Systemic Hypertension in Low-Gradient Severe Aortic Stenosis With Preserved Ejection Fraction

Mackram F. Eleid, MD; Rick A. Nishimura, MD, MACC; Paul Sorajja, MD; Barry A. Borlaug, MD

Background—Low-gradient severe aortic stenosis with preserved ejection fraction is an increasingly recognized entity, and symptomatic patients may benefit from aortic valve replacement. However, systemic hypertension frequently coexists with low-gradient severe aortic stenosis, which itself may cause elevated left ventricular (LV) filling pressures with resultant symptoms of dyspnea.

Methods and Results—Symptomatic patients with hypertension (aortic systolic pressure >140 mm Hg) and low-gradient (mean gradient <40 mm Hg) severe aortic stenosis (aortic valve area <1 cm²) with preserved ejection fraction (ejection fraction >50%) who underwent invasive hemodynamic catheterization of the left and right sides of the heart received infusion of intravenous sodium nitroprusside to reduce blood pressure and arterial afterload. At baseline, patients had severe hypertension (aortic systolic pressure, 176±26 mm Hg), pulmonary hypertension (mean pressure, 39±12 mm Hg), elevated LV end-diastolic pressure (19±5 mm Hg), and reduced stroke volume (33±8 mL/m²). All measures of afterload were reduced with nitroprusside (P<0.001 for all). Nitroprusside reduced mean pulmonary artery pressure (25±10 mm Hg) and LV end-diastolic pressure (11±5 mm Hg; P<0.001 for both compared with baseline). Aortic valve area (0.86±0.11 to 1.02±0.16 cm²; P=0.001) and mean gradient (27±5 to 29±6 mm Hg; P=0.02) increased with nitroprusside.

Conclusions—Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction is associated with elevated LV filling pressures and pulmonary hypertension. Treatment of hypertension with vasodilator therapy results in a lowering of the total LV afterload, with a decrease in LV filling pressures and pulmonary artery pressures. These findings have important implications for the management of patients with low-gradient severe aortic stenosis with preserved ejection fraction and hypertension. (Circulation. 2013;128:1349-1353.)

Key Words: aortic valve stenosis □ hypertension □ stroke volume

Low-flow, low-gradient (LG) severe aortic stenosis (AS) with preserved ejection fraction (EF) is an increasingly recognized entity with discordant AS severity criteria that pose a clinical management dilemma. Although treatment is controversial, it is generally recommended that such patients undergo aortic valve replacement when symptomatic and no other cause is found for symptoms. However, systemic hypertension frequently coexists in this patient population, and the increased arterial afterload may itself cause elevated left ventricular filling pressures, which could play a major role in producing symptoms of dyspnea.

Editorial see p 1281
Clinical Perspective on p 1353

We hypothesized that in patients with systemic hypertension and LG severe AS, there are 2 obstructions in series whereby treating systemic hypertension may result only in a reduction in left ventricular (LV) filling pressures. Additionally, because hypertension may result in inaccuracy of AS severity determination, we wished to study the acute effects of treating hypertension on measures of AS severity. Accordingly, we examined the effects of sodium nitroprusside in patients with LG severe AS and preserved EF who underwent invasive hemodynamic catheterization of the right and left sides of the heart, specifically evaluating the effect on LV filling pressures and pulmonary pressures.

Methods

Patients

The Mayo Clinic Institutional Review Board approved this study. Between January 1, 2006, and May 1, 2013, symptomatic patients with LG (<40 mm Hg) severe AS (aortic valve area ≤1 cm² or aortic valve area index ≤0.6 cm²/m²) with preserved EF (>50%) as determined by transthoracic echocardiography who also underwent catheterization of the left and rights of the heart were studied prospectively (group 1). Patients were referred for hemodynamic catheterization for assessment of AS severity at the discretion of their treating physician. Exclusion criteria for the study were moderate or severe concomitant valvular heart disease (eg, aortic, mitral, or tricuspid regurgitation), reduced LV EF (≤50%), age <18 years, and complex congenital heart disease. Clinical characteristics, including symptoms, comorbidities, and echocardiography and hemodynamic data, were recorded. For comparison, patients with LG severe AS and reduced EF (≤50%) who underwent hemodynamic catheterization of the left and right sides of the heart with nitroprusside infusion during the same time period were included (group 2).

