We agree with Dr. Epstein’s suggestion that increase in rate by administration of atropine need not always reduce the incidence of arrhythmias and might even increase that incidence. We feel, however, that the findings of Han, of Epstein, and of Scherlag are not necessarily in conflict because an increase in rate can, in fact, make reentrant extrasystoles either appear or disappear. We agree with Dr. Epstein’s caveat that the view that increase in heart rate necessarily leads to a decrease in arrhythmias is an overly simple rule on which to base therapy.

Andrew L. Wit, Ph.D.
Assistant Professor of Pharmacology
College of Physicians and Surgeons
of Columbia University
New York, New York

Paul F. Cranefield, M.D., Ph.D.
Associate Professor
The Rockefeller University
New York, New York

References

The authors reply:
To the Editor:

Drs. Wit and Cranefield’s letter concisely outlines their important contributions to the understanding of the relation between heart rate and reentry in isolated cardiac tissue. We also appreciate their attempt to reconcile our views with those of Dr. Han and co-workers. However, we do not believe the data obtained in the intact animal permits such a harmonious reconciliation.

First, let us clearly point out the differences between our experimental data and the commonly held interpretations of the data of Han et al. The latter authors demonstrated that temporal dispersion of ventricular refractory periods decreases and ventricular fibrillation threshold increases when heart rate is augmented under nonischemic conditions.1 These data thus indicate that electrical stability of the myocardium is enhanced by faster rates in the absence of ischemia. Although comparable data were not obtained during ischemia, these experiments provided the electrophysio-

logic rationale for the hypothesis that bradycardia is an unstable rhythm during acute myocardial infarction and that increasing heart rate would decrease the incidence of serious ventricular arrhythmias. We wish to emphasize that in the nonischemic model our findings are essentially in agreement with those obtained by Dr. Han et al. However, we questioned the validity of extrapolating these results to the ischemic myocardium, since we had demonstrated that increasing heart rate, even from baseline rates as slow as 30 beats/min, increased ischemic injury.2 Thus, if greater ischemic injury increases the susceptibility of the intact heart to the development of serious arrhythmias (as one would intuitively expect), we hypothesized that deleterious electrophysiologic results would be found in the presence of ischemia. This turned out to be the case; during ischemia (left anterior descending coronary artery occlusion) we found that increasing heart rate increased the disparity of refractory periods and decreased ventricular fibrillation threshold.3 Both these changes suggest that during ischemia increasing heart rate leads to decreased electrical stability of the myocardium.

How do these results relate to the data of Drs. Wit and Cranefield? Obviously, because of the difference in experimental models, it is impossible to draw any definitive comparisons. Drs. Wit and Cranefield are working with an elegant in vitro preparation, i.e., isolated Purkinje fiber bundles. Of importance, this tissue does not perform mechanical work; hence, an increase in stimulus frequency would not substantially increase myocardial oxygen utilization and therefore the degree of ischemia. In contrast, the electrophysiologic measurements in our studies were obtained in working myocardium. Hence, this system is considerably more complex than that of Drs. Wit and Cranefield insofar as any increase in rate during coronary occlusion also leads to an increase in ischemia injury.2 On the basis of our results in the intact heart, it would appear that the augmentation of myocardial ischemia produced by faster heart rates seems to be the predominant influence during acute coronary occlusion; i.e., while disparity of refractory periods diminished when heart rate was increased in the absence of ischemia, it increased when heart rate was increased in the absence of ischemia, it increased when heart rate was raised in the presence of ischemia. The relative complexity of the situation present in the intact heart is further evidenced by our recent demonstration that vagal stimulation per se increases electrical stability of the ventricle.4 Thus, three factors will independently influence electrical stability of the intact heart when heart rate is increased with atropine during myocardial ischemia: the increase in heart rate, the increase in myocardial ischemia, and the decrease in vagal tone.

Finally, the interesting triphasic relation between rate of stimulation and reentrant impulses demonstrated by Drs. Wit and Cranefield in isolated Purkinje fibers is not found when heart rate is related to ventricular fibrillation threshold or disparity of recovery periods in the intact heart. The accompanying figure (fig. 2) demonstrates a stimulus-response curve covering a heart rate range from 60 to 180 beats/min. The relation between heart rate and the electrophysiologic variables.
measured is monophasic over the range of heart rate studied. Moreover, ischemic injury following coronary occlusion is also linearly related to heart rate, a finding that provides further support for the hypothesis that these electrophysiologic parameters are greatly influenced by the degree of myocardial ischemia.

Electrophysiologic studies are of critical importance in expanding our knowledge of the mechanisms responsible for the genesis of arrhythmias. Nonetheless, the most relevant experiment which would provide insight into how alterations in heart rate change the propensity for arrhythmias to develop during myocardial ischemia would be one that allows determination, in the intact heart, of the actual incidence of serious ventricular arrhythmias at different heart rates. In this regard, we have found consistently that during experimental acute coronary occlusion in the closed-chest sedated dog the incidence of serious ventricular arrhythmias tends to be greater when heart rate is increased from control levels by atropine. In addition, sinus bradycardia (heart rates of 40–60 beats/min), occurring spontaneously during coronary occlusion or induced by vagal stimulation, does not predispose to the development of serious ventricular arrhythmias.

What is clear from our studies, therefore, is that moderately severe bradycardia in itself does not appear to be associated with an increased incidence of serious arrhythmias during acute myocardial ischemia, and that increasing heart rate with atropine tends, if anything, to produce deleterious effects.

