Single Cardiac Vagal Fiber Activity, Acute Myocardial Ischemia, and Risk for Sudden Death

Donatella Cerati and Peter J. Schwartz

Experimental and clinical evidence indicates that high risk for sudden death is significantly correlated with post-myocardial infarction depression in two “markers” of vagal activity, heart rate variability and baroreflex sensitivity. The present experiments were designed to answer some of the questions generated by those findings. In 33 anesthetized cats, the neural activity of single cardiac vagal efferent fibers was recorded in control conditions and after injection of phenylephrine (n=33), before and during a 1-hour coronary artery occlusion (CAO) (n=17), and before and after removal of the left stellate ganglion (n=16). In the first minute after CAO, vagal activity increased by 35% from 1.66±0.37 to 2.57±0.62 impulses/sec (p<0.01); despite a slight decline, it remained for the entire CAO above the control values, to which it returned after CAO release. Of 17 cats, ventricular fibrillation occurred in nine (susceptible) and eight survived (resistant). Resistant and susceptible cats had different reflex vagal responses to CAO. Whereas the resistant cats had a 48% (p<0.01) increase by the second minute of CAO, susceptible cats had no change (−18%, p=NS) in vagal activity. These differences were independent of blood pressure changes. The increase in vagal efferent activity in response to the blood pressure rise induced by phenylephrine (baroreceptive reflex) was more marked in the resistant cats compared with the susceptible cats (+246±66% versus +80±14%, p<0.025). Just before the injection of phenylephrine, vagal activity was not different between resistant and susceptible cats (1.58±0.35 versus 1.48±0.30 impulses/sec, p=NS). In 16 cats, left stellectomy increased cardiac vagal efferent activity by 75% (p<0.01), and the reflex vagal activation secondary to phenylephrine was further enhanced (from 2.2±0.4 to 4.7±0.7 impulses/sec, p<0.001). These data demonstrate that 1) cardiac vagal efferent activity increases in response to acute myocardial ischemia—much more so among the animals destined to survive, 2) before CAO, susceptible and resistant animals can be identified by the vagal response to blood pressure increase (assessed clinically by baroreflex sensitivity) and not by tonic vagal activity (assessed clinically by heart rate variability), and 3) the findings with left stellectomy support the hypothesis that vagal activity decreases after myocardial infarction because of an increase, secondary to abnormal stretch of the cardiac mechanoreceptors, in cardiac sympathetic afferent traffic, which exerts a tonic restraint on vagal outflow. (Circulation Research 1991;69:1389–1401)

The relation between cardiac vagal efferent activity and lethal arrhythmias, so far explored by means of either vagotomy or of vagal stimulation mostly in anesthetized prepara-

From Centro di Fisiologia Clinica e Ipertensione (D.C., P.J.S.), Istituto di Clinica Medica II, Università di Milano, Milan, Italy, and Dipartimento di Medicina (P.J.S.), Università di Pavia, Pavia, Italy.

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Address for reprints: Peter J. Schwartz, MD, Professor of Medicine, Istituto di Clinica Medica II, Via F. Sforza, 35, 20122 Milan, Italy.

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The analysis of the baroreceptive reflex control of heart rate, mostly mediated via its vagal efferent arm, has allowed the early identification of conscious dogs with a healed myocardial infarction at high risk for ventricular fibrillation (VF) during acute myocardial ischemia.9,6 Subsequently, two clinical studies successfully used heart rate variability,7 a “marker” of vagal tone, and baroreflex sensitivity,8 a “marker” of vagal reflexes, for the identification of high-risk post-myocardial infarction patients. The experimental studies produced also two puzzling sets of data. First,
the myocardial infarction reduced baroreflex sensitivity in over two thirds of the animals. Second, whereas after a myocardial infarction both baroreflex sensitivity and heart rate variability had a predictive power, before a myocardial infarction only baroreflex sensitivity was able to discriminate between individuals at high or low risk after myocardial infarction.5,6

Altogether, these investigations have raised a host of new questions: Is the response of vagal effenter activity to acute myocardial ischemia indeed related to survival? Are heart rate variability and baroreflex sensitivity, markers of vagal activity, a valid counterpart of what actually happens to vagal neural activity? Could sympathetic afferent activity, as we have suggested,6 contribute to the depressed baroreflex sensitivity after myocardial infarction?

