stunned, while

resting MBF remains normal but ultimately progresses to hibernation [4]. Hallmarks of hibernation in these studies include increased glucose utilization and reduced resting MBF, the latter attributed to myocardial remodeling rather than to a stenosis-related decrease in resting MBF [5]. Importantly, these animal experimental studies identified an impairment of the coronary flow reserve rather than a stenosis-related reduction in coronary blood flow at rest as a major determinant of hibernation. Based on these observations, we postulated that viable myocardium in humans may also be associated with progressive impairments in the regional myocardial flow reserve (MFR). Therefore, we measured regional MBFs at rest and during pharmacologically induced hyperemia and the regional myocardial uptake of ^{18}F -fluorodeoxyglucose (FDG) as a tracer of glucose utilization in order to explore possible relationships between MBF and glucose uptake and to examine whether the findings made in animal experiments were indeed valid in human myocardial hibernation.

Materials and methods

Study population

Patients—Patients were recruited retrospectively from a study population referred between January 1997 and December 2003 to the UCLA Nuclear Medicine Service for myocardial viability assessment with quantitative positron emission tomography (PET) ^{13}N -ammonia MBF measurements at rest and during dipyridamole stress and FDG PET metabolic imaging. Exclusion criteria included unstable angina, recent myocardial infarction (<4 weeks), and idiopathic dilated cardiomyopathy. After obtaining a waiver by the UCLA Institutional Review Board (IRB), clinical data and PET image data were reviewed and analyzed. The study population consisted of 36 patients (28 men, age 59 ± 12 years) with coronary artery disease (CAD) and left ventricular (LV) dysfunction (LV ejection fraction $25 \pm 10\%$). Table 1 summarizes the patient characteristics.

Normal controls—Twenty age-matched healthy volunteers (age 58 ± 7 years, eight men) with a low probability (<5 %) of CAD based on absence of symptoms and coronary risk factors, a normal physical examination, and a normal resting ECG served as normal controls (Table 1). They were selected from our laboratory database; all had participated in IRB approved investigations and had given written informed consent [6, 7]. MBF had been measured in all with ^{13}N -ammonia PET at rest and during dipyridamole stress but none had been evaluated with FDG. They were included as a control group for comparison of flow measurements in the patients with ischemic cardiomyopathy.

PET

Imaging protocol—Participants refrained from caffeine and theophylline-containing beverages or medications for at least 24 h prior to the PET study. MBF was measured with ^{13}N -ammonia, first at rest and then during dipyridamole-induced hyperemia, followed by an evaluation of regional myocardial glucose uptake with FDG, using a PET system with a 15.5-cm axial field of view and an intrinsic spatial resolution of 4.5 mm at full-width at half-maximum (ECAT/EXACT HR+, Siemens/CT, Knoxville, TN, USA). ^{13}N -Ammonia images were acquired dynamically as described previously [8]. The final, 15-min image of the serially acquired image data was used for evaluating the relative distribution of MBF.

After acquisition of the baseline ^{13}N -ammonia study, hyperemia was induced with a 4-min i.v. infusion of 0.56 mg/kg dipyridamole followed 4 min later by an i.v. bolus of ^{13}N -ammonia (25–30 mCi). Heart rate (HR), blood pressure, and a 12-lead ECG were recorded at 1-min intervals; the rate-pressure product (RPP) was derived from the HR and systolic blood pressure during the initial 2 min and served as an estimate of cardiac work. FDG (8–10 mCi) was administered i.v. after an oral glucose load to stimulate insulin secretion or, when blood glucose levels were elevated, after i.v. short-acting insulin [9, 10] in order to promote myocardial glucose uptake. Acquisition of 20-min images began 60 min after the FDG administration.

