Aus der Medizinischen Klinik mit Schwerpunkt Kardiologie der

Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Potential Usefulness and Clinical Relevance of a Systematic Implementation of Transoesophageal Echocardiography in the Evaluation of Patients with Severe Aortic Stenosis and Low Gradient

zur Erlangung des akademischen Grades Doctor medicinae (Dr. med.)

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von

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List of Abbreviations

AR Aortic regurgitation

AS Aortic stenosis

AV Aortic valve

AVA Aortic valve area

AVAi Aortic valve area indexed

BAV Bicuspid aortic valve

BSA Body surface area

CAD Coronary artery disease

CSA Cross-sectional area

CE Continuity equation

CT Computer tomography

CW Continuous wave Doppler

EF Ejection fraction

EOA Effective orifice area

HBP High blood pressure

HF Heart failure

LA Left atrium

LFLG Low flow low gradient

LG Low gradient

LV Left ventricle

LVH Left ventricle hypertrophy

LVCO Left cardiac output

LVEF Left ventricle ejection fraction

LVOT Left ventricular outflow tract

MPG Mean pressure gradient

NYHA New York Heart Association

PLAX Parasternal long axis

PW Pulsed wave Doppler

SD Standard deviation

SV	Stroke volume
SVi	Stroke volume index
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
Vmax	Peak transvalvular velocity
VTI	Velocity time integral
Zva	Valvuloarterial impedance
2D	Two-dimensional
3D	Three-dimensional

0. Abstract

Background

Severe aortic stenosis with low gradient (AS-LG) is a challenging entity which demands careful echocardiographic assessment. Two-dimensional (2D) transthoracic echocardiography (TTE) assessment of the left ventricular outflow tract (LVTO) diameter is susceptible, to error due to suboptimal imaging quality or to morphological variations of the LVOT (i.e. sigmoid septum or sand hourglass shape) leading to an incorrect estimation of the aortic valve area (AVA) by continuity equation (CE). The purpose of this study was to evaluate the potential usefulness and clinical relevance of a systematic use of transoesophageal echocardiography (TOE) to measure the antero-posterior LVOT diameter for the AVA estimation by CE in patients with severe AS-LG.

Methods

In a cross-sectional design, 91 patients with severe AS-LG (aortic valve area <1 cm^2, mean transvalvular pressure gradient (MPG) < 40 mmHg) were systematically analyzed by TTE and TOE.

Results

TOE detected a higher percentage of morphological variations of the LVOT than TTE (rate of detection of sand hourglass-shaped LVOT TOE 43.9% vs. TTE 24.1%, p value 0.02).

Accordingly, the antero-posterior diameter of LVOT was larger by TOE than by TTE (2.1 ± 0.27 mm vs. 2.0 ± 0.23 mm, $p < 0.01$, respectively). In line with these findings, a significantly larger AVA by CE was found by using the diameters obtained from TOE rather than those obtained from TTE (AVA: 0.84 ± 0.19 cm^2 vs. 0.76 ± 0.14 cm^2; p value < 0.01; respectively). Use of TOE on a systematic basis led to a detection of moderate AS in patients previously diagnosed with severe AS-LG (rate of moderate AS 13.1%). Likewise, similar results were found using TOE systematically to measure the aortic annulus in AVA calculation by CE in patients with severe AS-LG (rate of moderate 35.1%).

Conclusion

The findings from this study suggest that a systematic use of TOE for the assessment of the LVOT diameter and thus AVA calculation by CE could result in the recategorization of AS as moderate in some patients with severe AS-LG.

Nevertheless, further larger studies are needed to validate these results, which could have relevance in the assessment of patients with severe AS-LG.

Zusammenfassung

Einleitung

Die Diagnostik der schweren Aortenklappenstenose mit niedrigem Gradienten (AS-LG) erfordert eine sorgfältige echokardiographische Untersuchung.

Die Messungen durch zweidimensionale (2D) transthorakale Echokardiographie (TTE) des antero-posterior linksventrikulären Auswurfstrakts (LVTO) sind eine häufige Fehlerquelle und könnten dazu führen, dass die Aortenklappenfläche (AVA) und das Schlagvolumens (SV) falsch eingeschätzt wird. In dieser Studie wurde es daher untersucht, den potenziellen Nutzen und die klinische Relevanz einer systematischen Anwendung der transösophagealen Echokardiographie (TOE) zur Messung des antero-posterioren LVOT-Durchmessers für die AVA-Schätzung durch CE bei Patienten mit schwerer AS-LG zu bewerten.

Methodik

In einer cross-sectionalen Studie wurden 91 Patienten mit schwerer AS-LG (berechnete Aortenklappenfläche <1 cm^2, mittlerer transvalvulärer Gradient (MPG) <40 mmHg), bei denen gleichzeitig ein TTE und eine TOE vorlag, eingeschlossen.

Ergebnisse

Die TOE führte zu einem höheren Nachweis von morphologischen LVOT-Schwankungen als der TTE (Nachweisrate der Sanduhr-förmigem LVOT-Morphologie: TOE 43,9% vs. TTE 24,1%, p-Wert 0,02). Der antero-posteriore Durchmesser der LVOT durch TOE größer als durch TTE (2,1 ± 0,27 mm gegenüber 2,0 ± 0,23 mm, p <0,01). In Übereinstimmung mit diesen Befunden wurde eine signifikant größere AVA durch CE unter Verwendung der aus TOE erhaltenen Durchmesser als TTE gefunden (AVA: 0,84 ± 0,19 cm^2 gegenüber 0,76 ± 0,14 cm^2; p-Wert <0,01; jeweils). Die systematische Anwendung von EVG führte bei Patienten, bei denen zuvor schweres AS-LG diagnostiziert worden war, zum Nachweis einer moderaten AS (Rate einer moderaten AS 13,1%). Ebenso wurden ähnliche Ergebnisse unter Verwendung systematischer EVG zur Messung des Aortenanulus bei der AVA-Berechnung durch CE bei Patienten mit schwerem AS-LG (Rate von moderaten 35,1%) gefunden.

Schlussfolgerung

Die Ergebnisse dieser Studie legen nahe, dass eine systematische Anwendung von TOE zur Beurteilung des LVOT-Durchmessers und damit der AVA-Berechnung durch CE bei einigen Patienten mit schwerem AS-LG als moderat einstufen könnte. Dennoch sind weitere größere Studien erforderlich, um diese Ergebnisse zu validieren, die für die Beurteilung von Patienten mit schwerem AS-LG relevant sein könnten**.**

1. Introduction

Aortic stenosis (AS) is the most prevalent entity among heart valve diseases in western countries and has a substantial impact on cardiovascular morbidity and mortality in the elderly population [1]. The estimated prevalence of AS in individuals aged 80 years is around 9,8% and it increases up to 3% after that age [2, 3].

The predominant etiology, in this age-group is calcific valve degeneration leading to an increase in valvar stiffness and a concomitant reduction in aortic valve area (AVA)[3-5].

For a correct and accurate diagnose of AS, it is essential to assign several diagnostic tools when grading the severity of valve stenosis by combining and integrating all echocardiographic data in the clinical presentation and not using only one specific measurement.

In daily practice the standard imaging modality for valve assessment is the two-dimensional (2D) transthoracic echocardiography (TTE), which noninvasively allows the assessment of AS severity. It is also a useful tool for decision-making and in terms of prognostic information [5, 6].

Considering a normal AVA around 3 - 4 cm^2, under normal hemodynamic conditions the transvalvular flow is laminar with a peak velocity less than 2 m/s [2].

According to the current guidelines, the classical definition of severe AS should meet the following criteria: an AVA <1.0 cm^2 or an indexed AVA <0.6 cm^2/m^2 of body surface area (BSA), a peak transvalvular velocity >4 m/s and a mean pressure gradient >40 mm Hg (MPG) or a combination of any of these [5-7].

In grading AS severity, the effective AVA as well as the MPG are crucial points directly related to the treatment of choice. The AVA is usually calculated by using the continuity equation, which, based on the principle of mass conservation, considers that the stroke volume (SV) ejected through the left ventricular outflow tract (LVOT), which passes through the stenotic orifice and thus SV at valve level, is equal to the SV at the LVOT [5-8].

However, the calculated LVOT cross-sectional area (CSA) and the derived AVA from the continuity equation assumes a LVOT geometry as a circular shape rather than ellipsoidal, which it indeed is, and therefore it could significantly underestimate the CSA of the LVOT and thus the true AVA and SV [9, 10].

In some cases an important discordance could be found between the severity criteria parameters, thus a low peak velocity (<4 m/s) with a low MPG (<40 mmHg), yet a small AVA (<1.0 cm^2). For this scenario of severe aortic stenosis with low gradient, an integrated approach is recommended in order to exclude measurement errors, particularly an underestimation of the LVOT area [5, 11].

The flow status, represented by the SV [5, 7], is an important parameter in the hemodynamic profile configuration of the AS. It is derived from two measurements: LVOT diameter and LVOT time velocity integral. Calculation of SV is one of the main pitfalls associated with the diagnosis of paradoxical low flow and/or low gradient AS [12-14].

On the other hand, none of the current recommendations has a standard approach for the use of transoesophageal echocardiography (TOE), and it is only indicated for those cases of poor TTE image quality or to assess the valve before transcatheter aortic valve implantation (TAVI)[7].

Severe AS-LG is a challenging entity, which demands careful echocardiographic assessment. Two-dimensional TTE assessment of the LVTO diameter is a common source of error in the setting of suboptimal imaging quality or morphological variations (such as sigmoid septum or hourglass shape) of the LVOT, which could lead to an incorrect estimation of AVA by CE.

The main purpose of the present study is to evaluate the potential usefulness and clinical relevance of TOE on a systematic basis for the assessment of the anterior-posterior LVOT diameter for the AVA calculation by CE in patients with severe AS-LG.

1.1 Anatomy perspective

The aortic valve is a semilunar valve situated between the aortic root and the left ventricle. It is formed by three leaflets or cusps supported by the aortic sinuses: right, left, and non-coronary leaflet. The right coronary leaflet rests on the muscular part of the interventricular septum, the left coronary leaflet is continuous with the anterior mitral leaflet and muscular interventricular septum, and the non-coronary leaflet is adjacent to the membranous septum and the anterior leaflet of the mitral valve,

Histologically, the aortic valve is composed of four tissue layers: the *endothelium*, the *ventricularis* with elastin rich fibers on the ventricular side, the *fibrosa*, on the aortic side, composed of fibroblasts and collagen fibers, and the *spongiosa* at the base of the leaflet, it is between the fibrosa and ventricularis layers, primarily formed of loose connective tissue, fibroblasts, mesenchymal cells and mucopolysaccharides [4, 15]. (Fig.1)

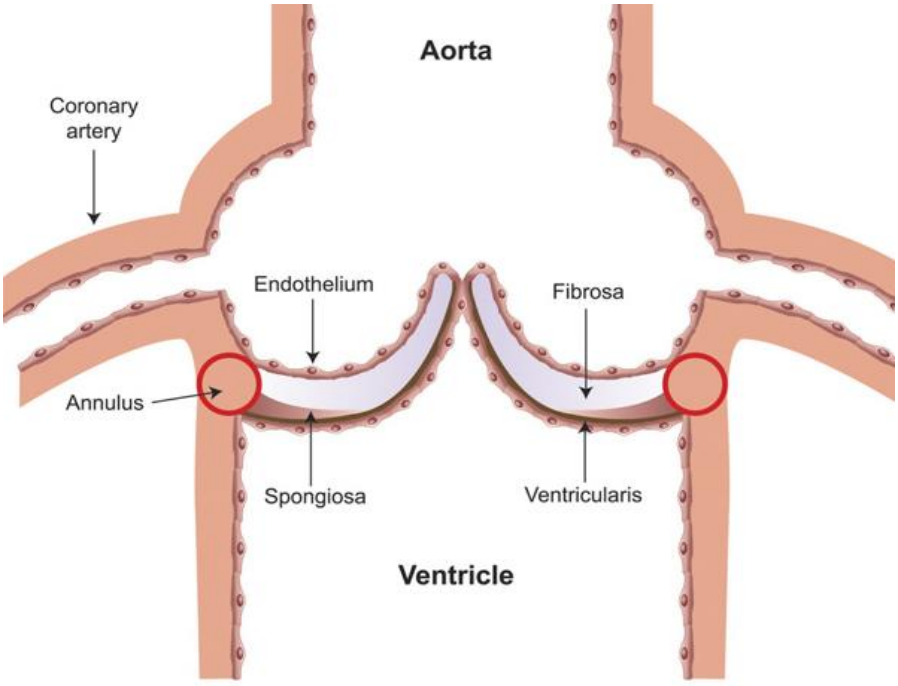


Figure 1. Aortic valve structure.
Aortic valve structure with the 4-layered valve cusps. Reproduced with permission from Dweck, M, et al. Calcific Aortic Stenosis A Disease of the Valve and the Myocardium[15].

At the base, the leaflets are attached to a collagenous network known as the annulus which facilitates their attachment to the aortic root and the dissipation of mechanical force. The fibrous interleaflet trigones are between the semilunar hinge lines of the cusps, and this attachment of

the semilunar lines to the aortic sinuses defines the anatomic annulus. The coronary arteries arise from the base of left and right coronary cusps. The left coronary ostium is frequently in the posterior part of the left sinus, and the right coronary ostium is anterior and superior in the right sinus. The lower position of the left coronary increases its risk for obstruction by a calcified aortic leaflet[14-16] (Fig. 2).

