Myocardial Muscarinic Receptor Upregulation and Normal Response to Isoproterenol in Denervated Hearts by Familial Amyloid Polyneuropathy

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Background—Patients with familial amyloid polyneuropathy, a rare hereditary form of amyloidosis, have progressive autonomic neuropathy. The disease usually does not induce heart failure but is associated with sudden death, conduction disturbances, and an increased risk of complications during anesthesia. Although cardiac sympathetic denervation has been clearly demonstrated, the postsynaptic status of the cardiac autonomic nervous system remains unelucidated.

Methods and Results—Twenty-one patients were studied (age, 39 ± 11 years; normal coronary arteries; left ventricular ejection fraction 68 ± 9%). To evaluate the density and affinity constants of myocardial muscarinic receptors, PET with $^{11}$C-MQNB (methylquinuclidinyl benzilate), a specific hydrophilic antagonist, was used. Cardiac β-receptor functional efficiency was studied by the heart rate (HR) response to intravenous infusion of isoproterenol (5 minutes after 2 mg of atropine, 5, 10, and 15 ng/kg per minute during 5 minutes per step). The mean muscarinic receptor density was higher in patients than in control subjects ($B_{\text{max}}$, 35.5 ± 8.9 versus 26.1 ± 6.7 pmol/mL, $P=0.003$), without change in receptor affinity. The increase in HR after injection of atropine as well as of MQNB was lower in patients compared with control subjects ($\Delta$HR after atropine, 11 ± 21% versus 62 ± 17%; $P<0.001$), consistent with parasympathetic denervation. Incremental infusion of isoproterenol induced a similar increase in HR in patients and control subjects.

Conclusions—Cardiac autonomic denervation in familial amyloid polyneuropathy results in an upregulation of myocardial muscarinic receptors but without change in cardiac β-receptor responsiveness to catecholamines. (Circulation. 2001; 104:2911-2916.)

Key Words: nervous system, autonomic amyloid receptors

Denervation induces receptor upregulation in skeletal muscle. In the heart, denervation may have consequences at the receptor level, but they remain controversial. Most experimental studies involved models of cardiac denervation different from that observed in humans. Heart failure is associated with parasympathetic functional denervation, as suggested by reduced parasympathetic tone on heart rate (HR) variability measurements. Nevertheless, increased adrenergic drive and plasma catecholamine level and downregulation of cardiac β-adrenergic receptors could participate in myocardial muscarinic receptor (MR) upregulation. Heart transplantation is apparently the simplest mechanism of denervation. First, however, no upregulation in β-adrenergic receptors or isoproterenol supersensitivity has been found in humans, probably because of the persistence of receptor stimulation by circulating catecholamines; second, the ventricular MR density could remain unchanged, possibly because the cell bodies of postganglionic parasympathetic nerves that reside inside the myocardial wall are not removed at surgery.

Familial amyloid polyneuropathy (FAP) is a rare hereditary form of amyloidosis predominant in Portugal, Japan, and Scandinavia. FAP type I, characterized by a progressive sensorimotor polyneuropathy with often severe autonomic neuropathy, is due to amyloid deposition of a genetic variant transthyretin (prealbumin) essentially produced by the liver. The Met-30 variant is by far the most common. The only effective treatment is liver transplantation, which can stop the disease progress or improve the neurological status. An increased risk of anesthetic complications, sinus node dysfunctions, disturbances of auriculoventricular and intraventricular conduction, and sudden death have been reported.
even in patients with pacemaker, with amyloid deposits found in the myocardium, in the conduction system, and in the sympathetic and parasympathetic nervous systems, FAP, rarely associated with atherosclerotic coronary disease and heart failure, creates pure lesions of cardiac innervation with, in particular, sympathetic denervation demonstrated by iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy. However, little is known about the postsympathetic status in FAP.

The present study was undertaken in patients with FAP to measure the myocardial MR density and affinity constants with the use of PET and 11C-methylquinuclidinyl benzilate (MQNB) as a tracer and to evaluate the functional responsiveness of cardiac β-adrenergic receptors to catecholamines with the use of the HR response to isoproterenol infusion.

