Effect of Submaximal Exercise on Vulnerability to Fibrillation in the Canine Ventricle

ALBERT K. DAWSON, PH.D., ARTHUR S. LEON, M.D., AND HENRY L. TAYLOR, PH.D.

SUMMARY The risk of instantaneous death due to ventricular fibrillation was compared in resting and exercised dogs. Three weeks before testing, all dogs had bipolar left ventricular stimulating electrodes implanted and a reversible snare was placed around the anterior descending coronary artery. The dogs were randomly assigned to either an exercise (13 dogs) or a control (12 dogs) group. We measured ventricular fibrillation threshold (VFTs) in all dogs before and after inducing ischemia by tightening the snare while the dogs stood at rest. The next day, nonischemic and ischemic VFTs were redetermined for control dogs at rest and for the exercise group during a treadmill run. No statistically significant changes were noted within and between groups in nonischemic or in ischemic VFTs at rest. In five exercise dogs, spontaneous ventricular fibrillation occurred during the first 8 minutes of the ischemic run. For the other exercise dogs, running increased the mean drop in VFTs during coronary occlusion by 23% (p < 0.01). These data suggest that moderate dynamic exercise may greatly enhance the risk of ventricular fibrillation and sudden death in the presence of myocardial ischemia. In the absence of ischemia, exercise does not appear to increase vulnerability to ventricular fibrillation.

SINCE THE PIONEER STUDIES of Wiggers and Wegria, measurement of the ventricular fibrillation threshold (VFT) by scanning the "vulnerable phase of ventricular systole" with an electrical stimulus has been considered a valuable tool for comparing the susceptibility of the ventricle to fibrillate in a variety of situations. Spontaneous fibrillation and fibrillation induced by electrical stimulation have been studied and found to have significant similarities. In both, the degree of inhomogeneity between myocardial fibers, represented by a dispersion in their recovery times, has a critical level that will result in fibrillation if exceeded. Hence, the VFT is used as an index of the degree of electrical inhomogeneity required to precipitate ventricular fibrillation. In general, factors that alter the experimental VFT appear to produce a parallel shift in susceptibility to spontaneous ventricular fibrillation. However, subtle differences in experimental methods and techniques may influence VFT measurements to the extent that measurements that appear to be made under similar circumstances yield dissimilar results. Also, it is uncertain whether data from anesthetized animals can be extrapolated to the conscious, intact animal.

Each year, 300,000-400,000 Americans die suddenly from coronary heart disease, most within 2 hours of the onset of symptoms. The work of Bruce and Kluge and of Friedman et al. suggests that rhythmic exercise greatly enhances the risk of instantaneous coronary death. Thompson et al. reported that the combination of strenuous treadmill exercise and simultaneous coronary occlusion was more likely to provoke ventricular fibrillation in dogs than coronary occlusion alone. An increased incidence of serious ventricular arrhythmias and associated mortality was also observed when coronary occlusion was performed immediately before or after exhaustive exercise. However, in the latter instance, the results were less conclusive. In view of the uncertainty surrounding the effects of rhythmic exercise on the vulnerability of the normal and the acutely ischemic heart to ventricular fibrillation, we decided to compare VFTs in the nonischemic and in the ischemic myocardium of conscious, intact dogs at rest and during moderate treadmill exercise.

Materials and Methods

Adult mongrel dogs of either sex that weighed 17-30 kg were studied. The dogs were familiarized with treadmill running and only those that were willing to run voluntarily at submaximal speeds were used in the study. On the day of surgery, each dog was anesthetized with an intravenous administration of 25-30 mg/kg sodium pentobarbital (Nembutal) and given 600,000 units of penicillin intramuscularly. Under aseptic conditions and positive pressure ventilation, a left thoracotomy was performed at the fifth intercostal space. The anterior descending coronary artery was isolated 1-1.5 cm distal to its origin and a snare made of surgical monofilament nylon (size 2) enclosed in a polyethylene sleeve (tubing size P.E. 320) was placed around it and anchored with two small sutures to the epicardium. Next, two corkscrew-tipped plantium-iridium electrodes (Medtronic Model 6917) were screwed into the left ventricular myocardium 1-3 cm apart and within the region of projected ischemia. The dog's chest was then closed and the distal ends of the electrode leads and the snare...
were buried in a subcutaneous pocket just caudal to the left scapular region.

