Electrical Stability of Acutely Ischemic Myocardium
Influences of Heart Rate and Vagal Stimulation

By Kenneth M. Kent, M.D., Ph.D., Eldon R. Smith M.D., David R. Redwood, M.B., M.R.C.P., and Stephen E. Epstein, M.D.

SUMMARY
Previous investigations have shown that a slower heart rate (HR) and myocardial ischemia independently diminish the electrical stability of the heart. It therefore was suggested that increasing heart rate during myocardial infarction might diminish the incidence of serious ventricular arrhythmias. However, since increased HR during experimental acute myocardial ischemia augments the degree of ischemia, an evaluation of the presumed "protective" effects of increased HR on the electrical stability of acutely ischemic myocardium was undertaken. The differences in refractory periods (RP) of eight contiguous areas of the left ventricle were determined as a function of HR. In nonischemic myocardium, the disparity of RP was less at an HR of 180 than 60. However, in ischemic myocardium the disparity increased in three of six animals as the HR was increased from 60 to 90, in seven of 10 animals as HR was increased from 60 to 120, and in all animals when the HR was increased from 60 to 180. The increased disparity of RP is believed to favor development of reentrant arrhythmia. The vulnerability of the heart to develop ventricular fibrillation was assessed by determining ventricular fibrillation threshold (VFT). During ischemia, VFT was not only an inverse function of HR but also was found to be independently influenced by electrical stimulation of the cervical vagus nerves. In the absence of vagal stimulation VFT was lowered in only one of four dogs as HR was increased from 50 to 90, but decreased 30% (P < 0.01) as HR reached 120 and 74% at 180 beats/min. When vagal stimulation was used to control HR VFT was lowered 37% as HR was increased from 50 to 60 to 90 (P < 0.05). We conclude that increasing HR within a physiologic range by diminishing vagal tone during myocardial ischemia decreases electrical stability of the ventricle by (1) increasing ischemia consequent to the rate-induced increase in myocardial oxygen requirements, and (2) a direct electrophysiologic action of the vagus on the ventricular myocardium.

Additional Indexing Words:
Ventricular fibrillation threshold Refractory periods Coronary occlusion
Acetylcholine Electrophysiology

The influence of heart rate on the incidence of arrhythmias during acute myocardial ischemia has been a topic of considerable controversy and speculation. Previous investigators have shown that both slower heart rates and acute myocardial ischemia lead to increased disparity of refractory periods ("temporal dispersion") between contiguous areas of myocardium and to decreased ventricular fibrillation threshold.1, 2 The increase in "temporal dispersion" and the decrease in fibrillation threshold indicated that the heart is more vulnerable to the development of reentrant arrhythmias and ventricular fibrillation. These results provided the electrophysiologic rationale for the hypothesis that increasing heart rates from bradycardic levels during acute myocardial ischemia should decrease the incidence of reentrant arrhythmias and ventricular fibrillation.3, 4 However, the beneficial effects of faster heart rates on disparity of refractory periods and fibrillation threshold were demonstrated only in nonischemic myocardium.1, 2 Moreover, it has been shown that when heart rate is increased during experimental acute coronary occlusion the degree of ischemic injury increases5, 6 and the incidence of ventricular fibrillation and ventricular arrhythmias tends to be greater.7 Therefore, we questioned the validity of extrapolating electrophysiologic data obtained in nonischemic myocardium to ischemic conditions. To determine whether the electrophysiologic alterations induced by changes in heart rate in
the presence of myocardial ischemia are different from those found in the absence of ischemia, we defined the relation of heart rate to disparity of refractory periods and ventricular fibrillation thresholds in the nonischemic and ischemic canine ventricle.

Methods

Mongrel dogs weighing from 13 to 15 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. The heart was exposed through a left thoracotomy and an adjustable ligature was placed around the left anterior descending coronary artery approximately 2 cm from its origin. Heart rate and systemic arterial pressure were recorded continuously: When heart rate was controlled by vagal stimulation, the right and left cervical vagi were isolated and stimulated through platinum electrodes. Pulses of 0.3-msec duration from 10 to 40 Hz were applied at intensities necessary to produce the desired heart-rate response.

