Muscarinic Receptor Upregulation in Patients With Myocardial Infarction
A New Paradigm

Alejandro N. Mazzadi, PhD; Julien Pineau, MD; Nicolas Costes, PhD; Didier Le Bars, PhD; Franck Bonnefoi, RA; Pierre Croisille, MD, PhD; Raphaë1 Porcher, PhD; Philippe Chevalier, MD, PhD

Background—Despite the major role attributed to myocardial vagal activity in left ventricular arrhythmogenesis in chronic myocardial infarction, the impact of infarction on left ventricular muscarinic receptor density remains unknown.

Methods and Results—Left ventricular muscarinic receptor density was measured in vivo by positron emission tomography using the specific antagonist $[^{11}C]$methylquinuclidinyl benzilate ($[^{11}C]$MQNB) in 11 patients 43±20 days after myocardial infarction and 9 healthy volunteers. The extent of myocardial damage was quantified by delayed contrast-enhanced MRI. Three short-axis slices from each subject were analyzed in matched positron emission tomography and MRI images. A 2-injection positron emission tomography protocol was used; $[^{11}C]$MQNB time-activity curves were obtained in 6 regions per slice and fitted to a 3-compartment ligand-receptor model. Four classes of myocardial regions were considered: normal (in volunteers); remote, supplied by healthy or <70% diameter reduction arteries and without MRI signs of damage; potentially damaged, supplied by infarct-related or >70% diameter reduction arteries and without signs of damage; and damaged, with damage. The muscarinic receptor density in remote (67±30 pmol/mL tissue; n=86) and potentially damaged (71±30 pmol/mL tissue; n=42) regions of patients was higher than in normal regions of volunteers (32±17 pmol/mL tissue; n=156; P<0.001). The muscarinic receptor density in damaged regions (42±21 pmol/mL tissue; n=58) was reduced compared with remote and potentially damaged regions (P<0.001) but was not significantly different from normal regions in volunteers (P=0.093).

Conclusions—Vagal control in patients with chronic myocardial infarction involves muscarinic receptor upregulation in remote nondamaged left ventricular regions. Our results suggest that the receptor density remains within normal values in myocardial regions containing damaged tissue. (Circ Cardiovasc Imaging. 2009;2:365-372.)

Key Words: myocardial infarction • receptors • tomography • MRI

Parasympathetic tone is a strong modulator of myocardial electric activity. Vagal stimulation opposes the postsynaptic sympathetic effect and decreases norepinephrine release from sympathetic nerve terminals. In cardiac myocytes, muscarinic acetylcholine receptor activation results in a marked decrease of calcium current in the presence of adrenergic stimulation.1 It is also well documented that acetylcholine influences the action potential duration of human ventricular myocytes,2 and, in humans, an increase of the QT interval during sleep has been associated with vagal stimulation.3

Myocardial ischemia and myocardial infarction (MI) drastically alter the autonomous nervous system, which has been suggested to contribute to the susceptibility of the infarcted left ventricle (LV) to arrhythmias and sudden cardiac death.4,5

In this context, the cardiac parasympathetic limb has been shown to play an important antiarrhythmicogenic role. Several experimental studies have convincingly demonstrated the antiarrhythmic action of muscarinic receptor activation during myocardial ischemia.6,7 In clinical practice, it is known that markers of decreased vagal activity are associated with an enhanced risk of ventricular arrhythmias and sudden cardiac death in patients with MI.8,9 However, though the important role of vagal control in arrhythmogenesis in MI is almost certain, a study of myocardial vagal innervation in infarcted patients has never been performed.

