Hemodynamic Effects of Intravenous Phentolamine in Low Output Cardiac Failure
Dose-Response Relationships

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SUMMARY Nineteen patients with chronic low output cardiac failure were studied before, during and after infusion of phentolamine in doses of 10, 20, 30 and 40 μg/kg/min. Significant reduction of left- and right-sided pressures and increases in cardiac index and heart rate (HR) were present within 15 minutes of starting phentolamine at the 10 μg/kg/min dose. Minimal additional effect was observed at 30 minutes. Increased dose from 10 to 20 μg/kg/min resulted in small but significant (P < 0.05) additional reduction in pressures and increases in HR. No additional significant changes occurred at doses of 30 or 40 μg/kg/min. Significant hemodynamic changes persisted for at least an hour (53 ± 3 min) after the phentolamine infusion was discontinued. Near maximal hemodynamic effects occur within 15 minutes of starting phentolamine infusion and can be achieved at doses of 10 to 20 μg/kg/min. Increased HR during phentolamine infusion may limit its usefulness in patients with ischemic heart disease.

AFTERLOAD REDUCTION using vasodilators is becoming a widely used and valuable adjunct in the management of patients with severe heart failure. Sodium nitroprusside has become one of the more popular intravenous vasodilators. Although the acute clinical and hemodynamic responses to nitroprusside are frequently dramatic, its extended use over several days may be associated with toxicity due to accumulation of thiocyanate. Additionally, some patients do not respond adequately to nitroprusside.

For these reasons, the efficacy of alternative vasodilators should be assessed in patients with severe heart failure. Among such agents, the alpha blocker phentolamine has been shown to exert beneficial hemodynamic effects when given intravenously to patients with heart failure. Previous studies have usually assessed the effects of phentolamine infused at a single dose. This study evaluates the acute hemodynamic effects of intravenous phentolamine infused at increasing dose levels in 19 patients with stable, chronic low output cardiac failure.

Materials, Methods and Procedures
Informed consent was obtained from each patient before the study.
All 19 patients studied were hospitalized for treat-
ment of severe cardiac failure. There were 18 males and one female. Ages ranged from 36–76 years, with an average of 57 years. Heart failure was considered to be the result of atherosclerotic heart disease in nine patients, primary myocardial disease in eight patients and hypertension in one patient. One patient had left ventricular dysfunction persisting after mitral valve replacement. Although several patients had murmurs of mitral and/or tricuspid regurgitation, valvular disease was not considered to be a major cause of heart failure. All patients had received digitalis and diuretic therapy before the study. These medications were usually omitted the morning of the study.

The patients were brought to the special hemodynamic research unit on the morning of the study. They were in a fasting state and had not received specific premedication. A #7F thermal dilution Swan-Ganz catheter was inserted into an antecubital vein and advanced under fluoroscopic control until the catheter tip was situated in the right or left pulmonary artery. The tip was positioned to yield a reliable wedge pressure (WP) waveform when the balloon was inflated, and pulmonary artery systolic pressure (PASP) and pulmonary artery diastolic pressure (PADP) waveform when the balloon was deflated. A satisfactory WP could not be obtained in two patients, and their PADP was utilized as an index for left ventricular filling pressure (LVFP). Right atrial pressure (RAP) was measured from the proximal lumen. Cardiac output (CO) was determined by averaging three or more thermal dilution curves obtained by injecting 10 cc of 0°C saline into the right atrium. A Model 9500 Edwards Laboratory CO computer was used to give on-line readout of CO. Arterial systolic pressures (ASP) and arterial diastolic pressures (ADP) were measured from an indwelling cannula in the radial or brachial artery. Pressures were measured from Statham 23DB transducers leveled at the midstem position. Mean pulmonary arterial pressures (MPAP) and mean systemic arterial pressures (MSAP) were determined by electrical damping. Heart rate (HR) was determined from a standard ECG lead which was monitored continuously. Pressures and ECGs were recorded on a multichannel photographic recorder run at various paper speeds. Arterial oxygen saturations (AO2) and pulmonary oxygen saturations (PAO2) were determined in 17 patients by oximetry, using an American Optical oximeter. Arterial lactates were measured in 11 patients using enzymatic techniques.3

The following calculations were made:

