Autonomic Mechanisms and Sudden Death

New Insights From Analysis of Baroreceptor Reflexes in Conscious Dogs With and Without a Myocardial Infarction

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We have suggested that among conscious dogs with a healed anterior wall myocardial infarction (MI) a depressed baroreflex sensitivity (BRS) carries a higher risk of developing ventricular fibrillation during a brief ischemic episode associated with an exercise stress test. The clinical and pathophysiological implications of our previous findings prompted the present study, which addressed three major questions: 1) Is, indeed, analysis of BRS after MI a specific and sensitive marker for sudden death—risk stratification? 2) Does MI modify BRS? 3) Does analysis of BRS before MI provide information about outcome during ischemic episodes occurring after MI? An anterior MI was produced in 301 dogs, and 4 weeks later, a 2-minute circumflex coronary artery occlusion beginning during the last minute of an exercise stress test could be performed in 192 animals. Ventricular fibrillation occurred in 106 (55%) dogs (susceptible to sudden death), whereas 86 (45%) dogs (resistant to sudden death) survived. BRS was assessed by the phenylephrine method and was expressed by the regression line relating RR intervals to blood-pressure changes. BRS was significantly lower among susceptible than among resistant dogs (9.1 ± 6.0 vs. 17.7 ± 6.5 msec/mm Hg, p<0.0001). The risk for sudden death increased from 20% (15 of 73 dogs) for a BRS greater than 15 msec/mm Hg to 91% (62 of 68 dogs) for a BRS less than 9 msec/mm Hg (p<0.001). An internal control study in 55 animals showed that BRS was reduced 4 weeks after MI compared with control conditions (13.5 ± 6.7 vs. 17.8 ± 6.6 msec/mm Hg, p<0.001) and that a reduction occurred in 73% of animals. Susceptible dogs and those that spontaneously died after MI had a lower BRS even before the MI (16.2 ± 5.9 vs. 22.2 ± 6.2 msec/mm Hg, p<0.001). The risk for sudden death after MI increased from 35% (nine of 26 dogs) for a BRS before MI greater than 20 msec/mm Hg to 85% (17 of 20 dogs) for a BRS before MI less than 14 msec/mm Hg (p<0.001). This study demonstrates that the presence of a reduced BRS is associated with a greater susceptibility to ventricular fibrillation during subsequent ischemic episodes. In the majority of dogs, BRS is reduced after an MI. The results in 192 conscious dogs with a healed MI indicate that analysis of BRS is a powerful tool for risk stratification not only after, but even before, the occurrence of an MI. (Circulation 1988; 78:969–979)

Despite the well-recognized importance of the autonomic nervous system in the genesis of life-threatening arrhythmias, particularly in ischemic hearts,1−5 attempts have been made only recently to use autonomic reflexes for the identification of individuals who have suffered myocardial infarction (MI) and who are at high risk for sudden cardiac death.6−8

In 1982, we6 reported that a depressed baroreflex sensitivity (BRS) was associated with an augmented risk for ventricular fibrillation in a clinically relevant experimental model for sudden cardiac death.

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Conscious dogs with a healed anterior wall MI underwent a 2-minute circumflex coronary artery occlusion while performing an exercise stress test; this combination of acute myocardial ischemia and physiologically elevated sympathetic activity triggered ventricular fibrillation in 60% of the animals.
(susceptible to sudden death), whereas the remaining 40% (resistant to sudden death) survived with few or no ventricular arrhythmias.9 Both of these response patterns were reproducible for a few months.10

The initial report,6 based on 11 susceptible and six resistant animals, stimulated two clinical prospective studies aimed at comparing BRS between patients after MI and matched controls11 and at assessing the relation between BRS, clinical variables, and mortality in patients with a first MI.12-14 It also raised several questions on important links between cardiovascular pathophysiology and clinical cardiology.

