Unexpected Interaction Between β-Adrenergic Blockade and Heart Rate Variability Before and After Myocardial Infarction

A Longitudinal Study in Dogs at High and Low Risk for Sudden Death

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Background Heart rate (HR) variability is a marker of tonic cardiac autonomic activity and contributes in assessing risk for sudden death after myocardial infarction. Recent clinical observations have indicated that attenuation of HR variability, which occurs after myocardial infarction, may be transient. This study addresses the issue of whether autonomic control of heart rate recovers at different rates after myocardial infarction in subjects at high and low risk for ventricular fibrillation (VF).

Methods and Results Thirty dogs, 22 with myocardial infarction and 8 sham-prepared animals, completed the study. Changes and recovery in cardiac autonomic activity after myocardial infarction were examined by measuring HR variability before and at defined intervals during the first 30 days after infarction. Each HR variability measurement was made before and after β-blockade in dogs at high (n=10) and low (n=12) risk for VF. Arrhythmia risk was determined on the basis of development of VF during exercise and transient myocardial ischemia 30 days after infarction. No sham-prepared animals developed VF. Preinfarction measurements of HR variability were not different between the groups before β-blockade, but HR variability increased much more in response to β-blockade in animals destined to be resistant compared with susceptible animals (289±26 to 369±35 msec, Δ27.7%, versus 270±36 to 283±34 milliseconds, Δ4.8%, respectively, P<.01). Immediately after infarction, HR variability was significantly attenuated in all dogs, but in the resistant dogs it recovered to pre-myocardial infarction levels within 10 days. After the infarction, β-blockade did not increase HR variability in either group of animals. Postoperative increases in HR variability from β-blockade were preserved in the sham group. Susceptible animals were characterized by a persistent attenuation of HR variability throughout the 30 days.

Conclusions The depression in HR variability produced by myocardial infarction has a clearly different temporal recovery pattern between low- and high-risk animals. After myocardial infarction, β-adrenergic blockade does not alter HR variability, thus preserving its predictive value. Before myocardial infarction, however, β-blockade increases HR variability only in the animals destined to be at low risk for lethal arrhythmias after the infarction. The recovery pattern of HR variability after myocardial infarction may contribute to the early recognition of individuals at high risk for sudden death. (Circulation. 1994;90:976-982.)

Key Words • heart rate • myocardial infarction • death, sudden • nervous system • receptors, adrenergic, beta

Cardiac autonomic balance, measured by heart rate (HR) variability,1,2 is altered early after myocardial infarction in humans3-7 and in experimental animals.8 Quantification of this alteration can predict mortality after myocardial infarction, especially the risk for arrhythmic death.3-7 Clinical observations show a trend toward significant recovery of cardiac autonomic activity within the first 2 months after myoccardial infarction.9 By 1 year, autonomic recovery does occur,10,11 but measurements are still attenuated compared with noninfarcted control subjects.12 Previous studies that examined autonomic recovery after myocardial infarction reported large variances12 in the measures of HR variability, indicating that the groups comprised subjects having a wide range of effective vagal control of heart rate, possibly at different levels of recovery or destined never to recover. Still, these studies have contributed to generation of the concept that vagal control of heart rate ultimately recovers after myocardial infarction. Recent observations indicate that depressed HR variability identifies high-risk patients even 2 years after myocardial infarction,13 which is potentially in conflict with the concept of time-dependent vagal recovery. Therefore, the temporal recovery patterns of HR variability after myocardial infarction remain controversial and clinically relevant.

Another unanswered question of clinical importance is how β-adrenergic blockade affects HR variability after myocardial infarction. Kleiger and colleagues4

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showed that mortality was reduced by use of β-blockers after myocardial infarction, but low HR variability (<50 milliseconds) in the presence of adrenergic blockade was still associated with twofold increase in mortality compared with patients on β-blockers, who had higher HR variability (>50 milliseconds). Cook et al. found that HR variability showed a moderate increase during β-adrenergic blockade in young healthy subjects, but the relevance of these results to older patients after myocardial infarction is unknown. A recent study in patients after myocardial infarction showed an increase in HR variability after β-adrenergic blockade, but the significance is obscure, since the sample size of the population used in the study was not reported. Overall, clinical studies are limited by their inability to provide information on a most critical issue: namely, whether or not a change in any given autonomic marker is associated with a change in risk status. The present study was designed to test the hypothesis that recovery of cardiac autonomic activity after myocardial infarction has prognostic significance.

