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Research paper

Assessment of aortic valve calcium load by multidetector computed tomography. Anatomical validation, impact of scanner settings and incremental diagnostic value

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ABSTRACT

Objectives: To validate aortic valve calcium (AVC) load measurements by multidetector row computed tomography (MDCT), to evaluate the impact of tube potential and slice thickness on AVC scores, to examine the accuracy of AVC load in distinguishing severe from nonsevere aortic stenosis (AS) and to investigate its effectiveness as an alternative diagnosis method when echocardiography remains inconclusive.

Methods: We prospectively studied 266 consecutive patients with moderate to severe AS who underwent MDCT to measure AVC load and a comprehensive echocardiographic examination to assess AS severity. AVC load was validated against valve weight in 57 patients undergoing aortic valve replacement. The dependence of AVC scores on tube potential and slice thickness was also tested, as well as the relationship between AVC load and echocardiographic criteria of AS severity.

Results: MDCT Agatston score correlated well with valve weight ($r = 0.82$, $p < 0.001$) and hemodynamic indices of AS severity (all $p < 0.001$). Ex-vivo Agatston scores decreased significantly with increasing tube potential and slice thickness (repeated measures ANOVA $p < 0.001$). Multivariate analysis identified mean gradient, the indexed effective orifice area, male gender and left ventricular outflow tract cross-sectional area as independent correlates of the in-vivo AVC load.

Conclusions: MDCT-derived AVC load correlated well with valve weight and hemodynamic indices of AS severity. It also depends on tube potential and slice thickness, thus suggesting that these parameters should be standardized to optimize reproducibility and accuracy.

1. Introduction

Calcific aortic valve (AV) disease is a slowly progressive disorder with a disease continuum that ranges from mild valve thickening without obstruction of blood flow, termed aortic sclerosis, to severe calcification with impaired leaflet motion, or aortic stenosis (AS). Active calcification and bone formation have been shown to play an important role in the disease progression.[1–6] Although microscopic accumulations of extracellular calcification are usually present even in the earliest stages of the disease,[1] more prominent calcifications as well as areas of frank bone formation do characterize the end-stages of the disease.

Although Doppler echocardiography is the preferred method for assessing the severity of AS, its feasibility is often limited by image quality, particularly in patients with poor echocardiographic windows. Defining the true severity of AS by use of Doppler echocardiography is also challenging as it relies on the combined assessment of valve area and mean transvalvular gradients. In up to 30% of subjects,[7] and in particular those with poor LV ejection

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Abbreviations and acronyms

AS	aortic stenosis
AV	aortic valve
AVC	Aortic valve calcification
AVR	Aortic valve replacement
EBCT	electron beam computed tomography
EOA	effective orifice area
EOAi	indexed effective orifice area
LV	left ventricle
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MDCT	multidetector row computed tomography
MPG	mean peak gradient
Vmax	peak transaortic flow velocity

fraction, these indices are discordant, leaving clinicians in doubt as to the true severity of AS. It has been suggested that measurement of aortic valve calcium (AVC) by X-Ray computed tomographic modalities may be helpful in this respect. The amount of AVC can indeed be readily quantified by use of electron beam computed tomography (EBCT) and multidetector row computed tomography (MDCT). Both of these modalities have been extensively validated for the quantification of coronary artery calcification,[8–11] and were more recently shown to permit quantification of AVC load as well.[12–14] Close correlations between the amount of AVC load and the hemodynamic severity of AS have been demonstrated,[14–17] suggesting that AVC load by EBCT or MDCT can be used as a surrogate to the hemodynamic quantification of AS severity. Although AVC load quantification has been anatomically validated and successfully used to differentiate between moderate AS and truly severe AS,[17,18] a wide variety of image acquisition protocols and scanner settings have been used across the published studies, raising concerns about the clinical applicability of the diagnostic thresholds reported in these studies.

Therefore, the aim of the present study was to validate AVC load measurements by MDCT, to evaluate the impact of scanner acquisition settings (tube potential and slice thickness) on AVC scores, to evaluate the correlation between AVC load and the hemodynamic indices of AS severity and to examine the accuracy of AVC load in distinguishing severe from nonsevere AS, defined on the basis of guidelines criteria.

