Usefulness of cardiovascular magnetic resonance imaging for the evaluation of valve opening and closing kinetics in aortic stenosis

Julio Garcia¹,², Philippe Pibarot¹, Romain Capoulade¹, Florent Le Ven¹, Lyes Kadem², and Éric Larose¹*

¹Quebec Heart and Lung Institute, Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, 2725 Chemin Sainte-Foy, Quebec, Canada G1V-4G5; and ²Laboratory of Cardiovascular Fluid Dynamics, Concordia University, 1515 Ste Catherine W, Montreal, Canada H3G-2W1

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Aims

The aims of this study were: (i) to determine the feasibility and reproducibility of the measurement of valve kinetic parameters by cardiovascular magnetic resonance (CMR) and (ii) to examine the association between these parameters and markers of a poor prognosis in patients with aortic stenosis (AS).

Methods and results

Eight healthy control subjects and 71 patients with AS (0.60 cm² ≤ EOA ≤ 1.90 cm²) underwent transthoracic echocardiography (TTE) and CMR. The valve opening slope (OS) and closing slope (CS) were calculated from instantaneous effective orifice area (EOA) curves obtained by CMR. Intra- and inter-observer variability were 4.8±3.9 and 5.0±4.1%, respectively, for OS, 3.8±2.9 and 4.0±3.1% for CS. OS was significantly related to the plasma level of NT-pro-brain natriuretic peptide (BNP) (r=−0.36, P=0.002), whereas the EOA or gradient were not.

Conclusion

This study demonstrates the excellent feasibility and reproducibility of CMR for the measurement of valve kinetic parameters in patients with AS. Larger studies are needed to confirm the incremental prognostic value of these new CMR parameters of aortic valve kinetics in patients with severe AS.

Keywords

Aortic stenosis • Echocardiography • Cardiovascular magnetic resonance • Aortic valve • Valve kinetics

Introduction

The valve effective orifice area (EOA) is one of the most frequently used parameters to quantify aortic stenosis (AS) severity and current ACC/AHA and ESC guidelines propose an EOA <1.0 cm² as the criteria to be utilized for the definition of severe stenosis.¹⁻² Transthoracic echocardiography (TTE) is the method generally utilized in clinical practice to measure the valve EOA and grade AS severity. Cardiovascular magnetic resonance (CMR) has emerged as a non-invasive, radiation-free accurate alternative method to measure EOA, and corroborate AS severity.³⁻⁸

Some previous TTE studies have suggested that the analysis of valve opening and closing kinetics, i.e. of the temporal changes in the EOA during systole, could provide incremental prognostic information beyond what is obtained for the standard EOA, i.e. the EOA averaged over the whole systole.⁹⁻¹³ However, the analysis of valve opening/closing kinetics by TTE is cumbersome, time consuming, and prone to measurement errors.

The objectives of this study were: (i) to determine the feasibility and reproducibility of the measurement of the valve leaflet opening/closing kinetics parameters by CMR; (ii) to identify the determinants of these parameters; and (iii) to examine the association between these parameters and markers of poor prognosis in AS: (i) the plasma level of brain natriuretic peptide (BNP) and (ii) the valvulo-arterial impedance.

Methods

Study population

Eight healthy control subjects and 71 asymptomatic patients with mild to severe AS (0.60 cm² ≤ EOA ≤ 1.9 cm²) underwent TTE and CMR
in the context of this study. Exclusion criteria were: age <21 years old, LV ejection fraction <50%, moderate or severe mitral or aortic regurgitation, poor TTE imaging quality, and standard contraindications to magnetic resonance imaging. All patients provided written informed consent to the study. The study was approved by the institutional review board.

**Clinical and laboratory data**

Clinical data included age, sex, weight, height, body surface area, body mass index, waist circumference, history of diabetes, and hypertension. Fasting blood samples were drawn to obtain NT-pro-BNP, glycaemia, insulinaemia, creatinine, and complete lipid profile using automated techniques standardized with the Canadian reference laboratory. The presence of metabolic syndrome was identified using the modified criteria proposed by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATPIII).