We have attempted to answer these questions by analyzing the “actual” cardiac vagal effenter activity and not one of its markers. In a series of conditions designed to provide an adequate setting for our questions, we have recorded the activity of single vagal effenter fibers dissected from the cardiac branch of the right vagus. This nerve contains the major contingent of vagal fibers directed to the sinus node.10

Materials and Methods

Surgery

Experiments were performed in 33 cats (2.5±0.5 kg) sedated by ketamine (15–20 mg/kg i.m. Ketalar, Parke-Davis, Morris Plains, N.J.) and anesthetized with α-chloralose (70 mg/kg i.v., Sigma Chemical Co., St. Louis, Mo.). The trachea was cannulated, and after a paralyzing dose (2–4 mg/kg) of gallamine triethiodide (Davis-Geck, Pearl River, N.Y.), the cats were artificially ventilated by a positive pressure pump (Harvard respirator, Harvard Bioscience, Mil- lis, Mass.). Tidal volume and respiratory rate were adjusted to keep blood gases and pH within physiological range throughout the experiment. The body temperature was maintained at 38±0.5°C using a heating pad. Polyethylene catheters were inserted into a femoral artery for recording arterial blood pressure (Statham P231DB pressure transducer, Gould Inc., Instrument Division, Cleveland, Ohio) and into a femoral vein for the administration of saline and drugs. The ribs from the first to the fourth on the right side were removed. The left anterior descending coronary artery was isolated, and a loose ligature was placed around the vessel just above the origin of the first diagonal branch. The two ends of the ligature were then passed through a plastic sleeve so that the artery could be reversibly occluded.

The cardiac branch of the right vagus nerve was traced to the heart as it passed under the aygous vein (Figure 1) and was prepared for neural recording, as previously described.11 The nerve was cut near the right atrium, immersed in warm mineral oil, divided into small bundles using fine forceps, and then placed across a bipolar platinum electrode. Careful splitting of small bundles under a light microscope (Wild M8, Wild Heerbrugg, Switzerland) was continued until one single fiber, with an acceptable signal-to-noise ratio, had been isolated. The neural activity was limited to cardiac vagal units by excising the right stellate ganglion and all of its connections. In 16 cats (according to protocol 2 below), the left stellate ganglion also was ablated.

Area at Risk

The “area at risk” was measured after death, from the isolated heart, by injection of methylene blue in the left anterior descending coronary artery immediately below the ligature while the left circumflex coronary artery was tied. The extent of the area at risk was expressed as the ratio between the weight of the area with a bluish color and the weight of the entire left ventricle.

Data Recording

The recording electrode was connected to an AC preamplifier (model P511, Grass Instrument Co., Quincy, Mass.) with a bandwidth of 10 Hz–10 KHz. The preamplifier output was connected in parallel to a loudspeaker, to a magnetic tape recorder (Racal Store 7 DS, Racal Recorder LDT, Hythe-Southampton, England), and to an oscilloscope (model D11, Tektronix Inc., Beaverton, Ore.). Blood pressure, electrocardiographic and neural activity were recorded on an eight-channel polygraph (model ES 1000, Gould) and were also fed into the tape recorder for subsequent analysis.

Experimental Protocols

After completion of surgery, a period of about 20–30 minutes was allowed for stabilization before starting the experiments with one of the following two protocols.

![Figure 1. Schematic drawing of the feline right cardiac nerves as seen from the ventral aspect. The ayzgos vein is cut to expose the cardiac branch of the vagus nerve as it enters the right atrium.](http://circres.ahajournals.org/lookup/doi/10.1161/01.CIR.69.10.1390)
Protocol 1 (n=17): Myocardial ischemia and ventricular fibrillation. This protocol had the following four aims: 1) to characterize the vagal response to coronary artery occlusion, 2) to examine potential correlations between the vagal response to acute myocardial ischemia and outcome, 3) to assess the effect of prolonged myocardial ischemia on vagal reflexes, and 4) to determine if, before coronary occlusion, either tonic or reflex vagal activity would differentiate between the animals that were going to die or to survive during coronary occlusion.

Arterial pressure was raised by intravenous injection of the pressor agent phenylephrine (15 μg/kg, Sigma). A 1-hour occlusion of the left anterior descending coronary artery was then performed. Five minutes before and 5 minutes after release of coronary occlusion, phenylephrine was administered again. Afterwards, the heart was excised, and the area at risk was evaluated.

