Research Paper

Depressed Systemic Arterial Compliance is Associated with the Severity of Heart Failure Symptoms in Moderate-to-Severe Aortic Stenosis: a Cross-Sectional Retrospective Study

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Abstract

Background: Patients with aortic stenosis (AS) may develop heart failure even in the absence of severe valve stenosis. Our aim was to assess the contribution of systemic arterial properties and the global left ventricular afterload to graded heart failure symptoms in AS.

Methods: We retrospectively reviewed medical records of 157 consecutive subjects (mean age, 71±10 years; 79 women and 78 men) hospitalized owing to moderate-to-severe degenerative AS. Exclusion criteria included more than mild aortic insufficiency or disease of another valve, atrial fibrillation, coronary artery disease, severe respiratory disease or anemia. Heart failure symptoms were graded by NYHA class at admission. Systemic arterial compliance (SAC) and valvulo-arterial impedance (Zva) were derived from routine echocardiography and blood pressure.

Results: Sixty-one patients were asymptomatic, 49 presented mild (NYHA II) and 47 moderate-to-severe (NYHA III–IV) heart failure symptoms. Mild symptoms were associated with lower SAC and transvalvular gradients, while more severe exercise intolerance coincided with older age, lower systolic blood pressure, smaller aortic valve area and depressed ejection fraction. By multiple ordinal logistic regression, the severity of heart failure symptoms was related to older age, depressed ejection fraction and lower SAC. Each decrease in SAC by 0.1 ml/m² per mmHg was associated with an increased adjusted odds ratio (OR) of a patient being in one higher category of heart failure symptoms graded as no symptoms, mild exercise intolerance and advanced exercise intolerance (OR: 1.16 [95% CI, 1.01–1.35], *P*=0.045).

Conclusions: Depressed SAC may enhance exercise intolerance irrespective of stenosis severity or left ventricular systolic function in moderate-to-severe AS. This finding supports the importance of non-valvular factors for symptomatic status in AS.

Key words: aortic valve stenosis; heart failure; vascular stiffness

Introduction

According to the current clinical practice guidelines, in severe aortic stenosis (AS) interventional therapy is recommended in the presence of any symptoms related to AS [1]. It is well recognized that heart failure can appear even in subjects with moderate AS and determination of their causal association with valve disease may be challenging. Impaired exercise tolerance is a result of an excessive left ventricular (LV) afterload that is influenced not only by AS severity but also systemic arterial compliance (SAC) and peripheral vascular resistance, both of which augment LV systolic pressure additively to valve disease [2,3].

In 2005 the group of Pibarot [3] proposed a new index, valvulo-arterial impedance (Zva) that represents a total LV hemodynamic load opposing blood ejection into the aorta, and combines both valvular and arterial factors. Zva is equivalent to an estimated LV pressure divided by stroke volume indexed to body-surface area (stroke volume index, SVI) and, like SAC, may be easily derived from peripheral blood pressure and routine cardiac ultrasound examination. An increased Zva and depressed SAC were associated with a higher prevalence of LV diastolic and systolic dysfunction independently of other covariates including aortic valve area (AVA) in 208 consecutive patients with moderate-to-severe AS, out of whom 154 were symptomatic [3]. Additionally, a higher Zva was linked to a depressed stress-corrected LV midwall shortening [4] and an elevated incidence of major cardiovascular events and aortic valve events in asymptomatic mild-to-moderate AS in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study [5]. Furthermore, increased Zva was associated with a history of syncope in moderate-to-severe AS [6], an excessive mortality in severe AS with preserved EF (including 35% with paradoxically low flow [7]) and asymptomatic moderate-to-severe AS [8], and reduced event-free survival in asymptomatic moderate-to-severe severe AS [9,10] upon multivariate adjustment.

Dulgheru et al. [11] have recently reported that increased Zva and older age were the only multivariate determinants of reduced peak oxygen uptake in 62 asymptomatic subjects with moderate-to-severe AS and preserved EF. To the best of our knowledge, associations between SAC or Zva and graded heart failure symptoms in AS have not been investigated so far. Thus, our aim was to estimate the contribution of altered systemic arterial properties and the global LV afterload to graded symptomatic status in degenerative AS.

