Baroreceptor Reflex Control of Heart Rate: A Predictor of Sudden Cardiac Death

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SUMMARY To explore the possibility that the analysis of autonomic reflexes could identify subgroups at high risk of ventricular fibrillation, we studied chronically instrumented mongrel dogs randomly divided into two groups. Twelve dogs served as controls and 17 were studied 3–4 weeks after anterior wall myocardial infarction (MI). After recovery, the dogs were given bolus i.v. injections of phenylephrine, 10 μg/kg, and nitroprusside, 100 μg/kg, to raise or lower systolic arterial pressure 30–50 mm Hg. The RR intervals were plotted against the systolic pressure during the preceding beats, and the slope (baroreflex slope) was determined by least-squares-fit linear regression. On a subsequent day, the left circumflex coronary artery was occluded for 2 minutes, beginning with the last minute of an exercise stress test and continuing for 1 minute after the cessation of exercise (MI group only). The dogs could be divided into two groups based on their response to this test; 11 dogs (65%) had ventricular fibrillation (susceptible), whereas six dogs (35%) did not (resistant). The baroreflex slope (control 20.49 ± 8.59; resistant 10.95 ± 4.68; susceptible 4.60 ± 1.77 msec/mm Hg) and the heart rate response to a 30-mm Hg increase in arterial pressure (control −56.5 ± 14.8; resistant −40.0 ± 12.2; susceptible −12.9 ± 5.0 beats/min) for the susceptible dogs were significantly different from those of the control and resistant dogs. This may indicate that the resistant dogs have a greater capability to activate strong vagal reflexes, which reduce vulnerability to ventricular fibrillation. We conclude that anterior wall MI significantly attenuates the baroreflex control of heart rate and that analysis of the heart rate response to arterial pressure increases allows identification of subgroups of dogs at higher risk for ventricular fibrillation. A prospective study in patients with MI is warranted.

EARLY IDENTIFICATION of patients with ischemic heart disease at high risk for sudden death is a prerequisite for the use of aggressive preventive measures. Conversely, a more conservative approach may be used in low-risk patients. Important progress has been made in the risk stratification for both sudden and nonsudden cardiovascular deaths.1–3 However, identifying patients at a high risk for ventricular fibrillation remains elusive. Some of these patients have been identified,4, 5 but the underlying mechanisms, whether persistent electrical instability or major hemodynamic impairment, have not been clarified.

A large body of evidence indicates that the autonomic nervous system plays a critical role in triggering ventricular fibrillation.6–10 In particular, vagal activation is generally viewed as protective,11 while increased sympathetic activity predisposes the heart to ventricular fibrillation.12, 13 Conversely, both pharmacologic14 and surgical15, 16 antiadrenergic interventions protect against sudden death due to ventricular fibrillation.

Surprisingly, there has been no attempt to use autonomic reflex changes to discriminate among patients at high or low risk for sudden death. Changes in heart rate mediated by baroreceptor reflex can provide a meaningful way to assess autonomic neural control of the heart. Takeshita et al.17 found that myocardial ischemia attenuates baroreflex control of heart rate in response to arterial pressure increases. Clinical studies suggest18, 19 that baroreflex function may be altered after myocardial infarction (MI), as drug-induced hypotension may not be associated with tachycardia.

The purpose of this study was to determine whether there is a relationship between autonomic reflex control of heart rate and susceptibility to sudden death that would identify subgroups at higher risk.

Methods

Thirty-four mongrel dogs that weighed 14.5–25 kg were chronically instrumented to measure aortic pressure, left circumflex coronary blood flow, and the ECG. The dogs were randomly assigned to two groups: 12 controls and 22 in which an MI was produced.

Surgical Preparation

The dogs were given thiopental sodium (Pentothal, Abbott Laboratories), 25 mg/kg i.v., as a preanesthetic, and anesthesia was maintained by the inhalation of a halothane, nitrous oxide and oxygen mixture. A left thoracotomy was performed in the fourth intercostal space. The left circumflex coronary artery was dissected from the surrounding epicardial fat, and an 8–mHz continuous-wave Doppler flow transducer and a pneumatic occluder were placed around this vessel. A heparinized, saline-filled catheter was placed into the aorta through the left common carotid artery. Insulated silver-coated copper wires were sutured to the epicardial surface of both the left and right ventricles and were later used to record the ECG.

