Hemodynamic Consequences of Afterload Reduction in Patients with Chronic Aortic Regurgitation

JAMES L. BOLEN, M.D., AND EDWIN L. ALDERMAN, M.D.

SUMMARY Nitroprusside was used to reduce afterload in 13 patients with isolated, severe aortic regurgitation. The drug significantly lowered mean aortic pressure, pulse pressure, left ventricular end-diastolic pressure and left ventricular volume. Total ventricular, or angiographic, cardiac index was generally unaffected, but forward cardiac index was improved significantly in 8 of 13 patients. Augmentation of forward cardiac index was seen in patients with sub-normal resting forward cardiac index, in patients with decidedly elevated end-diastolic pressure, and in those with depressed resting ejection fractions. Regurgitant fraction fell with nitroprusside in six patients and remained unchanged in seven. Total stroke work index was diminished in all patients. These data show that afterload reduction in patients with severe aortic regurgitation may improve hemodynamics by reducing aortic regurgitation or by improving ventricular pump function. The lowered total stroke work, reduced ventricular size and improved forward cardiac index imply that afterload reduction may benefit left ventricular failure and delay progressive ventricular dysfunction in patients with aortic regurgitation.

NITROPRUSSIDE has significant and favorable effects upon hemodynamics in patients with mitral regurgitation, acute myocardial infarction, and chronic ischemic heart disease. In mitral regurgitation, the benefit arises primarily by reducing regurgitant volume and pulmonary venous pressure and by increasing forward cardiac output. In patients with primary muscle dysfunction, the peripheral vasodilatory properties of nitroprusside improve left ventricular function by reducing impedance to ventricular ejection resulting in improved cardiac output, stroke volume and ejection fraction.

We have examined the response of patients with significant aortic regurgitation to afterload reduction with nitroprusside. Detailed hemodynamic and angiographic data, obtained on patients with stable severe valvular lesions, suggest beneficial effects.

Methods

Thirteen patients with isolated severe aortic regurgitation were studied during cardiac catheterization. Informed consent was obtained in each case. Those with evidence at the time of catheterization and angiography of significant mitral stenosis (valve area < 2.0 cm²), mitral regurgitation, or mean aortic valve gradient > 10 mm Hg were excluded. Right-sided pressures were recorded using Statham P23Db transducers and left-sided pressures using fluid-filled catheters and Micron MP-15 transducers. Forward cardiac indices (Cl₂) were determined using the Fick method or duplicate indicator dilution curves using indocyanine green dye, injected into the pulmonary artery and sampled in the descending aorta. Pressures and gradients were computer-determined and manually checked. Resting ventriculography was performed in the 30° right anterior oblique projection, and ventricular volumes and ejection fraction were determined using a video-disc light-pen computer system. Fifteen minutes after angiotensin, sodium nitroprusside was administered via a peripheral vein with adjustment of the rate to reduce mean aortic pressure by approximately 25%. In some patients, because of the relatively low mean resting aortic pressures, this could not be accomplished without producing symptomatic hypotension, and pressure reductions were, therefore, limited to 15%. Stability of the desired pressure was confirmed for 15 minutes, and then repeat pressures and forward cardiac index were measured and left ventricular angiography was performed under these new conditions.

Angiographic, or total left ventricular, cardiac index is calculated by multiplying angiographic stroke index by heart rate. Left ventricular stroke work index (SW₁LV) equals (LV stroke index) x (mean LV systolic pressure during ejection) x (0.0136). Regurgitant fraction is given by the formula RF = (Cl₁LV – Cl₂)/Cl₁LV. Statistical results are expressed as mean ± standard error of the mean. Student's t-test for matched pairs was used to compare control and nitroprusside data.