Cardiac Index (CI) = CO/body surface area
Stroke Index (SI) = CI/HR
Left Ventricular Stroke Work Index (LVSWI) = (MSAP – WP) × SI × 13.6/1000
Systemic Arteriolar Resistance (SAR) = (MSAP – RAP)/CO
Pulmonary Arteriolar Resistance (PAR) = (MPAP – WP)/CO

After obtaining control measurements, phentolamine infusion was started at a dose of 10 μg/kg/min and measurements were repeated in 15 minutes. The dose was then increased by 10 μg/kg/min and measurements were made 15 minutes after each dose adjustment. Accordingly, all 19 patients were studied during control and phentolamine infusion at the 10 and 20 μg/kg/min doses. Fourteen of the 19 patients were also studied at the 30 μg/kg/min dose, and nine of the 19 patients were studied at all four phentolamine doses. Statistical analysis was determined by the Student t test for paired data. Comparisons were made between the 10 μg/kg/min dose and the second set of control values (19 patients), between the 20 and 10 μg/kg/min doses (19 patients), between the 30 and 20 μg/kg/min doses (14 patients), between the 40 and 30 μg/kg/min doses (9 patients) and between the post-infusion and control measurements (16 patients). A P value > 0.05 was considered not significant (NS). In order to see whether progressive hemodynamic changes occurred during phentolamine infusion at a constant dose, measurements were made in six patients 15 minutes and 30 minutes after beginning the 10 μg/kg/min phentolamine infusion. Hemodynamic measurements were also obtained in 16 of the 19 patients at an average of 53 minutes after the phentolamine infusion was discontinued.

Results

Mean and sem for all measured parameters before, during and following phentolamine infusion are listed in table 1.

Control Measurements

Two sets of control measurements were obtained 15 minutes apart in 16 of the 19 patients. There were no significant differences between the two measurements for any parameter. In all 19 patients, control CI was reduced (≤ 2.6 l/min/m², average 1.9 l/min/m²), and LVFP was increased (≥ 12 mm Hg, average 19 mm Hg).

Response to Phentolamine

Dose-Response Relationships

All 19 patients were studied during both the 10 μg/kg/min (P-10) and 20 μg/kg/min (P-20) infusions. At the P-10 infusion, significant (P < 0.001) decreases in both left- and right-sided pressures occurred with MSAP falling from 83 ± 3 mm Hg to 77 ± 3 mm Hg, MPAP from 42 ± 3 mm Hg to 35 ± 2 mm Hg and LVFP from 25 ± 2 mm Hg to 19 ± 2 mm Hg. Coincident with the fall in pressures, CI increased from 1.9 ± 0.1 l/min/m² to 2.8 ± 0.2 l/min/m², and AO2–PAO2 difference decreased from 45 ± 3 to 28 ± 2% (P < 0.001). HR was also significantly increased from 87 ± 3 beats/min to 94 ± 3 beats/min (P < 0.001), and thus increases in stroke volume (SV) and LVSWI, although significant at the 0.001 level, were of lesser magnitude than the increases in CI. Values obtained during the P-20 infusion, when compared with those obtained during the P-10 infusion, showed further significant reduction in all pressures except for ASP, with MSAP falling to 74 ± 3 mm Hg (P < 0.01), MPAP falling to 32 ± 3 mm Hg (P < 0.01) and LVFP falling to 17 ± 2 mm Hg.
Table 1. Mean ± SEM for Each Parameter at Control, During Phentolamine Infusion at 10, 20, 30 and 40 μg/kg/min and During the Postinfusion Period. Significance Determined by Student t test for Paired Data Comparing P-10 to Control, P-20 to P-10, P-30 to P-20, P-40 to P-30 and Postinfusion to Control.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>10 μg/kg/min</th>
<th>20 μg/kg/min</th>
<th>30 μg/kg/min</th>
<th>40 μg/kg/min</th>
<th>Postinfusion</th>
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<tr>
<td>No. of Pts</td>
<td></td>
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<td>19</td>
<td>14</td>
<td>9</td>
<td>16</td>
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<td>ASP mm Hg</td>
<td>123 ± 5</td>
<td>114 ± 5*</td>
<td>110 ± 6</td>
<td>105 ± 7†</td>
<td>108 ± 11</td>
<td>113 ± 6†</td>
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<tr>
<td>MASP mm Hg</td>
<td>85 ± 3</td>
<td>77 ± 3*</td>
<td>74 ± 3†</td>
<td>70 ± 4</td>
<td>71 ± 5</td>
<td>*77 ± 3</td>
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<td>60 ± 2*</td>
<td>56 ± 2†</td>
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<tr>
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<td>31 ± 2</td>
<td>24 ± 2*</td>
<td>*22 ± 2</td>
<td>24 ± 2</td>
<td>24 ± 2</td>
<td>*25 ± 2</td>
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<td>LVFP mm Hg</td>
<td>25 ± 2</td>
<td>19 ± 2*</td>
<td>*17 ± 2</td>
<td>18 ± 2</td>
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<td>RAP mm Hg</td>
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<td>7 ± 2</td>
<td>10 ± 2</td>
<td>*9 ± 2</td>
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<td>HBP beats/min</td>
<td>87 ± 3</td>
<td>94 ± 3*</td>
<td>*98 ± 3</td>
<td>97 ± 5</td>
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<td>CI l/min/m²</td>
<td>1.9 ± 0.1</td>
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<td>3 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>*2.7 ± 0.1</td>
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<td>SI cc/beat</td>
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<td>*29 ± 2</td>
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<td>LVSWI G-M</td>
<td>19 ± 2</td>
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<td>21 ± 1</td>
<td>20 ± 2</td>
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<td>SAR mm Hg</td>
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<td>PAR mm Hg</td>
<td>5 ± 0.5</td>
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<td>3.2 ± 0.4</td>
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<td>*3.4 ± 0.6</td>
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</table>

