Extent of Cardiac Sympathetic Neuronal Damage Is Determined by the Area of Ischemia in Patients With Acute Coronary Syndromes

Ichiro Matsunari, MD; Ullrich Schricke, MD; Frank M. Bengel, MD; Hans-Ullrich Haase, MD; Petra Barthel, MD; Georg Schmidt, MD; Stephan G. Nekolla, PhD; Albert Schoemig, MD; Markus Schwaiger, MD

Background—Prior studies have demonstrated that acute ischemic injury causes sympathetic neuronal damage exceeding the area of necrosis. The aim of this study was to test the hypothesis that sympathetic neuronal damage measured by 123I-metaiodobenzylguanidine (MIBG) imaging would be determined by the area of ischemia as reflected by area at risk in patients undergoing reperfusion therapy for acute coronary syndromes.

Methods and Results—In 12 patients, the myocardium at risk was assessed by 99m Tc-sestamibi SPECT before reperfusion, and infarct size was measured by follow-up 99m Tc-sestamibi SPECT 1 week later. All patients also underwent 123I-MIBG SPECT within a mean of 11 days after onset. The SPECT image analysis was based on a semiquantitative polar map approach. Defect size on the 123I-MIBG or 99mTc-sestamibi SPECT was measured for the left ventricle (LV) with the use of a threshold of $-2.5$ SD from the mean value of a normal database and was expressed as %LV. The 123I-MIBG defect size ($47\pm18\%LV$) was larger than the infarct size ($27\pm23\%LV$, $P<0.001$) but was similar to the risk area ($49\pm18\%LV$, $P=NS$). Furthermore, the 123I-MIBG defect size was closely correlated with the risk area ($r=0.905$, $P<0.001$).

Conclusions—Sympathetic neuronal damage measured by 123I-MIBG SPECT is larger than infarct size and is closely related to risk area, suggesting high sensitivity of neuronal structures to ischemia compared with myocardial cells. (Circulation. 2000;101:2579-2585.)

Key Words: nervous system, autonomic ▪ coronary disease ▪ tomography

Sympathetic nerve fibers in the heart travel parallel to the vascular structures on the surface of the heart and penetrate into the underlying myocardium.1 Prior experimental studies have demonstrated that disruption of cardiac sympathetic nerve fibers by interventions that affect the epicardium, such as transmural myocardial infarction or phenol application, resulted in sympathetic denervation within viable myocardium distally to the site of intervention.2–4

In a canine study using a balloon occlusion followed by reperfusion, however, Wolpers et al5 found that acute ischemia causes reduced retention of $^{11}$C-hydroxyephedrine, a catecholamine analog, in reperfused myocardium without evidence of necrosis, which was paralleled by reductions in tissue norepinephrine content. In that study, the severity of neuronal damage measured by $^{11}$C-hydroxyephedrine retention was related to the severity of reduction in regional blood flow during ischemia, suggesting a direct effect of ischemia on sympathetic nerve terminals. Furthermore, clinical studies using 123I-metaiodobenzylguanidine (123I-MIBG) to assess cardiac sympathetic innervation have shown that sympathetic neuronal injury is present even in patients without distinct myocardial infarction (eg, unstable angina).6,7 These observations suggest that the sympathetic dysfunction within viable myocardium in the setting of acute ischemia may be caused by the simple fact that the sympathetic neurons are more sensitive to ischemia than the myocytes, rather than the disruption of nerve fibers by transmural infarction and subsequent denervation of the distal site. If this is true, the area of acute ischemia would determine the extent of sympathetic neuronal injury. With the use of a recently developed radiolabeled technique, such an area of acute ischemia and thus “myocardium at risk” can be measured accurately in vivo with 99mTc-sestamibi and SPECT if the tracer is injected before reperfusion therapy.8,9

The aim of this study was to test the hypothesis that sympathetic neurons are more susceptible to ischemia than the myocardial cells and therefore the extent of sympathetic

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neuronal damage is determined by the area of acute ischemia as reflected by myocardium at risk in patients undergoing reperfusion therapy for acute coronary syndromes.

