

Aortic Valve Calcium Score as Measured by Native Vs. Contrast Enhanced Computer Tomography and the Implications for the Diagnosis of Severe Aortic Stenosis in TAVR Patients With Low Gradient Aortic Stenosis.

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Abstract

Purpose

we compared between patients with low gradient (LG) and high gradient (HG) severe aortic stenosis (AS) as regard the burden of aortic valve calcium (AVC) using different methodologies. Moreover, we evaluated the accuracy of published thresholds for the diagnosis of severe AS in both groups.

Methods

we measured the calcium volume and score using Agatston methodology in non-contrast (n-c) CT and with modified and fixed 850 Hounsfield unit (HU) thresholds in contrast enhanced (ce) CT.

Results

The medians (IQR) of Agatston score, score with 850 HU and modified thresholds were 1288 AU (750-1815), 101 (65-256), 701 (239-1632), respectively. The calcium volume in ceCT using fixed 850 HU thresholds is significantly lower than the assessed volume in ncCT or in ceCT using modifiable threshold.

LG patients were more obese; BMI 31.2 (29.1-35.1) vs 27.6 (26-31) and presented more with coronary artery disease (71.4% vs 40%). AF was documented in 42% in LG-patients vs 30% in HG patients. LVEF was severely depressed (less than 30%) in 28.6% in LG-patients. LG patients were more symptomatic (NYHA \geq III in 71.4% patients vs 42%). The LG patients had smaller anatomy: annulus diameter 23.5mm (21.5-27) vs 25mm (23-25.5), LVOT diameter 23mm (20-20) vs 25mm (23-26.7mm). The annulus geometry was more eccentric; eccentric index 0.23 (0.19-0.27) vs 0.11 (0.1-0.2). Agatston score and calcium volume were lower in patients with LG; 1641AU (1292-1990) vs 928AU (572-1284) and 1537mm³ (644-1860) vs 286mm³ (160-700), respectively. Only 20% of patients with LG had Agatston score less than the previously supposed AVC score threshold for the diagnosis of severe AS (>2000AU in men and >1200 in women). The elimination of ncCT from the protocol reduced significantly the radiation dose by 400.3 \pm 140 mGy*cm and 2.4 \pm 2.8mSv.

Conclusion

The diagnosis of severe LGAS should not depend on a single parameter as calcium score. The measurement of calcium score in contrast CT underestimate the calcium load significantly.

Introduction

Calcific aortic stenosis (AS) is often, although not solely, an age-related condition in which scarring and degeneration of the aortic valve (AV) promotes deposition of calcium within it ([Pawade, Newby et al. 2015](#)). Computer tomography (CT) is a well-established method for the quantification of aortic valve calcium (AVC). Most prior studies have used non-contrast (nc) CT to assess AVC as part of the evaluation of AS severity. The cut-off values for this purpose differed between males and females (\geq

2000 or ≥ 3000 for men and ≥ 1200 or ≥ 1600 for women (Clavel, Pibarot et al. 2014; Zamorano, Gonçalves et al. 2016). The CT protocol used in these studies was similar to that used by Agatston for calcium scoring of coronaries (Agatston, Janowitz et al. 1990). AVC not only can aid in determining the severity of AS, but also can predict prognosis in AS patients. (Clavel, Pibarot et al. 2014). These cut off values are only validated in patients with high gradient AS (HG AS) (Clavel, Messika-Zeitoun et al. 2013). Discordant AS would encompass classical low flow low gradient (cLFLG), paradoxical LFLG, normal flow LG, and also patients with mean pressure gradient (PG) > 40 mm Hg and aortic valve area index (AVAi) > 0.6 cm². Clavel and colleagues have reported that only 50% of patients with discordant AS had higher values than the cut off value. Patients with discordant AS also had a lower AVC burden (Veulemans, Piayda et al. 2021), and this group of patients accounts for approximately 30% of TAVR patients. The PG across the AV is determined not only by the AV area, but also independently by flow in the LVOT, AVC-load, and systemic arterial compliance (Clavel, Messika-Zeitoun et al. 2013). Veulemans et al. showed that CT can differentiate the severity of LG AS only in men (Veulemans, Piayda et al. 2021). This study evaluated the AVC in contrast enhanced CT (ceCT) with fixed threshold of 600 Hounsfield (HU). This fixed threshold could underestimate the calcium (Bittner, Arnold et al. 2016), especially in patients with discordant AS and low AVC burden. Even a multicenter trial only included few patients with discordant AS (161 from nearly thousand patients) (Pawade, Clavel et al. 2018). The evaluation of AVC using ceCT in patients with LG AS is therefore quite limited. Thus, we aimed to evaluate the AVC in both native and ceCT in patients with HGAS and in patients with LGAS.

