Cardiac Autonomic Dysfunction in Brugada Syndrome

Thomas Wichter, MD, FESC; Peter Matheja, MD; Lars Eckardt, MD; Peter Kies, MD; Klaus Schäfers, PhD; Eric Schulze-Bahr, MD; Wilhelm Haverkamp, MD; Martin Borggrefe, MD, FESC; Otmar Schober, MD, PhD, FESC; Günter Breithardt, MD, FESC; Michael Schäfers, MD

Background—Patients with Brugada syndrome present with characteristic ECG abnormalities (atypical right bundle-branch block and ST-segment elevation) and life-threatening ventricular tachyarrhythmias despite structurally normal hearts. Involvement of the autonomic nervous system is suggested by the occurrence of ventricular tachyarrhythmias and sudden death at rest or during sleep and by changes of typical ECG signs under pharmacological modulation of the myocardial autonomic tone.

Methods and Results—This study investigated the presynaptic cardiac neuronal reuptake of norepinephrine (uptake 1) in 17 patients with Brugada syndrome and 10 age-matched control subjects with the use of the norepinephrine analogue [123I]m-iodobenzylguanidine ([123I]-MIBG), single-photon emission CT (SPECT), and quantitative 33-segment bull’s-eye analysis. Regionally reduced [123I]-MIBG uptake was present in 8 (47%) of 17 patients with Brugada syndrome but in none of the control subjects. Quantitative analysis showed segmented reduction of [123I]-MIBG uptake in the inferior and septal left ventricular wall in patients with Brugada syndrome compared with control subjects ($P<0.05$). No correlation was found between the findings of [123I]-MIBG-SPECT and clinical characteristics of the study patients.

Conclusions—The present study demonstrated an abnormal [123I]-MIBG uptake in patients with Brugada syndrome, indicating presynaptic sympathetic dysfunction of the heart. These findings may have potential impact on the pathophysiology and arrhythmogenesis in patients with Brugada syndrome. Future quantitative investigations of the presynaptic and postsynaptic sympathetic and parasympathetic branches of the cardiac autonomic nervous system may clarify whether these observations represent a primary adrenergic dysfunction or an imbalance between sympathetic and parasympathetic innervation of the heart. (Circulation. 2002;105:702-706.)

Key Words: Brugada syndrome ■ death, sudden ■ nervous system, autonomic ■ tomography ■ norepinephrine

Ventricular fibrillation and sudden cardiac death are mostly attributed to structural heart disease, with the majority occurring in the setting of acute or chronic myocardial infarction. Overall, only 6% to 12% of the individuals who experienced sudden death were found to have no structural heart disease.1 These individuals were classified as having “idiopathic ventricular fibrillation” or “unexplained cardiac arrest.”2 After some earlier case reports and a small series by Martini et al,3 Brugada and Brugada4 in 1992 identified a new category of patients without structural heart disease but with specific ECG abnormalities who survived an episode of cardiac arrest or died suddenly from ventricular fibrillation. They described the “syndrome of right bundle branch block, persistent ST segment elevation, and sudden cardiac death,”4,5 also known as Brugada syndrome6–8 (Figure 1).

The pathophysiology of Brugada syndrome is still under investigation. Interestingly, unlike other diseases, ventricular fibrillation and sudden death mainly occur in the resting state, predominantly during sleep.9,10 The typical ECG changes are variable over time and can be modulated by exercise or pharmacological interventions that interact with the cardiac autonomic innervation. For example, ECG signs of Brugada syndrome are diminished during exercise and isoproterenol infusion. In contrast, they may be unmasked or intensified by antiadrenergic drugs (β-blockers), α-adrenergic receptor stimulators (norepinephrine), parasympathomimetic drugs (edrophonium), or sodium channel blockers (ic, ajmaline, flecainide, or procainamide).11,12 The acute intravenous administration of the latter has been used as a diagnostic test to unmask the typical ECG abnormalities in patients or family members with suspected Brugada syndrome.12

