# Valve opening and closing kinematic assessment in patients with aortic stenosis

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**Introduction:** Valve effective orifice area (EOA) is one of the most frequently used parameters to quantify aortic stenosis (AS) severity and current guidelines propose an EOA<1.0cm² as the criteria of severe stenosis [1, 2]. Transthoracic echocardiography (TTE) is widely used for grading AS severity. Previous studies have suggested that the analysis of valve opening and closing kinetics, i.e. of the temporal changes in 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 [3-5]. The objectives of this study were: 1- to determine the feasibility and reproducibility of the measurement of the valve leaflet opening/closing kinetics parameters by CMR; 2- to identify the determinants of these parameters; and 3- to examine the association between these parameters and two powerful predictors of prognosis in AS patients: i) the plasma level of Brain Natriuretic Peptide, and ii) a multi-parametric risk score proposed by Monin et al [6].

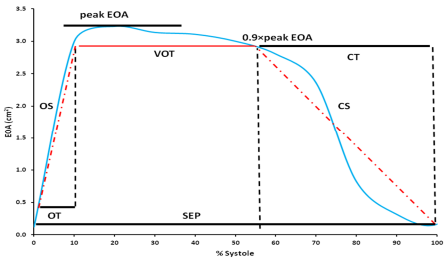


**FIGURE 1: Measurement of aortic valve opening and closing kinetic parameters by CMR.** The graph shows the temporal changes in effective orifice area (EOA) during systole, OT and OS are the opening time and slope, respectively, VOT is the valve opening time above 90% of peak EOA, SEP is the systolic ejection period and CT and CS are the closing time and slope, respectively.

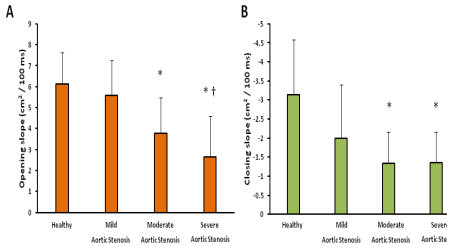


**FIGURE 2: Comparison of valve opening and closing kinetic parameters according to presence and severity of aortic stenosis.** Panel A: Valve opening slope; Panel B: valve closing slope. *: p<0.001 with healthy; †: p<0.001 with mild.

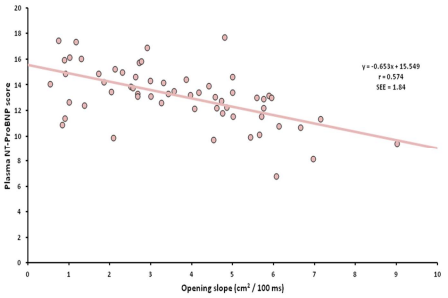


**FIGURE 3: Correlation between valve opening slope with the multiparametric risk score.**

**Methods:** Eight (8) healthy control subjects and 60 patients with mild to severe AS (0.60 $cm^2 \leq EOA \leq 1.79$ $cm^2$) underwent TTE and CMR in the context of this study. TTE measurements were performed according to the ASE guidelines [2]. CMR study was performed after TTE study with the use of a 1.5 Tesla scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands). A standard LV and aortic examination were performed for acquisition planning. In addition, through-plane phase-contrast imaging was performed in the LVOT upstream from the aortic valve annulus plane and in the ascending aorta (Ao) [7]. 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 x 208. For each patient, CMR encoding velocity (range from 150 to 550 cm/s) was optimally defined to avoid signal wrap. To determine the temporal changes in EOA during systole, we calculated the instantaneous EOA as follows: $EOA_{CMR}$ (t) = Q (t) / $Vmax_{Ao}$ (t), where Q (t) is the instantaneous flow in the LVOT and $Vmax_{Ao}$ (t) is the instantaneous maximal velocity of transvalvular flow. To characterize valve opening and closing kinetics, we calculated the following parameters (Figure 1): i) Opening slope (OS): slope of the instantaneous EOA/t curve from onset of systole to the first time point when EOA becomes > 0.9× peak systolic EOA and ii) Closing slope (CS): slope between first time point after peak systole where EOA decreases below 0.9×peak EOA and the end of systolic phase. These parameters were expressed in $cm^2$/100ms. The intra- and inter- observer variability was performed in a subset of 15 studies by two blinded observers. To assess the prognostic value of valve kinetic parameters, we examined the relationship between these parameters and: 1) the plasma level of NT-Pro BNP; 2) a multi-parametric risk score proposed by Monin et al [6]. This score was calculated with the use of the formula: Score=[peak aortic jet velocity (m/s)×2]+[natural logarithm of NT-ProBNP(pg/ml)×1.5]+1.5 (if female gender).

