Clinical Use of Sodium Nitroprusside in Chronic Ischemic Heart Disease

Effects on Peripheral Vascular Resistance and Venous Tone and on Ventricular Volume, Pump and Mechanical Performance

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SUMMARY

Although hemodynamic benefit has been shown with sodium nitroprusside (NP) in acute coronary pump failure, complete understanding of the mechanisms of action of the agent on the cardiocirculation and its value in chronic ventricular dysfunction are lacking. This investigation evaluates the effects of NP on the systemic and regional arterial and venous beds and on cardiac dynamics, ventricular volumes, contractile state and myocardial energetics in long-standing congestive heart failure. Twelve patients with chronic coronary pump dysfunction received NP infusion to lower systolic pressure to 95-105 mm Hg. Left ventricular (LV) function was assessed directly by angiographic volumes and high fidelity pressure, and peripheral circulatory dynamics were determined simultaneously by forearm arterial and venous plethysmography. NP reduced mean arterial pressure (MAP) from 88.2 to 73.4 mm Hg (P < 0.05) and significantly (P < 0.05) enhanced the variables of LV performance: LV end-diastolic pressure (EDP) diminished from 18.5 to 9.9 mm Hg; ejection fraction rose from 0.47 to 0.55; percent of LV segmental shortening increased; and isovolumic and ejection indices of contractility improved. Concomitantly, NP reduced the indices of myocardial oxygen demands of ventricular tension time index and LVED volume index. These salutary effects on LV performance and energetics occurred secondary to peripheral arterial and venous dilation (P < 0.05) produced by NP: total systemic vascular resistance was lowered from 1590 to 1310 dynes sec cm⁻²; forearm vascular resistance diminished from 46 to 37 mm Hg/ml/100 gm/min; and forearm venous tone fell from 14.2 to 10.1 mm Hg/cc. Depressed stroke index (SI) and cardiac index (CI) increased (P < 0.05) with NP, despite the fall in LVEDP, when ventricular filling pressures with the agent were at levels slightly above normal. Dextran infusion given with NP to restore LVEDP to moderately elevated values increased SI and CI (P < 0.05) when NP alone produced no change in stroke output. Thus, the peripheral vasodilator properties of nitroprusside improve LV function by reducing impedance to ventricular ejection, while MVO₂ is diminished by decreasing LV preload and afterload through relaxing actions on both systemic arterial and venous smooth muscle. These LV unloading effects of nitroprusside in chronic congestive heart failure are most beneficial in patients with marked pump dysfunction and greatly elevated LVEDP and peripheral vascular resistance.

Additional Indexing Words:

Coronary artery disease  Congestive heart failure  Dextran infusion
LV afterload  LV preload  LV unloading
Myocardial oxygen consumption  Vasodilator therapy  Ventricular function

Although conventional treatment of congestive heart failure consists of digitalis glycosides and diuretics,¹ there has been considerable interest recently in improving cardiac performance by the new therapeutic approach of producing alterations in ventricular loading with the use of peripheral vasodilator drugs.⁵-¹⁰ Thus, reduction of the impedance to left ventricular ejection by decreasing systemic vascular resistance with nitroprusside has elevated cardiac output and...
diminished ventricular filling pressure, while lowering myocardial oxygen needs in refractory cardiac failure due to acute myocardial infarction, mitral regurgitation or severe hypertension.\textsuperscript{2, 5, 7-10, 14} Although the salutary hemodynamic effects of the agent have been demonstrated by these reports, knowledge has been incomplete concerning the precise mechanism of action of nitroprusside on the heart and peripheral circulation. Further, the effects of nitroprusside on ventricular size have only been inferred from hemodynamic observations\textsuperscript{6} and quantification of alterations in ventricular volumes in response to the agent have not been carried out in patients without mitral regurgitation.

