IJC Heart & Vasculature 51 (2024) 101357

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Functional aortic valve area differs significantly between sexes: A phase-contrast cardiac MRI study in patients with severe aortic stenosis

Felix Troger [a], Christian Kremser [a], Mathias Pamminger [a], Sebastian J Reinstadler [b], Gudrun C Thurner [c], Benjamin Henninger [a], Gert Klug [d], Bernhard Metzler [b], Agnes Mayr [a,*]

[a] University Clinic of Radiology, Medical University of Innsbruck, Anichstrasse 35 6020, Innsbruck, Austria
[b] University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University of Innsbruck, Anichstrasse 35 6020, Innsbruck, Austria
[c] Institute of Pathology, Neuropathology and Molecular Pathology, Medical University of Innsbruck, Müllerstraße 44 6020, Innsbruck, Austria
[d] Department of Internal Medicine, County Hospital Bruck an der Mur, Tragoesser Strasse 1 8600, Bruck an der Mur, Austria

ARTICLE INFO

Keywords:
Aortic Stenosis
Cardiovascular MRI
Sex Differences
Phase-Contrast MRI

ABSTRACT

Background: Aortic stenosis (AS) is one of the most prevalent valvular heart-diseases in Europe. Currently, diagnosis and classification are not sex-sensitive; however, due to a distinctly different natural history of AS, further investigations of sex-differences in AS-patients are needed. Thus, this study aimed to detect sex-differences in severe AS, especially concerning flow-patterns, via phase-contrast cardiac magnetic resonance imaging (PC-CMR).

Methods: Forty-four severe AS-patients (20 women, 45 % vs. 24 men, 55 %) with a median age of 72 years underwent transthoracic echocardiography (TTE), cardiac catheterization (CC) and CMR. Aortic valve area (AVA) and stroke volume (SV) were determined in all modalities, with CMR yielding geometrical AVA via cine-planimetry and functional AVA via PC-CMR, the latter being also used to examine flow-properties.

Results: Geometrical AVA showed no sex-differences (0.91 cm^2, IQR: 0.61–1.14 vs. 0.94 cm^2, IQR: 0.77–1.22, $p = 0.322$). However, functional AVA differed significantly between sexes in all three modalities (TTE: $p = 0.044$; CC/PC-CMR: $p < 0.001$). In men, no significant intermethodical biases in functional AVA-measurements between modalities were found ($p = 0.278$); yet, in women the particular measurements differed significantly ($p < 0.001$). Momentary flowrate showed sex-differences depending on momentary opening-degree (at 50 %, 75 % and 90 % of peak-AVA, all $p < 0.001$), with men showing higher flowrates with increasing opening-area. In women, flowrate did not differ between 75 % and 90 % of peak-AVA ($p = 0.191$).

Conclusions: In severe AS-patients, functional AVA showed marked sex-differences in all modalities, whilst geometrical AVA did not differ. Inter-methodical biases were negligible in men, but not in women. Lastly, significant sex-differences in flow-patterns fit in with the different pathogenesis of AS.

1. Introduction

Aortic stenosis (AS) is considered the most common valvular heart disease in the Western world [1]. Although several differences between men and women in this disease entity have already been reported – including pathophysiology, clinical presentation and prognosis [2–4] – there are still no sex-sensitive classifications or guidelines. Some studies even suggested that the choice of the respective management, especially in severe AS, also leads to different outcomes between the sexes concerning morbidity and mortality [5–7]. Due to its complex hemodynamics, a further characterization and sex comparison of flow patterns in AS would be of particular interest, among others because of its primary diagnostic tool being transthoracic echocardiography (TTE) [1], which is mainly based on flow measurements. Especially in terms of the

Abbreviations: AS, Aortic Stenosis; AV, Aortic Valve; AVA, Aortic Valve Stenosis; BSA, Body Surface Area; CC, Cardiac Catheterization; CMR, Cardiovascular Magnetic Resonance Imaging; ECG, Electrocardiogram; EDV, Enddiastolic Volume; EDVi, Enddiastolic Volume Indexed by Body Surface Area; EF, Ejection Fraction; ESV, Endsystolic Volume; ESVi, Endsystolic Volume Indexed by Body Surface Area; IQR, Interquartile Range; LV, Left Ventricle/Ventricular; MM, Myocardial Mass; MMi, Myocardial Mass Indexed by Body Surface Area; PC-CMR, Phase-Contrast Cardiovascular Magnetic Resonance Imaging; SV, Stroke Volume; SVi, Stroke Volume Indexed by Body Surface Area; TTE, Transthoracic Echocardiography.

* Corresponding author at: University Clinic of Radiology, Medical University of Innsbruck, Anichstrasse 35 A-6020, Innsbruck, Austria.
E-mail address: a.mayr@i-med.ac.at (A. Mayr).

https://doi.org/10.1016/j.ijcha.2024.101357
Received 3 January 2024; Received in revised form 1 February 2024; Accepted 2 February 2024

primary pathogenetic development of AS, with women showing more fibrotic valve changes, whilst men tend to have a higher valvular calcium load [2], it seems reasonable that these changes might have a different effect on poststenotic flow dynamics as well. Furthermore, these sex-specific alterations could have a crucial impact on classification and grading of AS. Over the last few years, cardiovascular magnetic resonance imaging (CMR) has emerged to be a helpful tool in the diagnostic workup of valvular heart disease [1]. In particular, phase contrast-CMR (PC-CMR) has been shown to provide accurate measurements in investigating flow properties, especially in aortic stenosis assessment, with a high intra- and interobserver reproducibility [8–10]. Thus, the aims of this present study were: a) to assess the geometric aortic valve area (AVA) via cine-planimetry, b) to determine the functional AVA via TTE (routine standard), cardiac catheterization (CC; gold-standard) and PC-CMR, c) to characterize flow patterns above the stenotic valve via PC-CMR and to finally d) evaluate sex-specific differences in these measurements.

