Evidence for Chronic Stunning in Pigs

James A. Fallavollita, MD; John M. Canty, Jr, MD

Background—Viable, chronically dysfunctional myocardium can have normal or reduced resting flow. We previously produced hibernating myocardium with reduced resting flow in pigs with a chronic stenosis and hypothesized that hibernation is preceded by chronic stunning with normal resting perfusion.

Methods and Results—Pigs instrumented with a proximal left anterior descending coronary artery (LAD) stenosis were studied 1 or 2 months later in the closed-chest anesthetized state. Stenosis severity increased from 74±5% at 1 month to 83±6% at 2 months and was accompanied by anteroapical hypokinesis (wall motion score, 2.1±0.1 at 1 month and 1.5±0.3 at 2 months; normal=3). Resting perfusion was similar in normal and dysfunctional regions, but the deposition of 18F-2-deoxyglucose (FDG) varied. At 1 month, subendocardial FDG deposition by excised tissue counting was similar in each region (0.034±0.006 mL · g⁻¹ · min⁻¹ LAD region versus 0.032±0.004 mL · g⁻¹ · min⁻¹ in normal regions, P=NS). At 2 months, subendocardial FDG deposition was increased (0.084±0.025 mL · g⁻¹ · min⁻¹ LAD region versus 0.042±0.017 mL · g⁻¹ · min⁻¹ in normal regions, P<0.05). Increases in FDG uptake were inversely related to LAD subendocardial flow reserve during adenosine (3.5±0.6 at 1 month versus 1.4±0.2 at 2 months, P<0.01).

Conclusions—These data indicate a progression of physiological adaptations in pigs with viable, chronically dysfunctional myocardium. As coronary flow reserve decreases, fasting FDG uptake increases. Flow at rest remains normal, consistent with “chronic stunning,” and contrasts with reduced flow and increased FDG characteristic of hibernating myocardium in similarly instrumented pigs after 3 months. This temporal progression of adaptations supports the hypothesis of a transition from a physiological phenotype of stunning to hibernation. (Circulation. 1999;99:2798-2805.)

Key Words: stunning, myocardial hibernation fluorodeoxyglucose

Clinical studies have demonstrated a spectrum of physiological abnormalities that are associated with viable, chronically dysfunctional myocardium. At one extreme are patients in whom the dysfunction is associated with reduced resting flow and preserved metabolic uptake of 18F-2-deoxyglucose (FDG) that has been called “hibernating myocardium.” At the other extreme are patients in whom regional dysfunction occurs with normal perfusion, referred to as chronically stunned. Chronically dysfunctional myocardium is undoubtedly related to episodes of acute ischemia in both conditions, but the interrelation between these 2 states remains unclear and is controversial.1–3 One possibility is that areas of reduced perfusion at rest may be the result of an admixture of viable tissue and subendocardial scar, partial volume effects in dysfunctional regions, or attenuation with conventional single photon tracers.2,3 Arguing against this are animal studies using microspheres to assess regional perfusion that have demonstrated chronic dysfunction with histologically viable myocardium and both reduced and normal resting flow.4–7 This suggests that coronary artery disease may result in both chronic stunning and hibernation. If so, there may be a transition from stunning to hibernation as stenosis severity increases and flow reserve is compromised, as we previously hypothesized during progressive ameroid stenosis in dogs.6 Because it would be difficult to resolve this issue in clinical studies because of the lack of information regarding the temporal progression of events and detailed histology, we studied pigs with a chronic LAD stenosis at time points before that at which we previously demonstrated hibernating myocardium (3 to 4 months).4 The results demonstrate a transition from chronic stunning to hibernation with variability in FDG uptake that appears to be related to regional coronary flow reserve.

