

# Influence of Myocardial Ischemia and Infarction on Autonomic Innervation of Heart

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The vagus and sympathetic nerves link the heart to the central nervous system, carrying information from the heart over neural afferents and to the heart over neural efferents. Although it is generally well accepted that the autonomic nervous system can promote, precipitate, or prevent the development of cardiac arrhythmias, the mechanisms by which this transpires are incompletely understood. Several excellent recent reviews provide an overall discussion of the role of the autonomic nervous system and the genesis of cardiac arrhythmias.<sup>1,2</sup> This review will focus on selected recent observations concerning autonomic innervation of the heart, the effects of myocardial ischemia and infarction on such innervation, and how some of these changes can modulate the development of cardiac arrhythmias.

## Autonomic Innervation of Heart

### Extracardiac Nerves

Numerous studies to determine extracardiac neural innervation to the heart reveal that although significant overlap and complex patterns exist, in general autonomic neural input to the heart exhibits some degree of "sidedness." The right sympathetic and vagus nerves affect the sinus node more than the atrioventricular (AV) node, whereas the left sympathetic and vagus nerves affect the AV node more than the sinus node. Precise points of entry of parasympathetic nerves to the sinus and AV nodal regions have recently been described.<sup>3</sup> On the right, vagal input to the superior atrial and sinus nodal regions is by neural projections along the superior vena cava-right atrial junction, azygos vein, right pulmonary vein complex, and dorsal surfaces of the common pulmonary vein complex. On the left, vagal input to the sinus nodal region is quantitatively less,

but the pathways of innervation are similar to those on the right. Both right and left vagal fibers to the AV node enter the heart at the junction of the inferior vena cava and inferior left atrium and can be eliminated by excision of the triangular fat pad located at this junction. Pathways are so discrete that vagal fibers to the sinus or AV nodes can be selectively interrupted, with preservation of sympathetic innervation.<sup>3</sup> Such interruption can result in denervation supersensitivity to acetylcholine.<sup>4</sup> Sympathetic fibers to the canine sinus node on the right are primarily from the right stellate cardiac nerve, which follows the superior vena cava and azygos vein to the pulmonary plexus and right atrium. On the left, the ventrolateral nerve courses laterally over the aorta and pulmonary artery where it receives branches from the recurrent laryngeal nerve and provides the major sympathetic innervation to the AV node.<sup>5-7</sup>

Most efferent sympathetic impulses are transmitted to the canine ventricles by way of the ansae subclaviae, branches of the right and left stellate ganglia. The sympathetic innervation to the ventricle follows a course along the dorsal wall of the common pulmonary artery into the plexus supplying the main left coronary artery. The sympathetic nerves are distributed to the myocardium in superficial epicardial layers,<sup>8-11</sup> primarily along coronary arterial pathways, and then penetrate the myocardium. On the right side, the major route to the heart is the recurrent cardiac nerve; on the left, the major route is the ventrolateral cardiac nerve. Although regional differences in norepinephrine and choline acetyltransferase concentrations occur between and within cardiac chambers<sup>12-15</sup> and individual cardiac nerves preferentially innervate relatively localized parts of the ventricles,<sup>16-20</sup> in general, stimulation of the right sympathetic chain shortens refractoriness on the anterior portion of the ventricles, whereas activation of the left primarily affects refractoriness of the posterior surface of the ventricles. Again, overlapping areas of distribution occur.

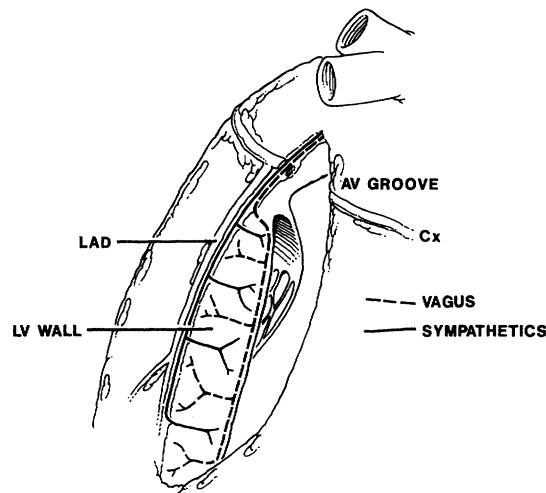
Histological studies suggest that transmural differences in innervation may also exist, with the endocardium less well innervated by sympathetic nerves but better innervated with parasympathetic nerves.<sup>21,22</sup> However, changes in repolarization elicited by neural stimulation are equivalent in endocardium and over-

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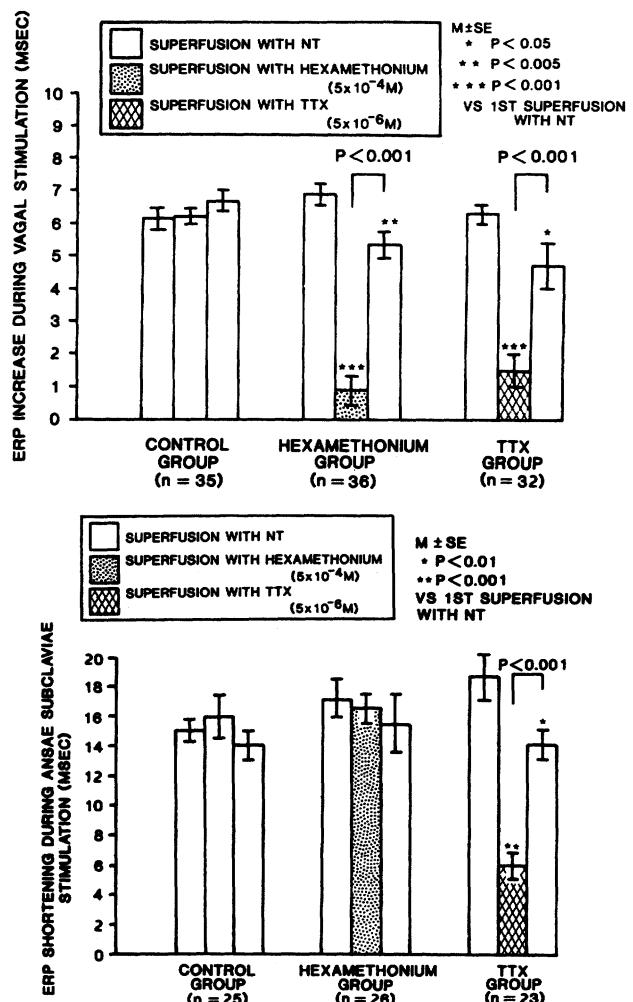
**FIGURE 1.** Schematic of sagittal view of left ventricular (LV) wall showing pathways of vagal and sympathetic afferent and efferent nerves. Postganglionic sympathetic axons are located superficially in periadventitia of coronary arteries; postganglionic vagal axons cross the atrioventricular (AV) groove in subepicardium but are located in subendocardium. Cx, circumflex coronary artery; LAD, left ventricular descending coronary artery.