After 2–3 weeks of recovery, each dog was reanesthetized with 25–30 mg/kg of Nembutal. Under aseptic conditions, the distal ends of the leads and snare were exposed and VFTs were determined by a method similar to that used by Bacaner. Briefly, a constant-current generator built in our laboratory by Robert Bohrer was used to deliver a single rectilinear 2-msec pulse through the myocardial electrodes. The generator output was calibrated at the beginning of each experiment using a model 7704A Tektronix oscilloscope with a model 7A22 differential amplifier. Periodic checks on the calibration were made during the course of each experiment. Three nonischemic and one ischemic VFTs were measured in each dog and the values recorded in milliamps. To measure nonischemic VFTs, the output of the constant-current generator was set initially at 10 mA. Then, the vulnerable period of the cardiac cycle was scanned by the single rectilinear pulse with one pulse delivered every tenth sinus beat or every 5 seconds, whichever time was longer. The R wave from a modified lead III ECG was used to synchronize each stimulus pulse delivered. Usually, the exact range of the vulnerable period for any given dog was easily recognized, because a stimulus falling outside this range only produced a single extrasystole, while one applied within this time frame most often resulted in two or more premature complexes. If ventricular fibrillation did not result from a given vulnerable period scan, the constant current output was increased by 2 mA and the scan repeated. This procedure was continued until ventricular fibrillation was induced and the VFT was recorded as the minimal current required to produce fibrillation. To obtain the ischemic VFT, the snare around the anterior descending coronary artery was rapidly tightened by an amount predetermined during surgery (and reaffirmed at necropsy) to produce complete occlusion. A stopwatch was then started and the ischemic changes in the myocardial electrogram were monitored continuously from one of the myocardial electrodes for the first 8 minutes. After this initial phase, scanning of the vulnerable period with the 2-msec pulse was begun. The procedure was the same as that used to measure the nonischemic VFT except that the initial constant-current generator setting was 2 mA. A record of time into the occlusion vs stimulus intensity (mA) up to the point of ventricular fibrillation was charted for each dog. This time course was then followed in all subsequent ischemic VFT determinations in these dogs. In all cases, defibrillation was accomplished by DC transthoracic countershock delivered after 15–30 seconds of fibrillation. For the ischemic VFT determination, countershock defibrillation usually was followed by a bolus infusion of 50 mEq of sodium bicarbonate (i.v.), snare release, and countershock again if reperfusion ventricular fibrillation occurred. After successful resuscitation, the myocardial electrogram was monitored for signs of return to normal. Coronary artery occlusion was never maintained longer than 20 minutes. The VFT determinations made while the dogs were anesthetized with Nembutal served as a screening process to give forewarning of any major complications that might arise when the dogs were studied in the conscious state. In this way, dogs that were unduly difficult to resuscitate after 15–30 seconds of fibrillation and dogs that spontaneously fibrillated during the first 8 minutes of coronary occlusion were eliminated from the study at this stage.

Baseline VFTs

After the initial VFT determinations under anesthesia, each dog was allowed 1 week to recover. Three nonischemic followed by one ischemic VFTs were then redetermined in each dog during a single day while the dog was conscious and standing quietly at rest. The procedure used for these baseline measurements was identical to that described above. After the baseline measurements were completed, each dog was randomly assigned to either an exercise or a control group.

Treatment VFTs

One or 2 days later, treatment VFTs were determined in all dogs in a manner similar to that used for baseline determinations. For the control group, treatment VFTs were measured while the dogs were again standing quietly at rest. For the exercise group, treatment VFTs were measured while each dog ran on a motor-driven treadmill at 3.0–3.5 mph and 30% grade. Each dog was allowed to rest for at least 45 minutes outside the treadmill room between each exercise VFT measurement. As in all other cases, the three nonischemic measurements were followed by a single ischemic determination, all four being completed within a single day. During each ischemic determination, the coronary snare was closed and the stopwatch and treadmill were started as quickly as possible. After the initial 8 minutes of occlusion, scanning of the vulnerable period was begun and progressed at such a rate that for any given time on the stopwatch, the level of stimulation (mA) was the same as the time-matched stimulus intensity used in the same dog at baseline. This consistency was maintained for both control and exercise groups.

Necropsy

After determination of treatment VFTs, each dog was killed and its heart removed. The hearts were sectioned and examined for macroscopic evidence of infarct. Functional adequacy of the snare was also checked.

