Renal Effects of Nitroprusside and Hydralazine in Patients with Congestive Heart Failure

John J. Cogan, M.D., Michael H. Humphreys, M.D., C. Jeffrey Carlson, M.D., and Elliot Rapaport, M.D.

SUMMARY The acute effects of nitroprusside infusion and intravenous hydralazine on renal hemodynamics and function were evaluated in nine male patients with severe, low cardiac output, congestive heart failure (CHF). Both drugs resulted in marked systemic hemodynamic improvement. Nitroprusside had a more profound effect on pulmonary artery pressure, while hydralazine produced a greater elevation in cardiac output. Significant decreases in both systemic and pulmonary vascular resistance and pulmonary capillary wedge pressure with increases in stroke volume and stroke work index were noted with both drugs. Total renal resistance decreased and renal blood flow (RBF) significantly increased with both drugs, while the distribution of cardiac output to the kidney remained depressed. Glomerular filtration rate (GFR) did not change significantly with either drug, although increases in GFR were seen in selected patients in whom RBF increased by more than 10% from control. The fraction of plasma filtered decreased toward normal with both drugs and excretion of total cations was significantly increased. These changes all represent improvements in systemic and renal hemodynamic abnormalities occurring in patients with CHF; their maintenance during long-term therapy would facilitate patient management.

THE RECENT APPROACH of modifying ventricular loading with vasodilators (afterload reduction) has been shown to be useful in the treatment of advanced heart failure. Among these agents, nitroprusside and hydralazine have been extensively investigated and found to be beneficial in restoring hemodynamics toward normal. Through their arteriolar vasodilating effect, both agents result in consistently increased cardiac output. Decreases in left ventricular filling pressure and pulmonary vascular resistance owing to venous vasodilation are more pronounced with nitroprusside. Despite these salutary hemodynamic changes, it is still unclear what effect these drugs may have on regional blood flows and function. In particular, the renal response to afterload-reducing agents is unclear. The object of this study was to investigate the response of the kidney to vasodilator therapy in patients with low cardiac output (CO) congestive heart failure. Specifically, we measured the acute effects of nitroprusside infusion and intravenous hydralazine on renal blood flow (RBF), glomerular filtration rate (GFR), renal resistance and electrolyte excretion, and confirmed their effect on hemodynamics.

Methods

Nine consecutive patients with congestive heart failure of 6 months to 7 years duration were studied. The clinical characteristics are presented in table 1.

The mean age was 51.3 years. All patients had an S3 gallop, eight had a left ventricular apical impulse consistent with dilatation and/or hypertrophy, seven had a right ventricular heave, five had hepatic enlargement, six had dependent edema, and four had pulmonary rales. Two patients had pulsatile neck veins consistent with tricuspid insufficiency. All patients had cardiomegaly on chest x-ray, and the two patients with coronary artery disease had old myocardial infarction patterns on the ECG. Echocardiographic examination in seven patients showed the left ventricular end-diastolic diameter to be greater than 5.9 cm in four, and the right ventricular diameter to be greater than 2.5 cm in five. There was mitral-septal separation consistent with reduced left ventricular ejection fraction in five.

The protocol, approved by the Committee on Human Research, University of California, San Francisco, was explained to each patient and written consent was obtained. Patients with a serum creatinine greater than 1.5 mg/dl or a history of allergy to the study drugs were excluded.