In addition, there have been relatively little clinical data on the value of nitroprusside infusion in long-standing ischemic cardiac dysfunction. Moreover, no information is available on the usefulness of the drug in chronic coronary heart failure not associated with severe valvular incompetence. Therefore, the purpose of this investigation was to determine the actions of nitroprusside on both the resistance and capacitance vessels of a specific peripheral vascular bed, that of the forearm, and to discern the effects of the potent vasodilator on cardiac pump and muscle performance by the direct assessment of chamber volumes, ejection fraction, extent and velocity of shortening, contractile state and myocardial oxygen consumption of the left ventricle in patients with chronic ischemic heart disease. In addition, the value of maintaining optimal ventricular preload concomitant with the reduction of impedance to ejection is evaluated by combining volume expansion therapy with nitroprusside infusion.

\section*{Methods}
Twelve patients, 9 male and 3 female, aged 43 to 61 years (average 54 years) with arteriographically documented coronary artery disease received sodium nitroprusside (NP) infusion during diagnostic cardiac catheterization. Nine patients had electrocardiographic and angiographic evidence of prior myocardial infarction and ten patients had left ventricular dysfunction with end-diastolic pressure above 12 mm Hg (14 to 51 mm Hg, average 20 mm Hg). Each patient was taking 0.25 mg digoxin daily; none had received anti hypertensive drugs and beta adrenergic blocking agents had not been administered for at least 3 days prior to catheterization. Sodium nitroprusside was prepared on the day of infusion by dissolving 25 mg NP crystals in 500 cc normal saline and passing the solution through a micropore filter.\textsuperscript{5, 8} Thirty minutes after angiographic measurements and immediately after obtaining control cardiac hemodynamic and forearm plethysmographic data, intravenous NP infusion was begun. The agent was individualized to gradually lower intra-arterial systolic pressure to 95-105 mm Hg, thereby affecting maximal vasodepressor response in each patient while maintaining systemic perfusion pressure within safe limits. The mean rate of NP administration was 63 \textmu g/min (range 25-100 \textmu g/min). Upon reaching the desired blood pressure, the infusion was maintained at a constant rate for 10 minutes and cardiac hemodynamic, forearm plethysmographic and angiographic studies were repeated sequentially. In 4 patients in whom LVEDP was substantially reduced to 4-8 mm Hg following nitroprusside, 300-500 cc of low molecular weight dextran (Rheomacrodex) was infused to restore end-diastolic pressure to 12-15 mm Hg and cardiac hemodynamics were measured.

Cardiac output (CO) was determined in duplicate in each patient before and after NP by the dye dilution technique with injection into the left ventricle and sampling at the brachial artery. Calculations utilized for determining cardiovascular variables pre and post NP included total systemic vascular resistance (TSVR) = 80 (\overline{P} - RA/CO) where \overline{P} = mean arterial pressure and RA = mean right atrial pressure; tension time index (TTI) in mm Hg sec/min = the product of mean left ventricular pressure during ejection determined by planimetry and systolic ejection time multiplied by heart rate.\textsuperscript{17} In 7 patients instantaneous rate of intraventricular pressure rise (dP/dt) at the common peak isovolumic developed pressure (CPIP) of 50 mm Hg corrected for left ventricular end-diastolic volume index (LVEDV): (dP/dt_max)/LVEDV,\textsuperscript{18} was obtained utilizing a high-fidelity micromanometer catheter.

Biplane left ventricular cineangiograms were obtained in 10 patients in the 30° right and 60° left anterior oblique projections on 35 mm film taken at 64 frames/sec using the Phillips 9-inch image amplifier system. The ventricle was opacified with 45-60 cc of Hypaque-M 76% (Winthrop) containing sodium and meglumine diatrizoates injected at 250-350 pounds per square inch through an angiocatheter. Tracings of left ventricular end-diastolic and endsystolic endocardial silhouettes were obtained in the right anterior oblique position and chamber volumes were quantified by the area-length method.\textsuperscript{19} Ejection fraction was calculated as the ratio of angiographically determined stroke volume to end-diastolic volume.\textsuperscript{19} Angiographic mean velocity of circumferential fiber shortening (mean \upsilon_{cf}) in circumferences (circ)/sec was determined by the equation (\sigma_{DED} - \sigma_{DES})/\sigma_{DED} \times ejection time, where \sigma_{DED} = end-diastolic circumference, \sigma_{DES} = end-systolic circumference and ejection time = interval separating end-diastolic and end-systolic cine frames in seconds.\textsuperscript{20} Correction for isovolumic contraction was accomplished by subtracting 0.05 seconds from the total ejection time. Extent of left ventricular segmental shortening was determined as the percent of systolic shortening along each of four reference axes, the major length axis measured from the midpoint of the aortic valve plane to the left ventricular apex and three minor axes equidistant along and perpendicular to the major axis.

