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⁻²) 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, 1,21-23 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 described 4 or as the commercially
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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 intraarterial pressure tracing. While this ratio, when corrected for LV end-diastolic volume index [(dVe/dt)/LVEDV in units of ml per sec/ml per m^3], 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 determined by calculating 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 \( m^2 \) \( (P < 0.05) \) (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).

In contrast, for the four subjects in whom cardiac index rose, the decline in LVEDP maintained LV filling pressures of at least 10 mm Hg. In contrast to NP, cardiac index increased for all of the subjects receiving PH, from 2.60 ± 0.21 to 3.02 ± 0.24 liters/min per \( m^2 \) \( (P < 0.02) \) (Fig. 4B). Also, unlike results with NP, only one subject given PH demonstrated a fall in LVEDP below 10 mm Hg and in this individual the decline was only to 9 mm Hg. In contrast to results with NP and PH, the average cardiac index of 2.83 ± 0.25 liters/min per \( m^2 \) was unaltered by NTG \( (P > 0.05) \) (Fig. 4C). There was substantial variability in cardiac output during action of NTG; in five of the nine subjects cardiac index decreased in response to the agent. This decline in cardiac index occurred in the five subjects in whom the post-NTG LVEDP was lowest (average = 7 mm Hg), while in the remaining four subjects who showed an increase in cardiac index LVEDP remained substantially higher (average = 12 mm Hg) after NTG.

Mean control stroke work index (30.7 ± 4.5 g-m/m\(^2\)) was unchanged in the group of subjects receiving NP (Fig. 5A). As for cardiac output, the direction of change in SWI was related to the level to which LVEDP fell during NP infusion: SWI rose when LVEDP declined to a value no lower than 10 mm Hg (Fig. 5A), while SWI fell when LVEDP was below 10 mm Hg after NP. In contrast, stroke work index increased in each of the six subjects given PH (Fig. 5B) with the mean value of 29.6 ± 3.4 increasing to 32.0 ± 3.1 g-m/m\(^2\) \( (P < 0.02) \). It was observed that after PH LVEDP was higher than after NP. Unlike NP and PH, NTG lowered SWI in the majority of subjects. (Fig. 5C). While the average control SWI of 33.3 g-m/m\(^2\) was not reduced...
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.

**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.

Nitroglycerin (NTG) on left ventricular ejection fraction (EF).

**Figure 6** Alterations in mean left ventricular ejection rate, (dVe/dt)/LVEDV, induced by nitroprusside (NP), phentolamine (PH), and nitroglycerin (NTG). C = control.

**Figure 7** Alterations in mean left ventricular ejection rate, (dVe/dt)/LVEDV, induced by nitroprusside (NP), phentolamine (PH), and nitroglycerin (NTG). 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 declined from 6.1 ± 2.9 to 3.0 ± 1.2 mm Hg/ml (-42%, P < 0.05) (Fig. 11G).

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nitroglycerin (NTG) on left ventricular-end diastolic volume index (LVEDVI). C = control.

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, nitroprusside, 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,10 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 predomi-
nant 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 resis-
tance.14-18,24-26. Further, our findings provide an expla-
nation 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
to was than with impedance to its ejection. Thus, left
ventricular end-diastolic pressure and volume were mark-
edly 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 imped-
ance 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 pri-
marily 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 ventricu-
lar 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 magni-
tude 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 car-
diac output and systemic arterial blood pressure. In con-
trast, 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 satisfac-
torily 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 myocar-
dial oxygen consumption, although each agent lowers ven-
tricular wall tension, the principal determinant of MVo2,24
NTG through its predominant vasodilator action and conse-
quently 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 effect caused by sublingual NTG and the relatively
equal venodilation and arteriolar dilation caused by intrave-
nous 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 relaxa-
tion of systemic arteriolar and venous smooth muscle. In
contrast, it is probable that the effects of PH are fundamen-
tally somewhat different from those of NTG and NP
because of the differences in relative importance of α-recep-
tors in the systemic resistance and capacitance beds.

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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 I, 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 from the cell membrane. In the present investigation we tested this...
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