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Invasive Hemodynamic Evaluation

All patients underwent hemodynamic catheterization of the left and right sides of the heart in the fasting state with conventional 6F and 7F fluid-filled catheters within 90 days of transthoracic echocardiography. Invasive hemodynamic measurements were obtained before any pharmacological or physical maneuvers or fluid administration. LV end-systolic pressure was measured by examining individual simultaneous aortic and LV tracings and identifying the point of crossover between aortic and LV pressures. Mean LV diastolic pressure was calculated as an estimate of left atrial pressure. For aortic valve area assessment, simultaneous pressures were taken from 2 separate sampling catheters in the central aorta and LV with digital acquisition (3- to 5-millisecond samples) for offline storage and review using proprietary software (CathCoding, Mayo Clinic, Rochester, MN). Cardiac output was determined by the thermodilution technique or the Fick method, indexed to body surface area, and used to determine stroke volume index. For the Fick method, oxygen consumption was measured by expired gas analysis at the time of catheterization (Medical Graphics Corp, St. Paul, MN). The Gorlin formula was used to calculate aortic valve area.4

Invasive Assessment of Afterload

Effective arterial elastance, a lumped measure of arterial load that combines the effects of resistive and pulsatile loading, was calculated from the ratio of LV end-systolic pressure (mm Hg) to stroke volume index (mL/m2). Total systemic arterial compliance was calculated as the ratio of stroke volume index to aortic pulse pressure. Systemic vascular resistance index (dynes·s/m2·cm5) was calculated as follows: (mean aortic pressure−mean right atrial pressure) ÷ cardiac index (L·min−1·m−2).6

Nitroprusside Administration

Sodium nitroprusside was administered to determine the effects of afterload reduction on AS severity. Exclusion criteria for administering nitroprusside included baseline systolic blood pressure <100 mm Hg, mean arterial pressure <60 mm Hg, or history of allergic reaction to the medication. Nitroprusside was started at a 0.25-μg·kg−1·min−1 intravenous infusion and increased in increments of 0.5 to 1 μg·kg−1·min−1 every 5 minutes. The predetermined end points to stop the infusion included a maximal dose of 10 μg·kg−1·min−1, an aortic valve mean gradient ≥40 mm Hg, an aortic mean pressure <60 mm Hg, or intolerable symptoms or side effects. Cardiac output and aortic valve mean gradient were determined both at baseline and at peak nitroprusside infusion in all patients. Patients were classified as having flow reserve if the stroke volume index increased by ≥20% with nitroprusside.10

Statistical Analysis

Wilcoxon rank-sum tests were used for comparing independent samples, and Wilcoxon signed-rank tests were used for comparing pre-treatment and posttreatment measures in the same individuals with an a priori significance defined as P < 0.05. Fisher exact tests were used to compare categorical variables. Spearman rank correlation was used to examine relationships between individual variables. Statistical analysis was performed with SPSS (SAS software version 12.0; SAS Inc, Cary, NC).

Results

Baseline Characteristics

Clinical characteristics and medications are shown in Table 1. Patients in group 1 were symptomatic and elderly (mean age, 78±6 years), and most (83%) had a history of treated hypertension. Group 2 had similar characteristics except for a lower EF (36% versus 66%; P < 0.001) and higher serum creatinine (1.7±0.4 versus 1.2±0.5 mg/dL; P = 0.04).

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics</th>
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<tbody>
<tr>
<td><strong>Group 1, HTN-LGSAS</strong> (n=18)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
</tr>
<tr>
<td>Known hypertension, n (%)</td>
</tr>
<tr>
<td>Known coronary artery disease, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
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<tr>
<td>Serum creatinine, mg/dL</td>
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<tr>
<td>Medications, n (%)</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
</tr>
<tr>
<td>β-Blocker</td>
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<tr>
<td>Calcium channel blocker</td>
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<tr>
<td>Diuretic</td>
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<tr>
<td>Nitrate</td>
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</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; HTN, hypertension; and LGSAS, low-gradient severe aortic stenosis.

