Systemic Hypertension in Low Gradient Severe Aortic Stenosis with
Preserved Ejection Fraction

Running title: Eleid et al.; Hypertension and low gradient aortic stenosis

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Abstract

**Background**—Low gradient (LG) severe aortic stenosis (AS) with preserved ejection fraction (EF) is an increasingly recognized entity, and symptomatic patients may benefit from aortic valve replacement. However, systemic hypertension frequently coexists with LG severe AS, 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 mmHg) and LG (mean gradient <40 mmHg) severe AS (aortic valve area <1 cm²) with preserved EF (EF >50%) who underwent invasive hemodynamic left and right heart catheterization 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 LV end diastolic pressure (19±5 mmHg) 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 mmHg) and LV end diastolic pressure (11±5 mmHg) (p<0.001 for both as compared to 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 mmHg, p=0.02) increased with nitroprusside.

**Conclusions**—Systemic hypertension in LG severe AS with preserved EF 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 LG severe AS with preserved EF and hypertension.

**Key words:** hypertension, aortic stenosis, ejection fraction, vasodilator, low gradient, afterload
Introduction

Low flow, low gradient (LG) severe AS with preserved ejection fraction (EF) is an increasingly recognized entity with discordant AS severity criteria that poses a clinical management dilemma \(^1\). Although treatment is controversial, it is generally recommended that such patients undergo aortic valve replacement when symptomatic and no other etiology is found for symptoms \(^2\).

However, systemic hypertension frequently co-exists 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.

We hypothesized that in patients with systemic hypertension and LG severe AS there are two obstructions in series whereby treating systemic hypertension only may result in a reduction in left ventricular 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 right and left heart catheterization, specifically evaluating the effect on left ventricular 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 mmHg) severe AS (aortic valve area ≤ 1 cm\(^2\) or aortic valve area index ≤ 0.6 cm\(^2\)/m\(^2\)) with preserved EF (> 50%) as determined by transthoracic echocardiography who also underwent left and right heart catheterization 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 (e.g. aortic, mitral or tricuspid regurgitation), reduced left ventricular EF (≤ 50%), age < 18 years, and complex congenital heart disease. Clinical characteristics including symptoms, co-morbidities, echocardiography and hemodynamic data were recorded. For comparison, a group of patients with LG severe AS and reduced EF (≤ 50%) who underwent hemodynamic left and right heart catheterization with nitroprusside infusion during the same time period were included (Group 2).

**Invasive Hemodynamic Evaluation**

All patients underwent hemodynamic left and right heart catheterization in the fasting state using conventional 6 and 7 French fluid-filled catheters within 90 days of transthoracic echocardiography. Invasive hemodynamic measurements were obtained prior to any pharmacologic 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 left ventricular diastolic pressure was calculated as an estimate of left atrial pressure. For aortic valve assessment, simultaneous pressures were taken from two separate sampling catheters in the central aorta and LV with digital acquisition (3 to 5 ms samples) for offline storage and review using proprietary software (CathCoding, Mayo Clinic, Rochester, MN). Cardiac output was determined by the thermodilution technique or by the Fick method, indexed to body surface area, and was 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 Corporation., St. Paul, MN). The Gorlin formula was used to calculate aortic valve area.
Invasive Assessment of Afterload

Effective arterial elastance (Ea), 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 (mmHg) to stroke volume index (mL/m²)^5-7. Total systemic arterial compliance (Ca) was calculated from the ratio of stroke volume index to aortic pulse pressure^8,9. Systemic vascular resistance index (SVRI, dyn·sec·m²/cm⁵) was calculated from (mean aortic pressure – mean right atrial pressure * 80) / cardiac index (L/min/m²)^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 mmHg, mean arterial pressure < 60 mmHg, or history of allergic reaction to the medication. Nitroprusside was started at 0.25 mcg/kg/min IV infusion and increased in increments of 0.5 – 1 mcg/kg/min every 5 minutes. The predetermined end points to stop the infusion included a maximal dose of 10 mcg/kg/min, aortic valve mean gradient > 40 mm Hg, 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 (SVI) increased by ≥ 20% with nitroprusside^10.

Statistical Analysis

Wilcoxon rank sum tests were used for comparing independent samples and Wilcoxon signed rank tests for comparing pre- and post-treatment 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 using SPSS (SAS software version 12.0, Cary, NC).

Results

Baseline Characteristics

Clinical characteristics and medications are shown in Table 1. Patients in group 1 were symptomatic, elderly (mean age 78 ± 6 years) and most (83%) had a history of treated hypertension. Group 2 had similar characteristics with the exception of lower ejection fraction (36% vs. 66%, p<0.001) and higher serum creatinine (1.7 ± 0.4 vs. 1.2 ± 0.5, p=0.04).