Methods

2.1 Study population:

Multi-slice CT (MSCT) images from all patients who underwent TAVR in 2020 at our institution (Zentralklinik Bad Berka) were reviewed. The CT data was available and interpretable in 311 out of 340 patients. We excluded patients with valve-in-valve TAVR.

2.2 Pre-procedure cardiac CT angiography

For all patients, we analysed the MSCT images, which were performed as standard-of-care pre-TAVR. Patients were evaluated using a Siemens Somatom Definition Edge scanner (Siemens Medical Solutions) using collimation of 0.6 mm at a fixed pitch of 0.2 with an injection of 70 ml of iopamidol (Ultravist-370; Bayer Vital Pharma). A dedicated protocol was formulated, with kV and tube current modified according to the patient's size. Image acquisition for the heart was performed with retrospective ECG gating. CT Digital Imaging and Communications in Medicine (DICOM) data were analysed using Siemens syngo software, Syngo Via, for TAVR Planning.

Measurement of calcium volume

The calcium score and volume of the aortic valve and each cusp were evaluated by the specialist (ME) using three different methodologies: 1. in ncCT imaging using a threshold of 130 Hounsfield (HU), 2. in

ceCT scans using a modifiable threshold and a fixed threshold of 850 and 600. The modification of Hounsfield was used; thus, 100 HU were added to the luminal attenuation HU (Bettinger, Khalique et al. 2017), Figure 1. In patients with LG AS the cardiac output was measured to assure that stroke volume index is $\leq 35\text{ml/m}^2$.

Assessment of radiation dose

Radiation exposure was measured according to the methods previously described by Shnayien and colleagues. The dose-length product (DLP) was obtained from an automatically generated protocol that was based upon the CT dose index (CTDI) and was measured in $\text{mGy}\cdot\text{cm}$. The effective dose (E) was measured in mSv and was derived from the DLP as suggested by the European Guidelines on Quality Criteria for Computed Tomography. Thus, we used a conversion coefficient (k) of 0.017 and the following formula: $E = k \times \text{DLP}$. The size-specific dose estimates (SSDE) is given in mGy, and was determined by ... E by multiplying conversion coefficients as a function of the sum of the lateral and anteroposterior dimensions with CTDI. (Shnayien, Bressemer et al. 2020).

3. Statistical analysis

Continuous variables were tested for normality of distribution by using the Shapiro-Wilk test. Normally distributed variables were expressed as mean \pm standard deviation. For non-normally distributed variables, the median and inter-quartile range (IQR) were calculated and tested for statistical significance with the Mann-Whitney U test. Categorical variables were compared by chi-square statistics. Statistical analyses were performed with SPSS (version 24.0; IBM Corporation, Armonk, NY). A two sided $P < .05$ was considered statistically significant.

Results

The median (IQR) of BMI was 29.1 (26.2-31.2) and of BSA was 1.91 (1.75-1.93).

The medians (IQR) of Agatston score, score with 850 HU and modified thresholds were 1288 AU (750-1815), 101 (65-256), 701 (239-1632), respectively. The calcium volume in ceCT using a fixed 850 HU threshold is significantly lower than the assessed volume obtained with modifiable threshold for both ncCT or ceCT. Calcium volume with the 850 HU threshold was 101mm^3 (65-256), with the modified HU threshold was 701 (239-1632) and in ncCT 1537mm^3 (644-1860). More calcification was found in the non-coronary cusp (NCC), 300mm^3 (119-750), and in the right coronary cusp (RCC), 289mm^3 (82-550), than in the left coronary cusp (LCC), 150mm^3 (41-500). The elimination of ncCT from the protocol significantly reduced the radiation dose by $400.3 \pm 140 \text{ mGy}\cdot\text{cm}$ and $2.4 \pm 2.8 \text{ mSv}$.

