Aortic Stenosis From the Perspective of the Current Guidelines

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Abstract:

Aortic stenosis (AS) is one of the most common valvular diseases encountered in clinical practice. It is most frequently caused by degenerative aortic valve fibrosis and calcification, and in a lesser number of cases by the calcification of congenital deformed aortic valve (bicuspid); it may occasionally develop after rheumatic fever.

Valve fibrosis and calcification lead to progressive valve restriction, obstruction and increased afterload with left ventricle remodelling for normalization of wall tension and cardiac output. During time, such hypertrophic and fibrotic myocardium deteriorates, resulting in heart failure. Generally, current guidelines of the European Society of Cardiology (ESC) recommend aortic valve replacement (AVR) when the aortic valve is severely stenotic and the patient is symptomatic. Most asymptomatic patients with severe AS should be managed conservatively, except for those with systolic LV dysfunction, an abnormal exercise test, very severe aortic stenosis, severe valve calcification, markedly elevated cardiac biomarkers, and severe pulmonary hypertension without other explanation.

This article will review our current understanding of the pathophysiology of AS and provide detailed information about clinical presentation, diagnostic procedures, disease course, and different treatment strategies for various groups of these patients.

Keywords: aortic stenosis, aortic valve replacement, transcatheter aortic valve implantation.

Sažetak:

Stenoza aorte (AS) jedna je od najčešćih bolesti srčanih valvulau kliničkoj praksi. Najčešće je uzrokovana degenerativnom fibrozom aortnih zalistaka i kalcifikacijom, dok su rjeđi razlozi kongenitalno deformirane zalisci aorte (bikuspidalni) ili posljedice reumatske groznice.

Fibroza i kalcifikacija valvula dovode do progresivnog ograničenja, opstrukcije i povećanog after-loada koje dovodi do remodeliranja lijeve klijetke kako bi se kompenzirala napetost zida i ejekcijska frakcija. Tijekom tog vremena, takav hipertrofični i fibrotični miokardij se pogoršava, što dovodi do zatajenja srca. Općenito, sadašnje smjernice Europskog kardiološkog društva (ESC) ukazuju na zamjenu aortnih valvula (AVR) kada je ona ozbiljno stenotična i pacijent je simptomatičan. Većini asimptomatskih bolesnika s teškom AS treba upravljati konzervativno, osim onih s disfunkcijom sistolne LV, abnormalnim testom napora, teškom aortnom stenozom, teškom kalcifikacijom valvula, izrazito povišenim srčanim biomarkerima i teškom plućnom hipertenzijom bez daljnjeg objašnjenja.

Ovaj članak će se prikazati pregled i naše sadašnje razumijevanje patofiziologije AS-a i te će pružiti detaljne informacije o kliničkoj slici, dijagnostičkim postupcima, tijeku bolesti i različitim strategijama liječenja za različite skupine bolesnika sa aortnom stenozom.

Ključne riječi: aortna stenoza, zamjena aortnih zalistaka, transkatetersna implantacija valvula

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Introduction

Calcific aortic stenosis (AS) is present at around 2% and 12% of patients aged ≥65 and ≥75 years, respectively (1-6). In the last group, severe aortic stenosis is present at 3.4% of patients. With the aging of the population, the number of individuals with AS is expected to increase twofold to threefold in developed countries in the coming decades[1-6].

Valvular AS may be a consequence of superimposed calcification of congenital bicuspid valve, normal trileaflet valve and rheumatic diseased valve. Also, it is important to evaluate possible obstruction of left ventricular (LV) outflow which may occur above the valve (supravalvular stenosis) or below the valve (discrete subvalvular stenosis). Finally, hypertrophic cardiomyopathy may cause subaortic obstruction[1,2].

Calcific (formerly "senile" or "degenerative") aortic valve disease, affecting a congenital bicuspid or normal trileaflet valve, is now the most common cause of AS in adults[1,2]. It may be a consequence of normal degenerative process as well as due to influence of atherosclerotic promoting factors, i.e. dyslipidemia, hyperglycemia, arterial hypertension, smoking, obesity, etc[1-11]. It is important to emphasize that aortic sclerosis, even in the absence of valve obstruction or known cardiovascular disease, is associated with an increased risk of myocardial infarction (MI) and cardiovascular and all-cause mortality[2,5].

Pathophysiology of Aortic Stenosis

Due to chronic valve obstruction and increased afterload, the ventricle typically undergoes hypertrophic remodeling (concentric remodeling, concentric hypertrophy, or eccentric hypertrophy) characterized by myocyte hypertrophy and increased wall thickness. It reduces wall stress (afterload) and maintains LV ejection performance. But, increased or maladaptive (insufficient) LV remodeling may be associated with more severe ventricular dysfunction and heart failure (HF) symptoms, as well as higher mortality[13-15].

