SUMMARY

The effects of chronic oral vasodilator therapy were studied in a group of patients with refractory congestive heart failure. Fifteen patients were treated acutely with intravenous sodium nitroprusside and sublingual isosorbide dinitrate. After continuous therapy with nitroprusside and isosorbide dinitrate for up to 72 hours the patients were then placed on isosorbide dinitrate and oral phenoxymethylamine. Hemodynamic responses to nitroprusside, isosorbide dinitrate, and phenoxymethylamine with isosorbide dinitrate were determined. After a mean follow-up of seven months, nine patients who were receiving isosorbide dinitrate and phenoxymethylamine underwent repeat hemodynamic studies.

Beneficial effects of acute vasodilator therapy included a significant reduction in pulmonary capillary wedge pressure and systemic vascular resistance, and significant increases in cardiac index and stroke work index. Mean arterial blood pressure and heart rate were unchanged. During the period of chronic vasodilator administration, no other change in basic therapy was made. In the nine patients who underwent repeat therapy with isosorbide dinitrate and phenoxymethylamine (3-21 months), the favorable effects observed acutely were maintained. All patients demonstrated symptomatic improvement with minimal side effects.

The beneficial hemodynamic responses that are noted with acute vasodilator therapy in patients in advanced congestive heart failure are maintained with oral therapy on a chronic basis.

A NUMBER OF RECENTLY PUBLISHED STUDIES have demonstrated the effectiveness of vasodilating agents in the acute management of refractory congestive heart failure. Cohn et al. have described the use of vasodilator drugs in the chronic management of a patient with intractable congestive heart failure secondary to ischemic heart disease.

In the current study we determined the effects of chronic oral vasodilator therapy in a group of patients with refractory heart failure secondary to a variety of etiologies and compared these effects with those achieved acutely with nitroprusside.

Materials and Methods

Patient Population

Fifteen patients were referred for study who were judged to be refractory to maximal conventional therapy for congestive heart failure. All patients were on a low sodium diet, oral digoxin in what was considered maximal therapeutic dose range, and furosemide in doses ranging from 120 to 800 mg per day. Six patients had been at bed rest from two to six months. All patients were judged to be class 4 (New York Heart Association classification).

Ten patients had undergone cardiac catheterization to exclude the presence of surgically remediable lesions. The remaining five had primary myocardial disease on the basis of history, physical exam, chest X-ray, electrocardiogram, and echocardiogram. Careful medical evaluation was done to rule out extra-myocardial factors which might contribute to the intractable state of myocardial dysfunction. All patients at the time of referral were hospitalized because of refractory congestive heart failure. The patients and diagnoses are listed in table 1.

Four of the five with ischemic cardiomyopathy had undergone cardiac catheterization. Each demonstrated diffuse coronary disease with poor left ventricular function and were judged not to be operative candidates. Each had experienced one or more prior infarctions. The fifth patient with ischemic disease had experienced three prior myocardial infarctions, recurrent ventricular tachycardia, and episodic acute pulmonary edema. No patient experienced an acute myocardial infarction within six months prior to the period of study.

Two patients had a viral cardiomyopathy, four an alcoholic myopathy, one postpartum cardiomyopathy, and two had cardiomyopathy of unknown cause. The remaining patient had undergone aortic valve replacement for rheumatic valvulitis five years prior to study. Follow-up catheterization showed no evidence of prosthetic valve dysfunction and normal coronary arteries.

The purpose of the study was carefully explained to each patient and his family and informed written consent was obtained.

Hemodynamic Measurements

Right atrial (RA), pulmonary artery (PA), and pulmonary capillary wedge (PCW) pressures were measured through a balloon-tip triple lumen catheter. Monitoring and recording of the pressures were done on Hewlett-Packard 7702B and 780-9 recorders utilizing Hewlett-Packard 1280 C pressure transducers. Cardiac outputs (CO) were performed in triplicate by the thermodilution technique utilizing the same catheter.