Protocol 2 (n=16): Effect of left stellectomy. This protocol aimed at determining if the presence or absence of the tonic cardiac afferent sympathetic activity mediated by the left stellate ganglion had an effect on tonic and reflex vagal activity. In 16 cats, phenylephrine (15 μg/kg) was injected to raise arterial pressure before and after left stellectomy.

Statistical Analysis

Results are reported as mean±SEM. The firing rate of vagal fibers was calculated in impulses per second. Because of the individual variability in the control nervous activity between animals, the neural responses were also expressed as percent changes from baseline. Vagal activity in every control condition and during and after coronary occlusion was evaluated for periods of at least 1 minute; after injection of phenylephrine, it was measured during the phase of rapid increase in arterial blood pressure. The normality of the distribution of changes in vagal activity after 2 minutes of coronary artery occlusion was assessed by a goodness of fit test over five classes of vagal responses. Multiple analysis of variance was used to determine the significance of the differences among groups. Paired or unpaired Student t tests were used, as appropriate, to analyze the differences between means in two groups. Significance was accepted for values of p<0.05 for the two-tailed hypothesis, unless otherwise specified. In specific cases, as detailed in “Results,” one-tailed tests were used, since we were testing a single hypothesis and not its opposite.

Results

Characteristics of the Vagal Fibers

Eighteen of the 33 recordings (one for each experiment) were obtained from filaments with only one active fiber; in the remaining 15 recordings, two or three active fibers were present, but the differences in the height of the action potentials were such that one single fiber could always be clearly identified and its activity could be calculated separately. Only one fiber was analyzed per experiment.

Five fibers (15%) had a constant cardiac rhythm. All the fibers recorded in this study responded to blood pressure increases with a marked increase in firing rate, thus fulfilling the criteria for vagal fibers under baroreceptive control. Conversely, they decreased their activity whenever blood pressure was decreased. An example of a vagal efferent fiber with cardiac rhythm and this behavior is shown in Figure 2.

Protocol 1: Myocardial Ischemia and Ventricular Fibrillation

In 17 cats, before the phenylephrine injection, mean blood pressure was 78±4 mm Hg, and vagal activity was 1.52±0.23 impulses/sec. Heart rate was 166±8 beats/min and remained almost constant throughout the experiment because of the removal of most neural connections to the sinus node as a result of right stellectomy and right cardiac vagotomy.

Coronary artery occlusion. Just before the onset of coronary artery occlusion, vagal activity was 1.66±0.37 impulses/sec. It increased during the first minute by 35% to 2.57±0.62 impulses/sec (p<0.01) and declined slightly by the second minute to 1.95±0.47 impulses/sec but tended to be higher compared with the control values. Meanwhile, mean blood pressure in control conditions was 85±5 mm Hg and decreased in the first and second minute (70±4 and 63±4 mm Hg, respectively, p<0.001). Thus, the answer to our first question was that, in the overall population, vagal activity initially increased despite a reduction in blood pressure and then tended to plateau at a somewhat higher level compared with control.

Within this group, nine cats (53%) developed VF within the first 3 minutes of acute myocardial ischemia. These cats were defined as “susceptible,” a current and useful terminology. The remaining eight cats (47%) survived coronary artery occlusion and were defined as “resistant” to VF. The vagal response was then analyzed separately for the resistant and for the susceptible cats; this provided the answer to our second question.

In susceptible cats, cardiac vagal activity did not change significantly during acute myocardial ischemia; it was 1.43±0.38 impulses/sec in the control condition and 1.17±0.34 impulses/sec (−18%, p=NS) 2 minutes after the onset of coronary occlusion. A very different response was observed in the cats resistant to VF; cardiac vagal activity (1.91±0.66 impulses/sec in the control condition) increased by 48% (p<0.01) to 2.83±0.83 impulses/sec by the second minute of acute myocardial ischemia (Table 1; Figure 3). In the first minute, vagal activity had increased in both groups but somewhat more among the resistant cats (+69% in resistant cats versus +39% in susceptible cats, p=NS). Vagal activity just before occlusion was not significantly different between the two groups (1.91±0.66 impulses/sec for resistant cats versus 1.43±0.38 impulses/sec for susceptible cats, p=NS). The risk of developing VF was inversely related (p<0.01) to the extent of vagal
activation by the second minute of occlusion; VF occurred in two of nine (22%) of the cats that increased their vagal activity by more than 25% and in seven of eight (87%) of those whose vagal increase was <25%. The relative risk was 3.94, thus indicating a fourfold increase (p<0.01) according to vagal response. The changes in vagal activity, during coronary artery occlusion and independent of outcome, were normally distributed (χ²=2.87, p>0.05).

