Anesthesiology
V 44, No 6, Jun 1976

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.[57,135,136,195,275] Sinus bradycardia (heart rate less than 60 beats/min), an ominous finding in these situations, has often been treated with anticholinergics,[1,36,144,231,287] but severe ventricular arrhythmias have been reported to occur after the use of atropine and related compounds in such circumstances.[116,134,209,217] A controversy has arisen about the use of vagolytic agents in the post-myocardial infarction period.[186] 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 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.[5] It is therefore not surprising to detect a high incidence of bradycardia and bradyarrhythmias in patients admitted soon after AMI[287] or in patients reached very quickly by a mobile coronary care unit.[36,231] The explanation of this early bradycardia is not clear, yet Hinkle[126] 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
LVET = 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
V_{max} = maximal rate of rise of the action potential or maximal rate of phase 0 depolarization
VT = ventricular tachycardia

* Assistant Professor, Department of Anesthesiology.
† Professor and director, Department of Anesthesiology.
Received from the Department of Anesthesiology, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106. Accepted for publication February 12, 1976. Supported in part by NIH Grant GM 19599-03.
Address reprint requests to: Paul Dauchot, M.D., Department of Anesthesiology, University Hospitals of Cleveland, 2065 Adelbert Road, Cleveland, Ohio 44106.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

TABLE 1. Incidences of Bradycardia after Acute Myocardial Infarction

	Number of Cases	Incidence of Bradycardia (Per Cent)
Adgey *et al.*[2]	284	44
Binder and Sbertoli[23]	300	2
Chadda *et al.*[35]	66	45
Chapman[36]	269	12
Grauer *et al.*[98]	84	24
Haden *et al.*[104]	50	14
Lown *et al.*[197]	300	25
Pantridge and Adgey[231]	794	74
Reichmut[237]	104	30
Rotman *et al.*[244]	539	26
Webb *et al.*[287]	74	55

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

	Inferior (Per Cent)	Anterior (Per Cent)
Webb *et al.*[287]	77	32
Adgey *et al.*[2]	53	24
Grauer *et al.*[98]	13	5
George and Greenwood[91]	43.8	12.7
Chadda *et al.*[35]	54	14

bradycardia and other signs of vagal activity were also more evident.[144,148] This can be explained anatomically: 90 per cent of inferior MI's occur by occlusion of the right coronary artery (RCA).[145] In 55 to 65 per cent of cases, the blood supply, which centrally enters the sinus node,[146] comes from the RCA.[143,148,149,163] In 85 to 90 per cent of cases the A-V node artery springs from the right coronary artery as well.[143,148,149,164] Conventional staining techniques, light microscopy, electron microscopy, and cholinesterase staining methods[146] demonstrate many vagal receptors and cholinergic nerve endings located in the posterior wall of the right atrium. These receptors and nerve endings exist in the region of the S-A node and in the posterior part of the A-V groove.[148,300] Therefore, occlusion of the RCA with subsequent ischemia, hypoxia, acidosis, and accumulation of metabolic degradation products[147,301] in this poorly perfused area may stimulate vagal receptors located in the vicinity. The sinus node pacemaker cells are relatively resistant to hypoxia,[147] but disturbances in the propagation of impulses at the junction of the sinus node and Purkinje cells may prolong S-A conduction and slow heart rate.[148]

After experimental coronary occlusion in animals, decreases,[44,72,83,92,184] increases,[94,131,132,155,246] or inconsistent changes[257] 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.[130,138,190] 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] Pain[84] and fear of death[148] are said to cause vago-vagal bradycardia. Receptors located in the esophagus can trigger vagal reflexes causing bradycardia and syncope.[250] In patients suffering from AMI, even the ingestion of hot beverages can provoke bradycardia that could be prevented by atropine.[101]

Baroreceptor reflex: Blood levels of catecholamines are often elevated after AMI.[153,168,173,239,266] 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 hypothalamus[179] and is related, to some extent, to the actual sympathetic tone. Levy and co-workers[188] showed that a pre-existing

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

elevated sympathetic tone produced a stronger cholinergic decelerating response. Grodner *et al.*[100] experimentally inhibited the sympathetic stimulation and positive chronotropic effect of norepinephrine with vagal stimulation and acetylcholine. In the presence of high sympathetic tone, Levy[189] and Dempsey[59] 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.[285]

Reflexes originating from intracardiac receptors: Cardiac chemo and mechanoreceptors initiate the reflexes that travel along the sympathetics[125,205] or the vagi. In 1867, von Bezold and Hirt caused bradycardia, hypotension and apnea in animals[20] by injecting veratrine into coronary arteries. In the late 30's, Jarish thought that the sensory receptors for this triad were located in the heart.[151] Dawes identified the location of the receptor responsible for the reflex apnea in the lungs[55] and established that the chemoreceptors that trigger hypotension and bradycardia were localized in the heart.[54] The injection of contrast dye during cardiac catherization and coronary angiography can cause bradycardia and asystole.[213] This bradycardia is thought to be partly triggered by a reflex vagal inhibition of the sinus node.[89] Evidence suggests that reflexes originating in mechanoreceptors play a role in the bradycardia, hypotension and depressed ventricular activity found after AMI.[301] 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.[11,172] Receptors that trigger the afferent limb of this reflex have been found on the epicardial surface of the left ventricle[262] and in the ventricles.[38,42,230,249] 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.[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.[176] Gellhorn and coworkers[91] 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[229] and in the atria.[230] This reflex arc, receptor–hypothalamus–autonomic cardiovascular efferent, can be blocked by bilateral vagotomy. Atropine administration, however, will only diminish[11] or prevent[41,229] 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,[11,167] and although atropine has been reported to influence receptor discharges,[226] the afferent vagal pathway is largely unaffected by atropine.

Chemoreceptor reflexes: Hypotension and shock, very often associated with AMI,[3,24,122,254] are followed by serious acid–base disturbances[123] and hypoxemia.[14,80,288] Severe acute hypercapnia causes slowing of heart rate.[205] Bradycardia has been related to hypoxemia,[104] which can be triggered by the carotid body chemoreceptors[50,62,175,176] and is modulated by the activity of higher nerve centers and ventilation patterns.[50,51] Atropine does not completely abolish this hypoxic bradycardia.[62]

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 hypertension were two other vascular components of this reflex. The metabolic consequences are an increase in Pa_{CO_2}, increases in plasma concentrations of organic acids and potassium, and a reduction in *p*H. This reflex bradycardia can be blocked by bilateral vagotomy or by atropine, thus demonstrating the vagal origin of the cardiodeceleration. In man, this diving or oxygen-conserving reflex can be simulated by immersing the face in ice-cold water with or without breath-holding. The efferent cardiovascular responses include bradycardia, peripheral vasoconstriction, decreased cardiac output and left ventricular

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

work.[86,192,264,291] The diving reflex is less developed in man than in other species.[176] Yet, Wolf[297] and Richter[241] 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.[301] This vagally mediated bradycardia can be exaggerated by acidosis, since acidemia can enhance vagal reflexes.[141,194] Several studies discuss these reflexes in greater detail.[10,104,150,172]

Some investigators were unable to reproduce the bradycardia after experimental acute coronary occlusion. However, when occlusion is preceded by bilateral vagotomy or atropine,[44] experimental ligation of the sinus node artery in dogs can result in bradycardia that does not respond to atropine.[21] The denervated heart slows after coronary occlusion.[43] However, a denervated heart is deprived of vagal tone and will consequently not respond to atropine.[75,280] 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 *p*H of the myocardial surface.[201] Since the sinus node is located 1 mm or less beneath the epicardial surface,[142] an acidic *p*H may exert a negative chronotropic effect.[147] Since pericarditis is not uncommon after AMI,[63,74,142,148,191,225] that inflammatory process may contribute to the bradycardia.[142,148]

The sensitivity of autonomic Purkinje fibers: The more distally a Purkinje cell is located in the conduction system, the less automaticity it possesses.[261] However, milieu changes, such as hypoxia,[277] 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[168,173,180,229] will also augment automaticity of these fibers, and an existing post-MI hypoxia will increase even more the sensitivity of these Purkinje fibers to epi- and norepinephrine,[128] so that they become quite active. These sensitized fibers are ready to assume pacemaker function in the presence of a depressed sinus node. Associated slow conduction and uni- or bidirectional block can set the stage for reentry, resulting in relatively slow idioventricular rhythms.[196,263,295]

