Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction

An experimental preparation for sudden cardiac death

PETER J. SCHWARTZ, M.D., GEORGE E. BILLMAN, PH.D., AND H. LOWELL STONE, PH.D.

ABSTRACT The relationship between activity of the autonomic nervous system, myocardial ischemia, and malignant arrhythmias has been investigated in a new experimental preparation for sudden death. Fifty-seven dogs were chronically instrumented and studied under control conditions (n = 15) and 1 month after production of an anterior myocardial infarction (n = 42). The protocol consisted in occluding the left circumflex coronary artery for 2 min, commencing at the last minute of an exercise stress test and extending through the first minute after cessation of exercise. With this protocol, ventricular fibrillation was observed in 40% of normal dogs and 66% of dogs with infarction. In 14 dogs with infarction, left stellectomy reduced the incidence of ventricular fibrillation to zero (p < .001). The reflex changes in heart rate elicited within the first minute of ischemia during exercise in the animals that survived (from 204 ± 14 to 198 ± 31 beats/min, −6) were opposite those in animals that had ventricular fibrillation (from 208 ± 24 to 229 ± 30 beats/min, +21) (p < .05). The ischemia-induced reduction in heart rate despite continuation of exercise suggests the presence in the dogs that survived of active vagal reflexes that may have played an important role in the maintenance of cardiac electrical stability. This preparation has the potential to induce ventricular fibrillation consistently in conscious animals by the interaction of a few clinically relevant factors (acute myocardial ischemia, submaximal exercise and its cessation, sympathetic and vagal reflexes, and heart rate) and offers the possibility of acquiring further insights into the mechanisms of malignant arrhythmias and evaluating novel strategies for targeted prevention.


TARGETED prevention of sudden cardiac death depends on an adequate understanding of the mechanisms of and the factors leading to ventricular fibrillation, as well as an understanding of their relative roles. Basic electrophysiologic experiments, usually performed in isolated hearts or in open-chest preparations, are designed to identify these factors and their probable modes of action, but comprehension of their relative roles in the clinical setting requires experiments in unanesthetized animals.

Necessary to achieve this goal are the identification of the most critical factors, the capability of controlling them, the potential for consistently eliciting ventricular tachyarrhythmias by the use of physiologic triggers, the possibility of reasonably applying experimental findings to the clinical problem, and above all a sound working hypothesis on pathophysiologic mechanisms. We,1,3 as others,4 have suggested that the interaction between acute myocardial ischemia and disturbances in the autonomic nervous system plays a key role in sudden cardiac death, particularly when these factors occur in a myocardium that is electrically unstable because of preexisting ischemic damage or because of specific alterations in cardiac innervation.5

Exercise is associated with striking changes in autonomic activity and with abrupt rebounds in vagal activity upon cessation. Surprisingly, arrhythmias associated with acute myocardial ischemia and occurring during exercise have received only sporadic attention.6 A prior anterior myocardial infarction is one of the most significant risk factors for subsequent sudden death.7 Acute myocardial ischemia elicits an excitatory
cardiodecardiac sympathetic reflex, which plays a decisive role in the genesis of the early ventricular arrhythmias. There is increasing evidence that ischemia occurring at a site different from that of a previous infarction is clinically important.

We have combined these conditions in a conscious animal preparation to study the onset of ventricular fibrillation (VF) during the interaction of the following factors before and after production of an anterior myocardial infarction: acute myocardial ischemia, exercise and its cessation, vagal and sympathetic reflexes, and heart rate. The potential to control and manipulate these factors allows us to acquire new insights into their relative roles and to evaluate measures that might help in preventing sudden cardiac death.

Methods

Fifty seven mongrel dogs weighing 14.5 to 25 kg were used in the study.

