The Effects of Heart Rate, Myocardial Ischemia and Vagal Stimulation on the Threshold for Ventricular Fibrillation


SUMMARY The minimum current required to cause ventricular fibrillation was determined by electrical stimulation of the normal or ischemic canine left ventricle. The threshold for ventricular fibrillation in the normal heart decreased when the heart rate was rapid. Strong vagal stimulation did not affect the ventricular fibrillation threshold when the heart rate was fixed. The fall in the ventricular fibrillation threshold in the presence of acute myocardial ischemia was greater and more prolonged when the heart rate was rapid. These findings indicate the importance of the immediate correction of tachycardia in patients suffering from acute myocardial infarction.

Although it is known that most deaths from acute myocardial infarction occur early in the attack, and that ventricular fibrillation is the cause of death in the majority, knowledge of the factors which predispose to the development of ventricular fibrillation is still far from complete.

There has been increasing controversy about the effects of change in heart rate on ventricular irritability. The high incidence of ventricular fibrillation at the onset of acute clinical myocardial infarction and the high incidence of bradyarrhythmias at this time suggest that slow heart rate may be one factor involved in the development of ventricular fibrillation. Experimental evidence in favor of this was provided by the early studies of Han et al., which indicated that in the dog slow heart rates lead to a fall in ventricular fibrillation threshold and to an increase in the frequency of ventricular arrhythmias after coronary occlusion.

There is now both experimental and clinical evidence that inappropriate acceleration of the heart in the presence of acute myocardial ischemia may increase the vulnerability of the heart to fibrillation, and experimental evidence that slowing of the heart may reverse this effect.

Additional problems were raised by the study of Kent and co-workers. They claim that stimulation of the vagus nerve in the absence of any change in heart rate results in a 200% increase in the threshold current required to produce ventricular fibrillation in the nonischemic heart. This is surprising since even high doses of lidocaine do not have such a marked effect. The Bethesda group placed both fibrillating electrodes on nonischemic myocardium. Such nonischemic tissue may not exhibit the same reduction in the threshold current required to produce ventricular fibrillation after ligation of the coronary artery as the ischemic zone. In view of these problems, and in view of the importance of control of heart rate in patients with acute myocardial infarction, it was decided to investigate the effects of changes in heart rate and of vagal stimulation on the ventricular fibrillation threshold in the ischemic and in the non-ischemic myocardium.

Methods

Adult greyhounds of both sexes (weight 19–30 kg) were anesthetized by the intravenous injection of sodium pentobarbitol 30 mg/kg, and ventilated by a Palmer Ideal pump, initially with room air, at a rate of 18 per min and a stroke volume of 13 ml/kg. These pure-bred dogs have hearts with a weight comparable to that of man. The heart was exposed through the fifth left intercostal space and a bipolar platinum pacing electrode was sutured to the left atrial appendage. Two bipolar platinum electrodes for stimulation, and recording electrograms, and the two fibrillating electrodes were sutured to the anterior surface of the left ventricle. In those experiments in which the coronary arteries were occluded the ligatures were placed around the

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Ventricular Fibrillation Threshold

The ventricular fibrillation threshold was determined using the method of Shumway et al. as modified by Han. A quartz crystal oscillator (Devices Digitimer, Type 3290) provided three sets of pulses; the time interval between each set could be accurately and independently varied. The first set of pulses triggered an isolated Devices stimulator at regular intervals; this was used to pace the heart at the basic cycle length (300-1500 msec) through the bipolar atrial or ventricular electrodes (fig. 1). After each eighth basic driving stimulus the second output pulse triggered a Devices Type 2521 gated pulse generator which produced a train of square-wave pulses (5 msec duration; 100 Hz; variable amplitude) from a second isolated stimulator. This pulse train was delivered to the epicardium through the fibrillating electrodes, initially two German silver plates (20 mm x 9 mm), but later two stainless steel needles (6 mm long; gauge 21) mounted 2 cm apart on an epoxy resin base. The third set of output pulses was used to trigger the sweep of a Tektronix 502A dual-channel oscilloscope on which was displayed the unipolar ventricular epicardial electrogram. During pacing of the heart at a rate of 200/min, the onset and duration of the train of pulses from the fibrillating electrodes were adjusted until it began 20-40 msec after depolarization of the left ventricle and continued until the end of the T wave. The train of pulses did not extend beyond the end of the T wave, and produced only a single ventricular response. The amplitude of the pulse train was determined from the voltage drop across a precision 1000 ohm resistor in the input circuit to the heart, and displayed differentially on the second channel of the oscilloscope. The amplitude of the pulse train was increased in steps of 1 mA, and the minimum current to produce ventricular fibrillation was determined. External defibrillation was carried out within 30 seconds, and at least ten minutes was allowed to elapse before a further threshold determination was made.

