Systemic pressure does not directly affect pressure gradient and valve area estimates in aortic stenosis in vitro

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Aims
Hypertension is a frequent finding in patients with aortic stenosis (AS). However, controversial data about the influence of systemic blood pressure on the quantification of AS have been published.

Methods and results
Various models of AS (plates and biological valves) were studied in an in vitro circuit. Valve areas were calculated with the Doppler continuity equation and the Gorlin formula. Systolic systemic pressures were increased from 80 to 200 mmHg while flow rates were maintained constant. In addition, a computational fluid dynamics (CFD) model was constructed to test the effect of systemic pressures on pressure gradient and valve area estimates.

When systemic pressure was raised, pressure gradients as well as valve areas did not change (mean difference 3.4 ± 1.8 mmHg, range 0.4–6.8 mmHg; mean difference 0.01 ± 0.03 cm², range −0.02 to 0.05 cm²). By multivariable analysis, neither valve area nor pressure gradient were independently affected by systemic pressure. In addition, CFD analysis revealed no effect of systemic pressure on pressure gradient and valve area.

Conclusion
Our results suggest that blood pressure itself does not directly affect pressure gradients and valve area estimates in AS. Thus, when observed in vivo, these changes are most likely due to afterload-related variations of ejection fraction and, therefore, flow rate.

Keywords
Aortic stenosis • Haemodynamics • Hypertension

Introduction
Aortic stenosis (AS) is a highly prevalent disease in industrialized countries affecting between 2 and 7% of the elderly population.1,2 Up to 50% of AS patients have been reported to suffer from additional systemic hypertension.3,4 Although this combination is so frequent, the possible effect of blood pressure changes on the assessment of AS has gained little attention while the impact of flow has extensively been studied.5–15 Few clinical studies, which evaluated the association between blood pressure and estimated pressure gradients and valve areas, have yielded varying results.7,16–18 Clinical data are, however, difficult to interpret since the interventions used to induce blood pressure changes cause a complex combination of changes of peripheral resistance, ejection fraction and transvalvular flow rate. Thus, in humans it is almost impossible to study changes exclusively caused by variation of systemic pressure. An experimental setting appears more appropriate to evaluate this question, however, only two experimental studies on the topic were carried out19,20 and they have yielded opposite results. While Kadem et al.19 recently reported that hypertension may lead to a decrease of pressure gradients in AS in an experimental animal model, another study showed a linear increase of pressure gradients with rising systemic pressure.20

Thus, the important question whether variation in blood pressure itself influences pressure gradient and valve area measurements independently of secondary flow changes and whether
blood pressure has therefore to be considered in the assessment of AS still remains unclear. To resolve this question we used a well-controlled in vitro circulation model, applying both Doppler and catheter technique to assess stenosis severity, and in addition established a computational fluid dynamics (CFD) model. By all the three methods, the impact of blood pressure on pressure gradients and valve area estimates in AS was carefully assessed.

**Methods**

**Experimental model**

The modular in vitro flow circuit used in this study has previously been described in detail (Figure 1). It consists of ventricular and aortic section, a compliance chamber and a reservoir. Aorta, compliance chamber and reservoir are made of Plexiglas and connected by silicone tubes. The system is driven by a computer-controlled piston pump (Vivitro Inc.), which generates stroke volumes (SV) from 10 to 100 mL. Ejection pressure can be varied from 0 to 300 mmHg, pulse rate from 30 to 120 b.p.m., and ejection time from 100 to 700 ms. Flow rate was measured with an ultrasonic flowmeter (Transonic Systems Inc.) that was calibrated against timed collections. In the present study the flow probe was placed between pump and stenosis. Pressure taps 10 mm proximal and 50 mm distal to the stenosis were connected to electronic pressure transducers (Peter van Berg, Hellige signal amplifier) by fluid filled catheters. Physiological pressures were maintained by adjusting pump characteristics, distal compliance, and resistance. An aortic diameter of 4.0 cm was chosen to minimize pressure recovery (22). A bioprosthetic valve between ventricle and test section avoided backflow when plates with circular orifices served as models of stenotic valves. The test section has been designed to allow optimal alignment of Doppler beam and flow across the stenosis. To mount bioprostheses in the circuit, they were sutured into silicon rings, which were fixed on Plexiglas rings. A water glycerol solution (60% water, 40% glycerol), which approximates the viscosity of blood at a temperature of 22.5 °C (3.5 c.p.), served as test fluid. 10 g/L cornstarch were added to facilitate Doppler measurements. Doppler, pressure- and flow tracings were simultaneously recorded and transferred to a data acquisition system (Hellige GmbH, PC) for further analysis, which was performed with commercially available software (Famos 3.0). The utilized set-up resulted in Doppler, flow, and pressure tracings very similar to the in vivo setting. Peripheral resistance ranged from 960 to 4267 dyn s cm⁻² (mean 2240 ± 835 dyn s cm⁻²).

