Review Article

Bradycardia after Myocardial Ischemia and Its Treatment with Atropine

Paul Dauchot, M.D.,* and J. S. Gravenstein, M.D.†

Anesthesiologists are occasionally involved in the treatment of patients who have acute or recent myocardial infarction (MI) for emergency surgery, revascularization procedures of the myocardium or in emergency rooms and intensive care units. Sinus bradycardia (heart rate less than 60 beats/min), an ominous finding in these situations, has often been treated with anticholinergics, but severe ventricular arrhythmias have been reported to occur after the use of atropine and related compounds in such circumstances. A controversy has arisen about the use of vagolytic agents in the post-myocardial infarction period. We, therefore, review below: 1) the incidence and etiology of bradycardia after acute myocardial infarction (AMI); 2) the relationship between bradycardia and morbidity or mortality after AMI; 3) the value or dangers of atropine in the treatment of bradycardia after AMI.

The Incidence and Etiology of Bradycardia after Acute Myocardial Infarction

INCIDENCE

The incidences of patients reported as experiencing bradycardia after AMI in different

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series range from 2 to 74 per cent (table 1). The time of observation and the location of the MI may explain this diversity. The sooner AMI was diagnosed, the more often bradycardia was found. It is therefore not surprising to detect a high incidence of bradycardia and bradyarrhythmias in patients admitted soon after AMI or in patients reached very quickly by a mobile coronary care unit. The explanation of this early bradycardia is not clear, yet Hinkle found evidence in a prospective study of 300 middle-aged men that the presence of sustained relatively slow heart rates was linked to dysfunction of the cardiac pacemaker and to a higher risk of sudden cardiac death. Bradycardia is more often associated with an inferior MI (table 2). This type of MI involves the diaphragmatic part of the ventricle and, in earlier days, was called posterior MI. In a series of cases with a higher percentage of inferior MI,

ABBREVIATIONS

AMI = acute myocardial infarction
A-V = atrioventricular
BBB = bundle-branch block
DRP = disparity of refractory period
IZE = ischemic zone epicardium
LAD = left anterior descending coronary artery
LCA = left coronary artery
LVEF = left ventricular ejection time
MI = myocardial infarction
PEP = pre-ejection period
PVC = premature ventricular contraction
RCA = right coronary artery
S-A = sinoatrial node
VF = ventricular fibrillation
VFT = ventricular fibrillation threshold
Vmax = maximal rate of rise of the action potential or maximal rate of phase O depolarization
VT = ventricular tachycardia

501
TABLE 1. Incidences of Bradycardia after Acute Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Number of Cases</th>
<th>Incidence of Bradycardia (Per Cent)</th>
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</thead>
<tbody>
<tr>
<td>Adgey et al.5</td>
<td>284</td>
<td>44</td>
</tr>
<tr>
<td>Binder and Shortt23</td>
<td>300</td>
<td>2</td>
</tr>
<tr>
<td>Chadda et al.25</td>
<td>66</td>
<td>45</td>
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<tr>
<td>Chapman26</td>
<td>269</td>
<td>12</td>
</tr>
<tr>
<td>Grauer et al.28</td>
<td>84</td>
<td>24</td>
</tr>
<tr>
<td>Haden et al.104</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Lown et al.37</td>
<td>300</td>
<td>25</td>
</tr>
<tr>
<td>Pantridge and Adgey231</td>
<td>794</td>
<td>74</td>
</tr>
<tr>
<td>Reichman277</td>
<td>104</td>
<td>30</td>
</tr>
<tr>
<td>Rotman et al.211</td>
<td>539</td>
<td>26</td>
</tr>
<tr>
<td>Webb et al.287</td>
<td>74</td>
<td>55</td>
</tr>
</tbody>
</table>

TABLE 2. Bradycardia after Acute Myocardial Infarction Related to Infarction Location

<table>
<thead>
<tr>
<th></th>
<th>Inferior (Per Cent)</th>
<th>Anterior (Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webb et al.287</td>
<td>77</td>
<td>32</td>
</tr>
<tr>
<td>Adgey et al.25</td>
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<td>Grauer et al.28</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>George and Greenwood31</td>
<td>43.8</td>
<td>12.7</td>
</tr>
<tr>
<td>Chadda et al.25</td>
<td>54</td>
<td>14</td>
</tr>
</tbody>
</table>

of impulses at the junction of the sinus node and Purkinje cells may prolong S-A conduction and slow heart rate.149

After experimental coronary occlusion in animals, decreases,142,152,203,164 increases,144,161,152,155,216 or inconsistent changes257 in heart rate have been reported. Differences in techniques may explain these contrasting observations, since the studies vary with respect to open versus closed chests, conscious versus anesthetized animals, the sites of the occlusion in the coronary artery, and the time intervals between occlusion and recording.

