Efficacy of Ambulatory Systemic Vasodilator Therapy with Oral Prazosin in Chronic Refractory Heart Failure

Concomitant Relief of Pulmonary Congestion and Elevation of Pump Output Demonstrated by Improvements in Symptomatology, Exercise Tolerance, Hemodynamics and Echocardiography

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SUMMARY  The long-term efficacy of the new oral vasodilator, prazosin (PZ), was evaluated in nine patients with refractory heart failure due to chronic coronary heart disease. Ventricular function was assessed by cardiac catheterization, echocardiography, and treadmill testing; symptomatic evaluation was carried out for two to four months. One hour following 2-7 mg PZ, control left ventricular filling pressure was reduced (32 to 18 mm Hg, P < 0.001) and cardiac index was elevated (1.95 to 2.80 L/min/m², P < 0.001) for a 6-hour period. After two weeks of PZ 2 to 7 mg four times daily, echographic end-diastolic dimension fell (5.7 to 5.4 cm, P < 0.001) while shortening fraction increased (27.6 to 30.2%, P < 0.005). Treadmill exercise duration increased from 209 to 317 seconds (P < 0.001). Symptoms diminished throughout the duration of follow-up (mean 94 days) with improvement in NYHA functional class (3.7 to 2.2, P < 0.001). Thus, prazosin possesses sustained nitroprusside-like balanced dilator actions on the systemic arterial and venous systems and is effective in the ambulatory management of chronic severe heart failure.

THE BENEFITS OF VASODILATOR THERAPY in patients with severe heart failure are now recognized.1-28 Thus ventricular unloading with intravenous nitroprusside produces improvement of cardiac dysfunction from acute and chronic coronary artery disease,2 4-6, 8-10, 15, 17, 18, 21-23 valvular heart disease,5, 8, 22 and cardiomyopathies.10 The salutary hemodynamic effects of this systemic vasodilator agent are related to its equal relaxation of the vascular smooth muscle of both the peripheral resistance and the capacitance vessels.23 As the result of this balanced dilator action on the systemic venous and arterial beds, ventricular preload reduction is accompanied by decline in aortic impedance, thereby leading to relief of pulmonary congestion simultaneously with enhancement of cardiac output. However, attempts to continue the benefits of such balanced ventricular unloading therapy in ambulatory patients with chronic heart failure have been difficult because of the lack of an oral vasodilator drug with both arterial and venous relaxing properties. Thus the nitrates, which principally cause venodilation, are capable of reducing ventricular preload and pulmonary congestion2, 15, 14, 16, 19, 20-25 but lack consistent effects on systemic impedance and therefore produce minimal alterations of cardiac output.14, 16, 18, 22-25
Hydralazine, on the other hand, improves cardiac output by means of impedance reduction via peripheral arterial dilation; however, the agent is without systemic venous effects and therefore pulmonary congestion is not substantially improved.\textsuperscript{27, 28} Although the combination of hydralazine with long-acting nitrates has been shown to diminish pulmonary congestion and enhance pump performance,\textsuperscript{29, 30} chronic hydralazine therapy may be associated with sodium retention, the development of drug tolerance, and the induction of the systemic lupus erythematosus syndrome.\textsuperscript{31-34}

Recent observations in our laboratories have shown that prazosin, a new oral vasodilator antihypertensive agent which is a quinazoline derivative, structurally unrelated to other antihypertensive agents available in the United States, has balanced vasodilator effects on the systemic arteriolar and venous beds.\textsuperscript{35} Further, we have also demonstrated that a single ingested capsule of prazosin produces sustained nitroprusside-like improvement in cardiac performance (unpublished observations). Therefore, the present study was undertaken to determine whether chronic oral prazosin therapy might be useful in ambulatory treatment of chronic refractory congestive heart failure to improve the symptoms of marked dyspnea and fatigue characteristic of this condition. In this study, myocardial performance was objectively assessed utilizing graded treadmill exercise tests, echographic indices of cardiac function, and ventricular hemodynamics obtained by heart catheterization, as well as serial evaluation of heart failure symptomatology.

