Correlation Between Scintigraphic Evidence of Regional Sympathetic Neuronal Dysfunction and Ventricular Refractoriness in the Human Heart

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Background. Denervation supersensitivity has been proposed as a mechanism for the relationship between ventricular arrhythmias and the sympathetic nervous system. Evaluation of this phenomenon in humans has become feasible only recently with the development of noninvasive scintigraphic methods for evaluating the pattern of sympathetic innervation. The purpose of this study was to determine if scintigraphic evidence of sympathetic neuronal dysfunction correlates with measurements of ventricular refractoriness and to evaluate the phenomenon of denervation supersensitivity in humans.

Methods and Results. Eleven patients with a history of sustained ventricular tachycardia or sudden cardiac death who were referred for placement of an implantable defibrillator participated in this study (seven men and four women; age, 51±18 years). Preoperative scintigraphic evaluation of the pattern of sympathetic innervation was performed with 11C-hydroxyephedrine in conjunction with positron emission tomography. At the time of surgery, ventricular refractoriness was determined in regions of myocardium demonstrating normal and reduced 11C-hydroxyephedrine retention in the baseline state and during an infusion of norepinephrine. Scintigraphic evaluation demonstrated regions of reduced 11C-hydroxyephedrine retention in each patient. The effective refractory period in areas of myocardium that demonstrated reduced 11C-hydroxyephedrine retention was significantly longer than in areas of myocardium demonstrating normal 11C-hydroxyephedrine retention (273±32 versus 243±32 msec, p<0.001). Norepinephrine shortened the effective refractory period in regions of myocardium demonstrating normal and reduced 11C-hydroxyephedrine retention to a similar degree.

Conclusions. There is a correlation between scintigraphic evidence of sympathetic neuronal dysfunction and ventricular refractoriness in the human heart. These observations help validate the use of scintigraphic techniques for evaluation of sympathetic innervation and may assist in the further evaluation of the relation between the sympathetic nervous system and ventricular arrhythmias.

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KEY WORDS • nervous system, sympathetic • denervation • refractoriness • 11C-hydroxyephedrine

Sympathetic denervation and denervation supersensitivity have been observed after myocardial infarction in animal models. These phenomena can be evaluated in humans as noninvasive scintigraphic evaluation of the pattern of sympathetic innervation of the human heart is possible with either 123I-radioiodinated metaiodobenzylguanidine (MIBG) or 11C-hydroxyephedrine (HED). With these agents, scintigraphic evidence of sympathetic neuronal dysfunction has been demonstrated in patients with coronary artery disease and in patients with an idiopathic dilated cardiomyopathy. However, an electrophysiological correlate to scintigraphic evidence of sympathetic neuronal dysfunction has never been demonstrated in humans.

Therefore, the purpose of this study was to determine if scintigraphic evidence of sympathetic neuronal dysfunction correlates with measurements of ventricular refractoriness and to determine if the phenomenon of denervation supersensitivity can be demonstrated in humans by evaluating the change in refractoriness during a catecholamine infusion in regions of myocardium with and without scintigraphic evidence of sympathetic neuronal dysfunction.

In this study, the pattern of sympathetic innervation was evaluated using HED, a norepinephrine analogue that shares the same uptake-1 and vesicular storage mechanisms as naturally occurring norepinephrine. When used in conjunction with positron emission tomography, HED allows quantitative noninvasive evaluation of the sympathetic nervous system in the human heart. Because HED is not metabolized by monoamine oxidase in the cytosol of sympathetic nerve terminals, retained HED activity reflects the uptake and storage of HED by adrenergic nerve terminals. Animal studies have confirmed that tissue retention of HED correlates closely with the concentration of norepinephrine in tissue, and studies in transplant patients have demonstrated low nonspecific binding of HED.
Methods

