Pharmacological Mechanisms for Left Ventricular Unloading in Clinical Congestive Heart Failure

Differential Effects of Nitroprusside, Phentolamine, and Nitroglycerin on Cardiac Function and Peripheral Circulation

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SUMMARY We compared cardiocirculatory actions of the commonly employed systemic vasodilators, intravenous (iv) nitroprusside (NP), iv phentolamine (PH), and sublingual nitroglycerin (NTG), causing left ventricular (LV) unloading in 29 chronic coronary subjects with congestive failure to determine whether they produce disparate responses in LV function by different relaxing actions on systemic resistance and capacitance beds. Each drug equally lowered systemic arterial pressures to a small extent, whereas heart rate rose slightly with NTG. Cardiac catheterization showed a decline in end-diastolic pressure with NTG (19 to 8 mm Hg) which was greater (P < 0.05) than with NP and PH (21 to 11). Cardiac index increased (P < 0.05) during NP (2.68 to 2.93 liters/min per m²) and PH (2.60 to 3.02) but was unchanged (2.83) by NTG. Stroke work increased with PH, ejection fraction rose with NP and PH, and mean ejection rate increased with each, whereas pressure-time per minute fell and end-diastolic volume decreased with each agent. Total systemic vascular resistance declined (P < 0.001) during NP and PH (1,475 to 1,200 dynes sec cm⁻⁵) but was unchanged (1,487) by NTG. Plethysmographically, forearm vascular resistance (FVR) decreased (P < 0.01) with NP and PH (61.6 to 39.1 mm Hg/ml per 100 g/min) but not (52.4) by NTG. The decreases in venous tone (VT) with NTG (18.2 to 9.3 mm Hg/ml) and NP (18.5 to 9.8) were greater (P < 0.05) than with PH (18.8 to 13.1). FVR/VT percent changes of 0.96, 1.62, and 0.53 with NP, PH, and NTG indicated balanced systemic arteriovenous relaxation by iv NP, greater arteriolar dilation with iv PH, and predominant venous dilation by sublingual NTG. Thus, vasodilators produce disparate modifications of LV function by their differing alterations of preload and impedance, which are dependent upon relative extents of relaxation of systemic resistance and capacitance vessels characteristic of each agent as used clinically.

ALTHOUGH efficacy of left ventricular (LV) unloading in congestive heart failure is well documented,¹⁻¹⁹ it is not known whether a given unloading agent has characteristic properties which are unique and which confer relative advantages in different clinical settings. Thus, in this investigation we considered the possibility that nitroprusside (NP), phentolamine (PH), and nitroglycerin (NTG), the peripheral vasodilator drugs used most often to produce cardiac unloading in patients, might exert disparate effects on ventricular preload and afterload through their potentially different relaxing actions on the vascular smooth muscle of the systemic resistance and capacitance beds. Despite previous observations describing the effects of a single vasodilator drug on cardiac function,¹⁻⁹ there is no information which compares the unloading mechanisms and sites of action of these agents on the peripheral arteriolar and venous systems or the resulting modifications in hemodynamic variables in patients with congestive heart failure. Accordingly, the present investigation was carried out to quantify and contrast both the primary actions on the peripheral circulation and the consequent effects on cardiac performance of intravenous (iv) sodium NP, iv PH, and sublingual NTG in a large group of patients with severe chronic LV dysfunction due to coronary heart disease.

Methods

The study population was a group of 29 patients, 21 male and eight female, 43–68 years in age (mean = 56 years), who had chronic, stable, and arteriographically documented coronary artery disease and congestive heart failure and who did not have mitral regurgitation. The cardiac effects of iv NP, iv PH, and sublingual NTG were evaluated on 22 patients (who constitute group I) by hemodynamic and ventriculographic measurements made during elective diagnostic cardiac catheterization. In the other seven patients (group II), the peripheral circulatory actions of the drugs were assessed by forearm plethysmography. Administration of digoxin and diuretics to all patients was discontinued 2 days prior to the studies; none was receiving antihypertensive agents or other medications. The present study was conducted with approval of our institutional Committee on Human Investigation and after informed consent was obtained from all subjects.

