Beneficial effects of dopamine combined with intravenous nitroglycerin on hemodynamics in patients with severe left ventricular failure

HENRY S. LOEB, M.D., JAMES P. OSTRENGA, M.D., WILLIAM GAUL, M.D., JEFFREY WITT, M.D., GREGORY FREEMAN, M.D., PATRICK SCANLON, M.D., ROLF M. GUNNAR, M.D.

ABSTRACT  Hemodynamic effects of dopamine and intravenous nitroglycerin alone, and in combination, were studied in 27 patients with severe left ventricular failure. Dopamine alone increased cardiac index from 1.8 to 2.5 l/min/m² but also increased wedge pressure from 24 to 30 mm Hg and heart rate from 88 to 101 beats/min. Arterial oxygen saturation fell from 92% to 87% (p < .001). Nitroglycerin alone had a lesser effect on cardiac index (1.8 to 2.2 l/min/m²) but decreased wedge pressure from 26 to 16 mm Hg and heart rate from 91 to 86 beats/min. Arterial oxygen saturation fell from 91% to 90% (NS). Combined dopamine and nitroglycerin administration resulted in optimal hemodynamics, with cardiac index of 2.9 l/min/m², wedge pressure of 17 mm Hg, and heart rate of 96 beats/min. Arterial oxygen saturation remained low at 88% in spite of the reduction in left ventricular filling pressure, which probably reflects increased intrapulmonary right-to-left shunting coupled with increased pulmonary blood flow. These results suggest that the combination of dopamine with intravenous nitroglycerin should be considered for patients with severe left ventricular dysfunction who require temporary pharmacologic support.

Circulation 68, No. 4, 813–820, 1983.

TEMPORARY pharmacologic support of patients with chronic severe left ventricular dysfunction is frequently required either during episodes of deterioration or before definitive diagnostic or therapeutic procedures. Although a variety of intravenous inotropic and vasodilator drugs are available for this purpose, the selection of a specific drug or combination of drugs remains largely empiric.

Dopamine, a catecholamine with significant inotropic activity, has potential advantages for use in patients with advanced low-output cardiac failure because of its selective effect on promoting blood flow to renal and splanchnic beds via stimulation of nonadrenergic vasodilator receptors in these areas. Although dopamine infusion may reduce an elevated left ventricular filling pressure in some patients with heart failure, other patients may show a significant increase in filling pressure associated with the development of pulmonary congestion or edema. The possible mechanisms of dopamine-induced elevation of left ventricular filling pressure, particularly at higher doses, are many and include increased preload and afterload due to excessive α-receptor-mediated vasoconstriction, excessive tachycardia, and/or myocardial ischemia in patients with severe coronary artery disease. In addition, in patients with chronic heart failure, the inotropic response to dopamine may be diminished by prior myocardial catecholamine depletion or by “down regulation” of myocardial β-receptors secondary to prolonged compensatory sympathetic stimulation. In such patients the high doses of dopamine required to obtain an adequate inotropic effect may be associated with excessive and undesirable α-receptor stimulation.

Nitrates have been shown to be effective venodilators and are particularly useful in lowering left ventricular filling pressure in patients with severe left ventricular failure. Since intravenous nitroglycerin has recently been approved for clinical use, it seemed reasonable to evaluate the use of dopamine combined with intravenous nitroglycerin in a group of patients with advanced chronic left ventricular failure. Our results suggest that this combination offers significant advantages over either drug administered alone and may be ideally suited for patients with severe left ventricular...
dysfunction who require temporary pharmacologic support.

Methods and materials

The patients studied were all men who were hospitalized for symptoms of chronic low-output cardiac failure (NYHA class III or IV) in spite of treatment with digitals and diuretics. Ages ranged from 33 to 66 years and averaged 57 years. Informed consent was obtained from each patient before the study. Nine patients had arteriosclerotic heart disease documented by coronary arteriography (six patients) or postmortem examination (three patients). Nine patients had no or insignificant coronary artery disease as determined by angiography and were considered to have primary myocardial disease. Of the remaining nine patients who did not undergo angiography, six were considered to have primary myocardial disease on the basis of clinical findings. In no patient was valvular heart disease considered to be the major cause of heart failure.