Surgical preparation. The animals were given 25 mg/kg iv thiopental sodium (Pentothal, Abbott Laboratories) as a preanesthetic and a surgical plane of anesthesia was maintained by the inhalation of a halothane, nitrous oxide, and oxygen mixture. With aseptic procedures, a left thoracotomy was performed in the fourth intercostal space. The left circumflex and the left descending coronary arteries were carefully dissected from the surrounding epicardial fat, and both an 8 MHz continuous-wave Doppler flow transducer and hydraulic occluder were placed around each vessel. Insulated silver-coated copper wires were sutured to the epicardial surface of both the left and right ventricles to record the electrocardiogram and/or to pace the heart. Nylion monofilament sutures were placed around the caudal and cephalic poles of the left stellate ganglion. The sutures were then buried subcutaneously and a stainless steel nut was tied to these lines to facilitate their future localization. In some animals a solid-state pressure transducer (Konigsberg, Model P4.5) was positioned in the left ventricle through an incision in the apical dimple.

In 42 animals an experimental myocardial infarction was then produced. A modified two-stage occlusion was performed on the left anterior descending coronary artery approximately one-third the distance from its origin. The vessel was partially occluded for 20 min and then tied off. In addition, two to three branches from the left anterior descending coronary artery were ligated proximal to the occlusion site.

All lead wires were tunneled under the skin to exit from the dorsal surface of the neck. Pentazocine lactate (Tanwin Winthrop Laboratories, 30 mg im) was given approximately every 8 hr for the first 24 hr to control postoperative pain. We adhered to the guidelines of the American Physiological Society on the care and treatment of experimental animals.

Postoperative treatment of the animals with infarcts. The animals with infarcts were placed in an intensive care setting and treated to prevent the development of early ventricular fibrillation. The animals were given 100 mg im of lidocaine HCl (Xylocaine, Astra Laboratories) before surgery, which was supplemented (60 mg iv) during each stage of the Harris two-stage occlusion. At the completion of the operation the dogs were placed in a quiet recovery area, the electrocardiogram was monitored, and a lidocaine intravenous drip (100 µg/ml) in lactated Ringer's solution was maintained at the rate of 1 ml/min for the first 24 hr after myocardial infarction was produced. The animals were then given 500 mg im of procainamide HCl (Pronestyl, E. R. Squibb & Sons, Inc.) twice daily for the next 4 days.

Experimental protocol. One month after production of myocardial infarction, while the animals were resting on a laboratory table, the balloon occluder around the circumflex coronary artery was inflated to produce acute myocardial ischemia and the occlusion was maintained for 2 min. The coronary occlusion at rest was done to determine whether major arrhythmias occurred when myocardial ischemia was not associated with exercise. Several days later all animals were subjected to submaximal exercise stress test. The animals ran on a motor-driven treadmill for 12 to 18 min while the workload increased every 3 min (4.8 kph, 0% grade during first 3 min; 6.4 kph, 12% grade during the last 3 min period). During the last minute of the exercise test the left circumflex coronary artery was occluded; the treadmill was then suddenly stopped and the occlusion was maintained for a second minute (figure 1). Coronary occlusion was begun when the animal completed 17 min of exercise or when a heart rate close to 220 beats/min was reached. Large steel plates were placed across the animal's chest so that electrical defibrillation (American Optical Corp., Model 6217) could be performed with minimal delay. Electrocardiograms, heart rate, and coronary flow were monitored throughout the exercise test. Flow velocity in the left circumflex coronary artery was measured to verify completeness of the occlusion.

Measurements. Recordings of flow velocity in the left circumflex and left descending coronary arteries, left ventricular pressure, and the electrocardiogram were made on an eight-channel Beckman type RM direct-writing oscillograph. The first derivative of left ventricular pressure (dP/dt) was obtained by an analog differentiator with a time constant of 0.01 sec and a frequency response linear to 65 Hz. The electrocardiogram was used to trigger a cardiotachometer to measure heart rate. The signals were also recorded on magnetic tape (Ampex FR-1300) for later analysis. The infarct size was determined by the nitroblue tetrazolium enzymatic staining technique and was reported as a percentage of the left ventricle.