All cardiac medications, including digitalis, diuretics and vasodilators, were discontinued 24-48 hours before the study. The patients were taken to the catheterization laboratory where, without premedication and under fluoroscopic control, a Swan-Ganz thermodilution catheter was inserted into the pulmonary artery. A #5F polyethylene catheter was placed percutaneously in either a femoral or radial artery, and in seven patients, a Foley catheter was positioned in the urinary bladder and connected to gravity drainage. The patients were then transported from the catheterization laboratory to the neighboring coronary care unit, where the arterial line and Swan-Ganz catheter were connected to Hewlett-Packard 1280 pressure transducers and monitored with Hewlett-Packard 7820SB digital pressure amplifiers. Pressure contours were displayed on a Hewlett-Packard 78304A unit. A bipolar ECG lead was connected to a Hewlett-Packard 782031 digital pulse...
Table 1. Summary of Pertinent Clinical Information

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Etiology of CHF</th>
<th>Duration of CHF (years)</th>
<th>New York Heart Association Class</th>
<th>Drugs before study</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>CAD &amp; Etoh</td>
<td>1</td>
<td>IV</td>
<td>Digoxin, triamterene</td>
</tr>
<tr>
<td>2*</td>
<td>28</td>
<td>M</td>
<td>PMD</td>
<td>1</td>
<td>III</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>3*</td>
<td>24</td>
<td>M</td>
<td>PMD</td>
<td>7</td>
<td>III</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>CAD</td>
<td>2</td>
<td>III</td>
<td>Digoxin, furosemide, prazosin</td>
</tr>
<tr>
<td>5*</td>
<td>36</td>
<td>M</td>
<td>AI</td>
<td>$\frac{1}{2}$</td>
<td>III</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>MR</td>
<td>4</td>
<td>III</td>
<td>Digoxin, furosemide, prazosin, alpha-methyl-dopa</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>CAD</td>
<td>6</td>
<td>III</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>M</td>
<td>MR</td>
<td>$\frac{1}{2}$</td>
<td>IV</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>M</td>
<td>Hypertension</td>
<td>2</td>
<td>IV</td>
<td>Digoxin, furosemide, isosorbide dinitrate</td>
</tr>
</tbody>
</table>

*History of intravenous drug abuse.

Abbreviations: CAD = coronary artery disease; Etoh = alcoholic cardiomyopathy; PMD = primary myocardial disease; AI = aortic insufficiency; MR = mitral regurgitation; CHF = congestive heart failure.

A pulmonary loading dose of sodium paraaminohippurate (Merck, Sharp, and Dohme, Inc., West Point, Pennsylvania) and iothalamate meglumine (Malinkrodt, Inc., St. Louis, Missouri) was followed by a constant infusion of these compounds in isotonic dextrose in water at 1 ml/min for renal clearance measurements. The patients remained supine for the entire protocol, with the head of the bed elevated 20–30°, and were allowed free access to water during the study.

The protocol involved four separate periods: control 1, nitroprusside, control 2 and hydralazine. After the completion of urine collections and hemodynamic measurements during control 1, sodium nitroprusside (Roche Laboratories, Nutley, New Jersey), was administered at a starting dose of 5 μg/min. The infusion rate was gradually increased until thermodilution cardiac outputs showed that the increase in output had plateaued. The mean infusion rate was 131 μg/min (range 7–425 μg/min). At this time, urine collections and hemodynamic measurements were repeated. The nitroprusside was discontinued and the patient allowed to return to baseline for 30–90 minutes. Repeat control measurements (control 2) were then taken in a similar manner. After control 2, hydralazine (CIBA Pharmaceutical Company, Summit, New Jersey), was administered intravenously, 5 mg every 10–20 minutes. The mean total dose of hydralazine averaged 34 mg (range 10–60 mg). One and one-half to 2 hours after the first dose of hydralazine was given, measurements were again made.

Heart rate, systemic arterial pressure, pulmonary artery pressure, and pulmonary capillary wedge (PCW) pressures were recorded twice during each of the four periods; the two measurements in each period were averaged. The pulmonary artery diastolic pressure was used in two patients as an approximation of left atrial pressure when the PCW pressure could not be obtained. CO was measured by the thermodilution technique using a Santa Barbara Technology 1700 cardiac output computer (Santa Barbara, California). At least five measurements of CO were done twice during each period. The following were derived from these data: cardiac index (CI) = CO/body surface area in square meters (m²); total systemic resistance (TSR) = mean systemic arterial pressure (MAP)/CO; pulmonary vascular resistance = (mean pulmonary artery pressure − mean PCW)/CO; stroke volume (SV) = CO/heart rate; stroke volume index (SVI) = SV/m²; left ventricular stroke work index (LVSWI) = (aortic systolic pressure − aortic diastolic pressure) × 0.8 + (aortic diastolic pressure − PCW) × 0.136 × SVI.

