Atropine and Acute Myocardial Infarction

To the Editor:

In a recent paper by Epstein et al., a comparison was made between our study and that of Scherlag et al. on the relationship between heart rate and the likelihood of coronary occlusion in dogs. The paper indicated that, in contrast to our results, Scherlag et al found that increasing heart rate during coronary occlusion provoked ventricular arrhythmias and fibrillation, and vagal stimulation often reduced ventricular ectopic activity. I would like to point out that these two studies are markedly different in experimental design and, therefore, are not comparable. We observed the incidence of ventricular premature beats within 5 min of the start of coronary occlusion at various heart rates between 75 and 150/min. In most instances the duration of occlusion was 1-3 min since the arterial clamp was removed immediately with the appearance of ventricular premature beats. In the study of Scherlag et al., ventricular tachycardia or fibrillation was provoked by increasing heart rate to 200/min by atrial pacing during coronary occlusion of longer durations lasting up to 20 min.

As previously observed by us, the effects of coronary occlusion on electrophysiologic properties of the ventricular myocardium are variable depending on the time of observation relative to the start of occlusion. Coronary occlusion produces an initial decrease in diastolic threshold, refractory period, and conduction time in the affected area within 2-3 min after the start of occlusion, followed by a marked increase in these parameters with the continuation of occlusion. It is possible that excitability and conductivity are initially increased because of moderate myocardial ischemia, but they are subsequently depressed when the myocardium becomes severely ischemic. Our observations on the relationship between heart rate and the incidence of ventricular premature beats were made during this initial phase of increased excitability and conductivity, when the ectopic beats are more likely to be due to the discharge of automatic Purkinje fibers. The increased excitability is also expected to facilitate focal reexcitation resulting from increased asynchrony of repolarization at the boundary between the normal myocardium and the moderately ischemic myocardium with accelerated repolarization process. The observed increase in the incidence of premature beats at slower heart rates may, then, be due to an increase in the degree of asynchrony of repolarization between the normal and moderately ischemic areas. It has been shown that, during conduction (partial occlusion) of a coronary artery which produces a sustained decrease in refractory period in the affected myocardium, presumably due to moderate ischemia, the difference in refractory periods between the normal and moderately ischemic areas is indeed increased at slower heart rates.

In contrast, Scherlag et al. showed that ventricular tachycardia and fibrillation are provoked by increasing the heart rate to 200/min by atrial pacing during a longer period of coronary occlusion when excitability and conductivity are expected to be markedly depressed in the affected area as a result of severe ischemia. Such ventricles should be more vulnerable to fibrillation since reentry and fractionation of wavefronts are more likely to occur because of the presence of areas of depressed excitability and conductivity. It has been shown that the ventricle with prolonged coronary occlusion could be more readily fibrillated by premature beats, including those with relatively longer coupling intervals. When the extremely rapid heart rate is imposed on such ventricles, it may decrease the arterial pressure and coronary flow and further increase the degree of ischemia, resulting in further depression of excitability and conductivity in the ischemic area. Under these circumstances, rapid ventricular beats are certain to produce deleterious electrophysiologic effects since they are, in effect, a series of premature beats that are capable of inducing reentrant beats and fractionation of wavefronts leading to ventricular fibrillation. Therefore, it is not surprising to observe that the temporal dispersion of excitability is increased and fibrillation threshold is decreased during the rapid pacing of 180/min in the ventricle with coronary occlusion.

I agree with Epstein et al. that atropine has the capability of increasing the heart rate enough to produce deleterious effects in patients with acute myocardial infarction. This potential danger led to their reservation on the advisability of self-administration of atropine by patients in the absence of close medical supervision. However, it has been recognized that increasing the ventricular rate by means of atropine or cardiac pacing has a definite place in the management of bradycardia and ventricular ectopic activity in the setting of coronary care unit. The monitoring of electrocardiogram and blood pressure would help determine whether the patient will be benefited by an increase in the heart rate. An increase in the arterial pressure resulting from an increase in the ventricular rate would certainly be beneficial in the patient whose bradycardia is associated with hypotension. The close medical observation will also allow more judicious administration of atropine or the use of a temporary pacemaker to achieve a ventricular rate just high enough to suppress the ectopic activity without
decreasing the arterial pressure and coronary blood flow.