Table 2 shows hemodynamic findings at baseline. In group 1, pulmonary hypertension was present in all patients (mean pressure, 39±12 mm Hg) with elevated pulmonary arteriolar resistance (4.41±2.93 Wood units). LV filling pressures were severely elevated (end-diastolic pressure, 19±5 mm Hg; mean diastolic pressure, 13±4 mm Hg). Systemic hypertension was present in all patients (aortic systolic pressure, 176±26 mm Hg; diastolic pressure, 75±13) with a widened pulse pressure (101±26 mm Hg). Cardiac index and stroke volume index were low (2.4±0.4 L·min−1·m−2 and 33±6 mL/m2). Invasive measures of afterload were all abnormal at baseline (Table 2). In group 1, aortic systolic pressure closely correlated with LV end-diastolic pressure (r=0.64, P<0.001). Mean pulmonary artery pressure correlated with aortic systolic pressure (r=0.34, P=0.047). There was no significant relationship between aortic systolic pressure and cardiac index (r=-0.24, P=0.15) or mean aortic valve gradient (r=-0.18, P=0.29).

Group 2 patients tended to have a higher resting heart rate and lower cardiac index and stroke volume index than group 1 patients (Table 2). Aortic systolic, mean, and pulse pressures were lower in group 2 compared with group 1 (Table 2), but LV filling pressures and pulmonary pressures were similar. Invasive measures of arterial afterload were similar between groups (Table 2).

Hemodynamic Effects of Nitroprusside

All patients tolerated nitroprusside with no adverse effects. The mean peak dose of nitroprusside was 1.3±0.9 μg·kg−1·min−1 in group 1 and 0.8±0.4 μg·kg−1·min−1 in group 2. All arterial afterload measures improved with nitroprusside in both groups (Table 2). Nitroprusside decreased mean aortic, LV end-diastolic and mean diastolic, and mean pulmonary artery

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pressures ($P<0.05$ for all; Table 2). Figure 1 shows representative hemodynamic tracings in a patient with LG severe AS and severe systemic hypertension before and after nitroprusside. The online-only Data Supplement shows the individual pressure tracings and hemodynamic data of the remaining 17 patients in group 1 and the 6 patients in group 2.

### AS Severity

In group 1, the mean gradient increased from $27\pm5$ to $29\pm6$ mm Hg ($P=0.02$) and the aortic valve area increased from $0.86\pm0.11$ to $1.02\pm0.16$ cm$^2$ ($P=0.003$) after nitroprusside infusion. Only 4 patients had no increase in aortic valve area with lowering of systemic aortic pressure (see the online-only Data Supplement). Individual changes in the aortic valve area and mean gradient are shown in Figure 2.

In group 2, the mean gradient increased from $24\pm4$ to $27\pm5$ mm Hg ($P=0.01$), and there was a nonsignificant increase in aortic valve area ($0.89\pm0.10$ to $0.98\pm0.12$ cm$^2$; $P=0.21$). Two patients had a decrease in aortic valve area with nitroprusside (see the online-only Data Supplement).

### Discussion

The present investigation highlights the importance of considering the characteristics of the arterial circulation in addition

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**Table 2. Effect of Sodium Nitroprusside on Low-Gradient Severe Aortic Stenosis Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1, HTN-LGSAS (n=18)</th>
<th>Group 2, Reduced EF–LGSAS (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before NTP</td>
<td>After NTP</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±14</td>
<td>76±14</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>39±12</td>
<td>25±10</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance, Wood units</td>
<td>4.41±2.93</td>
<td>2.68±1.41</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure, mm Hg</td>
<td>19±5</td>
<td>11±5</td>
</tr>
<tr>
<td>Left ventricular mean diastolic pressure, mm Hg</td>
<td>13±5</td>
<td>8±4</td>
</tr>
<tr>
<td>Aortic systolic pressure, mm Hg</td>
<td>176±26</td>
<td>108±14</td>
</tr>
<tr>
<td>Aortic diastolic pressure, mm Hg</td>
<td>75±13</td>
<td>54±12</td>
</tr>
<tr>
<td>Aortic mean pressure, mm Hg</td>
<td>115±17</td>
<td>77±15</td>
</tr>
<tr>
<td>Aortic pulse pressure, mm Hg</td>
<td>101±26</td>
<td>54±14</td>
</tr>
<tr>
<td>Stroke volume index, mL/m$^2$</td>
<td>33±8</td>
<td>36±7</td>
</tr>
<tr>
<td>Cardiac index, L·min$^{-1}$·m$^{-2}$</td>
<td>2.44±0.40</td>
<td>2.70±0.51</td>
</tr>
<tr>
<td>Effective arterial elastance, mm Hg·mL$^{-1}$·m$^{-2}$</td>
<td>4.86±1.30</td>
<td>2.75±0.77</td>
</tr>
<tr>
<td>Total arterial compliance, mL·m$^{-2}$·mm Hg</td>
<td>0.37±0.12</td>
<td>0.71±0.25</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne·s·m$^2$/cm$^4$</td>
<td>3441±640</td>
<td>2155±827</td>
</tr>
<tr>
<td>Mean aortic valve gradient, mm Hg</td>
<td>27±5</td>
<td>29±6</td>
</tr>
<tr>
<td>Aortic valve area, cm$^2$</td>
<td>0.86±0.11</td>
<td>1.02±0.16</td>
</tr>
</tbody>
</table>