In 22 dogs, an experimental MI was produced. A modified two-stage occlusion20 was performed on the left anterior descending coronary artery approximately one-third of the distance from its origin. The vessel was partially occluded for 20 minutes and then tied off. In addition, two to three branches from the left anterior descending coronary artery were ligated proximal to the occlusion. The leads to the cardiovascular instru-
mentation were tunneled under the skin to exit on the back of the dog’s neck. Pentazocine lactate (Talwin Winthrop laboratories), 30 mg i.m., was given approximately every 8 hours for the first 24 hours to control postoperative pain.

Prevention of Early Cardiac Arrhythmias

The dogs subjected to MI were placed in an intensive care setting. The therapy described below was given to prevent early cardiac arrhythmias. The dogs received 100 mg of lidocaine HCl i.m. (Xylocaine, Astra Laboratories) before surgery, which was supplemented (60 mg i.v.) during each stage of the Harris two-stage occlusion. After surgery, the dogs were placed in a quiet recovery area, the ECG was monitored, and a lidocaine drip infusion (100 μg/ml in lactated Ringer’s solution) was maintained at the rate of 1 ml/min for the first 24 hours after MI. The dogs were then given 500 mg of procaainamide HCl i.m. (Pronestyl, E. R. Squibb & Sons Inc.) twice daily for the next 3 days. These interventions seemed useful, as only four dogs died during this period. A fifth dog died from exsanguination through the catheter 2 weeks after MI.

Baroreceptor Reflex Testing

The dogs were allowed to recover for 3–4 weeks before baroreceptor reflex testing began. The dogs were placed on a laboratory table and a venous catheter was percutaneously placed in the cephalic vein to administer the vasoactive drugs. Arterial pressure was obtained from the aortic catheter with a Statham P23Db pressure transducer. Baroreceptor reflex control of heart rate was then assessed by the method of Smyth et al. The dogs were given injections of sodium nitroprusside dihydate, 100 μg/kg (Nipride, Roche Laboratories), and phenylephrine HCl, 10 μg/kg (Neo-Synephrine, Winthrop Laboratories) to raise or lower systolic arterial pressure 30–50 mm Hg. Each RR interval (and heart rate) was plotted as a function of the preceding systolic pressure. The analysis was performed beat by beat beginning only after the first noticeable change in RR interval. Control data were obtained by averaging over five successive beats immediately before the vasoactive drug was infused. A least-squares-fit linear regression was performed, and the reflex control of heart rate was expressed as the slope of the linear regression line (an index of baroreceptor reflex sensitivity). The slope was accepted for further analysis only if the correlation coefficient was 0.80 or greater.

Sudden Death Testing

Susceptibility to ventricular fibrillation was evaluated with a new experimental model in which malignant arrhythmias were consistently induced by a combination of exercise, acute myocardial ischemia and autonomic reflexes. The 17 dogs that survived MI were subjected to a submaximal exercise stress test. The dogs ran on a motor-driven treadmill for 15 minutes, while work load increased every 3 minutes (4.8 kph, 0% grade during first 3 minutes; 6.4 kph, 12% grade during the last 3 minutes). During the last minute of the exercise test, the left circumflex coronary artery was occluded; the treadmill was suddenly stopped and the occlusion maintained for an additional minute. The occlusion lasted 2 minutes. Large steel plates were placed across the dog’s chest so that electrical defibrillation could be performed with minimal delay. Arterial pressure, ECG and heart rate were monitored throughout the exercise test.