Methods

All experimental procedures and protocols conformed to institutional guidelines for the care and use of animals in research. Juvenile pigs (n=30) were fasted and premedicated with a mixture of Telazol (tiletamine 50 mg/mL and zolazepam 50 mg/mL) and ketamine (100

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mg/mL) (0.037 mL/kg IM) and given prophylactic antibiotics (cephalothin 50 mg/kg IV and gentamicin 5 mg/kg IM). The pigs were intubated, and anesthesia was maintained with halothane (0.5% to 2%) and oxygen (balance). Through a thoracotomy (fourth left intercostal space), the proximal left anterior descending coronary artery (LAD) was exposed with a 1- to 2-cm limited pericardiotomy, leaving the rest of the pericardium intact. The LAD was dissected free and instrumented with a stenosis having a fixed ID of 1.5 mm. Five animals were sham-instrumented to determine whether surgery resulted in wall motion abnormalities. The incision was closed, and the pneumothorax was evacuated. A single postoperative dose of antibiotics was repeated after the chest was closed, and an intercostal nerve block (2% lidocaine) and analgesics (butorphanol 0.025 mg/kg IM) were given postoperatively to alleviate pain.

Figure 1. Transmural perfusion at rest, during epinephrine, and during adenosine in animals with chronic LAD stenosis. Resting flow in dysfunctional LAD regions was similar to normally perfused regions, consistent with myocardial stunning. At 1 month (top), epinephrine increased flow similarly in both regions, but there was a moderate reduction in adenosine flow. During epinephrine at 2 months (bottom), flow to inner 2 thirds of LAD region failed to increase to same extent as normal regions. Although adenosine flow increased 6-fold in normal region, it was severely restricted in LAD territory and similar to flows during epinephrine. Endo indicates subendocardium; Mid, midmyocardium; Epi, subepicardium; and FT, full thickness.
Differential FDG Uptake in Chronically Stunned Myocardium

Experimental Protocol

Pigs were fasted overnight, and anesthesia was induced with the Telazol/xylazine (100 mg/mL) mixture (0.022 mL/kg IM). After intubation, anesthesia was maintained with halothane (0.5% to 1%) and oxygen (balance) supplemented with additional Telazol/xylazine (0.011 mL/kg IM PRN). A pigtail catheter was placed retrogradely and oxygen (balance) supplemented with additional Telazol/xylazine (100 mg/mL) mixture (0.022 mL/kg IM). After intubation, anesthesia was maintained with halothane (0.5% to 1%) and oxygen (balance) supplemented with additional Telazol/xylazine (100 mg/mL) mixture (0.022 mL/kg IM). After intubation, anesthesia was maintained with halothane (0.5% to 1%) and oxygen (balance) supplemented with additional Telazol/xylazine (100 mg/mL) mixture (0.022 mL/kg IM). Arterial pressure and reference withdrawal sam-

FDG Quantification by Ex Vivo Tissue Counting

An hour after the last pharmacological intervention (3 to 4 hours from study initiation), blood was obtained for metabolic substrate levels. Enzymatic colorimetric assays were used to quantify nones-

TABLE 1. Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Heart Rate, bpm</th>
<th>Systolic Aortic Pressure, mm Hg</th>
<th>Mean Aortic Pressure, mm Hg</th>
<th>LVEDP, mm Hg</th>
<th>RPP, bpm×mm Hg</th>
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<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1 mo</td>
<td>10</td>
<td>94±3</td>
<td>127±5</td>
<td>95±4</td>
<td>13±1</td>
<td>11 990±730</td>
</tr>
<tr>
<td>2 mo</td>
<td>10</td>
<td>92±6</td>
<td>136±7</td>
<td>101±5</td>
<td>16±1</td>
<td>12 380±870</td>
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<tr>
<td>Epinephrine</td>
<td></td>
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<td></td>
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<tr>
<td>1 mo</td>
<td>10</td>
<td>150±6*</td>
<td>130±4</td>
<td>102±3</td>
<td>11±1</td>
<td>19 400±600*</td>
</tr>
<tr>
<td>2 mo</td>
<td>9</td>
<td>139±11*</td>
<td>139±7</td>
<td>104±5</td>
<td>14±2</td>
<td>19 010±1230*</td>
</tr>
<tr>
<td>Vasodilation</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>10</td>
<td>107±6*</td>
<td>136±6</td>
<td>91±3</td>
<td>13±2</td>
<td>14 530±1110*</td>
</tr>
<tr>
<td>2 mo</td>
<td>9</td>
<td>101±9</td>
<td>135±7</td>
<td>89±4*</td>
<td>14±1</td>
<td>13 370±970</td>
</tr>
</tbody>
</table>

LVEDP indicates left ventricular end-diastolic pressure; RPP, heart rate×systolic blood pressure product. Values are mean±SEM.