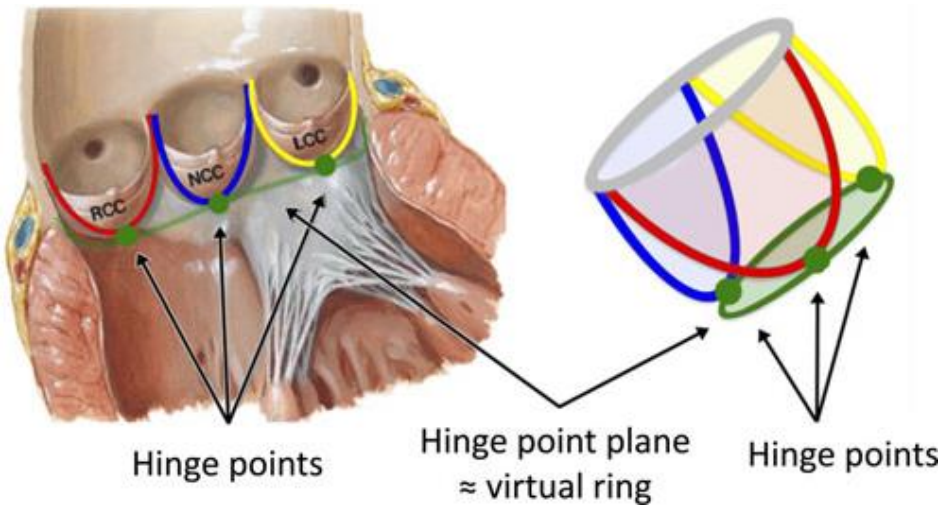


Figure 2. Anatomy of the aortic annulus.
The aortic annulus accounts for the tightest part of the aortic root and is defined as a virtual ring (shaded) with three anatomic hinge points of each attachments of the three aortic leaflets. Ao: Aorta; RCC: right coronary cusp, NCC: non coronary cusp, LCC: left coronary cusp. By Lang, R M, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults[14] . Reproduced with permission from Kasel, AM et al.

The most common congenital cardiac anomaly is the bicuspid aortic valve (BAV), an important anatomical variation that differs from the tricuspid normal aortic valve by including a larger and more circular annulus, larger sinus of Valsalva and ascending aorta, and more eccentric annular calcification [17]. The conduit between the left ventricular cavity and the ascending aorta is defined as the left ventricular outflow tract (LVOT), a complex musculomembranous channel or tunnel of about 25 mm length in the adult heart. This tunnel has a circumferential shape (an elliptical shape in some patients) and is formed posteriorly by the intervalvar fibrosa, which is in continuity with the anterior leaflet of the mitral valve, and anteriorly by the muscular and membranous interventricular septum[18,19] .
In other words, the LVOT is composed of a muscular component (i.e., the muscular portion of interventricular septum) and a fibrous component (i.e., the fibrous continuity between the aortic

and mitral cusps) [18]. Functionally, the LVOT CSA and flow are used to calculate stroke volume, cardiac output, and AVA by the continuity equation. In these calculations, the LVOT is assumed to be a uniform conduit but considering that the LVOT is a composite of adjoining structures, it is possible to find regional heterogeneity in its structure. On the other hand, the LVOT is a dynamic structure with variable changings in size and shape from end-diastole to peak systole. It is, in fact, a composite of adjoining structures, with possible regional heterogeneity in its structure[18-22].

The aortic root, a structure that is the direct continuation of the LVOT, emerges towards the AV. It is situated to the right and posterior to the subpulmonary infundibulum. The structure includes the aortic annulus, the interleaflet triangles, the semilunar aortic leaflets and their attachments, the aortic sinuses of Valsalva, and the sinotubular junction. It extends from the basal attachments of the aortic valve cusps within the LVOT to their distal attachment at the tubular portion of the aorta. The aortic annulus is, actually not a distinct anatomic structure but a virtual ring that may be drawn by joining the basal attachments of the three aortic cusps. The uppermost attachments of the leaflets, in the shape of a crown, form the true anatomic ring [14, 22-24] (Fig.3).

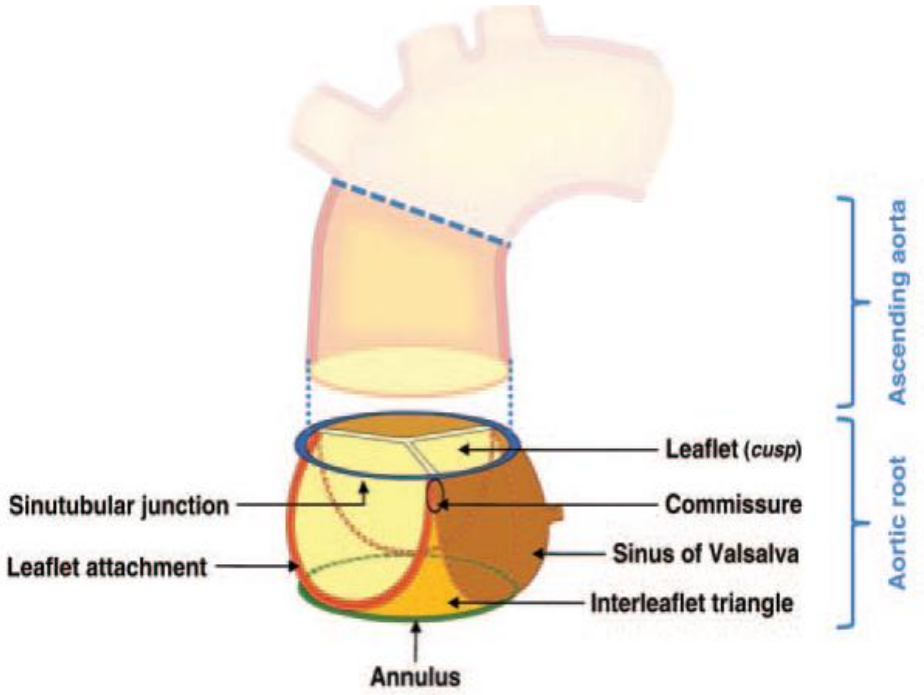


Figure 3. Anatomy of aortic root.
The structure includes: the aortic annulus, the interleaflet triangles, the semilunar aortic leaflets and their attachments, the aortic sinuses of Valsalva, and the sinotubular junction. Reproduced with permission from Sievers H, et al. The everyday used nomenclature of the aortic root components: the tower of Babel? [24].

1.2 Histopathology: from sclerosis to stenosis

The term "aortic valve sclerosis" is usually used to define a mild valve thickening without hemodynamic blood flow obstruction[4].

Early aortic histopathological manifestations of sclerosis are likely to be initiated by endothelial disruption. These are focal subendotelial lesions on the aortic side of the leaflet, originating due to increased or decreased shear stress, that could extend to the adjacent fibrosa layer with lipoprotein accumulation and depots, especially apolipoproteins B and E, LDL oxidation and inflammatory cell infiltrate. Later, as the valve degeneration progresses, the sclerosis turns into calcification, and although aortic sclerosis is clinically asymptomatic, it is associated with an increased morbidity and mortality, especially in coexistence with cardiovascular risk factors [25-28].

In animal studies, it has been shown that hypercholesterolaemia triggers endothelial dysfunction in the aortic valve with oxidative stress, inflammation and plaque development, as well as valve mineralization [24].

Valve calcification used to be thought to be a passive degenerative process with calcium attaching to the cusp's surface. However, emerging evidence indicates that calcific aortic valve disease is a continuum and progressive disorder, rather active than passive, similar to atherosclerosis. The mechanism of lipid deposition is very similar to the one that takes place in coronary atherosclerosis. The active calcification process of a tricuspid aortic valve is the major factor that leads in early stages to valve stiffness and later results in stenosis. The characteristic pattern of calcium depot is defined by a prominent mineral accumulation in the central and basal parts of leaflets without commissural fusion, resulting in a stellate-shaped systolic orifice [4, 5, 25-28].

Recent studies have documented that lipid-lowering treatment with rosuvastatin reduced the progression of AS as well as cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia. Furthermore, the treatment with rosuvastatin has an independent and dose-response association with incident AS[25, 28, 29].

1.3 Definition of severe aortic stenosis

The classical definition of aortic valve stenosis refers to a hemodynamic blood flow obstruction to the normal flow between the LV and the aorta. This blockage is caused by the calcification,

thickening and stiffness of valve cusps. The consequence is an alteration of the normal valve motion with impaired leaflet mobility[3].

The severity of AS in terms of echocardiographic findings is considered hemodynamically relevant when an AVA ≤ 1.0 cm² or an indexed AVA ≤0.6 cm²/m² of BSA, a peak transvalvular velocity ≥4 m/s and a mean pressure gradient ≥40 mm Hg (MPG) or a combination of any of these is present [5-7].

However, discrepancies in estimated flow status or stroke volume and a discordant low MPG for a severe valve area (<1cm^2) can be present. This is the entity known as low-flow/low-gradient AS (LF/LG) and it can be present in 30 to 50% of patients with severe AS [30] (Table 1).

Table 1. Classification of AS.

Modified from Baumgartner et al.[5]

	Aortic sclerosis	**Mild AS**	**Moderate AS**	**Severe AS**
Peak velocity (m/s)	<2.5 m/s	2.6 – 2.9	3.0 – 4.0	>4.0
Mean gradient (mmHg)	-	<20	20-40	>40
AVA (cm^2)	-	>1.5	1.0-1.5	<1.0
Indexed AVA (cm^2/m^2)	-	>0.85	0.60-0.85	<0.6

1.4 Classification of aortic stenosis: what do the guidelines say?

Current guideline recommendations for AS are based on the hemodynamic relevance of the heart valve disease (mild, moderate and severe), the symptomatic status of the patient, the flow state, the gradient (high or low) and the impact of AS on LV systolic function [5-7]. The recommended classification of AS is also a useful guide for therapeutic decision-making and the indication of aortic valve replacement (Table 1).

1.4.1 Stages of aortic valve stenosis: classification of the American Heart Association/American College of Cardiology (AHA/ACC)[7]

The AHA/ACC guideline [7] stratified AS based on patient symptoms, hemodynamic status and valve anatomy. This classification also considers the hemodynamic consequences of AS.

- **STAGE A**: Risk of AS with a pathological valve anatomy (bicuspid valve anomaly) or AV sclerosis, without symptoms or hemodynamic consequences. Aortic V. max (maximum velocity) <2m/s.

- **STAGE B: PROGRESSIVE AS:** Mild to moderate leaflet calcification of a bicuspid valve or a tricuspid valve, with some reduction of systolic motion or rheumatic valve changes with commissural fusion. No Symptoms. Early LV diastolic dysfunction may be present but with normal LVEF.
  ***Mild AS**:* Aortic V. max 2.0-2.9 m/s or a MPG <20 mmHg.
  Moderate AS: Aortic V. max 3.0-3.9 m/s or MPG 20-39 mmHg.

- **STAGE C: SEVERE AS, ASYMPTOMATIC:**

  STAGE C1: ASYMPTOMATIC SEVERE AS

  Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening. Aortic V.max >4 m/s or MPG ≥40 mm Hg. AVA typically ≤1.0 cm2 (or AVAi <0.6 cm2/m2). Very severe AS is an aortic V.max ≥5 m/s or MPG ≥60 mm Hg. LV diastolic dysfunction. Mild LV hypertrophy with normal LVEF. No Symptoms but exercise testing is reasonable to confirm status.

  STAGE C2: ASYMPTOMATIC SEVERE AS WITH LV DYSFUNCTION

  Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening. Aortic V.max ≥4 m/s or MPG ≥40 mm Hg. AVA typically ≤1.0 cm2 (or AVAi <0.6 cm2/m2). LVEF <50%. No Symptoms.

- **STAGE D: SEVERE AS, SYMPTOMATIC:**

  STAGE D1: SYMPTOMATIC SEVERE HIGH-GRADIENT AS

  Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening. Aortic V.max ≥4 m/s or MPG ≥40 mm Hg. AVA typically <1.0 cm2 (or AVAi <0.6 cm2/m2), but may be larger with mixed AS/aortic regurgitation (AR). LV diastolic

dysfunction. LV hypertrophy. Pulmonary hypertension may be present. Symptoms: exertional dyspnea or decreased exercise tolerance, exertional angina, exertional syncope or presyncope.

STAGE D2: SYMPTOMATIC SEVERE LOW-FLOW/LOW-GRADIENT AS WITH REDUCED LVEF (CLASSICAL LF-LG AS)

Severe leaflet calcification with severely reduced leaflet motion. AVA <1.0 cm2 with resting aortic Vmax <4 m/s or MPG <40 mm Hg. Dobutamine stress echocardiography shows AVA <1.0 cm2 with Vmax >4 m/s at any flow rate. LV diastolic dysfunction. LV hypertrophy. LVEF <50%. Symptoms: angina, syncope or presyncope and/or heart failure (HF).

STAGE D3: SYMPTOMATIC SEVERE LOW-GRADIENT AS WITH NORMAL LVEF OR PARADOXICAL LOW-FLOW SEVERE AS

Severe leaflet calcification with severely reduced leaflet motion. AVA <1.0 cm2 with aortic Vmax <4 m/s or MPG <40 mm Hg. Indexed AVA <0.6 cm2/m2 and stroke volume index <35 mL/m2. Measured when patient is normotensive (systolic BP <140 mm Hg). Increased LV relative wall thickness. Small LV chamber with low stroke volume. Restrictive diastolic filling. LVEF ≥ 50%. Symptoms: angina, syncope or presyncope.

1.4.2 Integrated approach according to the classification of the European Society of Cardiology (ESC)[5,6]

Recommendations of the latest guidelines from the ESC for the assessment of aortic valve stenosis and for the management of valve heart disease [6] are centered on an integrated approach for the diagnosis and classification of AS. (Fig. 6)

In cases where the MPG is are too low for a given small AVA, it is important to rule out measurement errors and to exclude other causes of discordant values, such as small body size, hypertension during the examination or underestimation of the LVOT diameter and flow rate.

According to the basic grading criteria of severe AS and discordant gradient values, SV and AVA, AS could be classified in:

- **Low-flow, low-gradient (LF/LG) AS with reduced EF**
- **LF/LG AS with preserved EF: Paradoxical LF/LG.**

- **Normal-flow, LG AS with preserved EF: obtained data should be reevaluated.**
  In those cases of discordant values and a reduced EF the performance of a Dobutamine stress-echocardiography would be helpful to evaluate changes in valve area, peak velocity and MPG under pharmacological stress and the contractile response to it and the existence of flow reserve[5,6].

