The Histology of Viable and Hibernating Myocardium in Relation to Imaging Characteristics

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OBJECTIVES
This study characterizes the histology of myocardium predicted to be hibernating using three different imaging techniques to explain the discordance among them.

BACKGROUND
Both radionuclide and functional imaging techniques were used to assess myocardial hibernation. The former have high sensitivity and the latter high specificity for predicting functional recovery.

METHODS
Nineteen patients underwent thallium-201 and 99m-technetium tetrofosmin myocardial perfusion imaging, and dobutamine magnetic resonance imaging (MRI), prior to coronary bypass grafting. Criteria for predicted hibernation for each technique were defined before operation. Postoperative criteria for scar and true hibernation were also defined. Biopsies were analyzed for myocyte volume fraction (MVF), glycogen deposition and pathologic cell features.

RESULTS
Thallium was most sensitive in predicting hibernation (88%) and MRI most specific (84%); and, although there was good agreement between thallium and tetrofosmin (85%), agreement between MRI and thallium (59%) or tetrofosmin (59%) was poor. For each technique, MVF was higher in segments predicted to be hibernating rather than scar (p < 0.05). The MVF was higher where both thallium and MRI predicted hibernation (0.77 ± 0.07) than in segments predicted by thallium alone (0.69 ± 0.13, p < 0.05). Proven hibernating segments had a higher MVF than scar (0.72 ± 0.11 vs. 0.6 ± 0.26, p < 0.05).

CONCLUSIONS
Preservation of myocyte fraction is an important determinant of functional recovery after revascularization. A higher myocyte fraction is required to maintain contractile reserve than to achieve significant tracer uptake. This explains the higher sensitivity of radionuclide imaging compared with dobutamine MRI in the identification of myocardial hibernation. (J Am Coll Cardiol 2002;39:428–35) © 2002 by the American College of Cardiology

Viable myocardium is myocardium that contains recognizable myocytes and is “alive.” Hibernating myocardium is viable, potentially ischemic and dysfunctional muscle that has the capacity to recover function after revascularization. Several imaging techniques have been used to characterize myocardium as viable and/or hibernating, and to make the clinically relevant distinction from infarcted tissue. The techniques rely upon different myocardial properties and hence they do not necessarily give the same results. Uptake of thallium-201 (thallium) or 99m-technetium-tetrofosmin (tetrofosmin) is a marker of integrity of the myocyte membrane (modulated by myocardial perfusion); uptake of 18F-fluorodeoxyglucose (FDG) is a marker of glucose metabolism (1), and functional imaging techniques such as stress echocardiography (2) or magnetic resonance imaging (MRI) (3) are markers of contractile reserve. None of the techniques, however, are perfectly accurate for the detection of hibernating myocardium, and discordance among the techniques is well recognized (4). Almost 30 years ago the equivalence of myocardial akinesia and infarction was first challenged by Rees et al. (5,6). More recent studies have suggested that hibernating myocardium contains a higher proportion of myocytes than myocardium that does not recover function after revascularization, and that there is glycogen deposition and loss of contractile protein (7–9). We have previously studied the comparative accuracies of three imaging techniques in identifying myocardial hibernation and found discordance between the radionuclide and functional methods (3). The aim of this study was to examine the histology of hibernating myocardium and to see whether these characteristics could explain differences between imaging techniques when used to detect viable and hibernating myocardium.

METHODS
Patients. Nineteen patients with ischemic left ventricular dysfunction were studied (18 men, median age 62 years, range 40 to 71 years). All patients gave informed consent, and the work was approved by our institution’s ethical committee. Patients were recruited from the waiting list for coronary bypass surgery. The principal inclusion criteria were left ventricular ejection fraction (LVEF) <35% and dyspnea as a major symptom. All had three-vessel coronary disease (defined as >70% luminal diameter stenosis) with evidence of inducible ischemia, and all had previous myo-
cardiac infarction (MI). Patients with significant valve disease, uncontrolled atrial fibrillation, permanent pacemaker or previous coronary bypass surgery were excluded.

**Imaging.** Preoperative imaging was performed within three months of surgery and included myocardial perfusion imaging (MPI) using thallium and tetrofosmin, and cine MRI at rest and during low-dose infusion of dobutamine. No patient underwent revascularization or sustained an MI between preoperative imaging and surgery. Postoperative imaging was performed three to six months after surgery and included thallium MPI and coronary arteriography to assess the success of revascularization, and resting MRI to assess changes in regional myocardial function.