Patient Population

This study was performed in 11 patients. Nine patients presented with sudden cardiac death, and two presented with hemodynamically unstable ventricular tachycardia. Each patient failed treatment with conventional antiarrhythmic agents or was referred directly for placement of an implantable defibrillator either because of the absence of inducible sustained monomorphic ventricular tachycardia during a baseline electrophysiology test or because of the need for coronary artery bypass graft surgery. Their clinical characteristics are described in Table 1. There were seven men and four women, and mean age was 51±18 years. Seven patients had coronary artery disease, with six having had a myocardial infarction 17 days to 6 years before their evaluation. Three patients had a nonischemic dilated cardiomyopathy, and one patient had no apparent structural heart disease. The mean left ventricular ejection fraction was 0.36±0.16. The results of scintigraphic imaging in these patients were compared with images obtained in a group of 14 volunteers who had no evidence of structural heart disease (eight men and six women; mean age, 38±6 years). Informed consent was obtained in each patient under an investigational protocol approved by the Human Research Committee at the University of Michigan.

Scintigraphic Imaging

Scintigraphic evaluation of the pattern of sympathetic innervation and resting myocardial perfusion was performed by positron emission tomography using a Siemens 931 15-slice whole body tomograph. Following placement of a 22-gauge IV cannula in an antecubital vein and positioning the tomograph with the aid of a scout image, a 15-minute transmission study was acquired using a retractable 68Ge ring source, for subsequent attenuation correction of the emission data. Neuronal imaging of the heart was performed following bolus injection of 20 mCi HED and a one-hour dynamic acquisition with 15 frames (framing rates 6×30 seconds, 2×60 seconds, 2×150 seconds, 2×300 seconds, 2×600 seconds, 1×1,200 seconds). The radioisotopy of HED has been previously described.13 After allowing 1 hour for 11C-decay, a static 10-minute myocardial blood flow image was collected as a single-frame study. This was performed to assess regional resting blood flow. This image was obtained either 60 seconds after injection of 40–60 mCi 82Rb or 3 minutes after injection of 20 mCi of 13N-ammonia. The HED and blood flow emission data were attenuation corrected and reconstructed by filtered backprojection using a Hanning filter with a cutoff of 0.3 cycles per pixel. Images were reoriented to the long and short axes of the left ventricle using a SUN workstation (SUN Microsystems Mountainview, Calif.).

Polar maps of relative tracer activity were generated from the short-axis blood flow and 30–40-minute HED images, using circumferential profiling analysis with a maximal search algorithm. The left ventricular myocardium is depicted on the map as eight short-axis slices from apex to the center to base peripherally, with all pixels normalized to the maximum in the heart. A normal data base was formed from the studies obtained in the 14 healthy volunteers for subsequent statistical comparison. The regional homogeneity of blood flow and HED retention in these 14 volunteers are depicted schematically in Figure 1. Patient map pixels falling more than 2.5 SDs below data base values were defined as abnormal. The extent of the left ventricle with abnormal ratio of blood flow to HED retention was expressed as a percentage of total polar map area.

![Figure 1. Charts of summary data of myocardial flow and 11C-hydroxyephedrine (HED) uptake in normal volunteers using a polar map approach. Tracer retention is normalized to peak myocardial uptake and expressed as a percentage. Relative tracer uptake at the apex is projected on the center of the map, and relative tracer uptake at the base is displayed toward the periphery. Left panel: Relative distribution of flow. Right panel: Relative retention of HED. Both myocardial flow and HED uptake are homogeneous throughout the ventricle. ANT, anterior; SEPT, septal; LAT, lateral; INF, inferior.](image-url)
Electrophysiological Testing

Electrophysiology tests were performed with subjects in the fasting state at least five half-lives after discontinuation of all antiarrhythmic drugs, including β-blockers. Standard quadripolar electrode catheters were inserted via the femoral vein and positioned at the high right atrium, across the tricuspid valve to record a His bundle electrogram, and at the apex of the right ventricle. A 5F catheter was inserted into the femoral artery for blood pressure monitoring. Leads V₁, I, and III, the intracardiac electrograms, and blood pressure were recorded at a paper speed of 25 mm/sec using a Siemens-Elma Mingograph 7 recorder. Programmed electrical stimulation was performed with a programmable stimulator (Bloom Associates Ltd., Reading, Pa.) with stimuli that were 2 msec in duration and twice-diastolic threshold. As many as three extrastimuli were delivered at drive train cycle lengths of 600, 400, and 350 msec. If sustained monomorphic ventricular tachycardia was not induced at the apex, programmed electrical stimulation with an identical protocol was repeated at the right ventricular outflow tract. Sustained ventricular tachycardia was defined as ventricular tachycardia of more than 30 seconds in duration or requiring cardioversion for termination due to hemodynamic instability.