In the present study, the following three questions were addressed: 1) Does analysis of BRS after MI indeed provide a sufficiently specific and sensitive marker for being at either high or low risk for subsequent sudden cardiac death? 2) Does MI really modify BRS? 3) Does analysis of BRS in animals before MI provide predictive information about their outcome when exposed to acute myocardial ischemia after MI?

The results indicate that analysis of BRS, not only after but even before MI, is a powerful tool for risk stratification. They also suggest that the presence of a reflex autonomic imbalance characterized mostly by reduced parasympathetic activity and to some extent by augmented sympathetic activity, as indicated by depressed BRS, is associated with a higher propensity to develop ventricular fibrillation during acute myocardial ischemia. Preliminary results have been presented.15

Materials and Methods

Three hundred seven dogs (weighing 17–25 kg) were entered in the study. The experiments were performed during 1981–1987 at the University of Oklahoma, Norman, Oklahoma, and during 1985–1987 at the University of Milan, Milan, Italy.

Surgical Preparation

The surgical procedure has been described already in detail.9 Briefly, dogs were given thiopental sodium (Pentothal Sodium, Abbott Laboratories, North Chicago, Illinois) 20 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. A Harris two-stage occlusion of the left anterior descending coronary artery was performed below the first diagonal branch. In six animals, the coronary artery was isolated, but occlusion was not performed; this group served as sham-operated controls. A 20-MHz flow probe and a hydraulic occluder were placed around the left circumflex coronary artery. A Tygon catheter was often inserted into the aortic arch for recording blood pressure. Two electrodes were sutured on the right atrial appendage to record a bipolar electrogram. All lead wires were tunneled under the skin to exit from the dorsal surface of the neck. Pentazocine lactate (Talwin, Winthrop Laboratories, New York, New York) 30 mg i.m. was given every 8 hours to control postoperative pain. The guidelines of the American Physiological Society and the American Heart Association on the care and treatment of experimental animals were adhered to throughout the study.

Arterial blood pressure was recorded for the evaluation of BRS before MI either from the femoral artery through a percutaneous stick with a 21-gauge needle or from the omocervical artery through a Tygon catheter positioned a few days earlier under short-lasting anesthesia. The distal end of the Tygon catheter was tunneled under the skin to exit from the back of the neck.

Baroreceptor Reflex Testing

Before testing, dogs were allowed to adapt to the laboratory environment for a few days to minimize any orienting response elicited by the new environment. The unsedated animals were then placed on a laboratory table, and with minimal physical restraint, a venous catheter was percutaneously placed in the cephalic vein to administer phenylephrine. A bipolar right atrial electrogram and the surface electrocardiogram were recorded from the epicardial leads and from needle electrodes placed in the standard limb lead configuration. BRS was then assessed by the method described by Smyth et al.16 Dogs were given a bolus injection of phenylephrine HCl 5–10 μg/kg (Neo-Synephrine, Winthrop Laboratories) to raise systolic pressure by 30–40 mm Hg. Baroreflex sensitivity was then expressed as the slope of the regression line relating RR intervals to systolic arterial pressure changes. The baroreceptor reflex tests were performed 4–5 weeks after MI in all surviving dogs and a few days before the production of MI in 85 animals. The majority (65%) of animals had two or three BRS tests in each condition (before and after MI).

Baroreceptor Reflex Analysis

BRS was calculated by analyzing every cardiac cycle after the first noticeable change in blood pressure; control data were obtained by averaging five consecutive beats preceding phenylephrine administration. Only sinus beats were analyzed; premature beats and the one immediately after, as well as ventricular escape beats, were excluded from the measurements. The RR intervals were manually measured, and BRS was always calculated before the exercise and ischemia test.

The variability sometimes present in a given animal between one BRS measurement and another and between the number of BRS tests performed, depending on slight protocol changes that occurred over the years, made necessary the adoption of arbitrary rules for data analysis and selection. These criteria, as listed below, are not necessarily better or more accurate than others; they were adopted to
avoid any possible bias in the choice of the final BRS value for a given animal and to ensure the reproducibility of these data by other investigators. BRS slopes were excluded from analysis when one of the following occurred: basal RR interval less than 400 msec (heart rate > 150 beats/min) or basal systolic blood pressure greater than 150 mm Hg.

