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Comparative Hemodynamic Effects of Inotropic and Vasodilator Drugs in Severe Heart Failure
ESTEBAN MIKULIC, M.D., JAY N. COHN, M.D., AND JOSEPH A. FRANCOSA, M.D.

SUMMARY In 12 patients with severe congestive heart failure (CHF) due to ischemic heart disease or nonischemic cardiomyopathy the hemodynamic response to intravenous infusion of sodium nitroprusside (N) was compared to that of dobutamine (D) 10 μg/kg/min. D and N produced comparable increases in cardiac output (CO) (2.8 to 5.8 L/min and 2.9 to 5.0 L/min, respectively), but, compared to N, D caused a higher arterial pressure (99.3 vs 86.2 mm Hg, P < 0.01) and heart rate (102.5 vs 95.3, P < 0.05) and less reduction in pulmonary wedge pressure (PWP) (28.9 to 20.2 mm Hg vs 29.1 to 16.6 mm Hg, P < 0.05). In five additional patients N and D were studied separately and then were infused together. The combination resulted in a higher CO, lower PWP and greater reduction in systemic and pulmonary vascular resistances than either drug alone. Brachial arterial infusion of nitroprusside produced prominent forearm vasoconstriction in a dose less than 10% of the systemic dose, whereas vasodilatation with dobutamine was only modest even when 50% of the systemic dose was infused. Therefore, potent inotropic and vasodilator drugs produce similar and additive augmentation of left ventricular performance in heart failure. Reduction in vascular resistance with dobutamine probably is largely of reflex origin, but the vasodilatation itself may be an important determinant of the rise in cardiac output.

RECENT STUDIES from this and other laboratories have revealed that infusion of a vasodilator drug can result in significant improvement in left ventricular pump function in patients with heart failure.1-7 This functional improvement, which is characterized by a reduction in left ventricular filling pressure, an increase in stroke volume and no change in heart rate or in indices of left ventricular contractility, has been attributed to a reduction in impedance to left ventricular outflow.8 * The traditional means of improving left ventricular performance in the failing heart has been by administration of an inotropic drug. Since previously available inotropic agents exerted considerable effect on the peripheral circulation or heart rate, it has not been possible to evaluate in the intact circulation the effects of a pure inotropic intervention. Furthermore, a direct comparison of the relative effectiveness of vasodilator and inotropic therapy on the failing heart has not been reported previously.

The purpose of the present study was to compare in a group of patients with severe congestive heart failure the functional response of the left ventricle to infusion of sodium nitroprusside, a potent vasodilator with no direct cardiac effect,10,11 and dobutamine, an inotropic agent that is relatively devoid of peripheral vascular and chronotropic effects.12-15

Materials and Methods
Studies were performed in 21 hospitalized patients with class III or class IV congestive heart failure as defined by the New York Heart Association. In eleven patients the heart failure was thought to be on the basis of nonischemic myocardial disease due in some cases to excessive alcohol ingestion and in others to unknown cause. The absence of significant coronary artery disease was documented by angiography in nine of these patients. The other ten patients had severe ischemic heart disease with previous myocardial infarctions or documented multiple vessel coronary artery disease. All patients had had symptomatic heart failure for at least six months and had been treated with digitalis and diuretics without complete relief of symptoms. Digitalis therapy was continued on a daily basis throughout the study period, but diuretics were withheld on the day of study. Patients gave informed, written consent for performance of the studies.

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All studies were carried out without premedication and with the patient supine or as nearly supine as was compatible with comfortable breathing. In 17 patients a Swan-Ganz balloon tipped catheter was inserted via the basilic or femoral vein and advanced into the pulmonary artery so that balloon inflation occluded the pulmonary artery and allowed recording of pulmonary wedge pressure. In two patients the catheter could not be advanced into the pulmonary artery and in three other patients balloon occlusion of the pulmonary artery could not be accomplished throughout the entire study. The brachial artery or femoral artery was cannulated for pressure recording and blood sampling. All pressures were recorded using Statham P23Db transducers and a multiple channel Hewlett-Packard recorder. Cardiac output was determined by the indicator dilution technique with indocyanine green dye injected into the pulmonary artery and sampled from the aorta or brachial artery.