**MRI.** We performed an MRI using a 1.5 Tesla system (Picker International, Ohio). Preoperative images were acquired at rest and during a peripheral infusion of dobutamine at 5 and 10 μg/kg/min, while postoperative images were acquired at rest. Cine gradient echo images were acquired in the vertical and horizontal long-axis planes and in basal and apical short-axis planes as previously described (3).

**Thallium scintigraphy.** Stress was performed using adenosine infused at 140 μg/kg per min for 6 min combined with bicycle exercise in increments to 75 W if tolerated. Eighty megabecquerels (MBq) of thallium was injected at 4 min, and images were acquired immediately afterwards (stress images) and after 4-h redistribution (redistribution images). A separate-day resting study was also performed with 80 MBq of thallium injected at rest followed by immediate (early rest) and 4-h delayed imaging (late rest). Tomograms were reconstructed in the vertical and horizontal long-axis and short-axis planes (3).

**Tetrofosmin scintigraphy.** Stress was performed in an identical manner to that used for thallium MPI. 250 MBq of tetrofosmin was given during stress, and the images were acquired 30 min later without an intervening fatty meal. Four hours after the stress injection, 750 MBq of tetrofosmin was injected at rest and images acquired after a 30-min delay. Image processing was identical to that described for thallium MPI.

**Image analysis.** Magnetic resonance images were analyzed by two experienced observers independently. A nine-segment model of the left ventricle was used with basal and apical parts of the septum, anterior, lateral and inferior walls, together with the apex. Endocardial motion was scored visually using a five-point scale and systolic myocardial thickening using a four-point scale (Table 1). Left ventricular volumes were calculated at end-diastole and end-systole using a biplane area-length technique (10). Stroke volume and ejection fraction were derived. Radioluclide images were analyzed in a similar fashion by two observers unaware of MRI findings. Tracer uptake was scored using a five-point scale (Table 1) where the grades corresponded approximately to uptake of 100% to 70%, 70% to 50%, 50% to 30%, 30% to 0% of maximum, but taking into account normal variations such as inferior attenuation.

**Postoperative imaging.** Postoperative assessment included stress-redistribution thallium MPI, resting cine MRI, and coronary angiography. One week before the postoperative studies, medication was adjusted to be the same as for the preoperative studies. Coronary arteriograms were analyzed by a single observer, unaware of the other imaging findings. Coronary territories were assigned as anterior wall, septum and apex to the left anterior descending artery, lateral wall to the circumflex artery and inferior wall to the right coronary artery (or to the circumflex artery depending upon dominance). Four segments were excluded from analysis because of inadequate bypass (assessed angiographically or from persistent ischemia) or because of perioperative myocardial damage (assessed from the postoperative thallium score).

**Definitions.**
- **Normally perfused myocardium:** preoperative resting function grade ≥2 and stress thallium uptake grade ≥3 without reversibility.
- **Inducible ischemia:** preoperative resting function grade ≥2 and improvement of thallium uptake between stress and late-rest imaging of grade ≥1.
- **Myocardial scar:** preoperative resting function grade ≤1 and no improvement after surgery.
- **True hibernation:** preoperative resting function grade ≤1 and postoperative improvement of at least one grade.
- **Thallium viable:** preoperative thallium uptake in late-rest images grade ≥2.

| Table 1. Semi-Quantitative Scoring Used to Assess Function From Resting and Dobutamine Magnetic Resonance Imaging, and Uptake of Both Thallium and Tetrofosmin |
|---|---|---|---|---|---|---|
|  | −1 | 0 | 1 | 2 | 3 | 4 |
| Endocardial motion | Paradoxical | Akiness | Severe hypokinesis | Mild hypokinesis | Normal |
| Tracer uptake | Absent | Severely reduced | Moderately reduced | Mildly reduced | Normal |

Scores were assigned to each of nine myocardial segments.
Thallium-predicted hibernation: thallium viable and preoperative resting function grade ≤1.

Tetrofosmin viable: preoperative tetrofosmin uptake in rest images grade ≥2.

Tetrofosmin-predicted hibernation: tetrofosmin viable and preoperative resting function grade ≤1.