Materials and Methods

Patients

We retrospectively reviewed medical records of 157 consecutive patients (mean age, 71 ± 10 years; 79 women and 78 men) hospitalized in a tertiary care center in 2008–2013 owing to moderate-to-severe degenerative AS defined as a calculated AVA ≤1.5 cm^2 (or AVA index ≤0.9 cm^2/m^2 body-surface area) or mean transvalvular pressure gradient ≥25 mmHg [1]. Exclusion criteria encompassed age below 50 years, more than mild coexisting aortic insufficiency, concomitant moderate or severe disease of another valve, atrial fibrillation, a history of myocardial infarction, coronary revascularization or a diameter stenosis of ≥50% of at least one major epicardial artery segment on coronary angiography, significant peripheral artery disease or carotid stenosis, severe respiratory disease or anemia, body-mass index over 35 kg/m^2, endocrinological disorders except for diabetes, severe renal insufficiency (estimated glomerular filtration rate below 30 ml/min per 1.73 m^2), malignant or inflammatory disorders, and other relevant coexistent diseases or significant abnormalities in routine laboratory tests. The ethics committee of our university was notified about the planned analysis, similar to our previous report based on a retrospective data analysis [12].

Data collection

Demographical and clinical patients' characteristics were recorded from discharge letters and hospital records with heart failure symptoms graded by New York Heart Association (NYHA) functional classification at admission. Available measures of stenosis severity and LV structure and function were derived from transthoracic echocardiography and included peak and mean transvalvular pressure gradient, calculated AVA, LV volumes, EF and LV mass. Transvalvular pressure gradients were obtained from continuous Doppler recordings by the modified Bernoulli formula. AVA was computed according to the standard continuity equation using the ratio of subvalvular to transvalvular time-velocity integrals. In agreement with the current recommendations EF was calculated by the biplane Simpson's method [13]. LV mass index was estimated by the modified Devereux formula from M-mode measurements [14].

In addition, we computed an estimate of SAC as SVI divided by brachial pulse pressure measured at the time of echocardiographic examination [3,15]. Zva was calculated in a simplified manner because aortic diameter at the level of the sinotubular junction could not be obtained from a retrospective analysis of medical records. This limitation precluded the computa-

tion of the so-called net mean aortic gradient that takes taking into account not only transvalvular gradient at the vena contracta but also pressure recovery distal to the narrowed valve as proposed by Briand et al. [3] on the basis of the equation developed by Baumgartner et al. [16]. Thus, Zva was derived as the sum of systolic blood pressure and mean transvalvular pressure gradient divided by SVI, i.e. by a simplified approach which was nonetheless frequently used previously [7-11,17].

Statistical analysis

Data are shown as mean and standard deviation, or numbers (n) and percentages. The patients were divided into 3 subgroups according to the degree of exercise intolerance i.e. asymptomatic subjects with no evidence of exertional dyspnea and/or fatigue or a syndrome of fluid retention in available medical records, and those with a history of mild or advanced heart failure symptoms by NYHA functional class at admission. The accordance with a normal distribution was confirmed by Kolmogorov-Smirnov test and homogeneity of variances by Levene's test. Intergroup differences were estimated by one-way analysis of variance (ANOVA) followed by the Tukey honest significant difference test for unequal n for continuous variables, and chi-squared test for categorical data. Bivariate associations were assessed by Pearson's correlation coefficients (r).

In order to identify independent determinants of the severity of symptoms, multiple ordinal logistic regression was performed, including only variables for which the P value in a univariate analysis was below 0.10. Odds ratios (OR) with 95% confidence intervals (CI) for the predictor variables have been shown for a patient being in one higher category of heart failure symptoms graded as no symptoms, mild exercise intolerance (NYHA II) and advanced exercise

intolerance (NYHA III–IV). OR represents a multiplicative rise in the odds of a patient presenting worse categorized heart failure symptoms associated with each increment in the predictor variable by a given value (for continuous characteristics) or an increase in the odds in the patients exposed to a factor of interest (for dichotomous data). First, according to the approach proposed by Bender and Grouven [18], the goodness-of-fit of the binary logistic regression models was confirmed by the Hosmer-Lemeshow test for each dichotomized response, i.e., symptomatic vs. asymptomatic subjects and those with advanced symptoms vs. the remainder; then the proportional odds assumption was validated by means of a score test. A P value <0.05 was inferred significant.

Results

Demographical and clinical characteristics of AS subjects by the presence and degree of heart failure symptoms are summarized in Table 1. Patients with mild symptoms tended to be more frequently men, whereas the presentation with advanced symptoms was related to an older age and weakly to lower mean blood pressure.

Echocardiographic measures, systolic blood pressure, pulse pressure, Zva and SAC are shown in Table 2. The prevalence of mild symptoms associated with a significantly lower SAC and decreased transvalvular pressure gradients compared to asymptomatic subjects. A more severe exercise intolerance coincided with a smaller AVA, lower systolic blood pressure and depressed EF (Table 2).

