Autonomic Neural Influences on the Dysrhythmias Resulting from Myocardial Infarction

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THE VAST majority of deaths associated with myocardial infarction occur within the first few hours of the acute attack and are secondary to ventricular dysrhythmias evolving to ventricular fibrillation. Although the precise mechanisms responsible for these lethal dysrhythmias remain elusive, a large body of data indicates that profound alterations in autonomic nervous system function occur during the early time interval. The purpose of this review is to: (1) examine the data obtained dealing with changes in autonomic activity during myocardial infarction; (2) present, when possible, the exact role exerted by each division of the autonomic nervous system; and (3) suggest areas of research that might be productive in further elucidation of the role of the autonomic nervous system in the development of dysrhythmias during myocardial infarction.

Role of the Parasympathetic Nervous System in Dysrhythmias Resulting from Myocardial Infarction

The influence of the parasympathetic nervous system has received considerable attention over the last several years due to the controversy concerning the administration of atropine during acute myocardial infarction. This controversy stems primarily from studies on animals and case reports which indicate that removal of vagal tone may have deleterious effect on rhythm. In contrast, recent clinical data indicate that the incidence of bradycardia is very high soon after myocardial infarction and may contribute to the genesis of ventricular fibrillation. To clarify these apparent discrepancies, the experimental data will be divided into four types of studies: (1) recording cardiac parasympathetic nerve activity, (2) enhancing the functional activity of the cholinergic nervous system to the heart, (3) administering atropine, and (4) surgically interrupting the vagal nerves to the heart.

1. Recording Parasympathetic Nerve Activity

Although several investigators have reported a change in afferent vagal activity during coronary occlusion, only one study has described changes that occur in efferent vagal fibers. In that study, increased activity occurred during a fall in arterial pressure. Therefore the increase in vagal activity was not due to an increase in baroreceptor activation but was more likely due to activation of cardiac vagal afferents, with an increase in efferent vagal tone.

2. Increasing Cardiac Efferent Vagal Activity

These studies all have been performed on animals with the exception of one preliminary report dealing with data obtained from patients. The consequence of increasing cholinergic activity to the heart depends on the time interval after the acute ischemic episode. This is probably due to the differences between early (first hour) and late (6-24 hours) dysrhythmias previously reviewed by several authors in detail and showing that early malignant dysrhythmias depend primarily on a reentrant mechanism whereas the relatively benign late dysrhythmias are a consequence of enhanced automaticity. Therefore, it is not surprising that the effect of altering activity of the parasympathetic nervous system also would depend on these time intervals. For example, vagal stimulation during the first hour after coronary occlusion either mitigated or terminated the rhythm disturbance, improved the rate of rise of the ischemic zone electrogram, increased the ventricular fibrillation threshold, reduced the incidence of serious ventricular dysrhythmias (i.e., reduced beats with R-R' < 0.43 sec), decreased the number of animals developing spontaneous ventricular fibrillation, and increased the time to onset of ventricular dysrhythmia. Furthermore, administration of edrophonium during this early interval also elevated the ventricular fibrillation threshold, an effect abolished by atropine. In one study, increased efferent vagal stimulation in the cat failed to enhance the beneficial effect already present.
presumably since the cat, unlike the dog, exhibits increased vagal tone with coronary occlusion, and increasing this influence further fails to confer additional protection.

On the other hand, 24 hours after coronary occlusion, vagal stimulation exacerbates the ventricular dysrhythmias due to the unmasking of enhanced ventricular automaticity. Likewise, at 5.5 hours after coronary occlusion, vagal stimulation or acetylcholine administration exacerbated cardiac arrhythmias, although the incidence of ventricular tachycardia and fibrillation was unchanged. In one preliminary study performed in patients during the first 24 hours after acute myocardial infarction, edrophonium failed to alter the incidence of premature beats during a 5-hour period, although coupled premature beats and ventricular tachycardia were more frequent in the treated group. This lack of beneficial effect and indeed deleterious effect was predictable from the studies on animals mentioned above and supports the contention that a beneficial influence might be anticipated only in the early, malignant period after the acute ischemic attack, although no definitive clinical data exist during this early time interval.