MRI-predicted hibernation: resting MRI functional grade ≤1, improving by ≥1 grades with dobutamine infusion.

Histology. Biopsies through the full thickness of the myocardium were taken during surgery using a metal cork borer of 2 mm internal diameter. Where practical, biopsies were taken from segments with normal perfusion, inducible ischemia, hibernation and myocardial scar as determined by preoperative imaging. It was not always possible to biopsy all of the tissue types in each patient. The samples were divided into epicardial and endocardial regions and immediately fixed using Zamboni’s fixative. Wax-embedded sections were stained using hematoxylin and eosin, periodic acid–Schiff reagent (PAS) and phosphotungstic acid. Samples were also processed for thin-section transmission electron microscopy and high-resolution light microscopy after fixing with 2.5% glutaraldehyde in 0.1 mol/l sodium cacodylate buffer at pH 7.3 for 2 h, followed by 2% osmium tetroxide for 2 h and dehydration. En bloc staining was performed with saturated uranyl acetate in 50% ethanol, and samples were embedded in epoxy resin. Ultrathin sections from the same blocks were examined by light microscopy after staining with 1% toluidine blue in a solution of 1% borax and 50% ethanol.

Myocyte structure was initially assessed from the semi-thin sections and then defined in more detail in directed ultrathin sections and by electron microscopy. The frequency of abnormal myocytes was assessed semi-quantitatively by two independent observers blinded to the origin of the specimen. Abnormal myocytes had reduced myofibrillar content, numerous rounded and small mitochondria and irregular nuclear envelopes (Figs. 1 and 2). Glycogen accumulation was analyzed and scored separately. A five-point scale was used: 0 = no pathological myocytes, 1 = 1% to 25% of pathological myocytes, 2 = 26% to 50%, 3 = 51% to 74% and 4 = >75% of pathological myocytes. A similar five-point scoring system was used for myocyte glycogen content assessed from the PAS-stained sections.

Morphometric analysis was used to assess the tissue fractions of myocytes, replacement and interstitial fibrous tissue, interstitial cells and blood vessels, using an 11×11 graticule. To overcome bias caused by different orientations of the myocytes in each sample, measurements from five randomly selected fields using two graticule orientations were averaged. Thereafter, values for the epicardial and endocardial regions for each sample were averaged to give a mean tissue fraction for the biopsy as a whole.

Statistics. Summary data are expressed as mean ± SD. Dependence between segmental measurements was tested using Pearson’s correlation coefficient. Although some significant correlations existed between tracer uptake scores in segments perfused by the same coronary artery, no significant correlations were seen between segmental measurements of myocyte volume fraction. Thus, independence between these measurements was assumed. Multiple regression analysis was used to compare myocyte volume fraction in each of the four myocardial categories (normally perfused, reversible ischemia, true hibernation and true scar) (11). True scar was taken as the reference category, and dummy variables were created to compare this with each of the other categories.

Figure 1. Thin-section electron micrograph illustrating typical features of a “pathological” myocyte, with large areas of cytoplasm (c) devoid of contractile proteins and full of glycogen, numerous small mitochondria (m) and an irregularly shaped nucleus (n). Certain sarcomeres are in a hypercontracted state (contraction bands [b]). Bar = 10 μm.
three. Sensitivity and specificity were calculated using conventional formulae, and these were compared using the McNemar test. Agreement between observers for categorical scoring was assessed using the unweighted kappa statistic. A p value of $<0.05$ was considered statistically significant. Analyses were performed using Stata version 6.0 (Stata Corp., College Station, Texas).

RESULTS

Clinical outcome. One patient died perioperatively, one died after operation and before follow-up and one patient defaulted from follow-up. Thus, 16 patients completed the full protocol. Mean LVEF increased from $23.0 \pm 8.1\%$ to $28.7 \pm 10.5\%$ ($p < 0.05$), and mean New York Heart Association (NYHA) functional class improved from $2.7 \pm 0.6$ to $1.5 \pm 0.7$. In patients who were followed, 38 of 59 biopsied segments were severely hypokinetic (functional grade 1) or worse before surgery, and 24 of these segments improved function following revascularization (truly hibernating). One segment appeared to have infarcted perioperatively and was excluded from analysis. Thallium MPI was the most sensitive technique for predicting hibernation ($88\%$) but was the least specific ($57\%$). Dobutamine MRI was the least sensitive ($46\%$) but the most specific ($84\%$) ($p < 0.05$). Tetrofosmin had intermediate sensitivity ($79\%$) and specificity ($69\%$). There was good agreement between thallium and tetrofosmin for the identification of viable but severely hypokinetic segments (33/38, 86%), but the agreement was not as good between thallium and dobutamine MRI (23/38, 60%) or between tetrofosmin and MRI (23/38, 60%).