During each period, urine was collected for renal clearance measurements. In the seven patients with bladder catheters, three 10–20-minute collections were made, and blood samples obtained at the midpoint of the first and third periods. In the other two patients, urine was obtained by spontaneous voiding during each period, with blood samples at the beginning and end of each period. All measurements during a single control or experimental period were averaged to provide a single value for each patient under each condition. GFR was calculated from the clearance of iothalamate, effective renal plasma flow (RPF) from the clearance of PAH, and RBF from RPF/(1 – hematocrit). Arterial hematocrit was measured in heparinized glass capillary tubes in each period. Filtration fraction (FF) was derived from the ratio GFR/RPF, and total renal resistance (TRR) from MAP/RBF. Plasma and urine were analyzed for PAH by the method of Harvey and Brothers,¹⁴ iothalamate by fluorescence excitation,¹⁵ and sodium and potassium by flame photometry using lithium as the internal standard. Sodium (U NaV), potassium
(U_KV), and total cation (U_{Na+K}V) excretion are expressed in μEq/min.

**Statistical Methods**

For each variable, the mean ± SD was calculated by standard methods. A two-tailed t test for the significance of the mean difference between paired samples was done for the measured parameters comparing control 1 and nitroprusside; control 2 and hydralazine; control 1 and control 2; and nitroprusside and hydralazine.

**Results**

The data are summarized in tables 2 and 3. There were no statistically significant differences between the two control periods in any of the variables measured. The clinical diagnosis of low-output congestive heart failure was substantiated by the extremely depressed CI and markedly elevated PCW pressure in all patients (table 2). Resting heart rate was somewhat elevated with normal MAP. Total systemic and pulmonary vascular resistances were moderately elevated. RBF was so depressed that despite the reduced CO, the ratio RBF/CO was only 10% (table 3). Likewise, resting GFR was decreased approximately 45% from average normal values. The FF was 0.30 ± 0.11, higher than the value of 0.20 seen in normal man. All of these findings are characteristic of the systemic and renal hemodynamic manifestations of low-output congestive heart failure.

**Hemodynamics (table 2)**

The end point used to evaluate drug effect was the occurrence of a plateau in CO augmentation despite further added doses of a drug. CI increased in all patients with both treatment drugs, and was significantly greater for hydralazine than for nitroprusside (70% vs 35%; p > 0.05). MAP fell with both drugs. The decrease in MAP with nitroprusside averaged 12% and with hydralazine 11%. TSR decreased in all patients with both agents: 35% with nitroprusside and 44% with hydralazine.

Mean pulmonary artery pressure decreased in all patients with nitroprusside and in five with hydralazine; the 24% decrease with nitroprusside was significantly greater than the 16% average decrease with hydralazine. PCW pressure fell in all patients with nitroprusside and in seven with hydralazine. The overall decrease in wedge pressure with nitroprusside averaged 29% from a control mean of 26 mm Hg. Pulmonary vascular resistance decreased in all patients with nitroprusside (34%) and in eight with hydralazine (40%).

LVSWI increased 28% with nitroprusside and 49% with hydralazine. All patients had an increase in LVSWI with hydralazine and seven had an increase with nitroprusside. When SVI and LVSWI were related to PCW pressure, hydralazine caused greater increases in SVI and LVSWI, while nitroprusside lowered PCW pressure more. This observation is consistent with the mixed effects of nitroprusside on resistance (arteriole) and capacitance (vein) vessels; hydralazine acts principally on resistance sites only.

