Right Ventricular Infarction Causes Heterogeneous Autonomic Denervation of the Viable Peri-infarct Area

Arif Elvan, MD; Douglas P. Zipes, MD

**Background**—Because efferent autonomic pathways to the right ventricle (RV) differ from the efferent autonomic projections to the left ventricle (LV), we assessed the effects of RV infarction on this innervation.

**Methods and Results**—We measured the ventricular effective refractory period (ERP) shortening in response to bilateral ansae subclaviae stimulation and ERP lengthening induced by bilateral vagal stimulation as markers of autonomic innervation before and after RV myocardial infarction (RVMI) produced by coronary ligation (n = 28 dogs) or intracoronary latex injection (n = 18 dogs) into a marginal branch of the right coronary artery in open-chest anesthetized dogs. In each dog, ERPs measured in viable peri-infarct area at two RV outflow tract (RVOT) sites and two septal and four lateral sites at the RV free wall after RVMI showed reduced or absent ERP shortening during bilateral ansae subclaviae stimulation laterally, septally, and at RVOT sites 3 hours after RVMI. ERP shortening in response to infused norepinephrine was still present. Bilateral vagal stimulation during background norepinephrine infusion (0.10 to 0.25 μg/kg per minute) lengthened the ERP at all test sites before latex injection. After transmural RVMI, vagally induced ERP prolongation was attenuated or lost at lateral, septal, and RVOT test sites.

**Conclusions**—RVMI causes sympathetic and vagal denervation at viable sites at the RVOT, lateral, and, to a lesser extent, septal sides of the viable peri-infarct area. Autonomic denervation in the RVOT might contribute to the development of ventricular tachyarrhythmias after the acute stage of myocardial infarction involving the RV. *(Circulation. 1998;97:484-492.)*

**Key Words:** infarction • ventricles • innervation

Isolated RVMI accounts for <3% of all cases of myocardial infarctions but is often associated with considerable morbidity and mortality.1–9 RVMI accompanies 30% to 50% of inferior wall myocardial infarctions and, to a lesser extent, posterior and anterior wall myocardial infarctions1–9 and is a strong predictor of arrhythmogenic, ischemic, and mechanical complications and high in-hospital mortality in patients with acute inferior wall myocardial infarction.1

Transmural LV myocardial infarction in patients and dogs produces afferent and efferent sympathetic and vagal denervation in viable myocardium apical to the infarcted area.10–15 Although the pattern of sympathetic and vagal nerve projections to the RV is similar to that of the LV, the efferent sympathetic nerve fibers to the RVOT are located not only in the superficial subepicardium but also intramurally and in the subendocardium.16 Therefore, we sought to assess the effects of RVMI on efferent sympathetic and vagal innervation of viable myocardium in the viable peri-infarct area in an open-chest canine model.

**Methods**

**Surgical Preparation**

Forty-six mongrel dogs of either sex weighing 20 to 25 kg were initially anesthetized with pentobarbital sodium (30 mg/kg), and anesthesia was maintained with α-chloralose (10 mg/kg per hour). The dogs were placed on a heating pad, intubated, and ventilated with room air using a volume-cycled respirator (model 607, Harvard Apparatus). Left femoral arterial blood pressure was monitored, and normal saline was infused into the left femoral vein at a rate of 100 to 200 mL/h to replace spontaneous fluid losses. The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. Depending on the coronary anatomy, one or more proximal marginal branches of the RCA were isolated for later occlusion. Two hook electrodes made from Teflon-coated wires, insulated except for their tips, were placed in myocardium at the lateral side of the RV free wall (Fig 1) for cathodal unipolar stimulation; the anodal electrode was a 33-mm-diameter metal disk placed in the abdominal wall. A bipolar plunge electrode in the RV was used to record the ventricular responses induced by extrastimuli. A thermistor (model 400, Yellow Springs Instrument) was used to monitor epicardial temperature, which was maintained at 36° to 38°C with an operating room table lamp and a heating pad. Data acquisition began 40 minutes after placement of the plunge electrodes.