*P<0.05 vs corresponding rest value.

FDG deposition were determined from a 1- to 1.5-cm midventricular ring. It was divided into 9 to 12 full-thickness wedges, which were subdivided into subendocardial, midmyocardial, and subepicardial layers. Samples were placed into tared vials and weighed, and annihilation gamma radiation at 511 keV was measured in a gamma counter (model 1470, Wallac Inc).

TABLE 2. Subendocardial and Full-Thickness Perfusion and Endocardial/Epicardial Ratios

<table>
<thead>
<tr>
<th></th>
<th>Subendocardial</th>
<th>Full-Thickness</th>
<th>Endo/Epi Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LAD</td>
<td>Normal</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>10</td>
<td>1.14±0.09</td>
<td>1.15±0.08</td>
</tr>
<tr>
<td>2 mo</td>
<td>10</td>
<td>1.01±0.10</td>
<td>1.01±0.10</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>10</td>
<td>1.84±0.10*</td>
<td>1.91±0.10*</td>
</tr>
<tr>
<td>2 mo</td>
<td>9</td>
<td>1.67±0.37‡</td>
<td>2.09±0.36*</td>
</tr>
<tr>
<td>Vasodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>10</td>
<td>3.67±0.54‡ ‡</td>
<td>6.35±0.51*</td>
</tr>
<tr>
<td>2 mo</td>
<td>9</td>
<td>1.51±0.32‡ ‡</td>
<td>5.26±0.76*</td>
</tr>
</tbody>
</table>

Values are mL · min⁻¹ · g⁻¹, ratio or mean±SEM.

*P<0.05 vs rest.
†P<0.05 vs 1 mo.
‡P<0.05 vs normal.

Histology

Myocardial rings apical and basal to the ring used for microsphere and FDG analyses were incubated in triphenyltetrazolium chloride to exclude myocardial necrosis. In addition, samples from the LAD and normal regions were immersed in Z-fix (Anatech Ltd) for histology. Thin sections were stained with Masson or Gomori trichrome stains.
Connective tissue staining was quantified with standard point counting techniques. 4

Data Analysis
Data are presented as mean±SEM. Flow and FDG in the LAD and normally perfused regions represent weighted means for all samples within a given region after the perfusion boundaries were determined from the circumferential distribution of perfusion during adenosine. 4 Measurements in the normal and LAD regions were compared by paired t tests. Differences during pharmacological interventions were assessed with an ANOVA and t tests with the Bonferroni correction for multiple comparisons. Experimental groups were compared by use of unpaired t tests. Values of P<0.05 were considered significant.

Results
All animals were in good health at the time of study. Infarctions >1% of left ventricular mass were present in 3 pigs, and they were excluded from analysis.

Regional Perfusion and Function in Chronically Stunned Myocardium
The distributions of perfusion and hemodynamics at rest, during submaximal epinephrine, and during pharmacological vasodilation with adenosine are summarized in Figure 1 and Tables 1 and 2. Hemodynamic parameters were similar between the 2 groups. Resting flow was similar in the LAD and normally perfused remote regions. Figure 2 shows representative left ventriculograms from each group. Despite normal values for resting perfusion, anteroapical hypokinesis and normally perfused remote regions. Figure 2 shows representative end-diastolic and end-systolic ventriculogram tracings with centerline analysis. 9 Anteroapical wall motion was reduced in animals studied 1 and 2 months after instrumentation compared with sham controls.