**Methods**

This investigation included nine patients with severe chronic ischemic congestive heart failure with prior myocardial infarction and arteriographically documented coronary artery disease (table 1). The nine individuals included four males and five females, mean age 61 years (range 41-72 years). Each patient had marked cardiac dysfunction causing dyspnea at rest and pronounced fatigue with minimal effort; seven also manifested severe orthopnea. All nine of these patients with refractory heart failure were already receiving digoxin and diuretics, as well as long-acting nitrates in seven. The duration of heart failure exceeded two years in seven patients and was present for at least eight months in the remaining two. Patients with anemia, chronic lung disease and valvular dysfunction were excluded. In each patient, ventricular dynamics and exercise performance were determined prior to initiation of prazosin therapy and these variables of cardiac and exercise function were repeated two weeks following treatment with 40-50 μg/kg of oral prazosin. During the course of the trial of this new systemic vasodilator agent, digitalis and diuretics were kept constant whereas long-acting nitrates were discontinued two days before control and post-prazosin measurements.

Ventricular function was assessed echocardiographically before and during prazosin. Echocardiography was performed with the subjects supine and head elevated 45 degrees with an Ekoline 20A echograph utilizing a 0.5 inch diameter 2.25 MHz transducer focused at 10 cm with a repetition rate of 1,000 impulses/sec. The signal from the echograph was displayed and recorded on an Electronics for Medicine Model DR8, multichannel oscilloscopic recorder. All echocardiograms were obtained with rigid adherence to the technique and criteria previously stressed for determining left ventricular dimensions which provide optimal relation to left ventricular volumes.\textsuperscript{36-38} Briefly, along the left sternal border at the location of the most prominent cardiac impulse or in the third or fourth intercostal space, the transducer was directed posteriorly and then angled until the characteristic echo of the anterior mitral leaflet was recorded. The transducer was then directed slightly inferior and lateral, and the echograph gain was adjusted until echoes were obtained from both left ventricular septal and endocardial surfaces just below the full excursions of the mitral leaflets in the area of the chordae tendineae. The transducer was then maintained in this position, and recordings were obtained at the constant respiratory phase of held mid-expiration.

All echocardiograms were calibrated and measurements were taken from identical areas of the left ventricle.\textsuperscript{39-41} The end-diastolic dimension of the endocardial surface was measured at 0.04 sec after the onset of the QRS complex, and the end-systolic dimension was determined by the nearest approximation of the septal and posterior internal walls during systole. Although echographic dimensions are difficult to measure precisely to less than 1 mm, we were able to estimate the ultrasound distances to this level of accuracy,\textsuperscript{42} as have other workers.\textsuperscript{43} Left ventricular shortening fraction was determined as the difference between end-diastolic dimension minus end-systolic dimension divided by the end-diastolic dimension.\textsuperscript{44} Mean rate of left ventricular circumferential fiber shortening (V\textsubscript{Cf}) was obtained as the differences between end-diastolic and end-systolic dimensions divided by the product of end-diastolic dimension and ejection time.\textsuperscript{45} The ejection time was calculated as the time from the beginning of the QRS complex to maximal anterior systolic motion of the left ventricular posterior wall less 50 msec for the pre-ejection period.\textsuperscript{46} Mean arterial

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<tr>
<th>Patient</th>
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Abbreviations: NYHA = New York Heart Association functional Class; A = anterior; I = inferior; P = posterior; MI = myocardial infarction; dig = digoxin 0.25 mg; furos = furosemide; iso = isosorbide dinitrate; NTG = long-acting nitroglycerin.
pressure was obtained as diastolic pressure plus one-third of the difference between systolic and diastolic pressures sphygmomanometrically.