**Computed tomography**

Aortic valve cusp calcification was quantified by multidetector computed tomography (CT) with the use of the volumetric method that identifies calcium within the cusps as areas of at least two contiguous pixels with a density ≥130 HU.

**Transthoracic echocardiography**

TTE studies were performed and analysed by two experienced echocardiographers according to the American Society of Echocardiography guidelines and included:

1. **Valve hemodynamics:** transvalvular pressure gradients were determined by the Bernoulli formula and the valve EOA was calculated by continuity equation: 
   \[ \text{EOA}_{\text{TTE}} = \frac{\text{SV}_{\text{LVOT}}}{\text{VTI}_{\text{Ao}}} = \frac{\text{VTI}_{\text{LVOT}} \times A_{\text{LVOT}}}{\text{VTI}_{\text{Ao}}} \]
   where \( \text{SV}_{\text{LVOT}} \) is the stroke volume measured in the LV outflow tract (LVOT), \( A_{\text{LVOT}} \) is the cross-sectional area of the LVOT and \( \text{VTI}_{\text{LVOT}} \) and \( \text{VTI}_{\text{Ao}} \) are the velocity-time integrals of the LVOT and transvalvular flow, respectively. AS severity was classified on the basis of TTE-derived EOA: normal (EOA >2.0 cm\(^2\)), mild (1.5 cm\(^2\) < EOA ≤ 2.0 cm\(^2\)), moderate (1.0 cm\(^2\) < EOA ≤ 1.5 cm\(^2\)), and severe (EOA ≤ 1.0 cm\(^2\)).

2. **LV geometry:** LV end-diastolic LV internal dimension and wall thickness were measured as recommend by the American Society of Echocardiography (ASE), the LV mass was calculated using the corrected formula of the ASE and indexed to height\(^2\).\(^{16,17} \)

3. **Parameters of LV systolic function:** the LV ejection fraction was measured by the biplane Simpson method and the peak systolic wave velocity of the mitral annulus (Sa) was measured by Doppler tissue imaging.

4. **Parameters of LV diastolic function:** peak velocity of the mitral annulus E-wave (Ea) was measured by Doppler tissue imaging and the ratio of the E-wave velocity to the A-wave velocity of the mitral flow (E/A ratio) measured by pulsed wave Doppler was calculated.

5. **Parameters of arterial haemodynamics:** systemic arterial compliance (SAC) was computed with the use of the formula: 
   \[ \text{SAC} = \frac{\text{SV}}{\text{PP}}, \] where SV, is the stroke volume indexed by the body surface area and PP is the pulse pressure. Systemic vascular resistance (SVR) was also estimated with the formula: 
   \[ \text{SVR} = \frac{80 \times \text{MAP}}{\text{CO}}, \] where MAP is the mean arterial pressure and CO is the cardiac output.

6. **Parameter of global LV haemodynamic load:** valvulo-arterial impedance (Zva) was calculated with the use of the formula:
   \[ Z_{\text{va}} = \frac{(\text{SAP} + \text{MPG})}{\text{SV}_{\text{i}}}, \] where SAP is the systolic arterial pressure and MPG is the mean transvalvular pressure gradient.\(^{18} \)

