Use of Phentolamine in Acute Myocardial Infarction Associated with Hypertension and Left Ventricular Failure

By David T. Kelly, M.B., Cesar E. Delgado, M.D., Dean R. Taylor, M.D., Bertram Pitt, M.D., and Richard S. Ross, M.D.

SUMMARY
In 11 patients with hypertension associated with acute myocardial infarction intravenous phentolamine decreased the elevated left ventricular filling pressure. Cardiac index increased with a small decrease in arterial pressure, and therefore the same or increased stroke work was achieved at a lower filling pressure. In patients with acute hypertension myocardial oxygen demand was decreased and this may tend to increase infarct size. The potentially beneficial effects were less great in patients with chronic hypertension antedating the myocardial infarction.

Additional Indexing Words:
Vasodilator therapy Myocardial oxygen consumption Catecholamines

A MAJOR objective of the modern therapy of myocardial infarction is to minimize the mass of myocardial muscle which is infarcted. Factors which increase myocardial oxygen consumption have been shown to increase infarct size and conversely, infarct size may be minimized by reducing myocardial oxygen consumption.1 Heart rate, ventricular volume, systemic arterial pressure, and the contractile state of the myocardium are the determinants of myocardial oxygen consumption.2, 3 An increase in any of these factors will result in an increase in myocardial oxygen demand and therefore, an increase in infarct size. One of these factors, systemic arterial pressure, is frequently elevated during the course of acute myocardial infarction and may adversely affect the course of the disease by increasing the area of ischemia and infarction. The systemic hypertension of myocardial infarction has been attributed to release of catecholamines from the heart.4 Arterial hypertension, especially that due to excessive catecholamines, is treatable and presents an attractive therapeutic possibility for the minimization of the mass of infarcted tissue.

Vasodilators have been used to treat patients with severe chronic heart failure following myocardial infarction5 and patients with acute myocardial infarction.6 We have used phentolamine to decrease arterial pressure in hypertensive patients with acute myocardial infarction and left ventricular dysfunction.

Methods and Subjects
Patient Population
Eleven patients with acute myocardial infarction were studied at an average time of 9 hours after the onset of symptoms. All had left ventricular failure as evidenced by rales in the lungs, gallop rhythm, and tachycardia. Eight patients were male, three female, six white, and four black. The average age was 53.7 years. Three patients had nontransmural infarction; the remainder had transmural infarction, four inferior and four anterior. All had abnormal elevation of the creatine phosphokinase enzyme. Three had suffered previous myocardial infarction. Six had a history of chronic hypertension which was confirmed by abnormal retinal vessels and electrocardiographic evidence of left ventricular hypertrophy. Two of these had been treated for chronic congestive failure previously. The remaining five patients had no previous history of hypertension or heart failure and had normal retinal vessels and no evidence of hypertrophy on the electrocardiogram. The patients had received oxygen, narcotics for pain, or xylocaine for ventricular irritability when present, but no cardiotonumotoric or diuretic drugs had been administered prior to the infusion of phentolamine. The procedure was explained to the patient and informed consent was obtained.

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Methods

A Swan-Ganz catheter was inserted in the right antecubital vein for right-heart catheterization. Arterial pressures were measured by an indwelling radial artery needle inserted percutaneously. Pressures were measured with Statham transducers and recorded with the electrocardiogram on a four-channel direct-writing recorder.* The mean pulmonary capillary wedge pressure was taken to represent left ventricular filling pressure. Cardiac output was measured in liters/min by injecting indocyanine green dye into the pulmonary artery and sampling at the radial artery. A Gilford densitometer and dynamic on-line calibration system was used.7 Two control observations of pulmonary artery wedge, arterial pressure, and duplicate cardiac outputs were made at 20-min intervals. Phentolamine was infused for 10–20 min at an initial dose of 0.75 mg/min using a Harvard infusion pump. If significant hemodynamic change occurred, measurements were taken after 10 min of infusion. If no change occurred the drug dose was doubled and measurements taken after 10 min of 1.5 mg/min. The infusion was then discontinued and the serial hemodynamic observations were made at 20-min intervals for an additional hour.

Calculations:

\[
\text{SWI (g/m^2)} = \frac{\text{SVI (MSP - PCW pr)} \times 13.6}{100}
\]

where \(\text{SWI} = \text{stroke work index, SVI = stroke volume index (mL/m^2), MSP = mean systolic arterial pressure (mm Hg), PCW pr = pulmonary capillary wedge pressure (mm Hg).}\)

Systemic vascular resistance (units) was calculated from the formula: (mean arterial pressure – right atrial pressure)/cardiac output (liters/min).

