Relation of the Contractile Reserve of Hibernating Myocardium to Myocardial Structure in Humans

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Background—Although dobutamine echocardiography (DE) is widely used to assess myocardial viability in humans, little is known about the relation between contractile reserve and myocardial structure.

Methods and Results—We evaluated 20 patients with coronary disease (64 ± 13 years old, ejection fraction 28 ± 7.5%) with DE (up to 40 μg · kg⁻¹ · min⁻¹), rest-redistribution ²⁰¹TI single photon emission CT, and quantitative angiography before bypass surgery. During surgery, patients underwent transmural myocardial biopsies (n=37) guided by transesophageal echocardiography to determine the extent of interstitial fibrosis and intracellular and interstitial proteins by histopathology and immunohistochemistry. Among the 37 segments biopsied, 16 recovered function as assessed 2 to 3 months later. Segments with postoperative functional recovery had more wall thickening at low-dose DE (28% versus 3%, P<0.001), higher thallium uptake (69% versus 48%, P=0.03), and less interstitial fibrosis (2% versus 28%, P<0.001). Quantitative angiographic parameters did not predict recovery of function. Segments with DE viability (contractile reserve and/or ischemia) had less fibrosis (2.7% versus 28%, P<0.001), less vimentin and fibronectin (both P<0.01), more glycogen (P=0.016), and higher thallium uptake (64% versus 35.5%, P<0.05) than those without viability. Viable segments by both DE and thallium had less fibrosis (1%) than those viable by 1 of the 2 techniques (9%) or not viable by both (28%, P=0.005). Thickening at low-dose DE correlated well with the extent of interstitial fibrosis (r=−0.83, P<0.01).

Conclusions—Contractile reserve during DE correlates inversely with the extent of interstitial fibrosis and the amount of fibronectin and vimentin and directly with rest-redistribution thallium uptake. (Circulation. 1999;100:490-496.)

Key Words: hibernation ■ echocardiography ■ pathology ■ scintigraphy

The term “hibernating myocardium” refers to a state of persistent ventricular dysfunction in the presence of coronary artery disease that may be reversed by revascularization. This may be an adaptive mechanism that preserves myocardial structural integrity and minimizes necrosis. However, the majority of patients have a mixture of necrotic and viable myocardium. The proportion of viable myocardium is a critical factor in determining the likelihood of functional recovery after successful revascularization. It is also susceptible to ischemia, dysrhythmia, and infarction. Several radionuclide and echocardiographic techniques have recently been evaluated for the detection of myocardial hibernation. ²⁰¹TI scintigraphy¹–⁴ is usually used with a rest-redistribution strategy. In fact, a significant correlation was noted between ²⁰¹TI uptake and interstitial fibrosis.³ Dobutamine echocardiography (DE) has emerged as a technique capable of predicting functional recovery after revascularization.⁶–¹¹ Although the majority of segments that recover function frequently exhibit augmented contractility in response to DE, some do not recover after successful revascularization. There are few data relating the contractile reserve of dysfunctional myocardium to myocardial structure. Therefore, the purpose of this study was to evaluate the relationship between the extent of viable myocardium by histopathology, resting perfusion as determined by rest-redistribution ²⁰¹TI, and the different contractile responses exhibited during DE. In addition, we investigated the relation between myocardial thickening during low-dose dobutamine and intracellular proteins as a measure of the contractile capacity and cellular degeneration. Vimentin and fibronectin in the interstitial space were evaluated as a measure of the replacement fibrosis and the accumulation of fibroblasts due to myocyte loss.

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Methods
The study enrolled 20 patients scheduled for coronary artery bypass surgery who were not included before (in previous studies) and who had stable ischemic heart disease and resting left ventricular dysynchrony in the distribution of ≥1 coronary arteries with ≥70% stenosis. The decision to operate was made before noninvasive testing. Test results did not change the management of the patients. 201TI single photon emission CT (SPECT) and DE were performed 2 to 5 days before bypass surgery. During surgery, transmural myocardial biopsies were obtained from the dysfunctional myocardial segments, guided by transesophageal echocardiography (TEE). Patients underwent 2D echocardiography 2 to 3 months after surgery to evaluate changes in left ventricular function.