lying epicardium. Thus, in the normal canine myocardium, sympathetic neural stimulation shortens refractoriness in epicardial sites equal to that in the underlying endocardial sites, whereas vagal stimulation prolongs refractoriness in epicardial sites equal to that in the underlying endocardial sites.<sup>23</sup>

#### Intracardiac Functional Pathways of Sympathetic and Vagal Innervation in Canine Ventricle

Recent functional studies of intracardiac neural pathways indicate that afferent vagal fibers cross the AV groove in the superficial subepicardium and then penetrate the myocardium, at which point they are probably located in the subendocardium. In contrast, afferent sympathetic fibers appear to be located in the superficial subepicardium throughout most of their course<sup>24</sup> (Figure 1). Similarly, sympathetic efferents are superficially placed,<sup>8-11,25</sup> whereas most efferent vagal fibers en route to the ventricle cross the AV groove within 0.25–0.5 mm of the epicardial surface<sup>26,27</sup> and dive intramurally, at which point they are located in the subendocardium.<sup>22,28</sup> Vagal efferent fibers crossing the AV groove are probably postganglionic axons with the ganglion cells located in the atria.<sup>29</sup>

A recently reported study<sup>30</sup> provides additional evidence that vagal and sympathetic nerves are located in the subepicardium, at least during part of their intraventricular course. Instillation of oxygenated normal Tyrode's solution containing hexamethonium (500  $\mu$ M), a ganglionic blocker, into the pericardial sac eliminates lengthening of ventricular refractoriness and sinus arrest induced by efferent vagal stimulation. Pericardial hexamethonium does



**FIGURE 2.** Bar graphs of effects of pericardial hexamethonium and tetrodotoxin (TTX). Top panel: Effects of epicardial superfusion with hexamethonium and TTX on changes in ventricular refractoriness induced by bilateral vagal stimulation. Lower panel: Effects of epicardial superfusion with hexamethonium and TTX on ansae subclaviae-induced prolongation of ventricular refractoriness. ERP, effective refractory period; NT, normal Tyrode's solution; n, number of test sites. Reproduced with permission.<sup>30</sup>

not affect shortening of refractoriness evoked by ansae subclaviae stimulation because only vagal ganglia are located on the epicardium (Figure 2). In contrast to the effects of hexamethonium, tetrodotoxin (5  $\mu$ M), a sodium channel blocker that interrupts axonal neurotransmission, when instilled in the pericardial space suppresses changes in refractoriness induced by both efferent vagal and ansae subclaviae stimulation (Figure 2) but does not affect changes in refractoriness induced by intravenous administration of norepinephrine or methacholine (not shown). These data indicate that tetrodotoxin instilled into the pericardial sac inhibits both efferent vagal and sympathetic neurotransmission but does not prevent the effector cell from responding to exogenous agonists. Thus, the site of action of tetro-

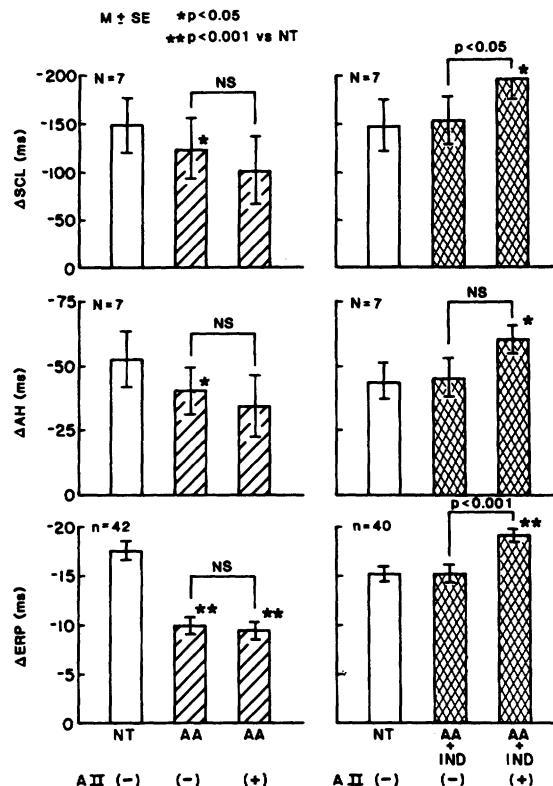
dotoxin must be presynaptic; therefore, both vagal and sympathetic axons must at some point be located superficially during their course in the heart.