ETIOLOGY OF BRADYCARDIA AFTER ACUTE MI

The mechanisms that may explain post-MI bradycardia can be divided into those involving the vagal and non-vagal systems. The effects of vagal stimulation on the automatic cells of the S-A node mimic the effects of acetylcholine in causing a decrease in the slope of diastolic depolarization, an increase in the maximal diastolic potential, a shift of the pacemaker to another site in the node, and impaired conduction in the node, resulting in S-A block and sinus arrest.150,152,190 Many reflexes can stimulate vagal efferent activity.

Vago-vagal reflexes: Stephenson re-emphasized recently the important contribution of vagal reflexes to bradycardia and bradyarrhythmias.271 Pain64 and fear of death143 are said to cause vago-vagal bradycardia. Receptors located in the esophagus can trigger vagal reflexes causing bradycardia and syncope.259 In patients suffering from AMI, even the ingestion of hot beverages can provoke bradycardia that could be prevented by atropine.161

Baroreceptor reflex: Blood levels of catecholamines are often elevated after AMI,152,168,172,239,266 This process is triggered by pain, stress, or endogenous blood-borne factors released from the ischemic area. The subsequent increase in blood pressure, which has been observed in the very early stages of AMI,148,290 can stimulate baroreceptors and produce bradycardia. Indeed, the magnitude of the bradycardic response can be modulated by the hypothalamus179 and is related, to some extent, to the actual sympathetic tone. Levy and co-workers188 showed that a pre-existing
elevated sympathetic tone produced a stronger cholinergic decelerating response. Grodner et al.\textsuperscript{101} experimentally inhibited the sympathetic stimulation and positive chronotropic effect of norepinephrine with vagal stimulation and acetylcholine. In the presence of high sympathetic tone, Levy\textsuperscript{103} and Dempsey\textsuperscript{29} also observed accentuation of the negative inotropic effect of vagal stimulation on the ventricle. Warner proposed a mathematical model showing the dominating influence of the vagal system in the regulation of heart rate.\textsuperscript{285}

Refluxes originating from intracardiac receptors: Cardiac chemo and mechanoreceptors initiate the reflexes that travel along the sympathetics\textsuperscript{125,210} or the vagi. In 1867, von Bezold and Hirt caused bradycardia, hypotension and apnea in animals\textsuperscript{50} by injecting ventricle into coronary arteries. In the late 30's, Jarish thought that the sensory receptors for this triad were located in the heart.\textsuperscript{131} Dawes identified the location of the receptor responsible for the reflex apnea in the lungs\textsuperscript{26} and established that the chemoreceptors that trigger hypotension and bradycardia were localized in the heart.\textsuperscript{54} The injection of contrast dye during cardiac catheterization and coronary angiography can cause bradycardia and asystole.\textsuperscript{213} This bradycardia is thought to be partly triggered by a reflex vagal inhibition of the sinus node.\textsuperscript{49} Evidence suggests that reflexes originating in mechanoreceptors play a role in the bradycardia, hypotension and depressed ventricular activity found after AMI.\textsuperscript{201} Increased vagal afferent activity has been reported to occur after experimental coronary occlusion in dogs that manifested the concomitant hemodynamic changes of bradycardia, hypotension and decreased ventricular performance.\textsuperscript{11,172} Receptors that trigger the afferent limb of this reflex have been found on the epicardial surface of the left ventricle\textsuperscript{252} and in the ventricles.\textsuperscript{58,47,230,249} Epicardial changes have been seen seconds after clamping the left anterior descending coronary artery (LAD), and increases in diastolic intramyocardial tissue pressure have been reported to occur during and after experimental coronary-artery occlusion.\textsuperscript{232} Changes in myocardial tissue pressure might influence vagal receptors and afferent vagal activity. Stimulation of these receptors from a bulging or stretching infarcted ventricular area will reach the hypothalamus via afferent vagal tracts.\textsuperscript{176} Gellhorn and co-workers\textsuperscript{241} showed that this input can be modulated depending on which part of the hypothalamus shows predominant activity. Vagal or sympathetic responses will follow. Other receptors have been demonstrated at the bifurcation of the main trunk of the left coronary artery\textsuperscript{229} and in the atria.\textsuperscript{220} This reflex arc, receptor–hypothalamus–autonomic cardiovascular effector, can be blocked by bilateral vagotomy. Atropine administration, however, will only diminish or prevent the bradycardia and will not affect the hypotension and decreased myocardial performance. Indeed, the latter is apparently influenced by the afferent vagal limb of a reflex that decreases sympathetic efferent tone,\textsuperscript{11,167} and although atropine has been reported to influence receptor discharges,\textsuperscript{276} the afferent vagal pathway is largely unaffected by atropine.

