Spatial Inhomogeneity of Sympathetic Nerve Function in Hibernating Myocardium

Andrew J. Luisi, Jr, MD; James A. Fallavollita, MD; Gen Suzuki, MD, PhD; John M. Canty, Jr, MD

**Background**—Although humans and swine with hibernating myocardium have an increased risk of sudden death, the contribution of chronic alterations in sympathetic nerve function is unknown. Acute transmural ischemia causes inhomogeneity in sympathetic innervation that may lead to lethal arrhythmias, but it is unclear whether similar abnormalities develop in response to chronic reversible ischemia.

**Methods and Results**—Swine were chronically instrumented with a left anterior descending coronary artery (LAD) stenosis that produced hibernating myocardium after 3 months. Resting subendocardial flow (LAD 0.75±0.14 versus 1.19±0.14 mL · min⁻¹ · g⁻¹, *P*<0.05) and wall thickening (LAD 15±3% versus 40±2%, *P*<0.05) were reduced compared with normal remote regions, without triphenyltetrazolium chloride evidence of necrosis. ¹³¹I-metaiodobenzylguanidine (MIBG) was used to assess integrity of the norepinephrine uptake-1 mechanism, and the spatial and transmural distributions were quantified by ex vivo counting. In hibernating myocardium, MIBG deposition was decreased in each layer, with the greatest reduction in the subendocardium (LAD subendocardium 0.28±0.02 versus 0.42±0.04 mL · g⁻¹ · min⁻¹ in normal, *P*<0.05; LAD subepicardium 0.31±0.03 versus 0.38±0.04 mL · g⁻¹ · min⁻¹ in normal, *P*<0.05). In contrast, there were no spatial alterations of MIBG deposition in sham-instrumented animals.

**Conclusions**—The sympathetic norepinephrine uptake-1 mechanism is impaired in hibernating myocardium. These findings raise the possibility that chronic alterations in sympathetic innervation contribute to the excess mortality seen in the setting of hibernating myocardium. (*Circulation. 2002;106:779-781.*)

**Key Words:** hibernation • myocardial stunning • nervous system, sympathetic • death, sudden • ischemia

Spatial variations in regional sympathetic innervation lead to inhomogeneity in cardiac repolarization and may increase the risk of arrhythmic sudden death.¹–³ Regional denervation occurs after myocardial infarction, and lethal arrhythmias may be related to nerve sprouting during reinnervation.⁴ Functional denervation has also been observed after brief coronary occlusions,⁵,⁶ as well as in viable risk areas of reperfused myocardial infarcts,⁷ which supports the view that sympathetic nerve function is exquisitely sensitive to ischemia.

Although transmural ischemia causes cardiac denervation, it is uncertain whether reversible subendocardial ischemia could chronically affect sympathetic nerve function and contribute to the risk of sudden death in patients with chronic ischemic heart disease. In support of this, clinical studies have demonstrated an increased mortality when patients with hibernating myocardium are not revascularized, and the excess risk is largely related to sudden death.⁸ This increased mortality is also seen in animal studies of chronic hibernating myocardium, in which the cumulative incidence of sudden death approaches 50% over 5 months.⁹

We hypothesized that hibernating myocardium exhibits regional inhomogeneity in sympathetic innervation that arises from chronic repetitive ischemia distal to a critical coronary stenosis. To test this, we evaluated the functional integrity of the sympathetic nervous system by characterizing the transmural deposition of ¹³¹I-metaiodobenzylguanidine (MIBG) in swine with chronic hibernating myocardium. The results demonstrate regional alterations in MIBG uptake, which may contribute to the pathophysiological sequelae of hibernating myocardium.

**Methods**
All procedures were performed in accordance with institutional guidelines. We chronically instrumented swine (n=8; Bippert’s Farms, Alden, NY) with a fixed-diameter Delrin stenosis to produce hibernating myocardium as described previously.¹⁰ Sham animals (n=4) underwent dissection of the left anterior descending coronary artery (LAD) without an occlusive stenosis. After 3 months, physiological studies were performed in the closed-chest sedated state (Teiizol/xylazine IM and propofol 2 to 5 mg · kg⁻¹ · min⁻¹ IV). A 5F Millar micromanometer was inserted into the left ventricle via a 6F introducer placed in the brachial artery by a percutaneous technique. Aortic pressure was monitored via the side port. We assessed resting function using echocardiography¹¹ and resting flow by injecting 2×10⁶ fluorescent microspheres into the left ventricle, while a reference withdrawal sample was taken from the side port of the introducer (6 mL/min).⁸–¹¹ Subsequently, vasodilated flow was determined during adenosine administration (0.9 mg · kg⁻¹ · min⁻¹) while phentylephrine was...
Transmural Variations in MIBG Deposition and Flow