$EF$ indicates ejection fraction; $HTN$, hypertension; $LGSAS$, low-gradient severe aortic stenosis; and $NTP$, nitroprusside.

*Significant difference ($P<0.05$) between groups 1 and 2.

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**Figure 1.** Representative hemodynamic tracings of a patient with low-gradient severe aortic stenosis and preserved ejection fraction with concomitant severe systemic hypertension. At baseline, there is a widened pulse pressure, delayed aortic (Ao) pressure upstroke, and severely elevated left ventricular (LV) and left atrial (LA) filling pressures. With nitroprusside and normalization of systemic pressure, the aortic pressure upstroke becomes less delayed and more rounded, consistent with only relative aortic stenosis, and LV filling pressures normalize. AVA indicates aortic valve area; LVEDP, left ventricular end-diastolic pressure; and SVI, stroke volume index.
to traditional measurements in the assessment of AS. Systemic hypertension in the presence of LG severe AS with preserved EF is associated with elevated LV filling pressures and pulmonary hypertension, which are reduced with the vasodilator sodium nitroprusside. These results have important implications for the management of the increasingly prevalent population of elderly patients with hypertension and LG severe AS with preserved EF. Often, such patients present with symptoms that are difficult to attribute solely to AS, and the clinician is faced with the challenge of adequately characterizing the severity of AS and its contribution to symptoms and determining whether the patient would benefit from aortic valve replacement. The decision to perform aortic valve replacement is a major one in this group of patients, not only because of the increased risk of surgery in the aging population but also because many patients may have only moderate AS, in which case aortic valve replacement would expose them to unnecessary risk and would not treat the underlying cause of symptoms.

There was a good correlation between aortic systolic pressure and LV diastolic pressures, highlighting the importance of ventriculoarterial coupling in patients with LG severe AS and preserved EF. Similar relationships have been shown in patients with heart failure and preserved EF in whom the ability of the myocardium to augment contractility in response to increases in afterload is impaired. The very large drop in systemic arterial pressure with fairly low-dose nitroprusside is also consistent with prior studies in heart failure with preserved EF. This dramatic response, likely related to a steep end-systolic pressure–volume relationship, underlines the importance of careful titration when short- or long-term vasodilator therapy is used in this group. The majority of patients with low stroke volume at baseline had a subsequent increase in stroke volume with nitroprusside. This highlights the observation that patients with hypertension and LG severe AS with preserved EF have 2 obstructions in series and that treatment of systemic hypertension may help reduce symptoms in addition to reducing cardiovascular risk.

In a previous study using an animal model of fixed supravalvular AS and acutely induced hypertension, mean gradient, stroke volume, and aortic valve area were all lower in the setting of systemic hypertension. With treatment of hypertension, there was a large increase in mean gradient with a relatively small increase in the aortic valve area such that the aortic valve area was still severely reduced. We observed a small increase in the mean gradient and stroke volume in the majority of patients with hypertension and LG severe AS with treatment of hypertension, suggesting that the degree of AS was not severe. However, in some patients, treatment of hypertension resulted in an increase in the mean gradient with either no change or a reduction in the valve area, suggesting severe AS. The heterogeneous responses to nitroprusside in this population of patients with LG severe AS and preserved EF underscore the importance of integrating all of the available hemodynamic information into the assessment, including not only the mean gradient and valve area data but also cardiac output, characteristics of the peripheral circulation (blood pressure, pulse pressure, measures of afterload), and the aortic pressure tracing morphology. Whether nitroprusside used to characterize AS severity results in clinically meaningful improvements in outcomes is uncertain and requires studies with long-term follow-up of clinical end points.