Methods

Patient Population
Twenty-one consecutive patients (9 men, 12 women; age, 39 ± 11 years) referred for liver transplantation were included in the study.

The inclusion criteria were (1) diagnosis based on clinical signs, including familial history of sensorimotor polyneuropathy and confirmed by histopathologic examination of biopsy specimens from rectal mucosa or peripheral nerves (TTR-Met-30, 20 patients; TTR-Ala-49, 1 patient); (2) normal coronary arteries on coronary angiography and normal coronary flow reserve (CFR) as assessed by intracoronary Doppler measurement at baseline and after injection of adenosine (CFR values: left anterior descending coronary artery, 2.6 ± 0.3; circumflex artery, 2.6 ± 0.4; right coronary artery, 2.6 ± 0.4); (3) normal left ventricular systolic function (radionuclide ejection fraction 68 ± 9%); and (4) sinus rhythm (patient 15 had a sentinel pacemaker).

The exclusion criteria were (1) diabetes; (2) congestive heart failure or valvular disease; and (3) therapy with drugs reported to interfere with autonomic nervous system.

During the screening of the patients, clinical data, ECG, and bidimensional and M-mode echocardiography results were gathered. The study was approved by our institutional ethics committee, and all patients gave informed consent.

Evaluation of Cardiac Autonomic Neuropathy

Heart Rate Variability
Analysis of HR variability, based on a 24-hour Holter ambulatory ECG recording, was performed with a methodology previously described. Nonspatial indexes (SDNN, RMSSD) and spectral power over 2 frequency regions of interest during day and night (low-frequency component, 0.02 to 0.15 Hz; high-frequency component, 0.2 to 0.3 Hz) were determined. Normal values were determined in 14 healthy control subjects (age, 39 ± 11 years).

MIBG Imaging
Cardiac sympathetic denervation was assessed by MIBG imaging with the use of standard methodology. MIBG uptake was calculated as the heart-to-mediastinum activity ratio on a 10-minute static acquisition performed at 20 minutes and 4 hours in the anterior view of the chest after intravenous injection of 300 MBq of MIBG. Cardiac MIBG washout rate was defined as percent change in cardiac activity between the early and delayed images. Normal values were determined in 12 healthy control subjects (age, 36 ± 12 years).

Plasma Catecholamine Assay
Plasma norepinephrine and epinephrine concentrations at rest were determined by high-performance liquid chromatography.

Evaluation of Cardiac Receptor Function

PET Protocol
PET was performed with a methodology previously described.

Data Acquisition and Experimental Protocol
11C-MQNB had a specific radioactivity ranging from 5 to 50 GBq/μmol at the time of the first injection. Dynamic series of images (62 images for each of the 63 cross sections: 10-second images during the first 2 minutes after labeled ligand injection and longer-duration images when radioactivity decreased) were recorded with 2D PET acquisitions with attenuation correction (ECAT EXACT HR+; Siemens). Experimental protocol included three intravenous injections: first, 180 MBq of 11C-MQNB; at 30 minutes, 0.3 mg of unlabeled ligand (displacement procedure); and at 60 minutes, a mixture of labeled (150 MBq) and unlabeled MQNB (0.3 mg) in the same syringe (coinjection). The HR was continuously monitored.

PET Data Analysis
For each myocardial slice, regions of interest were manually drawn on the 10-minute images: one encompassing the entire left ventricular myocardium and three segmental regions (septal, anterior, lateral). The homologous regions of interest were summed. The input function was obtained from a region of interest within the left ventricular cavity on the largest slice. 11C-MQNB time-activity curves were generated after correction for 11C decay and were expressed as picomoles per milliliter after dividing by specific radioactivity measured at time 0. Myocardial wall thickness was carefully measured by M-mode echocardiography, and PET data were corrected for losses in count recovery caused by the decreased thickness of the heart wall compared with the spatial resolution of the PET system. Spillover from the blood cavity to the myocardium was accounted for by use of a vascular fraction in the fitting procedure.