3. Effects of Administration of Atropine

Experimental results are inconsistent and inconclusive, because atropine has been shown to be beneficial, harmful, and without effect. LeRoy and colleagues reported that atropine reduced the incidence of ventricular fibrillation after circumflex coronary occlusion in both the anesthetized and conscious dog, but this conclusion was unfounded based on our statistical analysis of their data. Thus, atropine administration failed to produce any significant effect on the incidence of ventricular fibrillation. Two points should be made: (1) circumflex coronary occlusion in the dog produces primarily an inferior myocardial infarction, whereas left anterior descending (LAD) coronary occlusion results in primarily an anterior myocardial infarction; and (2) each of the previously presented studies demonstrating a beneficial influence of enhancing efferent vagal influences were performed in conjunction with LAD coronary occlusion. Indeed, in the same experimental model, atropine was found to be detrimental after anterior myocardial infarction, whereas no effect was seen after inferior myocardial infarction. Thus, the response to atropine may be dependent not only on the time interval after the acute episode but, also, on the exact location of the jeopardized myocardium. These hypotheses also are supported by several additional experimental studies of anterior myocardial infarction in conscious dogs. Atropine was found to: (1) suppress arrhythmias 24 hours after coronary occlusion; (2) obliterate the benign dysrhythmias (ventricular beats with R-R' > 0.43 sec) at this time period; (3) increase the frequency of both occlusion and release dysrhythmias at 10 minutes after occlusion, and (4) increase the incidence of ventricular fibrillation in the early interval in cats, an effect that was shown to be independent of changes in rate.

Thus it is apparent that, in experimental animals, a deleterious response to atropine is encountered when: (1) anterior myocardial infarction is present, (2) atropine is administered during the early interval after ischemia, and (3) the ventricular premature complexes have short coupling intervals.

In view of all the experimental data, it is not surprising that atropine has been found beneficial in patients suffering from acute myocardial infarction. Indeed, within this treated population of patients, the majority suffer from inferior myocardial infarctions and usually are treated several hours after the acute attack. The therapeutic value of atropine in these patients is to improve hemodynamics, and its use is confined to treating either bradycardia (rate < 50/min), bradycardia associated with hypotension, and/or heart block. These disorders are primarily a consequence of inferior myocardial infarction as opposed to an anterior locus. However, the recent clinical studies designed to evaluate the detrimental effects of atropine shown in experimental studies were performed several hours (5–7 hours) after the onset of the acute attack, and 76% of patients had an inferior infarction. In one clinical study, atropine was administered during the early time interval (66% of patients were treated within the 1st hour) but the majority of patients suffered from inferior infarction. Therefore, the decisive clinical studies evaluating the use of atropine during acute myocardial infarction should focus on those patients seen within the early time interval and those with a predominant anterior myocardial infarction. It should be noted that the incidence of bradycardia is high during anterior myocardial infarction when patients are seen within the first 30 minutes relative to the very low incidence seen several hours after an anterior infarction.

4. Surgical Section of Cardiac Parasympathetic Nerves

Only three studies have evaluated the influence of bilateral vagotomy, all during the early interval after LAD coronary occlusion. This procedure was without effect on the incidence of ventricular fibrillation in dogs, whereas, in the cat, this procedure resulted in a significant enhancement of the mortality rate, secondary to ventricular fibrillation. Furthermore, the effect was independent of changes in heart rate and therefore was due to removal of a protective influence of vagal tone, per se. The fact that the dog failed to demonstrate any significant rhythm alteration after vagotomy is not surprising, since the conscious dog shows a withdrawal of vagal tone after LAD coronary occlusion, with a resultant tachycardia.