**Types of stenosis**

Lucite plates (2 mm thickness) with central circular orifices of 0.75, 1.0, and 1.25 cm² served as models of rigid valve stenoses. In addition, a Carpentier Edwards 23 mm bioprostheses was used. The commissures of the bioprosthetic valve were sewed together to simulate valvular AS with a more flexible orifice.

**Doppler measurements**

A Vingmed CFM 800 (Vingmed Sound A/S) with a Duplex probe (2.5 MHz CW-Doppler) was used for continuous-wave and pulsed wave Doppler measurements. The ultrasound probe was coupled to the model with ultrasound gel (Gerosonic) by fluid filled catheters. Physiological pressures were maintained by adjusting pump characteristics, distal compliance, and resistance. An aortic diameter of 4.0 cm was chosen to minimize pressure recovery. A bioprosthetic valve between ventricle and test section avoided backflow when plates with circular orifices served as models of stenotic valves. The test section has been designed to allow optimal alignment of Doppler beam and flow across the stenosis. To mount bioprostheses in the circuit, they were sutured into silicon rings. A water glycerol solution (60% water, 40% glycerol), which approximates the viscosity of blood at a temperature of 22.5 °C (3.5 c.p.), served as test fluid. 10 g/L cornstarch were added to facilitate Doppler measurements. Doppler, pressure- and flow tracings were simultaneously recorded and transferred to a data acquisition system (Hellige GmbH, PC) for further analysis, which was performed with commercially available software (Famos 3.0). The utilized set-up resulted in Doppler, flow, and pressure tracings very similar to the in vivo setting. Peripheral resistance ranged from 960 to 4267 dyn s cm⁻² (mean 2240 ± 835 dyn s cm⁻²).

**Figure 1** Diagram of the circulation model: AM, amplifier; A/D, analogue-to-digital converter; D, Doppler probe; F, flow probe; P, pressure transducer; R, resistance; US, ultrasound device.
The cross-sectional area of the LVOT (CSA_{LVOT}) in our model was 3.8 cm². Mean systolic transvalvular flow rate (Q_{mean}) was obtained by dividing SV by systolic ejection time. Peak instantaneous pressure gradients (Δp_{peak}) were calculated according to the simplified Bernoulli equation:

$$\Delta p_{\text{peak}} = 4 \cdot V_{\text{max}}^2,$$  \hspace{1cm} \text{(2)}

where $V_{\text{max}}$ is the maximum transvalvular velocity as obtained by CW-Doppler. The mean pressure gradient (Δp_{mean}) was derived by averaging instantaneous pressure gradients over the ejection period. Effective aortic valve area (AVA_{Doppler}) was calculated using the continuity equation:\textsuperscript{33}

$$\text{AVA}_{\text{Doppler}} = \frac{\text{VTI}_{\text{LVOT}} \cdot \text{CSA}_{\text{LVOT}}}{\text{VTI}_{\text{AO}}},$$  \hspace{1cm} \text{(3)}