During the initial years of the study, only one determination of BRS was used. Subsequently, at least two BRS tests were performed in each animal on different days. The BRS value of a given dog was determined according to the following possibilities: 1) the two slopes were within 3 msec/mm Hg; the one with the highest r was chosen; 2) the two slopes differed by more than 3 and less than 6 msec/mm Hg; if the r of both slopes differed by less than 5%, the average of the two BRSs was calculated; if the r of both slopes differed by greater than 5%, the BRS with the highest r was chosen; 3) if the two slopes differed by greater than 6 msec/mm Hg, a third BRS test was performed; the two closest values were analyzed according to criteria 1 and 2, provided that they differed by less than 6 msec/mm Hg. In six dogs, the difference remained excessive, and these animals were excluded from subsequent analysis.

Exercise and Ischemia Test

Four weeks after the production of the anterior myocardial infarction, the susceptibility to sudden cardiac death was assessed by a test combining submaximal exercise and a brief episode of acute myocardial ischemia.9 Dogs performed an exercise stress test on a motor-driven treadmill for 12–18 minutes until heart rate reached values of approximately 210–220 beats/min. At the beginning of the last minute of exercise, an acute occlusion of the circumflex coronary artery was performed by inflating the hydraulic occluder, and it was maintained for an additional minute after cessation of exercise. The dogs had two steel paddles secured across their chests so that electrical defibrillation (Model 6217, American Optical, New York, New York) could be immediately accomplished whenever necessary.

Electrocardiograms, heart rate, arterial blood pressure, and coronary flow were monitored throughout the exercise test. Flow velocity in the left circumflex coronary artery was measured to verify completeness of occlusion.

Measurements

Recordings of aortic blood pressure, instantaneous heart rate, surface and epicardial electrocardiograms, and coronary flow were made simultaneously, in Oklahoma City, on an eight-channel R612 Beckman chart recorder (Redwood City, California) and on an eight-channel Ampex 2200 magnetic tape recorder (Schiller Park, Illinois) or, in Milan, on a six-channel Gould-Brush 260 chart recorder (Cleveland, Ohio) and on a seven-channel Racal 7DS magnetic tape recorder (Southampton, England). Blood pressure was measured by an Elec
tromedics MS20 transducer (Englewood, Colorado) in Oklahoma City and by a Statham P23ID transducer (Cleveland, Ohio) in Milan. Coronary flow was recorded by 20-MHz flowmeters built as described by Hartley and Cole.17

Statistical Analysis

Whenever an internal control study was made, statistical analysis was performed by the Student’s t test for paired data. One way analysis of variance (ANOVA) and Tukey’s test were used for group comparisons. Risk for sudden death was calculated by the χ² test. The validity,18 as a screening procedure, of the baroreflex test was determined by measuring its sensitivity, its specificity, and its predictive value.19 Data are expressed as mean ± SD, unless otherwise specified. Significance was accepted for values of p<0.05.

Results

An anterior wall MI was produced in 301 dogs. The subsequent events, including perioperative and postoperative (up to 4 weeks after MI) mortality and technical problems precluding the exercise and ischemia test (mostly rupture of the hydraulic occluder or a nonacceptable BRS test), are summarized in Figure 1.

The mortality after MI was 30% (89 of 301 dogs); this incidence compares quite well with and, thus, confirms the incidence already reported with this procedure in our previous studies: 26 of 64 (41%)20, five of 22 (23%)20; 14 of 42 (33%)20; eight of 26 (31%)20; and 14 of 52 dogs (27%)21 for a total of 67 of 206 dogs (32%). Among the 212 survivors, technical problems prevented the completion of the study in 20 dogs (9%) so that the exercise and ischemia test was performed in 192 dogs (Figure 1A). All these animals had the BRS test performed approximately 4 weeks after MI. In 85 dogs, BRS was studied also before the production of the MI (before MI); of these, 55 survived, and 51 of these survivors had a functioning instrumentation (as detailed in Figure 1B) so that they could undergo the exercise and ischemia test. This group of 85 dogs provides the data for the internal control study on the effect of MI on BRS and on the relation between BRS before MI and mortality after MI.

