Heart rate response to onset of exercise: evidence for enhanced cardiac sympathetic activity in animals susceptible to ventricular fibrillation

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Billman, George E. Heart rate response to onset of exercise: evidence for enhanced cardiac sympathetic activity in animals susceptible to ventricular fibrillation. Am J Physiol Heart Circ Physiol 291: H429–H435, 2006. First published February 24, 2006; doi:10.1152/ajpheart.00020.2006.—A large heart rate (HR) increase at the onset of exercise has been linked to an increased risk for adverse cardiovascular events, including cardiac death. However, the relationship between changes in cardiac autonomic regulation induced by exercise onset and the confirmed susceptibility to ventricular fibrillation (VF) has not been established. Therefore, a retrospective analysis of the HR response to exercise onset was made in mongrel dogs with healed myocardial infarctions that were either susceptible (S, n = 31) or resistant (R, n = 114) to VF (induced by a 2-min occlusion of the left circumflex artery during the last minute of exercise). The ECG was recorded, and time series analysis of HR variability (vagal activity index, the 0.24–1.04-Hz frequency component of R-R interval variability) was measured before and 30, 60, and 120 s after the onset of exercise (treadmill running). Exercise elicited significantly (ANOVA, P < 0.0001) greater increases in HR in susceptible dogs at all three times (e.g., at 60 s: R, 46.8 ± 2.3 vs. S, 57.1 ± 2.2 beats/min). However, the vagal activity index decreased to a similar extent in both groups of dogs (at 60 s: R, −2.8 ± 0.1 vs. S, −3.0 ± 0.2 ln ms2). β-Adrenoceptor blockade (BB, propranolol 1.0 mg/kg iv) reduced the HR increase and eliminated the differences noted between the groups [at 60 s: R (n = 26), 40.4 ± 3.2 vs. S (n = 31), 37.5 ± 2.4 beats/min]. After BB, exercise once again elicited similar declines in vagal activity in both groups (at 60 s: R, −3.6 ± 0.5 vs. S, −3.2 ± 0.4 ln ms2). When considered together, these data suggest that at the onset of exercise HR increases to a greater extent in animals prone to VF compared with dogs resistant to this malignant arrhythmia due to an enhanced cardiac sympathetic activation in the susceptible dogs.

β-adrenergic receptors; cardiac parasympathetic activity; heart rate variability; sudden cardiac death

THE IDENTIFICATION OF PATIENTS at the greatest risk for adverse cardiovascular events remains a major clinical challenge. It is well established that alterations in the cardiac autonomic regulation are linked with an increased risk for sudden cardiac death (12, 29). In particular, an enhanced cardiac sympathetic activation, coupled with an attenuated parasympathetic regulation, decreases the electrical stability of the heart and thereby facilitates the formation of malignant arrhythmias (12, 29). The quantification of this cardiac autonomic imbalance should help identify the patients with the greatest risk for life-threatening cardiac rhythm disorders, including ventricular fibrillation.

Numerous studies (2, 3, 6, 8, 11, 17, 22, 23, 32) have, in fact, demonstrated that low heart rate variability, typically measured over a 24-h period, or a reduced response to baroreceptor activation (baroreflex sensitivity) identifies postmyocardial infarction patients (or animals) at a high risk for lethal arrhythmias. For example, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) group found that postmyocardial infarction patients with either low heart rate variability or a reduced baroreceptor reflex sensitivity had a much greater risk of sudden death than those individuals with a well-preserved cardiac autonomic regulation (23). The greatest risk for mortality was observed in patients with a large reduction in both markers of cardiac autonomic regulation (23). However, there is, as yet, no consensus on what is the best heart rate variability technique to use, and a standardization of commercial systems is currently lacking (20). Furthermore, many of these autonomic markers require complex data processing techniques that are not readily available in the clinical setting. Simple and inexpensive markers of cardiac autonomic regulation are required to identify patients with the greatest risk for cardiac mortality.