**Renal Function (table 3)**

Nitroprusside infusion caused RBF to increase in seven of the nine patients; with hydralazine, RBF increased in eight of the nine. The mean increases were

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**Table 2. Hemodynamic Effects of Afterload Reduction**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nitroprusside*</th>
<th>p</th>
<th>Control</th>
<th>Hydralazine†</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (1/min/m²)</td>
<td>2.1 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>&lt;0.001</td>
<td>2.0 ± 0.6</td>
<td>3.4 ± 0.9</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>22.8 ± 5.1</td>
<td>16.2 ± 3.6</td>
<td>&lt;0.001</td>
<td>25.6 ± 5.4</td>
<td>19.4 ± 5.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>91.4 ± 13.5</td>
<td>89.3 ± 12.9</td>
<td>NS</td>
<td>93.9 ± 16.2</td>
<td>98.1 ± 13.2</td>
<td>NS</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>23.7 ± 7.5</td>
<td>32.2 ± 7.8</td>
<td>&lt;0.001</td>
<td>22.6 ± 8.4</td>
<td>35.6 ± 10.8</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84 ± 20.4</td>
<td>73.8 ± 15.6</td>
<td>&lt;0.002</td>
<td>88.6 ± 25.5</td>
<td>78.6 ± 24.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TSR (units)</td>
<td>23 ± 5.4</td>
<td>15.1 ± 3.9</td>
<td>&lt;0.001</td>
<td>27.2 ± 3.0</td>
<td>13.5 ± 4.8</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>38.8 ± 10.8</td>
<td>29.6 ± 7.8</td>
<td>&lt;0.001</td>
<td>41.3 ± 10.2</td>
<td>34.9 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>4.5 ± 2.4</td>
<td>3.0 ± 1.8</td>
<td>&lt;0.005</td>
<td>4.6 ± 2.4</td>
<td>2.7 ± 1.5</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>LVSWI (g-m/m²)</td>
<td>27.9 ± 12.3</td>
<td>35.6 ± 11.4</td>
<td>&lt;0.01</td>
<td>28.8 ± 16.2</td>
<td>42.9 ± 16.2</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

*Infusion rate of nitroprusside = 131 ± 49 μg/min.
†Total dose of hydralazine = 34 ± 6 mg.

Abbreviations: MAP = mean arterial pressure; PCW = mean pulmonary capillary wedge pressure; SVI = stroke volume index; CI = cardiac index; PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; TSR = total systemic resistance; LVSWI = left ventricular stroke work index; HR = heart rate.
Nitroprusside increased RBF 33% over control; hydralazine increased it 126%. Despite this greater average effect of hydralazine on RBF, the effects of the two drugs were not statistically different from each other. The increases in RBF seen with both nitroprusside and hydralazine were in proportion to the increases in CO. RBF was 9–10% of CO during control periods. After nitroprusside, RBF remained 10%, and after hydralazine, it was 13% of CO, a value not significantly greater than that during control or nitroprusside infusion.

The effects of afterload reduction of GFR are also illustrated in figure 1. There were no significant changes in GFR with either nitroprusside or hydralazine for the group as a whole. However, six patients responding to nitroprusside with an increase in RBF greater than 10% of control had an increase in GFR; these patients tended to have a subnormal control GFR (fig. 1). Two patients had a 10% fall in GFR when RBF changed little or decreased in response to nitroprusside. One patient had a moderate decrease in GFR with both drugs while RBF decreased with nitroprusside and was unchanged with hydralazine. GFR was near normal, however, during all periods in this patient. With hydralazine, six patients had an increase in GFR greater than 5% of control, one a decrease and two were unchanged.

