Combined Dopamine and Nitroprusside Therapy in Congestive Heart Failure

Greater Augmentation of Cardiac Performance by Addition of Inotropic Stimulation to Afterload Reduction

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SUMMARY The hemodynamic benefits of combining administration of dopamine with nitroprusside (NP) were evaluated in nine patients with chronic congestive heart failure due to ischemic, idiopathic myocardial or valvular cardiac disease. NP alone (68 μg/min) produced decline in left ventricular end-diastolic pressure (LVEDP) from 25.4 to 14.1 mm Hg (P < 0.01) but modest increase in cardiac index (CI) from 2.41 to 3.02 L/min/m² (P < 0.05). Dopamine alone (6 μg/kg/min) caused an elevation of CI to 3.36 (P < 0.01) but without decrease of LVEDP. Simultaneous infusion of the two agents resulted in favorable alterations in both hemodynamic variables: LVEDP decreased to 15.7 (P < 0.01) and CI increased to 3.52 (P < 0.01).

It is concluded that dopamine substantially enhances the effectiveness of nitroprusside therapy in congestive heart failure by providing concomitantly the principal beneficial actions of the vasodilator and dopamine used separately. Thus combined dopamine with NP treatment considerably raises CI while markedly reducing elevated LVEDP and provides a potentially efficacious pharmacologic modality for the treatment of severe congestive heart failure due to left ventricular dysfunction.

ALTHOUGH IT IS WELL ESTABLISHED that in patients with congestive heart failure cardiac performance may be substantially enhanced either by positive inotropic agents1-7 or by afterload reducing drugs,8-18 it is unknown if more benefit might be derived from the simultaneous utilization of both of these therapeutic approaches. The afterload reducing agent nitroprusside has been confined to heart failure patients without hypotension; the possibility remains, however, that the vasodilator drug might be employed beneficially even in cardiac dysfunction with lowered blood pressure by adding dopamine. In the present study it was considered that the positive inotropic agent, dopamine, infused concomitantly with nitroprusside, which reduces afterload, could enhance pump function to a degree unattainable with either agent alone. Accordingly this investigation was carried out in congestive heart failure patients to determine the comparative individual and combined actions of dopamine and nitroprusside on indexes of cardiocirculatory function.

Materials and Methods

The study population was comprised of nine patients, mean age 53 years (41–68 years), with chronic clinical congestive heart failure, New York Heart Association functional class III, requiring the outpatient administration of digitalis glycosides and diuretics. All nine patients underwent elective diagnostic left and right heart catheterization, left ventricular cineangiography and selective coronary arteriography. The etiology of cardiac dysfunction was ischemic heart disease in five patients, idiopathic congestive cardiomyopathy in three and primary mitral valvular regurgitation in one. All patients had elevated resting left ventricular end-diastolic pressures ≥18 mm Hg and seven had reduced cardiac indexes <2.50 L/min/m². Digitalis administration was discontinued 72 hours prior to catheterization in each case; because digoxin was the glycoside employed in each instance, it would be expected that most of the patients had subtherapeutic serum digoxin levels at the time of the investigation. All patients were studied in the basal state after an overnight fast and precatheterization medication consisted of intravenous diazepam, 5 mg. Informed consent was obtained from each patient.

All patients underwent complete right and left heart catheterization, left ventricular angiography in which 40 to 50 ml Hypaque was employed, and selective coronary arteriography. Left ventriculography was performed prior to coronary arteriography. Each patient had ventricular pressures measured serially for five minutes following angiography and a 10 minute period elapsed subsequent to coronary arteriography. Thus, the interval between administration of the bolus of contrast material and acquisition of control cardiocirculatory variables for the drug protocol was at least 25 minutes in each patient. A previous study indicates that left ventricular function and intravascular volume returned to a steady state within this time period.19

After obtaining control indexes nitroprusside was infused at a mean rate of 68 μg/min (40 to 100 μg/min) to lower systemic arterial systolic pressure to between 110 and 120 mm Hg and/or left ventricular end-diastolic pressure to between 10 and 15 mm Hg. When the desired pressures were attained, the nitroprusside infusion was maintained constant for 10 minutes and hemodynamic variables were remeasured. With the nitroprusside infusion continuing at the same rate, dopamine, 5–7 μg/kg/min (total dose 300–500 μg/min) was begun and the two agents were infused concomitantly for 10 minutes and all measurements were

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repeated. Nitroprusside was then terminated while the dopamine infusion was continued at a constant rate for an additional 20 minutes; the hemodynamic indexes were again determined during the final 5 minutes of dopamine administration. The sequence of infusion of nitroprusside and dopamine was reversed in four patients.