Exercise stress testing is commonly employed in most clinics to evaluate patients for the presence of coronary artery disease. Exercise-induced changes in heart rate could provide an economical means of identifying patients at risk for subsequent adverse cardiac events. Recently, an elevated heart rate increase at the onset of exercise has been linked to an increased risk for adverse cardiovascular events, including death (16). Patients with documented coronary artery disease that exhibited the largest increase in heart rate at exercise onset also had a greater risk for cardiac events (cardiac deaths and nonfatal myocardial infarctions) than did those subjects with a more modest heart rate increase. These authors (16) concluded that the change in heart rate elicited by exercise was a strong independent marker of risk for adverse cardiac events. Exercise provokes increases in heart rate both by increasing sympathetic and by reducing parasympathetic activity (28). The relative contribution of the withdrawal of the cardiac parasympathetic regulation or the activation of cardiac sympathetic nerves to the heart rate increase was not investigated in this study. These authors (16) did, however, speculate that the increase most likely reflected a rapid withdrawal of ongoing parasympathetic tone rather than as a result of the cardiac sympathetic nerve activation. It should also be noted that in this study the diagnosis of cardiac death was determined either by interviews of the next of kin, by interviews of the family physician, or from death certificates. As such, the number of deaths that resulted specifically from lethal arrhythmias was not determined. Thus the specific relationship between changes in cardiac autonomic regulation induced by exercise onset and the confirmed susceptibility to ventricular fibrillation has not been established.

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It was, therefore, the purpose of this study to investigate the relationship between the heart rate response to the onset of exercise, cardiac autonomic (both sympathetic and parasympathetic) regulation, and susceptibility to malignant arrhythmias. In particular, the hypothesis that an enhanced sympathoexcitatory activation rather than an accelerated parasympathetic inhibition with the corresponding increase in heart rate at exercise onset would be associated with an increased risk for ventricular fibrillation was tested. Time series analysis of heart rate variability was used to evaluate cardiac parasympathetic regulation in dogs with healed myocardial infarction that were subsequently found to be either susceptible or resistant to ventricular fibrillation. The sympathetic component of the heart rate response to exercise onset was evaluated by using the \( \beta \)-adrenoceptor antagonist propranolol.

**METHODS**

The principles governing the care and use of animals as expressed by the Declaration of Helsinki and as adopted by the American Physiological Society were followed at all times during this study. In addition, the Ohio State University Institutional Animal Care and Use Committee approved all the procedures used in this study.

Archived data from 245 (167 females and 78 males; weight, 17.9 ± 0.2 kg; age, 1–3 yr) heartworm-free, purpose-bred mongrel dogs were used in this study. A consecutive sequence of animals in which the ECG signal was of sufficient quality to determine heart rate variability rate throughout a submaximal exercise test was selected. In a subset of these animals (\( n = 57 \): males, \( n = 15 \); and females, \( n = 42 \)), the submaximal exercise test was also performed after pretreatment with the \( \beta \)-adrenoceptor antagonist propranolol HCl.

**Surgical preparation of canine model.** The surgical preparation of the dogs has been described in previous publications (5, 6, 8, 11, 18, 30). Briefly, the dogs were anesthetized, and, with the use of strict aseptic techniques, a left thoracotomy was made in the fourth intercostal space. The heart was exposed and supported by a pericardial cradle. A hydraulic occluder and a 20-MHz Doppler flow transducer were placed around the left circumflex coronary artery. Insulated silver-coated copper wires were sutured to the epicardial surface of the left and right ventricle for later use in recording a ventricular electrogram. The left anterior coronary artery was ligated, producing an anterior-wall myocardial infarction. All leads to the instrumentation were tunneled under the skin to exit at the back of the neck. Dogs were medicated to control postoperative pain and infection as described previously (5, 18).

**Exercise protocol.** Three to four weeks after surgery, the animals were trained to walk on a motor-driven treadmill for several days to familiarize them with the laboratory. Preexercise values of all the variables were obtained while the animals were standing on the treadmill before the onset of the running. The response to exercise was then assessed by using a submaximal exercise protocol previously described (6, 7, 18). Briefly, the treadmill exercise lasted a total of 18 min and was divided into 3-min blocks. The protocol began with a 3-min warm-up period during which the animal ran at 4.8 km/h, 0% grade. The speed was increased to 6.4 km/h, and the grade of the treadmill was increased every 3 min as follows: 0, 4, 8, 12, 16%. After the completion of 18 min of exercise, the treadmill was stopped, and the animal remained standing while the postexercise ECG was obtained.

