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Effect of Metaraminol During Acute Inferior Wall Myocardial Infarction Accompanied by Hypotension: Preliminary Study

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This study was designed to evaluate the effects of metaraminol (Aramine) in six patients with evolving acute inferior wall myocardial infarction accompanied by hypotension and warm limbs. There were 16 episodes of acute inferior wall ischemia, and the response to therapy was judged by evaluating blood pressure and ST segment and T wave abnormalities. Three patients received intravenous isosorbide dinitrate and two received streptokinase as the initial therapy. The mean ST segment elevation was significantly reduced (from 4.94 ± 1 to 0.5 ± 0.7 [$p < 0.0001$]) after metaraminol infusion was initiated. The average T wave height also decreased (from 6.8 ± 2 to −1.3 ± 2.5 mm [$p < 0.0005$]). The average heart rate decreased from 82 ± 11 to 69 ± 9 beats/min ($p < 0.05$) and the mean arterial blood pressure increased from 81 ± 12 mm Hg before metaraminol treatment to 126 ± 8 mm Hg after treatment. All these changes occurred within a few minutes after metaraminol therapy was instituted. In 12 episodes, accelerated idioventricular rhythm appeared concomitantly with the resolution of ST segment elevation.

Coronary angiography performed between 4 and 10 days after admission demonstrated significant obstruction in all infarct-related arteries, but none was totally occluded. Left ventricular function was normal in three patients and slightly hypokinetic in the inferior wall in two.

These results indicate that in a selected group of patients with acute inferior myocardial infarction, metaraminol administration (in certain hemodynamic circumstances) can alleviate acute ischemia within a few minutes and thereby reduce ischemic injury.

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Previous experimental studies (1–3) have demonstrated the beneficial effect of alpha-adrenergic agonists in reducing ischemic injury in experimental acute myocardial infarction in dogs. These findings have been extended to humans (4,5). Borer et al. (4) demonstrated reduction in myocardial ischemia in seven patients during acute myocardial infarction without heart failure by using phenylephrine to abolish nitroglycerin-induced hypotension.

The present study was undertaken to determine the effectiveness of therapy with metaraminol (Aramine) on the extent of ischemic injury in six patients with acute inferior wall myocardial infarction accompanied by hypotension and peripheral vasodilation.

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Methods

Study patients. Between February 1985 and March 1986, 106 patients were admitted to our intensive coronary unit with evidence of acute inferior acute myocardial infarction. Of these 106 patients, 6 (6%) fulfilled the criteria defined later for metaraminol therapy, and these patients formed the study group. There were two men and four women (range 40 to 73 years, mean 58). The onset of symptoms (chest pain) occurred 1 to 4 hours before the study.

Study protocol. According to our standard protocol, all patients who presented in the hyperacute phase of acute myocardial infarction received intravenous isosorbide dinitrate (provided that systolic blood pressure was >100 mm Hg and heart rate was <110 beats/min) and a continuous drip infusion of heparin sulfate. From December 1985, we started to give intravenous streptokinase, according to the protocol used by Ganz et al. (6); thus two patients in this study group received intravenous streptokinase as initial therapy. One patient who presented with hypotension received metaraminol as initial therapy.

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Metaraminol was administered only to patients who fulfilled all the following criteria: 1) ST segment elevation and a positive T wave without a Q wave in leads II, III and aVF during severe chest pain; 2) systolic blood pressure <90 mm Hg; 3) warm limbs; 4) no signs of heart failure; and 5) no clinical, electrocardiographic and echocardiographic signs of right ventricular infarction.

Metaraminol infusion (40 mg in 100 ml saline solution) began at a rate of 2 drops/min and the rate was increased rapidly to raise the systolic arterial pressure by 30 mm Hg. Systolic blood pressure was not allowed to exceed 130 mm Hg. Continuous electrocardiographic monitoring of the inferior lead that showed maximal ST segment elevation was done during the ischemic episode. Cuff blood pressures were recorded at intervals of 0.5 to 1 minute. The magnitude of ST segment elevation, T wave height and heart rate were recorded continuously. Metaraminol infusion was continued to maintain systolic blood pressure at approximately 120 mm Hg until the acute ischemic episode subsided and then was gradually stopped.

Angiographic data. Biplane left ventriculography and selective arteriography of both coronary arteries were performed in five patients because of recurrent ischemic episodes within 4 to 10 days after admission. Coronary stenosis of >70% of luminal diameter in any view was considered significant.