**TABLE 3. Anteroapical Wall Motion**

<table>
<thead>
<tr>
<th>Wall motion score</th>
<th>Sham</th>
<th>1 mo</th>
<th>2 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>2.6±0.1</td>
<td>2.1±0.1*</td>
<td>1.5±0.3*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>2.9±0.1</td>
<td>2.5±0.1†</td>
<td>2.1±0.1†</td>
</tr>
<tr>
<td>Centerline score (SD/chor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>−0.4±0.6</td>
<td>−1.8±0.1†</td>
<td>−2.2±0.2†</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>−0.1±0.5</td>
<td>−1.4±0.2†</td>
<td>−1.8±0.3†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.05 vs sham. †P<0.05 vs rest.

Stenosis severity averaged 74±5% at 1 month, causing a moderate restriction in vasodilated perfusion (full-thickness LAD flow, 3.87±0.40 versus 6.07±0.33 mL·min⁻¹·g⁻¹ in the normal region, P<0.001). Adenosine flows were higher than those during epinephrine in each myocardial layer (Figure 1, top). At 2 months, stenosis severity increased by only a small amount, to 83±6% (P=NS versus 1 month), but there was a pronounced attenuation of pharmacological vasodilator reserve (full-thickness LAD flow, 1.92±0.32 versus 5.36±0.55 mL·min⁻¹·g⁻¹ in the normal region, P<0.001). Flow in the LAD region during adenosine was similar to that during epinephrine (Figure 1, bottom).

Regional Variations in Fasting FDG Deposition
The deposition of FDG relative to the normally perfused myocardium for the 2 groups of animals is shown in Figure 3. At 1 month, there were no regional or transmural differences in deposition between the dysfunctional LAD region and the normally perfused myocardium (LAD subendocardium, 0.034±0.006 versus 0.032±0.004 mL·g⁻¹·min⁻¹ in normal, P=NS). In contrast, at 2 months, FDG deposition was increased in the LAD perfusion territory (LAD subendocardium, 0.084±0.023 versus 0.042±0.017 mL·g⁻¹·min⁻¹ in normal, P<0.05). The relative FDG deposition (LAD/normal) varied transmurally in the animals studied at 2 months and was significantly greater than 1 month on a full-thickness basis (2.0±0.3 versus 0.9±0.1, P<0.01) as well as in the inner 2 thirds of the myocardial wall. Free fatty acids, plasma glucose, and insulin were within the range expected for fasting animals (Table 4). There were no differences between 1 and 2 months. Although there was a wide range of fasting glucose values, regression analysis revealed no correlation with FDG uptake [relative FDG uptake=(0.029·plasma glucose)+1.37, r=0.09, P=NS].

Discussion
Our results indicate that pigs instrumented with an LAD stenosis for 1 or 2 months develop regional dysfunction in association with progressive reductions in coronary flow reserve. Resting flow in both groups is normal and consistent with a state of chronic myocardial stunning. Despite physiological features of chronic stunning at each time point, there were differential patterns of FDG uptake. This variability suggests that both coronary flow reserve and the length of time during which the heart is subjected to reversible ischemia are determinants of increased FDG uptake in viable dysfunctional myocardium.
Progression of Physiological Abnormalities in Viable, Chronically Dysfunctional Myocardium

The present results taken together with those of our previous study and results of others suggest that there is a transition from stunning to hibernation, as was previously reported in dogs with collateral-dependent myocardium and limited collateral vasodilator reserve. Figure 4 shows the relation among flow at rest, FDG uptake, and flow during vasodila-
tion from our previous study in relation to the present groups of animals. Figure 5 illustrates the relationship between relative subendocardial flow (LAD/normal) and wall motion.

The present results of viable dysfunctional myocardium associated with normal resting perfusion at 1 and 2 months are consistent with findings in clinical studies. After 3 months, however, we observed reductions in resting flow and increased FDG uptake that are consistent with findings in humans with collateral-dependent, hibernating myocardium. Importantly, dysfunction preceded reductions in resting perfusion, which is in marked contrast with experimental models in which flow is acutely reduced (short-term hiber-
nation). Thus, it seems likely that reductions in resting flow are a result rather than a cause of chronic contractile dysfunction.