2. Methods

2.1. Patient population

Between February 1st, 2013 and August 31st, 2015, we prospectively enrolled 266 consecutive patients with moderate to severe AS, defined as an effective orifice area (EOA) < 1.5 cm^2 and an indexed EOA (EOAi) < 0.9 cm^2/m^2. Patients with hemodynamic instability, left ventricular (LV) dysfunction, more than moderate aortic regurgitation or mitral valve disease, previous valve replacement or repair, or poor quality of echocardiographic data were not considered for inclusion. The study protocol was approved by the local ethical committee and all patients gave informed consent prior to inclusion into the study.

2.2. Doppler echocardiography measurements

Echocardiographic data were obtained with commercially available ultrasound systems as part of the usual patient's clinical workup. All patients underwent a comprehensive examination, including M-mode and 2-dimensional echocardiography, as well as Doppler examinations. All tests were conducted by experienced sonographers. Multiple transducer positions were systematically used to record maximal instantaneous and mean pressure gradients (MPG) across the aortic valve. The EOA was calculated by use of the continuity equation.[19] In patients with atrial fibrillation, 5 consecutive beats were systematically averaged. LV volumes and ejection fraction (LVEF) were calculated by use of the biplane Simpson method.[20]

2.3. Multidetector computed tomography measurements

The MDCT examinations were exclusively performed for the purpose of the present study protocol. All patients underwent MDCT within 10 ± 19 days of their echocardiographic examination. All MDCT examinations were performed by use of a helical 256-slice CT scanner (Brillance ICT, Philips Healthcare, Cleveland, Ohio, USA). Acquisition parameters were set as follows: tube potential of 120 kV, tube current of 250 mA, gantry rotation time of 330 ms, detector configuration of 32 × 0.625 mm, and pitch of 0.14–0.18. Contiguous non-overlapping slices of 2.5 mm were acquired in a craniocaudal direction during inspiratory breathhold and using prospective ECG-triggering at 75% of R-R interval and a CB filter. No contrast enhancement was needed and no beta-blockers were administered. The average of the total estimated effective radiation dose per CT scan was 0.89 ± 0.08 mGy and the average dose-length product was 64 ± 6 mGy cm.

2.4. Surgical specimens

The aortic leaflets of a subset of 57 patients (22 men, 35 women, mean age 73 ± 9 years, range 48–90 years) scheduled to undergo AV replacement (AVR) were collected at the time of surgery. The aortic leaflets were carefully dissected free from the aortic wall by cutting along the basal attachment, cleaned from any blood residues and immediately weighed on a high precision scale. The specimens were subsequently placed into the CT scanner to measure the AVC score ex-vivo using the above-mentioned protocol. Additional scans were performed by changing either the tube potential (80, 100 and 140 kV) or the slice thickness (1, 2, and 5 mm) in order to evaluate the impact of these parameters on AVC score. As transthoracic echocardiography cannot accurately diagnose a bicuspid valve configuration,[21] we also took valve morphology into account in the subset of patients in whom bicuspid morphology was surgically confirmed.

2.5. Measurement of aortic valve calcium

Measurements of AVC were performed on dedicated workstations with validated and commercially available software *(heartbeat calcium scoring; Philips Medical Systems)*. Calcifications were identified by using a threshold of CT attenuation of 130 Hounsfield Units (HU) for Agatston score and calcium volume and 100 HU for the calcium mass. Measurements were made in the axial view by a single investigator who identified the calcification corresponding to the aortic valve leaflets. For this, the aortic valve was visualized in multiple planes, including cross-sectional valve plane, to accurately exclude contiguous calcium in the mitral valve annulus, the aortic wall or the coronary arteries (Fig. 1). Agatston score, calcium volume and mass were reported as Agatston units (AU), cubic millimeters (mm^3) and milligrams (mg), respectively. To account for inter-individual variability in valve size, we used the AVC density, defined as AVC Agatston score indexed to the cross-sectional area of

the left ventricular outflow tract (LVOT), when necessary. In order to determine the intra- and inter-observer variability, AVC measurements in 20 consecutive patients were reassessed by the same investigator (J.B.) and a second investigator (B.G.) blinded to previous scoring.

