Regional Cardiac Sympathetic Denervation in Patients With Ventricular Tachycardia in the Absence of Coronary Artery Disease

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Objectives. The aim of this study was to determine whether patients with ventricular arrhythmias in the absence of coronary artery disease also have abnormalities in sympathetic innervation.

Background. We have previously shown by cardiac sympathetic scintigraphy using iodine-123-metaiodobenzylguanidine (I-123-MIBG) that patients with ventricular tachycardia after myocardial infarction have regional cardiac sympathetic denervation. It is not known whether patients with ventricular tachycardia in the absence of coronary artery disease also have regional cardiac sympathetic denervation.

Methods. We performed cardiac I-123-MIBG and thallium-201 single-photon emission computed tomographic (SPECT) scans at rest in 18 patients (mean age 47 ± 18 years) with cardiomyopathy (n = 6), left ventricular hypertrophy (n = 1), valvular disease (n = 2) or a structurally normal heart (n = 9) who presented with monomorphic (n = 15) or polymorphic (n = 3) ventricular tachycardia. These scans were compared with scans in 12 control patients without ventricular tachycardia (mean age 30 ± 17 years) who had cardiomyopathy (n = 3) or a structurally normal heart (n = 9). Cardiac sympathetic denervation was defined as myocardial areas having thallium uptake with reduced or absent I-123-MIBG uptake.

Results. Twelve (67%) of 18 patients with ventricular tachycardia had regional cardiac sympathetic denervation compared with 1 (8%) of 12 patients who did not have ventricular tachycardia (p = 0.002). In the nine patients with a structurally normal heart and ventricular tachycardia, five (55%) patients had regional cardiac sympathetic denervation compared with zero of nine control patients with a structurally normal heart (p = 0.029). Five patients underwent right ventricular radiofrequency ablation for ventricular tachycardia, and sympathetic denervation was adjacent to the ablation site in one of these patients.

Conclusions. Patients with ventricular tachycardia in the absence of coronary artery disease have abnormal cardiac sympathetic innervation detectable by cardiac sympathetic scintigraphy. The role of regional cardiac sympathetic denervation in arrhythmogenesis remains to be determined.

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Sympathetic innervation to the heart modulates arrhythmogenesis. Reduction of sympathetic input to the left ventricle (by left stellctomy) in patients with the long QT interval syndrome exerts antiarrhythmic effects (1), whereas sympathetic stimulation enhances arrhythmogenesis in many animal models (2,3).

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Sympathetic nerves to the ventricle lie in the subepicardium, penetrating intramurally to innervate the endocardium. Phenol painted on a discrete area in the epicardium interrupts both afferent and efferent sympathetic function, effectively denervating myocardium downstream from the injured area (4–6). Similarly, experimental transmural infarction in a canine model interrupts sympathetic nerve function, which then causes sympathetic denervation in viable myocardium apical to the infarct (5,7–10). The subsequent denervation supersensitivity to circulating catecholamines (11) has been implicated in the pathogenesis of arrhythmias (12,13).

To understand further the presence and potential importance of regional cardiac sympathetic denervation, noninvasive imaging of the cardiac sympathetic nervous system can be performed by single-photon emission computed tomography (SPECT) after administration of iodine-123-labeled metaiodobenzylguanidine (I-123-MIBG) (14–16). The latter, a guanethidine derivative, is a radiolabeled analog of norepinephrine and is taken up by the postganglionic presynaptic sympathetic nerve terminals with the same uptake mecha-
nism used for norepinephrine (17). Scintigraphy with this agent has been shown in both dogs (18,19) and humans (20–22) to be capable of locating regional defects in cardiac sympathetic innervation (17–20). In a canine model after myocardial infarction, Minardo et al. (19) correlated the presence of sympathetic denervation detected by 1-123-MIBG scintigraphy with sympathetic denervation detected by electrophysiologic techniques.

Sympathetic denervation has also been demonstrated scintigraphically in patients after myocardial infarction (20–22) and in patients with cardiomyopathy (23,24) or the long QT syndrome (25). Stanton and colleagues (20) showed that patients with a history of myocardial infarction and ventricular tachycardia have a high prevalence of sympathetically mediated tachycardia. They proposed a role for sympathetic denervation in the pathogenesis of ventricular tachycardia in patients after myocardial infarction (13).