Following echocardiographic estimation of ventricular function, each patient underwent determination of maximal exercise capacity using graduated multistage treadmill exercise tests before and during prazosin.\(^4\) Step one of the branching exercise protocol consisted of 1.97 miles/hour (MPH) at 0% grade maintained for 2 minutes, followed by 2.62 MPH at 0% grade for an additional 2 minutes (step two). If 70% of maximal predicted heart rate was achieved during step two, the speed was thereafter kept constant and the grade increased to 3.5%, 7% and 9% following every 2 minutes of exercise (steps three, four and five, respectively). If 70% of heart rate was not achieved at 2.62 MPH during step two, the treadmill speed was increased to 3.19 MPH for 2 minutes (step three) and then to 3.53 MPH (step four). If 70% of predicted heart rate was achieved at either of these latter two speeds, further exercise was conducted by increasing the grade every 2 minutes to 3.5%, 7% and 9% until the patient terminated the test because of dyspnea or fatigue. Although four patients developed angina pectoris during exertion, in none of the patients was it necessary to discontinue the exercise test because of chest pain. During the test, symptoms were evaluated and maximal total body oxygen consumption (\(V_O_2\)) was determined from established nomograms.\(^4\) Exercise test-assessed functional classification was thereby determined using estimated \(V_O_2\) in which \(V_O_2 < 10 \text{ml/kg/min} \) indicated functional class IV, \(V_O_2\) 11–15 functional class III, \(V_O_2\) 16–24 functional class II, while \(V_O_2 > 25\) indicated functional class I. In addition, the peak heart rate \(\times\) systolic blood pressure product, an index of myocardial oxygen consumption (\(MVO_2\)), was calculated.\(^4\)

Additionally, all nine patients underwent right heart catheterization with placement of the balloon-tipped thermodilution Swan-Ganz catheter in the pulmonary artery for assessment of cardiac performance prior to prazosin. In each of these patients intra-arterial blood pressure (BP), pulmonary artery (PA) pressures and triplicate thermodilution cardiac outputs (CO) were measured. The PA diastolic pressure was confirmed to be identical to PA wedge pressure and was thereafter used to measure left ventricular filling pressure (LVFP). The following parameters of cardiac performance were calculated: Total systemic vascular resistance (TSVR, dynes-sec-cm\(^{-4}\)) from \([(P - RA) \times 80]/CWO\) where \(P\) is mean BP, \(RA\) is mean right atrial pressure and 80 is the conversion factor for converting units of resistance into dynes; stroke work index (SWI, gm \(\cdot\) m/m\(^3\)) from \((P - LVFP) \times SI \times 0.00136\) where SI is stroke index (ml/beat/m\(^3\)); and pressure-time product per minute (PTM, mm Hg-sec/min) from SBP \(\times ET \times HR\) where SBP is systolic BP (mm Hg), ET is ejection time (sec) and HR is heart rate (beats/min).

The sequence of studies carried out in this investigation of prazosin were as follows. Prior to the agent, control echocardiographic determinations of ventricular function were obtained in duplicate together with sphygmomanometer blood pressure in the supine position. Then exercise testing was performed in the control period to determine maximal physical capacity limited by cardiac dysfunction. Upon completion of the exercise test, right heart catheterization was carried out to quantify hemodynamic variables. In each patient, with the Swan-Ganz catheter in place, 40–50 \(\mu g/kg\) (2 to 7 mg) prazosin was ingested. Cardiac hemodynamics were then remeasured every 30 minutes for six hours following administration of the agent. Following completion of the post-prazosin direct hemodynamic evaluation, the cardiac catheter and intra-arterial cannula were removed. Then each patient received 2 to 7 mg of oral prazosin four times daily on a chronic outpatient basis. The dose was individualized according to the response in blood pressure, left ventricular filling pressure and cardiac output to the initial administration of prazosin. Two weeks later, while the patients continued on prazosin, the echocardiographic and exercise evaluations were repeated.

In addition, symptomatic evaluation and physical examination of each patient were performed before and at weekly intervals following the initiation of oral prazosin therapy for a period of two to four months. Each patient maintained a diary of symptomatology including occurrence and degree of dyspnea, fatigue, orthopnea, chest pain and related difficulties. To aid in this self evaluation of the extent of symptoms, each patient classified dyspnea on a scale of 0 to 4 daily: 0 when none occurred, 1+ with more than ordinary activity, 2+ with ordinary physical activity, 3+ dyspnea at rest and 4+ orthopnea. In this manner, dyspnea was graded along with other symptomatology related to ventricular dysfunction to provide serial clinical function classification from I to IV according to the criteria of the New York Heart Association (NYHA).