5. Possible Mechanisms for the Protective Vagal Effects

As previously discussed, the dysrhythmias occurring during the early interval after myocardial ischemia may be due to a reentrant mechanism, whereas those relatively benign dysrhythmias occurring several hours later are primarily the result of enhanced automaticity. Since beneficial vagal influences are confined to this early interval, effects on reentrant mechanisms will be discussed.
Furthermore, the fact that the protective influence of vagal input is confined to those infarctions involving anterior areas may be explained by histological findings in the human and canine heart, demonstrating parasympathetic innervation exclusively to the Purkinje conduction network,28 anatomically located primarily in the anterior region of the heart. Although stimulation of efferent vagus nerves during the early interval has been shown to alleviate the dysrhythmia, an effect attributed to the bradycardia-induced15 stimulation of these nerves with rate held constant was not performed.16,18 Furthermore, several studies have ascribed the beneficial effects on rhythm to the vagus nerves per se, independent of changes in heart rate.3-5

The question remains as to how efferent vagal activation, apart from the rate effect, protects the ventricle from serious and often lethal dysrhythmias. Arrhythmias that occur within minutes of occlusion and last for several hours (i.e., arrhythmias responding in a positive fashion to cholinergic stimuli) appear to be dependent on the effects of ischemia on ventricular myocellular bodies. According to Wit and Bigger,17 "transmembrane action potentials have not been recorded from ischemic myocardium in the in situ heart during the early phase of ventricular arrhythmias, so the actual cellular electrical events which accompany these arrhythmias are a matter of conjecture." Additional information on the mechanism of the protective effect of the vagus may not be forthcoming until these experiments are performed, and the influence of vagal stimulation on ischemic-induced changes in electrical activity of ventricular muscle fibers has been assessed. However, studies in vitro14-16 have demonstrated that acetylcholine decreases phase four depolarization, increases maximum diastolic potential, and improves conduction velocity secondary to an increase in the velocity of upstroke, particularly if the response is premature.18 These responses are most likely due to an increase in $K^+$ conductance, and would be expected to improve conduction velocity and, possibly, obviate a slowed reentrant pathway. In addition, other investigators have put forward the hypothesis that the early malignant dysrhythmias are due to a slow inward calcium current secondary to inactivation of the fast response mediated by sodium.17,18 Acetylcholine has been shown to antagonize this slow calcium current, probably also due to an increase in $K^+$ conductance, and thus slow-response action potentials would fail to propagate thereby interrupting the reentrant circuit.17 Although available evidence suggests that the Purkinje system is not involved in the early malignant ventricular dysrhythmias,17 any reentrant circuit through an ischemic region presumably would be influenced by altered activity in the Purkinje conduction network.

Another mechanism that might account for the protective influence of the vagus nerves is inhibition of norepinephrine release from cardiac sympathetic nerve terminals.1 The arrhythmogenic influences of catecholamines are well known,20 and vagal stimulation has been shown to decrease norepinephrine output from postganglionic sympathetic nerves,29 thus preventing the deleterious effects of norepinephrine. This proposal recently has been examined by Lown and colleagues, with results indicating that the beneficial effect of the vagus is confined to antagonism of adverse sympathetic influences. However, the studies of Lown and co-workers30-32 all were performed under nonischemic conditions, and a recent preliminary study19 demonstrates that, with coronary occlusion, vagal stimulation stabilizes the electrical activity of the ventricle only when sympathetic tone is excluded. In summary, although the protective influence of the vagus nerves may be in part due to a reduction in sinus rate, a direct cardiac effect of acetylcholine released from vagus nerves appears to be a primary mechanism.

Role of the Sympathetic Nervous System in Dysrhythmias Resulting from Myocardial Infarction

Although there is general agreement from both clinical and experimental literature that the sympathetic nervous system exerts deleterious influences on dysrhythmias resulting from myocardial infarction, closer examination of the data reveals that firm conclusions cannot be drawn. At least six types of studies have been performed to evaluate the influence of the sympathetic nervous system on these dysrhythmias including: (1) recording of cardiac sympathetic nerve activity, (2) measurement of circulating and tissue catecholamines, (3) determination of the responsiveness of cardiac tissue to sympathetic stimuli, (4) increasing cardiac efferent sympathetic influences, (5) pharmacological attenuation of cardiac sympathetic neural activity, and (6) surgically denervating sympathetic nerves to the heart.

