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ORIGINAL PAPER

Hemodynamics of paradoxical severe aortic stenosis: insight from a pressure–volume loop analysis

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Abstract

Background Controversy exists about the pathophysiology of different hemodynamic subgroups of AS. In particular, the mechanism of the paradoxical low-flow, low-gradient (PLFLG) AS with preserved ejection fraction (EF) is unclear.

Methods A total of 41 patients with severe, symptomatic AS were divided into the following 4 subgroups based on the echocardiographically determined hemodynamics: (1) normal-flow, high-gradient (NFHG) AS; (2) low-flow, high-gradient AS; (3) paradoxical low-flow, low-gradient (PLFLG) AS with preserved EF and (4) low-flow, low-gradient (LFLG) AS with reduced EF. As part of the comprehensive invasive examinations, the analyses of the PV loops were performed with the IntraCardiac Analyzer (CD-Leycom, The Netherlands).

Results PLFLG was characterized by small left ventricular volumes as well as a decreased cardiac index, a decreased systolic contractility and a lower stroke work, than the conventional NFHG AS. Alterations in effective arterial elastance (2.36 ± 0.67 mmHg/ml in NFHG versus 3.01 ± 0.79 mmHg/ml in PLFLG, $p = 0.036$) and end-systolic elastance (3.72 ± 1.84 mmHg/ml in NFHG versus 5.53 ± 2.3 mmHg/ml in PLFLG, $p = 0.040$) indicated impaired vascular function and increased chamber stiffness.

Conclusions The present study suggests that the hemodynamics of PLFLG AS can be explained by two mechanisms: (1) stiffness of the small left ventricle with reduced contractility, and (2) increased afterload due to the impairment of vascular function. Both mechanisms have similarities to those of heart failure with preserved EF. This type of remodeling may explain the poor prognosis of PLFLG AS.

Keywords Aortic stenosis · Pressure–volume loops · Hemodynamics

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Abbreviations

AS	Aortic valve stenosis
AVA	Aortic valve area
BNP	B-type natriuretic peptide
EF	Ejection fraction
HFpEF	Heart failure with preserved ejection fraction
LFLG	Low-flow, high-gradient
NFHG	Normal-flow, high-gradient
PLFLG	Paradoxical low-flow, low-gradient
SVI	Stroke volume index
τ	Relaxation time constant

Introduction

Severe, symptomatic aortic valve stenosis (AS) is the most common reason for heart valve replacement [1, 2]. According to the current guidelines, a severe AS is certain if the

aortic valve area (AVA) is < 1 cm^2 and if the mean transaortic gradient is ≥ 40 mmHg [3]. However, a significant proportion of patients with AS have an AVA of < 1 cm^2, with a mean transaortic gradient < 40 mmHg [4]. This condition is explained by a reduced blood flow over the aortic valve, leading to a low gradient. On the one hand, there may be a limitation of the left ventricular ejection fraction (EF), which is associated with a low stroke volume [low-flow, low-gradient (LFLG) with reduced EF].

On the other hand, there is the low-flow, low-gradient AS with preserved EF, which is also called paradoxical AS due to the seemingly contradictory characteristic of low flow despite preserved EF [5]. The hemodynamics of this subgroup of AS are not fully understood. There is also controversy surrounding whether this subtype is a non-severe form of AS that should be treated as a moderate AS [6, 7] or if it is a particularly advanced form of severe AS with more severe myocardial damage and a poor prognosis [8, 9]. In the latter case, it is assumed that paradoxical AS has similarities to heart failure with preserved ejection fraction (HFpEF) due to the more pronounced myocardial hypertrophy and impaired relaxation [5, 10]. However, there are ambiguities concerning the exact pathophysiological mechanisms of paradoxical AS in comparison to other hemodynamic subgroups of AS.

Pressure–volume (PV) loop analysis is considered the gold standard for the investigation of myocardial hemodynamics [11]. Until now, however, this method has never been used in the analysis of the subgroups of AS. In this study, an invasive analysis of pressure–volume loops was performed on different hemodynamic subgroups of severe AS. The aim was to elucidate the underlying pathophysiological mechanisms of low-flow, low-gradient AS with preserved and reduced LVEF.

Methods

Between 2016 and 2017 this prospective study included consecutive, hemodynamically stable patients with severe symptomatic AS (AVA < 1 cm^2 and NYHA class ≥ II) who agreed to participate and who had an indication for aortic valve replacement. The exclusion criteria were as follows: any stenosis of another heart valve, more than moderate valvular regurgitation, shock, treatment in intensive care, therapy with catecholamines and left bundle branch block.

The patients were divided into four subgroups according to the echocardiographic criteria: (1) high-gradient, normal-flow AS (HGNF), defined as AVA < 1 cm^2, mean transaortic gradient ≥ 40 mmHg and stroke volume index (SVI) > 35 ml/m^2; (2) high-gradient, low-flow AS (HGLF), defined as AVA < 1 cm^2, mean transaortic gradient ≥ 40 mmHg and SVI ≤ 35 ml/m^2; (3) paradoxical low-gradient, low-flow (PLGLF) AS with preserved EF, defined as AVA < 1 cm^2, mean transaortic gradient < 40 mmHg, SVI ≤ 35 ml/m^2 and EF ≥ 50%; and (4) low-gradient, low-flow (LGLF) AS with reduced EF, defined as AVA < 1 cm^2, mean transaortic gradient < 40 mmHg, SVI ≤ 35 ml/m^2 and LVEF < 50% [3]. In all patients with LGLF AS, dobutamine echocardiography was performed to evaluate flow reserve [12].

