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ORIGINAL RESEARCH

Discordant Grading of Aortic Stenosis Severity: New Insights from an *In Vitro* Study

Jérôme Adda, MD[a], Viktoria Stanova, MSc[b], Anne-Sophie Zenses, MSc[b,c], Marie-Annick Clavel, DVM, PhD[c], Paul Barragan, MD[d], Guillaume Penaranda, MD[e], Gilbert Habib, MD, PhD[f], Philippe Pibarot, DVM, PhD[c], and Régis Rieu, PhD[b]

[a]Department of Cardiology, University Hospital Arnaud de Villeneuve, Montpellier, France; [b]Aix-Marseille University, LBA-UMRT24 IFSTTAR, Marseille, France; [c]Department of Cardiology, Quebec Heart and Lung Institute, Quebec, Canada; [d]Department of Cardiology, Polyclinique les Fleurs, Ollioules, France; [e]Département Statistiques, Laboratoire Alphabio, Marseille, France; [f]Department of Cardiology, Hospital La Timone, Insuffisance Cardiaque et Valvulopathie, Marseille, France

ABSTRACT

Background: Low gradient (mean gradient, < 40 mmHg) aortic stenosis (AS) may occur in conjunction with a small valve effective orifice area (EOA) < 1 cm^2. This discordant grading in AS severity raises challenges from both a diagnostic and therapeutic standpoint. We sought to identify echocardiographic markers of severe AS in normal and low flow conditions *in vitro*.

Methods: In an *in vitro* mock circulatory system, we tested 6 degrees of AS severity (3 severe and 3 nonsevere), and 3 levels of stroke volume (30, 50, 70 ml), heart rate (60, 80, 100 bpm), and mean arterial pressure (100, 120, 140 mmHg). MG and EOA were measured by Doppler-echocardiography.

Results: In normal flow conditions, a MG of 40 mmHg corresponded to an EOA of 0.85 cm^2, and an EOA of 1.0 cm^2 to a MG of 28 mmHg. The presence of EOA < 0.85 cm^2 and MG between 24 and 40 mmHg in the low-flow condition yielded a 100% specificity for severe AS. In normal flow conditions, these thresholds were respectively < 0.9 cm^2 and > 36 mmHg.

Conclusion: Low gradient AS may occur in severe AS in both low and normal flow conditions. The presence of a valve EOA < 0.85 cm^2 with an MG ≥ 25 mmHg may be used as a criteria to confirm severe AS in presence of low flow. In patients with normal-flow, a MG ≥ 37 mmHg is generally suggestive of severe AS.

Abbreviations: AS: aortic stenosis; EOA: effective orifice area; HR: heart rate; LFLG: low-flow low-gradient; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; MG: mean gradient; NFLG: normal-flow low-gradient; SV: stroke volume

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KEYWORDS Aortic stenosis; *in vitro*; low flow; low gradient; echocardiography

Introduction

Severe aortic stenosis (AS) is generally defined by a mean transaortic mean gradient (MG) ≥ 40 mmHg and an effective orifice area (EOA) ≤ 1 cm.[21,2] However, discordant grading (EOA < 1 cm^2 with MG < 40 mmHg) may occur with depressed or preserved LV ejection fraction and with low or normal flow.[3,4] Accordingly, three main subtypes of discordant grading with low gradient have been identified: (1) classical low-flow low-gradient (CLFLG) AS, related to low left ventricular ejection fraction (LVEF); (2) paradoxical low-flow low-gradient (PLFLG) AS, with normal LVEF and low flow defined as stroke volume index ≤ 35 ml/m^2, related to LV concentric remodeling, impaired longitudinal systolic function, and systemic hypertension[5]; and (3) normal-flow low-gradient (NFLG) AS (normal LVEF and stroke volume index > 35 ml/m^2) may be linked to discrepancies in the definition of severe AS, and is present in up to 25% of the patients.[6] In all these entities with discordant grading, the stenosis may be severe despite the presence of a low MG. It is thus essential to develop and validate echocardiographic criteria to differentiate true severe from pseudo-severe stenosis.

The objectives of this *in vitro* study were to determine the cut-points of MG and EOA that could be used to confirm the presence of severe stenosis in discordant grading in normal and low flow conditions.

Materials and methods

Experimental model

The *in vitro* circulatory system was previously described.[7] Briefly, the simulation system included anatomically shaped silicone-made left heart cavities and aorta, and simulation of the pulmonary and systemic circulations. Contraction of the left ventricle was achieved by a piston pump (Vivitro Inc.,

CONTACT Jérôme Adda j-adda@chu-montpellier.fr Centre Hospitalier Universitaire de Montpellier, Hopital Arnaud de Villeneuve, 371 avenue du doyen Gaston Giraud, Montpellier Cedex 5 34295, France.

Jérôme Adda and Viktoria Stanova are both first authors, as they contributed equally to this work.