Local electrolyte disturbances: When ischemia irreversibly injures the myocardium, the myocardial cells lose potassium, magnesium and phosphorus and take up sodium, chloride, and water.[48,152] This explains the presence of higher potassium levels in the blood of the coronary sinus after AMI.[33,48] In addition to their effect on rhythm and conduction,[76,82] high extracellular-to-intracellular potassium ratios can decrease the rate of spontaneous depolarization of autonomic cells, slowing heart rate by this mechanism.[128,270] In summary, much experimental evidence suggests that reflex vagal activity, probably enhanced by local phenomena, plays an important role in the bradycardia occurring after AMI. Clinical experience suggests that atropine is able to ameliorate this bradycardia.[1,2,3,35,36,56,69,71,93,119,181,197,237,287,298] However, other reports claim atropine has little effect in the treatment of sinus arrest after AMI[245] and a slow heart rate after MI to be refractory[25] or poorly responsive to atropine.[116]

The sick-sinus syndrome: This syndrome has been described to occur in Caucasians and in Negroes[139] and has also been called "the bradycardia–tachycardia syndrome,"[37,258] the "inadequate sinus mechanism,"[259] the "sluggish sinus node syndrome,"[273] "sinoatrial syncope,"[65] and "chronic sinoatrial heart block."[235] It has attained increasing importance in the last decade. The main characteristics have been reviewed by Rubenstein[245] and Ferrer.[79] Severe, persistent bradycardia and brief or prolonged periods of sinus arrest or complete S-A exit block that can be followed by escape rhythms, 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[203] and measurement of the sinoatrial conduction time,[61] are presently used to investigate and evaluate sinus node function. Both sinus node recovery time[204] and sinoatrial conduction time[267,268] can be abnormally

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

prolonged in the presence of sinus node dysfunction. It should be noted that in the prospective study of Hinkle,[126] 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,[65,204,235,241] but can be dangerous[241] and might further impair sinus node function when atropine elicits a "paradoxical" prolongation of the sinus nodal recovery time.[238]

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.[301] 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.[9,26,87,255] As a result, ventricular function is impaired and the ability to adjust cardiac output via stroke-volume variations is limited[150] 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.[251,292] This deleterious effect can be blocked by atropine. Histologically, Nonidez,[227] Napolitano[224] and others have demonstrated vagal innervation of the ventricles. The physiologic counterpoint was provided by Levy,[187] DeGeest,[58] Dagett,[49] Linden,[193] and others,[281] 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 Katoh[158] 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,[129,182] as in the case of an A-V node pacemaker that results in A-V dissociation.[282] This arrhythmia impairs ventricular filling[29] 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.[121,242] Since the ventricular pacemaker cells belong to the ventricular conductive system and their automaticity is probably not influenced by acetylcholine or vagal activity,[128] 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,[17,68] the clinical importance of this may be negligible.

The coronary vessels are also influenced by the vagus and cholinergic stimulation should produce coronary vasodilatation.[49,78,85,159,289] 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 MI[154] are not blocked by atropine.[32] However, by a different mechanism atropine can increase coronary blood flow by increasing heart rate, and with it, myocardial oxygen requirement.[96,171]

Bradycardia, Arrhythmias, and Conduction Disturbances after MI

Bradycardia itself can be the root of rhythm irregularities. In 1966, Han observed that slowly beating atria 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

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

after coronary occlusion when the basic rate was low.[108] He concluded that re-excitation of asynchronously repolarized adjacent fibers was responsible for the spontaneous generation of coupled beats. Singer[260] 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_{max}, and protracted conduction. Recycling this sequence could establish decreased resting membrane potentials, low-amplitude action potentials, and decremental conduction with uni- and bidirectional 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.[282,294,295]

In many animal experiments it has been shown that sinus bradycardia increased ventricular instability and lowered ventricular fibrillation threshold (VFT).[71,108,109,257] Leroy reported reduced mortality in dogs after acute occlusion of the LCA when the dogs were pretreated with atropine.[185] Madan found atropine decreased spontaneous ventricular activity after coronary ligation in dogs,[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.[34] 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_{pvc} 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_{pvc} intervals shorter than 0.43 seconds were often followed by severe ventricular arrhythmias (VF) and were considered malignant.[73] He noticed that atropine or pacing suppressed benign (R-R_{pvc} > 0.43 seconds) arrhythmias after coronary occlusion in dogs but was not very effective in abolishing the malignant (R-R_{pvc} < 0.43 seconds) arrhythmias.[73] In man, the limit between benign and malignant arrhythmias does not seem to be as well-defined, since de Soyza[60] did not find the R-R_{pvc} intervals to differ significantly between "benign" and "malignant" ventricular extrasystoles. Clinically, Scheinman *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.[256] The malignancy of closely coupled PVC's is well recognized, for they can produce the R-on-T phenomenon that precipates ventricular fibrillation.[64,114] 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.[147,198,201] It was observed that sinus bradycardia could be associated with an increased ectopic atrial activity,[93] 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[71,111,248] or ventricular paroxysmal tachycardia.[197] Whether vagal stimulation[71,111,148] caused these severe ventricular arrhythmias directly[197] or indirectly via the mechanism of atrial dysrhythmias is not clear. However, Sloman reported that bradycardia can lead to idioventricular tachycardia that can be effectively treated by atropine.[263] Norris failed to see major ventricular arrhythmias in patients who were bradycardic after AMI.[228]

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.[265] Hageman could elicit conduction abnormalities and bradydysrhythmias by stimulating small vagal nerves.[106]

Clinically, ventricular aberrant conduc-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

tion with bradycardia has been described,[81,234] and bradycardia has been linked to the appearance[210] and disappearance[10] of bundle-branch block. However, El-Sherif did not find evidence that could relate bradycardia-dependent block to enhanced automaticity.[70]

Inferior MI frequently causes disturbances in A-V conduction,[45] since the blood supply to the A-V node often arises from the right coronary artery.[147,161] Conduction in the A-V node is normally slow.[278,283] Ischemia aggravates slowing of conduction and produces various degrees of A-V block, facilitating reentry phenomena,[296] which can lead to atrial tachyarrhythmias. Pick[233] 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.[303] His-bundle electrograms have confirmed the existence of the A-V nodal bypass in man.[178] In general, MI with conduction abnormalities carries an unfavorable prognosis.[13,26,41,157,197] Imperial[140] found that bradycardia with AMI was associated with a lower mortality rate than tachycardia; others reported that bradycardia resulted in higher mortality.[22,23] While Chapman[76] found sinus bradycardia to be a good prognostic sign, Haden thought it was a poor one.[104]

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.[286] For years, however, clinical and experimental evidence that the heart rate should be accelerated in the bradycardic patient with AMI was accepted.[111,237] It was suggested that likely candidates for MI be provided with self-injectable ampules of atropine.[299] With the growing use of atropine for bradycardia, however, many reports that described frequent, severe ventricular ectopic activity appeared.[1,116,131,209,240,287,302,304] 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.[223] Nevertheless, it also occasionally elicited atrial fibrillation, ventricular tachycardia, and ventricular fibrillation.[217] 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,[257] caused myocardial ischemia in dogs that had experimental coronary stenosis,[224] enlarged a pre-existing ischemic injury,[205] and depressed left ventricular function.[207] A reduction of vagal tone with increased heart rate caused electrical stability of the ventricle,[166] produced rate-related S-T segment elevation,[236] caused a higher incidence of arrhythmias[156] of closely coupled PVC's ($R\text{-}R_{PVC} < 0.43$ seconds), and decreased myocardial performance as gauged by an increase in the PEP/LVET ratio and prolongation of the PEP.[274] Furthermore, after hypoxia higher rates produced less relaxation of the ventricular myocardium and more ventricular wall rigidity, which resulted in decreased ventricular filling.[289]

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-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

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.[165] 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.[76] 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.[133] Finally, Corr *et al.* produced evidence that after acute coronary occlusion, the efferent vagal tone can exert a salutary influence on the heart.[44] Myers *et al.* showed that vagal stimulation and bradycardia during experimental AMI had a protective effect.[219] Harrison and colleagues demonstrated that the electrical stability of the acute ischemic heart could be improved by giving anticholinesterases,[118] while, after stellectomy, coronary-artery occlusion produced less decrease in the VFT.[169] Kolman found that vagal stimulation enhanced the ventricular electrical stability in dogs with experimental coronary occlusion only in the presence of increased sympathetic tone.[174]

The electrical stability of the myocardium is already reduced in the presence of coronary artery disease[127] and after AMI, even if the heart is beating at a normal rate.[27,112,169] This may relate to the increased re-entrant activity seen after occlusion of the LAD in dogs.[110] 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.[113,257] Increased re-entrant activity precipates arrhythmias.[113,257]