Ligand Receptor Model
The ligand receptor model was a nonequilibrium, nonlinear, two-step model: transport of the ligand from the blood to a free ligand compartment and a classic ligand-receptor interaction. The model parameters characterizing the ligand-receptor interactions were the concentration of available receptors (B_s), the equilibrium dissociation constant K_d (ratio of the dissociation rate constant k_o to the association rate constant k_a), and the fraction of extravascular fluid (V_e) in which MQNB interacts with the receptors. The normal values were determined in 12 healthy control subjects (age, 39 ± 11 years).

Pharmacological Test With Isoproterenol Infusion
All patients and 6 healthy control subjects (age, 39 ± 6 years) underwent this test. After a 15-minute supeine resting period, the parasympathetic blockade was initiated with an atropine intravenous bolus of 2 mg, a dose known to block parasympathetic influence on HR in humans. Atropine, a competitive MR antagonist, was used first to evaluate parasympathetic tone and second to avoid a contribution from a reflex withdrawal of cardiac vagal tone to the tachycardia produced by isoproterenol. Five minutes after, incremental stepwise infusion of a freshly prepared solution of isoproterenol was started with a constant-infusion pump at 5, 10, and 15 ng/kg per minute for 5 minutes each. HR and blood pressure were recorded every 2.5 minutes. The change over postatropine baseline was used to define the dose–response relation to isoproterenol.

Statistical Analysis
All values are expressed as mean ± SD. MIBG data, HR variability indexes, and PET data were compared by Student’s t tests for unpaired samples between patients and control subjects and paired samples for PET regional analysis. For the pharmacological test, each variable was compared between patients and control subjects by the Mann–Whitney U test and by ANOVA for the global response to isoproterenol. A value of P < 0.05 was considered statistically significant.
Results

Clinical, Echocardiographic, and ECG Characteristics

Characteristics of the patients are summarized in Table 1. The duration of symptomatic disease varied from 6 months to 16 years. The polyneuropathy was at its beginning in 4 patients, mild in 9 (subjective symptoms), moderate in 6 (functional disturbances, patient able to undertake most activities of daily life), and severe in 2 (major functional disturbances, patient unable to undertake most activities of daily life). At echocardiography, left ventricular wall thickness was slightly increased (septum, 10.4±2.8 mm; posterior, 8.8±1.6 mm), with a characteristic but moderate granular sparkling appearance in 9 patients but with a normal cavity size. Conduction disturbances were frequent (4 first-degree and 1 second-degree atrioventricular block, 2 right bundle-branch block, 1 left bundle-branch block, and 1 left anterior fascicular block). Five pacemakers were implanted subsequently.

Evaluation of Cardiac Autonomic Neuropathy

Heart Rate Variability

HR variability analysis showed a noticeable scatter of values (Table 2). Only SDNN (standard deviation of all cycles) and LF/HF day (low frequency/high frequency, index of sympathovagal balance) were significantly different between patients and control subjects.

MBG Imaging

Cardiac MIBG uptake was markedly decreased in patients compared with control subjects (heart-to-mediastinum activity ratio at 20 minutes, 1.53±0.2 versus 1.87±0.26, P<0.001; at 4 hours, 1.43±0.28 versus 1.98±0.35, P<0.001). Cardiac MIBG washout rates were higher in patients than in control subjects (29±6.8% versus 21±6%, P=0.003).

Table 1. Characteristics of Patients With FAP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y, sex</th>
<th>Duration of Polyneuropathy, y</th>
<th>Degree of Polyneuropathy</th>
<th>Orthostatic Hypotension</th>
<th>H/M</th>
<th>Bmax</th>
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<td>+</td>
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<td>21</td>
<td>33, M</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>1.27</td>
<td>26.3</td>
</tr>
</tbody>
</table>

Degree of polyneuropathy: 0, beginning; +, mild; ++, moderate; ++++, severe; orthostatic hypotension: +, present; 0, absent; H/M, heart-to-mediastinum activity ratio; Bmax, MR density.

