Beneficial Effects of Afterload Reduction Therapy in Patients with Congestive Heart Failure and Moderate Aortic Stenosis

BARRY H. GREENBERG, M.D., AND BARRY M. MASSIE, M.D.

SUMMARY Patients with congestive heart failure have improved cardiac performance when afterload is reduced by drugs that lower systemic vascular resistance. However, in the presence of mild-to-moderate aortic stenosis, the response to such drugs is uncertain because the major impedance to left ventricular emptying may occur at the level of the aortic valve. To determine whether vasodilator therapy is useful in this setting, we evaluated the response to afterload reduction in 11 patients with severe congestive heart failure and reduced aortic valve area.

All patients underwent catheterization to document the severity of stenosis before study. Reduced valve area was due to native valve stenosis in three patients and to the presence of aortic prostheses in eight patients. A transvalvular gradient was measured in all patients. The peak gradient was 17 ± 3 mm Hg (mean ± SEM), and the aortic valve area index was 0.7 ± 0.1 cm²/m².

After optimal doses of either hydralazine (nine patients) or prazosin (two patients), cardiac index increased from 2.2 ± 0.1 to 3.3 ± 0.2 l/min/m² (p < 0.001) and stroke volume index increased from 28 ± 2 to 38 ± 2 ml/m² (p < 0.001). Systemic vascular resistance fell from 1649 ± 94 to 1061 ± 68 dyn-sec-cm⁻² (p < 0.001), and mean arterial pressure decreased from 93 ± 4 to 88 ± 4 mm Hg (p < 0.01). Hemodynamics were improved in all 11 patients regardless of valve area.

We conclude that patients with heart failure and mild-to-moderate aortic stenosis respond favorably to drugs that lower systemic vascular resistance. In such patients, resistance to ventricular emptying is determined predominantly by systemic vascular resistance rather than by aortic valve area.

A COMPENSATORY INCREASE in systemic vascular resistance frequently occurs in response to low cardiac output in patients with congestive heart failure. Recently, the potentially deleterious effect of increased afterload in patients with left ventricular dysfunction has been appreciated. Afterload reduction, using drugs that lower systemic vascular resistance, facilitates emptying of the impaired left ventricle and frequently results in improved cardiac performance and symptomatic improvement in such patients.

Patients with congestive heart failure may also have aortic stenosis that is not sufficiently severe to indicate valve replacement. Reduced aortic valve area may be due to disease of the native valve or to the presence of an aortic prosthesis. In such cases, the response to afterload reduction therapy is uncertain because resistance at the level of the aortic valve may contribute substantially to left ventricular afterload. If this were true, drugs that lower systemic vascular resistance would be expected to have little beneficial effect on cardiac performance and might be harmful.

To determine whether afterload reduction therapy is beneficial in patients with reduced aortic valve area, we evaluated the response of a group of patients with severe congestive heart failure and mild-to-moderate aortic stenosis to hydralazine or prazosin. Drugs whose predominant effect is to reduce systemic vascular resistance.

Methods

Patient Population

Eleven patients with severe congestive heart failure and reduced aortic valve area were evaluated. Their clinical and hemodynamic profile is shown in table 1. There were nine males and two females whose mean age was 59 ± 3 years (SEM). Three patients had native valve stenosis and eight had an aortic valve prosthesis.
All patients were in New York Heart Association functional class III–IV. Diagnostic cardiac catheterization and left ventricular angiography were undertaken before the drug trial in all patients. All patients had a transvalvular gradient. The aortic valve area index using the Gorlin formula was 0.7 ± 0.1 cm²/m². Aortic stenosis was considered to be mild or moderate in all but patient 9 (table 1), who had a 37-mm Hg gradient across a Starr-Edwards 9A, series 2400 aortic prosthesis. At surgery there was no evidence of prosthesis obstruction or dysfunction, and valve replacement was not undertaken in this patient. Based on the severity of stenosis, none of the remaining patients were considered to be candidates for valve replacement. Ejection fraction was 0.30 ± 0.02. Mitral regurgitation was noted in five patients and was felt to be clinically important in two. No patient had more than trivial aortic insufficiency. Two patients had coronary artery disease.