1. Recording of Cardiac Sympathetic Nerve Activity

Four studies12,34-36 have evaluated the alterations in cardiac efferent sympathetic activity during coronary occlusion. One43 demonstrated either a decrease or no change in inferior cardiac nerve discharge, although LAD coronary occlusion was maintained only for up to 2 minutes. In contrast, occlusion of either the LAD or circumflex coronary artery in cats for up to 90 seconds consistently enhanced efferent sympathetic tone from the T3 ramus, changes which were associated with S-T and T-wave alterations.45,46 In addition, increases in preganglionic efferent sympathetic nerve activity were seen in nearly all animals with main left coronary occlusion, changes consistently associated with the development of severe ventricular dysrhythmias, including ventricular fibrillation.12 Thus, it appears that efferent cardiac sympathetic discharge occurs within seconds after induction of myocardial ischemia. A preliminary study37 reports data to indicate that coronary occlusion results in increases in neural activity in several cardiac sympathetic nerves, whereas simultaneous decreases are seen in others. This asynchronous activation of cardiac neural input may be more arrhythmogenic than homogeneous activation38 and therefore of considerable importance in the generation of early ventricular dysrhythmias.
2. Measurement of Circulating and Tissue Catecholamines

Both plasma and urinary catecholamines are elevated after experimentally induced and human acute myocardial infarction. Increases in both norepinephrine and epinephrine have been observed, suggesting a role not only of sympathetic nerve terminals but also of the adrenal medulla. Indeed, large increases in epinephrine release from the adrenal gland have been reported in dogs and cats after coronary occlusion, as well as release of norepinephrine from the heart, with a result ant depletion of myocardial norepinephrine stores in ischemic regions. It appears that the increased release of catecholamines from ischemic heart muscle may be due to increased efferent sympathetic nerve activity rather than impaired neurotransmitter reuptake. However, the fact that depletion is far more pronounced from ischemic regions suggests that other factors may be involved. In isolated hearts devoid of centrally mediated efferent sympathetic input, anoxia induces a release of approximately one-fourth of the total cardiac catecholamine content within 3 minutes, an effect preventable by administration of tyramine 30 minutes prior to exposing the heart to anoxia. Thus, a tyramine-releasable pool of norepinephrine may be of primary importance and may be influenced by numerous substances released during the early ischemic process. Furthermore, potassium is known to be released within minutes after myocardial ischemia, and this ion has been shown to release norepinephrine, presumably due to a presynaptic site of action.

The stimulus for activation of cardiac efferent sympathetic nerves after myocardial ischemia is not fully understood, although a reflex originating in the heart or initiated by either chemical substances or metabolites from ischemic tissue or by physical changes in the mechanical properties of the myocardial tissue may be responsible. In addition, sympathetic activity may be increased by a decrease in baroreceptor stimulation, consequent to a reduction in systemic arterial pressure. Furthermore, the release of catecholamines from the adrenal gland may be secondary to activation of cardiac afferent vagal fibers with a resultant centrally mediated enhancement of efferent splanchnic discharge.

Perhaps the most controversial question is whether the increased release of catecholamines described initiates or exacerbates the ventricular dysrythmias. It would be anticipated that relatively homogeneous humoral effects of catecholamines (i.e., adrenal gland) on the heart would be far less arrhythmogenic than asynchronous neural input (i.e., localized release or efferent nerve activation). Several studies have reported a temporal relationship between catecholamine release and the development of ventricular dysrythmias (see citations in refs. 53 and 58). However, the fact that adrenal vein ligation did not alter the patterns of ventricular dysrythmias but did attenuate the incidence of ventricular fibrillation after experimental myocardial infarction suggests a role in the evolution of ventricular fibrillation. Likewise, continuous monitoring of plasma catecholamines during the first 48 hours after acute myocardial infarction in patients failed to demonstrate a temporal correlation between plasma catecholamines and ventricular dysrythmias, and this finding is in agreement with experimental findings in dogs. Thus, it appears that if catecholamine levels predispose the heart to serious rhythm disturbances after acute myocardial infarction, measurement of plasma or urinary catecholamines is not sufficiently sensitive to delineate a cause-effect relationship. Furthermore, particularly in clinical investigations, the anxiety of patients associated with hospital admission may result in large fluctuations in catecholamines.

