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Factors influencing dyspnea occurrence in patients with moderate and severe aortic stenosis

Short title: Factors influencing dyspnea occurrence in aortic stenosis

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INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease, particularly prevalent in the geriatric population, with calcific sclerosis affecting 40% of individuals over 75 years old and an overall prevalence of 10% in that age group [1, 2]. Approximately half of patients are asymptomatic at the time of severe AS diagnosis despite meeting echocardiographic criteria,

leading to delays in appropriate surgical treatment [3]. The paradigm of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) procedures shifts constantly, as recent studies demonstrate the feasibility of alternative access routes for TAVI [4] and SAVR [5] as well as, contradictory to the previous evidence, a benefit from performing percutaneous coronary intervention before a TAVI [6]. Each change to TAVI and SAVR procedures may require modified qualification criteria, as different factors affect the outcomes of each procedure [7]. Research on predictive factors for AS symptoms is limited, as only a few studies have been published on this topic [8, 9]. This study aimed to investigate the clinical parameters that predict the occurrence and the degree of severity of dyspnea in patients with AS.

METHODS

The study population consisted of 226 patients diagnosed with moderate or severe aortic stenosis and hospitalized between 2019 and 2024 at a single tertiary referral hospital. All considered hospital admissions were elective and all patients were admitted while in stable condition. The indication for each considered hospitalization was either the routine angiographic assessment of coronary heart disease or the diagnostic workup for qualifying for TAVI or SAVR procedures. All analyzed data were acquired retrospectively from the patients' electronic records.

Patients admitted due to acute coronary syndrome, with chronic obstructive pulmonary disease, non-degenerative aortic pathology, severe multivalvular heart disease, or any past surgical intervention involving the aortic valve were excluded from the study. The presence of any diagnosed or suspected congenital heart defect, except for the bicuspid aortic valve, also constituted an exclusion criterion. This study has been approved by the Local Bioethics Committee (No.118.0043.1.77.2024 from March 21, 2024).

The occurrence of dyspnea, angina (during the month before the admission) and syncope (during the year before the admission), as well as the presence of comorbidities and used medications (listed in Table 1), were assessed on the first day of hospitalization for each patient. Dyspnea severity was assessed using the New York Heart Association (NYHA) classification. N-terminal pro-B-type natriuretic peptide levels were measured in 169 patients. 180 patients underwent routine coronary angiography during their hospitalization. A reduction of >75% of the luminal diameter found in any of the main coronary arteries or their main branches was considered critical coronary stenosis.

Each patient underwent one routine echocardiographic examination by an experienced cardiologist during the first week of considered hospitalization. Basic echocardiographic parameters, namely aortic valve area (AVA), maximal aortic valve velocity (V_{max}), mean and maximal aortic valve pressure gradients ($AVPG_{mean}$ and $AVPG_{max}$), left ventricular ejection fraction, stroke volume (SV), left ventricular internal dimension at end-diastole (LVIDd), left ventricular posterior wall diameter at end-diastole, left atrium area and interventricular septum thickness at end-diastole, were measured for each patient. Cardiac output was measured in 222 patients, peak velocity of early diastolic transmitral flow (E) in 182 patients and peak velocity of early diastolic mitral annular motion (E') in 181 patients. For detailed measurement descriptions, see Supplementary material, *Table S1*. The cut-off for severe aortic stenosis was defined as either AVA <1 cm^2, V_{max}>4m/s, or $AVPG_{mean}$ >40 mm Hg [10]. The severe stenosis group was further divided into 4 categories depending on the $AVPG_{mean}$, left ventricular ejection fraction, and indexed stroke volume values (Supplementary material, *Figure S1*).

Categorical variables were compared using Pearson's χ^2 test. Data normality was assessed by the Shapiro–Wilk test. NYHA classes treated as ordinal variables were correlated with quantitative parameters using Spearman's rank correlation. The Student t-test or Wilcoxon rank sum test was used for two-group comparisons, and either one-way ANOVA or Kruskal–Wallis test was used for multiple-group comparisons. The multivariable regression models were chosen using the stepwise selection process. The threshold for statistical significance of all tests was set at P <0.05.

RESULTS AND DISCUSSION

This study included 226 patients with a median age of 77 years. As shown in Table 1, Severe AS was present in 84.1% of all patients. Dyspnea occurred in 75.5% of patients, angina in 51.3% and syncope in 14.6%.