LG AS patients were more obese than patients with HGAS; BMI 31.2 (29.1-35.1) vs 27.6 (26-31) and also presented more often with coronary artery disease (71.4% vs 40%). No significant difference was found as regard other patients' characteristics (see table 1). Atrial fibrillation was documented in 42% of the LG-patients vs 30% in high gradient patients. LVEF was severely depressed (less than 30%) in 28.6% of LG-

patients. The mean PG in LG was 32 mmHg (25-35 mmHg) vs 46 mmHg (42-59 mmHg). Interestingly, LG patients were more symptomatic (NYHA \geq III in 71.4% patients vs 42% of patients with high gradients).

LG patients had smaller dimensions in terms of their cardiac anatomy: annulus diameter 23.5 mm (21.5-27 mm) vs 25 mm (23-25.5 mm), LVOT diameter 23 mm (20-24 mm) vs 25 mm (23-26.7 mm). The annulus geometry of the LGAS group was more eccentric than in patients with HG AS, with an eccentricity index of 0.23 (0.19-0.27) vs 0.11 (0.1-0.2). The LVOT diameter to annulus diameter of the LGAS patients was also more conical in shape. Calcium volume and Agatston score was both lower in the LG patients; 1641 AU (1292-1990 AU) vs 928 AU (572-1284 AU) and 1537 mm³ (644-1860 mm³) vs 286 mm³ (160-700 mm³), respectively. Only 20% of patients with LG had an Agatston score higher than the published AVC score threshold for the diagnosis of severe AS.

Discussion

We report here that only 20% of severe AS patients with LG had a higher AVC volume when evaluated by MSCT than the published cutoff recommended for the diagnosis of severe AS. We also note that the mean AVC burden in this study was lower than in previously reported studies (Bittner, Arnold et al. 2016; Pawade, Clavel et al. 2018; Veulemans, Piayda et al. 2021). We included more patients with LGAS; however, even in patients with high gradient AS the calcium load was lower than in prior studies. Factors known to affect AVC burden include hyperlipidemia, diabetes, chronic kidney disease, male sex, and the presence of a LG. We included high risk patients with dyslipidemia (58%), diabetes (56.3%), and chronic kidney disease (17.6%). Thus, the risk profile in our study is comparable to that of prior studies, such as that of Aggarwal et al. In that study, the patients included had hyperlipidemia (67%), coronary artery disease (42%), and diabetes mellitus (24%), and the reported predictors of an increased AVC burden age, male sex, higher velocity, smaller aortic valve area, and smaller LVOT. Likewise, the mean aortic annulus diameter (23.5 mm) and mean aortic annulus area (485.5mm²) in our study were comparable to what Bittner, et al reported (24.2mm and 462mm², respectively). The AVC load in our patients was similar to the one in female patients with LG and in patients with AVA more than 1cm in the study of Veulemans et al, 1007 (521/1547). We found that the distribution of calcification was uneven, being more prominent in the NCC and the RCC and less so in the LCC. This is consistent with Veulemans, et al who found that in AS of all severities and etiologies AS entities, the NCC was the most calcified. Cheng et al also reported that the NCC had the most calcification and the LCC had the least calcification. (Cheng, Chang et al. 2017). In previous CT studies of TAVR, the incidence of LG AS was between 33-56% (Pawade, Clavel et al. 2018; Veulemans, Piayda et al. 2021), which is consistent with the 41.2% incidence we found. This high incidence of LG AS in TAVR patients highlights the importance of studying this entity. We demonstrate here that previously published CT-AVC thresholds are not applicable in LGAS. In keeping with our results, Pawade et al found, in a multicenter study with 918 patients, that CT-AVC thresholds (women 1377 Agatston units, men 2062 Agatston units) were accurate only in patients with HG AS but not in patients with LG AS. Furthermore, Veulemans and colleagues found that the AVC load thresholds were only useful for differentiating between moderate and severe AS in both males and females when the AS was

HG. In general, the assessment of calcium volume using the 850 HU threshold underestimates the volume of calcium. The accurate measurement of AVC is valuable as certain calcium distribution patterns may increase the risk for the need of permanent pacemaker implantation. (REF: Fujita, B 2016 Eur Heart J Cardiovasc Imaging) Thus, this

Limitations: Some of the limitations of this study are that it is a single-center study and that its design is retrospective and observational.