Supplemental data for this article can be accessed here.

Victoria, Canada). Both pump activation and signal acquisition were controlled with LabVIEW8.2 (National Instruments, Texas, USA) through a Compact RIO with field-programmable gate array (FPGA) controller and data acquisition system. Controlling enables physiological flow through the aortic valve following the standards for heart valve testing in normal flow conditions (ISO 5840-part 3). Systole duration (in ms) was set according to the following formula: (HR x 0.28 + 21) x 600/HR.

The systemic circulation was composed of a compliance, which accounts for the capacity of arteries and veins to accumulate and release some energy during the cardiac cycle, and a resistance, which models the total pressure loss. A pressure sensor was inserted into the silicon aorta to monitor the aortic pressure. The circulatory fluid was a saline mixture of water (53%) and glycerol (47%) mimicking blood viscosity (4 ± 0.2 cP) and maintained at 37°C.[8]

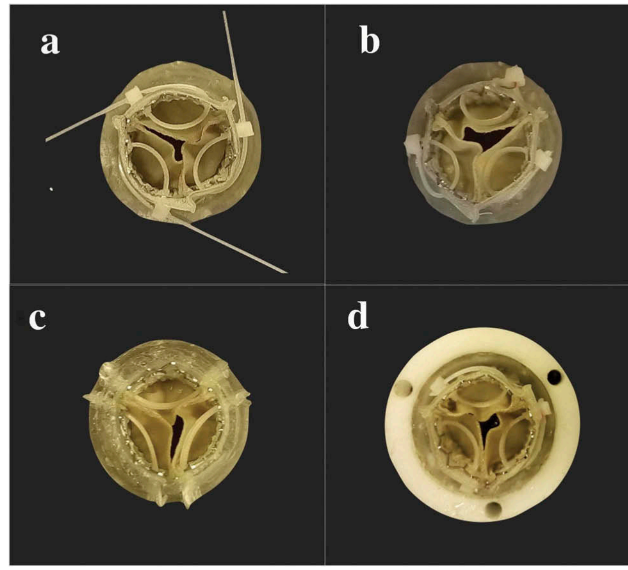

Figure 1. *In vitro* reproduction of the aortic stenosis. a: Placement of three clamp rings to reduce the opening of the leaflets of an Edward SAPIEN valve. b: The exceeding parts of the clamp rings are cut, allowing insertion of the valve inside the annuli (c and d).

Doppler echocardiographic measurements

Doppler echocardiographic measurements were performed using a General Electric Vivid 7 (GE Health Medical, Horten, Norway), with a 3.5 MHz probe. The transvalvular flow velocities, MG, and aortic velocity-time integral (VTI) were measured five times per condition by continuous-wave Doppler. Transvalvular flow was measured using an electromagnetic flowmeter (Model 501, Carolina Medical Electronics Inc., East Bend, USA) positioned immediately below the prosthesis and averaged over 100 cycles. Valve EOA was determined by the continuity equation, by dividing the stroke volume measured with electromagnetic flowmeter by the echocardiographic aortic VTI. Mean transvalvular flow rate (Q) was calculated by dividing the SV by the LV ejection time measured on the Doppler acquisitions.

Reproduction of the aortic stenosis

To reproduce an aortic stenosis, three clamp rings were inserted through the stent frame of a 23 mm Edwards SAPIEN transcatheter valve (Figure 1a–c). Depending on the length of the clamp rings, different degrees of valve restriction could be achieved. The aortic valve was then implanted in a 23 mm silicone annulus (Figure 1d).

A high-speed camera (SA3 Fastcam, Photron, Japan) was used to acquire 1,000 images per second en-face view of the valve videos during the cardiac cycle. Determination of the geometric orifice area (GOA) was performed using a "Region Based Active Contour Segmentation" program based on Matlab (Mathworks, Natick, MA, USA), after image calibration with a calibration pattern. The GOA was calculated at the maximal valve-opening frame (Figure 2).

To define the severity of a stenosis, we measured the EOA and the GOA in normal flow rate conditions (mean flow rate between 200 and 250 ml/s). Therefore, we considered it represented the true degree of stenosis of the valve, independent of any further change in stroke volume, heart rate or mean aortic pressure.

Six degrees of stenosis were determined as follows: no stenosis (control condition, maximal GOA 2.4 cm^2, maximal EOA 2.2 cm^2 in normal flow conditions), moderate stenosis (GOA 1.3 cm^2, EOA 1.1 cm^2), moderate-to-severe stenosis (GOA 1.2 cm^2, EOA 1.1 cm^2), severe stenosis (GOA 1.0 cm^2, EOA 0.9 cm^2), very severe stenosis (GOA 0.8 cm^2, EOA 0.8 cm^2), and extreme stenosis (GOA 0.5 cm^2, EOA 0.5 cm^2). For each degree of stenosis, three different values were applied for heart rate (HR: 60, 80, 100 bpm), stroke volume (SV: 30, 50, 70 ml), and mean aortic pressure (MAP: 100, 120, 140 mmHg). Assuming an average body surface of 1.7 m^2, these 3 SVs corresponded to normal flow (41 ml/m^2), low flow (29 ml/m^2), and very low flow (18 ml/m^2). Data were also divided depending on levels of mean transvalvular flow rate: high mean flow rate ($Q > 250$ ml/s), normal mean flow rate (Q 200–250 ml/s), and low mean flow rate ($Q < 200$ ml/s).