**Cardiovascular magnetic resonance imaging**

CMR studies were performed in comparable haemodynamic state (heart rate TTE = 63 ± 14 bpm vs. heart rate CMR = 64 ± 11 bpm, \( P = 0.54 \)). Imaging was performed with a 1.5 Tesla Philips Achieva scanner operating release 2.6 level 3 and dedicated phased-array cardiac coil during successive end-expiratory breath-holds (Philips Healthcare, Best, The Netherlands). Cine imaging of cardiac function was performed by the steady-state-free precession technique at 30 phases per cardiac cycle (with vectorcardiographic gating) in 8–14 parallel short-axis and two-chamber, four-chamber, and two orthogonal LVOT planes (8 mm thickness, 0 mm gap) providing complete coverage. Typical parameters included TR/TE of 3.4/1.2 ms, flip angle 40°, NEX of 1, yielding in-plane spatial resolution of 1.6 × 2 mm. Three-chamber long-axis through the aortic valve and orthogonal LVOT plane view were paired for positioning three contiguous cine slices (7 mm slice thickness, 0 mm gap) centred on the aortic valve tips at the maximum systolic opening. In addition, through-plane phase-contrast imaging was performed in the LVOT at 12 mm upstream from the aortic valve annulus plane (reference: 0 mm) and in the ascending aorta (Ao) at 10 mm downstream of the annulus (Figure 1).\(^{7,8} \)

Velocity flow imaging parameters consisted of: TR/TE of 4.60–4.92/2.76–3.05 ms, flip angle 15°, 24 phases, pixel spacing 1.32–2.07 mm, slice thickness 10 mm and acquisition matrix of 256 × 208. Each phase-contrast velocity mapping acquisition produced two cine images: one magnitude image and one phase image (Figure 1).

For each patient, peak aortic jet velocity measured by TTE was used to define CMR encoding velocity (CMR encoding velocity = 1.5 × peak velocity).
jet velocity; range from 150 to 550 cm/s) to optimally define resolution and avoid signal wrap.

CMR image analysis was performed by readers blinded to clinical and TTE results. A custom-made research application was developed using the Matlab software (Mathworks, Natick, MA, USA) to process and analyse velocity-encoded images. Regions of interest (ROIs) were defined on each of the 24 phases of magnitude images to include the lumen of the LVOT and of the Ao. The following measurements were performed within each ROI on matched phase images at LVOT and Ao positions.

Flow velocities within the ROI were used to determine the changes in instantaneous peak and average velocity ($V_{\text{average}}$) in the LVOT at the $12 \text{ mm}$ position during the cardiac cycle. The instantaneous LVOT flow rate was calculated by multiplying the instantaneous $V_{\text{average}}$ by the LVOT cross-sectional area.

The peak flow velocity within the ROI was used to determine the instantaneous peak aortic velocity at the Ao position.

**Valve kinetic parameters**

To determine the temporal changes in the EOA during systole, we calculated the instantaneous EOA as follows:

$$EOA_{\text{CMR}} (t) = \frac{Q (t)}{V_{\text{max, Ao}} (t)},$$  

(1)

where $Q (t)$ is the instantaneous flow in the LVOT and $V_{\text{max, Ao}} (t)$ is the instantaneous maximal velocity of the transvalvular flow.

To characterize valve opening and closing kinetics, we calculated the following parameters (Figure 2): (i) opening slope (OS): slope of the instantaneous EOA/$t$ curve from the onset of systole to the first time point when EOA becomes $>0.9 \times$ peak systolic EOA and (ii) closing slope (CS): the slope between first time point after peak systole where EOA decreases $<0.9 \times$ peak EOA and the end of systolic phase. These parameters were expressed in cm$^2$/100 ms. Furthermore, we computed other parameters of temporal valve dynamics as proposed by Weininger et al.:

$$T85 = \left( \frac{\text{# of frames} > 0.85 \times \text{peak systolic EOA}}{\text{# of systolic frames}} \right) \times 100,$$

$$T90 = \left( \frac{\text{# of frames} > 0.90 \times \text{peak systolic EOA}}{\text{# of systolic frames}} \right) \times 100,$$

where # means : number T85 and T90 represent the percentage of systolic period spent at $>85$ and $>90\%$ of peak EOA, respectively.

To evaluate the intra- and inter-observer variability, the measurements of the valve kinetic parameters were repeated in a subset of 15 studies (11 AS and 4 control subjects) by two-blinded observers.

