Rationale and design of SAVI-AoS: A physiologic study of patients with symptomatic moderate aortic valve stenosis and preserved left ventricular ejection fraction

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Abstract

Background: Moderate aortic valve stenosis occurs twice as often as severe aortic stenosis (AS) and carries a similarly poor prognosis. Current European and American guidelines offer limited insight into moderate AS (MAS) patients with unexplained symptoms. Measuring valve physiology at rest while most patients experience symptoms during exertion might represent a conceptual limitation in the current grading of AS severity. The stress aortic valve index (SAVI) may delineate hemodynamically significant AS among patients with MAS.

Objectives: To investigate the diagnostic value of SAVI in symptomatic MAS patients with normal left ventricular ejection fraction (LVEF ≥ 50%): aortic valve area (AVA) > 1 cm² plus either mean valve gradient (MG) 15–39 mmHg or maximal aortic valve velocity (AOV max) 2.5–3.9 m/s. Short-term objectives include associations with symptom burden, functional capacity, and cardiac biomarkers. Long-term objectives include clinical outcomes.

Methods and results: Multicenter, non-blinded, observational cohort. AS severity will be graded invasively (aortic valve pressure measurements with dobutamine stress testing for SAVI) and non-invasively (echocardiography during dobutamine and exercise stress). Computed tomography (CT) of the aortic valve will be scored for calcium, and hemodynamics simulated using computational fluid dynamics. Cardiac biomarkers and functional parameters will be serially monitored. The primary objective is to see how SAVI and conventional measures (MG, AVA and Vmax) correlate with clinical parameters (quality of life survey, 6-minute walk test [6MWT], and biomarkers).

Conclusions: The SAVI-AoS study will extensively evaluate patients with unexplained, symptomatic MAS to determine any added value of SAVI versus traditional, resting valve parameters.

Abbreviations: 6MWT, 6-minute walking test; AOV max, Maximal aortic valve velocity; AS, Aortic stenosis; AVA, Aortic valve area; CCS, Canadian Cardiovascular Society; IQR, Interquartile range; KCQ-QOS, Kansas City Cardiomyopathy Questionnaire Overall Score; LV, Left ventricle/ventricular; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; MAS, Moderate aortic stenosis; MG, Mean valve gradient; MDCT, Multi-detector computed tomography; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SAVI, Stress aortic valve index; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation/replacement.

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1. Introduction

Moderate aortic stenosis (AS) occurs twice as often as severe AS with a prevalence of 2.2% versus 1.1%, respectively [1]. A common misconception suggests that moderate AS (MAS) imparts a more favorable outcome than severe AS, but survival rates at one and five years of approximately 90% and 75% appear quite similar in both groups [1] Current European and American guidelines mainly focus on patients with severe AS, with little attention to MAS, especially with unexplained symptoms [2,3].

The indication for contemporary aortic valve intervention for symptomatic AS relies on a resting assessment, whereas the majority of patients experience symptoms during exertion. This potential discordance between resting evaluation and exercise symptomatology represents a conceptual inconsistency in grading AS severity [4]. We hypothesize that routine valvular stress testing might identify symptomatic patients with moderate AS at rest who would benefit from earlier intervention. Our prior mechanistic study demonstrated that resting assessments of AS severity cannot reliably predict stress conditions, and that many valves (both severely stenotic and after TAVI) do not behave like an orifice, as required for valve area calculations [5]. Furthermore, reliance on resting AVA carries additional limitations due to poor correlation with symptom burden, LV remodeling, and variable prognosis, even when less than the commonly used 1 cm² cutoff [6,7]. Consequently, we proposed the stress aortic valve index (SAVI) to quantify hemodynamics under stress conditions and provide an objective, relative measure of peak flow reduction due to valvular obstruction that could be corrected with device therapy [5,8].