All the patients gave written consent to participate in this study. The study protocol was approved by the local ethics committee (approval 4379-12, Ethics Committee of the Ruhr University Bochum). The study was supported by the German Heart Foundation.

Echocardiography and NT-pro-B-type natriuretic peptide

Immediately prior to the invasive investigations, transthoracic echocardiography was performed on the Vivid 7 or Vivid S70 (General Electric, Boston, MA, USA) according to current recommendations [12, 13]. The left ventricular ejection fraction was measured using biplane Simpson's rule method. Measurements of global longitudinal strain were performed by speckle tracking. The measurement of the left ventricular outflow tract in the parasternal axis was carried out with particular care to avoid measurement errors. The echocardiographic stroke volume was calculated using the cross-sectional area of the left ventricular outflow tract and the time–velocity integral from pulsed-wave Doppler of the left ventricular outflow tract. Transaortic gradients were calculated using the simplified Bernoulli equation (Fig. 1). The AVA was determined using the continuity equation. The quantification of concomitant valve diseases was done according to current recommendations [14]. Relative wall thickness (RWT) was calculated using the following formula:

$$RWT = (2 \times PWd)/LVEDD,$$

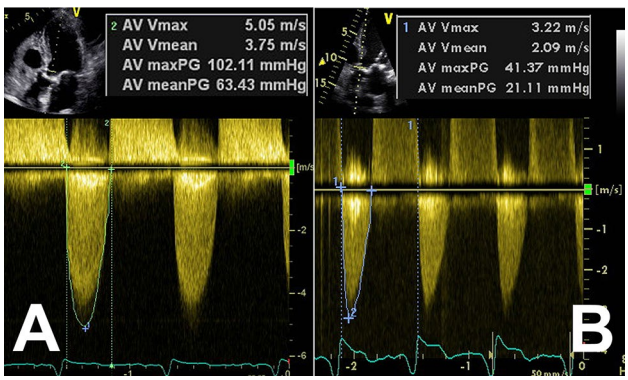

Fig. 1 **a** Echocardiography of a patient with normal-flow, high-gradient aortic stenosis and **b** echocardiography of a patient with paradoxical low-flow, low-gradient aortic stenosis with preserved ejection fraction

where PWd is posterior wall thickness in diastole and LVEDD is left ventricular end-diastolic diameter.

The valvuloarterial impedance Zva is considered a measure of global afterload and was calculated as:

$$Zva = (SAP + \Delta p)/SVI,$$

where SAP is systolic arterial pressure, Δp is mean systolic transaortic gradient, and SVI is stroke volume index [15].

The energy loss index (ELI) is considered a parameter that represents the energy loss over the AS and the poststenotic pressure recovery. Calculation required the cross-sectional area of the ascending aorta at the level of the sinutubular junction (AoA) and the aortic valve opening area (AVA):

$$ELI = (AVA \times AoA)/(AoA - AVA)/BSA,$$

where AVA is aortic valve orifice area, AoA is ascending aortic cross-sectional area, and BSA is body surface area [15].

On the day of the study, the plasma NT-pro- B-type natriuretic peptide (BNP) (normal value < 125 pg/ml) was determined. The blood samples were collected in tubes containing EDTA. After immediate centrifugation, the NT-pro-BNP was determined using an electro-chemiluminescence immunoassay kit (Roche, Basel, Switzerland).

Cardiac catheterization and PV measurement

The study was performed in stable patients without sedation and without catecholamines. Right heart catheterization was performed with a Swan–Ganz catheter (Edwards Lifescience Irvine, CA, USA). The measurements were carried out at least three times and were averaged. If the results of the individual measurements differed by > 10%, further measurements were made.

Systemic vascular resistance (SVR) was calculated using the formula:

$$SVR = 80 \times (MAP - RAPmean)/CO,$$

where MAP is the mean arterial pressure, RAPmean is the mean right atrial pressure and CO is the cardiac output.

Pulmonary vascular resistance (PVR) was calculated as:

$$PVR = 80 \times (PAPmean - PCWP)/CO,$$

where PAPmean is the mean pulmonary artery pressure, PCWP is the pulmonary capillary wedge pressure and CO is the cardiac output.

Both parameters were given in metric units ($dyn \times s \times cm^{-5}$).

The retrograde aortic valve passage opening was accomplished with a fluid-filled Langston dual-lumen pigtail catheter (Minneapolis, Minn., MN, USA) via an 8 F sheath. The measurement of left ventricular and aortic pressures was performed simultaneously (Fig. 2). The values of the following pressures were calculated using the average of at least

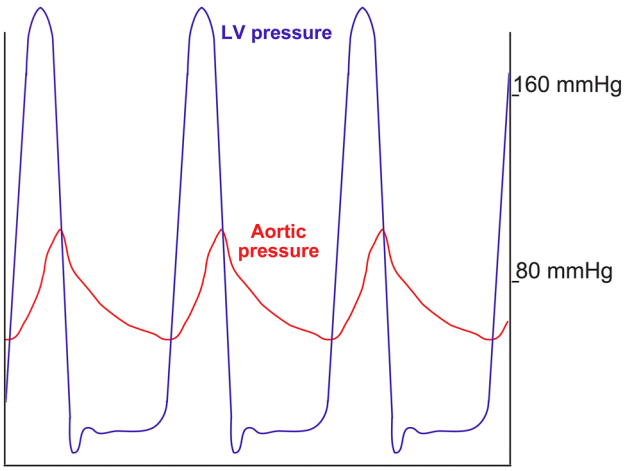

Fig. 2 Example of simultaneous pressure measurements in the left ventricle and aorta in a patient with normal-flow, high-gradient aortic stenosis

10 beats: the maximum left ventricular pressure, left ventricular end-diastolic pressure, diastolic and systolic aortic pressure, and mean transaortic pressure. The calculation of the invasively determined AVA was carried out by means of the Gorlin formula:

$$AVA = CO/HR \times ET \times 44.3 \times \sqrt{\Delta p},$$

where CO is cardiac output, HR is heart rate, ET is ejection time and Δp is mean transaortic gradient.