Baroreflex Sensitivity After Myocardial Infarction and Sudden Death

Of the 192 dogs that underwent the exercise and ischemia test, 106 (55%) developed ventricular fibrillation (susceptible), and 86 survived (resistant). Ventricular fibrillation almost always resulted from degeneration of very rapid ventricular tachycardia or flutter. Asystole and electromechanical dissociation were never observed.

When the BRS of animals without MI (controls, n = 85) was compared with that of the dogs after MI
(n = 192), BRS was found to be higher (19.6 ± 7.9 vs. 12.9 ± 7.6 msec/mm Hg, p < 0.001) (Figure 2).

BRS was significantly lower among susceptible dogs when compared with that of resistant dogs (9.1 ± 6.0 vs. 17.7 ± 6.5 msec/mm Hg, p < 0.0001) (Figure 2). Although the BRS of the susceptible dogs was markedly lower compared with the controls, no difference was present between the resistant dogs after MI and the controls (Figure 2).

Figure 3 shows the distribution of the individual values of BRS for the susceptible and the resistant dogs. The values between 9 and 15 msec/mm Hg encompass an arbitrarily defined gray area used for the purpose of identifying areas of high and of low risk. It is immediately evident that there was an excess of susceptible animals in the area below 9 msec/mm Hg as well as an excess of resistant animals in the area of BRS greater than 15 msec/mm Hg. These data allowed the calculation of risk for sudden death in respect to BRS measured 4 weeks after MI. The risk increased from 20% (15 of 73 dogs) for a BRS greater than 15 msec/mm Hg to 91% (62 of 68 dogs) for a BRS less than 9 msec/mm Hg (p < 0.001) (Table 1). When the individual changes of this internal control study were examined (Figure 4), it became evident that a reduction in BRS (change >3 msec/mm Hg) occurred in 73% of animals (40 of 55 dogs), whereas no change was present in 20% (11 animals), and an increase occurred in only 7% (four animals). An example of a major reduction in BRS after MI is shown in Figure 5.

The reduction in BRS after MI was not significantly different between susceptible (−6.4 ± 8.2 msec/mm Hg) and resistant dogs (−4.5 ± 7.2 msec/mm Hg).

Heart rate and blood pressure were not different before and 4 weeks after MI (99 ± 23 vs. 107 ± 21 beats/min and 130 ± 19 vs. 130 ± 16 mm Hg). Similarly, no difference was present when analyzing separately susceptible and resistant animals.

When the BRS of six dogs was compared before and after surgery without MI, no difference was found (16.1 ± 4.7 vs. 17.9 ± 4.0 msec/mm Hg, NS).
In detail, a decrease was found in only one of six dogs (17%), this incidence was significantly different ($p<0.05$) compared with that present after an MI (40 of 55 dogs, 73%).

**Baroreflex Sensitivity Before Myocardial Infarction and Sudden Death After Myocardial Infarction**

BRS values obtained before the creation of the MI were analyzed in relation to events after MI, including not only the outcome during the exercise and ischemia test but also the spontaneous mortality after MI. From the latter were excluded all perioperative deaths and the few related to an infection; included were 17 dogs that died suddenly or overnight during the first 4 weeks after MI (mostly during the 1st week) and in which the autopsy failed to show any significant abnormality other than the anterior wall MI. These 17 dogs were analyzed and formed the group of susceptible animals together with 23 dogs that survived the period after MI but that developed ventricular fibrillation during the exercise and ischemia test.