Thus the goal of this study is twofold. First, it aims to compare both invasive and non-invasive SAVI against traditional resting valve metrics in relation to symptom burden, functional capacity, and biomarkers in patients with MAS and unexplained symptoms. Second, this study will observe associations with clinical outcomes related to valvular disease between both SAVI and standard resting indices. We hypothesize that low SAVI (more marked AS during stress) will demonstrate a stronger correlation with symptom burden and will identify patients with a worse prognosis.

2. Methods

The SAVI-AoS study is a multicenter, non-blinded, observational trial. Each center will include patients with MAS and unexplained cardiac symptoms with a preserved left ventricular ejection fraction. The main endpoint will be measured at 1 year follow-up, after which the follow-up period extends to a total of 5 years. Ethical approval is required at each center and written informed consent from every subject. The study has been prospectively registered (clinicaltrials.gov NCT04514250).

2.1. Study population

Symptomatic patients with MAS are eligible for the study if meeting these inclusion criteria: age ≥ 50 years; MAS defined as an aortic valve area (AVA) > 1 cm² plus either AOV max of 2.5–3.9 m/s or MG 15–39 mmHg confirmed in the 3 months prior to enrollment by standard echocardiographic evaluation; and ability to undergo exercise stress testing. A detailed description of in- and exclusion criteria can be found in Table 1.

2.2. Study protocol

2.2.1. Screening

Symptoms will be assessed using the Canadian Cardiovascular Society (CCS) classification of angina pectoris, New York Heart Association (NYHA) classification of heart failure, and the presence of unexplained (pre)syncope. In MAS patients with such symptoms and no apparent alternative cause, invasive cardiac catheterization is justified according to contemporary guidelines to exclude a mischaracterization of valve severity. Eligible patients will be asked for written informed consent, which can be obtained before the clinical cardiac catheterization. If significant coronary artery disease is found, then the subject will be reported as screen failure.

Table 1

| Inclusion and exclusion criteria. |
|----------------------------------|
| 1. Hemodynamic criteria for aortic valve stenosis |
| AVA > 1 cm² |
| EITHER peak velocity 2.5–3.9 m/s OR mean gradient 15–39 mmHg |
| Exclusion: any of AVA ≤ 1 cm², peak velocity ≤ 4 m/s, or mean gradient ≥ 40 mmHg |
| Demographic criteria |
| Able to provide informed consent |
| Age ≥ 50 years |
| Able to undergo exercise testing (sub study) |
| Life expectancy ≥ 2 years |
| Alternative explanation for symptoms (exclusions) |
| PCI or CABG in past 3 months or near future |
| Impaired LVEF < 50% |
| Severe concomitant valvular disease (severe AI or MR, for example) |
| COPD GOLD 3 or 4, home oxygen dependency or ≥ 2 pulmonary inhalers (stable COPD GOLD 1 or 2 is permitted) |
| Important pulmonary hypertension (systolic pulmonary artery pressure > 50 mmHg) |
| Right ventricular dysfunction (defined by standard echocardiographic criteria) |
| Anatomic exclusion criteria |
| Unicuspid, bicuspid or non-calcified aortic valve |
| Hypertrophic cardiomyopathy or septal hypertrophy > 15 mm |
| Hemodynamically important intracardiac shunt (Qp/Qs > 2) |
| Contraindication for testing (exclusions) |
| Acute coronary syndrome in past 6 weeks |
| Unvascularized and severe coronary artery disease |
| Persistent atrial fibrillation with uncontrolled ventricular response (>100 beats/ min) |
| Prior adverse reaction to dobutamine |
| eGFR ≤ 30 mL/min or dialysis |
| Severe iodine contrast allergy |

ACS: acute coronary syndrome. AI: aortic insufficiency. AS: aortic stenosis. ASD: atrial septal defect. AVA: Aortic Valve Area. CABG: coronary artery bypass grafting. COPD: chronic obstructive pulmonary disease. eGFR: estimated glomerular filtration rate. GOLD: Global Initiative for Chronic Obstructive Lung Disease. LVEF: left ventricular ejection fraction. MR: mitral regurgitation. PCI: percutaneous coronary intervention. VSD: ventricular septal defect.
transthoracic echocardiography will measure non-invasive pressure gradients over the aortic valve for comparison, and blood pressure will be monitored non-invasively using a sphygmomanometer to calculate SAVI according to the formula provided in the next section. After the protocol is finished, the pressure wire will be pulled back to the guiding catheter to check for drift.