Because the pathogenesis of ventricular tachycardia in patients without coronary artery disease, particularly in those with a structurally normal heart, remains unclear, we speculated that abnormalities in cardiac sympathetic innervation may be critical in the pathogenesis of ventricular arrhythmia. The purpose of this study was to determine whether patients with ventricular arrhythmias in the absence of coronary artery disease also have abnormalities in sympathetic innervation.

Methods

Study patients. Twenty patients with documented ventricular arrhythmias in the absence of coronary artery disease underwent SPECT imaging after injection of I-123-MIBG. Inclusion criteria included ability to give informed consent, absence of coronary artery disease as detected by cardiac catheterization, echocardiography or exercise testing alone or in combination. Exclusion criteria included receiving medications known to interfere with I-123-MIBG uptake, such as calcium channel blockers, beta-adrenergic drugs or major tranquilizing agents (26). Two of the 20 patients who had no cardiac I-123-MIBG uptake and were subsequently found to be receiving medications known to inhibit I-123-MIBG uptake, were excluded from subsequent analysis. Clinical characteristics in the remaining 18 patients comprising Group I are shown in Table 1. Patients were judged as having a structurally normal heart if they had normal left ventricular dimensions, normal left ventricular systolic function and absent right ventricular abnormalities, as determined by echocardiography and cardiac catheterization. In addition, all patients with a structurally normal heart except for Patient 5 had normal thallium scans at rest. Patient 5 had an inferior thallium defect but was still included among those patients with a structurally normal heart because he had normal results on echocardiography and cardiac catheterization including left ventricular angiography. Patients with mitral valve prolapse without mitral regurgitation (Patient 7), the congenital long QT syndrome (Patient 8) and the acquired long QT syndrome (Patient 9) were considered to have a structurally normal heart. Fourteen of these 18 patients had coronary arteriographic findings confirming the presence of normal coronary arteries. The other four patients were women (26, 29, 40, and 67 years old, respectively) with no history suggestive of coronary artery disease. Two of these four patients had normal findings on exercise stress tests and echocardiography, one patient had a normal exercise stress test result with echocardiographic evidence of decreased left ventricular systolic function without regional wall motion abnormalities and one had normal echocardiographic findings and did not undergo exercise stress testing (Table 1). No patient in this group or the control group had diabetes mellitus or any diseases known to be associated with neuropathies.

Control group. The control patients (Group II) were 12 patients who underwent I-123-MIBG imaging and had both no evidence of coronary artery disease and no history of documented ventricular arrhythmias. Four of the 12 patients were normal, healthy volunteers with no known medical problems. Of the remaining eight patients, three showed no evidence of coronary artery disease by coronary arteriography; three others (11, 12 and 19 years old, respectively, and all within one family) had the diagnosis of familial hypertrophic cardiomyopathy with a family history of sudden death, and two other patients were women (25 and 46 years old, respectively) with no history of coronary artery disease and with normal findings on echocardiography and exercise stress testing. None of these 12 patients had defects on their thallium scans. Eight had no presenting symptoms (Table 1), but four had episodes of palpitation; electrophysiologic studies in these four failed to induce ventricular tachycardia.