Conclusion

The published CT AVC threshold for the diagnosis of severe AS is suboptimal for LG AS. We need to standardize the methodology used of calcium measurement in CT before TAVR in order to determine an appropriate threshold for AS in patients with LG.

Abbreviations

AVC aortic valve calcium

AU: arbitrary unit.

AS: aortic stenosis

CT: computed tomography.

CE: Contrast enhanced.

HU: Hounsfield Units

HG: high gradient

ID: implantation depth

LVOT: left ventricle outflow track.

LG: low gradient.

NPV negative predictive value

NCC non-coronary cusp

NC non contrast

PPV positive predictive value

ROC Receiver-operating characteristic

RCC right coronary cusp

TAVR transcatheter aortic valve replacement

Declarations

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Conflicts of interest/Competing interests: the authors report no financial relationships or conflicts of interest regarding the content herein.

Availability of data and material: all data are available on request at the Department of Cardiology, Zentralklinik Bad Berka, Germany.

Code availability: not available.

Authors' contributions: MG collected the data and did the provisional drafting of the manuscript. MG, EC and TO did the statistical analysis and the interpretation of data and helped in the drafting. PL, TK and HL revised the manuscript critically and give the final approval. All authors have read and approved the manuscript.

Ethics approval and consent to participate : our analysis looked retrospectively at outcomes for a cohort of patients treated as part of routine care and is in no way an add-on for purposes of research. This was done internally as part of an audit/evaluation, to improve our quality of care.

Consent for publication Not applicable, as this study was conducted retrospectively and was done internally as part of an audit/evaluation, to improve our quality of care. This is in line with the European regulations; https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf.

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Tables

Table 1: preoperative patients` characteristics.

	HG AS	LG AS	Total	P Value
	293 (61.2%)	186 (38.8%)	479	
Female n (%)	137 (46,8%)	82 (43.9%)	219 (45.6%)	0.5
Age median (IQR)	80 (77-83)	80 (78-83)	80 (77-83)	ns
BMI	27.6 (26-31)	31.2 (29.1-35.1)	29.1 (26.2-31.2)	0.04
EUROII median (SD)	26.6 (16.8)	28.2 (7.4)	27.1 (11)	0.07
STS Score	5.1 (4.8)	9.6 (14)	6.8 (8)	0.04
DM n (%)	133 (45.5%)	96 (51.3%)	229 (47.8%)	0.2
CLD n (%)	37 (12.6%)	36 (19.3%)	73 (15.2%)	0.06
CKD n (%)	69 (23.5%)	58 (31%)	127 (26.5%)	0.07
Stroke n (%)	15 (5,1%)	17 (9,1%)	32 (6.7%)	0.07
CABG n (%)	11 (3.8%)	15 (8%)	26 (5.4%)	0.04
Atrial fibrillation	84 (28.7%)	69 (36.9%)	153 (31.9%)	0.09
NYHA III/IV n (%)	178 (60.8%)	127 (67.8%)	304 (63.5%)	0.053

BMI: Body Mass Index; HTN: hypertension; CLD: Chronic Lung Disease; CKD: chronic kidney disease; NYHA: New York Heart Association. .

Table 2: preoperative TTE and CT characteristics.