*P < 0.001.
†P < 0.01.
‡P < 0.05.
| Abbreviations: ASP = arterial systolic pressure; MASP = mean arterial pressure; ADP = arterial diastolic pressure; PASP = pulmonary artery systolic pressure; MPAP = mean pulmonary artery pressure; PADP = pulmonary artery diastolic pressure; LVFP = left ventricular filling pressure; RAP = right atrial pressure; HR = heart rate; CI = cardiac index; SI = stroke index; LVSWI = left ventricular stroke work index; SAR = systemic arterial resistance; PAR = pulmonary arterial resistance; AO₂ = arterial oxygen saturation; PAO₂ = pulmonary artery oxygen saturation. |

(P < 0.02). Although at P-20, CI was further increased to 3.0 ± 0.2 l/min/m², this value was not significantly different than at the P-10 dose. At P-20, HR which averaged 98 ± 3 beats/min was, however, significantly increased (P < 0.05) from the P-10 value.

Fourteen patients were studied at the 30 μg/kg/min (P-30) dosage, and these values were compared to values present at the P-20 level in these patients. Except for ASP and ADP, there were no further significant changes in any of the parameters between the P-20 and P-30 dose levels.

Nine patients were studied at all four dose levels, and values during control and each dose level for these patients are illustrated in figures 1-6. None of the parameters measured at 40 μg/kg/min (P-40) was significantly changed from values obtained at the P-30 infusion rate in these patients.

Arterial lactate was normal during the control and did not change significantly throughout the study.

Time Course and Duration of Action

In six patients, measurements were obtained 15 and 30 minutes after starting phentolamine at the P-10

Figure 1. Mean and standard error for systemic arterial pressure during control (C) and during infusion of phentolamine at 10, 20, 30 and 40 μg/kg/min infusion rates. N = number of patients studied. Data shown is limited to the nine patients studied at all four phentolamine infusion rates.
dose and without changing the infusion rate. The major hemodynamic effects of phentolamine were present 15 minutes after starting the infusion. At 30 minutes, minimal additional changes in pressures or HR were observed. A small increase in CI between 15 and 30 minutes was seen in each of the six patients, averaging 0.35 l/min/m² (range 0.2-0.6 l/min/m²).

In 16 patients, measurements were obtained an average of 53 ± 3 minutes after phentolamine had been stopped. As can be seen in figure 7, the major effect of phentolamine appeared to persist throughout this post-infusion period, and hemodynamics remained significantly altered from control values.