Forearm plethysmography was carried out in 6 patients during cardiac catheterization using a mercury-filled rubber strain-gauge plethysmograph placed at the midforearm.\textsuperscript{21, 22} These studies were performed in the supine position with the forearm elevated so that venous pressure approached zero and the hand vessels were isolated from the forearm by inflation of a wrist cuff to suprasystolic pressure. A standard sphygmomanometer cuff was wrapped around the upper arm and, by utilizing a tank of compressed air with a pressure gauge preset at 30 mm Hg, inflation and deflation of the upper arm cuff was rapidly achieved by turning a stopcock. Forearm blood flow was calculated from
the change in forearm circumference during acute venous occlusion of the upper arm cuff and was expressed as ml/100 gm tissue. Simultaneous intra-arterial pressure was obtained through an indwelling brachial artery catheter placed into the opposite forearm. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow expressed in mm Hg/ml/100 gm/min. Each value for forearm blood flow and forearm vascular resistance was obtained by averaging 6 or more individual determinations.

Forearm venous tone was determined in 7 patients by acute occlusion and equilibration techniques utilizing an indwelling venous needle placed in the forearm just distal to the mercury-in-rubber strain gauge. In the acute method, the pressure-volume characteristics of the capacitance vessels were calculated by determining the ratio of the increment in venous pressure to the increment in forearm volume which occurred in the initial 10 seconds following inflation of the venous occlusion cuff to 30 mm Hg and were expressed in mm Hg/cc. In the equilibration technique, the upper arm venous occlusion cuff was suddenly inflated to 30 mm Hg and forearm venous pressure and circumference were permitted to equilibrate for 2 min. The tone of the venous capacitance vessels was calculated from the increments in volume and pressure which occurred during the 2 min period.

Results

Nitroprusside infusion at a constant rate for 10 minutes resulted in decline in mean arterial pressure in all patients (fig. 1A). The average control pressure of 88.2 ± 4.5 (SEM) fell to 73.4 ± 3.4 mm Hg (P < 0.01). For the entire group of patients, the mean heart rate of 74.8 ± 4.8 was unchanged following NP (fig. 1B). However, two characteristic subsets of patient responses were observed. In the patients with an increase in heart rate, LVEDP fell below 10 mm Hg (P < 0.05) and there was no significant change in stroke index with NP. In contrast, in the five remaining patients with no change or a slight decline in heart rate, LVEDP was reduced (P < 0.01) but remained above 10 mm Hg while stroke index increased (P < 0.05).

Left ventricular end-diastolic pressure decreased in each patient; the mean control LVEDP of 18.5 mm Hg ± 1.8 diminished to 9.9 mm Hg ± 1.5 (P < 0.01) (fig. 1C). In the seven patients with resting LVEDP below 18 mm Hg the percent decrease in LVEDP was greater (–57%, P < 0.05) and the stroke index decreased in six, compared to the five patients with control LVEDP above 18 mm Hg in whom the LVEDP declined by 35% and the stroke index increased in each. The response of cardiac index to NP infusion was dependent on the level to which LVEDP was reduced. Thus, the five patients whose LVEDP remained above 10 mm Hg with NP had a significant increase (P < 0.05) in cardiac index, while the seven patients whose LVEDP fell below 10 mm Hg had no change in this variable (2.8 L/min/m²). Stroke index was increased in all three patients whose control LVEDP was greater than 20 mm Hg and in three of four patients with LVEDP 16-20 mm Hg (fig. 2). In contrast, all patients with control LVEDP equal to or less than 15 mm Hg demonstrated a fall in stroke index. In the four patients who received dextran during NP infusion to return LVEDP to control levels (fig. 3), stroke index did not change significantly from control with NP alone but volume expansion concomitant
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Figure 2
Relation between LVEDP and stroke index before and during nitroprusside infusion. Vertical dashed line indicates upper limit of normal for LVEDP.