	HG AS	LG AS	Total	P Value
	293 (61.2%)	186 (38.8%)	479	
Max PG mmHg	71 (64-91)	48 (32-59)	63 (48.7-84.5)	< 0.05
Mean PG mmHg	46 (42-59)	32 (26-35)	41 (32.7-49.7)	< 0.05
AVA cm ²	0.83 (0.7-0.9)	0.7 (0.7-0.8)	0.75 (0.7-0.9)	ns
RVSP mmHg	38 (12)	50 (15)	41 (13)	< 0.05
LVEF %	54 (14)	47 (11)	51.2 (13)	ns
More than mod. MR	69 (23.3)	45 (24.2)	114 (23.8)	ns
More than mod.TR	37 (12.6)	37 (19.9)	74 (15.4)	< 0.05
Mean Annulus D (mm)	25mm (23-25.5)	23.5mm (21.5-27)	23.5 (23-26)	ns
Max Annulus D (mm)	26 (25-28)	26 (25-28)	26 (22-30)	ns
Min Annulus D (mm)	23 (20-24)	20 (19-24)	21.5 (20-24)	< 0.05
LVOT (mm)	25mm (23-26.7)	23 (20-20)	25 (22-26)	< 0.05
Eccentricity index	0.11 (0.1-0.2)	0.23 (0.19-0.27)	0.17 (0.1-0.21)	< 0.05
Annulus area (mm ²)	504 (412-510)	388.5 (332-510)	458 (394-510)	ns
Annulus perimeter (mm)	78.5 (74-83)	72 (68.2-81)	76 (73-83)	ns
MS (mm)	3 (2.5-4.9)	5 (4-5.2)	3.7 (2.6-5.1)	ns
Aortic tilting angel	44 (43-45)	44 (44-48)	44 (43-48)	ns
Calc score (Agaston)	1641(1292-1990)	928 (572-1284)	1288 (750-1815)	< 0.05
Calc score (850 HU)	254 (158-583)	86 (11-107)	141 (89-351)	< 0.05
Calc score (modified HU)	2069 (894-2477)	392.5 (216-947)	947 (384-2202)	< 0.05
AVC V (mm ³)	1537mm ³ (644-1860)	286mm ³ (160-700)	701 (239-1632)	< 0.05
AVC V (mm ³) (850 HU)	101 (65-256)	51 (8-77)	186 (114-426)	< 0.05
AVC V (mm ³) (modified HU)	1537 (649-1860)	266.5 (160-701)	701 (239-1632)	< 0.05
Calc. LCC V (mm ³) (modified HU)	220 (125/543)	33 (8/270)	150mm ³ (41-500)	< 0.05
Calc. RCC V (mm ³) (modified	500 (261/553)	34 (18/119)	289mm ³ (82-	< 0.05

HU)			550)	
Calc. NCC V (mm ³) (modified HU)	632 (262/799)	208 (111-300)	300mm ³ (119-750)	< 0.05

RBBB: right bundle branch block; LBBB: left bundle branch block; LAHB: links anterior hemiblock; PG: pressure gradient; AVA: aortic valve area; RVSP: right ventricular systolic pressure; LVEF: left ventricular ejection fraction; D: diameter; LVOT: left ventricular outflow tract; MS: membranous septum; Calc: calcification; DLZ: device-landing zone; LCC: left coronary cusp; NCC: non-coronary cusp; PPMI: permanent pacemaker implantation; RCC: right coronary cusp; AVC aortic valve calcification.

Table 3: operative and postoperative data.

	HG AS	LG AS	Total	P Value
	293 (61.2%)	186 (38.8%)	479	
THV size (mm)	27 (26-29)	26 (23-29)	26.5 (23.5-29)	<0.05
Type of THV				<0.05
Edward Sapien	174 (59.3)	111 (39.1)	285 (59.4)	
Evolut	75 (25.6)	40 (21.4)	115 (24)	
AccurateNeo	23 (7.8)	28 (15)	51 (10.6)	
Lotus	21 (7.2)	8 (4.3)	29 (6)	
30-days mortality	5 (1.7%)	3 (1.6%)	8 (1.7%)	NS
VARC Major bleeding	4 (1.4)	1 (0.5)	5 (1)	ns
Major vascular complication	8 (2.7)	8 (4.3)	16 (3.3)	ns
PPMI	49 (16.7)	32 (17.1)	68 (14.2)	ns
Acute kidney injury	36 (12.3)	32 (17.1)	68 (14.2)	ns
Non disabling cerebral stroke	6 (2)	5 (2.7)	11 (2.3)	ns

THV: transcatheter heart valve, VARC: valve academic research consortium, PPMI permanent pacemaker implantation.