**Methods**

**Patients**

We consecutively recruited 12 patients undergoing reperfusion therapy for acute coronary syndromes who met the following criteria: (1) chest pain of ≥30 minutes suggestive of myocardial infarction and <48 hours from onset, (2) significant ECG ST-T segment changes and/or T-wave inversion in ≥2 contiguous leads, and (3) injection of 99m Tc-sestamibi during acute chest pain before the interventional therapy. Patients were excluded if they (1) had historical or ECG evidence for prior myocardial infarction, (2) were diabetic or had significant valvular disease or pulmonary disease, (3) were premenopausal women, or (4) had clinical instability preventing transport to the nuclear laboratory within 6 hours of 99m Tc-sestamibi administration.

There were 10 men and 2 women with a mean age of 58 years (range, 42 to 74 years). All patients had successful reperfusion therapy (defined as restoration of TIMI grade II or III flow) by direct PTCA and stent implantation. Plasma creatine kinase level was obtained at a sampling rate of 2 to 4 hours for the first 2 days and 4 to 6 hours for 2 additional days. A predischARGE coronary angiography and left ventriculography were performed 2 weeks later. All patients gave written informed consent in accordance with the institutional Human Clinical Study Committee guidelines.

**Data Acquisition**

All patients underwent a first and follow-up 99m Tc-sestamibi imaging to assess sympathetic neuronal damage. Patient eligibility was established shortly after arrival to the emergency room. After giving informed consent, each patient received 20 to 30 mCi IV (740 to 1110 MBq IV) of 99m Tc-sestamibi during acute chest pain before therapy with coronary angioplasty was performed. Tomographic images were obtained 2 to 6 hours later after the intervention to assess the myocardium at risk. Infarct size was measured by a second resting 99m Tc-sestamibi SPECT performed an average of 6.5 days (range, 4 to 9 days) from onset. To assess sympathetic neuronal damage, 5 mCi (185 MBq) of 123I-MIBG was injected at rest, and imaging was started 30 minutes and 5 hours after injection on a separate day within a mean of 11 days (range, 6 to 19 days) from onset. All patients continued their cardiac medications, including β-receptor blockers, ACE inhibitors, ticlopidine, and aspirin.

All SPECT acquisitions were performed with a triple-head camera system (Multispect 3, Siemens AG) equipped with low-energy, parallel-hole collimators for 99m Tc-sestamibi or medium-energy collimators for 123I-MIBG to avoid the effects of septal penetration. Images were acquired in 64 matrices with an acquisition time of 40 seconds per projection for 99m Tc-sestamibi or 60 seconds for 123I-MIBG in 6° increments. An energy window centered on the 140±10.5-keV peak was used for 99m Tc-sestamibi; a window centered on 159±15.9 keV was used for 123I-MIBG. The image data were reconstructed over 180° from 45° right anterior oblique to 45° left posterior oblique by use of a Butterworth filter with a cutoff frequency of 0.45, order 5.

**Image Analysis**

Image data analysis was performed with a polar map approach developed in our laboratory. 

**Patient Characteristics**

<table>
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<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Culprit Vessel</th>
<th>Other Stenosed Vessel</th>
<th>Time to Reperfusion, h</th>
<th>Area at Risk</th>
<th>Infarct Size</th>
<th>30-min MIBG Defect Size</th>
<th>5-h MIBG Defect Size</th>
<th>CK&lt;sub&gt;iso&lt;/sub&gt; IU/L</th>
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Visual indicates defect size by visual interpretation (number of abnormal segments); Quant, defect size by quantitative measurements (%LV); CK<sub>iso</sub>, maximum creatine kinase; LVEF, LV ejection fraction; LAD, left anterior descending artery; LCx, left circumflex artery; and RCA, right coronary artery.
was defined as \(^{123}\)I-MIBG defect size minus infarct size, and the amount of salvaged myocardium was defined as myocardial area at risk minus infarct size. Both were expressed as %LV.

**Assessment of Defect Location**

To assess the location of defect area, the left ventricular myocardium was divided into apical, anterior, septal, lateral, and inferior regions. A region was arbitrarily considered to have a defect if the defect area was 50% of the assigned region.