**Discussion**

Alpha blocking agents have been used clinically in various types of low output states and clinical shock since the early studies of Nickerson and co-workers with phenoxybenzamine. Improved hemodynamic monitoring has been helpful in identifying patients most likely to respond favorably to alpha adrenergic blockade. Experience with chlorpromazine suggested that such patients could be characterized as having a markedly reduced CO accompanied by elevated ventricular filling pressures, and systemic resistance when arterial pressure was normal or only modestly reduced. In such patients, a small further reduction in arterial pressure attendant to alpha blockade is usually well-tolerated and associated with clearcut evidence of improved cardiac function and peripheral perfusion.

Although the use of both phenoxybenzamine and chlorpromazine can result in desirable hemodynamic effects, phentolamine offers certain advantages over these agents because of its relatively short duration of action and absence of central nervous system depression.

The effectiveness of phentolamine in improving hemodynamics in patients with severe heart failure has been documented by several investigators. Majid, Sharma and Taylor studied 12 patients with ischemic heart disease treated with phentolamine for three hours at a dose level of 1-2 mg/min. Patients were divided into two groups: those with incapacitating heart failure (six patients) and those with less severe heart failure (six patients). In both groups, phentolamine infusion was associated with significant improvement in CO and reduction in LVFP. Kelly et al. reported hemodynamic effects of phentolamine infused at a dose of 0.75-1.5 mg/min in 11 patients with left ventricular failure and hypertension following acute myocardial infarction. Significant improvement in CI and reduction in LVFP was present 10 minutes after the infusion was started and persisted for one hour after the infusion was discontinued. Henning et al. gave phentolamine in amounts of 10 to 40


FIGURE 4. Stroke index and stroke work index are relatively less affected by phentolamine than cardiac index.

FIGURE 5. Significant reduction in both systemic and pulmonary arteriolar resistance is observed at infusion rates of 10 µg/kg/min, with little additional change at higher doses.

µg/kg/min to 14 patients with acute pulmonary edema due to arteriosclerotic heart disease. During the infusion, pulmonary WP fell from an average of 20 mm Hg to 14 mm Hg, while CI increased from 1.9 l/min/m² to 2.5 l/min/m². These hemodynamic effects persisted for over 45 minutes after the infusion had been discontinued. Although increasing the infusion rate from 10–30 µg/kg/min was associated with further reduction in WP and ASP, maximal improvement in CI was observed at the lower (10 µg/kg/min) infusion rate.

Our own data confirm that of the above investigators. In our patients, we observed significant improvement in CI and reduction in LVFP within 15 minutes after starting phentolamine infusion at a dose of 10 µg/kg/min (equivalent to an infusion rate of 0.8 mg/min for an 80 kg patient). Although statistically significant additional reductions in left- and right-sided pressures and increases in heart rate were observed when the infusion rate was raised from 10–20 µg/kg/min, the magnitude of these changes was small compared to changes present at the initial 10 µg/kg/min dose. Further significant hemodynamic changes were not seen at the higher infusion rates of 30 or 40 µg/kg/min. Measurements obtained 15 and 30 minutes after the 10 µg/kg/min infusion had been started showed minimal change between 15 and 30 minutes. It appears, therefore, that a maximal hemodynamic effect can be expected within 15 minutes after beginning phentolamine infusion at a dose of 10–20 µg/kg/min, and it is not necessary to give higher doses or wait for an extended period before deciding whether the desired hemodynamic effect has been achieved. The effects of phentolamine persist to some extent for an hour or longer after the infusion has been discontinued, and, in this regard, phentolamine differs from nitroprusside and many adrenergic drugs, including isoproterenol and dobutamine, whose effects are largely dissipated within a few minutes after the infusion is stopped. Although this prolonged effect of phentolamine makes it somewhat difficult to compare its acute hemodynamic effects with other drugs, it may be clinically useful when circumstances prohibit an uninterrupted infusion at a constant rate.

The precise mechanisms of action of phentolamine have been controversial. The major effect of phentolamine seems to be arteriolar dilatation, with relatively less effect on the venous system in comparison to nitrates or nitroprusside. This effect
Figure 6. Arterial oxygen saturation (upper line) is not affected by phentolamine. The increase in pulmonary artery oxygen saturation (lower line) reflects the improved cardiac output.

