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Impact of stroke volume assessment by integrating multi-detector computed tomography and Doppler data on the classification of aortic stenosis

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Background: The prevalence of low flow low gradient (LFLG) severe aortic stenosis (AS) may be overrated due to underestimation of stroke volume in two-dimensional (2D) echocardiography. The implications of 3D imaging on stroke volume calculation for AS classification have not been elucidated. Integrating multi-detector computed tomography (MDCT) and Doppler data may improve diagnostic accuracy in patients with LFLG AS.
Methods: A total of 186 patients with severe AS evaluated for transcatheter aortic valve replacement were classified according to indexed stroke volume (SVI, cut-off 35 mL/m^2) and mean transaortic pressure gradient (cut-off 40 mm Hg). SVI was calculated using a) the biplane Simpson's method, b) left ventricular outflow tract (LVOT) velocity time integral (VTI) and LVOT diameter determined by 2D echocardiography, or c) LVOT VTI and LVOT area planimetered by MDCT.
Results: SVI assessed by the biplane Simpson's method was smaller than that obtained from 2D echocardiography LVOT diameter (29.5 ± 0.6 vs 34.9 ± 0.8 mL/m^2, $p < 0.001$). The latter was smaller than SVI calculated by integrating MDCT and Doppler data (47.5 ± 1.4 mL/m^2, $p < 0.001$). LFLG and paradoxical LFLG severe AS were diagnosed in 42.5% and 27.4% of patients using the biplane Simpson's method, in 30.1% and 16.7% using 2D echocardiography LVOT diameter, and in 17.2% and 8.1% when integrating MDCT and Doppler data.
Conclusions: The prevalence of LFLG and paradoxical LFLG severe AS was overestimated by 2.5- and 3.4-fold based on 2D echocardiography alone. Integration of MDCT and Doppler data should be considered for stroke volume assessment in the classification of severe AS.

1. Introduction

Aortic valve stenosis (AS) is one of the most frequent valve diseases in the Western world [1–3]. Given the increasing prevalence of AS with the ageing population and the implementation of less invasive treatment modalities, hemodynamic evaluation of AS patients is becoming increasingly important. The assessment of aortic valve disease is mainly based on two-dimensional (2D) echocardiography, and complementary imaging modalities are applied in unclear situations. Echocardiographic diagnosis of severe AS is based on mean transaortic pressure gradient > 40 mm Hg, maximal flow velocity > 4.0 m/s, and aortic valve area (AVA) < 1.0 cm^2 or <0.6 cm^2/m^2 when indexed to body surface area (BSA) [4–7]. However, quantification of aortic valve disease may be challenging, and hybrid approaches incorporating different imaging modalities have been proposed to improve diagnostic accuracy [8,9]. Subgroups among AS patients such as those with low flow low gradient (LFLG) severe AS need to be identified based on transaortic pressure gradients, left ventricular function, and stroke volume [9,10]. Given the worse clinical outcomes of patients with low flow patterns [11–15], identification of such patients is particularly important.

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Echocardiographic determinations of stroke volume are based on the calculation of left ventricular volumes and ejection fraction by the biplane Simpson's method, or, alternatively, by measurement of left ventricular outflow tract (LVOT) diameter and velocity time integral (VTI). Suboptimal image quality and foreshortened views may hamper correct assessment by the biplane Simpson's method. Further, measurement of LVOT diameter in 2D echocardiography may be influenced by oblique views or annular calcifications, and systematic errors may occur on top of these limitations because the rather elliptical shape of the LVOT is neglected in the calculation of stroke volume [16,17]. Two-dimensional imaging has indeed been shown to underestimate the LVOT area as compared to three-dimensional (3D) echocardiography and multi-detector computed tomography (MDCT) [16,18–20]. However, the impact of 3D imaging on stroke volume calculation and its implications for AS classification has not been elucidated, yet. Underestimation of stroke volumes in 2D echocardiography may lead to an overestimation of the prevalence of patients with low flow states, and stroke volume measurements based on 3D imaging such as MDCT may improve diagnostic accuracy and affect classification of patients with AS.