Individual variation was 5 to 10%. Cardiac output computations were performed by Edwards cardiac output computers, models 9500A or 9510. Arterial blood pressure (BP) was monitored either by a 20 gauge cannula inserted into the radial artery with the phasic and mean values recorded by the above equipment or, in those patients on follow-up who had an adequate and easily audible blood
pressure, by obtaining multiple cuff readings which were averaged. Where the cuff method was used, the mean arterial pressure (AP) was calculated arithmetically by the formula \( \frac{S + 2D}{3} \). This value agreed favorably when compared to a mean value obtained by electronic damping. Derived values were calculated as follows:

Cardiac Index (CI) = cardiac output (CO)/body surface area (BSA) \((\text{L}/\text{min}/\text{m}^2)\)

Stroke Volume Index (SVI) = SV/BSA \((\text{ml}/\text{m}^2)\)

Stroke Work Index (SWI) = SVI \((\text{BP} - \text{PCW})\) \((\text{1.36} \times 10^3 \text{ g-m}/\text{m}^3)\)

Systemic Vascular Resistance (SVR) = \(\frac{\text{BP} - \text{RA}}{\text{CO} \times 80} \text{ (dynes-sec cm}^{-5}\)

Pulmonary Vascular Resistance (PVR) = \(\frac{\text{PA} - \text{PCW}}{\text{CO} \times 80} \text{ (dynes-sec cm}^{-5}\)

**Vasodilator Therapy**

Electrocardiograms, chest films, echocardiograms, serum electrolytes, creatinine, CBC, lactic dehydrogenase, serum glutamic oxaloacetic transaminase, and creatine phosphokinase were obtained prior to vasodilator therapy. Baseline hemodynamic values were obtained with the patients receiving their usual medications. During the acute study period no change in the dosage of medication was made other than an observed consistent reduction in the need for diuretics. No patient was receiving any antihypertensive medication at the time of study. Nitrates were not required by any of the patients with ischemic heart disease for at least 24 hours prior to the study.

**Nitroprusside**

Sodium nitroprusside (NP) was administered after obtaining baseline values by means of a controlled flow infusion.* The infusion was begun at a dose of 15 \(\mu\text{g}/\text{min}\) and the dose gradually increased until a significant decrease in the pulmonary capillary wedge (PCW) pressure occurred or the mean arterial blood pressure (AP) fell more than 20 mm Hg. The dose range of nitroprusside administered was 15–150 \(\mu\text{g}/\text{min}\). When a constant infusion rate of nitroprusside was obtained hemodynamic measurements were repeated.

**Trinitroglycerin**

The nitroprusside infusion was discontinued and pressures were allowed to return to control levels. Eight patients then received 0.6 mg of trinitroglycerin (TNG) sublingually. Hemodynamic parameters were followed and CI determined at time intervals of 5, 15, 30, and 60 minutes, or until the pressures had returned to control levels.

**Isosorbide Dinitrate**

Twelve patients received sublingual isosorbide dinitrate (I) in a dose of 5 mg. Hemodynamic variables were monitored and CI determined at time intervals of 5, 15, 30, 60, and 90 minutes, or until pressures had returned to control levels.

**Continuous Therapy**

At the conclusion of the above interventions the patients were begun on a constant infusion of sodium nitroprusside, at a rate previously determined to be optimal and sublingual isosorbide dinitrate (5 mg) was given at an interval of every two hours. Therapy was continued for 24–72 hours in a special care unit with constant monitoring of electrocardiogram, arterial blood pressure, PA, and PCW pressures. Cardiac index determinations were made at periodic intervals. Digitalis, anti-arrhythmics, and diuretics were continued as needed. Assessment of subjective symptoms was noted. At the end of this period all in-dwelling catheters were removed and the patients were advanced to chronic therapy.

**Chronic Therapy**

Based on the objective and subjective response to continuous therapy, 12 patients were placed on an oral regimen of vasodilators to supplement their standard therapy. This consisted of sublingual isosorbide dinitrate (2.5–10 mg) every two hours while awake and phenoxybenzamine hydrochloride (10 mg capsules) given every 8 to 12 hours and the dosage was titrated for each patient. The dose of the latter was adjusted by arterial blood pressure response and the avoidance of significant orthostatic changes. The dosage and response were carefully evaluated before discharge. The patients were followed as outpatients by their own physicians and by the authors on a regular basis. Periodic blood chemistries, electrocardiograms, echocardiograms, chest X-rays, and physical assessment were performed. Repeat hemodynamic measurements were obtained in nine patients at various intervals after oral therapy was initiated. The results were analyzed using the Student's \(t\)-test and a \(P < 0.05\) was considered significant.

