A novel method for the assessment of valve effective orifice area using 4D flow shear layer detection method in patients with aortic stenosis

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Introduction: Valve aortic stenosis (AS) is the most common cause of valvular replacement, the severity of which is mainly evaluated by transthoracic Doppler echocardiography (TTE). In addition to interrogating peak velocities, TTE allows for the quantification of valve effective orifice area (EOA) as determined by the continuity equation [1]. In a previous study we have shown that EOA can be directly determined by 2D flow MRI velocity measurements downstream of the stenosis using the jet shear layer detection (JSLD) method, which is derived from the acoustical source term (AST) concept [2]. However, both TTE and 2D flow MRI rely on the measurement of local and single-directional velocities which results in an incomplete assessment of complex post-valve flow dynamics for a significant proportion of patients [3, 4]. 3D time-resolved phase contrast MRI with 3-directional velocity encoding (4D flow MRI) may improve EOA estimation by leveraging the advantages of the JSLD method and full volumetric coverage of ascending aortic 3D blood flow. Therefore, the objective of this study was to validate 4D flow MRI-based EOA estimation using an *in-vitro* stenosis phantom and *in-vivo* measurements of the JSLD-determined EOA, as compared to the 2D flow MR (n=50 subjects).

Methods: An *in-vitro* stenosis model (pipe Ø 33.5 ± 2.0 mm, stenosis Ø 10 ± 1.0 mm, EOA = 0.78 cm^2) filled with a blood-mimicking fluid was evaluated under steady flow (5.7 ± 0.5 L/min) for validation of the EOA technique. An *in-vivo* study included 50 participants: ten (10) healthy control subjects (5 females, age 39±11 years), 15 patients with tricuspid valves (6 females, age 58±15 years) with mild to severe AS (0.90 $cm^2 \leq$ EOA $\leq$ 3.95 cm^2) and 25 patients with bicuspid valves (6 females, age 44±11 years) with mild to severe AS (0.90 $cm^2 \leq$ EOA $\leq$ 4.56 cm^2). Evidence of aortic aneurysm and valve regurgitation was present in 73% and 58% of patients, respectively. All subjects had normal ejection fraction (>50%) and stroke volume (SV>60 ml). Imaging was performed at 1.5T and 3T (Espree, Avanto, Skyra, Siemens AG, Germany). Dynamic 2D cine imaging of the heart (steady-state free precession, flip angle=73-80, TE/TR=1.18-1.2/41-65, spatial/temporal resolution = 1.25-1.4×1.4-1.6×8 mm/29-49ms) provided a comprehensive overview over cardiac cycle of vascular morphology and valve function. Through-plane 2D phase-contrast imaging was performed in the left ventricular outflow tract (LVOT), upstream from the aortic valve annulus and in the ascending aorta (AAo) downstream from the annulus [2,3]. 4D flow MRI was acquired in a sagittal oblique 3D volume covering the thoracic aorta using prospective ECG gating and a respiratory navigator placed on the lung-liver interface [5]. Pulse sequence parameters were as follows: 1.5 T scan parameters ranged from TE/TR=2.3–3.4/4.8–6.6 ms, flip angle α=7–15° and temporal resolution=38.4–52.5 ms; the field of view was 340–400×200–300 mm, with a voxel size of 1.8–2.1×1.8–2.1×2.0–2.8 mm^3 (3 T scans used echo times=2.5 ms, repetition times=5.1 ms, flip angle α=7–15°, and temporal resolution=40.8 ms); the field of view was 400×308 mm with a voxel size of 2.1×2.1×2.4 mm^3. Velocity encoding was adjusted to minimize velocity aliasing (1.5-3.0 m/s). As a reference standard, EOA was calculated using the continuity equation ($EOA_{CE}=SV/VTI_{Ao}$, where SV is the LV stroke volume and VTI_{Ao} is the aortic velocity-time integral using 2D flow MRI). The JSLD method (EOA_{JSLD}) was employed to calculate EOA from 4D flow data by using AST($[\nabla(\omega \Lambda V)]$, where ω is vorticity and V is velocity field) to detect the post-valve jet-flow zone, i.e. EOA. Inter- and intra- variability was assessed in a subset of 15 patients by two blinded observers.