On a subsequent day, the submaximal exercise test was repeated after pretreatment with the \( \beta \)-adrenoceptor antagonist propranolol HCl (1.0 mg/kg iv, Sigma Chemical, St. Louis, MO). Previous studies (6, 11) demonstrated that this dose of propranolol completely abolished the response to the \( \beta \)-adrenoceptor agonist isoproterenol (1 \( \mu g/kg \) iv, Sigma Chemical) (6, 11). Propranolol was given as a bolus intravenous injection via a cephalic vein 3 min before the onset of exercise using a counterbalanced design. Thus approximately one-half the animals were first treated with this \( \beta \)-adrenoceptor antagonist followed on a subsequent day by a control (no drug) exercise test, whereas the remaining dogs first received a control exercise test followed by an exercise test after treatment with the \( \beta \)-adrenoceptor antagonist.

**Susceptibility classification: exercise plus ischemia test.** The susceptibility to ventricular fibrillation was tested as previously described (5, 6, 8, 11, 18, 30). Briefly, the animals ran on a motor-driven treadmill while workload progressively increased until a heart rate of 70% of maximum (~210 beats/min) had been achieved. During the last minute of exercise, the left circumflex coronary artery was occluded, the treadmill stopped, and the occlusion maintained for an additional minute (total occlusion time, 2 min). The exercise plus ischemia test reliably induced ventricular flutter that rapidly deteriorated into ventricular fibrillation. Therefore, large metal plates (11 cm in diameter) were placed across the animal’s chest so that electrical defibrillation (Zoll M series defibrillator, Zoll Medical, Burlington, MA) could be achieved with a minimal delay, but only after the animal was unconscious (10–20 s after the onset of ventricular fibrillation). ECG was recorded throughout the test, and left circumflex coronary blood flow was measured to confirm that the coronary occlusion was complete. This exercise plus ischemia test induced ventricular fibrillation in 131 (susceptible: males, \( n = 47 \); and females, \( n = 84 \)) animals, whereas the remaining 114 (resistant: males, \( n = 36 \); and females, \( n = 78 \)) never displayed malignant arrhythmias during this test.

**Data analysis.** All data are reported as means ± SE. The data were recorded by using either a Gould model 2800S eight-channel chart recorder (Gould, Cleveland, OH) or a Biopac MP-100 data acquisition system (Biopac Systems, Goleta, CA). A ventricular electrogram was recorded by using the leads sutured to the epicardium. Coronary blood flow was measured with a University of Iowa model 545C pulsed Doppler flowmeter (Iowa City, IA). Heart rate variability was obtained by using a Delta-Biometrics vagal tone monitor triggering off the ECG R-R interval (Urbana-Champaign). This device employs the time-series signal processing techniques as developed by Porges (27) to estimate the amplitude of respiratory sinus arrhythmia. Details of this analysis have been described previously (7). Briefly, the ECG signal was digitized at 1 kHz, and sequential R-R intervals were timed to the nearest millisecond. The nonperiodic baseline fluctuations were removed by using a moving third-order 21-point polynomial function. This procedure prevented leakage of trends and harmonics of nonsinusoidal periodic activity (i.e., transient changes) into the respiratory frequency component. Once the filtering procedures had been performed, the output of the moving polynomial was processed with a digital band-pass filter to extract the variance in the 0.24–1.04 Hz frequency band. The variance measure was then transformed to its natural logarithm to normalize the distribution of the variance estimates to limit the impact of large differences (i.e., outlying values). Heart rate and heart rate variability data were averaged over 30-s intervals, beginning 3 min before the exercise onset and continuing throughout the exercise session. The following time points were evaluated in the present study: the last 30 s before the onset of exercise, 0–30 s after exercise onset, 30–60 s after exercise onset, and 90–120 s after exercise onset. These average values are reported as times 0, 30, 60, and 120 s, respectively. The following three indexes of heart rate variability were determined: vagal activity index, the high-frequency (0.24–1.04 Hz) component of R-R interval variability; R-R interval range, the difference between the longest and shortest R-R interval for the same 30-s time period; and SD of the R-R intervals for the same 30-s time period.