The clinical characteristics and the variability of the typical ECG features under autonomic modulation indicate the potential role of the cardiac autonomic nervous system in the pathogenesis and arrhythmogenesis of Brugada syndrome.
The diagnosis of Brugada syndrome was made on the basis of typical ECG features, clinical arrhythmic events, and the absence of identifiable structural heart disease. Detailed noninvasive and invasive investigations included 2D echocardiography, left and right ventricular angiography, coronary angiography, MRI, and endomyocardial biopsy. No patient had ECG signs of left ventricular hypertrophy or prolongation of the QT interval. All patients underwent an invasive electrophysiological study involving programmed ventricular stimulation with up to 3 extrastimuli as previously reported and pharmacological provocation with the use of intravenous ajmaline (1 mg/kg within 5 minutes) to unmask or intensify ECG signs of Brugada syndrome.

All patients had characteristic ECG signs of Brugada syndrome with atypical right bundle-branch block and ST-segment elevation (Figure 1A). Thirteen patients had a history of survived cardiac arrest (n=8) or unexplained syncope (n=5). The remaining 4 patients had a family history of Brugada syndrome or unexplained premature cardiac arrest or sudden death. In these 4 asymptomatic patients, typical ECG abnormalities indicating Brugada syndrome were found during routine ECG examination. Genetic analyses disclosed a mutation in the cardiac sodium channel gene SCN5A in only 1 of the 15 patients tested.

Control Group
An age-matched group of 10 patients (5 men and 5 women aged 43±12 years, range 25 to 62 years, median 43 years; P=NS versus study patients) with medullary carcinoma of the thyroid gland served as a control group. They underwent ¹²³I-MIBG-SPECT imaging to exclude pheochromocytoma in the setting of multiple endocrine neoplasms. All control subjects had low-risk profiles with normal cardiovascular examination results, resting 12-lead ECGs, and exercise tests. No control subject was on drug treatment or had a history, sign, or symptom of cardiac disease or of diseases possibly affecting the cardiac autonomic nervous system.

Data Acquisition and Data Analysis

Data Acquisition
All patients and control subjects underwent ¹²³I-MIBG-SPECT imaging to assess cardiac norepinephrine release and reuptake in the heart. Details of the scanning procedure were reported and discussed elsewhere. Briefly, all subjects were off medication for at least 36 hours. After the thyroid gland was blocked with perchlorate, 300 MBq of ¹²³I-MIBG (Mallinckrodt Diagnostics) with a specific activity 280 to 420 MBq/mg was injected intravenously. SPECT images were acquired 4 hours after injection with the use of a 3-headed gamma camera (Multispect3, Siemens Medical Systems) equipped with low energy all purpose collimators.

To exclude abnormal myocardial perfusion despite normal epicardial coronary arteries (small-vessel disease), additional resting ⁹⁹mTc-tetrofosmin-SPECT was performed in the first 6 patients within 2 to 5 days after the ¹²³I-MIBG study. Because of normal perfusion SPECT images in all of these patients and the normal coronary angiograms and exercise tests in the entire study group, perfusion SPECT imaging was not continued in the subsequent patients to minimize radiation exposure.