Statistical analysis. A paired *t* test was used to compare each of the hemodynamic and electrocardiographic variables before and after administration of metaraminol. Differences were considered statistically significant at the $p < 0.05$ level. The time course of each hemodynamic and electrocardiographic variable was demonstrated in adequate curves; for each time point, the mean value ± 1 standard deviation was calculated.

Results

The six patients had a total of 16 acute ischemic episodes during the early stages of the acute myocardial infarction (two to four episodes for each patient). The effects of metaraminol on electrocardiographic variables, blood pressure and heart rate during each ischemic episode are presented in Figures 1 to 6.

Electrocardiographic variables. The mean ST segment elevation of the 16 ischemic episodes was significantly reduced (from 4.9 ± 1.2 to 0.5 ± 0.72 mm [$p < 0.0001$]) after metaraminol therapy (Fig. 1). The decrease in ST segment elevation was noticeable within 0.5 to 6 minutes after initiation of the metaraminol infusion (Fig. 2). The mean T wave height also decreased (from 6.8 ± 2 to 1.3 ± 2 mm [$p < 0.0005$]) during metraminol infusion and this decrease was noticeable within 0.5 to 6 minutes after initiation of therapy.

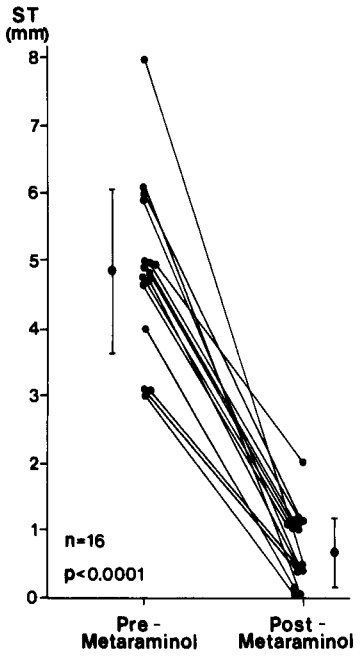
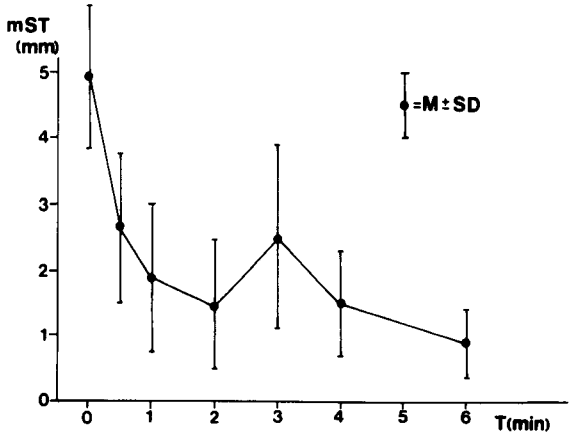


Figure 1. Changes in ST segment elevation in six patients with 16 ischemic episodes before and during metaraminol administration. Metaraminol produced a marked reduction in ST segment level.

Heart rate and arrhythmias. Administration of metaraminol decreased the average heart rate from 82 ± 11 to 69 ± 9 beats/min ($p < 0.05$), but in five episodes, the heart rate was unaltered (Fig. 3). In 12 episodes, accelerated idioventricular rhythm appeared concomitantly with the resolution of ST segment elevation (Fig. 4 and 5).

Blood pressure. The mean blood pressure before metaraminol was 81 ± 12 mm Hg, and increased to 125 ± 8 mm Hg ($p < 0.0005$) during drug infusion (Fig. 6). The increase in systolic blood pressure was noticable within 0.5

Figure 2. Time course of mean ST segment elevation during metaraminol infusion. There is a dramatic reduction in mean (M) ST segment level starting after 0.5 minute.



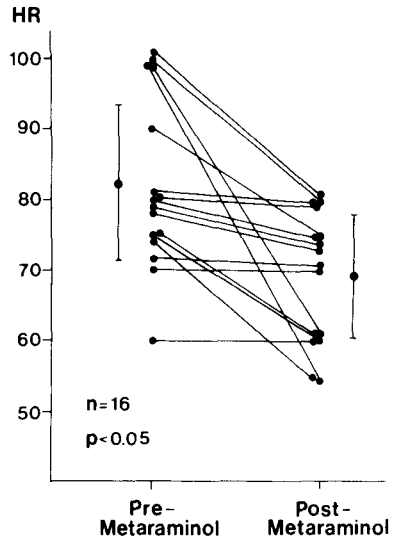


Figure 3. Changes in heart rate (HR) in six patients with 16 ischemic episodes during metaraminol administration.