The invasively measured valvuloarterial impedance (Zva) was calculated as:

$$Zvainv = (SAP + \Delta p)/SVI,$$

where SAP is systolic arterial pressure, Δp is mean systolic transaortic gradient, and SVI is stroke volume index.

Conductance catheter examination is considered the gold standard for the analysis of myocardial hemodynamics [11]. The principle of the conductance catheter technique is based on the measurement of the electrical conductance of the blood in the left ventricle [16, 17]. Therefore, a 7-French pressure–volume catheter (CD-Leycom, Zoetermeer, The Netherlands) was retrogradely inserted into the left ventricle, was positioned in the apex of the heart and was analyzed with an IntraCardiac Analyzer (CD-Leycom, Zoetermeer, The Netherlands). Measurements of left ventricular volume and left ventricular pressure were taken, and the ECG was connected. Immediately before the invasive examination, 2D echocardiography was performed to measure left ventricular volumes, cross-sectional area and time–velocity integral of the left ventricular outflow tract. These volume measurements were used to calibrate the conductance volume signal. Total left ventricular volume was calculated from a maximum of seven segmental volumes. The instantaneous PV relationships were visualized and pressure–volume curves

were performed. The following hemodynamic indices were determined: cardiac output, end-systolic pressure, end-diastolic pressure, maximum rate of change in left ventricular pressure (dP/dt_{max}), minimum rate of change in left ventricular pressure (dP/dt_{min}) and relaxation time constant (τ).

The Starling contractile state index was determined by dP/dt_{max} normalized for end-diastolic volume. Stroke work was calculated as the area of the pressure–volume loop. Effective arterial elastance was calculated by dividing end-systolic pressure by stroke volume. End-systolic elastance was determined by single beat estimation as previously described [18]. In addition, the volumes at an end-systolic pressure value of 100 mmHg (ESV_{100}) were determined [18, 19]. End-diastolic elastance was calculated from the ratio of end-diastolic pressure/end-diastolic volume. The ratio of end-systolic elastance and effective arterial elastance revealed the ventricular–arterial coupling [11].

Statistics

Numerical values are expressed as the mean ± standard deviation (SD). Continuous variables without normal distribution are summarized by the median (1st quartile, 3rd quartile). Continuous variables were compared between groups using an unpaired *t* test/ANOVA test (for normally distributed variables) or a Mann–Whitney *U* test/Kruskal–Wallis test (for non-normally distributed variables), when appropriate. χ^2 analysis was used to compare categoric variables. Comparisons between echocardiographic parameters and invasively measured parameters were performed by a paired, two-tailed *t* test. The relationship between the echocardiographic and invasive values with regards to the mean pressure gradients and AVA was analyzed by linear regression.

In order to avoid bias, sensitivity analysis was performed. For this purpose, results of PV loop analysis were adjusted for hypertension, diabetes and beta-blocker therapy. An initial maximal model was successively simplified by eliminating non-significant parameters in order to deliver a minimal model with significant predictors only.

All the reported probability values are two-tailed, and $p < 0.05$ was considered statistically significant. Analyses were performed with the SPSS statistical software package (version 24.0) and custom S scripts written for the environment R 3.2.1.

Results

A total of 41 patients with severe, symptomatic AS were included in this study. The clinical characteristics and distribution into subgroups are listed in Table 1. The patient subgroups did not differ significantly with respect to age, sex, body mass index or NYHA class. The patients with low-flow, low-gradient AS (both PLFLG and LFLG) had coronary artery disease more frequently than patients with high gradients. The patients with LFLG AS had significantly higher BNP levels and received diuretics more often than did the patients in the other subgroups (Table 1).

Echocardiography

For echocardiography, there was no difference between groups with respect to AVA or aortic valve area index. The mean transaortic gradient was lower in the low-gradient groups than in the high-gradient groups. Likewise, the SVI was lower in the low-flow groups than in the high-flow group. In contrast, the left ventricular EF was significantly lower in patients with LFLG AS than in all the other subgroups. The valvuloarterial impedance was significantly lower in NFHG AS than in the low-flow groups. Significant differences in frequencies of concomitant valvular regurgitation did not occur between groups. Moreover, there was no difference between the *E*/*E*′ ratio and the left atrial volume index (Table 2). Dobutamine echocardiography demonstrated flow reserve in all the patients with LFLG AS.

Invasive measurements

Cardiac catheterization confirmed the results of echocardiography. Even in the invasive measurement, calculated using the Gorlin formula, there was no difference between the subgroups with regard to AVA or to the aortic valve area index. The mean transaortic gradient showed similar changes to those measured by echocardiography (Table 3). The cardiac index was larger in the NFHG AS group than in all the other subgroups. Remarkably, the systolic arterial pressure, mean arterial pressure, and systemic vascular resistance were significantly higher in patients with PLFLG AS than in patients with NFHG AS. There were no significant differences in patient subgroups with respect to left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (Table 3).