Methods

Overview

Thirty dogs, 22 with a small anterior wall myocardial infarction and 8 prepared with the surgical procedure but no infarction (sham), completed the study. Each animal underwent HR variability analyses before and after β-blockade several days before the myocardial infarction and periodically during the 30 days immediately after the infarction. On day 30, each dog underwent an exercise test coupled with transient myocardial ischemia, and the outcome of the test determined risk status for sudden death: animals experiencing ventricular fibrillation during the transient myocardial ischemia were labeled susceptible (n=10), and those without ventricular fibrillation were labeled resistant (n=12). Values of HR variability were then correlated with risk status to assess the predictive value of the test.

Surgical Preparation

The surgical procedure used to create the myocardial infarction has been described in detail. Briefly, during anesthesia, the heart was exposed via a left fifth intercostal space thoracotomy, an arterial catheter was implanted in the aortic arch, and a Doppler flow probe (20 MHz) and distally placed pneumatic occluder were implanted around the circumflex branch of the left coronary artery. The left anterior descending coronary artery was ligated immediately proximal to the first major diagonal branch after a 30-minute subtotal stenosis. All instrumentation leads were exteriorized on the dorsal neck area. The eight sham-prepared animals had the same instrumentation as outlined above, including dissection of the left anterior descending coronary artery, but the artery was not ligated.

Every dog received immediate postoperative short-term analgesics (pentazocine lactate, 1 mg/kg IM) followed by a longer-acting analgesic (nalbuphine HCl, 0.5 mg/kg IM). Guidelines (National Institutes of Health, American Physiological Society, and American Heart Association) pertaining to the appropriate care and use of animals were strictly followed.

Acclimation to the Recording Environment

Our previous experience indicates that HR variability measurements are significantly altered after the dogs are acclimated to the recording environment and personnel. Therefore, each animal underwent measurement protocols several days before the actual recording period began. Additionally, if the HR was deemed to be too high compared with baseline measurements or if the behavior was considered to be inappropriate for basal autonomic recordings, measurements were postponed and redone after further acclimation. HR variability was not measured if any animal had signs of overt clinical illness.

Exercise and Ischemia Test

Dogs were evaluated for the risk of lethal arrhythmias by use of submaximal exercise stress tests on a motor-driven treadmill according to a protocol previously described. Specifically, dogs were exercised for approximately 12 to 15 minutes while the workload progressively increased every 3 minutes (3 mph at 0% grade, 4 mph at 0% grade, 4 mph at 4% grade, 4 mph at 8% grade, and 4 mph at 12% grade). The circumflex coronary artery was occluded when heart rate reached a target level of 210 to 220 beats per minute, which represents approximately 70% of the maximal heart rate attainable in a dog. Our experience with this protocol showed that vagal activity at this level of exercise is progressively but never completely withdrawn because it can be further modulated by vagolytic interventions. Continuous measurement of transthoracic ECG, beat-to-beat HR (from the ECG signal), phasic and mean arterial blood pressures, and phasic blood flow through the circumflex coronary artery were transcribed simultaneously on a direct-writing oscillograph (model 7D, Grass) while the dog initially stood on the treadmill and throughout the exercise stress test. When the target heart rate was reached, the pneumatic occluder surrounding the circumflex coronary artery was inflated for 2 minutes. The animal continued to exercise during the first minute, and exercise was stopped during the second minute. Ventricular fibrillation occurred in 10 of 22 dogs (45%) (susceptible), and those animals were defibrillated immediately. The remaining 12 animals (55%) had no sustained ventricular arrhythmias during exercise and myocardial ischemia (resistant). The occurrence of ventricular fibrillation in this model is known to be highly reproducible.

HR Variability

HR variability was measured in each animal, without and with β-blockade (atenolol 1 mg/kg IV), before the myocardial infarction and on days 5, 9, 13, 17, 21, 25, and 29 after the infarction. The preinfarction ECG recording was made after at least 7 days of laboratory acclimation. For all recordings, 25-minute ECG samples were obtained while the dogs were resting quietly, but not sleeping, on a padded and warmed table. The recording room was locked and kept quiet during data acquisition. Detailed methodology has been described. Briefly, a transthoracic modified lead I ECG was amplified (Grass 7P4 H), filtered at a low frequency (5 Hz) and high frequency (500 Hz), and digitized at 400 Hz. All digitally encoded files were analyzed with a commercially available program (Corazonix Corp). Premature ventricular complexes and their adjacent RR intervals were rejected by the software, in addition to electrical noise or other aberrant ECG signals. HR variability measurements were made only on visually confirmed sinus rhythm recordings. The RR interval data from 25 minutes of continuous ECG recordings were plotted as a frequency histogram distribution using 4-millisecond bins from which the mean RR interval and its SD were derived. Since the SD of the mean RR interval is influenced by the prevailing HR, another measurement, the coefficient of variance (quotient of the SD of the mean RR interval and the mean RR interval x 1000), was calculated to normalize HR variability to HR.