Results: The *in-vitro* test led to excellent agreement between the 4D flow derived EOA_{JSLD} = 0.78±0.02 cm^2 and the theoretical EOA = 0.79 cm^2 (obtained from potential flow theory). The *in-vivo* study showed a peak vorticity increase with AS severity (Fig 1.B). The valve EOA using 2D flow MRI and the continuity equation and correlated well with the 4D flow JSLD method (r= 0.95, p<0.001, Fig 1.C). Bland-Altman analysis between both EOA_{CE} and EOA_{JSLD} methods led to a small mean difference of -0.09±0.26 cm^2 and demonstrated good agreement (limits of agreement from 0.43 to -0.62 cm^2, Fig 1.D). Example normal and severe AS EOA_{JSLD} cases are shown in Fig 1.E. Inter-observer variability was excellent with only small absolute error of 7±6 %. Intra-observer absolute error was 2±2 % and 5±5 % for observer 1 and 2, respectively

Discussion and Conclusion: The main findings of this study were: 1) EOA_{CE} and 4D flow EOA_{JSLD} correlate and agree for the estimation of AS severity; 2) valve EOA_{JSLD} can be obtained with excellent reproducibility in patients with AS. In addition, the 4D flow JSLD method may prove useful to accurately grade aortic stenosis severity non-invasively without the need for stroke volume and the velocity-time integral, mitigating traditional sources of error when computing EOA. This is especially relevant given that AS severity assessment in elderly patients is often challenging due to the high incidence of low transvalvular pressure gradients and/or severe AS despite normal ejection fraction. This often results in the controversial "wait for symptoms" strategy to decide if a patient will undergo aortic valve repair [6,7]. In conclusion, this study showed that the EOA determined by the JSLD method can easily be obtained from 4D flow MRI measurements in aortic stenosis patients and is in excellent agreement with standard techniques. Furthermore, the proposed method may be useful for the assessment of other obstructive cardiovascular diseases (i.e. HOCM, other valves and/or aortic coarctation).

Acknowledgment: Grant support by NIH R01HL115828, NUCATS Dixon Award.

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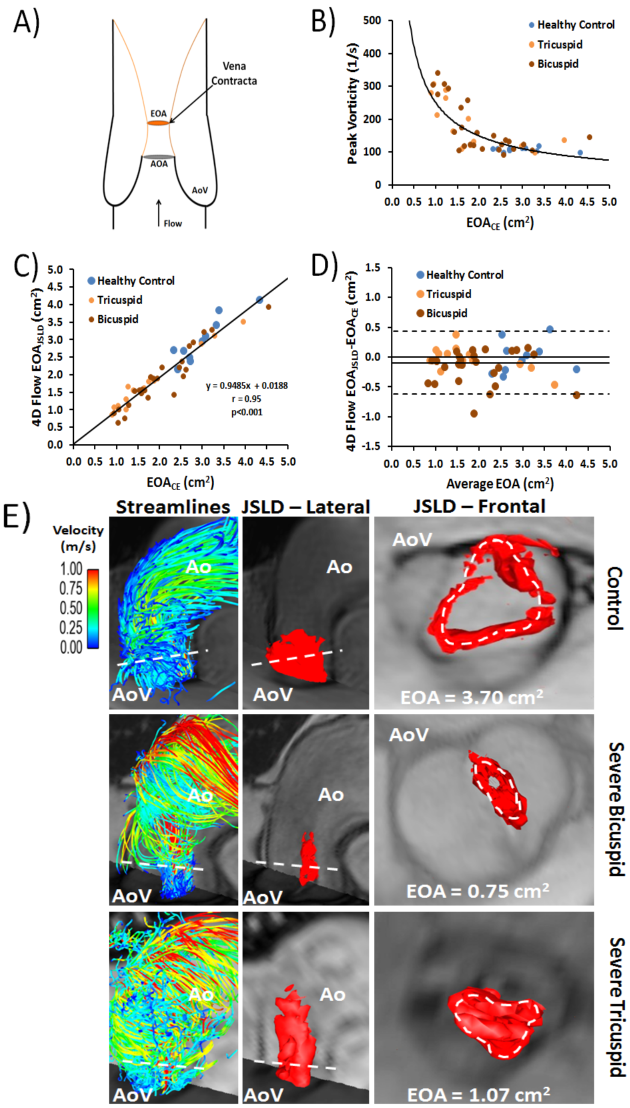

FIGURE 1: Valve effective orifice area assessment.
Panel A shows an idealized representation of transaortic valve flow separation. AOA is the anatomic orifice area and EOA is the valve effective orifice area at the vena contracta (smaller area of transvalvular flow reattachment, orange lines, and maximal velocity position), note AOA>EOA. Panel B shows the regression fit of the valve effective orifice area measured by continuity equation using 2D flow MRI (EOA_{CE}) and peak systolic vorticity. Panel C shows the regression fit of the EOA_{CE} and the 4D flow MRI EOA measured by the jet shear layer detection method (EOA_{JSLD}). Panel D shows the corresponding Bland-Altman agreement plot for both methods. Panel E shows three different cases (control, severe bicuspid and tricuspid aortic stenosis) using valve area estimation with the 4D flow jet shear layer detection method at peak systole. The first column illustrates the aortic flow velocity streamlines at peak systole; the second column shows a 3D lateral view of the acoustical source term (AST) structure, with the red iso-surface computed from 4D flow MRI data at peak systole; the third column shows a 3D frontal view of AST at peak systole. The dashed white line indicates transvalvular maximal velocity position, i.e. the vena contracta. Ao: Aorta, AoV: Aortic valve.