Echocardiographic Studies
Imaging was performed in the standard parasternal and apical views with the patient in the left lateral position (Hewlett Packard Sonos 2500, 2.5- or 3.5-MHz transducer). Short-axis tomograms were acquired at the level of the mitral valve, papillary muscles, and distal third of the left ventricle. Regional function was assessed according to the 16-segment model of the American Society of Echocardiography and graded from 1 to 5: 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesia, and 5 = dyskinesia. In addition, myocardial thickening in the dysfunctional segments was calculated from the parasternal short-axis views as (end-systolic thickness)−(end-diastolic thickness)/(end-diastolic thickness)/end-diastolic thickness. Measurements were performed offline in the segments with abnormal baseline function in triplicate and averaged by use of Digiosics EC500. Ejection fraction (EF) was quantified with the multiple-diameter method.12 The initial, follow-up, and DE studies were interpreted without knowledge of the scintigraphic and histopathological data. Regional function recovery was defined by an improvement of ≥2 grades based on previous work of reproducibility in our laboratory.4 To match myocardial segments with coronary distribution, the anterior wall, anterior septum, and apex were assigned to the left anterior descending coronary artery (LAD), the lateral wall to the circumflex artery, and the inferoposterior wall and inferior septum to the right coronary artery.

Dobutamine Echocardiography
Dobutamine infusion was started at 2.5 μg·kg−1·min−1 and increased at 3-minute intervals to 5, 7.5, 10, 20, 30, and 40 μg·kg−1·min−1. Images at baseline, 5 and 7.5 μg·kg−1·min−1, and peak dobutamine were digitized online in a quad-screen format to provide the most optimal assessment of viability.4 The responses of dysfunctional segments to dobutamine were classified as biphasic (improvement at low dose with worsening at high dose), worsening, no change, and sustained improvement (increased thickening without change at low dose with worsening at high dose). Any response during DE was considered indicative of viability.

Rest-Redistribution 201TI
Rest and 4-hour redistribution 201TI SPECT scans were performed after intravenous administration of 3 mCi of 201TI before surgery. A large-field-of-view rotating gamma camera with a high-resolution parallel-hole collimator was used. Thirty-two frames were acquired over a 180° arc (45° left posterior oblique to 45° left anterior oblique). The reconstructed images were oriented in the standard short axis, horizontal long axis, and vertical long axis for interpretation and quantification of 201TI uptake13 by experienced nuclear cardiologists unaware of all other data. Computerized polar maps of the 3-dimensional myocardial radioactivity were generated. The 16-segment model comparable to that for echocardiography was used. Myocardial 201TI activity was determined with a region of interest 40×40 pixels (matrix 128×128). The activity in each segment was normalized to the segment with the highest uptake. A maximal uptake of ≥60% at rest or redistribution was considered indicative of viability, as previously shown from our laboratory.13 Thallium defects were classified as reversible defects (≥60% uptake after redistribution, with ≥10% increase from rest to redistribution), fixed mild to moderate defects (≥60% uptake but no redistribution), and nonviable defects (<60%).

Quantitative Coronary Angiography
Selective coronary angiography of the right and left coronary arteries in multiple views was performed with the Judkins technique. Angiograms were analyzed by an automated edge-detection method using Cardiovascular and Angiographic Analysis System. The luminal diameter of the stenosed artery in the projection showing maximal severity, along with the adjacent normal reference segments, were measured at end diastole. Calibration was achieved by use of the Judkins catheter size. Stenosis was expressed as the percent reduction of the internal luminal diameter in relation to the normal reference segment (not considering poststenotic dilatation, coronary aneurysms, and ectatic segments). The length of the stenotic segment was also measured.

Transmural Left Ventricular Biopsies, Morphometric Analysis, and Immunohistochemistry
Transmural myocardial biopsies were obtained with a 20-mm, 14-gauge Tru-cut biopsy needle at the time of surgery, before cardioplegia. TEE was used to direct the biopsy to the selected segments, with 2 biopsies acquired per patient except for 3 patients in whom only 1 biopsy was obtained. For dysfunctional segments in the LAD distribution, biopsies were acquired between the LAD and its first or second diagonal branch, depending on the location of the stenosis and the position of the abnormal segment. For the right coronary artery distribution, biopsies were acquired from the inferior wall, and for the circumflex artery, they were obtained from the lateral wall.