2. Methods

2.1. Study population

Forty-four patients with severe AS (according to the 2021 guidelines of the European Society of Cardiology [1]) were consecutively enrolled in this prospective study. Overall, 20 women (45 %) and 24 men (55 %) were included. Arterial hypertension was present in 32 patients (73 %) and all of these patients had antihypertensive therapy (13 on beta blockers, 24 on ACE-/AT2-antagonists, 9 on calcium antagonists and 12 on diuretics). All participants underwent TTE, CC and CMR. In all modalities, AVA and left ventricular (LV) stroke volume (SV) were determined. TTE served as routine standard, providing AVA and SV via the continuity equation. CC acted as gold-standard, providing AVA via the Gorlin-formula and SV via the Fick-equation. Lastly, CMR yielded on one hand a geometrical AVA via planimetry using cine-images and on the other hand a functional AVA in PC-CMR, using a previously introduced equation [8]. PC-CMR was then also used to examine flow-patterns. Additionally, computed tomography was performed in 35 patients (80 %) to assess valvular calcium load. Written informed consent was obtained in all patients. The study was approved by the local ethics committee and was conducted in accordance to the Declaration of Helsinki.

2.2. Cardiovascular magnetic resonance imaging

All CMR scans were performed on a 1.5 Tesla clinical MR scanner (MAGNETOM Avantofit; Siemens Healthineers AG, Erlangen, Germany) 16 days (interquartile range (IQR): 1–30) after CC and 27 days (IQR: 10–49) after TTE. High-resolution cine-images in long- and short axis covering the LV (i.e. 10–12 slices) were acquired using a balanced steady state free precession (bSSFP) sequence with retrospective electrocardiographic (ECG) gating (slice thickness: 8 mm, interslice gap: 2 mm, echo time: 1.19 ms, repetition time: 2.83 ms, 22 lines per segments, temporal frame duration: 62.26 ms, frame rate: 25 frames per second, flip angle: 70°, field of view: 380x310mm, matrix: 320x260, voxel size: 2.6x1.8x8.0 mm^3, parallel imaging mode: GRAPPA (generalized autocalibrating partial parallel acquisition) with acceleration factor 2).

Blood flow through the aortic valve was measured and quantified via PC-CMR, using a modified free-breathing, velocity-encoded phase-contrast-protocol without through-plane correction for cardiac motion (spatial resolution: 1.3 × 1.3 × 8 mm, repetition time: 13.56 ms, echo time: 2.62 ms). Velocity encoding ranged from 300 to 800 cm/s, with 500 cm/s being used most often (n = 20). Retrospective ECG-triggering with 20 (n = 1), 50 (n = 37) or 128 (n = 6) phases per cardiac cycle was applied. Median heart rate during PC-CMR measurements was 66/min (IQR: 60–77), resulting in a mean reconstructed temporal resolution of 17 ms. One (n = 11), two (n = 1), three (n = 14) or five (n = 18) slices were set perpendicular to the aortic root to measure through-plane flow. In synopsis with three-chamber cine-stacks, distance from leaflet attachment plane to the respective measuring slice was determined, and in accordance to a recently published study, slices 10–20 mm above the valve were preferably used [11]. Standard software (Circle Cardiovascular Imaging, Calgary, Canada) was used to compute momentary flow volume and momentary peak velocity at each measuring point; the measuring range for peak velocity was defined as the single "fastest" pixel without including neighbouring pixels. Contours of aortic valve (AV) orifice were drawn manually on all images of the chosen measuring slice, and flow throughout the cardiac cycle was measured using velocity values of corresponding velocity-encoded images. SV was defined as forward blood flow minus reverse blood flow in the same layer during systole. AVA was then calculated as the ratio of flow and velocity [8], and the mean AVA over the systolic phase was used as "functional AVA by PC-CMR". Via plotting temporary flow volumes, velocities and, lastly, AVA determined in PC-CMR, several parameters to characterize flow were assessed: firstly, peak and mean velocity values were measured; duration of systole as well as the specific time intervals, during which the AV is opened more than a certain percentage of maximum opening (i.e. 50, 75 and 90 % of the peak AVA value via PC-CMR) were determined; lastly, mean flow during these opening intervals was measured, as is shown in Fig. 1.

To perform cine-planimetry, in every patient 3 cine images were acquired orthogonal to the aortic root (slice thickness: 5 mm, no interslice gap); the slice, which exactly recorded the valve opening was used