An example of the pattern of discharge of a vagal fiber in a resistant cat during the first 2 minutes of coronary occlusion is shown in Figures 4 and 5. In this cat, while blood pressure remained stable, a burst of vagal activity followed the first few seconds of occlusion and, after a brief return to the preocclusion levels, rose again to plateau at values almost double those in control. The nervous activity during these periods is shown in Figure 5.
TABLE 1. Vagal Activity During Coronary Artery Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Cardiac vagal activity (impulses/sec)</th>
<th>After coronary artery occlusion</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Resistant</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>3.6</td>
<td>3.26</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>2.33</td>
</tr>
<tr>
<td>4</td>
<td>6.05</td>
<td>10.26</td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>Mean±SEM</td>
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<td>3.23±0.98</td>
</tr>
<tr>
<td>Susceptible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>3.6</td>
<td>7.26</td>
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<tr>
<td>3</td>
<td>0.9</td>
<td>0.8</td>
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<tr>
<td>4</td>
<td>1.95</td>
<td>1.7</td>
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<tr>
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<td>0.6</td>
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<tr>
<td>6</td>
<td>0.2</td>
<td>0.3</td>
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<tr>
<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
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</tr>
<tr>
<td>Mean±SEM</td>
<td>1.43±0.38</td>
<td>1.99±0.73</td>
</tr>
</tbody>
</table>

Resistant, cats that did not develop ventricular fibrillation after acute myocardial ischemia; Susceptible, cats that developed ventricular fibrillation after acute myocardial ischemia.

The changes in cardiac vagal activity during the first 2 minutes of coronary artery occlusion in the resistant and susceptible groups are shown in Table 1. Among the cats destined to survive, vagal activity increased markedly during the first few minutes, when the risk for VF is greater, and then remained elevated. By contrast, the susceptible cats had only a modest increase in vagal activity, which very rapidly declined again just before the onset of VF. These different patterns are exemplified in Figure 3. Thus, the vagal response to acute myocardial ischemia correlates with survival.

This different pattern of neural responses could in theory depend on differences between the two groups of cats in their blood pressure response to ischemia or in the extension of the area at risk. Neither of these potential explanations accounts for our findings. Mean blood pressure was not significantly different in resistant and susceptible cats, both in control conditions (84±6 versus 86±7 mm Hg, respectively, p=NS) and after 2 minutes of coronary artery occlusion (70±6 versus 58±7 mm Hg, respectively, p=NS). Also, resistant and susceptible cats had comparable areas at risk (35±0.5% versus 35±1%, respectively, p=NS), thus ruling out the possibility that the different reflex vagal activation was dependent on a larger ischemic area in one group.

The analysis of vagal discharge in the resistant cats provided the answer to our third question, because vagal activity remained constantly elevated throughout the 60 minutes of coronary artery occlusion. Compared with the initial value of 1.91±0.66 impulses/sec, cardiac vagal activity was 3.06±1.08 impulses/sec at 30 minutes and 3.70±1.95 impulses/sec just before release. The pattern of discharge was monitored over this relatively long period (Figure 6). It is important to note that blood pressure declined markedly, particularly during the first few minutes, and that, despite baroreceptive reflexes, vagal activity increased significantly. Figure 6 also indicates that, at release of occlusion, vagal activity begins to return toward basal values.

![Figure 3](http://circres.ahajournals.org/)

**Figure 3.** Graphs showing the effect of coronary artery occlusion on vagal activity. Left panel: Bar graph showing cardiac vagal activity in 17 cats in control conditions and during the first 2 minutes of coronary artery occlusion. Data are expressed as impulses per second. Right panel: Graph showing cardiac vagal activity in control conditions and during the first 2 minutes of coronary artery occlusion in resistant (R, _n_ =8) and susceptible (S, _n_ =9) cats. Data are expressed as impulses per second. It is evident that the resistant cats had a significantly higher neural response than the susceptible cats. *p<0.01; **p<0.09.
Baroreceptive reflex. We investigated whether susceptible and resistant cats had a different response not only to myocardial ischemia but also to baroreceptive stimulation performed before coronary artery occlusion. Specifically, we tested the hypothesis that resistant cats would have a greater vagal efferent response, as suggested by our baroreflex sensitivity studies in conscious dogs.\(^5,6\) Table 2 summarizes the changes in mean blood pressure and in vagal cardiac activity that occurred during the phenylephrine injection.

