Transmural Myocardial Infarction in the Dog Produces Sympathectomy in Noninfarcted Myocardium

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SUMMARY Because sympathetic fibers travel in the subepicardium and generally follow the coronary arteries in a basal to apical course, we tested the hypothesis that transmural myocardial infarction that involves this subepicardial region interrupts sympathetic axons traveling through the infarct and produces sympathetic denervation at noninfarcted sites apical to the infarction. A rapidly hardening vinyl latex solution injected into the first diagonal branch of the left anterior descending coronary artery produced the transmural myocardial infarction by embolizing the vasculature. Ten dogs were studied 90 minutes after coronary artery embolization (acute) and 12 dogs were studied 7–21 days after infarction (chronic). The integrity of the sympathetic innervation was tested in an open-chest preparation of the acutely and chronically infarcted dogs by measuring endocardial and epicardial effective refractory period changes during left and right stellate stimulation. Additionally, regional myocardial norepinephrine content and fluorescence were examined in the chronically infarcted dogs. Transmural infarction was verified using nitroblue tetrazolium staining. In the 10 acutely infarcted dogs, left and right stellate stimulation shortened the effective refractory period at all 56 sites examined before infarction and at 30 sites basal or lateral to the infarct after embolization. Twenty-six noninfarcted sites apical to, but not within, the zone of infarction did not respond to left or right stellate stimulation after infarction. In the 12 chronically infarcted dogs, left and right stellate stimulation shortened the effective refractory period at all 20 sites basal to infarction. In noninfarcted sites apical to the infarction, left stellate stimulation did not shorten the effective refractory period at 23 of 41 sites, while right stellate stimulation was ineffective at 24 of 41 sites. Twelve of 41 sites apical to the infarct had normal effective refractory period shortening during left and right stellate stimulation. In both groups of dogs, norepinephrine infusion, 0.05 μg/kg/min, i.v., shortened the refractory period at all sites apical to the infarct that did not shorten refractory period in response to stellate stimulation. In chronically infarcted dogs, myocardial norepinephrine content was reduced at the denervated sites, and histologically reduced norepinephrine fluorescence in noninfarcted, denervated myocardium was found. We conclude that transmural myocardial infarction produces heterogeneous sympathetic denervation in noninfarcted sites apical to the area of necrosis. This denervation is probably the result of interrupting sympathetic nerves coursing from base to apex.

ALTHOUGH some sympathetic nerves innervate relatively specific and localized sites in the ventricle, several studies have shown that the anterior left ventricle receives its major efferent sympathetic nerve supply from nerves that course in the superficial subepicardium, most likely within the upper 0.25–0.50 mm. These nerves travel from base to apex along the coronary arteries,1,2 probably dive transmurally to innervate the endocardium,3 and modulate a variety of myocardial functions.1,4 It is known that myocardial ischemia disrupts autonomic neurotransmission within a region of developing infarction;5 but it is not known whether the zone of infarction inhibits neurotransmission to areas of viable, noninfarcted myocardium distal (apical) to the ischemic zone. This could occur if the infarction damaged axons traveling though it en route to more distal sites.

The goal of the present study was to produce a localized transmural myocardial infarction and test the hypothesis that such an infarction acutely disrupts sympathetic neural responses by interrupting efferent sympathetic nerve fibers passing from base to apex through the infarction and produces chronic sympathetic denervation of viable myocardium apical to the infarct.

Methods

We tested the acute and chronic effects of latex-induced transmural myocardial infarction. We produced transmural infarction by intracoronary injection of a rapidly hardening vinyl latex solution6,7 to eliminate the influence of collateral circulation found in the canine heart, and to ensure the production of transmural infarction that has been demonstrated using the coronary artery embolization technique.6,8

Acute Preparation

Ten healthy, adult male dogs that weighed 15–23 kg...
were anesthetized with sodium secobarbital (30 mg/kg i.v.). A midline incision was made in the neck, the right and left cervical vagi were isolated, the trachea was cannulated and the dogs were ventilated 10–14 times/min using a volume-cycled respirator (Harvard model 607). The left femoral artery and vein were cannulated with heparinized, saline-filled polyethylene tubing. The arterial catheter was connected to a Statham pressure transducer (P23Db) and Honeywell (model 1858 CRT) Visicorder to monitor arterial blood pressure. This catheter also served as a site to obtain arterial blood samples that were analyzed for pH, Po2, and PCO2 on an IL-813 automated blood gas analyzer. Ventilation was adjusted throughout the experiment to maintain arterial Po2 at a level greater than 85 mm Hg. Sodium bicarbonate was infused intravenously as needed to correct for base deficit and maintain arterial pH within 7.35–7.47.