For completeness, we should point out that once an arrhythmia appeared during acute coronary occlusion, increasing heart rate with either atropine or pacing often abolished both ventricular premature contractions that occurred late in the cardiac cycle and slow idioventricular rhythms. However, our data indicated that these types of ventricular arrhythmias are not harbingers of ventricular fibrillation and death. When the effects of increasing heart rate on closely coupled ventricular premature contractions (a rhythm disturbance that often leads to ventricular fibrillation) was assessed, we found that these ectopic beats were only infrequently abolished. Thus, although some clinicians may point to their personal experience when attesting to the efficacy of atropine in the treatment of arrhythmias occurring in the setting of acute myocardial infarction, it is of critical importance to determine whether the arrhythmias abolished were those which might have led to ventricular fibrillation, or whether the effect of atropine was merely cosmetic and the arrhythmias were of a relatively benign type which would not have altered the patient's prognosis even if left untreated.

In conclusion, an increase in heart rate may occasionally result in salutary effects on arrhythmias during acute myocardial infarction. However, we believe an expanding body of information concerning the relation between heart rate and serious ventricular arrhythmias suggests that the net effect of increasing rate may be deleterious in the large group of subjects with acute infarction who, with the exception of bradycardia, are otherwise stable. Therefore, it is our view that increasing heart rate from moderate levels of bradycardia in an otherwise stable patient is, on the basis of the information currently available, contraindicated.

STEPHEN E. EPSTEIN, M.D.
Chief, Cardiology Branch

DAVID R. REDWOOD, M.B., M.R.C.P.
Chief, Section on Cardiovascular Diagnosis

KENNETH M. KENT, M.D., PH.D.
Senior Investigator
Cardiology Branch
National Heart and Lung Institute
Bethesda, Maryland
Regional Left Ventricular Performance

To the Editor:

In their article on regional dyssynergy in postinfarct patients (Circulation 48:679, 1972) Field et al. have convincingly demonstrated a relationship between disorders of wall motion and overall ventricular function. Our only regret is the use of their theoretic spherical model to predict the functional state of the nonakinetik myocardium.

The principal error lies in their assumption that a ventricle with an akinetic segment would have a normal ejection fraction (EF) provided the nonakinetik segment functions normally and serves as the total circumferential length. This is implied in the derivation of equation 6 in the appendix. Given these conditions, the following a priori circumstances could evolve. A spherical ventricle with 50% of its hemisphere rendered akinetic would have its nonakinetik circumferential length equal to 50% of total length. If there were no change in the contractility of the nonakinetik myocardium, the stroke volume would be reduced by half whereas the end-diastolic volume derived from half the original circumferential length \((4/3\pi [0.5 L_a/2a]^3)\) would be reduced by 87.5%. This would produce a ventricle ejecting almost three times its end-diastolic contents which is clearly absurd.

Furthermore, the authors go on to derive a formula which is supposed to predict the EF of the akinetic ventricle assuming the nonakinetik segment is normal.

This is equation 7 which is reproduced as follows:

\[
\frac{SV_a}{4/3\pi (L_a/\pi)^3} = 0.67 \left( \frac{1-AS}{100} \right)^a
\]

where \(SV_a\) = stroke volume of the ventricle with akinesis, \(L_a\) = total circumferential length, and \(AS\) = akinetic segment expressed as a percent of total length.

Using our hypothetic ventricle with \(AS = 50\%\), it is clear that the left-hand expression would be \(0.67 \times 0.5 = 0.34\) whereas the right-hand expression would be \(0.67 \times (0.5)^a = 0.084\). The latter expression seriously underestimates the actual EF of the model and yet it was precisely this formula that was employed to predict the EF of the akinetic ventricles with presumably normal nonakinetik segments.

The authors then applied the above model to their data and found a curiously good fit (fig. 4). They mistakenly surmised that these patients had normal nonakinetik myocardial segments when in fact the predicted ejection fraction derived from the model was seriously underestimated. If their figures are correct, we would reinterpret the findings to indicate several possible conditions: (1) the nonakinetik segments were depressed in function; (2) despite the use of biplane analysis, contiguous areas of akinesis in other planes were present but not observed; or (3) there was significant paradoxical motion of the akinetic segments accounting for an overall reduction in ejection fraction.

We submit, however, that unless a more appropriate geometric model is developed, it would be hazardous to use the data derived from quantitative regional akinesis to predict the functional state of the nonakinetik myocardium.

ERNEST L. FALLEN, M.D., F.R.C.P.(C)

PETER HERSCOVITCH, B.Eng.

Division of Cardiology
McGill University Clinic
Royal Victoria Hospital
Montreal, P.Q., Canada

The authors reply:

To the Editor:

We appreciate the comments of Dr. Fallen and Mr. Herscovitch, who have however, incorrectly interpreted the derivation of our spherical model equation. They incorrectly state that we assumed, in equation 6 of our appendix, that "a ventricle with an akinetic segment would have a normal ejection fraction provided the nonakinetik segment functions normally and serves as the total circumferential length."

The derivation can best be understood by first considering equation 2 of our appendix. This is a general equation which states that the total end-diastolic circumferential length of a ventricle with akinesis \((L_a)\) can be divided into two components: the

\[
\frac{SV_a}{4/3\pi (L_a/\pi)^3} = 0.67 \left( \frac{1-AS}{100} \right)^a
\]
Atropine and Acute Myocardial Infarction: The authors reply:
STEPHEN E. EPSTEIN, DAVID R. REDWOOD and KENNETH M. KENT

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