Because the period of combined drug administration in the present study was limited to 10 minutes after attaining a steady rate, this investigation does not afford evaluation of the effects of prolonged infusion of dopamine and nitroprusside including the potential deleterious effects of extended inotropic stimulation on ischemic myocardium.

Duplicate measurements of cardiac output (CO) were made by the dye dilution and thermodilution techniques with the same method utilized in each patient. Calculations utilized to quantify cardiocirculatory variables included: total systemic vascular resistance [TSVR = 80 (P-R̄A)/ CO], where 80 is the conversion factor from mm Hg to dynes sec cm⁻³, P = mean systemic arterial pressure, R̄A = mean right atrial pressure; pressure-time per minute (PTM) in mm Hg sec per min = \( P \times ET \times HR \), where ET = left ventricular ejection time and HR = heart rate; and stroke work index (SWI) in g-m/m² = [(P-LVEDP) × SI × 13.6]/1000 where SI = stroke index. Statistical analyses were carried out by analysis of variance.

Results

Mean systemic arterial pressure (fig. 1A) was lowered by NP from 89.9 ± 4.4 to 77.7 ± 1.6 mm Hg (\( P < 0.01 \)); \( \overline{P} \) was unchanged from control (C) by dopamine. With simultaneous NP and dopamine infusion \( \overline{P} \) was reduced to 83.1 ± 3.6 mm Hg (\( P < 0.05 \) vs C; \( P < 0.05 \) vs dopamine alone). The mean heart rate of 74.8 beats/min was not changed significantly by NP (fig. 1B), dopamine or by combination of the two agents. Left ventricular end-diastolic pressure was lowered in each patient by NP; the mean control LVEDP fell from 25.4 ± 4.2 mm Hg to 14.1 ± 2.7 (\( P < 0.01 \)) (fig. 1C). LVEDP was unchanged from C by dopamine; and significantly reduced from C and dopamine alone by the combined infusion of NP with dopamine to 15.7 ± 2.8 mm Hg (\( P < 0.01 \) vs C; \( P < 0.01 \) vs dopamine). Cardiac index was augmented by both agents administered individually from C of 2.41 ± .10 L/min/m²: NP to 3.02 ± .22 (\( P < 0.05 \) vs C); dopamine to 3.36 ± .33 (\( P < 0.01 \) vs C; \( P < 0.05 \) vs NP). Concomitant infusion of NP and dopamine effected an even greater increase in cardiac index to 3.52 ± .34 L/min/m² (\( P < 0.01 \) vs C; \( P < 0.05 \) vs NP) (fig. 1D).

Each drug individually lowered TSVR from C of 1608 ± 105 dynes sec cm⁻⁴: NP to 1154 ± 78 (\( P < 0.05 \) vs C); dopamine to 1294 ± 91 (\( P < 0.05 \) vs C); and the combination of both agents lowered TSVR to 1072 ± 115 (\( P < 0.01 \) vs C) (fig. 2A). Pressure time per minute declined during NP infusion from C of 2166 ± 154 to 1875 ± 108 mg Hg sec per min.

**Figure 1.** Effect of NP, dopamine and the combination of NP with dopamine on (A) mean systemic arterial pressure (\( \overline{P} \)), (B) heart rate (HR), (C) left ventricular end-diastolic pressure (LVEDP) and (D) cardiac index (CI). C = control. Points are mean ± SEM.

**Figure 2.** Effect of NP, dopamine and the combination of NP with dopamine on (A) total systemic vascular resistance (TSVR), (B) pressure time per minute (PTM), and (C) stroke work index (SWI).
mm Hg sec/min (P < 0.05); this variable was unchanged by dopamine, but lowered by the combined NP and dopamine infusion to 1906 ± 115 (P < 0.05 vs C; P > 0.05 vs NP; P < 0.05 vs dopamine) (fig. 2B). Neither NP nor dopamine significantly altered SWI from C of 30.6 ± 4.11 g-m/m² (fig. 2C). However the combination of the two drugs augmented this index to 40.6 ± 3.24 (P < 0.05 vs C).