**Results**

**Hemodynamics**

At cardiac catheterization, heart rate was 80 ± 5 beats per minute during control (C) and remained unchanged throughout the six hours of measurement following administration of prazosin (PZ). Systemic arterial mean BP declined following PZ ingestion (fig. 1A). Thus, control mean BP of 99.7 ± 4.8 mm Hg was significantly reduced to 87.6 ± 6.5 mm Hg (P < 0.01) by 30 minutes after the agent with marked reduction in mean BP occurring at 60 minutes following oral PZ (77.7 ± 4.6 mm Hg, P < 0.001). Thereafter, mean BP remained significantly reduced (P < 0.001) for the duration of the study with the maximal effect lasting 2 hours and then gradually rising toward control during the final 3 hours, being still substantially lowered (86.0 ± 5.0 mm Hg, P < 0.001) at six hours following PZ administration.

Oral prazosin resulted in dramatic and sustained decline in the markedly elevated control left ventricular filling pressure of 32.0 ± 3.7 mm Hg (fig. 1B). Prazosin produced a decrease in LVFP at 30 minutes (23.4 ± 3.2 mm Hg, P < 0.01) with maximal reduction by 60 minutes (17.6 ± 1.9 mm Hg, P < 0.001). This marked reduction in LVFP induced by oral PZ persisted (P < 0.001) for the entire duration of the study; maximal diminution remained for the subsequent three hours with only a minimal tendency of LVFP to rise during the final two hours of observation, the six hour value being 19.7 ± 2.4 mm Hg (P < 0.001).

Simultaneously with the reduction of LVFP, oral PZ caused a striking and persistent increase in the control car-
diac index (CI) of 1.95 ± 0.12 (fig. 2A). After 30 minutes CI was elevated to 2.57 ± 0.12 L/min/m² (P < 0.001); maximal improvement occurred at 60 minutes (2.89 ± 0.11 L/min/m²; P < 0.001) and remained so for a three hour period with only a slightly less elevated CI 6 hours after PZ (2.41 ± 0.16 L/min/m²; P < 0.001). Stroke output (fig. 2B) also showed a similar enhancement from control of 25.4 ± 3.1 ml/beat/m² to 32.8 ± 3.1 ml/beat/m² (P < 0.001) at 30 minutes after oral PZ, increasing further to 36.3 ± 2.0 ml/beat/m² at 60 minutes (P < 0.001). This improvement persisted for the entire study duration; stroke output was 32.7 ± 3.1 ml/beat/m² (P < 0.001) six hours after the agent.

Total systemic vascular resistance was lowered by oral PZ throughout the duration of the study (fig. 3A), decreasing from control of 2314 ± 147 to 1528 ± 107 dynes-sec-cm⁻² at 30 minutes (P < 0.001), 1215 ± 99 at one hour (P < 0.001) and 1639 ± 138 dynes-sec-cm⁻² at six hours (P < 0.001) following prazosin. At the same time, stroke work index (fig. 3B) increased from control of 24.1 ± 4.6 to 29.0 ± 4.3 gm ∙ m/m² at 30 minutes (P < 0.01); thereafter maximal elevation of SWI was observed for the remainder of the study period; 30.1 ± 3.8 gm ∙ m/m² (P < 0.01) at 60 minutes and 29.9 ± 4.3 gm ∙ m/m² (P < 0.05) at six hours after the systemic vasodilator. This enhancement in cardiac performance was accomplished with less myocardial oxygen consumption estimated as pressure-time per minute which declined from control of 3175 ± 138 mm Hg-sec/min to 2931 ± 242 (P < 0.01) at 30 minutes, 2664 ± 170 (P < 0.001) at 60 minutes with the improvement in mechanical efficiency lasting for the study duration (PTM 2844 ± 199 mm Hg-sec per minute; P < 0.01) at six hours.