Results

Of 31 dogs that had VFT determinations while anesthetized with Nembutal, 25 qualified for the study and were randomized to the control (12 dogs) and the exercise (13 dogs) groups. The remaining six dogs were eliminated from the study for the following reasons. One dog went into spontaneous ventricular
fibrillation within 2 minutes of coronary occlusion under Nembutal. Two dogs had spontaneous ventricular fibrillation after snare release and resultant coronary reperfusion after measurement of the ischemic VFT under Nembutal. Both of these dogs required a number of additional countershocks to reestablish a stable heart pumping action. Two other dogs had idioventricular rhythms 24 hours after VFT measurements under Nembutal; a subsequent necropsy showed spotty subendocardial necrosis. No other abnormalities were revealed during necropsy in any of the remaining dogs. Finally, one dog was lost from the study at baseline due to spontaneous reperfusion ventricular fibrillation after the ischemic VFT measurement. A limited attempt to resuscitate this dog was unsuccessful. There were no other instances of spontaneous ventricular fibrillation in conscious dogs standing quietly at rest. ST-segment elevation was recorded from a unipolar subepicardial lead implanted in the area of induced ischemia (fig. 1). ST-segment elevation was moderately increased in 12 of the exercise group dogs and unchanged in just one during ischemia with exercise, compared with values during ischemia at rest.

**Nonischemic VFTs (table 1)**

A comparison of the mean nonischemic VFT values obtained at baseline and treatment showed no statistically significant change. Treadmill exercise in the absence of ischemia did not significantly alter the VFT.

**Ischemic VFTs (table 2)**

The mean difference (treatment vs baseline) in the control values for ischemic VFTs (0.2 ± 3.5 mA) was not significantly different from zero. However, the comparable mean for the exercise group (−4.4 ± 2.0 mA) was significantly different from zero and from the control group mean (p < 0.01). Five of the 13 exercised dogs had spontaneous ventricular fibrillation during the first 8 minutes of the ischemic treadmill run. Hence, VFT analysis for this group was limited to the remaining eight dogs.

**TABLE 1. Mean Nonischemic Ventricular Fibrillation Threshold for Exercise and Control Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Treatment†</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Control</td>
<td>37.0 ± 11.7</td>
<td>34.9 ± 10.2</td>
<td>−2.1 ± 5.1 (NS)</td>
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<tr>
<td>(n = 12)</td>
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<tr>
<td>Exercise</td>
<td>30.1 ± 9.6</td>
<td>31.6 ± 10.3</td>
<td>+1.5 ± 4.8 (NS)</td>
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<td>(n = 13)</td>
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Values are given in millamps (Mean ± SD).
*Baseline: both exercise and control groups standing at rest.
†Treatment: for exercise dogs—treadmill run; for control dogs—stand at rest.

**TABLE 2. Mean Ischemic Ventricular Fibrillation Threshold for Exercise and Control Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Treatment†</th>
<th>Difference</th>
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<tr>
<td>Control</td>
<td>20.2 ± 9.9</td>
<td>20.4 ± 10.7</td>
<td>+0.2 ± 3.5 (NS)</td>
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<tr>
<td>(n = 12)</td>
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<tr>
<td>Exercise</td>
<td>17.8 ± 9.4</td>
<td>13.4 ± 8.4</td>
<td>−4.4 ± 2.9 (p &lt; 0.01)</td>
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<td>(n = 8)</td>
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Values are given in millamps (mean ± SD).
*Baseline: both exercise and control groups standing at rest.
†Treatment: for exercise dogs—treadmill run; for control dogs—stand at rest.
**Coronary Occlusion and Heart Rate**

Figure 3 shows the effect of coronary occlusion on the heart rate for the exercise group. The ischemic heart rate values represent an average over the first 7 minutes of coronary occlusion or, in the cases of spontaneous ventricular fibrillation, an average of the sinus rate up until the time of a serious ventricular arrhythmia. Nonischemic heart rates were measured just before coronary occlusion during standing rest.
and after 3–4 minutes of treadmill running. There was a small but significant trend for the resting heart rate to accelerate immediately after coronary occlusion. For the exercise group, the heart rates (mean ± SD) immediately before and after coronary occlusion were 97.6 ± 23.7 and 108.8 ± 20.1 beats/min, respectively (p < 0.01). The control group showed a similar significant increase in heart rate before and after coronary occlusion (96.3 ± 13.8 and 114.1 ± 17.2 beats/min, respectively; p < 0.01). This trend was also evident for the exercise group during the run. The heart rates during the last (third) nonischemic run and the subsequent ischemic run were 202.6 ± 41.5 and 230.4 ± 39.7 beats/min, respectively (p < 0.01).