with NP increased stroke index significantly ($P < 0.05$).

The mean ejection fraction increased significantly from $0.47 \pm 0.05$ to $0.55 \pm 0.04$ ($P < 0.01$) following NP (fig. 4). Ejection fraction increased in each of the 7 patients with control values below normal and four of these patients attained normal levels after NP. There was an increase in the isovolumic index of contractility of $(dP/dt_{50})/LVEDV$ in 6 of 7 patients (fig. 5A). The mean control value of $3.9 \pm 0.44$ was elevated to $4.6 \pm 0.58$ mm Hg/sec/ml/m$^2$ ($P < 0.05$). The ejection index of contractility of mean $V_C$ increased in each of the 10 patients following NP from an average of $0.66 \pm .10$ to $0.90 \pm .11$ circ/sec ($P < 0.01$) (fig. 5B). The extent of left ventricular segmental shortening was enhanced during systole (fig. 6). Thus, percent of shortening increased in three of the four segments: minor axis II from 18 to 31% ($P < 0.05$), minor axis III from 24 to 38% ($P < 0.01$) and the major axis IV from 12 to 19% ($P < 0.05$).

Two measured factors relating to myocardial oxygen requirements were significantly reduced following NP infusion (fig. 7). In each patient tension time index was diminished with the mean value of $3300 \pm 230$ declining to $2600 \pm 196$ ($P < 0.01$) (fig. 7A). Similarly, left ventricular end-diastolic volume index (EDVI) was reduced from $113 \pm 12.4$ to $92 \pm 9.3$ cc/m$^3$ ($P < 0.01$) following NP (fig. 7B).

Total systemic vascular resistance fell in each patient with NP (fig. 8A). The average control value of $1590 \pm 110$ declined to $1310 \pm 114$ dynes sec cm$^{-5}$ ($P < 0.01$). Forearm vascular resistance (FVR) decreased in each patient following NP (fig. 8B). The control mean value of $46 \pm 8.4$ was reduced to $37 \pm 4.6$ mm Hg/ml/100 gm/min ($P < 0.05$). Forearm vascular resistance was most reduced in patients with the highest control values. Venous tone (VT) measured by the acute occlusion technique was diminished in each patient by NP from an average of $14.2 \pm 1.7$ to $10.1 \pm 1.6$ mm Hg/cc ($P < 0.01$) (fig. 8C). Additionally, forearm venous volume determined by the equilibration technique at 30 mm Hg increased from $1.16 \pm 0.07$ to $1.70 \pm 0.09$ ml/100 gm ($P < 0.01$), indicating that venous tone was diminished by NP.

Figure 9 relates the decline of EDVI to TSVR and of EDVI to forearm venous tone. In relation to the decrease in TSVR, the reduction of EDVI was not significantly greater (fig. 9A) than the fall in forearm.
venous tone (fig. 9B). Similarly, there was no significant relationship between stroke index and TSVR (fig. 10A) or between stroke index and forearm venous tone (fig. 10B).