Calculations based on direct flow and pressure measurements. Mean transvalvular flow (Q_{mean}) was determined by integrating the area under the flow curve and dividing it by the measured systolic ejection time. The mean pressure gradient (Δp_{mean}) was calculated by integrating the difference between ventricular and aortic pressure throughout systole and dividing it by the ejection period. A constant of 4.3 was used for calculation of the anatomic valve area (AVA_{Gorlin}) by the Gorlin formula:\textsuperscript{34}

$$\text{AVA}_{\text{Gorlin}} = \frac{Q_{\text{AO}}}{\sqrt{(4.3 \cdot \Delta p)}},$$  \hspace{1cm} \text{(4)}

### Test protocol

Experiments were carried out at mean flow rates of 2.0, 3.0, 4.0 and 5.0 L/min, SV ranged from 30 to 85 mL. Peak and mean systolic flow rates were kept constant at each set of experiments while poststenotic systolic pressure was increased in incremental steps of 20 mmHg from 80 to 200 mmHg. Poststenotic systolic pressures were thus intended to cover the whole range from hypotension to hypertension. Pulse rate was maintained at 60 b.p.m., with an ejection time ranging from 320 to 420 ms. Echo Doppler data were collected simultaneously with invasive pressure and flow measurements at each flow rate.

### Computational modelling

With CFD a two-dimensional axis-symmetric model of the LVOT, plates, simulating AS, and the aortic root were developed, with the dimensions used in the in vitro model. A computational mesh including 24 664 quadrilateral elements was generated. (Fluent 6.2 and Gambit 2.2; Fluent Inc., Lebanon, NH, implemented on a Dell Precision Workstation 670, 3.2 GHz dual processor unit).

The incompressible version of the Navier–Stokes equations was resolved in conjunction with the RNG (i.e. renormalization group method) based k-ε turbulence model, which is suitable for the simulation in the laminar–turbulent transition. Simulations were performed with fixed mass flow rates, according to the in vitro measurements. The outlet pressure was defined for outflow cross-section and set for three different given values (0–100–200 mmHg). Inflow pressure was calculated depending on this given outflow pressure and the given input flow. The walls were set as no-slip boundaries.

### Table 1: Mean values of Doppler and catheter velocity time integrals, valve area estimates and pressure gradients for each flow rate