Effects of Changes in Heart Rate on the Normal Myocardium

The effects of changes in heart rate on the ventricular fibrillation threshold were determined in 15 dogs. Both cervical vagus nerves were isolated, and the left divided. Two control determinations of ventricular fibrillation threshold were made, the right vagus was divided, and the observations were repeated. There was no difference in the fibrillation threshold before and after complete vagotomy.

The ventricular fibrillation threshold was then measured at heart rates of 200 per min (300 msec cycle), 150 per min (400 msec cycle), 100 per min (600 msec cycle), 70 per min (850 msec cycle), and 40 per min (1500 msec cycle) in sequence. These heart rates were produced by electrical stimulation of the left atrium through the pacing electrodes. When a rapid spontaneous heart rate (typically 140-160 beats per min) prevented regular pacing at the desired rate, the distal end of the right cervical vagus nerve was stimulated electrically (pulses of 1 msec duration and 5-12 V amplitude) at a frequency sufficient to reduce the sinus rate until it was just slower than the required rate. Stimulation of the vagus nerve was continued to reduce the sinus rate throughout the period of observations, and regular capture of the heart was then possible using the left atrial electrodes. The lowest rate, 40 per min, could only be achieved in nine dogs, owing to the development of a more rapid idioventricular rhythm in six. When the effects of the lowest heart rate had been determined, the measurements of ventricular fibrillation threshold were repeated at each heart rate in random order.

Mean arterial blood pressure was recorded from a Portex polythene catheter inserted into a carotid or femoral artery, and attached to a Consolidated Electrodyamics Type 4-327-L221 pressure transducer. The arterial blood pressure and the electrocardiogram (leads II and aVF, and the ventricular epicardial electrogram) were recorded continuously on a Devices M 8 recorder.

Effects of Changes in Heart Rate on the Ischemic Myocardium

The effects of a change in heart rate on the ventricular fibrillation threshold of hearts with an area of ischemic myocardium were studied in a group of 11 dogs. The ventricular
The fibrillation threshold was initially measured under control conditions, during atrial pacing at 200–207/min (300–290 msec basic cycle length). In four dogs it was also measured at a pacing rate of 100/min. Then the chest was reopened and, by ligation of one to three epicardial branches of the main anterior descending branch of the left coronary artery, an area of ischemia was produced around one of the electrodes used to deliver the fibrillating pulses to the surface of the left ventricle. The other electrode which produced fibrillation was outside the ischemic area. Acute ischemic injury after coronary artery occlusion was indicated by the development of marked ST-segment elevation on the epicardial electrogram recorded from the fibrillating electrode in the ischemic zone. The chest was immediately closed and further determinations were made of the threshold current to produce ventricular fibrillation at heart rates of 200–207 and 100/min in all 11 dogs. The variation in the faster heart rate was due to the necessity to pace at a slightly higher rate to capture the ventricles in some dogs with sinus tachycardia and heart rates approaching 200/min. The determinations of fibrillation threshold were repeated until 2 1/2–3 1/2 hours had elapsed from occlusion of the coronary arteries.

Three dogs were excluded from this study: one which developed spontaneous, irreversible ventricular fibrillation after coronary artery occlusion, one in which a heart rate of 100 could not be achieved owing to the intervention of a rapid idioventricular rhythm, and one in which two observations of ventricular fibrillation threshold could be made at a rate of 100 per min after ligation of the coronary artery.