Although a consistent change in GFR could not be confirmed statistically, an overall relationship between GFR and RBF could be distinguished in these patients. When the absolute changes in RBF and GFR were compared (fig. 2), increases in GFR occurred only when RBF also increased. This relationship appeared more pronounced with nitroprusside than with hydralazine. There was no apparent relationship between GFR and any change in renal or systemic resistance, the starting absolute RBF, or the control GFR.

![Response of renal blood flow (top) and glomerular filtration rate (GFR) (bottom) to vasodilator therapy with nitroprusside and hydralazine; points with lines represent means ± SEM. Renal blood flow increased regularly with both drugs; GFR did not increase significantly with either drug, but patients with lower control GFRs tended to increase GFR after drug infusion.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.96.5.932?bean安然為客人在11月5日, 2017年下载自http://circ.ahajournals.org)
Urine flow increased from 1.0 ± 0.4 ml/min during control 1 to 2.7 ± 1.9 ml/min during nitroprusside infusion. The increase from 1.9 ± 1.3 to 2.4 ± 2.1 ml/min after hydralazine was not significant. Total cation excretion (\(U_{Na} + U_K\)) increased with both nitroprusside and hydralazine; although both \(U_{Na}\) and \(U_K\) increased after drug administration, these increases were of marginal significance, except in the case of \(U_K\) after hydralazine (table 3). Although there was little change in GFR, the fraction of RPF filtered (table 3) fell toward normal owing to the marked increase in blood flow with both drugs.

Discussion

The acute hemodynamic effects of intravenous nitroprusside and hydralazine in our patients with low-output congestive heart failure are similar to those observed by other investigators.\(^2\) \(^3\) \(^6\) \(^10\) MAP decreased a small amount with both agents despite marked augmentation in CO, while an increase in heart rate did not occur. Nitroprusside affects both resistance and capacitance vessels, lowering left ventricular filling pressure as well as systemic resistance.\(^5\) \(^10\) Hydralazine has its principal effect on arteriolar resistance vessels.\(^2\) \(^3\) Although the effect of hydralazine on the ventricular function curves was somewhat different, we did observe a significant reduction in pulmonary vascular resistance and PCW pressure with this drug. The effect has been described,\(^2\) \(^5\) although Chatterjee and co-workers\(^3\) \(^4\) did not observe any significant change in wedge pressure in their patients. The difference between our results and those of Chatterjee et al. are probably due to the dose and route of administration. Packer et al.\(^12\) found significant reductions in PCW pressure only with higher doses of hydralazine (100 mg orally), a dose similar to that used by Franciosa et al.\(^2\) \(^5\)

Our results indicate that administration of these vasodilators to patients with CHF is associated with a marked increase in RBF and a decrease in TRR and FF. These responses seem directly attributable to the consequences of the drug infusions, and not to spontaneous or diurnal changes. In normal man, GFR is lowest at night and reaches maximum values during late morning;\(^16\) patients with pathologic states of sodium retention such as CHF or cirrhosis of the liver exhibit a reversal of this normal diurnal pattern.\(^17\) \(^18\)

However, the prompt improvement in renal hemodynamics seen in our study were temporally very closely related to drug administration and, in the case of nitroprusside, were rapidly reversed when the drug infusion was stopped. The longer half-life of hydralazine precluded a final, post-drug control period in these acute studies. Moreover, the magnitude of the increase in RBF is much greater than generally reported to occur as a result of diurnal fluctuations.\(^16\)

It is also possible that the discontinuation of digitalis preparations and diuretics before the study could have resulted in an unstable background due to progressive diminution of the pharmacologic effects of these agents during the study period. If anything, this would be expected to produce a deterioration of renal and cardiac function, yet vasodilator therapy was nevertheless very successful in improving systemic and renal hemodynamics. The comparability of the second control period, after nitroprusside infusion, to the initial control, also suggests that this drug did not cause any long-lasting effects that might have influenced the response to the subsequently administered hydralazine. Thus, the pattern of renal response to these vasodilating agents appears directly attributable to the agents themselves and not to variations associated with the experimental design.