BRS in the condition before MI was significantly lower among the susceptible animals compared with the resistant (16.2 ± 5.9 vs. 22.2 ± 6.2 msec/mm Hg, $p<0.001$). Figure 6 shows the individual BRS values with an arbitrarily defined gray area between 14 and 20 msec/mm Hg for the purpose of identifying areas of high and low risk; it also allowed for a distinction between those animals that died spontaneously in the phase after MI and those that died during the exercise and ischemia test. As a consequence of the higher BRS in the animals without MI, the arbitrary gray area, used to define areas including adequate numbers of animals, had to encompass higher values. Similar to what is shown in Figure 3 for BRS after MI, it is evident that there was an excess of susceptible animals in the area of BRS less than 14 msec/mm Hg, whereas such a clear distinction was not present in animals with a BRS greater than 20 msec/mm Hg. These data

### Table 1. Baroreflex Sensitivity and Sudden Death in Dogs After Myocardial Infarction

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<th>BRS sensitivity (msec/mm Hg)</th>
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<th>Percentage</th>
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<td>$&gt;20$</td>
<td>4/32</td>
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<td>62/68</td>
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<td>$&lt;4$</td>
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$n$, 192 dogs.
animal developed ventricular fibrillation during MI.

5. FIGURE a for Baroreflex dogs

The produced an after allowed the calculation of risk greater 3 msec/mm Hg occurs.

allowed the calculation of risk for sudden death after an MI with respect to BRS measured before MI. The risk increased from 35% (nine of 26 dogs) for a BRS 20 msec/mm Hg or greater to 85% (17 of 20 dogs) for a BRS less than 14 msec/mm Hg (p<0.001) (Table 2). The sensitivity of the BRS test was somewhat lower compared with the study after MI, 43%, but both specificity and predictive value remained quite satisfactory, 89% and 85%, respectively.

No difference in BRS was present between the dogs that died spontaneously after the MI and those that died while performing the exercise and ischemia test (16.9 ± 6.4 vs. 16.1 ± 5.8 msec/mm Hg).

The simultaneous examination of Figures 3 and 6 provided more information relevant to the effect of MI on BRS. After MI, a large number of animals (67 of 192, 35%) had BRS less than 9 msec/mm Hg, which is in striking contrast to the few (three of 68, 4%) (p<0.0005) that had these values before MI. This observation is quite consistent with the finding shown in Figure 4, namely, that MI reduced BRS in the majority of animals.

Discussion

This study in conscious dogs with a healed myocardial infarction demonstrates that analysis of BRS in the period after MI allows the identification of a large subgroup at a very high risk for sudden death. It demonstrates also, with an internal control analysis, that BRS is reduced in the majority of animals after MI, and it provides the first evidence that even in control conditions, that is, before MI, a depressed BRS constitutes a marker of higher risk for subsequent sudden death.

The results yielded by the analysis of baroreceptor reflexes in a conscious animal model of sudden cardiac death offer new insights on the mechanisms underlying the complex relation between the autonomic nervous system, acute myocardial ischemia, and life-threatening arrhythmias. The feasibility of
baroreflex sensitivity evaluation in humans adds to the clinical implications of this study.

Animal Model for Sudden Death

Ventricular fibrillation in this preparation was induced by the combination of clinically relevant factors such as transient myocardial ischemia occurring at a time of physiologically elevated sympathetic activity in a conscious animal with a healed myocardial infarction. The various characteristics of the exercise and ischemia test have been described in detail, including the hemodynamic profile of resistant and susceptible dogs. The present larger study, which confirms the reproducibility of the main characteristics of this animal model, also provides additional information on the relation between heart rate and outcome.

Just before beginning exercise on the treadmill, the heart rate of susceptible animals had been found to be higher (approximately 25 beats/min) than that of resistant animals. In the present study, no difference in heart rate was present between the two groups when heart rate was examined in resting conditions. This observation would suggest that susceptible animals may not be grossly different from the resistant ones at rest but that they may respond differently to various stresses, for example, standing in preparation for exercise or during acute myocardial ischemia.