Infarct Size Estimation

When the experimental protocols were completed, the animals were killed with an overdose of pentobarbital (100 mg/kg IV), and the hearts were immediately removed. Infarct size was measured in 8 of the 10 susceptible and 11 of the 12
resistant dogs with the tetrazolium enzymatic staining technique. The left ventricle was isolated and cut through a line perpendicular to the long axis from the apex in 1-cm slices and incubated at 38°C in a buffered 5% tetrazolium blue solution for 20 minutes. The infarct zone was identified by only two investigators (P.B.A., E.V.) to avoid excessive subjective variation. Normal and infarcted tissues were then carefully dissected, and the infarct size was expressed as a percentage of total left ventricle and septal wall mass.

Statistics

Statistical significance of the data was determined by ANOVA suitable for repeated measures, and mean differences were assessed with Tukey's test. Data are presented in the test as the mean±SEM unless otherwise noted. An α level of P<.05 was considered statistically significant, and changes are significant unless otherwise noted.

Results

Heart Rate

HRs in all groups of dogs were equivalent before surgery (Fig 1A). After myocardial infarction, HRs were persistently higher in susceptible animals throughout the recording period (76±5 beats per minute pre-infarction versus 89±5 beats per minute day 29 after infarction, P<.05). Compared with preinfarction conditions, resting HRs in resistant dogs were higher immediately after the infarction but were not significantly different by day 17 (72±4 beats per minute preinfarction, 82±4 beats per minute day 5 after infarction, 76±5 beats per minute day 17 after infarction). Sham-prepared dogs had a transient elevation in heart rate after surgery but returned to presurgical levels within 5 days (Fig 1A).

Atenolol significantly reduced HR before surgery in all dogs as shown in Figs 2A (resistant), 3A (susceptible), and 4A (sham). Early after myocardial infarction, adrenergic blockade had no influence on heart rate (Figs 2, 3, and 4), but its effect became evident in all dogs from day 5 after surgery.

SD of the Mean RR Interval

SD of the mean RR interval measurements before the infarction were not different between groups (289±26 milliseconds, resistant; 270±36 milliseconds, susceptible; 285±24 milliseconds, sham; Fig 1B). However, before surgery an important difference already
The effects of atenolol on the SD of the mean RR interval after surgery are shown in Figs 2B, 3B, and 4B. Only on day 5 after myocardial infarction, but not thereafter, did β-blockade slightly but significantly increase the SD of the RR intervals in the resistant animals (from 178±22 to 215±23 milliseconds; P=.02) (Fig 2B). β-Blockade did not significantly alter the SD of the RR intervals in the susceptible animals before or at any point after myocardial infarction (Fig 3B). In contrast to the infarcted animals, sham-prepared dogs had significant changes in SD of the mean RR interval after β-blockade before and on each day after surgery (Fig 4B).

Coefficient of Variance

To ensure that the changes in HR variability after myocardial infarction and β-blockade were not simply due to changes in HR, the coefficient of variance was calculated to normalize HR variability to the prevailing HR (SD of the mean RR interval/mean RR interval×1000). Baseline values for the coefficient of variance from all dogs before and after surgery are shown in
Fig 1C. Before myocardial infarction, the groups were not different. Measurements for resistant and susceptible animals decreased early after myocardial infarction but were different between the two groups of dogs by 9 days (303±21 versus 194±29, respectively, P<.001). This significant difference was maintained for each recording thereafter. Coefficient of variance values in sham animals were not significantly changed by the surgical intervention (300±27 presurgery versus 275±50 at day 5 postsurgery, P=.42).