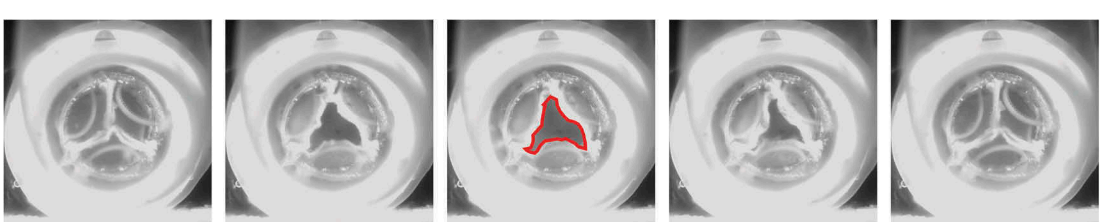

Figure 2. Main frames of a cardiac cycle obtained with high-speed camera imaging in the moderate-to-severe condition. The red line shows the maximal geometric orifice area.

Statistical analysis

Relationship between EOA and MG or EOA and Q was assessed with an exponential regression model. Sensitivity, specificity and positive and negative predictive values were calculated for different cut-points of MG and EOA in order to identify severe AS in low flow and normal flow conditions with discordant grading (small EOA with low gradient). For the purpose of this analysis: no stenosis, moderate stenosis and moderate-to-severe stenosis were considered nonsevere AS, and the other categories (severe, very severe, and extremely severe) were considered severe. All statistical analyses were performed with SPSS Statistics version 24 (IBM corp., Armonk, USA). A value of $p < 0.05$ was considered significant.

Results

Relationship between EOA and MG

There was an inverse exponential relationship between EOA and MG, respectively, for SV 70, 50 and 30 ml, $r^2 = 0.93$, 0.93, and 0.91, all $p < 0.0001$ (Figure 3).

In normal flow conditions (SV 70 ml; SV index 41 ml/m^2 with a body surface area of 1.7 m^2), an EOA of 1 cm^2 corresponded to a MG of 28 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.85 cm^2.

In low-flow conditions (SV 50 ml; SV index 29 ml/m^2), an EOA of 1 cm^2 corresponded to a MG of 16 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.66 cm^2.

Finally, in very low-flow conditions (SV 30 ml; SV index 18 ml/m^2), an EOA of 1 cm^2 corresponded to a MG of 6 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.42 cm^2.

The correlations between MG and EOA are also presented according to the mean flow rate categories: Q > 250 ml/s, Q 200–250 ml/s, or Q < 200 ml/s (Supplementary Figure 1). In high flow conditions (Q > 250 ml/s), an EOA of 1 cm^2 corresponded to a MG of 33 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.9 cm^2. In normal flow conditions (Q 200–250 ml/s), an EOA of 1 cm^2 corresponded to a MG of 21 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.74 cm^2. In low flow conditions (Q <200 ml/s, an EOA of 1 cm^2 corresponded to a MG of 9 mmHg, and a MG of 40 mmHg corresponded to an EOA of 0.51 cm^2.

EOA and MG thresholds for severe AS

In normal flow conditions (SV 70 ml), MG ranged from 23 to 36 mmHg in moderate-to-severe AS, and from 33 to 53 mmHg in the severe AS condition (Table 1 and Figure 4). Similarly, EOA could range from 0.9 to 1.1 cm^2 in moderate-to-severe AS, and from 0.8 to 0.9 cm^2 in the severe AS condition (Figure 5).

Table 2 and Figure 6 present the results of the ROC analyses (cut-off values for MG and EOA) to predict severe AS despite low gradient in case of discordant grading (EOA < 1 cm^2 and MG < 40 mmHg). In low gradient AS situations, regardless of the flow, the area under curve (AUC) of MG and EOA were respectively 0.81 (95% confidence interval CI 0.77–0.89, $p < 0.0001$) and 0.99 (95% CI 0.99–1, $p < 0.0001$). Specifically, a MG between 36 and 40 mmHg or an EOA < 0.85 cm^2 had a 100% specificity for severe AS.

In low flow conditions and MG<40 mmHg, the AUC of MG and EOA were respectively 0.99 (95% confidence interval CI 0.99–1, $p < 0.0001$) and 1 (95% CI 1–1, $p < 0.0001$). A cutoff for MG of 24 mmHg yielded a 100% specificity and a 86% sensitivity for severe AS. An EOA < 0.85 cm^2 had a 100% specificity and sensitivity for severe AS.