**Baroreflex Sensitivity and Myocardial Infarction**

Although a reduction in BRS has been occasionally reported in a few patients with an MI, only recently a specifically targeted study involving an adequate number of patients after MI and age-matched control individuals has been performed, demonstrating that despite considerable overlapping BRS was significantly lower among patients after MI. Interestingly, in most patients, this reduction was a transient phenomenon lasting only a few months.

The main limitation of these clinical studies lies in the necessity of drawing conclusions based on cross-sectional group comparisons due to the extreme difficulty to perform a longitudinal, internal control study. For this reason, the clinical studies can suggest at most that MI has or has not a direct influence on the reflex control of heart rate. The present study, by comparing BRS before and after MI within the same animals, has demonstrated that in the condition after MI BRS was indeed reduced compared with the control state. This change occurred in the vast majority of dogs (73%); however, the remaining animals constitute one fourth of the population and may represent a potentially confounding factor in small-sized clinical studies. The lack of reduction in BRS among sham-operated dogs confirms that the decrease observed in the present experiments was indeed due to the MI and not to surgery alone.

The mechanism by which BRS was reduced after MI is not as yet defined but is likely to involve derangements in the neural activity of cardiac origin. The central nervous system receives tonic sensory input from the atria and the ventricles by vagal afferent fibers; both may be damaged, or their function may be altered by an MI. The changes in the geometry of a beating heart secondary to the presence of a necrotic and noncontracting segment may quite conceivably increase beyond normal the firing of sympathetic and vagal afferent fibers by mechanical distortion of the sensory endings. Such a sympathetic excitation affects and impairs the baroreceptor reflex; that is, it interferes with the physiological increase in the activity of vagal fibers directed to the sinus node. Similar

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**Figure 6.** Plot of baroreflex sensitivity before myocardial infarction (MI) in 68 animals and its relation with susceptibility to sudden death after MI. In this case, the arbitrary gray zone extends from 14 to 20 msec/mm Hg. , Animals susceptible to sudden death during the exercise and ischemia test. , Animals that died suddenly during the first 4 weeks after MI. , Animals that survived during the exercise and ischemia test. Note how few animals have baroreflex sensitivity less than 9 msec/mm Hg. For further details, see text.

**Table 2. Baroreflex Sensitivity Before Myocardial Infarction and Sudden Death in Dogs After Myocardial Infarction**

<table>
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<tr>
<th>Baroreflex sensitivity (msec/mm Hg)</th>
<th>Sudden death (n)</th>
<th>Percentage</th>
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<td>&gt;20</td>
<td>9/26</td>
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<td>14–20</td>
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<td>&lt;14</td>
<td>17/20</td>
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n, 68 dogs.
effects have unexpectedly been reported also after activation of vagal afferents by posterior ischemia.30

Alternatively or in combination, a reduction in the upstroke velocity of arterial blood pressure, secondary to a diminished myocardial contractility, could affect the discharge of the carotid sinus and aortic nerves resulting in the attenuation of the baroreceptor reflex.31 Against this possibility seems to mitigate the recent finding, among patients after MI, of no correlation between BRS and several variables of left ventricular function.14 So far, there is nothing to suggest that the BRS reduction after MI depends on alterations involving the carotid baroreceptors or the sinus node response to acetylcholine. The possibility of an alteration of the central integration of the baroreceptor input cannot yet be discounted.

**Baroreflex Sensitivity and Sudden Death**

This study, performed in almost 200 conscious dogs 1 month after an anterior MI, demonstrates conclusively that a depressed (<9 msec/mm Hg) BRS identifies a subgroup of animals at very high (91%) risk for developing ventricular fibrillation during an episode of acute myocardial ischemia. It has also been possible to identify a level of BRS (>20 msec/mm Hg) above which this risk for sudden death is remarkably low (12%).

The unusually large number of animals studied was necessary to allow reasonably accurate conclusions in terms of risk. BRS proved to be a highly specific (93%) test with a satisfactory sensitivity (58%).