Thallium-201 scintigrapy. A thallium-201 scintigram at rest was performed in 27 of the 30 patients; 3 others (1 patient in Group I and 2 patients in Group II) underwent thallium-201 scintigraphy as part of an exercise test. The protocol for the thallium-201 scans at rest was as follows: Patients were given an intravenous injection of 2.1 to 2.9 mCi of thallium-201. Twenty to 40 min after injection, cardiac images were obtained using 20% energy windows centered over the thallium-201 photopeak (80 keV) on a commercially available gamma camera equipped with a low energy, all-purpose collimator. Tomographic images were obtained with a rotating camera from right anterior oblique to left anterior oblique in an 180° arc at 3° per step (20 s per frame) yielding 60 sequential images. Single-photon emission computed tomographic images were then reconstructed using a 0.35/8 Butterworth filter to display between 8 and 16 tomographic slices through the short, vertical long and horizontal long axes. For the three patients who underwent thallium-201 scintigraphy in conjunction with treadmill exercise testing, the protocol was modified as follows: The patients were given an intravenous injection of 2.5 to 2.9 mCi of thallium-201 1 min before completion of exercise. Images were obtained in a manner similar to that described for the
Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Presenting Symptom or Arrhythmia</th>
<th>Cardiac Disease</th>
<th>Echocardiographic Results</th>
<th>Result of Stress Test</th>
<th>Cardiac Catheterization Results</th>
<th>TL-MIBG Results</th>
<th>EPS Results</th>
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</table>
| Group I
| 1     | 50/M     | VTNS   | SNH                            | NI             | NI                       | NI CA, NI LV            | Denervation, anteroseptal        | VTNS           | VT        |
| 2     | 24/M     | VT     | SNH                            | NI             | NI                       | NI CA                | Denervation, posterolateral and inferopical | VT            |
| 3     | 72/M     | VT     | SNH                            | NI             | NI                       | NI CA                | Denervation, anterolateral       | VTNS           | VT        |
| 4     | 69/F     | VTNS   | SNH                            | NI             | NI                       | NI CA, NI LV            | Denervation, inferor            | VTNS           | VT        |
| 5     | 44/M     | VT     | SNH                            | NI             | NI                       | NI CA, NI LV            | Denervation, anterolateral       | VTNS           | VT        |
| 6     | 61/M     | VT     | SNH                            | NI             | NI                       | NI CA, NI LV            | Denervation, anterolateral       | VTNS           | VT        |
| 7     | 27/M     | VT     | SNH, MVP                       | NI             | NI                       | NI CA, NI LV            | Denervation, anterolateral       | VTNS           | VT        |
| 8     | 26/F     | PMVT   | SNH, L QT                      | NI             | NI                       | NI                    | Denervation, anteroseptal        | PMVT/Vfib      |
| 9     | 40/F     | PMVT   | SNH, L QT                      | NI             | NI                       | NI                    | Denervation, anteroseptal        | Vfib           |
| 10    | 70/M     | VT     | LVH                            | LVI            | NI                       | NI CA                | Denervation, inferior and lateral | VT1            |
| 11    | 79/F     | VT     | MR, LV dil, MR                 | LV dil, MR     | NI                       | NI CA, MR             | Denervation, inferior            | VT1            |
| 12    | 31/M     | VT     | AR                             | AR             | NI                       | NI CA                | Denervation, apical             | VT1            |
| 13    | 36/F     | VT     | CMP/bx                         | NI             | NI                       | NI CA                | Denervation, anteroseptal        | VTNS           | VT        |
| 14    | 45/F     | VT     | DCM, LV dil                    | DCM, LV dil    | NI                       | NI CA                | Denervation, inferior            | VTNS           | VT        |
| 15    | 47/M     | VTNS   | DCM                            | DCM            | NI                       | NI CA, DCM            | Denervation, inferior            | VTNS           | VT        |
| 16    | 27/M     | VT     | DCM                            | DCM            | NI                       | NI CA                | Denervation, inferopical         | VTNS           | VT        |
| 17    | 29/F     | VT     | DCM                            | DCM            | NI                       | NI                    | Denervation, inferoicpical        | VTNS           | VT        |
| 18    | 67/M     | PMVT   | DCM                            | DCM            | NI                       | NI CA, DCM            | Denervation, inferoicpical        | VTNS           | VT        |
| Group II
| 19*   | 21/M     | None   | SNH                            | NI             | NI                       | NI                    | Denervation, inferior            | Ni            |
| 20*   | 26/M     | None   | SNH                            | NI             | NI                       | Ni                   | Denervation, inferior            | Ni            |
| 21*   | 37/M     | None   | SNH                            | NI             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 22*   | 43/M     | None   | SNH                            | Ni             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 23    | 40/F     | Palp   | SNH                            | Ni             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 24    | 23/F     | Palp   | SNH                            | Ni             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 25    | 66/F     | None   | SNH, Indet, Minor irreg        | Indet          | Minor irreg             | Ni                   | Denervation, inferior            | Ni            |
| 26    | 59/F     | Palp   | SNH                            | Ni             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 27    | 16/F     | Palp   | SNH, MVP                       | Ni             | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 28*   | 19/M     | None   | HCMi                           | HCM            | Ni                       | Denervation, inferior        | Ni            |
| 29*   | 12/F     | None   | HCMi                           | HCM            | Ni                       | Ni                   | Denervation, inferior            | Ni            |
| 30*   | 11/F     | None   | HCMi                           | HCM            | Ni                       | Ni                   | Denervation, inferior            | Ni            |

