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Abnormalities of Cardiac Sympathetic Innervation in Arrhythmogenic Right Ventricular Cardiomyopathy
Quantitative Assessment of Presynaptic Norepinephrine Uptake and Postsynaptic β-Adrenergic Receptor Density With Positron Emission Tomography

Thomas Wichter, MD; Michael Schäfers, MD; Christopher G. Rhodes, MSc; Martin Borggreve, MD, FESC; Hartmut Lerch, MD; Adriaan A. Lammertasma, PhD; Flemming Hermansen, MD; Otmar Schober, MD, PhD; Günter Breithardt, MD, FESC, FAC; Paolo G. Camici, MD, FESC, FAC, FRCP

Background—The frequent provocation of ventricular tachycardia by stress or catecholamines and the efficacy of antiarrhythmic drugs with antiadrenergic properties suggest an involvement of the cardiac adrenergic system in arrhythmogenesis in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Previous studies demonstrated abnormalities of the presynaptic uptake-1 assessed by 123I-MIBG–single-photon emission computed tomography.

Methods and Results—This study investigated neuronal reuptake of norepinephrine (uptake-1) and β-adrenergic receptor density in 8 patients with ARVC and 29 age-matched control subjects. All subjects underwent positron emission tomography with the volume of distribution (Vd) of [11C]hydroxyephedrine (11C-HED) used to assess presynaptic norepinephrine reuptake, the maximum binding capacity (Bmax) of [11C]CGP-12177 (11C-CGP-12177) to assess postsynaptic β-adrenergic receptor density, and [15O]H2O for quantification of myocardial blood flow. Patients with ARVC demonstrated a highly significant global reduction in postsynaptic β-adrenergic receptor density compared with that in control subjects (Bmax of 11C-CGP-12177: 5.9 ± 1.3 vs 10.2 ± 2.9 pmol/g tissue, P < 0.0007), whereas the presynaptic uptake-1 tended toward reduction only (Vd of 11C-HED: 59.1 ± 25.2 vs 71.0 ± 18.8 mL/g tissue, NS). There were no differences in myocardial blood flow between the groups, and plasma norepinephrine was within normal limits in patients and control subjects.

Conclusions—The findings demonstrate a significant reduction of myocardial β-adrenergic receptor density in patients with ARVC. This may result from a secondary downregulation after increased local synaptic norepinephrine levels caused by increased firing rates of the efferent neurons or as the result of impaired presynaptic catecholamine reuptake. These findings give new insights into the pathophysiology of arrhythmogenesis in ARVC, with potential impact on diagnostic evaluation and therapeutic management. (Circulation. 2000;101:1552-1558.)

Key Words: cardiomyopathy ▪ ventricular tachycardia ▪ nervous system, autonomic ▪ receptors, adrenergic, beta ▪ tomography

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is frequent as an underlying disease in young patients with ventricular tachycardia (VT) and sudden death.1–3 These arrhythmias often occur during physical exercise or mental stress and may be provoked by intravenous catecholamine infusion during electrophysiological study (catecholamine sensitivity).4,5 In contrast, ventricular tachyarrhythmias are frequently suppressed by an antiarrhythmic drug regimen with antiadrenergic properties.5,6

The pathophysiological mechanisms of these observations in patients with ARVC are still under investigation. However, the clinical findings suggest an involvement of the cardiac sympathetic nervous system. Recently, abnormalities of the myocardial sympathetic function were demonstrated by reduced presynaptic uptake of [123I]meta-iodobenzylguanidine (123I-MIBG) with the use of single-photon emission computed tomography (SPECT).7 On the basis of these studies, we hypothesized that abnormalities of myocardial sympathetic function are present and may contribute to the arrhythmogenesis in ARVC. Reduced presynaptic uptake of radionuclide tracers may result from increased neuronal firing rates or impaired function of the
presynaptic norepinephrine transporter (uptake-1). Either condition would result in elevated concentrations of synaptic norepinephrine that could lead to a subsequent downregulation of β-adrenergic receptors on the postsynaptic membranes. To test this hypothesis, we assessed quantitatively the presynaptic uptake-1 and the postsynaptic β-adrenergic receptor density in patients with ARVC with the use of positron emission tomography (PET) with the norepinephrine analogue 1[(11C)]hydroxyephedrine (11C-HED)8 and the β-adrenergic receptor antagonist S-[11C]-CGP-12177 (11C-CGP-12177).9

Methods

Subjects

Study Patients

Eight patients (4 men, 4 women; age 37±8 years, range 26 to 50; median 34 years) with ARVC and documented VT were investigated. ARVC was diagnosed according to the criteria proposed by an international study group on ARVC.10 The clinical characteristics of the study patients are summarized in Table 1.