In humans, the LV parasympathetic limb can be investigated in vivo and noninvasively using positron emission tomography (PET) and the specific muscarinic antagonist $[^{11}C]$methylquinuclidinyl benzilate ($[^{11}C]$MQNB). This methodology allows for the absolute quantification of...
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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No. (Age, y)</th>
<th>Days After MI†</th>
<th>ECG Findings</th>
<th>Infarct-Related Artery</th>
<th>Coronary Artery Disease</th>
<th>Coronary Angioplasty</th>
<th>Enzymes Peak CK/Troponin, IU</th>
<th>MRI LVEF±, %</th>
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<td>LCX</td>
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<td>1600/37</td>
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<td>400/9</td>
<td>59</td>
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<td>LCX/RCA</td>
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<td>RCA/LCX</td>
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</table>

Mean±SD 43±20 1783±1402/26±22 54±10

STEMI indicates ST-segment elevation MI; nSTEMI, non-ST-segment elevation MI; Inf, inferior; Ant, anterior; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; CK, creatine kinase enzyme; EF, ejection fraction; NA, not available.

*Patients without regional mechanical dysfunction as visually assessed by cine-MRI.
†Time from MI until imaging studies.
‡Computed at the time of imaging studies.

postsynaptic muscarinic receptors (muscarinic receptor density [Bmax] in pmol/mL tissue), but it requires a 3-injection protocol and complex mathematical modeling.10,11 Because this approach appears difficult for clinical use, its application in patients has been very limited,12-14 and no imaging studies have assessed LV muscarinic receptors in patients with MI.

In this descriptive study, we quantified the LV Bmax in infarcted patients using a simplified and validated 2-injection PET-protocol11 and [11C]MQNB. The location and extent of myocardial damage were estimated by delayed contrast-enhanced MRI.

Methods

Population

The ethics committee of our institution approved the study protocol. Written informed consent was obtained from each subject.

Nine healthy male volunteers were free of cardiac disease based on clinical history and examination and ECG exploration, and MRI in 5 of them (volunteers 2, 4, 5, 6, and 7).

There were 11 male patients with their first MI (Table 1) diagnosed by an association of chest pain (>30 minutes), ECG signs of ischemia (ST-segment alterations), and troponin increase.15 All patients had echocardiography within the first 24 hours after MI, angiographic evidence of coronary atherosclerosis, and successful reperfusion therapy by coronary stenting. No patient had diabetes or any other condition that would interfere with the autonomic system. Subjects underwent MRI and PET within the same day.

PET

A Siemens ECAT EXACT HR+ 63-slice whole-body PET tomograph was used. For photon attenuation correction, a transmission scan was performed for 10 minutes with 3 removable rotating sources of 18F-FDG. To assess the muscarinic receptors, a previously optimized and validated 2-injection PET protocol11 was used (tracer injection and coinjection). At t=0, approximately 2.7 MBq/kg body wt [11C]MQNB was intravenously injected over a period of 15 seconds. Thirty minutes later, 2.7 MBq/kg of labeled and 0.2 mg of unlabeled MQNB was injected. Acquisition (3D mode) lasted 70 minutes. Emission scans were reconstructed with all corrections (filtered backprojection method) in a 128×128 matrix, using a Hanning filter (cutoff frequency, 0.4 mm−1). The scan sequence consisted of 59 frames: 12 images ×10 seconds, 4×120 seconds, 5×240 seconds, 12×10 seconds, 16×30 seconds, and 10×180 seconds. The heart rate (bpm) and arterial blood pressure were monitored 3 to 5 minutes before each injection and every 2 minutes after each injection until 8 minutes.

Analyses were performed in 3 reoriented LV short-axis slices (8-mm thick): basal (7 cm from the apex), midventricular (5 cm), and apical (3.5 cm). A static [11C]MQNB image was constructed by adding frames between 18 to 26 minutes (Figure 1A). Six myocardial regions/slice (~3 cm3 each) were drawn in the static image from right ventricle insertion (Figure 1A). Regions were then superimposed on the corresponding dynamic series, and regional time-activity curves (TACs) were obtained (Figure 2). The input blood function was available from a region drawn in the basal LV cavity (~1 cm3). The plasma function used as input was calculated considering that ~85% of blood radioactivity was in the plasma.10 The TACs were corrected from partial volume effects using the geometric transfer matrix (GTM) method.16 Nine PET-emitting structures per slice, drawn on the static [11C]MQNB image, were considered: 6 myocardial regions, the liver, and the right and left ventricular cavities (Figure 3). The GTM, containing activity recovery and cross-contamination factors, was constructed from the point spread function of the scanner and inverted. The resulting matrix included correction factors accounting for spill-over and spill-out effects and was applied to all TACs. The corrected TACs were used as input for fitting the model.