Results

Thirteen patients were studied (table 1). Ages ranged from 27 to 72; there were ten males and three females. Two patients (#3 and 6) had a history of rheumatic fever. The remaining patients had either congenitally deformed valves or undefined abnormalities as the basis for aortic regurgitation. Four patients had coronary arteriography and in only one (#10) was a significant lesion (95% right coronary narrowing) found. No other patient had angina, electrocardiographic evidence of prior myocardial infarction, or segmental ventricular contraction abnormalities. No patient had acute aortic regurgitation or recent dramatic change in clinical state.

Pressure and Output Measurements

Aortic pressure was significantly lowered in every case. Average systolic/diastolic pressure declined from 154 ± 8/58 ± 4 to 115 ± 4/48 ± 2 (P < 0.01) and mean aortic pressure from 92 ± 5 to 71 ± 3 (P < 0.01) (fig. 1, table 1). Aortic systolic pressure was reduced an average of 25%; diastolic, 17%; and mean, 23%. Nitroprusside narrowed the pulse pressure in each instance. Nitroprusside infusion did not significantly affect the heart rate.

Left ventricular end-diastolic pressure was lowered to nor-
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<th>Ao S/D (mean) (mm Hg)</th>
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<th>CI(f) (F or D) (L/min/m²)</th>
<th>RF</th>
<th>SWI (g/m²)</th>
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Mean: C = control; NP = nitroprusside; D = dye output; F = Fick output.

Abbreviations: RA = right atrium; PA = pulmonary artery; LVEDP = left ventricular end-diastolic pressure; Ao = aorta; CI(lV) = total left ventricular cardiac index; CI(f) = forward cardiac index, RF = regurgitant fraction; SWI = stroke work index; EDV = end-diastolic volume; EF = ejection fraction; C = control; NP = nitroprusside; D = dye output; F = Fick output.
NITROPRUSSIDE IN AORTIC REGURGITATION/Bolen, Alderman

Normal values (<15 mm Hg) in six of seven patients with abnormally high resting left ventricular end-diastolic pressures. Similar reductions in pulmonary artery and wedge pressures occurred. Control mean right atrial pressures were abnormal in two patients and were reduced to normal values by nitroprusside.

Left ventricular (angiographic) cardiac index in most instances was little affected by afterload reduction (6.4 to 6.7 L/min/m², NS) (fig. 2). However, two patients (#10 and 11) exhibited increases of left ventricular cardiac index greater than 20%. These responses were caused by an increased stroke index and ejection fraction. It is possible that in some cases nitroprusside resulted in obliteration of ventricular margins by trabeculations in such a way that the end-systolic volume is underestimated. Two patients (#8 and 12) showed declines in CLV greater than 20%. In both patients, right atrial pressure was severely reduced by nitroprusside (3 to 0 mm Hg; 12 to 2 mm Hg), as was left ventricular end-diastolic pressure (7 to 2 mm Hg; 23 to 6 mm Hg). Both patients experienced pronounced shrinkage of end-diastolic volume suggesting that the fall in ventricular output in these two patients was probably due to a disproportionate decline in venous return to the heart.

Forward cardiac index (CLV) was significantly increased from 2.4 L/min/m² to 2.8 L/min/m² (P < 0.05) (fig. 3). It was augmented more than 10% in eight of 13 patients, unchanged in four, and decreased more than 10% in one patient. In three of the eight with improved forward output, this response was due primarily to a decrease in regurgitant fraction; in three it was due to an increase in ejection fraction; and in the remaining two it was due to both an increase in ejection fraction and a decrease in regurgitant fraction. In the four patients without change in CLV, no significant

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Comparison of pressures before and during nitroprusside infusion. There is significant diminution in systolic and diastolic aortic pressure, aortic pulse pressure, left ventricular end-diastolic pressure and mean pulmonary artery pressure.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Total left ventricular cardiac index before and during nitroprusside infusion. Increased CLV was seen in two patients and decreases in three. Overall, however, CLV was not significantly changed by afterload reduction.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Forward cardiac index during the control condition and during nitroprusside infusion. A significant increase in CLV was seen in eight patients and a significant decrease occurred in only one patient. Of those nine patients with a subnormal CLV (<2.5 L/min/m²), CLV increased in six and remained unchanged in three.
alterations were seen in ejection fraction, stroke index or regurgitant fraction.