*Patients 19 to 22 were the four normal healthy volunteers. **Ventricular tachycardia only inducible with isoproterenol. #Spontaneous ventricular tachycardia with isoproterenol. §Patients 28 to 30 were from the same extended family. AR = aortic regurgitation; bx = by biopsy; CA = coronary arteries; CMP = cardiomyopathy; DCM = dilated cardiomyopathy; EPS = electrophysiologic study; F = female; HCM = hypertrophic cardiomyopathy; Indet = indeterminate; irreg = irregularities; L QT = long QT; LV = left ventricle; LV dil = left ventricular dilation; LVH = left ventricular hypertrophy; M = male; MR = mitral regurgitation; MVP = mitral valve prolapse; Ni = noninducible; Ni = normal; Palp = palpitation; PMVT = polymorphic ventricular tachycardia; pt = patient; SNH = structurally normal heart; TL-MIBG = thallium-201 imaging with iodine-123-metaiodobenzylguanidine; Vfib = ventricular fibrillation; Vfib = ventricular flutter; VT = ventricular tachycardia, VTNS = nonsustained ventricular tachycardia.

rest study immediately after exercise (stress) and 4 h later (redistribution). Only the redistribution images were used to compare with the I-123-MIBG images.

Iodine-123-metaiodobenzylguanidine imaging. High purity I-123-MIBG was synthesized according to previously published criteria (27) at a specific activity of 7 to 10 mCi/mg. Patients received an injection of 2.6 to 6.1 mCi of I-123-MIBG after completion of the thallium scan (at rest or redistribution) or on a separate day from the thallium scan. Images were obtained between 2 and 4 h after administration of I-123-MIBG to allow for the extraneurovesicular clearance of I-123-MIBG uptake (28). The technique for obtaining cardiac images after I-123-MIBG administration was similar to the protocol described for the thallium-201 images except for the 20% energy window, which was centered over the I-123-MIBG photopeak (159 keV).
Interpretations of the I-123-MIBG and thallium-201 cardiac images were performed by nuclear medicine physicians (R.W.B. and H.N.W.) who were unaware of the patients' clinical history. Sympathetic denervation was defined to be present when areas showed "thallium/MIBG mismatch," that is, areas of myocardium demonstrated perfusion on the thallium-201 scan but had reduced or absent uptake on the I-123-MIBG scan (Fig. 1). Iodine-123-metaiodobenzylguanidine (I-123-MIBG) images were used for sustained, nonsustained and polymorphic ventricular tachycardia induced after isoproterenol infusion. Standard definitions of the presentation of ventricular tachycardia and had detailed electrophysiologic mapping of the origin of the ventricular tachycardia (31). The sites of ventricular tachycardia foci in these five patients were identified fluoroscopically and then compared with sites of regional sympathetic denervation identified on the SPECT scans to determine the proximity of the ventricular tachycardia focus to the area of sympathetic denervation. Patients 1, 5 and 7 had I-123-MIBG scintigraphy within 2 days after radiofrequency ablation of the ventricular tachycardia focus, and Patients 2 and 12 had I-123-MIBG scintigraphy before ablation.

Statistics. The Fisher exact test was used to compare categoric variables and the unpaired $t$ test was used to compare continuous data between the two groups. A $p$ value $< 0.05$ was considered significant.

