Coronary Artery Occlusion in the Conscious Dog

Effects of Alterations in Heart Rate and Arterial Pressure on the Degree of Myocardial Ischemia

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SUMMARY

 Bradycardia, with or without hypotension, frequently occurs in the early phases of acute myocardial infarction. To determine the relative effects of alterations in heart rate and blood pressure on the degree of ischemic injury, the left anterior descending coronary artery was occluded for 15-min periods in closed-chest conscious dogs by inflating a balloon cuff previously implanted around the artery. The degree of myocardial ischemia was estimated by summing the S-T elevation recorded from 12 myocardial electrodes. Heart rate was increased by atropine or pacing and decreased by electrical stimulation of the vagus nerve. Hypotension was produced by venesection (average decrease in mean BP, 56 mm Hg). At normal arterial pressures there was a positive correlation between percent change in heart rate (range 30–215 beats/min) and percent change in S-T elevation (y = 0.75 X + 30.2, r = 0.93, P < 0.01). When myocardial ischemia was induced during hypotension and bradycardia, S-T elevation totaled 68 mv at 15 min of ischemia. When heart rate was increased to control levels in the presence of hypotension S-T elevation during myocardial ischemia was greater (mean difference 29 mv, P < 0.05). In contrast, when blood pressure was increased to control in the presence of bradycardia, S-T elevation in seven of 10 dogs was less than during hypotension and bradycardia. Thus, during experimental acute myocardial ischemia, hypotension induced by hemorrhage increases ischemic injury, and bradycardia reduces it. It is concluded that in acute myocardial ischemia increases in heart rate, even from slow baseline rates, may be deleterious to the myocardium. It remains to be determined whether alterations in the degree of myocardial ischemia induced by hemorrhagic hypotension are analogous to those caused by the type of hypotension that often accompanies bradycardia occurring during acute myocardial infarction in man.

Additional Indexing Words:
Atropine  Pacing  Bradycardia
Tachycardia  Hypotension

BRADYCARDIA, with or without hypotension, occurs in a high percentage of patients seen soon after the onset of symptoms of myocardial ischemia. Since bradycardia is believed to predispose the heart to the development of ventricular ectopic rhythms,1-4 it has been suggested that if atropine were administered to the patient with bradycardia shortly after the onset of ischemic symptoms

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This drug might, by increasing heart rate, result in a substantial decrease in the number of prehospital arrhythmic deaths.\(^5\)

If this concept is valid its importance as a public health measure cannot be overstated since it has been estimated that two thirds of deaths from ischemic heart disease, the majority due to disturbances in rhythm, occur in the prehospital phase of acute myocardial infarction.\(^6\)\(^-\)\(^8\) However, studies in our laboratory suggest that atropine, administered within the first 2 hours of experimental acute myocardial ischemia, is not consistently effective in preventing or abolishing those arrhythmias leading to ventricular fibrillation and death.\(^9\) Indeed, it appears that when atropine is administered prophylactically shortly after the onset of experimental acute myocardial ischemia, the incidence of ventricular arrhythmias increases.\(^10\) Moreover, results obtained from open-chest anesthetized dogs have suggested that increases in heart rate increase the degree of ischemia produced during acute coronary occlusion.\(^11\)\(^,\)\(^12\) The relationship between these results observed when the heart rate was approximately 200 beats/min and heart rates present under more basal circumstances is necessarily uncertain. Nevertheless, if the beneficial effects of atropine administered during acute myocardial ischemia are equivocal, it is all the more important to determine whether atropine could potentially be deleterious; i.e., do moderate atropine-induced increases in heart rate raise myocardial oxygen consumption sufficiently to increase myocardial ischemia? Furthermore, hypotension is not infrequently associated with bradycardia during acute myocardial infarction. It would be important, therefore, to determine the relative effects of bradycardia and hypotension under these circumstances.

The present investigation was designed to study the effects of alterations in heart rate and blood pressure on the degree of myocardial ischemia occurring during acute occlusion of the anterior descending coronary artery of the dog. In order to reduce the number of physiologic variables caused by operation and anesthesia, we produced myocardial ischemia in the closed-chest conscious dog by inflating a balloon cuff implanted around the left anterior descending coronary artery at a previous operation. The degree of myocardial ischemia was estimated by measuring the amount of S-T segment elevation recorded from leads attached to myocardial electrodes implanted at the same operation into the area supplied by the left anterior descending coronary artery.