A left thoracotomy at the fifth intercostal space was performed and the lungs were gently retracted. To produce neural decentralization of the heart,9, 10 the ansae subclaviae were isolated as they exited from the stellate ganglia, doubly ligated and transected. The cervical vagi were doubly ligated and transected at this time. Miniature shielded bipolar stimulating electrodes (Ealing Manufacturing Co.) were positioned on the left and right ansae subclaviae to stimulate efferent sympathetic nerves to the heart. Stimuli were square-wave pulses (4 msec, 7–9 V, 2–4 mA) delivered at a rate of 3–5 Hz from a constant current source. This frequency has been described as the “tonic” rate of activity11, 12 for the cardiac sympathetic nerves and produces shortening of the effective refractory period (ERP) without excessively increasing heart rate.

The pericardium was opened, 5–7 mm of the first diagonal branch of the left anterior descending coronary artery (LAD) were isolated, and two silk ligatures were placed underneath the artery. Because isolation of the coronary artery might interrupt sympathetic fibers traveling in the adventitia, after coronary artery dissection, refractory period determinations were performed before and during stellate stimulation to ensure that all areas tested were not denervated by the coronary artery isolation. All sites tested in this study had ERP shortening during left and right stellate stimulation after the coronary artery isolation. Endocardial and epicardial bipolar plunge electrodes, constructed of two Teflon-coated stainless steel wires threaded through a 21-gauge needle and bent at the tip to form a hook, were positioned above (basal) and below (apical) the zone that potentially would be made ischemic by the latency injection of the artery. Each endocardial electrode was placed beneath an epicardial electrode. The electrode positions, area of latency injection, and the area of potential sympathetic denervation are shown in figure 1. A banjo thermistor (YSI probe, model 425) was secured to the epicardial surface of the left ventricular free wall, and epicardial temperature monitored. Rectal temperature was also monitored, and a heating blanket and lamp were used to keep epicardial and core temperature within a range of 37–39°C.

Control ERPs were obtained (see below) before and during sympathetic nerve stimulation. Then, the ligature at the origin of the diagonal branch was tied and retracted, the distal ligature positioned in such a manner as to prevent bleeding due to retrograde flow, and the diagonal branch cannulated with PE-50 catheter. The cannula was secured in the artery, and 0.3–0.5 ml of vinyl latex solution (Carolina Biological Supply) was rapidly injected into the artery through the cannula to embolize the vasculature.6 7 The cannula was removed, the proximal ligature left in place, and the distal ligature tied tightly around the embolized artery. Preliminary experiments had demonstrated that after embolization, 60–90 minutes were required for the preparation to stabilize before reproducible ERP determinations could be made. ERPs in the acute infarct study were measured 90 minutes after embolization. In two additional dogs, only acetone, the vehicle in which the latex was dissolved, was injected.

Chronic Preparation
Twelve adult male mongrel dogs, 15–26 kg, were anesthetized with sodium secobarbital (30 mg/kg i.v.), intubated and artificially ventilated with room air using a constant-volume respirator. Using sterile technique,
the chest was opened at the fifth left intercostal space, the lungs were gently retracted and the pericardium was opened and sutured to the wound edges to support the heart. Five to 7 mm of the first diagonal branch of the LAD were isolated and two silk ligatures placed underneath. The artery was cannulated and 0.3–0.5 ml of vinyl latex solution injected as described for the acute preparation. In four additional dogs, the coronary artery was ligated and cannulated but latex was not injected into the vessel. The chest was closed in layers, negative pressure breathing established, and the dogs were allowed to recover. Postoperative antibiotics were administered for 5 days to prevent infection, and at the time of the second procedure all dogs were in good health. Seven to 21 days after coronary embolization, the dogs were prepared for study in a manner similar to that described for the acutely infarcted dogs. The dogs were anesthetized, ventilated and the previous incision at the left fifth intercostal space was reopened. Dogs were neurally decentralized and the ansae subclaviae prepared for stimulation as described above. Bipolar endocardial and epicardial plunge electrodes were positioned above and below the zone of infarction. This region was easily identified on the epicardial surface by visualizing the area of necrotic tissue and the red vinyl latex present in the artery. Epicardial and rectal temperatures were monitored carefully and maintained by the method described above. ERPs were measured before and during sympathetic nerve stimulation.