Echocardiography

Echographic assessment of cardiac performance was performed prior to PZ therapy and two weeks after this oral agent was chronically administered. In all nine patients PZ resulted in decline in left ventricular (LV) dimensions at both end diastole (EDD) and at end systole (ESD). Thus, LVEDD decreased from 5.7 ± 0.4 to 5.4 ± 0.4 cm (P < 0.001) (figs. 4A and 5) with PZ therapy, while LVESD diminished from 4.2 ± 0.4 to 3.9 ± 0.4 cm (P < 0.001) (figs. 4B and 5). In addition, chronic oral PZ resulted in increase in shortening fraction from 27.6 ± 6.5 to 30.2 ± 4.5% (P < 0.005) (fig. 4C), while mean normalized VCF increased from 0.86 ± 0.17 to 0.94 ± 0.19 circumferences/sec (P < 0.025) (fig. 4D).
Resting BP prior to exercise was significantly reduced by PZ. Systolic BP decreased from 132.6 ± 8.9 to 112.6 ± 6.7 mm Hg (P < 0.001), while diastolic BP declined from 83.5 ± 3.6 to 75.2 ± 2.6 mm Hg (P < 0.001). Resting mean BP was reduced from 100.4 ± 5.4 to 88.3 ± 6.1 mm Hg (P < 0.001). Resting heart rate was unchanged by PZ; control 80 ± 4 to 77 ± 4 beats/min. Orthostatic hypotension was not observed in any patient with PZ; control standing systolic BP declined 5.0 ± 1.5 mm Hg and only 7.2 ± 2.0 mm Hg with PZ.

Exercise capacity was assessed prior to PZ therapy and two weeks after continuous treatment with the vasodilator agent. The aforementioned hemodynamic and echographic improvements in cardiocirculatory variables induced by PZ resulted in enhanced exercise capacity. All patients were able to exercise for a longer period, the mean duration of exercise improving from 209 ± 39 to 317 ± 50 seconds (P < 0.001) (fig. 6A). In addition, maximal total body oxygen consumption (VO$_{2}$) increased from 10.2 ± 1.4 to 13.7 ± 1.7 ml/kg/min (P < 0.01) (fig. 6B). This improvement in exercise tolerance was accomplished at less cardiac oxygen requirements as reflected by the reduction of the double product of heart rate and systolic BP, an indirect index of myocardial oxygen consumption (MVO$_{2}$). Control double product was significantly decreased at peak exercise during chronic PZ therapy from 20,536 ± 1458 to 17,538 ± 1088 units (P < 0.001) (fig. 7C). Since maximal exercise heart rate was not significantly altered (control 122 ± 7 and PZ 128 ± 8 beats per minute) (fig. 7A), the reduction in heart rate · blood pressure product was accomplished by decline in peak exercise systolic BP from 165.0 ± 8.7 to 137.3 ± 3.9 mm Hg (P < 0.001) (fig. 7B).

Symptomatology

The mean duration of follow-up of PZ therapy was 94 days (64–127 days). Symptomatology due to heart failure was greatly improved with PZ in all nine patients (fig. 8). Prior to initiation of prazosin, despite therapy with digoxin and diuretics, all patients had marked dyspnea and fatigue (NYHA functional class IV in seven patients and class III in the remaining two patients). Figure 8 shows considerable decrease in heart failure symptoms achieved with chronic oral prazosin therapy in individual patients. Of the seven class IV patients prior to PZ, the oral vasodilator reduced heart failure symptoms to class III in three and to class II in four. Similarly, symptomatology was diminished in the two class III patients to class II in one and to class I in the other with PZ.

Discussion

This investigation demonstrates that chronic impedance and preload reduction therapy induced by the new systemic oral vasodilator, prazosin, markedly enhances cardiac performance in patients with severe coronary heart failure persisting despite treatment with digoxin and diuretics. It is emphasized that this salutary effect occurred when prazosin was substituted for long-acting nitrates. Thus, by such an addition of prazosin to the therapeutic regimen, concomitant with improvements in hemodynamic (figs. 1–3) and
FIGURE 5. Representative example of the effects of oral prazosin therapy on echographic left ventricular dimensions in a patient with chronic coronary heart disease. The left panel was obtained prior to the agent and the right panel was recorded two weeks after beginning the agent 4 mg four times daily. IS = interventricular septum; PW = left ventricular posterior wall. During prazosin the end-diastolic dimension decreased from 5.9 to 5.7 cm while the end-systolic dimension declined from 5.3 to 5.1 cm.