Studies on Isolated Purkinje Fibers

Twenty greyhounds of both sexes, weight 18–35 kg, were anesthetized by the intravenous administration of sodium pentobarbital (30 mg/kg). The beating heart was removed, placed in a modified Krebs’ solution at room temperature, and bubbled with a 95% oxygen and 5% carbon dioxide gas mixture. The strand of Purkinje fibers running free in the left ventricular cavity from the ventricular septum to the posterior papillary muscle was excised, and fixed to a paraffin block in a tissue bath (volume 11 ml), by pins through the attached ventricular muscle. All side connections of the main strand were cut. Care was taken throughout to prevent stretching of the fibers. Fibers which showed spontaneous activity during stimulation at 30 per min were discarded. The tissue bath was perfused with modified Krebs’ solution at a rate of 10 ml/min, and temperature 36.5 ± 1.0°C (mean and range). The 95% oxygen and 5% carbon dioxide gas mixture was bubbled through both the fluid in the reservoir and that in the tissue bath. The composition of the solution was (mM): Na+, 145.8; K+, 4.5; Mg++, 1.5; Ca++, 2.7; Cl-, 133.4; HCO3-, 25; H2PO4-, 1.8; Glucose, 5. The pH was 7.41 ± 0.01 (mean ± SE of four determinations in four experiments).

Unipolar extracellular potentials were recorded from tungsten electrodes mounted on separate micromanipulators. Fine tungsten wire (diameter 40 μ) was etched electrolytically in an aqueous solution of sodium nitrate and potassium hydroxide to a rounded tip, diameter approximately 20 μ, and mounted in drawn glass capillary tubing. The electrode was fixed to the glass and insulated with epoxy resin (Araldite, CIBA), so that less than 1 mm projected beyond the insulation material. The resistance between the individual electrodes and the indifferent electrode, a grounded Ag-AgCl plate, was 1,800–3,000 ohms. The electrodes were connected separately to the two input channels of a Tektronix Model 502 dual-beam oscilloscope and the two separate biphasic potentials (amplitude 1.5–2.0 mv) were recorded on 35 mm film using an Asahi Pentax single lens reflex camera.

Basic driving and test stimuli, each of intensity four times threshold and of variable duration, were delivered from an isolated stimulator (Devices) to the septal end of the Purkinje strand through two silver electrodes insulated to their tip (diameter 1 mm). The cathode was always nearer to the recording electrodes than the anode. A Digitimer quartz crystal oscillator provided a series of pulses, programmed to trigger the oscilloscope, to determine the frequency of the basic driving stimuli (S1) and during determinations of the refractory period to provide a variable delay after each eight driving stimuli before discharge of a test stimulus (S2).

The conduction velocity of the Purkinje fiber preparations was determined from the distance between the two recording electrodes and the time interval between the peaks of the single action potentials recorded at each site.

The duration of the effective refractory period was defined as the shortest possible S1-S2 interval between two propagated responses, where S1 was the basic driving stimulus to the preparation and S2 the test stimulus consistently causing a premature second response after each eight driving stimuli.

Results

Effects of Changes in Heart Rate on the Normal Myocardium

The threshold current required to cause ventricular fibrillation was determined at a number of different heart rates in two groups of dogs. In the first set of experiments (group A; ten dogs) the duration of the train of pulses to the ventricle was adjusted during pacing of the heart at 200/min so that the train began after the QRS complex, continued until the end of the T wave, and produced only one ventricular response. The fibrillation threshold was then determined using this fixed train duration during pacing of the heart at 200–40/min. In order to exclude incomplete scanning of the vulnerable period at slow heart rates, the length of the pulse train was varied at each heart rate (200–40/min) to include only the period from early systole until the end of the T wave in another group of five dogs (group B).