2.6. Statistical methods

Statistical analyses were performed using the SPSS version 19.0 (SPSS inc., IBM, Chicago, IL) software. Continuous variables are expressed as mean ± standard deviation (SD) unless otherwise stated and were compared using a standard Student *t*-test or Mann-Whitney test, as appropriate. Categorical variables are expressed as counts and percentages and were compared using the χ^2 test. Correlations between hemodynamic, tomographic and anatomic data were tested using linear or exponential regressions as appropriate. The effect of variation of tube potential and slice thickness was tested using a one-way ANOVA for repeated measures followed by a Bonferroni post-hoc test. Multiple regression analysis was used to assess independent correlates of the Agatston score. Receiver operating characteristic (ROC) curves were used to identify the best cut-off values (by use of the Youden index) of AVC scores for differentiating between severe and nonsevere AS on the basis of guidelines-defined Doppler echocardiographic thresholds (MPG $\geq$ 40 mmHg, peak transvalvular flow velocity (V_{max} > 4 m/s, EOAi < 0.6 cm^2/m^2)). Their predictive value was evaluated by computing the area under the ROC curves. All tests were two sided and a *p*-value of 0.05 or less was considered statistically significant.

3. Results

3.1. Baseline clinical, hemodynamic and echocardiographic characteristics

Baseline clinical, hemodynamic and echocardiographic characteristics of the study population are shown in Table 1. Men were younger than women, had larger body surface area (BSA), displayed higher prevalence of dyslipidemia, smoking history, coronary artery disease, and lower glomerular filtration rate. From an echocardiographic point of view, all patients demonstrated calcified aortic valves. No significant differences in AS severity markers were found between men and women. However, men had slightly lower LVEF, higher mean transvalvular flow rate, larger left ventricular volume and LVOT diameter.

3.2. Ex-vivo and in-vivo validation of aortic valve calcium by MDCT

Amongst the 57 aortic valve specimens harvested at the time of AVR, 35 were tricuspid and 22 were bicuspid. Bicuspid valves displayed higher AVC scores in comparison with tricuspid valves. However, this difference was no longer significant after indexation of the AVC scores to the LVOT cross-sectional area (Table 2).

The ex-vivo Agatston score correlated well with valve weight by pathology ($r = 0.93$, $p < 0.001$). As shown in Fig. 2, a similarly good correlation was observed between valve weight and either the in-vivo Agatston score ($p = 0.86$, $p < 0.001$), the in-vivo calcium volume ($r = 0.80$, $p < 0.001$) or the in-vivo calcium mass ($r = 0.85$, $p < 0.001$).

3.3. Impact of tube potential and slice thickness on Agatston scores

Fig. 3 shows the impact of varying tube potential and slice thickness on the ex vivo Agatston scores. As shown, the AVC Agatston score decreased by 21% when increasing potential from 80 to 140 kV ($p < 0.001$ by repeated measures ANOVA). Similarly, the AVC Agatston score decreased by 23% when increasing slice thickness from 1 to 5 mm ($p < 0.001$ by repeated measures ANOVA). Dependence of AVC Agatston score on tube potential and slice thickness was seen for any degree of AVC.

3.4. The uni- and multivariable determinants of AVC load

Uni- and multivariable determinants of AVC Agatston score are shown in Table 3. As shown, after multivariable analysis, only the MPG, the EOAi, male gender and the LVOT cross-sectional area were found to be significantly and independently associated with high AVC Agatston score.

3.5. Relation of AVC scores to hemodynamic indices of AS severity

All hemodynamic indices of AS severity (EOAi, MPG and V_{max}) correlated with AVC Agatston score by MDCT, both in males and