On the morning of the study all patients, who had fasted and had not received any drugs, were brought to a special hemodynamic research unit. A No. 7F thermal dilution Swan-Ganz catheter was inserted in an antecubital vein and was 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 (PASP) and diastolic (PADP) pressure waveform when the balloon was deflated. 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 ml of 0°C saline into the right atrium. A Model 9500 Edwards Laboratory cardiac output computer was used to give on-line readout of CO. Arterial systemic (ASP) and diastolic (ADP) pressures were measured from an indwelling catheter in the radial or brachial artery. All pressures were obtained from Statham 23Db transducers leveled at the midstch position. Mean pulmonary (MPAP) and mean systemic arterial (MAP) pressures were determined by electrical damping. Heart rate (HR) was determined from a standard electrocardiographic (ECG) lead that was monitored continuously. Pressures and ECGs were recorded on a multichannel photographic recorder run at various paper speeds. Arterial (ART O₂) and pulmonary oxygen saturations were determined with an American Optical oximeter.

Calculations were made with the following formulas: cardiac index (CI) = CO/body surface area, stroke index (SI) = CI/HR, left ventricular stroke work index (LVSWI) = (MAP - WP) × SI × 13.6/1000, systemic arteriolar resistance (SAR) = (MAP - RAP)/CO, and pulmonary arteriolar resistance (PAR) = (MAP - WP)/CO.

Two sets of control measurements were obtained 15 min apart in 10 of the 27 patients. In these 10 patients differences between the first and second control measurements were not significant. In the remaining 17 patients, a single set of control measurements was obtained before drug infusion. The order of drug infusion was randomized by drawing from a sealed envelope. Dopamine was given first in 17 patients and nitroglycerin was first in 10 patients. Both drugs were administered with an automated (IVAC) infusion system after dilution of the drug with 5% dextrose in water to concentrations of 800 μg/ml for dopamine and 400 μg/ml for nitroglycerin. Each drug was titrated separately as follows: dopamine was started at 2 μg/kg/min with dose increments of 1 μg/kg/min every 10 min until WP was greater than 28 mm Hg; HR was greater than 120 beats/min, or a maximum dose of 6 μg/kg/min was given. In our experience2 doses above 6 μg/kg/min frequently lead to undesirable tachy-
dose of dopamine alone were compared with a full dose of dopamine combined with a half dose of nitroglycerin. This combination resulted in a significant reduction in all measured pressures and resistances, a significantly lower HR (p < .02), and higher CI, SI, and LVSWI. Neither ART $\text{O}_2$ nor AVO$_2\Delta$ were changed.

A full dose of dopamine alone when compared with a full dose of dopamine combined with a full dose of nitroglycerin yielded similar results, except that HR was no longer significantly lower than that with dopamine alone while AVO$_2\Delta$ was lower (p < .02).

**Effects of nitroglycerin alone vs nitroglycerin combined with dopamine** (table 2). Values obtained during a full dose of nitroglycerin alone were compared with values obtained during a full dose of nitroglycerin combined with a half dose of dopamine. This combination resulted in significantly higher mean values for HR, SI, and CI, and lower values for SAR, PAR, ART $\text{O}_2$ and AVO$_2\Delta$, while both systemic and right-sided pressures were similar. When compared with a full dose of nitroglycerin alone, combined nitroglycerin and dopamine at full doses yielded significantly higher mean values for ASP, CI, SI, and LVSWI, and lower mean values for SAR, PAR, and AVO$_2\Delta$, while MAP, ADP, and right-sided pressures were not increased. The ART $\text{O}_2$ of 88% during nitroglycerin plus dopamine was significantly less (p < .02) than the mean value of 90% during nitroglycerin alone.

**Discussion**

The desired hemodynamic goals of short-term intravenous drug therapy in patients with advanced low-output cardiac failure includes augmentation of forward output and peripheral perfusion plus reduction in backward failure and pulmonary congestion. An additional important goal, particularly in patients with coronary disease, is the maintenance of an adequate
coronary perfusion pressure and avoidance of myocardial ischemia.

Of the inotropic drugs available for continuous intravenous infusion, both dobutamine and dopamine have been shown to significantly augment CO in patients with advanced heart failure. However, when these drugs are used alone, an elevated left ventricular filling pressure may fall only slightly or, in the case of dopamine, may actually increase.2,3 Additionally, both dobutamine and dopamine may increase net myocardial oxygen demand unless preload and myocardial wall tension are concurrently reduced sufficiently to offset the direct inotropic and chronotropic actions of these drugs.