### Hemodynamic Measurements

Measurements of right atrial, pulmonary artery and pulmonary artery wedge pressures were obtained using a Swan-Ganz triple-lumen, balloon-tipped catheter (Edwards Laboratories, Santa Ana, California). Cardiac output was measured through the same catheter using a bedside computer (9520 Thermodilution Computer, Edwards Laboratories). Arterial pressure was measured either directly by means of a small catheter in the brachial artery, with the mean determined electronically, or by sphygmomanometer, with the mean arterial pressure (MAP) derived from the formula:

\[
MAP = D + \frac{(S - D)}{3}
\]

where S is the peak systolic pressure and D the end-diastolic pressure. Systemic vascular resistance (SVR) was derived in the following manner:

\[
SVR = \frac{MAP - RAP}{CO} \times 80
\]

where MAP = mean systemic arterial pressure in mm Hg, RAP = right atrial pressure in mm Hg, CO = cardiac output in liters/minute and 80 is the factor for converting resistance units to dyn-sec-cm⁻¹.

### Vasodilator Administration

All patients were clinically stable at the beginning of and throughout the study. All patients were receiving digitalis and diuretic agents, which were continued without change during the study.

After stable, reproducible measurement of heart rate, pressures and cardiac output during the control state, either hydralazine, 50–75 mg, or prazosin, 1–2 mg, was administered. Measurements were repeated hourly and, using the methods previously described, dosages were increased until maximal beneficial effects were obtained. Patients were maintained on maximal dose therapy for an additional 24 hours before final measurements were obtained 2–3 hours after a dose of the drug. Final drug doses ranged from 50–100 mg of hydralazine every 8–12 hours and 6–8 mg of prazosin every 8 hours (table 2). No patient was switched from one drug to the other because of poor response.

Statistical analysis was accomplished by means of a paired t test for comparison of before- and after-hydralazine values.

### Results

The effects of afterload reduction therapy on pressures and flow are shown in table 2. Nine patients...
received hydralazine and two patients received prazosin (table 2).

Maximal drug therapy resulted in a small but significant drop in arterial pressure, from $93 \pm 4$ to $88 \pm 4$ mm Hg, while heart rate increased slightly, from $82 \pm 3$ to $85 \pm 3$ beats/min. Right atrial, pulmonary artery and pulmonary artery wedge pressures did not change significantly.

A significant reduction in systemic vascular resistance, from $1649 \pm 94$ to $1061 \pm 68$ dyn-sec-cm$^{-5}$, resulted in increases in cardiac index ($2.2 \pm 0.1$ to $3.3 \pm 0.2$ l/min/m$^2$) and stroke volume index ($28 \pm 2$ to $38 \pm 2$ ml/m$^2$).

Within the range of mild-to-moderate stenosis in our patients (aortic valve area index ranged from $0.4$ to $1.2$ cm$^2$/m$^2$), the severity of stenosis did not appear to be related to the response to drug therapy. Patient 9 had the greatest degree of stenosis (aortic valve area index $0.4$ cm$^2$/m$^2$), but still increased cardiac index by 52% and stroke volume index by 39% without a reduction in arterial pressure when systemic vascular resistance was reduced from $1270$ to $811$ dyn-sec-cm$^{-5}$.

Although several patients developed transient, mild side effects from vasodilator therapy (nausea or headache), these symptoms resolved in all cases and medication was not discontinued for this reason in any patient. None of our patients developed evidence of myocardial ischemia while receiving therapy.

**Discussion**

This study shows that afterload reduction therapy improves cardiac performance in patients with heart failure despite the presence of mild-to-moderate aortic stenosis.

All patients in our group who received afterload reduction therapy showed evidence of improved cardiac performance. Overall, there was a 50% increase in cardiac index and a 38% increase in stroke volume index. Similar results have been obtained in patients with heart failure who were without evidence of aortic valve disease when either hydralazine or prazosin was administered. Although a rapid tachyphylaxis to the beneficial effects of prazosin has been noted, this phenomenon was not observed in the two patients in our series who received this drug.

Although a significant fall in mean arterial pressure was noted in our patients, the absolute reduction, from $93 \pm 4$ to $88 \pm 4$ mm Hg, was small and not clinically significant. Only patient 8 experienced a reduction in arterial pressure $\geq 10$ mm Hg (table 2). This patient was hypertensive during the control period, and after a dose of 100 mg of hydralazine, mean arterial pressure was reduced from $120$ to $103$ mm Hg. The lack of major change in arterial pressure despite a marked reduction in systemic vascular resistance resulted from the substantial increase in cardiac output. The maintenance of arterial pressure is particularly important in this group of patients, because a fall in coronary perfusion could be especially deleterious in patients with aortic stenosis.