Histology. Fifty-nine biopsies were obtained and 58 were analyzed. There was significant histologic heterogeneity within each biopsy, but in general each of the four tissue types (normal, ischemic, hibernating, scar) had different degrees of fibrosis, manifested as both interstitial fibrosis and separate islands of connective tissue representing local infarction. Tissue classified as scar had extensive replacement of myocytes by fibrous tissue, and in some areas of full thickness infarction fibrous tissue occupied most of the biopsy. On light microscopy, the appearance of the myocytes varied from normal to pathologic, with severe depletion of myofibrillar proteins on toluidine blue and phosphotungstic acid hematoxylin staining. These cells were PAS positive, suggesting glycogen accumulation. On transmission electron microscopy, the pathologic cells had consistent features of reduced myofibrillar content, glycogen accumulation, numerous rounded and small mitochondria and irregular nuclear envelopes. The changes primarily affected the perinuclear area, although complete depletion of the contractile apparatus within a given sectional view was occasionally seen. Partially affected cells had preservation of sub-sarcolemmal contractile proteins and partial preservation of Z-band structure in the actin/myosin free zones. These features were seen in all four types of tissue (including the normally perfused myocardium), which may reflect the very poor ventricular function of this group of patients.

Table 2 shows the histologic characteristics of myocardial segments according to tissue type. As defined above, segments with normal perfusion and inducible ischemia were characterized by preoperative thallium MPI and had preserved resting wall motion by MRI; segments with true hibernation and scar were classified by pre- and postopera-

Figure 2. Histologic sections stained with phosphotungstic acid/hematoxylin. (A) Image comparable to the electron micrograph in Figure 1 and demonstrating light microscopic appearance of loss of myocyte contractile apparatus (contractile proteins stain dark purple; most cells demonstrate cytoplasm devoid of protein [c]). (B) Nonrecovering (infarcted) segment again showing abnormal myocytes but with a high fibrous tissue content (f). (C) Hibernating tissue again showing a high proportion of myocytes depleted in contractile protein, but with relatively low volume fraction of fibrous tissue compared to B.
Table 2. Histologic Characteristics of Myocardial Segments According to Tissue Type (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Normally Perfused (n = 7)</th>
<th>Inducible Ischemia (n = 7)</th>
<th>True Hibernation (n = 24)</th>
<th>True Scar (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte fraction</td>
<td>0.75 ± 0.11†</td>
<td>0.75 ± 0.11†‡</td>
<td>0.72 ± 0.11*</td>
<td>0.60 ± 0.26‡‡</td>
</tr>
<tr>
<td>Mean glycogen deposition score</td>
<td>0.8 ± 1.0</td>
<td>1.5 ± 0.8</td>
<td>1.1 ± 0.9</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Mean pathologic cell score</td>
<td>1.4 ± 1.0</td>
<td>1.5 ± 0.9</td>
<td>1.5 ± 1.1</td>
<td>1.1 ± 0.9</td>
</tr>
</tbody>
</table>

Table 3. Histologic Characteristics of Segments Predicted to Be Hibernating or Scarred Using Each of the Three Preoperative Imaging Techniques