**Relationship between valve kinetic parameters and risk markers of adverse events**

To assess the prognostic value of valve kinetic parameters, we examined the relationship between these parameters and: (i) the plasma level of NT-pro-BNP which have been shown to predict occurrence symptoms and adverse events prior and after AVR in patients with AS; (ii) valvulo-arterial impedance ($Z_{\text{va}}$) which has been shown to be a powerful independent predictor of outcomes in patients with AS.

**Statistical analyses**

Results are expressed as mean ± SD. Comparisons between groups (mild vs. moderate vs. severe AS or tricuspid vs. bicuspid valve) were performed with the use of one-way ANOVA or Student's
Results
Seventy-one patients with mild to severe AS (64% men, age 65 ± 14 years) and eight healthy subjects (75% men, age 34 ± 8 years) were included in this study. Valve morphology was bicuspid in 24% of AS patients and 30% had a severe stenosis. The inter-group comparisons of the clinical and echocardiographic variables are presented in Supplementary data online, Table SA1. Some of the data presented in this paper have been published in two previous articles from our group.7,8 However, these previous studies included ≤45 patients and did not include the data of valve kinetic parameters.

Feasibility and reproducibility of CMR valve kinetic parameters
The measurements of valve OS, CS, T85, and T90 were feasible in all healthy subjects and AS patients (Figure 3). Intra- and inter-observer variability were 4.8 ± 3.9 and 5.0 ± 4.1%, respectively for OS, 3.8 ± 2.9 and 4.0 ± 3.1% for CS, 5.1 ± 9.6 and 7.7 ± 12.5% for T85, and 10.9 ± 18.4 and 11.38 ± 17.8% for T90. In the Bland–Altman analysis, the mean absolute difference between measurements was: (i) for OS: intra-observer: −0.04 ± 0.12 (limits of agreement from −0.28 to 0.2), inter-observer: −0.10 ± 0.17 (−0.43 to 0.24); (ii) for CS: intra: 0.01 ± 0.04 (−0.06 to 0.09), inter: −0.01 ± 0.15 (−0.3 to 0.28); (iii) for T85: intra 3 ± 6 (−10 to 15), inter: 2 ± 4 (−6 to 9); (iv) for T90: intra: 4 ± 8 (−12 to 21), inter: 1 ± 8 (limits of agreement from −16 to 16). Each valve kinetic parameter required a 1–2 min computation time after scanning and flow segmentation.

Valve kinetic parameters according to stenosis severity and valve morphology
Figure 3 shows the temporal changes in the EOA during systole for healthy control subjects as well as patients mild, moderate, and severe AS. Patients with AS had lower OS and CS compared with healthy controls (Figures 3 and 4, Supplementary data online, Table SA1). Among AS patients, the reduction in OS and CS was more pronounced in patients with more severe AS (Figures 3 and 4, Supplementary data online, Table SA1). There was no significant association between valve morphology (bicuspid vs. tricuspid) and valve opening kinetics (Figure 3 and Supplementary data online, Table SA1).

Correlates of valve kinetic parameters
OS correlated with age, parameters of LV geometry and function (LV end-diastolic internal dimension, relative wall thickness ratio, Sa-wave and Ea-wave), and parameters of AS severity (valve EOA and transvalvular gradient) (Table 1). CS correlated with age, body surface area, LV end-diastolic internal dimension, SAC, and parameters of AS severity (Table 1). T85 and T90 correlated with LV end-diastolic internal dimension and LV mass index (Table 1). OS and CS did not correlate with heart rate (r = −0.04, P = NS and r = −0.018, P = NS, respectively). There was no significant correlation between parameters of valve kinetics and the degree of aortic valve calcification measured by CT.

Discussion
The main findings of this study are: (i) The measurements of valve opening and closing kinetics can be achieved with excellent feasibility and reproducibility in patients with AS. (ii) The valve kinetic parameters correlate with conventional indices of stenosis severity as well as parameters of LV geometry and function. (iii) There is a strong association between valve OS and plasma level of NT-pro-BNP, a previously validated risk marker in AS.