**Experimental Protocol — Acute Infarction**

To maintain a constant paced cycle length throughout each experiment during refractory period measurements, the pacing cycle length chosen was 30 msec shorter than the minimum cycle length achieved during 1 minute of left and right sympathetic stimulation. ERPs were measured before coronary artery injection of latex and before and during left and right ansae subclaviae stimulation. Control (no sympathetic nerve stimulation) ERP measurements were made 20 minutes after completing neural manipulations and inserting the bipolar plunge electrodes. After control measurements, either the left or right ansae subclaviae (the order of stimulation was chosen randomly) were stimulated for at least 3 minutes and ERP values remeasured. Unilateral sympathetic stimulation was then discontinued and the heart was allowed to recover for 10 minutes. Control ERPs were obtained and the opposite pair of ansae subclaviae was stimulated for 3 minutes. Then, ERPs were measured once again. This procedure was followed whenever sympathetic nerve stimulation was performed.

The ERP was determined at each electrode site using the extrastimulus (S2) technique with bipolar rectangular stimuli of 2 msec duration at twice diastolic threshold delivered from a digital stimulator (Medtronic model 5325) through an isolation transformer. Diastolic threshold was constant at each site tested to ± 0.5 mA throughout the experiment or the data were discarded. A train of 15 basic stimuli (S1, the cycle length determined as described above) was followed by S2 that initially produced a propagated ventricular response. The ventricular response was recorded in lead II of the ECG and from multiple bipolar electrodes in the ventricle and displayed on a storage oscilloscope (Tektronix model D11) at a rapid sweep speed. The S1S2 interval interval was shortened by 1-msec intervals until failure to capture occurred. Then, the S1S2 was increased by 5 msec and the shortening of the S1S2 was repeated 30 seconds later. Each test site was stimulated at least twice before moving to another test site. A repeat ERP measurement yielded a value within 1 msec of the first, or the data were discarded. The ERP was defined as the longest S1S2 that failed to capture the ventricle. The paced (basic) cycle length (S1S2; 250–280 msec) was maintained constant throughout each experiment.

Preinfarction ERPs were measured before and during sympathetic nerve stimulation. Then, 0.3–0.5 ml of latex solution was injected directly into the first diagonal branch through a PE-50 catheter. The preparation was allowed to stabilize for 90 minutes and the ERP measurements were repeated before and during sympathetic stimulation. Twenty minutes after recovery from the last period of sympathetic nerve stimulation, ERP values were obtained before and during i.v. infusion of norepinephrine, 0.05 μg/kg/min, to test the ERP response to an infused neuromediator.

Four to 6 hours after occlusion, the heart was fibrillated and excised with the electrodes still in place. The left ventricle was separated from the rest of the heart and cut in a breadloaf fashion from base to apex (fig. 2). Tissue slices were obtained, rinsed in cold tap water and placed in a solution of distilled water (288 ml), phosphate buffer (32 ml, pH 7.4) and nitroblue tetrazolium (100 mg, Sigma Co.) at 37°C for 7–12 minutes. Nitroblue tetrazolium, a formazan stain for myocardial dehydrogenase enzyme activity, delineates infarcted myocardium. With this method, we verified electrode position with respect to the infarct as well as the transmural nature of the infarct. No data presented were obtained from electrode sites located within the region of latex distribution and myocardial infarction.

The ERP data for the electrode sites were categorized into one of three groups, based on the electrode anatomic location and response to sympathetic nerve stimulation: (1) regions above (basal to) the infarction demonstrating ERP shortening during sympathetic nerve stimulation before and after coronary occlusion; (2) regions below (apical to) the infarction where ERP values shortened during sympathetic nerve stimulation before infarction, but did not shorten after infarction; and (3) regions below (apical or lateral to) the infarction that exhibited ERP shortening during sympathetic nerve stimulation before and after infarction. Sites with ERP shortening ≤ 2 msec during left or right sympathetic nerve stimulation that previously demonstrated ERP shortening greater than 5 msec during sympathetic stimulation were considered to be sympa- thetically denervated.
Experimental Protocol — Chronic Infarction