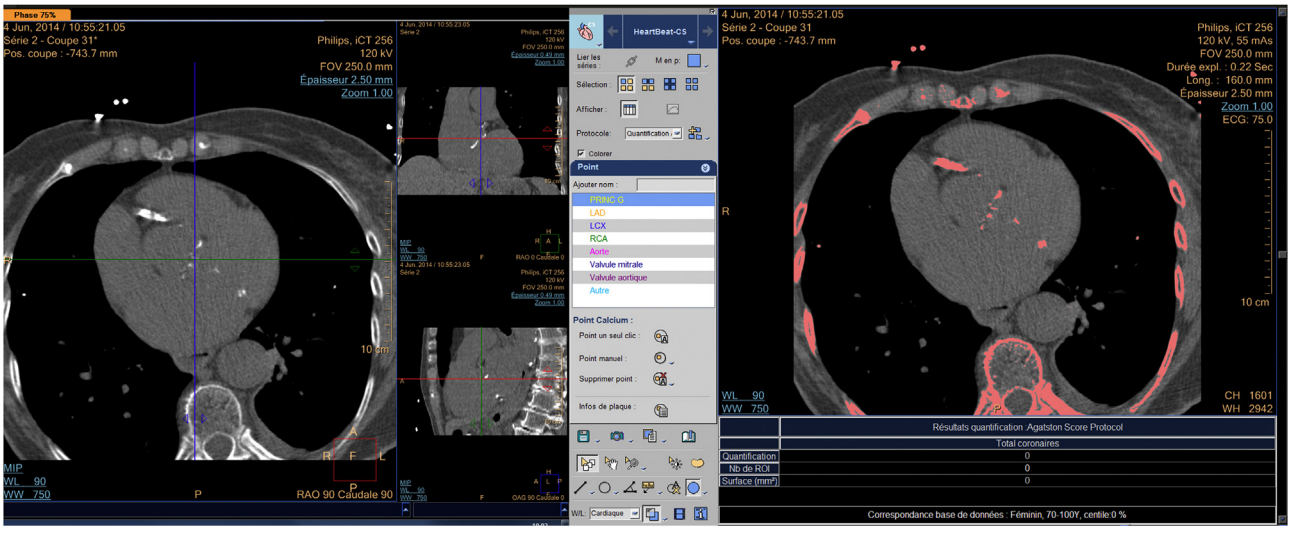

Fig. 1. Aortic valve calcium scoring. Calcium scoring software on the right and CT-viewer, allowing images reconstruction and visualization of calcifications in multiple planes, on the left.

Table 1
Baseline demographic, clinical and echocardiographic characteristics.

	Overall (n = 266)	Women (n = 115)	Men (n = 151)	p-value
Demographic and clinical characteristics				
Age, y	77 ± 10	79 ± 9	75 ± 10	<0.001
Weight, kg	75 ± 16	67 ± 14	80 ± 14	<0.001
Height, cm	166 ± 9	159 ± 7	171 ± 7	<0.001
Body surface area, kg/m^2	1.8 ± 0.2	1.7 ± 0.2	1.9 ± 0.2	<0.001
Heart rate, beat/min	69 ± 12	71 ± 13	67 ± 12	0.24
Systemic hypertension, n (%)	206 (77)	95 (83)	111 (74)	0.08
Dyslipidemia, n (%)	181 (68)	67 (58)	114 (76)	0.003
Diabetes, n (%)	54 (20)	20 (17)	34 (23)	0.30
Smoking, n (%)	109 (41)	16 (14)	93 (62)	<0.001
Family history, n (%)	45 (17)	17 (15)	28 (19)	0.42
Coronary artery disease, n (%)	119 (45)	41 (36)	78 (52)	0.01
Atrial fibrillation, %	61 (23)	30 (26)	31 (21)	0.29
GFR, mL/min	65 ± 28	75 ± 27	58 ± 27	<0.001
NYHA class III/IV, n (%)	71 (27)	37 (32)	34 (23)	0.12
Angina, n (%)	78 (29)	28 (24)	50 (33)	0.12
Syncope, n (%)	22 (8)	13 (11)	9 (6)	0.12
Baseline echocardiographic and Doppler data				
LVEDVi, mL/m^2	58 ± 15	55 ± 15	60 ± 15	0.02
LV ejection fraction, %	59 ± 7	61 ± 7	58 ± 6	0.001
LV mass index (g/m^2)	84 ± 67	87 ± 96	82 ± 30	0.57
LV stroke volume index, mL/m^2	41 ± 10	42 ± 11	40 ± 9	0.14
LA volume, mL/m^2	71 ± 33	73 ± 36	69 ± 31	0.31
LVOT diameter, cm	2.1 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	<0.001
Mean transvalvular flow rate, mL/s	212 ± 53	212 ± 53	235 ± 54	<0.001
V_{max}, cm/s	371 ± 89	370 ± 94	371 ± 84	0.92
Mean pressure gradient, mmHg	35 ± 17	35 ± 18	35 ± 17	0.95
EOA, cm^2	0.88 ± 0.29	0.84 ± 030	0.91 ± 0.27	0.06
EOAi, cm^2/m^2	0.48 ± 0.16	0.50 ± 0.18	0.47 ± 0.14	0.17