2.2.3. Stress echocardiography

A substudy in selected patients will include stress ergometry using a supine bike with simultaneous echocardiography. (Fig. 1: Panel B) Predicted target heart rate and workload will be determined in advance based on age, sex, and height. A 12-lead electrocardiogram will be recorded during exercise to determine the heart rate and monitor for ST-segment or rhythm changes. After standard baseline images, the stress protocol will be started at 25 Watt with incremental workload of 25 Watt every 2 min [12]. At each stage, the aortic valve gradient will be evaluated by echocardiography and the blood pressure will be measured. In some centers, estimated central aortic pressure can be obtained additionally by mathematical transformation of radial tonometry pressure [13]. The patient will continue until symptoms or limiting fatigue develops, severe gradients are measured (e.g. mean aortic gradient 60–80 mmHg, maximal aortic velocity 5.0–5.5 m/s), or the cardiologist terminates the protocol according to other standard indications. Offline aortic valve mean pressure gradients (ΔP) will be traced and SAVI calculated as \( \frac{1}{1 + \Delta P / \text{systolic blood pressure}} \) as per the supplemental appendix of our previous publication [5].

2.2.4. Cardiac computed tomography scan

A baseline cardiac MDCT scan with ECG-gating capability will be used to calculate the valvular calcium score, which correlates with aortic stenosis severity (and is recommended by European guidelines) and can evaluate aortic valve and LVOT anatomy. (14) For aortic valve calcium scoring, the Agatston method will be used: a calcium score of > 2000 AU in men and > 1200 AU in women suggests more severe AS [15]. At least one full heart beat will be recorded to measure systolic and diastolic parameters. This scan will be used to simulate pressure gradients non-invasively by computational fluid dynamics as part of a substudy. (Fig. 1: Panel C) At 1 year the valvular calcium score will be reimaged for comparison with the baseline measurement.

2.3. Endpoints

The primary endpoint is the correlation of baseline clinical parameters (quality of life survey [KCCQ-OS], 6MWT, and biomarkers) with SAVI and each of MG, AVA, and AOV max.

Secondary endpoints will include correlations between invasive and noninvasive SAVI measurements to explore whether stress assessment of the aortic valve can be evaluated non-invasively or whether it requires invasive hemodynamic measurement for acceptable precision. The same will be done with the cardiac CT scans that will be analyzed to see whether computational fluid dynamics can accurately simulate invasive SAVI. Other objectives will compare SAVI with standard AS indices for quality of life (KCCQ-OS), functional status (6MWT), cardiac biomarkers

Fig. 1. Panel A: invasive setup for SAVI measurements. Ao: Aorta. LV: left ventricle. Panel B: Supine ergometer stress set-up. Panel C: computed tomography based computational fluid dynamics analysis. LA: left atrium. Asterisk: pressure sensor.
(NT-pro B-type natriuretic peptide, high sensitivity cardiac troponin), and CT aortic valve calcium score.

Additionally SAVI will be compared against standard indices of AS for a composite clinical endpoint of hospital admission for heart failure, angina or syncope, arrhythmia (atrial fibrillation, ventricular tachycardia), valvular intervention (SAVR, TAVI, balloon valvuloplasty), death of any cause, and cardiac death.

2.4. Follow-up

Subjects will be followed for a period of 5 years after enrolment. A 1-year follow-up will be done during an outpatient visit. Follow-up thereafter can occur via the electronic medical record, by telephone, or in person depending on local circumstances. During the follow-up interview, subjects will be asked about clinical events, functional capacity, medications, and symptoms of angina and heart failure. Clinical events will not be centrally adjudicated. Existing quality databases or electronic medical records, if applicable, can be leveraged for this study to track subjects after enrollment. A flowchart of these study parameters and investigations can be found in Fig. 2.