These studies suggest that substances in the pericardial fluid, whether normally secreted or present due to disease, can modulate autonomic neural transmission to the heart. For example, the pericardium normally synthesizes prostaglandins, and under certain circumstances, such as increased myocardial work and oxygen consumption, substantial release of pericardial prostaglandin occurs. We have found recently that prostaglandins instilled into the pericardial sac or secreted into the pericardial fluid as a response to pericardial introduction of arachidonic acid produce an antisympathetic action and reduce the shortening of sinus cycle length, atrium-His conduction (AH interval), and refractoriness of the right and left ventricular myocardium induced by ansae subclaviae stimulation. Pericardial prostaglandins also prevent intra-aortic angiotensin II (Ang II) (30 ng/kg/min) from augmenting the effects of ansae subclaviae stimulation on these variables (Figure 3). Epicardial superfusion with arachidonic acid plus indomethacin (1 µg/ml) eliminates the prostaglandin increase and restores the electrophysiological responses to ansae subclaviae stimulation and Ang II infusion. Because epicardial superfusion with prostaglandin E<sub>2</sub> or prostacyclin solution does not blunt the shortening of refractoriness induced by intravenous infusion of norepinephrine, the actions of pericardial prostaglandin are more likely due to a prejunctional modulation of cardiac sympathetic neurotransmission than to an alteration in postjunctional responsiveness.<sup>31</sup>

These data offer the possibility that an increased concentration of prostaglandins in the pericardial fluid in response to various stimuli may constitute a physiological negative-feedback control mechanism that regulates efferent sympathetic stimulation of the heart. Thus, when efferent sympathetic input to the heart is heightened or plasma catecholamines are increased, the pericardium could produce prostaglandin I<sub>2</sub> and other prostaglandins, which would bathe the cardiac sympathetic nerves and limit efferent sympathetic input to the heart and further release of catecholamines. Finally, because epicardial superfusion with arachidonic acid does not affect cardiac responses to efferent vagal stimulation or afferent vagal or sympathetic reflexes produced from the heart,<sup>31</sup> pericardial prostaglandins may act to suppress arrhythmia development in various situations, including acute myocardial ischemia.<sup>32</sup>

#### Effects of Myocardial Ischemia and Infarction Cardiac Reflex Responses

It has been known for many years that ischemia or infarction and reperfusion can trigger cardiac reflexes.<sup>33-36</sup> For example, acute inferoposterior myocardial ischemia or infarction often results in bradycardia and hypotension, whereas anterior myocardial



**FIGURE 3.** Bar graphs of effects of stimulation of prostaglandin release into pericardial fluid on changes in cardiac electrophysiological variables elicited by bilateral ansae subclaviae stimulation. Left panels: Efferent sympathetic-induced shortening of spontaneous sinus cycle length ( $\Delta SCL$ ), atrium-His interval ( $\Delta AH$ ), and ventricular effective refractory period ( $\Delta ERP$ ) determined during controlled superfusion with normal Tyrode's solution (NT) and subsequent superfusion with arachidonic acid (AA; 3 µg/ml) with and without intra-aortic infusion of angiotensin II (A II; 30 ng/kg/min). Right panels: Data obtained from additional seven dogs that received AA plus indomethacin (IND; 1 µg/ml). N, number of test dogs, n, number of ventricular test sites. Reproduced with permission.<sup>31</sup>

ischemia more frequently evokes tachycardia and hypertension.<sup>35,37-42</sup> A greater density of receptors on vagal afferents in the inferoposterior wall of the left ventricle may be responsible for the enhanced vaso-depressor and cardioinhibitory reflexes in response to ischemia in that area or to veratridine or nicotine injected into the left circumflex coronary artery or locally applied.<sup>43</sup> Prostaglandins released during myocardial ischemia and reperfusion stimulate chemosensitive but not mechanosensitive nerve endings in the ventricles and may be responsible for the reflex inhibition of sympathetic nerve activity that results from activation of cardiac sensory vagal endings in the left ventricle.<sup>42</sup>

#### Ischemia- or Infarction-Produced Afferent Denervation

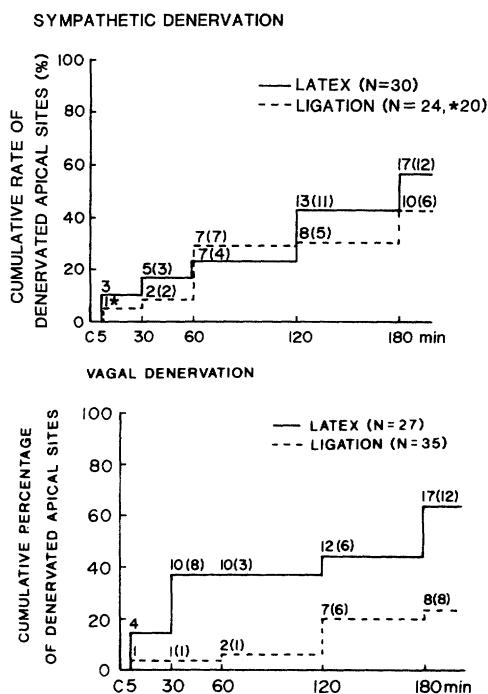
However, ischemia or infarction, in addition to stimulating mechanosensitive and chemosensitive

sensory nerve endings in the ischemic myocardium, might impair neurotransmission. Axons could become ischemic, infarcted, or dysfunctional because they lie in an ischemic myocardial milieu that might adversely affect neural function. If this were the case, then myocardium apical to the site of ischemia or infarction, but not otherwise involved in the process, might lose normal innervation because nerve fibers serving the apex but traveling through an ischemic segment located more basally might develop impaired function. Thus, myocardial injury that was either functional and transient or anatomical and permanent could disrupt autonomic neural transmission. The interaction between ischemically damaged myocardium and altered neural innervation could result in cardiac arrhythmias.

Myocardial ischemia or infarction has been shown to interrupt cardiac reflexes<sup>44</sup> soon after the onset of coronary occlusion.<sup>45</sup> Several minutes after creating transmural myocardial ischemia, the sympathetic reflex elicited from the epicardium of the ischemic area or apical to it becomes interrupted or attenuated when the myocardial blood flow in the epicardial test site decreases to approximately 40% or less of the control value. In contrast, nontransmural ischemia does not attenuate the epicardial sympathetic reflex but does attenuate the vagal vasodepressor response, as would be expected from the functional pathways described previously (Figure 1). A 15-minute coronary occlusion followed by reperfusion produces reversible attenuation of vagal epicardial reflexes. Loss of these reflex responses so quickly after the onset of ischemia and return with reperfusion suggests initial functional neural impairment.