The specimens were fixed in 10% buffered formalin, processed through a series of ethanol solutions, embedded in paraffin, and cut into sections (3 μm). The sections were stained with hematoxylin–eosin, Mallory’s trichrome stain (for the extent of fibrosis, Figure 1), and periodic acid–Schiff stain (for the amount of glycogen, Figure 2). Fibrosis, which stains purple with the trichrome stain, was distinguished from the pink myocardium and quantified with a computer image analysis technique using the Optima Bioscan software.14 It was then expressed as percent of the total biopsied section. Immunohistochemistry was performed for detection and semiquantification of intracellular proteins (desmin, actin), vimentin, and fibronectin. The proteins and glycogen content were semiquantified as 0 = absent, 1 = present sparingly and focally, 2 = present in up to half of the specimen, and 3 = present in more than half of the specimen.

Statistics
Continuous data are presented as median (first and third quartiles) and mean±SD where appropriate. ANOVA and Dunn or Tukey tests were used to compare the pathology data. 201TI uptake, and angiographic variables among the 4 different responses during DE. These methods were also used to compare results among the following 3 groups of segments: group 1 = no viability by both thallium and DE, group 2 = viability by thallium or DE, and group 3 = viability by both thallium and DE. The Mann-Whitney rank sum test or unpaired t test was applied for the comparison of the different echocardiographic, scintigraphic, angiographic, and histopathological variables between viable and nonviable segments as well as between segments with and without functional recovery. Paired t test was used to compare the preoperative and postoperative ejection fraction. Regression analysis was used to correlate thickening (at baseline and during DE) and percent thallium uptake, extent of fibrosis, and postbypass function. Significance was at P<0.05.
Results

The 20 patients (16 men, age 64±13 years, range 36 to 81 years) had a mean EF of 28±7.5% (range 16% to 43%). All but 2 had 3-vessel disease. Fourteen patients had redistribution thallium before surgery. They all had complete revascularization with 2 to 3 grafts per patient, and none developed postoperative ischemic events. Late after surgery, 39 (of 225) dysfunctional segments improved by 2 grades and 15 by 1 grade. Five segments deteriorated by 1 grade, and 1 segment deteriorated by 2 grades. After bypass surgery, a small increase in EF was observed but did not reach statistical significance (28±7.5% versus 31±10%; P=0.3). Although EF did not change in the majority of patients, an increase of ≥8% (range 8% to 24%) was seen in 8 patients. These 8 patients had more viable segments (10±4 versus 6±2; P=0.031).

Relation of Functional Recovery to Interstitial Fibrosis, DE, and Thallium Uptake

Thirty-seven myocardial segments were biopsied: 16 akinetic and 21 severely hypokinetic. Sixteen segments recovered (1 akinetic and 15 severely hypokinetic). Compared with segments that did not recover function, those with recovery had less interstitial fibrosis [2.7% (0% to 7.4%) versus 20% (5.3% to 51.5%), P=0.002] and higher thallium uptake (69±20% versus 49±18%, P=0.002). Furthermore, these segments had more systolic thickening at baseline (18% versus 0%, P=0.003) and in response to low-dose DE (28% versus 3%, P<0.001) compared with those without recovery. All segments that recovered had <17% interstitial fibrosis. In contrast, the majority of segments that did not recover function (17 of 21) had >17% interstitial fibrosis. Reversible thallium defects as well as mild to moderate fixed defects had less interstitial fibrosis than nonviable defects [% fibrosis: 0% (0% to 13.5%) versus 3.2% (0% to 7.5%) versus 49.6% (25.7% to 70.7%), respectively; ANOVA P<0.001, both reversible and fixed mild to moderate defects P<0.05 versus nonviable defects]. End-diastolic wall thickness and quantitative angiographic parameters were not different between segments with and without recovery of function.