In 1929, Johnson reported that nitroprusside caused an increase in RBF when injected into an isolated, pump-perfused kidney.\(^19\) This study was the first to document a direct vasodilatory effect of nitroprusside on the kidney. In an isolated, denervated kidney, perfused orthotopically from the femoral artery of a second dog, RBF increased when nitroprusside was administered to the intact animal.\(^20\) Renal perfusion pressure was controlled in this study, and no increase in GFR occurred despite the increase in RBF. Hydralazine has also been shown to increase RBF without augmenting GFR in normal and hypertensive patients\(^21\) and in dogs.\(^22\) These observations have been duplicated with a number of vasodilating agents infused into experimental animals. The increase in RBF produced by vasodilators, in association with constancy in GFR, results in a decrease in TRR and FF. In our patients with congestive heart failure, administration of nitroprusside or hydralazine also increased RBF without a significant change in GFR. As a consequence, the abnormally elevated FF and TRR so characteristic of renal hemodynamics in congestive heart failure were improved toward normal values.
Thus, afterload reduction exerted a beneficial effect on renal as well as systemic hemodynamics in these patients.

It is interesting to speculate on the mechanisms influencing GFR in this study. Four major determinants of GFR have been identified: the net hydrostatic pressure gradient across the glomerular capillary membrane ($\Delta P$), the colloid osmotic pressure across the capillary generated by the plasma proteins ($\Delta \pi$), the glomerular ultrafiltration coefficient ($K_f$), and glomerular plasma flow (GPF). In the dog, $\Delta P$ exceeds $\Delta \pi$ at the end of the glomerular capillary, a situation referred to as filtration pressure disequilibrium. This situation is characterized by a relatively small effect of GPF on GFR: increases in GPF produced by volume expansion or vasodilating agents are not accompanied by increases in GFR, and $\Delta P$ is the primary determinant of GFR. In the rat, however, filtration pressure equilibrium occurs, a setting in which increases in GPF are associated with proportional increases in GFR. The failure of vasodilating agents to increase GFR in the rat despite marked increases in plasma flow has been interpreted as due to a decrease in $K_f$ offsetting the increase in GPF.

The forces governing glomerular ultrafiltration in man have been less well defined, but it is likely that filtration pressure disequilibrium exists, because increases in RPF produced by vasodilating agents are not accompanied by increases in GFR. Measurement of renal hemodynamics in patients with CHF supports this formulation, because GFR is often well preserved despite marked reductions in RBF. This would suggest that $\Delta P$ is the primary determinant of GFR in both normal man, and patients with congestive heart failure. Assuming that $\Delta \pi$ (determined chiefly by plasma protein concentration) and $K_f$ were not changed by vasodilator administration in our patients with congestive heart failure, GFR would be influenced by $\Delta P$ and GPF. It seems reasonable to assert that at least a portion of the increase in RBF caused by the drugs would pass through the glomerular circulation, leading to an increase in GPF. The fact that GFR on average was unchanged despite this increase in GPF would suggest that GFR in these patients was not sensitive to GPF and, therefore, that glomerular dynamics might be operating under conditions of filtration pressure disequilibrium. However, GFR rose in many of the patients after drug administration, even though the average changes were not significant. Also, MAP decreased during drug therapy, in some cases quite markedly. As a consequence, $\Delta P$ in all likelihood also decreased, thereby leading to a decrease in glomerular ultrafiltration. It seems likely that the lack of overall change in GFR reflects the resultant of these two competing factors, the decrease in arterial pressure and $\Delta P$ offsetting any increase in GPF produced by an increase in GPF. Our data suggest that increases in GFR may indeed occur in response to vasodilator therapy in some patients if arterial pressure does not fall appreciably. To this extent, glomerular dynamics in these patients with congestive heart failure may be operating under conditions of filtration pressure equilibrium, as opposed to the situation in normal man. The observations of Judson and associates are also consistent with this view. The alternative possibility, that vasodilators decrease $K_f$ and thereby restrict the increase in GFR due to increased plasma flow, cannot be assessed in man at present.