Figures

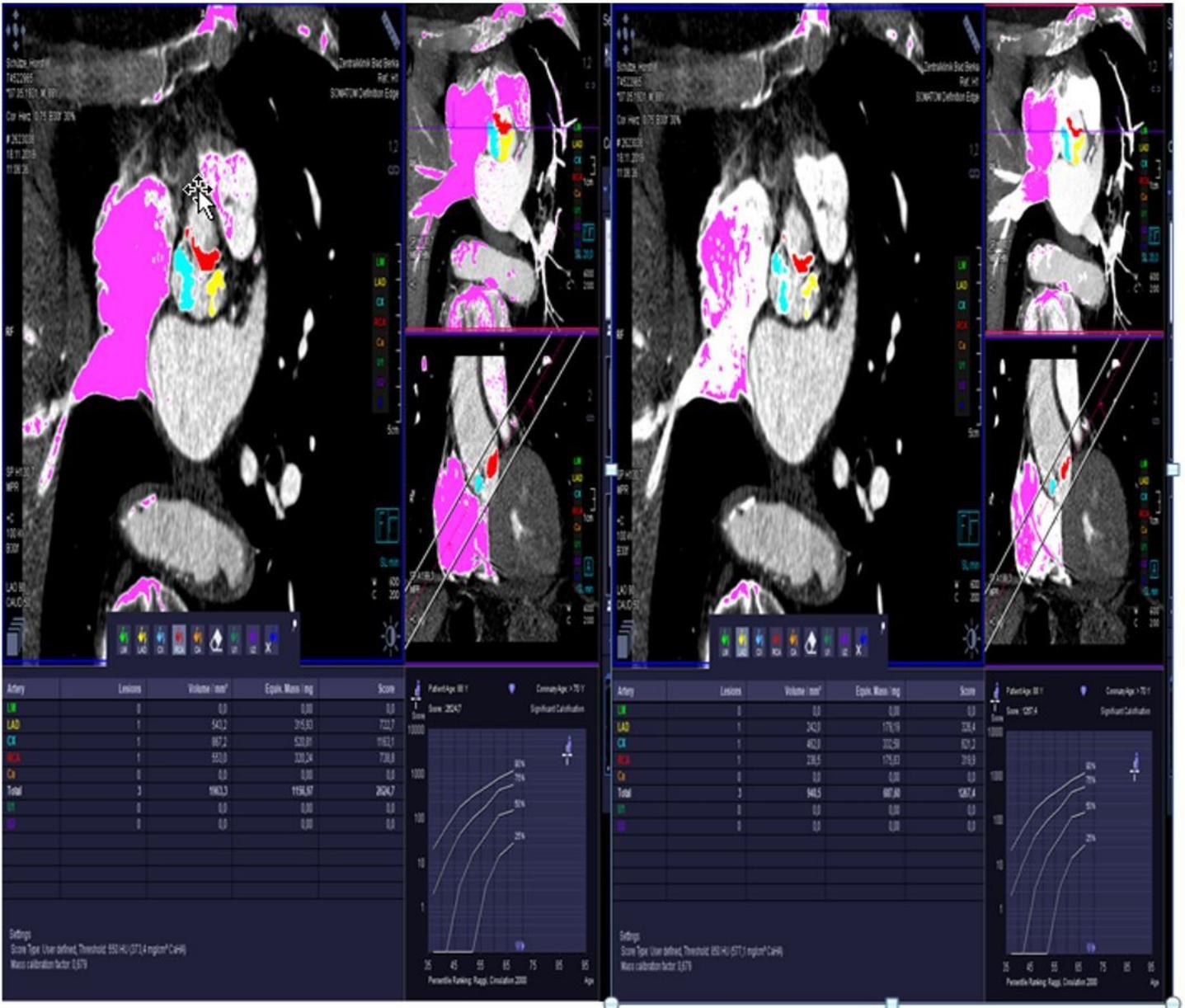


Figure 1

calcium score and volume measurement use different HU threshold leads to change the score and volume significantly (to the right with 850 HU threshold and to the left with modifiable threshold).