<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Predicted Hibernating</th>
<th>Scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thallium</td>
<td>(n = 31)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Myocyte fraction</td>
<td>0.75 ± 0.15*</td>
<td>0.57 ± 0.25*</td>
</tr>
<tr>
<td>Glycogen deposition score</td>
<td>0.9 ± 0.8</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>Pathologic cell score</td>
<td>1.6 ± 1.0</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>Tetrofosmin</td>
<td>(n = 26)</td>
<td>(n = 18)</td>
</tr>
<tr>
<td>Myocyte fraction</td>
<td>0.74 ± 0.12*</td>
<td>0.62 ± 0.24*</td>
</tr>
<tr>
<td>Glycogen deposition score</td>
<td>1.0 ± 0.9</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>Pathologic cell score</td>
<td>1.6 ± 1.0</td>
<td>1.3 ± 0.9</td>
</tr>
<tr>
<td>MRI</td>
<td>(n = 16)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Myocyte fraction</td>
<td>0.78 ± 0.08*</td>
<td>0.64 ± 0.21*</td>
</tr>
<tr>
<td>Glycogen deposition score</td>
<td>1.0 ± 0.8</td>
<td>1.1 ± 1.0</td>
</tr>
<tr>
<td>Pathologic cell score</td>
<td>1.8 ± 1.1</td>
<td>1.3 ± 0.9</td>
</tr>
</tbody>
</table>

For all three imaging techniques, myocyte volume fraction was higher in the segments predicted to be hibernating rather than scar.

*p < 0.05.
MRI = magnetic resonance imaging.

tive resting function. Hibernating segments contained a higher fraction of myocytes than scar and a similar fraction compared with segments with preserved function. Glycogen deposition and pathologic changes including myofibril loss did not differ among groups. The presence of ischemia did not affect the histologic characteristics of segments with preserved function.

Imaging and structure. There was good agreement between observers for scoring of tracer uptake (total agreement 75%, kappa 0.79) and moderate agreement for scoring of MRI wall motion (66%, kappa 0.59) and thickening (59%, kappa 0.50). There was a relationship between preoperative resting function and myocyte content. Mean myocyte fraction in segments with function grade 2 or 3 (normal or mild hypokinesia) was 0.75 ± 0.11, grade 1 (severe hypokinesia) 0.74 ± 0.09, and grade 0 or −1 (akinesis or dyskinesia) was 0.65 ± 0.25 (p = 0.08).

Table 3 shows the histologic characteristics in segments predicted by each of the three imaging techniques to be hibernating or scarred. It must be emphasized that these are predicted by pre- and postoperative resting function. Myocyte fraction was significantly higher in segments with true hibernation as defined previously compared with segments with preserved function. Segments predicted to be hibernating had higher myocyte fraction than those predicted to be scarred, and this was statistically significant for thallium, tetrofosmin and MRI. Glycogen deposition did not differ between predicted hibernating and predicted scarred segments.

Figure 3 shows the mean myocyte fraction in segments predicted by each of the imaging techniques to be hibernating compared with true hibernation assessed by postoperative recovery of function. For all three techniques the myocyte fraction was significantly higher in segments correctly identified as hibernating (true positive) than in segments correctly identified as scar (true negative). Segments that were predicted to be hibernating but did not recover function (false positive) had a higher myocyte fraction than scar, whereas segments that were predicted to be scar which did recover function (false negative) had intermediate myocyte content.

Figure 4 shows that myocyte fraction in segments predicted to be hibernating by both thallium and MRI (0.77 ± 0.07) was significantly higher than in those predicted by thallium alone (0.69 ± 0.13) (p < 0.05) and was higher than in those predicted to be scar by both techniques (0.55 ± 0.27) (p = 0.06). This implies that a higher myocyte fraction is required to maintain contractile reserve than to achieve significant uptake of tracer, and this most likely explains the greater sensitivity of thallium imaging for the detection of viable myocardium than dobutamine MRI or echocardiography. In segments with true hibernation there was a relationship between myocyte fraction and the degree of improvement in function after surgery. Thus, myocyte fraction in segments improving by ≥2 grades was 0.83 ± 0.03 compared with 0.69 ± 0.11 in those improving by one grade (p = 0.1).