There was a marked difference in the ventricular fibrillation threshold at different heart rates (fig. 2). Results were similar in the two groups of dogs in which the length of the train of impulses was fixed (group A) or varied in duration (group B). The threshold current was maximal during stimulation at 70/min. Reduction in heart rate from 70 to 40/min did not cause a significant increase in the fibrillation threshold (five dogs in group A; four dogs in group B). In both groups when the heart rate was increased from 70 to 100/min there was a significant fall in the amount of current required to produce ventricular fibrillation (P < 0.05), and a further decrease when the heart rate was increased to 150/min (P < 0.05). The fibrillation threshold during pacing at 200/min was not significantly different from that at a heart rate of 150/min.
In the second group of four dogs both vagi were divided and the ventricular fibrillation threshold at a ventricular rate of 200/min was determined in each dog, during atrial pacing (at 200/min) without vagal stimulation, during regular ventricular pacing without vagal stimulation, and during regular ventricular pacing with strong electrical stimulation of the distal ends of both vagus nerves in separate bipolar electrodes. Complete heart block with sinus arrest and transient ventricular asystole was produced in all four dogs by the strong vagal stimulation, and the left ventricle was then paced via a bipolar epicardial electrode at a rate of 200/min while the ventricular fibrillation threshold was determined. The mean values for the ventricular fibrillation threshold at a ventricular rate of 200 under the three conditions are shown in figure 4. There was no significant difference between the fibrillation threshold obtained during atrial pacing without vagal stimulation and either of the estimations made during ventricular pacing, with or without maximal vagal stimulation.

**Effects of Change in Heart Rate in the Presence of β-Adrenoceptor Blockade**

The sympathetic nerves to the heart were not divided in any of these experiments. Theoretically a change in the sympathetic drive to the heart could accompany the increase in heart rate, and contribute to the fall in the threshold current required to produce ventricular fibrillation.

In another group of four dogs the threshold current for fibrillation, determined at a pacing rate of 200/min (26.5 ± 5.6 mA), was significantly less than that during a period of pacing at 70/min with vagal stimulation (35.9 ± 4.6 mA; *P < 0.05*). Propranolol (0.2 mg/kg intravenously) reduced the rate of the unpaced hearts by 36 ± 4 beats/min. The fibrillation thresholds, determined
again at a pacing rate of 200/min (25.6 ± 3.9 mA), and at 70/min during vagal stimulation (35.8 ± 4.5 mA), showed no significant change from the results obtained under the corresponding conditions before the administration of propranolol. There was still a significant fall in the fibrillation threshold when the heart rate was increased from 70 to 200/min (P < 0.05).

Effects of Change in Heart Rate on Ischemic Myocardium

The ventricular fibrillation threshold fell acutely within ten minutes of occlusion of the coronary arteries. The mean values for fibrillation threshold in eight dogs before and at 30 min periods after the production of myocardial ischemia at heart rates of 100 and 200 beats/min are shown in figure 5. After occlusion the fibrillation threshold was similar at heart rates of 100 and 200/min, thus abolishing the relationship which had existed prior to production of ischemia. However 30 minutes after coronary artery occlusion, there was a steady increase in fibrillation threshold during pacing at a rate of 100/min, and by 60–90 minutes it was higher than the control value for the faster rate. In contrast, the threshold at the faster rate of 200/min remained depressed below the control level for 150–180 minutes before eventually returning toward the pre-ischemic level. Analysis of the variance of these grouped observations showed that after 30 minutes the difference between the fibrillation threshold at a heart rate of 100/min and that at 200/min was significant (P < 0.05). Therefore in the presence of ischemia, apart from the initial 30 min period after coronary artery occlusion, the ventricular fibrillation threshold was greater at the slower heart rate, and fell when the heart rate was increased to 200 per min.

Effects of Changes in Stimulation Frequency on Isolated Purkinje Fibers

The previous results in the nonischemic hearts suggested that the reduction in fibrillation threshold which accompanied an increase in heart rate was due to a direct effect of change in rate on the heart, rather than an effect mediated by autonomic nerves. Thus observations of the effects of changes in stimulation rate on isolated cardiac tissue were made in 20 Purkinje fibers removed from the left ventricle of 20 dogs.