The rate-pressure-time product was taken as the product of heart rate, mean systolic arterial pressure, and left ventricular ejection time (measured from the beginning of the upstroke to the dicrotic notch of the arterial pressure, in msec, recorded at 200 mm/sec).

Results

The results of the initial observations, after 10 min of phentolamine infusion and 1 hour after this infusion had been discontinued are shown in table 1 and figures 1 and 2. Phentolamine infusion was associated with significant changes in systemic arterial pressure, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance. Phentolamine decreased arterial pressure from a mean of 130 ± 13 to 108 ± 13 mm Hg, the pulmonary capillary wedge pressure from 19.5 ± 3.7 to 9.6 ± 3.6 mm Hg, and systemic resistance from 28 ± 6.4 to 14.1 ± 3.6 units. The cardiac index increased from 3.0 ± 5 to 3.9 ± 0.9 liters/min/m². The stroke work index was unchanged (65 ± 10 to 65 ± 11 g/m²/m). There is some variation, but overall the same work was done at a lower filling pressure as illustrated in figure 3. The mean heart rate in the total group of 11 patients did not change significantly, but as can be seen in table 1 and figure 1, there is a wide variation in the heart rate both before and after the infusion.

Two patients with chronic hypertension developed chest pain in association with tachycardia during phentolamine infusion and pain subsided when the drug was stopped. There were no other sequelae of the study. The data suggested that patients with chronic hypertension developed a faster heart rate during phentolamine infusion than the acutely hypertensive patients as all patients except one (no. 7) increased their heart rate with phentolamine infusion. Because of this possible difference in response the data were analyzed with respect to blood pressure, heart rate, and the rate-pressure-time product in the acute and chronic groups as plotted in figure 4.

Six patients had chronic hypertension which was well documented prior to admission. The blood pressure in this group, initially slightly higher than in the acute hypertensives, decreased by the same amount. The heart rate increased during phentolamine infusion and remained higher 1 hour later.

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*Brush Mark 240, Brush Inc.
### Table 1

**Hemodynamic Findings in 11 Patients**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Blood pressure (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac index (liters/min/m²)</th>
<th>Systemic resistance (units/m²)</th>
<th>SWI (g/m²)</th>
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</thead>
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<td>Acute Hypertension</td>
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<td>114</td>
<td>92</td>
<td>100</td>
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<td>116</td>
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<tr>
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<td>88</td>
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<td>5</td>
<td>134</td>
<td>120</td>
<td>116</td>
<td>23</td>
<td>16</td>
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<tr>
<td>Chronic Hypertension</td>
<td>6</td>
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<td>116</td>
<td>22</td>
<td>8</td>
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<td>124</td>
<td>120</td>
<td>19</td>
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<td>Mean ± SD</td>
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<td>102</td>
<td>105</td>
<td>19.5</td>
<td>9.6</td>
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<tr>
<td></td>
<td>±14</td>
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<td>±11</td>
<td>±3.7</td>
<td>±3.6</td>
<td>±4.1</td>
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<tr>
<td>P values*</td>
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<td>&lt;0.05</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: PCW = pulmonary capillary wedge pressure; B = control before phentolamine; A = after 10 min of phentolamine infusion; 1 hr = 1 hr after phentolamine was discontinued; SWI = stroke work index.

*P value represents the difference between B and A, and 1 hour as calculated by paired Student t test.
Chemoreceptors supplied by the coronary arteries have been identified as a cause.\textsuperscript{9} Catecholamines, primarily norepinephrine, are released from the damaged myocardium in infarction\textsuperscript{4} and are an important cause of this hypertension. The quantity released is thought to be proportional to the size of the infarct.\textsuperscript{10, 11} Since norepinephrine has been shown to increase both myocardial oxygen requirements and experimental infarct size, the size of the infarct may be increased.\textsuperscript{1} This is especially likely if the catecholamine release is associated with an increased left ventricular filling pressure and concomitant increases in wall stress and myocardial oxygen consumption.\textsuperscript{3} While beta-sympathetic blockade with propranolol has been shown to reduce myocardial oxygen requirements and experimental infarct size,\textsuperscript{1} the negative inotropic effects and the fear of inducing further left ventricular dysfunction have limited its routine clinical application. Phentolamine has a minor beta-adrenergic effect which may tend to increase myocardial oxygen consumption, but the main action produces alpha-adrenergic blockade and vascular smooth muscle dilation.\textsuperscript{12} This decreases both afterload and preload, and thus, myocardial oxygen requirements. The potential infarct size, therefore, should be reduced as ventricular function improves.