Figure 3 illustrates the PV loops of the various hemodynamic subgroups (Fig. 3). Stroke work was significantly higher in the NFHG AS group compared to all the other subgroups. In addition, dP/dt_{max} was higher in NFHG AS compared to low-gradient AS (PLFLG and LFLG). Effective arterial elastance was lowest in the NFHG AS group. End-systolic elastance, an expression of contractility and chamber stiffness, was higher in LFLG AS and higher in PLFLG AS compared to NFHG AS. Figure 4 illustrates the differences between end-systolic elastance and effective arterial elastance in patients with NFHG and PLFLG AS (Fig. 3). Remarkably, neither τ nor end-diastolic elastance showed significant differences among the groups.

Table 1 Clinical characteristics in patients' subgroups of severe aortic stenosis

	Group 1 NFHG ($n=15$)	Group 2 LFHG ($n=6$)	Group 3 PLFLG ($n=14$)	Group 4 LFLG ($n=6$)	p value
Age (years)	71.9 ± 11.2	82.2 ± 4.9*	77.1 ± 7.6	79.5 ± 2.1	0.083
Female gender (*n*, %)	4 (27)	3 (50)	6 (43)	3 (50)	0.656
Body mass index (kg/m^2)	29.1 ± 3.8	27.4 ± 4.5	26.6 ± 3.4	29.7 ± 5.4	0.411
NYHA class (II/III/IV) (*n*)	7/4/4	3/1/2	4/10/0	1/5/0	0.161
Cardiovascular diseases					
Hypertension (*n*, %)	13 (87)	3 (50)	14 (100)†	6 (100)†	0.013
Diabetes mellitus (*n*, %)	5 (33)	0 (0)	5 (36)	3 (50)†	0.280
CAD (*n*, %)	6 (40)	1 (17)	11 (79)*,†	6 (100)*,†	0.005
CABG (*n*, %)	0 (0)	0 (0)	3 (21)	1 (16)	0.190
Atrial fibrillation (*n*, %)	1 (7)	2 (33)	4 (29)	3 (50)*	0.175
Cardiovascular drugs					
ACEI/ARBs (*n*, %)	10 (67)	6 (100)	14 (100)*	5 (83)	0.054
Beta-blockers (*n*, %)	9 (60)	2 (33)	12 (86)†	6 (100)†	0.031
Diuretics (*n*, %)	7 (47)	3 (50)	7 (50)	6 (100)*,†,‡	0.144
ARA (*n*, %)	1 (7)	0 (0)	0 (0)	2 (33)‡	0.056
Laboratory measurements					
GFR (ml/min)	61.1 ± 18	61.5 ± 11.2	63.2 ± 13.9	50.7 ± 22	0.593
BNP (pg/ml) (quartile)	565 (164–1063)	1756 (580–4177)	536 (149–1660)	5206 (1059–7641)*,†,‡	0.042

NFHG normal-flow, high-gradient, *LFHG* low-flow, high-gradient, *PLGLF* paradoxical low-flow, low-gradient, *LFLG* low-flow, low-gradient, *NYHA* New York Heart Association, *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARA* aldosterone receptor antagonist, *GFR* glomerular filtration rate, *BNP* B-type natriuretic peptide

*Significant difference versus group 1

†Significant difference versus group 2

‡Significant difference versus group 3

Comparison between echocardiography and invasive measurements

The echocardiographically measured AVA was significantly higher than the invasively measured AVA (0.68 ± 0.14 cm^2 versus 0.62 ± 0.18 cm^2, $p=0.015$). The correlation between both parameters was moderate ($r=0.470$, $p=0.001$). Noteworthy, no patient had an AVA of ≥ 1 cm^2 in the echocardiography or invasive examinations. The mean transaortic gradient was lower with echocardiography compared with invasive measurement (39.6 ± 14.8 mmHg versus 43.7 ± 16.6 mmHg, $p=0.004$). Both values showed a good correlation ($r=0.844$, $p<0.001$).

Discussion

In this prospective study, we examined patients with symptomatic severe AS with an AVA < 1 cm^2. Based on hemodynamic parameters (mean gradient, SVI, EF), the patients were divided into different subgroups (Table 1). In our study, we first examined the different hemodynamic subgroups of severe AS using invasive PV loop measurements. We were able to demonstrate that many myocardial properties of PLFLG AS are fundamentally different compared to "conventional" NFHG AS. The results of our study suggest that the "paradoxical" AS is characterized by increased chamber stiffness and by a restriction in vascular function (Fig. 4). This type of remodeling may explain the limited prognosis of this disease.