Results

The clinical features of the 18 study patients (Group I) and 12 control patients (Group II) are shown in Table 1. The mean age of the study patients (48 ± 19) exceeded the mean age of the control patients (30 ± 16, $p = 0.015$). However, for the subgroup of patients with a structurally normal heart, the mean ages between the study group (46 ± 18) and the control group (35 ± 16) did not differ significantly ($p = Ns$). The presenting arrhythmia for the study group was monomorphic sustained ventricular tachycardia ($n = 12$), monomorphic nonsustained ventricular tachycardia ($n = 3$) or polymorphic ventricular tachycardia ($n = 3$). The cardiac diagnoses for these 18 patients were cardiomyopathy ($n = 6$), left ventricular hypertrophy ($n = 1$), mitral regurgitation with left ventricular dilatation ($n = 1$), bicuspid aortic valve with mild aortic regurgitation ($n = 1$) and structurally normal heart ($n = 9$). All patients with a structurally normal heart and Patients 10 to 13 had normal left ventricular systolic function. Of the nine patients with a structurally normal heart, one had mitral valve prolapse and two had a long QT (duration 480 and 550 ms, respectively) before their arrhythmia.

Of the 12 control patients (Group II), 3 had hypertrophic cardiomyopathy and 9 had a structurally normal heart. One of the latter nine patients had mitral valve prolapse.

Results of iodine-123 metaiodobenzylguanidine-thallium scans. The interpretation by the observers was concordant in 28 (93%) of 30 cases as to the presence or absence of regional cardiac sympathetic denervation (that is, I-123-MIBG–thallium mismatch). In Patient 1 the final interpretation was minimal sympathetic denervation, whereas in Patient 30 the I-123-MIBG scan was considered to be normal. Twelve (67%) of the 18 Group I patients had regional cardiac sympathetic denervation demonstrated by I-123-MIBG scans compared with only 1 (8%) of 12 of the Group II patients ($p = 0.002$, Fig. 2 and 3). The myocardial areas showing regional cardiac sympathetic denervation were inferior ($n = 5$), inferoapical ($n = 3$), posterolateral ($n = 1$), lateral ($n = 1$), anteroseptal ($n = 2$), apical ($n = 1$) and anterolateral ($n = 1$) (Fig. 4). Two of the 12 patients from Group I had sympathetic denervation involving more than one area. Patient 28 from Group II had inferior regional...
Ventricular tachycardia focus versus area of denervation. Five patients underwent successful radiofrequency ablation of ventricular tachycardia. Patients 2 and 7 did not have evidence for sympathetic denervation. The sites of the ventricular tachycardia focus and the sites of sympathetic denervation in the other three patients are shown in Figure 5. Patients 1, 5 and 12 had evidence for sympathetic denervation in the left ventricle while the ventricular tachycardia focus was ablated in the right ventricular outflow tract. It is possible that Patient 1 had sympathetic denervation at or near the area of the ventricular tachycardia ablation site. However, because sympathetic scintigraphy of the right ventricle was not performed, it is unknown whether any of the five patients also had sympathetic denervation involving the right ventricle. Patient 12 had recurrent ventricular tachycardia with a right bundle branch block configuration within 2 months of successful radiofrequency ablation for right ventricular outflow tract tachycardia.
eral left ventricle remote from the radiofrequency ablation site in the
right ventricular anterior wall. In Patient 1, sympathetic denervation was in the an-
teroseptal region in the left ventricle adjacent to the right ventricular
site of radiofrequency ablation. In Patient 5, it was in the anterolat-
eral left ventricle remote from the radiofrequency ablation site in the
right ventricular anterior wall. In Patient 12, it was in the inferoap-
tical left ventricle remote from the radiofrequency ablation site in the
right ventricular outflow tract.

Discussion

Major observations. We believe that our study is the first
to demonstrate abnormalities in cardiac sympathetic func-
tion detected by I-123-MIBG scintigraphy in patients with-
out coronary artery disease who had ventricular tachycar-
dia. The abnormal sympathetic scintigraphic findings are
probably due to regional cardiac sympathetic denervation,
as has been shown in animal and human studies (19,32).
However, it is possible that the I-123-MIBG defects may be
a more sensitive marker of epicardial myocardial injury that
is not detectable by conventional imaging modalities. The
finding of I-123-MIBG defects in patients with an apparently
structurally normal heart indicates that these patients actu-
almente do not have a structurally normal heart but, rather, have
evidence suggestive of cardiac sympathetic dysfunction.
Whether this sympathetic dysfunction is a result of a neu-
ropathy or other myopathic processes and whether its pres-
ence is important to the genesis of ventricular tachycardia
cannot be established from this study.