Measurements of the valve EOA in AS was initially based on the assumption that the orifice area remains constant throughout LV ejection. Because during each single ejection, the transvalvular flow increases from zero, at the onset of valve opening, to a maximum and then decreases back to zero, some investigators have, however, hypothesized and then demonstrated that the EOA changes throughout ejection.9–13,26,27 Doppler echocardiography may be used to determine the instantaneous EOA at each time point in the cardiac cycle and thus calculate the rate of change in the EOA during ejection. Using this method, Bermejo et al.11 observed that AS patients with a slow valve opening rate had worse clinical outcomes than those with a rapid opening rate. In another study, the rate of change in instantaneous EOA during ejection was an independent predictor of the rate of haemodynamic progression in patients with asymptomatic AS.12 These studies suggest that the analysis of valve opening kinetics may provide incremental information regarding pathophysiology of AS, which is unrevealed by conventional indices of stenosis severity. Nonetheless, the estimation of valve kinetic parameters by TTE is cumbersome and is subject to large measurement errors, thereby explaining why this method has not been implemented in the clinical setting. Indeed, the LVOT and transvalvular jet velocities are obtained from different cardiac cycles, which do not
necessarily have the exact same time duration and haemodynamic conditions. Furthermore, the LVOT diameter is assumed to remain constant during the systolic phase, which is not necessarily true. These limitations may yield to large errors in the measurement of OS, CS, T85, and T90 by Doppler echocardiography. The present study demonstrates the usefulness, feasibility, and reproducibility of CMR to determine the temporal changes in the EOA during systole and to measure the valve OS and CS. A recent study also reported that CMR can be used to assess the dynamic changes in the EOA. The method used in this previous study was, however, different from the one (i.e. continuity equation method) proposed in the present study. Indeed, in this previous study, temporal changes in the valve EOA were derived from the systolic variations of the area of the post-stenotic turbulent flow at its smallest convergence (i.e. proximal vena contracta). From the curve of the instantaneous EOA, the authors then
calculated T85, which represents the proportion of the systolic period spent over 85% of the maximum EOA. In the present study, T85 and T90 were, however, inferior to OS to predict NT-pro-BNP levels.

The number of adverse events (n = 7) in this study was too small to directly examine the relationship between valve kinetic parameters and clinical outcomes. Nonetheless, valve OS was found to be a good predictor of the plasma level of NT-pro-BNP.

Table 1  Correlates of valve kinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Opening slope (cm²/100 ms)</th>
<th>Closing slope (cm²/100 ms)*</th>
<th>T85 (%)</th>
<th>T90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r P-value</td>
<td>r P-value</td>
<td>r P-value</td>
<td>r P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.32 0.004</td>
<td>0.43 &lt;0.001</td>
<td>−0.04 NS</td>
<td>−0.1 NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.26 0.02</td>
<td>−0.39 &lt;0.001</td>
<td>0.2 NS</td>
<td>0.21 NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic internal dimension (mm)</td>
<td>0.35 0.002</td>
<td>−0.36 0.001</td>
<td>0.19 NS</td>
<td>0.22 0.05</td>
</tr>
<tr>
<td>Relative wall thickness ratio</td>
<td>−0.35 0.003</td>
<td>0.26 0.026</td>
<td>0.03 NS</td>
<td>−0.01 NS</td>
</tr>
<tr>
<td>LV mass index (g/m².7)</td>
<td>0.01 NS</td>
<td>−0.12 NS</td>
<td>0.28 0.029</td>
<td>0.25 0.046</td>
</tr>
<tr>
<td>Sa-wave (cm/s)</td>
<td>0.37 0.001</td>
<td>−0.03 NS</td>
<td>−0.08 NS</td>
<td>−0.07 NS</td>
</tr>
<tr>
<td>Ea-wave (cm/s)</td>
<td>0.24 0.038</td>
<td>−0.16 NS</td>
<td>−0.04 NS</td>
<td>0.04 NS</td>
</tr>
<tr>
<td>Systemic arterial compliance (mL m⁻² mmHg⁻¹)</td>
<td>0.16 NS</td>
<td>−0.33 0.003</td>
<td>0.12 NS</td>
<td>0.16 NS</td>
</tr>
<tr>
<td>Mean transvalvular gradient (mmHg)</td>
<td>−0.52 &lt;0.001</td>
<td>0.33 0.004</td>
<td>−0.01 NS</td>
<td>−0.04 NS</td>
</tr>
<tr>
<td>Valve effective orifice area (cm²)</td>
<td>0.54 &lt;0.001</td>
<td>−0.51 &lt;0.001</td>
<td>0.08 NS</td>
<td>0.14 NS</td>
</tr>
</tbody>
</table>