Renal vasodilation regularly increases $U_{\text{NaV}}$ and $U_{\text{R}}$V in experimental animals. This effect has been attributed to the decrease in colloid osmotic pressure and increase in hydrostatic pressure in the postglomerular capillary circulation caused by vasodilation. These in turn lead to diminished reabsorption of filtrate in the proximal tubule and subsequent natriuresis and kaliuresis. This effect in our patients was small and only achieved statistical significance when total cation excretion was considered. The reasons for this modest response could reflect the tendency toward hypotension produced by these agents, which thereby limits their natriuretic effects, and also indicate a high degree of distal compensation for increased delivery out of the proximal tubule. LeJemtel and co-workers found no consistent increase in 24-hour urine sodium excretion despite augmented cardiac output after afterload reduction in patients with congestive heart failure, while Judson and colleagues observed an increase in $U_{\text{NaV}}$ after acute hydralazine administration.

The effects of nitroprusside or hydralazine administration on systemic and renal hemodynamics in intact animals and man have been somewhat controversial. In the intact dog, nitroprusside decreased total peripheral resistance and MAP without increasing CO; these changes were associated with decreases in GFR, RBF and $U_{\text{NaV}}$. Similarly, nitroprusside failed to increase RBF when administered to seven normal subjects in one study, and decreased both RBF and arterial pressure in a study of anesthetized patients undergoing nephrolithotomy. In a few of our patients, the same phenomena were observed: hypotension appeared to predominate, and RBF either did not change or even fell. Thus, the beneficial effect of afterload reduction on renal hemodynamics appears dependent on the ability of CO to increase sufficiently to maintain arterial pressure at or near baseline levels. Similar results to those in our study were obtained by Judson and associates after intravenous administration of hydralazine. Arterial pressure fell from 129 to 110 mm Hg in their patients, and was accompanied by improvement in both systemic and renal hemodynamics and an increase in electrolyte excretion. Their results suggest that a fall in blood pressure well within the renal autoregulatory range may still permit the beneficial hemodynamic consequences of hydralazine to be manifested. Our patients as a group had lower MAP, near the lower end of the autoregulatory range, and it fell less markedly after vasodilator therapy.

The renal fraction of CO was not altered with administration of either nitroprusside or hydralazine, suggesting that the increase in RBF was not out of
proportion to flow through other vascular beds. However, this interpretation depends critically on $C_{PAH}$ as an indicator of RBF. Renal extraction of PAH ($E_{PAH}$) was not measured in our patients; if vasodilator therapy decreased $E_{PAH}$, then $C_{PAH}$ would underestimate RPF and hence RBF. To the extent of this effect, RBF would then assume a greater proportion of CO then the 10–13% estimated using $C_{PAH}$ uncorrected for extraction. Pagani, Vatner and Braunwald8 have demonstrated that nitroprusside infusions have different effects on regional blood flows in conscious dogs. The coronary circulation showed the most pronounced decrease in resistance and increase in blood flow to nitroprusside, with mesenteric and renal beds showing a lesser response. The iliac circulation actually showed an increase in resistance and a decrease in flow. Evidence also exists to indicate that hydralazine may have different effects on various regional vascular beds. Whatever the changes in distribution of CO caused by these agents in our patients, the renal response appeared closely related to the increase in CO that resulted.