**Results**

**Sodium Nitroprusside**

The hemodynamic changes observed with nitroprusside administration are detailed in table 2. The mean responses, standard error of the mean, and \(P\) values are listed. No significant changes in heart rate (HR) or mean arterial pressure (MAP) were observed. Mean right atrial (MRAP),
pulmonary artery (MPAP), pulmonary capillary wedge (MPCW) pressures and systemic vascular resistance (SVR) were uniformly decreased. The individual responses varied but those patients with control values closer to normal tended to show a lesser degree of change, consistent with the observations of others.1, 6 Figure 1 shows the individual responses of the pulmonary capillary wedge pressure to nitroprusside infusion and the direction and magnitude of change in the cardiac index. In all cases the PCW fell and in all but one case the CI rose. In that case the CI was unchanged as the PCW was reduced. The increase in mean stroke work index (SWI) was commensurate with an increase in stroke volume (SV) and decrease in PCW. No electrocardiographic evidence of acute ischemia was observed.

The changes in pulmonary vascular resistance (PVR) were variable, with the reduced mean value not quite reaching statistical significance (0.1 > P > 0.05). The majority of patients with an elevated PVR did show some reduction. The elevated PVR observed was consistent with chronic left ventricular failure.

In several patients during the course of the nitroprusside infusion, a noticeable reduction in ventricular ectopy was observed as hemodynamic improvement occurred.

**Trinitroglycerin**

Table 3 shows the time of peak hemodynamic effect and duration of action of 0.6 mg sublingual trinitroglycerin in eight patients. The mean peak effect occurred 8.5 min after administration and the mean duration of action was 36 min. This is consistent with the time course of action as reported by Gold et al.6 At the time of peak effect the percent reduction in PCW is shown.

**Isosorbide Dinitrate**

The time of peak effect and duration of action of 5 mg sublingual isosorbide dinitrate was noted in the same eight patients and is shown in table 4. The mean peak effect occurred at 19 min and the mean duration of action was 72.5 min. The percentage reduction in PCW is presented. The major difference observed for the doses used was in the duration of action rather than in the magnitude of the response. The response of the mean PCW and time course of action of TNG compared to that of isosorbide dinitrate is shown in figure 2.

**Table 2. Hemodynamic Response to Sodium Nitroprusside Infusion**

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<thead>
<tr>
<th>Patient</th>
<th>HR (beats/min)</th>
<th>MABP (mm Hg)</th>
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<th>MPCW (mm Hg)</th>
<th>CI (L/min/m²)</th>
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*Abbreviations: HR = heart rate; MABP = mean arterial blood pressure; MPAP = mean right arterial pressure; MPAP = mean pulmonary artery pressure; MPCW = mean pulmonary capillary wedge pressure; CI = cardiac index; SWI = stroke work index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; C = control; NP = sodium nitroprusside.*

**Figure 1** Individual responses of wedge pressure and cardiac index to nitroprusside administration.
patients is shown in table 5. In three patients the data collection was incomplete for accurate analysis. A decrease in heart rate was observed but was not significant. As with nitroprusside the MABP was not significantly reduced and CI rose. The individual responses of the CI to changes in PCW with isosorbide dinitrate are shown in figure 3. In 11 of 12 patients the CI rose as the PCW fell. One patient maintained the same CI with a marked reduction in filling pressure.

The mean SWI rose, and as with nitroprusside, the increase was not accompanied by electrocardiographic evidence of ischemia. The fall in mean SVR was significant but the response of the PVR was variable. Elevated values tended to show some reduction but the mean response was not significant.

Continuous Therapy

An example of the hemodynamic response of a representative patient to both acute and continuous therapy is depicted in figure 4. Following the determination of the responses and duration of action of nitroprusside, trinitroglycerin, and isosorbide dinitrate, continuous therapy with constant nitroprusside infusion and 5 mg of sublingual isosorbide dinitrate given every two hours was begun. The responses during and at the end of 36 hours of therapy showed a reduction in SVR and PCW with an increase in CO. During continuous therapy each of the 12 patients in whom data collection was complete demonstrated a marked

Table 4. Duration and Magnitude of Effect of Isosorbide Dinitrate

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<tr>
<th>Patient</th>
<th>Peak effect (min)</th>
<th>Duration of effect (min)</th>
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The results indicate that the initial favorable responses seen acutely can be maintained by continuous treatment for periods up to 72 hours.