Intraoperative Measurements of Refractoriness

All patients underwent placement of an implantable defibrillator using a median sternotomy approach. After the heart was exposed and before placement of the implantable defibrillator lead system, the arterial pressure and sinus cycle length were determined. Four unipolar plunge electrodes constructed by threading a Teflon-coated single steel wire through a 21-gauge needle were then placed in the regions identified before surgery to have normal and reduced HED retention. Placement of these electrodes by the surgeon was guided by a detailed map of the pattern of HED uptake obtained from the positron emission tomography images. Efforts were made to position the electrodes in the midmyocardium by inserting the electrodes approximately 6 mm into the myocardium before withdrawal of the needle. Two electrodes were placed in regions of myocardium demonstrating normal HED retention and perfusion, and two electrodes were placed in regions of myocardium demonstrating reduced HED retention and normal perfusion. In patients with matching defects of HED retention and perfusion, the second pair of electrodes was placed in a region of myocardium demonstrating reduced HED retention and perfusion. The indifferent anode was attached to the chest wall. Pacing was performed using a programmable stimulator (Bloom Associates) with pulses 2 msec in duration and a current intensity twice the stimulation threshold.

Ten minutes after placement of the plunge electrodes, the diastolic threshold was determined. The mean diastolic threshold in regions of myocardium demonstrating reduced myocardial flow and reduced HED retention (1.4±1 mA) was greater than that observed in regions of myocardium demonstrating normal myocardial flow and normal HED uptake (0.4±0.2 mA) and in regions of myocardium demonstrating normal myocardial flow and reduced HED uptake (0.3±0.2 mA; p<0.01). The ventricular effective refractory period at each site was determined using a pacing drive cycle length of 500 msec, a drive train duration of 12 beats, and an intertrain pause of 3 seconds. A ventricular extrastimulus was initially introduced after every 12th ventricular paced beat initially at a coupling of 290 msec, and the coupling interval was decreased in 10-
msec steps until ventricular capture failed to occur. The coupling interval of the extrastimulus then was increased in 2-msec steps until ventricular capture occurred. The effective refractory period was defined as the longest extrastimulus coupling interval that failed to capture with an extrastimulus current strength of twice the stimulation threshold. The effective refractory period was determined twice at each site. Data were considered reproducible and acceptable for analysis only if the two determinations of the effective refractory period did not differ by more than 4 msec.\textsuperscript{14} The order of sites at which the effective refractory period was determined was randomized. The electrophysiologist was blinded to the site at which ventricular effective refractory periods were being measured.

**Norepinephrine Infusion**

After measurement of baseline arterial pressure, sinus cycle length, and the effective refractory period at each site, norepinephrine was infused at a rate of 0.1 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}. This infusion rate of norepinephrine was selected because it is within the range of rates used clinically and in prior experimental studies of denervation supersensitivity.\textsuperscript{2,15,16} After at least 10 minutes of norepinephrine infusion to allow a steady state to be achieved, the arterial pressure, sinus cycle length, and effective refractory period at each site were reetermined. If the diastolic threshold changed by more than 4 mA compared with baseline values, the site was considered unstable, and the data were excluded from analysis.

The phenomenon of denervation supersensitivity has been demonstrated in animal models with both isoproterenol and norepinephrine.\textsuperscript{2} Norepinephrine was selected as the catecholamine to be used in this study because HED is an analogue of norepinephrine and both are taken up by presynaptic nerve terminals. Because neuronal uptake and metabolism of norepinephrine constitute the major determinant of synaptic cleft concentrations,\textsuperscript{17} the potential for observing denervation supersensitivity in regions of reduced HED retention may be greater for norepinephrine than for isoproterenol.

**Statistical Analysis**

The effective refractory periods at sites demonstrating normal HED retention and perfusion, reduced HED retention but normal perfusion, and reduced HED retention and reduced perfusion were compared using ANOVA. The effect of norepinephrine on arterial blood pressure, sinus cycle length, and effective refractory period at each site was determined using paired two-tailed \textit{t} tests. In all cases, \( p < 0.05 \) was considered significant. All data are expressed as mean±1 SD.