In conclusion, the acute administration of hydralazine and nitroprusside resulted in systemic and renal hemodynamic improvement in patients with advanced congestive heart failure. TRR was decreased by both drugs and RBF significantly increased. The percentage of CO received by the kidney was initially reduced and was not markedly changed after administration of both agents. GFR was not changed with either hydralazine or nitroprusside, even though mean arterial pressure fell significantly with each agent; in selected patients in whom RBF increased by more than 10% from control, increases in GFR were seen. FF decreased toward normal with both medications. The excretion of total cation was significantly elevated over control with both drugs. These changes all represent corrections toward normal in the systemic and renal hemodynamic abnormalities occurring in congestive heart failure. The maintenance of these responses during long-term therapy would facilitate the management of patients with severe congestive heart failure.

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References


Effect of Hydralazine on Renal Failure in Patients with Congestive Heart Failure

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SUMMARY Hydralazine is known to improve cardiac function in patients with congestive heart failure (CHF), but its effects on renal function in CHF are less clear. Sodium retention is known to occur with long-term use of hydralazine to treat hypertension; if this occurs in patients with CHF it could be deleterious. Therefore, in a metabolic unit we studied renal effects of hydralazine in patients with stable class III or IV CHF. In a single-blind study, the patients were given placebo twice daily for 3 days (period P-1), 100 mg of oral hydralazine twice daily for 3 days (period P-H), and placebo for 3 more days (period P-2). The average 24-hour creatinine clearance was 69.7 ± 7.7 ml/min (mean ± SEM) in P-1, increased to 76.3 ± 9.0 ml/min with hydralazine (p < 0.01) and fell again when hydralazine was stopped (P-2) to 68.5 ± 7.8 ml/min (p < 0.02). Though the slight improvement in sodium excretion was not statistically significant (60.2 ± 12.1 mEq in P-1, 64.5 ± 12.4 mEq in P-H, 52.3 ± 7.7 mEq in P-2), serum osmolality decreased from 288 ± 1.8 mosM in P-1 to 283 ± 1.9 mosM in P-H (p < 0.02) and rose to 286 ± 1.9 mosM in P-2 (NS). During the three periods, serum sodium, chloride, potassium, carbon dioxide, blood urea nitrogen, creatinine and glucose were unchanged, as were weight and urine volume. Systolic blood pressure was 109.6 ± 3.6 mm Hg in P-1, 110.1 ± 3.9 mm Hg in P-H (NS), and 114.2 ± 5.0 mm Hg in P-2 (p < 0.05). Diastolic blood pressure, heart rate and respirations were unchanged. Thus, we found no evidence of sodium or water retention during hydralazine administration in patients with CHF, and renal function was actually improved, as evidenced by the increased creatinine clearance.

HYDRAZALINE improves left ventricular performance in patients with congestive heart failure (CHF) and may be effective for long-term oral therapy of patients with chronic CHF. However, hydralazine can lead to sodium and fluid retention when used to treat hypertension, and sodium retention has been reported during administration of hydralazine in a patient with CHF. Such a response to hydralazine in patients with CHF might limit the value of this drug for long-term therapy or necessitate larger doses of diuretics. The present study assesses the effects of hydralazine on renal function and sodium balance in patients with CHF.

Methods

Nine male patients with New York Heart Association functional class III or IV heart failure (three class IV and six class III) who were on conventional therapy were studied. The patients were ages 47–64 years (average 59 years). Three of the patients had primary myocardial disease and six had ischemic heart disease. Exclusion criteria included: insulin-dependent diabetes mellitus, severe pulmonary disease (PO2 < 50 mm Hg or PCO2 > 50 mm Hg), renal insufficiency (BUN > 40 mg/dl or creatinine > 2.0 mg/dl), abnormal serum electrolytes, angina requiring nitrate therapy, myocardial infarction within the past 3 months, significant primary heart valve disease, hypertension requiring nonguandant antihypertensive agents or heart failure due to restrictive heart disease. After giving written informed consent, the patients were admitted to a special diagnostic and treatment unit (SDTU) of the Minneapolis Veterans Administration Medical Center for evaluation. All patients were clinically stable with a steady body weight when admitted to the SDTU. All patients were

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