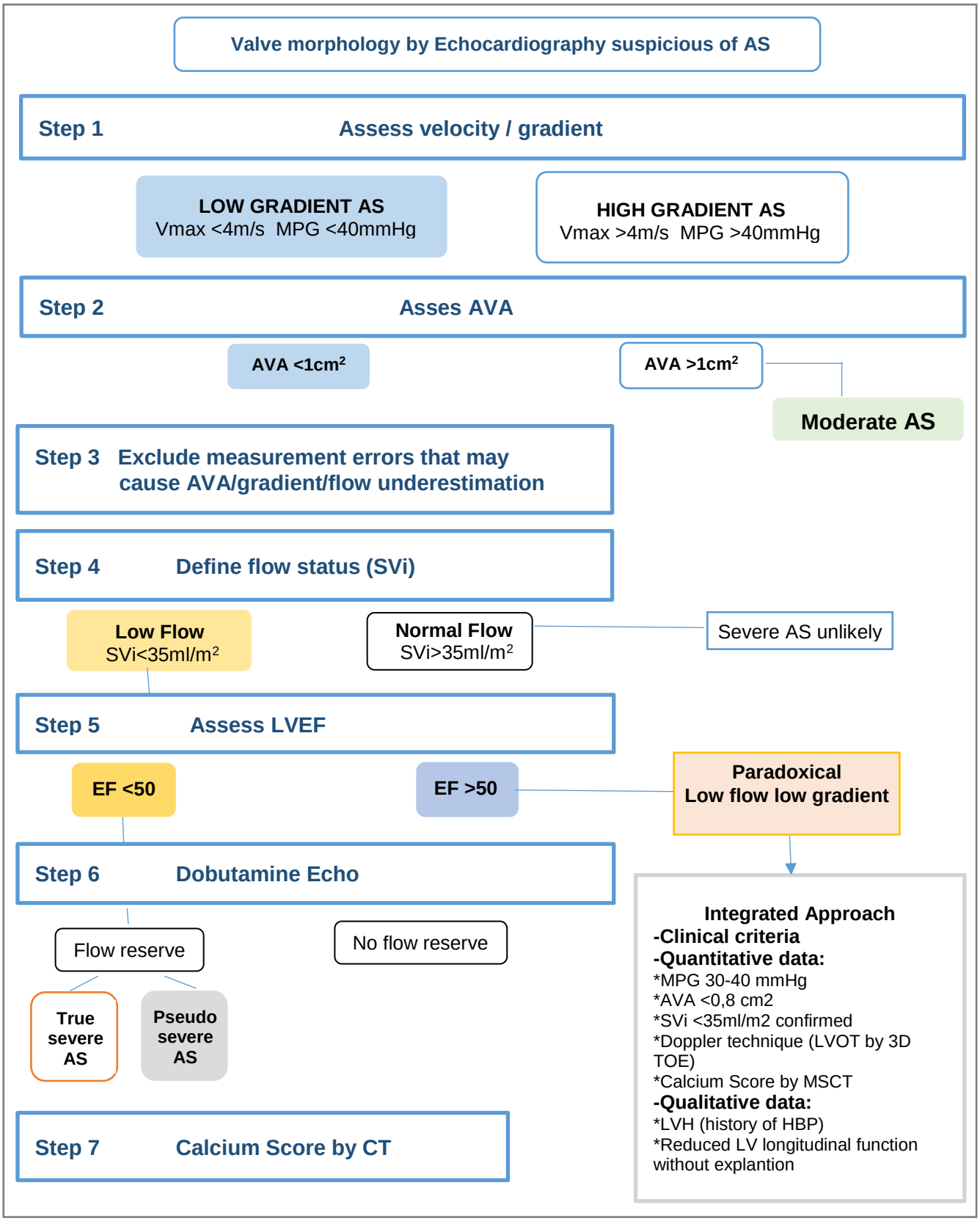


Figure 4. AS severity grading.
Integrated approach to grading AS severity. Modified with permission from Baumgartner et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update of the European Association of Cardiovascular Imaging and the American Society of Echocardiography[5,6].

1.5 Pathophysiology: reasons for low gradient in aortic stenosis

Normally, during the cardiac cycle, the SV is ejected from the left ventricle (LV) to the aorta through the AV, which has a normal area of around 3 to 4 cm^2. Under normal hemodynamic conditions, a small pressure gradient exists between the LV and the aorta throughout the midsystole, and along the second half of the systole this gradient would be inverted due to a flow deceleration in the aorta, resulting afterwards in valve closure[15, 31].

AS is characterized by a progressive calcium deposition on the valve surface, which gradually leads to a valve orifice narrowing with a consequent commissural fusion and eventually LVOT obstruction [25, 31]. The valve area correlates inversely to the square root of the pressure gradient. This means that for a normal contractile function and normal vascular load conditions, decreases in AVA smaller than 1.5 cm^2 result in important increases of the pressure gradient. In other words, the narrower the valve orifice, the faster the transvalvular jet velocity and thus the higher the pressure gradient [31-33].

Clinical evidence shows that the average reduction of the AVA in an emerging mild AS would be around 0.1cm^2/year. It has been seen that in the natural evolution of AS, once any of the typical symptoms of AS -angina, syncope or heart failure- are present, the existing reduced orifice is considered to be at least <1cm^2. In elderly patients who also have coronary heart disease the rate of valve disease progression is faster than in those who do not have this association [34-40].

Once the outflow obstruction on the LV takes place, the LV must overcome the valve stenosis. The progressive increase in ventricular afterload leads to the development of a compensatory septal hypertrophy. At the beginning of the disease, the hypertrophy tends to normalize the parietal stress, but with AS progression this compensation will be no longer effective and the chronic increased afterload will afterwards lead to left ventricular systolic dysfunction with abnormal ventricular filling and mitral regurgitation [31-34]. It is also at that moment that the representative symptoms mostly appear. The appearance of clinical manifestations characterize the natural evolution of the stenotic valve disease [5, 34-38].

Nevertheless, the progression of AS and the performance of a pressure gradient do not only rely on valvar stiffness, but also on the anatomy and functional characteristics of the myocardial muscle. The LV in association with the elastic properties of the arterial system, would determine the hemodynamic and clinical profile of the heart valve disease. In other words, the degree of valvar obstruction in addition to the systemic arterial compliance and/or to an increase in systemic vascular resistance determine LV afterload [31-36].

At a compensated stage of AS, an increase of systolic pressure in the LV is based on the development of a concentric remodeling, which according to Laplace law (wall stress= pressure x radio/2 thickness) will be helpful to reduce the parietal stress at the expense of an increase in wall thickness[36, 37]. At this point, both LVEF and flow status are normal.

The chronic pressure overload subsequently induces more concentric remodeling and LV hypertrophy. This mechanistic pattern of the LV in association with the reduction in AVA, the fibrosis, the elevated vascular load, the decrease in contractility and the possibly associated coronary disease contribute to the rise of end systolic volume and parietal stress. Once the ability of compensatory ventricular hypertrophy is exceeded, the direct consequence is a reduction in EF and functional mitral regurgitation. All of these together contribute to an augmentation in end diastolic pressure or preload and once transmitted to the left atrium and pulmonary capillary will boost the consecutive appearance of dyspnea at different degrees of exertion [15, 34-40].

The functional development of AS in relation to EF, MPG and SV determines the different clinical presentations of the disease. According to the guidelines, an SV <35 ml/m2 is by definition a low flow state and it is a frequent cause of low gradient AS[5, 7, 41].

The transvalvular flow rate affects the maximum aortic velocity and thus the mean pressure gradient. At minimal decreases of SV and transvalvular flow rate, gradients will also reduce, a phenomenon known as a pseudo-normalization of the gradient, meaning that in cases of low flow (classical LF-AS), it is expected to be related to a reduced ventricular systolic function.

On the other hand, it has been seen that a low flow, low gradient AS can also exist with a preserved LV ejection fraction, which is known as “paradoxical low flow AS”. Years ago, Hachicha and colleagues[13] first described the coexistence of a severe AS and a discordant low gradient despite a preserved EF -“paradoxical low flow low gradient (LF-LG) severe AS”-, and the apparent discrepancy was justified as a potential impairment in intrinsic myocardial function.

It was also proposed that a low flow could be the consequence of the LV concentric remodeling and the diastolic dysfunction with impaired LV filling and reduced left cavity size. In most of the cases of calcific AS, the coexistence of a chronic systolic hypertension is frequent, and this can be consequently the origin of a reduced ventricular and arterial compliance [40-42]. It adds an arterial load to the subsequently increased afterload in the LV due to elevated valvular load . This parameter can be estimated with the valvuloarterial impedance (Zva) by dividing the MPG and systolic blood pressure by the SVi [40-43]. The valvuloarterial impedance evaluates the global afterload, which represents the valvular obstruction and the systemic vascular load, and it has

an important predictive value as seen in some recent investigations. In case of a LF-LG AS, the Zva can be pathologically high (>4,5 mmHg/ml) [44-50] (Figure 5).

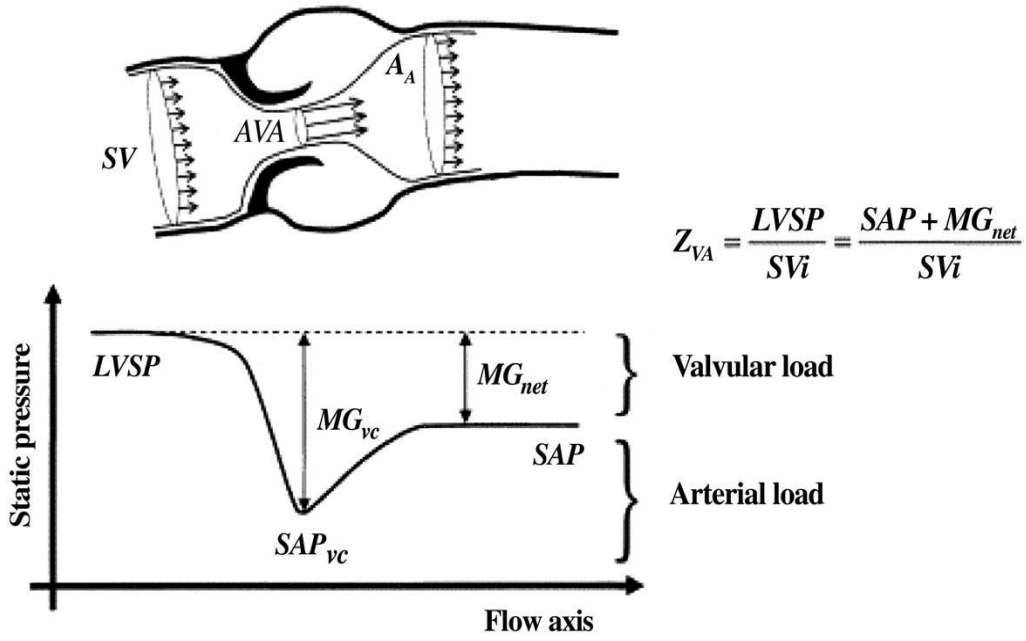


Figure 5. Flow and pressure.
Graphic representation of the flow and static pressure across the left ventricular outflow tract (LV), aortic valve (AV), ascending aorta during systole. AA aortic cross-sectional area, AVA effective aortic valve area; LVSP leftventricular pressure, MG net transvalvular pressure gradient after pressure recovery, MGvc transvalvular pressure gradient at the vena contracta ; SAP systolic aortic pressure, SAPvc systolic aortic pressure at the vena contracta, SV stroke volume, SVi indexed stroke volume , ZvA valvulo-arterial impedance. With permission from Briand et al. Reduced systemic compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implication for diagnosis and treatment[46.]

Conversely, it has been proposed that the low flow state is not due to an elevated afterload but related to intrinsic myocardial disease with an increased subendocardial fibrosis and less cavity size as in ischemic heart disease (35, 39-44), which would also be associated to a reduced longitudinal systolic function[48, 50]. For this reason, the recommendation in patients with LG-AS is to perform the echocardiographic assessment under normal systolic blood pressure [5-7, 41-48].
Another important aspect is the so-called pressure recovery phenomena. In AS the flow should pass through the stenotic orifice coming from a high pressure zone to overcome an obstacle. The zone where the flow jet is the smallest and the flow acceleration is the highest is the vena

contracta, which represents the EOA[40]. The EOA of the valve corresponds to the cross-sectional area of the vena contracta [34, 40, 51] (Figure 6).

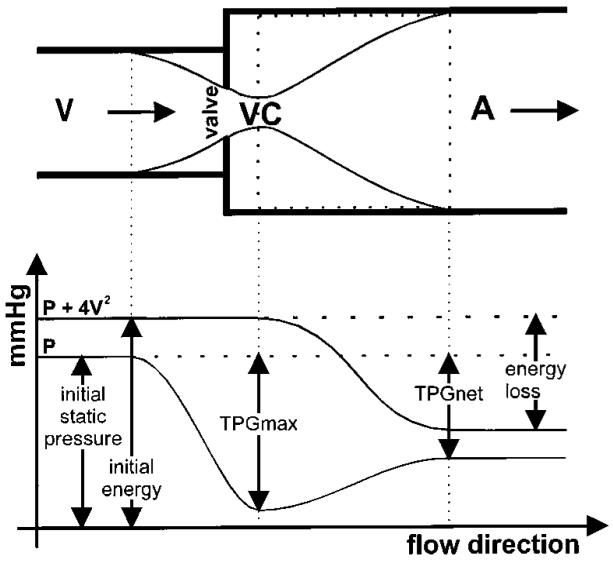


Figure 6. Pressure recovery phenomenon.
Schematic representation of pressure recovery phenomenon. System composed of left ventricle, aortic valve and ascending aorta, with the corresponding static pressure (P) and energy in terms of total pressure (P+4V). V is for left ventricular outflow tract; VC is for vena contracta; A is for aorta. With permission from Garcia D, et al. Assessment of Aortic Valve Stenosis Severity: A New Index Based on the Energy Loss Concept[51].