Muscarinic Receptor System Characterization

The ligand-receptor model was a nonequilibrium, nonlinear model previously described in depth.10,11 Briefly, the model included 3 compartments corresponding to labeled ligand concentrations: ligand in the arterial blood (compartment 1), free ligand in the tissue (compartment 2), and ligand specifically bound to the muscarinic receptors (compartment 3). The model considers 2 steps: transfer of the ligand from the blood (compartment 1) to a tissue compartment as free or nonspecifically bound ligand (compartment 2) and a classic ligand-receptor interaction (between compartments 2 and 3). Irreversible and nonspecific binding was assumed to be unidentifiable. It was shown previously11 that a good estimation of Bmax (pmol/mL tissue) is obtained by fitting the model to TACs obtained by 2-injection PET protocol (Figure 1D).
A 1.5-T MRI unit (Sonata Maestro Class, Siemens) was used with ultrafast gradient amplitude and a 2–phased-array chest coil. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA, 0.2 mmol) was intravenously injected after Cine-MRI. Seventeen short-axis delayed contrast-enhanced (CE) images (5-mm thick; Figure 1B) covering the LV were acquired 10 minutes after injection. The analysis of CE images was performed as previously described.\textsuperscript{17}
in 3 short-axis slices homologous to PET slices. Epicardial and endocardial contours were traced, and 6 regions per slice were generated. The mean signal intensity for each region was normalized to the average signal intensity of 3 control regions (from different slices) selected for the minimal mean value of signal intensity in the slice and supplied by a healthy or <70% diameter reduction arteries. To quantify the extent of enhancement (ie, the size of myocardial damage), CE images were converted into binary images (signal intensity values 1 or 0; Figure 1C). Pixel values >200% of the average signal intensity in control regions were set to 1.19

**PET and MRI Registration**

Circumferential registration (in-plane registration) between MR slices during diastole and PET slices was carefully achieved by taking into account the relative apex-to-base location from the long-axis MRI localizer view and matching landmark locations such as right ventricle insertion and papillary muscle location.18 The location of the vascular beds was considered as usual in LV polar maps: regions 6 to 1 (left anterior descending artery territories), 2 to 3 (right coronary artery), and 4 to 5 (left circumflex artery).

**Regional Characterization**

In volunteers, all myocardial regions were considered as normal. In patients, 3 classes of regions were considered: remote, supplied by healthy or by <70% diameter reduction arteries (as determined by angiography), and without signs of myocardial damage (as determined by MR binary CE images); potentially damaged, supplied by infarct-related or >70% diameter reduction arteries and without damage; and damaged regions, with MR signs of damage (regional extent of enhancement ≥10%; see Results).

**Statistical Analysis**

The distribution of age and basal heart rate in patients and healthy volunteers were compared using t tests. Changes in heart rate after the MQNB injections were evaluated using the paired t test.

Mean values were compared across territories or regions using mixed-effects ANOVA. Random subject and random slice effects (nested within the subject) were used to account for a correlation between measurements in the same subject and the same slice. The covariance structure of random effects and residuals was selected on the basis of Akaike information criterion (AIC). The goodness-of-fit of the models was assessed by inspecting Pearson residuals using quantile-to-quantile plots and the Shapiro-Wilks test of normality. When slice effects were not found to improve the model fit, they were removed from the final model. Post hoc 2-by-2 comparisons were carried out when the global effect was significant. To account for multiple testing, probability values were corrected using the Holm method. The variance stabilizing arcsine transformation of percentages was used to analyze the extent of enhancement.

In patients, the relationship between the mean Bmax in remote regions and age, basal heart rate, damage extent, and time after infarction was evaluated using the Spearman rank correlation coefficient (ρ). In volunteers, the relationship between the mean Bmax in normal regions and age was similarly evaluated.