Of the 22 subjects comprising group I, seven received NP, prepared as previously described⁵ or as the commercially

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available form, Nipride. Thirty minutes after control left ventriculography and immediately after obtaining control cardiac hemodynamic data, iv NP was begun and the rate of administration was adjusted to gradually lower intra-arterial systolic pressure to 95-105 mm Hg. This provided a maximal vasodepressor response while maintaining systemic pressure within safe limits. The mean rate of NP infusion was 76 μg/min (35-120 μg/min). When the desired blood pressure had been obtained, a stable circulatory state was achieved by maintaining the NP infusion at a constant rate for 10 minutes. Measurement of cardiac hemodynamics and ventricular angiographic studies were repeated during the continued NP administration. Six patients in group I received PH administered intravenously as a 5.0-mg bolus followed by constant infusion (mean = 1.3 mg/min; range = 0.75-2.0 mg/min) at a rate adjusted to lower systemic systolic pressure to 95-105 mm Hg. Hemodynamic and ventriculographic measurements were obtained as described for NP. In the three of the 13 subjects receiving NP or PH who had the highest systolic pressures prior to drug administration, this variable was lowered to slightly above 105 mm Hg; for two subjects we used NP and for one, PH. Nine patients in group I received sublingual NTG as a tablet of 0.4 mg. Hemodynamic and angiographic measurements were made at the time of maximum reduction in systemic arterial pressure; this occurred between 5 and 10 minutes after drug administration; this time also corresponded to the greatest decrease in left ventricular end-diastolic pressure (LVEDP).

Duplicate measurements of cardiac output (CO) were made by the dye-dilution technique in each of the 22 subjects in group I, before and during administration of each agent. Calculations used to quantify cardiocirculatory variables included: total systemic vascular resistance (TSVR) = (P - RA)/CO, where 80 is the factor to convert mm Hg to dynes sec cm^{-1}; P = mean systemic arterial pressure; RA = mean right atrial pressure; pressure-time per minute (PTM) in mm Hg sec per min = P x ET x HR, where ET = left ventricular ejection time and HR = heart rate; and stroke work index (SWI) in g·m/m² = [(P - LVEDP) x SI x 13.6]/1,000, where SI = stroke index.

Biplane LV cineangiograms were recorded in the 30° right and 60° left anterior oblique projections on 35-mm film at 64 frames/sec, using the Philips 9-inch image-amplifier system. Tracings of LV end-diastolic and end-systolic endocardial silhouettes were obtained in the right anterior oblique position, and chamber volumes were quantified by the area-length method. Ejection fraction was calculated as the ratio of angiographically determined stroke volume to end-diastolic volume. Mean LV ejection rate was determined angiographically by the relation dVe/dt, where Ve = ventricular volume and t = time. This describes the systolic change in ventricular volume as stroke volume with respect to time measured from the simultaneous systemic intra-arterial pressure tracing. While this ratio, when corrected for LV end-diastolic volume index [dVe/dt/LVEDV in units of ml per sec/ml per m²], is analogous to the angiographically determined mean rate of circumferential fiber shortening (Vcf)¹, the mean LV ejection rate represents a three-dimensional alteration and thereby provides an improved characterization of the functional state of the entire ventricle in contrast to mean Vcf which describes a linear dimensional change. Thus, in the present investigation of the comparative effects of vasodilator agents which influence cardiac loading conditions in patients with regional abnormalities of contraction, LV ejection rate afforded a more precise measure of ventricular function than mean Vcf.