Nine patients had a subnormal resting forward output (< 2.5 L/min/m²), six of whom improved with nitroprusside (fig. 3). Of the six who increased, CI₅ was elevated into the normal range in four patients. With the exception of patient 5, the most favorable results in improving CI₅ were in those patients with decidedly elevated left ventricular end-diastolic pressures which were brought into the normal range (7–12 mm Hg). Afterload reduction in patients with initially normal ventricular filling pressures did not benefit, or even worsened, forward output. In summary, an improvement in CI₅ may be anticipated if the resting CI₅ is subnormal and if resting left ventricular end-diastolic pressure is significantly elevated.

By virtue of the reduced systolic pressure, total (LV) stroke work index and minute work index were reduced in all 13 patients (P <0.01; table 1). Hence, for 12 of 13 patients, forward cardiac index was increased or maintained at a time when the ventricle performed significantly less work.

**Ventriculographic Measurements**

Regurgitant volume during nitroprusside infusion was decreased in six patients, unchanged in six and increased in one patient. Regurgitant fraction, which reflects changes in both left ventricular and forward output, fell significantly in six patients and remained essentially unchanged in the remaining seven. In four of the six patients in whom regurgitant fraction fell, the forward output improved. In three of the six, the decrease in regurgitant volume came about primarily as a result of a decrement in CIₑLV. There were no identifiable hemodynamic differences (resting end-diastolic volume, left ventricular end-diastolic pressure, regurgitant fraction, or degree of afterload reduction) between those who decreased regurgitation and those who did not.

Left ventricular end-diastolic volume was decreased by more than 10% during nitroprusside in 8 of 13 patients and remained unchanged in four (fig. 4). Neither the initial ventricular volume nor the magnitude of afterload reduction seemed to predict the magnitude of end-diastolic volume diminution. Stroke volume remained unchanged in eight patients, increased in two and fell in three. Ejection fraction rose by .10 or more in five patients with a significant overall increase (.53 to .59, P <0.05) (fig. 5). Both patients with markedly depressed resting ejection fraction (4 and 11) experienced improvement. Forward cardiac output improved in five of the six patients who increased ejection fraction, and end-diastolic volume fell significantly in five of these six. However, there seemed to be no other features to identify these six patients who improved ejection fraction as compared with the group which did not.

**Discussion**

Few data are available on the effects of afterload reduction on hemodynamics in patients with aortic regurgitation. The observation that the Austin-Flint murmur softens after amyl nitrite inhalation has been taken as evidence that regurgitation is lessened by lowered blood pressure. Delius and Enghoff found that the administration of amyl nitrite in patients with aortic regurgitation resulted in a decrease in mean arterial pressure, a diminution in left ventricular end-diastolic pressure, and an increase in effective stroke volume in most cases.

It is clear from previous studies in mitral regurgitation that afterload reduction with nitroprusside may enhance forward output by decreasing the regurgitant volume or by improving ventricular pump function by lowering impedance. Chatterjee et al. found that afterload reduction by nitroprusside in patients with severe mitral regurgitation significantly augmented forward cardiac index and stroke

**Figure 4.** Effects of nitroprusside upon end-diastolic volume. End-diastolic volume was reduced in nine of 13 patients; the mean reduction was 15%.

**Figure 5.** Ejection fraction in the control condition and during nitroprusside infusion. Ejection fraction rose by .10 or more in five patients and remained essentially unchanged in eight. The ejection fractions in the two patients in whom it was below .40 both increased substantially.
index by virtue of a reduction in regurgitant fraction. An improvement in ventricular pump function was also suggested since depressed resting ejection fractions were increased by nitroprusside. Similar reduction in regurgitant fraction and improvement of forward cardiac index was found by Goodman et al. in studying 14 patients with chronic rheumatic mitral regurgitation. It is of interest that the majority of these patients, in contrast with the patients described by Chatterjee et al., who tended to have mitral regurgitation on the basis of papillary muscle dysfunction, had normal ejection fractions at rest which were not increased by nitroprusside. Hence, the hemodynamic improvement seen in the patients with normal resting function was primarily the result of reduced regurgitation rather than a direct beneficial effect of lowered systolic impedance upon pump function.