**Discussion**

Therapy directed primarily toward reducing left ventricular loading conditions including both the impedance to ejection and diastolic volume has resulted in substantial hemodynamic improvement in certain patients with left ventricular failure due to acute myocardial infarction or mitral regurgitation in chronic coronary heart disease. This mode of treatment represents a departure from the traditional management of pump failure directed fundamentally at increasing lowered myocardial contractile state with positive inotropic agents which may secondarily influence cardiac diastolic loading by reducing ventricular volume and produce variable effects on peripheral vascular resistance. However, when refractory pump failure results from the marked impairment of a large number of myocardial contractile units, an increase in the inotropic state of the remaining functioning myocardium may be insufficient to adequately enhance cardiac function. Moreover, prolonged use of agents with potent positive inotropic properties may have deleterious effects related to elevation of myocardial oxygen requirements (MVO₂). Since facilitation of ventricular emptying with consequent enhancement of stroke volume is the major objective of therapy for cardiac failure principally due to ventricular disease, reduction in impedance to left ventricular ejection accomplished by systemic arteriolar dilation may achieve this goal in intractable heart failure even without simultaneous administration of cardiotonic agents, while also diminishing MVO₂. Furthermore, concomitant systemic venodilation may reduce ventricular preload with attendant salutary effects on circulatory congestion and MVO₂.

In the present investigation in patients with chronic coronary heart disease and left ventricular dysfunction, nitroprusside produced only mild to moderate reductions in blood pressure (average −17%) (fig. 1A) which were accompanied by either an increase (+16%, 7 patients) or essentially no change (average −4%, 5 patients) in heart rate (fig. 1B). Since the fall in mean arterial pressure was not significantly different between these two subgroups (−15.6% and −20.5%), it is unlikely that the small variation in the magnitude of arterial pressure change accounts for the different heart rate responses in the two groups with NP. With regard to the relation between LVEDP and heart rate following NP, the markedly elevated LVEDP was considerably reduced in the patients in whom heart rate was unchanged with the LVEDP remaining above 10 mm Hg. In contrast, in the group whose heart rate rose, the mildly elevated LVEDP fell to less than 10 mm Hg. Additionally, there was a substantial augmentation in stroke index in the patients with unaltered heart rates, while stroke index was unchanged or fell slightly in those whose heart rates increased. Thus, in chronic ischemic heart disease, reduction in afterload by NP coupled with maintenance of a moderately elevated filling pressure resulted in a significant (P < 0.05) increase in stroke index without altering heart rate (fig. 2). In contrast, little or no change in stroke index occurred with a compensatory increase in heart rate in chronic coronary patients in
whom elevated left ventricular filling pressures fell to normal levels (fig. 2).

The importance of maintaining left ventricular filling pressure at an optimally elevated level combined with reducing afterload is further exemplified by carrying out volume expansion during NP infusion. Thus, four of the patients who had marked reductions in LVEDP to below 10 mm Hg and simultaneous declines in stroke index with NP alone, then received dextran during constant NP infusion to return LVEDP to the mildly increased control levels (fig. 3). At this elevated filling pressure, with the extent of afterload reduction remaining constant, there was a rise in stroke index in each patient to levels considerably above preNP control values. Thus, it is apparent that maximal pump performance with NP is attained in ventricular dysfunction when markedly elevated LVEDP is only lowered to levels which are somewhat above normal. Through careful adjustment of ventricular loading by reducing afterload with NP and increasing preload with volume expansion in instances in which LVEDP falls below suboptimal levels, maximal enhancement of stroke volume and cardiac output is attained. Previous reports on the value of volume expansion in acute myocardial infarction have indicated that LVEDP levels of 15-18 mm Hg are usually optimal for cardiac output without producing pulmonary congestion.25, 26

Although enhancement of systolic emptying is the primary goal of therapy for cardiac pump failure, the effect of nitroprusside on left ventricular ejection fraction in the absence of mitral regurgitation is not known. Therefore, a major objective of the present study was to quantify the actions of NP on this sensitive measure of ventricular performance. Nitroprusside infusion resulted in substantial augmentation of ejection fraction in all patients in whom this variable was depressed and normal values were obtained in the majority (fig. 4). Further, ejection fraction was not altered in those with normal control levels.