The data were compared by using ANOVA for repeated measures (NCSS statistical software, Kaysville, UT). For example, the effect of exercise onset on the heart rate variability data (heart rate; vagal activity index, i.e., 0.24–1.04 Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range) in the...
susceptible and resistant dogs was analyzed by using a two-way ANOVA [group (2 levels) × time (4 levels)] with repeated measures on one factor (time). A similar two-factor ANOVA with repeated measures on one factor was used to compare the effects of the β-adrenoceptor blockade (BB) on the heart rate variability response to exercise onset in the susceptible and resistant dogs. Because repeated-measures ANOVA depends on the homogeneity of covariance, this sphericity assumption (i.e., the assumption that the variance of the difference scores in a within-subject design is equal across the groups) was tested using Mauchley’s test (19). If the sphericity assumption was violated, then the F ratio was corrected with Huynh-Feldt correction (19). If the F ratio was found to exceed a critical value ($P < 0.05$), then the difference between the means was determined with Scheffé’s test.

**RESULTS**

**Susceptibility classification.** The exercise plus ischemia test induced ventricular fibrillation in 131 of the 245 (susceptible) animals, whereas the remaining 114 (resistant) dogs did not develop malignant arrhythmias. There were no sex differences between the groups. The susceptible dogs included 84 females (64.1%) and 47 males, whereas the resistant group was composed of 78 females (68.4%) and 36 males.

**Control heart rate variability measures.** The heart rate response and the change in heart rate response to exercise onset for both groups are shown in Fig. 1. These data were obtained during the first stage of the exercise stress test (i.e., with the animals running at 4.8 km/h, 0% grade). Because the heart rate responses to exercise onset were similar in both male and female dogs (e.g., change at 60 s; resistant, male 50.4 ± 4.9, female 44.5 ± 2.4 beats/min; susceptible, male 57.5 ± 3.5, female 55.8 ± 2.7 beats/min), the data were combined for all subsequent analyses. Exercise onset elicited a significant increase in heart rate (exercise effect, $F_{3/725} = 663.39$, $P < 0.0001$) with larger (group effect, $F_{1/242} = 8.96$, $P < 0.003$) increases in the susceptible dogs compared with the resistant animals at each time point (Fig. 1, *top*). The preexercise heart rate was similar in both the susceptible (127.1 ± 8 beats/min) and the resistant (126.3 ± 2.1 beats/min) dogs. As a consequence, the susceptible dogs also exhibited a significantly (group × exercise interaction, $F_{3/725} = 7.55$, $P < 0.0001$) greater change (i.e., increase) in heart rate at each time point after the onset of exercise (Fig. 1, *bottom*).

The heart rate variability and the change in heart rate variability response to exercise onset for both groups are shown in Fig. 2. Once again, there were no obvious sex differences in either the susceptible (vagal activity index, change at 60 s, female $−2.9 ± 0.2$ vs. male $−3.2 ± 0.2$ ln ms$^2$) or resistant (vagal activity index, change at 60 s, female $−2.7 ± 0.1$ vs. male $−3.0 ± 0.3$ ln ms$^2$) dogs. Therefore, the male and female data have been combined for all subsequent comparisons. Exercise onset provoked large reductions (exercise effect, $F_{3/725} = 510.5$, $P < 0.0001$) in the high-frequency component of the R-R interval variability (a marker of cardiac vagal regulation, 0.24 to 1.04 Hz). In a similar manner, heart rate variability was lower (group effect, $F_{1/242} = 8.70$, $P < 0.01$, susceptible vs. resistant animals.
0.002) in the susceptible dogs compared with the resistant animals (Fig. 2, top). However, there was no significant group × exercise interaction \([F_{3/725} = 1.32, P = 0.27\), not significant (NS)]. As such, the change in heart rate variability did not differ between the two groups of animals (Fig. 2, bottom). Similar results were obtained for R-R interval range and SD of R-R interval; exercise onset elicited similar changes in both the susceptible and resistant dogs (e.g., change at 60 s, SD of R-R interval, susceptible, \(-37.3 \pm 2.9\) vs. resistant, \(-41.5 \pm 3.0\) ms; R-R interval range, susceptible, \(-109.2 \pm 7.0\) vs. resistant, \(-111.3 \pm 7.5\) ms). These data suggest that, despite larger heart rate increases induced by the exercise onset in the susceptible compared with the resistant dogs, cardiac vagal regulation (i.e., the change in these variables) decreased to a similar extent in both groups. Thus exercise onset provoked a similar parasympathetic withdrawal in the susceptible and resistant dogs.