SAC correlated to Zva ($r = -0.69$, P <0.001), SVI ($r = 0.71$, P <0.001), systolic blood pressure ($r = -0.44$, P <0.001), pulse pressure ($r = -0.47$, P <0.001), LV mass index ($r = 0.37$, P <0.001) and age ($r = -0.24$, P = 0.004).

Table 1. Demographical and clinical patients' characteristics by heart failure symptoms.

Characteristic	No symptoms n = 61	NYHA II n = 49	NYHA III–IV n = 47	P value[a]
Age, years	68 ± 11	71 ± 9	74 ± 9*	0. 005
Female gender, n (%)	35 (57)	18 (37)	26 (55)	0.07
Body-mass index, kg/m²	29.0 ± 4.6	29.9 ± 5.1	28.4 ± 4.9	0.31
Hypertension, n (%)	47 (77)	44 (90)	38 (81)	0.21
Diabetes mellitus, n (%)	20 (33)	17 (35)	17 (36)	0.93
Chronic kidney disease, n (%)	12 (20)	11 (22)	12 (26)	0.77
Mean blood pressure, mmHg	90 ± 11	92 ± 11	87 ± 12	0.12
Drugs, n (%)				
Diuretics	42 (69)	39 (80)	37 (79)	0.34
ACE inhibitors	26 (43)	25 (51)	22 (47)	0.89
Beta-blockers	33 (54)	24 (49)	20 (43)	0.49
Statins	36 (59)	30 (61)	29 (62)	0.95

Data are presented as mean ± SD or n (%).

[a]By ANOVA or chi-squared test for continuous and categorical data, respectively.

*P <0.05 vs. asymptomatic patients.

Abbreviations: ACE: angiotensin-converting enzyme; NYHA: New York Heart Association functional class.

Table 2. Echocardiographic indices, systolic blood pressure, pulse pressure, Zva and SAC by heart failure symptoms.

Characteristic	No symptoms n = 61	NYHA II n = 49	NYHA III–IV n = 47	P value by ANOVA
AVA, cm²	0.94 ± 0.34	1.01 ± 0.27	0.86 ± 0.29†	0.04
Peak aortic gradient, mmHg	71 ± 31	57 ± 30*	68 ± 32	0.04
Mean aortic gradient, mmHg	44 ± 21	34 ± 20*	41 ± 22	0.04
Systolic blood pressure, mmHg	131 ± 15	137 ± 16	129 ± 17†	0.03
Pulse pressure, mmHg	60 ± 14	67 ± 15	63 ± 16	0.07
EF, %	57 ± 10	51 ± 14	49 ± 12*	0.01
LV mass index, g/m²	147 ± 54	141 ± 45	166 ± 63	0.17
SVI, ml/m²	37 ± 10	35 ± 10	36 ± 14	0.67
Zva, mmHg per ml/m²	5.1 ± 1.7	5.2 ± 1.4	5.7 ± 2.3	0.36
SAC, ml/m² per mmHg	0.65 ± 0.23	0.54 ± 0.18*	0.57 ± 0.22	0.03

Data are presented as mean ± SD.
*$P <0.05$ vs. asymptomatic patients, †$P <0.05$ vs. NYHA-II patients by Tukey's test.
Abbreviations: AVA: aortic valve area; EF: ejection fraction; LV: left ventricular; NYHA: New York Heart Association functional class; SAC: systemic arterial compliance; SVI: stroke volume index; Zva: valvulo-arterial impedance.

Table 3. Multiple ordinal logistic regression analysis of predictors of the severity of heart failure symptoms graded as no symptoms, mild exercise intolerance and advanced exercise intolerance.

Predictor variable	Wald statistic	Odds ratio (OR) of a patient being in one higher symptomatic category	
		Mean OR (95% CI)	P value
Age (per 10-year increment)	9.45	1.70 (1.21–2.39)	0.002
Gender (men vs. women)	0.04	1.03 (0.75−1.42)	0.85
AVA index (per 0.1-cm² decrement)	1.66	1.14 (0.93−1.41)	0.19
EF (per 10% decrement)	7.64	1.42 (1.11−1.81)	0.006
SAC (per decrease of 0.1 ml/m² per mmHg)	4.11	1.16 (1.01−1.35)	0.045

CI: confidence interval; other abbreviations as in Table 2.

Owing to the results of intergroup comparisons, age, gender, AVA, EF and SAC were included in the multiple ordinal logistic regression with the categorized severity of heart failure symptoms as a dependent variable. As mean transaortic pressure gradient correlated closely to peak transaortic gradient (r = 0.97, $P <0.001$) and AVA index ($r = −0.62$, $P <0.001$), only the latter was entered into the regression. Additionally, because of the previously mentioned relations between SAC, systolic blood pressure and pulse pressure, blood pressure was not included in the regression model. Multivariate analysis revealed the association of heart failure symptoms severity with an older age, depressed EF and decreased SAC (Table 3).