The conduction velocity was maximal during stimulation at a rate of 30/min (2.08 ± 0.01 m/sec), and fell with each increase in stimulation rate (fig. 6). When the stimulation frequency was increased from 60 to 120 per min there was a significant fall in conduction velocity (P < 0.01) and further decreases in conduction velocity followed successive increases to 180, 240 and to 300/min, when it was 1.91 ± 0.01 m/sec.
m/sec. In five preparations the conduction velocities were determined repeatedly at the different rates of stimulation over a seven hour period; there was no significant alteration from the initial results.

The effective refractory period, determined in 16 of the Purkinje fibers, fell from 262 ± 7 msec during stimulation at 60/min, to 208 ± 5 msec at 120/min, and 165 ± 6 msec at 240/min. The conduction velocities of the last conducted premature beats, at the onset of the effective refractory periods in these isolated Purkinje fibers, were less than those of the regular stimuli, but did not vary significantly with change in stimulation rate (1.73 ± 0.09 m/sec at 60/min; 1.68 ± 0.11 m/sec at 120/min; and 1.85 ± 0.07 m/sec at 240/min).

Discussion

The present results show that increasing the heart rate from 70 to 100–200/min in the nonischemic dog heart reduces the electrical current required to produce ventricular fibrillation and that stimulation of the vagus nerves does not increase the threshold current for fibrillation. Within 30 minutes of the onset of acute myocardial ischemia the threshold current required to cause ventricular fibrillation is reduced to the same level at heart rates of 100 and 200/min, but thereafter the threshold current required is greater during pacing at 100 than at 200/min. Some two hours after occlusion of the coronary arteries the threshold current during pacing at 100/min approaches control values, but it remains depressed for three hours or so when the pacing rate is 200/min.

The conduction velocities of the isolated Purkinje fibers from normal hearts were also maximal during stimulation at 30–60/min, and fell with increases in the rate of stimulation. Similar observations have been made on normal-amplitude Purkinje fibers surviving over the endocardial surface of one and three-day old infarcts; as the rate of stimulation is increased the conduction velocity falls to a similar extent as in the fibers from the normal hearts (Allen, unpublished observations). Earlier reports indicate that the transmembrane potential and rate of depolarization of Purkinje fibers also fall as the frequency of stimulation is increased. With a change in stimulation rate from 60 to 120 and 240/min there was a fall in the duration of the refractory period, but no change was recorded in the conduction velocity of the last premature response before the onset of the refractory period, close to the vulnerable period of the intact heart. This suggests that slow conduction in the main Purkinje fiber network is not the main cause of the fall in fibrillation threshold which follows an increase in heart rate. The effects of rapid stimulation on local responses to electrical stimuli could not be studied with the extracellular electrodes, although such local responses can greatly influence the fibrillation threshold of the in situ heart.

Ventricular fibrillation was produced in the present studies by the application of a train of relatively large current pulses to the ventricle at the end of systole. Heterogeneities in the duration of refractory periods, conduction velocities and excitabilities have been demonstrated between different regions of the heart at this time. These heterogeneities reflect differences in the transmembrane potentials, and rate and amplitude of depolarization and the duration of the action potentials in cardiac tissues. The present results show that with an increase in the stimulation frequency there is a small decrease in the conduction velocity of isolated Purkinje fibers, and a large decrease in the fibrillation threshold of the in vivo heart. The disparity in the size of these two effects suggests that the fall in fibrillation threshold which follows an increase in stimulation frequency is due to differences in the refractory periods, the conduction velocities and the excitabilities of tissues other than the main Purkinje fiber network. We have not examined the effects of changes in stimulation frequency on the Purkinje fiber-ventricular muscle junction, or on ischemic or nonischemic ventricular muscle. The gating mechanism of the Purkinje fiber-ventricular muscle junction frequently shows nonuniform responses to rapid stimulation, with delayed conduction and 2:1 conduction block, although the refractory period of the Purkinje fibers is closer to that of nonischemic ventricular muscle under these conditions.

In the nonischemic heart the results in the present study are in conflict with those of Han et al. We did not find that the fibrillation threshold was highest during pacing at 200/min, and decreased with reduction in the pacing rate to 86/min. However, there are several differences between the studies which may account for this disagreement. Han et al. crushed the sino-atrial node, cut the autonomic effector nerves to the heart, paced the right ventricle, and determined the ventricular fibrillation threshold in the right ventricle. It is known that the threshold current required to produce ventricular fibrillation in the right ventricle is very much lower than in the left.