The blood flow is laminar and not compressible. When the laminar flow passes a stenotic valve, it will suffer a deceleration of approximately 0.5 cm before the obstruction site. This deceleration causes turbulence with small high velocity vortexes and a decrease in pressure. This means that when the generated flow contraction passes through the obstruction, a part of the potential energy will be reconverted into kinetic energy, which results in an acceleration of flow and pressure drop. The vortex turbulences cause a considerable part of the kinetic energy to be irreversibly released as heat. But another part of the kinetic energy will be reconverted to recover the previously decreased pressure. This is known as pressure recovery phenomenon and its magnitude depends directly on the relationship between the valve and the size of the aorta. The greater the flow turbulence, the less available energy to be recovered as pressure when the valve is smaller relative to the aorta[40, 43, 51].

This phenomenon is important for the clinical implications and possible discrepancies between the results when assessing the gradient invasively in comparison with the echocardiographic assessment [51].

1.6 Echocardiography in aortic stenosis: the standard diagnostic modality

The typical symptoms of aortic stenosis are dyspnea, syncope and/or angina. Clinical signs are a late peaking systolic murmur, heard at the base with a louder intensity in midsystole and with a radiation to the carotids, a louder S2 and possibly a fourth heart sound at the end of the diastole[52, 53].

On the basis of such clinical presentation, further evaluation modalities should be performed in order to diagnose an underlying aortic valve disease.

Echocardiography represents the primary diagnosis method of heart valve disease and is the key tool for the assessment and severity evaluation of AS [5-7]. Clinical decision-making is based on the results obtained from echocardiographic imaging, and it is for that reason that image quality and measurement accuracy are of cardinal importance. It is also relevant for the evaluation of the consequences of severe AS such as LV compensation for AS, systolic function, EF, aortic root dimensions and associated mitral valve disease [6, 7, 52].

The basic assessment consists of a combination of 2D views (parasternal short- and long-axis, five-chamber view and three-chamber view) in order to do a qualitative assessment of the valve. The number of cusps and their mobility, thickness and calcification are determined. The severity of valve calcification can be semi-quantitative estimated as mild, moderate, or severe according to the degree of valve thickening and echogenicity. The amount valve calcification predicts clinical outcomes[5, 54].

Measurements by Doppler can reveal the level of obstruction, valve flow velocities, transvalvular pressure gradients and hemodynamic parameters such as EF and SV [5-7], and the combination of Doppler parameters is helpful in determining the severity of a possible concomitant valve regurgitation [6, 52].

However, an accurate assessment requires an in-depth adjustment of technical details and it is highly dependent on the experience of the observer.

The standard hemodynamic parameters recommended (Evidence Level I) for the clinical practice are the aortic peak velocity, the mean pressure gradient (MPG) and the aortic valve area (AVA) calculated by the continuity equation (CE) [2,5,6].

1.7 AS peak jet velocity

Measurements of aortic peak velocity should be performed from multiple acoustic windows (apical five- and three-chamber view and supraesternal) using continuous-wave (CW) Doppler ultrasound to record the highest forward flow, which is to say the antegrade peak systolic velocity.

It is recommended to use the color Doppler signal to guide the evaluation of flow velocities, because if there is a concomitant mitral regurgitation with an eccentric jet, this could interfere in the CW signal.

In patients with sinus rhythm three beat recordings are enough, but in case of atrial fibrillation or other irregular rhythms an average of five beats is mandatory[5, 31].

The velocity curve should be smooth with a well-defined outer edge, and afterwards this edge can be carefully traced (Figure 7).

1.8 Mean pressure gradient (MPG)

The MPG is the most robust parameter in AS severity grading[5]. It represents the instantaneous gradients between the LV and the aorta happening during the ejection period. It can only be calculated from the envelope tracing of the aortic CW Doppler signal. It is not possible to calculate the MPG with mean velocity and the simplified Bernoulli equation using the maximum gradient[2,5,31] (Figure 7).

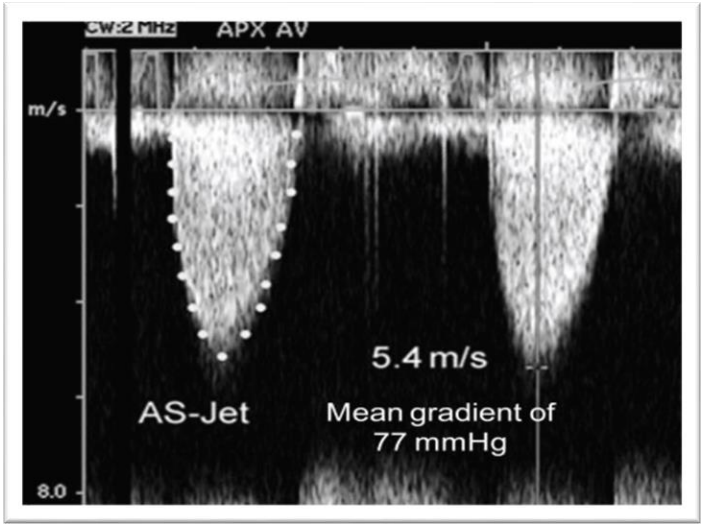
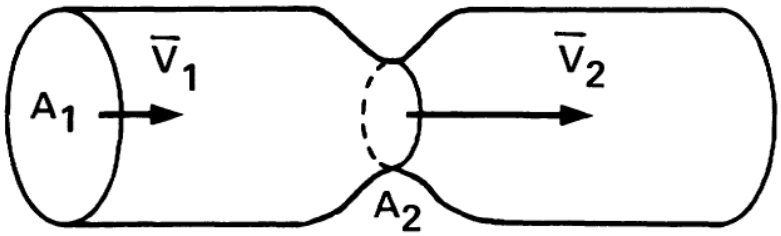


Figure 7. MPG and peak velocity assessment.
Measurements of MPG and peak velocity performed with CW Doppler from aortic peak velocity of a severe AS. With permission from Baumgartner et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update of the European Association of Cardiovascular Imaging and the American Society of Echocardiography[5].

1.9 AVA by continuity equation (CE)

The CE represents the standard calculation of the AVA and is based on the concept that the systolic volume ejected through the LVOT to the aorta passes through a stenotic valve and thus the volume at the valve orifice is equal to the LVOT volume [5, 31, 55].

The volume flow passing through a CSA is the same, as the CSA times flow velocity over the ejection, which is to say that when a flow passing through a conduit is a laminar flow, it is considered to be equal to the mean velocity times the cross-sectional area of the orifice. If the flow is constant, the CSA points is inversely proportional to the ratio of the mean velocities at two different. This means that if the velocity and flow at a stenotic valve is known, its area can be calculated from the flow divided by the mean velocity of the stenotic jet (Figure 8)[5,8,31].



$$Q = A_1 \times V_1 = A_2 \times V_2$$

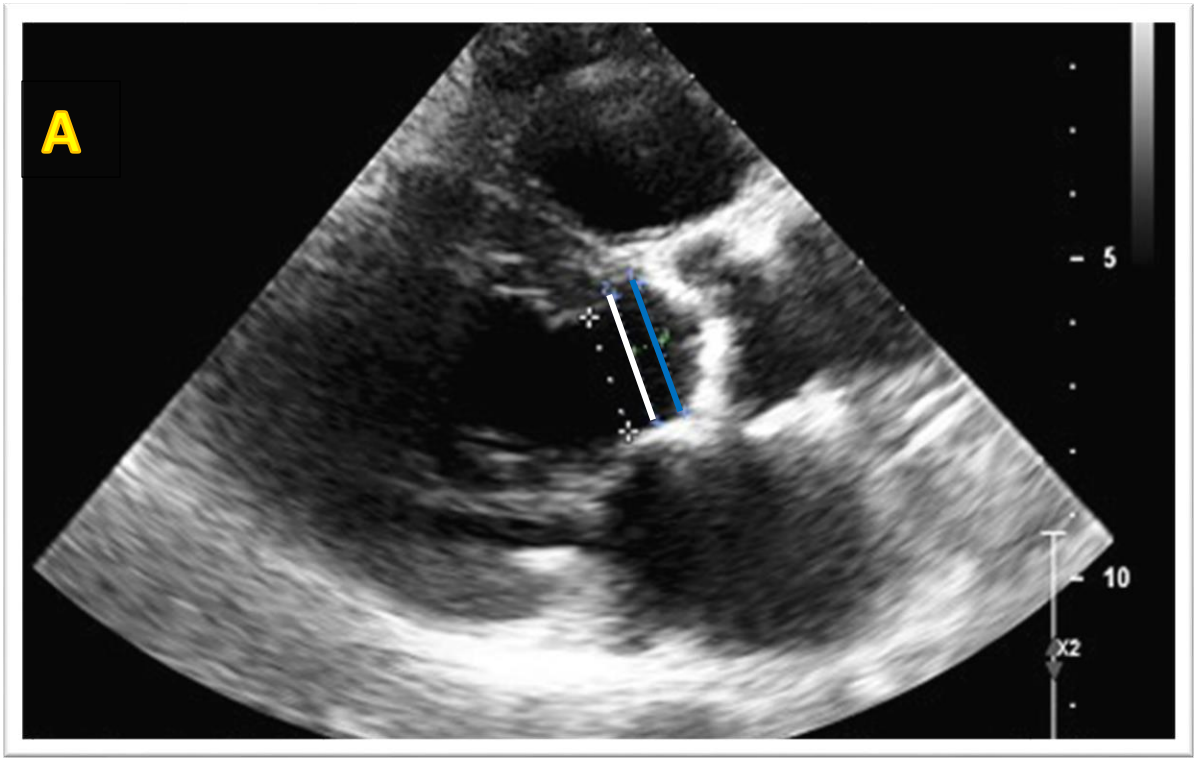
$$A_1 / A_2 = V_2 / V_1$$

Figure 8. Estimation of stenotic valve area.
Illustration of the hemodynamic principle of estimation of stenotic valve area, where A is the CSA and V is the velocity. If A1,V1 and V2 are known, the stenotic area A2 can be derived as Q/V2 x A = cross-sectional area (CSA); Vmean velocity; Q = flow. With permission from Zoghby et al. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography[8].

For the calculation it is necessary to measure the diameter of the LVOT to obtain the CSA:

$$CSA_{LVOT} = \pi . (\text{LVOT diameter} / 2)^2$$

The LVOT diameter should be measured in the parasternal long-axis view from inner to inner edge of the endocardium in midsystole using a zoom-in. (Figure 9)



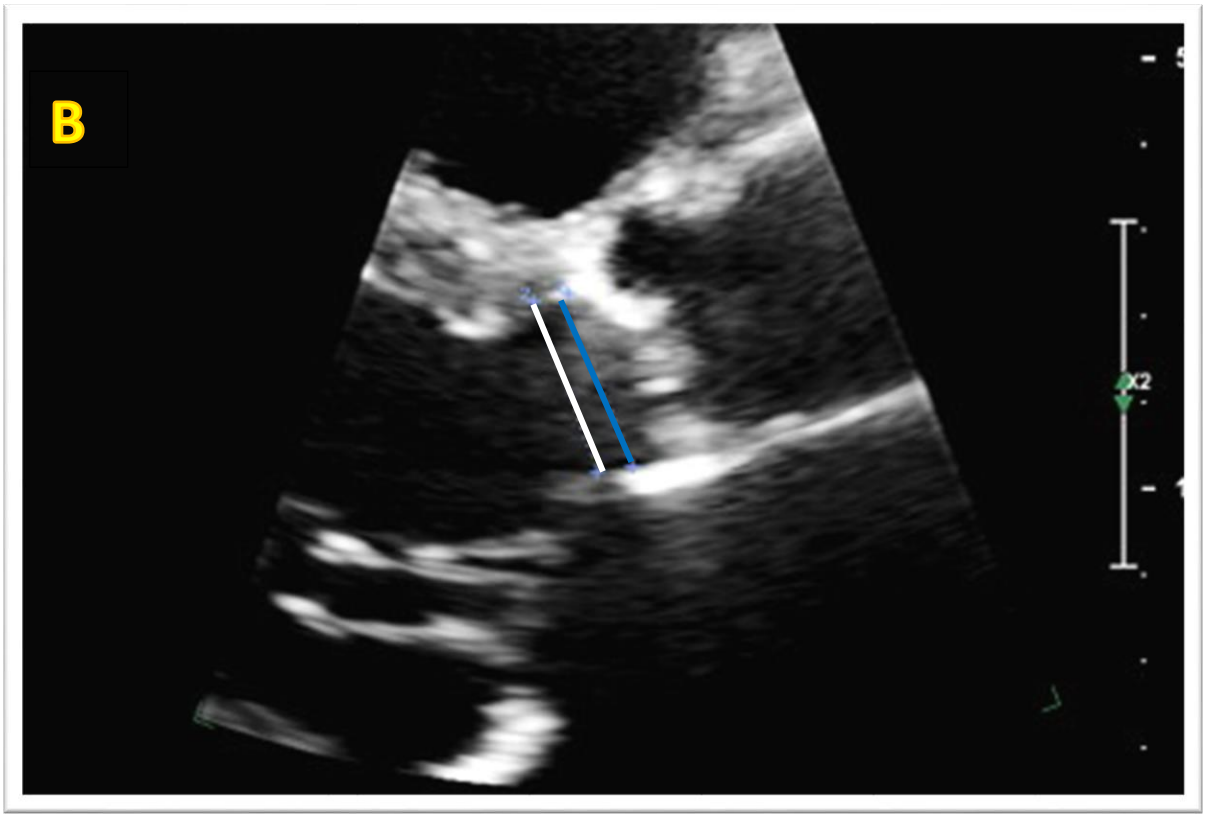


Figure 9. Transthoracic LVOT diameter assessment.
A: Parasternal long axis. LVOT diameter measured in midsystole. The white line represents the LVOT diameter within 1 cm of the aortic annulus; the blue line shows the diameter measured at the annulus. **B:** LVOT zoom-in view from the same patient.