Data analysis. The resting and exercise data were analyzed either directly or, whenever left ventricular pressure had been recorded, from the analog magnetic tape recording by a digital computer (PDP 11/34) programmed to sample the data every 5 msec over 5 beats. The computer averaged the data points for the 5 beats and also calculated dP/dt. The heart rate was otherwise averaged over a 5 sec period before exercise (with the animal standing on the treadmill), immediately before the onset of the occlusion, and 1 min into the period of occlusion (immediately before the cessation of exercise). Data are reported as

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EXERCISE

FIGURE 1. Outline of the experimental protocol. At the beginning of the last minute of an exercise stress test, with progressively increasing workload on a treadmill, the circumflex coronary artery was occluded for 2 min. After 1 min of exercise plus ischemia, the treadmill was stopped and myocardial ischemia continued for the second minute after cessation of exercise. CAO = coronary arterial occlusion.
Results

Fifty-seven dogs were instrumented and 42 of them had an anterior myocardial infarction produced at the time of surgery, while the remaining 15 dogs served as controls. In seven of the control animals myocardial infarction was subsequently produced by inflation of a hydraulic occluder and the studies were repeated. Fourteen (33%) of the 42 dogs died within the first 72 hr after myocardial infarction. Results will be presented separately for the 15 dogs studied in control conditions, for the 35 studied after myocardial infarction, and for the 14 dogs with myocardial infarction that were also studied after left stellectomy.

The reproducibility of the results was assessed by repeating the exercise plus ischemia test 6 and 12 weeks after the first test (10 and 16 weeks after myocardial infarction). Nine dogs that developed VF during the first test were reexamined after 6 weeks, and eight of nine again had VF when they repeated the exercise plus ischemia test.

An outline of the complete protocol and of the conditions in which the various dogs were studied is shown in figure 2.

Coronary occlusion at rest. A 2 min occlusion of the circumflex coronary artery was performed on 33 animals while they were resting. Twelve of these animals had no or minor arrhythmias when later exposed to the exercise plus ischemia test, while the remaining 21 developed VF. In no instance were arrhythmias (more than one premature ventricular contraction) observed during this episode of acute ischemia in a resting condition. However, a significant difference (ANOVA, p < .001) was observed when the increase in heart rate induced by the coronary arterial occlusion in the dogs that later survived the exercise plus ischemia test (10.2 ± 19.1 beats/min) was compared with that induced in the animals that subsequently had VF (49.2 ± 14.0 beats/min).

Controls. Fifteen dogs were studied with the exercise plus ischemia test in control conditions, i.e., without prior myocardial infarction. Eight animals (53%) showed ventricular arrhythmias and six (40%) had VF, most of these episodes occurring within a few seconds after cessation of exercise.

In several of these control animals, just after the beginning of coronary arterial occlusion and despite continuation of exercise, heart rate decreased by a considerable amount (30 to 50 beats/min in some cases) instead of increasing as expected. All of these animals survived the exercise plus ischemia test without having arrhythmias. The average heart rate in all the control dogs was 99 ± 19 beats/min before exercise; during exercise just before the coronary arterial occlusion the average heart rate was 198 ± 22 beats/min, and after 1 min of myocardial ischemia, just before the treadmill was stopped, it was 198 ± 32 beats/min (table 1). However, when the data for the dogs that survived and for those that died were examined separately (table 1),

**TABLE 1**

Exercise plus ischemia test: heart rate (beats/min) and outcome

<table>
<thead>
<tr>
<th></th>
<th>Before Ex</th>
<th>During Ex before CAO</th>
<th>1 min CAO before end of Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>15</td>
<td>99 ± 19</td>
<td>198 ± 32</td>
</tr>
<tr>
<td>MI</td>
<td>35</td>
<td>105 ± 23</td>
<td>211 ± 17</td>
</tr>
<tr>
<td>MI + LSGx</td>
<td>14</td>
<td>120 ± 19</td>
<td>218 ± 24</td>
</tr>
<tr>
<td>Control surv.</td>
<td>9</td>
<td>102 ± 15</td>
<td>195 ± 15</td>
</tr>
<tr>
<td>Control dec.</td>
<td>6</td>
<td>94 ± 26</td>
<td>202 ± 32</td>
</tr>
<tr>
<td>MI surv.</td>
<td>12</td>
<td>111 ± 17</td>
<td>209 ± 11</td>
</tr>
<tr>
<td>MI dec.</td>
<td>23</td>
<td>102 ± 23</td>
<td>212 ± 23</td>
</tr>
<tr>
<td>All surv.</td>
<td>21</td>
<td>108 ± 16</td>
<td>204 ± 14</td>
</tr>
<tr>
<td>All dec.</td>
<td>29</td>
<td>95 ± 28</td>
<td>208 ± 24</td>
</tr>
</tbody>
</table>

Ex = exercise; CAO = coronary arterial occlusion; MI = dogs with myocardial infarction; LSGx = dogs with left stellectomy; Surv. = survivors; Dec. = deceased.