In the akinetic segments without recovery (n=15), median percent fibrosis was 24.5% (in 13 of 15 segments, interstitial fibrosis ≥17%). All except 1 of these 15 segments had thallium uptake <60% (exception: 61%). The majority of these segments (11 of 15) had no response to DE. Likewise, hypokinetic segments that did not recover (n=6) had a median percent fibrosis of 17% and a median thallium uptake of 54%.

Figure 1. Top, Transmural myocardial biopsy visualized under low power, stained with trichrome stain from an akinetic anterior wall that did not recover and had no inotropic reserve during DE. Notice subendocardial interstitial fibrosis that extends through roughly half of specimen. Bottom, High-power view of top. F indicates fibrosis; M, myocardium.

Figure 2. Periodic acid–Schiff staining for glycogen shows its accumulation in hibernating myocardium (top arrow, glycogen deposits; bottom arrow, vacuolated myocytes). This specimen is from a hypokinetic lateral wall that recovered and had a sustained response to DE.
Relation of Myocardial Viability by DE to Interstitial Fibrosis and Thallium Uptake

Myocardial segments were classified into 2 groups according to DE: viable (any response to dobutamine, n=23) and nonviable (no response, n=14), regardless of postoperative functional recovery. Viable segments by DE had less interstitial fibrosis [median: 2.7% (0% to 5.9%) versus 28.2% (20% to 62.5%), P<0.001] and higher thallium uptake (64±28% versus 35.5±12.6%, P=0.01). Furthermore, viable segments had thicker myocardium (1.2 versus 0.9 cm, P=0.025) and more thickening at low-dose DE (26% versus 0%, P<0.001). The severity of the stenosis (length, absolute diameter of the stenotic vessel, and percent diameter stenosis) as well as collateral vessels were not different between viable and nonviable segments. Among viable segments by DE, those that recovered had less fibrosis (2.5±4.7% versus 10.3±8.4%, P=0.03).

Nine segments had a biphasic response to DE, 9 sustained response, 5 worsening, and 14 no change in function. The percent interstitial fibrosis was similar among segments with biphasic [2.7% (0% to 4.3%)], sustained [0% (0% to 8.8%)], and worsening [5.7% (0% to 9%)] responses to DE. Segments with no response to DE, however, had significantly more fibrosis [28.2% (20% to 62.5%), P<0.001]. Similarly, percent thallium uptake was higher in segments with biphasic (73±21%), sustained (70±20%), and worsening (67±16.5%) responses than in those with no response (35.5±12.6%, P=0.003). None of the angiographic variables were significantly different among the 4 groups of responses.

On the basis of concordance of viability diagnosis by DE and thallium tomography, 3 groups of segments were defined, as follows: group 1, no viability by both DE and thallium uptake (n=11); group 2, viability by either DE or thallium (n=8); and group 3, viability by both DE and thallium (n=8). Recovery of function did not occur in any group 1 segments but in all group 3 segments. Six of the 8 group 2 segments recovered. Interstitial fibrosis was highest in group 1 (28%) and lowest in group 3 (1%), with group 2 having an intermediate value (9%, ANOVA P=0.005) (Figure 3). Group 2 segments were composed of 5 segments that were viable by thallium only (3 of 5 segments recovered, % fibrosis 13%) and 3 segments that were viable by DE only (all recovered, % fibrosis 4.7%). Group 3 segments had a higher thallium uptake (85%) than group 2 (61%) and group 1 (39%).

Significant correlations were present between the extent of interstitial fibrosis and percent thallium uptake (r=−0.7, P<0.001), thickening at baseline (r=−0.57, P<0.001), and thickening at low-dose DE (nonlinear regression, r=−0.83, r²=0.69, P<0.001) (Figure 4). Likewise, a significant correlation was present between percent thallium uptake and baseline thickening (r=0.64, P=0.001) and thickening at low-dose dobutamine (r=0.76, P=0.001). Similar correlations between DE and percent thallium uptake were present when all segments were analyzed. At follow-up, the thickening fraction was related significantly to the percent of interstitial fibrosis (r=−0.7, P<0.001) (Figure 5), thallium uptake (r=0.47, P=0.025), and thickening at low-dose dobutamine (r=0.76, P=0.001).
**Glycogen Content in Hibernating Myocardium**

The glycogen content was similar in segments with postoperative functional recovery and those without (semiquantitative median score for both was 2, \( P > 0.1 \)). Viable segments by DE, however, had more glycogen than nonviable segments (Table). Segments with biphasic, sustained, and worsening responses during DE had more glycogen than segments with no change in function (scores: 2, 2, and 2.25 versus no change, 1.5, \( P = 0.08 \)).