After control measurements of pressures and cardiac output 12 patients received an intravenous infusion of sodium nitroprusside (100 μg/ml) at a rate of 15 μg/min which was increased at 3 min intervals until pulmonary arterial wedge pressure was reduced by 40% or until systolic arterial pressure fell to 95 mm Hg. The average infusion rate at the time of stabilization was 83.9 μg/min. Pressures and flows were remeasured at this time and the infusion of nitroprusside was discontinued. After a minimum of 30 minutes during which pressures and outputs were allowed to return to control levels, repeat control measurements were obtained and an infusion of dobutamine was begun in gradually increasing doses until an infusion rate of 10 μg/kg/min was achieved. After this stable infusion rate had been maintained for at least 15 minutes and the pressures were stable cardiac outputs were again measured. This dose of dobutamine was selected because in previous studies the response to dobutamine was demonstrated to be dose-dependent and 10 μg/kg/min produced a striking effect in all subjects.

In five additional patients nitroprusside and dobutamine were studied as above but without measuring cardiac output again during the recontrol period. Immediately after studies were completed during dobutamine infusion the nitroprusside infusion was restarted at the previously established dose and pressures and output were measured again when hemodynamics had stabilized during infusion of both drugs.

In four other patients with heart failure forearm blood flow was measured by venous occlusion plethysmography utilizing a Whitney mercury-in-rubber resistance gauge applied to the upper forearm and a matching Wheatstone bridge. Changes in arm girth were recorded during 15 seconds of venous occlusion produced by an arm cuff filled acutely from a reservoir whose pressure was maintained at 50 mm Hg. Sodium nitroprusside or dobutamine was then infused directly into the brachial artery on that side using a motor-driven Harvard infusion pump. The dose of the drugs was progressively increased until forearm flow had increased by at least 3–4 fold. Concentration of the infusate was adjusted so that at no time did infusion rate exceed 1.4 ml per minute. The order of drug infusions was varied, and 30–60 minutes was allowed after completion of one drug infusion before the other was instituted.

Cardiac output (CO) was calculated by semilog replot of the indicator dilution curves. Systemic vascular resistance (SVR) and pulmonary arteriolar vascular resistance (PVR) were calculated by the standard formulae. Systolic ejection time (ET) in milliseconds was measured from the beginning of the upstroke to the dicrotic notch of the brachial arterial pressure recorded at a paper speed of 100 mm/sec. Mean systolic pressure was calculated by planimetry. Mean systolic outflow resistance (MSOR) was calculated by the formula: (MSP × ET)/SV. Mean systolic ejection rate in ml/sec was calculated as the stroke volume divided by ET in seconds. Tension-time index was calculated from the formula: MSP × SV × ET. Forearm blood flow was calculated from the slope of the change in forearm girth corrected for calibration of the gauge and for the initial forearm girth.

**Results**

Hemodynamic data in the 12 patients receiving nitroprusside and dobutamine sequentially are shown in table 1 and figure 1. During infusion of nitroprusside most patients reported an improvement in their dyspnea and cessation of their sweating if this had been present prior to infusion. Some who were somnolent or confused appeared to become more alert during the infusion. During infusion of dobutamine a similar clinical response was noted although several patients complained of the sensation of palpitations, even when little change in heart rate was noted.