Patient Selection

The main exclusion criteria of our study were signs or symptoms of heart failure and a history of treatment with β-blockers or other drugs (including amiodarone) affecting the sympathetic nervous system. Because of the potential influence on tracer uptake and/or metabolism, patients after catheter ablation and those with diabetes mellitus, pulmonary, renal, liver, or autoimmune disease were also excluded from the study. In 1 case (patient 8), an implantable cardioverter-defibrillator had been implanted subpectorally by a transvenous approach. However, there was no interference of the device with the field of view during the PET scans.

Control Groups

For the studies with 11C-HED and [15O]H2O, the control group consisted of 10 healthy volunteers (mean age 35±7 years, range 23 to 46, median 33 years). For the 11C-CGP-12177 scans, a control group of 19 subjects (mean age 44±16 years, range 21 to 65, median 45 years) was investigated. All control subjects had low-risk profiles, normal examination results, resting 12-lead ECGs, and exercise tests. No control subject was receiving drug treatment or had a history, medication, smoking, and caffeine-containing drinks for at least 36 hours. Investigations were performed in the nonsedated resting state after fasting for ≥4 hours.

On the first day, PET scanning consisted of a transmission scan, a 1[15O]CO emission scan for blood volume, an 11C-HED dynamic emission scan for presynaptic uptake-1 function, and an [15O]H2O dynamic emission scan for resting myocardial blood flow (MBF). On the second day, transmission and [15O]CO emission scans were recorded in addition to an 11C-CGP-12177 dynamic emission scan for the assessment of postsynaptic β-adrenergic receptor density.

During the PET scans, blood pressure was monitored at 15-minute intervals. Heart rate and cardiac rhythm were monitored with continuous 12-lead ECG recording. Plasma norepinephrine was measured at the beginning and the end of each scanning procedure. Arterialized venous blood was sampled at a rate of 2.5 mL/min from the vein of a heated hand by means of a peristaltic withdrawal pump and a bismuth germanate (BGO) detection system for monitoring the input function.11 Additional blood samples were taken to calibrate the BGO detection system, measure whole blood/plasma ratios, and assay HED metabolites in plasma.

The left ventricle was centered in the scanner field of view by the use of a rectilinear scan recorded during the exposure of external germanium-68 ring sources. This was followed by a transmission

### TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>VT</th>
<th>CL, ms</th>
<th>Hx of VT, mo</th>
<th>Syncope</th>
<th>EXERC</th>
<th>ISO</th>
<th>EPS</th>
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<td>33</td>
<td>sVT</td>
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<td>91</td>
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<td>+</td>
<td>0</td>
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<td>sVT</td>
<td>290</td>
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<td>sVT</td>
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<td>25</td>
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<td>+</td>
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<td>4</td>
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<td>sVT</td>
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<td>+</td>
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<tr>
<td>Total</td>
<td>4M, 4F</td>
<td>37±8</td>
<td></td>
<td>298±101</td>
<td>95±87</td>
<td>n=4</td>
<td>n=4</td>
<td>n=1</td>
<td>n=4</td>
</tr>
<tr>
<td>Control (n=10)</td>
<td>5 M, 5 F</td>
<td>35±7</td>
<td></td>
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<td>Control (n=19)</td>
<td>13 M, 6 F</td>
<td>43±15</td>
<td></td>
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</tbody>
</table>

CL, indicates cycle length; EPS, electrophysiological study; EXERC, exercise tests; Hx of VT, history of arrhythmia; ISO, isoproterenol infusion; ±, presyncope (under Syncope); and VT, ventricular tachycardia (s, sustained; ns, nonsustained).

Informed Consent

All patients and control subjects gave written informed consent to the study protocol, which was approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee.

Data Acquisition and Data Analysis

Cardiac presynaptic and postsynaptic sympathetic function was assessed by dynamic PET (ECAT 931 to 08/12, Siemens/CTI), allowing the simultaneous acquisition of 15 planes. Raw scan data were stored on a MicroVax-II computer (Digital Equipment Corp) and transferred to a SUN workstation for normalization, attenuation correction, and reconstruction. The resulting images were further analyzed as reported previously,11 with the use of software developed under MatLab mathematical software packages (The MathWorks Inc).

Study Protocol

In patients with ARVC, the measurement of cardiac presynaptic and postsynaptic sympathetic functions was performed in the same patient on 2 consecutive days. None of the patients or control subjects had previously received β-blockers. All subjects were off medication, smoking, and caffeine-containing drinks for at least 36 hours. Investigations were performed in the nonsedated resting state after fasting for ≥4 hours.