Concerning the mechanism of the increase in lowered ejection fraction produced by nitroprusside, it was observed that stroke volume and cardiac output increased in those individuals who were characterized by marked elevation of LVEDP prior to the agent. Therefore, in patients with the greatest impairment of left ventricular function, this elevation of stroke output with NP was achieved by substantial rise in ejection fraction which was afforded by reduction in impedance to ejection while maintaining a relatively high filling pressure (fig. 2). Thus, in the severely abnormal hemodynamic setting of very high LVEDP with low stroke volume in chronic ischemic heart disease, ejection fraction rose principally by the decline in impedance predominating over the decrease in preload with the administration of the systemic vasodilator in this condition. In contrast, there was little change in ejection fraction in patients with only

**Figure 7**
Effects of nitroprusside on two indices of myocardial oxygen consumption. Panel A, tension time index (TTI) and panel B, end-diastolic volume index (EDVI). Dashed horizontal lines represent upper limits of normal.

**Figure 8**
Effects of nitroprusside on (A) total systemic vascular resistance (TSVR), (B) forearm vascular resistance (FVR) and (C) venous tone (VT).
mild to moderate elevation of control LVEDP since filling pressures became normal with NP; consequently, stroke volume and cardiac output were unaltered in these individuals in whom the decline in impedance was equally counterbalanced by fall in preload (fig. 2). These findings in chronic ischemic heart disease are consistent with the previous studies in acute myocardial infarction in which stroke volume and cardiac output were raised by NP only in patients with elevated LVEDP.

Although the principal actions of nitroprusside on ventricular function are mediated by mechanical unloading of the heart via the direct systemic vasodilator actions of the drug, the effects of this agent on cardiac contractility were also examined in this study. The depressed contractile state prior to NP was improved minimally but significantly by the drug as assessed by isovolumic and ejection inotropic indices (fig. 5). These estimates of contractility were significantly increased, although to a lesser extent, even without normalization for preload; therefore the rise in these inotropic indices was not due solely to decreases in end-diastolic volume and circumferences with NP. Since nitroprusside does not possess direct inotropic properties on experimental papillary muscles, the modest enhancement of contractile state in our patients is likely the result of mild reflex sympathetic discharge due to the decline in arterial pressure and/or decrease in ventricular ischemia resulting from reduction in over-all myocardial oxygen requirements. This indirect increase in contractility probably contributes to a small degree to the improvement in ventricular function caused by nitroprusside, but the major salutary actions of the agent on cardiac performance are the result of reduced ventricular loading.

In addition to increased velocity of shortening (fig. 5B), the extent of ventricular shortening during ejection was enhanced by nitroprusside (fig. 6). This improvement in systolic wall excursion was observed in both normally contracting and hypokinetic ventricular segments but not in akinetic or dyskinetic areas. The principal mechanism of the enhanced extent of left ventricular shortening of the smaller heart following NP appears to be the reduction in impedance to ventricular emptying.

Concomitant with the beneficial alterations of hemodynamics induced by nitroprusside, the agent also favorably influences indices of myocardial energetics. Thus, the unloading of the ventricle by systemic vasodilation decreases the end-diastolic volume (fig. 7B) and systolic pressure (fig. 1A), thereby decreasing ventricular wall tension, the principal determinant of MVO₂. In terms of the major factors governing myocardial oxygen requirements, the decline in wall tension lowering MVO₂ is essentially unopposed, since heart rate was not altered (fig. 1B) and contractile state was only minimally affected (fig. 5). This over-all reduction of the principal determinants of MVO₂ produced by nitroprusside was reflected by the diminution of the ventricular tension-time index (fig. 7A) in the present investigation. In contrast to positive inotropic drugs which raise MVO₂ and beta adrenergic blocking agents which depress the contractile state, nitroprusside is unique in its ability to enhance ventricular function while lowering indices of myocardial oxygen requirements.