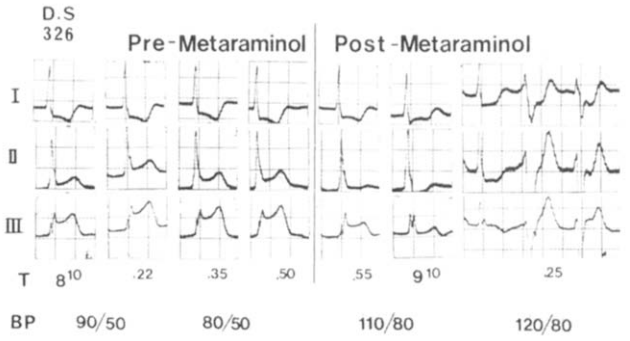


Figure 5. Influence of isosorbide dinitrate and metaraminol on ST segment elevation in a 73 year old woman with acute inferior myocardial infarction. Isosorbide dinitrate administration during 40 minutes caused a decrease in blood pressure (BP) and an increase in ST segment elevation. Metaraminol administration caused a rapid decrease in ST segment elevation within 5 minutes and the appearance of accelerated idioventricular rhythm (115 beats/min) after 25 minutes.

to 2 minutes (Fig. 4 and 5). In three patients, the low systolic blood pressure occurred during isosorbide dinitrate infusion, and in two patients during streptokinase therapy. One patient presented with hypotension before starting any drug therapy. There was an inverse relation between blood pressure and the extent of ST segment elevation (Fig. 4). When blood pressure increased, there was a concomitant decrease in ST segment level ($r = 0.9151$).

Angiographic findings. The right coronary artery was significantly obstructed in four patients, and the circumflex artery was obstructed in one patient. None of these infarct-related arteries was totally obstructed, and there was anterograde flow. There was no evidence of thrombus. Two patients also had significant left anterior descending coronary artery disease. Biplane left ventriculography revealed normal left ventricular function in three patients and slight inferior hypokinesia in the remaining two patients.

Figure 4. Influence of streptokinase and metaraminol on ST segment elevation in a 40 year old woman with acute inferior myocardial infarction. **A,** Streptokinase administration caused a decrease in blood pressure, but did not reduce ST segment elevation within 50 minutes. **B,** Metaraminol administration caused a decrease in ST elevation and bradycardia (40 beats/min) within 2 minutes. **C,** Accelerated ventricular rhythm (85 beats/min) appeared after 5 minutes. **D,** Nearly complete resolution of ST segment elevation appeared 20 minutes after metaraminol administration. BP = blood pressure.

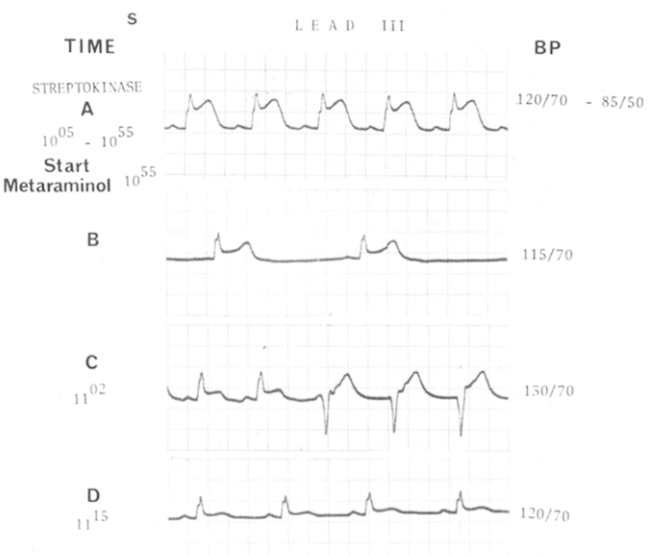
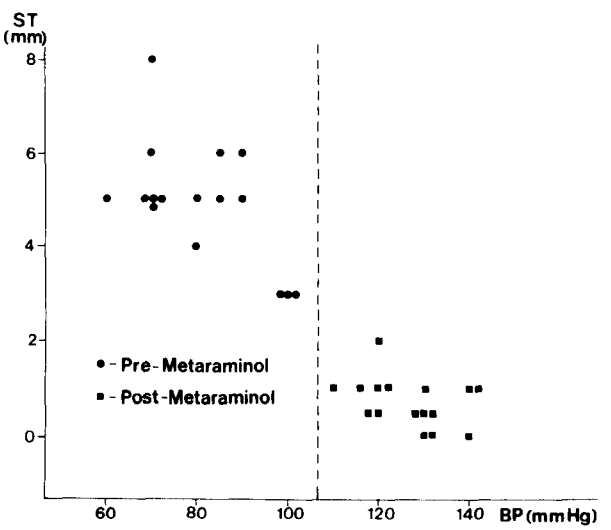


Figure 6. Relation between the ST segment level and systolic blood pressure (BP) before and during metaraminol infusion in 16 ischemic episodes. There is an inverse relation between the ST segment level and blood pressure ($r = -0.9151$).