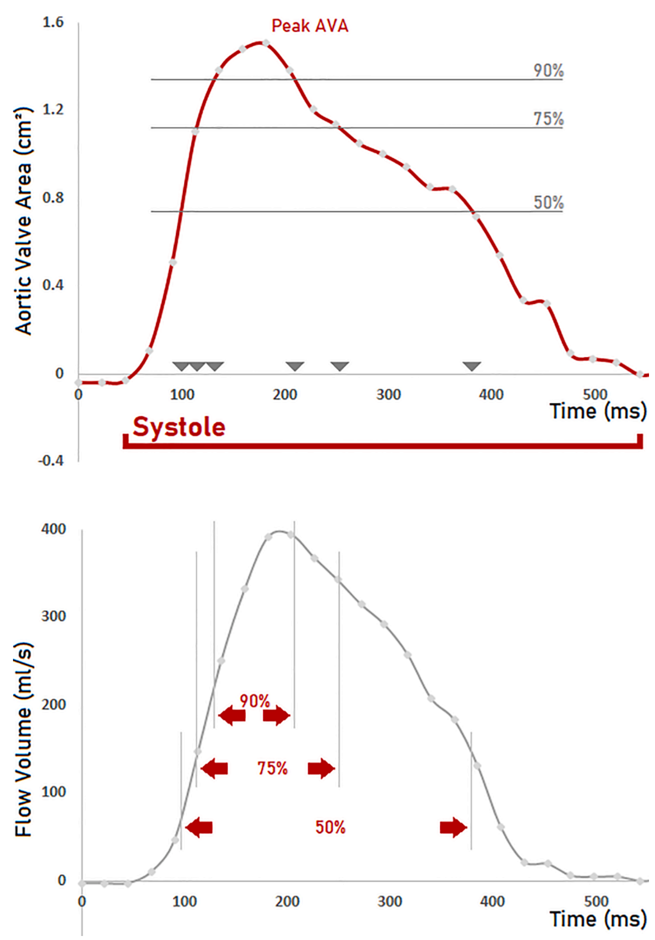

Fig. 1. Graphs showing the dynamics of AVA opening and momentary flow volume in a female patient with severe aortic stenosis, depicting the specific time intervals examined in our study. Note: The PC-CMR-generated AVA-values analysed in this study represent the mean value of valve opening area during systole. *AVA: aortic valve area, SV: stroke volume.*

for planimetry of the anatomical AVA. For volumetric measurements, standard software (Circle Cardiovascular Imaging, Calgary, Canada) was used for post-processing analyses with semi-automatic detection of LV endo- and epicardial borders. Papillary muscles were excluded from myocardial mass (MM) and included in the LV volume. MM, end-diastolic volume (EDV) and end-systolic volume (ESV) were then divided by the body surface area (BSA) [m^2] to obtain indexed values (MMi, EDVi and ESVi, respectively). To calculate BSA, the Du Bois formula was used [12]. In 3 patients (7 %), no adequate cine-images were available. CMR image analysis were performed blinded to clinical, echocardiographic and clinical data.

2.3. Echocardiography

All patients underwent a comprehensive TTE examination, including assessment of the aortic valve by measuring SV and AVA via the continuity equation and LV ejection fraction (EF) by the Simpson method. Median heart rate was 69/min (IQR: 60–80). All echocardiographic analyses were performed by two experienced cardiologists with a TTE EACVI-certification, blinded to clinical, invasive and CMR data. AS was evaluated and classified according to current guidelines by the European Society of Cardiology [1].

2.4. Cardiac catheterization

All patients underwent left and right heart catheterization. A Swan-Ganz catheter was used for hemodynamic measurements. LV end-systolic and –diastolic pressures were recorded. Cardiac output was determined according to Fick principle [13], SV was then calculated by dividing cardiac output by the respective heart rate (71/min, IQR: 62–80). Dividing SV by the BSA yielded SVi. AVA was calculated using the Gorlin-formula [14].

2.5. Statistical analysis

SPSS Statistics 26.0 (IBM, Armonk, NY, USA) was used for statistical analyses. All results for continuous variables are expressed as medians with IQR. To test for significant differences between two groups, Mann-Whitney-test was used. To test for inter-methodical biases within patients in multiple modalities, a Friedman test for related samples was applied. To evaluate the agreement between two methods, Pearson correlation coefficient (r) as well as Bland-Altman analysis were used; limits of agreement were defined as mean difference plus or minus 1.96x standard deviation. A p-value < 0.05 was considered as statistically significant. According to sample size estimation, a sample size of at least 40 patients was needed to ensure a 95 % confidence level.

3. Results

3.1. Baseline patient characteristics

At the time of study inclusion, participant age was 72 years (IQR: 66–77). Twenty participants (45 %) were biological women and 24 were biological men (55 %). According to TTE (continuity equation), 23 patients (52 %) had low flow states (i.e. SVi < 35), with no sex-specific differences in flow-states (45 % low-flow in women, n = 9, vs. 58 % in men, n = 14, p = 0.378).

Overall, there were no significant sex-specific differences in baseline characteristics, which are listed in Table 1. Measurements of AVA and SV in the different modalities plus calcium scoring by CT are listed in Table 2.

3.2. Geometrical AVA

The geometrical AVA determined via planimetry in cine-CMR images was 0.91 cm^2 (IQR: 0.70–1.18) and showed no significant sex-specific difference (women: 0.91 cm^2, IQR: 0.61–1.14 vs men: 0.94 cm^2, IQR: 0.77–1.22, p = 0.332).

Table 1
Baseline characteristics.

	All patients (n = 44)	Women(n = 20)	Men(n = 24)	p-value
Age, years	72 (66–77)	73 (69–78)	72 (63–77)	0.486
Body Mass Index, kg/m^2	26 (23–30)	25 (21–33)	26 (24–29)	0.604
Low Flow, n (%)	23 (52)	9 (45)	14 (58)	0.378
Mitral Regurgitation, n (%)	35 (80)	17 (85)	18 (75)	0.413
Bicuspid AV, n (%)	16 (36)	9 (45)	7 (29)	0.277
Risk profile				
Smokers, n (%)	15 (34)	7 (35)	8 (33)	0.890
Hypertension, n (%)	32 (73)	17 (85)	15 (63)	0.138
Dyslipidemia, n (%)	31 (70)	15 (75)	16 (67)	0.692
Diabetes mellitus, n (%)	11 (25)	6 (30)	5 (21)	0.536
Coronary Artery Disease, n (%)	30 (68)	15 (75)	15 (63)	0.327
Clinical presentation				
AS symptoms, n (%)	39 (89)	18 (90)	21 (88)	0.883
- Vertigo	16 (36)	9 (45)	7 (29)	0.324
- Syncope	5 (11)	3 (15)	2 (8)	0.555
NYHA class, n (%)				
- I	2 (5)	0 (0)	2 (8)	0.403
- II	8 (18)	3 (15)	5 (21)	
- III	27 (61)	12 (60)	15 (63)	
- IV	7 (16)	5 (25)	2 (8)	
CCS class, n (%)				
- I	5 (11)	2 (10)	3 (13)	0.868
- II	16 (36)	8 (40)	8 (33)	
- III	17 (39)	7 (35)	10 (42)	
- IV	5 (11)	3 (15)	2 (8)	
Lab parameters				
nt-pro-BNP, ng/l	572 (182–983)	589 (283–983)	486 (136–1076)	0.383
Troponin T, ng/l	13 (9–20)	12 (6–16)	16 (10–22)	0.064
Cholesterole, mg/dl	177 (144–204)	177 (151–209)	181 (141–204)	0.869

AS: aortic stenosis, AV: aortic valve, CCS: Canadian Cardiovascular Society grading of angina pectoris, nt-pro-BNP: n-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association classification.