Thus, although it is well known that ischemia triggers cardiac reflexes,<sup>33–42</sup> the data given above indicate that ischemia can also inhibit them. Therefore, the resultant physiological response may be a balance between inhibiting and activating actions of ischemia and may also be anatomically determined. For example, reflex activation may occur when it originates at ischemic sites in the basal or lateral borders of the ischemic zone, whereas the response originating at more apical locations may be inhibited. Perhaps reflex activation and inhibition have different time courses or different responses to transmural or nontransmural ischemic locations or to mechanosensitive or chemosensitive stimulation.

One subject of special interest is painless ischemia.<sup>46</sup> Because afferent sympathetic fibers appear to mediate cardiac pain sensation, it is possible that some patients have a form of "autodenerivation." Ischemia could interrupt afferent neurotransmission with elimination of pain perception. Recovery of neurotransmission would occur with reperfusion, so that another episode of ischemia, perhaps localized differently (e.g., sparing the epicardium), might then produce pain in the same patient. A sensory neuropathy has been used to explain altered anginal perceptual threshold in diabetics<sup>47</sup>



**FIGURE 4.** Graphs of sympathetic and vagal denervation plots. Top panel: Cumulative percentage of sympathetically denervated apical sites divided by number of total apical test sites ( $N$ ) shown on ordinate as function of time. —, Data from dogs with latex coronary injection; ---, data from dogs with coronary ligation; figures without parentheses, cumulative number of denervated test sites (total number of sites that had shown shortening of effective refractory period  $\leq 2$  msec at least once by that moment of determination); figures in parentheses, number of test sites that showed shortening of effective refractory period  $\leq 2$  msec at that moment of determination. Presentation in this fashion is necessary because some sites showed variation in response around cutoff value. For example, 120–180 minutes after latex injection, four new sites (17 minus 13) became denervated, whereas only 12 of the 17 sites still exhibited shortening of effective refractory period  $\leq 2$  msec at 180 minutes. The remaining five sites that had shown shortening of effective refractory period  $\leq 2$  msec at least once by 120 minutes now exhibited refractory period shortening  $>2$  msec at 180 minutes after infarction. Cumulative rate of denervated sites did not differ between dogs receiving latex injection and those receiving coronary artery ligation ( $p=0.41$ ). C, control before coronary occlusion.

\*Data from one dog that developed ventricular fibrillation were not included at 5 minutes after ligation. Bottom panel: Plot showing cumulative percentage of vagally denervated apical sites is shown as in top panel and was greater in dogs receiving latex injection than in dogs with ligation of coronary arteries ( $p<0.002$ ). Reproduced with permission.<sup>49</sup>

and supports the concept of denervation as a possible cause of painless ischemia.

#### Ischemia- or Infarction-Produced Efferent Denervation

Transmural myocardial ischemia or infarction also alters efferent sympathetic and vagal presynaptic

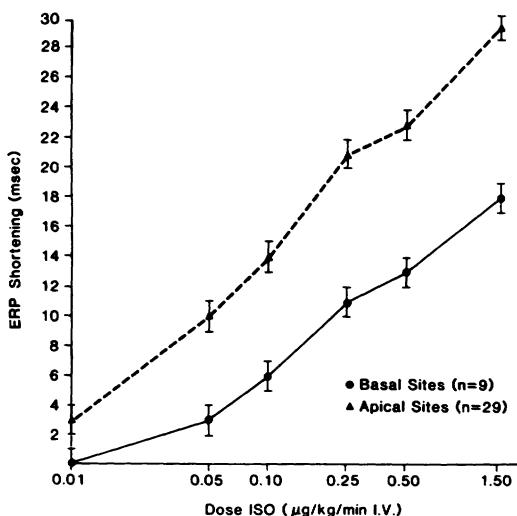


FIGURE 5. Plots of denervation supersensitivity. Dose-response curves of effective refractory period (ERP) shortening in response to various concentrations of isoproterenol (ISO) are given for sites basal and apical to infarction. Reproduced with permission.<sup>63</sup>

function, probably by affecting neural transmission over axons located within the zone of ischemia or infarction, and produces efferent sympathetic and vagal denervation at noninfarcted sites apical to that zone (Figure 4).<sup>48-50</sup> Myocardium within the ischemic area may become denervated.<sup>51</sup> As predicted from the schematic in Figure 1, a subendocardial infarction that spares the epicardium interrupts vagal innervation but not sympathetic transmission.<sup>48-50,52</sup> The noninfarcted myocardial rim overlying a subendocardial infarction also has a transiently depressed response to sympathetic nerve stimulation, possibly due to local factors released by the adjacent infarct.<sup>53</sup>

Heterogeneous loss of functional efferent sympathetic innervation in noninfarcted apical sites occurs as early as 5–20 minutes after transmural ischemia created by coronary occlusion, with more complete denervation progressing with time. Some sites may undergo partial denervation initially, which progresses with time.<sup>49</sup> Of interest, the activity of tyrosine hydroxylase, a neurochemical marker for sympathetic innervation, decreases significantly in the ischemic left ventricle only after about 5 hours of ligation of the left anterior descending coronary artery.<sup>54</sup>

Ischemia-produced efferent vagal denervation follows a similar time course as that of efferent sympathetic denervation.<sup>49</sup> However, the activity of the enzyme critical for the synthesis of acetylcholine, choline acetyltransferase, does not decrease significantly until many hours after coronary ligation.<sup>54</sup>

From these observations, it appears likely that early denervation is due to functional changes in neural activity with measurable decreases in transmitter concentration or enzyme activity lagging behind and following the onset of actual tissue damage as the infarction develops and progresses over time.

