Atropine and Acute Myocardial Infarction

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Of the 600,000 people who die each year in the United States from acute myocardial infarction, approximately two thirds die prior to receiving medical attention.1–3 On the basis of data gathered by mobile coronary care units, it appears that most of these deaths result from ventricular fibrillation.4 Clearly, then, any intervention that can successfully modify or eliminate those factors which predispose to the development of ventricular fibrillation during the prehospital phase of acute myocardial infarction will have a profound influence on the natural history of coronary artery disease.

One hypothesis that has evolved recently which bears directly on this problem is that bradycardia may be an important factor predisposing to the development of ventricular fibrillation in many patients dying within minutes or hours of the onset of infarction.5–8 This hypothesis has gained support because of the following clinical and experimental observations: (1) the incidence of bradycardia (heart rate ≤ 60 beats/min) during acute myocardial infarction exceeds 40% in the first few hours of the attack;9 (2) the incidence of ventricular tachycardia in hospitalized patients has been reported to be higher in patients with bradycardia;10 (3) it has been observed that ventricular ectopic activity present during bradycardia is abolished following atropine-induced tachycardia;10,11 (4) several papers on acute myocardial infarction have suggested that bradycardia is associated with a relatively poor prognosis compared to that in patients with normal heart rates;5,11–15 (5) the cardiac output and arterial pressure of patients with acute myocardial infarction and complete heart block seem to be optimal when the ventricles are paced at a rate of 100 beats/min;16 (6) the incidence of ventricular ectopic beats occurring during acute myocardial ischemia in the open-chest anesthetized dog is inversely related to the ventricular rate;17 (7) the duration of the ventricular refractory period in contiguous areas of myocardium is more variable during bradycardia,18 a phenomenon believed to be associated with a greater propensity for the development of reentrant arrhythmias; (8) bradycardia has been shown experimentally to decrease the fibrillation threshold of ventricular myocardium;18 (9) and bradycardia may lead to a fall in blood pressure in some patients with acute myocardial infarction and thereby increase the degree of myocardial ischemia.19,20

The implication of these observations seems straightforward: bradycardia with or without associated hypotension is a potentially dangerous rhythm frequently encountered in the prehospital phase of acute myocardial infarction. In 1966, mainly as a result of these considerations, atropine began to be administered routinely for the treatment of bradycardia occurring during the early phase of acute myocardial infarction by physicians who were transported rapidly to the patient by mobile coronary care units.9 Atropine was considered indicated, not only in the patient with acute myocardial infarction who had severe bradycardia with associated hypotension or ventricular ectopic activity, but also in the patient who manifested even minor degrees of bradycardia and who was otherwise entirely stable.9

Subsequently, the concept that the treatment of bradycardia with atropine may

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produce salutary effects in patients experiencing acute myocardial infarction was considerably extended by the suggestion that, were atropine made available to patients for self-administration while awaiting medical aid, many patients dying before medical attention arrived might be salvaged. This is an exciting proposal; it would represent an intervention on a grand scale aimed at reduction of the single most important cause of death in Americans before age 65. It is especially attractive since it is commonly believed that a moderate increase in heart rate under such circumstances rarely has any deleterious effects.\textsuperscript{5, 21} Considering the potential public health importance of this innovative approach, a critical assessment of the relevant evidence is merited.

Discussion

First, what is the evidence that patients with acute myocardial infarction and associated bradycardia have an increased mortality when compared to patients without bradycardia? We have reviewed the literature relating to survival of hospitalized patients after acute myocardial infarction. Utilizing figures obtained from those studies with adequate data,\textsuperscript{12, 13, 15, 22-28} the mortality rates of patients with and without untreated sinus bradycardia were calculated. It was found that 46 of 346 patients with bradycardia (heart rate of 60 beats/min or less) died (a mortality of 13\%) in contrast to 563 of 2012 patients with heart rates greater than 60 (28\%). In four studies it was possible to compare the mortality rates of patients with sinus bradycardia to those with heart rates of 61-99\textsuperscript{22, 28} or to those with heart rates of 61-99 beats/min and without any detected arrhythmia.\textsuperscript{23, 26} Of those patients with bradycardia, 16 of 214 died (7.5\%) compared with 30 of 347 (8.6\%) with "normal" heart rates. These results may be deceiving since it is possible that the type of infarction leading to bradycardia is by nature more benign than the type of infarction unassociated with bradycardia; thus, it can be argued that the low mortality rate of the group with bradycardia would be even lower if all such patients were treated with atropine.

It also is possible that the low in-hospital mortality rate reflects a selection factor, since the patients admitted to the hospital with bradycardia may represent only a small subgroup of a large cohort most of whom died before receiving medical attention. Nevertheless, the fact remains that the available data do not support the contention that bradycardia is associated with an increased mortality rate in patients hospitalized with an acute myocardial infarction.