**Methods**

Thirty mongrel dogs weighing from 15 to 22 kg were studied. They were anesthetized with sodium thiopental, 25 mg/kg, and anesthesia was maintained with halothane and oxygen using intermittent positive pressure. The heart was exposed through a left thoracotomy. The anterior descending branch of the left coronary artery was mobilized between 2 and 3 cm from its origin and an inflatable silicone rubber balloon 7 mm in width was sutured around the artery. The tube from this balloon was brought out onto the chest wall. Myocardial S-T segment changes were recorded by means of Teflon-insulated electrode wires implanted at a depth of 3–5 mm into the

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**Figure 1**

Anterior view of the heart showing the site of occlusion of the anterior descending branch of the left coronary artery and the method of insertion and distribution of the myocardial electrodes.

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myocardium in the area of distribution of the left anterior descending coronary artery (fig. 1). The proximal ends of these wires were attached to a multiiotilet plug sutured to the skin of the chest wall. After pacing wires were attached to the right and left atrial appendages, the pericardium was resutured loosely and the thoracotomy closed.

The dogs were studied 5–7 days postoperatively. They were sedated with morphine (1–1.5 mg/kg im) and diazepam (1.5–2 mg/kg im). A reference electrocardiogram for determination of heart rate and rhythm was recorded throughout the studies either from the atrial leads or, during the pacing studies, from a unipolar limb lead. The myocardial electrograms were recorded as unipolar leads with the limb leads serving as the ground electrode. S-T segment elevation, recorded on a multichannel direct-writer recorder at a paper speed of 25 mm/sec and at a sensitivity of 5 mv/cm was measured as the deflection from the isopotential at a point 100 msec after the onset of the QRS deflection. The results in each dog were expressed as a summation of the S-T segment elevation of all 12 leads in millivolts (Σ S-T). Studies in which arrhythmias or aberrant conduction occurred were not used for analysis. Heart rate before, during, and after coronary occlusion was computed from the mean of several R-R intervals. Arterial pressure was measured by a 4 inch no. 20 Teflon catheter inserted into the femoral artery by the Seldinger technic and connected to a Statham 23 Db pressure transducer. Manometer zero was set at the level of the midthorax.

The effects of occlusion of the left anterior descending coronary artery were studied as follows:

In order to establish reproducibility of the method, repeated 5-min occlusions of the coronary artery were carried out by rapid inflation of the balloon cuff. Each occlusion was separated from that preceding it by a 60-min recovery period. A constant heart rate during the occlusions was maintained by atrial pacing. S-T segment elevation was measured before each occlusion and at 5 min of occlusion.

The effect of increasing heart rate was studied by comparing the summated S-T segment elevation after 5-min periods of occlusion at control heart rates with the elevation after 5-min periods of occlusion at higher rates induced by intravenous atropine. The order of the pairs of occlusions was randomized. In order to determine whether atropine exerted an effect on myocardial ischemia entirely by means of its effect on heart rate, the effects of occlusion on S-T segment elevation following atropine were compared with those during rate-matched atrial pacing.

Bradyarrhythmia (range 30–50 beats/min) was induced by electrical stimulation of the right vagus nerve exposed under local anesthesia in the neck. The S-T elevation after 5-min occlusions during slow heart rates was compared with the S-T elevation after 5-min occlusions at control heart rates.

The effects of alteration in arterial pressure were studied at control heart rates and during bradyarrhythmia induced by right vagal stimulation. Hypotension was induced and maintained during the period of coronary occlusion by means of venesection of from 500 to 800 ml of blood. Blood was removed over a period of about 10 min, and 10 min were allowed for stabilization before the coronary artery was occluded. To determine the time course of the S-T changes occurring during ischemia at control and hypotensive arterial pressures, the occlusion was maintained for 15 min and measurements of S-T elevation were made before occlusion and at 5, 10, and 15 min of occlusion.

In order to determine whether the degree of myocardial ischemia could be altered by changes in the experimental conditions during the course of coronary occlusion, the effects of an increase or decrease in heart rate were studied as follows:

1. After 15 min of coronary occlusion under conditions of bradycardia and normal blood pressure the heart rate was increased to control values by reducing the level of vagal stimulation. Recordings for the measurement of S-T segment response were taken 1 min after attaining the new rate.

2. After 15 min of coronary occlusion under conditions of control heart rate and normal blood pressure S-T elevation was measured after the heart rate was reduced for 1 min by vagal stimulation.

The degree to which hypotension could be reversed by increasing heart rate during the course of coronary occlusion was also determined: after 15 min of occlusion under conditions of bradycardia and hypotension heart rate was increased to control values by reducing vagal stimulation. Arterial pressure and S-T elevation were recorded 1 min later.