Definition of viable and nonviable regions by polar map analysis—On the reoriented short- and long-axis myocardial images and the corresponding polar maps, the relative distributions of MBF and FDG uptake were evaluated visually and semiquantitatively, using the standard American Heart Association recommended 17-segment model and the Munich Heart software [11]. As described previously and consistent with guidelines by the American Society of Nuclear Cardiology [1, 9, 10], myocardium with the highest ^{13}N -ammonia activity on the rest perfusion images (5 % of the sectors with the highest activity) was defined as 100 % and served as reference for normalization of regional ^{13}N and ^{18}F activity concentrations. Regional ^{13}N activity concentrations on the rest images in the patients were compared to a normal reference database obtained previously in 20 normal volunteers [12]. Regional decreases in ^{13}N activity concentrations 2.5 SDs below the mean were defined as perfusion defects and differences between ^{18}F and ^{13}N activity concentrations 15 % were defined as “mismatch,” whereas differences <15 % were defined as “match.” Further, segments with ^{13}N activity concentrations between –1.0 and –2.5 SDs and 15 % difference between ^{13}N -ammonia and FDG uptake were also defined as mismatches. Segments with ^{13}N activity concentrations 4.5 SDs below the mean were defined as matches regardless of the difference between ^{13}N -ammonia and FDG uptake. Myocardial regions with perfusion-metabolism mismatches and matches were defined as viable and nonviable myocardium, respectively. The operational terms “viable” and “nonviable” refer to the potential reversibility or non-reversibility of contractile function of hypoperfused myocardial regions following revascularization. Regions with the highest ^{13}N activity concentration at rest were defined as remote myocardium. When both viable and nonviable patterns were found in the same segment, the assigned category was based on the tissue type with the greatest segment extent.

Estimates of the myocardial glucose extraction—Disproportionate increases in myocardial FDG uptake relative to MBF as a hallmark of viability reflect increases in the regional myocardial glucose extraction. As the net uptake of a radiotracer is the product of its extraction and MBF, a semiquantitative measure of the extraction of FDG and thus of glucose can be derived from the ratio of the relative regional radiotracer concentrations of FDG (glucose net uptake) and ^{13}N -ammonia (MBF) and was defined as E (FDG). The difference in regional FDG and ^{13}N -ammonia concentrations as another measure of the regional FDG extraction was also evaluated.

Determination of regional MBF—In the patients, regions of interest (ROI) were assigned manually to myocardium defined as viable, nonviable, and remote on the polar maps assembled from the reorientated late ^{13}N -ammonia short-axis images (Fig. 1). Together with an ROI placed in the LV blood pool, the ROIs were then copied to the initial, 2-min serially acquired images for the rest and the dipyridamole studies. From the resulting time-activity curves, estimates of regional MBF at rest and during hyperemia were obtained as described previously [8]. In the normal controls, time-activity curves were generated for the entire LV myocardium and the LV blood pool with ROIs assigned automatically by the analysis software program. The time-activity curves were corrected for partial volume effect, assuming a 1-cm thickness for the LV myocardium, and for activity spillover from blood to myocardium. The MFR was estimated as the ratio of hyperemic to baseline MBF. MBFs and MFRs were measured in all segments with perfusion defects, with the exception of eight segments with spillover fractions ≥ 0.80 at rest or stress as they would lead to errors in flow estimates.

Statistical analysis

Data are presented as mean $\pm$ SD. Hemodynamic results at baseline and after dipyridamole stimulation in patients and in normal controls were compared with Student's *t* test for paired or unpaired data as appropriate. All other parameters including ^{18}F -FDG and ^{13}N -ammonia activity concentrations, E(FDG), MBFs, and MFR in remote, viable, and nonviable regions in the patients and in normal controls were compared by analysis of variance (ANOVA) followed by post hoc testing (the Bonferroni with equal variance assumed or the Dunnett's T3 test with equal variance not assumed). The relationships between MFR and E(FDG) and MBF and FDG uptake were analyzed by least squares regression analysis. Significance was considered as two-sided if $p < 0.05$ using SPSS software (Version 13.0, Chicago, IL, USA) for statistical analysis.

Results

Hemodynamic findings

At baseline, HR (70 ± 13 vs 60 ± 8 bpm, $p < 0.05$) and the corresponding RPP ($8,387 \pm 2,094$ vs $7,191 \pm 1,257$ mmHg $\times$ min, $p < 0.05$, respectively) in the patients were higher than those in the normal controls. After dipyridamole stimulation, HR (82 ± 13 vs 86 ± 10 bpm, respectively) and corresponding RPP ($9,376 \pm 2,579$ vs $9,697 \pm 1,820$ mmHg $\times$ min, respectively) had increased in patients ($p < 0.05$) and in controls ($p < 0.0001$) and no longer differed between the two groups ($p > 0.05$).