**Effect of BB on heart rate variability.** The exercise test was repeated in 57 dogs [susceptible \((n = 31)\): males, \(n = 7\), and females, \(n = 24\); and resistant \((n = 26)\): males, \(n = 8\), and females, \(n = 18\)]. Once again there were no obvious sex differences in the heart rate response (e.g., change at 60 s; resistant: male, 42.5 ± 5.4, and females, 44.5 ± 2.4 beats/min; and susceptible: males, 39.4 ± 3.8, and females, 39.9 ± 3.8 beats/min) for either group, and, as such, the male and female data have been combined for all subsequent analyses. The heart rate response and the change in heart rate response to exercise onset for both groups are shown in Fig. 3. BB reduced the preexercise heart rate in both groups (resistant: before BB, 126.3 ± 4.2; and after BB, 112.8 ± 4.0 vs. susceptible: before BB, 127.1 ± 3.6; and after BB, 117.7 ± 2.7 beats/min). This intervention also attenuated the heart rate response to exercise onset in both the resistant and susceptible animals and abolished the differences (group effect, \(F_{1/55} = 1.32, P = 0.26\), NS) between the two groups, such that the heart rate increase at exercise onset was similar in both groups (group × exercise interaction, \(F = 2.13, P = 0.10\), NS). In other words, after BB, exercise onset elicited similar heart rate (Fig. 3, top) and change in heart rate (Fig. 3, bottom) responses in both the susceptible and resistant dogs.

The effects of BB on the heart rate variability response and the change in heart rate variability response to exercise onset for both groups are shown in Fig. 4. Once again there were no obvious sex differences in the heart rate variability response in either the susceptible (male, \(-2.6 \pm 0.8\) vs. female, \(-3.3 \pm 0.5\) ln ms\(^2\)) or the resistant (male, \(-3.7 \pm 0.8\) vs. female, \(-3.6 \pm 0.6\) ln ms\(^2\)) dogs. Therefore, the male and female data have been combined for all subsequent analyses. BB reduced preexercise heart rate variability to a similar extent in both the susceptible (vagal activity index; before BB, 6.8 ± 3.3; and after BB, 4.8 ± 0.4 ln ms\(^2\)) and the resistant dogs (vagal
activity index; before BB, 7.2 ± 0.3; and after BB, 6.0 ± 0.4 ln ms^2). As in the control (no drug) studies, exercise onset provoked large (exercise effect, F_{3/165} = 85.11, \( P < 0.0001 \)) reductions in the high-frequency component of the R-R interval variability (a marker of cardiac vagal regulation, 0.24 to 1.04 Hz) (Fig. 4, \textit{top}). After BB, heart rate variability was lower in the susceptible dogs (group effect, \( F_{1/55} = 4.84, P < 0.04 \)). However, the change in heart rate variability did not differ (group × exercise interaction, \( F_{3/165} = 0.38, P = 0.8 \), NS) between the two groups of animals (Fig. 4, \textit{bottom}). Similar results were obtained for R-R interval range and SD of R-R interval; exercise onset elicited similar changes in both the susceptible and the resistant dogs (e.g., change at 60 s; SD of R-R interval, susceptible, −27.6 ± 4.0 vs. resistant, −34.0 ± 6.8 ms; R-R interval range, susceptible, −108.3 ± 14.3 vs. resistant, −94.7 ± 15.9 ms). Thus BB eliminated the larger heart rate increases induced by exercise onset in the susceptible compared with resistant dogs without altering reductions in the various indexes of heart rate variability (i.e., cardiac vagal regulation decreased to a similar extent) in both groups. When considered together, these data suggest that exercise onset provokes larger increases in heart rate in dogs susceptible to ventricular fibrillation than in animals resistant to this malignant arrhythmia as the result of an enhanced \( \beta \)-adrenoceptor activation rather than as the consequence of a more rapid withdrawal of cardiac parasympathetic regulation.

**DISCUSSION**

The major findings of this study were 1) heart rate increased to a greater extent at the onset of exercise in animals confirmed to be susceptible to ventricular fibrillation than in dogs that were resistant to malignant arrhythmias; 2) exercise onset elicited similar reductions in heart rate variability, a noninvasive index of cardiac parasympathetic regulation (7, 14, 17, 18, 32), in both groups of dogs; and 3) the differences in the heart rate increase induced by the onset of exercise in the two groups were eliminated with administration of the \( \beta \)-adrenoceptor antagonist propranolol. These data suggest that exercise onset provokes larger increases in heart rate in dogs susceptible to ventricular fibrillation than in animals resistant to this malignant arrhythmia. Furthermore, the elevated heart rate response noted for the susceptible dogs resulted from an enhanced \( \beta \)-adrenoceptor activation rather than as a consequence of a more rapid withdrawal of cardiac parasympathetic regulation.