Recent efforts in this field were surveyed by Epstein,[72] who found ample evidence that increasing heart rate in the acute ischemic heart decreases the electrical stability of the myocardium. He concluded that cardioacceleration 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.[36,84,91,147,197] 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,[5] and nodal re-entrant tachycardia has been observed after atropine.[6] 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.[111,113]

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.[293]

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.[90,247] Stimulation of the posterior hypothalamus has been linked with degenerative lesions of the myocardium.[107,279] Cerebral hypoxia increases the susceptibility of the heart to atrial and ventricular fibrillation.[272] During hypoxia, mesencephalic stimulation can induce severe ventricular arrhythmias in the cat.[212] Diazepam is a valuable antagonist of ventricular arrhythmias induced by elective stimulation of structures of the limbic system in the same animal.[253] Natural sleep can substantially reduce the frequency of premature ventricular contractions in man. This was most significant in patients who had coronary disease.[199]

Increasing electrical instability is not the

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

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[162] and, in health, correlates well with myocardial oxygen consumption.[31,66] The adjustment of the coronary blood flow occurs mainly through an autoregulatory system in which, besides other chemical and neurohumoral factors,[95] the P_{O_2} of the coronary sinus[18] or the myocardium itself[222] plays a most important role. An increasing heart rate augments myocardial oxygen consumption[28,252] and coronary blood flow.[170,298]

Since ventricular myocardium extracts 75 per cent of the arterial coronary oxygen content,[222] the A-V oxygen difference in the normal beating heart is already 12 vol per cent.[137] 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.[97] When the heart of a patient suffering from angina is paced at high rates, the coronary blood flow may actually decrease,[170] or at least increase relatively less than would be expected from the increase in heart rate.[298] 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[228] and some even beneficial.[30,165] Atropine should be used with caution in the treatment of bradycardia in acute myocardial infarction. Atropine is not a harmless drug[72] and should not be administered routinely to the bradycardic patient. The potentially deleterious effects of atropine should be balanced against its benefits,[98] and a critical reassessment in the treatment of bradycardia after acute MI is needed.[88] The cardiovascular effects of atropine[19,99] make this drug useful in the treatment of bradycardia associated with hypotension,[36,115,-181,276,287] escape rhythms,[256,301] and conduction disturbances[15,287] 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.[244] 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.[1,35,231,301] 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.[13,71,181,287] 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,[105,177] but not on A-V conduction.[52]

The individual susceptibilities of different muscarinic receptors to atropine are well known.[124] Genetic defects,[117] anesthesia,[77,-95,218] age,[53,220] exercise,[12,46,161] neurologic diseases,[8] heart disease,[67] uremia,[200] metabolic[196] and endocrine disorders,[120] drugs,[160,208] 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.[53,220] This may be due to poor vascularization of sinus node. Interruption of the main blood supply to the sinus

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

node in dogs causes atropine-resistant bradycardia.[78] 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.[171] 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.[267]

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[16] or by a sequential injection of both drugs. According to Foldes,[243] 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,[53,204] 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.[183,214] 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.[99]

References

1. Adgey AA, Mulholland HC, Geddes JS, et al: Incidence, significance and management of early bradyarrhythmias complicating acute myocardial infarction. Lancet 295:1097–1101, 1968
2. Adgey AA, Geddes JS, Allen JD, et al: Acute phases of myocardial infarction. Lancet 301: 501–504, 1971
3. Agress CM, Binder MJ: Cardiogenic shock. Am Heart J 54:458–477, 1957
4. Agruss NS, Rosin EY, Adolph RJ, et al: Significance of chronic sinus bradycardia in elderly people. Circulation 46:924–930, 1972
5. Akhtar M, Damato AN, Caracta AR: Electrophysiologic effects of atropine on atrioventricular conduction studied by His bundle electrogram. Am J Cardiol 33:333–343, 1974
6. Akhtar M, Damato AN, Batsford WP, et al: Induction of atrioventricular nodal reentrant tachycardia after atropine. Am J Cardiol 36:286–291, 1975
7. Alessi R, Nusinowitz M, Abiloskov JA: Nonuniform distribution of vagal effects on the atrial refractory period. Am J Physiol 194: 406–410, 1958
8. Amorin DS, Goday RA, Manco JC, et al: Effects of acute elevation in blood pressure and of atropine on heart rate in Chagas' disease. Circulation 38:289–294, 1968
9. Amsterdam EA: Function of the hypoxic myocadium. Experimental and clinical aspects. Am J Cardiol 32:461–471, 1973
10. Andersen HT: Physiological adaptions in diving vertebrates. Physiol Rev 46:212–243, 1965
11. Ascanio G, Barrera F, Lautsch V, et al: Role of reflexes following myocardial infarction. Am J Physiol 209:1081–1088, 1965
12. Astrand PO, Ekblom B, Goldbarg AN: Effects of blocking the autonomic nervous system during exercise. Acta Physiol Scand 82:18A–19A, 1971
13. Atkins JM, Leshin SJ, Blomquist GR, et al: Ventricular conduction blocks and sudden death in acute myocardial infarction. N Engl J Med 288:281–287, 1973
14. Ayres SM, Mueller H, Gianellis S Jr, et al: The lung in shock. Alveolar capillary gas exchange in the shock syndrome. Am J Cardiol 26:588–594, 1970
15. Baird IM, Randhawa MR: Intravenous atropine in bradycardia due to coronary infarction. Lancet 1:711–712, 1965
16. Baraka A: Safe reversal. (2) Atropine–neostigmine mixture. Br J Anaesth 40:30–36, 1968
17. Bayley JC, Greenspan K, Elizari MV, et al: The effects of acetylcholine on automaticity and conduction within the proximal His–

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

Purkinje specialized conduction system. Circ Res 30:210–216, 1972
18. Berne RM: Regulation of coronary blood flow. Physiol Rev 44:1–29, 1964
19. Berry JN, Thompson HK, Miller E, et al: Circulatory effects of atropine. Changes in cardiac output, stroke volume and central venous pressure induced by atropine in man. Am Heart J 58:204–213, 1959
20. Bezold von A, Hirt L: Ueber die Physiologischen Wirkungen des Essigauren Veratrins. Unters Physiol Lab Würzburg 1:75–176, 1867
21. Billette J, Elharrar V, Porlier G, et al: Sinus slowing produced by experimental ischemia of the sinus node in dogs. Am J Cardiol 31:331–335, 1973
22. Billings FT, Kalstone BM, Spencer JL, et al: Prognosis of acute myocardial infarction. Am J Med 7:356–370, 1949
23. Binder M, Sbertoli MW: Cardiac arrhythmias. Their prognostic value in acute myocardial infarction. Ill Med J 108:321–324, 1955
24. Binder M: The mechanism and treatment of shock in acute myocardial infarction. Prog Cardiovasc Dis 1:206–218, 1958
25. Birchfield RI, Menefee EE, Bryant GDN: Disease of the sino-atrial node associated with bradycardia, asystole, syncope and paroxysmal atrial fibrillation. Circulation 16:20–26, 1957
26. Bleifeld W, Hanrath P, Mathey D: Acute myocardial infarction. V. Left and right ventricular hemodynamics in cardiogenic shock. Br Heart J 36:822–834, 1974
27. Boineau JP, Cox JL: Slow ventricular activation in acute myocardial infarction; a source of re-entrant premature ventricular contractions. Circulation 48:702–713, 1973
28. Boerth RC, Covell JW, Pool PE: Increased myocardial oxygen consumption and contractile state associated with increased heart-rate in dogs. Circ Res 24:725–734, 1960
29. Braunwald E: Symposium on cardiac arrhythmias—Introduction with comments on the hemodynamic significance of atrial systole. Am J Med 37:665–669, 1964
30. Braunwald E: Control of myocardial oxygen consumption. Am J Cardiol 27:416–432, 1971
31. Braunwald E, Sarnoff SJ, Case RB, et al: Hemodynamic determinants of coronary blood flow; effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow. Am J Physiol 142:157–163, 1958
32. Brown AM: Motor innervation of the coronary arteries of the cat. J Physiol (Lond) 198: 311–328, 1968
33. Case RB, Nasser MG, Crampton RS: Biochemical aspects of early myocardial ischemia. Am J Cardiol 24:766–775, 1966
34. Chadda KD, Banka VS, Helfant RH: Rate dependent ventricular ectopia following acute coronary occlusion. The concept of an optimal antiarrhythmic heart rate. Circulation 49:654–658, 1974
35. Chadda KD, Lichstein E, Cupta PK, et al: Bradycardia–hypotension syndrome in acute myocardial infarction. Reappraisal of the overdrive effects of atropine. Am J Med 59:158–163, 1975
36. Chapman BL: Prognostic factors in acute myocardial infarction treated in a coronary care unit. Aust NZ J Med 1:53–62, 1971
37. Cheng TO: Transvenous ventricular pacing in the treatment of paroxysmal atrial tachyarrhythmias alternating with sinus bradycardia and standstill. Am J Cardiol 22:874–879, 1968
38. Chevalier PA, Weber KC, Lyons GW, et al: Hemodynamic changes from stimulation of left ventricular baroreceptors. Am J Physiol 227:719–728, 1974
39. Chung DK, Jacobs WH: Effect of atropine on isorhythmic A-V dissociation. W Va Med J 67:38–39, 1971
40. Cohen SI, Voukydis P: Disappearance of bundle branch block with slowing of normal heart rate. Am Heart J 85:727–731, 1973
41. Col JJ, Weinberg L: The incidence and mortality of intraventricular conduction defects in acute myocardial infarction. Am J Cardiol 29:344–350, 1972
42. Coleridge HM, Coleridge JCG, Kidd C: Cardiac receptors in the dog with one particular reference to two types of afferent endings in the ventricular wall. J Physiol (Lond) 174:323–339, 1964
43. Corday E, Gold H, De Vera LB, et al: Effects of cardiac arrhythmias on the coronary circulation. Ann Intern Med 50:535–553, 1959
44. Corr PB, Gillis R: Role of the vagus in the cardiovascular changes induced by coronary occlusion. Circulation 49:86–96, 1973
45. Cosby RS, Bilitch M: *In* Heart Block. New York, McGraw-Hill, 1972, p 89
46. Craigh FN: Effect of atropine, work and heat on heart rate and sweat production in man. J Appl Physiol 4:826–833, 1951–1952
47. Cullumbine H, Miles S: The effect of atropine sulfate on men exposed to warm environments. Q J Exp Physiol 41:162–179, 1956
48. Cummings JR: Electrolyte changes in heart tissue and coronary venous plasma following coronary occlusion. Circ Res 8:865–870, 1960
49. Daggett WM, Nugent GC, Carr PW, et al: Influence of vagal stimulation on ventricular contractility, oxygen consumption and coronary flow. Am J Physiol 212:8–18, 1967
50. Daly MdB, Scott MJ: The cardiovascular effects of hypoxia in the dog with special reference to the contribution of the carotid body chemoreceptor. J Physiol (Lond) 173:201–214, 1964
51. Daly MdB, Scott MJ: An analysis of the primary cardiovascular effects of stimulation of the carotid body chemoreceptors in the dog. J Physiol (Lond) 162:555–575, 1962