3.3. Functional AVA

Functional opening area was determined in three different ways. In TTE, AVA via the continuity equation was 0.79 cm^2 (IQR: 0.63–0.91) and showed a significant difference between women (0.70 cm^2, IQR: 0.54–0.84) and men (0.83 cm^2, IQR: 0.68–0.99; p = 0.044). Then, determined via CC using the Gorlin-equation, AVA was 0.64 cm^2 (IQR: 0.51–0.78) and showed a significant difference between the sexes (women: 0.51 cm^2, IQR: 0.39–0.62 vs. men: 0.75 cm^2, IQR: 0.66–0.88; $p < 0.001$). Finally, according to PC-CMR, functional AVA was 0.75 cm^2 (IQR: 0.60–0.94) with a significant bias between female (0.62 cm^2, IQR: 0.56–0.75) and male participants (0.90 cm^2, IQR: 0.73–0.99; $p < 0.001$).

3.4. Stroke volume assessment

Volumetric SV was 84 ml (IQR: 75–96) and showed no significant sex difference (women: 79 ml, IQR: 75–86 vs. men: 91 ml, IQR: 80–100, p = 0.070). Concerning sex-specific differences, SV was significantly lower in women when assessed by CC and PC-CMR (both $p < 0.005$). In TTE, there was no significant difference (p = 0.278). Indexed SV values are listed in Table 2.

3.5. Flow assessment

At assessing flow properties via PC-CMR, firstly the duration of

Table 2
CMR, TTE, CC and CT measurements.

	All patients	Women	Men	p-value
Cine Planimetry	**n = 44**	**n = 20**	**n = 24**	
AVA, cm^2	0.91 (0.70–1.18)	0.91 (0.61–1.14)	0.94 (0.77–1.22)	0.322
Cine CMR	**n = 41**	**n = 18**	**n = 23**	
SVi, ml/m^2	49 (39–52)	49 (40–52)	46 (38–52)	0.655
Ejection Fraction, %	68 (60–75)	74 (67–78)	63 (51–70)	**0.001**
EDVi, ml/m^2	75 (56–83)	63 (54–79)	76 (59–89)	0.109
ESVi, ml/m^2	21 (15–31)	15 (13–28)	30 (17–33)	**0.002**
MMi, g/m^2	70 (63–90)	63 (57–75)	86 (69–94)	**0.002**
TTE	**n = 44**	**n = 20**	**n = 24**	
AVA (cont. equ.), cm^2	0.79 (0.63–0.91)	0.70 (0.54–0.84)	0.83 (0.68–0.99)	**0.044**
SVi (cont. equ.), ml/m^2	35 (30–44)	38 (33–44)	32 (29–43)	0.364
Cardiac Catheterization	**n = 44**	**n = 20**	**n = 24**	
AVA, cm^2	0.64 (0.51–0.78)	0.51 (0.39–0.62)	0.75 (0.66–0.88)	**< 0.001**
SVi (Fick), ml/m^2	29 (25–33)	28 (24–30)	31 (28–35)	**0.005**
PC CMR	**n = 44**	**n = 20**	**n = 24**	
AVA, cm^2	0.75 (0.60–0.94)	0.62 (0.56–0.75)	0.90 (0.73–0.99)	**< 0.001**
SVi, ml/m^2	44 (33–56)	40 (31–44)	51 (36–58)	**0.028**
CT	**n = 35**	**n = 15**	**n = 20**	
Calcium Score	1119 (475–1989)	443 (262–1489)	1756 (959–2836)	**0.005**

AVA: aortic valve area, CT: computed tomography, EDVi: end-diastolic volume, ESVi: indexed end-systolic volume, MMi: indexed myocardial mass, SVi: indexed stroke volume, TTE: transthoracic echocardiography.

different valve opening degrees (50 %, 75 % and 90 % of maximum opening area) was measured as well as the mean flow rate during these intervals. In women, the whole systolic phase was significantly longer than in men (413 ms, IQR: 352–432 vs. 354 ms, IQR: 339–394; $p = 0.028$). The time interval in which the valve was open > 50 % of the respective peak AVA was longer in women (291 ms, IQR: 264–318 vs. 258 ms, IQR: 227–288, $p = 0.007$). The mean flow during systole and at different opening degrees (50 %, 75 % and 90 % of peak AVA) was at all measured intervals significantly higher in men (all $p < 0.001$). Within sex-groups, all these mean flow values differed from each other in men (all $p < 0.005$); in women, mean flow rate at 75 % and 90 % did not significantly differ ($p = 0.191$). PC-CMR flow measurements are listed in Table 3. Box plots showing a direct comparison of these flow rates are illustrated in Fig. 2.