ERPs were measured before and during left and right ansae subclaviae stimulation at each of the bipolar electrode sites as described for the acute infarction preparation. In six dogs, norepinephrine, 0.05 μg/kg/min, was infused intravenously and changes in ERP were recorded. At the end of the experiment, the hearts were fibrillated and then excised with the electrodes still in position. The location of the electrodes with respect to the infarct was visually confirmed and the electrode sites categorized into one of three groups as described for the acute infarction preparation. In the six dogs in which norepinephrine was not infused, the hearts were placed in iced saline and multiple endocardial and epicardial biopsies taken from tissue adjacent to normally responsive (i.e., normally innervated) and sympathetically denervated electrode sites. These biopsies were examined for myocardial norepinephrine content, histologic evidence of necrosis and catecholamine histofluorescence.

Myocardial Norepinephrine Determination

Myocardial norepinephrine content was determined in tissue samples frozen in liquid nitrogen and stored at −30°C until analysis. The samples were homogenized in 5–10 volumes (w:v) of 0°C 0.1N perchloric acid. An appropriate aliquot was then analyzed for norepinephrine using a radioenzymatic assay. Each sample was quantitated in duplicate; an internal standard of 500 pg norepinephrine was used for each sample. Sensitivity of the assay was 1.5 pg and the coefficient of variation of the assay was 4.0%.

Catecholamine Histofluorescence

Additional samples of cardiac tissue taken after sacrifice were dissected into blocks for histofluorescence histochemistry, quickly frozen in isopentane chilled to −125°C in liquid nitrogen and stored either in liquid nitrogen or at −95°C in a low-temperature freezer until studied. The frozen pieces of tissue were subsequently frozen to a chuck and cut on a cryostat (Hacker-Bright) at −30°C. The sections were picked up on clean glass slides, exposed to glyoxylic acid according to the method of de la Torre, and examined with a Leitz Orthoplan microscope equipped with Ploem epillumination accessories. Sections from each region.
were viewed and photographed on the day they were cut to minimize the effects of photodecomposition and diffusion.

Data Analysis

All results in this study are expressed as mean ± SEM. The statistical significance of difference was determined using the appropriate t test for paired or unpaired data. When multiple group comparisons were made, a one-way analysis of variance was performed. When an analysis of variance demonstrated significance, a Scheffé test was used to determine significance between individual means. Significance was considered to be present if p < 0.05. Statistical techniques were taken from Snedecor and Cochran.

Results

Acute Infarction Study

Acute experiments were performed during which we measured ERPs at 62 endocardial and epicardial electrode sites. Values obtained at six sites subsequently were excluded from analysis because after nitroblue tetrazolium staining, the electrodes were found to lie within the infarct region.

Results are grouped as described in Methods. Before sympathetic stimulation and creation of infarction, control ERP values were not different above or below the level of the area to be infarcted (fig. 3, column C) (p > 0.05, analysis of variance). Left and right sympathetic nerve stimulation shortened ERP to a similar degree at all 20 sites above the infarction and at 36 electrode sites examined below (apical to) the area of potential infarction. Analysis of variance showed no statistically different responses among the three groups.

Figure 4 shows values from the same areas of the heart 90 minutes after coronary artery embolization. ERP measurements before sympathetic stimulation were not statistically different from each other (column C, 134 ± 3 vs 131 ± 3 vs 137 ± 5 msec), or from values obtained before infarction in each area. Both left (p < 0.05) and right (p < 0.02) sympathetic nerve stimulation significantly shortened ERPs measured at 20 sites above the infarction, and at 10 sites (left, p < 0.05; right, p < 0.02) apical to and distant from the infarction. Additionally, all sites above (p < 0.02) and below (p < 0.02) the infarction demonstrated a significant shortening of the ERP during i.v. infusion of norepinephrine. Electrode sites close to the apical side of the infarction did not demonstrate ERP shortening during either left (131 ± 3 to 131 ± 3 msec) or right (131 ± 3 to 129 ± 3 msec) sympathetic nerve stimulation, but i.v. norepinephrine infusion produced a significant decrease (p < 0.02) in the ERP at all 26 sites tested.

In two dogs whose data are not included in this study, ERP changes during sympathetic nerve stimulation were determined at eight sites basal and 12 sites apical to the coronary artery 90, 120 and 180 minutes after the artery was doubly ligated, cannulated and injected with 0.3 ml of acetone. ERPs changed the same amount during sympathetic nerve stimulations after ligation of the coronary artery and injection of acetone as they did before ligation. Small subendocardial infarctions were identified in both hearts after 6 hours of ischemia using nitroblue tetrazolium.