3. Determination of the Responsiveness of Cardiac Tissue to Sympathetic Stimuli

The heart subjected to coronary occlusion may be hypersensitive to the arrhythmogenic effects of catecholamines. This has been demonstrated in canine, as well as in porcine hearts, with epinephrine, norepinephrine, isoproterenol, and efferent sympathetic nerve stimulation. These exaggerated responses appear to develop within minutes after coronary occlusion and may persist for as long as 12 days.

4. Increasing Cardiac Efferent Sympathetic Influences

In experimental animals, psychological stress has been shown to decrease the latency time for the onset of ventricular fibrillation subsequent to coronary occlusion and electrical stimulation of the left stellate ganglia reduces the ventricular fibrillation threshold, an effect independent of heart rate alterations. In contrast, stimulation of the right stellate ganglion increases the ventricular fibrillation threshold, a difference attributable to the differing anatomical distribution of the postganglionic neurons. Furthermore, electrical stimulation of central sympathetic centers (i.e., posterior hypothalamus in dogs) results in a high incidence of ventricular fibrillation (i.e., 62.5%) after coronary occlusion, whereas no animals exhibit fibrillation during stimulation prior to coronary occlusion. Thus it appears that a major factor in the genesis of ventricular fibrillation after acute myocardial infarction may be centrally mediated sympathetic neural input.

5. Pharmacological Attenuation of Cardiac Sympathetic Neural Activity

Numerous pharmacological agents have been used to attenuate adrenergic influences to the heart during myocardial infarction, and conflicting results have been obtained. Myocardial depletion of catecholamines with reserpine has no significant influence on ventricular dysrythmias, including ventricular fibrillation after coronary occlusion and may actually exacerbate the dysrythmias. This paradoxical effect may be due to the unaffected adrenal catecholamines combined with postsynaptic supersensitivity and/or to additional, postsynaptic effects of the drug. Pretreatment with reserpine has been shown to decrease the incidence of ventricular fibrillation associated with coronary reperfusion,
infusion of 6-hydroxydopamine into the left coronary artery has been shown to decrease the mortality incidence due to ventricular fibrillation subsequent to coronary occlusion significantly.76

In contrast to the negative findings with reserpine, a number of investigators have reported that pretreatment with propranolol (0.08–0.31 mg/kg) attenuates the incidence of ventricular dysrhythmias77 and fibrillation96, 78–81 after coronary occlusion, despite employing doses that result in incomplete β-receptor blockade.82, 83 Indeed, in several of the above studies, as well as others, when doses sufficient to produce complete β-receptor blockade were used, no significant alteration of ventricular fibrillation incidence was seen.7, 80, 81 However, pretreatment with practolol in doses that produce complete β-adrenergic blockade significantly reduces the incidence of ventricular fibrillation after coronary occlusion,75, 76 suggesting possibly intrinsic pharmacological differences between propranolol and practolol. One difference between these two drugs is their dissimilar effects on potassium release. Potassium is released from the ischemic region within minutes after coronary occlusion and may play a primary role in generating the subsequent dysrhythmia.82 Catecholamines have been shown to have a biphasic effect on potassium release (i.e., increases and decreases),84 and propranolol blocks the beneficial decrease in potassium release84 mediated by β1 receptors, whereas practolol does not possess this potential detrimental influence.84 Another difference that has been described recently is that propranolol decreases while practolol increases the duration of the diastolic period for subendocardial perfusion.85 In addition, propranolol, but not practolol, un-masks detrimental α-receptor-mediated vasoconstriction in the ischemic region.86 Studies in patients with these two drugs also suggest that a difference exists. Except for an initial small-scale study in patients,87 several groups have reported that prophylactic propranolol treatment of patients with coronary artery disease failed to attenuate the incidence of sudden death,88–90 whereas a more recent trial with practolol in patients with acute myocardial infarction demonstrated a significant decrease in cardiac deaths over a 3-year period, an effect confined to the first 2 hours after the acute attack and primarily in patients with previous anterior myocardial infarctions.90 Thus, it is likely that intrinsic differences exist between β-blocking drugs.