**Statistical Methods**

Regression analysis was employed to determine the statistical significance of the changes in S-T elevation induced by alterations in heart rate. Student's t test was used to compute the significance of paired data. Mean values are expressed with standard error of the mean in parentheses.
Results

Effects of Coronary Occlusion

S-T segments recorded from the intramyo-cardial electrodes were slightly elevated under control preocclusion conditions (average \( \Sigma \) S-T elevation 17.5 ± 1.3 mv). In those experiments in which heart rate was increased by atropine or atrial pacing no further increase in preocclusion S-T segment elevation was observed. In those experiments in which hypotension was induced by venesection, S-T segment elevation before coronary occlusion increased to an average of 29 ± 2.5 mv (\( P < 0.005 \)).

Following complete occlusion of the left anterior descending coronary artery by rapid inflation of the balloon, the amount of S-T elevation began increasing in less than 1 min. Following release of the balloon there was rapid resolution of the S-T segment changes and a return to preocclusion values within 2 min. As seen in figure 2, myocardial leads situated in the central zones of distribution of the left anterior descending coronary artery demonstrated more marked S-T segment elevation after 5 min of occlusion than those leads in marginal zones.

Reproducibility of the Method

There was no significant change in the degree of S-T segment elevation between pairs of 5-min occlusions performed at the same heart rate and blood pressure (\( \Sigma \) S-T elevation: 86.6 ± 17 vs 78.6 ± 17.7 mv, \( \text{NS; } N = 8 \)). When repeated occlusions of the left anterior descending coronary artery of 15-min duration were performed at matched heart rates and control pressures, the S-T changes at 5, 10, and 15 min were also highly reproducible (fig. 3). This reproducibility occurred despite two or more interventions performed between the pairs of control occlusions.

Effects of Alterations in Heart Rate

When 5-min occlusions were carried out at control heart rates (average 97 beats/min) and at faster heart rates induced by atropine (range 120–215 beats/min), there was a positive correlation between percentage increase in heart rate and S-T elevation (\( Y = 0.72 \times + 7.78; r = 0.81, P < 0.01; \) fig. 4). The effects of atropine appeared to be rate related since there were no significant differences between \( \Sigma \) S-T elevation after 5 min of occlusion when heart rate was increased by atropine or by rate-matched atrial pacing (fig. 5).

Figure 2

Effect of alterations in heart rate on the degree and distribution of S-T segment elevation at 5 min of occlusion. The figure shows the results of three consecutive occlusions in the same dog. The leads are numbered in order (1–12) from left to right across the area of distribution of the occluded anterior descending coronary artery. In each panel the lower data points represent the S-T elevation in each lead recorded before occlusion, and the upper data points the values obtained at 5 min of occlusion. The shaded areas depict the increases in S-T segment elevation in mv that occurred during each occlusion.
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Figure 3
Effect of repeated 15-min occlusions at normal heart rate and arterial pressure. The data points represent the means of the results in eight dogs. Between pairs of control occlusions in each animal, at least two other 15-min occlusions were performed at hourly intervals to study the effect of alterations in heart rate and arterial pressure. Despite this the S-T changes during the control occlusions were highly reproducible. There was no significant difference in the Δ S-T segment elevation between pairs either before occlusion or at 5, 10, and 15 min of occlusion.

Decreasing heart rate to 30–80 beats/min by electrical stimulation of the right vagus nerve caused a significant reduction in the degree of S-T segment elevation produced by 5 min of coronary occlusion (figs. 6 and 7). There was no significant alteration in mean arterial pressure between occlusions at control heart rates and those during bradycardia (124 vs 118 mm Hg, NS). When occlusions were performed during hypotension, slower heart rates also were associated with lesser degrees of S-T segment elevation (fig. 8).

Effects of Alteration in Arterial Pressure
At control heart rates (average 102 ± 1 beats/min) coronary occlusion during hypotension (average mean pressure 68 ± 4 mm Hg) produced significantly greater increases in the degree of S-T segment elevation than when occlusion was carried out at control blood pressure (average mean pressure 120 ± 5 mm Hg). These increases were significant whether calculated either as absolute values or as the increase from control preocclusion values, and they were observed as early as 5 min of occlusion (fig. 9). At control heart rates with normal arterial pressures, S-T elevation totaled 75 ± 16 mv at

Figure 4
Effect of increase in heart rate at normal arterial pressures on the degree of S-T segment elevation at 5 min of occlusion in 15 dogs.