FIGURE 6. Treadmill exercise evaluation of the effects of chronic prazosin therapy (2 to 7 mg, four times daily) in 9 chronic heart failure patients two weeks after initiation of ambulatory therapy (PZ) compared to control exercise (C). Exercise duration (Panel A) and maximal total body oxygen consumption (Panel B) were increased in all patients with prazosin.
The hemodynamic and echocardiographic observations in the present series of patients indicate that the beneficial symptomatic effects of prazosin resulted from relatively equal dilator actions of the drug, such that peripheral arterio-dilation produced decline in aortic impedance while venodilation promoted venous pooling. The former action caused enhanced ventricular emptying so that the lowered ejection fraction was raised, while the latter action resulted in decline of venous return to the heart with decrease in cardiac chamber volume and relief of pulmonary congestion. These effects of oral prazosin therapy were exemplified by reduction in systemic vascular resistance (fig. 3A) and diminution in intraventricular echographic dimensions (figs. 4A, 4B and 5). The enhanced cardiac output (fig. 2A) combined with the decrease in elevated left ventricular filling pressure (fig. 1B) afforded by prazosin thereby permitted increased exercise tolerance (fig. 6) with less inducement of fatigue and dyspnea (fig. 8).

Concerning the clinical application of the various systemic vasodilator agents in the management of congestive heart failure, nitroprusside, phentolamine and trimethaphan have been the most useful intravenous drugs.1-5, 6-12, 16, 17, 18, 20-23 Of these parenteral vasodilators, the most frequently used and beneficial agent has proved to be nitroprusside administered by infusion.2, 4-6, 8-10, 15, 17, 18, 21-23 The premier role of nitroprusside derives from its balanced vasodilator direct effects on the systemic resistance and capacitance vessels.23 Thus, nitroprusside permits relief of pulmonary congestion concomitantly with enhancement of ventricular output. Previous plethysmographic studies from our laboratories have demonstrated that oral prazosin has systemic vasodilator effects comparable to those of parenteral nitroprusside.23 Further, we have shown by direct hemodynamic measurements that these peripheral circulatory actions of oral prazosin are translated into dramatic improvements in markedly deranged cardiac dynamics in a large group of patients with chronic ischemic heart disease.44 The present comprehensive investigation extends these previous observations by demonstrating that oral prazosin also objectively enhances functional capacity by exercise testing and chronically improves heart failure symptoms during long-term ambulatory therapy with the agent, as well as cor-

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**Figure 7.** Treadmill exercise evaluation of the effects of chronic prazosin therapy (2 to 7 mg, four times daily) in all nine chronic heart failure patients two weeks after beginning ambulatory therapy (PZ) compared to control exercise (C). Maximal heart rate (Panel A) was not significantly affected, while peak systolic blood pressure (BP) was reduced (Panel B), and maximal heart rate (HR) x systolic BP product was diminished (Panel C) in patients during prazosin.

**Figure 8.** Symptomatic evaluation of the efficacy of prazosin therapy (2 to 7 mg, four times daily) in all nine chronic heart failure patients during the duration of follow-up (mean 94 days) of the agent (PZ) compared to control symptoms (C). PZ improved New York Heart Association (NYHA) functional classification in all patients from an average control class of 3.7 to 2.2. The NYHA functional class is indicated by the Roman numerals I-IV and the number of patients is indicated within the boxes during the C and PZ periods.
raborting its beneficial influence on cardiac function by hemodynamic measurements and echographic determinations of ventricular mechanics.