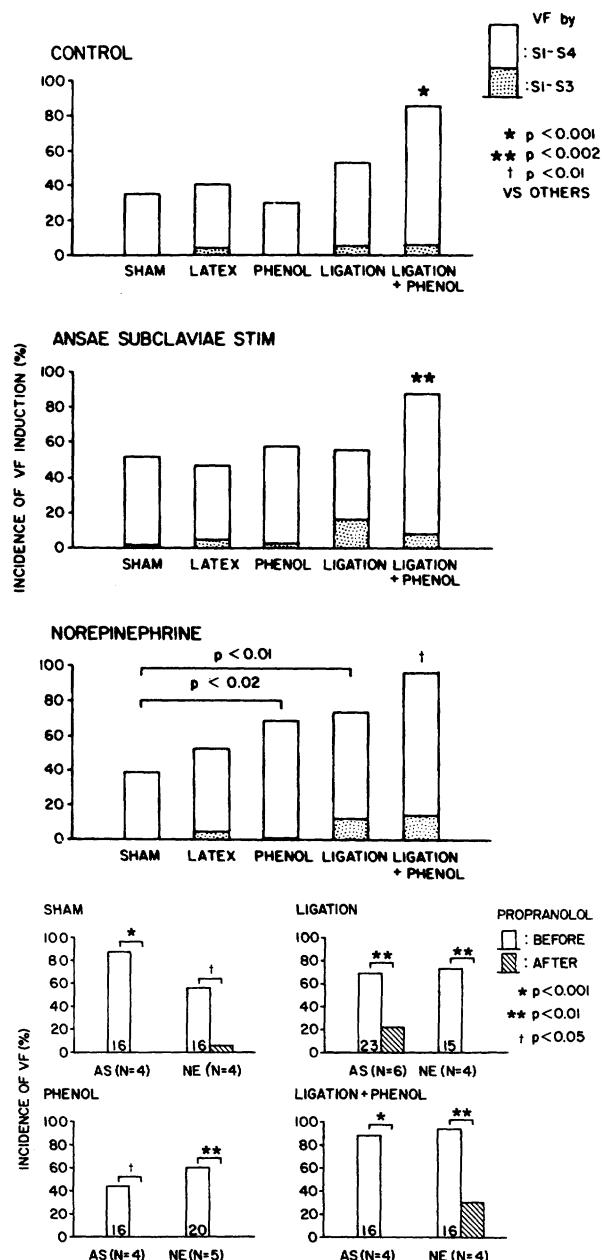
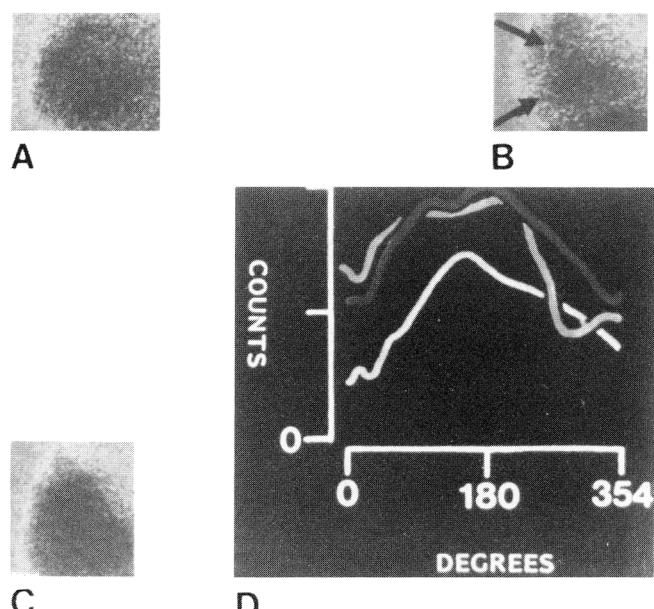


FIGURE 6. Bar graphs of denervation supersensitivity and arrhythmias. Top panel: Incidence of ventricular fibrillation (VF) induced by premature ventricular stimulation. Open bars: Rate of induction of VF by three extrastimuli during basic ventricular drive (S1-S3). Bottom panel: Prevalence of induction of VF before (open bars) and after (hatch bars) propranolol injection during ansae subclaviae stimulation (AS) or norepinephrine infusion (NE). Figures in parentheses are numbers of dogs, and those in open bars are total number of test sites. Reproduced with permission.<sup>65</sup>

The cardiac response to ischemia or infarction is also influenced by the "myocardial history." For example, four 5-minute episodes of coronary occlusion and reperfusion dramatically limit infarct size of the myocardium that is later subjected to 40 minutes of sustained ischemia, compared with myocardium that did not experience prior ischemia.<sup>55</sup> Although



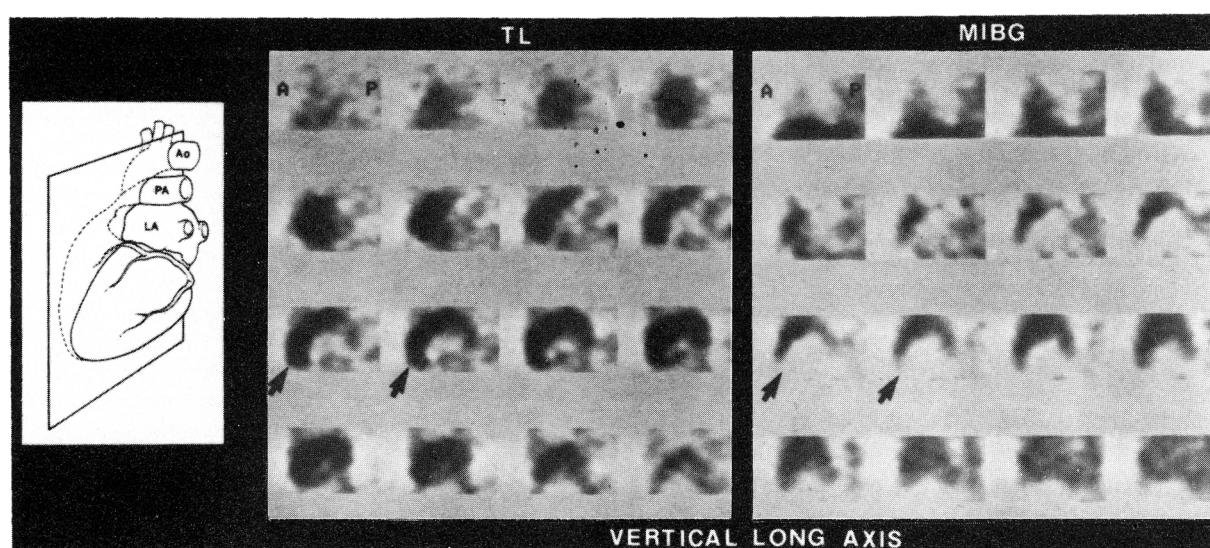
**FIGURE 7.** Scintigraphic cardiac images after latex injection into left anterior descending coronary artery. Panel A: Left lateral preoperative metaiodobenzylguanidine (MIBG) image showing homogeneous uptake. Subsequent MIBG images show anteroapical defect obtained 7 weeks after latex injection (panel B) and homogeneous uptake obtained 14 weeks after latex injection (panel C). Angular circumferential profiles of myocardial activity obtained preoperatively (line starting in middle of graph), 7 weeks postoperatively (line starting at top of graph), and 14 weeks postoperatively (line starting at bottom of graph) (panel D). Reproduced with permission.<sup>69</sup>