The decision to examine BRS in normal dogs and to relate it to the occurrence of sudden death after the production of an MI in the same animals has disclosed an intriguing and exciting fact. Indeed, before this study, the possibility that the analysis of autonomic reflexes in normal individuals might identify a subgroup at increased risk for sudden death after the occurrence of an MI had not even been considered. The present results show that normal dogs with a BRS less than 14 msec/mm Hg have a very high risk (85%) of dying suddenly either during the first few days after an MI or during a transient ischemic episode associated with a submaximal exercise stress test.

An important concept is that the wide differences in BRS already present in the normal animals reflect individual variability; myocardial infarction displaces the entire range toward lower values, thus increasing the chances for a condition associated with a higher risk.

Because the initial report of an association between depressed BRS in animals after MI and susceptibility to sudden death has already led to prospective studies in patients after MI11–14, the present finding indicating that this association is present also in animals without an MI opens a range of possibilities with significant clinical implications. A rational analysis of the latter requires, however, an understanding of pathophysiological mechanisms underlying these observations.

**Baroreflex Sensitivity and Sudden Death: Mechanisms**

Why are the animals with the most depressed BRS more vulnerable to malignant arrhythmias? A depressed BRS reflects reduced vagal activity that is probably combined with elevated sympathetic activity, although the vagal component is largely dominant.22 This concept derives from the observation that baroreflex sensitivity increases after β-blockade in most,32–36 but not all,37,38 studies. The lack of univocal results may partly be explained by the findings that β-blockade increases BRS only among patients less than 40 years of age39 and that in our experimental model this seems to happen only among susceptible animals.36 Along the same lines, Goldstein40 found that BRS is inversely correlated with plasma norepinephrine. Thus, it seems that the heart-rate response to elevations in blood pressure, which is primarily due to vagal activation, is also modulated by the opposing effect of either tonic or phasic sympathetic activity. This means that the susceptible animals are likely to have an autonomic imbalance resulting in a relative sympathetic dominance.

Three issues have to be examined: the effects of sympathetic and of vagal activity on cardiac electrical stability and the relation between autonomic effects at the sinus node and at the ventricular level.

Enhancement of susceptibility to ventricular fibrillation due to augmented sympathetic activity has been repeatedly demonstrated, particularly in the setting of acute myocardial ischemia.1–5,41–44 In the present study, sympathetic hyperactivity is deleterious not only because of its direct electrophysiological effects but also because it produces a further increase in an already physiologically elevated heart rate. This, in turn, increases the severity of ischemia and precipitates ventricular fibrillation.

The relation between vagal activity and ischemia-related malignant arrhythmias has been less clearly defined, particularly in the conscious state.3,45 Most studies have shown protective effects of vagal stimulation, electrical or pharmacological.46–52 Detrimental effects of vagotomy53,54 or of atropine administration55 have also been reported, but results are less concordant55,56 and seem to largely depend on the site of coronary occlusion.57 Vagal stimulation protects also from reperfusion arrhythmias.58 Recently, a method has been developed to perform electrical vagal stimulation in the conscious dog,8 and it has been found that in the present model of combined exercise and ischemia it has a striking antifibrillatory effect, which is largely dependent on the heart rate reduction.59 Even if the potential for direct vagal effects on ventricular electrophysiological properties exists,60–62 an important component is the antagonism of adrenergic influences.53–66 The enhancement of vagal effects in the presence of elevated sympathetic activity67 is particularly important in our preparation that involves both exercise and myocardial
ischemia. This “accentuated antagonism”\textsuperscript{68} is present also in the conscious dog.\textsuperscript{69} Thus, a greater electrical stability can be expected in those individuals capable of more powerful vagal responses. Whether due to direct electrophysiological actions or, as it seems more likely, to a reduced heart rate with beneficial anti-ischemic effects, this protective role of vagal activity is critical for the understanding of our results that show protection from ventricular fibrillation in those animals with unimpaired baroceptive reflexes.