**Spontaneous Fibrillation During Exercise**

Five of the 13 exercise group dogs had spontaneous ventricular fibrillation during the initial 8 minutes of the ischemic run. These five dogs had a higher mean ischemic exercise heart rate than the other eight dogs in this group (241.6 ± 22.7 vs 223.4 ± 47.6 beats/min, respectively; NS). Table 3 shows that the baseline VFTs for these five dogs was within the usual range for all of the other dogs in this study (tables 1 and 2). The drop in VFT during coronary occlusion at standing rest for this subgroup of five dogs ranged from 3 mA (14%) to 20 mA (67%). This compared favorably with values in the other dogs at baseline for both the exercise and the control group. (The mean drops in VFT were 35% and 45%, respectively.)

**Discussion**

Studies in both animals and man have shown that the increase in myocardial oxygen consumption, which accompanies positive inotropic and chronotropic interventions, increases damage caused by coronary ischemia. Bloor et al.11 found that the reduction in VFT 15 minutes after coronary occlusion correlated well with infarct size determined at necropsy. These reports are in agreement with the results observed in the present study. The increase in ST-segment elevation over resting levels induced by coronary occlusion during treadmill exercise possibly represents an extension or intensification of the ischemia during exercise beyond that experienced at rest. This is in agreement with the observed associated increased drop in VFT during exercise in the presence of ischemia. The method used to record subepicardial potentials does not permit us to quantify the degree or extent of ischemia. However, Becker12 has observed that tachycardia during acute myocardial infarction results in a redistribution of coronary flow such that subendocardial flow actually decreases as the rate increases. The risk of instantaneous death (death within minutes of the onset of myocardial ischemia) is reported to be enhanced in both pacing- and exercise-induced high heart rates. If we regard exercise simply as a means of evoking tachycardia, our results are in agreement with those obtained by Epstein et al.,5 who observed that the VFT was not affected by heart rate in the nonischemic heart but decreased with increasing heart rate during ischemia. However, James et al.14 reported that VFT dropped with increasing heart rate in the nonischemic situation and showed no heart-rate-related changes during the first 30 minutes of ischemia, and Han et al.15 found that the nonischemic VFT decreased with decreasing heart rate. At first one might find it difficult to reconcile the apparent wide variability in results among these studies. However, there were several differences in the methods used that may account for these discrepancies. Although all three of these studies used pentobarbital anesthesia and acute dog preparations, the technique for scanning the vulnerable period, the breed of dog (mongrel or purebred greyhound) and the degree of basal cardiac autonomic tone all differed. At least two major differences in methods exist between these three studies and ours. First, we used an intact, unanesthetized preparation. Second, the heart rate acceleration of exercise is associated with other complex physiologic responses. Although heart rate is a major correlate and determinant of myocardial oxygen consumption,16 contractility and myocardial wall tension, which also increase during exercise, may be even more important.17 Hence, the combined effect of changes in these and other parameters during exercise are important considerations in acute myocardial ischemia.

The apparent discrepancies among studies cited above might prompt one to question the significance of VFT measurements. However, the parallel between a shift in VFT and a corresponding change in susceptibility to spontaneous ventricular fibrillation has generally been upheld.2,3 The primary sources of the "discrepancies" may be differences in animal preparations and stimulation procedures. Gaum et al.18 observed a discordance during acute myocardial ischemia between the VFT as measured with a train of stimuli and the actual electrical stability of the heart. However, Shumway et al.,19 using a single-pulse stimulation technique similar to ours, reported no such discrepancy when the stimulation site was within the ischemic zone. We observed that a drop in VFT due to ischemia tended to persist well beyond the 6–8 minutes that Gaum et al.14 found was required for the ischemic VFT to return to and exceed the nonischemic level.