the mechanism of this protective effect of preconditioning ischemia is unknown, one hypothesis is that repeated episodes of ischemia regionally deplete catecholamines so that the final ischemia takes place in "sympathectomized" myocardium that can withstand the effects of ischemia better than ischemic myocardium with a normal catecholamine content.<sup>56</sup> In reality, the opposite occurs. Preconditioning ischemia without an increase in collateral blood flow to the ischemic myocardium actually preserves the efferent sympathetic response during the first hour of the subsequent sustained ischemia and preserves the efferent vagal response for at least 3 hours.<sup>57</sup> Thus, the concept of regional sympathectomy does not explain

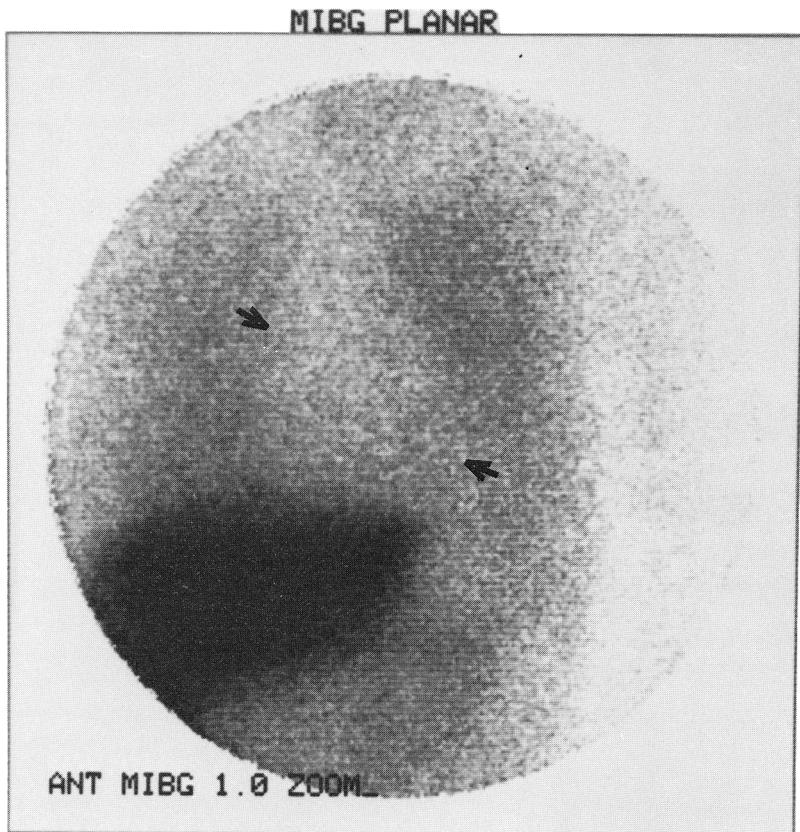
the basis of preconditioning ischemia. However, understanding the mechanism might provide insight into how the heart can be made more resistant to the effects of ischemia and related arrhythmias.

#### *Mechanisms of Denervation Caused by Ischemia or Infarction*

Initial loss of vagal and sympathetic neural responsiveness after acute myocardial ischemia is probably due to functional derangement of nerve action, as suggested above, rather than to structural changes. Because the denervated myocardium responds normally to infused norepinephrine, postjunctional target cell dysfunction is not likely.<sup>48,58</sup> Prejunctional



**FIGURE 8.** Single photon emission computed tomographic images of patient with denervation after inferior myocardial infarction. Note that apex (arrows) is perfused as demonstrated by thallium-201 (TL) images. Metaiodobenzylguanidine (MIBG) images show a defect in apex. Images progressed from medial (top left) to lateral (bottom right). A, anterior; Ao, aorta; LA, left atrium; P, posterior; PA, pulmonary artery. Reproduced with permission.<sup>70</sup>



**FIGURE 9.** Planar metaiodobenzylguanidine (MIBG) image in patient after cardiac transplantation, showing anterior view. Dark shadow on lower left represents liver. MIBG uptake in lungs outlines central paler area that represents cardiac silhouette (arrows) without MIBG uptake. Study performed with Marshall Stanton, MD, and Henry Wellman, MD.

altered neural function may be due to ischemic changes in the nerves themselves or to the fact that the nerves lie in ischemic myocardium where the pH may be 6.8 or less, extracellular K<sup>+</sup> may be 12 mM or higher,<sup>59</sup> and PO<sub>2</sub> is less than 50 mm Hg. In addition, adenosine<sup>60</sup> and other substances released by the ischemic myocardium may alter neural function.