In patients with dyspnea, AVA (P = 0.008) and SV (P = 0.04) values were lower, and age was higher (P = 0.001) than in the patients without dyspnea (Table 1). When comparing the dyspnea severity between high-gradient AS category vs. combined low-gradient AS categories (LG-NF, pLG-LF and cLG-LF), severe dyspnea was significantly more prevalent in the combined low-gradient categories (NYHA I–II: 59% vs. 39.5%; NYHA III–IV: 41% vs. 60.5%; P = 0.04). Greater NYHA class was correlated with higher age (P <0.001), higher N-terminal pro-B-type natriuretic peptide (P = 0.001), lower E' (P = 0.01), and lower AVA (P = 0.003) (Supplementary material, *Table S2*). Individual comorbidities were not associated with higher dyspnea prevalence.

Uni- and multivariable logistic regression models with the occurrence of dyspnea (NYHA II–IV) as the dependent variable were specified using the demographic and selected echocardiographic parameters (Supplementary material, *Table S3*). Significant parameters achieved after the stepwise selection were age (P <0.001; OR, 1.07; 95% CI, 1.03–1.10), $AVPG_{mean}$ (P = 0.01; OR, 1.28; 95% CI, 1.06–1.57) and LVIDd (P = 0.01; OR, 1.65; 95% CI, 1.16–3.06).

Decreased AVA, SV, and E', as well as increased LVIDd and $AVPG_{mean}$, were associated with the occurrence of dyspnea. AVA was the echocardiographic parameter most strongly correlated with dyspnea severity. Although increased aortic valve pressure gradient correlates with worse clinical outcomes of AS, irrespective of symptoms [11], we have found that in patients with severe dyspnea, the low-gradient categories were more common than the high-gradient category.

This is a retrospective study with all its inherent limitations. Complete echocardiographic parameters were not always available, which limits the possibility to assess other factors contributing to the symptoms, such as diastolic function and pulmonary hypertension. The study population was relatively small and heterogeneous, with a substantial prevalence of confounding comorbidities. As the study based on documentation records, it only included symptoms which can be assessed reliably from this source. Fractional flow reserve measurement was not performed in a substantial number of patients with coronary artery disease, therefore the cut-off for plausible significant lesion was set to 75%.

Narrowed aortic value leads to the pressure overload of the left ventricle and pulmonary vascular congestion, reflected by the increased transvalvular gradients during systole and increased filling pressure of the left ventricle during the diastole [12], with the latter being already linked with a dyspnea presence by an increased E/E' ratio in two different studies [8, 9].

The assessment of cardiac hemodynamics and symptomatic presentation can be used for the prognostic risk stratification in patients with AS [13, 14]. This study was focused on patients' characteristics prior to the potential TAVI or SAVR procedures. How the observed associations between dyspnea and echocardiographic parameters change after those procedures may be a subject of further research.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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Table 1. Quantitative and qualitative parameters in relation to dyspnea occurrence

Variable	Total n = 226[a]	Dyspnea		*P*-value
		Yes n = 171	No n = 55	
Age, years old	77 (69–83)	78 (70.5–83.5)	73 (65.5–79.5)	0.001
BMI, kg/m^2	28.4 (5)	28.4 (5.2)	28.4 (4.5)	0.73
NT-proBNP, pg/ml (n=169)	1613 (420.0–3345.0)	1800 (535.0–4060.0)	1154.5 (315.8–2299.0)	0.03
Sex				
Male	116 (51.3%)	87 (50.9%)	29 (52.8%)	0.93
Female	110 (48.7%)	84 (49.1%)	26 (47.3%)	
Syncope	33 (14.6%)	27 (15.8%)	6 (10.9%)	0.50
Angina	116 (51.3%)	93 (54.4%)	23 (41.8%)	0.14
NYHA class				
I	55 (24.3%)	-	-	-
II	76 (33.6%)	-	-	-
III	75 (33.2%)	-	-	-
IV	20 (8.8%)	-	-	-
Medications				
Beta-blockers	161 (71.2%)	121 (70.8%)	40 (72.7%)	1