Data Analysis
As described earlier, the regional ¹²³I-MIBG uptake of the left ventricular myocardium was measured quantitatively in each patient with the use of a 33-segment bull’s-eye analysis as the percentage uptake relative to the segment with maximal uptake (100%). Abnormal reduction of ¹²³I-MIBG uptake was defined as a reduction of tracer uptake by >2 SD of the mean value of the same segment in the control group. A patient study was classified as abnormal if it showed at least 3 adjacent segments with reduced tracer uptake that were not exclusively located in the most basal segments of the bull’s eye. The extent of affected left ventricular myocardium was assessed by calculating the total area of abnormal segments of the polar map. For each segment of the bull’s eye, the mean±SD of ¹²³I-MIBG uptake was calculated and compared with the corresponding segment in the control group. A nonparametric U test (Mann-Whitney) was used to test for the significance of differences in the regional ¹²³I-MIBG uptake between patients and control subjects. The correlation between the presence or absence of abnormal ¹²³I-MIBG uptake and clinical patient characteristics was tested with the use of a x² test or Mann-Whitney U test as appropriate. A value of P<0.05 was considered significant.
Tetrofosmin-perfusion SPECT revealed homogeneous tracer uptake in all of the 6 patients with Brugada syndrome investigated, although 4 of them showed significant reduction of regional 123I-MIBG uptake.

All 123I-MIBG scans in the control group showed homogeneous uptake in the entire left ventricular myocardium. In the patients with Brugada syndrome, 103 (18.4%) of 561 segments showed a significant reduction of 123I-MIBG uptake. SPECT images were classified as abnormal in 8 (47%) of 17 patients, with 79 (29.9%) of 264 segments demonstrating reduced tracer uptake (Figure 2). Table 2 summarizes the regional distribution, defect area, and mean tracer uptake in patients with an abnormal 123I-MIBG scan. In the inferior and inferoseptal wall, 123I-MIBG uptake was reduced (P<0.05, Figure 3). However, no correlation was found between the results of 123I-MIBG-SPECT and the clinical characteristics of the study patients. In particular, there was no relation to age, sex, family history, spontaneous or inducible sustained ventricular tachyarrhythmias, syncope, or cardiac arrest.

Discussion

SPECT imaging with the use of 123I-MIBG as a norepinephrine analogue enables noninvasive and quantitative assessment of the norepinephrine turnover as a result of the release and reuptake at the presynaptic site. The present study used quantitative 123I-MIBG-SPECT to further elucidate the nature of suggested autonomic dysfunction and investigated for the first time in vivo the presynaptic adrenergic function in a considerably large cohort of patients with the rare condition of Brugada syndrome. The results strongly suggest an abnormal presynaptic myocardial innervation demonstrating a regional reduction of tracer reuptake in 47% of the patients. They confirm and extend previous observations by radionuclide studies using 123I-MIBG-SPECT, which demonstrated regional reduction of transporter-mediated neuronal catecholamine reuptake (uptake 1) in 2 case reports of Brugada syndrome.16,17 In contrast, Miyazaki et al11 did not find abnormalities of 123I-MIBG-SPECT in 3 of 4 patients with Brugada syndrome and concluded that autonomic dysfunc-

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Short-axis (top) and vertical long-axis (bottom) slices of 123I-MIBG-SPECT (middle and right columns) and matching 99mTc-tetrofosmin-SPECT (left column) of a patient with symptomatic Brugada syndrome (patient No. 5 from Table 1). 123I-MIBG uptake is locally reduced in inferior and inferolateral myocardial wall despite homogeneous myocardial blood flow (99mTc-tetrofosmin-SPECT). In this patient, additional early image acquisition (10 minutes post-injection) was performed. This illustrates kinetics of 123I-MIBG in inferior wall, showing accelerated washout of 123I-MIBG from early (middle column) to delayed (right column) images, resulting in regional defect in image acquired 240 minutes post-injection. Ant indicates anterior; Lat, lateral; Inf, inferior; and Sept, septal wall.

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<th>EPS Event</th>
<th>Resting MBF</th>
<th>123I-MIBG-SPECT</th>
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<td>Abnormal</td>
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EPS indicates electrophysiological study; F, female; M, male; MBF, myocardial blood flow; N, no; ND, not done; nsVT, nonsustained ventricular tachycardia; pVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; and Y, yes.
tion may not be a primary disease process. However, their patient population was small, and their $^{123}$I-MIBG-SPECT imaging protocol was not explained.