Polar map findings

In the age-matched normal controls, myocardial perfusion was homogeneous. No regional defects were noted on visual and quantitative polar map analysis, both at rest and during hyperemia, further confirming that these healthy volunteers were indeed free of significant CAD. In the 36 patients with ischemic cardiomyopathy, the polar map analysis of the baseline studies identified 34 viable and 36 nonviable regions (Table 2). The extent of viable and nonviable myocardium averaged 16 ± 16 % (range 8.1–50.4 %) and 18 ± 15 % (range 8.1–63.5 %), respectively ($p > 0.05$). Of the patients, 8 had viable regions only, 14 had nonviable

regions only, and the remaining 14 patients had both viable and nonviable myocardial regions. No additional perfusion defects were noted on the stress ^{13}N -ammonia images; in only 12 of the 34 viable regions were the flow defects more severe on the stress images, while the defect severity remained unchanged in the remaining 22 viable regions.

As summarized in Table 2, regional ^{13}N activity concentrations and thus relative myocardial perfusion were on average more severely reduced in nonviable than in viable regions (43 and 38 % on average, respectively) when compared to remote regions. Despite this statistically significant difference, individual flow reductions varied considerably between patients or regions so that there was a wide overlap of defect severities between viable and nonviable regions (Fig. 2). Further, relative FDG uptake and thus glucose utilization were, as expected, significantly more reduced in nonviable than in viable regions ($p<0.0001$). When compared to remote myocardium, the relative FDG uptake in viable regions considerably varied between patients. In 32 % of viable regions it was higher than and in 68 % viable regions equal to or lower than that in remote myocardium. Finally, glucose extraction as reflected by $E(\text{FDG})$ was 24 % higher in viable than in nonviable regions ($p<0.0001$) and 65 % higher than in remote regions ($p<0.0001$). Furthermore, the FDG to ^{13}N -ammonia differences in viable myocardial regions ranged from 10 to 31.5 % (average 20.6 ± 5.8 %) and were significantly higher than those in nonviable regions (average 5.4 ± 10.2 %, $p<0.0001$).

Regional MBF and MFR

We compared MBF at rest and after dipyridamole administration in both viable and nonviable regions to their remote regions. As summarized in Table 3, MBF at rest in remote regions of the patients was similar to that in the normal volunteers, but was significantly diminished in both viable and nonviable regions. Rest MBFs were on average 38 % lower in viable and 51 % lower in nonviable regions ($p<0.001$) than in remote myocardium, ranging from 0.15 to 0.81 ml/min per g in viable and from 0.13 to 0.56 ml/min per g in nonviable regions, again demonstrating a considerable overlap of resting MBFs between viable and nonviable regions (Fig. 2).

Further, dipyridamole stress significantly increased MBF in all regions (see Table 3). However, the flow response to the dipyridamole-induced vasodilation in remote myocardium of patients remained significantly below that in the normal volunteers (70 ± 45 % vs 174 ± 67 % average increases, $p<0.0001$, respectively). Hyperemic flows were even more severely reduced in viable and nonviable regions, when compared to normal controls or to remote myocardium. Moreover, hyperemic stress flows were lower in nonviable than in viable regions ($p=0.002$).

Correspondingly, MFRs in remote myocardium of patients were significantly attenuated in comparison to normal controls (Fig. 3). MFRs were diminished even more severely in viable and nonviable regions compared to remote regions (by 18 and 28 %, respectively) or the normal controls but did not differ significantly between viable and nonviable regions ($p>0.05$).

Myocardial glucose uptake and MBF

The relative FDG uptake was significantly associated with regional MBFs at rest in viable regions. It declined with lower MBFs but disproportionately less so that FDG concentrations disproportionately increased relative to successively declining flows. No such association was observed in nonviable regions (Fig. 4). As shown in Table 2, E(FDG) as a measure of the glucose extraction was higher in viable (1.40 ± 0.14) than in remote (0.9 ± 0.20 , $p < 0.0001$) or nonviable regions (1.13 ± 0.21 , $p < 0.0001$). In order to account for FDG uptake in remote myocardium and to estimate more directly the contribution of myocardial viability to the FDG extraction, E (FDG) in viable regions was normalized to that in remote regions. The resulting ratio of the extraction in viable over remote myocardium averaged 1.65 ± 0.50 , suggesting that myocardial viability was associated with an on average 65 % augmentation of the regional glucose extraction.