The main finding, and the answer to our fourth question, was that the increase in vagal activity in response to similar blood pressure increases induced by phenylephrine was more marked in the resistant cats compared with the susceptible cats (4.36±0.73 versus 2.47±0.49 impulses/sec, respectively, \(p<0.05\) by one-tailed test; +246±66% versus +80±14%, respectively, \(p<0.025\)). Despite the variability in spontaneous vagal activity among individual cats, the patterns of response to blood pressure increase were very consistent and quite different in the two groups, as shown in Figure 7. By contrast, in control condition (i.e., before infusion of phenylephrine), the level of tonic vagal activity was not different between resistant and susceptible cats (1.58±0.35 versus 1.48±0.30 impulses/sec, respectively, \(p=NS\)), as also shown in Figure 7.

These striking differences in the vagal response to baroreceptive stimulation, between resistant and susceptible cats, were not dependent on variability in the procedure or in the hemodynamic response. The latencies in the blood pressure rise were similar in the two groups (12.1±0.9 seconds for susceptible cats versus 11.9±0.9 seconds for resistant cats, \(p=NS\); the individual values for each cat are reported in Table 2. The increase in mean blood pressure was similar in resistant and susceptible cats (55±6 versus 46±6 mm Hg, respectively, \(p=NS\)).

Prolonged myocardial ischemia affected the vagal response to the blood pressure increase. The response of vagal cardiac activity to blood pressure increase was significantly blunted near the end of occlusion (+128±79% 5 minutes before release versus +246±66% in control conditions, \(p<0.05\)) (Figure 8). Neural responsiveness tended to return to control values after release (+185±52%, \(p=NS\)). There were no differences in the mean blood pressure increase during these two injections of phenylephrine (44±7 mm Hg before and 48±8 mm Hg after release of occlusion, \(p=NS\)).

Protocol 2: Effect of Left Stellectomy

In 16 cats, the heart rate was 176±4 beats/min before and 157±4 beats/min after left stellectomy (\(p<0.001\)). Mean blood pressure was 85±2 mm Hg before and 82±3 mm Hg after left stellectomy (\(p=NS\)).

Removal of the left stellate ganglion did significantly increase both tonic and reflex vagal activity, as shown in Figure 9. The resting level of cardiac vagal activity increased from 1.2±0.2 to 2.1±0.3 impulses/sec (+75%, \(p<0.01\)). Based on the inhibitory effect of sympathetic afferent stimulation on vagal outflow,\(^1\) our present study tested the one-way hypothesis that removal of the left stellate ganglion would lead to a more powerful baroreceptor reflex (i.e., to a greater vagal response to the blood pressure increase). This was indeed our finding; vagal activity after left stellectomy and after the injection of phenylephrine was 4.7±0.7 versus 2.2±0.4 impulses/sec (\(p<0.001\)) with an increment of 134±24% versus 86±18% (\(p<0.05\)). Figure 10 illustrates clearly how the number of vagal impulses directed toward the

\[\text{FIGURE 4. Time course showing vagal activity before and during acute myocardial ischemia. An example of the pattern of discharge of a single cardiac vagal efferent fiber in a resistant cat in control conditions and during the first 2 minutes of coronary artery occlusion, when an increase in firing rate occurred, is shown. Data are expressed as impulses per second and were averaged every 5 seconds. Top panel: Time course of mean blood pressure (MBP). Bottom panel: Histogram of cardiac vagal activity. The beginning of the occlusion is marked by the arrow. A, B, and C indicate representative points for which the actual neural recording is shown in Figure 5.} \]
sinus node, at the same level of elevated blood pressure, is considerably higher after removal of the left stellate ganglion.

This major difference cannot be explained on the basis of the hemodynamic changes associated with phenylephrine injection, because there were no differences in the mean blood pressure increase before and after left stellectomy (56±5 versus 60±6 mm Hg, respectively, p=NS) and also because the latency to blood pressure increase was similar (13.3±0.9 versus 12.5±0.4 seconds, respectively, p=NS).