Table 2. Heart Rate Variability

<table>
<thead>
<tr>
<th></th>
<th>Low-Frequency Component, ms²</th>
<th>High-Frequency Component, ms²</th>
<th>LF/HF Ratio</th>
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<tr>
<td></td>
<td>Day</td>
<td>Night</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SDNN, ms</td>
<td>RMSSD, ms</td>
<td>Day</td>
</tr>
<tr>
<td>Patients</td>
<td>103±43</td>
<td>55±62</td>
<td>728±1445</td>
</tr>
<tr>
<td>Control subjects</td>
<td>153±34</td>
<td>38±9</td>
<td>1220±759</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>NS</td>
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</table>

SDNN indicates standard deviation of N-N intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent N-N intervals; LF, low-frequency component; and HF, high-frequency component.
Figure 1. Example of scintigraphic results in patient with severe FAP. A, Very low myocardial MIBG uptake in anterior view of chest 4 hours after injection (heart-to-mediastinum activity ratio, 1:1). H indicates heart; M, mediastinum. B, Tomographic transaxial cross-sectional image of heart 10 minutes after injection of 11C-MQNB. Left ventricular (LV) myocardial and cavity regions of interest are drawn. C, Time-activity curve in three-injection experiment: 180 MBq of 11C-MQNB at time 0, 0.3 mg of unlabeled ligand at 60 minutes (displacement procedure), coinjection of labeled (150 MBq) and unlabeled ligand (0.3 mg) at 30 minutes (displacement procedure), coinjection of labeled (150 MBq) and unlabeled ligand (0.3 mg) at 60 minutes. Circles are measurements in LV region of interest. Solid line corresponds to fitting procedure obtained from model.

Plasma Catecholamine Concentration
Slightly low or normal values were found in patients for plasma concentrations of norepinephrine (297 ± 147 ng/L; normal, 210 to 350 ng/L) and epinephrine (63 ± 54 ng/L; normal, 63 to 133 ng/L).

Global and Regional Left Ventricular Muscarinic Receptor Density
Figure 1 depicts an example of scintigraphic results in a patient. The mean MR density was higher in patients than in control subjects (35.5 ± 8.9 vs. 26.1 ± 6.7 pmol/mL, P = 0.003) (Table 3 and Figure 2). The values of the other parameters were not significantly different. In patients, the receptor density was higher (P = 0.008) in the septal regions than in the anterior regions and higher (P = 0.001) in the anterior regions than in the lateral regions (27.5 ± 9.2, 26.4 ± 6.8, 24.8 ± 8.7 pmol/mL, respectively), without differences in regional wall thickness (septum, 8.6 ± 0.8 mm; posterior, 8.7 ± 0.7 mm).

TABLE 3. PET Results

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control Subjects</th>
<th>P</th>
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<tr>
<td>B'(_{raw}) , pmol/mL</td>
<td>35.5 ± 8.9</td>
<td>26.1 ± 6.7</td>
<td>0.003</td>
</tr>
<tr>
<td>V_o, mL/mL</td>
<td>0.25 ± 0.1</td>
<td>0.20 ± 0.1</td>
<td>NS</td>
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<tr>
<td>k_a, mL per pmol - min^-1</td>
<td>0.06 ± 0.04</td>
<td>0.09 ± 0.08</td>
<td>NS</td>
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<tr>
<td>k_d, min^-1</td>
<td>0.27 ± 0.1</td>
<td>0.27 ± 0.12</td>
<td>NS</td>
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<tr>
<td>K_e, pmol/mL</td>
<td>3.7 ± 1.6</td>
<td>2.6 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>F_v</td>
<td>0.34 ± 0.07</td>
<td>0.37 ± 0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

B'(_{raw}) indicates MR density; V_o, volume of reaction; k_a, association rate constant; k_d, dissociation rate constant; K_e, equilibrium dissociation constant; and F_v, vascular fraction.

Figure 2. Individual left ventricular MR density. Significantly higher mean MR density was found in patients (n = 21) compared with control subjects (n = 12).

Slight differences in regional wall thickness were found (septum, 10.4 ± 2.8 mm; posterior, 8.8 ± 1.6 mm, P < 0.001). In control subjects, the receptor density was not significantly different in the septal, anterior, and lateral regions (27.5 ± 9.2, 26.4 ± 6.8, 24.8 ± 8.7 pmol/mL, respectively), without differences in regional wall thickness (septum, 8.6 ± 0.8 mm; posterior, 8.7 ± 0.7 mm).