Disparity of Refractory Periods

The disparity of refractory periods was measured by suturing a small circular disc with a central electrode and eight additional electrodes placed in two concentric circles (2 mm apart) onto the epicardium of that portion of the ventricle subsequently made ischemic. The threshold voltage for each individual electrode was determined by stimulating late in the cardiac cycle long after the refractory period. The voltage was then increased 30%, and the interval between the basic pacing stimulus and the test stimulus was shortened until no propagated response occurred. This stimulus interval was taken as the relative refractory period. The degree of disparity of refractory periods was defined as the maximum difference of the eight refractory periods measured in each animal during a given intervention. This procedure was similar to that described by Han et al. The duration of the refractory periods as well as the threshold voltage was quite variable during the first few minutes of ischemia. However, after 8–12 min of ischemia these parameters were stable and it was at this time that the disparity of refractory periods was measured. In general, the refractory periods during ischemia shortened at the faster heart rates (120 and 180) and lengthened at slower rates.

Effect of Heart Rate

Two groups of dogs were studied. In the first group heart rate was controlled by slowing the intrinsic sinus node rate to less than 50 beats/min by bilateral stimulation of the cervical vagi, and then pacing the left ventricle to the desired rate through the central electrode of the disc. The intensity of vagal stimulation was thereafter held constant throughout the course of the experiments in each dog. The disparity of refractory periods was determined at heart rates of 60 and 180 beats/min in six dogs and at 60 and 120 beats/min in four dogs, under both nonischemic and ischemic conditions. In the second group heart rate was controlled by ventricular pacing after induction of complete heart block by 1 ml 10% formalin injected into the atrioventricular (A-V) node region. The disparity of refractory periods was studied in this preparation in six dogs at heart rates between 50 and 180 beats/min under ischemic conditions only.

The sequence of heart rates studied in each group was randomized. In addition, by retesting the initial intervention at the end of the procedure in five animals, we found no changes as a function of time or as a result of the experimental interventions.

Effect of Vagal Stimulation

Two dogs were studied at a fixed heart rate to determine the effect of vagal stimulation alone on disparity of ventricular refractory periods. Ventricular rate was held constant at 180 beats/min by electrically pacing the left ventricle. The disparity of refractory periods was determined under nonischemic and ischemic conditions with and without cervical vagal stimulation. When the vagus was stimulated the intensity of stimulation was set at that level required to slow the sinus atrial rate to 50 beats/min.

Ventricular Fibrillation Threshold

A train of pulses, each 2 msec in duration and 8 msec apart, was delivered through two platinum electrodes sutured to the left ventricle outside of the region of subsequent ischemia. The train of pulses was begun 80 msec after the onset of ventricular activation, and continued 50 msec after the end of the T wave in lead II of the ECG. Current was augmented in 4-ma increments (measured with a Hewlett-Packard current probe and displayed on a storage oscilloscope) until ventricular fibrillation supervened. Ventricular fibrillation threshold was defined as the current (in ma) required to produce fibrillation. This procedure was similar to that described by Han. Ventricular defibrillation was accomplished within 30 sec after the initiation of fibrillation by a DC current (capacitor discharged) applied to the heart through two 6-cm electrodes. The interventions were randomized. Furthermore, the results of two control animals, each fibrillated two times at a constant heart rate under ischemic and two times under nonischemic conditions over 4 hours, demonstrated no changes in the fibrillation threshold for either condition over this time period.

Effect of Heart Rate

The effect of heart rate on ventricular fibrillation threshold was determined in two groups of animals. In the first group (14 dogs), heart rate was controlled by slowing the sinus node rate to less than 50 beats/min by cervical vagal stimulation, and then pacing the ventricle to the desired rate. Heart rates of 60 and 180 were studied under nonischemic conditions, and in six of the animals studies also were conducted during ischemia. In the second group (eight dogs) heart rate was controlled by right ventricular pacing after complete heart block had been induced by injection of formalin into the A-V node. The effect on fibrillation threshold of heart rates of 60 and 180 (three animals), or 50, 90, and 120 (five animals) were studied during
ischemia. No vagal stimulation was employed in this second group.

Effect of Vagal Stimulation

The effects of cervical vagal stimulation on the fibrillation threshold at a fixed heart rate were determined in six animals under nonischemic conditions. Heart rate was maintained constant at 180 beats/min by ventricular pacing. When the vagus was stimulated, the intensity of stimulation was set at that level required to slow the sinus rate to 50 beats/min. Ventricular fibrillation threshold under control conditions and under conditions of cervical vagal stimulation was obtained in each animal.

Effect of Increasing Heart Rate by Decreasing Vagal Stimulation

In another group of five animals, ventricular fibrillation thresholds were determined during ischemia when heart rate was varied between 50 and 90 beats/min by changing the intensity of vagal stimulation. Heart rate was controlled only by cervical vagal stimulation and ventricular pacing was not employed.

Statistical analysis of the results was performed by comparing the paired responses in each animal and the changes analyzed by Student's t test for paired data.