2.5. Data analysis

Echocardiographic and CT images will be analyzed by experienced cardiac imagers and radiologists. An analyses of images and invasive hemodynamics will be performed by a central core lab blinded to other study results. An overview of echocardiographic and CT parameters for analysis is shown in Table 2.

2.6. Statistical analysis

At baseline, patient and imaging characteristics will be summarized using standard descriptive statistics. The primary outcome correlate valve metrics (like SAVI, AVA, mean gradient, and maximal velocity) with baseline clinical parameters (KCCQ-QS quality of life, functional status via a 6MWT, biomarkers of cardiac stress, and aortic valve calcium scoring). We anticipate a continuous, direct relationship between valve severity and worse clinical parameters (for example, lower SAVI will likely correlate with more valve calcium). The Pearson correlation coefficient will quantify the strength of this association for each valve metric and each clinical parameter and can be presented as a 4x5 matrix of correlation coefficients (4 valve metrics and 5 clinical parameters). Furthermore, we hypothesize that SAVI will display weak correlations with traditional valve metrics (AVA, mean gradient, and maximal velocity), indicating that stress conditions provide additive information. In order to examine discordant cases further, McNemar analysis will stratify each baseline clinical parameters into 4 groups based on SAVI and 1 traditional valve metric using binary thresholds. Due to the exploratory nature of this study and lack of impact on treatment, no adjustments will be made for multiple statistical testing.

To investigate the relationship between clinical outcomes related to valve metrics (SAVI, AVA, mean gradient, and maximal velocity), a survival analysis will be conducted. Assuming that tests for proportional hazards are met during the 1-year period (using both visual inspection of

Table 2

| Transthoracic echocardiographic and CT parameters | At baseline | 12 months – 5 years FU |
|-----------------------------------------------|------------|-----------------------|
| Transthoracic echocardiogram                  | X          | X                     |
| DSE                                           | X          | X                     |
| BSE                                           | X          | X                     |
| Coronary angiography incl. SAVI measurements   | X          | X                     |
| Cardiac CT (full cycle; AVA; LVOT anatomy)    | X          | X                     |
| Aortic valve calcium scoring                   | X          | X (*)                 |
| Biomarker profile (troponin; BNP)             | X          | X                     |
| Quality of life (KCCQ)                        | X          | X                     |
| 6-minute walking test                          | X          | X                     |

DSE: dobutamine stress echo. BSE: bike stress echocardiography. FU: follow up. LVOT: left ventricular outflow tract. CT: computed tomography. KCCQ: Kansas City Cardiomyopathy Questionnaire. AVA: aortic valve area * aortic valve calcium scoring is once repeated at year one.

Fig. 2. study flowchart. CAD: coronary artery disease. 6MWT: six-minute walk test. KCCQ: Kansas City Cardiomyopathy Questionnaire. SAVI: stress aortic valve index.
the event curves and Schoenfeld residuals), both univariate and multi-variable Cox models will examine time to first cardiac hospital admission (e.g. heart failure, angina, syncope), valvular intervention (TAVI, SAVR, or balloon valvuloplasty), new-onset arrhythmia (atrial fibrillation or ventricular arrhythmia), or all-cause death (both cardiac and non-cardiac). Multivariable models will include SAVI plus 1 traditional valve metric from among AVA, mean gradient, and maximal velocity. All valve metrics will be studied both as continuous parameters and also binary variables (using SAVI = 0.70, mean gradient = 30, maximal velocity = 3.5, and AVA = 1.5 for thresholds). In order to examine discordant cases further, McNemar analysis will stratify 1-year binary events into 4 groups based on SAVI and 1 traditional valve metric using binary thresholds.