In normal flow conditions (SV 70 ml) and MG < 40 mmHg, the AUC of MG and EOA were respectively 0.86 (95% confidence interval CI 0.78–0.96, $p < 0.0001$) and 1 (95% CI 1–1, $p < 0.0001$). A MG between 36 and 40 mmHg yielded a 100% specificity and

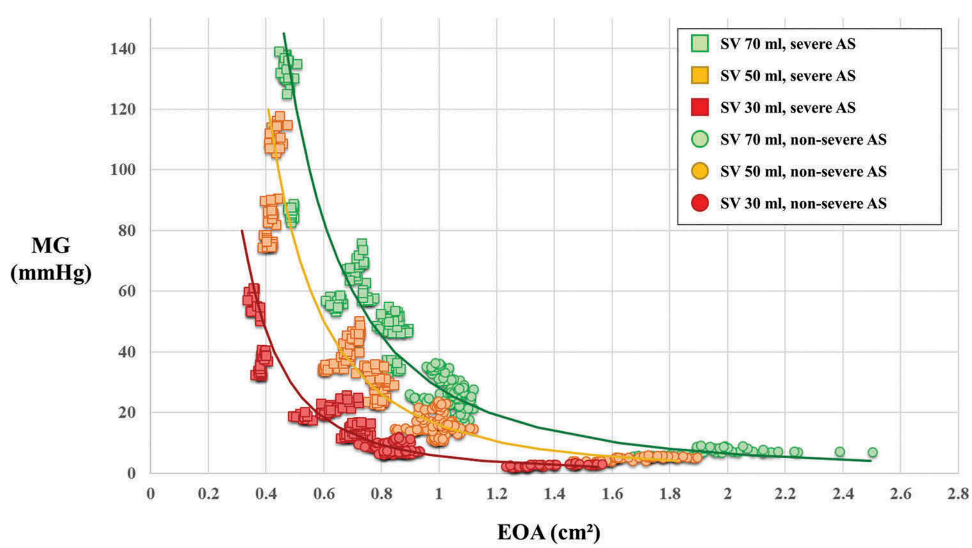

Figure 3. Correlation between mean gradient (MG) and effective orifice area (EOA) according to flow level. Squares: severe aortic stenosis. Circles: nonsevere aortic stenosis. Green: Normal flow – stroke volume (SV) 70 ml (SV: index: 41 ml/m^2); orange: low flow – SV: 50 ml (stroke volume index: 29 ml/m^2); red: very low flow – SV: 30 ml (stroke volume index: 18 ml/m^2). Stroke volume index was calculated assuming a body surface area of 1.7 m^2.

Table 1. Values of mean gradient (mmHg) and effective orifice area (cm^2) in all stenosis degrees, depending on flow and flow rate. Minimal and maximal values are shown. EOA: effective orifice area, MG: mean gradient, SV: stroke volume, Q: mean aortic flow.

		No stenosis	Moderate	Moderate-to-severe	Severe	Very severe	Extreme
		[Min – Max]	[Min – Max]	[Min – Max]	[Min – Max]	[Min – Max]	[Min – Max]
SV 70 ml	MG (mmHg)	5–9	17–28	23–36	33–53	53–76	84–139
	EOA (cm^2)	1.7–2.4	1.0–1.2	0.9–1.1	0.8–0.9	0.6–0.8	0.5
SV 50 ml	MG (mmHg)	5–6	11–16	14–24	22–36	34–50	75–116
	EOA (cm^2)	1.5–1.8	1.0–1.1	0.85–1.0	0.7–0.85	0.6–0.7	0.4–0.5
SV 30 ml	MG (mmHg)	2–3	6–7	8–12	12–17	18–26	32–61
	EOA (cm^2)	1.2–1.5	0.8–0.9	0.7–0.9	0.7–0.8	0.5–0.7	0.3–0.4
Q > 250 ml/s	MG (mmHg)	7–9	24–28	29–36	46–53	57–76	127–139
	EOA (cm^2)	1.9–2.4	1.0–1.2	1.0–1.1	0.8–0.9	0.7–0.8	0.5
Q 200–250 ml/s	MG (mmHg)	5–6	11–26	20–26	28–37	38–59	89–116
	EOA (cm^2)	1.7–1.8	1.0–1.1	0.9–1.0	0.8–0.9	0.6–0.7	0.4–0.5
Q < 200 ml/s	MG (mmHg)	2–5	6–16	8–20	12–24	18–36	32–91
	EOA (cm^2)	1.2–1.8	0.8–1.1	0.7–1.0	0.7–0.8	0.5–0.7	0.3–0.4