The left ventricle was centered in the scanner field of view by the use of a rectilinear scan recorded during the exposure of external germanium-68 ring sources. This was followed by a transmission

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A blood volume scan was performed with the inhalation of $^{15}$O-labeled carbon monoxide ($[^{15}$O]CO) delivered through a face mask at a constant rate of 500 mL/min and a radioactive concentration of 3 MBq/mL over 4 minutes. After 1 minute, to allow for tracer equilibration, a 6-minute emission scan was initiated, during which 4 venous blood samples were taken to measure blood radioactivity. Myocardial blood volume (mL/mL of region of interest, ROI) was calculated by relating the regional concentration of radioactivity in the $[^{15}$O]CO scan to the mean concentration of radioactivity in the blood samples (a value of 1.06 g/mL was assumed for the density of blood). Extravascular tissue volume ($V_{ev}$, mL tissue/mL ROI) was calculated by subtracting the blood volume image from the normalized transmission scan.15

Myocardial Blood Flow

Resting MBF (in mL · min$^{-1}$ · g$^{-1}$) was measured after the administration of an intravenous bolus (555 MBq) of $[^{15}$O]H$_2$O and dynamic emission scanning for 5.5 minutes.14 MBF was calculated with the use of a single compartment model.13,14 The perfusable tissue fraction ($t_f$, mL exchangeable tissue/mL ROI) was obtained from the $[^{15}$O]H$_2$O scan data and used to correct the $[^{15}$O]-HED scan information for partial volume effects and to calculate the perfusable tissue index (PTI = $t_f$/$V_{ev}$).15

Presynaptic Neuronal Catecholamine Reuptake

Presynaptic neuronal catecholamine reuptake was measured by intravenous administration of the norepinephrine analogue HED labeled with $^{1}$C. The uptake of $^{1}$C-HED uptake was previously reported to correlate well with the activity of the presynaptic norepinephrine. $^{11}$C-HED was measured by direct N-methylation of metaraminol with $[^{11}$Cl]methyl iodide in sulfone.8 The compound was purified with the use of high-performance liquid chromatography to provide an isotonic buffered aqueous solution for injection. The blood volume and transmission scans were normal at baseline and during the scans without significant differences between the groups. A 12-lead ECG recording confirmed the absence of complex ventricular arrhythmias during the PET scans in all patients and control subjects.

Hemodynamic Parameters

In patients with ARVC, heart rate and blood pressure were normal at baseline and during the scans without significant differences between the groups. A 12-lead ECG recording confirmed the absence of complex ventricular arrhythmias during the PET scans in all patients and control subjects.

Plasma Norepinephrine

In patients with ARVC, plasma norepinephrine concentrations were within normal limits, were not different from the control group (1.23 ± 0.23 vs 1.42 ± 0.71 nmol/L; NS), and remained constant during the scans. There was no correlation between plasma norepinephrine concentrations and presynaptic neuronal catecholamine reuptake ($^{11}$C-HED) or postsynaptic $\beta$-adrenergic receptor density ($^{11}$C-CGP-12177).

Myocardial Blood Flow

In patients with ARVC, global MBF at rest ($1.01 ± 0.25$ vs $0.97 ± 0.25$ mL · min$^{-1}$ · g tissue$^{-1}$; NS) and the perfusable tissue index ($0.94 ± 0.06$ vs $0.94 ± 0.09$; NS) were normal and not different when compared with that in control subjects. No regional differences were observed in either group.
Myocardial Sympathetic Function

Global \( V_d \) of HED was reduced by 17% in ARVC patients compared with control subjects (5.9±1.3 vs 10.2±2.9 pmol/g tissue), which was highly significant \((P<0.0007)\). There was no correlation between presynaptic and postsynaptic function in each patient \((r=0.39; \text{NS})\). No statistical differences were detected in regional presynaptic \(^{11}\text{C}-\text{HED} \) uptake or postsynaptic \( \beta \)-adrenergic receptor density in either group. A clear regional reduction of \(^{11}\text{C}-\text{HED} \) uptake was present in 4 patients with ARVC (Figure 2).