The central point of disagreement between the present results and those of Kent and co-workers, is our failure to confirm during either atrial or ventricular pacing at 200/min that stimulation of the vagus nerves causes a large increase in the threshold current for ventricular fibrillation in the nonischemic heart (from 26 mA to 85 mA during ventricular pacing in their study). The reasons for this are not clear. In the present study the vagal stimulation had a similar profound effect on cardiac rhythm (sinus arrest) as in the study of Kent et al. (sinus rate slowed to 50 per min). There were two minor differences in technique. First, the duration of the train of fibrillatory pulses extended 50 msec beyond the end of the T wave in the study by Kent et al.; in the present study it stopped at the end of the T wave. Second, both vagus nerves were divided in all of the present experiments. However, division of the vagus nerves in three of the experiments of Kent et al. did not modify the effects of vagal stimulation, although no data were given. The present experiments were undertaken on large pure-bred greyhounds and those of Kent et al. on smaller mongrel dogs. There may be some difference in the distribution of the vagus nerves and acetylcholine receptors in the ventricles of the two breeds of dogs, or some difference due to the larger mass of the greyhound ventricles. However, it is interesting that, despite a large increase in the threshold current for ventricular fibrillation when the heart rate was held constant during vagal stimulation, Kent et al. did not find any decrease in the temporal dispersion of recovery of excitability under these conditions. Our finding that stimulation of the vagus nerves has no effect on the fibrillation threshold of the nonischemic heart is in agreement with the earlier conclusion of Hoffman et al. that vagal stimulation does not have a significant effect on the fibrillation threshold of the nonischemic heart.
not alter ventricular excitability. Our present results are also consistent with those of Lown’s group, who stimulated the right ventricular endocardium with single pulses in dogs anesthetized with chloralose. Heart rate was kept constant in their study. Stimulation of the vagus nerves did not raise the ventricular fibrillation threshold unless the sympathetic nerves were stimulated simultaneously.

The measurement of the fibrillation threshold at different heart rates during ischemia was an attempt to determine whether the relationship we had shown in the normal myocardium obtained in the presence of ischemia. With the exception of the very early postocclusion phase (< 60 min) a similar relationship obtained as in the nonischemic state. The duration of the period of reduced fibrillation threshold (150-180 min) was longer than that found in the study of Burgess et al. in which similar branch arteries were ligated but ventricular vulnerability was determined using pulse trains of variable duration and fixed current amplitude. As in the study of Kerzner et al., idioventricular rhythm (at a rate of 50-90/min) supervened if the heart rate was reduced below 100/min during the period 30-180 minutes after occlusion of the coronary artery. This prevented the determination of fibrillation threshold at ventricular rates less than 100/min. Hence, while the present results show a similar trend to those of Kent and co-workers and extend their findings to a longer period of acute myocardial ischemia and to an increase in heart rate from 100 to 200/min, we are unable to comment on the increase in fibrillation threshold observed by them when the heart rate was reduced from 90 to 50/min by vagal stimulation alone. Our studies in the nonischemic heart suggest that reduction in heart rate below 70/min produces no further increase in fibrillation threshold.

Clinical experience of acute myocardial infarction indicates that sinus tachycardia is not infrequent in the first hour after the onset of symptoms, during movement of such patients to hospital, and after the administration of excessive doses of atropine. Sinus tachycardia predisposes to ventricular arrhythmias in these patients. There is experimental evidence that rapid heart rates will increase the degree and severity of myocardial ischemic injury and necrosis. The present experimental data indicate that increased heart rate (greater than 100/min) will also reduce the fibrillation threshold of the ischemic ventricle. Prehospital administration of preparations which correct inappropriately slow or rapid heart rates after acute myocardial infarction clearly has merit. Beneficial effects have been recorded from the administration of a combination of atropine and beta-adrenoceptor blocking drug, sotalol. However, despite correction of abnormal heart rates, patients remain highly vulnerable to ventricular fibrillation during the first half hour after the onset of the coronary attack.

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