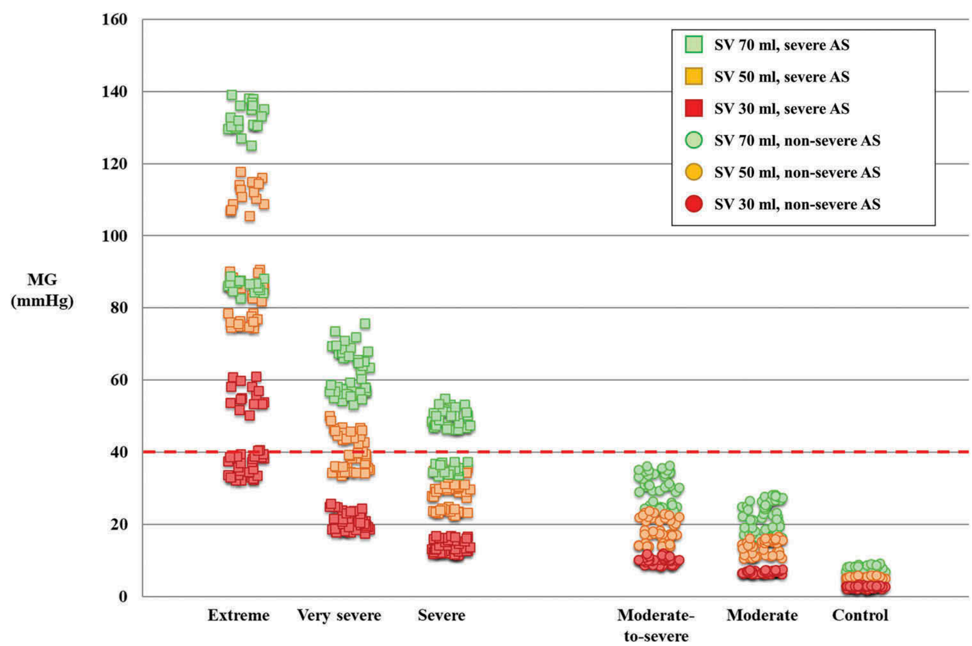

Figure 4. Distribution of MG according to degree of stenosis and level of flow. Squares: severe aortic stenosis. Circles: nonsevere aortic stenosis. Green: Normal flow – stroke volume (SV) 70 ml (SV index: 41 ml/m^2); orange: low flow – SV: 50 ml (SV index: 29 ml/m^2); red: very low flow – SV: 30 ml (SV index: 18 ml/m^2). Stroke volume index was calculated assuming a body surface area of 1.7 m^2. The red dotted line represents a MG of 40 mmHg.

a 33% sensitivity for severe AS. An EOA < 0.88 cm^2 had a 100% sensitivity and specificity for severe AS. Moreover, cases with NFLG pattern and a Q > 255 ml/s all had moderate AS.

Figure 7 shows the relationship between EOA and mean aortic flow. There was a significant increase of the EOA from the lowest to the highest values of Q, in all stenosis severities ($p <$ 0.0001 for all). The same increase was observed with the GOA (p < 0.0001 for all stenosis severities). This increase was observed whether the flow was <200 ml/s ($p < 0.0001$ for all), or > 200 ml/s ($p < 0.0001$ for all but moderate-to-severe stenosis $p = 0.0002$), except in the moderate stenosis condition, for which no increase was observed beyond 200 ml/s (p =ns).

Discussion

To our knowledge, our study is the first to assess *in vitro* the relationship between EOA, mean gradient, stroke volume, and heart rate, in different degrees of stenosis.

The main findings of this study are as follows: (1) in case of low-flow, low-gradient AS, a MG ≥ 25 mmHg, and an EOA < 0.85 cm^2 are supportive of the presence of severe AS; (2) in normal-flow low-gradient AS, the thresholds supportive of severe AS are respectively ≥ 37 mmHg and < 0.9 cm^2; and (3) normal-flow low-gradient AS is unlikely to be severe if the mean transvalvular flow rate is > 255 ml/s.