Results

Disparity of Refractory Periods

Effect of Heart Rate

The results were similar whether heart rate was controlled by ventricular pacing when the intrinsic heart rate was slowed to 50 beats/min by vagal stimulation or controlled by ventricular pacing in the presence of complete heart block. In the dogs with vagal stimulation, in nonischemic myocardium, the maximum difference of refractory periods of the myocardium under the eight electrodes tended to decrease (average 46%) as heart rate was increased from 60 to 180; it decreased 30% as heart rate was increased from 60 to 120 ($P < 0.02$, fig. 1, left). However, opposite results were obtained in ischemic myocardium (fig. 1, right). As heart rate was increased from 60 to 180 beats/min, the disparity of refractory periods increased 88% ($P < 0.02$), and when the rate was increased from 60 to 120 it increased in three of the four dogs so tested. The average increase was 57%. In six dogs with induced heart block and ventricular pacing, heart rates were

![Figure 1](image_url)

*The influence of heart rate on the disparity of refractory periods in the absence of ischemia (left) and during ischemia (right). Six animals were studied at heart rates of 60 and 180 under both ischemic and nonischemic conditions. Four animals were studied at 60 and 120 under both conditions.*
studied between 50 and 180 in three to four steps to determine the heart rate at which disparity of refractory periods began to increase (fig. 2). Increasing heart rate to 90 beats/min from 50-60 beats/min resulted in increased disparity of refractory periods in three dogs tested, but not in two. As heart rate was increased to 120/min, the disparity of refractory periods increased in four of six animals and large increases in the disparity of refractory periods occurred when heart rate was increased to 180 beats/min in all of the three dogs tested.

**Effect of Vagal Stimulation**

There was no change in the disparity of refractory periods of ischemic or nonischemic myocardium in two dogs when the cervical vagi were stimulated and heart rate was held constant by ventricular pacing.

**Ventricular Fibrillation Threshold**

**Effect of Heart Rate**

The current required to produce ventricular fibrillation in 14 animals showed no consistent relation to heart rate in nonischemic myocardium, whereas in the ischemic myocardium, ventricular fibrillation threshold was inversely related to heart rate. Figure 3 depicts the results obtained in six animals which were tested during both ischemic and nonischemic conditions. An average of 89 ± 31 (SEM) ma was required to produce fibrillation during ischemia at a heart rate of 60 beats/min, but only 38 ± 6 ma was required to produce fibrillation at a heart rate of 180 beats/min \( (P < 0.02) \).

The levels to which heart rate had to be increased to diminish ventricular fibrillation threshold during ischemia was determined by studying the influence of smaller increments in heart rate on fibrillation threshold. In the absence of vagal stimulation (ventricular rate altered by ventricular pacing in dogs with heart block), fibrillation threshold diminished slightly in only one of four dogs when heart rate was increased from 50 to 90 beats/min but decreased an average of 30% when heart rate was increased to 120 (fig. 4, \( P < 0.01 \)). In an additional group of three dogs ventricular fibrillation threshold was studied when heart rate was increased from 60 to 180/min. At the faster heart rate in nonischemic myocardium, whereas in the ischemic myocardium, ventricular fibrillation threshold was inversely related to heart rate.

---

**Figure 2**

Disparity of refractory periods as a function of heart rate in six animals during ischemia.

**Figure 3**

The current required to produce ventricular fibrillation—ventricular fibrillation threshold—as a function of heart rate in the absence of ischemia (left) and during ischemia (right) in six animals.
STABILITY OF ISCHEMIC MYOCARDIUM

Figure 4

Ventricular fibrillation threshold as a function of heart rate in four animals under ischemic conditions. Heart rate was controlled by ventricular pacing after production of complete heart block.

rate fibrillation threshold decreased an average of 74%.

**Effect of Vagal Stimulation**

To determine the effect of vagal stimulation on fibrillation threshold, dogs were studied at constant ventricular rate (ventricles paced at 180/min) under control conditions and when the cervical vagi were stimulated at an intensity that slowed the sinus (atrial) rate to 50 beats/min. A large increase in ventricular fibrillation threshold was observed in six animals during vagal stimulation (fig. 5). The current required to produce fibrillation averaged 26 ± 3 ma in the absence of vagal stimulation and 85 ± 13 ma when the vagi were stimulated ($P < 0.025$).