Discussion

The present study has shown that cardiac vagal efferent activity increases during acute myocardial ischemia—much more so among those animals destined to survive compared with those that develop VF. It has also provided the evidence that, in control conditions, the reflex vagal responses to blood pressure increases discriminate between the animals that will or will not develop VF during a subsequent coronary artery occlusion; such a discrimination is not provided by analysis of the tonic vagal activity. Finally, by demonstrating that cardiac sympathetic afferent activity mediated by the left stellate ganglion exerts a tonic restraint on both tonic and reflex vagal activity, the present study provides a potential mechanism for the unforeseen finding of a reduction in both tonic and reflex vagal activity after a myocardial infarction. These data have pathophysiological as well as clinical implications.

FIGURE 5. Electroneurogram (ENG) of the single cardiac vagal efferent fiber shown in Figure 4 in the control condition and during the first 2 minutes of coronary artery occlusion (CAO). Panels A, B, and C correspond to A, B, C on Figure 4. Panel A: Control conditions. Panel B: Beginning of the first minute of CAO. Panel C: After 90 seconds of CAO.
Characteristics of the Preparation

The relation between vagal activity and cardiac events has traditionally been studied with one of the following methodologies: 1) markers of vagal activity, such as heart rate variability or baroreflex sensitivity, 2) interruption of neural traffic by vagotomy, 3) prevention of muscarinic receptor activation by atropine, and 4) recordings of neural activity from the

Table 2. Vagal Activity During Phenylephrine Injection

<table>
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<tr>
<th>Cat</th>
<th>Control</th>
<th>Stimulus</th>
<th>Latency (sec)</th>
<th>ΔMBP (mm Hg)</th>
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<tbody>
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<tr>
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<tr>
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<td>Susceptible</td>
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<tr>
<td>Mean±SEM</td>
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<td>2.47±0.49</td>
<td>12.1±0.9</td>
<td>46±6</td>
</tr>
</tbody>
</table>

Stimulus, peak effect of phenylephrine on blood pressure; Latency, time from the phenylephrine injection to the peak in mean blood pressure; ΔMBP, change in mean blood pressure; Resistant, cats that did not develop ventricular fibrillation after acute myocardial ischemia; Susceptible, cats that developed ventricular fibrillation after acute myocardial ischemia.
cervical vagus and of multifiber or whole-nerve activity from smaller branches.

All of these methods have some merit, and they may all provide useful information, if data are cautiously interpreted. Their main limitation is that they do not provide direct quantitative information on the amount of neural impulses, and hence of acetylcholine release, that reach the sinus node and the heart in general. Heart rate variability and baroreflex sensitivity are just markers of vagal activity and, as such, require validation. Recording from the cervical vagus does not allow identification of the organ innervated by those specific nerve fibers (lungs, heart, stomach, or gut). Recording from multifiber preparations or from the whole nerve may be quite misleading because the neural activity is quantified not by direct count of individual action potentials (spikes) but by counting whatever passes through a window discriminator exceeding a selected voltage. This method has been seriously criticized by two careful quantitative analyses. 13,14 Andresen and Yang 14 have concluded that “interactions among spike trains ... lead to serious underestimation of activity levels” and that “interpretation of results of multifiber or whole nerve recordings whether analyzed with integrative, time-averaging, or spike counting techniques need to be viewed with caution.”

The present study is based on recordings of single vagal fibers according to the technique described in 1972 by Kunze. 10 These fibers are largely directed to the sinus node and to the ventricles, because the atrioventricular node is primarily innervated from the left vagus. Electrical stimulation of this small vagal branch markedly decreases heart rate. 10 There

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**Figure 7.** Responses of cardiac vagal activity (impulses/sec) in resistant and susceptible cats plotted against increases in mean blood pressure (BP) after phenylephrine injection. Left and middle panels: Individual responses. Right panel: Mean response of each group. Open circles represent susceptible cats, and filled circles represent resistant cats.

**Figure 8.** Bar graph showing response to phenylephrine before and during coronary artery occlusion. Responses of cardiac vagal activity to phenylephrine injection in resistant cats are expressed as percent change of nervous activity from the control value. Data are shown before (control) and after 55 minutes of coronary artery occlusion. Values are expressed as mean±SEM. *p<0.05.