**Actin, Desmin, Vimentin, and Fibronectin in Hibernating Myocardium**

Vimentin and fibronectin (Figure 6) were present in smaller amounts in segments with postoperative functional recovery compared with segments with unchanged function (vimentin median score: recovery = 0.25 versus no recovery = 1, \( P = 0.02 \); fibronectin: recovery = 0 versus no recovery = 1, \( P = 0.005 \)). Similarly, they were less frequently present in viable segments by DE regardless of postoperative function (Table). Segments with a biphasic, sustained, or worsening response to dobutamine had less vimentin (scores: 0.5, 0.5, and 0.25 versus 2.25, respectively, \( P = 0.002 \) and fibronectin (scores: 0, 0, and 0.25 versus 1.75, respectively, \( P = 0.024 \)) than segments with no response. The accumulation of these proteins paralleled the extent of interstitial fibrosis. With

**Histopathology, Immunohistochemistry, and \( { }^{201} \)TI Uptake in Viable and Nonviable Myocardium by DE**

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<tr>
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<th>Viable</th>
<th>Nonviable</th>
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<tr>
<td>Interstitial fibrosis</td>
<td>2.7% (0%–5.9%)</td>
<td>28.2%* (20%–62.5%)</td>
</tr>
<tr>
<td>Maximum thallium uptake</td>
<td>64±28%</td>
<td>35.5±12.6%*</td>
</tr>
<tr>
<td>Thickening at low-dose DE</td>
<td>26% (20%–30%)</td>
<td>0%* (0%–0.75%)</td>
</tr>
<tr>
<td>Glycogen score</td>
<td>2 (1.8–2.7)</td>
<td>1.5* (0–1.8)</td>
</tr>
<tr>
<td>Vimentin score</td>
<td>0.5 (0–0.65)</td>
<td>2.25* (2–3)</td>
</tr>
<tr>
<td>Fibronectin score</td>
<td>0 (0–0.35)</td>
<td>1.75* (1.5–2.75)</td>
</tr>
<tr>
<td>Actin score</td>
<td>2.5 (2–3)</td>
<td>2.2 (1.5–2.5)</td>
</tr>
<tr>
<td>Desmin score</td>
<td>1.75 (1.5–2.8)</td>
<td>1.7 (1.5–2.5)</td>
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*\( P < 0.05; \) first and third quartiles in parentheses.

>17% fibrosis, the scores were 2 to 3, whereas with less fibrosis, they were ≤2.

The intracellular proteins desmin (Figure 7) and actin had a somewhat higher distribution in viable than in nonviable segments (Table). These trends were also observed in segments with postoperative functional recovery compared with those without (desmin score: 2 versus 1.5, respectively, \( P = 0.07 \); actin score: 3 versus 2.5, respectively, \( P = 0.3 \)). Desmin and actin had a relatively similar distribution among the 4 groups of segments classified by DE response, with both proteins being least present in segments with no response to DE.

**Discussion**

Our study shows that the dobutamine response of viable myocardium in humans is inversely related to the extent of interstitial fibrosis as quantified by tissue morphometry. Vimentin and fibronectin were more frequently present in segments without any response to DE. The increase in these proteins reflects the replacement fibrosis due to myocyte loss, which reduces the contractile reserve. Furthermore, the systolic function after revascularization is dependent on the extent of interstitial fibrosis and can be predicted noninvasively with rest-redistribution \( { }^{201} \)TI uptake and myocardial thickening in response to DE.