Values are n (%) or mean ± SD. GFR: glomerular filtration rate; NYHA: New York Heart Association. EOA: effective orifice area; EOAi: indexed EOA; LVEDVi: indexed left ventricular end-diastolic volume; LV: left ventricle; LA: left atrium; LVOT: left ventricular outflow tract; Vmax: peak aortic flow velocity.

Table 2
Comparison of AS severity and AVC load in tricuspid and bicuspid valves.

	Tricuspid (n = 35)	Bicuspid (n = 22)	P-value
EOA, cm^2	0.71 ± 0.20	0.80 ± 0.23	0.17
EOAi, cm^2/m^2	0.40 ± 0.11	0.42 ± 0.11	0.41
Mean pressure gradient, mmHg	44 ± 18	46 ± 15	0.67
Vmax, cm/s	412 ± 77	421 ± 67	0.66
Agatston AVC score, AU	2489 ± 1238	3534 ± 1777	0.011
Agatston AVC density, AU/cm^2	779 ± 400	974 ± 574	0.14
LVOT diameter, cm	2.0 ± 0.2	2.2 ± 0.2	0.002

Values are n (%) or mean ± SD. EOA: effective orifice area; EOAi: indexed EOA; LVOT: left ventricular outflow tract; Vmax: Peak aortic flow velocity.

females ($p < 0.001$). Fig. 4 shows the correlation between AVC Agatston score and EOAi and MPG. Yet, for similar degrees of AS severity, AVC Agatston score was larger in males than in females.

Table 4 shows the best thresholds calculated in males and females for distinguishing severe from nonsevere AS based on guidelines recommended thresholds for EOAi, MPG and V_{max}. As expected, these thresholds are larger in males than in females. They are also larger when defining AS severity on the basis of MPG (2168 AU [645 AU/cm^2]) or V_{max} (2031 AU [604 AU/cm^2]) than on that of the EOAi (1741 AU [518 AU/cm^2]).

4. Discussion

The aim of the present study was to anatomically validate AVC load by MDCT, to examine the influence of scanner settings on the obtained measurements and to evaluate the possible accuracy and incremental diagnostic value of AVC load scores in distinguishing severe from nonsevere AS based on guidelines criteria. Our main results can be summarized as follows:

- The 3 AVC load scores (Agatston score, calcium volume and calcium mass) are highly correlated with AV weight and with hemodynamic parameters of AS severity;
- AVC Agatston scores are negatively impacted by tube potential and slice thickness;
- The MPG, EOAi, gender, and LVOT cross-sectional area are the main independent determinants of AVC load;
- For similar degrees of AS severity, AVC load is higher in males than in females even after indexation. As a consequence, thresholds distinguishing severe from nonsevere AS are also larger in males than females.
- For similar degrees of AS severity, bicuspid valves have higher absolute AVC score in comparison with tricuspid valves but similar AVC density. Consequently, same thresholds can be used for all valve morphologies but it is imperative to use the indexed values.

4.1. Methods for assessing AVC load

Our study evaluated different scoring systems for quantifying AVC load. These scoring systems were initially designed for the quantification of coronary artery calcification. The Agatston score was initially introduced to overcome partial volume effects related to slice thickness in EBCT examinations, by multiplying pixel density by a correction factor.[7] Later, volume and mass scores were proposed to improve the accuracy of calcium scoring by MDCT.[22–24] Our study demonstrated that all 3 approaches are highly correlated with absolute valve weight, used as surrogate to AVC content. We also found that despite similar degrees of AS severity, women have less AVC than men.