**Figure 9.** Graph showing effects of left stellectomy on cardiac vagal activity (impulses/sec) in control conditions and after phenylephrine (PHE) injection. PRE-LSGx, before left stellectomy; POST-LSGx, after left stellectomy. *p<0.01; **p<0.005; ***p<0.001.
CONTROL

BP

ENG

mmHg

250

150

50

LEFT STELLECTOMY

BP

ENG

mmHg

250

150

50

1 sec

1 sec

FIGURE 10. Tracings showing activity of a single cardiac vagal efferent fiber at the same blood pressure (BP) levels induced by phenylephrine before (top panel) and after (bottom panel) left stellectomy. The fiber shows a pulse-synchronous activity. In each panel, the upper tracing shows BP, and the lower tracing shows the electroneurogram (ENG).

is very limited doubt about the destination of the vagal impulses, and the neural activity can be exactly quantified without fear of artifacts.

Vagal Responses to Ischemia

The sympathetic reflex responses to acute myocardial ischemia were investigated and defined by our group more than 20 years ago using the single fiber recording technique.\textsuperscript{15} Strangely enough, information is very scanty about neural efferent vagal activity in response to coronary artery occlusion. This actually seems to be limited to a few multifiber recordings made by Gillis in 1971.\textsuperscript{16} The present study provides the first thorough description of the vagal neural response to acute myocardial ischemia and of its behavior during a 1-hour coronary occlusion.

Vagal efferent activity increases in response to coronary occlusion, and this response overrides the baroreceptor reflex, because it takes place despite a reduction in blood pressure. The artery occluded was the left anterior descending coronary artery, which makes the reflex increase in vagal activity even more significant because, despite some exceptions,\textsuperscript{17,18} it is the occlusion of the circumflex coronary artery, with the attendant ischemia of the inferior left ventricular wall, that is thought to generate the more impressive
vagal responses, experimentally and clinically. This reflex response is secondary to activation of afferent vagal fibers whose sensory endings are largely mechanoreceptors. After the first few minutes of ischemia, vagal efferent activity stabilizes at a level higher than in the control condition and remains there until release of coronary occlusion, when it returns toward the control values.

A major difference was found between the vagal responses to myocardial ischemia of the cats that survived compared with those of the cats that developed VF. With due caution and considering that alpha-chloralose does not alter vagal efferent traffic, it seems reasonable to compare the present findings with previous data obtained in conscious dogs. The more marked reflex vagal activation present among the resistant cats is in full agreement with the observation that the conscious dogs that were more likely to survive a transient myocardial ischemia were those that had signs of valid vagal reflexes during the first minute of occlusion, that is, reductions in heart rate or no increases despite ischemia and continuation of exercise. Moreover, the present findings help to elucidate the relation between vagal responses and survival, suggested by the study in conscious dogs and demonstrated here. The link between augmented vagal activity and enhanced survival is the reduction from 100% to 10% (p < 0.001) produced by vagal stimulation in the incidence of VF during acute myocardial ischemia in 30 high-risk conscious dogs with a healed myocardial infarction. That study demonstrated that by electrically augmenting vagal activity at the beginning of coronary artery occlusion VF could be prevented, an effect partly independent of the reduction in heart rate. The present study demonstrates that those animals responding spontaneously to acute myocardial ischemia with stronger vagal discharges are much less likely to develop VF. Only one of the several vagal branches had been sectioned, thus still allowing release of acetylcholine to effectively reach the ventricles. The mechanisms underlying the vagally mediated protection from VF have been analyzed in detail elsewhere; they involve the antagonism of sympathetic activity, the control of heart rate with its effect on myocardial oxygen consumption, and the direct electrophysiological actions of acetylcholine.

**Vagal Activity and the Risk for Sudden Death**

Experimental and clinical data demonstrated that after a myocardial infarction both heart rate variability and baroreflex sensitivity can help to identify individuals at low or at high risk for VF during an episode of acute myocardial ischemia. By contrast, before a myocardial infarction (i.e., in control conditions), only baroreflex sensitivity and not heart rate variability was found to be associated with outcome during a subsequent episode of acute myocardial ischemia. From these data based on markers of vagal activity, it would have been rather reasonable to infer that, in control conditions, association with the risk of developing VF during acute ischemia would have been found only with vagal reflexes (e.g., baroreceptor reflex) and not with resting vagal activity. This inference had to be tested. Our protocol demonstrated that the impulse activity of single cardiac vagal efferent fibers during blood pressure elevations was indeed significantly higher among the resistant cats. By contrast, vagal firing was identical among the two groups when blood pressure was normal; that is, resting or tonic vagal activity was the same in resistant and in susceptible cats.