Role of cardiac sympathetic innervation. The human ven-
tricle is profusely innervated with sympathetic fibers that
modulate the electrophysiologic properties of the specialized
and working fibers (33). Enhanced sympathetic tone or
reduced parasympathetic tone, inferred by loss of sinus cycle length variability or reduced baroreceptor sensitivity,
have been demonstrated to be associated with increased incidence of sudden cardiac death after myocardial infarc-
tion (34–38).

It is now well established in dogs (7–10,18,19) and hu-
mans (20–22) that myocardial infarction causes regional areas of sympathetic denervation. These denervation sites
subsequently exhibit denervation supersensitivity that is
manifested by an exaggerated electrophysiologic response to
circulating catecholamines (11,12). Dogs with regional car-
diac sympathetic denervation and sympathetic supersensi-
tivity are more likely to have inducible ventricular fibrillation
that can be prevented by propranolol (12). The correlation of
regional cardiac sympathetic denervation with ventricular
arrhythmias in humans has also been demonstrated, al-
though intravenous beta-adrenergic blockade failed to pre-
vent induction of ventricular tachycardia (20). We have
hypothesized that patients with coronary artery disease can
develop regional cardiac sympathetic denervation and symp-
pathetic supersensitivity after episodes of myocardial infarc-
tion that, in the presence of increased cardiac sympathetic
activity, create heterogeneous ventricular excitation and
repolarization patterns that can cause ventricular arrhyth-
mas (13). Consistent with this hypothesis is the finding of an
increase in cardiac sympathetic activity documented by
excessive cardiac norepinephrine overflow in patients who
have survived an aborted episode of sudden cardiac death
(39). Whether this hypothesis is more applicable to the origin
of less organized rhythms such as ventricular fibrillation
compared with ventricular tachycardia is not known. Nev-
evertheless, the beneficial effects of beta adrenergic blockers
on cardiac death in patients after myocardial infarction may, in part, be due to blocking the supersensitive response
to norepinephrine and eliminating the electrophysiologic heterogeneity.

Any damage to the mycardium should be capable of
interrupting neural axons, creating areas of sympathetic (and
vagal) denervation followed by denervation supersensitivity.
Abnormal I-123-MIBG patterns have been found in patients
with dilated cardiomyopathy (23,24). Prior studies in hyper-
tensive rats (40) have demonstrated intramyocardial intersti-
tial fibrosis and microscopic scarring; therefore, it is not
surprising that I-123-MIBG defects would be observed in
patients with left ventricular hypertrophy from hyperten-
sion. However, there are no apparent reasons for the pa-
tients without structural heart disease to have regional
cardiac sympathetic denervation. Obviously, it is possible
that they do have structural damage that is not apparent
using the relatively gross clinical tests available. Biopsies
were not routinely obtained in these patients, and they might
have revealed cellular abnormalities. Whatever the mecha-
nism, in this study there was an increased prevalence of
focal I-123-MIBG defects in patients with ventricular ar-

Figure 5. Schematics representing locations of successful ventricu-
lar tachycardia radiofrequency ablation and areas of sympathetic
denervation for three patients. Superimposed short-axis slices of the
left ventricle are shown with the anterior and posterior right
ventricular (RV) walls. The black circles represent areas where
radiofrequency ablation eliminated ventricular tachycardia, and the
lightened areas represent sympathetic denervation within the left
ventricle.

a) Patient 1

b) Patient 5

c) Patient 12

RV Anterior Apex
Septum

RV

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rhythmias compared with the control group. This increased prevalence of focal I-123-MIBG defects among patients with ventricular tachycardia was particularly noteworthy in the subgroup of patients with structurally normal hearts.