**Effect of Increasing Heart Rate by Decreasing Vagal Stimulation**

Since vagal stimulation per se greatly influenced fibrillation threshold, and since fibrillation threshold did not consistently diminish when heart rate was increased by ventricular pacing to 90 beats/min from 50–60 beats/min, the effects of increasing heart rate on ventricular fibrillation threshold was assessed when heart rate was increased during ischemia by lowering the intensity of vagal stimulation. Under these circumstances, ventricular fibrillation threshold during ischemia decreased an average of 37% ($P < 0.05$) as the heart rate was increased to 90 beats/min from 50–60 beats/min (fig. 6).

**Figure 5**

The effects of cervical vagal stimulation on the ventricular fibrillation threshold in six animals under nonischemic conditions at a constant heart rate of 180 beats/min. In three of the animals, the vagi were decentralized with no significant change in the response.
myocardial infarction die before receiving medical aid,\textsuperscript{8-10} most from ventricular fibrillation. The observation that bradycardia occurred in a substantial percentage of patients early in the course of acute myocardial infarction\textsuperscript{11,12} led to the hypothesis that increasing heart rate with atropine in such patients might considerably reduce the incidence of potentially fatal ventricular arrhythmias. The studies of Han et al.\textsuperscript{1,2} which demonstrated that slower heart rates and acute myocardial ischemia independently decrease fibrillation threshold (i.e., increase the vulnerability of the heart to the development of ventricular fibrillation) and increase disparity of refractory periods of contiguous areas of myocardium were interpreted as providing the electrophysiologic rationale for this hypothesis.\textsuperscript{3,4} The present investigation demonstrates that the observations of Han et al. cannot be extrapolated to heart rate changes during ischemia. We found that, although disparity of refractory periods is increased by slowing heart rate in the nonischemic myocardium, it is decreased when heart rate is slowed in the ischemic ventricle. Moreover, the electrical instability of the ventricle, as assessed by measuring fibrillation threshold, is also decreased during acute myocardial ischemia when heart rate is slowed. The protective effect of a slow heart rate during ischemia is also demonstrated by the observation that while ischemia lowered fibrillation threshold and increased disparity of refractory periods at faster heart rates, these deleterious changes were not found when ischemia was produced at a heart rate of 60 beats/min (figs. 1 and 3).

The studies of Scherlag et al.\textsuperscript{13} provide additional data which demonstrate that increasing heart rate during acute myocardial ischemia leads to deleterious electrophysiologic effects. They showed that faster heart rates reduce the initial deflection of local electrograms recorded from ischemic tissue, a finding believed to reflect impaired ability of the action potential to propagate effectively (decremental conduction). Thus, an increase in heart rate during acute myocardial ischemia appears to cause at least two electrophysiologic changes that may be responsible for the greater vulnerability of the ventricle to fibrillation under these circumstances: (1) it increases the disparity of recovery periods in contiguous areas of myocardium; (2) it produces changes that predispose to decremental conduction. Both of these alterations would lead to slow, inhomogeneous spread of impulses resulting in the establishment of multiple sites of reentrant activity.

\textbf{Systemic Arterial Pressure}

Although there often was a transient change of mean systemic pressure with large changes in heart rate, pressure returned to control levels (± 10 mm Hg) before any determinations were made during each of the experimental interventions.

\textbf{Discussion}

Over 50% of patients experiencing an acute

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig6}
\caption{Ventricular fibrillation threshold as a function of heart rate in five animals during ischemia. Heart rate was controlled by vagal stimulation only.}
\end{figure}
fractionation of wavefronts, and eventually ventricular fibrillation.

The mechanism responsible for the rate-related development of these deleterious electrophysiologic changes is most likely related to the fact that increasing heart rate, even from rates as slow as 35–45 beats/min, augments the degree of ischemic injury during acute coronary occlusion. It would therefore appear that although a faster heart rate reduces inhomogeneity of refractory periods under nonischemic conditions, this favorable effect is overridden during coronary occlusion when the faster rate results in enhanced metabolic demands and consequently increased ischemia.

Our results also demonstrated that vagal stimulation per se has a profound effect on ventricular fibrillation thresholds. When the ventricles were paced at a constant rate to obviate the effects that alterations in heart rate might have on fibrillation threshold, stimulation of the cervical vagi at intensities that slowed the sinus (atrial) rate to 50 beats/min increased fibrillation threshold by an average of 200%. Although it is well known that the vagal trunk contains some sympathetic as well as vagal fibers, it is unlikely that the increase in fibrillation threshold produced by vagal stimulation was due to stimulation of the sympathetic fibers since Han et al. have shown that specific stimulation of cardiac sympathetic nerves produces deleterious electrophysiologic changes in the canine myocardium.