Low-flow, high-gradient AS

The different stages of severe symptomatic AS are distinguished by the mean gradient (high- and low-gradient AS), the SVI (normal and low-flow AS) and the EF (preserved and reduced) [4]. In LFHG AS, there is a high mean gradient despite having a low flow across the aortic valve. Usually, LFHG AS is classified into "high-gradient" AS [1]. However, Clavel et al. described recently that LFHG is a subgroup of AS with particularly severe aortic valve obstruction [5]. In our study, we examined LFHG AS invasively for the first time. These patients had a non-significant trend toward a smaller valve opening area compared to the normal-flow, high-gradient AS (Table 2). In addition, compared to NFHG AS, LFHG AS was characterized by (1) reduced SVI, cardiac index and stroke work and (2) elevated valvuloarterial impedance, systemic vascular resistance, effective arterial

Table 2 Echocardiographic measurements in patients' subgroups of severe aortic stenosis

	Group 1 NFHG ($n=15$)	Group 2 LFHG ($n=6$)	Group 3 PLFLG ($n=14$)	Group 4 LFLG ($n=6$)	p value
AVA_{echo} (cm^2)	0.68 ± 0.1	0.58 ± 0.17	0.68 ± 0.14	0.75 ± 0.16	0.215
$AVAI_{echo}$ (cm^2/m^2)	0.35 ± 0.05	0.32 ± 0.13	0.37 ± 0.11	0.38 ± 0.09	0.316
Mean $gradient_{echo}$ (mmHg)	50 ± 13.3	54.3 ± 7.1	29.2 ± 5.3*,†	23.7 ± 2.8*,†,‡	< 0.001
SVI (ml/m^2)	43.7 ± 6.1	28.6 ± 3*	29.9 ± 4.7*	25 ± 6.3*	< 0.001
LVEDV (ml)	135 ± 28	111 ± 39	84 ± 24*	132 ± 34‡	0.003
LVESV (ml)	55.3 ± 22.6	61.3 ± 27.2	31.2 ± 13.4*,†	93 ± 24.5*,‡	< 0.001
LV ejection fraction (%)	61.1 ± 9.3	50.8 ± 12.9	62.4 ± 7.9†	33.2 ± 7.1*,†,‡	0.001
Diastolic IVS (mm)	1.54 ± 0.34	1.48 ± 0.34	1.44 ± 0.23	1.47 ± 0.31	0.950
Relative wall thickness	0.6 ± 0.12	0.67 ± 0.16	0.68 ± 0.19	0.59 ± 0.1	0.772
Global longitudinal strain (%)	15.5 ± 4.1	13.5 ± 3.4	13.4 ± 2.4	8.2 ± 2.5*,†,‡	0.008
$Z_{va\ echo}$ ($mmHg/ml \times m^2$)	4.1 ± 0.71	6.39 ± 0.69*	5.98 ± 1.89*	6.72 ± 2*	< 0.001
Energy loss index (cm^2/m^2)	0.39 ± 0.07	0.29 ± 0.05*	0.43 ± 0.14†	0.4 ± 0.06	0.052
AR (grade 0/1/2/3)	3/11/1/0	2/2/2/0	7/4/3/0	3/2/1/0	0.244
MR (grade 0/1/2/3)	3/11//0	2/3/1/0	8/6/0/0	0/5/1/0‡	0.142
TR (grade 0/1/2/3)	3/11/1/0	0/5/1/0	3/10/1/0	0/3/3/0	0.155
E/*E*′ ratio	13.8 ± 6.2	13.6 ± 4.8	13.1 ± 5.7	16.2 ± 4.4	0.592
LAVI (ml/m^2)	40.1 ± 12.6	39.1 ± 12.5	36 ± 14	42.5 ± 7.8	0.553
RAVI (ml/m^2)	23.5 ± 12.3	24.1 ± 15.9	24.8 ± 13.4	35.3 ± 23.9	0.788

NFHG normal-flow, high-gradient, *LFHG* low-flow, high-gradient, *PLGLF* paradoxical low-flow, low-gradient, *LFLG* low-flow, low-gradient, *AVA* aortic valve area, *AVAI* aortic valve area index, *SVI* stroke volume index, *LV* left ventricular, *IVS* interventricular septal thickness, Z_{va} valvuloarterial impedance, *AR* aortic regurgitation, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *LAVI* left atrial volume index, *RAVI* right atrial volume index

*Significant difference versus group 1

†Significant difference versus group 2

‡Significant difference versus group 3

elastance and ventricular–arterial coupling. Therefore, our study suggests that LFHG AS also has altered hemodynamics compared to NFHG AS (Fig. 3).

Low-flow, low-gradient AS with reduced EF

There is an LFLG AS with reduced EF in approximately 5–10% of all patients with severe AS. This is a severe case of AS in combination with systolic heart failure [5]. The most common cause of this severe case is concomitant coronary heart disease, especially in patients with a previous myocardial infarction. Due to the loss of myocardial contractility, the left ventricle is no longer capable of creating a sufficiently high left ventricular pressure. The cardiac output and the stroke volume, and thus the blood flow over the severe stenosed aortic valve, are lowered. The prognosis of this form of AS is particularly unfavorable, even in the case of surgical or interventional therapy [20]. In our study, the LFLG AS cases showed significant differences in many hemodynamic parameters compared to the NFHG AS group, as well as compared to the paradox LFLG AS group (Tables 1, 2, 3). Basic characteristics of LFLG AS compared to NFHG AS are increased end-systolic volumes, a decreased cardiac index, a decreased contractility of LV, and a decreased stroke work (Table 3). In addition, the end-systolic elastance, the effective arterial elastance and ventricular–arterial coupling were elevated (Table 3). The changes in these parameters in the LFLG AS cases are similar to those of systolic heart failure [11] and may explain the poor prognosis of the disease [21].

Low-flow, low-gradient AS with preserved EF—paradoxical AS

In the last 10 years, PLFLG AS, in particular, has been the focus of attention because the correct diagnosis is a clinical challenge [8, 22], the prognosis of the disease is controversially discussed [6, 9, 23] and the pathophysiology is not fully understood [7, 8, 10].