One of the major factors responsible for the transition from stunning to hibernation may be the physiological significance of a stenosis. As illustrated in Figure 4, progression in stenosis severity was associated with a transition from stunning to hibernation between 2 and 3 months. Vasodilated subendocardial perfusion fell from 1.51±0.32 to 1.05±0.15 mL/min/g (P=0.16), with a corresponding attenuation of stress-induced perfusion during submaximal epinephrine infusion (1.67±0.37 at 2 months versus 0.84±0.11 mL/min/g at 3 months, P<0.05). Interestingly, the reduction in adenosine flow reserve was unchanged because resting flow decreased in hibernating myocardium (subendocardial adenosine flow/resting flow, 1.4±0.2 at 2 months versus 1.3±0.2 at 3 months, P=NS). These data support the hypoth-
esis that hibernation may reflect an adaptation that is induced once flow reserve is critically compromised to minimize ischemia during subsequent episodes of increased demand, as we have previously speculated.

Other possible explanations for the transition from chronic stunning to hibernation seem less likely. Complete coronary occlusion was infrequent in chronically stunned compared with hibernating pigs in our previous study (18% versus 73%), yet Mills et al demonstrated reduced resting flow in pigs when all of the stenoses were patent. The transition to hibernating myocardium cannot be explained by myocardial scar, because we found a similar regional increase in connec-
tive tissue in pigs with chronically stunned and hibernating myocardium (6.6±0.9% at 2 months versus 6.2±0.9% at 3 months, P=NS). Untested hypotheses include a downregu-
lation of demand resulting from disassembly of the contractile apparatus in hibernating but not chronically stunned myocardium. Finally, time may be an independent determi-
nant of whether hibernating myocardium develops.

The presence of a temporal transition from chronic stunning to hibernation may help resolve some of the conflicting experimental data in clinical as well as animal studies that have resulted in varying speculation and conclusions regarding the relationship of these physiological entities. The role of PET in detecting reversible dyssynergy was originally

### Table 4. Fasting Substrate and Insulin Levels

<table>
<thead>
<tr>
<th></th>
<th>Free Fatty Acids, mEq/L</th>
<th>Glucose, mmol/L</th>
<th>Insulin, μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo (n=6)</td>
<td>0.65±0.12 (0.32–1.15)</td>
<td>3.9±1.2 (1.6–9.6)</td>
<td>0.27±0.02 (0.021–0.032)</td>
</tr>
<tr>
<td>2 mo (n=6)</td>
<td>0.56±0.09 (0.28–1.10)</td>
<td>6.9±1.2 (2.3–11.5)</td>
<td>0.29±0.02 (0.021–0.034)</td>
</tr>
</tbody>
</table>

Values are mean±SEM (range).
described by Tillisch et al., who demonstrated that a mismatch pattern between FDG uptake and reduced regional flow predicted viability, whereas matched reductions in FDG uptake and resting flow were consistent with irreversibly damaged myocardium. Importantly, however, more than half of the patients in their study demonstrated reversible dyssnergy in the presence of normal resting flow consistent with stunning and, a priori, myocardial viability. In other studies, myocardium with normal resting flow constitutes a significant fraction of reversibly dyssynergic regions. Although the stability and chronicity of such changes remains to be established, our results support the notion that reversible dysfunction can occur with both normal and reduced resting flow.

Because animals were studied only once, we cannot delineate the mechanisms by which acute ischemia caused dysfunction in this model. Myocardial stunning has been demonstrated after brief occlusions as well as during demand-induced ischemia. Cyclic flow reductions due to platelet aggregates can result in transient coronary occlusion and has been reported distal to critical ameboid stenoses. Spontaneous demand-induced stunning has been demonstrated after physiological increases in myocardial oxygen demand in pigs with ameboid occluders. Either mechanism may have been the cause of repetitive ischemia leading to chronic dysfunction, and continuous monitoring will be required to assess their relative importance.