Heart rate was unchanged during nitroprusside infusion, but cardiac output rose significantly and there were significant reductions in arterial pressure, pulmonary arterial and wedge pressure and systemic and pulmonary arteriolar

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**Table 1. Hemodynamic Effects of Nitroprusside and Dobutamine in 12 Patients with Congestive Heart Failure**

<table>
<thead>
<tr>
<th>HR</th>
<th>Systolic AP</th>
<th>Diastolic AP</th>
<th>Map</th>
<th>FAD</th>
<th>PCW</th>
<th>CO</th>
<th>CI</th>
<th>SVR</th>
<th>PVR</th>
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</thead>
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<tr>
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<td>±0.3</td>
<td>±0.1</td>
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<td>Nitroprusside Mean</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
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<td>Recontrol Mean</td>
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<td>1.5</td>
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<td>Dobutamine Mean</td>
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<td>141.2</td>
<td>82.2</td>
<td>93.3</td>
<td>34.1</td>
<td>20.2</td>
<td>5.8</td>
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</table>

Abbreviations: HR = heart rate (beats/min); AP = arterial pressure (mm Hg); Map = mean arterial pressure (mm Hg); FAD = mean pulmonary artery pressure (mm Hg); PCW = pulmonary wedge pressure (mm Hg); CO = cardiac output (L/min); CI = cardiac index (L/min/m²); SVR = systemic vascular resistance (dynes-sec-cm⁻²); PVR = pulmonary vascular resistance (dynes-sec-cm⁻²).
resistances. Pressure and output returned to pre-infusion levels after nitroprusside was discontinued. During dobutamine infusion systolic arterial pressure and cardiac output rose significantly while pulmonary arterial and wedge pressures and systemic and pulmonary vascular resistances fell. Heart rate increased insignificantly.

Since the recontrol measurements before the dobutamine infusion were practically identical to the control observations prior to nitroprusside infusion, it was possible to compare directly the data during dobutamine infusion to that during nitroprusside infusion (fig. 2). The hemodynamic pattern was quite similar, with cardiac output and systemic and pulmonary arteriolar resistances at similar levels. The main differences were that heart rate was slightly higher during dobutamine infusion whereas arterial, pulmonary arterial and pulmonary wedge pressures were lower during nitroprusside infusion.

Left ventricular ejection dynamics differed during administration of the two drugs (fig. 3). Ejection time was significantly prolonged during nitroprusside infusion whereas it was not significantly altered from control values during dobutamine infusion. Since stroke volume was slightly higher during dobutamine infusion, the mean systolic ejection rate was greater during dobutamine than during nitroprusside, although both drugs significantly increased the rate over control values. Although mean systolic pressure was increased by dobutamine and reduced by nitroprusside, both drug infusions resulted in similar decrements in mean systolic outflow resistance.

Since systolic pressure and heart rate were higher during dobutamine infusion than during nitroprusside, the heart rate-blood pressure product was significantly higher, as was the tension-time index.

When nitroprusside and dobutamine were infused in com-
Nitroprusside combination (Dobutamine) in five subjects, the hemodynamic effects were greater than when the drugs were given in the same dose independently (table 2, fig. 4). The cardiac output was higher during combination therapy, the mean arterial pressure was lower than during dobutamine alone and the systemic vascular resistance was consequently lower than during either drug infusion given alone. The cardiac output rose less in these five subjects during infusion of nitroprusside alone and dobutamine alone than the average response to these drugs in the other 12 patients. The apparently diminished response to these drugs in this small subgroup of patients appears to be a chance occurrence, since the drugs were administered identically.

Nitroprusside infused into the brachial artery produced dose-dependent forearm vasodilatation. The threshold for vasodilatation ranged from 0.6 to 4 μg/min, which represented in these patients an average of 2.5% of the systemic dose effective in improving left ventricular performance in these individuals. The dose-response curve was sharp, flow increasing to more than three times resting flow with local infusion of 10% of the systemic dose. Intra-arterial dobutamine also exerted a mild vasodilator effect but the threshold was noted at a dose ranging from 15 to 100 μg/min, which represented an average of 8.1% of the systemic dose (10 μg/kg/min) (fig. 5). The dose-response curve to dobutamine was flat, flow increasing to only twice resting flow with local infusion of half the systemic dose (5 μg/kg/min), a dose that has a prominent systemic effect.18