Miller et al., in studying 12 patients with chronic pump dysfunction from coronary artery disease, found that nitroprusside significantly lowered left ventricular end-diastolic pressure and increased depressed ejection fractions. When a markedly elevated left ventricular end-diastolic pressure was reduced, but to levels slightly above normal, improvement was noted in stroke index and cardiac index. If a near-normal left ventricular end-diastolic pressure was reduced to a relatively low value, no improvement in cardiac index resulted.

Our data show that, in general, the consequences of afterload reduction in patients with aortic regurgitation are beneficial, but that important heterogeneity of response exists. Reductions in mean arterial pressure, left ventricular end-diastolic pressure and mean pulmonary artery pressure are consistently recorded (fig. 1). Forward cardiac index is augmented by nitroprusside in the majority of patients (fig. 3). Thus, the improvement in forward output was accomplished either by an increase in ejection fraction or decrease in regurgitant fraction or combination of both. However, the total or left ventricular cardiac index is usually unaffected by afterload reduction (fig. 2), a result that is consistent with previous studies showing that total cardiac output in patients with severe aortic regurgitation is little affected by exercise.

The consistent reduction in left ventricular stroke work index and minute work index coupled with general improvement in forward cardiac index translate into improved myocardial oxygen supply/demand ratio. The reduction in ventricular size following nitroprusside would also tend to lessen myocardial oxygen requirements by reducing wall tension. Nitroprusside would be expected to benefit the relationship of myocardial oxygen delivery to requirements.

The improved ejection fraction after nitroprusside in patients with markedly depressed resting ejection fractions is consistent with the results observed in cardiomyopathy patients, with or without regurgitant lesions. In patients with chronic ischemic heart disease and failure, depressed ejection fractions almost invariably respond to nitroprusside. Similar results were found in studying patients with chronic mitral regurgitation. Our data in patients with chronic aortic regurgitation confirm that those individuals who exhibit left ventricular dysfunction at rest, as manifested by a depressed resting ejection fraction, will tend to benefit from afterload reduction.

The regurgitant volume did not consistently decline following nitroprusside which contrasts with the uniform fall in regurgitation in patients with mitral regurgitation. A possible explanation is that the diastolic aortic-to-left-ventricular gradient is not always greatly altered by nitroprusside. Our data show that aortic diastolic pressure is less affected than systolic pressure. These observations probably account for the variability in degree of regurgitation with afterload reduction in patients with aortic insufficiency.

Clinical Implications

These data support the feasibility of using afterload reduction in patients with severe aortic regurgitation to assist in the temporary treatment of severe congestive failure or inadequate peripheral perfusion, unresponsive to an adequate trial of digitalis and diuretics. The patient likely to benefit from afterload reduction would, in general, have the following characteristics: 1) depressed forward cardiac index; 2) distinctly elevated left ventricular end-diastolic pressure; 3) reduced ejection fraction; and 4) elevated systolic left ventricular pressure. Careful monitoring of aortic pressure and pulmonary artery wedge pressure would be advisable to assure that excessive reduction in left ventricular filling pressure is not produced. The advantages in such patients would be decreased ventricular size, augmentation of forward stroke index and decreased stroke and minute work index.

By inference, these data provide a rationale for control of systolic blood pressure in patients with chronic aortic regurgitation. The effects of a smaller ventricular volume, possibly decreased regurgitant fraction and lowered ventricular work would seem beneficial in order to delay progressive ventricular dysfunction in patients with aortic regurgitation.

Acknowledgment

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References

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