Relations Between Muscarinic Receptors and Other Variables
Despite a similar basal HR between patients and control subjects (72 ± 14 versus 64 ± 9.4 bpm), the maximal HR, reached 6 to 8 minutes after coinjection (ie, after 0.6 mg of MQNB), was lower in patients than in control subjects (ΔHR 12 ± 19% versus 58 ± 33%, P < 0.001). The individual MR density in patients did not correlate with maximal HR, the degree of polyneuropathy, the duration of symptomatic disease, the norepinephrine or epinephrine concentrations, HR variability indexes, or with the cardiac MIBG uptake at 4 hours.

Pharmacological Testing
Atropine Injection
The HR in patients scarcely increased with atropine (88 ± 17 versus 80 ± 15 bpm; ΔHR, 11 ± 21%, P = 0.01) (Figures 3 and 4), contrasting with an important increase in control subjects (109 ± 14 versus 68 ± 10 bpm; ΔHR, 62 ± 17%, P < 0.001).

Isoproterenol Infusion
Isoproterenol infusion induced a similar HR increase in patients compared with control subjects (Figures 3 and 4), associated with a similar decrease in arterial blood pressure.

Figure 3. Change in HR and blood pressure (BP) during atropine injection followed by isoproterenol (I) infusion. *Comparison with postatropine baseline values. †P < 0.001 vs control subjects (right).
The fact that parasympathycolysis with MQNB or MR supersensitivity. In dogs treated with an antagonist treatment has been described in heart.2,22 This indicates the absence of acetylcholine fixed on MR and then available for displacement.

Commonly, the expression of receptors is affected by the degree of receptor activation. Thus, chronic exposure to receptor agonists decreases receptor expression (downregulation), whereas chronic inhibition of the receptors increases receptor expression (upregulation). For example, MR upregulation after chronic antagonist treatment has been described in animals with MR supersensitivity.24 In dogs treated with an irreversible acetylcholinesterase inhibitor, increasing the amount of endogenous acetylcholine available for MR activation, a downregulation of myocardial MR was observed with the use of 1\(^{13}\)C-MQNB and PET, confirmed in vitro with the use of \(^{3}\)H-MQNB.25 Thus, in FAP, increase in MR appears to be a consequence of parasympathetic denervation.

Discussion
Cardiac autonomic neuropathy in FAP induces an increase in myocardial MR density, even in patients with very mild diseases, with preserved cardiac \(\beta\)-adrenergic receptor responsiveness to catecholamines.

Muscarinic Receptors
FAP is characterized by both sensorimotor and autonomic neuropathy, with symptoms such as alternating diarrhea and constipation, orthostatic hypotension, urinary retention, and dry mouth and eyes. Cardiac sympathetic denervation was established by the striking decrease in myocardial MIBG uptake, indicating a decrease in presynaptic catecholamine stores similar to that reported in transplanted human heart. The fact that parasympathycolysis with MQNB or atroline had no effect or only a minimal effect on HR in FAP despite the presence of MR upregulation, is consistent with cardiac parasympathetic denervation.14 As in transplanted heart,2,22 this indicates the absence of acetylcholine fixed on MR and then available for displacement.

Commonly, the expression of receptors is affected by the degree of receptor activation. Thus, chronic exposure to receptor agonists decreases receptor expression (downregulation), whereas chronic inhibition of the receptors increases receptor expression (upregulation). For example, MR upregulation after chronic antagonist treatment has been described in animals with MR supersensitivity.24 In dogs treated with an irreversible acetylcholinesterase inhibitor, increasing the amount of endogenous acetylcholine available for MR activation, a downregulation of myocardial MR was observed with the use of 1\(^{13}\)C-MQNB and PET, confirmed in vitro with the use of \(^{3}\)H-MQNB. Thus, in FAP, increase in MR appears to be a consequence of parasympathetic denervation.