Table 2 shows hemodynamic findings at baseline. In group 1, pulmonary hypertension was present in all patients (mean pressure 39 ± 12 mmHg) with elevated pulmonary arteriolar resistance (4.41± 2.93 WU). Left ventricular filling pressures were severely elevated (end diastolic pressure 19 ± 5 and mean diastolic pressure 13 ± 4 mmHg). Systemic hypertension was present in all patients (aortic systolic pressure 176 ± 26 and diastolic pressure 75 ± 13) with a widened pulse pressure (101 ± 26 mmHg). Cardiac index and stroke volume index were low (2.4 ± 0.4 L/min/m² and 33 ± 8 mL/m²). Invasive measures of afterload were all abnormal at baseline (Table 2).

In group 1, aortic systolic pressure closely correlated with left ventricular 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 (Table 2). Aortic systolic, mean and pulse pressure were lower in group 2 compared to group 1 (Table 2), but left ventricular 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 mcg/kg/min in group 1 and 0.8 ± 0.4 mcg/kg/min in group 2. All arterial afterload measures improved with nitroprusside in both groups (Table 2). Nitroprusside decreased mean aortic, LV end and mean diastolic, and mean pulmonary artery 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 supplementary appendix shows the individual pressure tracings and hemodynamic data of the remaining 17 patients in group 1 and the 6 patients in group 2 (appendix).

**Aortic stenosis severity**

In group 1, the mean gradient increased from 27 ± 5 to 29 ± 6 mmHg (p=0.02) and the aortic valve area increased from 0.86 ± 0.11 to 1.02 ± 0.16 cm² (p=0.003) after nitroprusside infusion. There were only 4 patients who had no increase in aortic valve area with lowering of systemic aortic pressure (appendix). Individual changes in the aortic valve area and mean gradient are shown in Figure 2.

In group 2, the mean gradient increased from 24 ± 4 to 27 ± 5 mmHg (p=0.01) and there was a non-significant increase in the aortic valve area (0.89 ± 0.10 to 0.98 ± 0.12, p=0.21).

There were 2 patients that had a decreased in the aortic valve area with nitroprusside (appendix).

**Discussion**

The present investigation highlights the importance of considering the characteristics of the arterial circulation in addition to traditional measurements in the assessment of aortic stenosis.
Systemic hypertension in the presence of LG severe AS with preserved EF is associated with elevated LV filling pressures and pulmonary hypertension that are reduced with the vasodilator sodium nitroprusside. These results have important implications for 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, its contribution to symptoms, and whether the patient would benefit from AVR. The decision to perform AVR is a major one in this group of patients, not only due to the increased risk of surgery in the aging population, but also because many may only have moderate AS, in which case AVR would expose them to unnecessary risk and not treat the underlying cause of symptoms.

There was a good correlation between aortic systolic pressure and left ventricular 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, where 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 is likely related to a steep end-systolic pressure volume relationship, and underlines the importance of careful titration when utilizing acute or chronic vasodilator therapy 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 two 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\textsuperscript{14}. 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 and a larger increase in the aortic valve area with treatment of hypertension, suggesting that the degree of aortic stenosis 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 underscores 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 using nitroprusside to characterize AS severity results in clinically meaningful improvements in outcomes is uncertain and requires studies with long term follow-up of clinical endpoints.

This study also has important implications for the management of paradoxical low flow, LG severe AS. When systemic hypertension is present in symptomatic patients with low gradient severe AS and preserved ejection fraction, it would be prudent to treat the hypertension with medical therapy prior to consideration of aortic valve replacement. As demonstrated herein, treatment of hypertension results in a beneficial decrease in the total left ventricular afterload and reduces left ventricular filling pressures and pulmonary artery pressures. If treatment of the
hypertension results in resolution of symptoms, continued medical therapy would be reasonable. Treatment of the 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 primarily dependent on changes in flow\textsuperscript{15}. Re-measurement 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 following treatment of hypertension is necessary to determine if 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, a decrease in LV filling pressures and pulmonary artery pressures. These findings have important implications for the management of patients with LG severe AS with preserved EF and systemic hypertension.
Conflict of Interest Disclosures: None.

References:


**Table 1. Clinical Characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Group 1: HTN-LGSAS (n=18)</th>
<th>Group 2: Reduced EF LGSAS (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>78 ± 10</td>
<td>77 ± 6</td>
<td>0.37</td>
</tr>
<tr>
<td>Female sex</td>
<td>12 (67%)</td>
<td>3 (50%)</td>
<td>0.63</td>
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<tr>
<td>Symptomatic</td>
<td>17 (100%)</td>
<td>6 (100%)</td>
<td>1.00</td>
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<td>Body mass index (kg/m²)</td>
<td>31 ± 6</td>
<td>28 ± 3</td>
<td>0.27</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>66 ± 5</td>
<td>36 ± 15</td>
<td>&lt;0.001</td>
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<td>Known hypertension</td>
<td>15 (83%)</td>
<td>4 (67%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Known coronary artery disease</td>
<td>1 (39%)</td>
<td>4 (67%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (28%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>3 (17%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.2 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitor/ ARB</td>
<td>8 (44%)</td>
<td>2 (33%)</td>
<td>1.00</td>
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<tr>
<td>Aldosterone antagonist</td>
<td>3 (17%)</td>
<td>3 (50%)</td>
<td>0.14</td>
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<tr>
<td>Beta blocker</td>
<td>14 (78%)</td>
<td>4 (67%)</td>
<td>0.62</td>
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<tr>
<td>Calcium channel blocker</td>
<td>2 (11%)</td>
<td>1 (17%)</td>
<td>0.45</td>
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<tr>
<td>Diuretic</td>
<td>10 (56%)</td>
<td>5 (83%)</td>
<td>0.35</td>
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<tr>
<td>Nitrate</td>
<td>3 (17%)</td>
<td>0 (0)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; HTN, hypertension; LGSAS, low gradient severe aortic stenosis
Table 2. Effect of Sodium Nitroprusside on Low Gradient Severe AS Hemodynamics.

| Table 2. Effect of Sodium Nitroprusside on Low Gradient Severe AS Hemodynamics. |
|---------------------------------|--------------------|--------------------|---|--------------------|--------------------|---|
|                                | Group 1: HTN-LGSAS (n=18) | Group 2: Reduced EF LGSAS (n=6) | P  | Before NTP | After NTP | Before NTP | After NTP | P  |
| Heart rate (bpm)               | 74±14               | 76±14               | 0.32 | 92±23       | 82±22       | 0.25 |
| Mean pulmonary artery pressure (mmHg) | 39±12         | 25±10               | <0.001 | 40±15       | 32±17       | 0.13 |
| Pulmonary arteriolar resistance (WU) | 4.41±2.93    | 2.68±1.41           | 0.001 | 5.18±3.78   | 3.72±2.15   | 0.13 |
| Left ventricular end diastolic pressure (mmHg) | 19±5         | 11±5                | <0.001 | 20±6        | 12±7        | 0.03 |
| Left ventricular mean diastolic pressure (mmHg) | 13±5         | 8±4                 | <0.001 | 14±6        | 9±5         | 0.13 |
| Aortic systolic pressure (mmHg) | 176±26             | 108±14               | <0.001 | 131±30*     | 105±21       | 0.03 |
| Aortic diastolic pressure (mmHg) | 75±13             | 54±12               | <0.001 | 67±12       | 55±10       | 0.03 |
| Aortic mean pressure (mmHg)    | 115±17             | 77±15               | <0.001 | 92±16*      | 74±12       | 0.03 |
| Aortic pulse pressure (mmHg)   | 101±26             | 54±14               | <0.001 | 64±28*      | 50±19       | 0.03 |
| Stroke volume Index (mL/m²)    | 33±8               | 36±7                | 0.13 | 26±11       | 35±10       | 0.03 |
| Cardiac index (L/min/m²)       | 2.44±0.40          | 2.70±0.51           | 0.09 | 2.23±0.46   | 2.75±0.49   | 0.06 |
| Effective arterial elastance (mmHg/ml/m²) | 4.86±1.30 | 2.75±0.77       | <0.001 | 4.84±1.56   | 2.78±0.77   | 0.03 |
| Total arterial compliance (mL/m²/mmHg) | 0.37±0.12 | 0.71±0.25       | <0.001 | 0.45±0.16   | 0.77±0.29   | 0.03 |
| Systemic vascular resistance index (dyn·s/cm³/m²) | 3441±840 | 2155±827        | <0.001 | 3253±1238   | 2098±709   | 0.03 |
| Mean aortic valve gradient (mmHg) | 27±5          | 29±6                | 0.02 | 24±4        | 27±5        | 0.03 |
| Aortic valve area (cm²)         | 0.86±0.11          | 1.02±0.16           | 0.001 | 0.89±0.10   | 0.98±0.12   | 0.19 |

Legend: * indicates significant difference (p<0.05) between groups 1 and 2
Abbreviations: EF, ejection fraction; HTN, hypertension; LGSAS, low gradient severe aortic stenosis; NTP, nitroprusside

Figure Legends:

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.

**Figure 2.** Individual changes in the aortic valve area and mean gradient with sodium nitroprusside in patients with hypertension and low gradient aortic stenosis and preserved ejection fraction. In the majority of patients, there was a small increase in the mean gradient and a larger increase in the valve area.
Figure 1

**Baseline**
- Mean gradient 22 mmHg
- SVI 23 mL/m$^2$
- AVA 0.7 cm$^2$

**Nitroprusside**
- Mean gradient 26 mmHg
- SVI 34 mL/m$^2$
- AVA 1.0 cm$^2$
Figure 2
Systemic Hypertension in Low Gradient Severe Aortic Stenosis with Preserved Ejection Fraction
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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.