In our sample of 57 collected valves, bicuspid valves displayed higher absolute AVC Agatston scores in comparison with tricuspid

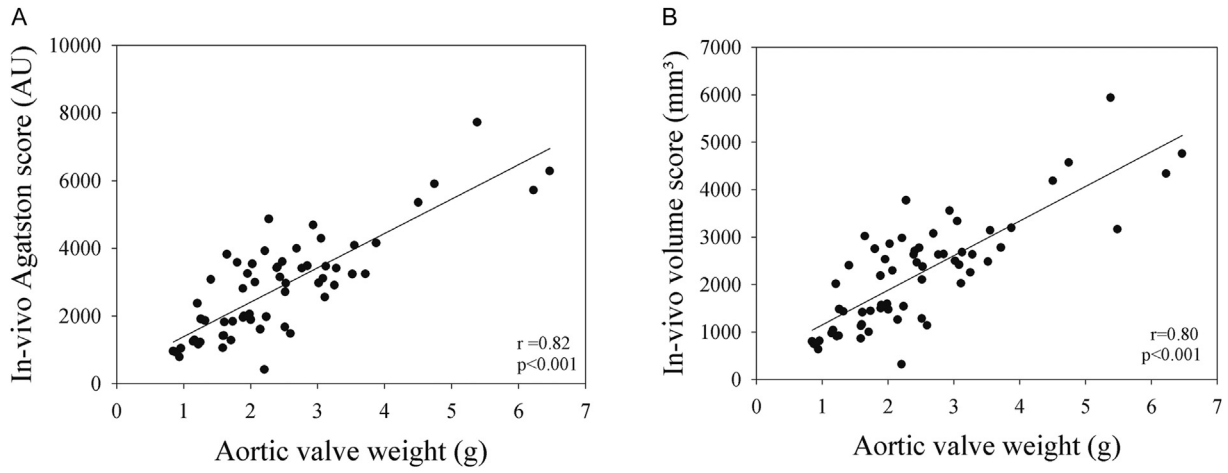

Fig. 2. Dotplots showing the relationship between aortic valve weight and in-vivo Agatston score (panel A), in-vivo volume score (panel B) and in-vivo mass score (panel C).

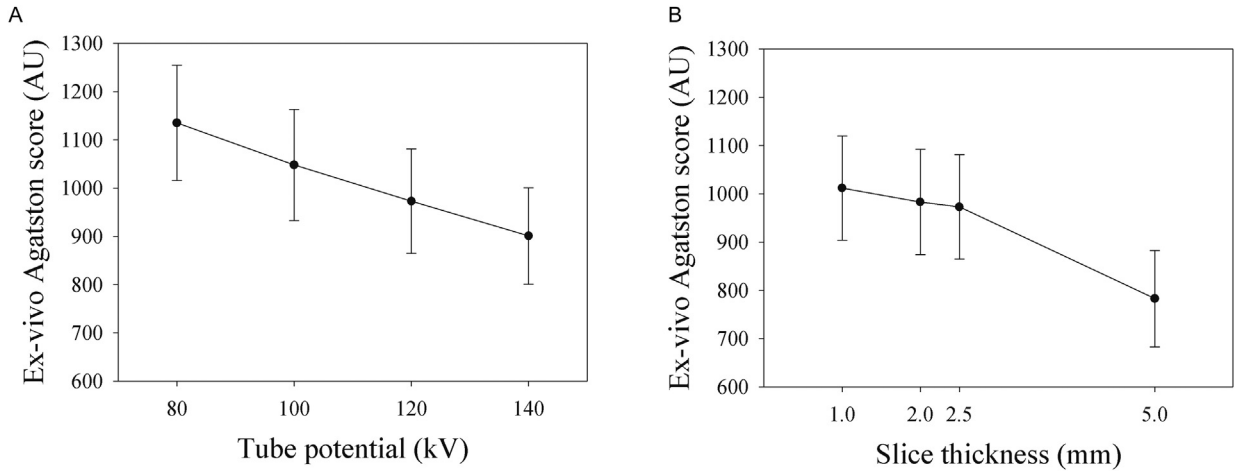

Fig. 3. Mean plot showing the relationship between the ex-vivo Agatston score and tube potential (panel A) or slice thickness (panel B). Error bars indicate SEM.

valves, despite similar degrees of AS severity. However, this difference was no longer significant after indexation of AVC score to LVOT cross-sectional area, which suggests that their apparently larger AVC load mostly reflects the amount of tissue needed to cover the larger LVOT areas seen in patients with bicuspid as opposed to tricuspid aortic valves (Table 2). This could potentially have important clinical implications, as it suggests that AVC density should probably be preferred to absolute AVC scores when evaluating AS severity on the basis of AVC load measurements. Similar observations were recently reported by Clavel et al.[25] when comparing valve weight in bicuspid and tricuspid aortic valves. This contrasts, however, with the observations of Ferda et al.[26] who reported similar AVC loads among bicuspid and tricuspid aortic valves. Unfortunately, these authors did not measure the LVOT cross-sectional area in their study, make it difficult to compare their results with ours. More studies are thus probably needed to solve this issue.