The direct action of prazosin on vascular smooth muscle involves inhibition of the enzyme phosphodiesterase. The resultant increased levels of intracellular cyclic AMP appear responsible for relaxation of the systemic vessels produced by prazosin. Interestingly, PZ-induced phosphodiesterase inhibition in the heart causes elevation of myocardial cyclic GMP and cardiac sympathetic responsiveness is diminished. Thus, baroreceptor-mediated adrenergic stimulation of the heart is attenuated by prazosin. This observation is consistent with the lack of heart rate increase with the decline in systemic blood pressure at rest with prazosin, as well as the similar rise in peak exercise heart rate with the agent compared to control exercise despite the lesser rise in blood pressure with exertion during prazosin (fig. 7A). This lack of increased frequency of contraction coupled with reduction of left ventricular intramyocardial tension, reflected by the fall in resting PTM with prazosin and the decline in heart rate ∙ blood pressure double product with exercise with PZ (fig. 7C), appears to account for the consequent improvement in the myocardial oxygen supply-demand relation with the systemic vasodilator in the present patients with ischemic heart disease.

Presently, the topical and oral long-acting nitrates are the principal vasodilators being employed for ambulatory management of patients with congestive heart failure. However, in common with sublingual nitroglycerin, these agents primarily reduce ventricular preload without substantially affecting aortic impedance. Therefore, while pulmonary congestion is relieved by nitrates, cardiac output is only minimally and inconsistently influenced by these agents. Although hydralazine recently has been shown to improve ventricular performance by raising cardiac output, it has little to no affect on left ventricular filling pressure. While the combination of hydralazine with long-acting nitrates has been demonstrated both to improve pulmonary congestion by lowering ventricular preload and to reduce fatigue by increasing cardiac output, oral prazosin offers the advantage of a single drug which effectively accomplishes the same therapeutic purposes without the disadvantages of hydralazine side effects.

Further, our clinical experience with prazosin in heart failure therapy has indicated the agent does not cause serious untoward actions; only transient headache and mild nausea were noted in two patients which did not require discontinuance of the drug. Of additional importance is that we have not observed orthostatic hypotension with the careful and individualized use of prazosin in relieving severe heart failure symptomatology, apparently because the agent did not lower left ventricular preload below the upper limits of normal (fig. 1B).

Systemic vasodilators have been shown to have beneficial effects on myocardial ischemia in acute and chronic coronary artery disease. Thus there is clinical and experimental evidence that nitroprusside and trimethaphan reduce the extent of clinical and experimental myocardial infarct size by virtue of improvement in myocardial energetics, decrease in myocardial oxygen demand and improvement of coronary collateral flow. While the peripheral circulatory effects of prazosin are similar to those of nitroprusside, its effects on coronary flow and myocardial ischemia are as yet unknown. Nevertheless, in our heart failure patients ventricular internal chamber dimensions were consistently reduced (figs. 4A, 4B and 5) together with decline in arterial pressure (fig. 1A) which would be anticipated to result in substantial diminution in intramyocardial wall tension and cardiac oxygen demand. Indeed, resting myocardial oxygen requirements, as estimated by the indirect index of pressure-time per minute decreased considerably in all of our patients.

Consistent with the postulated reduction of MVO₂ with prazosin, the five patients with angina pectoris in addition to heart failure symptoms reported substantial decrease in angina frequency while on prazosin. Furthermore, in the four patients who developed ischemic chest discomfort during control treadmill exercise, two of these individuals were without angina with treadmill exercise on prazosin despite 34% greater duration of exercise. Since peak systolic blood pressure rise was 17% less (fig. 7B) while maximal heart rate was similar at maximal exercise (fig. 7A), in the nine patients comparing control to prazosin exercise testing, the double product of heart rate and systolic blood pressure at peak exercise was diminished 17% during prazosin (fig. 7C). These results indicate that the oral systemic vasodilator may reduce myocardial ischemia and angina pectoris in patients with coronary disease and heart failure.

Though similar improvements in myocardial energetics may also pertain to coronary patients with ventricular ischemia without heart failure, it should be noted that reduction of ventricular preload to less than peak normal values of filling pressure by prazosin in such patients without heart failure could result in the lowering of cardiac output and systemic hypotension. Therefore, the potential decrease in coronary flow may exceed the decline in MVO₂ in this instance, thereby adversely affecting myocardial oxygen balance leading to exacerbation of ventricular ischemia. However, in patients with acute myocardial infarction and heart failure, infarct size might be anticipated to be reduced by improvement in myocardial oxygen requirements effected by prazosin-induced decrease of left ventricular afterload.

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