*aPlease note that the sign of CS is negative.

Figure 4  Comparison of valve opening and closing kinetic parameters according to presence and severity of aortic stenosis. (A) Valve opening slope; (B) valve closing slope; (C) percent time spent at >85% of peak aortic valve area (T85); (D) percent time spent at >90% of peak aortic valve area (T90). *$p < 0.001$ with healthy; †$p < 0.001$ with mild.
Increased BNP or NT-pro-BNP levels have been shown to predict occurrence symptoms and adverse events prior and after AVR in patients with severe AS. Of interest in the present study, the association with this risk marker appeared to be stronger with the OS than with the conventional indices of stenosis severity (i.e., EOA and gradient). This finding may be, at least in part, related to the fact that valve OS not only reflects the valve stenosis severity per se but also the consequences of the stenosis on the LV geometry and function. As opposed to what was reported by Lim et al., NT-pro-BNP did not correlate with standard parameters of AS severity (i.e., EOA and gradients) in the present study. This may be explained, at least in part, by the differences in the study populations: the study of Lim et al. included only patients with severe AS and a large proportion of these patients were symptomatic, whereas in the present study, 30% of patients had severe AS and none had symptoms. The findings of our study also suggest that OS might be useful to identify more advanced stage of the valvular disease as well as to detect subclinical impairment of myocardial function.

Valvulo-arterial impedance has been shown to be a powerful independent predictor of adverse events in patients with AS. The lack of correlation between OS and valvulo-arterial impedance may be, at least in part, related to the fact that the impedance reflects the global LV haemodynamic burden, which includes both the valvular load and the arterial load. On the other hand, OS is a marker of the valve disease, per se, as well as its repercussion on LV function but it does not reflect the arterial load.

The assessment of valve kinetic parameters might also be useful to improve risk stratification in patients with low-flow, low-gradient AS, and reduced or preserved LV ejection fraction, but this aspect deserves further studies in this specific population.

**Study limitations**

Accurate estimation of valve kinetics is dependent on the temporal resolution which is essentially determined by sequence acquisition time. New promising fast acquisition flow sequences and hardware (i.e. parallel imaging) could help overcoming this limitation. The number of patients with AS was too small to determine the association between valve kinetic parameters and clinical outcomes.

This study included predominantly (70%) patients with mild/moderate AS. Further studies in larger series of patients with severe AS are needed to confirm the incremental prognostic value of these parameters measured by CMR.

**Conclusions**

This study shows that temporal changes in the valve EOA can easily be obtained by CMR in AS patients and that parameters of valve opening and closing kinetics can be measured with excellent feasibility and reproducibility. The valve OS correlates better with the plasma level of NT-pro-BNP than standard parameters of AS severity in this population that includes predominantly patients with mild or moderate AS. Larger studies are needed to confirm the incremental prognostic value of these new CMR-derived parameters of aortic valve kinetics, particularly in the subset of asymptomatic patients with severe AS.

**Supplementary data**

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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**Conflict of interest:** none declared.

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