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

52. Das G, Talhers FN, Weissler AM: New observations on the effect of atropine on the sinoatrial and atrioventricular nodes in man. Am J Cardiol 36:281–285, 1975
53. Dauchot PJ, Gravenstein JS: Effects of atropine on the electrocardiogram in different age groups. Clin Pharmacol Ther 12:274–280, 1971
54. Dawes GS: Studies on veratrum alkaloids, VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridin. J Pharmacol Exp Ther 89:325–343, 1947
55. Dawes GS, Comroe JH Jr: Chemoreflexes from the heart and lungs. Physiol Rev 34: 167–201, 1954
56. D'Cunha GF, Hughes G, Friedberg HD: Immediate treatment of myocardial infarction. Wis Med J 70:111–112, 1971
57. DeBakey ME, Dietrich EG, Liddicoat JE: Acute left ventricular myocardial infarction. Successful excision. Bull Cardiovasc Res Center 8:8, 1969
58. Degeest H, Levy MH, Zieske H, et al: Depression of ventricular contractility by stimulation of the vagus nerve. Circ Res 17:222–235, 1965
59. Dempsey PJ, Cooper T: Ventricular cholinergic receptor systems: Interaction with adrenergic systems. J Pharmacol Exp Ther 167:282–290, 1969
60. de Soyza N, Bissett JK, Kane JJ: Ectopic ventricular prematurity and its relationship to ventricular tachycardia in acute myocardial infarction in man. Circulation 50: 529–533, 1974
61. Dhingra RC, Wyndham C, Amat-Y-Leon F: Sinus nodal responses to atrial extrastimuli in patients without apparent sinus node disease, Am J Cardiol 36:445–462, 1975
62. Downing SW, Remensnijder JP, Mitchell JH: Cardiovascular responses to hypoxic stimulation of the carotid bodies. Circ Res 10:675–685, 1962
63. Dressler W: Management of pericarditis secondary to myocardial infarction. Prog Cardiovasc Dis 3:134–144, 1960
64. Dhurandar RN, MacMillan RL, Brown KW: Primary ventricular fibrillation complicating acute myocardial infarction. Am J Cardiol 27:347–351, 1971
65. Easley RM, Goldstein S: Sinoatrial syncope. Am J Med 50:166–177, 1971
66. Eckenhoff JE, Hafkenschiel JH, Landmesser CN, et al: Cardiac oxygen metabolism and control of the coronary circulation. Am J Physiol 149:634–649, 1947
67. Eckberg DL, Drabinsky M, Braunwald E: Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 285:877–883, 1971
68. Eliakim M, Bellet S, Tawil E, et al: Effect of vagal stimulation and acetylcholine of the ventricle. Circ Res 9:1372–1379, 1961
69. El-Sherif N: Paroxysmal atrial flutter and fibrillation, induction by carotid sinus compression and prevention by atropine. Br Heart J 34:1024–1028, 1972
70. El-Sherif N, Scherlag BJ, Lazarra R, et al: Pathophysiology of bradycardia-dependent-block in the canine proximal His–Purkinje system after acute myocardial ischemia. Am J Cardiol 33:529–540, 1974
71. Epstein SE, Redwood DR, Smith ER: Atropine and acute myocardial infarction. Circulation 45:1273–1278, 1972
72. Epstein SE, Goldstein RE, Smith ER, et al: The early phase of acute myocardial infarction. Pharmacological aspects of therapy. Ann Intern Med 78:918–936, 1973
73. Epstein SE, Beiser GD, Rosing DR, et al: Experimental myocardial infarction. Characterization and treatment of the malignant premature ventricular contraction. Circulation 47:446–453, 1973
74. Erhardt LR: Clinical and pathological observations in different types of acute myocardial infarction. Acta Med Scand (suppl) 560: 59, 1974
75. Essex HE, Herrick JF, Mann FC, et al: The effect of atropine on the coronary blood flow of trained dogs with denervated and partially denervated hearts. Am J Physiol 138:683–686, 1943
76. Ettinger PO, Regan TJ, Oldewurtel HA: Hyperkalemia, cardiac conduction and the electrocardiogram. Am J Cardiol 88:360–371, 1974
77. Farman JV: Circulatory effects of atropine during halothane anesthesia. Br J Anaesth 39:226–235, 1967
78. Feigl EO: Parasympathetic control of coronary blood flow in dogs. Circ Res 25:509–519, 1969
79. Ferrer MI: The sick sinus syndrome. Circulation 57:635–641, 1973
80. Fillmore SJ, Guimaraes AC, Scheidt SS, et al: Blood gas changes and acute pulmonary hemodynamics following acute myocardial infarction. Circulation 45:583–591, 1972
81. Fisch C, Zipes DP, McHenry PL: Rate dependent aberrancy. Circulation 48:714–724, 1973
82. Fisch C: Relation of electrolyte disturbances to cardiac arrhythmias. Circulation 47:408–425, 1973
83. Flameng W, Schaper W, Lewi P: Multiple experimental coronary occlusions without infarction. Effects of heart rate and vasodilatation. Am Heart J 85:767–776, 1973
84. Fluck DC, Olsen E, Pentecost BL, et al: Natural history and clinical significance of arrhythmias after acute cardiac infarction. Br Heart J 29:170–189, 1967
85. Folkow B, Frost J, Unas B: Action of acetylcholine, adrenalin, and noradrenalin on the coronary blood flow of the dog. Acta Physiol Scand 17:201–205, 1949