<table>
<thead>
<tr>
<th>Valve</th>
<th>Flow rate (L/min)</th>
<th>VTILVOT (m)</th>
<th>VTIALVOT (cm²)</th>
<th>AVA – Cont. (cm²)</th>
<th>AVA – Cath. (cm²)</th>
<th>Mean dp – Doppler (mmHg)</th>
<th>Mean dp – Catheter (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological</td>
<td>2.0</td>
<td>88.4 ± 3.1</td>
<td>12.8 ± 0.3</td>
<td>0.62 ± 0.02</td>
<td>0.66 ± 0.02</td>
<td>17.5 ± 1.4</td>
<td>18.3 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>103.7 ± 5.7</td>
<td>13.2 ± 0.4</td>
<td>0.61 ± 0.02</td>
<td>0.67 ± 0.01</td>
<td>28.6 ± 1.7</td>
<td>30.8 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>115.8 ± 6.4</td>
<td>15.4 ± 0.4</td>
<td>0.62 ± 0.02</td>
<td>0.66 ± 0.02</td>
<td>43.8 ± 2.4</td>
<td>40.2 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>133.0 ± 7.4</td>
<td>19.5 ± 0.5</td>
<td>0.63 ± 0.03</td>
<td>0.66 ± 0.02</td>
<td>52.0 ± 3.7</td>
<td>48.8 ± 2.3</td>
</tr>
<tr>
<td>Plate 1.25 cm²</td>
<td>2.0</td>
<td>50.8 ± 1.0</td>
<td>8.2 ± 0.2</td>
<td>0.68 ± 0.02</td>
<td>0.77 ± 0.01</td>
<td>7.7 ± 0.5</td>
<td>9.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>75.2 ± 1.8</td>
<td>13.1 ± 0.2</td>
<td>0.68 ± 0.02</td>
<td>0.77 ± 0.01</td>
<td>15.4 ± 0.6</td>
<td>14.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>89.2 ± 3.3</td>
<td>16.5 ± 0.3</td>
<td>0.72 ± 0.02</td>
<td>0.76 ± 0.02</td>
<td>22.0 ± 1.2</td>
<td>24.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>110.0 ± 4.2</td>
<td>19.6 ± 0.3</td>
<td>0.70 ± 0.02</td>
<td>0.78 ± 0.03</td>
<td>33.8 ± 2.4</td>
<td>36.2 ± 2.1</td>
</tr>
<tr>
<td>Plate 1.0 cm²</td>
<td>2.0</td>
<td>58.0 ± 2.3</td>
<td>7.2 ± 0.2</td>
<td>0.71 ± 0.01</td>
<td>0.70 ± 0.02</td>
<td>9.8 ± 1.3</td>
<td>7.0 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>81.6 ± 2.6</td>
<td>10.3 ± 0.4</td>
<td>0.69 ± 0.02</td>
<td>0.67 ± 0.02</td>
<td>20.5 ± 2.6</td>
<td>16.5 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>103.0 ± 3.8</td>
<td>12.6 ± 0.4</td>
<td>0.71 ± 0.02</td>
<td>0.69 ± 0.01</td>
<td>33.5 ± 3.5</td>
<td>28.6 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>122.0 ± 5.3</td>
<td>16.5 ± 0.5</td>
<td>0.78 ± 0.02</td>
<td>0.70 ± 0.03</td>
<td>46.5 ± 3.7</td>
<td>41.1 ± 3.6</td>
</tr>
<tr>
<td>Plate 0.75 cm²</td>
<td>2.0</td>
<td>74.5 ± 2.0</td>
<td>8.9 ± 0.2</td>
<td>0.47 ± 0.02</td>
<td>0.51 ± 0.02</td>
<td>19.3 ± 0.9</td>
<td>17.80 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>103.5 ± 3.8</td>
<td>11.9 ± 0.5</td>
<td>0.45 ± 0.02</td>
<td>0.52 ± 0.01</td>
<td>35.5 ± 2.9</td>
<td>31.80 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>124.2 ± 5.2</td>
<td>14.5 ± 0.6</td>
<td>0.47 ± 0.03</td>
<td>0.51 ± 0.01</td>
<td>50.3 ± 3.1</td>
<td>47.10 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>135.4 ± 6.5</td>
<td>16.8 ± 0.6</td>
<td>0.49 ± 0.02</td>
<td>0.52 ± 0.02</td>
<td>56.7 ± 3.7</td>
<td>52.70 ± 4.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. VTI indicates velocity time integral; AO, aorta; LVOT, left ventricular outflow tract; AVA, aortic valve area, Cont., continuity equation; Cath., catheter; dp, pressure gradient.
The CFD calculations were carried out, considering blood as a Newtonian fluid. A constant blood viscosity value of 0.0035 kg/m s and an average constant density value of 1020 kg/m³ were applied for each CFD simulation.

**Statistical analysis**

Results are expressed as mean ± SD. Agreement between Doppler and catheter gradients and estimated valve areas was analyzed with the Bland Altman method. Multiple linear regression models were performed to test the dependence of catheter valve area on flow (in L/min), systemic pressure (in mmHg) and orifice size (individual categories against one reference category). The same analysis was done with the target variables Doppler valve area, catheter pressure gradient, and Doppler pressure gradient. A P-value < 0.01 was considered as significant to account for multiplicity of testing. Model assumption was checked by normal probability plot of the residuals and by calculating the variance inflation factors (vif) to look for collinearity. The model assumptions were fulfilled as there was no hint on a deviation of the residuals from a normal distribution and all vif were < 1.5. All tests were two-sided, statistical analyses was done using SAS 9.1.

**Results**

Peak pressure gradients across the various stenoses ranged from 14.7 to 122.5 mmHg (mean 51.3 ± 24.1 mmHg) by catheter technique and from 15.2 to 128.0 mmHg (mean 55.8 ± 26.4 mmHg) by Doppler. Mean pressure gradients ranged from 9.1 to 58.4 mmHg (mean ± SD, 33.2 ± 15.7 mmHg) by catheter technique and from...