Data Analysis

All data were recorded on a Beckman RM recorder. The slope, as determined by linear regression, was treated as a response variable and analyzed by one-way analysis of variance. Newman-Keul’s multiple-range test was used to make comparisons. Specifically, the hypothesis that anterior wall myocardial infarction attenuated the baroreceptor reflex control was tested (null hypothesis — anterior wall myocardial infarction does not alter the baroreceptor reflex control of heart rate). The hypothesis that sudden cardiac death could be predicted from the baroreflex slope was also tested (null hypothesis — the baroreflex slopes in the dogs that had ventricular fibrillation are not different from those in dogs that did not). To avoid possible bias, we calculated the baroreflex slopes before the dogs were tested on the treadmill. Control heart rate and systolic arterial pressure were obtained by averaging over the last five beats before the drug infusion. The changes in heart rate for a 30-mm Hg increase and a 30-mm Hg decrease in systolic aortic pressure were also calculated. The myocardial infarct size was determined by the nitroblue tetrazolium enzymatic staining technique and reported as percent of the left ventricle involved. These data were compared as described above.

Results

Effect of Myocardial Infarction

ECG and arterial pressure recordings after phenylephrine injection for a control dog and a dog that survived MI are shown in figure 1. For any given arterial pressure, the RR interval was more prolonged in the control dog. A similar pattern was observed in all the dogs. For a 30-mm Hg increase in systolic aortic pressure, heart rate decreased by 56.5 ± 14.8 beats/min, whereas after MI the decrease was only 26.0 ± 8.6 beats/min. Similarly, the baroreflex slope was significantly reduced after MI (controls 20.49 ± 8.59 vs post-MI 6.84 ± 4.31 msec/mm Hg). Resting heart rate and blood pressure were similar in both groups (table 1).

Susceptibility to Ventricular Fibrillation

The dogs that survived MI could be divided into two groups based on their response to the combined exercise and acute myocardial ischemia test. Eleven dogs (65%) developed ventricular fibrillation and were considered susceptible to sudden death. Six dogs (35%) did not have life-threatening arrhythmias and were considered resistant. In five of the six resistant dogs, the heart rate decreased during the exercise-ischemia
test. This contrasts with the further increase in heart rate invariably observed at the time of the coronary occlusion in the susceptible dogs.

The regression analyses for two MI dogs, one resistant and one susceptible to ventricular fibrillation, are presented in figure 2. The slopes for 11 MI dogs are displayed in figure 3. The baroreflex slope was significantly reduced in the susceptible dogs compared with the resistant dogs (figure 4, table 1). Both the total slope (response to increases and decreases in arterial pressure plotted as one function) and the response to phenylephrine (increased arterial pressure) were significantly attenuated ($F_{2,26} = 20.04, p < 0.001$ and $F_{2,26} = 11.71, p < 0.001$, respectively). In fact, there was very little overlap between the groups; 90% of the resistant group had a slope greater than 10.72 msec/mm Hg, and 90% of the susceptible dogs had slopes less than 6.17 msec/mm Hg. However, the RR-interval response to an arterial pressure decrease was much more variable, and there was no significant difference between the groups ($F_{2,26} = 3.31, NS$).

The average heart rate reduction for a 30-mm Hg increase in systolic arterial pressure was significantly reduced in the susceptible dogs compared with both the control and resistant dogs ($F_{2,26} = 41.89, p < 0.001$) (fig. 5). The heart rate response to arterial hypotension, however, were not significantly different between the groups ($F_{2,26} = 0.40, NS$). When heart rate rather than RR interval was plotted against systolic arterial pressure, the results were similar (phenylephrine response: control $-6.63 \pm 1.6$ beats/min/mm Hg; resistant $-3.22 \pm 1.0$ beats/min/mm Hg; susceptible $-0.49 \pm 0.2$ beats/min/mm Hg).

The mean predrug heart rate and the systolic arterial pressure were similar in all groups. The resistant and susceptible dogs had MIs of similar size (table 1).

**Discussion**

This study presents a very reliable means of identifying subpopulations of dogs vulnerable to sudden cardiac death. Baroreceptor reflex control of heart rate, as measured by the slope of the RR interval plotted against systolic arterial pressure, was significantly reduced by anterior wall MI. The dogs that exhibited the greatest reduction in slope (smallest slope) invariably had ventricular fibrillation during the exercise-ischemic event.