**Measurement of ERP**

The ERPs were determined with the extrastimulus technique using a programmable stimulator (Krannert Medical Engineering) as reported previously.11–20 The ERP, determined to the nearest 1 ms, was defined as the longest S1S2 interval at which S2 failed to produce a ventricular response. The ERPs were determined in triplicate and averaged.
Neural Stimulation

**Bilateral Ansae Subclaviae Stimulation**

The ansae subclaviae were isolated as they exited from the stellate ganglia, doubly ligated, and cut. Shielded bipolar electrodes were placed on the right and left anterior and posterior ansae subclaviae and connected to a programmable nerve stimulator (Pulsar 4; Frederick Haer). Stimuli were rectangular 4-ms pulses delivered at a frequency of 2 to 4 Hz and 3 to 4 V. Ansae SS intensity was increased until a 10 to 30 mm Hg increase in mean systemic arterial blood pressure was produced. Determination of the refractory period was started 2 minutes after the onset of neural stimulation. After the experiment norepinephrine was infused at dosages of 0.20 to 0.25 μg/kg per min, and ERPs were remeasured. The conditions of neural stimulation were kept constant in each experiment.

**Bilateral Vagal Stimulation**

Two Teflon-coated wire electrodes were embedded in the cardiac end of each vagal nerve. Rectangular pulses of 4-ms duration were delivered at a frequency of 20 Hz and 0.1 V greater than that required to produce asystole for the right vagal nerve and asystole or complete AV block for the left vagal nerve. Effects of VS were determined during norepinephrine infusion before and 3 hours after infarction (0.20 to 0.25 μg/kg per minute). Ten minutes after the baseline ERP values were obtained, coronary occlusion was performed by latex injection or coronary ligation. In the group of dogs that underwent latex injection (n=18), the isolated marginal branch was cannulated with a PE-50 catheter, and 0.5 mL latex solution was injected to produce transmural RVMI as in previous studies on LV myocardial infarctions.12-15 In 23 dogs, depending on the coronary anatomy, one or more marginal branches of the RCA were ligated in a one-stage manner to produce transmural non-transmural infarction. ERPs were then determined at 20, 60, 120, and 180 minutes after coronary occlusion. It took ≤15 to 20 minutes to determine the ERPs during each session; the data presented at 20 minutes, for example, were obtained at 20 to 40 minutes after coronary occlusion. In an additional 5 dogs, we examined the ERP responses to norepinephrine infusion before and 3 hours after infarction produced by coronary artery ligation.

After the experiment, the heart was fibrillated and excised with the electrodes still in place. The RV was separated from the remainder of the heart and cut in slices from base to apex. Each slice was rinsed in cold tap water and placed in a solution of distilled water, phosphate-buffered saline, and NBT (Sigma Chemical) at 37°C for 20 minutes. In viable myocytes, NBT is reduced to form a dark purple diformazan precipitate with intracellular diaphorases that use NADH or NADPH as electron donors. The infarcted tissue remains unstained. With this method, we verified the electrode position with respect to the infarction as well as the transmural nature of the infarction. No data presented were obtained from electrode sites located within the region of latex distribution or myocardial infarction.

**Data Analysis**

As reported previously,11-20 sites were considered completely sympathetically denervated if stimulation of bilateral ansae subclaviae shortened the ERP ≥9 ms before coronary occlusion but ≤2 ms after coronary occlusion. Test sites were considered partially sympathetically denervated if the ERP shortening induced by bilateral SS was attenuated ≥60% after coronary occlusion. In 3 sites of dogs receiving latex injection and 2 sites of dogs receiving coronary ligation, SS during the 3 hours after infarction shortened ERP ≤2 ms on one occasion and 3 to 6 ms on one or more different occasions, indicating some oscillation around the cutoff value. These sites were considered to be completely sympathetically denervated. Three sites with <9-ms shortening of ERP before coronary occlusion were excluded from the study because of possibly insufficient effects of SS.

Sites were considered to be completely vagally denervated if bilateral VS prolonged ERP ≥3 ms before coronary artery occlusion but ≤1 ms after coronary occlusion. Test sites were considered partially vagally denervated if the ERP prolongation produced by bilateral VS was reduced ≥60% after coronary occlusion. In 3 sites of dogs receiving latex injection and 1 site of dogs receiving coronary ligation, VS during the 3 hours after infarction lengthened ERP ≤1 ms on one occasion and 2 to 3 ms on one or more different occasions, representing some variations around the cutoff value. These sites were considered to be completely vagally denervated. Four test sites with <3-ms prolongation of ERP before coronary occlusion were excluded from the analysis because of possibly insufficient effects of VS.

