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Impact of Pre-Intervention Transaortic Flow Rate Versus Stroke Volume Index on Mortality Across the Hemodynamic Spectrum of Severe Aortic Stenosis

Implications for a New Hemodynamic Classification of Aortic Stenosis

Transvalvular flow rate (FR), which is stroke volume divided by left ventricular ejection time (in milliliters per second), is physiologically likely to be a better marker of transvalvular flow in patients with severe aortic stenosis (AS) compared with stroke volume index (SVi), a traditional marker of flow, as the former represents ejection flow and the latter ejection volume. It has previously been shown that pre-intervention FR can predict mortality in patients with low gradient severe AS beyond SVi (1). However, the value of pre-intervention FR across the severe AS population, irrespective of gradient status, is unknown. We aimed to assess the relative value of transvalvular FR versus SVi before aortic valve intervention for the prediction of mortality in patients with severe AS.

We prospectively collected the data from retrospectively conducted echocardiographic examinations in 774 patients with aortic valve area (AVA) <1 cm^2 who underwent aortic valve intervention between 2010 and 2014. The outcome assessed was time to all-cause mortality. Receiver-operating characteristic curve analysis with endpoint mortality at 1 year was used to identify the best cutoff value of FR from the maximum sum of sensitivity and specificity. Kaplan-Meier survival curves and log-rank p values were used to evaluate the impact of specific variables on mortality. Univariate and multivariate Cox regression analyses were performed to identify predictors of mortality.

The mean patient age was 73.1 ± 12 years, with low left ventricular ejection fraction (LVEF) (<50%) in 164 patients (21.2%). Almost all patients (723 of 743 [97.2%]) were symptomatic (New York Heart Association functional classes II to IV). The mean AVA was 0.71 ± 0.17 cm^2, and the mean aortic valve gradient was 46.3 ± 16.4 mm Hg. The mean LVEF, SVi, and FR were, respectively, 58.9 ± 12.3%, 38.8 ± 10.2 ml/m^2, and 216.9 ± 52 ml/s.

During a median follow-up period of 3.66 years (interquartile range: 2.55 to 4.93 years), 144 deaths (18.6%) occurred. Among age, clinical risk factors, New York Heart Association class, resting LVEF, AVA, mean gradient, left ventricular mass index, left ventricular ejection time, European System for Cardiac Operative Risk Evaluation II score, concurrent coronary artery bypass grafting, and type of and time to aortic valve intervention, FR was an independent predictor of mortality (hazard ratio [HR]: 0.99; 95% confidence interval [CI]: 0.98 to 0.99; $p = 0.005$), whereas SVi was not (HR: 0.98; 95% CI: 0.94 to 1.01; $p = 0.06$), when the 2 were assessed in separate models containing the same variables to avoid collinearity. When patient risk was assessed in a hierarchical manner with addition of SVi to a baseline model containing clinical risk factors, LVEF, AVA, mean gradient, operative parameters, and left ventricular ejection time, the global chi-square statistic did not change (from 108.07 to 109.4, $p = 0.23$). In contrast, the addition of FR changed the chi-square statistic significantly from 108.07 to 117.03 ($p = 0.005$). Furthermore, the significance was retained even when FR and SVi were added to the baseline model (**Figure 1A**).

The receiver-operating characteristic curve indicated an optimal cutoff of rest FR at 211 ml/s (area under the curve = 0.704, $p < 0.005$, with sensitivity of 74% and specificity of 56%). The study population was divided into 4 groups according to flow and gradient (cutoffs of 211 ml/s and 40 mm Hg, respectively). In the normal-flow, high-gradient group, 33 of 292 patients (11.3%) died, as opposed to 19 of 126 patients (15.1%) with normal-flow,