Chemoreceptor reflexes: Hypotension and shock, very often associated with AMI,\textsuperscript{224,225,226} are followed by serious acid–base disturbances\textsuperscript{123} and hypoxemia.\textsuperscript{149,288} Severe acute hypercapnia causes slowing of heart rate.\textsuperscript{295} Bradycardia has been related to hypoxemia,\textsuperscript{104} which can be triggered by the carotid body chemoreceptors\textsuperscript{50,62,175,176} and is modulated by the activity of higher nerve centers and ventilation patterns.\textsuperscript{50,231} Atropine does not completely abolish this hypoxic bradycardia.\textsuperscript{225}

In 1870, Paul Bert made the first observation of diving-induced bradycardia in ducks. Later, Charles Richet related this bradycardia to an oxygen-conserving mechanism; vasoconstriction in skin and viscera and hypotension were two other vascular components of this reflex. The metabolic consequences are an increase in $P_{aCO_2}$, increases in plasma concentrations of organic acids and potassium, and a reduction in $pH$. This reflex bradycardia can be blocked by bilateral vagotomy or by atropine, thus demonstrating the vagal origin of the cardioacceleration. In man, this diving or oxygen-conserving reflex can be simulated by immersing the face in iced cold water with or without breath-holding. The afferent cardiovascular responses include bradycardia, peripheral vasoconstriction, decreased cardiac output and left ventricular
The diving reflex is less developed in man than in other species. Yet, Woll and Richter pointed to similarities between the oxygen-conserving reflex and the adaptive reflexes of animals and man to stressful or disastrous situations. Seen in that perspective, bradycardia after MI might have facets of an oxygen-conserving reflex. This vagally mediated bradycardia can be exaggerated by acidosis, since acidemia can enhance vagal reflexes. Several studies discuss these reflexes in greater detail. Some investigators were unable to reproduce the bradycardia after experimental acute coronary occlusion. However, when occlusion is preceded by bilateral vagotomy or atropine, experimental ligation of the sinus node artery in dogs can result in bradycardia that does not respond to atropine. The denervated heart slows after coronary occlusion. However, a denervated heart is deprived of vagal tone and will consequently not respond to atropine. This indicates that mechanisms other than those vagally mediated may be responsible for the slowing of the heart after AMI.

Pericarditis: Ligature of the LAD in primates causes a decrease of the pH of the myocardial surface. Since the sinus node is located 1 mm or less beneath the epicardial surface, an acidic pH may exert a negative chrono- or tachy effect. Since pericarditis is not uncommon after AMI or other inflammatory process, it may contribute to the bradycardia.

The sensitivity of autonomic Purkinje fibers: The more distally a Purkinje cell is located in the conduction system, the less automatically it possesses. However, milieu changes such as hypoxia can increase the slope of phase 4 spontaneous depolarization so much that threshold potential is reached, resulting in an action potential. Increased catecholamine levels found after AMI will also augment automaticity of these fibers, and an existing post-MI hypoxia will increase even more the sensitivity of these Purkinje fibers to epinephrine and norepinephrine, so that they become quite active. These sensitized fibers are ready to assume pacemaker function in the presence of a depressed sinus node.

Atrial tachycardia and atrial fibrillation are cardinal features.