Chronic Infarction Study

In 12 dogs, chronic studies were performed during which we measured ERPs at 68 electrode sites. Data from seven of these electrode sites were excluded from the study because at postmortem examination, the electrodes were found to lie within the infarcted region.

Figure 5 shows the ERP values for regions similar to those described in the acute infarction studies. No significant differences (p > 0.05) in ERP existed among the three regions during control conditions before sympathetic stimulation. At all 20 sites above the infarction, left (p < 0.05) and right (p < 0.05) sympathetic stimulation significantly shortened ERP. Intravenous infusion of norepinephrine in six dogs significantly (p < 0.02) decreased ERP at the sites measured above the infarct.

Twelve of 41 sites not infarcted by embolization and below (apical to) the transmural infarct showed significant ERP shortening during left (p < 0.02) and right (p < 0.02) sympathetic stimulation (fig. 5). The ERP
failed to shorten in 18 sites below the infarct during left and right sympathetic nerve stimulation (completely denervated), yet demonstrated a significant shortening in ERP during norepinephrine infusion ($p < 0.02$). In 11 remaining sites (table 1), the ERP significantly shortened during left but not right sympathetic stimulation at six sites and during right but not left sympathetic stimulation at five sites.

Myocardial norepinephrine content determined from tissue biopsies taken from the six dogs that did not receive i.v. norepinephrine infusions are shown in table 2. Innervated sites showed significantly higher ($p < 0.005$) myocardial norepinephrine content at both endocardial and epicardial sites than did the denervated sites.

Histologic study of tissue from the biopsy sites revealed all areas consisted of normal endocardial and epicardial muscle with no evidence of necrosis or ischemic damage to the muscle (figs. 6A and 6B). Histologic and histofluorescent analysis for catecholamine-containing neurons demonstrated significant qualitative differences between the normally innervated and the functionally denervated areas. Histologically normal nerve fibers and catecholamine histofluorescence were seen in the normally innervated areas (fig. 6C), while denervated regions apical to the infarct demonstrated few viable nerve fibers and markedly reduced histofluorescence (fig. 6D).

Four dogs underwent chronic coronary artery ligation as described above, but latex was not injected. The dogs were allowed to recover and were restudied 1 week later. One dog had a small subendocardial infarction and the three other dogs had no identifiable region of infarction, as demonstrated by nitroblue tetrazolium. We did not find areas of efferent sympathetic denervation in any of these four dogs.

**Discussion**

**Major Findings**

The results of this study indicate that a 90-minute occlusion produced by injecting rapidly hardening latex into the first diagonal branch of the LAD inhibited ERP shortening during sympathetic stimulation in
areas of viable, noninfarcted endocardium and epicardium situated apically to the infarct. Interruption of neurotransmission was heterogeneous, since all sites examined apical to the transmural infarct were not sympathetically denervated. These denervated sites, although no longer responsive to sympathetic nerve stimulation, still demonstrated normal ERP shortening in response to blood-borne norepinephrine. Seven to 21 days after chronic transmural infarction induced by latex injection, electrophysiologic evidence of sympathetic denervation was still present in viable, noninfarcted myocardial sites on the apical side of the infarct. As with the acute occlusion, sympathetic denervation was heterogeneous and some sites had intact innervation from only one side of the sympathetic chain. Infused norepinephrine still significantly shortened ERPs at sites that were neurally denervated. Histologic evidence of necrosis was not found in the sympathetically denervated tissue. Evidence for nerve disruption and degeneration was seen, as demonstrated by an 84% reduction in norepinephrine content in the endocardium and an 88% reduction in the epicardium. While these reductions were not as large as those reported in earlier phenol denervation studies22,23 or after complete ventricular sympathectomy,22,23 the depletion was striking. While tissue samples were taken from denervated myocardium containing the bipolar electrode, relatively large samples (0.2–0.4 g) were used. The heterogeneous nature of the sympathetic denervation may have resulted in the inclusion of completely denervated and partially denervated myocardium in some tissue samples, while other samples consisted of totally sympathetically denervated tissue. Indeed, in 10 of the 21 denervated tissue biopsies assessed for myocardial norepinephrine content, values of less than 90 pg norepinephrine/g myocardium (less than 10% of the norepinephrine content found at the normally innervated sites) were seen. Thus, examination of norepinephrine content provides support for the observed functional denervation.