**Results**

**Scintigraphic Results**

Figure 2 shows blood flow and HED images in a normal volunteer. Myocardial blood flow and HED retention are homogeneous throughout the entire left ventricle. Figure 3 shows an example of a patient with coronary artery disease (patient 5). This 60-year-old
A man with a history of a prior anterior wall myocardial infarction presented with sudden cardiac death, which occurred at rest and was associated with an elevation in the creatine kinase to 855 IU (13% MB fraction). Regional myocardial perfusion was reduced in the anterior wall, consistent with a prior anterior wall myocardial infarction. The corresponding scintigraphic images demonstrate a more extensive area of reduced HED retention that extends in a circumferential fashion beyond the region of myocardium that demonstrated reduced myocardial perfusion. Figure 4 shows an example of a patient with an idiopathic dilated cardiomyopathy (patient 9). This 31-year-old man presented with sudden cardiac death. Regional myocardial blood flow demonstrated a small perfusion abnormality in the midinferolateral wall, consistent with fibrosis. The corresponding HED scintigraphic images show heterogeneous areas of reduced HED retention in parts of the anterior, lateral, and inferior walls of the left ventricle.

Table 2 summarizes the results of regional HED retention and myocardial perfusion. In patients with coronary artery disease, the region of myocardium demonstrating reduced HED retention was similar in size to the region demonstrating reduced perfusion (matched defect) in four patients. The region of reduced HED retention was longer than the region demonstrating reduced perfusion in three patients (mismatched defect). In these three patients, the region of reduced HED retention extended in a circumferential fashion beyond the region demonstrating reduced myocardial perfusion.

**Table 2. Results in Patients Using 11C-Hydroxyephedrine**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart disease</th>
<th>Defect location</th>
<th>11C-Hydroxyephedrine pattern</th>
<th>% Flow</th>
<th>% 11C-Hydroxyephedrine</th>
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CAD, coronary heart disease; IDC, idiopathic dilated cardiomyopathy; % Flow, percent of left ventricle demonstrating reduced myocardial perfusion; % 11C-Hydroxyephedrine, percent of left ventricle demonstrating reduced retention of 11C-hydroxyephedrine.
Cardial perfusion. In the four patients without coronary artery disease, the region of reduced HED retention was larger than the region demonstrating reduced perfusion in three patients. The fourth patient (patient 10) demonstrated normal perfusion and only a very slight abnormality in HED retention, which was localized to the inferior wall of the left ventricle.

Baseline Measurements of Refractoriness

Figure 5 shows the relation between refractoriness and the pattern of HED retention in patient 8. The effective refractory period measured in the region of myocardium demonstrating reduced uptake was longer than the effective refractory period measured in the region of myocardium demonstrating normal HED uptake. The relation between refractoriness and the scintigraphic pattern of sympathetic innervation observed in this patient was representative of that observed in the majority of patients in this study.

The mean baseline effective refractory period in areas of myocardium that demonstrated reduced HED retention was significantly greater than the mean baseline effective refractory period in areas of myocardium that demonstrated normal HED retention (277±32 versus 242±30 msec; p<0.001; Figure 6). When analyzed according to the pattern of perfusion and HED retention, the mean baseline effective refractory period was greater in areas of myocardium demonstrating reduced perfusion and reduced HED retention than in areas of myocardium demonstrating normal HED retention and normal perfusion (294±16 versus 263±27 msec; p=0.048; Figure 7). The effective refractory period at both types of sites demonstrating reduced HED retention was greater than the effective refractory period at sites demonstrating normal HED retention (p<0.01).