3.6. Inter-methodical differences

Regarding inter-methodical biases between AVA-determination, there were no significant differences between different modalities in men (all $p > 0.09$), with the largest inter-methodical bias being between planimetric and invasive AVA (0.21 cm^2 [IQR: −0.07 to 0.50], $p = 0.094$). In women, planimetric AVA differed significantly from invasive determination (bias: 0.39 cm^2 [IQR: 0.13–0.63], $p < 0.001$) and from PC-CMR (bias: 0.24 cm^2 [IQR: 0.00–0.50], $p = 0.014$), TTE differed significantly from invasive determination (bias: 0.19 cm^2 [IQR: 0.07–0.27], $p < 0.001$) and invasive determination differed significantly from PC-CMR (bias: −0.17 cm^2 [IQR: −0.21 to 0.00], $p = 0.014$); there were no significant inter-methodical differences in women between planimetric AVA and TTE (0.23 cm^2 [IQR: −0.04 to 0.44], $p = 0.142$) as well as between PC-CMR and TTE (bias: −0.06 cm^2 [IQR: −0.25 to 0.08], $p = 0.327$). Inter-methodical biases within sex groups are depicted in Fig. 3. Correlation of AVA values was moderate between CC and PC-CMR (r: 0.497, $p < 0.001$) and low between TTE and PC-CMR (r: 0.365, $p = 0.015$). Corresponding scatter and Bland-Altman plots are shown in Fig. 4.

Table 3
Flow dynamics in aortic stenosis patients measured via phase-contrast cardiac magnetic resonance imaging.

	All patients (n = 44)	Women(n = 20)	Men(n = 24)	p-value
Stroke volume, ml	83 (55–109)	69 (53–84)	101 (60–120)	**0.003**
Peak velocity, m/s	3.8 (3.2–4.6)	3.6 (3.2–4.7)	4.0 (3.2–4.6)	0.671
Mean velocity, m/s	2.3 (2.0–2.7)	2.2 (1.8–2.7)	2.3 (2.0–2.7)	0.741
Duration of systole, ms	380 (345–421)	413 (352–432)	354 (339–394)	**0.028**
Time open > 50 % of peak AVA, ms	271 (241–303)	291 (264–318)	258 (227–288)	**0.007**
Time open > 75 % of peak AVA, ms	188 (143–252)	206 (151–261)	174 (118–234)	0.147
Time open > 90 % of peak AVA, ms	76 (34–151)	81 (39–175)	76 (32–130)	0.556
Mean flow during systole, ml/s	202 (154–286)	169 (148–194)	279 (202–316)	**< 0.001**
Mean Flow at > 50 % opening, ml/s	258 (201–363)	229 (182–252)	346 (269–398)	**< 0.001**
Mean Flow at > 75 % opening, ml/s	302 (233–392)	258 (215–284)	381 (287–488)	**< 0.001**
Mean Flow at > 90 % opening, ml/s	308 (252–440)	256 (191–299)	409 (304–492)	**< 0.001**

AVA: aortic valve area.

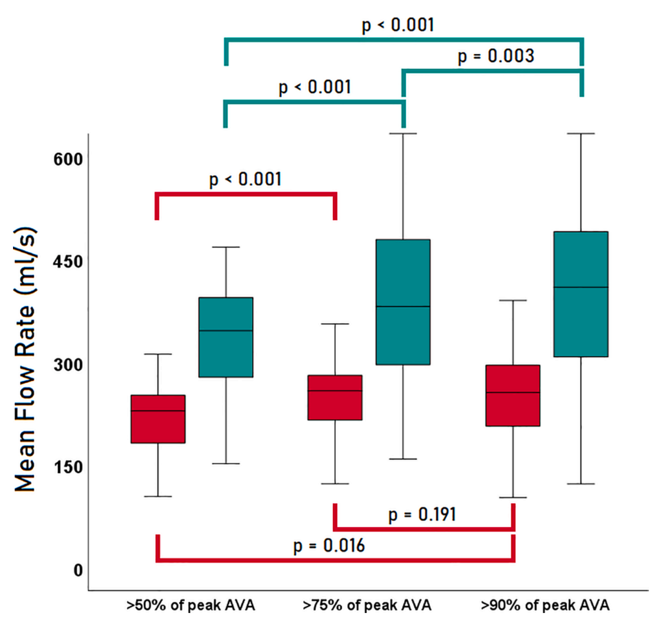

Fig. 2. Box plots of inter-sex comparison between mean flow rates at different opening degrees (red: women, green: men). *AVA: aortic valve area.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This study represents the first investigation of sex-specific differences in severe aortic stenosis via PC-CMR. Our findings can be summarized as follows: a) planimetric measurement of valve opening did not differ between sexes; b) the functional AVA showed significant differences between men and women in all three modalities used: TTE, CC as well as CMR; c) flow assessment by PC-CMR showed considerable differences between male and female AS patients; and lastly, d) significant inter-methodical biases were only found in women.

This analysis highlights that the well-known divergent natural history of AS in men and women is reflected in substantial sex-specific