An additional important observation made in this study relates to the impact of tube potential and slice thickness on AVC measurements. Indeed, increasing tube potential and slice thickness was found to result in significant reductions of measured Agatston scores. The dependence of Agatston scores on tube potential was rather linear between 80 and 140 kV. By contrast, the dependence on slice thickness was marginal below 2.5 cm but became significant between 2.5 and 5 cm. The dependence of Agatston scores on tube potential has been described before, in phantom experiments.[27,28] For example, Deprez et al. demonstrated that increasing tube potential from 80 to 140 kV resulted in a 22% decrease in calculated Agatston scores.[28] We made very similar findings in the present study. We indeed observed that increasing tube potential from 80 to 140 kV was associated with a 21%

Table 3
Uni- and multivariable determinants of AVC Agatston score >1741 AU.

Covariates	Univariable analysis		Multivariable analysis	
	Odd Ratios	p value	Odd Ratios	p value
Mean gradient (per 1 mmHg)	1.13	<0.001	1.12	<0.001
EOAi (per 1 cm^2/m^2)	0.02	<0.001	0.12	0.019
Male gender	2.31	0.001	3.22	0.002
LVOT area (per 1 cm^2)	1.43	0.079	2.78	0.002
History of HTN	0.53	0.05		
Hypercholesterolemia	1.59	0.08		
Smoking	1.28	0.34		
Age (per 1 yr)	1.00	0.76		
CAD	0.94	0.82		
Diabetes mellitus	0.96	0.89		

CAD: coronary artery disease; EOAi: indexed effective orifice area; HTN: systemic hypertension; LVOT: left ventricular outflow tract.

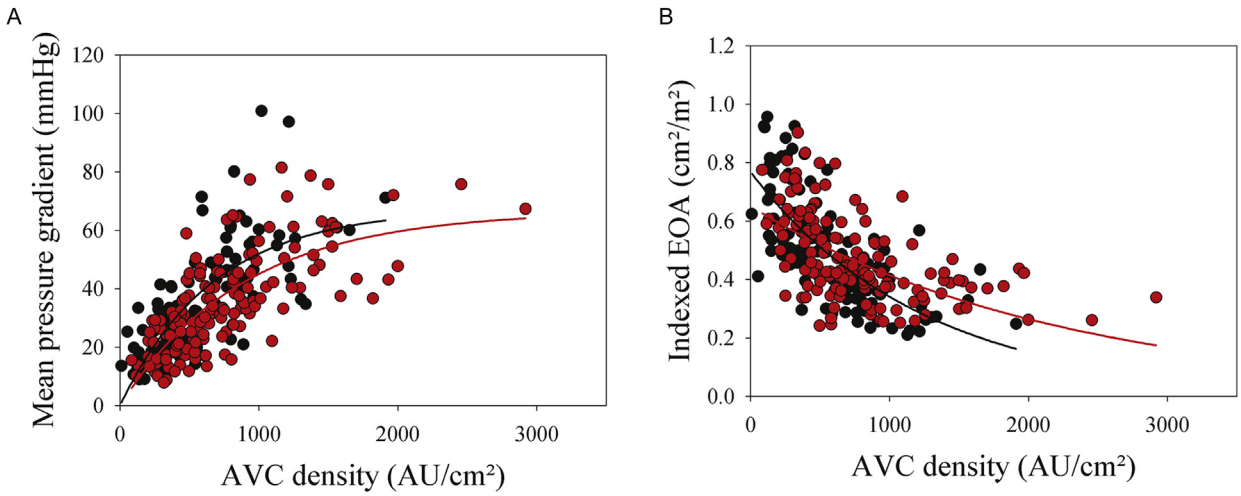

Fig. 4. Dotplots showing the relationship between AVC load and the mean transaortic pressure gradient (panel A) or the indexed effective orifice area (panel B) in both men (black dots) and women (red dots).