Data are expressed as mean ± SD. Statistical analysis was performed by analysis of variance.
it became evident that the heart rate response to myocardial ischemia during exercise was significantly different between the two groups (ANOVA, p < .05). Among the survivors, heart rate decreased by 14 beats to 181 ± 21 beats/min; among the animals that died it increased by 26 beats to 228 ± 24 beats/min.

**Animals with infarcts.** Thirty-five dogs were studied 3 to 4 weeks after myocardial infarction, seven of which had been studied before myocardial infarction. The incidence of arrhythmias induced during the exercise plus ischemia test was higher than that in dogs without myocardial infarction, as expected; 26 dogs (74%) had arrhythmias and 23 (66%) had VF. However, this difference was not statistically significant.

VF most often occurred within a few seconds after cessation of exercise, while coronary occlusion was still maintained. Figure 3 shows an example typical of this pattern. It is worth noting that shortly after coronary occlusion major ischemic changes developed but lasted for only a few seconds despite continuation of occlusion. In a minority of animals ventricular arrhythmias or ventricular flutter, which rapidly deteriorates into VF, occurred shortly after coronary occlusion while the dogs were still running (figure 4). The infarct size was 23 ± 7% of left ventricular mass and was identical (23 ± 5% vs 23 ± 8%) among the dogs that survived and those that did not survive the exercise plus ischemia tests.

In the 35 dogs with myocardial infarction, heart rate before exercise was 105 ± 23 beats/min, increasing to 211 ± 17 beats/min just before the coronary arterial occlusion and to 217 ± 33 beats/min at the end of exercise. When the heart rate responses of both groups were analyzed separately, it was found that, as for the control dogs, the survivors had a somewhat higher heart rate before exercise (111 ± 17 vs 102 ± 23 beats/min; ANOVA, NS) and attained the same heart rate when the coronary occlusion was performed. Once more the differences emerged within the first minute of myocardial ischemia as the heart rate of

**FIGURE 3.** Example of the most frequent sequence of events during the exercise plus ischemia test. This dog had at rest an unusually low heart rate (HR) at rest, which increased rapidly with exercise. After 12 min of exercise the heart rate was already 230 beats/min and coronary arterial occlusion (CAO) was produced. Within a few seconds major ischemic changes appeared but were short lived, as indicated by the two continuous strips. Exercise ended after 1 min of occlusion, and within 1 sec ventricular flutter appeared and rapidly deteriorated into VF. Coronary arterial occlusion was immediately released, without benefit.
survivors was not modified (207 ± 30 vs 209 ± 11 beats/min, −2; ANOVA, NS) while the heart rate of animals that died increased by 21 beats (233 ± 34 vs 212 ± 23 beats/min; ANOVA, p < .05). The relationship between the outcome and the heart rate responses to myocardial ischemia during exercise is shown in figure 5.

**Animals with infarcts and left stellectomy.** Fourteen dogs with myocardial infarctions were also studied with the exercise plus ischemia test after left stellectomy. Ten of them had either ventricular tachyarrhythmias (n = 2) or VF (n = 8) when studied after myocardial infarction and before left stellectomy. The incidence of arrhythmias decreased dramatically after left stellectomy, when only two dogs (14%) had premature ventricular contractions and none had VF. One of the two dogs that had sporadic premature ventricular contractions after left stellectomy had no arrhythmias when studied after myocardial infarction and before left stellectomy. The incidence of VF in dogs with infarcts after left stellectomy (0/14) when compared with that observed in dogs with infarcts (23/35) is significantly different ($\chi^2 = 18.45$, $p < .001$); the same is also true when the incidence of VF is compared with that observed in the same animals after myocardial infarction but before left stellectomy (8/14) ($\chi^2 = 15.3$, $p < .001$).