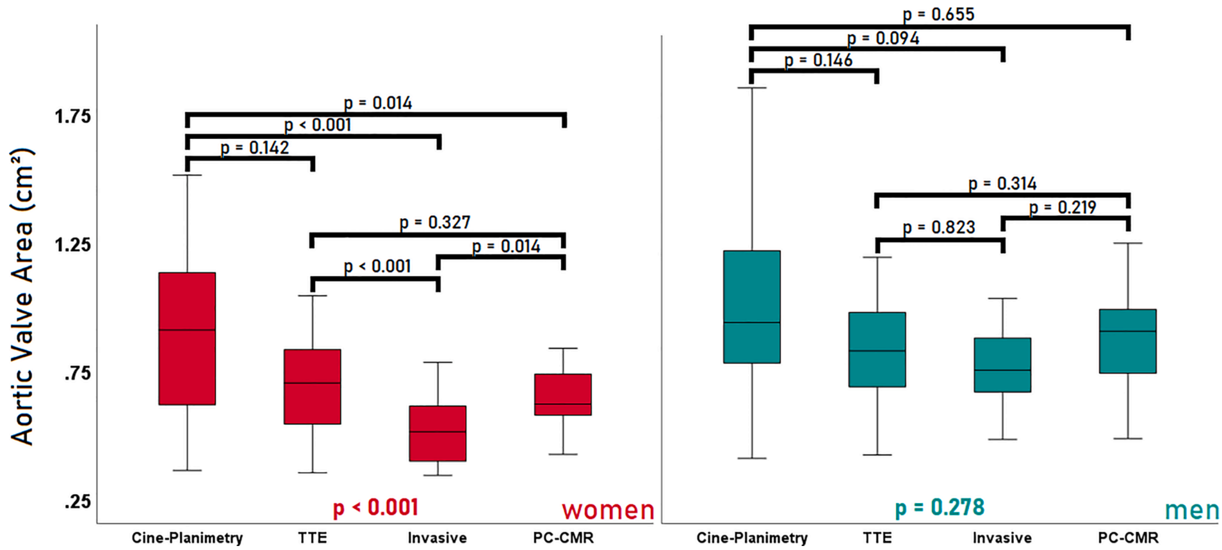

Fig. 3. Box plots of inter-methodical comparison of aortic valve area determination within different sex groups. *PC-CMR: phase-contrast cardiac magnetic resonance imaging, TTE: transthoracic echocardiography.*

differences in various aspects of imaging based aortic valve evaluation.

In this present study, the geometric AV orifice area as assessed via cine-planimetry did not show any sex-specific differences. This finding reflects the fact that there is no sex-sensitive grading of AS [1], but rather easily objectifiable parameters used to classify AS that do not consider differences in the development of AS between men and women. According to a study by Repanas et al., planimetry in CMR tends to overestimate continuity equation in TTE [15]. A similar result was generated by Levy et al. [16]. These findings were also shown in our study, although these differences did not reach a significant level, whether overall nor within sex groups. Debl et al. found a good correlation between planimetric assessment and CC as well as trans-esophageal echocardiography [17], however in all these studies no statements about sex differences were made. There are currently no studies available investigating on differences in geometric/planimetric AVA between men and women.

When assessing functional AVA, it becomes apparent that the geometric AVA by planimetry generally yields the highest AVA values, whilst the invasive evaluation via CC yields the lowest. Especially in women, geometric AVA differed markedly from invasive assessment and PC-CMR measurements, with median biases of at least 0.19 cm^2 each. Even within functional AVA measurements, CC differed significantly from TTE and PC-CMR in women, whilst in men there were no significant differences. When comparing valvular calcium load, men had markedly more calcified valves than women, which is in line with a study by Linde et al., assessing calcium burden in 69 severe AS patients via CT prior to valve replacement [18]. Simultaneously, this finding underlines the already reported different natural history between men and women, with the AV in women being more prone to fibrotic rather than calcific changes [2]. Apparently, the different presentation of the valve not only implies different clinical presentation of the respective patient [4,5], but even leads to women being referred later to surgical or transcatheter valve replacement [2,3] and having different outcomes after valve replacement [19]. Interestingly, when dichotomized at the median valvular calcium score (1119 AU), we found no significant difference between patients above and below this value, neither in AVA and SV values (all modalities), mean and maximum flow velocities nor momentary flow volumes (PC-CMR) (all $p > 0.05$). This indicates that valvular calcium load (considering the low sample size) apparently had no major impact on our measurements. There were no differences between men and women in the prevalence of arterial hypertension, however some authors also reported a possible influence of hypertension and/or hypertrophy on PC-CMR measurements, being mostly grounded on a concomitant increase of SV [20]. As for our study, hypertension did not cause any significance in inter- or intra-methodical biases (all $p > 0.1$). It seems reasonable that these differences in presentation and management are an important implication of its pathophysiology, which also would be a sensible explanation for the discrepancies in AVA estimation observed in our study. Moreover, our study shows that the geometric AVA differs much more from the functional AVA in women, leading to a potential overestimation of the 'true' AVA in women.

The most considerable differences found in our study were seen in flow dynamics, mainly expressed in mean flow rates over specific time intervals. Independent of the opening degree, men had higher flow rates than women. Besides, the flow rate increased depending on opening degree in men, but apparently reached a plateau between 75 % and 90 % opening in women, with even higher values at 75 % opening than at 90 % (if not significant). This finding is probably also due to the distinct pathophysiology (calcification vs. fibrosis) [2], presumably resulting in calcific valves maintaining a more "logical" valve dynamic with higher flow rates at higher opening degrees. The fibrotic changes on the other hand apparently lead to the valve showing a maximum flow rate possibly restricting the LV-SV by plateauing at certain rates, thus maybe contributing to the fact that a paradoxical low-flow low-gradient situation is more common in women [21]. Again, there are hardly any comparable studies available describing flow properties in AS via PC-CMR with focus on sex differences, however, there are partly marked differences between men and women detectable.

Lastly, the fact that in our study the inter-methodical biases were very much in favor of male patients could be primarily a result of the more common occurrence (and maybe more thorough diagnostic workup) of AS in men before 70 years of age [22], and on the other hand the simpler quantifiability of AV calcifications that both led to a years-long neglect of fibrosis as an alternative pathophysiological mechanism [23]. Altogether, these findings go along with some authors suggesting that "male AS" and "female AS" should be regarded as different disease entities and that the inclusion of sex aspects in the diagnostic workup are eventually inevitable [5,24].

Perspectively, the implementation of sex-specific differences in the management of AS would mark a further step in this direction, with some studies having already shown differences in outcome after surgical or transcatheter valve repair [5,25].