The effect of propranolol on ventricular fibrillation threshold following coronary occlusion is controversial. Two groups have reported that propranolol significantly increases the ventricular fibrillation threshold,91, 92 while one group has reported no effect.93 In terms of fibrillation incidence, sotalol in adequate β-receptor blocking doses is effective in reducing the occurrence of fibrillation following coronary occlusion in some studies,53, 80, 81 but not in others.94 In contrast, a rather consistent finding is that β-receptor blockade in experimental animals 24 hours after coronary occlusion is without any significant antiarrhythmic effect.90–98 Any antiarrhythmic influence is seen at doses of propranolol several times higher than needed for complete β-receptor blockade.93, 97–100

Clinical reports suggest that, in patients during the first few hours after acute myocardial infarction, administration of drugs that block β-adrenergic receptors results in a significant antiarrhythmic effect,101–105 whereas this effect is markedly reduced in patients 24 hours after the onset of acute myocardial infarction.106 However, none of the results of these studies suggested that the subsequent mortality rate was altered by the antiarrhythmic influence.

Bretylium has been shown to decrease the mortality incidence in experimental animals subjected to coronary occlusion,107 increase the ventricular fibrillation threshold in ischemic hearts,108 and shorten the duration of time spent in a ventricular arrhythmia.109 Likewise, clinical results suggest that this drug may decrease the frequency of ventricular dysrhythmias after myocardial infarction,110 particularly in patients with anterior myocardial infarction.111 It is not yet clear whether the antidysrhythmic influence of bretylium is due to its interaction with catecholamines or to a nonspecific direct membrane effect of the agent.

6. Surgical Section of Cardiac Sympathetic Nerves

Two specific points pertaining to the review of these studies are: (1) the data from several authors often are misquoted or misinterpreted; and (2) an alteration of PVC frequency does not necessarily imply a reduction in the mortality rate. For example, as early as 1936, Cox and Robertson112 suggested that acute stellate ganglionectomy reduced mortality from ventricular fibrillation, although statistical evaluation of their data indicates that mortality rates of control and denervated groups were not significantly different. Furthermore, either acute or chronic bilateral stellate ganglionectomy combined with bilateral removal of the chain ganglia has no significant influence on the incidence of ventricular fibrillation after coronary occlusion,52, 113–117 despite the conclusions of two of these studies112, 114 and the finding that bilateral stellatecetomy prevents the fall in ventricular fibrillation threshold normally seen after coronary occlusion.106 However, denervation techniques do reduce the frequency of premature ventricular complexes.115, 116, 117

In contrast to the negative findings on mortality incidence described above, several authors have indicated that bilateral removal of the stellate ganglia plus the chain ganglia from T1 through T5 either 24 hours118 or 3 weeks prior119 to coronary occlusion significantly attenuates the incidence of ventricular fibrillation. This apparent paradox might be best explained by the studies of Ebert and colleagues32, 115 wherein neither acute (1-hour) cardiac neural ablation (i.e., technique of Cooper and colleagues120) nor chronic (i.e., 3 weeks) bilateral stellate ganglionectomy significantly attenuated the incidence of ventricular fibrillation. In contrast, chronic cardiac neural ablation did significantly attenuate the incidence of ventricular fibrillation occurring after coronary occlusion. The difference in response of the denervated groups was due to virtual depletion of catecholamines in nonischemic tissue with the latter chronic technique, whereas only
partial depletion of catecholamines was seen with the former techniques. Thus, it appears that cardiac catecholamine stores may play a key role in the genesis of ventricular fibrillation after acute myocardial infarction (see previous section on tissue catecholamines). Although total depletion of catecholamines attenuates the incidence of ventricular fibrillation, all animals died within 36 hours due to either cardiac failure or asystole, suggesting a primary role of the sympathetic nervous system in the maintenance of hemodynamic function after acute myocardial infarction.