Table 4
Optimal AVC Agatston score thresholds to distinguish severe from nonsevere AS.

		AVC load threshold	AUC	Se	Sp	P-value
EOAi < 0.6 cm^2/m^2	Overall	1741 AU (518 AU/cm^2)	0.83 ± 0.03	73%	85%	<0.001
	Female	1342 AU (434 AU/cm^2)	0.84 ± 0.04	72%	76%	<0.001
	Male	1977 AU (554 AU/cm^2)	0.84 ± 0.04	70%	87%	<0.001
GM > 40 mmHg	Overall	2168 AU (645 AU/cm^2)	0.85 ± 0.02	80%	77%	<0.001
	Female	1765 AU (571 AU/cm^2)	0.88 ± 0.03	89%	81%	<0.001
	Male	2556 AU (716 AU/cm^2)	0.88 ± 0.03	84%	80%	<0.001
V_{max} > 4 m/s	Overall	2031 AU (604 AU/cm^2)	0.85 ± 0.02	83%	73%	<0.001
	Female	1765 AU (571 AU/cm^2)	0.87 ± 0.04	89%	80%	<0.001
	Male	2460 AU (689 AU/cm^2)	0.87 ± 0.03	86%	77%	<0.001

AUC values are mean ± SEM.

decrease in calculated Agatston scores, a value quite similar to those observed in Deprez et al. phantom studies.

Finally, we observed that the optimal AVC load tresholds differ when using MPG or V_{max} as opposed to the EOAi to define AS severity. Indeed, higher AVC load were associated with severe AS defined as a MPG >40 mmHg or with a V_{max} > 4 m/s than with an EOAi <0.6 cm^2/m^2. The data presented here suggest that AV considered to be severely stenotic on the basis of an EOAi <0.6 cm^2/m^2 are often less calcified and in the end probably also less severe than AV considered to be severely stenotic on the basis of MPG or V_{max}. As use of these echocardiographic cut-off values often generate inconsistent grading of the severity of AS, our study provides evidence that AVC load measurement adds incremental diagnostic value to the Doppler echocardiographic assesment of AS severity. AVC load measurement by MDCT can thus be helpful when echocardiographic examination cannot provide a conclusive diagnosis.

4.2. Clinical implications

Our observations may have important clinical implications. AVC load measurements are indeed increasingly used to confirm the severity of AS in patients presenting with difficult clinical situations, such as low flow - low gradient AS. In this respect, our study supports this approach, as AVC load appears to be an excellent surrogate marker of true AS severity. Our study nonetheless confirms that different AVC thresholds should be used for men and women even after indexation of AVC scores. It also shows that similar AVC load tresholds can be used in bicuspid and tricuspid valves, provided that the data are normalized to size of the LVOT, bicuspid valves being usually larger than tricuspid valves. Finally, because tube potential and slice thickness independently influence Agatston scores, one should be very cautious when using severity thresholds published in the literature if the scanners settings used in those studies differ from those used in his own daily clinical practice. Caution should also be exercised when interpreting the results of multicentric registries that have not standardized the image acquisition protocols across the different participating centers.

4.3. Study limitations

Our study has several limitations which should be acknowledged. Firstly, AVC score may overestimate AS severity in patients with large annuli, a limitation that can be overcome by indexing the AVC score to the LVOT cross-sectional area (AVC density). Secondly, we evaluated the morphology only in excised valves as it is difficult to accurately differentiate bicuspid from tricuspid valves in vivo by transthoracic echocardiography. Since absolute AVC load differs between bicuspid and tricuspid valves, but AVC density does not, this latter should probably be routinely used to avoid misinterpretation of calcium scores in patients in whom it is difficult to ascertain the underlying valve morphology.

5. Conclusion

The present study shows that AVC load by MDCT correlates well with hemodynamic indices of AS severity and can be used as a

helpful surrogate index of AS severity whenever the final echocardiographic diagnosis remains uncertain. Our study also shows that scanner acquisition settings, and particularly tube potential and slice thickness, need to be standardized in order to obtain reproducible and accurate results.

Acknowledgments

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Conflicts of interest

None.

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