Degenerative lesions of the S-A node are often found. These are associated with defects of the atrial and A-V node specialized conductive tissue. This helps to explain the complexity of ECG patterns encountered in the sick-sinus syndrome. Two techniques, measurement of the sinus node recovery time and measurement of the sinoatrial conduction time, are presently used to investigate and evaluate sinus node function. Both sinus node recovery time and sinoatrial conduction time can be abnormally
prolonged in the presence of sinus node dysfunction. It should be noted that in the prospective study of Hinkle,28 death due to coronary-artery disease was linked to a "sustained relative bradycardia" and the latter to sinus node dysfunction. The use of atropine in the sick-sinus syndrome is not only ineffective,65,294,255,211 but can be dangerous251 and might further impair sinus node function when atropine elicits a "paradoxical" prolongation of the sinus nodal recovery time.258

The Relationship between Bradycardia and Morbidity or Mortality after AMI

CARDIAC PERFORMANCE AND BRADYCARDIA AFTER MI

In general, bradycardia with heart rates of less than 50 beats/min is associated with decreased cardiac output.291 In the presence of a fixed heart rate, a demand for increased cardiac output can be met only by increasing stroke volume.4,102,294 However, moderate or severe acute ischemia, which cripples the myocardium, decreases cardiac output and stroke volume and increases left ventricular filling pressure and left ventricular end-diastolic pressure.9,291,97,255 As a result, ventricular function is impaired and the ability to adjust cardiac output via stroke-volume variations is limited120 or nonexistent. In addition to producing bradycardia, vagal effects on atrial and ventricular contractility and pacemaker shift can further aggravate a poor ventricular performance.

Vagal stimulation has a marked negative inotropic effect on the atrial myocardium, and ventricular filling can become inadequate or incomplete.251,252 This deleterious effect can be blocked by atropine. Histologically, Nonidez,257 Napolitano251 and others have demonstrated vagal innervation of the ventricles. The physiologic counterpart was provided by Levy,197 deGees,24 Dugot,29 Linden,251 and others,291 who showed that vagal influence on ventricular performance had a negative inotropic effect.

By the beginning of this century, Zahn,300 Meek,215,216 and later Kato,126 had already demonstrated that vagal stimulation can shift the pacemaker within the sinus node or from the sinus node to lower located automatic cells. A slow sinus rate can unmask the activity of a lower pacemaker,29,196 as in the case of an A-V node pacemaker that results in A-V dissociation.292 This arrhythmia impairs ventricular filling29 and, by itself, decreases stroke volume and cardiac output.197 Atropine can often be used successfully to reverse A-V dissociation to sinus rhythm.29,84 When the pacemaker is further displaced downward via vagal mediation, a progressive slowing of ventricular heart rate can result and eventually lead to ventricular asystole. This arrhythmia is reported to be a frequent cause of sudden death following AMI.121,212 Since the ventricular pacemaker cells belong to the ventricular conductive system and their automaticity is probably not influenced by acetylcholine or vagal activity,129 atropine would have little or no influence on these slow idioventricular rates unless the drug could re-establish the dominance of the higher pacemakers. While some reports do claim cholinergic influence on the proximal part of the His-Purkinje system,17,26 the clinical importance of this may be negligible.

The coronary vessels are also influenced by the vagus and cholinergic stimulation should produce coronary vasodilatation.49,78,231,229,299 This effect is thought to be small,18 and there are conflicting observations about the direct influence of atropine on the coronary vascular tone.78,103 The reactive vasodilatation and increase in blood flow through the non-obstructed part of the coronary bed that occur after MI154 are not blocked by atropine.22 However, by a different mechanism atropine can increase coronary blood flow by increasing heart rate, and with it, myocardial oxygen requirement.56,171

BRADYCARDIA, ARRHYTHMIAS, AND CONDUCTION DISTURBANCES AFTER MI

Bradycardia itself can be the root of rhythm irregularities. In 1966, Han observed that slowly beating atra of the normal dog heart could experience ectopic activity when triggered by premature stimuli.109 Furthermore, the ventricular fibrillation threshold was decreased at lower driving frequencies,109 and ectopic beats occurred in the dog's ventricle.
after coronary occlusion when the basic rate was low.\textsuperscript{196} He concluded that re-excitation of asynchronously repolarized adjacent fibers was responsible for the spontaneous generation of coupled beats. Singer\textsuperscript{200} showed in the isolated dog heart that slow-frequency stimulation produced prolongation of the diastolic interval, providing the Purkinje fibers with ample time for spontaneous phase 4 depolarization. The resulting ectopic ventricular beat was characterized by a low action potential, small \( V_{\text{max}} \), and protracted conduction. Recycling this sequence could establish decreased resting membrane potentials, low-amplitude action potentials, and decremental conduction with unidirectional block that could be aggravated by increased stretch, hypoxia, hypercarbia, and changes in \( K^+ \). Once conduction abnormalities are established, re-entry phenomena are facilitated, creating a vicious circle that can perpetuate ectopic ventricular activity and rhythms.\textsuperscript{202,204,205}