As an alternative to inotropic therapy, intravenous vasodilators have become popular for short-term management of patients with severe left ventricular failure. Sodium nitroprusside, which acts on both the venous and arterial systems,10 has been shown to result in significantly lower WP and HR when compared with dobutamine at doses that augmented CO to the same extent.11,12 Recently, intravenous nitroglycerin has become commercially available; however, its role in the management of patients with severe left ventricular failure has yet to be defined. Theoretically nitroglycerin may offer certain advantages over nitroprusside, particularly when used in combination with inotropic drugs. Its more potent action on venous vs arterial smooth muscle13 should make it possible to effectively reduce preload without causing excessive hypotension, which could compromise coronary and peripheral perfusion. Nitroglycerin dilates the large conduit
coronary vessels\textsuperscript{14, 15} and may augment flow to areas supplied by stenotic coronary vessels\textsuperscript{16}; this is in contrast to nitroprusside, which dilates coronary resistance vessels and may reduce flow to ischemic myocardium.\textsuperscript{17} Additionally, prolonged nitroprusside administration may cause accumulation of toxic levels of thiocyanate,\textsuperscript{18} whereas intravenous nitroglycerin can be given safely for extended periods.\textsuperscript{13}

Leier et al.\textsuperscript{9} compared intravenous nitroglycerin with nitroprusside in 10 patients with congestive failure. At doses that exerted a similar reduction in left ventricular filling pressure, nitroprusside resulted in a greater increase in CO and reduction in arterial pressure than did nitroglycerin. Effects on limb and hepatic blood flow were similar and renal blood flow, which fell significantly during nitroglycerin treatment, was unchanged with nitroprusside. Thus, although intravenous nitroglycerin is well tolerated and is very effective in reducing elevated pulmonary and left-sided filling pressures in patients with severe acute or chronic heart failure, it is generally less effective than inotropic drugs or sodium nitroprusside in augmenting CO and systemic blood flow.

To achieve optimal hemodynamic effects, combined intravenous therapy with inotropic and vasodilator drugs has been advocated. The combination of dobutamine with nitroprusside,\textsuperscript{11, 19, 20} dobutamine with nitroglycerin,\textsuperscript{21} and dopamine with nitroprusside\textsuperscript{22, 23} or sublingual isosorbide dinitrate\textsuperscript{24} have each been reported to result in more favorable hemodynamics than achieved with the inotropic or vasodilator drugs administered separately.

Our experience with 27 patients with severe low-output cardiac failure clearly demonstrated that the combination of intravenous nitroglycerin with dopamine resulted in major hemodynamic improvement not obtainable with either drug used alone. Figure 1 shows that dopamine increased both systemic and right-sided pressures. WP increased in two-thirds of our patients from a mean of 24 to 30 mm Hg for the group. We\textsuperscript{3, 25} have previously reported increases in filling pressure during dopamine administration in some patients with left ventricular failure, cardiogenic shock, or septic shock, which appears to be a reflection of α-adrenergic-mediated vasoconstriction of resistance and/or capacitance vessels that dopamine can exert, particularly at higher doses.\textsuperscript{26-28} We believe this feature of dopamine markedly limits its usefulness as a single drug for inotropic support of patients with impaired left ventricular function, and if a single inotropic drug is desired dobutamine would be preferable. On the other hand, dopamine, unlike dobutamine, has unique non-adrenergic-mediated renal and mesenteric vasodilator properties\textsuperscript{1} that might be highly desirable in patients with low-output states and reduced renal blood flow. As can be seen in figure 1, the combined use of intravenous nitroglycerin with dopamine markedly reduced the high WP and right-sided pressures to levels essentially the same as with nitroglycerin alone. Arterial pressures, although also reduced, remained well above hypotensive levels. Therefore, nitroglycerin would seem to have advantages over nitroprusside in patients with borderline hypotension.

The fact that intravenous nitroglycerin resulted in major reduction of left ventricular filling pressure, pulmonary artery pressure, and RAP with only a modest fall in systemic arterial pressure probably reflects the greater relative effect nitroglycerin has on venous vs arterial smooth muscle, and to some extent distinguishes it from most other vasodilators used for treatment of patients with heart failure. Since patients with

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Pressure measurements (mean ± SEM) during the initial control period and during infusion of dopamine and nitroglycerin alone and in combination. The order of drug administration was different than illustrated in the figure. C = control; D = dopamine; N = nitroglycerin; N/2 = half dose nitroglycerin; D/2 = half dose dopamine.}
\end{figure}
advanced heart failure have a depressed Starling function curve, CO will be minimally affected by even large changes in preload. Nitroglycerin, therefore, would not be expected to markedly lower systemic and coronary perfusion pressures in such patients. To the contrary, reduction of elevated intracavitary diastolic pressures could augment subendocardial perfusion, and reduction in wall tension should reduce myocardial oxygen demand with a net effect of improving the myocardial oxygen supply and demand relationship. Although the hemodynamic responses we observed are compatible with these concepts, we did not measure myocardial blood flow or oxygen consumption in our patients, nor was it possible from clinical or electrocardiographic observations to demonstrate effects of the drugs alone or in combination on the relationship between myocardial oxygen supply and demand. Such studies should be undertaken in the future.