![Figure 2](image-url)
9.8 to 64.0 mmHg (mean 35.2 ± 16.6 mmHg) by Doppler. Valve area estimates ranged from 0.41 to 0.80 cm², mean 0.61 ± 0.12 cm², by Doppler continuity equation and from 0.43 to 0.78 cm², mean 0.62 ± 0.11 cm², by the Gorlin formula, based on catheter measurements.

Table 1 shows mean values of Doppler and catheter pressure gradients, valve area estimates, and velocity time integrals for each flow rate.

Agreement between Doppler and catheter pressure gradients as well as calculated valve areas was good [mean difference 3.6 ± 2.8 mmHg, limits of agreement −2 (95% CI −2.94 to −1.06) to 9.2 (95% CI 8.26–10.14) for pressure gradients and 0.01 ± 0.05 cm², −0.09 (−0.11 to −0.07) to 0.11 (0.09–0.13) cm² for valve areas] (Figure 2A and B).

Effect of systemic pressure on pressure gradients and calculated valve areas

Circulation model

When poststenotic systolic pressure was raised from 80 to 200 mmHg while maintaining peak and mean systolic flow constant, peak and mean pressure gradients as well as valve area estimates did not show clinically relevant changes. The mean difference between pressure gradients at baseline (80 mmHg) and at maximum poststenotic pressure (200 mmHg) was 3.4 ± 1.8 mmHg, range 0.4 to 6.8 mmHg. For estimated valve areas the mean difference between baseline and maximum systemic pressure was 0.01 ± 0.03 cm², range −0.02 to 0.05 cm². Results were similar for rigid orifices (plates) (Figure 3A and B) and stenotic bioprostheses (Figure 4A and B).

Multiple regression analysis with the target variables Doppler and catheter valve area, and the independent variables flow, systemic pressure and orifice size yielded a significant influence of flow (P < 0.0001 and P < 0.0001) and orifice size (P < 0.0001 and P < 0.0001), but no effect of systemic pressure on valve areas by Doppler as well as catheter technique.

Similarly, systemic pressure did not impact on catheter and Doppler pressure gradients, whereas flow (P < 0.0001 and P < 0.0001) and orifice size (P < 0.0001 and P < 0.0001) significantly affected catheter as well as Doppler pressure gradients. The results of the multivariable regression analysis are shown in Table 2.

Computational modelling

When poststenotic systolic pressures were raised from 80 to 200 mmHg while mean systolic flow rates were kept constant, computational modelling confirmed the results obtained by Doppler and catheter measurements. It demonstrated that velocity and pressure distributions across stenosis and outflow chamber were independent from poststenotic pressures at constant systolic flow rates. Figure 5 depicts velocity and pressure maps as obtained by computational modelling in a simulation setting of the 1.0 cm²
rigid stenosis at a mean systolic flow rate of 2 L/min and systemic pressures of 80 mmHg (top) vs. 200 mmHg (bottom). Figure 6 compares velocity and pressure maps at a mean systolic flow rate of 5 L/min and systemic pressures of 80 mmHg (top) vs. 200 mmHg (bottom).

### Discussion

Systemic hypertension is a very common disease, and also affects up to 50% of patients with AS.\(^1,3,4\) Because the frequency of this combination has grossly been underestimated in the past the impact of hypertension on the assessment of AS has gained little attention. More recently, several clinical, animal, and in vitro studies on this topic have been carried out\(^7,16–19\) and it has been postulated that systemic hypertension indeed influences the assessment of AS independently of afterload-related flow changes.\(^18\)

Clinical studies on the issue\(^7,16–18\) are difficult to interpret, because changes of blood pressure cause various physiological changes of peripheral resistance, ejection fraction, and transvalvular flow rate. Two of the studies showed an increase of mean pressure gradients mediated by the administration of nitroprusside\(^7\) and ACE (angiotensin-converting enzyme) inhibitors\(^16\) while calculated valve areas remained unchanged. In the study by Khot et al.,\(^7\) a concomitant increase of SV was also documented. In the work by Chockalingam et al.\(^17\) ACE inhibitors caused an increase of ejection fraction while pressure gradients as well as valve areas remained unchanged.