Thus, when the heart has not yet suffered a myocardial infarction, vagal reflexes and not vagal tone carry a prognostic value for lethal arrhythmias during acute myocardial ischemia.

Despite the encouraging concordance between the data with heart rate variability and with baroreflex sensitivity when compared with those obtained by direct recording of neural vagal activity, it is fair to keep in mind that both markers are based on the behavior of the sinus node, which is under the opposing influences of sympathetic and vagal activity. Thus, according to the level of sympathetic activity, these markers may not always accurately reflect vagal efferent activity. Despite this word of caution, the main message from these data is that the direct neural recording has fully confirmed our previous conclusions on the relation between vagal activity and risk for sudden death, based on the use of markers such as baroreflex sensitivity and heart rate variability.

**A Mechanism for Depression of Vagal Efferent Activity After Myocardial Infarction**

The unexpected observation that, among conscious dogs with a healed myocardial infarction, many had a depressed baroreflex sensitivity was rapidly supported by several lines of evidence. Two clinical studies indicated that, when compared with sex- and age-matched healthy controls, a significant portion of post–myocardial infarction patients had values either of the high-frequency peak of power spectral analysis of heart rate variability or of baroreflex sensitivity well below the normal range for the healthy population. In these two studies, the phenomenon was transient in most patients. The clinical studies are unavoidably limited by being group comparisons, because of the objective difficulty of studying the same individual in control conditions and after a myocardial infarction. This limitation is compounded by the large range of normal values. Experimental cardiology does not suffer from this limitation, and we were able to study 55 conscious dogs before and also 1 month after a myocardial infarction. By using internal control analysis and thus eliminating the problem of individual variability, we definitively demonstrated that after myocardial infarction baroreflex sensitivity decreases in >70% of the animals and does not change in 20% of them. Always using internal control analysis, we also found that heart rate variability decreases after myocardial...
infarction only in those dogs destined to develop VF during the exercise and ischemia test.  

These investigations have generated the novel concept that myocardial infarction impairs often, and transiently, the vagal control of the heart. This concept has important practical implications because, as now demonstrated by the relation between reduced vagal activity and augmented risk for lethal arrhythmias, it may help to explain the high risk for sudden death particularly in the first few months after myocardial infarction.

However, none of these studies has explained the mechanism underlying the reduction in vagal activity after a myocardial infarction. We had proposed, as a two-component working hypothesis, that myocardial infarction would often augment sympathetic efferent traffic and that this, in turn, could reduce vagal efferent activity. The presence of a necrotic and noncontracting segment may alter the geometry of the beating heart and increase beyond normal the firing of sympathetic and vagal afferent fibers by mechanical distortion of their sensory endings. In addition, these afferent fibers may be damaged or their function may be altered by myocardial infarction.

The second component of this hypothesis depends on a previous study in which we used the same technique used here. In 1973 we showed that electrical stimulation of afferent cardiac sympathetic nerves inhibits tonic vagal efferent activity and blunts the baroreceptor-mediated reflex vagal increase in response to a blood pressure elevation. This finding was supported by the subsequent demonstration that selective removal of the tonic cardiac afferent sympathetic traffic resulted in a potentiation of the reflex bradycardia that follows an increase in blood pressure.

To test the first component of the hypothesis would require recording the same single afferent sympathetic fibers before and a few weeks after myocardial infarction in the same animals; this is technically not feasible. Nonetheless, the concept involved is supported by a sufficiently large body of knowledge. To test the second component would require studying vagal efferent activity at normal and elevated blood pressure levels before and after removal of cardiac sympathetic afferent activity; this was done. The present data indicate clearly that both resting reflex vagal efferent activity are under tonic restraint exerted by cardiac afferent sympathetic activity. It follows that, whenever this activity increases, there will be a further reduction in vagal efferent activity (i.e., depressed heart rate variability) with impairment of vagal reflexes (i.e., reduced baroreflex sensitivity).

Thus, our working hypothesis is supported by the new set of experimental results and, by assuming a different mechanical impact of scars of varying size and location, may also account for the large individual variability in the degree of depression of the vagal control of the heart after a myocardial infarction.

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