Diuretics	141 (62.4%)	107 (62.6%)	34 (61.8%)	0.97
ACEi/ARB	127 (56.2%)	93 (54.4%)	34 (61.8%)	0.47
Statins	144 (63.7%)	112 (65.5%)	32 (58.2%)	0.38
Calcium channel blockers	62 (27.4%)	20 (11.7%)	43 (78.2%)	0.14
Critical CS (n = 180)	46 (25.6%)	33 (19.3%)	13 (23.6%)	0.85
Moderate AS	36 (15.9%)	20 (11.7%)	16 (29.1%)	0.002
Severe AS	190 (84.1%)	151 (88.3%)	39 (70.9%)	
AS category (n=190)				
cLG-LF	19 (10%)	18 (10.5%)	1 (1.8%)	0.004
pLG-LF	15 (7.9%)	10 (5.8%)	5 (9.1%)	
HG	147 (77.4%)	114 (66.7%)	33 (60%)	
LG-NF	9 (4.7%)	9 (5.3%)	0 (0%)	
Diabetes mellitus	87 (38.5%)	65 (38.0%)	22 (40.0%)	0.79
Prior MI	35 (15.5%)	25 (14.6%)	10 (18.2%)	0.69
Smoking history	33 (14.6%)	45 (26.3%)	17 (30.9%)	0.65
Arterial hypertension	187 (82.7%)	142 (83.0%)	45 (81.8%)	1
Stroke/TIA	28 (12.4%)	22 (12.9%)	6 (10.9%)	0.70
PCI	62 (27.4%)	48 (28.1%)	14 (25.5%)	0.84
AF	75 (33.2%)	59 (34.5%)	16 (29.1%)	0.46
CKD	104 (46.0%)	83 (48.5%)	21 (38.2%)	0.18

Dyslipidemia	140 (61.9%)	112 (65.5%)	28 (50.9%)	0.052
AVA, cm^2	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.8 (0.6–1.1)	0.008
AVAi, cm^2/m^2	0.4 (0.3–0.5)	0.4 (0.3–0.4)	0.4 (0.4–0.6)	0.02
$AVPG_{mean}$, mm Hg	46.1 (34.2–57)	46.6 (35–57.7)	42.4 (29.7–52.1)	0.08
$AVPG_{max}$, mm Hg	73.7 (58.4–92.2)	74.4 (60.9–95)	68.7 (50.3–86.1)	0.08
LVEF, %	55 (49.3–60)	55 (49.5–60)	55 (49–63.5)	0.36
LA Area, cm^2	26 (22.5–31)	25.9 (22.6–31.4)	26 (22.4–29.8)	0.69
LVIDd, cm	4.8 (4.4–5.2)	4.9 (4.5–5.3)	4.7 (4.3–5.1)	0.17
LVPWd, cm	1.1 (1–1.2)	1.1 (1–1.2)	1.1 (1–1.2)	0.34
IVSd, cm	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.2 (1.1–1.4)	0.23
SV, ml	71 (54.7–88)	70.6 (23.9)	78.6 (26.5)	0.04
SVi, ml/m^2	39.1 (12.8)	38.1 (12.6)	42 (13.2)	0.05
E, m/s (n = 182)	0.9 (0.7–1)	0.9 (0.7–1)	0.8 (0.6–1)	0.33
E', cm/s (n = 181)	6 (5–7)	5.5 (5–7)	5.5 (5–7)	0.06
CO, l/min (n = 222)	5.2 (4.2–6.4)	5.2 (4.2–6.4)	5.3 (4.9–6.3)	0.36

Continuous data are presented as mean (SD) or median (IQR) depending on normality. Categorical data are presented as counts with percentages (% of the count given for each column)

[a]If not stated otherwise

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; AS, aortic stenosis; BMI, body mass index; CKD, chronic kidney disease; MI, myocardial infarction; TIA, transient ischemic attack; PCI, percutaneous coronary intervention. AVA, aortic valve area; AVAi, aortic valve area index; $AVPG_{mean}$, mean aortic valve pressure gradient; $AVPG_{max}$, maximal aortic valve pressure gradient; cLG-LF, classical low-gradient low-flow; CO, cardiac output; CS, coronary stenosis; E, peak velocity of early diastolic transmitral flow; E', peak velocity of early diastolic mitral annular motion; HG, high gradient; LA, left atrium; LG-NF, low-

gradient normal-flow; LVEF, left ventricular ejection fraction; LVIDd, Left ventricular internal dimension at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pLG-LF, paradoxical low-gradient low-flow; SV, stroke volume; SVi, stroke volume index; IVSd, interventricular septum thickness at end-diastole; V_{max}, aortic valve peak velocity