The data in this study are expressed as mean±SEM. Both one-way repeated measures ANOVA and Newman-Keuls comparisons were used to compare the baseline ERPs and ERP response to sympathetic stimulation or VS. Statistical significance was set at $P<.05$.
TABLE 1. Changes in Baseline ERP in Sympathetic Denervation Experiments

<table>
<thead>
<tr>
<th>Before Coronary Occlusion</th>
<th>After Coronary Occlusion, min</th>
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<tr>
<td></td>
<td>20</td>
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<tr>
<td>RVOT sites without complete denervation (n=8)</td>
<td>166±3.7</td>
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<tr>
<td>RVOT sites with complete denervation (n=9)</td>
<td>172±4.0</td>
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<tr>
<td>Septal sites (n=18)</td>
<td>169±2.1</td>
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<tr>
<td>Lateral sites (n=36)</td>
<td>166±3.5</td>
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<tr>
<td>RVOT sites without complete denervation (n=7)</td>
<td>162±3.2</td>
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<tr>
<td>RVOT sites with complete denervation (n=7)</td>
<td>164±3.4</td>
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<tr>
<td>Septal sites (n=16)</td>
<td>159±3.1</td>
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<tr>
<td>Lateral sites (n=32)</td>
<td>160±2.9</td>
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ERPs of RV test sites measured before SS. Values are mean±SEM and expressed in ms. Differences in ERP before and after coronary occlusion were not statistically significant (P=NS).

Results

Sympathetic Denervation

Dogs With Latex Injection of a Marginal Branch of RCA

In all 9 dogs that received latex injection into a marginal branch of the RCA, transmural myocardial infarction was demonstrated with NBT staining, and complete sympathetic denervation was achieved in at least one RVOT test site in each dog over a period of 3 hours. Baseline ERPs of RV test sites are shown in Table 1. The cumulative rate of complete and partial sympathetic denervation of the test sites is shown in Fig 2. In this figure, the results of complete and partial sympathetic denervation in latex-induced infarctions and ligation-induced infarctions are combined, and the insert shows the relative distribution of these changes.

In the 9 dogs with RVMI produced by latex injection, 3 of the 17 RVOT test sites exhibited complete sympathetic denervation as early as 20 minutes after latex injection. Nine of 17 RVOT test sites became completely denervated 180 minutes after latex injection, but none of the lateral and septal test sites did so (Fig 3). Three of the 8 RVOT test sites without complete denervation, 5 of the 18 septal sites, and 19 of the 36 lateral test sites became partially denervated (ie, ERP shortening induced by bilateral SS was attenuated ≥60% after coronary occlusion) 180 minutes after latex injection (Fig 3). Shortening of ERP in response to norepinephrine was present at all sites (Fig 3), except for 1 RVOT test site that was located in the infarct area. This latter site was excluded from the data analysis.

Dogs With Ligation of Marginal Branches of RCA

The number of ligated marginal branches supplying the lateral RV free wall depended on the coronary anatomy of the dog (average, 2.4±0.3 ligations; n=11 dogs). Three dogs in the coronary ligation group that developed a nontransmural myocardial infarction as demonstrated by NBT staining showed no sympathetic denervation. These dogs demonstrated relatively constant ERP values over the 3-hour test period and are used as time controls (Table 2). Their data are not included in Fig 2.

Eight dogs had transmural RV infarction as demonstrated with NBT staining. Baseline ERPs of test sites are shown in Table 1. In 1 of the 8 dogs with transmural myocardial infarction, no complete sympathetic denervation was achieved at any RVOT test site. In the remaining 7 dogs, complete sympathetic denervation occurred at least 1 RVOT test site. In 1 of the 7 dogs, ventricular fibrillation was induced during ERP measurement 20 minutes after coronary ligation. Data obtained after the application of defibrillation DC shock (20 J) were excluded from the analysis. Complete sympathetic den-
ervation occurred at 7 of the 14 RVOT test sites 180 minutes after coronary occlusion (Fig 4). Partial denervation (ie, ERP shortening induced by bilateral SS attenuated ≥60% after coronary occlusion) occurred at 15 of the 32 lateral test sites 180 minutes after coronary ligation. At the remaining 7 RVOT and 16 septal test sites, responses to SS were slightly attenuated over time (Fig 4). Two RVOT test sites located in the infarct zone as demonstrated by NBT staining did not show a shortening of ERP in response to norepinephrine 180 minutes after coronary occlusion and consequently were not included in the data analysis.