**Discussion**

Ventricular pump function usually is defined by the Frank-Starling curve, which relates end-diastolic fiber length to stroke volume, stroke work or cardiac output. In practice, the filling pressure of the left ventricle is substituted for the fiber length, even though compliance changes of the chamber may alter the relationship between fiber length and pressure. In the presence of left ventricular failure depressed pump function may be improved by the administration of an inotropic drug that increases the force of myocardial contraction and shifts the Frank-Starling relationship upward and to the left resulting in a higher stroke volume or stroke work for any given end-diastolic pressure or fiber length. Such an improvement in pump function has been demonstrated in the past during administration of digitalis, norepinephrine, and other sympathomimetic amines. In recent studies it has also been demonstrated that a vasodilator drug, by reducing outflow resistance or impedance, also results in an improvement in pump function.

**Table 2. Hemodynamic Effects of Nitroprusside and Dobutamine Singly and Together in Five Patients with Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>Systolic AP</th>
<th>Diastolic AP</th>
<th>AP</th>
<th>PA</th>
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<th>CO</th>
<th>CI</th>
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<th>PVR</th>
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<tr>
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<td>Dobutamine (D)</td>
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<td>126.4</td>
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<tr>
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**Figure 4.** Mean changes in five patients of pulmonary wedge pressure (PWP) and stroke volume (SV) during infusion of nitroprusside (N) followed by dobutamine (D) and then the combination (D + N).

**Figure 5.** Effect of brachial arterial infusion of nitroprusside (N) and dobutamine (D) on forearm blood flow in four patients with heart failure. The percent change in forearm blood flow is plotted in relationship to the intraarterial infusion rate of the drugs expressed as a fraction of the intravenous dose needed to produce systemic hemodynamic effects.
characterized by a reduction in left ventricular filling pressure and chamber size accompanied by an increase in stroke volume and stroke work. This response has been achieved during administration of nitroprusside, phentolamine, nitroglycerin, trimethaphan and hydralazine.

The present study confirms that both an inotropic agent and a vasodilator drug may significantly improve left ventricular pump function in patients with severe heart failure. Indeed, the magnitude of the augmentation in left ventricular performance was similar with these two agents, which probably are the most potent and selective vasodilator and inotropic drugs available for clinical use. Extensive studies have revealed that nitroprusside’s action is limited to relaxation of smooth muscle and therefore its hemodynamic effect must be attributed to dilation of arteries, arterioles or the venous capacitance vessels. In contrast, dobutamine is an agent that has quite selective actions on myocardial contractility. Although the drug has both alpha and beta adrenergic stimulating properties, and therefore exerts an effect on peripheral vessels, the balance of alpha and beta stimulating properties in the periphery results in relatively little direct peripheral vascular action; the effects of infusion of the drug are then predominantly related to its action on the myocardium. It is also interesting that dobutamine exerts little effect on heart rate despite its prominent effect on myocardial contractility.

Despite the markedly divergent sites of action of these two agents, the circulatory effects of these drugs in the patients with congestive heart failure in the present series were remarkably similar. Cardiac output increased to a similar extent with both drugs, and pulmonary capillary wedge pressure was reduced. Although infusion of dobutamine was associated with a slight but significant rise in systolic pressure whereas infusion of nitroprusside was associated with a significant reduction in both systolic and diastolic arterial pressure, the total systemic vascular resistance and pulmonary vascular resistance were reduced similarly with the two drugs. Neither nitroprusside nor dobutamine significantly altered heart rate from control levels, but the heart rate during dobutamine infusion was significantly faster than during nitroprusside infusion, reflecting a slight increase during dobutamine and a slight reduction during nitroprusside. In addition wedge pressure, which was reduced with both drugs, remained significantly higher during dobutamine infusion than during nitroprusside infusion.

Further evidence that these two agents are working through independent mechanisms was obtained when the two drugs were infused together. In all instances the combination of nitroprusside with dobutamine resulted in a higher cardiac output and usually a lower pulmonary wedge pressure than when either drug was infused alone.