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

86. Folinsbee L: Cardiovascular response to apneic immersion in cool and warm water. J Appl Physiol 36:226–232, 1974
87. Franciosa JA, Guvha NH, Limas CJ: Arterial pressure as a determinant of left ventricular filling pressure after acute M.I. Am J Cardiol 34:506–512, 1974
88. Friedberg CK: Symposium—Myocardial infarction (Part I). Introduction. Circulation 45:179–188, 1972
89. Frink RJ, Merrick B, Lowe HM: Mechanism of bradycardia during coronary angiography. Am J Cardiol 35:17–22, 1975
90. Gellhorn E: The significance of the state of the central autonomic nervous system for quantitative and qualitative aspects of some cardiovascular reactions. Am Heart J 67: 106–119, 1964
91. George M, Greenwood TW: Relation between bradycardia and the site of acute myocardial infarction. Lancet 293:739–740, 1967
92. Gillis RA: Role of the nervous system in the arrhythmias following coronary occlusion in the conscious dog. Am Heart J 81:677–684, 1971
93. Goel BG, Han J: Atrial ectopic activity associated with sinus bradycardia. Circulation 42:853–859, 1970
94. Goldstein RE, Karsh RB, Smith ER, et al: Influence of atropine and of vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in closed chest dogs. Circulation 47: 1180–1196, 1973
95. Gyl-Rodriguez JA, Payne JP, Potter DR: Some cardiovascular effects of intravenous atropine in patients anaesthetized with halothane. Br J Pharmacol 40:571 P +, 1970
96. Gorlin R, Smith MH, Fletcher HP: Studies on the regulation of the coronary circulation. I: Atropine induced changes in cardiac rate. Am J Med 25:37–42, 1958
97. Gorlin R: Regulation of coronary blood flow. Br Heart J 33:suppl 9–14, 1971
98. Grauer LE, Gershen BJ, Oklando MM, et al: Bradycardia and its complication in the prehospital phase of acute myocardial infarction. Am J Cardiol 32:607–611, 1973
99. Gravenstein JS, Perkins HM: The effect of neostigmine, atropine and ephedrine on heart rate in man. ANESTHESIOLOGY 27:298–303, 1966
100. Grodner AS, Lahritz HG, Pool PE, et al: Neurotransmitter control of sino-atrial pacemaker frequency in isolated rat atria and in intact rabbits. Circ Res 27:867–873, 1970
101. Gross L, Malaya R: Extrinsically induced arrhythmia in acute myocardial infarction. JAMA 228:1021–1024, 1974
102. Guyton AC: Regulation of cardiac output. N Engl J Med 277:805–812, 1967
103. Guzman SV, Swenson E, Jones M: Intercoronary reflex: Demonstration by coronary angiography. Circ Res 10:739–745, 1962
104. Haden RF, Rapport MI, McNerney JJ: The significance of sinus bradycardia in acute myocardial infarction. Dis Chest 44:168–173, 1963
105. Haeyes AH, Copelan WH, Ketchum JS: Effects of large intramuscular doses of atropine on cardiac rhythm. Clin Pharmacol Ther 12: 482–486, 1971
106. Hageman GR, Randall WC, Armour JA: Direct and reflex cardiac bradydysrhythmias from small vagal nerve stimulations. Am Heart J 89: 338–348, 1975
107. Hall RE, Sybers HD, Greenhoot JH, et al: Myocardial alterations following hypothalamic stimulation in the intact conscious dog. Am Heart J 88:770–776, 1974
108. Han J, DeTraglia J, Millet D, et al: Incidence of ectopic beats as a function of basis rate in the ventricle. Am Heart J 72:632–639, 1966
109. Han J, Millet D, Chizzonitti B, et al: Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. Am Heart J 71:481–487, 1966
110. Han J, Goel BG, Hanson CS: Re-entrant beats induced in the ventricle during coronary occlusion. Am Heart J 80:778–784, 1970
111. Han J: Mechanisms of ventricular arrhythmias associated with myocardial infarction. Am J Cardiol 24:800–813, 1969
112. Han J: Ventricular vulnerability during acute coronary occlusion. Am J Cardiol 24:857–864, 1964
113. Han J: The concepts of re-entrant activity responsible for ectopic rhythms. Am J Cardiol 28:253–262, 1971
114. Han J, Goel BG: Electrophysiologic precursors of ventricular arrhythmias. Arch Intern Med 129:749–755, 1972
115. Han J: Atropine and acute myocardial infarction. Circulation 47:429–431, 1973
116. Harris A, Bluestone R: Treatment of slow heart rates following acute myocardial infarction. Br Heart J 28:631–637, 1966
117. Harris WS, Goodman RM: Hyperreactivity to atropine in Down's syndrome. N Engl J Med 279:407–410, 1968
118. Harrison LA, Harrison LH, Kent KM: Enhancement of electrical stability of acutely ischemic myocardium by edrophonium. Circulation 50:99–102, 1974
119. Harvey WP: Some pertinent physical findings in the clinical evaluation of acute myocardial infarction. Circulation 40: (suppl 4) 175–181, 1969
120. Heimbach DM, Crout R: Effect of atropine on the tachycardia of hyperthyroidism. Arch Intern Med 129:430–432, 1972
121. Hellerstein HK, Turell DJ: The mode of death in coronary artery disease. An electrocardiographic and clinicopathological correlation, Sudden Cardiac Death. Edited by B Surawicz, ED Pellegrina. New York, Grune and Stratton, 1964, p 17
122. Hellerstein HK, Brofman BL, Caskey WH:

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

Shock and myocardial infarction. Am Heart J 44:407–427, 1952
123. Helmers C, Mogensen R, Nerlander E, et al: Acid–base disturbances in patients with acute myocardial infarction. Acta Med Scand 194:421–426, 1973
124. Henderson VE: On the sensitivity of different nerve endings to atropine. J Pharmacol Exp Ther 21:99–102, 1923
125. Hess GL, Zuperku EJ, Coon RL, et al: Sympathetic afferent nerve activity of left ventricular origin. Am J Physiol 227:543–546, 1974
126. Hinkle LE, Carver ST, Plakun A: Slow heart rates and increased risk of cardiac death in middle-aged men. Arch Intern Med 129: 732–748, 1972
127. Hinkle LE, Carver ST, Stevens M: The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. Am J Cardiol 24:629–650, 1969
128. Hoffman BF, Cranefield PF: The physiological basis of cardiac arrhythmias. Am J Med 37: 670–684, 1964
129. Hoffman BF: The genesis of cardiac arrhythmias. Prog Cardiovasc Dis 8:319–329, 1966
130. Hoffman BF: Autonomic control of cardiac rhythm. Bull NY Acad Med 43:1087–1096, 1967
131. Hood WB, McCarthy B, Lown B: Myocardial infarction from coronary artery ligation in dogs; hemodynamic effects of isoproterenol and acetylstrophantidin. Circ Res 21:191–199, 1967
132. Hood WB, Joison J, Kumar R, et al: Experimental myocardial infarction. Production of left ventricular failure by gradual coronary occlusion in intact conscious dogs. Cardiovasc Res 4:73–83, 1970
133. Hope RR, Williams DO, El-Sherif N, et al: The efficacy of antiarrhythmic agents during acute myocardial ischemia and the role of heart rate. Circulation 50:507–514, 1974
134. Horgan J: Atropine and ventricular tachyarrhythmia. JAMA 223:693, 1973
135. Hultgren HN, Miyagawa M, Buch W, et al: Ischemic myocardial injury during cardiopulmonary bypass. Am Heart J 85:167–176, 1973
136. Hunter PR, Enrey-Walder P, Bauer GE, et al: Myocardial infarction following surgical operations. Br Med J 4:725–728, 1968
137. Hurst JW, Logue RB, Schlant RC, et al (editors): Metabolism of the heart, The Heart. Third edition. New York, McGraw-Hill, 1970, p 117
138. Hutter OF, Trautwein W: Vagal and sympathetic effects of the pacemaker fibers of the sinus venosus of the heart. J Gen Physiol 39: 715–733, 1955
139. Ikeme AC, D'Arbela PG, Somers K: The sick-sinus syndrome in Africans. Am Heart J 89:295–300, 1975
140. Imperial EC, Carballo R, Zimmerman H: Disturbances of rate, rhythm and conduction in acute myocardial infarction. Am J Cardiol 5:24–29, 1960
141. Jacoby J, Ziegler C, Hamelberg W, et al: Cardiac arrhythmia: Effects of vagal stimulation and hypoxia. ANESTHESIOLOGY 16:1004–1008, 1955
142. James TN: Pericarditis and sinus node. Arch Intern Med 110:305–311, 1952
143. James TN, Burch GE: The atrial coronary arteries in man. Circulation 17:90–98, 1958
144. James TN: Posterior myocardial infarction. J Mich St Med Soc 60:1409–1412, 1961
145. James TN: Myocardial infarction and cardiac arrhythmias. Circulation 24:761–766, 1961
146. James TN: Cardiac innervation: Anatomic and pharmacological relations. Bull NY Acad Med 43:1041–1086, 1967
147. James TN: The coronary circulation and conduction system in acute myocardial infarction. Prog Cardiovasc Dis 10:410–449, 1968
148. James TN: Pathogenesis of arrhythmias in acute myocardial infarction. Am J Cardiol 24:791–799, 1969
149. James TN: Coronary circulation in acute myocardial infarction. Br Heart J 32: (suppl) 138–144, 1974
150. James TN: Sudden death related to myocardial infarction. Circulation 45:205–214, 1972
151. Jarish A, Richter H: Der Berzold Effekt—Eine Vergesse Kreislaufreaktion. Klin Wochenschr 1:185–187, 1939
152. Jennings RB, Sommers HM, Kaltenbach JP: Electrolyte alterations in acute myocardial ischemic injury. Circ Res 14:260–269, 1964
153. Jewitt DE, Reid D, Thomas M, et al: Free noradrenaline and adrenaline excretion in relation to the development of cardiac arrhythmias and heart failure in patients with acute myocardial infarction. Lancet 296: 635–641, 1969
154. Joyce E, Gregg DE: Coronary artery occlusion in the intact unanesthetized dog Intercoronary reflexes. Am J Physiol 213:64–70, 1967
155. Kahn MI, Hamilton JT, Manning GW: Early arrhythmias following experimental coronary occlusion in conscious dogs and their modification by adrenoreceptor blocking drugs. Am Heart J 86:347–365, 1973
156. Karsh RB, Orlando M, Norman D, et al: Ineffectiveness of prophylactic atropine in decreasing arrhythmias and enhancing survival following acute coronary artery occlusion in the conscious dog. Am J Cardiol 29: 273, 1972
157. Kastor JA: Atrioventricular block (second of two parts). N Engl J Med 292:572–574, 1975
158. Katoh Y: Experimental study on shifting of the pacemaker. Jap Circ J 28:733–757, 1964
159. Katz LN, Joachim K: Observations on the innervation of the coronary vessels in the dog. Am J Physiol 126:395–401, 1939
160. Kaupman JH, Yapchai R: Atropine–digitalis tolerance test. Geriatrics 23:112–116, 1968
161. Keck EW: Herzzeitvolumen, Herzfrequenz