In another group of 5 dogs with ligation of marginal branches of RCA, shortening of ERP in response to norepinephrine before and 3 hours after coronary occlusion was more pronounced at the RVOT test sites than at lateral and septal sites (Fig 5). In these dogs, the ERPs were determined during bilateral SS and then during norepinephrine infusion before coronary occlusion and 3 hours after coronary occlusion. Four RVOT test sites showed complete denervation and 5 RVOT test sites did not exhibit complete denervation 3 hours after coronary occlusion. There were no differences in ERP responses to bilateral SS or norepinephrine infusion between RVOT sites with and without complete sympathetic denervation.

**Vagal Denervation**

**Dogs With Latex Injection of a Marginal Branch of RCA**

In 9 dogs receiving intracoronary latex injection, 3 of the 36 lateral sites and 1 of the 18 RVOT sites were involved in myocardial infarction; therefore, data from these sites were excluded. Baseline ERP of test sites are shown in Table 3. Cumulative rate of complete and partial vagal denervation after latex- and ligation-induced infarctions are shown in Fig 6. In the 9 dogs with RVMI produced by latex injection, as early as

<table>
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<tr>
<th>TABLE 2. Changes in ERP Induced by SS in Five Dogs With Nontransmural RVMI</th>
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<tr>
<td>RVOT sites (n=10)</td>
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<tr>
<td>Septal sites (n=9)</td>
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<tr>
<td>Lateral sites (n=18)</td>
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</table>

Values are mean±SEM and expressed in ms.

*P<.05 compared with before occlusion.
20 minutes after coronary occlusion, 3 RVOT test sites exhibited complete vagal denervation. Complete vagal denervation was achieved in 11 of 17 RVOT test sites 3 hours after latex injection (Fig 7). Partial vagal denervation occurred at 17 of the 33 lateral sites, 7 of the 16 septal sites, and 2 of the 6 RVOT test sites without complete denervation over a period of 3 hours. Lengthening of the refractory period in response to bilateral VS was significantly attenuated after coronary occlusion over a period of 3 hours at all test sites (Fig 7).

**Dogs With Ligation of Marginal Branches of RCA**

The number of marginal branches ligated was dependent on the coronary anatomy of the dog (average, 2.2±0.5 ligations; 12 dogs). The difference in the number of ligated marginal branches of the RCA between the vagal denervation group and sympathetic denervation group was not statistically significant (P=NS).

The ERP data obtained from 5 dogs were excluded from statistical analysis because dogs had no infarction or nontransmural myocardial infarction and/or because dogs developed multiple ventricular fibrillation episodes during refractory period measurements during infusion of norepinephrine after coronary ligation. Ventricular defibrillation was accomplished promptly with the epicardial application of direct current shocks (20 J), but because it has been previously shown that defibrillating shocks significantly affect neural responsiveness, these dogs were excluded from data analysis.

In the remaining 7 dogs, 5 showed transmural myocardial infarction and 2 showed nontransmural myocardial infarction. Baseline ERPs of tested sites are shown in Table 3. The cumulative rate of complete and partial vagal denervation after coronary ligation is shown in Fig 6. Complete vagal denervation occurred at RVOT test sites but not at lateral or septal test sites. Seven of the 13 RVOT sites showed complete vagal denervation over a period of 3 hours (Fig 8). Partial vagal denervation was achieved at 11 of the 26 lateral test sites. The ERP lengthening in response to bilateral VS was markedly attenuated at the lateral test sites (n=26) and RVOT sites that showed complete vagal denervation, whereas it was slightly reduced at the septal test sites (n=12) and RVOT test sites (n=6) without denervation (Fig 8).