The presence of regional cardiac sympathetic denervation in patients without coronary artery disease may be arrhythmogenic by the same mechanisms proposed for patients with coronary artery disease, as noted previously. The need for catecholamine infusion to initiate ventricular tachycardia during electrophysiologic testing, the clinical benefits of beta adrenoceptor or calcium channel blockade and precipitation of ventricular tachycardia by exercise all support the importance of sympathetic stimulation. However, there were six patients in Group I with ventricular tachycardia who had normal cardiac sympathetic scintigraphy. Therefore, it is possible that the presence of sympathetic denervation is not entirely clear. Abnormalities in thallium scintigraphy have been found in some patients with the long QT syndrome (25). The pathogenesis is not entirely clear (46). Abnormalities in left ventricular wall motion have been noted in I-123-MIBG scintigraphy; their occurrence as a normal phenomenon in I-123-MIBG scintigraphy may be secondary to the decrease in myocardial norepinephrine concentrations in the apex compared with the base (42, 43) or just a result of normal myocardial apical thinning.

In this study, only 1 (8%) of 12 patients without ventricular arrhythmias had evidence of sympathetic denervation; this patient had hypertrophic cardiomyopathy and a family history of sudden cardiac death. During the follow-up period, this patient experienced syncope but did not undergo electrophysiologic testing. None of the nine control patients with a structurally normal heart had sympathetic denervation.

No patient in the control group had dilated cardiomyopathy. Prior studies (23, 24) on patients with dilated cardiomyopathy indicated that I-123-MIBG uptake was directly related to left ventricular ejection fraction. However, these studies did not comment on the presence of ventricular arrhythmias in those patients who underwent sympathetic scintigraphy. Although the presence of I-123-MIBG defects may be a nonspecific finding, in patients with idiopathic dilated cardiomyopathy the presence of regional cardiac sympathetic denervation detectable by I-123-MIBG was a specific finding in patients with a structurally normal heart, usually limited to those with documented ventricular arrhythmias.

Wilber et al. (44) recently demonstrated the results of I-123-MIBG scans performed in five patients 1 to 4 months after radiofrequency ablation of adenosine-sensitive ventricular tachycardia. Four patients had normal scan results, whereas one patient had diffusely diminished uptake of I-123-MIBG. The difference in findings between our report and that of Wilber et al. (44) is probably due to differences in study patients and in timing of I-123-MIBG scintigraphy. In our unselected patients with different ventricular arrhythmias, various mechanisms were responsible for their ventricular tachycardias. Furthermore, I-123-MIBG scans were performed at the time patients presented to our institution in our study, whereas in the study of Wilber et al. (44) the scans were performed 1 to 4 months after radiofrequency ablation.

The long QT syndrome. Two patients in Group I had a long QT interval. In one patient (mentioned in a prior report (20)), MIBG scintigraphy was normal, but regional cardiac sympathetic denervation was demonstrated in the other. Both of these patients had a structurally normal heart. The long QT syndrome has been attributed to abnormal sympathetic innervation, possibly with increased left-sided versus decreased right-sided sympathetic stimulation (45), although the pathogenesis is not entirely clear (46). Abnormalities in MIBG scintigraphy have been found in some patients with the long QT syndrome (25).
Sympathetic denervation and electrophysiologic testing. Inducibility of ventricular tachycardia at electrophysiologic study was not significantly correlated with the presence of sympathetic denervation, although there was a trend toward this correlation. The small number of patients may have been insufficient to reveal a significant difference between those with and without tachycardia inducibility. However, the lack of correlation may also be explained by the decreased reliability of electrophysiologic testing in inducing ventricular tachycardia in patients without than in patients with coronary artery disease (47).

Limitations. In this report sympathetic denervation was diagnosed using I-123-scintigraphy. Iodine-123-labeled metaiodobenzylguanidine is taken up by postganglionic sympathetic neurons by the same uptake mechanism used for norepinephrine. Therefore, one could argue that an I-123-MIBG defect represents failure of uptake and not truly sympathetic denervation. Furthermore, because we performed I-123-MIBG scintigraphy 2 to 4 h after injection of the tracer, it is also possible that MIBG defects represent normal uptake with enhanced release of MIBG, which also may not represent true sympathetic denervation (48). Because we did not perform I-123-MIBG scans immediately after injection, we do not know whether these patients would have had early uptake of MIBG. Studies in patients after acute myocardial infarction (23) and with dilated cardiomyopathy (21) have revealed that initial I-123-MIBG scans demonstrate significantly more MIBG uptake than is seen on delayed imaging. This initial uptake was thought to be due to nonspecific uptake (28.49), although more recently published data suggest that early nonspecific MIBG uptake (uptake 2) in humans is not significant (48).