The aim of this study was therefore to assess the effect of the integration of MDCT and Doppler data on stroke volume calculation in patients with severe AS, and to determine its implications for the classification of AS into different subgroups, particularly LFLG severe AS. In a complementary analysis, assessment of stroke volume was compared between 3D transesophageal echocardiography (3D-TEE) and the integration of MDCT and Doppler data.

2. Methods

2.1. Patients

A total of 186 patients with severe AS (aortic valve area [AVA] < 1.0 cm^2 or indexed AVA [AVAI] < 0.6 cm^2/m^2), who were evaluated for transcatheter aortic valve replacement (TAVR), and who underwent a comprehensive 2D echocardiographic examination including transthoracic ($n = 99$, 53.2%) or transesophageal ($n = 87$, 46.8%) echocardiography as well as an MDCT ($n = 186$, 100%) were included in the analysis. All imaging procedures were performed between February 2009 and January 2014 at the University Hospital Zurich, Switzerland. Patients with suboptimal image quality of the aortic valve and root as well as the left ventricle were excluded from the analysis. Written informed consent was obtained from all patients, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Echocardiography

Transthoracic (TTE) and TEE images were obtained in accordance with the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) and performed using commercially available ultrasound systems (Philips iE33, Philips Healthcare, Andover, MA, USA; GE Vivid 7, GE Healthcare, Milwaukee, WI, USA) and a Philips X7-2t probe for 3D-TEE imaging. Measurement of left ventricular dimensions and assessment of AS were performed according to ASE/EAE recommendations [6,21,22]. Aortic valve area was calculated using the continuity equation [6]. Classification of LFLG severe AS was performed utilizing a cut-off value of 35 mL/m^2 for SVI and 40 mm Hg for mean transaortic pressure gradient. Paradoxical LFLG included the patients with LFLG severe AS and preserved left ventricular ejection fraction (>50%) [10].

2.3. Multi-detector computed tomography (MDCT)

Multi-detector computed tomography was performed using a 128-slice dual-source computed tomography system (Somaton Definition Flash, Siemens Healthcare, Forchheim, Germany) with the following parameters: a quality reference tube current-time product of 130 mAS/rotation using automatic tube current modulation (CAREDose; Siemens), a reference tube voltage of 100 kVp using automated attenuation-based tube voltage selection (pitch 3.2, gantry rotation time 0.25 s). The reconstructed slice thickness was 0.6 mm with an increment of 0.4 mm using a soft tissue convolution kerne (Bv36) [20,23]. For image acquisition, a bolus of 45 mL Iopromide (Ultravist 300, 300 mg/mL, Bayer Schering Pharma, Berlin, Germany) was injected at a flow rate of 5 mL/s, followed by a second bolus of 35 mL at a flow rate of 2.5 mL/s. Then, 60 mL saline solution was injected at the same flow rate. Bolus tracking in the ascending aorta was performed with a signal attenuation threshold of 100 Hounsfield Units at 120 kVp.

The scan ranged from the apex of the lungs to the lesser trochanter of the femur. The start time of CT acquisition at the most cranial position of the chest was automatically calculated by the CT software in accordance to prospective ECG gating based on the previous 10 heart beats in order to time the data acquisition to arrive at the sinotubular junction at 60% of the RR-interval. Acquisition was performed without premedication, as coronary assessment was not the aim of these examinations. For quantitative analysis, the centerline of the aortic root and the ascending aorta was drawn semi-automatically (3mensio benzslicer 4.3, Bilthoven, The Netherlands). The aortic annulus was defined at the level of the lowest insertion point of each aortic leaflet. The LVOT area was planimetered 5 mm below the aortic annular plane (Fig. 1) [24].