**Pathophysiology of Hibernating Myocardium**

Hibernating myocardium, as noted here, is characterized by an intact sarcolemmal function (preserved thallium uptake), an increase in glycogen content, and relatively preserved intracellular proteins. Conversely, myocardial segments without postoperative functional recovery have a predominance of fibrosis and an abundance of vimentin and fibronectin. Hibernating myocardium downregulates its function in adaptation to the reduced flow reserve\textsuperscript{15,16}; some segments become hypokinetic and others akinetic, with a relatively weak correlation of baseline function to the extent of interstitial fibrosis. This highlights the important role of DE and thallium scintigraphy in these
patients. Depending on the amount of viable muscle mass, these segments may have an inotropic response to dobutamine. This is modulated by the complex interaction between coronary flow reserve, increased oxygen demand, and cellular function. We and others have noted that the postoperative function is dependent in part on the extent of interstitial fibrosis. Other important determinants include the duration of disease, the extent of cellular degeneration, and the success of revascularization.

Response of Viable Myocardium to Dobutamine

Factors that determine the contractile reserve of viable myocardium include interstitial fibrosis, sarcoplasmic reticulum function, myocardial blood flow at rest, and coronary flow reserve. We noted a strong inverse correlation between thickening at low-dose dobutamine and the extent of interstitial fibrosis (% fibrosis accounted for 69% of the observed thickening at low-dose DE). These observations parallel the findings of inverse correlations between thallium as well as technetium uptake and interstitial fibrosis. Importantly, we noticed that viable myocardium and subsequent recovery are most frequent when both DE and thallium SPECT predicted viability and least when both were negative. In the few cases with discrepancy, the extent of interstitial fibrosis was intermediate. In addition, the cellular function of viable myocytes plays an important role. Other changes include the disorganization of the sarcomeric proteins with loss of myofilaments and thus a reduction in the contractile reserve. With regard to the interstitial proteins, the abundance of fibronectin and vimentin noticed by us and others parallels the interstitial fibrosis and the accumulation of fibroblasts that develop in response to myocyte loss. Energy stores are also different between viable and nonviable myocytes. More glycogen was present in viable myocardium (defined by DE thickening at low-dose DE). These observations parallel the findings of inverse correlations between thallium as well as technetium uptake and interstitial fibrosis. Importantly, we noticed that viable myocardium and subsequent recovery are most frequent when both DE and thallium SPECT predicted viability and least when both were negative. In the few cases with discrepancy, the extent of interstitial fibrosis was intermediate. In addition, the cellular function of viable myocytes plays an important role. Other changes include the disorganization of the sarcomeric proteins with loss of myofilaments and thus a reduction in the contractile reserve. With regard to the interstitial proteins, the abundance of fibronectin and vimentin noticed by us and others parallels the interstitial fibrosis and the accumulation of fibroblasts that develop in response to myocyte loss. Energy stores are also different between viable and nonviable myocytes. More glycogen was present in viable myocardium (defined by DE response), possibly reflecting increased glucose utilization with stress, previously noted in hibernating myocardium but not in regions with normal function. It is also possible that this is the result of glycolytic enzyme depletion favoring glucose storage as glycogen. With regard to myocardial blood flow, previous work using SPECT has shown that inotropic reserve occurred more frequently when rest perfusion was normal than when it was reduced. Likewise, we and others made similar observations with myocardial contrast echocardiography. Because the inclusion criteria mandated the presence of severe coronary stenosis, none of the angiographic variables related to baseline function or to thickening at low-dose DE and thus failed to predict functional recovery.

Limitations

 Coronary flow reserve is an important determinant of the response to dobutamine. This was not measured because it would have necessitated repeat angiography. We also did not evaluate other determinants of inotropic reserve, including the adrenergic system and the enzymatic machinery of the hibernating myocardium. There were few viable akinetic segments in this series, which limits our conclusions pertaining to this group of segments. Also, the relatively small number of biopsied segments precludes the complete evaluation of the ultrastructural correlates of the different responses to DE. In addition, one biopsy was obtained per dysfunctional segment. Because we used TEE to guide these core biopsies, we believe that our specimens indeed reflect well the core tissue in these segments. Although more specimens could have been obtained, this was greatly limited by patient safety.

Acknowledgments

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