**Discussion**

The present study used quantitative PET to further elucidate the nature of previously suggested sympathetic dysinnervation and investigated for the first time in vivo both the presynaptic \(^{11}\text{C}-\text{HED} \) and postsynaptic \(^{11}\text{C}-\text{CGP-12177} \) adrenergic function in patients with ARVC. The results provide clear evidence of abnormal sympathetic myocardial innervation in patients with ARVC and demonstrate a severe and highly significant reduction of postsynaptic \( \beta \)-adrenergic receptor density \((B_{\text{max}} \text{ of } ^{11}\text{C}-\text{CGP-12177}) \) that has not been investigated in ARVC before our studies. Although abnormalities of the presynaptic function \((V_d \text{ of } ^{11}\text{C}-\text{HED}) \) were not significant in the limited number of patients included in the present study, the results confirm and extend our previous observations by radionuclide studies performed with \(^{123}\text{I}-\text{MIBG-SPECT} \), which consistently demonstrated regional reduction of transporter-mediated neuronal catecholamine reuptake (uptake-1) in ARVC.

**Potential Mechanisms of Sympathetic Dysinnervation in ARVC**

**Hypoperfusion**

Myocardial hypoperfusion with reduced tracer uptake can be excluded as a mechanism of sympathetic dysinnervation in ARVC because the distribution volume \((V_d) \) for \(^{11}\text{C}-\text{HED} \), being the ratio of influx and efflux rates, is independent of changes in MBF. In addition, coronary angiography as well as MBF \(([^{15}\text{O}]\text{H}_2\text{O-PET}) \) were normal in all patients with ARVC.

**Figure 1.** Results of quantitative PET in patients with ARVC compared with control subjects (mean values indicated by horizontal lines). Top, Presynaptic norepinephrine reuptake \((V_d \text{ of } ^{11}\text{C}-\text{HED}) \) showed trend toward reduction in ARVC (NS). Bottom, Postsynaptic \( \beta \)-adrenergic receptor density \((B_{\text{max}} \text{ for } ^{11}\text{C}-\text{CGP-12177}) \) was significantly reduced \((P<0.0007)\) in ARVC compared with control subjects.

**Myocardial Sympathetic Function**

Global \( V_d \) of HED was reduced by 17% in ARVC patients compared with control subjects (59±25 vs 71±19 mL/g tissue), which was, however, not statistically significant \((P=0.22)\). Global maximum binding capacity \((B_{\text{max}})\) for CGP-12177 was reduced by 42% in ARVC compared with control subjects (5.9±6.25 vs 7.1±6.19 mL/g tissue), which was, however, not statistically significant \((P<0.0007)\).

**Table 2. Results of the Study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma NE, nmol/L</th>
<th>MBF, mL/min·g(^{-1})</th>
<th>PTI, t/V\text{ev}</th>
<th>(^{11}\text{C}-\text{HED}, V_d/t_f, mL/g)</th>
<th>(^{11}\text{C}-\text{CGP-12177, } B_{\text{max}}/V_{\text{ev}}, \text{pmol/g})</th>
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<td>1.01</td>
<td>26.6</td>
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<td>2</td>
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<td>0.85</td>
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<tr>
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<td>0.98</td>
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</tr>
<tr>
<td>4</td>
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<td>0.94</td>
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<td>0.87</td>
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<td>7.45</td>
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<td>6</td>
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<td>7.14</td>
</tr>
<tr>
<td>8</td>
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<td>0.95</td>
<td>104.4</td>
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<td></td>
<td>1.23±0.23</td>
<td>1.01±0.25</td>
<td>0.94±0.06</td>
<td>59.1±25.2</td>
<td>5.9±1.3</td>
</tr>
<tr>
<td>Control (n=19)</td>
<td>1.00±0.21</td>
<td>1.00±0.21</td>
<td>1.00±0.21</td>
<td>59.1±25.2</td>
<td>5.9±1.3</td>
</tr>
<tr>
<td>Control (n=10)</td>
<td>1.42±0.71</td>
<td>0.97±0.25</td>
<td>0.94±0.09</td>
<td>71.0±18.8</td>
<td>&lt;0.0007</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine; MBF, myocardial blood flow; PTI, perfusable tissue index; and HED, hydroxyephedrine.
Denervation

In ARVC, myocardial atrophy and fibrofatty replacement progresses from the subepicardium toward the subendocardium. Because sympathetic nerve fibers travel in the subepicardium, localized presynaptic sympathetic denervation may occur early in the course of the disease process before functional abnormalities become apparent. However, the findings of the present study do not support the presence of such a denervation process underlying sympathetic dysinnervation in ARVC. Analysis of the tracer clearance rate from the myocardium revealed substantially higher blood flow–corrected $k_2$ values ($k_2/MBF$) for the 4 subjects who had a reduced $V_d$ for $^{11}$C-HED (subjects 1, 4, 6, and 7), whereas this parameter was normal for the 4 subjects with normal or high values of $V_d$. The blood flow–corrected uptake values ($K_1/MBF$) were normal for both of these subgroups. These findings strongly support a reduced uptake-1 to release ratio and argue against a loss of neurons. Moreover, the finding of normal values of perfusable tissue index in these patients would not be consistent with an increase in adipose or fibrous tissue.