To date, stroke volume is assumed to be reduced due to increased left ventricular hypertrophy, due to impaired diastolic left ventricular filling, and due to reduced left ventricular systolic longitudinal function [5, 22, 24, 25]. In addition to decreased stroke volume, other factors, such as atrial fibrillation, mitral regurgitation, mitral stenosis or

Table 3 Invasive hemodynamic measurements in patients` subgroups of severe aortic stenosis

	Group 1 NFHG ($n=15$)	Group 2 LFHG ($n=6$)	Group 3 PLFLG ($n=14$)	Group 4 LFLG ($n=6$)	p value
Aortic valve $area_{inv}$ (cm^2)	0.6 ± 0.16	0.48 ± 0.17	0.66 ± 0.21	0.65 ± 0.14	0.242
$AVAI_{inv}$ (cm^2/m^2)	0.31 ± 0.09	0.26 ± 0.13	0.35 ± 0.08	0.33 ± 0.07	0.112
Mean $gradient_{inv}$ (mmHg)	54.9 ± 13.2	60.8 ± 13.5	30.5 ± 4.9*,†	28.8 ± 7.2*,†	< 0.001
Cardiac index (l/m^2)	2.74 ± 0.73	1.67 ± 035*	2.06 ± 0.7*	1.42 ± 0.49*	0.001
SAP (mmHg)	121 ± 22	128 ± 26	140 ± 18*	128 ± 14	0.079
DAP (mmHg)	68.7 ± 17.3	75.7 ± 25.9	74.1 ± 13.4	76.7 ± 14.7	0.732
MAD (mmHg)	87 ± 17.5	95.8 ± 27.5	102 ± 16.2*	99.5 ± 13.6	0.120
LV max. pressure (mmHg)	196 ± 24	204 ± 31	176 ± 23*,†	160 ± 12*,†	0.004
SVR ($dyn \times s \times cm^{-5}$)	1431 ± 402	1895 ± 516*	2222 ± 644*	1790 ± 657	0.006
LVEDP (mmHg)	17.6 ± 6.6	18 ± 6.1	13.4 ± 6.3	15 ± 4.5	0.359
SW (ml × mmHg)	14,727 ± 4162	9460 ± 2476*	8201 ± 2701*	5583 ± 2198*,†	< 0.001
dP/dt_{max} (mmHg/s)	1689 ± 344	1604 ± 331	1433 ± 273*	1253 ± 304*	0.046
dP/dt_{min} (mmHg/s)	− 1596 ± 218	− 1656 ± 317	− 1465 ± 318	− 1267 ± 286*,†	0.056
SCI (mmHg/ml/s)	13.2 ± 4.5	16.7 ± 8.6	18.5 ± 5.9*	10.1 ± 3.3‡	0.039
τ (ms)	32.9 ± 5.4	33.3 ± 3.2	32.4 ± 4.1	35.5 ± 4.1	0.592
E_A (mmHg/ml)	2.36 ± 0.67	4.46 ± 1.59*	3.01 ± 0.79*,†	4.22 ± 1.79*	0.006+
E_{ES} (mmHg/ml)	3.72 ± 1.84	3.99 ± 24	5.53 ± 2.3*	1.59 ± 0.47*,‡	0.001+
ESV_{100} (ml)	33.7 ± 15.8	35.8 ± 18	20.9 ± 8.4*,†	68.1 ± 23*,†,‡	0.001
E_{ED} (mmHg/ml)	0.14 ± 0.07	0.19 ± 0.12	0.17 ± 0.08	0.13 ± 0.07	0.546
E_A/E_{ES}	0.75 ± 0.33	1.51 ± 0.75*	0.63 ± 0.26†	2.59 ± 0.67*,†,‡	< 0.001+
PCWP (mmHg)	16.4 ± 7.3	18.8 ± 12	14.2 ± 6.2	20.7 ± 7.1	0.325
PAMP (mmHg)	26.7 ± 10.4	27 ± 12.9	23.2 ± 8.7	34.2 ± 12.8‡	0.327
RAMP (mmHg)	9.73 ± 5.5	9.83 ± 5.31	7.3 ± 3.3	12.7 ± 4.8‡	0.139
PVR ($dyn \times s \times cm^{-5}$)	203 ± 113	236 ± 108	204 ± 138	316 ± 214	0.498

NFHG normal-flow, high-gradient, *LFHG* low-flow, high-gradient, *PLGLF* paradoxical low-flow, low-gradient, *LFLG* low-flow, low-gradient, *AVAI* Aortic valve area index, *SVI* stroke volume index, Z_{va} valvuloarterial impedance, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *MAD* mean arterial pressure, *LV* left ventricular, *LVEDP* left ventricular end-diastolic pressure, *SW* stroke work, *SCI* Starling contractile state index, τ relaxation time constant, *EA* effective arterial elastance, *EES* end-systolic elastance, ESV_{100} end-systolic volume at fixed pressures of 100 mmHg, *EED* end-diastolic elastance, *EES/EA* ventricular–arterial coupling, *SVR* systemic vascular resistance, *PCWP* pulmonary capillary wedge pressure, *PAMP* pulmonary artery mean pressure, *RA* right atrial mean pressure, *PVR* pulmonary vascular resistance

*Significant difference versus group 1

†Significant difference versus group 2

‡Significant difference versus group 3

+Remains significant after adjusting for age, hypertension, diabetes and beta-blocker therapy (see supplementary table 1)

right heart failure, are considered explanations of PLFLG AS pathophysiology [5].