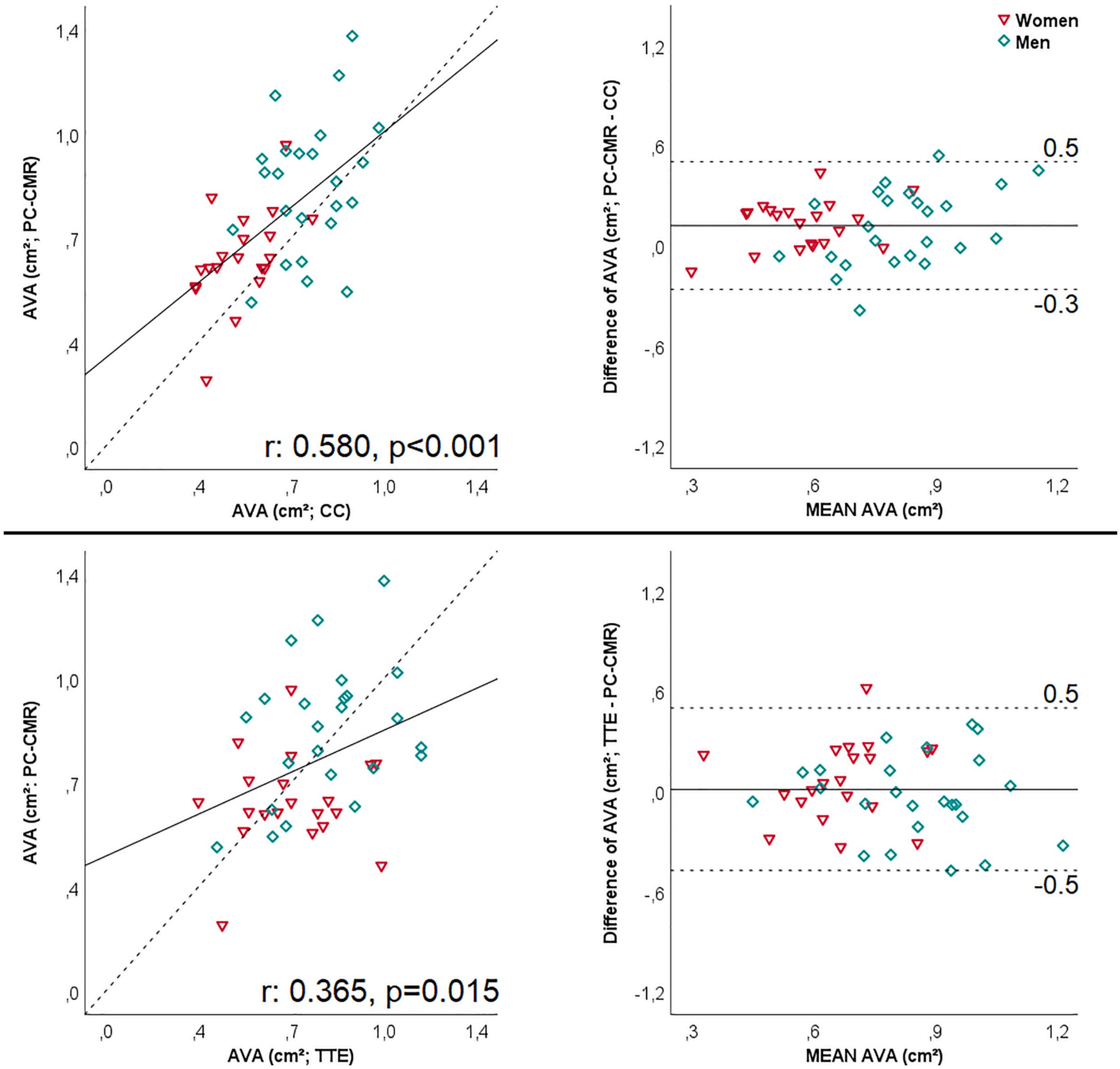

Fig. 4. Scatter plots (left, with interpolated and calibrated line, the latter as dashed line) and Bland-Altman plots (right, with mean value and limits of agreement, the latter as dashed lines) of inter-methodical comparison of AVA assessment between PC-CMR and CC (above) and between PC-CMR and TTE (below), respectively. The red triangles represent women, the green squares men. *AVA: aortic valve area, CC: cardiac catheterization, PC-CMR: phase-contrast cardiac magnetic resonance imaging, TTE: transthoracic echocardiography)*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. Limitations

We do acknowledge that this study bears some limitations: firstly, the CMR protocol used in this study was not entirely uniform in all patients, as over the course of the years the number of obtained slices and phases per examination was continuously increased; anyway, in all of our patients we were able to use an appropriate slice position (i.e. distance above the valve) and compute momentary flow in an adequate number of phases. Another issue regarding echocardiography is the fact that due to single assessment we were not able to perform intra- and interobserver analysis in our TTE measurements; nevertheless, the echocardiographers acting in our study are certified experts in this field, furthermore a study by Pouleur et al. in 2007 showed an excellent reproducibility for this method [26]. Lastly, the number of patients in this study is expandable, however, there are no comparable studies investigating on a similar number of AS patients via PC-CMR.

5. Conclusion

In this present study, it was shown that in patients with severe AS, there were no differences in geometrical AVA between sexes. However, the functional AVA yielded in three different modalities showed marked differences between men and women. There were virtually no inter-methodical biases in men, whilst in women there were partly distinct discrepancies. Lastly, significant sex-differences in calcium load and flow-patterns substantiate the different natural history of AS between the sexes.

Ethics approval and consent to participate

Prior to study inclusion, written informed consent was given by all participants. The study received approval by the local research ethics committee.