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The authors reply:
To the Editor:

We appreciate the opportunity of responding to some of the questions raised by Dr. Han in his letter. Dr. Han makes a very important point when he emphasizes that his own observations (demonstrating that slower heart rates during experimental acute myocardial infarction increase the incidence of ventricular premature beats) were made mainly within the first 1–3 min of onset of acute coronary occlusion. We certainly do not question the importance of these results, given this time frame and the fact that open-chest anesthetized dogs were used with the attendant increase in circulating catecholamines, faster control heart rates, etc. However, it is questionable how relevant the data are to the problem we were mainly concerned with; i.e., the advisability of giving atropine to the patient with bradycardia and acute myocardial infarction. In this circumstance, practical considerations make it virtually impossible for any therapeutic intervention to be applied for the first few minutes after onset of infarction. It therefore seems to us that this important clinical question relates not so much to the first 3 min of the onset of myocardial infarction but to the effects of increasing heart rate on the incidence of ventricular premature contractions and ventricular fibrillation over the course of the first 1–3 hours after onset of acute infarction.

Dr. Han is not entirely accurate in suggesting that the time course of onset of ventricular arrhythmias after coronary occlusion is different in dogs and Dr. Scherlag's studies1,2 was very different. Moreover, although interpretation of Dr. Scherlag's paper is complicated when evaluating the results following the very fast-paced heart rates, Dr. Han neglects to mention another phase of the study in which these investigators reported that ventricular slowing produced by vagal stimulation caused disappearance of ventricular ectopic beats in all instances. Nevertheless, interpretative difficulties do remain since this study was not specifically designed to answer the question we were interested in exploring. We therefore investigated the effects of atropine (using a randomized study design) on ventricular arrhythmias over the first few hours of acute coronary occlusion in the closed-chest conscious dog.3 This model was chosen so that the relative arrhythmic potential of a physiologic range of heart rate could be evaluated. We found that the incidence of serious ventricular arrhythmias was directly related to the spontaneous heart rate; i.e., slower heart rates (< 60 beats/min) were accompanied by a lower incidence of ventricular ectopic activity and ventricular fibrillation. Moreover, we found that when compared to a saline-treated control group the incidence of ventricular arrhythmias and ventricular fibrillation was higher in dogs whose baseline heart rates were increased from a mean of 88–107 beats/min by an infusion of atropine.

A second aspect of the problem raised in Dr. Han's letter is the influence of heart rate on electrophysiologic parameters that may influence the incidence of ventricular arrhythmias. Dr. Han and his co-workers demonstrated that both ischemia and bradycardia independently increase the disparity of the length of ventricular refractory periods (thereby favoring development of reentrant arrhythmias) and decrease ventricular fibrillation threshold.4 While we do not question these experimental results, we do wonder whether some of the conclusions derived from these results are entirely valid. For example, several authors have interpreted these data as supporting the hypothesis that increasing the heart rate of a patient with an acute myocardial infarction who has bradycardia will diminish the risk of arrhythmic death. Although this may be true, it appeared somewhat tenuous to us to extrapolate data obtained in the absence of ischemia to the ischemic situation since, to our knowledge, Dr. Han has never published studies showing that a slower heart rate during acute myocardial infarction leads to deleterious electrophysiologic effects (with the exception of a figure5 illustrating temporal dispersion data obtained from only a single dog).

Our own skepticism originated from the finding that increasing heart rate, even from rates as slow as 30–40/min, increased the degree of ischemic injury in the closed-chest conscious dog,6 a result which suggested to us that altering heart rate might have very different electrophysiologic effects in the presence of ischemia. When this hypothesis was tested, we indeed

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