**Discussion**

**Major Findings**

RVMI produced by intracoronary latex injection or ligation of marginal branches of the RCA caused selective complete
sympathetic and vagal denervation in the viable peri-infarct area at the RVOT side of the infarction. After latex-induced infarction, partial sympathetic and vagal denervation occurred at the lateral, RVOT, and septal sides of the infarction. After ligation-induced infarction, partial denervation was observed only at the lateral side of the infarction, and the autonomic responsiveness at the septal and RVOT sites without denervation was attenuated. This pattern of denervation after RVMI differs from that after LV infarction.11 The shortening of ERP at the RVOT test sites produced by norepinephrine infusion, but not by bilateral SS, was more pronounced before and 3 hours after coronary occlusion compared with septal and lateral test sites.

**Sympathetic Denervation**

In the present study, we observed selective complete efferent sympathetic denervation at viable test sites located at the RVOT side of the infarction. Partial denervation occurred at the lateral, septal, and RVOT sides of the infarction produced by latex injection. The shortening of ERPs in response to bilateral SS after latex-induced RV infarction was attenuated at the RVOT, lateral, and septal sites without apparent complete denervation. However, the septal and lateral sites exhibited less attenuation in shortening of ERPs during bilateral SS after coronary ligation-induced RVMI (Figs 3 and 4). This pattern of denervation in the viable peri-infarct zone after RVMI differs from that after LV infarction.11 Barber et al11 have shown that bilateral SS in dogs after LV myocardial infarction shortened the ERPs at sites basal to the infarction. However, approximately one third of the tested sites located apical to, but not within, the zone of infarction no longer responded to SS after LV infarction.11

Ito and Zipes16 have shown that the efferent sympathetic fibers are located in the subepicardium and project to the RV perpendicular to the right lateral AV groove or the LAD. The sympathetic fibers to the RV myocardium near the RCA stem predominantly from the right lateral AV groove. RV myocardium close to the LAD receives sympathetic fibers from both the right lateral AV groove and areas close to the LAD. They16 also have shown that the sympathetic innervation of the RVOT differs from the remainder of the RV and from the LV. Efferent sympathetic fibers to the RVOT originate both from the right lateral AV groove near the origin of the RCA and from areas near the LAD. In the RVOT region, sympathetic fibers are located both in the superficial subepicardium and deep myocardium.

**RVOT Response to Norepinephrine**

Interestingly, in the present study, we observed a more pronounced ERP shortening to a standard concentration of norepinephrine infusion at the RVOT test sites compared with that at septal and lateral test sites. This latter observation is not due to denervation supersensitivity (ie, chronically denervated sympathetically denervated myocardium becoming supersensitive to the effects of infused catecholamines). The explanation might be a higher density of β-adrenergic receptors or a higher sensitivity of these receptors for catecholamines in this region.

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Table 3: Changes in Baseline ERP During Norepinephrine Infusion in Vagal Denervation Experiments

<table>
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<tr>
<th></th>
<th>Before Coronary Occlusion</th>
<th>After Coronary Occlusion, min</th>
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<tr>
<td></td>
<td>20</td>
<td>60</td>
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<tr>
<td>Nine dogs with transmural RVMI from latex injection of a marginal branch of RCA</td>
<td>RVOT sites without complete denervation (n=6) 151±4.2</td>
<td>149±3.8</td>
</tr>
<tr>
<td></td>
<td>RVOT sites with complete denervation (n=11) 152±3.6</td>
<td>150±3.7</td>
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<tr>
<td></td>
<td>Septal sites (n=16) 149±3.4</td>
<td>146±3.3</td>
</tr>
<tr>
<td></td>
<td>Lateral sites (n=33) 147±4.0</td>
<td>149±3.6</td>
</tr>
<tr>
<td>Seven dogs with transmural RVMI from ligation of a marginal branch of RCA</td>
<td>RVOT sites without complete denervation (n=6) 145±3.9</td>
<td>145±4.1</td>
</tr>
<tr>
<td></td>
<td>RVOT sites with complete denervation (n=7) 149±4.2</td>
<td>148±3.8</td>
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<tr>
<td></td>
<td>Septal sites (n=12) 144±4.5</td>
<td>146±4.1</td>
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<tr>
<td></td>
<td>Lateral sites (n=26) 151±3.6</td>
<td>149±3.3</td>
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Values are mean±SEM and expressed in ms. Difference in ERP before and after coronary occlusion was not statistically significant (P=NS).