These findings are different from those observed in denervated transplanted heart, with a PET study indicating a similar MR density2 and with a pharmacological study demonstrating a comparable negative inotropic effect of a parasympathetic agonist in patients with transplants and control subjects.26 This may be explained by the fact that surgical parasympathetic denervation is preganglionic, in contrast with sympathetic denervation. Therefore, postganglionic parasympathetic neurons in the donor heart may remain intact and interact with the regulation of the postsynaptic MR, as suggested by evidence of subnormal myocardial content of acetylcholine after heart transplantation in rats.27

The lack of basal tachycardia in patients with FAP despite parasympathetic denervation may be due to abnormalities of the sinus node function caused by amyloid infiltration or the increase in MR coupling to the inhibitory guanine nucleotide-binding protein (G\(_i\)). In dilated idiopathic cardiomyopathy, the maximal HR after 0.6 mg of MQNB inversely correlated with the individual MR density in patients, indicating a link between the left ventricular receptor number and its biological function. Moreover, MR upregulation appears to be associated with increased G\(_i\)-binding protein levels.4 In mouse hearts with highly expanded pools of \(\beta\)-adrenergic receptors by transgenic overexpression, spontaneous receptor activation not reduced by propanolol was shown, indicating a ligand-independent receptor signaling.28 In FAP, no such relation was found, probably because of the difference in mechanism of denervation. In heart failure, increased MR density is an adaptive mechanism to parasympathetic tone decrease, turning off sustained \(\beta\)-agonist stimulation. The homogeneous nature of this mechanism could explain a relation between two kinds of MR property expression: left ventricular MR density and HR after MR antagonist use (ie, without agonist fixed at MR level) reflecting its biological specific function. In contrast, myocardial involvement in FAP is perhaps more heterogeneous, possibly because of length-dependent degeneration of fibers.29

\(\beta\)-Adrenergic Responsiveness to Isoproterenol
Because there is no uptake of isoproterenol by the adrenergic nerve terminals, any change in sensitivity to isoproterenol indicates a postsynaptic involvement, such as altered density or function of \(\beta\)-adrenergic receptors. Thus, the absence of increased sensitivity of patients with FAP to isoproterenol, found in the present and in another study, appears to be consistent with the absence of \(\beta\)-receptor-mediated supersensitivity despite sympathetic denervation. This difference in MR and \(\beta\)-adrenergic receptor regulation is probably due to the absence of circulating neuromediator for the parasympathetic system. Although myocardial catecholamine release by sympathetic neurons is interrupted in patients with FAP, the persistence of catecholamine production by the adrenergic system is associated with the lack of reuptake by the sympathetic nerves terminals in the myocardium are probably sufficient to maintain the \(\beta\)-receptor stimulation.

Heart Rate Variability
HR variability analysis showed a reduced variance, suggesting heart denervation, but spectral components were not different from those of control subjects. Similar data were observed in Chagas’ disease, another disease with cardiac denervation. However, in FAP, there was a loss of the circadian rhythmicity without a decrease in the HF component and so without sympathovagal balance increase during day. This is probably similar to the lack of increase in LF and decrease in HF components during standing in Chagas’ disease or in diabetes during standing or tilt.
Limitations of the Study
In FAP, the HR response to isoproterenol was normal. However, it is not possible to distinguish the role of receptor-binding properties from the one of postreceptor changes (functional activity of G-protein subunits). Cardiac β-adrenergic receptor density measurement with PET will be performed in another series of patients.

Clinical Implications
MRs mediate the parasympathetic control of heart function, with an inhibitory influence causing both bradycardia and negative inotropic response, in contrast to β-adrenergic receptors. Cardiac sympathetic and parasympathetic denervations do not have the same consequences on postsynaptic receptors in FAP. Denervation increases myocardial MR density, but without change in cardiac β-receptor responsiveness to catecholamines. This probably explains the depression of cardiac automaticity and conductivity during anesthesia with agents such as suxamethonium (succinylcholine) with structural similarity to acetylcholine, and the prompt response to therapeutic infusion of isoproterenol. Whether heterogeneous cardiac autonomic denervation, sympathetic and parasympathetic imbalance, and the loss of the HR circadian rhythmicity could be responsible for an excess of sudden death, even in patients with a pacemaker, is to be determined by further study. Alternately, a beneficial effect of an increase in parasympathetic tone after pacemaker implantation, as could be obtained with an agonist medication in these patients with increased myocardial MR density, could be expected through a diminution of ventricular excitability.

References
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