Experimental evidence that has some bearing on this point has been obtained recently in our laboratory in collaboration with Drs. Karsh, Orlando, and Norman.\textsuperscript{29} This study was designed to define the effects that alterations in heart rate have on the type and course of arrhythmias occurring during the early phase of acute myocardial infarction in the closed-chest unanesthetized dog. We found that the incidence of serious ventricular arrhythmias was directly related to the spontaneous heart rate present after balloon occlusion of the left anterior descending coronary artery; i.e., slower heart rates were accompanied by a lower incidence of ventricular ectopic activity and ventricular fibrillation. These results in the dog obviously are not directly applicable to myocardial infarction in man since with this experimental preparation heart rates of less than 60 beats/min occur relatively infrequently. Thus, although the definitive studies remain to be performed, the available clinical and experimental evidence suggests that bradycardia during acute myocardial infarction may be associated with a decreased rather than an increased mortality.

Second, what is the evidence that the type of ventricular premature contractions or ventricular tachycardia that occurs during sinus bradycardia necessarily leads to ventricular fibrillation and death? Of relevance to this question are the observations of Lown and coworkers\textsuperscript{10} who found that the incidence of ventricular tachycardia was nearly one-third greater in patients with bradycardia than without; however, they also reported that the patients with sinus bradycardia had the lowest mortality of any of the other subgroups.
analyzed. Although it may be argued that the patients with bradycardia, if left untreated, might have had a high mortality, it is equally possible that not all premature ventricular contractions and not all types of ventricular tachycardia predispose to a fatal outcome and therefore may not necessarily merit aggressive therapy. For example, it is commonly recognized that ventricular fibrillation is more likely when a premature ventricular depolarization interrupts the T wave, and a rating system for estimating the relative malignancy of ventricular arrhythmias has been proposed.30

Thus, a precedent exists for ascribing less lethal potential to certain types of premature ventricular contractions; it is also possible that some types of premature ventricular contractions are so rarely the harbingers of ventricular fibrillation and death that they can, for practical purposes, be considered “benign”? It is quite interesting that several reports have appeared in the literature indicating that “slow ventricular tachycardia” (idioventricular tachycardia) occurring in patients with acute myocardial infarction may be “benign” insofar as it does not seem to lead to a fatal outcome.31-33 It has even been suggested that this type of ventricular tachycardia need not be treated.31-33 In this regard, we recently analyzed the types of arrhythmias that occurred prior to the onset of ventricular fibrillation when acute coronary artery occlusion was produced in the closed-chest unanesthetized dog.29, 34 Of 127 dogs studied, 34 developed ventricular fibrillation. Prior to ventricular fibrillation, all 34 dogs had ectopic ventricular beats that followed a preceding beat by less than 0.43 sec (equivalent to a heart rate of 140 beats/min); ventricular fibrillation never appeared in the dogs that had only those ventricular ectopic beats or ventricular tachycardia with longer R-PVC intervals. Moreover, preliminary clinical evidence has been reported suggesting that during the prehospital phase of acute myocardial infarction the only ECG finding of predictive value for determining the subsequent development of serious ventricular arrhythmias is premature ventric-
ular contractions with a short coupling interval.35 Thus, there is both clinical and experimental evidence suggesting that not all ventricular ectopic activity should be viewed as potentially catastrophic. Whether such “benign” arrhythmias represent the predominant type of ventricular ectopic activity that occurs during bradycardia has not as yet been determined.

Third, what is the evidence that atropine abolishes with reasonable frequency those arrhythmias which untreated might lead to ventricular fibrillation or death? In this regard, we have observed recently that although atropine is extremely effective in abolishing what we have termed benign ventricular arrhythmias during coronary occlusion in the closed-chest conscious dog, it was considerably less effective in abolishing those arrhythmias associated with the eventual development of ventricular fibrillation.34

It must be emphasized that the data suggesting that ventricular arrhythmias can be divided into benign and malignant types are based mainly on results from the experimental animal and may not be applicable to man. Nevertheless, these results do raise questions that must be answered by more exhaustive clinical studies. If, indeed, such a distinction can be made, we must then ascertain the relative incidence of these two types of arrhythmias and the relative efficacy of increasing heart rate in abolishing the type of arrhythmia that seems to predispose to the development of ventricular fibrillation and death. In other words, we must determine whether changes leading to a reduction in risk occur as a result of our antiarrhythmic interventions, or whether the resulting changes serve only to reassure the physician.

Fourth, although mild degrees of hypotension frequently are associated with the bradycardia occurring during acute myocardial infarction, what is the evidence that an increase of mildly depressed blood pressure produced by increasing heart rate enhances survival? There would appear to be little reason to doubt the beneficial effects of atropine administered to a pale, cold, and
diaphoretic patient with severe bradycardia and profound hypotension. However, there is no evidence that severe hypotension occurs very frequently during acute myocardial infarction. It appears that the patient more commonly presents with moderate bradycardia and mild hypotension. Although hypotension has been shown experimentally to increase the degree of ischemic injury produced by coronary occlusion,19, 20 patients with acute myocardial infarction observed in a coronary care unit who had hypotension unassociated with clinical evidence of vasoconstriction or impaired regional perfusion did not have a significantly higher mortality than patients without hypotension.10 In addition, the effect on ischemic injury of raising pressure by increasing heart rate is complicated by the fact that, although increasing pressure is beneficial, increasing rate is deleterious. Thus, if hypotension is only mild, the net effect on ischemic injury of small increases in pressure and moderate increases in rate actually may be to increase the degree of ischemia.