Coefficient of variance measurements increased significantly in response to β-adrenergic blockade before surgery in the resistant dogs (from 331±21 to 368±24; P<.05) (Fig 2C) and sham dogs (from 300±27 to 349±49; P<.05) (Fig 4C). In contrast to these groups, the preinfarction coefficient of variance from the susceptible animals had a trend toward decrease after β-blockade, but the change did not reach statistical significance (from 327±33 to 302±24, P=.20) (Fig 3C).

After surgical intervention, the coefficient of variance increased significantly after β-blockade only in the sham animals (Figs 2C, 3C, and 4C).

Infarct Size Estimation

Hearts from 8 of the 10 susceptible and 11 of the 12 resistant animals were available for infarct size estimation. The myocardial infarction averaged 13.4±0.9% (range, 9.5% to 16.4%) of the left ventricular mass in the susceptible animals and 13.6±1.6% (range, 9.0% to 27.2%) in the resistant dogs (P=NS).

Discussion

The present study provides a longitudinal analysis on the evolution of HR variability after a myocardial infarction with two features not readily available in clinical investigations. One is the comparison of HR variability after myocardial infarction with values before the infarction, which allows a correct assessment of the extent of recovery; the other is the comparison between animals at low and at high risk for sudden cardiac death, which allows a refined assessment of the prognostic value of HR variability. Three main findings emerged, and they all have significant clinical implications.

The first is that myocardial infarction produces a depression in HR variability that shows a strikingly different temporal evolution between low- and high-risk animals. Among resistant dogs, the depression is quite transient, since HR variability returns to pre-myocardial infarction values within 10 days. In contrast, HR variability in susceptible dogs remains significantly depressed at 1 month after the infarction.

The second finding is that after myocardial infarction, β-adrenergic blockade, highly effective in preventing ventricular fibrillation in this animal model,20,21 does not alter HR variability. Specifically, the expected increase in HR variability after β-adrenergic blockade is absent in all dogs after myocardial infarction. Thus, treatment with β-blockers would not be a confounding factor in the analysis of HR variability.

The third finding is the unexpected and intriguing observation that before myocardial infarction, β-blockade increases HR variability only in the animals destined to be at low risk for lethal arrhythmias after the infarction. This raises the possibility that individuals at high risk for arrhythmic death after a myocardial infarction can be identified very early, even before the infarction.

HR Variability After Myocardial Infarction

Previous clinical studies found that HR variability is diminished within 2 weeks after myocardial infarction3-7,9,10,12 and significantly recovers within 6 months to 1 year.9,10,12 In contrast, cardiac sympathetic activity increases after acute myocardial infarction and decreases over time.8 Parallel to these observations is the decrease in baroreflex sensitivity that takes place shortly after myocardial infarction and that recovers between 1 and 3 months.11

The design of the present study has provided information about several issues that are not easily obtained in clinical studies. After myocardial infarction, both low- and high-risk animals underwent repeated assessments of HR variability. The objective and noncontroversial occurrence of ventricular fibrillation was used to identify the high- and low-risk animals. Recovery patterns after the infarction and the influence of β-blockade on HR variability were examined separately by internal control analysis. Most importantly, 30 days after the myocardial infarction, all dogs were exposed to the same situation of risk, namely, a brief episode of acute myocardial ischemia in the presence of a healed myocardial infarction while sympathetic activity was elevated physiologically by exercise. This step provides a fundamental difference from clinical studies. Indeed, depending on the extent of their coronary artery disease, many patients may never experience a new ischemic event. They therefore escape the true assessment of their arrhythmic risk.

The particular conditions of the exercise and ischemia test apply specifically to arrhythmias, which are mechanistically related to myocardial ischemia coupled with elevated sympathetic activity. The applicability of findings generated from this canine model of autonomically mediated ventricular arrhythmias during myocardial ischemia to clinical sudden cardiac death has recently been reviewed.22

The present data indicated that HR variability recovered in the resistant animals within 10 days of the infarction and at that time was similar to that of the noninfarcted sham-operated animals. Depression in HR
variability was not due to the stress of the thoracotomy, since the sham-operated animals had insignificant changes in HR variability after the surgery. Additionally, the recovery patterns observed were not due to differences in the infarct size, which, consistent with previously published data from our laboratory, were not different between the resistant and susceptible animals. Thus, the different recovery characteristics in cardiac autonomic activity between the two groups of animals did not depend on differences in the extent of left ventricular damage from the coronary artery ligation.