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

und Schlagvolumen, Blutdruck und peripherer Strömungswiderstand bei Hunden unter der Einwirkung von körperlicher Arbeit und der Gabe von Katecholaminen und Atropin. Arch Kreislaufforsch 48:78–118, 1965

162. Kelman GR: The heart. Cardiac energy requirements. Applied Cardiovascular Physiology. New York, Appleton-Century-Crofts; London, Butterworths, 1971, p 137
163. Kennel AJ, Titus JL: The vasculature of the human sinus node. Mayo Clin Proc 47: 556–561, 1972
164. Kennel AJ, Titus JL: The vasculature of the human atrioventricular conduction system. Mayo Clin Proc 47:562–571, 1972
165. Kent KM, Smith ER, Redwood DR, et al: The deleterious electrophysiologic effects produced by increasing heart rate during experimental coronary occlusion. Clin Res 30:379, 1972
166. Kent KM, Redwood DR, Smith ER, et al: Electrical stability of acutely ischemic myocardium: Influences of heart rate and vagal stimulation. Circulation 47:291–298, 1973
167. Kezdi P, Kordenat RK, Misra SN: Reflex inhibitory effect of vagal afferents in experimental myocardial infarction. Am J Cardiol 33:853–860, 1974
168. Klein RF, Troyer WG, Thompson HK, et al: Catecholamine excretion in myocardial infarction. Arch Intern Med 122:476–482, 1968
169. Kliks BR, Burgess MJ, Abildskov JA: Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion. Am J Cardiol 36:45–49, 1975
170. Knoebel SB, McHenry PL, Bonner AJ: Myocardial blood flow in coronary artery disease. Effect of right atrial pacing and nitroglycerin. Circulation 47:690–696, 1973
171. Knoebel SB, McHenry PL, Phillips JF, et al: Atropine-induced cardioacceleration and myocardial blood flow in subjects with and without coronary artery disease. Am J Cardiol 33:327–332, 1974
172. Kolatat T, Ascanio G, Tallarida RJ, et al: Action potential in the sensory vagus at the time of coronary infarction. Am J Physiol 213:71–78, 1967
173. Kones RJ: The catecholamines: Reappraisal of their use for acute myocardial infarction and the low cardiac output syndromes. Crit Care Med 1:203–220, 1973
174. Kolman BS, Verrier RL, Lown B: The effect of vagus nerve stimulation upon vulnerability of the canine ventricle. Role of sympathetic–parasympathetic interactions. Circulation 52: 578–585, 1975
175. Korner PJ: The role of the arterial chemoreceptors and baroreceptors in the circulatory response to hypoxia in the rabbit. J Physiol (Lond) 180:279–303, 1965
176. Korner PJ: Integrative neural cardiovascular control. Physiol Rev 51:312–367, 1971
177. Kottmeier CA, Gravenstein JS: The parasympathomimetic activity of atropine and atropine methylbromide. ANESTHESIOLOGY 29: 1125–1133, 1968
178. Krishnaswami V, Geraci AR: Accelerated A-V conduction associated with complete A-V block. Am Heart J 88:463–466, 1974
179. Kumada M, Schramm LP, Altmansberger RA, et al: Modulation of carotid sinus baroreceptor reflex by hypothalamic defense response. Am J Physiol 228:34–35, 1975
180. Lammerant J, DeHerodt P, DeSchryver C: Direct release of myocardial catecholamines into the left heart chambers. The enhancing effect of acute coronary occlusion. Arch Int Pharmacodyn Ther 163:219–226, 1966
181. Lancet: Atropine after myocardial infarction. Editorial. Lancet 2:1183–1184, 1972
182. Laslett EE: A case exhibiting a slow atrioventricular rhythm. Heart 6:81–86,1915–1917
183. Lawson JJ: Cardiac arrest following the administration of neostigmine. Br J Anaesth 28:336–337, 1956
184. Lengyel L, Caramelli Z, Montfort J, et al: Initial E.C.G. changes in experimental occlusion of the coronary artery in nonanesthetized dogs with closed thorax. Am Heart J 53:334–338, 1957
185. Leroy GV, Fenn GK, Gilbert NC, et al: The influence of xanthine drugs and atropine on the mortality rate. Am Heart J 23:637–643, 1942
186. Letters to the editor: Atropine and acute myocardial infarction. Circulation 47:429–431, 1973
187. Levy MN, Ng M, Lipman RI, et al: Vagus nerve and baroreceptor control on ventricular performance. Circ Res 18:101–106, 1966
188. Levy MN, Ng M, Martin P, et al: Sympathetic and parasympathetic interactions upon the left ventricle of the dog. Circ Res 19:5–10,1966
189. Levy MN, Zieske H: Effect of enhanced contractility on the left ventricular response to vagus nerve stimulation in the dog. Circ Res 24:303–311, 1969
190. Levy MN, Zieske H: Comparison of the cardiac effects of vagus nerve stimulation and acetylcholine infusions. Am J Physiol 216:890–897, 1969
191. Lichtstein B, Liu HM: Pericarditis complicating acute myocardial infarction: Incidence of complications and significance of electrocardiogram on admission. Am Heart J 87:246–252, 1974
192. Lin YC: Autonomic nervous control of cardiovascular response during diving in the rat. Am J Physiol 227:601–605, 1974
193. Linden RJ: Function of nerves of the heart. Cardiovasc Res 6:605–626, 1972
194. Linden RJ, Norman J: The effect of acidemia on the response to stimulation of autonomic nerves to the heart. J Physiol (Lond) 200: 51–71, 1969
195. Lindensmith GG, Meyer BW, Ellis EE: Surgery for non-contracting ventricular segments of the myocardium. Circulation 37: (suppl VI) 128, 1968