Follow-up. Two patients underwent successful angioplasty and three underwent coronary artery bypass surgery. All six patients are free of symptoms with no sign of heart failure.

Discussion

Rapid resolution of ST segment elevation as a marker of reperfusion. The results of this investigation show that administration of metaraminol in a selected group of patients with acute inferior myocardial infarction accompanied by hypotension can dramatically reduce ST segment elevation and T wave height within a few minutes. It is well recognized that acute ST segment changes can serve as an index of subsequent ischemic damage, and that a decrease in the magnitude of ST segment elevation reflects a reduction in the ischemic injury to the myocardium. A rapid decrease in ST segment elevation is one of the manifestations of reperfusion induced by intracoronary thrombolytic therapy (6–8). It has also been shown to be a reliable noninvasive marker of reperfusion during intravenous thrombolytic therapy (9). Recently, Hackworthy et al. (10) found a relation between the rate of resolution of ST segment elevation and the degree of perfusion of the infarct artery in patients with acute myocardial infarction in the absence of therapeutic intervention. They also demonstrated that a relation between the rate of decline in ST segment elevation and the time to peak level of serum creatine kinase, which is further evidence that the rate of resolution of ST segment elevation reflects myocardial perfusion. In their 19 patients with acute inferior myocardial infarction, spontaneous ST segment resolution occurred between 2 and 8 hours.

Ganz et al. (9) demonstrated that ST segment resolution was achieved 36 ± 26 minutes after the start of intravenous streptokinase infusion in evolving acute myocardial infarction. According to our experience and that of others (11), with administration of intravenous nitrates during acute myocardial infarction, it takes at least 15 minutes for the ST segment to decrease significantly. Gold et al. (12) showed a 77 ± 8% decrease in ST segment elevation within 30 minutes after the administration of intravenous propranolol in seven patients with acute anterior wall infarction. Leinbach et al. (13) showed an 84% decrease in ST segment elevation after 1 hour in five patients by using an intraaortic balloon pump during acute myocardial infarction without shock. None of the interventions just described, however, produce ST segment resolution in as short a time as shown in our study.

Effect of metaraminol. Previous experimental studies (1–3) have demonstrated the beneficial effect of alpha-adrenergic agonists such as methoxamine in reducing ischemic injury in experimental acute myocardial infarction in dogs. In these experiments, the alpha-adrenergic agonists were used in addition to nitroglycerin to prevent the decrease in blood pressure and reflex tachycardia. Borer et al. (4) extended this finding to humans and demonstrated a reduction in myocardial ischemia by using intravenous nitroglycerin in combination with phenylephrine only in patients without heart failure.

In our study, we used metaraminol, which is predominantly an alpha-adrenergic agonist. Its overall effects are similar to those of norepinephrine, but it is much less potent (14). The cardiovascular actions in human patients are reflected in a sustained increase in systolic and diastolic pressures due almost entirely to vasoconstriction and usually accompanied by a marked reflex bradycardia. Its action on $beta_1$-receptors in the myocardium is less prominent than that of other sympathomimetic amines such as isoproterenol, which act mainly on beta-receptors. Although dopamine in high doses causes vasoconstriction—an action similar to that of metaraminol—it still exerts a positive inotropic and chronotropic effect on the myocardium, which frequently causes tachycardia (14). In our experience, tachycardia or other tachyarrhythmias are very rare with the use of metaraminol.

How metaraminol acts on the coronary circulation in humans is unclear, but it is known to increase coronary blood flow in dogs (15). Metaraminol was used in 12 patients during acute myocardial infarction in 1964 by Malmcrona et al. (16), who demonstrated an increase in blood pressure, a decrease in heart rate and a higher stroke volume during metaraminol infusion, hemodynamic changes similar to those observed in our study group. However, these investigators made no comment on electrocardiographic changes.

Patient selection. The selection of appropriate candidates for metaraminol therapy was done carefully because of the well known risk of aggravating ischemic injury by administration of sympathomimetic amines. We excluded patients with heart failure because it was shown experimentally (17) and in human patients (4) that elevation of systemic arterial pressure above normal levels can result in the extension of ischemic injury. Patients with peripheral vasoconstriction were also excluded because any further increase in vasoconstriction is unnecessary and can be harmful. Thus, metaraminol therapy was instituted only if the patients were hypotensive, in the hyperacute phase of acute inferior myocardial infarction without peripheral vasoconstriction and heart failure and if there was no clinical sign of right ventricular infarction. We did not observe similar patients with acute anterior myocardial infarction.