Figure 3 depicts the individual and combined actions of NP and dopamine on the relationship between cardiac index and LVEDP: NP alone effected marked leftward but modest upward shifts in ventricular function, whereas dopamine greatly augmented cardiac index without significant change in filling pressure. In contrast, simultaneous infusion of the two agents achieved the same reduction in left ventricular end-diastolic pressure as NP alone, while reaching the same increase in cardiac index as with dopamine alone.

**Discussion**

To accomplish the principal objective in the treatment of cardiac pump dysfunction — facilitation of ventricular emptying — two divergent therapeutic modalities have been successfully applied in clinical congestive heart failure. The traditional approach has consisted of increasing the force and velocity of myocardial contraction with inotropic stimulating agents. More recently afterload reducing drugs have been utilized to enhance cardiac output through lowering of impedance to left ventricular ejection and thereby improving pump function secondarily. While each of these two methods is beneficial in certain clinical circumstances, they also possess disadvantages which limit their usefulness in other specific settings.

Nitroprusside, which is efficacious in congestive heart failure accompanied by elevated, normal or minimally reduced systemic arterial pressure, is contraindicated as the sole drug in the treatment of cardiac dysfunction with hypotension and shock. Dopamine, due to its powerful positive inotropic properties and differential regional vasodilator and vasoconstrictor actions is the preferred agent at present in most hypotensive conditions of cardiac etiology. However, the usefulness of dopamine is limited in severe pulmonary edema due to its failure to uniformly lower left ventricular filling pressure (fig. 1C). Therefore, pulmonary venous congestion may not be relieved and left ventricular end-diastolic volume and wall tension, the most important determinants of myocardial oxygen consumption, are not reduced during the concomitant oxygen increase in contractile state. Accordingly substantial augmentation of myocardial oxygen demand may result. The failure of dopamine to predictably lower left ventricular preload simultaneously with increase of ejection fraction and modest decline of systemic vascular resistance (fig. 2A) appears to result from the agent's constrictor action on the capacitance bed which promotes venous return thereby maintaining ventricular filling pressure.

From the present investigation it was shown that the concomitant administration of dopamine with nitroprusside to patients with congestive heart failure affords maximum benefit from the principal salutary actions of each agent and thereby provides hemodynamic improvement unattainable with either agent alone (fig. 3). Moreover the combined infusion of NP and dopamine obviates the major potential disadvantages of the individually administered drugs and thereby broadens the spectrum of clinical conditions in which NP and dopamine may be successfully applied.

The principal advantage afforded by NP added to dopamine compared to dopamine administered singly is related to reduction in left ventricular preload. Thus, although cardiac output is not appreciably augmented by the addition of NP to the positive inotropic agent, the dopamine-related increase in stroke output is achieved at a much lower left ventricular end-diastolic pressure when nitroprusside is concomitantly infused, so that there are both marked upward and leftward shifts in this relation (fig. 3). Additionally, the increase in myocardial oxygen needs related to dopamine-induced augmented contractile state may be partially offset by the decline in left ventricular preload and hence may improve cardiac efficiency compared to dopamine administered singly.

Dopamine added to nitroprusside provides two major hemodynamic advantages compared to NP alone. First, cardiac output is augmented to a greater extent by the
simultaneous administration of the two agents versus NP separately. Furthermore, it is anticipated that the excessive preload-dependent decline in cardiac output observed in certain patients given NP alone\textsuperscript{51, 52} would be abolished by dopamine. Secondly, maintenance of systemic arterial pressure by dopamine allows the potential extension of nitroprusside therapy to patients with pump failure complicated by mild or moderate hypotension.

In conclusion, despite continued major efforts to formulate an ideal cardiotonic agent for the therapy of left ventricular failure, at the present time such a drug is lacking. The combined use of dopamine and nitroprusside, however, affords the important beneficial actions of each agent while offsetting its principal disadvantages, thereby allowing extension of the use of the drugs to clinical conditions impractical with either agent alone. Thus simultaneous infusion of dopamine and nitroprusside appears to provide an efficacious and rational pharmacologic modality for the treatment of severe chronic congestive heart failure resulting from left ventricular dysfunction due to a variety of causes, and uniquely well suited for application in patients with ischemic heart disease and reduced systemic blood pressure.

References

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