In many animal experiments it has been shown that sinus bradycardia increased ventricular instability and lowered ventricular fibrillation threshold (VFT).\textsuperscript{21,102,103,237} Leroy reported reduced mortality in dogs after acute occlusion of the LCA when the dogs were pretreated with atropine.\textsuperscript{195} Madan found atropine decreased spontaneous ventricular activity after coronary ligation in dogs;\textsuperscript{202} while Chadda observed that, although the total number of ventricular premature beats was much higher at slow heart rates, the incidence of severe arrhythmias was the same whether the heart was paced at slow or fast rates.\textsuperscript{24} However, all these experiments did not fully evaluate the influence of increasing heart rate on the electrical ventricular stability and the ventricular fibrillation threshold in the acutely ischemic myocardium.

Epstein differentiated two types of post-coronary-artery-occlusion arrhythmias in dogs. Arrhythmias with R-R intervals (time between the R deflection of the EKG of the beat immediately preceding the PVC and the R excursion of the PVC complex) longer than 0.43 seconds were called “benign” because they never triggered severe ventricular ectopic rhythms. Arrhythmias with R-R intervals shorter than 0.43 seconds were often followed by severe ventricular arrhythmias (VF) and were considered malignant.\textsuperscript{73} He noticed that atropine or pacing suppressed benign (R-R intervals > 0.43 seconds) arrhythmias after coronary occlusion in dogs but was not very effective in abolishing the malignant (R-R intervals < 0.43 seconds) arrhythmias.\textsuperscript{23} In man, the limit between benign and malignant arrhythmias does not seem to be as well-defined, since de Soyza\textsuperscript{20} did not find the R-R intervals to differ significantly between “benign” and “malignant” ventricular extrastoles. Clinically, Scheinman \textit{et al.} observed that increasing heart rate by atropine very often abolished PVC’s in general in man suffering from post-myocardial-infarction bradycardia; however, looking particularly at patients who had closely coupled premature beats, they found that atropine could terminate these arrhythmias in only one of three patients.\textsuperscript{256} The malignancy of closely coupled PVC’s is well recognized, for they can produce the R-on-T phenomenon that precipitates ventricular fibrillation.\textsuperscript{64,314} However, the potential hazard of late coupled PVC’s in man is less well established.

Bradycardia after AMI has been correlated with arrhythmias in man.\textsuperscript{147,192,201} It was observed that sinus bradycardia could be associated with an increased ectopic atrial activity,\textsuperscript{83} which could be terminated by atropine, indicating the presence of a vagal mechanism. Often, ectopic atrial activity has been related to vagal stimulation. These atrial rhythm abnormalities have been shown to lead to ventricular fibrillation\textsuperscript{21,111,248} or ventricular paroxysmal tachycardia.\textsuperscript{197} Whether vagal stimulation\textsuperscript{21,111,138} caused these severe ventricular arrhythmias directly or indirectly via the mechanism of atrial dysrhythmias is not clear. However, Sloman reported that bradycardia could lead to idioventricular tachycardia that can be effectively treated by atropine.\textsuperscript{253} Norris failed to see major ventricular arrhythmias in patients who were bradycardic after AMI.\textsuperscript{258}

Bradycardia can also be associated with A-V conduction disturbances. Although sinus bradycardia can occur without significant alteration in conduction, parasympathetic stimulation can reciprocally influence pacemaker activity and impulse conduction.\textsuperscript{252} Hageman could elicit conduction abnormalities and bradydysrhythmias by stimulating small vagal nerves.\textsuperscript{106} Clinically, ventricular aberrant conduc-
tion with bradycardia has been described, and bradycardia has been linked to the appearance of bundle-branch block. However, El-Sherif did not find evidence that could relate bradycardia-dependent block to enhanced automaticity.

Inferior MI frequently causes disturbances in A-V conduction, since the blood supply to the A-V node often arises from the right coronary artery. Ischemia aggerates slowing of conduction and produces various degrees of A-V block, facilitating re-entrant phenomena, which can lead to atrial tachyarrhythmias. Pick reviewed other mechanisms that may produce cardiac arrhythmias, such as concealed conduction and conduction of impulses through ventricular pre-excitation pathways, (e.g., James, Kent and Mahaim fibers), which themselves possess unusual electrophysiologic properties. His bundle electrograms have confirmed the existence of the A-V nodal bypass in man. In general, MI with conduction abnormalities carries an unfavorable prognosis.