Theoretical consideration of the effect of metaraminol on ischemia. In all of our patients, the ischemic episodes were probably a consequence of reduction in flow, rather than increase in demand (there was no hypertension or tachycardia in any patient). The accepted theories explaining the reduction of flow during acute myocardial infarction are: 1) mechanical—coronary thrombosis usually superimposed

on a discrete atherosclerotic coronary stenosis (18); and 2) dynamic coronary obstruction—whether by active constriction (coronary spasm) or passive collapse.

Maseri et al. (19,20) postulated that vessel occlusion with interruption of distal flow can occur only when tone is increased. Ganz (21) postulated that a drastic reduction in flow can occur in a severely stenosed artery as a result of a decrease in distending pressure causing passive collapse of the vessel. The causes of passive change in stenotic area could be: 1) a decrease in perfusion pressure (hypotension) that leads to an increased resistance to flow across a stenotic artery (22), and 2) coronary arteriolar dilation (whether the result of augmentation of myocardial oxygen demand or application of vasodilators) and decrease in resistance distal to an elastic stenosis, which causes a decrease in distal coronary artery and distending pressures, thereby increasing the stenosis and the resistance to flow (23,24).

The dramatic effect of metaraminol in our study could possibly be explained by the "passive collapse" theory. In our patients, isosorbide dinitrate administration caused a decrease in systolic blood pressure (decreased perfusion pressure) and possibly coronary arteriolar dilation (decreased resistance) and hence a passive collapse. By giving metaraminol, we raised the blood pressure and coronary perfusion pressure and opened the collapsed artery. The rapid resolution of the ST segment elevation indicates reperfusion. The appearance of accelerated idioventricular rhythm in five patients concomitantly with resolution of ST segment elevation further supports reperfusion (25). If coronary spasm was the underlying mechanism causing ischemia in our patients, one would expect metaraminol, a potent vasoconstrictor, to aggravate it. Another possible explanation of the beneficial effect of metaraminol could be the significant slowing of heart rate and subsequent reduction in myocardial oxygen demand. However, the fact that the heart rate was unaltered in five episodes despite a dramatic ST segment resolution is contrary to this explanation.

In three of our patients, hypotension could have been caused by nitrate administration, and in two other patients, by streptokinase therapy. Although we cannot exclude the possibility that the beneficial effects observed are, indeed, due to the combined effect of metaraminol and isosorbide dinitrate or streptokinase therapy, the almost immediate result observed with metaraminol strongly implies that the beneficial effects were mainly related to this agent. This is well exemplified in the representative cases (Fig. 4 and 5). In addition, in one patient who received only metaraminol, results were similar to those in the other patients.

Angiographic and ventricular data. In all patients, the infarct-related artery was severely obstructed (90 to 95%) but still patent. As stated before, passive collapse can occur only in severely stenosed arteries. There was no evidence of thrombus formation, and it could be speculated that by increasing the distending pressure, the thrombus was being washed distally and its formation was prevented. The fact that every time the blood pressure decreased there was an increase in ST segment elevation makes it unlikely that thrombus formation was the primary event.

Three patients had normal left ventricular function and two had only slight hypokinesia in the inferior wall on ventriculography 4 to 10 days after the acute episodes, which can be ascribed to the shortening of the ischemic period by metaraminol infusion.

Limitations of study. Our study has not provided sufficient hemodynamic data to explain the observed beneficial effects of intravenous metaraminol. Procedures such as an arterial line and a Swan-Ganz catheter were not done because of the dramatic nature of the ischemic episodes and the immediate response to metaraminol infusion. Because of the preliminary nature of these results, we are currently conducting a prospective clinical trial that will include all the hemodynamic variables on a larger group of patients with acute myocardial infarction in other sites.

Clinical application. Our results indicate that in a highly selected group of patients with acute inferior wall myocardial infarction, metaraminol administration, if properly used, can alleviate acute ischemia within a few minutes and thereby reduce ischemic injury. Our documentation of the absence of a deleterious effect of this drug is also of great importance because other agents causing greater acceleration of heart rate or vasoconstriction, or both, may exacerbate ischemic injury. Our study also provides clinical support to the "passive collapse" theory and thereby contributes to the current controversy concerning the mechanism of dynamic coronary obstruction.

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