This study also has important implications for the management of paradoxical low-flow, LG severe AS. When systemic hypertension is present in asymptomatic patients with LG severe AS and preserved EF, it would be prudent to treat the hypertension with medical therapy before aortic valve replacement is considered. As demonstrated here, treatment of hypertension results in a beneficial decrease in the total LV afterload and reduces LV filling pressures and pulmonary artery pressures. If treatment of hypertension results in resolution of symptoms, continued medical therapy would be reasonable. Treatment of hypertension may also be of benefit in the determination of the severity of the AS. In patients with systemic hypertension and LG severe AS, the severity of AS may be overestimated, as seen in the present study. These findings are similar to a Doppler echocardiographic study of acutely induced hypertension using handgrip or phenylephrine that demonstrated an inverse relationship between the change in blood pressure and aortic valve area that was
dependent primarily on changes in flow.\textsuperscript{15} Remeasurement of aortic valve hemodynamics should be repeated after normalization of blood pressure in these patients.

Limitations
Although the present study represents a small series of patients, each underwent a comprehensive invasive hemodynamic assessment of AS severity before and after the novel administration of the vasodilator sodium nitroprusside. Although the patients were studied prospectively and consecutively, selection bias may be present. Further studies on a large number of patients with outcome data after treatment of hypertension are necessary to determine whether the aortic valve hemodynamics during nitroprusside infusion are beneficial in the evaluation and management of this group of patients.

Conclusions
Systemic hypertension in LG severe AS with preserved EF is associated with low output, elevated LV filling pressures, and pulmonary hypertension. Treatment of hypertension with vasodilator therapy results in a beneficial decrease in the total LV afterload and a decrease in LV filling pressures and pulmonary hypertension. These findings have important implications for the management of patients with LG severe AS with preserved EF and systemic hypertension.

Disclosures
None.

References

CLINICAL PERSPECTIVE

Low-flow, low-gradient severe aortic stenosis with preserved ejection fraction is an increasingly recognized entity with discordant aortic stenosis severity criteria. Although treatment is controversial, it is generally recommended that such patients undergo aortic valve replacement when symptomatic and no other cause is found for symptoms. Systemic hypertension frequently coexists in this patient population, and the increased arterial afterload may itself cause elevated left ventricular filling pressures, which could play a major role in producing symptoms of dyspnea. In this study, symptomatic patients with hypertension (aortic systolic pressure >140 mmHg) and low-gradient (mean gradient <40 mmHg) severe aortic stenosis (aortic valve area <1 cm\textsuperscript{2}) with preserved ejection fraction (ejection fraction >50%) underwent invasive hemodynamic catheterization of the left and right sides of the heart and received infusion of intravenous sodium nitroprusside to reduce blood pressure and arterial afterload. At baseline, patients had severe hypertension (aortic systolic pressure, 176±26 mmHg), pulmonary hypertension (mean pressure 39±12 mmHg), elevated left ventricular end-diastolic pressure (19±5 mmHg), and reduced stroke volume (33±8 mL/m\textsuperscript{2}). Nitroprusside reduced mean pulmonary artery pressure (25±10 mmHg) and left ventricular end-diastolic pressure (11±5 mmHg; \textit{P}<0.001 for both compared with baseline). Aortic valve area (0.86±0.11 to 1.02±0.16 cm\textsuperscript{2}; \textit{P}=0.001) and mean gradient (27±5 to 29±6 mmHg; \textit{P}=0.02) increased with nitroprusside. Treatment of hypertension with vasodilator therapy resulted in a lowering of the total left ventricular afterload, with a decrease in left ventricular filling pressures and pulmonary artery pressures. These findings have important implications for the management of patients with low-gradient severe aortic stenosis with preserved ejection fraction and hypertension.
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SUPPLEMENTAL MATERIAL

Supplemental Figures 1 and 2 Legend: Individual hemodynamic tracings before and after nitroprusside in patients with hypertension and low gradient (LG) severe aortic stenosis (AS) and preserved ejection fraction (patients 1-17 (patient 18 is shown in Figure 1)) and patients with LG severe AS and reduced ejection fraction (second page, patients 1-6). Abbreviations: AVA, aortic valve area; MG, mean gradient; NTP, nitroprusside; SVI, stroke volume index.