Although most of the hemodynamic improvement observed following phentolamine administration in patients with advanced heart failure can be explained by its known vasodilating action and resulting unloading effect, there is evidence to suggest that phentolamine may also exert direct cardiac effects. Increases in HR have been observed in the majority of patients during intravenous or following orally administered phentolamine. In the present study, mean HR increased from an average of 87 beats/min during control to 98 beats/min during phentolamine infusion of 20 μg/kg/min. Because increased HR during vasodilator therapy has been ascribed to the lowering of ventricular filling pressure to suboptimal levels, we compared the HR response during phentolamine in six patients with normal sinus rhythm, whose LVFP remained at 20 mm Hg or above (change from 33 to 28 mm Hg), with that of the six patients also in normal sinus rhythm whose LVFP during phentolamine was under 20 mm Hg (change from 22 to 10 mm Hg). In the group with persistently elevated LVFP, HR increased by an average of 11%, which was similar to the average increase in HR of 14% which occurred in the six patients with the lower LVFP. Each of the six patients whose LVFP remained high during phentolamine infusion maintained a MSAP of 70 mm Hg or above, whereas each of the six patients with lower LVFP had a MSAP below 70 mm Hg during phentolamine infusion.

Thus, in our patients, the increase in HR during phentolamine did not appear to depend on a large reduction in LVFP or the development of severe hypotension. Furthermore, in a group of 12 patients who also had severe chronic heart failure in whom similar measurements were made during nitroprusside infusion, we found no increase in HR in spite of a reduction in LVFP from 28 to 20 mm Hg, and in MSAP from 88 to 76 mm Hg.

These observations suggest that, unlike many other vasodilator agents in clinical use, the effects of phentolamine on HR may not totally depend on baroreceptor reflex mechanisms. In the experimental animal, the cardiac responses to phentolamine can be largely...
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prevented by administration of propranolol14 or by pretreatment with reserpine,15 suggesting that direct or indirect adrenergic mechanisms may be important. Similar results in patients were observed by Zahir and Gould,16 who showed that propranolol or reserpine attenuated the increased HR and fall in arterial pressure after a 5 mg bolus injection of phentolamine. Phentolamine appears not to exert a direct inotropic effect on isolated cat papillary muscle17 and, therefore, its cardiac effects may depend on norepinephrine release.10 From these data, it appears that the hemodynamic improvement observed during phentolamine infusion may be the result of combined peripheral (reduced afterload) plus cardiac (increased contractility) effects.

Increased HR during phentolamine infusion might be of clinical importance when the drug is used in patients with coronary disease and myocardial ischemia. In our patients, the product of HR × ASP was not significantly altered by phentolamine at the 20 μg/kg/min dose (10,700 ± 500 mm Hg × beats/min vs 10,900 ± 640 mm Hg × beats/min). However, since changes in ventricular volume, contractility and aortic perfusion pressure are also important with regard to myocardial oxygen needs and delivery, and since neither myocardial blood flow nor coronary sinus lactate or oxygen were measured, the net effect of phentolamine infusion on the balance between myocardial oxygen demand and supply is uncertain. Experimental studies suggest that phentolamine, compared to nitrates and nitroprusside, may have an adverse effect on coronary collateral function18 and may increase the degree of ischemic injury induced by coronary constriction.19 However, since hemodynamic and metabolic improvement has been observed with both phentolamine and nitroprusside in patients with heart failure due to coronary artery disease, the clinical implication of these experimental investigations is uncertain.

Our studies, although limited to patients with stable chronic heart failure, showed that phentolamine was an effective agent for temporarily improving hemodynamics in such patients. We have not studied phentolamine in acute heart failure, but others18 have reported favorable results in patients with acute pulmonary edema. Although the effects of phentolamine in patients who fail to respond adequately to sodium nitroprusside has not been defined, such a trial would seem to be indicated. In addition, phentolamine might be a reasonable alternative to nitroprusside in patients with heart failure when the required duration of therapy or nitroprusside dosage is likely to result in thiocyanate toxicity. Presently, the cost and availability of intravenous phentolamine, which is supplied as 5 mg ampules in lyophilized form, make it an expensive and cumbersome agent to administer by continuous infusion over several hours or days. The role of phentolamine in the future management of patients with severe heart failure has not been determined.

References

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