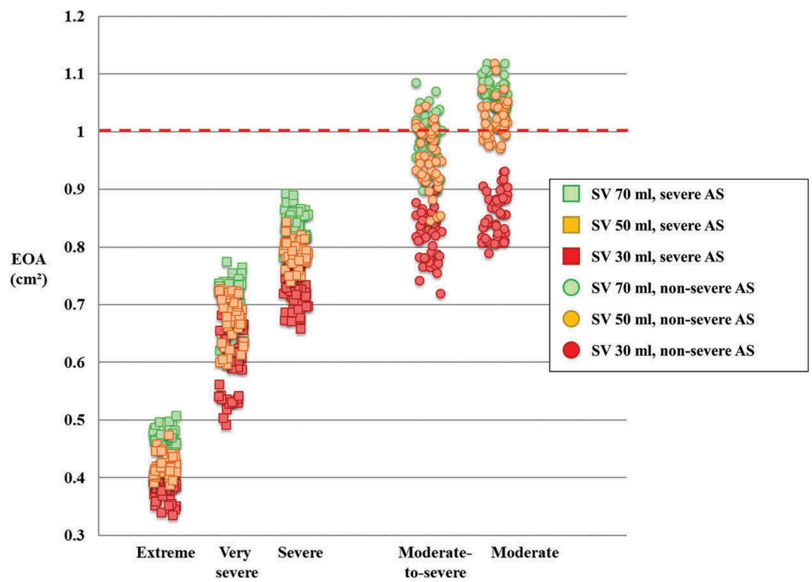

Figure 5. Distribution of valve EOA according to degree of stenosis and level of flow. Squares: severe aortic stenosis. Circles: nonsevere aortic stenosis. Green: Normal flow – stroke volume (SV) 70 ml (SV index: 41 ml/m^2); orange: low flow – SV: 50 ml (SV index: 29 ml/m^2); red: very low flow – SV: 30 ml (SV index: 18 ml/m^2). Stroke volume index was calculated assuming a body surface area of 1.7 m^2. The red dotted line represents an EOA of 1 cm^2. For better readability, control condition was removed.

Table 2. Sensitivity, specificity and predictive value of mean gradient and effective orifice area for severe aortic stenosis in low gradient, low-flow low-gradient and normal-flow low-gradient aortic stenosis. EOA: effective orifice area, LFLG: low-flow low-gradient, MG: mean gradient, NFLG: normal-flow low-gradient, PPV: positive predictive value, NPV: negative predictive value.

		Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
Low gradient						
MG						
	> 36 mmHg	17%	100%	100%	54%	
	> 23 mmHg	100%	43%	65%	100%	1.8
	> 30 mmHg	74%	77%	77%	74%	3.2
EOA						
	< 0.85 cm^2	95%	100%	100%	95%	
	< 0.88 cm^2	100%	97%	97%	100%	33.0
	< 0.87 cm^2	99%	97%	97%	99%	33.0
LFLG						
MG						
	> 24 mmHg	86%	100%	100%	92%	
	> 22 mmHg	100%	87%	83%	100%	7.7
	> 23 mmHg	97%	93%	90%	98%	13.9
EOA	< 0.85 cm^2	100%	100%	100%	100%	
NFLG						
MG						
	> 36 mmHg	33%	100%	100%	33%	
	> 33 mmHg	100%	67%	97%	100%	3.0
	> 35 mmHg	67%	80%	91%	45%	3.4
EOA	< 0.88 cm^2	100%	100%	100%	100%	

Definition of severe AS

According to the latest ESC[1] and ACC/AHA[2] guidelines, a severe aortic stenosis is defined by a MG ≥ 40 mmHg and an EOA ≤ 1.0 cm^2. However, different clinical studies have shown that inconsistencies exist in the definition of severe AS, whether by echocardiography[9] or by catheterization.[10] In these clinical studies, 34 to 38% of patients had an EOA < 1.0 cm^2 in spite of a MG < 40 mmHg. Moreover, these discrepancies occurred whether SV was low or normal, supposing that low flow was not the only explanation for the low gradient AS pattern. Some authors suggested to lower the cut-off for severe AS to 0.8 cm^2 in order to reconcile the discrepancies between EOA and MG.[9] However, in this *in vitro* study, we found that an EOA between 0.8 and 1.0 cm^2 could correspond to moderate AS, but also be associated with severe LFLGAS or high gradient AS. Other clinical studies also reported that patients with an EOA between 0.8 and 1.0 cm^2 and high or low gradient have worse outcomes compared to patients with an EOA > 1.0 cm^2, and harbor a major survival benefit with AVR compared to conservative management.[11,12] Lowering the cutoff would lead to a lowering of sensitivity for outcomes from 91% to 61%, which is not acceptable in clinical practice.

Paradoxical low-flow low-gradient AS

Low gradient AS has long been limited to AS with depressed LVEF (classical low LVEF low-flow low-gradient AS). Over the last decade, new entities have emerged, associating low gradient, normal LVEF, and low flow (paradoxical low-flow low-gradient AS, PLFLG) or normal flow (NFLG AS).