The extraction of glucose in viable regions was related to the MFR. As Fig. 5 shows, E(FDG) in viable regions correlated significantly and inversely with regional MFRs ($p < 0.05$). This correlation remained statistically significant ($p < 0.05$) even if the one data point for a flow reserve of 2.96 was excluded from the analysis (see Fig. 5, panel a). Regions with the most severely reduced MFR were thus associated with the highest glucose extraction. Additionally, E(FDG) normalized to remote myocardium increased even further, reaching peak values at MFRs of less than 1. No such correlation was found in nonviable regions ($p > 0.05$). No statistically significant associations between rest MBF and E(FDG) were found in viable ($r = -0.21$, $p > 0.05$) or nonviable regions ($r = -0.15$, $p > 0.05$). A similar, statistically significant, inverse correlation was found when the regional FDG to ^{13}N -ammonia differences in viable regions as another measure of the FDG extraction were compared to MFR ($r = -0.51$, $p = 0.002$).

E(FDG) in viable regions ranged from 1.17 to 1.69 with a median value of 1.39. To identify possible determinants of the magnitude of the FDG extraction, E(FDG) in viable regions were sorted by the median E(FDG) into a low and a high extraction group. Resting MBF did not differ significantly between the two groups (Table 4). However, hyperemic flows ($p < 0.005$) and MFR ($p < 0.05$) were significantly lower in the high than in the low E(FDG) group so that severely diminished MFRs were associated with the highest extraction of glucose.

Discussion

The main findings of the current study are as follows: (a) Relative and absolute flow reductions were on average less severe in viable than in nonviable myocardial regions but varied considerably between patients and regions so that flow reductions alone do not fully discriminate between viable and nonviable myocardium. (b) Flow responses to pharmacologic vasodilation in remote myocardium of ischemic cardiomyopathy patients were significantly attenuated as compared to controls, likely due to mild discrete coronary stenoses, diffuse epicardial and/or microvascular coronary disease. (c) Hyperemic flows in viable myocardial regions significantly exceeded those in nonviable myocardium, while MFRs were comparable. (d) The extraction of FDG and thus of glucose in viable myocardial regions correlated inversely with the MFR but was not associated significantly with resting

flow, implicating a severe impairment of the flow reserve rather than a stenosis-related decrease in coronary blood flow at rest as the major determinant of myocardial viability. This is consistent with findings in animal experimental models of hibernating myocardium that suggest that reduced flows at rest in viable myocardium in human ischemic cardiomyopathy may be a “consequence rather than a cause of adaptive myocardial remodeling” and that the reduced flow at rest reflects and induces the development of metabolic alterations including a downregulation of mitochondrial oxygen consumption [5, 13, 14].

Study limitations

There are several limitations to the current investigation. First, the study is retrospective as it includes consecutive patients who had been referred for clinical viability assessment and quantification of rest and stress MBF. Because the goal of the study was to examine possible associations between MBF and glucose uptake in viable myocardial regions, the retrospective nature of the study was unlikely to have affected the results. Second, echocardiographic and coronary angiographic data were not available in all patients. While of interest and while potentially offering information on structural alterations accounting for the impairments in rest and stress flows and on their effects on regional wall motion, they would have contributed little information on the association between myocardial glucose uptake and MBF at rest and during hyperemic stress as the major focus of the current investigation. Third, as another potential limitation, ROIs for perfusion defects were assigned manually according to the perfusion-metabolism patterns as seen on the ^{13}N -ammonia and FDG PET images rather than employing the standard 17-segment model. Yet, this manual ROI assignment allowed more precise and selective evaluation of glucose uptake and flows in “mismatch” and “match” regions. Fourth, it might have been interesting to relate regional wall motion disturbances to perfusion and metabolism patterns. Yet, such correlation of contractile function with flow and metabolism was beyond the scope of the current investigation that sought to explore possible associations between blood flow and metabolism. Finally, FDG uptake was not quantified; nevertheless, the comparison of FDG uptake in hypoperfused relative to remote myocardium together with normalization of the FDG uptake to MBF should offer sufficient information for defining regional differences in glucose utilization. Further, information on post-revascularization changes in global and regional contractile function was unavailable. However, the presence of myocardial viability was defined in this study by criteria that had previously been used for identifying myocardial viability and that was found to be predictive of post-revascularization changes in regional wall motion [1, 15].