In figure 2, changes in HR, CI, SI, and resistances are illustrated. During single drug administration, dopamine was more effective than nitroglycerin in augmenting CO; however, the maximal increases in CI, SI, and LVSWI, and reductions of SAR and PAR occurred when dopamine and nitroglycerin were administered together in full doses.

The chronotropic effects of dopamine resulted in an increase in HR from 88 to 101 beats/min. Although most patients with chronic heart failure tolerate such increases in HR, and none of our patients experienced angina or ischemic ECG changes during dopamine infusion, tachycardia would generally be considered undesirable in patients with heart failure and coexistent coronary artery disease. When nitroglycerin was combined with a full dose of dopamine, mean HR tended to be lower than with dopamine alone, although the difference was significant only for dopamine plus a half dose of nitroglycerin (101 vs 95 beats/min, p < .02). It was also of interest that nitroglycerin alone reduced mean HR from 91 to 86 beats/min (p < .01). The tendency for nitroglycerin alone or in combination with dopamine to reduce HR could be the result of reduced work of breathing secondary to reduction of central blood volume and left ventricular filling pressure. Additional mechanisms related to autonomic reflexes under the influence of pulmonary vascular or cardiac chamber stretch receptors must also be considered, but their role in modifying HR in response to drugs such as nitroglycerin remains speculative. Whatever the mechanism, it appears that in some patients with heart failure the addition of nitroglycerin can significantly reduce potentially undesirable tachycardia that occurs when dopamine is given alone.

The overall effect of the infusions on left ventricular performance is shown in figure 3, which is a plot of left

![Figure 2](http://circ.ahajournals.org/)

![Figure 3](http://circ.ahajournals.org/)
ventricular filling pressure vs LVSWI. With dopamine alone the plot moved up but to the right, whereas with nitroglycerin alone or in combination with dopamine the plot moved up and to the left, suggesting maximal improvement in left ventricular performance.

In a previous study,\(^3\) we compared the hemodynamic effects of dopamine with those of dobutamine in patients with severe chronic heart failure. We observed a fall in ART O\(_2\) during dopamine infusion in association with elevation of WP to above 30 mm Hg. Although increased CO per se may result in arterial hypoxemia by increasing flow to nonventilated or poorly ventilated lungs,\(^29,30\) ART O\(_2\) did not fall during dobutamine infusion in spite of similar increases in CO. In view of this, plus the fact that WP rose with dopamine but not with dobutamine, we felt that pulmonary congestion best explained the arterial hypoxemia we observed during dopamine infusion.

In the present study, we again observed a significant reduction in ART O\(_2\) from 92% to 87% during dopamine infusion. Of 25 patients in whom ART O\(_2\) was measured immediately before and during dopamine infusion, 12 had a reduction in ART O\(_2\) of 5% or more. Comparing these 12 patients with the remaining 13 patients (figure 4), it was again apparent that as a group the patients having the greatest fall in ART O\(_2\) during dopamine infusion had higher mean values for left ventricular filling pressures both before and during dopamine. We were surprised, therefore, that the addition of nitroglycerin to dopamine had little effect on ART O\(_2\) in spite of its marked effect on lowering the elevated left ventricular filling pressure. For the 12 patients with 5% or more reduction of ART O\(_2\) during dopamine (figure 5), the combination of dopamine plus nitroglycerin lowered left ventricular filling pressure from 36 to 25 mm Hg; however, ART O\(_2\) increased only slightly from 84% to 86%. It seems, therefore, that arterial hypoxemia during combined dopamine-nitroglycerin infusion is due at least in part to factors other than pulmonary congestion. In our patients, nitroglycerin alone resulted in a slight (but insignificantly) reduction of ART O\(_2\) from 92% to 90%. Others have reported arterial hypoxemia during nitroglycerin therapy\(^31,32\) and have ascribed it to increased intrapulmonary right-to-left shunting. It seems likely, therefore, that in the present study, increased pulmonary blood flow coupled with increased shunting during combined dopamine-nitroglycerin infusion may have offset the beneficial effects on arterial oxygen-
ation expected from the nitroglycerin-induced reduction of left ventricular filling pressure.

In summary, in our patients with chronic heart failure, the combination of dopamine plus intravenous nitroglycerin resulted in major overall hemodynamic improvement not obtainable with either drug given alone and accordingly could be advocated for similar patients requiring temporary pharmacologic support.

References

Beneficial effects of dopamine combined with intravenous nitroglycerin on hemodynamics in patients with severe left ventricular failure.
H S Loeb, J P Østreng, W Gaul, J Witt, G Freeman, P Scanlon and R M Gunnar

Circulation. 1983;68:813-820
doi: 10.1161/01.CIR.68.4.813

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/68/4/813

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/