An example of the protective effect of left stellectomy is shown in figures 6 and 7. In figure 6, the electrocardiogram, left ventricular dp/dt, left ventricular pressure, and circumflex coronary arterial flow velocity are shown after 17 min of exercise just before coronary occlusion, at cessation of exercise, and 10 sec later. The appearance of life-threatening ventricular tachyarrhythmias, indicative of impending VF, suggested a modification of the protocol involving an anticipated release of the occlusion. After a second run of ventricular tachycardia the animal underwent left stellectomy, and a few days later the exercise plus ischemia test was repeated (figure 7); this time no arrhythmias occurred even though the occlusion was maintained, as under the regular protocol, for 2 min.

In the dogs with myocardial infarction and left stellectomy, heart rate before exercise was somewhat higher, compared with the postinfarction condition (120 ± 19 vs 105 ± 23 beats/min; ANOVA, NS) and
LAboratory investigation–Ventricular arrhythmia

FIGURE 5. Relationship between outcome and the heart rate (HR) at the moment of coronary occlusion during exercise and after 1 min of myocardial ischemia. Top, Actual data. Middle, Changes from the levels reached before occlusion in control dogs and dogs with infarction. It is evident that the dogs that died during the test had increased heart rates in response to myocardial ischemia. The control dogs that survived had an opposite change, i.e., their heart rates decreased. The dogs with infarction that survived had apparently lost their capability to have significantly decreased heart rates in response to coronary occlusion but had no further increases. Bottom, Pooled data from dogs with and without myocardial infarction. The survivors and the dogs that died were different not because of their heart rates at the moment of ischemia but because of their heart rate response to the first minute of ischemia.

increased to 218 ± 24 beats/min just before coronary occlusion. However, with myocardial ischemia there was no further change, with heart rate remaining at 220 ± 34 beats/min. The antiarrhythmic effect of left stellectomy was preserved despite the fact that heart rate was even slightly higher than that attained in the group with myocardial infarction and without left stellectomy. The double product (heart rate × left ventricular systolic pressure) was somewhat lower in the dogs with myocardial infarction alone compared with that in the dogs with myocardial infarction and left stellectomy (1.1 × 10⁴ vs 1.4 × 10⁴ beats/min·mm Hg⁻¹) and there was no difference at the end of exercise (3.2 × 10⁴ vs 3.2 × 10⁴ beats/min·mm Hg⁻¹). Thus the antiarrhythmic effect of left stellectomy cannot be explained on the basis of a reduced myocardial oxygen consumption, of which the double product represents an index.

Role of heart rate. The possibility was investigated that the heart rate attained during exercise and myocardial ischemia could be the decisive factors in triggering VF in our animal preparation. In four dogs that had VF during the exercise plus ischemia test, the 2 min coronary arterial occlusion was performed again while the heart rate was kept at the same level reached at the occurrence of VF by atrial pacing. Two days after defibrillation, a 2 min coronary arterial occlusion was performed while the animals rested quietly on a laboratory table; no arrhythmias occurred, but heart rate was considerably lower, so that the protection may have depended on the lower heart rate. Thus the 2 min coronary occlusion was repeated on a subsequent day while the animals were resting, but heart rate was kept at the same level attained during exercise by atrial pacing. Arrhythmias did not occur in these animals despite 2 min of ischemia at this faster heart rate, indicating that for VF to occur in these dogs, both acute myocardial ischemia and a high heart rate had to be associated with the autonomic changes induced by exercise and its cessation.

Discussion

This study shows that in the presence of a healed myocardial infarction, a critical combination of acute myocardial ischemia and physiologically elicited high sympathetic tone can consistently induce malignant ventricular arrhythmias in the conscious dog.

Analysis of the experimental preparation. The evidence obtained from the victims and the successfully resuscitated survivors of sudden cardiac death indicates that acute myocardial infarction is responsible in only 25% of cases.¹¹ On the basis of current knowledge, it is reasonable to assume that VF frequently occurs when an episode of acute myocardial ischemia occurs in a heart with advanced ischemic disease. If this opinion is accepted, a transient ischemic episode with the accompanying autonomic reflexes in a heart with reduced electrical stability would be the most frequent cause of sudden cardiac death.