Chronic Therapy

The effects of long-term sublingual isosorbide dinitrate and oral phenoxycbenzamine therapy were assessed in follow-up studies. Repeat hemodynamic measurements were obtained in nine patients. Of the remaining three in whom continuous therapy data was available, one died with ventricular arrhythmias two days after starting oral therapy and two are alive and well but unavailable for repeat catheterization. The duration of oral therapy at time of reassessment ranged from three to 21 months. The PCW, CI, echocardiographic left ventricular end-diastolic diameter, and duration of oral treatment are shown in table 6 under chronic therapy.

Compared to the control period, chronic oral vasodilator therapy over a mean of seven months was marked by reduced HR (P < 0.05), MABP (P < 0.05), MPCW (P < 0.001), SVR (P < 0.02), and Dd (P < 0.001). The CI (P < 0.02) and SWI (P < 0.02) were increased. During oral therapy, the enhanced SWI was not accompanied by clinical or electrocardiographic evidence of increased ischemia. The reduced MABP (P < 0.001) and improved CI (P < 0.001) obtained during acute continuous therapy were thus maintained during the chronic administration of isosorbide dinitrate and phenoxycbenzamine.

The reduction in cavity size measured by serial chest X-rays was not as evident as reduced LV cavity size measured by echocardiography. Each of the nine restudied patients showed relief of pulmonary vascular congestion on follow-

Figure 2 Mean duration of action of trinitroglycerin (TNG) compared to isosorbide dinitrate (I) as measured by changes in the pulmonary capillary wedge pressure (MPCW) in eight patients.

Figure 3 Individual responses of wedge pressure and cardiac index to isosorbide dinitrate administration.
up films but only three showed a measurable reduction in cardio-thoracic ratio.

The present status of each patient in the original study group is listed in Table 1. Of the original 15 patients entered into the study, three have died: one at two days, as noted above; one after two weeks on oral therapy with recurrent myocardial infarction; and the third four and one-half months after entering the study, of a noncardiac cause. All 12 of the survivors are judged to be clinically improved. Five patients have returned to full or part-time employment. One of the latter has also resumed his college studies on a full-time basis. All are currently being followed by their private physicians in conjunction with periodic follow-up by the authors. Their usual drug therapy has been continued in addition to the oral vasodilator agents. Diuretic requirements have been reduced.

**Table 5. Hemodynamic Response to Isosorbide Dinitrate**

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<tr>
<th>Patient</th>
<th>HR (beats/min)</th>
<th>MAPB (mm Hg)</th>
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*Patients 3, 4, and 6 not included; see text.

**Side Effects**

Periodic electrocardiograms, physical examination, and laboratory determinations have revealed minimal untoward effects. Two patients have noted sexual impotency. One patient had an uncomplicated episode of orthostatic hypotension during early oral therapy adjustment and three have noted mild nasal congestion. These effects are probably related to the phenoxybenzamine. None have noted any central nervous system or gastrointestinal symptoms. The dosage range of phenoxybenzamine has been from 20 to 80 mg per day. No adverse reactions associated with nitrates have been observed. At time of recatheterization, after follow-up hemodynamic values were obtained, each patient was given a sublingual isosorbide dinitrate tablet. Each showed a further reduction in PCW and increase in CI suggesting that tolerance to the nitrates had not developed during the follow-up period.

**Discussion**

The traditional therapy for congestive heart failure has relied upon digitalis and diuretics to reduce pulmonary venous pressure and re-establish cardiac reserve. The mechanical performance of the left ventricle is affected by the functional capacity of the muscle itself (contractility), the end-diastolic fiber length (preload), and the forces opposing ventricular ejection (afterload). A refractory state occurs when any further diuretic-induced reduction in preload moves a patient to an unfavorable position on a ventricular function curve and the inotropic stimulus of digitalis is insufficient to compensate for the reduced ventricular function. As cardiac output falls, blood pressure is supported by a catecholamine-mediated increase in SVR.