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, $^{11}$C-HED), acceleration of tracer washout, and subsequent downregulation of postsynaptic $\beta$-adrenergic receptor density in patients with heart failure or pheochromocytoma. However, in patients with ARVC, the present study and other reports have shown that plasma catecholamines are not elevated. These findings suggest that increased synaptic norepinephrine confined to the heart or enhanced myocardial sensitivity to catecholamines rather than elevated plasma levels may be responsible for increased sympathetic activity of the myocardium in ARVC. Increased norepinephrine concentrations in the synaptic cleft may result either from increased presynaptic release (firing rates of efferent sympathetic nerve fibers) or from decreased synaptic clearance (uptake-1) of norepinephrine. Subsequently, this would result in some degree of competitive inhibition of intraneuronal tracer reuptake ($V_d$ for $^{11}$C-HED) and in a downregulation of postsynaptic $\beta$-adrenergic receptor density ($B_{max}$ for $^{11}$C-CGP-12177), thus providing the most convincing hypothesis for sympathetic dysinnervation in ARVC patients as reported in the present study.
Recent in vitro studies in adult rat cardiac myocytes reported norepinephrine-stimulated apoptosis mediated by β-adrenergic stimulation of intracellular cAMP and subsequent activation of protein kinase A, which increased calcium influx, thus inducing apoptotic cell death. In patients with ARVC, increased synaptic concentrations of norepinephrine therefore may not only increase the propensity to ventricular tachyarrhythmias but may contribute to the progression of myocardial atrophy mediated by apoptotic cell death, which recently has been discussed as a pathogenetic mechanism in ARVC.

**Sympathetic Dysinnervation and Arrhythmogenesis**

An imbalance of the sympathetic tone is considered to increase the propensity to develop ventricular arrhythmias in various cardiac diseases and conditions. Increased sympathetic activity with abnormal adrenergic stimulation of the myocardium may result from increased norepinephrine concentrations in the synaptic cleft, which may be modulated by physical exercise or exogenous exposure to catecholamines. This may cause changes of cellular CAMP production and protein phosphorylation, which may affect the spatial heterogeneity of calcium transients and subsequently increase the dispersion of repolarization and enhance the propensity for ventricular tachyarrhythmias. Frequent stimulation of postsynaptic β-adrenergic receptors may subsequently lead to downregulation of β-adrenergic receptor density (Figure 3). These mechanisms may (in part) be reversible by antiadrenergic drugs (β-blockade). Therefore, the results of the present study are in line with previous investigations that proved good clinical efficacy of β-blockers in combination with class-III antiarrhythmic agents for the treatment of ventricular tachyarrhythmias in patients with ARVC.

**Study Limitations**

Although the number of patients investigated in the present study is small, they represent a carefully selected and well-characterized cohort. The diagnosis of ARVC was made on the basis of detailed noninvasive and invasive investigations, and only patients without previous treatment with β-blockers were included.

Because of the limited spatial resolution of the PET scanner, it was not possible to perform accurate quantitative measurements in the thin right ventricular wall. Improvement of spatial resolution by the use of ECG gating was not possible because quantification of presynaptic and postsynaptic measurements requires dynamic PET scanning with acquisition of short time frames.

Regional abnormalities of presynaptic adrenergic function were not as extensive as previously reported in studies using 123I-MIBG SPECT and were found in only 4 patients with ARVC in the present study. This may be explained by patient selection, which was not based on the results of preceding 123I-MIBG scanning but rather on the absence of previous treatment with antiadrenergic drugs. Additional reasons may include the limited number of patients investigated in the present study and differences in tracer characteristics between 123I-MIBG and 11C-HED.

The catecholamine concentration in the synaptic cleft and the firing activity of the efferent sympathetic nerves were not measured directly. Therefore, although a causal interrelation between high synaptic norepinephrine concentrations and downregulated β-adrenergic receptor density is a probable and suitable explanation, it remains hypothetical.

**Conclusions**

The results of the present study provide convincing evidence of abnormal sympathetic myocardial innervation in ARVC with significant reduction of postsynaptic β-adrenergic density. These findings not only give new insights in the arrhythmogenesis of ARVC but may have therapeutic implications, because pharmacological interventions resulting in a normalization of synaptic norepinephrine concentrations and postsynaptic β-adrenergic receptor density in the heart might reduce the propensity for ventricular tachyarrhythmias and sudden death in patients with ARVC.

**Acknowledgments**

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**References**