In our study, patients with PLFLG AS had significantly lower mean transaortic gradients, lower end-diastolic volumes, stroke volumes, and cardiac output than patients with NFHG AS (Tables 2, 3). By contrast, we were able to demonstrate that PLFLG AS is not characterized by advanced diastolic dysfunction compared to "conventional" NFHG AS. This is probably due to advanced diastolic dysfunction in all subtypes of severe AS. In our study, neither the echocardiographically determined parameter, E/E', the invasively measured parameter, left ventricular end-diastolic pressure, nor the parameters τ and end-diastolic elastance measured by means of PV loops were different in the subgroups PLFLG and NFHG AS (Tables 2, 3). Additionally, there were no differences among the subgroups in the incidence of atrial fibrillation, mitral valve regurgitation, or the extent of right heart failure (Tables 1, 2, 3).

However, in contrast to NFHG AS, in PLFLG AS, the dP/dt_{max} and stroke work were reduced, and the aortic systolic and mean blood pressures, the systemic resistance, the valvuloarterial impedance, the effective arterial elastance and the end-systolic elastance were significantly increased (Tables 2, 3). Notably, the systolic and mean blood pressures were significantly higher in patients with PLFLG AS compared to patients with NFHG AS, despite more intensive antihypertensive drug therapy (Table 1).

Of particular interest are the end-systolic elastance and the effective arterial elastance, which are parameters that can only be obtained by the measurements of the PV loops.

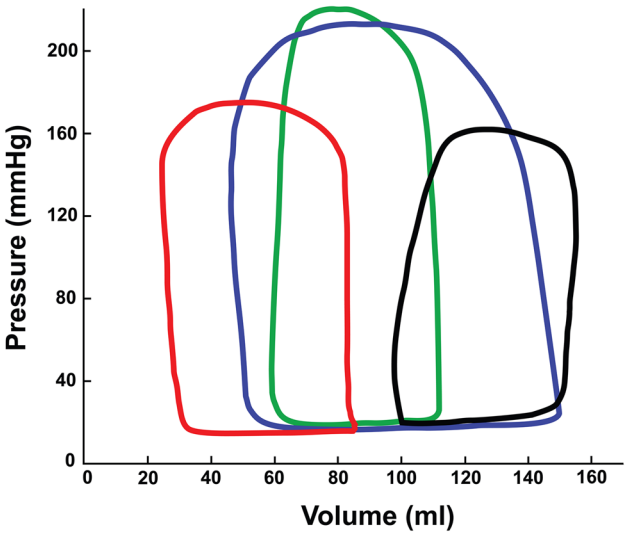

Fig. 3 Representative pressure–volume curves of different hemodynamic subgroups of severe aortic stenosis (blue line: normal-flow, high-gradient aortic stenosis, green line: low-flow, high-gradient aortic stenosis, red line: paradoxical low-flow, low-gradient aortic stenosis with preserved ejection fraction, black line: low-flow, low-gradient aortic stenosis with reduced ejection fraction)

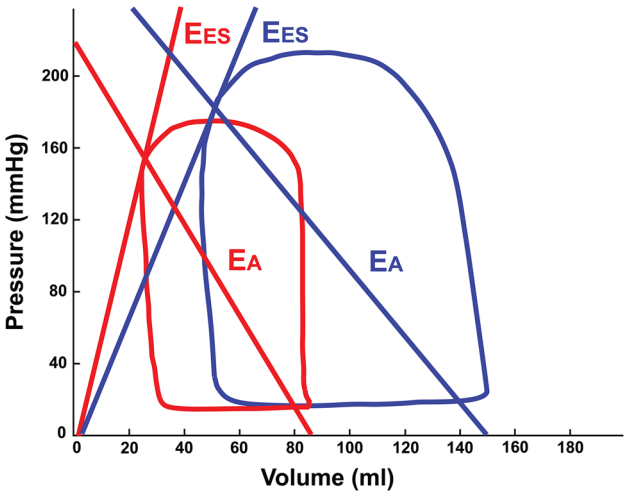

Fig. 4 Representative pressure–volume curves of normal-flow, high-gradient aortic stenosis (blue line) and paradoxical low-flow, low-gradient aortic stenosis with preserved ejection fraction (red line). *Ees* end-systolic elastance, *Ea* effective arterial elastance

The end-systolic elastance provides information about the contractile function of the ventricle and is also a measure of chamber stiffness [11]. In contrast, the effective arterial elastance is a measure of the total mean and the pulsatile load of the vessels in the heart [11, 18, 19]. Both end-systolic elastance and effective arterial elastance are significantly higher in paradoxical LFLG AS compared to NFHG AS.

Previous studies have described that end-systolic elastance and effective arterial elastance were significantly higher in patients with HFpEF than in normotensive controls [26, 27]. Therefore, our study suggests that paradoxical LFLG AS have hemodynamic similarities to HFpEF.

In summary, our study demonstrates that the hemodynamics of PLFLG AS can be explained by two mechanisms: (1) a disturbance of ventricular function due to a smaller end-diastolic volume in combination with an impairment of systolic contractility, and (2) an increased afterload due to the abnormal vascular and aortic valve function (Table 2, 3, 4).

Limitations

Relatively few patients with severe AS were included in this study. In addition, the subgroups of the study were relatively small. Nonetheless, the present study is the largest study that has performed a measurement of PV loops in severe AS. In particular, the extent of invasive measurements gathered in this study should be emphasized. In addition, we were the first to conduct a PV loops study in patients with PLFLG AS. End-diastolic elastance was measured by end-diastolic pressure and end-diastolic volume rather than by acute occlusion of the vena cava. The approach of our study was less invasive and consistent with the methods of other studies using PV loops. The present study was not sufficient to make statements about the prognosis of the subgroups of AS. To better estimate the prognostic significance of hemodynamic parameters, larger studies with more patients would be required.