While some authors23,24 have demonstrated that the norepinephrine content of the base of the heart is greater than the norepinephrine content in more apical areas, we do not feel this significantly influenced our results or interpretation. Although all denervated sites were located apical to the site of infarction and many of the normally innervated sites were basally located, the extent of norepinephrine depletion (endocardium 84%, epicardium 88%) at the denervated (apical) sites was eight to 20 times greater than previously reported base to apex differences23,24 in normal canine hearts. Additionally, the norepinephrine content at the denervated sites approached levels reported in previous studies22,23,25,26 in which complete sympathetic denervation was confirmed.

Catecholamine fluorescence was greatly reduced in the denervated myocardium, while regions basal to the infarct showed normal catecholamine fluorescence. Small qualitative differences in catecholamine histo-fluorescence also have been described with respect to a base-to-apex distribution,27 but virtual absence of evidence for histofluorescent activity has only been reported in studies where sympathetic denervation was found.28 Our observations demonstrated almost complete absence of catecholamine histo-fluorescence at the electrode sites found to be functionally denervated with respect to ERP shortening during sympathetic stimulation, while marked histofluorescence was seen at the sites with ERP shortening during sympathetic stimulation.

### Intraventricular Route of Sympathetic Fibers

Previous studies have demonstrated that the efferent sympathetic nerves from the stellate ganglia reach the anterior left ventricle by coursing in the epicardium along the coronary arteries.1,2 These fibers originate in the region of the LAD and travel in a general base-to-apex direction. These and more recent studies1-3,29 have shown that the left ventricular sympathetic fibers probably course in the upper 0.25–0.50 mm of the subepicardium and can be eliminated functionally when this region of the heart is damaged or removed. For example, phenol application eliminates changes in ventricular contractile force and left ventricular ERP in response to sympathetic stimulation in regions of the ventricle apical to the area of application.1-3,29 Phenol

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**TABLE 2. Left Ventricular Norepinephrine Concentrations at Denervated and Nondenervated Electrode Sites in Chronically Infarcted Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Endocardium</th>
<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondenervated</td>
<td>858 ± 212</td>
<td>898 ± 205</td>
</tr>
<tr>
<td>(8)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>140 ± 26*</td>
<td>104 ± 22*</td>
</tr>
<tr>
<td>(10)</td>
<td>(11)</td>
<td></td>
</tr>
</tbody>
</table>

**Values are mean ± SEM.**

Number in parentheses indicates the number of sites sampled.

Norepinephrine values are pg norepinephrine/g myocardium.

*p* < 0.005 from control.
destroys cells 0.25–0.50 mm deep and thus interrupts the sympathetic nerves traveling to this area.

Discussion of Model

The effectiveness of vinyl latex \(^6,7\) and Omniflex \(^8\) in interrupting collateral blood flow to the atria and ventricles of the canine heart has been demonstrated. One of the goals of the present study was to produce a localized transmural myocardial infarction in the region of the first diagonal of the LAD that would involve the subepicardial region, where the efferent cardiac sympathetic nerves have been shown to travel. \(^1-3,29\)

Euler et al. \(^6\) and Eaton and Bulkley \(^8\) showed that embolization of coronary arteries effectively and reproducibly resulted in transmural myocardial infarction within the distribution of the artery. Histochemical and histologic analyses of the infarcts created in the

![Figure 6](image-url)
present study demonstrated similar findings with latex injection. We created an infarct that was transmural and localized enough so as not to severely compromise left ventricular function. In separate experiments, ligation of the diagonal branch and injection of acetone, the vehicle in which the latex was suspended, directly into the artery did not produce the efferent sympathetic denervation that occurred in the transmural infarct studies. Thus, the diluent appeared to play no role. It could be argued that the latex itself produced sympathetic denervation. This is not likely, considering its inert properties. Latex was used only as a means of producing transmural infarction. Dogs that sustained simple ligation of the first diagonal branch and developed small endocardial infarctions demonstrated no areas of sympathetic denervation. Apparently, an infarction involving more than the subendocardium is necessary to interrupt the efferent cardiac sympathetic nerve fibers.