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<th>Endo</th>
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<tr>
<td>MIBG deposition, mL · g⁻¹ · min⁻¹</td>
<td>0.28±0.02*</td>
<td>0.42±0.04</td>
<td>0.32±0.03*</td>
<td>0.44±0.05</td>
<td>0.31±0.03*</td>
<td>0.38±0.04</td>
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<td>Resting flow, mL · g⁻¹ · min⁻¹</td>
<td>0.75±0.14*</td>
<td>1.19±0.14</td>
<td>0.99±0.09</td>
<td>1.13±0.12</td>
<td>0.92±0.11</td>
<td>0.86±0.09</td>
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<td>Vasodilated flow, mL · g⁻¹ · min⁻¹</td>
<td>0.70±0.13*</td>
<td>4.70±0.58</td>
<td>1.56±0.33</td>
<td>5.71±0.47</td>
<td>2.20±0.38*</td>
<td>4.81±0.33</td>
<td>0.32±0.04</td>
<td>0.97±0.07</td>
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<tr>
<td>Flow reserve</td>
<td>1.10±0.24*</td>
<td>4.48±0.87</td>
<td>1.63±0.34</td>
<td>5.67±0.95</td>
<td>2.61±0.46*</td>
<td>6.26±1.02</td>
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Endo indicates subendocardium; Epi, subepicardium. Mean±SEM.

*P<0.05, LAD vs. Remote.

The major new finding from the present study is that hibernating myocardium exhibits chronic spatial inhomogeneity in the norepinephrine uptake-1 mechanism, as reflected by reductions in MIBG deposition. Although these changes are similar to those reported in viable myocardium after transmural infarction, they occur in the absence of myocardial necrosis and are most pronounced in the LAD region.

### Discussion

The major new finding from the present study is that hibernating myocardium exhibits chronic spatial inhomogeneity in the norepinephrine uptake-1 mechanism, as reflected by reductions in MIBG deposition. Although these changes are similar to those reported in viable myocardium after transmural infarction, they occur in the absence of myocardial necrosis and are most pronounced in the LAD region.

Figure 1. Top, Circumferential distribution of MIBG and adenosine flow in representative animal. Midventricular ring was sectioned into 12 pieces, and triphenyltetrazolium chloride staining showed no evidence of infarction. MIBG was reduced in hibernating LAD region and corresponded closely to area at risk of ischemia, as reflected by circumferential distribution of perfusion during adenosine. Bottom, Relative circumferential distribution of MIBG uptake in full-thickness samples from all hibernating and sham-instrumented animals. There were significant reductions in MIBG in LAD region of swine with hibernating myocardium. In contrast, there was no spatial variation in sham-instrumented controls in which LAD was dissected. PDA indicates posterior descending coronary artery.
subendocardium. This raises the possibility that inhomogeneity of sympathetic innervation arising from reversible ischemia may contribute to the increased risk of sudden cardiac death when hibernating myocardium cannot be revascularized.8

Approximately 50% of myocardial MIBG deposition is dependent on the presynaptic norepinephrine uptake-1 mechanism. The remainder is nonspecific uptake and not affected by denervation.15 Although controversy exists as to whether acute reductions in MIBG uptake reflect the uptake-1 mechanism after acute infarction,13–15 β-adrenergic–mediated changes in myocardial function2 and α-adrenergic coronary vasoconstriction6 in response to sympathetic nerve stimulation are immediately attenuated after brief reversible episodes of transmural ischemia. In addition, animal models have shown that reductions in MIBG activity are associated with reductions in tissue norepinephrine content and sympathetic nerve density, which supports the use of MIBG as an index of sympathetic nerve function in the chronic setting.13

The circumferential reduction in MIBG uptake in hibernating myocardium paralleled the area of chronically reduced flow reserve and is consonant with the observation that sympathetic denervation corresponds to the area at risk of ischemia in ST-elevation myocardial infarcts.7 This supports the notion that the propensity of a region to develop spontaneous ischemia is closely linked to the development of sympathetic denervation. There was also a modest transmural gradient in MIBG deposition, with greater reductions found in the subendocardium, where flow reserve was critically impaired. Compared with normal remote regions, the 32% relative reduction in MIBG that we found in the subendocardium of hibernating myocardium exceeded the ~18% difference noted in the subendocardium of dysfunctional, normally perfused myocardium adjacent to transmural infarction.14 In contrast, the relative differences in subepicardial MIBG were similar (19% and 17%, respectively). The reduction in subepicardial MIBG could reflect an increased sensitivity of sympathetic nerves to even modest reductions in flow reserve and transient demand-induced ischemia. An alternate possibility is that they arise from transient total coronary occlusion and supply-induced ischemia from cyclical platelet aggregation before the development of total coronary occlusion, as previously described in amiodarone cludcer models.16 Finally, it is also possible that factors unrelated to ischemia could contribute to subepicardial denervation, as they do in normally perfused border zones adjacent to transmural infarction.14

Clinical Implications
Our data raise the possibility that regional inhomogeneity in sympathetic nerve function may be one of the determinants of increased mortality from sudden death in patients with hibernating myocardium. This is also consistent with the high rate of sudden death in the swine model of hibernating myocardium,9 which we have demonstrated to be associated with the development of ventricular tachycardia that degenerates rapidly into ventricular fibrillation (unpublished observations). Although additional studies are necessary, imaging the integrity of the sympathetic nervous system may provide an approach to stratify risk of sudden death in patients with hibernating myocardium and depressed left ventricular function.

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References
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