Once the CSA is calculated, it can be incorporated into the CE as follows:

$$\mathbf{AVA\ (cm^2) = (CSA_{LVOT} \times VTI_{LVOT}) / \ VTI_{AV}}$$

where VTI AV and VTI LVOT are the velocity time integrals of transvalvular and LVOT flow, respectively. The VTI from the LVOT is obtained with pulsed-wave Doppler recorded from an apical window in either five-chamber view or in apical long-axis view (Figure 10). All recommended standard recordings, technical specifications and measurements for AS quantification are displayed in Table 2.

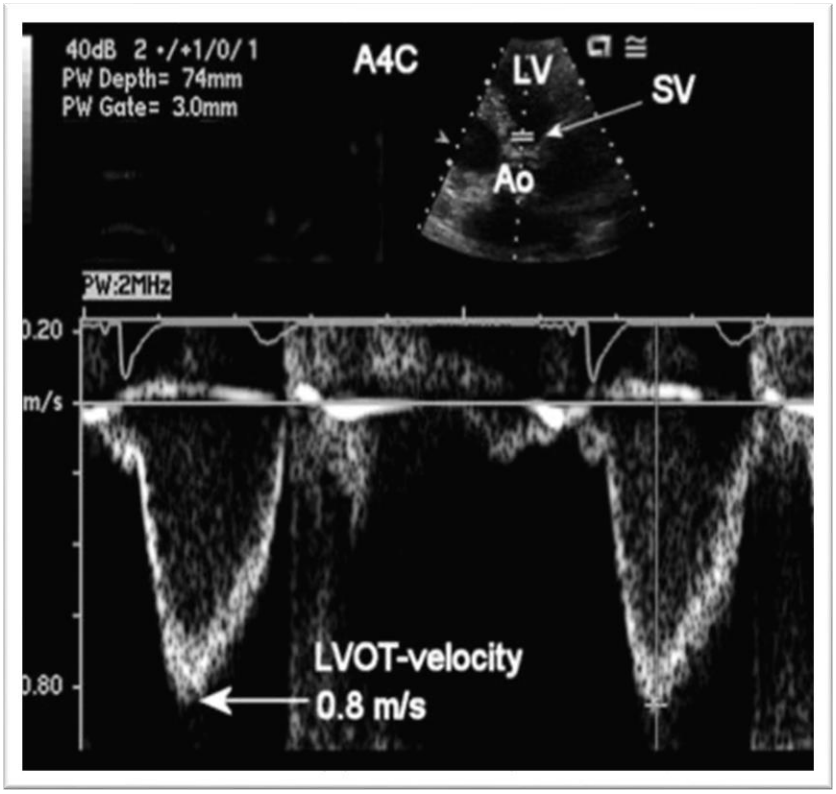


Figure 10. LVOT Doppler assessment.
PW Doppler from LVOT and measurement of VTI from a five-chamber view. With permission from Baumgartner et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update of the European Association of Cardiovascular Imaging and the American Society of Echocardiography[5].

Table 2. Recommendation for AS quantification: measurement and data recording.

Modified with permission from Baumgartner et al. Recommendations for the echocardiographic assessment of aortic valve stenosis: a focused update of the European Association of Cardiovascular Imaging and the American Society of Echocardiography[5].

Data element	Recording	Measurement
LVOT diameter	-2D PLAX -Zoom mode -Adjust gain to optimize tissue interface	–Inner edge to inner edge –In midsystole –Parallel to the AV or at the site of velocity measurement –Diameter to calculate circular CSA of LVOT
LVOT velocity	-Pulsed-wave Doppler -Apical long-axis view or 5C -Sample volume positioned just on LV side of valve and moved carefully into the LVOT if required to obtain laminar flow curve -Velocity baseline and scale adjusted to maximize size of velocity curve -Time axis (sweep speed) 50–100 mm/s -Low wall filter setting -Smooth velocity curve with a well-defined peak and a narrow velocity range at peak velocity	–Maximum velocity from peak of dense velocity curve –VTI traced from modal velocity
AS jet velocity	-CW Doppler (dedicated transducer) -Decrease gain, increase wall filter, adjust baseline, curve and scale to optimize signal -Multiple acoustic windows (e.g. apical, suprasternal, right parasternal) -Velocity range and baseline adjusted so velocity signal fits but fills the vertical -Gray scale spectral display with expanded time scale	–Maximum velocity at peak of dense velocity curve. –Avoid noise and fine linear signals –VTI traced from outer edge of dense signal –Mean gradient calculated from traced velocity curve –Report window where maximum velocity obtained
Valve anatomy	-Parasternal long- and short-axis views -Zoom mode	–Assess valve calcification –Assess cusp mobility and commissural fusion –Identify number of cusps in systole, raphe if present

2. Hypothesis

Severe AS-LG is a challenging entity which demands careful echocardiographic assessment. Two-dimensional TTE for the measurement of the LVOT diameter is susceptible to error in the setting of suboptimal imaging quality or morphological variations of the LVOT, such as sigmoid septum or hourglass-shaped septum, which may lead to an inaccurate estimation of the AVA by CE.

The objective of the present study is to evaluate the potential usefulness and clinical relevance of a systematic use of TOE in the echocardiographic assessment of patients with severe AS-LG to measure the anterior-posterior LVOT diameter for its implementation in the CE for AVA calculation.

3. Material and methods

In this cross-sectional study a cohort of 91 patients with severe AS who underwent 2D and Doppler TTE and TOE were retrospectively analyzed. All echocardiographic studies were reviewed offline.

3.1 Study population and clinical data

The study population consisted of 91 subjects aged >18 years who were referred to the echocardiography laboratory between January 2014 and October 2019 with findings of severe AS, defined according to the latest guidelines[5,7] as an AVA <1.0 cm2 (AVA indexed to BSA <0.6 cm2/m2) with low gradient (MPG <40 mmHg) of the native aortic valve by TTE.

Subjects with severe aortic regurgitation and/or severe mitral regurgitation, infective endocarditis, prosthetic valves, congenital heart disease, supra or subvalvular aortic stenosis, or presenting dynamic left ventricular outflow tract obstruction were excluded.

Demographic data of the patients were obtained by a retrospective review of existing clinical records. Clinical data included age, gender, history of smoking, documented diagnosis of hypertension, dyslipidemia (patients on lipid-lowering medication or, in the absence of such treatment, patients with documented plasma low-density lipoprotein cholesterol level >160 mg/dL), diabetes, obesity (body mass index >30 kg/m2), and coronary heart disease (history of myocardial infarction, coronary artery stenosis on coronary angiography, or regional wall motion abnormality on echocardiogram).

The patients with severe AS-LG were described as symptomatic if they presented dyspnea (New York Heart Association functional class >II) and/or a syncope event, and/or typical angina pectoris.

Demographics and clinical characteristics are described in Table 3.

3.2 Echocardiographic data

Comprehensive 2D and Doppler TTE and TOE examinations were performed in all patients with a commercial ultrasound system (Vivid-7 and E9, General Electric, and Epic7, Philips Medical Systems) equipped with 3.5 MHz or M5S transducers. Additionally, 3D TOE multiplane measurements were assessed in a subgroup of patients. The complete echocardiographic and Doppler examinations were performed in all patients, in accordance with current guidelines [5,14].

Data were stored digitally and analyzed in offline modus on a workstation (EchoPAC, GE Medical Systems). Three to five cardiac cycles in cine loop format were recorded for the offline analysis.

In order to optimize image quality, the tissue interface gain was adjusted and filters set at a high level. In the transthoracic modality, the following views were performed: paraesternal long- and short-axis view, LV apical long-axis or five-chamber, three-chamber, four-chamber and two-chamber views.

Additionally, TOE measurements were assessed at 0°, 45°, 90°, 120°, upper oesophageal, middle oesophageal. All echocardiographic data are displayed in Tables 4 and 5.

3.2.1 LVOT cross-sectional area (CSA) measurement and stroke volume (SV) assessment

Measurements of the LVOT diameter were performed in both TTE as in TOE. The CSA LVOT by TTE derived from the LVOT diameter, measured on a zoomed parasternal long-axis view, in midsystole, from inner edge to inner edge just below the insertion of the AV leaflets, between 0.5 and 1 mm below the aortic annulus[5].

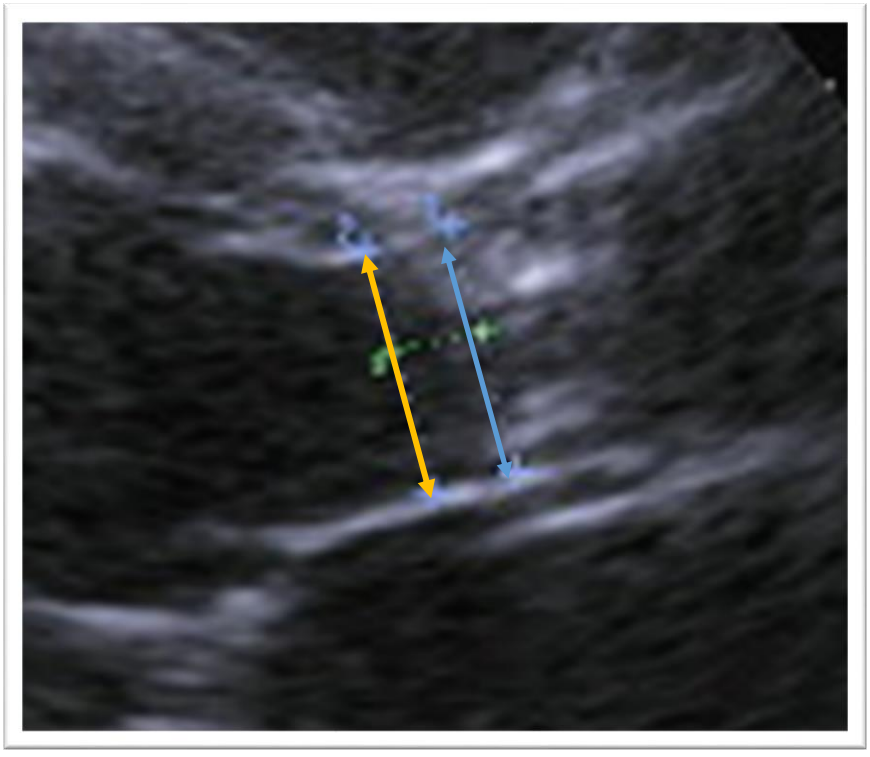


Figure 11. Measurement of LVOT by TTE.
The LVOT diameter is measured at 0.5-1 mm below the aortic annulus (yellow arrow) from a zoomed PLAX. LVOT diameter measured at the level aortic annulus (blue arrow), drawn from the insertion of the aortic cusp at the level of ventricular septum to the insertion of the aortic cusp at the level of the anterior mitral leaflet.

The CSA LVOT was estimated according to the conventional formula:

$$\mathbf{CSA_{LVOT} = \pi . (LVOT\ diameter / 2)^2}$$

In TOE in the 45° view it was performed cross-sectionally in order to show the aorta and the LVOT in midesophageal long-axis view (between 120° and at 140°) with zoom in the LVOT. The assessment of CSA the LVOT was also carried out during midsystole from inner edge to inner edge (Figure 11).

At 120° it was traced a multiplanar view to show the aortic valve in three-dimensions.

At the LV apical long-axis view, recordings of velocity were obtained through the aortic valve with continuous wave Doppler (CW) and through the LVOT using pulsed-wave Doppler (PW) and carefully positioning the sample volume, with a length of 3-5mm, on the LVOT proximal to the region of flow acceleration. After that, the maximum velocity and the velocity time integral curve (VTI) of the aortic valve and LVOT were opportunely recorded [5].

Stroke volume calculation as:

$$\mathbf{SV = VTI_{LVOT} \times CSA_{LVOT}\ (cm^2)}$$

where the VTI LVOT flow was previously calculated by PW from the apical five-chamber view. The result of the SV was indexed for body surface area to have SVi.

The left ventricle volumes and ejection fraction (EF) were assessed using the biplane Simpson method from the LV apical four- and two-chamber views and based on the TTE.

3.2.2 Aortic annulus measurement

Assessment of aortic annulus was performed by TTE and TOE in the PLAX and in 120°, respectively, in zoom mode at the level of the base implantation from non-coronary and right coronary cusps from inner edge to inner edge, in midsystole (Figures 11 and 12).