Regional myocardial perfusion and MBFs

Consistent with earlier findings in patients with ischemic cardiomyopathy [16], flow at rest in remote myocardium was comparable to that in the normal volunteers and thus was fully preserved. By contrast, flow responses in remote myocardial regions to dipyridamole stimulation were severely diminished (60 % lower than in normal volunteers). Obstructive as well as diffuse nonobstructive disease of the epicardial coronary vessels or microvascular disease most likely accounted for the severely diminished flow response.

Based on the polar map analysis of resting perfusion and myocardial FDG uptake, flows were, by definition, invariably reduced in viable and nonviable myocardial regions. Yet, these flow reductions varied considerably in severity between regions and patients so that, despite a statistically significant difference between the average values, the magnitude of individual flow reductions is of limited value for accurately distinguishing between viable or nonviable myocardium.

Assays of the tissue morphology [17] and comparison studies with late contrast-enhanced cardiac magnetic resonance imaging [18] have shown a close, inverse relationship between regional flow reductions at rest and the degree of transmural tissue fibrosis. For example, regional ^{13}N -ammonia concentrations as a measure of transmural MBF declined linearly with increasingly transmural tissue fibrosis as determined histopathologically in patients with ischemic cardiomyopathy [17, 19]. The non-fibrotic transmural fraction consists of living myocytes, either normal or abnormal or “hibernating” or “remodeled” myocytes [5, 14], which account for most of the remaining transmural flow. Whether perfusion differs quantitatively between populations of abnormal and of normal myocytes (i.e., flow per volume of cells) still awaits clarification. If abnormal myocytes are associated with lower perfusion, it might explain the reduced flow in hibernating myocardium that is rich in abnormal myocytes. Observed differences in the perfusable tissue index, i.e., the fraction of myocardium capable of rapidly exchanging water, likely representing the transmural fraction of living myocytes, were related to differences in the severity of perfusion defects between viable and nonviable regions [20]. Importantly, estimates of absolute flows, when normalized to the perfusable tissue index and thus to the volume of cells, were identical for both nonviable and viable regions and thus argue against possible perfusion differences as an explanation for the reduced flow.

Regional myocardial glucose utilization and MBF

Relevant to the current findings are earlier observations of a modest though statistically significant correlation between the fraction of abnormal myocytes and the regional FDG uptake [17, 19], implicating abnormal or hibernating myocytes in viable regions as a major determinant of FDG and, by inference, glucose uptake. In the current investigation in patients with ischemic cardiomyopathy, relative FDG uptake (i.e., normalized to relative perfusion) was significantly higher in viable than in nonviable regions. However, when compared to remote myocardium, individual values of FDG uptake in viable regions varied considerably between patients. It was higher than or equal to that in remote myocardium in some patients and reduced in others though less than regional MBF. A similar variability had been observed previously in patients with type 2 diabetes where FDG uptake in remote myocardium depended on the amount of short-acting insulin administered prior to the FDG injection [10]. The variability is also consistent with observations in an animal experimental model of hibernation [21]. Studies under fasting conditions with low uptake of FDG in normal myocardium were associated with relative increases of FDG uptake in hibernating myocardium. However, when euglycemic-hyperinsulinemic clamping was employed in order to promote FDG uptake in remote myocardium, FDG uptake in hibernating regions was reduced or equal to that in remote myocardium.

Mechanisms underlying such variability in relative FDG uptake in viable myocardium include differential expression of glucose transporter isoforms as assays of human hibernating myocardium have suggested [22, 23]. An upregulation of the insulin-independent glucose transporter 1 (GLUT1) would render hibernating myocardium less responsive to changes in substrate availability and thus substrate selection that are mediated through the insulin-sensitive GLUT4. For example, fasting-induced increases in circulating fatty acid levels suppress glucose utilization and thus FDG in normal myocardium but only to a lesser extent in hibernating myocardium. Conversely, insulin stimulation increases glucose utilization and thus FDG uptake in normal myocardium but to a lesser extent in hibernating myocardium.