In the seven subjects in group II, forearm plethysmography was carried out with a mercury-filled rubber strain gauge placed around the mid-forearm as previously described. NP, PH, and NTG were administered in succession to attain the same hemodynamic end points described for subjects in group I. Effects of each of the three vasodilator agents were assessed in all seven group II subjects in a sequential manner by a protocol which allowed at least 15 minutes for measured variables to return to control values between cessation of NP and administration of PH, and at least 20 minutes between cessation of PH and institution of NTG. These studies were performed with subjects in the supine position and with the forearm elevated so that venous pressure approached zero; the hand vessels were isolated from the forearm by inflation of a wrist cuff to a suprasystolic pressure. A standard sphygmomanometer cuff was wrapped around the upper arm and, by using a container of compressed air with a special pressure gauge preset at 30 mm Hg, forearm venous occlusion was rapidly achieved by inflation of the upper arm cuff by regulating a stopcock. Forearm blood flow was calculated from the change in forearm circumference during acute venous occlusion and was expressed as ml/100 g of tissue per min. Simultaneous measurement of intra-arterial pressure was obtained through an indwelling brachial artery catheter placed in the opposite forearm. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow expressed in units of mm Hg/ml per 100 g per min. The values for forearm blood flow and forearm vascular resistance during control periods and during drug administration were obtained by averaging at least six individual determinations for each agent.

Forearm venous tone was determined for six patients both by the acute occlusion and equilibration techniques, using an indwelling needle placed in a forearm vein just distal to the mercury-in-rubber strain gauge. By the acute method, the pressure-volume characteristics of the capacitance vessels were calculated by determining the ratio of the increment in forearm venous pressure to the increment in forearm volume which occurred during the initial 10 seconds after inflation of the venous occlusion cuff to 30 mm Hg. This is expressed in units of mm Hg/ml. By the equilibration technique, the upper arm venous occlusion cuff was suddenly inflated to 30 mm Hg and forearm venous pressure and volume were permitted to equilibrate for 2 minutes. The distensibility of the venous capacitance vessels of the forearm was calculated from the increments in volume and pressure which occurred in the forearm during the 2-minute period of equilibration.

**Results**

**GROUP I (CARDIAC FUNCTION)**

Infusions of NP and PH at constant rates for 10 minutes reduced systolic and mean systemic arterial pressures in all
subjects (Fig. 1). The average control systolic pressure of 122.4 ± 6.8 (SEM) mm Hg fell to 99.3 ± 4.6 (-19%, P < 0.001) during infusion of NP (Fig. 1A), while PH caused a decline in systolic pressure from 124.2 ± 5.4 mm Hg to 107.6 ± 3.9 (-14%, P < 0.005) (Fig. 1B). NP lowered mean arterial pressure from 82.4 ± 5.6 to 74.8 ± 5.2 mm Hg (-9%, P < 0.005) (Fig. 1D) and PH reduced mean arterial pressure from 97.0 ± 3.5 to 79.9 ± 3.3 mm Hg (-8%, P < 0.005) (Fig. 1E). Similarly, sublingual NTG reduced the average systolic pressure from 134.0 ± 7.5 to 111.6 ± 5.4 mm Hg (-17%, P < 0.001) (Fig. 1C) and mean arterial pressure from 86.2 ± 3.4 to 75.1 ± 3.8 mm Hg (-12%, P < 0.001) (Fig. 1F). The mean heart rate of 79.6 ± 6.7 was not changed significantly by NP (P > 0.05) (Fig. 2A) or by PH (P > 0.05) (Fig. 2B). NTG, in contrast, elevated heart rate minimally from 85.3 ± 5.9 to 90.1 ± 6.2 beats/min (P < 0.02) (Fig. 2C); however, the mean percent increase in this variable with NTG was not significantly (P > 0.05) greater than with NP or PH.

LVEDP declined in each subject after administration of NP, PH, or NTG (Fig. 3). The mean control LVEDP fell from 20.6 ± 2.6 to 11.4 ± 1.8 mm Hg (-45%) (P < 0.001) during NP infusion (Fig. 3A); from 20.3 ± 2.1 to 12.3 ± 1.5 mm Hg (-39%) (P < 0.005) with PH (Fig. 3B); and from 19.2 ± 2.3 to 7.7 ± 1.9 mm Hg (-60%) (P < 0.001) after NTG (Fig. 3C). The decline in LVEDP with NTG was significantly greater (P < 0.05) than with NP or PH.