Nevertheless, the correlation of sympathetic denervation by electrophysiologic testing to defects on I-123-MIBG scintigraphy has been demonstrated in the dog model (19) and suggests that focal MIBG defects result from regional adrenergic dysfunction rather than a global process such as enhanced turnover of catecholamines. At present, the exact mechanism by which regional adrenergic dysfunction produces focal MIBG defects is unclear. Further confirmatory data have been provided by Calkins and colleagues (32), who demonstrated a correlation between sympathetic denervation by refractory period responses and sympathetic defects detected by positron emission tomography using a different neurotransmitter (C-11 hydroxyephedrine), an agent that shares the same uptake mechanism as I-123-MIBG. These studies (19,32) suggest that scintigraphic evidence of decreased localization of norepinephrine analogues (I-123-MIBG or C-11 hydroxyephedrine) represents sympathetic denervation. With the present state of the art, it is difficult to prove in humans the presence of regional cardiac sympathetic denervation by applying techniques that we have used in dogs, such as sympathetic nerve stimulation and norepinephrine infusion while measuring effective refractory period responses at multiple left ventricular sites. Accurate identification of stimulation sites to matched areas of denervation by I-123-MIBG scintigraphy is difficult. Furthermore, we believed that there was no justification for obtaining myocardial biopsy specimens to assess norepinephrine myocardial concentration in denervated areas.

The mean age of the control group in this study was significantly less than that of the study group; however, the control group included three patients between 11 and 19 years old from one family with hypertrophic cardiomyopathy. Although it is possible that regional cardiac sympathetic denervation occurs with the aging process, there was great overlap among ages in both groups of patients (with and without denervation). Furthermore, in the subgroup of patients with a structurally normal heart there was no significant difference between ages in the study and control groups. Patients as young as 19 years demonstrated regional cardiac sympathetic denervation, whereas patients as old as 66 years had normal I-123-MIBG scans. Thus, it does not appear that sympathetic denervation is merely an aging phenomenon.

Another limitation may be that the spectrum of cardiac diseases present between both groups was different. However, the findings of this study were still valid when comparing the subgroup of patients with structurally normal hearts. The comparison of the areas of sympathetic denervation with the sites of origin of ventricular tachycardia was limited by comparisons of fluoroscopic images with SPECT scans. Some patients may have had right ventricular regional sympathetic denervation that was not detectable by our standard SPECT scanning techniques.

In addition, three patients had I-123-MIBG scintigraphy after radiofrequency ablation. However, one of these patients had a normal I-123-MIBG scintigram after receiving 28 radiofrequency applications, whereas another patient had sympathetic denervation at a site remote from the ablation. Other investigators failed to find focal MIBG defects in patients imaged 1 to 4 months after radiofrequency ablation of ventricular tachycardia (44). Although we cannot exclude an abnormal I-123-MIBG scintigram resulting from radiofrequency ablation, it is unlikely because of the findings from the two patients just described and because radiofrequency ablation causes limited subendocardial lesions while sympathetic nerves traverse through the subepicardium.

Conclusions. We have described abnormalities in sympathetic innervation of the human heart in patients with ventricular arrhythmias in the absence of coronary artery disease and, for the first time, in patients with an apparently structurally normal heart. In some of the patients with ventricular tachycardia, the defects seen on I-123-MIBG scintigraphy were the only detectable structural cardiac abnormalities. The findings from this study indicate that regional cardiac sympathetic denervation is present in many patients with ventricular tachycardia who do not have coronary artery disease, including patients with a structurally normal heart. The presence of regional cardiac sympathetic denervation may play a role in arrhythmogenesis in patients without apparent heart disease or, at the very least, may be
a marker for cardiac abnormalities not apparent by conventional testing.

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References