**Statistical Analysis**

Data were expressed as mean±SD. Comparisons of paired mean values were performed by use of repeated-measures ANOVA and Bonferroni’s multiple comparisons test. Linear regression was performed by least-squares analysis. Segmental agreement in a defect location was evaluated by \(k\) statistics. Statistical significance was defined as \(P<0.05\).

**Results**

**Angiographic, Scintigraphic, and Enzymatic Results**

Patient characteristics and scintigraphic results are summarized in the Table. Most patients (9 of 12) had an infarct-related artery in the left anterior descending artery and had complete occlusion of the culprit artery (10 of 12) at the time of coronary intervention. Time to reperfusion from onset was variable, ranging from 2.5 to 48 hours, but most patients had reperfusion at early time points (median, 4.5 hours). When an elevated serum peak creatine kinase level at least twice the upper limit established in our laboratory (80 U/L) was considered evidence of myocardial infarction, 11 of 12 patients developed acute myocardial infarction. The mean LV ejection fraction was 53±18%.

When the visual interpretation was compared with the quantitative measurements, there were close correlations between the number of abnormal segments by visual scoring and defect size by quantitative analyses for the area at risk (\(r=0.903, P<0.001\)), infarct size (\(r=0.941, P<0.001\)), and \(^{123}\)I-MIBG images (\(r=0.889, P<0.001\)). On the basis of these results, we used the quantitative data for further analysis, because quantitative analysis is generally more objective and reproducible. Infarct size measured by the second \(^{99}\)Tc-sestamibi imaging was closely correlated with either LV ejection fraction (\(r=-0.836, P<0.001\)) or serum maximal creatine kinase levels (\(r=0.903, P<0.001\)).

**Comparison of Myocardium at Risk, Infarct Size, and \(^{123}\)I-MIBG Defect Size**

The relationships between the myocardial area at risk and infarct size and between the area at risk and MIBG defect size are shown in Figure 1. Although there was a significant correlation between the risk area and infarct size (\(r=0.769, P<0.01\)), the area at risk (49±18% LV) was significantly larger than the infarct size (27±23% LV, \(P<0.001\)). Similarly, although the \(^{123}\)I-MIBG defect size was significantly correlated with the risk area (\(r=0.750, P<0.01\)), the MIBG defect size (47±18% LV) was significantly larger than the infarct size (27±23% LV, \(P<0.001\)).

The relationships between \(^{123}\)I-MIBG defect size and area at risk and between \(^{123}\)I-MIBG/\(^{99}\)Tc-sestamibi mismatch size and the amount of salvaged myocardium are plotted in Figure 2. The \(^{123}\)I-MIBG defect size was closely correlated with risk area (\(r=0.905, P<0.001\)) and was similar to risk area (47±18% LV versus 49±18% LV, respectively; \(P=NS\)). Similarly, the mismatch size was closely correlated with the amount of salvaged myocardium (\(r=0.859, P<0.001\)) and was similar to the amount of salvaged myocardium (20±15% LV versus 22±15% LV, respectively; \(P=NS\)).

Figure 3 displays polar maps of myocardial area at risk, infarct size, and \(^{123}\)I-MIBG images from a male patient.
Figure 3. Polar maps of myocardium at risk (left) and infarct size (center) and $^{123}$I-MIBG (right) images from male patient with inferior myocardial infarction (patient 10 in Table). Top, Original maps; Bottom, those with quantified defect areas filled with white. Ant indicates anterior; Sep, septal; Lat, lateral; and Inf, inferior.
with inferior myocardial infarction (patient 10 in the Table). The area at risk image shows a large defect that involves the inferior to inferolateral wall. After reperfusion, defect size remarkably decreased, from 37.8%LV to 13.3%LV. The 123I-MIBG defect (34.8%LV), on the other hand, was similar to the area at risk in both size and location.