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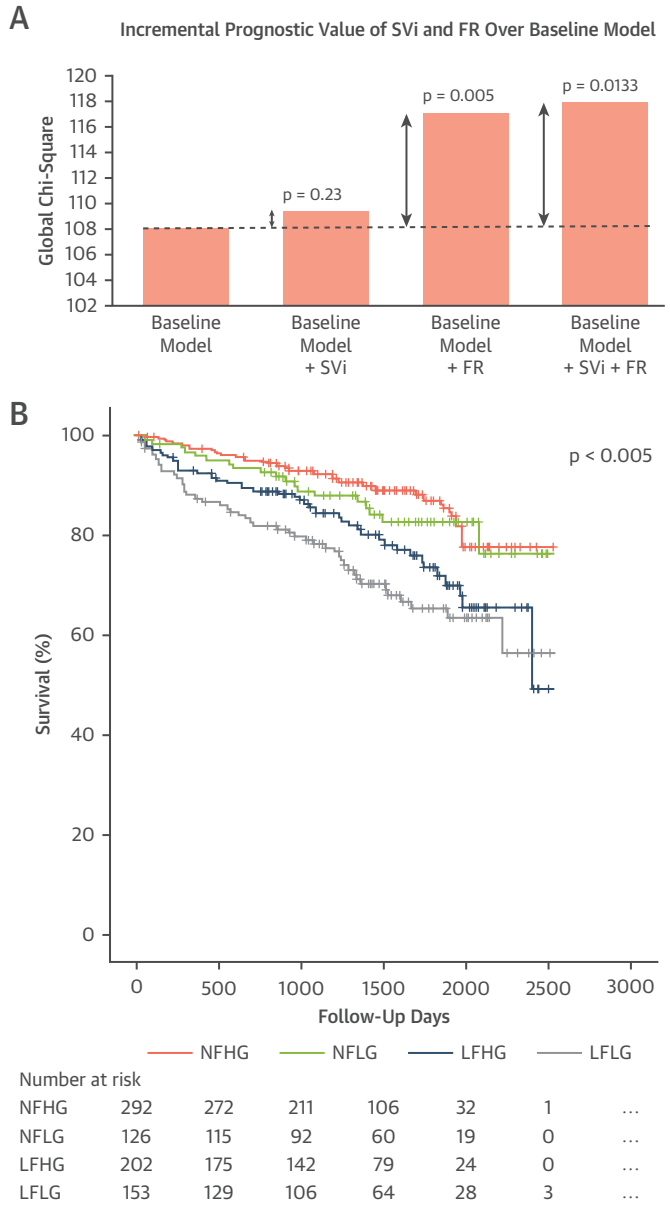
FIGURE 1 Incremental Prognostic Value of Flow Rate Over Baseline Model and Severe Aortic Stenosis Stratification Based on a Flow Rate of 211 ml/s and a Mean Gradient of 40 mm Hg



(A) Flow rate (FR) showed incremental value ($p = 0.005$) when added to a baseline model including standard clinical, operative, and echocardiographic variables for assessment of patient risk, whereas stroke volume index (SVi) did not ($p = 0.23$) (global chi-square values on y axis). **(B)** The low-flow, low-gradient (LFLG) group had the worst survival, followed by the low-flow, high-gradient (LFHG) group and the normal-flow groups (log-rank $p < 0.005$).

low-gradient AS, 45 of 202 patients (22.3%) with low-flow, high-gradient AS, and 47 of 153 patients (30.7%) with low-flow, low-gradient (LFLG) AS ($p < 0.005$). The unadjusted Kaplan-Meier survival curves of the different FR and mean gradient groups are shown in Figure 1B (log-rank $p < 0.005$). There was no difference in mortality between LFLG patients with LVEFs <50% (classical LFLG AS) (19 of 54 patients [35.2%] died) and LFLG patients with LVEFs >50% (paradoxical LFLG AS) (28 of 99 patients [29.3%] died) ($p = 0.24$). FR and gradient classification of AS independently predicted mortality beyond the clinical risk factors, LVEF, and procedural parameters (HR: 1.21; 95% CI: 1.08 to 1.36; $p = 0.002$), whereas SVi and gradient classification did not (HR: 1.13; 95% CI: 0.99 to 1.27; $p = 0.06$).

This study extends previous observations that pre-operative assessment of FR can predict mortality following aortic valve intervention beyond clinical risk factors, LVEF, and SVi in patients with predominantly symptomatic severe AS to both the low- and high-gradient AS groups. Forward transaortic flow (FR), physiologically, is a better determinant of tissue perfusion than LVEF or stroke volume, which are surrogate markers of cardiac efficiency but an inadequate determinant of tissue perfusion. Furthermore, this study also shows for the first time that flow-gradient classification by FR predicted outcome beyond the clinical risk factors and left ventricular systolic function following aortic valve intervention.

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