**Results:** Sixty patients with mild to severe AS (65% men, age 64±15 years) and eight healthy subjects (75% men, age 34±8 years) were included in this study. Valve morphology was bicuspid in 27% of AS patients. The 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. Patients with AS had lower OS and CS compared to healthy controls (Figures 2). Among AS patients, the reduction in OS and CS was more pronounced in patients with more severe AS. There was no significant association between valve morphology (bicuspid vs. tricuspid) and valve opening kinetics. OS correlated with age, parameters of LV geometry and function (Table 1). CS correlated with age, body surface area, LV end-diastolic internal dimension and parameters of AS severity (Table 1). OS was significantly related to the plasma level of NT-proBNP (r=-0.35; p=0.006; Table 2), whereas valve EOA or transvalvular gradient were not. On multivariate analysis, after adjustment for these variables and EOA, reduced OS was the sole factor independently associated with higher plasma levels of NT-proBNP (Table 2). Among clinical, TTE, and CMR parameters, OS was the one providing the best correlation (r=-0.57, p<0.001) with the multi-parametric risk score proposed by Monin et al., (Figure 3).

**Discussion and Conclusion:** The main findings of this study are: 1) The measurement of valve opening and closing kinetics can be achieved with excellent feasibility and reproducibility in patients with AS. 2) The valve kinetic parameters correlated with conventional indices of stenosis severity as well as parameters of LV geometry and function. 3) There was a strong association between valve OS and well-established risk markers. The number of adverse events 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 plasma level of NT-proBNP and of the multi-parametric risk score which was found to be a powerful predictor of clinical outcomes in asymptomatic patients with severe AS. Of interest in the present study, the association with these risk markers appeared to be stronger with the OS than with the conventional indices of stenosis severity (i.e. EOA and gradient). The assessment of valve kinetic parameters might also be useful to differentiate pseudo- versus true- severe AS and 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. In conclusion, this study demonstrates the excellent feasibility and reproducibility of CMR for the measurement of valve kinetic parameters in patients with AS. The OS appears to compare favorably with conventional indices of stenosis severity to predict risk of poor prognosis.

**TABLE 1.** Correlates of valve kinetic parameters.

| | Opening slope ($cm^2$/100ms) | | Closing slope ($cm^2$/100ms)* | |
|---|---|---|---|---|
| | r | p-value | r | p-value |
| Age (years) | -0.31 | 0.011 | 0.44 | <0.001 |
| Body surface area ($m^2$) | 0.21 | NS | -0.36 | 0.004 |
| Left ventricular end-diastolic internal dimension (mm) | 0.32 | 0.009 | -0.36 | 0.003 |
| Relative wall thickness ratio | -0.32 | 0.011 | 0.21 | NS |
| LV mass index (g/$m^{2.7}$) | 0.01 | NS | -0.12 | NS |
| Sa-wave (cm/s) | 0.35 | 0.005 | -0.06 | NS |
| Mean transvalvular gradient (mmHg) | -0.51 | <0.001 | 0.34 | 0.004 |
| Valve effective orifice area ($cm^2$) | 0.54 | <0.001 | -0.53 | <0.001 |

*Please note that the sign of CS is negative.

**TABLE 2.** Univariate and multivariate determinants of plasma NT-ProBNP levels.

| | Univariate Analysis | | | Multivariate Model 1 | | | Multivariate Model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| Correlates | β coeff±SE | r | p-value | β coeff±SE | r | p-value | β coeff±SE | r | p-valu |
| Age (years) | 0.031 ± 0.008 | 0.441 | <0.001 | 0.019 ± 0.009 | 0.263 | 0.06 | 0.019 ± 0.01 | 0.266 | 0.06 |
| Left ventricular mass index (g/$m^{2.7}$) | 0.031 ± 0.013 | 0.323 | 0.016 | 0.017 ± 0.012 | 0.174 | NS | 0.017 ± 0.012 | 0.178 | NS |
| E/Ea ratio | 0.086 ± 0.028 | 0.288 | 0.027 | 0.014 ± 0.04 | 0.046 | NS | 0.014 ± 0.041 | 0.045 | NS |
| Systemic arterial compliance (mL.$m^{-2}$.$mmHg^{-1}$) | -1.087 ± 0.399 | -0.337 | 0.008 | -0.773 ± 0.393 | -0.232 | 0.06 | -0.767 ± 0.399 | -0.23 | 0.06 |
| Effective orifice area ($cm^2$) | -0.531 ± 0.489 | -0.141 | NS | - | - | - | -0.079 ± 0.549 | -0.021 | NS |
| Opening slope ($cm^2$/100ms) | -0.187 ± 0.066 | -0.351 | 0.006 | -0.172 ± 0.062 | -0.313 | 0.008 | -0.165 ± 0.079 | -0.3 | 0.04 |

**Legend:** The log transform of NT-proBNP was used for this analysis. Multivariate Model 1 includes only variables that were significantly (p<0.05) associated with plasma BNP levels on univariate analysis. Multivariate Model 2 includes the same variables and valve effective orifice area. β coeff: regression coefficient β; SE: standard error.

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**References:** 1. Bonow RO et al. Circulation 2008; 118(15):e523-661. 2. Baumgartner H et al. JASE 2009; 22(1):1-23. 3. Arsenault M et al. JACC 1998;32(7):1931-7. 4. Beauchesne LM J et al. JASE 2003; 16(9):958-64. 5. Lester SJ et al. Circulation 2000; 101(16):1947-52. 6. Monin JL et al. Circulation 2009; 120(1):69-75. 7. Garcia J et al. JCMR 2011; 13(1):25.