Nevertheless, although considerable uncertainty still exists regarding the potential effects on mortality of atropine treatment of bradycardia in otherwise stable patients with acute myocardial infarction, the possibility remains that the drug does exert salutary effects. It therefore might be argued that if atropine is rarely harmful it should be administered on the chance that it might favorably alter the prognosis in many patients with bradycardia and acute myocardial infarction. However, in a randomized study of acute myocardial infarction produced in the closed-chest conscious dog, we found that when compared to a saline-treated control group the incidence of ventricular arrhythmias and ventricular fibrillation was higher in dogs whose baseline heart rates were increased from a mean of 88 to 107 beats/min by an infusion of atropine.29 In addition, atropine has been shown to increase the degree of myocardial ischemia in the closed-chest dog.36 Finally, it appears that in the absence of hypotension any increment in heart rate, even from baseline values as low as 30 beats/min, is associated with an increase in the degree of myocardial ischemia.36 It should be pointed out that these findings are not incompatible with the observations that an increase in heart rate produced during acute myocardial infarction in man16 or in the experimental animal21 may be associated with an increase in the pumping performance of the heart. Thus, the quantity of nonischemic myocardium present may be sufficient to augment cardiac performance in response to a faster heart rate even though this results in an extension of the ischemic zone.

With these considerations in mind, it should be noted that the classical experimental studies most frequently referred to in support of the hypothesis that bradycardia leads to deleterious electrophysiologic changes during acute myocardial ischemia were not conducted during ischemia. That is, while Han and co-workers18 demonstrated that both ischemia and bradycardia independently increased temporal dispersion and decreased ventricular fibrillation threshold, the effects of bradycardia on these parameters were not examined during myocardial ischemia. Thus, if bradycardia decreases ischemic injury occurring during coronary artery occlusion,36 it seemed conceivable that under these circumstances bradycardia might actually decrease temporal dispersion and increase fibrillation threshold. Indeed, the results of Scherlag and co-workers37 would support such a hypothesis. These investigators studied the mechanisms responsible for ventricular arrhythmias due to coronary ligation in the open-chest anesthetized dog. In contrast to the studies of Han et al.,18 it was found that increasing heart rate during coronary occlusion provoked ventricular arrhythmias and ventricular fibrillation, and vagal stimulation often reduced or terminated ventricular ectopic activity. Moreover, an increased heart rate produced electrophysiologic changes that have been associated with decremental conduction, a condition favoring the development of reentrant arrhythmias. To gain a more direct answer to the question raised concerning the interpretation of the studies of Han et al.,18 we
employed similar techniques but investigated the effects of increasing heart rate on temporal dispersion and fibrillation threshold during ischemia. The results of this study, performed in collaboration with Dr. Kenneth Kent, indicate that increasing heart rate during ischemia does not produce beneficial electrophysiologic effects. In fact, when heart rate was increased during ischemia, in most dogs temporal dispersion increased and fibrillation threshold diminished.

Conclusions

The preceding discussion is not intended as a brief against the concept that atropine should be used to treat bradycardia in a patient who is suffering from acute myocardial infarction but who otherwise is clinically stable. Rather, its purpose is to reemphasize the fact that much is still unknown about both the potential beneficial and deleterious effects of atropine in this situation. That atropine may eventually turn out to be important in the treatment of bradycardia occurring during acute myocardial infarction is a definite and exciting possibility. An often cited example of such a salutary effect is the patient with bradycardia and coexisting severe hypotension who almost invariably experiences marked clinical improvement when heart rate and blood pressure are raised subsequent to administration of atropine. However, a new therapeutic concept cannot be defended by anecdotal reports; rather, an extensive data base must be developed so that the net effects of treatment can be determined. To this end, studies must be performed: (1) to determine not only the prevalence and relative severity of hypotension when bradycardia is present in the patient experiencing acute myocardial infarction but, more importantly, the frequency with which hypotension and bradycardia are associated by the time the patient has recognized that something serious has occurred and would be prepared psychologically to self-administer an antiarrhythmic agent; (2) to determine whether mild hypotension occurring in association with bradycardia in a patient who is otherwise stable increases mortality during the prehospital phase of acute myocardial infarction; (3) to determine whether arrhythmias associated with bradycardia can be divided into benign and malignant types; and (4) if such a division is valid, to determine the relative efficacy of atropine in treating malignant arrhythmias. It is only after we have this information that the eventual role of atropine in the treatment of patients with acute myocardial infarction can be rationally defined.

References


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