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Figure 6. Cumulative percentage of completely vagally denervated RVOT sites and partially denervated lateral, septal, and RVOT test sites after latex- and ligation-induced RVMI in the same manner as in Fig 2. Insert shows the distribution of these changes. See text for details.
Figure 7. Lengthening of ERP induced by VS in 9 dogs with transmural myocardial infarction produced by latex injection into a marginal branch of the RCA. In 11 test sites at the RVOT side of the infarction, ERP prolongation in response to VS was ≤ 1 ms on one or more occasions after coronary occlusion and according to our criteria these sites were designated as completely denervated (Den).

None of the RVOT test sites exhibited spontaneous restoration of the ERP response toward baseline values at more than one consecutive ERP measurement episode. ERP lengthening in response to bilateral VS was significantly attenuated after coronary occlusion over a period of 3 hours at all test sites. ERP prolongation during VS is plotted over time (minutes). For format and abbreviations, see Fig 3.

Figure 8. Lengthening of ERP induced by VS in 7 dogs with RVMI (5 transmural and 2 nontransmural) produced by coronary ligation. For format and abbreviations, see Fig 3. See text for details.
However, the exact mechanism must be delineated in future studies. Denervation supersensitivity was not noted in the present study, probably because of the short time course of the experiments.17-19

**Vagal Denervation**

The pattern of vagal denervation was similar to that of sympathetic denervation. Functional denervation occurred heterogeneously and gradually over a period of 3 hours after coronary occlusion. Ito and Zipes16 have shown that the functional efferent vagal pathways to the RV are located superficially at the right lateral AV groove and then dive into the myocardium at 10 to 15 mm from the AV groove, when all vagal fibers become intramural. RV myocardium near the RCA receives vagal fibers mainly from the right lateral AV groove, whereas myocardium near the LAD receives vagal innervation both from the right lateral AV groove and from regions near the LAD. Vagal fibers to the RVOT are located deep in the myocardium, and the innervation pattern does not differ from the remainder of the RV. Our findings are compatible with the latter study, showing that transmural and nontransmural myocardial infarction causes complete vagal denervation at the RVOT side of the infarction. Vagal denervation at the RVOT side of the peri-infarct zone might be due to innervation of this area, with nerve fibers projecting mainly from the RCA and traveling through the infarcted myocardium. The innervation of lateral and septal sides stems from both the RCA and left coronary artery and thus exhibit partial denervation, but not complete elimination, of vagally induced ERP prolongation at these test sites after infarction.

**Cause of Denervation**

Vagal and sympathetic responses became lost or attenuated at the RVOT test sites and became attenuated at the lateral and septal test sites only within 20 minutes after coronary occlusion, with additional sites losing responsiveness over time. The time course of denervation is concordant with that of previous studies.12 The reason for selective complete denervation at the RVOT side of the peri-infarct zone might be innervation of this area with nerve fibers projecting mainly from the RCA and traveling through the infarcted tissue. The lateral and septal sides apparently receive nerve fibers from the regions of both RCA and left coronary artery, which might explain the partial denervation or attenuation, but not complete elimination, of autonomic responsiveness of refractoriness at these test sites.

In this study, as in previous studies12-15 of LV infarction, some RVOT test sites that were initially designated as completely denervated by our arbitrary criteria subsequently showed responses to neural stimulation that exceeded the complete denervation cutoff value. Metabolic changes may play a role,17-19 but the exact mechanism of this phenomenon remains unexplained. Because little is known about the blood supply to the cardiac nerve fibers, it is still unclear whether neural denervation results because due to ischemia in the nerve fibers, as in the contiguous myocardial fibers, or whether exposure to certain substances in the ischemic environment through which the axons pass causes functional denervation.18 Complete denervation of the nonischemic myocardium situated at the RVOT side of the peri-infarct area is best explained by the alteration of neurotransmission in the axons traveling through the infarcted myocardium. The myocardial fibers located septally and laterally receive innervation from nerve fibers traveling along the LAD and left circumflex artery, which may explain the partial denervation or attenuation of autonomic responses at these test sites. Collateral blood flow to the septal and lateral sides of the infarction may partially explain the absence of complete or partial denervation after coronary ligation-induced infarction. Collateral blood flow cannot account for the absence of complete denervation at the lateral and septal test sites after RVMI produced by latex injection, because latex embolizes collaterals and produces a transmural myocardial infarction.