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

196. Lloyd-Mostyn RH, Watkins PJ: Defective innervation of heart in diabetic autonomic neuropathy. Br Med J (Lond) 3:15–17, 1975
197. Lown B, Vassaux C, Hood WB, et al: Unresolved problems in coronary care. Am J Cardiol 20:494–508, 1967
198. Lown B, Temte JV, Arter WJ: Ventricular tachyarrhythmias. Clinical aspects. Circulation 48:1364–1380, 1973
199. Lown B, Tykocinski M, Garfein A: Sleep and ventricular premature beats. Circulation 48: 691–701, 1973
200. Lowenthal DT, Reidenberg MM: The heart rate response to atropine in uremic patients, obese subjects before and during fasting and patients with other chronic illnesses. Proc Soc Exp Biol Med 139:390–393, 1972
201. McNamara JJ, Soeter JR, Suehiro GT, et al: Surface pH changes during and after myocardial ischemia in primates. J Thorac Cardiovasc Surg 67:191–194, 1974
202. Madan BR, Gupta RS: Acetylcholine and atropine in ventricular arrhythmias following coronary occlusion in the dog. Arch Int Pharmacodyn Ther 178:43–52, 1969
203. Mandel W, Hayakawa H, Danzig R: Evaluation of sino-atrial node function in man by overdrive suppression. Circulation 54:59–66, 1971
204. Mandel WJ: Assessment of sinus node function in patients with the sick sinus syndrome. Circulation 46:761–769, 1972
205. Manley ES, Nash CB, Woodbury RA: Cardiovascular responses to severe hypercapnia of short duration. Am J Physiol 207:634–640, 1964
206. Maroko PR, Kjekshus JK, Sobel BE, et al: Factors influencing infarct size following experimental coronary artery occlusions. Circulation 43:67–82, 1971
207. Maroko PR, Libby P, Braunwald E: Effect of pharmacologic agents on the function of the ischemic heart. Am J Cardiol 32:930–936, 1973
208. Marta JA, Davis HS, Eisele JH: Vagomimetic effects of morphine and Innovar® in man. Anesth Analg (Cleve) 52:817–821, 1973
209. Massumi RA, Mason DT, Amsterdam EA, et al: Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardia. N Engl J Med 287:336–338, 1972
210. Massumi RA: Bradycardia-dependent bundle branch block. Circulation 38:1066–1073, 1968
211. Master AM, Dack S, Jaffe HI: Partial and complete heart-block in acute coronary artery occlusion. Am J Med Sci 196:513–529, 1938
212. Mauck HP Jr, Szumski AJ, Fu TS et al: The effect of acute hypoxia on cardiac dysrhythmias induced by mesencephalic stimulation. Am Heart J 87:197–202, 1974
213. McIntosh HD: Cooperative study on cardiac catherization. Chapter 5, Arrhythmias. Circulation 37–38, suppl III, 1968, pp 27–35
214. McIntosh RR: Death following injection of neostigmine. Br Med J 1:852, 1949
215. Meek WJ, Eyster JAE: Experiments on the origin and propagation of the impulse in the heart. IV, The effect of vagal stimulation and of cooling on the location of the pacemaker within the sino-auricular node. Am J Physiol 34:368–383, 1914
216. Meed WJ, Eyster JAE: Experiments on the origin and propagation of the impulse in the heart. III, The effect of vagal stimulation on the location of the pacemaker, the location of the pacemaker in auriculo-ventricular rhythm, and the effect of vagal stimulation on this rhythm. Heart 5:227–243, 1914
217. Mogensen L, Orinius E: Arrhythmic complications after parasympatholytic treatment of bradyarrhythmias in a coronary care unit. Acta Med Scand 190:495–498, 1971
218. Munchow OB, Denson IS: Modifications by light cyclopropane and halothane anesthesia of the chronotropic effect of atropine in man. Anesth Analg (Cleve) 44:782–790, 1965
219. Myers RW, Pearlman AS, Hyman RM, et al: Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial infarction. Circulation 49:943–947, 1974
220. Nalefski LA, Brown CFG: Action of atropine on the cardiovascular system in normal persons. Arch Intern Med 86:898–907, 1950
221. Napolitano L, Willmann VL, Hanlon CR, et al: Intrinsic innervation of the heart. Am J Physiol 208:455–458, 1965
222. Nasser MG: The Coronary System in Cardiovascular Dynamics. Third edition. Edited by RF Rushmer. Philadelphia–London–Toronto, W. B. Saunders, 1970, pp 275–276
223. Needl JB, Allen AT, Coleman E, et al: Cardiac rate and rhythm changes with atropine and methscopolamine. Clin Pharmacol Ther 17:290–295, 1975
224. Neill WA, Oxendine J, Phelps N, et al: Subendocardial ischemia provoked by tachycardia in conscious dogs. Am J Cardiol 35:30–36, 1975
225. Niarchos AP, McKendrick CS: Prognosis of pericarditis after myocardial infarction. Br Heart J 35:49–54, 1973
226. Nishi K: Effects of atropine on chemoreceptor discharge in the carotid body of the cat. Brain Res 23:292–297, 1970
227. Nonidez JF: Studies on the innervation of the heart. Am J Anat 65:361–413, 1939
228. Norris RM, Mercer CJ, Yeates SE: Sinus rate in acute myocardial infarction. Br Heart J 34:901–904, 1972
229. Okinaka S, Keda M, Hashiba K, et al: Pressoreflex arising from left coronary artery. Jap Circ J 27:575–584, 1963
230. Paintal AS: Vagal afferent fibers. Ergeb Physiol 52:75–156, 1963
231. Pantridge JF, Adgey AAJ: Pre-hospital coronary care: The mobile coronary care unit. Am J Cardiol 24:666–673, 1969
232. Peyster RG, Stuckey JH: Diastolic intramyocardial tissue pressure before, during and after temporary occlusion of the left de-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

scending coronary artery. J Thorac Cardiovasc Surg 67:343–348, 1974
233. Pick A: Mechanism of cardiac arrhythmias. From hypothesis to physiologic facts. Am Heart J 86:249–269, 1973
234. Probst P, Hunter J, Gamble O, et al: Investigation of atrial aberration as a cause of altered P wave contour. Am Heart J 86:516–522, 1973
235. Rasmussen K: Chronic sinoatrial block. Am Heart J 81:38–47, 1947
236. Redwood DR, Smith ER, Epstein SE: Coronary artery occlusion in the conscious dog: Effects of alterations in heart rate, and arterial pressure on the degree of myocardial ischemia. Circulation 46:323–332, 1972
237. Reichmut J: Treatment of bradycardic rhythm disorders in myocardial infarction. Schweiz Med Wochenschr 100:182–184, 1970
238. Reiffel JA, Bigger JT, Giardina EV: "Paradoxal" prolongation of sinus node recovery time after atropine in the sick sinus syndrome. Am J Cardiol 36:98–104, 1975
239. Richardson JA, Woods EF, Bagwell EE: Circulating epinephrine and norepinephrine levels in coronary occlusion. Am J Cardiol 5:613–618, 1960
240. Richardson S: Adverse effect of atropine during myocardial infarction. JAMA 228:1414–1416, 1974
241. Richter CP: On the phenomenon of sudden death in animal and man. Psychosom Med 19:191–198, 1957
242. Rokseth R, Hatle L: Sinus arrest in acute MI. Br Heart J 33:639–642, 1971
243. Rosner V, Foldes FF: The effect of atropine and neostigmine on heart rate and rhythm. Br J Anaesth 43:1066–1074, 1971
244. Rotman M, Wagner GS, Wallace AG: Bradyarrhythmias in acute myocardial infarction. Circulation 45:703–722, 1972
245. Rubenstein JJ, Schulman CL, Yurchak PM, et al: Clinical spectrum of the sick-sinus syndrome. Circulation 46:5–13, 1972
246. Rushmer RF, Watson N, Harding D, et al: Effects of acute coronary occlusion on performance of right and left ventricles in intact, unanesthetized dogs. Am Heart J 66:522–531, 1963
247. Rushmer RF, Smith DA Jr: Cardiac control. Physiol Rev 39:41–68, 1959
248. Sakamoto T, Yamade T, Hiesima K: Ventricular fibrillation induced by conducted sinus or supraventricular beat. Circulation 48: 438–442, 1973
249. Salisbury PF, Cross CE, Rieben PA: Reflexes from left ventricle. Circ Res 8:530–534, 1960
250. Sapru RP, Griffiths PH, Guz A: Syncope on swallowing. Br Heart J 33:617–622, 1971
251. Sarnoff SJ, Brockmann SK, Gillmore JP, et al: Regulation of ventricular contraction, influence of cardiac sympathetic and vagal stimulation on atrial and ventricular dynamics. Circ Res 8:1100–1107, 1969
252. Sarnoff SJ, Braunwald E, Welch GH Jr, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension–time index. Am J Physiol 192: 148–156, 1958
253. Saunders BA, Jenkins LC: Cardiac arrhythmias of central nervous system origin. Possible mechanism and suppresion. Can Anaesth Soc J 20:617–628, 1973
254. Scheidt S, Ascheim R, Killip T: Shock after acute myocardial infarction. A clinical and hemodynamic profile. Am J Cardiol 26:556–564, 1970
255. Scheidt S, Wilner G, Fillmore S, et al: Objective hemodynamic assessment after acute myocardial infarction. Br Heart J 35:908–916, 1973
256. Scheinman MM, Thornburn D, Abbott JA: Use of atropine in patients with acute myocardial infarction and sinus bradycardia. Circulation 52:627–633, 1975
257. Scherlag BJ, Helfant RH, Haft JI et al: Electrophysiology underlying ventricular arrhythmias due to coronary ligation. Am J Physiol 219:1665–1671, 1970
258. Short DS: The syndrome of alternating bradycardia and tachycardia. Br Heart J 16:208–214, 1954
259. Silverman LF, Mankin HT, McGoon DC: Surgical treatment of an inadequate sinus mechanism by implantation of a right pacemaker electrode. J Thorac Cardiovasc Surg 55:264–270, 1968
260. Singer DH, Lazzara R, Hoffman F: Interrelationships between automaticity and conduction in Purkinje fibers. Circ Res 21:537–558, 1967
261. Singer DH, Ten Eick RE: Electrophysiology of the heart and genesis of arrhythmias, Cardiac and Vascular Diseases. Volume I, chapter 12. Edited by HL Conn Jr, O Horwitz. Philadelphia, Lea and Febiger, 1972, p 188
262. Sleight PA: A cardiovascular depressor reflex from the epicardium of the left ventricle in the dog. J Physiol (Lond) 173:321–343, 1964
263. Sloman G, Dowling J, Vohra J: Prevention and treatment of ventricular dysrhythmias. Br Heart J 33: suppl, 1971, pp 165–170
264. Song SH, Lee WK, Chung A, et al: Mechanism of apneic bradycardia in man. J Appl Physiol 27:323–327, 1969
265. Spear F, Moore EN: Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system in the dog. Circ Res 32:27–41, 1973
266. Staszweska-Barcza J: The reflex stimulation of catecholamines during the acute state of myocardial infarction in the dog. Clin Sci 41:419–439, 1971
267. Steinbeck G, Luderitz B: Comparative study of sinoatrial conduction time and sinus node recovery time. Br Heart J 37:956–962, 1975
268. Strauss HC, Saroff AL, Bigger JT, et al: Premature atrial stimulation as a key to the understanding of sino-atrial conduction in man. Presentation of data and critical review of literature. Circulation 47:86–93, 1973
269. Stuckey JD, Pitt M, Sloman G: Atropine solu-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024