Advanced coronary atherosclerosis that mimics the human condition is difficult to produce in experimental preparations. For this reason we¹²,¹³ and others¹⁴–¹⁶ have begun to study animals with a healed myocardial infarction. Although not yet ideal, this represents an important step forward in comparison with those studies in which acute myocardial ischemia is produced in hearts with an entirely normal coronary circulation. The clinical relevance is further increased when the
experiments are performed in unanesthetized animals.

We have previously investigated the effect of a 10 min occlusion of the circumflex coronary artery in conscious and resting dogs with a healed anterior myocardial infarction. The significance of our findings was somewhat limited by a major effect on left ventricular function, and we thought it necessary to reduce the length of the ischemic episode without reducing its arrhythmogenic potential. This brief myocardial ischemic episode had to occur at a time of a naturally elicited high sympathetic tone. Sympathetic activation at the time of even a brief myocardial ischemic episode most often precipitates threatening ventricular arrhythmias.

Exercise was selected because it is a condition accompanied by high sympathetic activity and because of its clinical relevance. Furthermore, submaximal exercise was used in this study because similar levels of activity may be frequently reached by postinfarction patients under normal living situations while they are unlikely to engage in strenuous exercise. It is worth noting that the heart rates reached at the time of the circumflex arterial occlusion (198 ± 22 to 211 ± 17 beats/min for the control and postinfarction dogs) represent 70% of maximum heart rate for dogs. As an example, the heart rate reached by postinfarction patients during a normal and necessary physical activity such as sexual intercourse is 117 ± 14 beats/min, which corresponds to 65% of maximum heart rate for healthy men.

The effects of the interaction between coronary arterial occlusion and exercise have been investigated by Lown and associates. Their primary goal was to determine whether exercise facilitates the occurrence of malignant arrhythmias when combined with acute myocardial ischemia. They found that VF did not occur in exercising dogs 3 days or 1 hr after a fixed coronary arterial occlusion. Subsequently, they performed a coronary occlusion during strenuous exercise, which resulted in several instances of VF. Their study differs from ours in that their dogs had intact hearts and exercise was "strenuous," as also suggested by the end point of either major arrhythmia or exhaustion.

The sequence of events in the current protocol was selected so that only the first minute of coronary occlusion would be simultaneous with exercise, while the second minute of occlusion would be in the postexerci-
cise phase. This has allowed a differentiation of arrhythmias induced by ischemia plus exercise from those induced by ischemia plus cessation of exercise. In addition, reperfusion-related arrhythmias could be distinguished from arrhythmias related to cessation of exercise, even if a 2 min occlusion is too short to generate them.22 The interest in this latter phase is due to the fact that in human beings, the majority of sudden cardiac deaths related to exercise occurs shortly after termination of exercise.23 The vast majority of dogs that had VF during the exercise plus ischemia test did so within seconds after cessation of exercise. With the limitations inherent in an experimental study, this preparation may grossly mimic the condition of patients with prior myocardial infarctions who engage in a physical activity and have a brief reduction in coronary flow, perhaps caused by coronary spasm, leading to acute myocardial ischemia, cardiac pain, and arrest of exercise.

Thus in this preparation VF was induced by the specific interaction of the following factors: acute and transient myocardial ischemia, exercise and its cessation, activation of sympathetic and vagal reflexes, and heart rate. By performing the coronary occlusion during exercise and at rest, by keeping heart rate controlled if needed, and by selectively interfering with the effect of autonomic reflexes either pharmacologically (with α- or β-adrenergic blockade and with atropine) or surgically (with left or right stellectomy or vagotomy), we can determine the relative roles of these factors in the genesis of malignant arrhythmias in this preparation. Indeed, we have already acquired new insights on the mechanisms that relate the autonomic nervous system to the susceptibility to VF.24

Autonomic reflexes and heart rate. Myocardial ischemia excites both vagal25, 26 and sympathetic27 afferent fibers of cardiac origin. This can lead to vagally mediated depressor reflexes28 and/or to sympathetic cardiovascular excitatory reflexes.29 The existence of the latter in neurally intact anesthetized dogs has been questioned by Felder and Thames.30 The excitation of cardiac sympathetic afferent fibers also reflexly and selectively inhibits the activity of efferent cardiac vagal fibers.31 Thus activation of sympathetic afferent fibers
has the potential of impairing vagally mediated maintenance of an optimal heart rate, thereby facilitating the occurrence of a dangerous tachycardia.