Additionally, we will compare SAVI physiology and methodology (invasive versus non-invasive, both using dobutamine) using Bland-Altman analysis. The percentage of subjects with SAVI < 0.7 will inform the design of a future outcomes trial targeting this potentially higher risk subgroup. We anticipate that a two-dimensional scatterplot of SAVI (Ao/LV during dobutamine) versus Ao/LV at baseline will show a large and unpredictable heterogeneity of response, as we have already demonstrated for severe [5] and low-gradient aortic stenosis [8]. Finally, we will perform a Bland-Altman analysis to compare invasive SAVI against SAVI simulated from the cardiac CT scans using computational fluid dynamics.

The sample size is calculated with the primary goal of this study in mind: to document the association between SAVI and baseline clinical parameters. In our prior publication [6], SAVI had a stronger correlation coefficient (r = 0.831) than resting AVA (r = 0.555) with the peak flow reduction due to the stenotic valve. We assume that symptoms, as reflected in the baseline clinical parameters (KCCQ), are mainly associated with this reduction in flow. In order to detect a 0.831–0.555 = 0.276 differential correlation, a sample size of 100 subjects is necessary. Additionally, to refine the estimate of the prevalence of low SAVI in moderate AS, defined by resting AS measurements, we assume that symptoms, as reflected in the baseline clinical parameters (KCCQ), are mainly associated with this reduction in flow. In order to detect a 0.831–0.555 = 0.276 differential correlation, a sample size of 100 subjects is necessary. Additionally, to refine the estimate of the prevalence of low SAVI in moderate AS, defined by resting AS measurements, we assume that symptoms, as reflected in the baseline clinical parameters (KCCQ), are mainly associated with this reduction in flow. In order to detect a 0.831–0.555 = 0.276 differential correlation, a sample size of 100 subjects is necessary.

3. Results

The baseline characteristics and results from the first 10 enrolled patients can be found in Table 3. Per study inclusion criteria, all patients had a normal ejection fraction and were symptomatic. At baseline, the mean echocardiographic MG was 26 mmHg, AVA was 1.4 cm^2 and AoV max was 3.4 m/s. The echocardiographic MG matched the invasive MG of 25 mmHg. The mean baseline aortic/LV ratio (resting conditions) was 0.82. Based on prior publications [5,8] this indicates non-severe AS at rest. However, after the administration of dobutamine, the average SAVI was 0.67, indicating severe AS under stress conditions (<0.7 as per our previous work). (5)The baseline aortic calcium score for males was 1766 AU (IQR 1285 to 2374) and for females 1679 AU (IQR 937 to 1775) and the individual calcium scores associated with the presence of severe, as well as non-severe AS.

4. Discussion

Mild-to-moderate aortic stenosis (MAS) may have a similar effect on long-term clinical outcomes as severe AS (1), and symptomatic MAS patients often have no alternative explanation for their symptoms. It is therefore reasonable to question whether the current categorization framework for AS adequately captures the clinically important factors that determine symptom status and adopt stress physiology for the assessment of symptomatic MAS. SAVI offers a new and validated metric