Discussion

Our salient finding is that depressed systemic arterial compliance was associated with the severity of heart failure symptoms irrespective of AVA or EF in moderate-to-severe degenerative AS. That impaired systemic arterial properties were related to worse graded heart failure symptoms, supplements previous observations indicative of a limited predictive value of classical indices of stenosis severity or LV function with regard to symptomatic status in AS.

Predictors of symptomatic status in aortic stenosis

Over 10 years ago, Tongue et al. [19] identified impaired LV longitudinal shortening but not EF as an independent predictor of the presence of symptoms, mainly exertional dyspnea or angina, in addition to age and lower AVA index in moderate-to-severe AS. That study suggested the association of symptomatic status with LV longitudinal systolic function, governed by subendocardial fibers known to be more susceptible to microvascular ischemia due to an imbalance between decreased myocardial perfusion and increased systolic wall stress in AS. This observation was later extended by Weidemann et al. [20] who found graded associations with the degree of myocardial fibrosis – detected mainly at the subendocardial layer – for higher NYHA functional class, lower systolic mitral ring displacement and depressed LV longitudinal strain rate but not LV radial strain rate, EF or AVA. In line with these findings, the selective impairment of LV longitudinal contraction was described in patients with clinically asymptomatic severe AS and an abnormal response to exercise [21]. With regard to diastolic dysfunction, Dalsgaard et al. [22] observed that symptomatic status in severe AS was independently related not to AVA but to invasive and noninvasive indices of increased LV filling pressure. In keeping with this report, Dahl et al. [23] identified moderate or severe diastolic dysfunction as an independent determinant of the prevalence of symptoms in severe AS.

Importantly, the contribution of vascular factors to LV load was already suggested in 2003 by Antonini-Canterin et al. [2] who reported that patients with

coexisting hypertension and symptomatic AS presented with a similar degree of symptoms despite larger AVAs compared to normotensive subjects, probably because of an additional burden imposed on the left ventricle due to hypertension itself. In accordance with this early observation, Briand et al. [3] found a higher prevalence of symptoms, elevated systolic blood pressure, systemic vascular resistance and Zva, as well as an increased occurrence of LV systolic and diastolic dysfunction in severe AS and depressed SAC compared to their control counterparts with normal SAC despite similar indexed AVA. Furthermore, Ramamurthi et al. [24] observed an almost 2-fold higher prevalence of excessive vascular load in symptomatic vs. asymptomatic patients with moderate or severe AS.

However, the vast majority of the above cited cross-sectional studies aimed at the search for determinants of symptomatic status in AS either did not differentiate between exertional dyspnea, angina and syncope pooling all these AS manifestations together [2,3,19,22-24] or limited their analysis to a history of syncope [6], while we have focused our attention on NYHA functional class. Importantly, Park et al. [25] described characteristic intracardiac hemodynamic profiles for each type of presenting symptoms (syncope, dyspnea, and chest pain) in patients with severe AS with more advanced diastolic dysfunction associated with exertional dyspnea despite similar AVA and EF. It is noteworthy that, according to Dulgheru et al. [11], a negative association of Zva and peak oxygen consumption was maintained in multiple regression in 62 asymptomatic moderate-to-severe AS patients. Additionally, in that study [11] neither AVA nor EF was related to exercise capacity, whereas univariate correlations between peak oxygen consumption and tissue Doppler indices of systolic and diastolic LV function lost significance upon multivariate adjustment. That the role of vascular factors may be predominant in this setting, was also suggested by Rajani et al. [26] who observed that only decreased SAC and closely interrelated higher pulse wave velocity were univariate correlates of depressed exercise time in 101 patients with asymptomatic moderate-to-severe AS. Because they have not observed such a relationship for Zva [26], their results are in part compatible with our findings. Of note, Roşca et al. [27] observed independent associations of an index of aortic rigidity but not Zva with LV longitudinal deformation, E/E' ratio and B-type natriuretic peptide concentrations in 48 consecutive patients with severe AS. Finally, total arterial compliance, depressed in severe AS, not only did not increase with exercise in contrast to control subjects, but this impairment was a negative determinant of the exercise-induced increase

in stroke flow [28], which further strengthens the potential importance of altered systemic arterial properties for impaired exercise tolerance in AS.