Comparison between the effects of atropine and rate-matched atrial pacing on Δ S-T segment elevation at 5 min of occlusion. The results of pairs of occlusions in each dog are connected by the lines.
15 min of occlusion; during hypotension it totaled 104 ± 17 mv (P < 0.005). Expressing these results as the increase from preocclusion values, the increases averaged 57 ± 15 mv vs 73 ± 16 mv (P < 0.01). In 10 dogs in which the effect of hypotension at slow heart rates was studied, the results were more variable. In seven, increases in the degree of S-T elevation were greater than when occlusion was carried out at control blood pressures and matched slow heart rates. In the other three dogs the S-T changes were less during occlusions with hypotension than during those at normal pressures.

Effects of Simultaneous Reduction in Heart Rate and Arterial Pressure

At the heart rates and pressures studied it was found that during coronary occlusion the deleterious effects on the degree of myocardial ischemia produced by hypotension were offset by the beneficial effects of bradycardia. Thus, there were no significant differences in absolute S-T elevation or in change in elevation from control after 5, 10, or 15 min of occlusion whether occlusion was produced during bradycardia and hypotension or during control heart rate and normal blood pressure (fig. 10).

Alterations of Heart Rate during Ischemia

After 15 min of occlusion under conditions of bradycardia and normal blood pressure, increase in heart rate from an average of 57 to 105 beats/min for 1 min resulted in further S-T elevation (62 vs 73 mv, mean difference 11 ± 3, P < 0.02). There was a small, although significant, increase in arterial pressure induced by the increase in heart rate (114 vs 123 mm Hg, mean difference 9 ± 3, P < 0.05).

When heart rate was decreased by vagal stimulation after 15 min of occlusion at normal heart rates and normal blood pressures, 3 S-T elevation after 1 min tended to decrease, although this did not achieve statistical significance (135 vs 125 mv, mean difference 10 ± 5). As with the preceding intervention, there was a small but significant change in arterial pressure with the decrease in heart rate (112 vs 98 mm Hg, mean difference 14 ± 4, P < 0.05).

Following 15 min of coronary occlusion performed under conditions of bradycardia and hypotension, the low blood pressure could be only partially corrected by increasing heart rate to control values for 1 min (mean difference 10 ± 2 mm Hg, P < 0.02). At the same time 3 S-T elevation became significantly higher compared with the value at 15 min (86 vs 94 mv, mean difference 8 ± 2, P < 0.02).

Discussion

The validity of any conclusions evolving from this investigation is necessarily based on the validity of the assumption that changes in
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Figure 7
The effect of alteration in heart rate at normal arterial pressures on the degree of S-T segment elevation at 5 min of occlusion.

Figure 8
Effect of decrease in heart rate during hypotension on the degree of S-T segment elevation during 15-min occlusions. The data points depict the mean values obtained in seven dogs. Occlusions at slow heart rates resulted in a significant decrease in Σ S-T segment elevation compared with occlusions at normal heart rates at 5, 10, and 15 min of occlusion (P < 0.05).

Figure 9
Effect of decrease in blood pressure on the degree of Σ S-T segment elevation during 15-min occlusions at normal heart rates. The differences between occlusions at normal pressures and hypotension were significant (P < 0.05) whether the results at 5, 10, and 15 min of occlusion were expressed as absolute values of S-T elevation or as the increase from control (pre-occlusion) values.
Effects of simultaneous alteration in heart rate and arterial pressure on the degree of S-T segment elevation during 15-min occlusions. There was no significant difference between pairs of occlusions whether the results at 5, 10, and 15 min were expressed as absolute values of Σ S-T elevation or as the increase from control (preocclusion) values.

Figure 10

The degree of ischemia are reflected by changes in the amount of S-T segment elevation as determined from intramyocardial electrodes. The results of several investigations suggest that such an assumption is reasonable. Wegria et al. demonstrated that the appearance of S-T segment and T-wave changes in an epicardial lead was related to the severity of coronary artery obstruction, and Sayen et al. showed that coronary occlusion resulted in S-T segment changes at least as early as the appearance of changes in oxygen tension and in muscle contraction when both the ECG and oxygen tensions were recorded from the same intramyocardial platinum electrodes. Moreover, biochemical evidence indicating a correlation between S-T segment changes and ischemia has been presented by Scheuer and Brachfeld who found that when S-T segment changes were detected by epicardial electrodes lactate production was always present. Similarly, Case et al. found correlations between the onset of S-T changes recorded from epicardial electrodes and alterations in pH, lactate production, and potassium efflux. Finally, in an extensive and carefully controlled study of this problem, it has been shown recently that there is a close correlation between the extent and magnitude of early elevation of the S-T segments in epicardial recordings following coronary occlusion and the magnitude and extent of cellular damage estimated by depression in myocardial CPK activity.