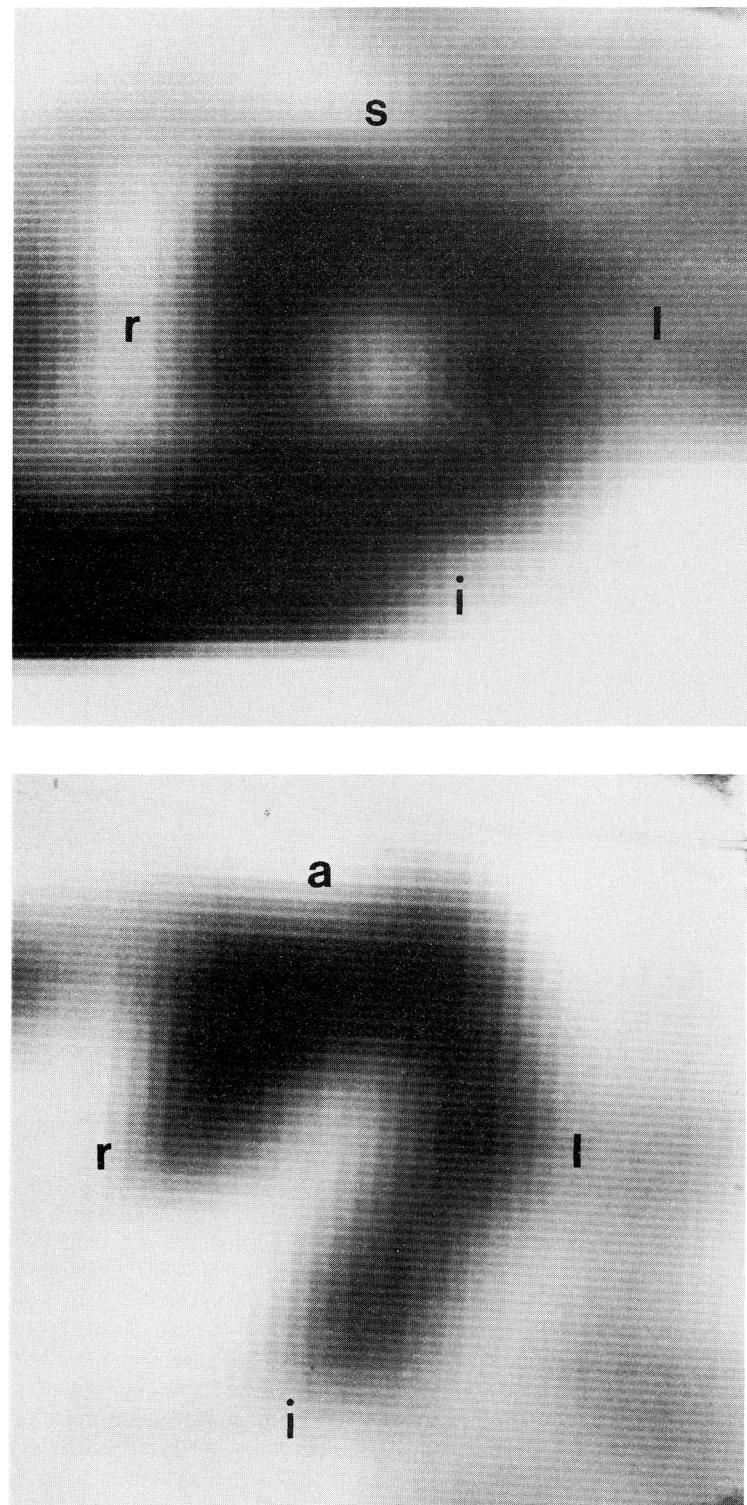
Several of these possibilities have been tested.<sup>58</sup> If the diagonal branch of the left anterior descending coronary artery is occluded but perfused with hypoxic normal Tyrode's solution (i.e., ischemia is still present but without buildup of ischemic metabolites), acute efferent sympathetic denervation of apical myocardium does not occur. On the other hand, if the occluded artery is perfused by a hypoxic Tyrode's solution containing 12 mM K<sup>+</sup> and 10 μM adenosine (pH 6.8), apical denervation promptly results. When these substances are instilled into the pericardial cavity (i.e., exposing the epicardial segments of these nerves to a superfusion of several metabolites found in the ischemic myocardium while avoiding any interruption in blood flow), similar denervation responses result. Thus, accumulation of metabolites in the ischemic myocardium through which the nerves pass is sufficient to produce neural dysfunction in myocardium apical to the ischemic site. Ischemia of the nerves themselves is not necessary. Of course, axonal ischemia in addition to neural modulation by accumulation of other ischemic metabolites is not

excluded by this study and may impair neural function still further.<sup>58</sup>

#### *Denervation Supersensitivity, Arrhythmogenesis, and Reinnervation*

Tissue deprived of its nerve supply responds in an exaggerated fashion to certain agents, a phenomenon called "denervation supersensitivity."<sup>61,62</sup> Sympathetic supersensitivity, manifest by an exaggerated shortening of refractoriness during both norepinephrine and isoproterenol infusions with an upward and leftward shift in the dose-response curves, occurs in apical denervated regions of the left ventricle (Figure 5).<sup>63,64</sup> The mechanism responsible for this type of supersensitivity is not clear because there is no difference in the density of β-adrenergic receptors ([<sup>125</sup>I]-cyanopindolol) in denervated apical compared with normal basal myocardium. β-Adrenoceptor coupling (GTP plus isoproterenol-stimulated adenylate cyclase activity) is slightly but not significantly greater in the apical than in the basal region. Further, muscarinic modulation of β-receptor coupling (oxotremorine attenuation of GTP plus isoproterenol-stimulated adenylate cyclase activity) is not significantly different between apical and basal sites. However, the fact that isoproterenol also produces a supersensitive response suggests a postjunctional mechanism.<sup>63,64</sup>

After transmural myocardial infarction, some dogs demonstrate shortening of refractory period in



**FIGURE 10.** Normal metaiodobenzylguanidine (MIBG) image in patient with long QT syndrome. Top panel: Tomographic image slicing across cavity of left ventricle, giving a short-axis view. *s*, Superior; *i*, inferior; *r*, right; *l*, left. Bottom panel: Transverse view of left ventricle. *a*, Anterior; *i*, inferoposterior; *r*, right; *l*, left. Study performed with Marshall Stanton, MD, and Henry Wellman, MD.

selected apical sites in response to ansae subclaviae stimulation (i.e., no apparent sympathetic denervation), yet they show a supersensitive response of refractory period shortening to infused norepinephrine at these same sites.<sup>63,65</sup> It is possible that these sites become partially denervated from the infarction and that this partial denervation is sufficient to permit development of sympathetic supersensitivity.