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**Table 1. The Effects of Myocardial Infarction on Heart Rate, Systolic Aortic Pressure, and Baroreflex Slope**

<table>
<thead>
<tr>
<th>Slope (msec/mm Hg)</th>
<th>Control dogs (n = 12)</th>
<th>Resistant dogs (n = 6)</th>
<th>Susceptible dogs (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>20.49 ± 8.59</td>
<td>10.95 ± 4.68*</td>
<td>4.60 ± 1.77**</td>
</tr>
<tr>
<td>PhE only</td>
<td>26.08 ± 15.37</td>
<td>17.91 ± 8.61*</td>
<td>4.41 ± 2.26**</td>
</tr>
<tr>
<td>NP only</td>
<td>11.17 ± 7.77</td>
<td>7.25 ± 5.13</td>
<td>4.53 ± 2.74</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>115.9 ± 26.6</td>
<td>128.2 ± 15.0</td>
<td>109.4 ± 23.4</td>
</tr>
<tr>
<td>APsys (mm Hg)</td>
<td>122.6 ± 17.7</td>
<td>125.2 ± 18.8</td>
<td>125.4 ± 21.4</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of left ventricle</td>
<td></td>
<td>23.2 ± 5.5</td>
<td>21.7 ± 7.4</td>
</tr>
<tr>
<td>ΔHR (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mm Hg APsys increase</td>
<td>$-56.5 \pm 14.8$</td>
<td>$-40.0 \pm 12.2^{*}$</td>
<td>$-12.9 \pm 5.0^{*}$</td>
</tr>
<tr>
<td>30 mm Hg APsys decrease</td>
<td>$87.4 \pm 26.7$</td>
<td>$76.4 \pm 47.2$</td>
<td>$75.4 \pm 33.6$</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

* $p < 0.05$ vs control.

$^{*} p < 0.01$ vs control.

$^{*} p < 0.01$ vs resistant.

Abbreviations: PhE = phenylephrine; NP = nitroprusside; HR = heart rate; APsys = systolic arterial pressure.
FIGURE 2. Regression analyses for two dogs that survived infarction, one resistant and one susceptible. There is a large slope difference and the correlation coefficients are relatively high. The response to phenylephrine and nitroprusside is expressed as one regression line (total slope). AP sys = systolic arterial pressure.

FIGURE 3. Regression analysis for all dogs that survived infarction. The solid lines represent susceptible dogs, the dashed lines resistant dogs. The response to phenylephrine and nitroprusside is expressed as one regression line (total slope). AP sys = systolic arterial pressure.

FIGURE 4. Composite slopes for all dogs. Total RR interval response to both an increase and a decrease in pressure. PhE = phenylephrine (10 µg/kg) response; NP = nitroprusside (100 µg/kg) response. *p < 0.05 vs control dogs. **p < 0.01 vs control dogs. **p < 0.01 vs resistant dogs. Plotted as mean ± sd.

Myocardial Infarction and Baroreflex

These results are consistent with the findings of both experimental and clinical studies. Takeshita et al. found that acute myocardial ischemia attenuated the baroreflex-mediated reduction in heart rate response to arterial pressure increases. The baroreflex slope was reduced more than 50% during ischemia, and returned to control levels after the release of the occlusion. Toubes and Brody examined the peripheral vascular component of the baroreflex and found that after experimental coronary embolization, hindlimb vascular resistance no longer increased in response to systemic arterial hypotension.

Indirect clinical evidence suggests that baroreflex function is impaired by myocardial infarction. Several studies have shown that reflex tachycardia in response to drug-induced hypotension is often absent or reduced in ischemic heart disease patients, as is reflex vasoconstriction. Bennett et al. found that the heart rate response to both the Valsalva maneuver and lower body negative pressure was attenuated in patients 1 year after MI, and baroreflex slope was demonstrably reduced (control 11.5 msec/mm Hg, MI patients 2.5 msec/mm Hg). Eckberg et al. used the pressor drug technique to evaluate baroreflex-mediated changes in heart rate and found that patients with the most advanced heart disease had the smallest heart rate reductions.
tion may be important during acute myocardial ischemia, they probably contribute very little to the changes after MI. The hemodynamic consequences of MI may contribute more to this baroreflex slope reduction. MI decreases the upstroke velocity of systolic arterial pressure, which is an important determinant of carotid sinus nerve activity and, hence, of the baroreceptor reflex. Alterations in upstroke velocity may therefore contribute significantly to the reduction of baroreflex slope after MI.