An earlier study pointed toward the potential of this previously unevaluated marker of cardiac autonomic regulation for the identification of patients at risk for adverse cardiovascular events. Falcone and coworkers (16) examined the heart rate increase elicited by a standard symptom-limited exercise stress test in 458 patients with documented coronary artery disease. They found that the patients with the largest increase in heart rate (≥12 beats/min above the median value of the distribution) also had a greater risk for adverse cardiovascular events (cardiac death and nonfatal myocardial infarction) during a 3.7–9 yr follow-up period. The exercise-induced increase in heart rate change reliably predicted an adverse outcome even when adjusted for potential confounding factors. They concluded that the heart rate response to exercise onset was a simple and widely available parameter that could prove to be clinically useful as an independent marker for patients at high risk for adverse cardiac events. Furthermore, they speculated that the accelerated heart rate increase in patients that experienced adverse cardiac events resulted from a more rapid withdrawal of cardiac parasympathetic regulation rather than from an augmented sympathetic activation in the high-risk patients. However, it should be emphasized that these investigators did not determine the cause of cardiac death (death due to ventricular fibrillation, asystole, electromechanical dissociation, acute heart failure, etc.) or evaluate the contribution of changes in cardiac regulation to the heart rate response to exercise onset. Thus the specific relationship between the exercise-induced changes in heart rate and the confirmed susceptibility to malignant arrhythmias remained an unanswered question.

The present study confirms and extends these clinical findings by demonstrating for the first time that the onset of exercise provokes a different cardiac autonomic response in animals in which ventricular fibrillation was induced by myocardial ischemia than in those dogs in which this intervention failed to provoke ventricular arrhythmias. Specifically, the onset of exercise provoked significantly larger increases in heart rate in animals that subsequently developed ventricular fibrillation than in those dogs that proved to be resistant to this malignant arrhythmia. As previously noted, heart rate could increase as the result of either an increased withdrawal of cardiac parasympathetic activity or from an enhanced activation of cardiac sympathetic efferent nerves (28). In the present study, cardiac parasympathetic regulation was evaluated by using various indexes of heart rate variability (7, 14, 15, 18, 32), whereas cardiac sympathetic activation was inhibited by using a nonselective \( \beta \)-adrenoceptor antagonist. If the enhanced heart rate increase at exercise onset noted in the susceptible animals resulted from an augmented parasympathetic withdrawal, then one would expect greater reductions in the various indexes of heart rate variability in the susceptible than in the resistant dogs. However, exercise onset elicited similar reductions in heart rate variability in both groups of animals. Conversely, if the elevated heart rate response to exercise onset resulted as a consequence of an enhanced cardiac sympathetic activation, then one would predict that BB would both reduce the heart rate response to exercise and eliminate any differences noted between the susceptible and resistant dogs. In the present study, the \( \beta \)-adrenoceptor antagonist propranolol did, in fact, abolish the enhanced heart rate response in the susceptible dogs, such that after this intervention, exercise provoked similar heart rate changes (accompanied by similar reductions in heart rate variability) in both the susceptible and resistant dogs. When considered together, these data strongly suggest that an elevated heart rate response to the onset of exercise in animals prone to ventricular fibrillation resulted from an enhanced \( \beta \)-adrenoceptor activation rather than as the consequence of a more rapid withdrawal of cardiac parasympathetic regulation.

In the present study, it must be emphasized that a rapid withdrawal of parasympathetic activity (decrease in the indexes of heart rate variability) also contributed significantly to the heart rate increase induced by exercise onset in both the susceptible and resistant dogs. Similar findings have been previously reported for humans (1, 15) and dogs (6, 7, 18). However, in addition to this rapid withdrawal of cardiac vagal regulation, the susceptible dogs exhibited a further increase in...


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heart rate due to an enhanced sympathetic activation because this increase was eliminated by BB. A large sympathetic component to the exercise-induced tachycardia has also been reported in cats (33). This enhanced cardiac sympathetic regulation at the onset of exercise in animals susceptible, compared to those resistant to ventricular fibrillation, contrasts with the autonomic response after the termination of exercise.