Data are displayed as mean±SD or as median. Average group differences estimated by mixed-effects ANOVA are displayed as estimate and standard error (SE); they may deviate from the differences of observed means when observations per subject are unbalanced. Whenever necessary, the normal distribution of data and equality of standard deviations across groups were tested using the Kolmogorov-Smirnov test and the equal variance test, respectively. P<0.05 was considered significant.

**Results**

**Population Characteristics**

Five of the healthy volunteers (50±11 years; n=9; P=0.249 versus patients; Table 2) underwent MRI, which revealed no mechanical dysfunction.

Patient characteristics are given in Tables 1 and 2. The therapeutic regimen at the time of the study (43±20 days after MI) was standardized and included β-blockers (except in patient 5, who was taking calcium channel blockers),
antiplatelet agents, and statins. There were no arrhythmic events between the infarction and the imaging study or during the 1-year period after the study.

MRI and Angiography
Three short-axis MRI slices per subject and 6 regions per slice were considered.

In 5 volunteers (90 regions), delayed MRI revealed a higher enhancement in apical territories (normalized signal intensity 1.32 ± 0.26 versus 1.19 ± 0.17, P = 0.015 and 1.03 ± 0.19, P < 0.001 in the midventricular and basal territories, respectively). No significant differences were found between the septal (1.24 ± 0.24; regions 1 to 2), inferolateral (1.10 ± 0.18; regions 3 to 4), and anterolateral (1.20 ± 0.29; regions 5 to 6) territories (P = 0.066). In volunteers, the extent of enhancement at the regional level varied from 0% to 7% (median, 1%; Figure 4). Based on 7% in volunteers, regions with ≥10% enhancement were considered damaged.

In 11 patients, 186 regions were analyzed (2 MRI slices were discarded due to quality image problems) (Figure 4); 86 were remote (angiographic and MRI criteria), 42 were potentially damaged (angiographic and MRI criteria), and 58 damaged (MRI criterion). The extent of enhancement in the 3 slices varied from 0.1% in patient 3 (ie, without MRI signs of damage) to 23.2% in patient 5 (Table 2). In damaged regions, the extent of enhancement varied from 10% (by definition) to 100% (transmural damage).

PET Findings: Relationship With Delayed MRI and Angiography
The baseline heart rate was similar in volunteers and patients (61 ± 12 and 57 ± 9 bpm; P = 0.470; Table 2) and remained unchanged after the first protocol injection. The second injection (containing 0.2 mg MQNB) resulted in a slight and transient increase in heart rate that was not significant in volunteers (61 ± 12 to 64 ± 17 bpm; P = 0.230) but significant in patients (54 ± 9 to 58 ± 9 bpm; P = 0.047).

In 9 volunteers, 156 regions were analyzed (3 slices per subject, except for 2 slices in volunteer 4) for muscarinic receptor estimation (Bmax). The regional Bmax was not significantly associated with the relative apex-to-base position (34 ± 17, 32 ± 16, and 29 ± 17 pmol/mL tissue for apical, midventricular, and basal regions, respectively, P = 0.351) but with the relative circumferential position (35 ± 19, 29 ± 12, and 28 ± 16 pmol/mL tissue for septal, inferolateral, and anterolateral regions, respectively, P = 0.460). The mean Bmax in the normal regions was 32 ± 17 pmol/mL tissue, and the mean value per subject varied from 12 ± 6 (volunteer 3) to 55 ± 7 pmol/mL tissue (volunteer 1) (Table 2). The average Bmax values per volunteer were lower in older subjects, but the association with age was not significant (ρ = −0.577; P = 0.087).