**Consideration of the Experimental Model**

Previous studies14,15 have shown that in the canine heart 4 to 21 days after transmural myocardial infarction or dissection of the AV groove, elimination of responses in ERP to sympathetic stimulation or VS are accompanied by the biochemical evidence of denervation of sympathetic or vagal fibers. In the present study, because only a limited number of sites were sampled, more extensive denervation may exist than suggested by the data presented.

We studied the autonomic changes up to 3 to 4 hours after coronary occlusion. Earlier reports11,17 have demonstrated that histochemical changes indicative of autonomic neural denervation take place within days. In the present study, no histochemical studies were performed to confirm the functional alterations in neural responsiveness; therefore, it might be more accurate to refer to the autonomic alterations as neural dysfunction, rather than as neural denervation, because we did not obtain histochemical proof of the latter.

The criteria for denervation were arbitrary in the present study as they have been used in previous studies.12-19 It took 15 minutes to determine the duration of ERPs both in the control state and during nerve stimulation. Although it is possible that minor changes in ERP might occur during these 15 minutes, this did not seem to be an important source of error. Tables 1 through 3 show that the baseline ERPs were stable during the experiments. It is unlikely that electrotonic interactions between infarcted and noninfarcted areas took place; however, we cannot totally exclude this possibility.

Myocardial blood flow was not determined in the present study. The site of electrode placement with respect to the infarction was determined with the use of NBT staining. This determination, in addition to the fact that infusion of norepinephrine shortened ERPs at the test sites, suggests that there were still viable, functioning adrenergic receptors at the completely or partially denervated test sites and that there appeared to be sufficient blood flow to distribute the infused norepinephrine to these test sites. Latex was injected to embolize collaterals and produce a transmural myocardial infarction in the present study as in previous studies.12-16 Because of its inert properties, it is not likely that latex itself interrupted both sympathetic and vagal responses. Dogs with ligation of marginal branches of RCA tended to have infarctions with less epicardial involvement than did dogs with infarctions produced by intracoronary latex injection. In the present study, vagal and sympathetic dener-
vations tended to occur more slowly after RVMI produced by coronary ligation compared with after latex-induced infarction. RVMI produced by ligation of marginal branches of the RCA alone also interrupted both sympathetic and vagal responses; therefore, autonomic denervation after latex-induced RVMI is very likely due to the infarction and not to the latex.

**Clinical Implications**

Zehender et al. have shown in their series of 200 patients with acute inferior wall myocardial infarctions that more than half had RV involvement. Those patients had a risk of dying in the hospital seven to eight times that for patients with acute inferior wall myocardial infarctions who did not have evidence of RV involvement. They have also shown that the poor outcome in their patients could not be explained on the basis of more severe damage to the LV in these patients. Yusuf et al. have suggested that the poor outcome in patients with inferior wall myocardial infarction with RV involvement may be due to an increase in serious ventricular arrhythmias, advanced AV block, and cardiac rupture.

The experimental RVMI model used in the present study differs from the usual clinical setting. In the majority of patients with RVMI, the RV is involved as an extension of LV infarction. In many cases, the RV free wall is not involved in the infarction. Patients with acute RVMI have acute RV dysfunction that can improve gradually to become almost normal in time.

These issues limit the direct clinical applicability of the present study.

It has been shown that sympathetic denervation was arrhythmogenic in dogs with LV myocardial infarction 4 to 22 days after denervation. Although arrhythmia induction was not tested in the present study, it is quite possible that the heterogeneous development of sympathetic and vagal denervation at the lateral, septal, and outflow tract sides of the RVMI might contribute to the development of ventricular tachyarrhythmias in the acute stage of infarction.

**Acknowledgments**

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**References**


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