Thus, if the magnitude of S-T segment elevation recorded from intramyocardial electrodes does reflect the degree of ischemic myocardial injury, our results suggest that at normal blood pressure or during hypotension the severity of myocardial ischemia occurring during acute coronary artery occlusion is directly related to alterations in heart rate. The beneficial effect of a reduced heart rate on myocardial ischemia is probably due in large part to the resulting decrease in myocardial oxygen consumption; it also is possible that the prolongation in total diastolic time per minute caused by slower heart rates favorably affects coronary collateral flow, and thereby may provide a second mechanism contributing to the salutary effects of bradycardia.

It is important to emphasize that these results were obtained during the production of acute ischemia in closed-chest conscious dogs, thereby obviating many of the interpretive difficulties that would have been inherent in an infarct model employing open-chest anesthetized dogs in which control heart rates are usually quite rapid. In this regard, Maroko et al. demonstrated in three open-chest dogs that when heart rate was increased an average of 62 beats/min from control values averaging 136 beats/min, the degree of S-T segment elevation also increased. As a result of these findings we were not surprised to find in our own investigation the close correlation between increases in S-T segment elevation and increases in heart rate when heart rate was increased from control values averaging 97 beats/min. We anticipated, however, that when heart rate was progressively slowed, a point would be reached at which a further decrease in heart rate would lead to a deterioration in the degree of myocardial ischemia either because of an increase in heart rate.
size and therefore wall stress, or because of an inability of the heart to maintain an optimal coronary perfusion pressure. It was therefore somewhat surprising when we were not able to detect any consistent nadir of ischemic electrocardiographic change even when heart rate was decreased to as low as 30 beats/min (fig. 6). Thus, we found that ischemic injury was directly related to heart rate over the entire range of heart rate studied, from 30 to 215 beats/min.

Hypotension, a frequent accompaniment to the bradycardia present during acute myocardial ischemia, could theoretically alter the degree of ischemia during coronary occlusion in several ways. By decreasing myocardial wall tension, oxygen consumption of the heart would tend to be reduced and ischemia decreased. Alternatively, a decrease in coronary perfusion pressure could further decrease blood flow to ischemic areas and result in greater injury. Moreover, systemic hypotension could evoke deleterious reflex changes. Our findings that hemorrhagic-hypotension did indeed increase the degree of myocardial ischemia in both central and peripheral areas of ischemia confirm the findings of Maroko et al. in the open-chest anesthetized dog and indicate that the oxygen-sparing effects of a decreased afterload are more than outweighed by the deleterious effects resulting either reflexly or from the decrease in myocardial perfusion pressure. It remains to be determined whether alterations in the degree of myocardial ischemia induced by hemorrhagic-hypotension are analogous to those caused by the type of hypotension that often accompanies bradycardia occurring during acute myocardial infarction in man.

In summary, our results indicate that bradycardia exerts a protective effect on the degree of ischemia provided arterial pressure is maintained; hemorrhagic-hypotension, on the other hand, exerts a deleterious effect. Although conclusions based upon these findings may not be directly applicable to acute myocardial ischemia as it occurs in man, the results do raise issues that have an important bearing on patient management, particularly in the early phases of acute myocardial infarction. For example, the finding that hemorrhagic-hypotension is deleterious to the myocardium during acute ischemia suggests that, when bradycardia is associated with hypotension, administration of atropine may have salutary effects, provided a substantial increase in arterial pressure accompanies the increase in heart rate. Relevant to this point are studies indicating that when hypotension accompanies the bradycardia present in patients during acute myocardial infarction, atropine is almost always successful in raising pressure. However, since our results also indicate that atropine has the capacity to exert deleterious effects on the degree of ischemia, even in the presence of slow heart rates, the advisability of administering this agent to patients with acute ischemia and either normal or only mildly depressed blood pressure is unclear. The ultimate decision concerning the use of atropine in this situation will have to be based on whether an increase in heart rate can protect against the development of those arrhythmias associated with ventricular fibrillation and death, and whether increases in mortality result from the type of mild-to-moderate hypotension that often accompanies bradycardia occurring during acute myocardial infarction in man.

References
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