A reduction in arterial pressure while reducing myocardial oxygen requirements could also reduce
The effects of phentolamine on heart rate, arterial mean pressure, and rate-pressure-time product in the acute and chronic hypertensive patients. The five patients with acute hypertension are denoted by the word ACUTE and the six patients with chronic hypertension by the word CHRONIC. The bar histogram represents the mean and 1 σ in 11 patients. The cross-hatched columns are the control findings before phentolamine, the open columns after 10 min of phentolamine infusion, and the dotted columns 1 hour after phentolamine was discontinued. Arterial pressure has the same directional change in both groups. Heart rate did not change significantly at 10 min or 1 hour in the acute group. The chronic group had a significant increase in rate (P < 0.05) which persisted for 1 hour. The rate-pressure-time product decreased (P < 0.02) at 10 min and 1 hour in the acute group but remained unchanged in the chronic.

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coronary blood flow to an ischemic area. It might well, however, improve flow to the ischemic area of the endocardium by favorably altering intramyocardial pressure, and hence the distribution of blood flow across the myocardium. As our patients improved hemodynamically the imbalance between oxygen demand and supply in the ischemic myocardium may have been favorably altered even though arterial pressure decreases slightly. Although we did not find relief of chest pain and arrhythmias during vasodilatory therapy in acute myocardial infarction other workers have and they suggested the oxygen supply to the ischemic myocardium may be improved. While left ventricular function was improved in all patients with hypertension, in some with preexisting chronic hypertension heart rate increased when systemic vascular resistance fell. This is probably secondary to increase baroreceptor activity attempting to maintain the chronically fixed level of hypertension. As seen in figure 4, those patients with chronic hypertension did not, because of the increase in heart rate, decrease their estimated myocardial oxygen demands. Two patients (nos. 10 and 4) who developed tachycardia had further precordial chest pain. Because this increase of heart rate was seen only in chronic hypertensive patients, information about the customary level of blood pressure in these patients present prior to infarction may be helpful as if the blood pressure is not further elevated during the acute phase of myocardial infarction; administration of phentolamine may not be indicated as the lowering of blood pressure below its normal level; plus the tachycardia may decrease oxygen supply to the ischemic area. Plasma catecholamine levels after infarction would be particularly helpful in this group of patients. Phentolamine has been used by Majid et al. in normotensive patients with persistent left ventricular dysfunction following myocardial infarction. They showed a fall in systemic vascular resistance was associated with considerable improvement in both systemic and pulmonary congestion. Similarly, Franciosa et al. have used the smooth muscle dilator nitroprusside and Gold et al., nitroglycerin in the therapy of left ventricular dysfunction associated with normotensive myocardial infarction with an improvement in left ventricular dysfunction. Phentolamine was given in relatively low dosage and for a short time in these patients. Majid et al. have shown that prolonged infusion of phentolamine resulted in considerable improvement and without tachyphylaxis. As the major effect is to counter increased catecholamines present in acute myocardial infarction, prolonged therapy during the hypertensive phase is probably not indicated as the left ventricular filling pressure.
remains in the normal range in most patients following a short infusion. No systematic controlled series of patients with acute hypertensive syndrome associated with myocardial infarction have been followed, but in several patients followed in our unit, routine initial hemodynamics have shown markedly elevated systemic and wedge pressure both of which took about 48 hours to subside in the absence of therapy. These patients were not known to have had significant previous hypertension. Thus, phentolamine probably considerably shortens the time course of acute hypertension and high left ventricular filling pressure in these patients.

Although there are as yet no controlled comparative trials, reduction of left ventricular afterload may offer advantages over current therapy for left ventricular dysfunction associated with hypertension complicating myocardial infarction as it enhances pump function at the same time as myocardial oxygen requirements are decreased. Routine therapy of patients with signs of congestion in acute myocardial infarction have included diuretics and digoxin. Diuretic therapy reduces ventricular preload and relieves pulmonary congestion but does not improve left ventricular function and may cause a fall in cardiac output and systemic pressure. Digitalis increases myocardial oxygen requirements and has not been found to effectively improve left ventricular function in the early stages of myocardial infarction. Primary inotropic agents such as norepinephrine tend to increase myocardial oxygen requirements and the size of experimental infarction. Volume expansion has the same effect. The ideal agent for the therapy of left ventricular dysfunction associated with myocardial infarction would: (1) increase oxygen delivery to the ischemic area, (2) reduce overall myocardial oxygen requirements, and (3) result in an improvement in left ventricular function and relieve pulmonary congestion. While none of the currently available pharmacologic approaches to the therapy of left ventricular dysfunction associated with myocardial infarction satisfy all these requirements, phentolamine fulfills the last two of the above criteria and would appear to be worthy of further exploration and clinical application in patients with transient hypertension complicating acute myocardial infarction. In patients with chronic hypertension associated with myocardial infarction the reduction in pulmonary congestion and improved left ventricular function may not, however, be associated with reduced myocardial oxygen consumption due to a compensating increase in heart rate.

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