Our results demonstrate that the capability of reflexly decreasing heart rate in response to increases in arterial pressure is markedly reduced after MI.

**Baroreflexes and Sudden Death**

The baroreflex slopes for the resistant and susceptible dogs were strikingly different, which immediately suggested a difference in the autonomic control of the heart in these two groups of dogs. Despite the novel approach used in this study, our findings were not unexpected, as a strict relationship between baroreceptor reflexes and vulnerability to ventricular fibrillation is logical on the basis of current knowledge. A steep baroreflex slope in response to an increase in blood pressure reflects primarily the activation of vagal efferent nerve fibers coupled, to some extent, with reduced sympathetic efferent activity. Thus, the resistant dogs seem to have a greater capability to reflexly increase their vagal tone than the susceptible dogs.

Verrier, Lown and associates showed that enhanced vagal tone decreases susceptibility to ventricular fibrillation. They also showed that vagal activation can oppose the decrease in the ventricular fibrillation threshold induced by sympathetic stimulation. Moreover, they found that vagal stimulation antagonizes the increases in ventricular vulnerability associated with either coronary occlusion or psychological stress. Five of six resistant dogs had a marked decrease in heart rate during the brief coronary occlusion during exercise, which further demonstrates a propensity for powerful vagal reflexes, as disclosed by the baroreflex testing, in these dogs.

Conversely, the almost flat baroreflex slopes in the susceptible dogs may indicate a relatively greater sympathetic activation. Preliminary experiments indicate that β-adrenergic blockade substantially increases the baroreflex slope in the susceptible dogs, but only slightly alters the slope in both the resistant and control dogs. The association between high sympathetic activity and increased vulnerability to ventricular fibrillation is well established.

Thus, the analysis of the autonomic reflexes induced by baroreceptor activation allows for the identification of subgroups of dogs that are either more or less vulnerable to ventricular fibrillation triggered by acute myocardial ischemia.

**Critique of the Study**

The pharmacologic method for evaluating baroreflex function has been widely used since its description by Smyth et al. and has provided valuable insight into...
circulatory reflex regulation. This technique is both easy to perform and yields reliable quantitative data. However, as Eckberg\textsuperscript{10} pointed out, this approach has two inherent limitations.

First, it treats the RR interval arterial pressure curve as a linear rather than a sigmoidal function. Therefore, arterial pressure elevations that occur within either the threshold or the saturation portions of the curve produce smaller calculated slopes than do pressure changes confined to the linear portion of the curve. Second, drugs that increase arterial pressure by vascular smooth muscle excitation will also cause the smooth muscle layers that contain the pressure receptor units to contract, thereby altering the baroreceptor firing pattern or frequency.

To circumvent these problems, we used only regression lines that displayed a large correlation coefficient (> 0.80) during an induced pressure change of 30–50 mm Hg. Pressure changes of this magnitude have been routinely reported to extend well within the linear portion of the baroreceptor curve.\textsuperscript{10} In addition, similar slope reductions were noted when heart rates rather than RR interval were plotted against systolic pressure. The heart rate reductions in response to 30-mm Hg pressure increases were significantly different in the groups.

Presumably, the effects of phenylephrine at the receptor sites would be similar in both the control and MI dogs. Thus, drug-induced changes in receptor function should be independent of myocardial ischemic injury and vulnerability to sudden death. This problem should therefore not be a major concern in this study.

Whenever susceptibility to sudden death is assessed experimentally, a critical issue is the relevance to the clinical condition. The occurrence of ventricular fibrillation in our model depends solely on the interaction between the following clinically relevant factors: acute myocardial ischemia, exercise and its cessation and the interaction between vagal and sympathetic reflexes.\textsuperscript{32} Baroreflex testing can be used to predict the results of the interaction between vagal and sympathetic reflexes.

Clinical Significance

Extrapolation of these data to the clinical setting seems possible even when one considers species differences.\textsuperscript{33} The baroreflex slope and the heart rate reductions associated with phenylephrine injections may prove useful for identifying patients vulnerable to ventricular fibrillation. Identifying MI patients at high risk for sudden death by their cardiac autonomic response to changes in blood pressure merits careful examination.

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