Does a powerful baroreceptive reflex imply that the obviously augmented vagal activity to the sinus node extends to the ventricles as well? The high specificity of the cardiac innervation,\textsuperscript{70,71} the central organization of cardiovascular reflexes,\textsuperscript{72} and a recent article by Inoue and Zipes\textsuperscript{73} indicate clearly that this extrapolation is unwarranted. A heart-rate response typical of increased vagal activity does not at all exclude the possibility of dominant sympathetic activity at ventricular and vascular levels (e.g., the diving reflex, hypoxia, and inferior myocardial ischemia). However, the most frequent reflex response is synergistic, that is, one limb of the autonomic nervous system is excited with simultaneous inhibition of the other limb.\textsuperscript{72} Few facts are relevant here. The reduction in rate produced by the baroreflex is accompanied by a reflex withdrawal of sympathetic activity that is generalized and extends to the ventricles. The animals with higher BRS are also those with significant reductions in heart rate during acute myocardial ischemia despite continuation of exercise\textsuperscript{7,9}; thus, those animals that respond with strong vagal reflexes to blood-pressure increases are likely to respond similarly to acute myocardial ischemia or at least to inferior wall myocardial ischemia. The animals with the greatest sinus node response to the baroreflex test are those less prone to sudden death during myocardial ischemia, and conversely, those with the most reduced BRS are those more vulnerable to ventricular fibrillation. This does not mean that the baroreflex test predicts the autonomic changes at ventricular level during myocardial ischemia but indicates that the baroreflex test can often predict the outcome during an ischemic episode, which is what really matters. Although, as correctly stated,\textsuperscript{73} the use of spontaneous or reflex changes in heart rate as an indicator of what might happen at the ventricular level would certainly be naive, their use to identify individuals at varying risk of life-threatening events seems a promising exploitation of the current notions of cardiovascular pathophysiology.

**Baroreflex Sensitivity and Sudden Death: Clinical Implications**

The results of the present study have multiple clinical implications. The single most important finding is that, independently from the presence of a myocardial infarction, a depressed BRS, as assessed by the intravenous bolus injection of phenylephrine, can correctly identify a relatively large group of animals at very high risk of developing ventricular fibrillation during acute myocardial ischemia.

The preliminary data from the ongoing prospective study on patients after MI\textsuperscript{13} bear a striking similarity with the experimental results. The BRS of the deceased patients is markedly lower than that of the survivors, independently of infarct location. Moreover, among patients with depressed BRS (>1 SD below the mean), mortality was 40% compared with 2.9% among the other patients. Among patients after MI, mortality is inversely correlated with heart-rate variability.\textsuperscript{74,75} A careful analysis by Bigger and others\textsuperscript{76} provides additional evidence for a decreased parasympathetic activity among the patients with reduced heart-rate variability. These three clinical studies\textsuperscript{13,74,75} indicate that the risk of a subsequent cardiac death for patients after MI increases when either a depressed BRS or a reduced heart-rate variability is present. Both conditions suggest the presence of a derangement in the autonomic balance due to a reduced vagal activity probably associated with increased sympathetic activity.

The growing understanding of the mechanisms and conditions underlying states of increased susceptibility to ventricular fibrillation might guide new strategies for prevention. The demonstration that daily exercise improves depressed BRS and reduces the incidence of sudden death in dogs after MI\textsuperscript{10} and that vagal stimulation during acute myocardial ischemia is not only highly protective but is also feasible in the conscious state\textsuperscript{59} are relevant examples of new approaches for the prevention of sudden cardiac death.

**Acknowledgments**

A study carried out over a 7-year period is based on the contributions of too many to allow a fair recognition. This study would have not been possible without the inspiration and support of our late partner and friend, Dr. H.L. Stone. Critical contributions to the organization and structure of the animal core including methodological refinements have been provided by Drs. S.S. Hull and R.D. Stith. We are grateful to Dr. D. Cerati for contributions to the data analysis and to D.T. Dickey, B.R. Fitts, and G. Stout for their technical assistance.

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