One of the principal objectives of this investigation was to determine the mechanism of ventricular un-
loading produced by nitroprusside. The profound effects of NP on cardiac function would be anticipated to be the result of actions of the drug on the peripheral circulation, since NP has no direct inotropic properties. Therefore, the actions of the agent were evaluated on both the systemic resistance and capacitance beds. Nitroprusside resulted in reduction of total systemic vascular resistance (fig. 8A) which is consistent with previous findings. The present study extends these observations of the vasodilator effects of NP to the specific vascular bed of the forearm (fig. 8B). Moreover, initial information is provided concerning knowledge of the actions of nitroprusside on the systemic venous system. Thus, forearm venous tone determined by two methods was diminished by NP (fig. 8C). Therefore, nitroprusside possesses the ability to directly relax both arterial and venous smooth muscle in the systemic vasculature.

The observations in this study allow a comparison of the relative vasodilator properties and resultant hemodynamic effects of nitroprusside with the rapidly acting nitrates, sublingual nitroglycerin and inhaled amyl nitrite. We have shown previously that sublingual nitroglycerin exerts a predominant systemic venodilator effect and consequently lowers stroke volume and cardiac output in normal subjects and in patients with ventricular dysfunction due to acute myocardial infarction. In contrast, inhaled amyl nitrite produces profound systemic arteriolar dilatation which results in elevation of cardiac output. Thus, sublingual nitroglycerin predominantly reduces ventricular preload which may transiently relieve pulmonary edema, while inhaled amyl nitrite principally diminishes impedance to ventricular ejection. The findings herein indicate that the vasodilator actions of nitroprusside are intermediate between sublingual nitroglycerin and inhaled amyl nitrite. Thus, NP infusion produced balanced dilation of the systemic arterial and venous beds, since stroke volume and cardiac output were unchanged (fig. 1D and 10) in our total group of patients. Consistent with the theory that NP equally reduces preload and impedance in terms of ventricular performance are our findings that ejection fraction rose while end-diastolic volume declined (figs. 4, 7 and 9).

In conclusion, the present study in patients with chronic ischemic heart disease demonstrates that the over-all mechanical unloading effect of nitroprusside on cardiac performance is dependent on the hemodynamic setting in which the agent is administered. When ventricular function is normal or minimally to moderately impaired, stroke output is usually unaltered while LVEDP falls, since preload is reduced to the same extent as is the impedance to ejection. However, when ventricular function is moderately to markedly abnormal, stroke index and cardiac output rise concomitant with decrease in LVEDP. Therefore, in the condition of severe left ventricular dysfunction with marked elevation of LVEDP, the effect of NP of reducing impedance is greater than of diminishing preload in terms of stroke output. The relatively flattened nature of the depressed ventricular function curve characteristic of a markedly impaired contractile state allows the reduction in impedance produced by NP to be expressed hemodynamically as a rise in stroke output with decrease in LVEDP. In patients in whom reduction in ventricular contractility is not markedly impaired, with LVEDP only mildly to moderately increased, lowered stroke output can be improved by combining NP with volume expansion to keep the ventricle preloaded at the top of the ascending limb of its function curve. Thus, new understanding of the cardiocirculatory mechanisms of action of nitroprusside have been provided herein by demonstration of the relaxing properties of the agent on the systemic venous bed as well as on the arteriolar vessels, and the effects of these peripheral vasodilator actions on ventricular volumes, ejection fraction, contractile state and myocardial energetics have been quantified. Finally, this information should be valuable in the more rational clinical use of nitroprusside in pump dysfunction consequent to acute coronary disease, as well as in the temporary improvement of patients with long-standing severe left ventricular failure due to chronic ischemic heart disease and other types of cardiac disorders.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Robert Kleckner, the secretarial assistance of Barbara Giles, Gail Garnas, Wanda McIntyre and Nancy Carston, and the medical artistry of Kathryn Marr.

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Clinical use of sodium nitroprusside in chronic ischemic heart disease. Effects on peripheral vascular resistance and venous tone and on ventricular volume, pump and mechanical performance.

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_Circulation_. 1975;51:328-336
doi: 10.1161/01.CIR.51.2.328

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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