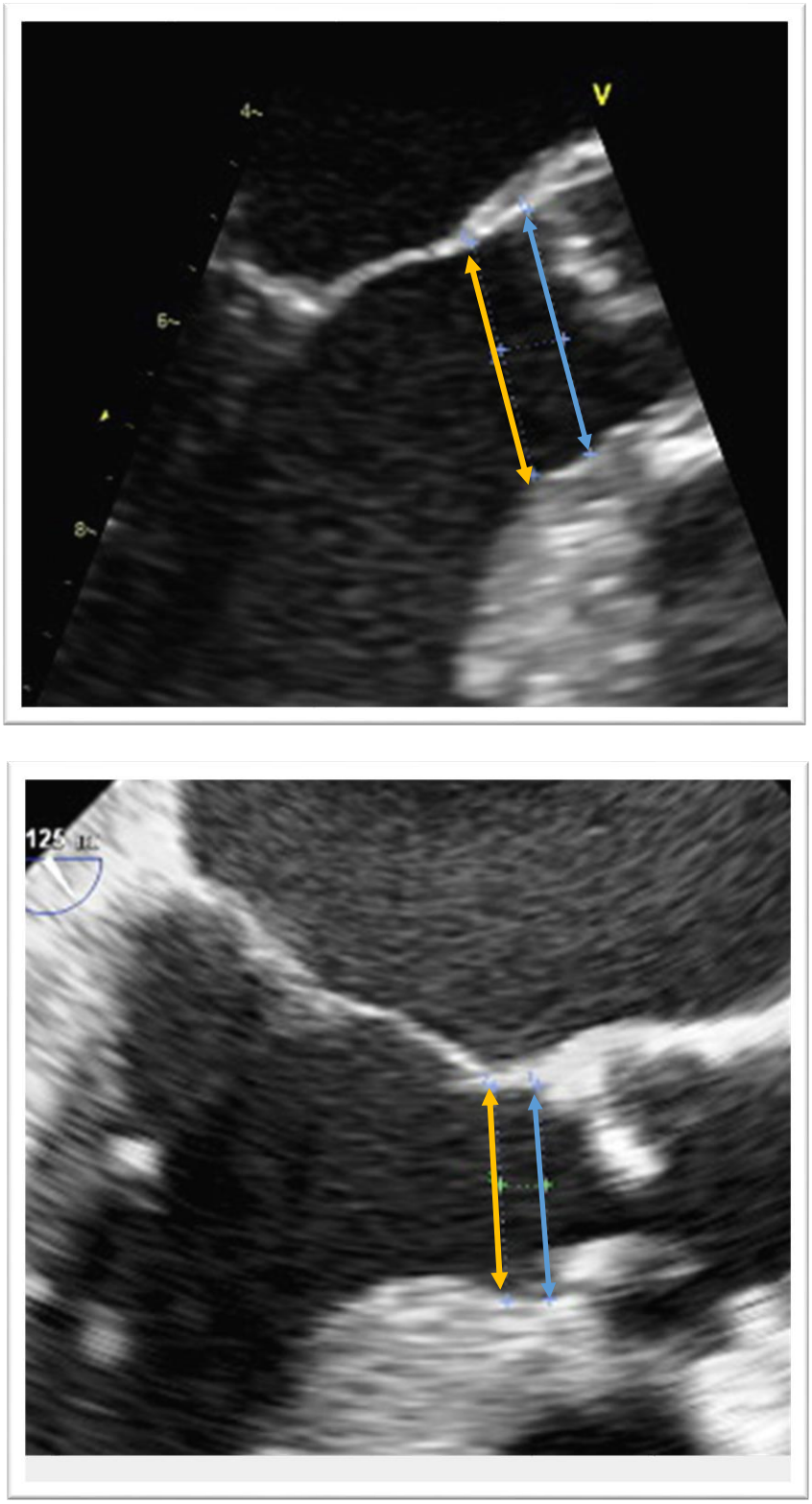


Figure 12. Measurement of LVOT by TOE.
From a zoomed parasternal long-axis view, the left ventricular outflow tract (LVOT) diameter was measured during midsystole at the level of the aortic annulus (blue arrow) and 0.5-1mm below the aortic annulus (yellow line).

3.2.3 Aortic valve stenosis quantification

In accordance with current recommendations[5,6], the initial evaluation of AS severity included the following parameters:

1)-AS peak jet velocity, measured with CW Doppler and recording the highest velocity from apical acoustic windows,

2)-mean transvalvular gradient, calculated as the difference in pressure between the LV and the aorta in systole,

3)-aortic valve area, calculated by using the continuity equation as follows:

$$AVA\ (cm^2) = (CSA_{LVOT} \times VTI_{LVOT}) / VTI_{AV}$$

where VTI AV and VTI LVOT are the velocity time integrals of transaortic and LVOT flow, respectively. The resulting AVA was afterwards indexed for BSA.

3.2.4 LV systolic function

The LVEF was assessed in all patients with the biplane Simpson method. The LV cardiac output (LVCO) was calculated as follows:

$$LVCO = SV \times HR$$

where HR is the heart rate and SV the stroke volume, the product of that was then indexed for BSA.

3.3 Statistical analysis

Quantitative variables are expressed as mean ± standard deviation (SD). Categorical variables are shown as percentage. Differences in continuous variables between the two groups were analyzed using the Student's t-test and between the groups using the analysis of variance. Categorical variables were compared by chi-square test, the Fisher exact-test, and the McNemar test as appropriate. All statistical analyses were performed with SPSS 23.0 (IBM) and MedCalc 19.1(MedCalc Software bvba).

The cut off p-value of <0.05 was considered statistically significant.

4. Results

The results of the present study show that among the selected group of patients the tendency was to be elderly, to be overweight, to have diabetes (59%), a high prevalence of systemic hypertension (97%) and dyslipidemia (64%). Almost all of the patients were symptomatic at the time of evaluation (99%) and the predominant symptom was dyspnea NYHA Class III (84%). Most of the patients were in sinus rhythm and 22% had atrial fibrillation by the time of evaluation. At the time of the study, a considerable number of them (89%) had an average systolic and diastolic blood pressure at the moment of the study of 124 mmHg and 71 mmHg, respectively (Table 3).

The baseline clinical and echocardiographic characteristics of the patients in this study are provided in Tables 3 and 4.

Table 3. Baseline clinical characteristics

Variable	Value (n=91)
Demographics	
Age >75y	79 ± 6.9
Female (%)	47
Body surface area, cm^2/m^2	1.87 ± 0.21
Body mass index, kg/m^2	28.95 ± 5.31
Cardiovascular risk factors	
Diabetes (%)	59
Hypertension (%)	97
Dyslipidemia (%)	64
Symptoms of AS	
Dyspnea NYHA III-IV (%)	84
Angina (%)	18
Syncope (%)	20
Hemodynamic status	
Systolic blood pressure (mmHg)	124 ± 13.8
Diastolic blood pressure (mmHg)	71 ± 10.7
Heart rate (beats/min)	73 ± 12.5
Comorbidities	
CAD (%)	63
Atrial fibrillation (%)	22

Table 4. Echocardiographic characteristics

Variable	(n=91)
Ejection fraction (Simpson) (%)	55.4 ± 1.5
Stroke volume (mL)	54 ± 1.7
Stroke volume indexed (mL/m^2)	28.6 ± 0.8
LA volume indexed (mL/m^2)	36.1 ± 2.4
LVOT	
-$V_{max,}$ (m/s) -VTI (cm) -Mean gradient (mm Hg)	0.56 ± 0.2 19 ± 4.7 1.62 ± 1.5
Aortic valve	
- $V_{max,}$ (m/s) - VTI (cm) - Mean gradient (mm Hg)	3.27 ± 0.4 77.2 ± 13.5 26.8 ± 6.8

4.1 Assessment of LVOT

In the selected cohort of 91 patients with diagnosis of severe LG-AS (area <1cm2 and mean gradient <40mmHg), it was possible to achieve a better characterization of the LVOT and an accurate assessment of its anterior-posterior diameter by performing TOE rather than TTE. The assessment of the diameters of the LVOT by both methods is described in Table 5.

Table 5. Echocardiographic measurements of LVOT diameters

Variable	TTE	TOE	P value
LVOT diameter (cm)	2.00 ± 0.23	2.10 ± 0.27	< 0.01
Aortic annulus (cm)	2.06 ± 0.20	2.21 ± 0.25	< 0.01

Patients previously diagnosed as severe AS-LG were reclassified into moderate by incorporating the values obtained in the CSA calculation and afterwards in the CE. Thus, when the severity grade was reassessed, a total of 13.1% of the patients previously diagnosed as severe LG-AS by TTE were determined to actually have a moderate AS. In these cases, the severity reclassification was done with the LVOT diameter obtained from TOE. This may suggest a possible reduction in the prevalence of severe AS. Hence, the analysis of the LVOT morphology in both cohorts detected an hourglass-shaped LVOT or sigmoid septum. This was easier to detect by TOE than by TTE (43.9% vs 24.1%, respectively. p 0.02).

Figure 13 shows the variations observed in septal morphology by TOE, in three different patients.

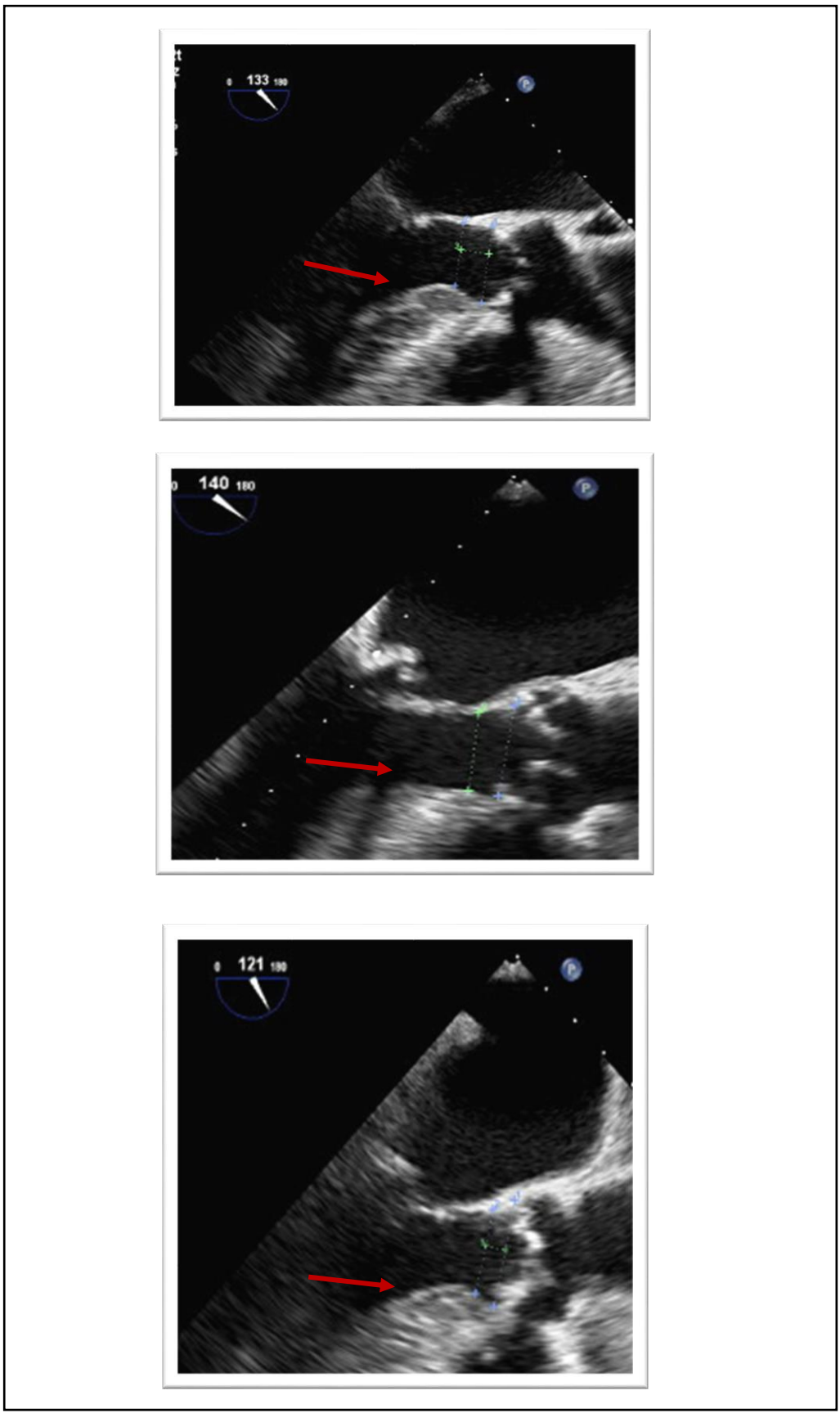


Figure 13. LVOT pattern by TOE.
TOE at PLAX between 120° and 140° in three patients with severe AS-LG. The LVOT has a sand hourglass shape (red arrow). Note the septal bulge pattern.

4.2 AVA calculation

The assessment of the AVA in the cohort studied showed significant inconsistencies. By implementation of the standard method of TTE to obtain the LVOT diameter, the calculated AVA was 0.76 ± 0.14 cm². In contrast, the continuity equation-based AVA estimated with the diameter measured at the aortic annulus from the TTE was larger than the one derived from the LVOT diameter. The resulting AVA using the annulus diameter obtained from TTE was 0.82 ±0.17 cm². In contrast, when the assessment was derived from TOE and the calculations derived from those estimated at the aortic annulus, the corresponding AVA was 0.94 ± 0.22 cm² (p <0.01). Additionally, when the continuity equation-based AVA was calculated using the LVOT diameter from TOE, the valve area was significant larger than the one obtained by TTE (0.84 ± 0.19 cm² (p <0.01)). Apart from this, we also performed a 3D multiplane AVA planimetry in the TOE in a subgroup of 53 patients, and the resulting values were even larger: the corresponding value was 1.18 ± 0.23 cm². (Table 6 and Figure 14). A point of interest is the resulting AVA when it is calculated according to the stroke volume. Using the SV estimated by the Simpson's biplane method, the corresponding AVA was 0.72 ±0.19 cm² (p <0.01).

Thus in summary, TOE detected a significantly higher percentage of morphological variations of the LVOT such as sigmoid septum or hourglass-shaped LVOT than TTE (rate 43.9% vs 24.1%, p value 0.02, respectively). In line with these findings, the anterior-posterior diameter of the LVOT was larger by TOE than by TTE (2.1 ± 0.27 mm vs. 2.0 ± 0.23 mm, p < 0.01, respectively). Accordingly, a significantly larger AVA by CE using TOE than TTE was found (AVA: 0.84 ± 0.19 cm² vs. 0.76 ± 0.14 cm²; p value < 0.01; respectively), which led to a detection of moderate AS using systematic TOE in patients with severe AS-LG (rate of moderate AS 13.1%). Likewise, similar results were found using TOE systematically to measure the aortic annulus in the AVA calculation by CE in patients with severe AS-LG (rate of moderate AS 35.1%) (Table 7 and Figure 15).

Table 6. Aortic valve area (AVA) (cm^2) calculation by continuity equation using different variables in TTE and TOE.