**Potential Mechanisms of Autonomic Dysfunction in Brugada Syndrome**

**Hypoperfusion**
Myocardial hypoperfusion with reduced tracer uptake can be excluded as a mechanism of sympathetic dysfunction in Brugada syndrome because exercise stress testing, coronary angiography, and myocardial perfusion ($^{99m}$Tc-tetrofosmin-SPECT, n=6) were normal in all patients with Brugada syndrome.

**Increased Sympathetic Activity**
High levels of circulating plasma catecholamines have been suggested as a potential mechanism for the diffuse reduction of presynaptic tracer uptake ($^{123}$I-MIBG, $^{1}$C-hydroxyephedrine), acceleration of tracer washout, and the subsequent downregulation of postsynaptic β-adrenergic receptor density in patients with heart failure or pheochromocytoma. Increased sympathetic activity confined locally to the heart may result either from increased presynaptic release (firing rates of efferent sympathetic nerve fibers) or from decreased synaptic clearance (uptake 1) of norepinephrine. Subsequently, increased concentrations of norepinephrine in the synaptic cleft would result in some degree of competitive inhibition of intraneuronal tracer reuptake and in a downregulation of postsynaptic β-adrenoceptor density. This mechanism of adrenergic dysfunction has been demonstrated in patients with idiopathic right ventricular outflow tract tachycardia and arrhythmogenic right ventricular cardiomyopathy. In these conditions, however, ventricular tachyarrhythmias are frequently capable of being provoked by exercise or catecholamines and of being suppressed by antiadrenergic therapy. In contrast, in the Brugada syndrome, ventricular arrhythmias and sudden death occur mainly at rest or during sleep, suggesting parasympathetic dominance to be a triggering factor. Moreover, ST-segment elevation is augmented by β-blockade or parasympathetic stimulation, whereas it diminishes or disappears with β-adrenergic stimulation. For these reasons, increased sympathetic activity appears to be very unlikely as a mechanism of the impaired presynaptic reuptake of norepinephrine in patients with Brugada syndrome as assessed by $^{123}$I-MIBG-SPECT imaging in the present study.

**Decreased Sympathetic Activity**
In consequence, an impairment of the presynaptic adrenergic function is the most likely mechanism of reduced presynaptic $^{123}$I-MIBG reuptake in patients with Brugada syndrome. This presynaptic dysfunction may be related to a reduction in the number or function of effent sympathetic neurons with a subsequent reduction of norepinephrine release to the synaptic cleft and/or a reduction of transport capacity for the reuptake of norepinephrine (or $^{123}$I-MIBG) from the synaptic cleft. Such abnormalities may be induced by either sympathetic denervation or modulation of neuronal activity. The latter may be influenced by various factors, including a reduction of sodium channel activity or an increase of parasympathetic activity with vagal dominance.

**Autonomic Imbalance and Arrhythmogenesis**
An imbalance of the autonomic tone is considered to increase the propensity to develop ventricular arrhythmias in various cardiac diseases. In conditions with exercise- or catecholamine-sensitive ventricular tachyarrhythmias, such as idiopathic ventricular tachycardia and hypertrophic or arrhythmogenic right ventricular cardiomyopathy, an increased sympathetic activity with abnormal adrenergic stimulation of the myocardium has been discussed as a potential pathophysiological mechanism.

In patients with Brugada syndrome, however, a reduced adrenergic activity with subsequent dominance of the parasympathetic tone may be discussed as a mechanism of autonomic imbalance. A lack of sympathetic drive and acetylcholine stimulation reduce cAMP production, with a potential impact on protein phosphorylation and spatial heterogeneity of calcium transients, which may be arrhythmogenic. This imbalance may be even more intense at times of physiological downregulation of adrenergic activity, which partly explains the propensity for ventricular tachyarrhythmias and sudden death at rest or during sleep in Brugada syndrome.