The dogs with infarction had, in comparison with the controls, a slightly higher heart rate both at rest and during exercise just before coronary occlusion. The difference increased somewhat after 1 min of ischemia, which suggests the presence of reduced vagal reflexes after a myocardial infarction or the necessity to compensate for a reduced left ventricular function by increasing heart rate.

The most meaningful information was discovered when the heart rate responses of the surviving animals was compared with that of the animals that died (figure 5). Among control dogs the heart rate response to the first minute of myocardial ischemia showed striking differences. The resistant dogs had an overall decrease of 14 beats/min despite continuation of exercise, while the susceptible dogs had an overall increase of 26 beats/min. A similar pattern was found among the dogs with myocardial infarctions. The susceptible dogs had an overall increase in heart rate (+24 beats/min), while the resistant dogs had a slight reduction (-2 beats/min). Even when the 2 min coronary occlusion was performed at rest, the increase in heart rate of the susceptible animals was greater (49 vs 10 beats/min) than that of the resistant animals. This strongly suggested that protection from VF is associated with dominant vagal reflexes elicited by acute myocardial ischemia, while susceptibility to VF was associated with dominant sympathetic reflexes. It is certainly possible that in the susceptible dogs, left ventricular dysfunction could have contributed to the reduced vagal response.

What causes vagal reflexes to predominate during the exercise plus ischemia test in some dogs? To some extent, the reflexes described by Thames et al.

may be involved, i.e., reduction in heart rate and in sympathetic efferent activity after circumflex arterial occlusion due to activation of vagal receptors, which are thought to be more numerous in the inferior wall of the left ventricle. In all of the dogs, myocardial ischemia was induced by occluding the circumflex coronary artery, which should theoretically have resulted in similar degrees of reductions in heart rate. It seems reasonable to surmise that the preexisting anterior myocardial infarction might have impaired left ventricular function and made the left ventricle more dependent on the blood supply through the circumflex coronary artery. Left ventricular dysfunction might reduce upstroke velocity of arterial blood pressure and thus, coupled with simultaneous stimulation of vagal and sympathetic receptors, might elicit more pronounced sympathetic reflexes, leading to an increase in heart rate. Thus the end result reflects the algebraic summation of the opposite adrenergic and cholinergic influences.

We were surprised to find that some animals had a significant decrease in heart rate (30 to 50 beats/min) at the time of coronary occlusion despite continuing exercise. This implied the presence of a powerful vagal reflex. Moreover, these animals had no malignant arrhythmias, which raised the question of the possibility of identifying in advance which animals would survive the exercise plus ischemia test. To assess autonomic reflexes, and in this case particularly vagal reflexes, we analyzed the changes in RR interval or in heart rate induced by an elevation in blood pressure. The dogs that survived the exercise plus ischemia test had a significantly greater reduction in heart rate (-40 ± 12 vs -13 ± 5 beats/min) in response to a 30 mm Hg increase in systolic blood pressure compared with the dogs that had VF on the treadmill. This suggested that the dogs resistant to VF had a greater capability to activate vagal reflexes, which had been shown to reduce vulnerability to VF. Conversely, an impaired potential for vagal reflexes identified a subgroup of postinfarction dogs at very high risk for sudden death.

Thompson and Lown postulated from their data that the risk of major arrhythmias was related to the peak heart rate generated by exercise. Their statement is almost certainly correct if coronary occlusion is performed at an extremely high heart rate, probably in excess of 260 beats/min. Our results suggest a different and more specific conclusion. At lower heart rates, between 210 and 250 beats/min, the most critical factor seems to be the balance between the autonomic reflexes elicited by acute myocardial ischemia and perhaps the exercise capacity rather than the heart rate per se. Indeed, the heart rates reached during exercise at the time of coronary arterial occlusion in the dogs that eventually died and in dogs that survived were almost identical (208 ± 24 vs 204 ± 14 beats/min) (table 1). Therefore this was not the decisive factor. In contrast, the heart rate attained after 1 min of ischemia during exercise, and particularly the directional changes in heart rate, was much more clearly associated with the outcome. The loss of the ability to either reduce heart rate during ischemia or at least to prevent substantial increases was clearly associated with higher risk of VF (figure 5). This tendency was evident even when coronary arterial occlusions were performed at rest. The reflex control of heart rate reflects the sympathetic-parasympathetic interaction at the level of the sinus node. The importance of high vagal
activity to oppose high sympathetic activity is consistent with recent concepts on the susceptibility to VF and particularly the concept that the vagi exert their protective action by antagonizing elevated sympathetic activity in the heart.