**Location of 123I-MIBG Defect and Myocardium at Risk**

Figure 4 shows the agreement between area at risk and MIBG defect on a regional basis. The complete agreement in localization between area at risk and 123I-MIBG images occurred in 55 of 60 segments (κ=0.832), leaving only 5 segments from 3 patients discordant, indicating that there is close agreement in defect location between the myocardium at risk and 123I-MIBG images.

**Discussion**

This study directly and quantitatively compares sympathetic neuronal damage measured by 123I-MIBG SPECT with the myocardium at risk measured by 99mTc-sestamibi SPECT. The major findings of this study were that (1) sympathetic neuronal damage measured by 123I-MIBG SPECT was larger than infarct size but was similar to the area of myocardium at risk and (2) 123I-MIBG defect was closely correlated with myocardium at risk in both size and location.

**Sympathetic Neuronal Function and 123I-MIBG**

Sympathetic nerve fibers are characterized by multiple nerve endings that are filled with vesicles containing catecholamines. Norepinephrine, the dominant transmitter in the sympathetic nervous system, is synthesized from the amino acid tyrosine by several enzymatic steps and stored within the storage vesicles in the sympathetic nerve terminals. Nerve stimulation leads to norepinephrine release, which occurs as vesicles fuse with the neuronal membrane and expel their contents by exocytosis. Most of the norepinephrine released undergoes reuptake in the nerve terminal (uptake-1 mechanism) and recycles into the vesicles or is metabolized in the cytosol of the nerve terminal.

123I-MIBG, a catecholamine analog, is taken up into the neuron via uptake-1 in a manner similar to that for norepinephrine, is not metabolized, and thus marks the location of functioning nerve terminals. Hence, the assessment of 123I-MIBG uptake allows unique characterization of alterations in regional sympathetic nerve function.

**Effect of Ischemia on Sympathetic Neurons and 123I-MIBG Uptake**

Prior experimental studies have demonstrated that the myocardial injury that affects the subepicardial layer, such as transmural infarction, could disrupt autonomic neuronal transmission and therefore that the myocardium apical to the site of infarction would lose normal innervation because nerve trunks travel from base to apex in the subepicardial layer of the myocardium. In a canine study by Dae et al, who produced transmural and nontransmural infarctions and compared 123I-MIBG and 201TI images with tissue norepinephrine content and histological findings, transmural infarction produced 123I-MIBG uptake defects distal to the 201TI defects, whereas nontransmural infarction showed matched defects between 123I-MIBG and 201TI, with minimal extension of the denervated area beyond the infarct zone. However, a greater reduction in 123I-MIBG activity relative to 201TI was present within the viable tissue, suggesting that the sympathetic nerves may be more sensitive to ischemia than cardiomyocytes. The results of the present study using a quantitative technique showed a larger 123I-MIBG defect than infarct size measured by 99mTc-sestamibi SPECT in most patients. This is consistent with numerous studies in CAD demonstrating larger 123I-MIBG defects than perfusion defects.6,7,16 In particular, a larger 123I-MIBG defect than perfusion defect was observed even in patients with no evidence of distinct myocardial infarction, such as unstable angina, suggesting that the ischemic threshold for the production of sympathetic neuronal damage is lower than that for cardiomyocytes. This was confirmed by the results of the present study that clearly showed that the area of 123I-MIBG abnormality closely agreed with that of acute ischemia (ie, myocardium at risk) in both size and location.

It should be noted that all our patients underwent aggressive reperfusion therapy, resulting in a considerable amount of salvaged myocardium. This is similar to the conditions in prior experimental studies.5 Using 11C-hydroxyephedrine as a tracer for cardiac sympathetic innervation, Wolpers et al found reduced tracer retention in postischemic myocardium that was related to the severity of flow reduction during coronary occlusion. In a clinical study by Allman et al in patients who underwent reperfusion therapy for acute myocardial infarction, the reduced retention of 11C-hydroxyephedrine was observed not only distal but also lateral to the sites of infarction. In this regard, the results indicate that the area of sympathetic neuronal damage within viable myocardium as reflected by 123I-MIBG/perfusion mismatch is determined by the amount of salvaged myocardium.
ischemic periods resulted in early functional changes in the presynaptic sympathetic neuron (ie, the nonexocytotic release of norepinephrine via the neuronal uptake carrier in reverse of its normal transport direction), but as ischemic time increased (ischemia >40 minutes), irreversible structural changes occurred, usually at ≈2 to 4 hours,19 which is similar to the time window from symptom onset to reperfusion in the patients in this study. It is not likely that cardiac sympathetic reinnervation occurred during the study period (mean, 11 days) and thus affected the results. Although reinnervation after myocardial infarction has been reported in canine studies,1 the reinnervation process seems to be slow, at least several months, in humans.13,16