Imperial found that bradycardia with AMI was associated with a lower mortality rate than tachycardia; others reported that bradycardia resulted in higher mortality. While Chapman found sinus bradycardia to be a good prognostic sign, Haden thought it was a poor one.

The Values or Dangers of Atropine in the Treatment of Bradycardia after AMI

In 1933, Wayne and Laplace reported that atropine prolonged the pain associated with post-exercise tachycardia and decreased the working capacity of patients suffering from angina. For years, however, clinical and experimental evidence that the heart rate should be accelerated in the bradycardic patient with AMI was accepted. It was suggested that likely candidates for MI be provided with self-injectable ampules of atropine. With the growing use of atropine for bradycardia, however, many reports that described frequent, severe ventricular ectopic activity appeared. Some clinicians preferred methscopolamine over atropine because this derivative exerts fewer CNS effects, since it does not readily cross the blood–brain barrier. Methscopolamine increased heart rate more consistently than atropine, but produced more nodal arrhythmias and conduction disturbances. Nevertheless, it also occasionally elicited atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. Eventually, there was increasing concern about the usefulness or safety of parasympatholytic agents in the treatment of the post-MI bradycardia. More experimental work was initiated to investigate the effect of higher heart rates on the electrical stability of the myocardium and its VFT.

Extensive work with experimental acute coronary occlusion in dogs and cats indicated that atrial pacing with increased heart rate exacerbated ischemic S-T changes, accelerated the incidence of ventricular tachycardia and fibrillation, caused myocardial ischemia in dogs that had experimental coronary stenosis, enlarged a pre-existing ischemic injury, and depressed left ventricular function. A reduction of vagal tone with increased heart rate caused electrical stability of the ventricle, produced rate-related S-T segment elevation, caused a higher incidence of arrhythmias of closely coupled PVC's (R-R < 0.43 seconds), and decreased myocardial performance as gauged by an increase in the PEP/LVET ratio and prolongation of the PEP. Furthermore, after hypoxia higher rates produced less relaxation of the ventricular myocardium and more ventricular wall rigidity, which resulted in decreased ventricular filling.

Some methods to evaluate the electrical instability of the myocardium are available. The ventricular fibrillation threshold (VFT) is assessed by applying graded, premature trains of pulses to the ventricular myocardium for the duration of the ST-T segment and T wave. The lowest level of electrical stimulation at which ventricular fibrillation occurs is called the VFT.

Under normal conditions, contiguous myocardial areas show uniformity in their refractory periods. This allows a regular and homogeneous spread of the cardiac impulses. In some special situations the lengths of the refractory periods of adjacent areas differ widely, creating electrical instability by allowing depolarization currents to re-enter a freshly repolarized area while many surrounding myocardial zones are still in a re-
fractory state. This produces anarchy in impulse conduction. The higher the disparity in refractory period (DRP), the more precarious the electrical stability of the myocardium.

The influence of heart rate on both VFT and DRP in the acutely ischemic ventricle has been documented by Kent. Increase in heart rate lowers the VFT and increases the DRP. Slowing of the heart rate has the opposite effects.

Other experiments also show the deleterious effects of increasing heart rate on the ischemic heart. When clamping of the LAD results in experimental MI in dogs, ventricular tachycardia precedes the appearance of VF. Ventricular tachycardia and ventricular arrhythmias are always forecast by a delay in the activation of the epicardium of the ischemic zone (IZE). Such a delay can be associated with regional hyperkalemia. Increasing heart rate hastened the appearance of the delay in IZE activation and, by the same token, the occurrence of ventricular arrhythmias leading to ventricular fibrillation. Finally, Corr et al. produced evidence that after acute coronary occlusion, the efferent vagal tone can exert a salutary influence on the heart. Myers et al. showed that vagal stimulation and bradycardia during experimental AMI had a protective effect. Harrison and colleagues demonstrated that the electrical stability of the acute ischemic heart could be improved by giving anticholinesterases, while, after stellatectomy, coronary-artery occlusion produced less decrease in the VFT. Kolman found that vagal stimulation enhanced the ventricular electrical stability in dogs with experimental coronary occlusion only in the presence of increased sympathetic tone.