This study was designed to measure the relative risk of ventricular fibrillation associated with moderate rhythmic exercise. Our findings suggest that in con-

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<th>Table 3. Baseline Ventricular Fibrillation Thresholds for Spontaneous Ventricular Fibrillation Subgroup of Exercised Dogs (n = 5)</th>
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<td>29</td>
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<tr>
<td>Mean ± SD</td>
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Values are given in milliamps.
contrast to the enhanced risk observed during exercise in the presence of myocardial ischemia, there did not appear to be increased risk with exercise in the non-ischemic heart. In addition, all five episodes of spontaneous ventricular fibrillation occurred within the first 7.5 minutes of ischemic exercise, which suggests that the risk of fibrillation is greatest during the first few minutes of ischemia. This point is in agreement with the findings of Axelrod et al., who observed that in eight of 10 dogs, the maximum drop in VFT after coronary occlusion occurred within 2 minutes and began to return to normal after approximately 6 minutes. There was also a trend in our study for the dogs with the highest exercise heart rate to be most prone to spontaneous ventricular fibrillation. This is in agreement with the observations of other investigators.8,13

No association was found between the magnitude of VFT drop with ischemia during the baseline period and the likelihood of spontaneous ventricular fibrillation during ischemic exercise. The degree of ischemic VFT lowering at rest appears not to be a reliable predictor of the predisposition to spontaneous ventricular fibrillation during exercise. The phrases “at rest” and “during exercise” are important, because the absence of a relationship between the drop in VFT with ischemia and the likelihood of spontaneous ventricular fibrillation in this study cannot be generalized. A more comprehensive examination would have required studying the time course of the ischemic VFT in much greater detail.

The time course of VFT during ischemia is a complex phenomenon, and fluctuations have been observed by a number of investigators.18,20,2,23 all of whom agreed that VFT falls rapidly after coronary occlusion, reaches a nadir and then begins to return toward the nonischemic level. However, the actual time of occurrence of the nadir varied widely among these studies, from a minimum of 1.1 minutes to a maximum of 30–60 minutes. The time course appears to be extremely dependent on the methods of measuring ischemic VFT. Possibly, a relationship exists between the ischemic VFT at its nadir and the likelihood of spontaneous fibrillation. There are two reasons why we did not examine this point. First, we wanted the opportunity to document spontaneous ventricular fibrillation unbiased by electrical myocardial stimulation. Second, we felt it necessary for humane reasons to minimize the number of fibrillation-defibrillation episodes in the conscious animal. Ischemic fibrillatory episodes, especially those which occur spontaneously, are very difficult to resuscitate. We could successfully resuscitate only one of the five dogs that had spontaneous fibrillation during exercise in the presence of myocardial ischemia. However, for any given dog, the intensity (mA) of ventricular stimulation during ischemic exercise was identical to the time-matched intensity used during ischemic rest. Hence, the change in ischemic VFT between conditions of rest and exercise appears to be a valid point of comparison in this study.

The heart rate in our conscious dogs accelerated after occlusion of the anterior descending coronary artery. This phenomenon has also been observed in our laboratory in open-chested dogs under morphine-chloralose anesthesia (unpublished data) as well as in conscious and anesthetized preparations of other investigators. If large enough, this increase in heart rate may add to the already substantial risk of instantaneous death after coronary occlusion. In contrast, Feola et al.26 and Corr and Gillis27 reported that bradycardia usually followed occlusion of the circumflex coronary artery in the dog and occlusion of the anterior descending coronary artery in the cat.

In conclusion, the results of this study are in close agreement with those of Thompson and Lown,8 who found that the simultaneous pairing of strenuous exercise with coronary occlusion caused a high mortality rate. Our observations also suggest that the combination of moderate exercise and sudden coronary occlusion not only increases risk of ventricular fibrillation, but also may increase ischemic myocardial damage beyond that caused by occlusion alone while in the resting state. The increase in heart rate, contractility and wall stress, with their concomitant increase in myocardial oxygen consumption and possible redistribution of coronary blood flow,12 probably contributes significantly to the increased drop in VFT and the greater risk of spontaneous ventricular fibrillation during ischemic exercise. Significantly, exercise alone produced no increase in vulnerability to ventricular fibrillation. Thus, our observations indicate that rhythmic exercise is well tolerated in the normal heart, but can contribute to a catastrophic outcome during the first few minutes of acute myocardial ischemia.

Acknowledgment

The authors thank Earl Levens for his valuable technical assistance.

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Effect of submaximal exercise on vulnerability to fibrillation in the canine ventricle.
A K Dawson, A S Leon and H L Taylor

Circulation. 1979;60:798-804
doi: 10.1161/01.CIR.60.4.798
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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