### Table 3: Baseline characteristics and results.

| Characteristic                        | Summary (n = 10) |
|--------------------------------------|-----------------|
| Age (years)                          | 76.8 ± 5.4      |
| Male                                 | 6 (60%)         |
| Ejection fraction (%)                | 10 (100%)       |
| Normal (>50%)                        | 10 (100%)       |
| Risk factors                         | Hypertension    |
|                                      | 10 (100%)       |
| Dislipidaemia                        | 7 (70%)         |
| Diabetes mellitus                    | 3 (30%)         |
| Cardiac history                      | Prior myocardial infarction |
|                                      | Prior PCI       |
|                                      | Prior CABG      |
|                                      | 2 (20%)         |
| Cerebral vascular disease            | 1 (10%)         |
| Peripheral vascular disease          | 1 (10%)         |
| COPD                                 | 1 (10%)         |
| Atrial fibrillation                  | 4 (40%)         |
| Permanent pacemaker                  | 1 (10%)         |
| Symptoms                             | Angina          |
|                                      | 3 (30%)         |
| Heart failure (NYHA II or higher)    | 8 (80%)         |
| Syncope                              | 1 (10%)         |
| Baseline KCCQ                        | 59.1 ± 27.4     |
| 6-minute walk test (m)               | 311.9 ± 106.1   |
| Cardiac biomarkers                   | Troponin (ng/L) |
|                                      | NT-pro B-type natriuretic peptide (pg/mL) |
|                                      | 318.0 [186-1155.5] |
| Aortic valve hemodynamics and other echocardiographic parameters |  |
| AVA (cm²) by continuity              | 1.4 ± 0.3       |
| Echo mean aortic valve gradient (mmHg) | 26.0 ± 5.6     |
| Echo peak aortic valve velocity (m/s) | 3.41 ± 0.34    |
| Stroke volume index (mL/m²)          | 50.9 ± 8.8      |
| Dimensionless index rest             | 0.35 ± 0.07     |
| Invasive mean aortic valve gradient (mmHg) | 25.3 ± 8.9     |
| Baseline aortic/LV pressure ratio    | 0.82 ± 0.06     |
| Peak dobutamine aortic/LV pressure ratio (SAVI) | 0.67 ± 0.09   |
| Diastolic dysfunction grade II or higher | 2 (20%)         |
| Aortic valve anatomy by CT           | Calcium score baseline (AU) |
|                                      | M: 1766         |
|                                      | (1285–2374)     |
|                                      | F: 1679 (937–1775) |

AVA: aortic valve area. CABG: coronary artery bypass grafting. COPD: chronic obstructive pulmonary disease. KCCQ: Kansas City Cardiomyopathy Questionnaire. LV: left ventricular. NT: N-terminal. PCI: percutaneous coronary intervention. SAVI: stress aortic valve index. Values are N (%), mean ± SD, or median (IQR) as appropriate. AU: Agatston Units. TTE: trans thoracic echocardiography. M: male. F: female.

to quantify the reduction in peak flow induced by the stenotic valve and hence the potential for device therapy to improve physiology. SAVI-AoS is an observational study designed to understand the clinical potential for an alternative perspective in many MAS patients. Ongoing but distinct studies for patients with low-gradient AS include ROTAS (NCT03667365), looking at preserved LVEF ≥ 50% but an intermediate AVA = 0.8–1.0 cm^2, TAVR UNLOAD (NCT02661451), looking at reduced LVEF < 50% with MAS and heart failure, PROGRESS (NCT04889872) and Expand TAVR II Pivotal Trial (NCT05149755), looking at symptomatic MAS with LVEF ≥ 20% and > 20%, respectively. SAVI has been designed to help improve clinical decision making with respect to intervention (Fig. 3).

4.1. Limitations

A limitation of this study is that it is not powered for clinical outcomes as its primary endpoint. An overview of the first ten study subjects is provided in Table 3.
5. Conclusions

The SAVI-AoS study will evaluate whether “valvular stress testing” in patients with symptomatic moderate aortic stenosis (MAS) may identify patients who might benefit from earlier aortic valve intervention, to be tested in subsequent clinical trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101063.

References

[1] G. Strange, S. Steward, D. Celermajer, D. Prior, G.M. Scalia, T. Marwick, M. Iton, M. Joseph, J. Codde, D. Playford, Poor Long-Term Survival in Patients With Moderately Aortic Stenosis, J Am Coll Cardiol. 74 (15) (2019) 1851–1863.

[2] H. Baumgartner, V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, et al., ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease, Eur Heart J. 38 (36) (2017 Sep 21) 2739–2791.