Of possible relevance to the concept that vagal activity may reduce the susceptibility of the ventricle to arrhythmias during acute myocardial ischemia are the findings of Scherlag et al. These investigators showed that, during ischemia, ventricular ectopic beats could be abolished by vagal stimulation, a result attributed to a decrease in heart rate (and thereby decrease in myocardial ischemia). Our results are compatible with this interpretation, but also suggest that part of the beneficial effect may have been caused by a direct electrophysiologic action of the vagus on the ventricle.

The observation that vagal stimulation enhances electrical stability of the ventricles adds to other observations indicating that vagal efferents play an important physiologic role in controlling ventricular function. Thus, considerable anatomic evidence exists for the presence of cholinergic innervation of the ventricles. In addition, vagal stimulation reduces ventricular contractility and acetylcholine slows the rate of firing of idioventricular pacemakers in dogs with complete idioventricular block. More recently, acetylcholine has been found to alter the configuration of action potentials in the proximal portion of the His-Purkinje conduction system of the dog.

Definitive evidence relating to the mechanism by which vagal stimulation directly decreases vulnerability of the ventricle to fibrillation is lacking. The present investigation, however, demonstrates that the vagus does not influence disparity of refractory periods in contiguous areas of epicardium. This is compatible with the findings that vagal stimulation has no effect on transmembrane action potential of ventricular epicardium studied in vivo. Whether or not vagal stimulation alters the electrical homogeneity of the terminal arborization of the Purkinje system in ventricular muscle, the Purkinje system itself, or the Purkinje-muscle junction is not known. In this regard, there are two conflicting studies in the literature: while Hoffman and Cranefield reported that acetylcholine (10 µg/ml) had no effect on the characteristics of the action potential of Purkinje fibers, Bailey et al. showed in a more recent study that acetylcholine (4 µg/ml) depressed the slope of diastolic depolarization and increased the rise time, amplitude, and conduction velocity of action potentials recorded in the proximal portion of the His-Purkinje system of the canine ventricle. If the results of the latter study reflect a physiologic function of the vagus on propagation of the ventricular action potential, then vagal stimulation might minimize any tendency for decremental conduction to occur within the His-Purkinje system and thereby create a less favorable electrophysiologic environment for reentrant arrhythmias.

It is important to note that although the greatest alterations in disparity of refractory periods and fibrillation threshold occurred when heart rate was increased to unphysiologic levels, changes were observed even over the rather narrow range of heart rate commonly observed during acute myocardial infarction in man. Thus, the disparity of refractory periods increased in several of the dogs studied when heart rate was raised to 90 beats/min from 50 to 60 beats/min by ventricular pacing. Moreover, although fibrillation threshold diminished in only one of four animals when heart rate was increased by ventricular pacing from 50 to 90 beats/min it diminished in all animals tested (by an average of 37%) when the same change in heart rate.
was brought about by diminishing the intensity of vagal stimulation.

In summary, the results of the present investigation demonstrate that in experimental acute myocardial ischemia (1) increasing heart rate per se increases nonhomogeneity of refractory periods in contiguous areas of myocardium and increases the vulnerability of the ventricle to fibrillation, and (2) reducing vagal tone, independent of changes in heart rate, leads to increased electrical instability of the heart. Both of these effects would be potentially deleterious consequences of increasing the heart rate with atropine during acute myocardial infarction. These results are compatible with other studies performed in this laboratory in which we demonstrated an increased tendency for serious ventricular arrhythmias to develop when heart rate was increased by atropine during experimental acute myocardial infarction in the closed-chest conscious dog. Although it is unknown whether these electrophysiologic and arrhythmic observations are relevant to the situation of acute myocardial infarction as it occurs in man, serious ventricular arrhythmias appearing after the administration of atropine to patients with acute myocardial infarction have recently been reported. A critical reassessment of the role of atropine in the treatment of patients with acute myocardial infarction is therefore essential.

References

7. Karsh RB, Orlando M, Norman D, Epstein SE: Ineffectiveness of prophylactic atropine in decreasing the incidence of arrhythmias or enhancing the survival during acute coronary occlusion in conscious dogs. In press
15. Cooper T: Terminal innervation of the heart. In Nervous Control of the Heart, edited by Randall WC. Baltimore, Williams and Wilkins Co., 1965
Electrical Stability of Acutely Ischemic Myocardium: Influences of Heart Rate and Vagal Stimulation
KENNETH M. KENT, ELDON R. SMITH, DAVID R. REDWOOD and STEPHEN E. EPSTEIN

_Circulation_. 1973;47:291-298
doi: 10.1161/01.CIR.47.2.291
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/47/2/291

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/