In 11 patients, a total of 186 regions were analyzed (3 slices per subject, except for patient 1). The Bmax in remote regions was approximately 2-fold higher than the Bmax of normal regions (average difference, 32 pmol/mL tissue; SE, 9; P < 0.001) (Table 2). The Bmax was similar in remote and potentially damaged regions (average difference, 2 pmol/mL tissue; SE, 3; P = 0.420) but reduced in damaged regions (average difference, 15 pmol/mL tissue; SE, 2; P < 0.001 versus remote; average difference, 13 pmol/mL tissue; SE, 3; P < 0.001 versus potentially damaged) (Table 2). No significant difference was found between damaged and normal regions (average difference, 17 pmol/mL tissue; SE, 9;
Several studies have suggested that the preservation of cardiac parasympathetic activity after myocardial infarction is associated with autonomic cardiac denervation. Recent studies have demonstrated that muscarinic receptor upregulation in chronic MI is characterized by muscarinic receptor upregulation in remote nondamaged LV regions and that receptor density remains within normal values in myocardial regions containing damaged tissue. Whether a loss of vagal control after MI is associated with the heart’s capacity to increase muscarinic receptors warrants further studies.

Several alterations have been described in the remote regions of patients with coronary artery disease. However, these alterations were reported in the advanced stages of the disease and are not expected in patients with relatively recent MI, successful coronary reperfusion, and relatively well-preserved mechanical function. In the present study, we carefully selected remote regions by combining angiographic and MRI information; regions supplied by arteries with >70% diameter reduction were not considered to avoid territories with repetitive transient ischemia (“repetitive stunning”). In remote regions, the enhancement detected by MRI was very low, as expected in nondamaged tissue. Moreover, previous PET studies revealed normal ranges of perfusion, glucose utilization, and oxidative metabolism in the remote regions of patients with a recent infarct. Consequently, regions characterized as remote in this study satisfied the required conditions for the rational use of the 3 compartment ligand-receptor model. For instance, the patency of the related artery, in addition to a normal microvasculature, could ensure the correct delivery, distribution, and washout of \([11C]MQNB\), which is why we concluded an upregulation of muscarinic receptors in remote, nondamaged regions. On the other hand, damaged regions (MRI enhancement \(\geq 10\%\)) have been associated with numerous alterations, such as cellular necrosis, edema, and increased permeability volume distribution. These pathological conditions could restrict receptor quantification when mathematical modeling is used.

Several myocardial postsynaptic alterations in pathological conditions reveal the potential adaptive role of parasympathetic innervation. The ventricular upregulation of muscarinic receptors was reported in animal models involving myocardial energetic imbalance, such as paced-induced heart failure. Such an upregulation was not found in the atria of dogs in a pacing model in which the number of receptors was determined in the intact cell. The upregulation was also described in conditions of reduced receptor activation, such as chronic treatment with antagonists or in patients with familial amyloid polyneuropathy, a hereditary disease associated with autonomic cardiac denervation. Recent studies also suggest that ventricular parasympathetic reinnervation could occur after denervation, such as that arising from infarction. Chen et al reported that muscarinic receptors, the distribution of parasympathetic nerves, and baroreflex sen-
tivity in rats were increased 1 week after vagotomy, suggesting that denervation induces parasympathetic overactivity. Thus, the upregulation of ventricular muscarinic receptors in this study appears to be an adaptive phenomenon related to parasympathetic denervation in patients with MRI signs of tissue damage consistent with MI.

Interestingly, we found that the approximate infarct size did not correlate with the receptor density in remote regions. The most striking evidence was found in patient 3, who presented with clinical signs of infarction. In this patient, we failed to detect MRI signs of myocardial damage, probably due to the small infarct size, or the apical location of the infarct (the apex is not appropriately imaged by short-axis images). Thus, though the infarct size in patient 3 could be expected to be very moderate, the receptor density in remote regions was approximately 3-fold higher than in normal volunteers. Consequently, we hypothesize that a lack of receptor activation secondary to parasympathetic denervation could only partially explain receptor upregulation after infarction and that other mechanisms probably participate in this overexpression.

Clinical Implications
Myocardial infarction leads to ventricular sympathetic denervation followed by sympathetic reinnervation.27–29 Although the extent and characteristics of such reinnervation remain uncertain, it is clear that infarction results in the heterogeneous distribution of sympathetic innervation and thus in differential sympathetic activity. This heterogeneity could play a modifier role as a substrate of reentry that favors life-threatening ventricular arrhythmias.