PLFLG AS was defined as a LVEF ≥ 50%, a SV ≤ 35 ml/m^2 and an indexed EOA ≤ 0.6 cm^2/m^2 with a MG < 40 mmHg.[5] Although many studies have shown a better prognosis after surgery[6,13], these results were not replicated in other studies, with a prognosis similar to moderate aortic stenosis.[14–16] Two studies found that MG tends to increase during follow-up in PLFLG, supporting conclusion that this form of AS represents an intermediary stage between moderate and severe AS.[17,18] On the other hand, other studies found that natural history of PLFLG AS has a distinct trajectory and does not evolve toward high gradient AS.[19,20] Nonetheless, a meta-analysis

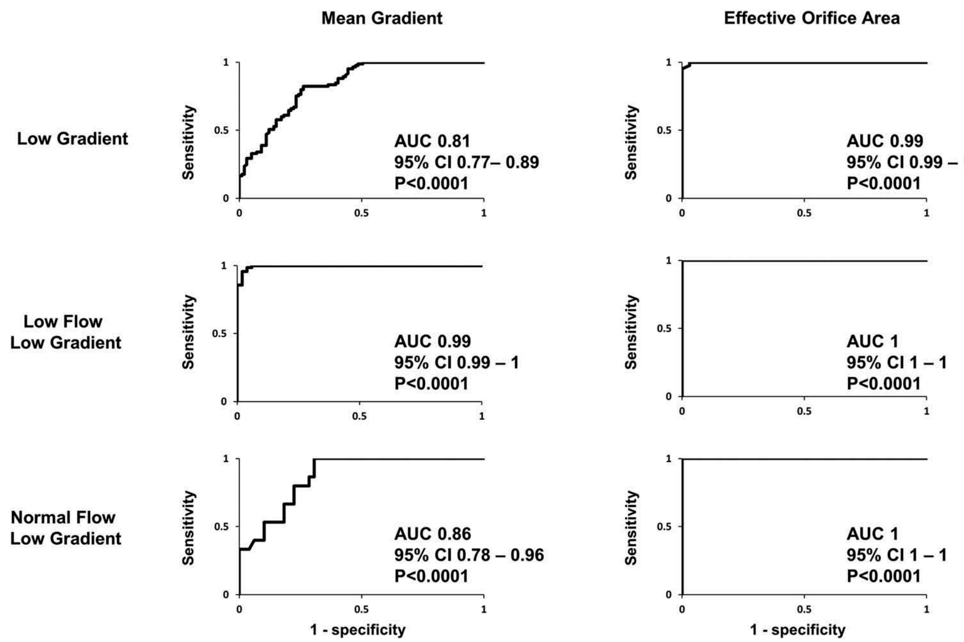

Figure 6. Receiver-operating characteristic (ROC) curve analyses to detect severe aortic stenosis with MG and EOA, in low gradient, low-flow low-gradient, and normal-flow low-gradient aortic stenosis.

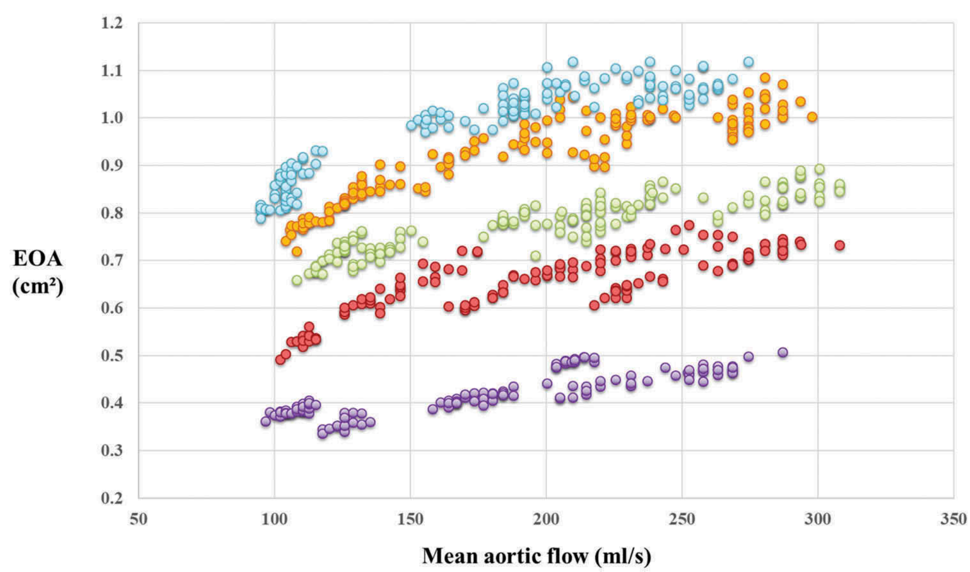

Figure 7. Valve EOA according to mean transvalvular flow rate. Purple: extreme stenosis; red: very severe stenosis; green: severe stenosis; orange: moderate-to-severe stenosis; blue: moderate stenosis. For better readability, control condition was removed.

including these studies demonstrated the beneficial impact of aortic valve replacement in patients with low gradient AS, regardless of the flow status: low or normal.[21]

Stress echocardiography studies showed that by increasing the SV, about two thirds of PLFLG were confirmed as severe AS.[22,23] These findings are consistent with those of the present study showing that, in low flow conditions, a large proportion of cases presented a low gradient despite the presence of a severe AS, and a high gradient when the flow was increased to the normal levels.