tion administered with an automatic device in the coronary care unit. Am J Cardiol 32:988–994, 1973
270. Surawicz B: Arrhythmias and electrolyte disturbances. Bull NY Acad Med 43:1160–1180, 1967
271. Stephenson HE: Yes, Virginia, there is a vagovagal reflex. Chest 64:3–5, 1973
272. Szekeres L, Papp G: Effect of arterial hypoxia on the susceptibility to arrhythmia of the heart. Acta Physiol Acad Sci Hung 32:143–153, 1967
273. Tabatznik B, Mower MM, Samson EB, et al: Syncope in the "sluggish sinus syndrome." Circulation 40:200 (suppl III), 1969
274. Talano JV, Ronan JA Jr: The effect of sinus tachycardia on the phases of left ventricular systole during acute myocardial infarction in man. Am Heart J 87:428–434, 1974
275. Tarhan S, Moffit EA, Taylor WF, et al: Myocardial infarction after general anesthesia. JAMA 220:1451–1454, 1972
276. Thomas N, Woodgate D: Effect of atropine in bradycardia and hypotension in acute myocardial infarction. Br Heart J 28:409–413, 1966
277. Trautwein W: Generation and conduction of impulses in the heart as affected by drugs. Pharmacol Rev 15:277–332, 1963
278. Tse WW: Evidence of presence of automatic fibers in the canine atrioventricular node. Am J Physiol 225:716–723, 1973
279. Van Bogaert A, Jacob W: Répercussions fonctionnelles et anatomiques de la stimulation hypothalamique. Arch Mal Coeur 67: 577–586, 1974
280. Wallace AG, Schaal SF, Sugimoto T, et al: The electrophysiologic effects of beta-adrenergic blockade and cardiac denervation. Bull NY Acad Med 43:1119–1137, 1967
281. Wang HH, Blumenthal MR, Wang SC: Effect of efferent vagal stimulation on coronary sinus outflow and cardiac work in anesthetized dogs. Circ Res 8:271–277, 1960
282. Watanabe Y, Dreifus LS: Newer concepts in the genesis of cardiac arrhythmias. Am Heart J 76:114–135, 1968
283. Watanabe Y, Dreifus LS: Factors controlling transmission with special reference to A-V conduction. Am Heart J 89:790–803, 1975
284. Warner HR, Toronto AF: Regulation of cardiac output through stroke volume. Circ Res 8:549–552, 1960
285. Warner HR, Russell RO: Effect of combined sympathetic and vagal stimulation on heart rate in the dog. Circ Res 24:567–573, 1969
286. Wayne EJ, Laplace LB: Observations on angina of effort. Clin Sci 1:103–129, 1933
287. Webb SW, Adgey AA, Pantridge JF: Autonomic disturbance at onset of acute myocardial infarction. Br Med J 3:89–92, 1972
288. Weil MH, Shubin H: Shock after acute myocardial infarction. Current understanding of hemodynamic mechanisms. Prog Cardiovasc Dis 11:1–17, 1969
289. Weisfeldt ML, Armstrong P, Schully HE: Incomplete relaxation between beats after myocardial hypoxia and ischemia. J Clin Invest 53:1626–1636, 1974
290. Weiss M: The early rise of blood pressure in coronary artery thrombosis. Am Heart J 17: 103–105, 1939
291. Whayne TF Jr, Smith TN, Eger EI II, et al: Reflex cardiovascular responses to stimulated diving. Angiology 23:500–508, 1972
292. Williams JF, Sonneblick EH, Braunwald E: Determinants of atrial contractile force in the intact heart. Am J Physiol 209:1061–1068, 1968
293. Wit AL, Hoffman BF, Cranefield PF: A possible cause of slow conduction and reentry in myocardial infarction. Circulation 44: (suppl 2) 85, 1971
294. Wit AL, Hoffman BF, Cranefield PF: Slow conduction and reentry in the ventricular conducting system. I, Return extrasystole in canine Purkinje fibers. Circ Res 30:1–10, 1972
295. Wit AL, Cranefield PJ, Hoffman BF: Slow conduction and reentry in the ventricular conducting system. II, Single and sustained circus movement in networks of canine and bovine Purkinje fibers. Circ Res 30:11–22, 1972
296. Wit AL, Rosen MR, Hoffman BF: Electrophysiology and pharmacology of cardiac arrhythmias. II, Relationships of normal and abnormal electrical activity of cardiac fibers to genesis of arrhythmias. B. Reentry, Section II. Am Heart J 88:798–806, 1974
297. Wolf S: Sudden death and the oxygen conserving reflex. Am Heart J 71:840–841, 1966
298. Yoshida S, Ganz W, Donoso R: Coronary hemodynamics during successive elevation of heart rate by pacing in subjects with angina pectoris. Circulation 44:1062–1071, 1971
299. Yu PN: Prehospital care of acute M.I. Circulation 45:189–204, 1972
300. Zahn A: Experimentelle Untersuchungen uber Reizbildung und reizleitung im atrioventrikularknoten. Pfluger's Arch. fur die Gesamte Physiologie des Menschen und der Tiere. CLI:247–278, 1913
301. Zipes DP: The clinical significance of bradycardic rhythms in acute myocardial infarction. Am J Cardiol 24:814–825, 1969
302. Zipes DP, Knoebel SB: Rapid rate dependent ventricular ectopy. Adverse responses to atropine-induced rate increase. Chest 62: 255–258, 1972
303. Zipes DP, DeJoseph RL, Rothbaum DA: Unusual properties of accessory pathways. Circulation 49:1200–1211, 1974
304. Zsigmond EK, Matsuki A, Sharatabadi C, et al: Atropine and cardiac arrhythmias. N Engl J Med 288:635, 1973
305. Zucker IH, Gilmore JP: Atrial receptor discharges during acute coronary occlusion in the dog. Am J Physiol 277:360–363, 1974

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/44/6/501/296663/0000542-197606000-00008.pdf by guest on 18 April 2024