Cardiac index rose during NP infusion, from 2.68 ± 0.22 to 2.93 ± 0.20 liters/min per m² (P < 0.05) (Fig. 4A) despite the concomitant fall in LV filling pressure. The three subjects whose cardiac index was unchanged by NP showed considerable reductions in LVEDP (to 9, 6, and 4 mm Hg).
FIGURE 5 Relation between stroke work index (SWI) and left ventricular end-diastolic pressure (LVEDP) before and during (arrow) nitroprusside, phentolamine, and nitroglycerin (NTG). Vertical dashed line indicates upper limit of normal (12 mm Hg) for LVEDP. The average results for the three agents are shown by the thick arrows.

Effects of nitroprusside (NP), phentolamine (PH) and nitroglycerin (NTG) on left ventricular ejection fraction (EF). Dashed horizontal lines indicate lower limit of normal for EF. C = control.

Total systemic vascular resistance (TSVR) was decreased in each subject by NP and PH (Fig. 10A and B, respectively). The mean control value of 1390 ± 116 declined to 1130 ± 109 dynes sec cm⁻¹ (P < 0.001) during NP infusion, and from 1550 ± 119 to 1270 ± 112 dynes sec cm⁻¹ (P < 0.001) during PH administration. In contrast, after NTG, the response of TSVR was variable and thus there was no change from the control value of 1487 ± 212 dynes sec cm⁻¹ (P > 0.05) (Fig. 10C).

GROUP II (PERIPHERAL CIRCULATION)

During infusion of NP and PH forearm vascular resistance decreased in each subject from 57.8 ± 8.2 to 31.0 ± 6.9 mm Hg/ml per 100 g per min (−44%, P < 0.005) and from 65.5 ± 8.7 to 47.3 ± 7.1 mm Hg/ml per 100 g per min (−37%, P < 0.02) with NP and PH, respectively (Fig. 11A and B). NTG, however, did not alter forearm vascular resistance significantly (P > 0.05) from the control value of 52.4 ± 9.1 mm Hg/ml per 100 g per min (Fig. 11C).

Forearm venous tone measured by the acute occlusion technique was lowered in each subject by NP (Fig. 11D) from 18.5 ± 4.7 to 9.8 ± 2.9 mm Hg/ml (−48%, P < 0.02), and during infusion of PH was reduced from 18.8 ± 5.3 to 13.1 ± 2.9 mm Hg/ml (−23%, P < 0.05) (Fig. 11E). After NTG, forearm venous tone declined markedly from 18.2 ± 6.1 to 9.3 ± 4.8 mm Hg/ml (−53%, P < 0.01) (Fig. 11F). The decline in forearm venous tone was significantly greater with NTG (P < 0.05) than with PH.

The response of forearm venous tone to the three vasodilator agents measured by the equilibration method was consistent with the results obtained by the acute occlusion technique. Thus, with NP, forearm venous tone declined from 14.3 ± 4.1 to 8.5 ± 3.6 mm Hg/ml (−40%, P < 0.01), and during infusion of PH forearm venous tone
CARDIAC UNLOADING THERAPY / Miller et al. 131

Nitropresside Phentolamine NTG

**Figure 9** Effects of nitropresside (NP), phenolamine (PH), and nitroglycerin (NTG) on left ventricular-end diastolic volume index (LVEDVI). C = control.

Cardiac Index decreased from 13.5 ± 2.9 to 9.3 ± 3.4 mm Hg/ml (−31%, P < 0.05). With NTG, forearm venous tone was considerably reduced from 13.9 ± 3.7 to 6.1 ± 2.8 (−56%, P < 0.005). As with the acute occlusion technique, the decline in forearm venous tone was significantly greater with NTG (P < 0.05) than with PH.