Although the clinical study protocol provided for measures to promote and standardize glucose uptake in normal myocardium, as for example, stimulation of insulin secretion by oral glucose administration or supplemental doses of short-acting insulin [9, 10], variations in glucose utilization nevertheless persisted and probably accounted for some of the inter-patient differences in FDG uptake. Normalization of the regional FDG uptake to regional perfusion, providing a measure of the regional FDG extraction, reduced some of this variability. The index of the regional myocardial extraction of FDG was found to correlate inversely with the regional MFR. Moreover, normalization of the FDG extraction in viable regions for the FDG extraction in remote myocardium amplified the inverse correlation with regional MFRs as it more accurately reflected the contribution of hibernating myocytes to the overall glucose utilization. Normalized E(FDG)s for MFRs in the range of 0.5–1.5 were as much as two to three times higher than in myocardial regions with greater than 1.5 MFRs. The observed relationship between the normalized FDG extraction and the regional MFR in the current study is remarkably similar to that found in an animal experimental model of myocardial hibernation where FDG deposition was highest in myocardial regions with MFRs of less than 1.5 [24]. Severe reductions of MFR were thus associated with the highest FDG extraction and thus glucose utilization. The magnitude of the FDG extraction was also inversely related with hyperemic flows but not significantly with resting MBFs.

If, as mentioned above, the extraction of FDG corresponds to the number of hibernating or remodeled FDG-avid myocytes, then, as also postulated previously [24], severe reductions of MFR might indeed represent a critical determinant for inducing “adaptations consistent with myocardial hibernation” in humans. The absence of a statistically significant correlation of resting MBFs and the FDG extraction as observed in the patients suggests that decreases in regional rest flows do not depend primarily on a stenosis-related restriction of coronary blood flow at rest but rather are secondary to adaptive alterations of viable or hibernating myocardium [5, 14]. Current findings may lay an important framework for future studies assessing alterations in MFR or coronary vascular health in response to medical therapy, interventional or surgical revascularization, or different forms of stem cell therapies. Monitoring the flow responses to different forms of medical interventions in ischemic cardiomyopathy with serial PET flow measurements may provide new mechanistic insights into the remodeling process in cardiomyopathy patients. Importantly, severe reductions in MFR, comparable to those in myocardial regions with the highest glucose extraction, are associated with poor long-term outcomes of patients with hypertrophic, dilated as well as ischemic cardiomyopathy [16, 25, 26], possibly due to progressive loss of

viable myocardium [27]. Therefore, current observations might suggest that improvements or restoration of the coronary flow reserve should be the primary goal of therapeutic strategies in order to prevent further myocardial remodeling and to facilitate recovery of contractile function.

Conclusion

The observed interactions between MFR and glucose utilization in viable myocardium in human ischemic cardiomyopathy are indeed consistent with those observed in an animal experimental model of myocardial hibernation. As observed in animal experimental studies, the residual MFR appears to be a major determinant of downstream functional, morphologic, and metabolic remodeling. It further appears that some degree of MFR is essential to maintain tissue viable. Whether further reductions in the MFR will result in loss of viability or whether an initial adaptive process ultimately progresses to loss of myocytes and tissue fibrosis awaits clarification.

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Abbreviations

MBF	Myocardial blood flow
MFR	Myocardial flow reserve
LV	Left ventricular
FDG	¹⁸ F-fluorodeoxyglucose
CAD	Coronary artery disease
HR	Heart rate
RPP	Rate-pressure product
ROI	Regions of interest
E (FDG)	Extraction of FDG as the ratio of the relative regional radiotracer concentrations of FDG (glucose uptake) and ¹³ N-ammonia (MBF)

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Fig. 1.

Polar map analysis of viable, nonviable, and remote myocardium and assignment of ROI for measurements of MBF. Normal remote (*green*), viable (*blue*), and nonviable (*red*) myocardial regions were defined by polar map analysis of rest ^{13}N -ammonia and the differences between ^{13}N -ammonia and FDG images. ROIs for viable, nonviable, and remote myocardium in polar maps of the dynamically acquired ^{13}N -ammonia images are manually drawn at rest, then copied to the stress polar maps. Regional rest and dipyridamole flows together with the MFR are shown in the lower panel

Fig. 2. Relative flow reductions and MBFs at rest in viable myocardial regions (*VM*) and nonviable myocardial regions (*NVM*). Note the considerable overlap of flow values between the two kinds of regions

Fig. 3.
MFRs in normal controls (*NLS*), in remote myocardial regions (*RM*), viable myocardial regions (*VM*), and nonviable myocardial regions (*NVM*)

Fig. 4.
Relative FDG uptake in comparison to regional MBF at rest (% FDG, relative regional FDG uptake)

Fig. 5.