Heart rate recovery after exercise has been shown to be an independent predictor of mortality across substantial and diverse population groups (10, 13, 21, 24–26). For example, Cole et al. (10) demonstrated in a multicenter study of 5,234 individuals that abnormal heart rate recovery after submaximal exercise predicted death, even after adjustment for various confounding factors; Nishime et al. (25) published similar results from a total of 9,454 patients. Our laboratory (31) recently demonstrated that dogs susceptible to ventricular fibrillation also exhibited a slower heart rate recovery after the cessation of exercise than did those animals that were resistant to malignant arrhythmias. Heart rate variability was depressed to a greater extent in the susceptible compared with the resistant dogs, and, furthermore, both the heart rate recovery and heart rate variability differences were eliminated by prior treatment with the cholinergic antagonist atropine (31). As such, the attenuated heart rate recovery seen in the animals subsequently shown to be susceptible to ventricular fibrillation almost certainly resulted from reduced parasympathetic recovery after exercise. These studies suggest that animals susceptible to ventricular fibrillation exhibit differing autonomic responses to exercise onset and the termination of exercise. The animals susceptible to ventricular fibrillation display an enhanced sympathetic activation at the onset of exercise but an impaired cardiac parasympathetic reactivation after exercise.

The mechanism responsible for the exaggerated cardiac autonomic response to exercise in the dogs susceptible to ventricular fibrillation was not investigated in the present study. However, retrospective analysis of myocardial infarction size of these dogs revealed that the susceptible dogs had larger infarctions than the resistant animals (susceptible, n = 55, 14.5 ± 1.0%; and resistant, n = 28, 10.8 ± 1.8%). One would predict that mechanical function would be compromised to a greater extent in those animals with the larger infarction. This impairment may become even more obvious when cardiac metabolic demand is increased during exercise. As a consequence, a greater increase in cardiac sympathetic activity might be required to maintain cardiac output in these animals. In other words, heart rate must increase to a greater extent in these animals to compensate for the relatively poor cardiac (reduced stroke volume) function in the animals with large myocardial infarctions. Indeed, our laboratory (9) has reported that left ventricular diastolic pressure increased to a greater extent during submaximal exercise in the susceptible animals compared with more modest changes in the resistant dogs. Furthermore, patients with myocardial infarctions that have poor ventricular function also have an increased risk for ventricular arrhythmias and sudden cardiac death (4). Thus the adjustments made in the cardiac regulation to compensate for an impaired contractile function may increase the risk for malignant arrhythmias.

It should be acknowledged that in the present study neither cardiac vagal activity nor cardiac sympathetic efferent nerve activity was directly evaluated. However, a number of previous investigations have verified that heart rate variability provides an accurate representation of parasympathetic function (7, 14). In a similar manner, the β-adrenoceptor antagonist propranolol eliminated the enhanced heart rate response in the susceptible animals without altering the exercise-induced changes in heart rate variability. The onset of exercise provoked similar heart rate increases and heart rate variability decreases in both the susceptible and in the resistant dogs after β-adrenoceptor inhibition. However, in agreement with previous studies (7, 8, 18), exercise elicited larger reductions in heart rate variability after BB. This accentuated heart rate variability response to exercise onset is consistent with an enhanced withdrawal of cardiac vagal regulation. To maintain cardiac output in the face of increased metabolic demand elicited by exercise, larger reductions in cardiac parasympathetic regulation would be required when sympathetic activation of the heart has been disrupted by BB. When these data are considered together, it is reasonable to conclude that the methods used in the present study provide a reliable indirect assessment of cardiac autonomic regulation.

In summary, exercise onset provoked larger increases in heart rate in dogs susceptible to ventricular fibrillation than in animals resistant to these malignant arrhythmias. This exercise-induced heart rate increase was accompanied by similar reductions in various indexes of heart rate variability in both groups of animals. In contrast, the heart rate response differences noted between the two groups of dogs were completely eliminated by the prior treatment with propranolol. When considered together, these data suggest that the elevated heart rate response noted for the susceptible dogs resulted from an enhanced β-adrenoceptor activation rather than as the consequence of a more rapid withdrawal of parasympathetic regulation. Because exercise stress testing is a widely used technique to evaluate coronary artery disease in patients, the heart rate response to exercise onset could prove to be a simple and inexpensive indicator of the risk for life-threatening arrhythmias in these patients.

GRANTS

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