Whereas the mechanism of the reduction in vascular resistance during infusion of nitroprusside can be attributed simply to its direct vasodilator properties, the mechanism of the vasodilator effect of dobutamine is less clear. One possibility would be that in the setting of high vascular resistance in patients with congestive heart failure the direct action of dobutamine on beta adrenergic receptors would predominate over its effect on alpha adrenergic receptors and result in a reduction in vascular tone.

In an attempt to study this possibility, the drugs were infused in progressively increasing doses into the brachial artery of patients with heart failure while forearm blood flow was measured. Nitroprusside infusion at doses averaging 2.5% of the systemic dose produced prominent vasodilation, whereas dobutamine had only a modest dilator effect with a threshold more than three times that of nitroprusside when the intra-arterial dosage was related to the systemic dose. If the forearm bed can be assumed to be representative of peripheral vascular effects, these data make it unlikely that the fall in systemic vascular resistance during dobutamine intravenous infusion is primarily related to a direct vasodilator effect of the drug.

An alternate explanation for the vasodilator effect of dobutamine is that its direct cardiac effect results in relaxation of heightened vascular tone, possibly in part by virtue of baroreceptor stimulation of an increased rate of left ventricular ejection. Furthermore, since vasodilation alone produces such a prominent increase in cardiac output in patients with heart failure, it is attractive to postulate that the increase in output observed with such inotropic drugs as dobutamine, dopamine and isoproterenol may be due largely to vasodilation rather than directly to inotropism.

Since the drugs produce similar improvement in left ventricular pump performance and their combined effects seem to be additive, the selection of the appropriate therapy for a given patient with severe heart failure should be based on other differences between the agents. The rise in systolic arterial pressure produced by dobutamine may be helpful in clinical situations in which pretreatment pressure is critically reduced. On the other hand, the higher arterial pressure and slightly faster heart rate during dobutamine treatment as compared to nitroprusside treatment is indicative of a higher myocardial oxygen consumption that could be deleterious in the presence of ischemic heart disease. When arterial pressure falls to dangerously low levels during nitroprusside therapy, the addition of dobutamine usually is effective in supporting pressure and further augmenting the cardiac output. Since dobutamine has not yet been approved for marketing, dopamine could be substituted clinically with the likelihood that the systemic hemodynamic response would be somewhat similar.

The regional distribution of the increased cardiac output in response to nitroprusside and dobutamine has not been studied. Data on their relative effects on renal and visceral perfusion would probably provide further distinguishing features that could be used in selecting the proper drug for particular clinical situations.

Although our studies explored only the intravenous effects of these agents, the results suggest that oral administration of a combination of an inotropic and vasodilator drug might be effective in managing patients who remain symptomatic despite treatment with digitalis and diuretics. Orally effective vasodilator regimens are already available and new orally effective inotropic drugs are being developed.

References
The Influence of Heart Rate on Pulmonary Arterial-Left Ventricular Pressure Relationships at End-diastole

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SUMMARY Increased resistance to blood flow stemming from structural and functional abnormalities of the lungs may cause pressure in the pulmonary artery to exceed that in the left ventricle at the end of ventricular diastole. This study explores the possible contribution of heart rate to the diastolic pressure gradient observed in the presence of acutely induced hypoxia. Pulmonary hemodynamics were examined in mongrel dogs with chronic atrioventricular dissociation and norepinephrine in man. Circ Res 36: 174, 1975


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AS A CONSEQUENCE of increased resistance to pulmonary blood flow, pulmonary arterial pressure exceeds that in the left ventricle at the end of diastole in certain cardiopulmonary disorders. In some patients this diastolic pressure gradient may be ascribed to external encroachment on the bed by diffuse parenchymal disease or to obstruction of the bed from within by thromboemboli or other pulmonary vascular lesions. In other patients the vasoconstrictor effects of alveolar hypoxia and acidemia contribute to the gradient. In a previous consideration of factors regulating the gradient in patients with chronic obstructive lung disease, 61% of the observed variation in the gradient could be ascribed to abnormal gas exchange. While heart rate also appeared to be related to the level of the gradient, addition of this factor to multiple regression analysis of the determinants of the
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