However, from these clinical data it cannot be clarified, whether blood pressure may still impact on pressure gradient and estimated valve area in AS apart from flow-mediated changes. This appears even more uncertain as results from experimental studies were contradictory\(^19,20\).

The more recent publication by Kadem et al.\(^19\) postulates that the severity of AS may partially be masked in the presence of hypertension since increasing systemic pressure caused a decrease of pressure gradients and increase in valve area. This conclusion was drawn from a study on pigs with supravalvular AS, modelled by banding of the ascending aorta. However, although average cardiac output remained constant in this study, mean systolic flow rates significantly decreased when hypertension was induced. This decrease of systolic flow could explain the decrease of pressure gradients. The increase of the simultaneously estimated orifice areas with increasing pressure is more difficult to explain. As, AS was created by banding of the ascending aorta. However, although average cardiac output remained constant in this study, mean systolic flow rates significantly decreased when hypertension was induced. This decrease of systolic flow could explain the decrease of pressure gradients. The increase of the simultaneously estimated orifice areas with increasing pressure is more difficult to explain.

In contrast to these data, the in vitro study by Razzolini et al.\(^20\) demonstrated a small but linear increase of pressure gradients across a 21 mm porcine bioprosthesis with rising systemic pressures. The authors do not offer an explanation for this observation. An increase in gradient without increase of flow would require a decrease in effective orifice area, which is however not supported

### Table 2 Results of the multivariable regression analysis

<table>
<thead>
<tr>
<th>Target variable</th>
<th>Independent variable</th>
<th>Regression coefficients with 95% CI</th>
<th>P-value</th>
<th>(R^2) of the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pressure gradient by catheter</td>
<td>Flow</td>
<td>10.06 (7.99–12.12)</td>
<td>&lt;0.0001</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Syst. pressure</td>
<td>–0.01 (–0.06 to 0.04)</td>
<td>0.8113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 0.75 cm(^2)</td>
<td>17.48 (15.69–19.28)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.0 cm(^2)</td>
<td>4.15 (2.51–5.79)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bio</td>
<td>17.99 (16.35–19.64)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.25 cm(^2)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pressure gradient by Doppler</td>
<td>Flow</td>
<td>12.03 (11.32–12.74)</td>
<td>&lt;0.0001</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Syst. pressure</td>
<td>0.01 (–0.01 to 0.03)</td>
<td>0.2691</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 0.75 cm(^2)</td>
<td>24.51 (22.24–26.77)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.0 cm(^2)</td>
<td>8.63 (6.56–10.71)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bio</td>
<td>21.79 (19.73–23.87)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.25 cm(^2)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVA by catheter</td>
<td>Flow</td>
<td>0.03 (0.02–0.04)</td>
<td>&lt;0.0001</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Syst. pressure</td>
<td>–0.00 (–0.00 to 0.00)</td>
<td>0.2630</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 0.75 cm(^2)</td>
<td>–0.28 (–0.30 to –0.25)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Plate 1.0 cm(^2)</td>
<td>–0.07 (–0.09 to –0.05)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bio</td>
<td>–0.23 (–0.26 to –0.21)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.25 cm(^2)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVA by Doppler</td>
<td>Flow</td>
<td>0.02 (0.02–0.03)</td>
<td>&lt;0.0001</td>
<td>0.94</td>
</tr>
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<td>Syst. pressure</td>
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<td>0.3538</td>
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<td></td>
<td>Plate 0.75 cm(^2)</td>
<td>–0.21 (–0.22 to –0.19)</td>
<td>&lt;0.0001</td>
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<td>Plate 1.0 cm(^2)</td>
<td>0.05 (0.03–0.06)</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td></td>
<td>Bio</td>
<td>–0.16 (–0.18 to –0.15)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plate 1.25 cm(^2)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AVA indicates aortic valve area; Bio, biological valve; Syst., systemic.
by fluid dynamics theory. In addition, this study is limited by the exclusive use of normal but not stenotic bioprostheses.