**HR Variability and β-Blocker Therapy**

The widespread use of β-adrenergic blocking therapy in post–myocardial infarction patients has generated concerns about the validity of risk stratification by HR variability; ie, therapy may modify the risk marker. Kleiger et al performed a subanalysis in patients treated with β-blockers and reported that 24-hour HR variability of <50 milliseconds was still associated with increased mortality compared with patients treated with β-blockers but with HR variability of >50 milliseconds. However, their study was not designed to determine whether β-blockers influence HR variability. Cook et al addressed this issue in normal young healthy adults and showed that HR variability increases after β-adrenergic blockade with atenolol.

These results are in agreement with our findings in the sham-prepared dogs and in the resistant animals before the myocardial infarction. However, the β-blocker–mediated increase in HR variability was no longer present after myocardial infarction. Additionally, after myocardial infarction, HR variability measured before and after β-blockade accurately predicted risk status in this population. Thus, β-adrenergic blockade does not impair the capability of HR variability to discriminate high- and low-risk subjects after myocardial infarction.

**Autonomic Activity Before Myocardial Infarction**

We have previously reported that baseline measurements of HR variability before myocardial infarction were not able to discriminate between resistant and susceptible dogs. This is at variance with the fact that baroreflex sensitivity is already lower before the infarction in the susceptible compared with the resistant animals. Both these findings were supported by a study in which “tonic” and “reflex” cardiac vagal efferent activity (assessed by the single-fiber recording technique) was measured in anesthetized cats before coronary artery occlusion. The animals destined to develop ventricular fibrillation during myocardial ischemia showed a marked impairment in the capability to increase vagal efferent activity in response to a blood pressure rise, ie, the baroreceptor reflex, but were not different in terms of “tonic” activity from the animals destined to survive. The present study adds a significant piece to this puzzle by showing that, before myocardial infarction, the response of HR variability to β-blockade is already different between the dogs destined to become resistant and susceptible after the infarction.

Taken together, these data strongly support the concept that there is great individual diversity in the autonomic make-up of normal individuals and that this diversity already contains important information pertaining to arrhythmic risk in case of future ischemic events. However, the mechanism underlying this difference remains a matter of speculation.

The previously reported increases in HR variability after β-blockade have been interpreted as being largely secondary to central modulation of cardiac reflexes, partly on the basis of reports that atenolol decreases tonic and reflex renal sympathetic nerve activity. This explanation, however, has to contend with the fact that atenolol does not cross the blood–brain barrier. The present data suggest that the proposed parasympathomimetic effect of atenolol either was lost or was much less effective in susceptible animals, thus producing the different responses to β-blockade that we had observed before myocardial infarction. This might reflect an individual predisposition of either genetic or environmental origin.

A tentative explanation for the differential effect of atenolol on HR variability before the infarction is possible. β-Blockade reduces the sensitivity of cardiac sympathetic afferents and therefore can be expected to dampen transient increases in sympathetic afferent activity. As a consequence, this reveals differences in cardiac vagal efferent activity resulting in higher HR variability in the resistant animals. Reduced baroreflex sensitivity among susceptible dogs before myocardial infarction has already indicated that these animals are less able to augment cardiac vagal activity. Similarly, one might expect that HR variability in dogs destined to become susceptible is also less likely to respond to β-blockade.

The occurrence of a myocardial infarction might further depress vagal efferent activity to act on the premorbid differences in autonomic activity found between high- and low-risk individuals. Vagal efferent depression probably occurs through a sympathovagal reflex resulting from the myocardial infarction. Increased sympathetic afferent traffic secondary to the mechanical consequences of the necrotic scar would produce inhibitory effects at the level of the central nervous system. The present results clearly indicate that further studies on the sympathovagal interaction in the central nervous system are needed to better understand the relation between the autonomic nervous system and the propensity toward sudden cardiac death.

Independent of the correct underlying mechanism, the finding that β-blockade produces different responses in HR variability according to the future risk of lethal arrhythmias during an ischemic episode opens exciting perspectives for early risk stratification among still healthy individuals. Highly relevant in this respect is the recent finding that exercise training improves all autonomic markers of vagal activity and strikingly reduces the risk for ventricular fibrillation not only in infarcted animals but also in animals with normal hearts. These data suggest that the combination of baroreflex sensitivity assessment and the response of HR variability to β-blockade may provide early identification of individuals potentially at risk for sudden death. These individuals, once identified, may be protected by a nonpharmacological intervention such as exercise training.
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References
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