Fasting FDG Uptake in Viable Chronically Dysfunctional Myocardium

Hibernating myocardium is accompanied by an increase in FDG uptake in the fasting state compared with normally perfused regions, yet FDG uptake is fairly uniform when assessed after stimulation of uptake by glucose or insulin. As illustrated in Figure 4, enhanced FDG uptake in chronically stunned pigs at 2 months and precedes the development of reductions in resting flow. Clinical data regarding fasting FDG uptake in chronically stunned myocardium are limited. Although it was not the primary focus of their report, Camici et al. found no regional variations in fasting FDG uptake before exercise (fractional FDG uptake, 0.11 ± 0.03 in coronary patients with regional dysfunction and normal flow versus 0.07 ± 0.04 in control subjects, P=NS). These observations support the notion that viable, chronically dysfunctional myocardium may be associated with normal FDG uptake, as we found in pigs instrumented for 1 month.

Although the factors responsible for the temporal variability in FDG uptake in the present study are unclear, the uniform distribution of FDG at 1 month suggests that the
myocardial adaptations that lead to an increase in glucose utilization are not simply related to resting dysfunction. One possibility is that there is a temporal lag in the development of increased FDG uptake, with stunning preceding changes in glucose transport. Alternatively, changes in FDG uptake may be related to the physiological significance of a coronary stenosis. Huang et al22 found fasting FDG uptake to increase with increasing stenosis severity in patients with chronic coronary artery disease. Because transmural FDG uptake is inversely related to adenosine perfusion (Figure 4), the propensity for a region to develop ischemia may determine whether FDG uptake is increased in the fasting state. Frequent episodes of ischemia could result in repetitive depletion of glycogen stores, and increased FDG may reflect glycogen repletion. This is also consistent with the inverse relation between fasting FDG uptake and regional coronary flow reserve that we previously demonstrated in hibernating myocardium.4 There could also be chronic alterations in the expression of myocardial glucose transporters induced in response to repetitive ischemia. Finally, there may be a regional variation in the lumped constant for FDG that may not reflect a true increase in glucose uptake.

Methodological Limitations
Contrast ventriculography is widely used in the evaluation of patients with coronary disease, but more sensitive techniques, such as wall thickening, would quantify the extent to which flow and function were dissociated. Although this would not have affected our conclusions regarding the presence of stunned myocardium at 1 and 2 months, we cannot determine whether function was disproportionately reduced compared with flow in hibernating pigs or whether there is superimposed myocardial stunning.

Ischemia23 and pharmacological stimuli24 rapidly alter myocardial glucose uptake. Our previous study in similarly instrumented animals with hibernating myocardium showed nearly identical measurements of FDG uptake by ex vivo counting following a similar pharmacological protocol and in vivo PET imaging without preceding interventions.4 This agreement supports the notion that 1 hour was sufficient for any effect of adenosine or epinephrine on glucose uptake to return to baseline before FDG administration.

Clinical Implications
There is controversy regarding the pathophysiological basis of viable, chronically dysfunctional myocardium in patients with coronary disease. Whereas dysfunction is a consequence of reversible ischemia in both chronically stunned and hibernating myocardium, our results demonstrate a progression in abnormalities that is consistent with a temporal transition from stunning to hibernation. This may be the result of progressive reductions in coronary flow reserve (ie, the propensity of a region to be subjected to ischemia). Alternatively, the transition from stunning to hibernation may require time and thus be dependent on the cumulative effects of reversible ischemia. This may explain the variability of resting flow measurements reported in experimental and clinical studies, in which coronary flow reserve is not always quantified and the chronicity of reduced function is largely unknown. Finally, enhanced fasting FDG uptake is not specific for hibernation, nor is it systematically present in chronically stunned myocardium. Nevertheless, the presence of enhanced FDG uptake may identify viable regions with the lowest flow reserve, in which revascularization to ameliorate ischemia may be most beneficial.

Acknowledgments
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References


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