All of our patients had evidence of marked left ventricular dysfunction as manifest by reduced ejection fraction and significant impairment in functional capacity. Both hydralazine and prazosin have been shown to improve cardiac performance in patients with left ventricular dysfunction by reducing the level of systemic vascular resistance. When afterload is reduced, left ventricular emptying is enhanced and stroke volume increases.

Mitrval regurgitation was demonstrated on left ven-
tricular angiography in patients 2, 6, 7, 8 and 11, and the lesion was felt to be hemodynamically important in patients 7 and 8 (table 1). Afterload reduction has been shown to be of benefit in patients with mitral regurgitation \(^{21-24}\) by redistributing total left ventricular stroke volume in a manner favoring forward cardiac output at the expense of regurgitant flow.\(^{44}\)

Regardless of which mechanism was responsible for the increase in cardiac index and stroke volume index in our patients, if the predominant resistance to ventricular emptying had been at the level of the aortic valve, a reduction in systemic vascular resistance would not have been expected to improve cardiac performance. If the capacity of the left ventricle to increase stroke volume were limited by aortic stenosis, the predominant effect of reducing systemic vascular resistance should have been a fall in arterial pressure rather than an increase in cardiac output. The results in our patients suggest that when the aortic valve area is reduced in the range of 0.4-1.2 cm\(^2/\text{m}^2\), the resistance to ventricular emptying at the level of the aortic valve is still relatively unimportant compared with systemic vascular resistance. Certainly, as the severity of aortic stenosis increases, the effects of the valvular resistance become increasingly important. We have not attempted to treat patients with more severe degrees of stenosis using afterload-reducing drugs because of the potentially harmful effects in such patients. Preliminary results on the use of nitroprusside in patients with critical aortic stenosis show that when resistance is reduced, arterial pressure falls and there is little change in cardiac index.\(^{28}\) As discussed below, we believe that patients with severe aortic stenosis and congestive heart failure should be considered as candidates for aortic valve replacement.

The overall effect of afterload reduction on the myocardial oxygen supply-demand ratio in patients with aortic stenosis is uncertain. Increased flow across a fixed stenosis would be expected to increase the transvalvular gradient, left ventricular systolic pressure and left ventricular wall tension. Alternatively, ventricular volume may be reduced by afterload reduction and wall tension is thus reduced. Awam et al.\(^ {26}\) could demonstrate no increase in myocardial oxygen consumption in patients with critical aortic stenosis treated with nitroprusside. Although afterload reduction did not precipitate myocardial ischemia in any of our patients, this factor should be considered when initiating afterload reduction therapy, particularly in patients with coronary artery disease.

All 11 of our patients had evidence of aortic stenosis documented by the presence of a transvalvular gradient and reduction in aortic valve area. The severity of stenosis was felt to be mild to moderate in all patients. In the three patients with valvular aortic stenosis (patients 1, 2 and 7, table 1), the valve disease was not considered sufficiently severe to have been the primary cause of heart failure. In the eight patients with an aortic valve prosthesis, the transvalvular gradient and calculated area index were felt to be within acceptable limits for the individual prosthesis. As noted recently, the presence of a prosthesis almost always results in some degree of "stenosis," despite an acceptable gradient and valve area for the model and series in question.\(^ {28}\) In patient 9, the 37-mm Hg gradient and calculated aortic valve area index of 0.4 cm\(^2/\text{m}^2\) was initially felt to be suggestive of prosthetic valve dysfunction. However, there was no evidence of obstruction or dysfunction at surgery and the prosthesis was not replaced.

When congestive heart failure is caused by critical aortic stenosis, valve replacement is the preferred approach, because both symptoms and survival appear to be improved.\(^ {97, 98}\) In addition, recent reports have cited improved systolic pump function after valve replacement in patients with critical aortic stenosis and impaired left ventricular function.\(^ {29-32}\) In our patients with heart failure in association with mild-to-moderate stenosis, no such benefits would be expected from valve replacement.

**Clinical Implications**

The use of afterload reduction therapy in patients with congestive heart failure and mild-to-moderate aortic stenosis appears to improve cardiac performance despite the presence of reduced aortic valve area. Changes in hemodynamics are similar to those previously shown in patients with heart failure who are without evidence of aortic valve disease.

Care should be taken not to overlook critical aortic stenosis in a native or prosthetic valve. In such cases, afterload reduction therapy may have deleterious effects on the cardiovascular system. Catheterization with simultaneous measurement of transvalvular gradient and cardiac output may be necessary to determine whether afterload reduction can be given safely or whether valve replacement should be considered.

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