The relative magnitude of the effects of the three vasodilator agents on the resistance and capacitance beds is shown in Fig. 12. We determined the ratio of the percent decline in forearm vascular resistance to the percent decline in forearm venous tone evaluated by the acute occlusion technique for each of the three vasodilator drugs. A ratio of unity (1.0) indicates a relatively equal extent of arteriolar and venous dilation. In the seven subjects who received each of the agents sequentially the ratio of forearm vascular resistance to venous tone (FVR/VT) was 0.96 ± 0.12 with NP, 1.62 ± 0.31 with PH, and 0.53 ± 0.21 with NTG.

**Discussion**

This investigation, carried out in subjects with chronic ventricular dysfunction consequent to coronary heart disease, examined the contrasting effects on cardiac performance of the three commonly employed ventricular unloading agents, nitropresside, phentolamine, and sublingual nitroglycerin. It also compared the differential actions of these vasodilator drugs on the peripheral resistance and capacitance beds. Although each drug reduced systemic arterial pressure by a similar extent (Fig. 1) and all three agents significantly lowered the elevated left ventricular end-diastolic pressure (Fig. 3), there was augmentation of cardiac index and ejection fraction only with NP and PH (Figs. 4 and 6). Because previous studies have demonstrated that NP, PH, and NTG do not possess direct positive inotropic actions, a possible variability between the agents in their inherent ability to cause myocardial stimulation cannot explain the disparate alterations in left ventricular function which they produced. Therefore, differences in the relative extents of their primary actions of direct relaxation of peripheral arterial and venous smooth muscle among the three agents must account for the dissimilar secondary modifications in cardiac hemodynamics observed in this investigation.

In this regard, NP and PH significantly reduced total systemic vascular resistance and lowered forearm vascular resistance in contrast to NTG, which did not alter these variables (Figs. 10 and 11). Furthermore, the decline in forearm venous tone induced by NTG was considerably greater than that effected by PH, whereas NP caused an intermediate reduction in this parameter (Fig. 11). Moreover, assessment of the relationship between the decrease in forearm vascular resistance and the reduction in forearm venous tone provided a quantitative comparison of the differential arteriolar and venous relaxing properties of the three vasodilator agents (Fig. 12). From this analysis it was determined that PH exerted a relatively greater dilator...
effect on the arteriolar tree, and NTG produced predominant relaxation of the venous bed, whereas NP caused similar degrees of dilation of both the resistance and capacitance beds.

Consistent with the results of the present investigation demonstrating the principal action of sublingual NTG to be on the peripheral venous system are prior studies which have shown that the nitrate usually causes a decline in cardiac output without affecting total peripheral vascular resistance.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) Further, our findings provide an explanation for the effects of NTG on cardiac performance which result from the agent's direct action on the peripheral circulation. Because the vasodilator action of sublingual NTG was exerted principally on the systemic capacitance bed, the preload of the left ventricle was reduced to a greater extent than was impedance to its ejection. Thus, left ventricular end-diastolic pressure and volume were markedly diminished by NTG in contrast to the agent's lack of effect on total systemic vascular resistance, a principal determinant of left ventricular impedance. Accordingly, it appears that NTG lowers cardiac output as a consequence of the predominance of its preload-reducing action over impedance reduction; therefore, only subjects who maintained LVEDP in the upper normal range or higher were capable of sustaining or increasing cardiac output after NTG (Fig. 4C).

PH, in contrast, exerted its principal dilator action on the systemic arterial bed. Consequently, this agent caused primarily a decrease in impedance to ventricular ejection and concomitant preservation of a left ventricular preload that was more optimal in terms of cardiac output. Thus, the substantial reduction in impedance with maintenance of preload resulted in a significant increase in cardiac output with PH (Fig. 4B). NP, on the other hand, through its balanced dilator actions on the peripheral arterial and venous systems, caused concurrent decreases in both ventricular impedance and preload. These vasodilator properties of NP resulted in either augmentation or reduction in cardiac output, depending on the degree to which LVEDP was decreased by infusion of this agent (Fig. 4A).