2.4. Indexed stroke volume (SVI) calculations

Indexed stroke volume was calculated using three different methods: 1) measurement of left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes obtained from 2D-TTE or 2D-TEE images utilizing the biplane Simpson's method and indexed to BSA [SVI biplane Simpson's method = (LVEDV − LVESV) / BSA]; 2) measurement of VTI determined at the level of the LVOT and the LVOT diameter assessed in 2D-TTE parasternal or 2D-TEE three-chamber long-axis views (SVI 2D echocardiography = $\pi \times$ (LVOT diameter / $2)^2 \times$ VTI), and 3) measurement of VTI determined at the level of the LVOT (2D echocardiography) and the LVOT cross-sectional area manually planimetered in MDCT (SVI MDCT Doppler data integration = LVOT area $\times$ VTI).

For calculation of left ventricular volumes, left ventricular endocardial borders were traced on apical four- and two-chamber views [22]. LVOT diameter was measured according to the inner edge to inner edge method 5–10 mm below the aortic valve annulus in mid-systole on a parasternal or three-chamber long-axis view, and VTI was measured in apical five-chamber view with the sample volume of the pulsed wave (PW)-Doppler placed 5–10 mm below the aortic valve annulus at the level of the LVOT diameter measurement. Both LVOT diameter and VTI measurements were averaged over 3 heart beats (5 or more heart beats if the patient had atrial fibrillation). To assess potential effects of annular calcifications on LVOT area planimetry in MDCT, in the 62/186 (33.3%) patients with annular calcifications, planimetry of the LVOT cross-sectional area was compared with and without inclusion of annular calcifications.

2.5. Comparison of three-dimensional transesophageal echocardiography (3D-TEE) and multi-detector computed tomography (MDCT)

In a second group of 37 patients with severe AS undergoing TAVR, SVI was measured 1) based on the VTI determined at the level of the LVOT and the LVOT cross-sectional area manually planimetered in 3D-TEE (SVI 3D-TEE = LVOT area $\times$ VTI), and 2) in MDCT Doppler data integration as described above. In analogy to MDCT, the 3D-TEE aortic annulus was defined at the level of the lowest insertion point of each aortic leaflet, and the LVOT area was planimetered in mid-systole 5 mm below the aortic annulus plane by off-line cropping of the 3D dataset using multiplanar reconstruction planes (QLAB, Philips, Andover, MA, USA).

2.6. Intra- and interobserver variability

To assess both intra- and interobserver variability for the assessment of LVOT dimensions in MDCT and 2D echocardiography, 20 patients were randomly selected and LVOT area and diameter measured by two independent observers.

2.7. Statistics

Continuous variables are presented as mean ± standard error of the mean (SEM) or median and interquartile range (IQR), respectively. Categorical variables are given as number and percentage. The Shapiro Wilk test was used to test for normality distribution, and the Levene's test to assess the homogeneity of variance. Non-parametric variables were analyzed with related-samples Friedman's two-way ANOVA by ranks and the Wilcoxon signed-rank test, or the Mann Whitney-*U* test as appropriate. Categorical variables were analyzed by the McNemar and the Cochran's Q test. Correlations between two variables were specified by the Pearson's and the Spearman's rank correlation coefficient. Intra- and interobserver variability for the measurement of LVOT area by MDCT and LVOT diameter in 2D echocardiography is described by intraclass correlation coefficients and the percentage of the mean absolute difference using Bland-Altman analysis. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed with SPSS for Windows 21.0 (Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Median age of the patients was 82 [75–89] years (53.2% male), and the majority of patients had hypertension and coronary artery disease. Mean transaortic pressure gradient was 43 ± 1 mm Hg, with 94/186 (50.5%) patients exhibiting a mean transaortic pressure gradient of ≤40 mm Hg. LVOT area calculated in 2D echocardiography was significantly smaller than the ones determined in MDCT ($p < 0.001$). AVAI calculated by 2D echocardiography was 0.39 ±