The electrical stability of the myocardium is already reduced in the presence of coronary artery disease and after AMI, even if the heart is beating at a normal rate. This may relate to the increased re-entrant activity seen after occlusion of the LAD in dogs. Thus, mechanisms that increase heart rate (e.g., atropine) will almost always facilitate A-V conduction so that more stimuli reach the ischemic zone and adjacent areas. When the ischemic heart beats at a higher frequency, the DRP between contiguous areas will grow and facilitate re-entrant activity.

Recent efforts in this field were surveyed by Epstein, who found ample evidence that increasing heart rate in the acute ischemic heart decreases the electrical stability of the myocardium. He concluded that cardiovacceleration is not always desirable and can indeed be harmful. The same basic relationships may account for the great number of clinical reports that correlate low mortality rate with the presence of sinus bradycardia after acute myocardial infarction. However, an increasing heart rate is not the only mechanism that renders the myocardium electrically unstable.

In the presence of premature atrial stimulation, atropine can increase aberrant ventricular conduction and inhibit the His-Purkinje system, and nodal re-entrant tachycardia has been observed after atropine. This could increase the electrical instability of an ischemic ventricle. Local hypoxia coinciding with high levels of circulating catecholamines increases the slope of slow depolarization of the His-Purkinje cells and enhances their automaticity in the ischemic myocardium. Premature ventricular contractions, ventricular arrhythmias and fibrillation can follow.

Slow, calcium-dependent action potentials that arise around the zone of infarction with high extracellular potassium and catecholamine concentrations may cause re-entry and arrhythmias.

The CNS may also be involved in generating or aggravating electrical myocardial instability. We have already mentioned the importance of the hypothalamic area in the generation of autonomic efferent traffic. Stimulation of the posterior hypothalamus has been linked with degenerative lesions of the myocardium. Cerebral hypoxia increases the susceptibility of the heart to atrial and ventricular fibrillation. During hypoxia, mesencephalic stimulation can induce severe ventriculararrhythmias in the cat. Diazepam is a valuable antagonist of ventricular arrhythmias induced by elective stimulation of structures of the limbic system in the same animal. Natural sleep can substantially reduce the frequency of premature ventricular contractions in man. This was most significant in patients who had coronary disease.

Increasing electrical instability is not the
only way in which cardioacceleration can imperil the ischemic heart. High heart rates appear to compromise the oxygen requirements of the ischemic myocardium as well. In the normal adult, coronary blood flow averages 250 ml/min\(^2\) and, in health, correlates well with myocardial oxygen consumption.\(^{21,66}\) The adjustment of the coronary blood flow occurs mainly through an autoregulatory system in which, besides other chemical and neurohumoral factors, the P\(_{12}\) of the coronary sinus\(^{18}\) or the myocardium itself\(^{22}\) plays a most important role. An increasing heart rate augments myocardial oxygen consumption\(^{22,23}\) and coronary blood flow.\(^{170,236}\)

Since ventricular myocardium extracts 75 per cent of the arterial coronary oxygen content,\(^{223}\) the A-V oxygen difference in the normal beating heart is already 12 vol per cent.\(^{127}\) Therefore, a rapidly beating heart cannot significantly increase oxygen extraction if coronary blood flow is not increased concomitantly. Tachycardia will also shorten diastole, the principal period of coronary blood flow. Coronary blood flow increases mainly as a result of decreased resistance in the coronary circulation. This satisfies the higher oxygen demand engendered by cardioacceleration. Arteriosclerosis of the coronary system limits this response.\(^{57}\) When the heart of a patient suffering from angina is paced at high rates, the coronary blood flow may actually decrease,\(^{70}\) or at least increase relatively less than would be expected from the increase in heart rate.\(^{226}\) Knoebel et al. observed a lowered response to the positive chronotropic effects of atropine in patients with cineangiographic evidence of obstructive coronary disease. The increase of coronary flow was lower than would be expected from the increase in heart rate. If it is assumed that oxygen consumption rose linearly with heart rate in these patients, the oxygen supply would have been marginal. Indeed, the prophylactic administration of atropine before cineangiography has been shown to produce anginal pain in patients who have obstructive coronary-artery disease.\(^{171}\)