Taking all these previous studies together, it remains unclear whether hypertension can independently affect the assessment of AS severity apart from secondary changes in flow rate caused by afterload-related changes in ejection fraction.

In the present study we used three independent methods to assess the influence of blood pressure variation on AS gradient and valve area estimates in a well-controlled in vitro flow circuit. All three methods (Doppler measurements, catheter measurements, and CFD simulation) showed similar results. Isolated changes of systemic pressure did not independently alter pressure gradients and valve area estimates in our model of AS. Thus, our results strongly indicate that changes of pressure gradients and valve area estimates were exclusively caused by changes of systolic flow rate.

Our findings are also supported by fluid mechanics theory. According to the Bernoulli equation the pressure difference between two points can be calculated in an incompressible fluid. In a rigid system the pressure difference is affected by flow velocity, friction, and gravitational energy but not by the systemic pressure.26

Most recently, the study by Little et al.18 very elegantly showed, that changes of blood pressure, which were induced by handgrip exercise or phenylephrine infusion, affected Doppler echo evaluation of AS severity in vivo. However, multivariable analysis revealed that only the mean flow rate independently predicted changes of AS severity index but not blood pressure. The correctness of this in vivo observation is well supported by the in vitro analysis of the present study.

**Clinical implications**

The present study has significant clinical implications as it strongly supports the fact that the presence of hypertension has no isolated influence on the assessment of AS independently of afterload-related secondary flow changes. In our in vitro setting systemic blood pressure appears to only affect measurements through an afterload-induced alteration of ejection fraction and thus cardiac output. However, further clinical studies will be needed to confirm the importance of the findings of this study. In vivo, significant changes of afterload by drug intervention or exercise can alter left ventricular ejection fraction and transvalvular flow rate. It has indeed been shown that the cautious use of antihypertensive drugs in AS patients can increase cardiac output and consequently pressure gradients.7,16 The present data, however, imply that as soon as ejection fraction, flow velocity, pressure gradient, and estimated valve area are all incorporated in the

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**Figure 5** Results of computational modelling in the 1.0 cm² rigid stenosis at a mean flow rate of 2 L/min: Contour plots were generated at systemic pressures of 80 (top, A and B) and 200 mmHg (bottom, C and D). Left, A and C: velocity maps, showing the contours of the velocity magnitude in m/s (maximum velocity red, minimum velocity blue). Right, B and D: pressure maps, showing the contours of absolute pressure in Pascal (maximum pressure red, minimum pressure blue).
assessment of AS, corruption of AS severity due to changes of systemic blood pressure is very unlikely.

**Study limitations**

Our *in vitro* model attempts to approximate the *in vivo* situation. However, it has stiff walls and rigid boundaries. It cannot entirely be excluded that complex interactions with reflected waves, differences in static and dynamic components, and compliance might exert a hitherto unknown effect.

Some of the used stenoses are a simplification of the complex three-dimensional structure of a stenotic valve.

Although glycerine–water solutions are Newtonian fluids, the addition of cornstarch causes non-Newtonian effects. However, due to the low concentration of cornstarch these effects should be minimal.

Despite these limitations the model allows a focused assessment of haemodynamic changes caused by isolated variations of systemic pressure or heart rate or flow rate, which is impossible in vivo.

**Conclusions**

The results of the present *in vitro* study suggest that blood pressure does not directly influence invasive or non-invasive pressure gradient and valve area estimates in AS independently of secondary flow changes. Therefore, variation of estimated valve area and pressure gradient with changing blood pressure, when observed in vivo, are most likely due to afterload-dependent changes in flow rate. Thus, changes in blood pressure should not bias the assessment of AS severity as long as valve area, pressure gradient, and flow are taken into consideration.

**Conflict of interest:** none declared.

**References**