DISCUSSION

Accuracy of imaging for predicting hibernation. We have confirmed previous findings that radionuclide techniques that assess the presence of viable myocytes directly are more sensitive than functional techniques that require contractile reserve for predicting recovery after revascularization (3). In contrast, functional techniques are more specific. We have also shown relatively good agreement between thallium and tetrofosmin for characterizing myocardial segments. This lack of specificity may not be a disadvantage because recovery of contractile function is only one of several mechanisms by which outcome in patients with ischemic
left ventricular function might benefit from revascularization. Abolition of ischemia may protect viable myocardium from ischemic arrhythmias, from stretching and remodeling, and from further loss of myocardium from apoptosis and necrosis. Our findings are similar to those of Perrone-Filardi et al. (4) who also reported greater sensitivity of thallium MPI than dobutamine echocardiography for predicting hibernation, with 84% agreement between the techniques in hypokinetic segments but only 43% agreement in akinetic segments. Panza et al. (12) have also shown that contractile reserve is more likely to be present in regions where thallium uptake is preserved than where it is reduced. Myocyte content. It seems likely that myocyte content is an important determinant of both resting function and of the likelihood of hibernating myocardium to recover after revascularization. We have certainly demonstrated a relationship between myocyte content and resting function. We have also shown that hibernating myocardium has a myocyte content similar to normally perfused or ischemic myocardium (which contracts well) but significantly greater than areas of scar. In addition, we have shown that the degree of functional improvement of hibernating myocardium following surgery bears some relationship to the magnitude of the myocyte content. These findings extend those of previous studies.

For instance, Maes et al. (9) showed that areas of preserved FDG metabolism but decreased resting perfusion (positron emission tomography [PET] mismatch, indicating hibernation) contained significantly less fibrous tissue (11%) than areas with both reduced FDG metabolism and perfusion (PET match, indicating scar) (35%). Dakik et al. (13) also reported less fibrosis (7.4%) in areas of hibernation compared with scar (31%). Assuming that myocyte fraction = 1 − fibrous fraction, our patients had higher degrees of fibrosis, but they also had significantly greater impairment of left ventricular function, with mean LVEF of 23%, compared with over 40% in other studies (8,12).

Of particular interest are the segments predicted to be hibernating by thallium but without contractile reserve by dobutamine MRI. We found that these segments had mean myocyte fraction of 0.69, which was significantly lower than
segments predicted to be hibernating by both techniques. Thus, it appears that a greater myocyte content is required to preserve contractile function than to achieve significant uptake of thallium, and this explains the greater sensitivity of this radionuclide technique for the prediction of hibernation. The mean myocyte content of 0.60 in areas of scar is higher than might be anticipated, but this is most likely because very thin areas were not biopsied so as to reduce the likelihood of complications. Thirteen segments that were truly hibernating but had no contractile reserve had a mean myocyte fraction of 0.69 and, therefore, it appears that the threshold for preserved contractile function is at least 0.7. It follows that very few segments would be expected to have contractile reserve in the absence of significant thallium uptake, and we identified only a single such segment.

We have previously shown (3) thallium to be more sensitive than tetrofosmin for detecting hibernation, but we now believe that our study may have compromised tetrofosmin in the detection of viable myocardium because the resting injection was given without nitrate cover. Because tetrofosmin does not redistribute after injection, viability may be underestimated in areas with reduced perfusion at rest. Other studies have demonstrated that this effect can be overcome by nitrates both for tetrofosmin (14) and for 99m-technetium 2-methoxyisobutylisonitrile (15).

Histopathology of hibernation. We have identified pathologic cells with reduced myofibril content, glycogen deposition, irregular nuclear envelopes and small mitochondria in all tissue subtypes, including myocardium with normal function and perfusion. Maes et al. (9) reported similar glycogen deposition in scar (24%) and in regions of PET mismatch (25%), although less deposition in normal tissue (12%), but in this study glycogen deposition and other changes were unrelated to the class of myocardium. Thus, in contrast with previous studies (16) we cannot confirm that the changes are specific to hibernation.

It has been suggested that the pathologic changes in myocytes are related to the duration of hibernation and that recovery depends upon resolution of the changes (17). Although myocardial fibrosis is unlikely to be reversible, restoration of myofibril content and regression of glycogen accumulation could be. Although it is possible that the differences between this study and others is related to more advanced disease in our patients, it is also possible that the changes are not the sole explanation for reduced function. For instance, reduced sensitivity of the contractile apparatus to $\text{Ca}^{2+}$ or a reduced storage capacity for $\text{Ca}^{2+}$ might be implicated (18,19). We have recently demonstrated reduced numbers and size of gap junctions in hibernating myocardium, with these findings being relatively specific for hibernation, which could be a further explanation for reduced function in hibernation (20). Thus, none of the imaging techniques currently available are able to assess all the changes related to hibernation, and it is unlikely that any can approach perfect accuracy for characterization of myocardium in ischemic left ventricular dysfunction.

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REFERENCES