The same arrhythmogenic setting has been suggested in congenital long QT syndrome.30,31 Interestingly, patients with this syndrome and those with MI both benefit from β-blockers. In patients with MI, the upregulation of muscarinic receptors (ie, increased endogenous β-blocking due to vagal stimulation) could act as the mechanism attenuating the arrhythmogenicity of heterogeneous sympathetic activity.

At present, only PET cardiac imaging can quantify muscarinic receptors in the ventricle. Our study using a simplified 2-injection protocol demonstrated the feasibility of this approach in the clinical setting. Baroreflex sensitivity and heart rate variability are grossly associated with vagal control of the heart, and they have been found to be useful risk stratifiers after MI. However, these markers are primarily indicators of parasympathetic innervation of the sinus node, not the ventricular myocyte. This fact may explain why currently available techniques fail to effectively stratify infarcted patients for the risk of ventricular arrhythmic events.32 Actually, in most studies using noninvasive testing, no differentiation is made between the mortality from all causes and mortality from sudden death. Additional studies on the relationship between ventricular muscarinic receptors and arrhythmogenesis may contribute to constructing a specific marker of arrhythmic sudden cardiac death.

Technical Considerations
The heart is usually considered to possess a single muscarinic receptor subtype (M2), but there is emerging evidence that M1 and M3 subtypes are also expressed in ventricles.33,34 In this study, we used a nonselective muscarinic antagonist for PET quantification; therefore, we cannot differentiate among different receptor subtypes.

In our 9 normal volunteers, PET estimated slightly higher receptor density than those previously published.11–14 The values (32±17 pmol/mL tissue; n=156) were higher and more scattered than those previously obtained using the same 2-injection protocol in 5 volunteers (25±7 pmol/mL tissue; n=5).11 These differences could be partially ascribed to the TACs being corrected for partial volume effects with the GTM method, whereas correction in previous studies were performed by taking into account the ventricle wall thickness and applying an experimental recovery factor; prior studies usually considered 1 large region covering the entire transaxial PET slice, whereas we included 3 short-axis slices and divided each of them into 6 regions.

The GTM method for partial volume effects (PVE) correction was formally validated for brain imaging.16 The principles of this method5 rely on the computation of the GTM by the convolution of delineated emitting regions by the response function of the scanner. Thus, the GTM method is not intrinsically dedicated to brain imaging. Moreover, in our cardiac study, GTM wasn't computed from MR images but directly from emitting structures drawn on the static PET images. Therefore, PET and MR image coregistration did not account for our PVE correction. Moreover, because TACs used for modeling Bmax were taken as the average activity in the regions and not at a voxel level, correction of the TACs based on the PVE factor for the whole region did not violate the hypothesis of regional homogeneity. The GTM values revealed that PVE corrections for myocardial regions were: the spill-in effect counted for 70%, spill-over effect between myocardial regions was approximately 2%, between myocardial regions and the left cavity was 7%, and between the liver and the 2 closest myocardial regions was 6% (0% elsewhere). Thus, the PVE correction of myocardial TACs essentially consisted in recovery of 30% of the activity measured in the region, decontamination of the activity of the frames after injections in the left cavity (6%), and decontamination of the activity in the 2 myocardial regions closest to the liver (6% of liver activity).

All patients (except patient 5) but none of the volunteers were taking β-blockers at the time of the study. Patient 5 was taking calcium channel blockers and had a similar Bmax as the rest of the patients. The therapeutic regimen in the patients was standardized and, to our knowledge, no work has reported the effect of these medications on vagal action.

Our results suggest that the receptor density remains within normal values in regions containing damaged tissue. Although technical considerations prevent us from making a firm statement about this topic, such a conclusion is possible. The rationale for this phenomenon is quite speculative. The PET is unable to correctly delineate intramyocardial territories and thus to correctly delineate damaged territories. In addition, damaged territories delineated by MRI could contain several ultrastructural alterations, potentially leading to denervation. The presence of an islet of viability in the scar tissue could explain some normal regional muscarinic expres-
sion. However, we prefer the hypothesis that most receptor expression comes from the peri-infarct territories in which metabolic activity could be normal or even increased.

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Disclosures

None.

References

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