**Technical Considerations**

In this study, we defined a defect by comparing uptake values of patients with those of age-matched normal subjects. Although a 60% cutoff threshold is well validated to define myocardium at risk and infarct size with 99mTc-sestamibi,8,9 this may not be applicable to 123I-MIBG, which has different physical and physiological characteristics from those of 99mTc-sestamibi. The distribution of 123I-MIBG in human hearts is physiologically heterogeneous in that inferior and septal 123I-MIBG uptake is lower than that of the anterior wall in normal subjects.19 Moreover, the activity distribution on SPECT images is generally not homogeneous because of soft tissue attenuation of the photon, which is true for both tracers. Our quantitative technique intrinsically considers this effect. Thus, it appears reasonable to define a defect on the basis of a normal database generated separately for each tracer. The quantitative technique used in this study closely correlated with the results of visual interpretation, which has been used as the reference standard in the literature.20 Furthermore, the infarct size measured by the second 99mTc-sestamibi images was correlated closely with clinical measures of myocardial necrosis (ie, peak creatine kinase levels and LV ejection fraction), providing a clinical validation to our quantitative technique.

For 123I-MIBG imaging, we used initial (30 minute) images rather than delayed (5 hours) images to be analyzed. Although a nonneuronal uptake mechanism for norepinephrine has been demonstrated to exist in experimental animal models,21 the contribution of nonneuronal accumulation to myocardial 123I-MIBG uptake is reportedly very low in humans.14 Thus, myocardial 123I-MIBG uptake on the initial image should represent functional integrity of cardiac sympathetic nerve terminals without considerable contributions of nonneuronal uptake of the tracer.

**Study Implications**

There is general agreement that the sympathetic nervous system plays an important role in the genesis of ventricular arrhythmias.1,22 The regional variation of presynaptic sympathetic function may be linked to some forms of ventricular arrhythmias and an increased incidence of sudden death.1,23 It was not clear, however, how such sympathetic neuronal damage is related to the area of acute ischemic injury, because no prior studies have directly measured the area of acute ischemia in comparison with 123I-MIBG uptake. In this regard, the results would provide insights into a better understanding of cardiac sympathetic neuronal damage in the setting of acute ischemia in humans.

**Study Limitations**

This study has several limitations. First, because of the relatively small sample size, it was not possible to investigate conclusively the exact incidence and extent of 123I-MIBG abnormalities, particularly in view of such clinical parameters as time to reperfusion from the onset. A further study involving a larger patient cohort is necessary to address this issue.

Second, none of the patients underwent reperfusion within a very short time period, such as <1 hour. Ischemic thresholds may exist to develop sympathetic nerve dysfunction. In a canine model,24 123I-MIBG uptake remained unchanged for up to 40 minutes of ischemia, which decreased as the tissue progressed from being ischemic to developing infarction. Thus, it remains unknown whether 123I-MIBG abnormality is induced by such a short ischemia in humans.

Finally, we did not include patients with chronic systemic diseases, such as diabetes mellitus, which are known to frequently coexist with CAD and to affect cardiac sympathetic innervation.25 Therefore, it is possible that the coexistence of such disease conditions could have modulated the results, which needs to be addressed in further studies.

**Conclusions**

Sympathetic neuronal damage measured by 123I-MIBG SPECT is larger than infarct size and is closely related to the area of ischemia as reflected by myocardium at risk, suggesting the high sensitivity of neuronal structures to ischemia compared with myocardial cells.

**Acknowledgments**

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