Implications of the Study

The major importance of this study is demonstration that a transmural myocardial infarction can interrupt neural innervation, and thus exert an effect on noninfarcted, otherwise apparently normal, myocardium. Holmgren et al. showed that left coronary artery occlusion in rat hearts resulted in a time-dependent loss of norepinephrine from adrenergic nerve terminals in the ischemic region. Significant decreases in myocardial norepinephrine content were demonstrable within the infarct 2½ hours after occlusion. This loss of norepinephrine was thought to be due to enhanced neurotransmitter release secondary to the ischemic process, and might signify neural interruption and degeneration.

Nonuniform electrophysiologic effects of right and left sympathetic nerve stimulation and left sympathetic nerve stimulation exert an arrhythmogenic potential in a variety of experimental settings. Neural influences modulate a variety of cardiac properties, including electrophysiologic alterations after acute myocardial ischemia. It is quite likely that myocardial infarction creates an area of autonomic imbalance not only in the ischemic area, but also in the nonischemic myocardium surrounding the infarction. With severe ischemia and infarction, neurotransmission to the infarction may cease. However, in regions of normal myocardium surrounding the infarction, sympathetic innervation remains heterogeneous for at least 3 weeks.

References

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Cardiovascular Reflexes Stimulated by Reperfusion of Ischemic Myocardium in Acute Myocardial Infarction

JEANNE Y. WEI, M.D., JOHN E. MARKIS, M.D., MICHAEL MALAGOLD, M.D., and EUGENE BRAUNWALD, M.D.

SUMMARY Acute myocardial infarction (AMI), especially of the inferior left ventricular wall, where most cardiac receptors with vagal afferents that are stimulated during coronary occlusion are located, is commonly associated with reflex hypotension and sinus bradycardia. To determine whether reperfusion of an acutely ischemic area can activate cardiac reflexes, changes in the heart rate, arterial pressure and rhythm were correlated with the time course and location of intracoronary thrombolytic therapy in 41 patients with AMI. Of the 27 patients with successful reperfusion, 17 developed significant transient bradycardia and hypotension and one became tachycardic and hypertensive at the time of recanalization. Spontaneous reversion of the bradycardia and hypotension occurred definitely in six patients and possibly in more (nine reverted after atropine and two after fluids). A positive correlation existed between the changes in heart rate and blood pressure, in contrast to the usual inverse relationship when baroreceptors are stimulated. Two of the three patients in whom reperfusion was transient also developed hypotension and bradycardia. In contrast, all 11 patients with persistent occlusion demonstrated no reflex cardiovascular changes during intracoronary thrombolytic therapy. Thus, successful reperfusion in AMI stimulates cardioinhibitory and vasodepressor (Bezold-Jarisch) reflexes. These findings raise the possibility that the transient hypotension and bradycardia observed during AMI, particularly inferior MI, may sometimes reflect the occurrence of spontaneous reperfusion of the acutely ischemic myocardium.

ACUTE myocardial infarction (AMI), especially of the inferior left ventricular wall, is often associated with transient hypotension and sinus bradycardia. Experimental evidence suggests that this cardiac reflex may result from activation of inhibitory cardiac receptors with vagal afferents located predominantly in the infarctoposterior wall of the left ventricle. Acute occlusion of the coronary artery and restoration of flow after prolonged occlusion have been associated with abrupt increases in discharge of left ventricular receptors in the cat. Whether reperfusion of ischemic myocardium also influences cardiac reflexes is not established. In the past, this question has not lent itself easily to investigation in humans, largely because reperfusion after acute coronary occlusion has not been widely studied until recently. However, the use of thrombolytic agents in conscious patients in the early hours of AMI permits an evaluation of the reflex effects associated with coronary reperfusion.

The present study was undertaken to assess the effect of reestablishment of coronary flow to ischemic myocardium on blood pressure and heart rate in humans. Because coronary spasm and perhaps its reversal as well as intracoronary contrast injection have elicited the hypotensive-bradycardic response, we hypothesized that reperfusion of acutely ischemic myocardium might activate cardiac reflexes. We sought to correlate the cardiovascular response with the site of myocardial reperfusion. Patients with AMI who also underwent intracoronary infusion of thrombolytic agents but in whom reperfusion was unsuccessful served as controls.

Methods

In 41 consecutive patients with AMI documented by history, elevation of serum CK-MB, acute electrocardiographic (ECG) changes, and arteriographic evidence of occlusion of the coronary artery supplying the...
Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium.
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