**Conclusion**

We cannot assume *a priori* that every bradycardia after MI is harmful; some may be considered benign\(^{226}\) and some even beneficial.\(^{20,165}\) Atropine should be used with caution in the treatment of bradycardia in acute myocardial infarction. Atropine is not a harmless drug\(^{22}\) and should not be administered routinely to the bradycardic patient. The potentially deleterious effects of atropine should be balanced against its benefits,\(^{29}\) and a critical reassessment in the treatment of bradycardia after acute MI is needed.\(^{29}\) The cardiovascular effects of atropine\(^{19,220}\) make this drug useful in the treatment of bradycardia associated with hypotension,\(^{36,115-181,276,265}\) escape rhythms,\(^{254,201}\) and conduction disturbances\(^{35,207}\) after coronary occlusion, even though atropine has been reported to worsen A-V conduction in this situation.\(^{211}\)

The incidence of A-V conduction disturbances after acute MI has been recently reviewed by Atkins.\(^{13}\) First-degree heart block and Mobitz type I block do respond well to atropine if treatment is necessary.\(^{214}\) However, a Mobitz type II block is usually located in the His-Purkinje system.\(^{157}\) Cholinergic influence on this part of the conduction system is small, so atropine will not be very efficient in reversing a Mobitz type II block. In transient acute complete A-V block, atropine has sometimes been used successfully.\(^{1,25,231,220}\) Generally the results of atropine treatment in this severe condition are unpredictable and, while atropine as well as isoproterenol can be used as a temporizing treatment, pacing is the treatment of choice. When atropine is given, it should be injected slowly and in small measured doses.\(^{1,13,21,181,265}\) Accurately calibrated infusion pumps have been used to satisfy these requirements.\(^{269}\) It is useful to remember that large intramuscular or small intravenous doses of atropine can produce vagomimetic effects on heart rate and rhythm,\(^{163,177}\) but not on A-V conduction.\(^{22}\)

The individual susceptibilities of different muscarinic receptors to atropine are well known.\(^{121}\) Genetic defects,\(^{17}\) anesthesia,\(^{77,95,218}\) age,\(^{22,229}\) exercise,\(^{12,46,161}\) neurologic diseases,\(^{8}\) heart disease,\(^{67}\) uremia,\(^{290}\) metabolic\(^{194}\) and endocrine disorders,\(^{120}\) drugs,\(^{160,220}\) and temperature\(^{47}\) can change chronotropic responses to atropine. Elderly patients with no known heart disease show a diminished positive or negative chronotropic response to atropine.\(^{33,220}\) This may be due to poor vascularization of sinus node. Interruption of the main blood supply to the sinus
node in dogs causes atropine-resistant bradycardia. A corollary to this finding may be the observation of Knoebel et al. that patients who had obstructive disease of two or three coronary vessels had a decreased chronotropic response to atropine. It is therefore, clearly necessary to titrate the administration of atropine according to response rather than to give bolus doses calculated by the patient's weight or surface area. Even with titration, however, one may overshoot and obtain an excessive increase in heart rate if vagal hyperactivity has overshadowed a high sympathetic tone. The developing cholinergic block unmasks the latter and results in an undesired, deleterious tachycardia.

A special situation deserves the attention of the anesthesiologist. After nondepolarizing muscle relaxants, neuromuscular blockade is reversed, either by a mixture of atropine and neostigmine or by a sequential injection of both drugs. According to Foldes, a clinically significant tachycardia occurs only when atropine (5–12 μg/kg) is injected 2 minutes before the administration of neostigmine. Since some patients have little or no chronotropic response to atropine, many anesthesiologists like to check the heart rate response to a vagolytic dose of atropine before injecting neostigmine in order to confirm the parasympathetic block. If the block is insufficient, neostigmine may cause an overwhelming parasympathomimetic effect that results in bradycardia, hypotension and cardiac arrest. Since failure of the heart to increase its rate after atropine may have its origin in the myocardium, an atropine-resistant bradycardia in and of itself may represent a contraindication to neostigmine. In myocardial infarction, on the other hand, tachycardia can be harmful, and these patients can be very sensitive to small doses of atropine. Therefore, any excessive increase in heart rate should be avoided during reversal of neuromuscular blockade in coronary occlusive disease.

More experimental and clinical investigation is required to determine whether it is preferable to allow patients with heart disease to recover spontaneously from their neuromuscular blockade or to use reversal techniques that avoid large increases or decreases in heart rate with atropine and neostigmine—two drugs that have different rates of onset and durations of action.

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