Clinical perspectives

Our study was the first study to investigate different subgroups of severe AS with PV loops. We identified fundamental differences in hemodynamics among the subgroups of AS. Hence, our study enables an improved understanding of the pathophysiology of AS subgroups. The LFLG AS group showed not only a reduced contractility, but also an end-systolic dilatation of the LV. Changes in effective arterial elastance, end-systolic elastance and ventricular–arterial coupling are similar to systolic heart failure. These results suggest that drug or device therapy for systolic heart failure may also be beneficial in these patients, regardless of aortic valve replacement.

In contrast, the PLFLG group was characterized by decreased left ventricular volumes, cardiac index, systolic contractility and increased end-systolic elastance compared to the "conventional" NFHG AS, indicating increased chamber stiffness. In addition, the alterations in the effective

arterial elastance indicate an abnormal vascular function. This means a double loading (aortic stenosis and vascular function) of the left ventricle with additive unfavorable changes in the left ventricular function. The results suggest that optimized therapy of arterial hypertension may be a suitable target for the treatment of patients with PLFLG AS, in particular both before and after aortic valve replacement [28].

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References

1. Kim WK, Hamm CW (2018) Transcatheter aortic valve implantation in Germany. Clin Res Cardiol 107(Suppl 2):81–87
2. Doenst T, Kirov H, Moschovas A et al (2018) Cardiac surgery 2017 reviewed. Clin Res Cardiol 107(12):1087–1102. https://doi.org/10.1007/s00392-018-1280-9 **(PMID: 29777372)**
3. Nishimura RA, Otto CM, Bonow RO, American College of Cardiology/American Heart Association Task Force on Practice Guidelines et al (2014) AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 63:2438–2488
4. Otto CM, Prendergast B (2014) Aortic-valve stenosis—from patients at risk to severe valve obstruction. N Engl J Med 371:744–756
5. Clavel MA, Magne J, Pibarot P (2016) Low-gradient aortic stenosis. Eur Heart J 37:2645–2657
6. Jander N, Minners J, Holme I et al (2011) Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation 123:887–895 **(Erratum in: Circulation. 2011;124:e336)**
7. Chhabra L (2016) Inconsistency of hemodynamic data in low-gradient severe aortic stenosis. J Am Coll Cardiol 67:2446–2447
8. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Sénéchal M, Pibarot P (2012) Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. J Am Coll Cardiol 60:1259–1267
9. Dayan V, Vignolo G, Magne J, Clavel MA, Mohty D, Pibarot P (2015) Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. J Am Coll Cardiol 66:2594–2603
10. Chin CWL, Ding ZP, Lam CSP, Ling LH (2016) Paradoxical low-gradient aortic stenosis: the HFpEF of aortic stenosis. J Am Coll Cardiol 67:2447–2448
11. Borlaug BA, Kass DA (2009) Invasive hemodynamic assessment in heart failure. Heart Fail Clin 5:217–228
12. Baumgartner H, Hung J, Bermejo J et al (2017) Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 30:372–392
13. Lang RM, Badano LP, Mor-Avi V et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28:1–39.e14
14. Lancellotti P, Tribouilloy C, Hagendorff A, Scientific Document Committee of the European Association of Cardiovascular Imaging et al (2013) Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 14:611–644
15. Briand M, Dumesnil JG, Kadem L et al (2005) Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. J Am Coll Cardiol 46:291–298
16. Baan J, Jong TT, Kerkhof PL et al (1981) Continuous stroke volume and cardiac output from intra-ventricular dimensions obtained with impedance catheter. Cardiovasc Res 15:328–334
17. Baan J, van der Velde ET, de Bruin HG et al (1984) Continuous measurement of left ventricular volume in animals and humans by conductance catheter. Circulation 70:812–823
18. ten Brinke EA, Klautz RJ, Verwey HF et al (2010) Single-beat estimation of the left ventricular end-systolic pressure-volume relationship in patients with heart failure. Acta Physiol (Oxf) 198:37–46
19. Burkhoff D, Mirsky I, Suga H (2005) Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 289:H501–H512
20. Tribouilloy C, Lévy F, Rusinaru D et al (2009) Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol 53:1865–1873
21. Schymik G, Tzamalis P, Herzberger V et al (2017) Transcatheter aortic valve implantation in patients with a reduced left ventricular ejection fraction: a single-centre experience in 2000 patients (TAVIK Registry). Clin Res Cardiol 106:1018–1025
22. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P (2007) Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation 115:2856–2864
23. Zheng Q, Djohan AH, Lim E et al (2017) Effects of aortic valve replacement on severe aortic stenosis and preserved systolic function: systematic review and network meta-analysis. Sci Rep 7:5092
24. Adda J, Mielot C, Giorgi R et al (2012) Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 5:27–35
25. Herrmann S, Störk S, Niemann M et al (2011) Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J Am Coll Cardiol 58:402–412
26. Kawaguchi M, Hay I, Fetics B, Kass DA (2003) Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 107:714–720
27. Borlaug BA, Paulus WJ (2011) Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 32:670–679
28. Gotzmann M (2018) Renin-angiotensin system blockade after TAVI: is there a link between regression of left ventricular hypertrophy and prognosis? Heart 104:628–629