Moreover, even if our study supports the concept that LFLG severe AS is a true physiological entity, attention should be paid to the potential for measurement errors. In the present study, in low-flow conditions (SV 50 ml), a MG of 30 mmHg corresponded approximately to an EOA of 0.75 cm^2. Similarly, although we found that a MG > 24 mmHg is in favor of severe AS in low flow conditions, EOA was always > 0.6 cm^2. Lower values of EOA in this setting should lead the echocardiographer to suspect an error in the LVOT diameter or VTI measurements.

Normal-flow low-gradient AS

Previous studies reported that there is a high proportion of patients with AS who harbor a normal-flow low-gradient AS pattern[6,15,24], characterized by an EOA < 1 cm^2 with a MG < 40 mmHg in the context of a normal LVEF and a normal flow defined as SV > 35 ml/m^2. In the absence of measurement errors, these patients have a better prognosis compared to PLFLG AS, and intermediate between moderate and severe AS.[14,15,25] Several studies reported that these patients with NFLG AS display a significant survival benefit with aortic valve replacement.[12,21] These patients also had better LV longitudinal systolic function assessed by 2D-strain, compared to PLFLG AS.[24]

The 2017 ESC guidelines consider that, in general, patients with NFLG AS are unlikely to have severe AS[1], but they provide a multi-parameter integrated approach to confirm AS severity and consider AVR in these patients. In the present study, we found normal-flow, low-gradient severe AS may occur but in specific hemodynamic conditions: i.e. a normal SV (70 ml) but with a mean transvalvular flow rate < 255 ml/s. In the clinical setting, a substantial proportion of patients may have a normal flow according to SV index but nevertheless a low mean transvalvular flow rate[26]; these patients generally have lower heart rates and longer LV ejection times. Therefore, in patients with normal flow (based on SV index > 35 mL/m2) and a low-gradient AS pattern, it is important to assess the mean transvalvular flow rate. If the flow rate is < 255 ml/s, the presence of severe AS is possible and further evaluation including, aortic valve calcium scoring by multidetector computed tomography, is required to confirm AS severity. On the other hand, if the flow rate is > 255 ml/s, the presence of a severe AS is unlikely.

Clinical implications

The main clinical implication of the present *in vitro* study is to propose cut-off values of EOA, MG, and Q that may be useful to assess the likelihood of severe AS in patients with low-gradient AS and preserved LVEF. Our study suggests that the stenosis is less likely to be severe in NFLG AS than in PLFLG AS. In patients with NFLG AS (SV index > 35 ml/m^2), the stenosis is unlikely to be severe if Q is > 255 ml/s. In those with Q < 255 ml/s, a MG ≥ 37 mmHg and an EOA < 0.9 cm^2 are supportive of the presence of severe AS. On the other hand, in patients with PLFLG AS (SV index ≤ 35 ml/m^2), a MG ≥ 25 and EOA < 0.85 cm^2 is supportive of severe AS. However, a decision should not be taken on these parameters and criteria only. In these patients considered likely to have severe AS, additional tests, such as aortic valve calcium scoring by CT, should be performed to confirm presence of severe AS and indication for AVR.

Study limitation

This *in vitro* study does not account for all factors that may influence the EOA-MG-flow relationship *in vivo*, including aortic compliance or indexation to body surface. In particular, a recent study reported that reduced arterial compliance, in addition to blood pressure, may result in a NFLG pattern despite the presence of a severe AS.[26] We could not test all possible degrees of stenosis and levels of SV and Q, but we focused on the most relevant values from a clinical standpoint. Although the design of the valve did not reproduce the exact situation and biomechanical behavior of the calcified native AS or the bicuspid aortic valve observed in humans, it probably allowed a better representation of AS than a round rigid orifice used in some previous *in vitro* studies.

It should also be noted that all cutoffs are based on EOA, which is the reference method to evaluate AS. It is not interchangeable with GOA, which usually shows higher values, and was not assessed in this study.

Conclusion

This *in vitro* study confirms from a fluid-mechanic standpoint the inherent discrepancies in the AS severity criteria of EOA and MG proposed in the guidelines for severe AS. In the present study, a MG of 40 mmHg indeed corresponded to an EOA of 0.85 cm^2 in normal flow conditions. We showed that a paradoxical low-flow low-gradient pattern occurs frequently in presence of true severe AS. In this entity, a MG ≥ 25 mmHg and an EOA < 0.85 cm^2 are strongly in favor of the presence of severe AS. In normal-flow low-gradient AS, a MG ≥ 37mmHg and an EOA < 0.9 cm^2 were supportive of the presence of severe AS. In this entity, the stenosis was unlikely to be severe if Q was > 255 ml/s.

ORCID

Jérôme Adda http://orcid.org/0000-0003-2548-6337
Marie-Annick Clavel http://orcid.org/0000-0002-8924-740X
Philippe Pibarot http://orcid.org/0000-0002-3607-279X

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