Variable	TTE	TOE	P value
Using LVOT diameter	0.76 ± 0.14 cm^2	0.84 ± 0.19 cm^2	< 0.01
Using aortic annulus	0.82 ± 0.17 cm^2	0.94 ± 0.22 cm^2	< 0.01
3D multiplane planimetry	n/a	1.18 ± 0.23 cm^2	< 0.01

Values expressed as mean SD
n/a not applicable

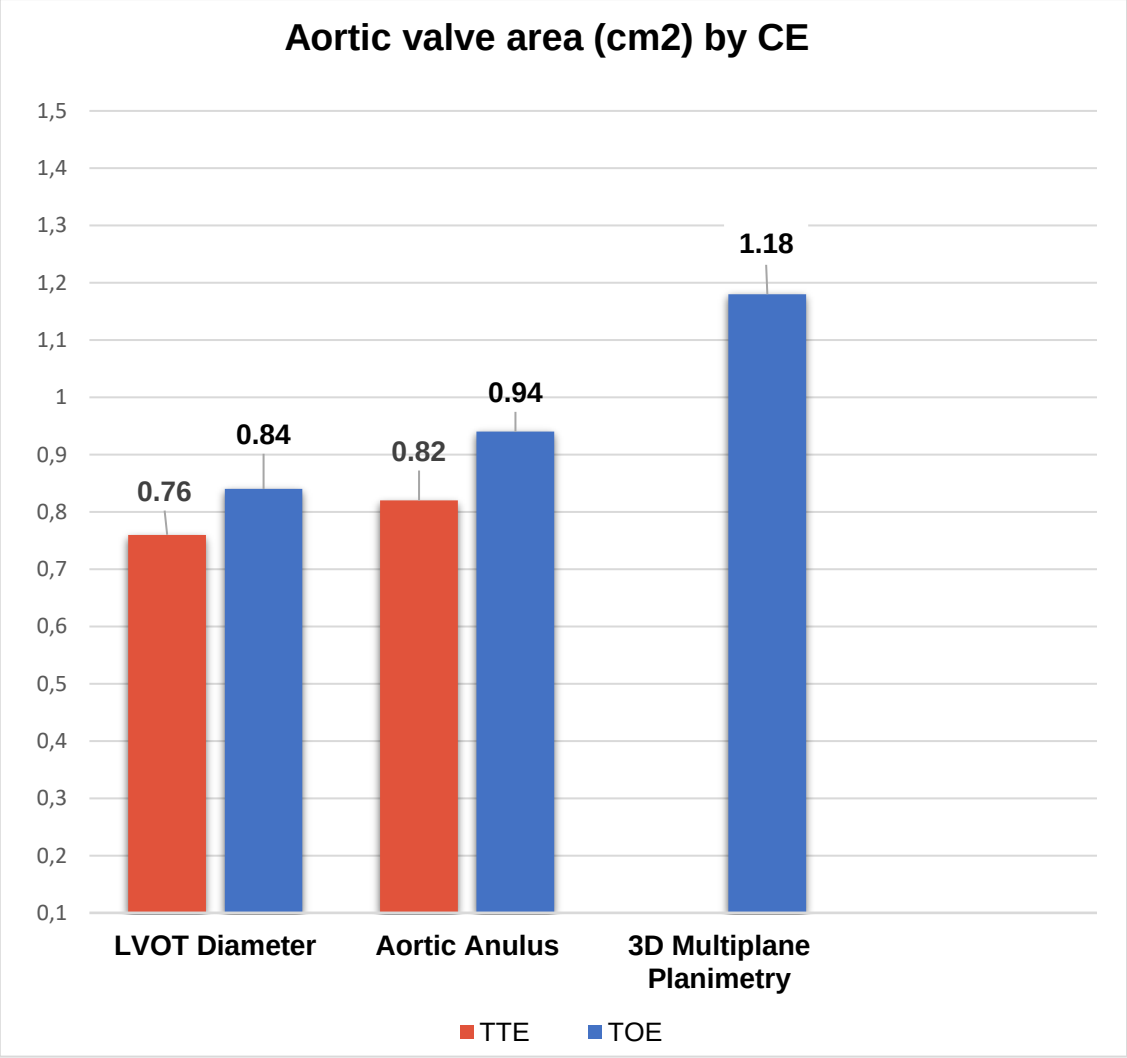


Figure 14. Aortic valve area.
AVA estimated by the continuity equation using different variables.

Table 7. Rate of moderate aortic stenosis (AS) by TTE and TOE using different variables.

Variable	TTE	TOE
Using LVOT diameter	n/a	13.1%
Using aortic annulus	8.7%	35.1%

Values expressed as mean.
n/a not applicable

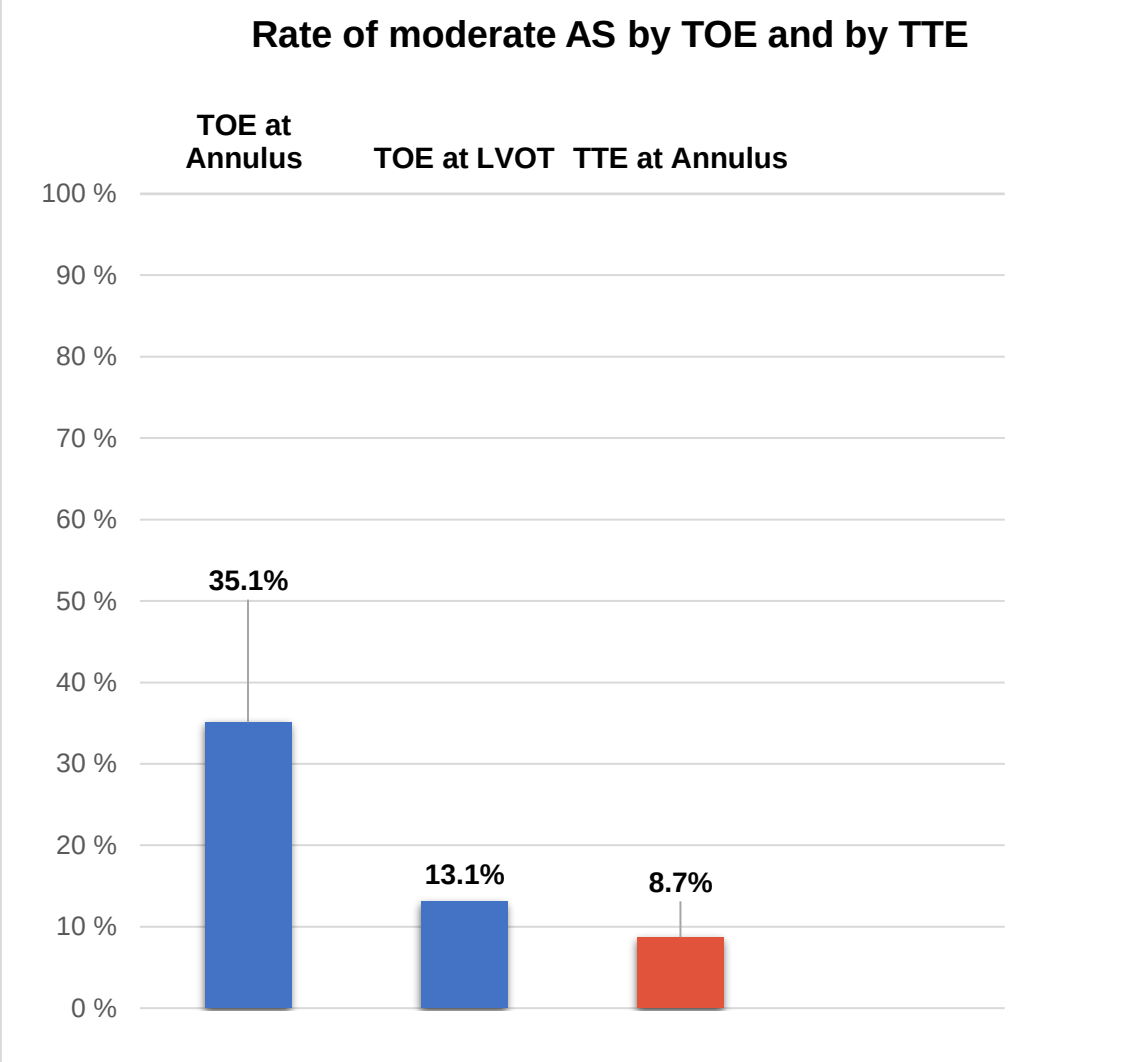


Figure 15. Rate of moderate AS.
Moderate AS by the assessment at the LVOT and at the annulus by TTE and TOE.

4.3 Stroke volume (SV) calculation

The SV assessment showed significant results. When the estimation was based on measurements of the LVOT diameter made by TTE, the resulting SV was 31.6 ±7.8 ml/m²; in contrast, by using the aortic annulus with TTE instead, the SV was 34.1 ± 9.7 ml/m². (Table 8) On the other hand, by estimating the SV through the LVOT diameter derived from TOE, the result was 34.9 ± 9.5 ml/m². Similarly, differences were seen by using the aortic annulus instead of the LVOT diameter measured with TOE; in those patients the SV was 39.1 ±11.5 ml/m². (Table 8)

When the biplane Simpson's method was used a statistical significance was observed. In this regard, the SV was 28.67 ± 7.7 ml/m²; all p value < 0.01.

Furthermore, the rate of normal SV (>35 ml/m²) among patients with a diagnosis of AS-LG with low flow (<35 ml/m²) determined by the standard method of LVOT diameter by TTE, also had a statistically significance; when the aforementioned methods were used, the rates were: 29.7%, 42.9%, 49.5%, 61.6% respectively (p < 0.001) (Table 9; Figure 16). Interestingly, when patients previously diagnosed as having a low flow severe AS- LG were reassessed with TOE, it was found that they actually had a normal flow (Table 10).

Table 8. Indexed stroke volume estimation by TTE and TOE.

Variable	TTE	TOE	P value
Using LVOT diameter	31.6± 7.8 ml/m²†	34.9 ± 9.5 ml/m²†	0.01
Using aortic annulus	34.1 ± 9.7 ml/m²†	39.1 ± 11.5 ml/m²†	< 0.01

†Values expressed as mean SD

Table 9. Rate of normal SV (>35ml/m2) calculated with TTE and TOE.

Variable	TTE	TOE
Using LVOT diameter	29.7%†	49.5%†
Using aortic annulus	42.9%†	61.6%†

†Values expressed as mean SD

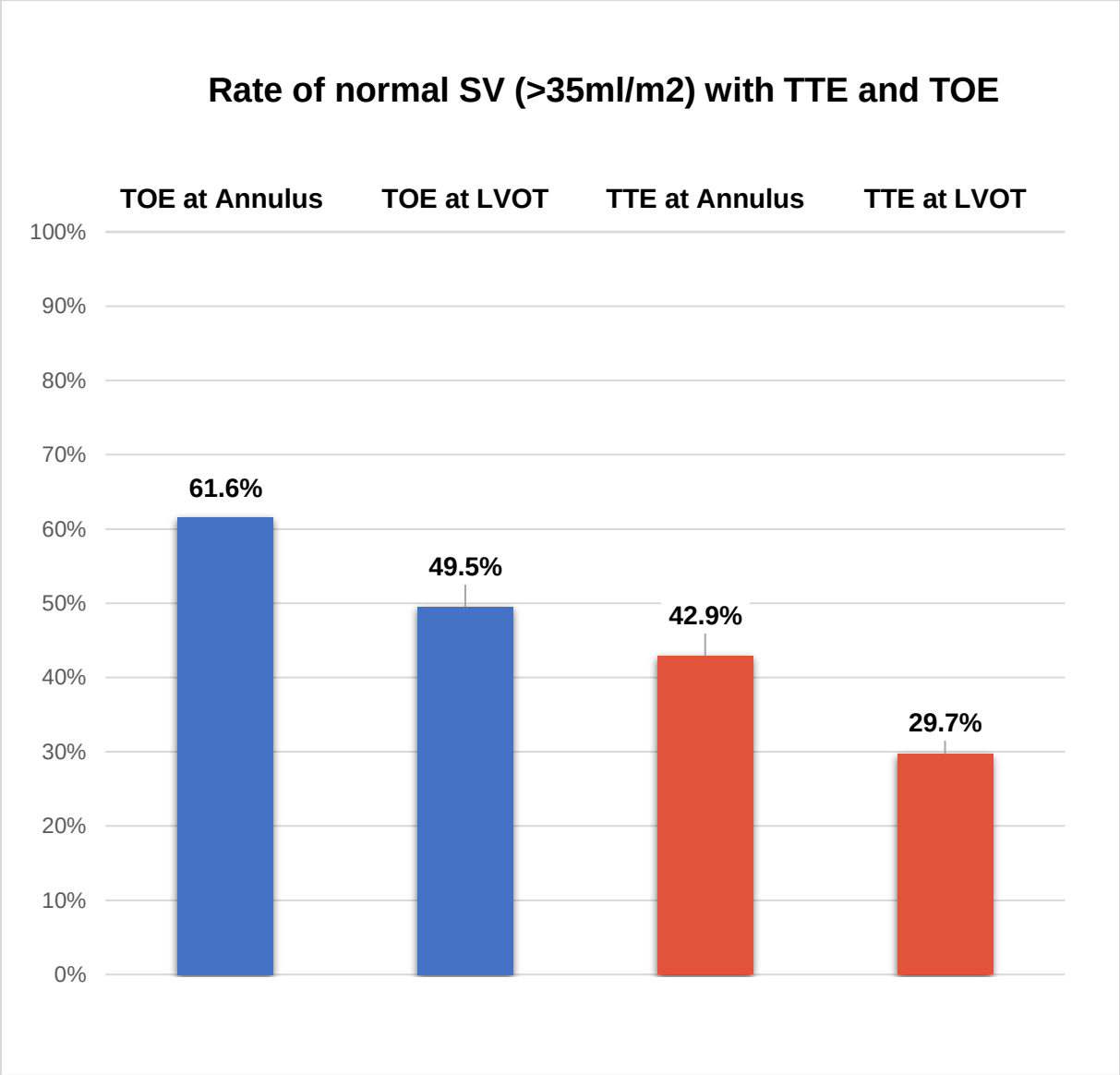


Figure 16. Rate of normal SV.
Estimation of normal SV by TOE and TTE using different variables.

Table 10. Rate of normal SV (>35ml/m^2) calculated with TOE in cases previously diagnosed by TTE as AS-LG and low flow.