MFR and extraction of FDG in viable regions. E(FDG), index of the regional FDG extraction as the ratio of relative FDG over relative ^{13}N -ammonia tissue concentrations; relative E(FDG) as shown on the ordinate of the figure, FDG extraction in viable myocardium normalized to E(FDG) in remote myocardium

Table 1

Demographics of patients and normal volunteers

Variables	Patient group (<i>n</i> = 36)	Normal group (<i>n</i> = 20)
Age (years)	59±12	58±7
M/F (<i>n</i>)	28/8	8/12
Smoking history/current smoker (%)	13 (36)	0
Hypertension (%)	8 (22)	0
Diabetes mellitus (%)	8 (22)	0
Hyperlipidemia (%)	10 (28)	0
Family history of CAD (%)	10 (28)	0
Obese (body mass index > 30) (%)	2 (6)	0
Prior PCI (%)	4 (13)	0
Prior CABG (%)	15 (42)	0
Prior PCI + prior CABG (%)	4 (13)	0
Coronary angiography (<i>n</i> = 16)		
One-vessel disease (%)	4 (25)	
Two-vessel disease (%)	6 (38)	
Three-vessel disease (%)	6 (38)	

PCI percutaneous coronary intervention, *CABG* coronary artery bypass grafting

Table 2

Regional tracer activity concentrations of ^{13}N -ammonia and ^{18}F -FDG in remote, viable, and nonviable myocardial regions

	Remote (<i>n</i> = 34)	Viable (<i>n</i> = 34)	Remote (<i>n</i> = 36)	Nonviable (<i>n</i> = 36)
^{13}N -ammonia (%)	87±6	54±10 *	84±7	48±9 *, **
FDG (%)	78±16	75±11	76±14	53±10 *, ***
E(FDG)	0.90±0.20	1.40±0.14 *	0.91±0.18	1.13±0.21 *, ***
Relative E(FDG)	1.65±0.50		1.29±0.34 ****	

Regional ^{13}N -ammonia and FDG concentrations are given in a percent of the maximum activity. E(FDG) is the ratio of regional FDG over regional ^{13}N -ammonia activity concentrations and serves as an index of the regional glucose extraction

* $p < 0.0001$ vs remote regions;

** $p < 0.01$ vs viable regions;

*** $p < 0.0001$ vs viable regions;

**** $p < 0.001$ vs viable regions

Blood flow and flow reserve (MFR) in viable, nonviable, normal remote regions, and in normals

MBF, ml/min per g	Normals (<i>n</i> = 20)	Ischemic cardiomyopathy patients			
		Remote (<i>n</i> = 34)	Viable (<i>n</i> = 34)	Remote (<i>n</i> = 36)	Nonviable (<i>n</i> = 36)
Rest	0.63±0.13	0.68±0.23	0.42±0.18*	0.66±0.21	0.32±0.09**
Dipyridamole	1.68±0.38***	1.10±0.33****	0.56±0.30****	1.08±0.36****	0.39±0.16****
MFR	2.74±0.67***	1.70±0.45	1.39±0.56	1.70±0.43	1.23±0.43****
Relative MFR		-0.18±0.25		-0.24±0.28	

*
 $p < 0.0001$ vs normals and remote regions;

**
p<0.05 vs viable regions;

 $p<0.0001$ vs remote, viable, and nonviable regions;

 $p < 0.0001$ vs rest MBF;

 $p < 0.0001$ vs remote regions;

p<0.005 vs rest MBF;

p<0.001 vs remote regions

Table 4

Comparison of rest and hyperemic MBFs and MFR in viable regions with high and low extraction of FDG

	High FDG extraction 1.40 (1.52±0.08)	Low FDG extraction <1.39 (1.28±0.07)	<i>p</i> value
Resting MBF (ml/min per g)	0.38±0.15	0.47±0.19	0.126
Stress MBF (ml/min per g)	0.42±0.17	0.70±0.34	0.005
MFR	1.19±0.41	1.59±0.63	0.036