Clinical implications

Our findings add to accumulating evidence supporting the clinical relevance of excessive arterial stiffness as demonstrated by Albu et al. [29] who observed that increased pulse wave velocity, an index of lower SAC, was the only significant predictor of LV diastolic dysfunction in 96 postmenopausal women without overt cardiovascular disease.

Taking into consideration the contribution of vascular components to exercise intolerance in AS, it may be hypothesized that interventions aimed at improving elastic properties of large arteries can delay symptom onset in AS. In a randomized placebo-controlled study Dalsgaard et al. [30] have recently shown that angiotensin-converting enzyme (ACE) inhibition with trandolapril – associated with a rise in SAC at day 3 – resulted in a lower LV end-systolic volume and decreased levels of N-terminal pro-B-type natriuretic peptide after a median follow-up of 7 weeks compared to placebo in 44 patients with severe AS, out of whom 32 were symptomatic. As B-type natriuretic peptides increase with the NYHA class [31] and predict the development of symptoms in AS [32], these findings appear consistent with the notion of hemodynamic benefits of ACE antagonists in AS. On the other hand, no effect of trandolapril on exercise capacity was found over the follow-up [30], which is somewhat contradictory to the report by Chockalingam et al. [33] who observed symptomatic improvement and better exercise tolerance after 1–3 months in 52 patients with severe symptomatic AS randomized to enalapril, although these effects were limited to those with a good tolerance of the drug. In addition, in a drug withdrawal study of 20 asymptomatic hypertensive subjects with moderate-to-severe AS Jiménez-Candil et al. [34] reported that stroke volume at peak exercise was higher when patients were taking ACE inhibitors, and correlated inversely to changes in systemic vascular resistance, nevertheless, exercise duration was unaffected by the medication.

Hence, further studies are warranted to determine if beneficial hemodynamic effect of ACE antagonists in AS observed in some clinical settings may be linked to their influence on arterial compliance or peripheral vascular resistance, as well as whether ACE inhibitors could favorably affect symptomatic status in patients unsuitable for or awaiting surgery or transcatheter aortic valve implantation. Importantly, as the results of these interventions are frequently suboptimal, the ACE inhibition-induced rise in SAC

could hypothetically be useful in postoperative management, e.g. in paradoxical low-flow, low-gradient severe AS associated with depressed SAC, pronounced LV myocardial fibrosis and a poorer clinical outcome after surgery than high-gradient AS [7,17,23,35,36].

Strengths and limitations of the study

The strength of our study was the ability to demonstrate an association of the severity of heart failure symptoms in AS with altered systemic arterial properties despite the use of only a retrospective analysis of routine medical records. Moreover, the study subjects represented a real-life population of consecutive patients with AS and we made every effort to limit the contribution of coexistent diseases to symptomatic status applying a wide set of exclusion criteria including significant coronary artery disease.

However, several limitations of the present study need to be acknowledged. First, heart failure symptoms were graded according to NYHA classification at admission although a better measure of exercise capacity would be advisable. Furthermore, assessment of symptoms in elderly AS patients is challenging because of a decreased physical activity of these subjects. Nevertheless, due to a retrospective study design with hospital discharge charts as source documentation, we could only include NYHA class, not a rarely used exercise tolerance test, in the final dataset. For the same reason, EF was the only index of LV systolic function. On the other hand, the NYHA class and EF still remain the basis of clinical decision-making in AS. Second, as mentioned previously in the Data collection subsection, Zva was derived by a simplified method [3,16] from the parameters available from our medical records. Third, although Doppler echocardiographic evaluation of AS should be performed when blood pressure control is optimal [37], this condition could not be unequivocally confirmed in all patients hospitalized during previous years. Finally, the lack of data on B-type natriuretic peptide – a marker of hemodynamic burden and adverse outcome [38] – as well as on the exact time of symptom onset constrains conclusions based on our cross-sectional analysis of associations between SAC and graded heart failure symptoms.

Conclusions

In summary, depressed systemic arterial compliance might enhance exercise intolerance irrespective of stenosis severity or left ventricular systolic function in moderate-to-severe degenerative AS, which supports the relevance of non-valvular factors for symptomatic status in AS. Whether medical therapy aimed at improving elastic properties of large arteries can relieve symptoms, especially in patients with moderate valve disease, or facilitate postoperative clinical improvement in AS, remains to be studied.

Abbreviations

ACE: angiotensin-converting enzyme; AS: aortic stenosis; AVA: aortic valve area; CI: confidence interval; EF: ejection fraction; LV: left ventricular; NYHA: New York Heart Association; OR: odds ratio; SAC: systemic arterial compliance; SVI: stroke volume index; Zva: valvulo-arterial impedance.

Acknowledgment

Competing Interests

The authors have declared that no competing interest exists.

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