Denervation supersensitivity elicits inhomogeneous autonomic and electrophysiological changes and makes the heart more vulnerable to electrical induction of ventricular arrhythmias (Figure 6).<sup>50,65</sup> Propranolol significantly attenuates this vulnerability. It is tempting to speculate that  $\beta$ -adrenoceptor blockade may reduce the incidence of sudden cardiac death after myocardial infarction<sup>66</sup> in part by attenu-

uating the effects of denervation supersensitivity on dispersion of refractoriness, conduction changes, or other electrophysiological properties.

Regional sympathetic denervation and supersensitivity could also modulate drug actions and cause the drugs to affect the myocardium heterogeneously. Such changes could provide another proarrhythmic mechanism.<sup>67</sup>

#### *Sympathetic Scintigraphy*

Because efferent denervation produced by epicardial phenol application or transmural infarction is postganglionic, reinnervation most likely occurs. We investigated whether <sup>123</sup>I-labeled metaiodobenzylguanidine (MIBG), a guanethidine analogue taken up by sympathetic nerve terminals,<sup>68</sup> could provide a scintigraphic image that would detect apical sympathetic denervation and possible reinnervation.<sup>69</sup> Dogs underwent MIBG imaging at various times after phenol application or transmural myocardial infarction. The results of MIBG scintigraphy were then correlated with electrophysiological responses obtained during ansae subclaviae stimulation and norepinephrine infusion to establish the presence of neural denervation, reinnervation, and supersensitivity. Thallium images were obtained concurrently to outline areas of normal blood flow and cell viability. Apical defects in the MIBG scan, which were associated with either normal perfusion by thallium or a thallium defect that was smaller than the MIBG defect, were found consistently in dogs that had apical sympathetic denervation.

Figure 7 demonstrates findings typical for the latex infarction model. Figure 7A shows a preoperative left lateral MIBG image, whereas an anteroapical defect is evident in Figure 7B (arrows) 7 weeks postinfarction. Figure 7C shows the corresponding left lateral image obtained 14 weeks postinfarction showing essentially complete resolution of the defect, consistent with reinnervation. Circumferential myocardial activity curves are shown in Figure 7D. The preoperative and reinnervation curves are parallel, whereas the 7 weeks postoperative curve derived from Figure 7B shows decreased activity beginning at 180° and corresponding to an anteroapical defect. These findings support the image interpretation of denervation 7 weeks after infarction followed by reinnervation 14 weeks after infarction.

For all images, the results of MIBG scintigraphy correlated accurately with the presence of denervation and reinnervation established by neuroelectrophysiological testing. Supersensitive refractory period shortening in response to norepinephrine infusion was present after denervation and persisted for more than 3 weeks after scintigraphic and electrophysiological evidence of reinnervation.<sup>69</sup>

This study<sup>69</sup> demonstrates that regional sympathetic denervation in the canine heart can be established noninvasively with a scintigraphic technique. The neuroelectrophysiological data provide evidence of the regional denervation shown by the MIBG

images. Thallium images exclude abnormalities in myocardial blood flow and cell viability as a cause of the defect in the MIBG image. Noted for the first time in this model is that sympathetic reinnervation after phenol- and infarction-induced denervation occurs at 8–17 weeks. Denervation supersensitivity is present even though reinnervation has occurred. Whether this persistence of supersensitivity is temporary and associated with incomplete reinnervation or is a permanent characteristic of reinnervation cannot be determined from the present study; it may be a cause of electrical myocardial instability.<sup>65</sup>

Preliminary studies with MIBG scintigraphy in humans have shown abnormalities in MIBG uptake after myocardial infarction similar to those seen in canine studies (Figure 8).<sup>70,71</sup> We found that 10 of 12 patients with spontaneous ventricular tachyarrhythmias after myocardial infarction exhibited regions of thallium-201 uptake indicating viable perfused myocardium, with no MIBG uptake. Such a finding is consistent with sympathetic denervation. One patient had frequent episodes of nonsustained ventricular tachycardia induced at exercise testing that was eliminated by  $\beta$ -adrenoceptor blockade. Eleven of the 12 patients had ventricular tachycardia induced at electrophysiological study both before and after metoprolol administration. Sympathetic denervation was also detected in two of seven postinfarction patients without ventricular arrhythmias. This study<sup>70</sup> provides evidence that regional sympathetic denervation occurs in humans after myocardial infarction and can be detected noninvasively by comparing MIBG and <sup>201</sup>Tl images. Although the presence of sympathetic denervation may be related to the onset of spontaneous ventricular tachyarrhythmias in some patients, it does not appear to be related to sustained ventricular tachycardia induced at electrophysiological study.

It is also possible to use MIBG to demonstrate noninvasively the disruption of myocardial sympathetic innervation in humans associated with a variety of disease states, such as during myocardial ischemia,<sup>72</sup> in patients with dilated cardiomyopathy<sup>73–75</sup> or hypertrophic cardiomyopathy,<sup>76</sup> and after cardiac transplantation.<sup>77</sup> We have found no cardiac sympathetic neural uptake of MIBG shortly after cardiac transplantation (Figure 9). MIBG scans in patients with arrhythmias directly attributable to sympathetic abnormalities such as the idiopathic long QT syndrome or dysautonomias might shed additional light on the pathogenesis of arrhythmias in these disease states. We found that MIBG scans were normal in one patient with the long QT syndrome and a family history of syncope and sudden death (Figure 10) and in a 26-year-old female patient with the long QT syndrome who had been resuscitated from ventricular fibrillation, but the scans were abnormal in two of three patients with hypertrophic cardiomyopathy and a family history of sudden cardiac death.

## Conclusions

In recent years, new information about extracardiac and intracardiac pathways has helped explain the effects of ischemia or infarction on cardiac neural innervation and the potential role the interaction between ischemia or infarction and the autonomic nervous system exerts on arrhythmia development. Use of modern imaging techniques may extend these concepts to patients and further delineate the mechanisms by which neural discharge affects arrhythmogenesis and sudden cardiac death.

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