Effects of Norepinephrine

Norepinephrine resulted in an increase in the mean blood pressure (82±10 versus 97±12 mm Hg; p<0.001) and did not alter the sinus cycle length (745±94 versus 705±116 msec; p=0.07). The mean arterial pressure increased by 11–32 mm Hg in each patient during a norepinephrine infusion. There was no apparent relation between the magnitude of change in the mean blood pressure and the change in the effective refractory period. Norepinephrine resulted in shortening of the effective refractory period in myocardium demonstrating normal HED retention and in myocardium demonstrating reduced HED retention (p=0.046 and 0.014, respectively; Figure 6). The degree of shortening of the ventricular effective refractory period was similar regardless of the pattern of HED retention (3.9±6 versus 5.4±7 msec, respectively; p=0.29). The change in the ventricular effective refractory period during a norepinephrine infusion in regions of myocardium demonstrating reduced HED retention did not differ regardless of whether the myocardial perfusion was normal or reduced (4±6 versus 6±8 msec; p=0.2).

Discussion

The results of the present study demonstrate a correlation between the scintigraphic pattern of sympathetic innervation of the heart and electrophysiological properties of the heart. The ventricular effective refractory period was longer in regions of myocardium that
demonstrated reduced HED retention compared with regions of myocardium demonstrating normal HED retention. An infusion of norepinephrine resulted in similar shortening of refractoriness in regions of myocardium demonstrating normal and reduced HED uptake, and therefore the phenomenon of denervation supersensitivity could not be demonstrated.

**Scintigraphic Imaging of Sympathetic Innervation**

Each of the control patients who underwent scintigraphic imaging demonstrated a normal pattern of HED retention. In contrast, scintigraphic imaging in each of the patients with malignant ventricular arrhythmias in this study demonstrated an inhomogeneous pattern of HED retention. These results suggest that the uptake and/or storage mechanisms for norepinephrine are impaired in certain regions of the heart and imply that these regions of the heart have abnormal neuronal function. The reduction in HED retention may result from either the absence or the dysfunction of sympathetic nerve terminals.

In patients with coronary artery disease, presumably infarcted regions of myocardium, as identified by a decrease in perfusion, uniformly demonstrated marked reduction in HED retention. Regions of myocardium that were presumed to be denervated and viable, as suggested by normal perfusion and reduced HED retention, were detected adjacent to the region of infarction in approximately one half of patients with coronary artery disease. These observations are consistent with prior experimental studies in dogs\(^5\),\(^16\),\(^18\) as well as in humans.\(^1\),\(^6\),\(^7\) Several investigators have demonstrated that transmural myocardial infarctions in dogs results in denervated viable myocardium distal to the zone of infarction, presumably due to damage to the sympathetic nerve trunks that travel in the subepicardium.\(^3\),\(^16\),\(^18\) Nontransmural infarctions result in denervated viable myocardium within the infarct zone, presumably due to local ischemic damage to sympathetic nerves.\(^18\)

In patients without coronary artery disease, perfusion was generally normal, yet regions of myocardium demonstrating reduced HED retention were detected in each patient. This finding is consistent with that of a prior study by Mitran et al\(^19\) who demonstrated abnormalities in MIBG uptake in 63% of patients with ventricular tachycardia in the absence of structural heart disease. Henderson et al\(^9\) also reported similar abnormalities in MIBG uptake in patients with idiopathic dilated cardiomyopathy.

**Baseline Measurements of Refractoriness**

The relation between the pattern of sympathetic innervation, determined noninvasively using HED, and refractoriness in humans has not previously been reported. In this study, the effective refractory period was longer at sites demonstrating reduced HED retention than at sites demonstrating normal HED retention. These results differ from those of prior experimental studies in animals, which have reported that refractoriness is similar in regions of myocardium demonstrating normal and reduced sympathetic innervation.\(^2\),\(^16\),\(^20\) These disparate results can be understood, at least in part, based on differences in study design. First, all prior studies of this phenomenon were performed in animal models following surgical cardiac denervation achieved by transecting the cervical vagi and the ansae subclavia. In contrast, this study was performed in patients with intact sympathetic innervation, which would result in shorter refractoriness in regions of myocardium that have normal sympathetic innervation compared with regions of myocardium in which sympathetic innervation was disrupted. Second, in prior studies refractoriness was determined only in regions of noninfarcted myocardium. Although the design of this study was similar to that of prior animal studies, only approximately one half of patients with coronary artery disease demonstrated a mismatched perfusion/HED retention defect. If a region of myocardium with normal perfusion and impaired HED uptake could not be identified, refractoriness was determined in a presumably infarcted region of myocardium demonstrating both reduced perfusion and reduced HED uptake. Prior studies have demonstrated that ventricular refractoriness is prolonged in infarcted regions of myocardium.\(^21\) Although the basis for the marked increase in refractoriness in presumably infarcted regions of myocardium demonstrating reduced perfusion and reduced HED uptake cannot be determined from this study, interruption of sympathetic innervation may play a role. The importance of interruption of sympathetic innervation is suggested by the finding that ventricular refractoriness was greater in regions of myocardium demonstrating impaired HED uptake and normal perfusion than in normal myocardium.