Two recent studies have presented evidence to suggest that simple cardiac denervation is far more complex than previously realized. For example, interruption of the left stellate ganglion attenuates the incidence of ventricular dysrhythmias, whereas right stellatectomy enhances the frequency of dysrhythmias including ventricular fibrillation. Thus, unilateral interruption of different sympathetic neural activity may be more arrhythmogenic than leaving the nerves intact, possibly due to the differential anatomical distribution of the neural fibers. Furthermore, interruption of sympathetic activity at the level of the dorsal roots into the spinal cord or interruption of spinal function from C4 to T6 significantly reduces the incidence of ventricular fibrillation, whereas interruption at the intercollicular level or at C1 leaving the spinal cord intact has no protective influence. Hence, it appears that activation of sympathetic afferents, known to occur with coronary occlusion, may activate a reflex confined to the spinal cord with subsequent enhancement of cardiac effenter sympathetic outflow.

Possible Mechanisms for the Deleterious Effect of Catecholamines

The electrophysiological effects of catecholamines have been reviewed in detail and this section will be confined to more recent advances, including the effect of catecholamines on slow response action potentials. Extracellular potassium in the ischemic region is known to be elevated within minutes after coronary occlusion, an alteration resulting in a decrease in the resting membrane potential. This may be sufficient to inactivate the normal sodium-mediated fast response and convert to slow response action potentials, with a resultant slowing of conduction velocity sufficient for a reentrant circuit. However, in the presence of high extracellular potassium, the increase in potassium conductance prevents propagation of the action potentials, and the reentrant circuit may be interrupted. In the presence of catecholamines, the slow response action potentials may reappear, and this may lead to slowing of conduction through the ischemic region, with sufficient dispersion of the impulse to result in not only premature ventricular complexes but also ventricular fibrillation. However, preliminary studies in dogs have suggested that sympathetic neural input enhances the conduction velocity in the ischemic region, and this agrees well with previous findings. Possibly, several areas of the ischemic region are depressed with complete conduction block, and catecholamines simply improve conduction enough through these areas to maintain a reentrant dysrhythmia.

Future Directions for Research

It should be apparent from the previous discussion that the influence of the autonomic nervous system on cardiac rhythm changes following acute myocardial infarction has not been fully clarified. Delineation is needed of the local electrophysiological effects of the autonomic nervous system under ischemic conditions in vivo. In the absence of this information, results obtained from studies using nonspecific pharmacological or surgical procedures will be difficult to interpret, especially in the evaluation of the role of adrenergic influences. Additional, possible fruitful areas of research include: (1) clarification of the interaction of cardiac sympathetic nerve activity with myocardial cellular function during myocardial infarction; (2) determination of the influence of the nervous system at different levels of the heart wall since innervation is regional (i.e., parasympathetic innervation of the ventricle is predominantly endocardial whereas sympathetic innervation is primarily epicardial and myocardial levels); (3) clarification of the role of the nervous system in the generation of the early as opposed to the late dysrhythmias, since it is probable that the underlying etiology is different; (4) clarification of the role of the nervous system as regards the site of infarction or the area of jeopardized myocardium; (5) clarification of the hemodynamic and cellular differences between various β-adrenergic blocking agents; (6) determination of the importance of intramyocardial release of noradrenaline independent of central adrenergic influences on these dysrhythmias; and (7) clarification of the electrophysiological differences between dysrhythmias occurring after coronary occlusion and those resulting from reperfusion.

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AUTONOMIC INFLUENCES ON DYSRHYTHMIAS/Corr and Gillis

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