The importance of heart rate in the occurrence of life-threatening arrhythmias seems to be primarily related to the underlying autonomic state, which is partially reflected by the changes that occur in heart rate.

Effect of left stellectomy. From the preceding analysis it would seem evident that high cardiac sympathetic activity played an important role in the genesis of the malignant arrhythmias associated with the exercise plus ischemia test. It was therefore logical to further test this possibility by investigating the effect of left stellectomy to evaluate potential preventive strategies.

The complete protection from VF in the 14 dogs tested after left stellectomy confirms our previous reports of the powerful antiarrhythmic effect of this procedure. When 32 conscious dogs with infarcts underwent a 10 min circumflex coronary artery occlusion, left stellectomy reduced the incidence of VF from 67% to 33%. This significant but incomplete protection afforded by left stellectomy reflects, in our opinion, the fact that the long duration of circumflex arterial occlusion in dogs with an anterior myocardial infarction significantly affected left ventricular function. Under these circumstances there are obvious limits to the antifibrillatory effect of any intervention. As recently analyzed, the protective effect of left stellectomy in ischemic heart disease results from the combination of the various direct electrophysiologic effects with significant salutary actions on the coronary circulation. These are essentially represented by an increased capability of the coronary bed to dilate, due to the removal of the dominant α-adrenergic receptor-mediated vasoconstrictor tone, which reduces both the extent and the severity of myocardial ischemia. Furthermore, left stellectomy largely prevents the negative effects on cardiac electrical stability from α-adrenergic receptor mechanisms. After left stellectomy heart rate increased, probably because of a reflex activation of the right stellate ganglion while left ventricular contractility was unaffected both at rest and during exercise in dogs with and without myocardial infarction. The effectiveness of left stellectomy depends to a great extent on the elimination of a major component of the arrhythmogenic sympathetic outflow to the heart and on the reduction of sympathetic afferent activity, which gives rise to excitatory reflexes and inhibits cardiac vagal efferent activity. Thus animals with a healed myocardial infarction are at a lower risk of sudden death at the time of a new ischemic episode occurring during physical exertion if their left stellate ganglion has been removed.

Clinical implications. Extrapolations to the clinical setting of data obtained from experimental animals should always be guarded. Nonetheless, some of the results obtained in this study may be used to gain insights into clinical problems.

The study provides greatly needed information on the effect of a brief episode of myocardial ischemia in conscious animals with a healed myocardial infarction. The occurrence of the ischemic episode during normal physical activity, such as submaximal exercise, accentuates its clinical significance. As pointed out by Myerburg et al., life-threatening arrhythmias occur most frequently in people with preexisting healed ischemic injury or myocardial infarction and the presumption or evidence of transient acute ischemia.

The importance of autonomic reflexes in protecting from or in precipitating VF is evident and suggests strategies for prevention. On one hand, antiadrenergic interventions such as left stellectomy (in human beings, high thoracic left sympathectomy) or β-adrenergic receptor blockade seem very encouraging. On the other hand, the possibility of increasing the propensity toward strong vagal reflexes offers new and exciting possibilities. Preliminary results with the use of daily exercise for 6 weeks in dogs with myocardial infarction at high risk for VF are very promising.

Our data also stress the importance of the state of the autonomic nervous system at the time of an acute ischemic episode and suggest that evaluation of autonomic reflexes in patients with myocardial infarction may contribute to identification of low- and high-risk subgroups.

We thank Tom Dickey and Gary Stout for excellent technical assistance and Lula Campbell for typing the manuscript.

References


Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death.

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Circulation. 1984;69:790-800
doi: 10.1161/01.CIR.69.4.790

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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