**Effect of Norepinephrine**

Norepinephrine resulted in an increase in the mean blood pressure, consistent with its known properties of \(\alpha\)-adrenergic stimulation; no change in the sinus cycle length; and a decrease in refractoriness in regions of myocardium demonstrating normal and reduced HED, consistent with its known properties of \(\beta\)-adrenergic stimulation.\(^15\)

The change in ventricular refractoriness during a norepinephrine infusion was no different in regions of myocardium demonstrating normal and reduced HED retention. This contrasts with the findings of prior studies in animal models that have reported that denervated viable myocardium distal to a zone of infarction, or created using phenol applied to the epicardium, demonstrates greater shortening of refractoriness in response to an isoproterenol or norepinephrine infusion than normally innervated areas of myocardium.\(^2\),\(^16\),\(^20\) Although the basis for the apparent absence of denervation supersensitivity in the patients enrolled in this study is uncertain, this may reflect the time dependence of sympathetic denervation. Prior studies have demonstrated the persistence of denervation supersensitivity in presumably infarcted areas of myocardium in the early postinfarction period or early after the application of phenol, with spontaneous resolution several months later.\(^16\) In this study, five or six patients with a prior myocardial infarction were studied more than 3 months after their myocardial infarction. The duration of heart disease in the remaining four patients without coronary artery disease is uncertain. It also is possible that denervation supersensitivity may have become apparent if higher doses of norepinephrine had been used. Although denervation supersensitivity has been demonstrated with norepinephrine infusion rates as low as 0.01 mg·kg\(^{-1}\)·min\(^{-1}\),\(^2\) the majority of animal studies have been performed using
infusion rates of norepinephrine significantly greater than those used in this study.\(^6,20\) And finally, it is possible that our failure to demonstrate denervation supersensitivity may have been due to the confounding alteration in the baroreceptor response. Norepinephrine resulted in an increase in the mean blood pressure in all patients in the study, which may have resulted in increased vagal tone and decreased sympathetic tone via the baroreceptor reflex.

**Study Limitations**

There are several limitations that were necessary to minimize the duration of the experimental protocol and reduce the risk to subjects. First, the effective refractory periods were not redetermined after the norepinephrine infusion was discontinued to confirm reproducibility. However, the effective refractory period was determined twice at each site under baseline conditions and during the norepinephrine infusion. Second, the effect of norepinephrine on the ventricular effective refractory period was determined at only a single infusion rate. Third, the majority of patients in this study did not have inducible monomorphic ventricular tachycardia. It is possible that different results might have been obtained if different patient selection criteria were used. However, these selection criteria were necessary to justify the surgical risk involved in a sternotomy. And finally, effective refractory periods and the response to norepinephrine were not examined in a control group of patients without malignant ventricular arrhythmias. Therefore, we cannot be certain if the scintigraphic evidence of sympathetic neuronal dysfunction detected in the patients in the present study are unique to patients with malignant ventricular arrhythmias or if they are common to the majority of patients with or without structural heart disease.

**Conclusions**

The results of the present study demonstrate that there is a correlation between scintigraphic evidence of sympathetic neuronal dysfunction and ventricular refractoriness in the human heart. Although the arrhythmogenic significance of scintigraphic evidence of sympathetic neuronal dysfunction and associated prolongation of refractoriness remains uncertain, these observations help validate the use of scintigraphic techniques for evaluation of sympathetic innervation in the human heart and may assist in the further evaluation of the relation between the sympathetic nervous system and ventricular arrhythmias. Further studies will be required to determine the prevalence and arrhythmogenic significance of scintigraphic evidence of neuronal dysfunction.

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**References**

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