**Study Limitations**
Although the number of patients with Brugada syndrome investigated in the present study is small, they represent a

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**TABLE 2. Distribution and Extent of Reduced Tracer Uptake in 264 Bull’s-Eye Segments in 8 of 17 Patients (47%) With Brugada Syndrome and Abnormal $^{123}$I-MIBG-SPECT**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Septal</th>
<th>Inferior</th>
<th>Lateral</th>
<th>Anterior</th>
<th>Apical</th>
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<td>Segments, n (%)</td>
<td>79 (29.9)</td>
<td>14 (5.3)</td>
<td>38 (14.4)</td>
<td>18 (6.8)</td>
<td>6 (2.3)</td>
<td>3 (1.1)</td>
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<tr>
<td>Bull’s-eye area, %</td>
<td>29.8±12.9</td>
<td>6.2±3.7</td>
<td>19.5±4.1</td>
<td>10.7±8.6</td>
<td>4.0±4.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Segment uptake, %</td>
<td>58.4±12.0</td>
<td>54.8±10.1</td>
<td>51.0±8.6</td>
<td>65.8±8.4</td>
<td>77.0±5.2</td>
<td>48.3±1.5</td>
</tr>
</tbody>
</table>

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**Figure 3.** Bull’s-eye display of differences of segmental $^{123}$I-MIBG uptake between control subjects and patients with Brugada syndrome. Central segments represent apical regions, and peripheral segments display basal regions of left ventricle. Non-parametric U tests (Mann-Whitney) were performed, and a value of $P<0.05$ was considered significant.
considerably large, carefully selected, and well-characterized cohort of a rare cardiac disorder. The true incidence and extent of sympathetic dysfunction may have been underestimated because the present study used relative quantification of SPECT imaging, which allows only the identification of regional abnormalities. Global or diffuse reductions of presynaptic adrenergic function, which may also be present in Brugada syndrome, can be detected by only absolute quantification with the use of advanced PET techniques. 20,21

Although the results of the present study indicate abnormal release and/or reuptake of norepinephrine to and/or from the synaptic cleft, the catecholamine concentration in the synaptic cleft and the firing activity of the efferent sympathetic nerves were not measured directly. In addition, the present study provides no information on the postsynaptic β-adrenergic receptor density in reaction to the presynaptic dysfunction and on the function of the parasympathetic branch of the cardiac autonomic nervous system. However, both aspects may be involved in the pathogenesis of Brugada syndrome.

Conclusions

The present study may be considered as a first step toward a more detailed understanding of the nature and pathogenetic impact of myocardial autonomic dysfunction in patients with Brugada syndrome. The results provide strong indication of presynaptic myocardial sympathetic dysfunction in Brugada syndrome. At the present time, it remains unclear whether the finding of an autonomic dysfunction represents a primary adrenergic disorder or an imbalance between sympathetic and parasympathetic innervation in these patients.

To further elucidate and characterize the role of the autonomic nervous system in Brugada syndrome, in vivo investigations of the sympathetic and parasympathetic branches are required, including quantitative assessment of presynaptic transmitter release and reuptake and of postsynaptic receptor density. The results of such studies may not only provide new insight into the pathophysiology and arrhythmogenesis of Brugada syndrome but may also have future therapeutic implications, because pharmacological interventions resulting in a normalization of autonomic imbalance may reduce the propensity for life-threatening ventricular tachyarrhythmias and sudden death in patients with Brugada syndrome.

Acknowledgments

This study was supported in part by grants from the Deutsche Forschungsgemeinschaft (SFB 556, Projects C1 and C4), Bonn, Germany, and the Alfried Krupp von Bohlen and Halbach Foundation, Essen, Germany. Drs. Wichert and Matheja were partly supported by grants from the Interdisciplinary Center for Clinical Research (BMBF 01 KS-9604), Münster, Germany.

References


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Circulation. 2002;105:702-706; originally published online December 31, 2001;
doi: 10.1161/01.HC0602.103677

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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