Afterload reduction by acute vasodilator treatment may result in an improvement in ejection fraction and thus allow for an enhanced cardiac output against reduced impedance. Furthermore, the reduction in residual end-systolic volume achieved by improved ejection results in a reduction in preload. The direct effects of nitroprusside and nitrates on venous tone produce an additional reduction in preload. This may be achieved without a commensurate reduction in

*FIGURE 4  Response of systemic vascular resistance (SVR), mean pulmonary capillary wedge pressure (MPWC), and cardiac output (CO) in a representative patient to acute and continuous therapy. Note the continued improvement with time during treatment with nitroprusside (NP) and isosorbide dinitrate (I). C = control; TNG = trinitroglycerin.*
CI because of the improved ejection characteristics of the ventricle.

An additional benefit of vasodilator therapy is a reduction in oxygen demand subsequent to a reduction in impedance to ejection (reduced pressure work) and to a reduction in wall tension secondary to the lower preload and thus decreased chamber radius. This is particularly important in patients with ischemic heart disease but is also operative in situations where subendocardial ischemia may result from unfavorable hemodynamic conditions even in the presence of normal coronary anatomy.19

In a number of patients with both primary myocardial disease and ischemic heart disease, mitral regurgitation caused by left ventricular dilatation, papillary muscle ischemia or both may develop. Vasodilators may directly or indirectly improve forward ejection in these patients by a reduction in impedance to ejection by reducing chamber size.20 In the present study the degree of mitral regurgitation could not be precisely estimated but a reduction in regurgitant flow may have been a significant factor in the hemodynamic improvement noted.

The major objective of our study was to determine the efficacy of chronic oral vasodilator therapy. All patients in the study group showed hemodynamic improvement with the acute reduction of afterload, demonstrating the same or an increased stroke volume at a lower left ventricular filling pressure. Follow-up studies demonstrated that chronically administered vasodilating agents resulted in comparable results. Afterload reduction did not result in a lowered mean arterial pressure or a reflex tachycardia, which would have had an adverse effect on the myocardial oxygen supply-demand relationship.

It had been observed that oral nitrates seem to exert a greater effect on venous than on arteriolar tone.5, 18 The hemodynamic result would be a disproportionate decrease in preload. In an attempt to achieve prolonged afterload reduction, phenoxybenzamine, an alpha-blocking agent, was added to the treatment regimen. It is possible that the major effect of the chronic therapy was a reduction in preload and the observed afterload reduction was secondary to an improved stroke volume. The direct contribution of alpha blockade could not be independently assessed. In the acute setting, however, preload reduction alone is probably not the major factor as, unlike the response with vasodilators, the stroke volume is not improved by a reduced venous return with tourniquets or phlebotomy.22

The results indicate that a sustained reduction in PCW pressure accompanied by a significant rise in CI can be achieved in the setting of refractory congestive heart failure by the use of isosorbide dinitrate and phenoxybenzamine on a chronic basis. The duration of action of isosorbide dinitrate appeared to be significantly greater than that of trinitroglycerin in the doses used. The improved efficiency of cardiac performance has allowed re-establishment of some degree of cardiac reserve in these patients and the reduction in pulmonary venous pressure has relieved the symptoms of dyspnea and orthopnea. The left ventricular chamber size as determined echocardiographically showed a small but consistent reduction with chronic therapy.

Despite the relatively few side effects seen in this study
with phenoxybenzamine, its slow time course of action and need for frequent follow-up in producing alpha blockade are potential disadvantages to its use. A potent oral medication which results in sustained vascular smooth muscle relaxation would be preferable to alpha blockade but no current medication fits those requirements. Investigation of certain antihypertensive medications for this purpose is underway. Despite these drawbacks this form of therapy appears to be safe, practical, and efficacious, a favorable hemodynamic response having been documented in nine patients.

The principle of chronic vasodilator therapy for the treatment of intractable congestive heart failure appears established: the continued search for more practical and better pharmacologic agents to achieve this end is clearly indicated.

Acknowledgments

The authors would like to acknowledge the technical assistance of Mr. Frank Titus, Mr. Joe Skidmore, Mr. Leonard Svidor, and the secretarial help of Mrs. Lori Fuees and Mrs. Pat Ritter.

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Circulation. 1976;53:322-328
doi: 10.1161/01.CIR.53.2.322
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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