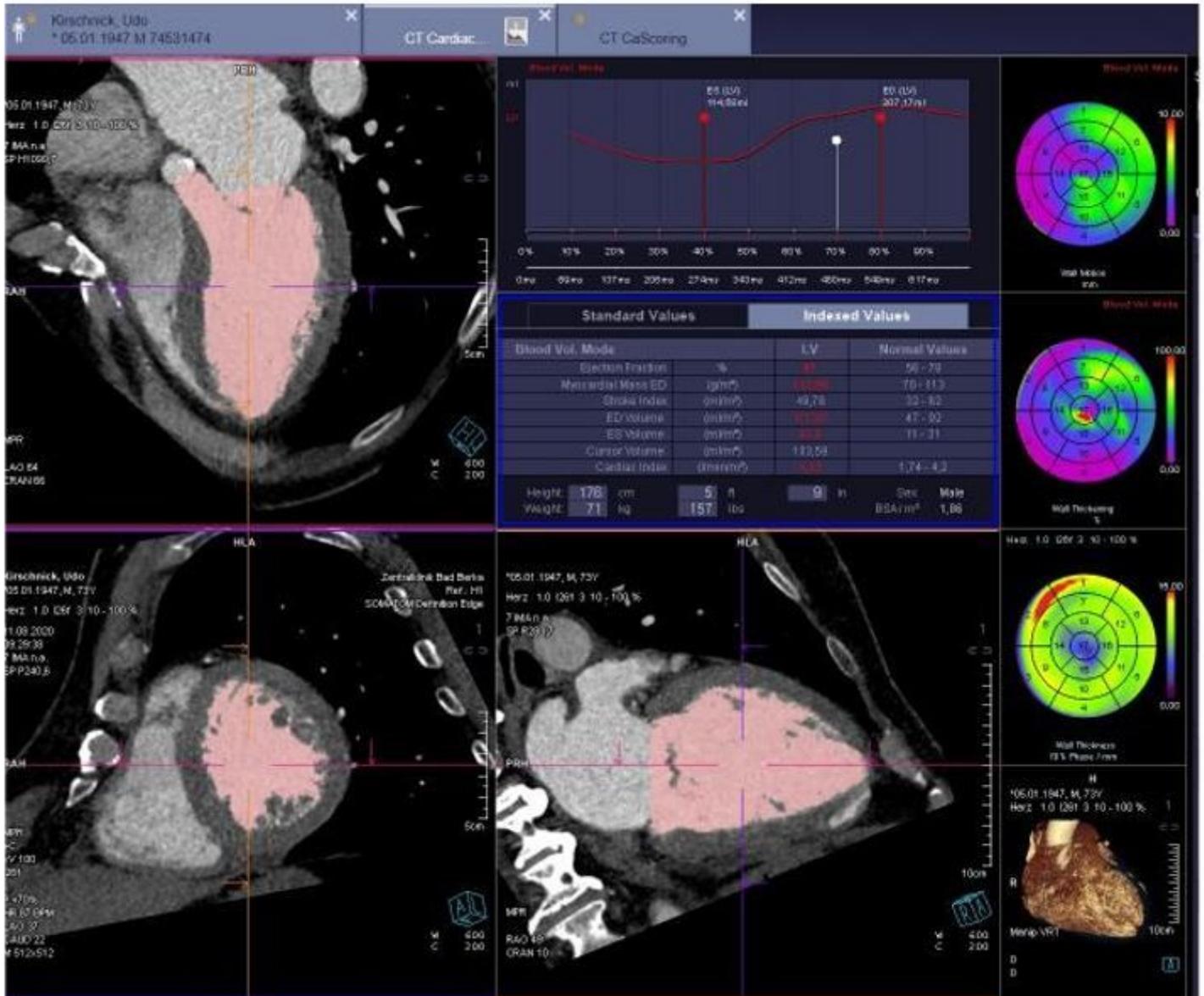


Figure 2

the use of the CT to measure the stroke volume especially in LG aortic stenosis.