Variable	TTE	TOE
Using LVOT diameter	n/a	28.2%[†]
Using Aortic Annulus	18.8%[†]	45.4%[†]

[†]Values expressed as mean SD
n/a: not applicable

5. Discussion

Severe aortic stenosis with low gradient (AS-LG) is a challenging entity which demands careful echocardiographic assessment. Two-dimensional transthoracic echocardiography measurement of the LVOT diameter is susceptible to serve as a source of error in the setting of a suboptimal imaging quality or morphological variations, i.e. sigmoid septum or hourglass shape of the LVOT, and it may eventually lead to an incorrect estimation of the AVA by CE.

The purpose of the present study was to evaluate the potential usefulness and clinical relevance of a systematic implementation of TOE in patients with severe AS-LG.

In a cross-sectional study, 91 patients with severe AS-LG (aortic valve area < 1 cm^2, mean transvalvular pressure gradient (MPG) < 40 mmHg) were systematically analyzed by TTE and TOE. TOE detected a significantly higher percentage of morphological variations of the LVOT such as sigmoid septum or hourglass-shaped LVOT than TTE (rate 43.9% vs 24.1%, p value 0.02, respectively).

In line with these findings, the anterior-posterior diameter of the LVOT was larger by TOE than by TTE. The implemented diameter measurements for the CE-based AVA calculation were the anterior-posterior diameter obtained at the level of the LVOT and at the aortic annulus level.

Accordingly, a significantly larger CE-based AVA and a better detection of moderate AS (rate of moderate AS 13.1%) were found by using TOE on a regular basis in patients with severe AS-LG. Likewise, similar results were found using TOE systematically to measure the aortic annulus in the AVA calculation by CE in patients with severe AS-LG (rate of moderate AS 35.1%).

The findings from this study may suggest that a systematic use of TOE to measure LVOT diameter in the CE-based AVA calculation would make possible a recategorization of a severe AS into a moderate AS in some of the patients previously diagnosed with severe AS-LG.

Hence, further larger studies are needed to validate the findings from the present study, which could have clinical and therapeutic relevance in the assessment of patients with severe AS-LG.

5.1 Accuracy of the LVOT assessment

Although current clinical evidence has shown theLVOT anatomy to be relatively elliptical and funnel-shaped rather than circular[9,10], in some patients the measurements of the LVOT diameter -mainly in 2D imaging- could have been wrongly assessed because of morphological variations

such as hourglass-shaped septum, which can make an accurate assessment of it more difficult. In the context of the AVA calculation this, could lead to an erroneous severity grading [3, 5, 33].

Despite the fact that the latest recommendations for AS severity assessment[5] have acknowledged the possible underestimation of the AVA due to the ellipticity of the LVOT, this also underscores the difficulty in incorporating the CSA calculation from an ellipse into daily practice. Thus, the assumed LVOT geometry has been consensually suggested to be circular.

One of the basic principles of Doppler echocardiography states that every section area determines a change in flow velocity. In other words, for a given flow volume calculation, the flow velocity integral should be multiplied by the CSA measured at the same level [2].

On account of this assumption, in this study was sought to investigate the AVA estimation by additionally using the anterior-posterior diameter of the LVOT measured by TOE and afterwards to recalculate the AVA. By using this method and recalculating the AVA of patients previously diagnosed by TTE as having a severe AS-LG, it was possible to determine that these patients actually had a moderate AS ($p<0.01$). This could suggest that the continuity equation-based AVA calculation using a LVOT diameter only assessed by 2D TTE underestimates the real valve orifice area.

AS in the elderly is characterized by a considerable valve disruption with different grades of calcification and commissural fusion (1,4). In cases of severe AV calcification, CE may not be accurate, since the calcium deposit on the valve interferes with a correct visualization in 2D of the LVOT and the corresponding measurement of its diameter by TTE. Recent studies have shown the relevance of three-dimensional echocardiography and a modest correlation of the AVA derived from 2D CE with the AVA derived from 3D echocardiography, especially when 3D imaging is obtained from TOE [19, 55-59] .

Current guidelines also recommend assessing the LVOT diameter in a zoomed-in view at the PLAX [5]. It is known that septal hypertrophy of the LV is the wall compensation to long-term pressure overload caused by chronic systemic hypertension, which contributes to defining the hemodynamic profile in patients with AS [34,36,39,46]. The LVOT remodelling in severe AS shows less distensibility and thus a greater stiffness during the systole [21]. When a scenario of LVOT remodelling, a considerable septal hypertrophy and a severe calcified valve appears, it makes a correct visualization of the LVOT extremely difficult. Thus errors in the assessment of the LVOT diameter might be amplified due to a poor definition of the inner borders of the endocardium. In such cases, the systematic implementation of TOE would play an important role, not only because it enables almost a direct view of the LVOT, but also because it allows a better morphological definition of both the septum and the LVOT.

Furthermore, in more than a half of the patients in this cohort, the morphology of the septum as observed by TOE was a sand hourglass shape. This conforms in appearance to a septal bulge, which represents an anatomical variation often seen and plausible to find in cases of AS with considerable septal hypertrophy.

5.2 Challenging the standard AVA Calculation

The assessment of the AVA is prone to measurement errors, particularly in elderly patients with severe calcified aortic valves. The standard evaluation of AS severity is based on the continuity equation (CE), which estimates the effective orifice area (EOA) at the vena contracta [5, 6, 31] reflecting the workload which the LV has to overcome in the case of valve stenosis. The calculation uses the AV VTI, the LVOT VTI and the LVOT diameter.

By echocardiography it is possible to measure the instant maximum gradient, which represents the place of the lowest pressure, the so-called vena contracta. Theoretically, the real EOA is at the vena contracta, where the flow acceleration is at the highest.

It is logical to assume the differences seen between invasive and non-invasive diagnostic approaches. In this matter, when comparing the AVA estimated with catheterization with the AVA calculated by Doppler, for an identical mean gradient the results of calculations are different. A possible explanation for this is given by the recovery pressure, a phenomenon that cannot be assessed with the echocardiographic method [51].

Based on the aforementioned, if we hypothetically consider the diameter of the LVOT and an average of aortic peak velocity between 3 m/s and 4 m/s, the corresponding AVA is less than a $1cm^2$. This could partially explain the discordance between area and gradient; moreover, this reflects that the recommended severity cutoff point might be lower to that value.

In this cohort the AVA calculation based on CE by TTE and TOE demonstrated inconsistencies. On the one hand, by using the standard CE method with the LVOT diameter assessed by TTE, the AS showed a more severe grade according to the valve orifice than by using the LVOT diameter assessed by TOE.

Some studies have shown that below the annulus the LVOT is more likely to be more dynamic than at the level of the annulus and in cases of septal bulge and hypertrophy it could lead to an underestimation of the LVOT diameter [39].

In this study, the measurements of the LVOT diameter were performed at the level of the annulus by TOE and TTE, respectively. Afterwards, for the standard AVA calculation by CE were employed the diameters obtained by both methods separately. The corresponding results

showed the AVA to be larger using the values obtained by TOE, especially those calculated at the level of the annulus than that measured below it.

Based on these findings and given the existing evidence, it seems to be a useful alternative to measure the LVOT diameter far from the septal basal hypertrophy or from the septal bulge and exactly at the level of the aortic annulus.

The histological structure of the aortic annulus is a fibrous complex formed by the interleaflet trigones. It offers a relatively stable basis for measurement, especially in the case of irregular heart rhythm, such as atrial fibrillation. Moreover, it would be a reproducible assessment.

A physiological measurement of AS is the estimated EOA; this represents a smaller area than the one assessed by planimetry. In fact, planimetry can only estimate the anatomic valve area and this might explain why these two measurements do not show identical values [2,5,31]. Additionally, when we analyzed AS severity by 3D multiplane planimetry with TOE in a subgroup of patients, in a considerable percentage of patients had indeed a moderate AS and not severe LG-AS.

5.3 Defining the flow status

According to the guidelines, the evaluation of AS severity should follow a step by step, integrated diagnostic approach. Even though, the AVA estimation by CE is routinely performed, it relies mainly on TTE. Thus far there is no gold standard method for the evaluation of AS severity.

It may seem quite clear that an assessment of severity grading by a single imaging modality, such as TTE, can present technical errors and some well-known limitations because of the procedure itself.

Severe LG-AS has a specific mechanism and is usually associated with a poor prognosis. However, in some cases the diagnosis of this condition is subject to erroneous measurements and a wrong assessment due to the methodology of flow estimation used. One of the reasons for a LG-AS can be the existence of a low flow status, which by definition corresponds to a SV <35 ml/m^2 [6,7]. Severity parameters of AS, especially gradient, are flow-dependent. In this respect, when the focus is set on the flow status, the present study took into consideration the SV as an important parameter of discordant values in AS severity grading, suggesting that there might be a considerable underestimation of the SV when using the LVOT diameter obtained from TTE in the calculation. Similar values were seen between the SV calculation through the LVOT diameter by TOE and when applying the aortic annulus diameter to the continuity

equation by TTE. Once more, these results show that TTE assessment of the LVOT is incorrectly estimated at the annulus partly because of the deficient image quality of 2D echocardiography, in addition to valve calcification and septal hypertrophy.

Current guidelines on valve heart disease describe an AS with a normal flow status unlikely to be severe. In the present study, the rate of a normal flow was higher both by assessing the LVOT diameter with TOE and by measuring at the annulus. This could mean that patients categorized as having a low flow status, when reanalyzed with TOE, actually have a normal flow. In this setting, the prevalence of severe AS changes and thus implies that a considerable percentage of the severe AS are actually moderate AS cases with normal flow.

Thus, the current evidence shows that although in daily clinical practice decisions are made based on the SV value obtained from the Doppler calculation, this is not advisable because this value is frequently underestimated.

On the other hand, it is also important to note that in this studied population, all patients had a stable blood pressure at the time of the echocardiographic evaluation. Precisely, 89% of the patients had normal blood pressure with a mean systolic and diastolic blood pressure value of 122 mmHg and 72 mmHg.

Clinical evidence shows that in AS-LG, among other factors, a low flow status (<35ml/m^2) is associated with a worse prognosis [7,13]. From the present results, one could assume that an underestimation of SV could be a direct consequence of the wrong measurement of the LVOT diameter obtained from TTE.

Considering that severity parameters are based on the results obtained through invasive valve catheterization, it does not seems to be feasible to compare to the findings by echocardiography. In other words, it is not possible to grade the severity of AS through echocardiography when the reference severity parameters in the guidelines come from the invasive valve assessment.

Current discussions circle around the accuracy of the AVA and its concordance with the MPG. In the present study the results are of a considerable relevance for patients who are potential candidates for aortic valve replacement.

Furthermore, it may also be acceptable to question where the arbitrary value of 35ml/min for SV comes from, since it is not possible to find relevant scientific literature and/or existing evidence for this threshold value, and the closest reference value to this, is the one measured invasively with catheterization.

5.4 Clinical implications

Whilst current guidelines only recommend treating severe symptomatic AS with reduced EF, it is essential to confirm whether or not a symptomatic patient has a truly severe LG-AS, in order to indicate valve replacement. The relevance of AS in the elderly population remains related to the general clinical presentation of the patients. This population often suffers from several co-morbidities, which can also mask the true clinical onset of AS.

Lately, improvements in valve replacement therapy and the increasing implementation of TAVI underline the need for an accurate assessment of the aortic ring in patients with severe AS, which has become a common measurement tool for decision-making. In this context, after the systematic assessment of the aortic valve, it is clear that the usual 2D TTE is not enough to define the correct diameter of the LVOT, at least not at the precise minor diameter of its elliptical part. This emphasizes the imprecision of 2D TTE for LVOT diameter assessment.

In this study, it was possible to demonstrate that the reassessment of LVOT diameter and AVA calculation with TOE defined more accurately the severity. This enables a group of patients who were previously diagnosed with severe AS-LG to be reclassified as having moderate AS.

Although some evidence suggests an elliptical geometry of the LVOT, measurements of the LVOT CSA that assume its diameter as a circumference could be more useful and clinically relevant. This logical assumption may be relevant not only because of its relative accessible estimation, but also because the size of aortic prostheses is estimated assuming a circular valve anatomy.

Furthermore, the majority of studies showing the prognostic relevance of severe AS have been performed using the standard CE-based AVA calculation (i.e. assessment of the anterior-posterior diameter of the LVOT).

The LVOT diameter remains of pivotal importance, as it has been shown in the present study with the systematic implementation of TOE for a better and more accurate assessment of the LVOT diameter and thus the AVA calculation.

6. Conclusion

Severe aortic stenosis with low gradient is a challenging entity which demands careful echocardiographic assessment. Two-dimensional transthoracic echocardiography assessment of the LVOT diameter is a source to error in the setting of suboptimal imaging quality or morphological variations of the LVOT, which may lead to an incorrect estimation of the aortic valve area by CE.

The purpose of this study was to evaluate the potential usefulness and clinical relevance of a systematic use of transoesophageal echocardiography to measure the anterior-posterior LVOT diameter for the calculation of the AVA by CE in patients with severe AS-LG.

TOE detected a significantly higher percentage of morphological variations of the LVOT such as sigmoid septum or hourglass-shaped LVOT, than TTE (rate 43.9% vs 24.1%, p value 0.02, respectively). In line with these findings, the anterior-posterior diameter of the LVOT was larger by TOE than by TTE. Accordingly, a significantly larger AVA by CE was found using TOE compare with TTE, which led to a detection of moderate AS using systematic TOE in patients with severe AS-LG (rate of moderate AS 13.1%). Likewise, similar results were found using TOE systematically to measure the aortic annulus in the AVA calculation by CE in patients with severe AS-LG (rate of moderate AS 35.1%).

These results evidence that it is possible to recategorize severe AS-LG into moderate AS by implementing an alternative method to the assessment of the LVOT by TOE.

Nevertheless, further larger studies are needed to validate the findings from this study, which could have clinical and therapeutic relevance in the assessment of patients with severe AS-LG.

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8. Affidavit

"I, **Rafaela Maria Pinto**, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic **"Potential Usefulness and Clinical Relevance of a Systematic Implementation of Transoesophageal Echocardiography in the Evaluation of Patients with Severe Aortic Stenosis and Low Gradient"**, independently and without the support of third parties, and that I used no other sources and aids than those stated. All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

_____

Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

9. Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

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