[3] C.M. Otto, R.A. Nishimura, R.O. Bonow, B.A. Carabello, J.P. Erwin, F. Gentile, H. Jneid, E.V. Krieger, M. Mack, C. McLeod, P.T. O’Gara, V.H. Rigolin, T.M. Sundt, A. Thompson, C. Toly, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation. 143 (5) (2021), https://doi.org/10.1161/CIR.0000000000000923.

[4] P. Das, H. Rimington, N. Smeeton, J. Chambers, Determinants of symptoms and exercise capacity in aortic stenosis: A comparison of resting haemodynamics and valve compliance during dobutamine stress, Eur Heart J 24 (2003) 1254–1263.

[5] Johnson NP, Zelis JM, Tomino PAL, Houthuijsen P, Bouwman RA, Brueren GRG, et al. Pressure gradient vs. flow relationships to characterize the physiology of a severely stenotic aortic valve before and after transcatheter valve implantation. Eur Heart J 2018 Jul 21;39(28):2646-2655.

[6] P. Mehrotra, K. Jansen, T.C. Tan, A. Flynn, J.W. Hung. Clinical features and prognosis of patients with isolated severe aortic stenosis and valve area less than 1.0 cm2, Heart 104 (3) (2018) 222–229.

[7] P. Mehrotra, K. Jansen, T. Tan, A. Flynn, S. Elmariah, M. Picard, J. Hung, Prognosis of Patients With Isolated Severe Aortic Stenosis: Are Outcomes Similar for All Patients With an Aortic Valve Area Less Than 1.0 cm2, J Am Coll Cardiol Elsevier BV 61 (10) (2013) E1937, https://doi.org/10.1016/S0735-1097(13)61937-3.

[8] J.M. Zelin, P.A.L. Tomino, D.T. Johnson, P. Balan, G.R.G. Brueren, I. Wijnbergen, R. L. Kirkeeide, N.H.J. Fijls, K.L. Gould, N.F. Johnson, Stress Aortic Valve Index (SAVI) with Dobutamine for Low-Gradient Aortic Stenosis: A Pilot Study, Struct Heart 4 (1) (2020) 53–61.

[9] D. Lu, R. Little, Q. Malik, D.J. Fernicola, M.D. Greenberg, N.J. Weissman, Accelerated dobutamine stress testing: Safety and feasibility in patients with known or suspected coronary artery disease, Clin Cardiol 24 (2) (2001) 141–145.

[10] J.A. San Román, R. Sanz-Ruiz, J.R. Ortega, M. Pérez-Paredes, M.J. Rollán, A. C. Muñoz, F. Segura, D. Jimenez, A. Camero, M. Pinedo, R. Arnold, I. Gómez, F. Fernández-Avilés, Safety and Predictors of Complications with a New Accelerated Dobutamine Stress Echocardiography Protocol, J Am Soc Echocardiogr 21 (1) (2008) 53–57.

[11] M. Shehata, Accelerated dobutamine stress testing: Feasibility and safety in patients with moderate aortic stenosis, Egypt Heart J 67 (6) (2015) 107–113.

[12] B. Redfors, P. Pibarot, L.D. Gillam, D. Burkhoff, J.J. Bax, B.R. Lindman, R. O. Bonow, P.T. O’Gara, M.B. Leon, P. Garencier, Stress Testing in Asymptomatic Aortic Stenosis, Circulation. 135 (20) (2017) 1956–1976.

[13] C.-H. Chen, E. Nevo, B. Fetics, P.H. Pak, F.C.P. Yin, W.L. Maughan, D.A. Kass, Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure, Validation of generalized transfer function. Circulation. 143 (5) (2021), https://doi.org/10.1161/CIR.0000000000000923.

[14] M.A. Clavel, D. Mesika-Zeitoun, P. Pibarot, S.R. Aggarwal, M. Macalou, P.A. Aroz, H.I. Michelenka, C. Caeff, E. Lausse, R. Capoulade, A. Vahanian, M. Enriquez-Sarano, The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study, J Am Coll Cardiol 62 (24) (2013) 2329–2338.