CRediT authorship contribution statement

Felix Troger: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christian Kremser:** Writing – review & editing, Methodology. **Mathias Pamminger:** Writing – review & editing, Investigation. **Sebastian J Reinstadler:** Writing – review & editing, Supervision. **Gudrun C Thurner:** Writing – review & editing. **Benjamin Henninger:** Writing – review & editing. **Gert Klug:** Writing – review & editing, Supervision, Conceptualization. **Bernhard Metzler:** Writing – review & editing. **Agnes Mayr:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Vahanian, F. Beyersdorf, F. Praz, et al., 2021 ESC/EACTS Guidelines for the management of valvular heart disease, Eur. J. Cardiothorac. Surg. 60 (4) (2021) 727–800.
[2] N. Cote, M.A. Clavel, Sex differences in the pathophysiology, diagnosis, and management of aortic stenosis, Cardiol. Clin. 38 (1) (2020) 129–138.
[3] C.G. Mihos, S.L. Klassen, E. Yucel, Sex-specific considerations in women with aortic stenosis and outcomes after transcatheter aortic valve replacement, Curr. Treat. Options Cardiovasc. Med. 20 (7) (2018) 52.
[4] A. Singh, D.C.S. Chan, J.P. Greenwood, et al., Symptom onset in aortic stenosis: relation to sex differences in left ventricular remodeling, JACC Cardiovasc. Imaging 12 (1) (2019) 96–105.
[5] S. Saeed, M.R. Dweck, J. Chambers, Sex differences in aortic stenosis: from pathophysiology to treatment, Expert Rev. Cardiovasc. Ther. 18 (2) (2020) 65–76.
[6] P.T.L. Chiam, K. Hayashida, Y. Watanabe, et al., Sex differences in patients undergoing transcatheter aortic valve replacement in Asia, Open Heart 8 (1) (2021).
[7] D. Bienjonetti-Boudreau, M.A. Fleury, M. Voisine, et al., Impact of sex on the management and outcome of aortic stenosis patients, Eur. Heart J. 42 (27) (2021) 2683–2691.
[8] F. Troger, I. Lechner, M. Reindl, et al., A novel approach to determine aortic valve area with phase-contrast cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 24 (1) (2022) 7.
[9] E. Guzzetti, H.P. Racine, L. Tastet, et al., Accuracy of stroke volume measurement with phase-contrast cardiovascular magnetic resonance in patients with aortic stenosis, J. Cardiovasc. Magn. Reson. 23 (1) (2021) 124.
[10] C. Cionca, A. Zlibut, L. Agoston-Coldea, T. Mocan, Advanced cardiovascular multimodal imaging and aortic stenosis, Heart Fail. Rev. 27 (2) (2022) 677–696.
[11] F. Troger, C. Tiller, M. Reindl, et al., Slice positioning in phase-contrast MRI impacts aortic stenosis assessment, Eur. J. Radiol. 1 (161) (2023).
[12] D. Du Bois, E. Du Bois, A formula to estimate the approximate surface area if height and weight be known, Nutrition 5 (5) (1989) 303–311.
[13] E. Shapiro, Adolf Fick–forgotten genius of cardiology, Am. J. Cardiol. 30 (6) (1972) 662–665.
[14] R. Gorlin, S.G. Gorlin, Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I, Am. Heart J. 41 (1) (1951) 1–29.
[15] T.I. Repanas, C.A. Papanastasiou, G.K. Efthimiadis, et al., Cardiovascular magnetic resonance as a complementary method to transthoracic echocardiography for aortic valve area estimation in patients with aortic stenosis: A systematic review and meta-analysis, Hellenic J. Cardiol. 62 (2) (2021) 107–111.
[16] F. Levy, L. Iacuzio, F. Civaia, et al., Usefulness of 3-Tesla cardiac magnetic resonance imaging in the assessment of aortic stenosis severity in routine clinical practice, Arch. Cardiovasc. Dis. 109 (11) (2016) 618–625.
[17] K. Debl, B. Djavidani, J. Seitz, et al., Planimetry of aortic valve area in aortic stenosis by magnetic resonance imaging, Invest. Radiol. 40 (10) (2005) 631–636.
[18] L. Linde, R. Carter-Storch, et al., Sex differences in aortic valve calcification in severe aortic valve stenosis: association between computer tomography assessed calcification and valvular calcium concentrations, Eur. Heart J. Cardiovasc. Imaging 22 (5) (2021) 581–588.
[19] L.E. Dobson, T.A. Fairbairn, S. Plein, J.P. Greenwood, Sex differences in aortic stenosis and outcome following surgical and transcatheter aortic valve replacement, J. Womens Health (Larchmt) 24 (12) (2015) 986–995.
[20] L. Bertelsen, J. Svendsen, L. Køber, et al., Flow measurement at the aortic root - impact of location of through-plane phase contrast velocity mapping, J. Cardiovasc. Magn. Reson. 18 (1) (2016) 55.
[21] Z. Hachicha, J.G. Dumesnil, P. Bogaty, P. Pibarot, Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival, Circulation 115 (22) (2007) 2856–2864.
[22] Y. Shan, P.A. Pellikka, Aortic stenosis in women, Heart 106 (13) (2020) 970–976.
[23] L. Simard, N. Cote, F. Dagenais, et al., Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: Is valvular fibrosis the explanation? Circ. Res. 120 (4) (2017) 681–691.
[24] V. Regitz-Zagrosek, S. Oertelt-Prigione, E. Prescott, et al., Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes, Eur. Heart J. 37 (1) (2016) 24–34.
[25] T. Sevilla, N. Ramos, M. Carnero, et al., Sex differences in clinical outcomes after aortic valve intervention for isolated severe aortic stenosis, J. Clin. Med. 12 (22) (2023).
[26] Pouleur AC, le Polain de Waroux JB, Pasquet A, Vancraeynest D, Vanoverschelde JL, Gerber BL. Planimetric and continuity equation assessment of aortic valve area: Head to head comparison between cardiac magnetic resonance and echocardiography. J Magn Reson Imaging. 2007;26(6):1436-43.