Certain important therapeutic implications emerge from these findings concerning the relative differences in magnitude of arterial and venous relaxation in response to systemic vasodilator drug usage in subjects with cardiac dysfunction. Sublingual NTG, with its ability to markedly lower left ventricular filling pressure at the expense of a slight reduction in cardiac output, is best suited for clinical application in the setting of severely elevated LVEDP occurring concomitantly with preservation of normal cardiac output and systemic arterial blood pressure. In contrast, PH is the most useful of the three agents in subjects with low cardiac outputs but without considerable elevation of left ventricular filling pressures and in whom a trial of volume expansion with augmented preload has not satisfactorily raised cardiac output. In contrast to NTG and PH, NP is optimally beneficial in the commonly encountered clinical condition of reduced cardiac output in association with marked elevations of left ventricular end-diastolic pressure. In this regard, NP is particularly efficacious in congestive heart failure complicating severe hypertension. However, while it has been pointed out that this agent may be hazardous clinically in the presence of diminished blood pressure, NP may be salutary when employed cautiously even in subjects with moderately reduced arterial pressure. Concerning the effects of NP, PH, and NTG on myocardial oxygen consumption, although each agent lowers ventricular wall tension, the principal determinant of \(\text{MV}_0\)\(^2\)\(^8\)\(^9\) NTG through its predominant vasodilator action and consequent reduction in ventricular preload and afterload appears to be particularly useful in limiting the extent of myocardial ischemia. Finally, it should be pointed out that the direct vasorelaxing actions of NTG and NP on isolated vascular smooth muscle might be similar. In the present investigation which was designed to compare the actions of NTG, NP, and PH in the manner these agents most commonly are employed clinically, it is possible that the predominant vasodilator caused by sublingual NTG and the relatively equal venodilation and arteriolar dilation caused by intravenous NP that we observed were, in part, due to the differences in routes of administration and disparate doses. However, the possibility also remains that NP and NTG may possess quantitatively different degrees of direct relaxation of systemic arteriolar and venous smooth muscle. In contrast, it is probable that the effects of PH are fundamentally somewhat different from those of NTG and NP because of the differences in relative importance of \(\alpha\)-receptors in the systemic resistance and capacitance beds.

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References

Calcium Accumulation and Enzymatic Activities of Subcellular Fractions from Aortas and Ventricles of Genetically Hypertensive Rats

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SUMMARY Subcellular fractions were obtained from aortas and ventricles of 6-month-old spontaneously hypertensive and normotensive Wistar rats by the use of differential and sucrose density gradient centrifugation. These preparations were studied to determine what alterations in calcium accumulation and enzymatic activities might be associated with hypertension. The total amount of calcium accumulation (in the presence of ATP and 17 μM free calcium) by the plasma membrane-enriched fraction from hypertensive rat aortas was significantly less than that from normotensive rats (11.3 ± 0.4 vs. 16.2 ± 1.6 μmol of calcium/g of protein, n = 8). In contrast the specific activities of the plasma membrane marker enzymes, 5'-nucleotidase and phosphodiesterase 1, were 80% and 40% greater, respectively, in the hypertensive than in the normotensive fractions. On the other hand, various fractions from ventricles of the two types of rats were generally similar in enzyme activities and calcium accumulation. The decreased rate of relaxation of aortas from spontaneously hypertensive rats may be caused by the decreased rate of calcium transport demonstrated in this study.

MANY CHANGES in the reactivity of vascular smooth muscle in hypertensive animals and man have been reported but little information is available concerning the possible underlying biochemical mechanisms. Since intracellular calcium activity is an important determinant of smooth muscle contractile state, an alteration in calcium regulation is a plausible cause of supersensitivity of strips of arteries from hypertensive animals to excitatory agents. Indeed, it has been suggested that increased sensitivity to potassium and norepinephrine, and decreased rate of relaxation of aortas from 6-month-old spontaneously hypertensive rats (SHR) may be due to decreased calcium extrusion by the cell membrane. In the present investigation we tested this...
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