Hypertrophic remodeling also impairs diastolic myocardial relaxation and increases stiffness[16,17], as modulated by cardiovascular and metabolic comorbidities[18]. Higher cardiomyocyte stiffness, increased myocardial fibrosis as a part of hypertrophic remodeling process, advanced-glycation end products, and metabolic abnormalities each contribute to increased chamber stiffness and higher end-diastolic pressures[16]. Increased chamber pressures, especially during diastole, leads to pulmonary hypertension in many patients with AS. The hypertrophied left ventricle, increased systolic pressure and prolongation of ejection increases myocardial oxygen consumption. Patients with AS may have normal epicardial coronary arteries, but decreased myocardial capillary density in the hypertrophied ventricle, increased LV end-diastolic pressure, and a shortened diastole decreases the coronary perfusion pressure gradient and myocardial blood flow. It creates an imbalance between myocardial oxygen supply and demand, especially in the subendocardium[1,2,16-18].

Clinical Presentation

Most patients presents with systolic murmur on physical examination, with confirmation of the diagnosis by echocardiography. The most common clinical presentation is a gradual decrease in exercise tolerance, fatigue, or dyspnea on exertion, due to LV diastolic dysfunction, elevated end-diastolic pressure and pulmonary congestion[1,2,19,20]. Also, exertional symptoms may be a consequence of the limited ability to increase cardiac output with exercise. More severe exertional dyspnea, with orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, reflects various degrees of pulmonary venous hypertension[1,2].

Angina during exertion is a frequent symptom, caused with imbalance of increased oxygen needs in hypertrophied myocardium and decreased delivery secondary to the excessive compression of coronary vessels. Syncope most often is caused by inadequate increase in cardiac output related to valvular stenosis, systemic vasodilatation during exertion and consequent brain hypoperfusion[1,2].

Diagnosis

Physical findings

The specific finding with severe AS is a slow-rising, late-peaking and low-amplitude carotid impulse (parvus and tardus)[2]. The ejection systolic murmur of AS typically is heard best at the base of the heart and radiation to the neck. It may become softer with failing ventricle. Splitting of second heart sound (S2) implies the aortic valve leaflets are flexible enough for creating an audible closing sound (A2). The intensity of the systolic murmur varies according to the duration of diastole (atrial fibrillation, premature beats). It is augmented by squatting, which increases stroke volume, and reduced during the strain of the Valsalva maneuver and standing due to the reduction of transvalvular flow[2].

Diagnostic testing

Echocardiography It is the standard approach for evaluating and following patients with AS and selecting them for operation. According to the guidelines[1,2,21], valve obstruction to LV outflow is graded as:

1) mild obstruction: aortic jet velocity of 2.0 - 2.9 m/sec, mean gradient ≤20 mm Hg, aortic valve area (AVA) 1.5 - 2.0 cm^2;
2) moderate obstruction: aortic jet velocity of 3.0 - 3.9 m/sec, mean gradient 20 - 39 mm Hg, AVA 1.0 - 1.5 cm^2; and
3) severe obstruction: aortic jet velocity of ≥4 m/sec, mean gradient ≥40 mm Hg, AVA ≤1.0 cm^2.

Furthermore, four categories of aortic stenosis can be defined[1,2,21]:

a) **High-gradient AS** (valve area <1.0 cm^2, mean gradient >40mmHg). Severe aortic stenosis can be assumed irrespective of whether LVEF and flow are normal or reduced.

b) **Low-flow, low-gradient AS with reduced ejection fraction** [valve area <1.0 cm^2, mean gradient <40mmHg, ejection fraction <50%, stroke volume index (SVi) <35mL/m2]. There is

LV dysfunction with reduced blood flow (SVI <35mL/m2). In this situation, dobutamine stress echocardiography (DSE) can help to distinguish between pseudo-severe and true severe AS. More precisely, DSE may allow iden-tification of the presence or absence of contractile reserve (flow reserve), which is defined as an increase in stroke volume ≥20% on dobutamine. In the absence of contractile reserve, no solid conclusions can be drawn with regard to severity of AS. In contrast, in the presence of a contractile reserve, differential diag¬nosis between true severe and pseudo-severe AS (reduced valve opening due to primary myocardial disease and limited contractile driving forces) may be possible. In true severe AS, a significant increase in transaortic gradients with increasing flow is observed whereas the calculated valve area remains small (e.g. mean gradient >40 mmHg and AVA < 1.0–1.2 cm^2 at peak stress). In pseudo-severe AS, gradients typically remain low, while the calculated valve area increases (e.g. mean gradient < 30–40 mmHg and AVA > 1.0–1.2 cm^2 at peak stress).

c) **Low-flow, low-gradient AS with preserved ejection fraction** [valve area <1.0 cm^2, mean gradient <40mmHg, ejection fraction >50%, SVi <35mL/m2]. This is typically encountered in the elderly and is associated with small ventricular size, marked LV hypertrophy and frequently a history of hypertension.

The diagnosis of severe aortic stenosis in this setting remains challenging and includes positive clinical criteria (typical symptoms without other explanation, elderly patient (>70 years)), qualitative imaging data (LV hypertrophy and reduced LV longitudinal function without other explanation) and quantitative imaging data (mean gradient 30-40 mmHg, AVA ≤ 0.8 cm^2, low flow (SVI <35 mL/m2). Finally, the degree of valve calcification by MSCT is related to aortic stenosis severity and outcome. Its assessment has therefore gained increasing importance in this setting.

d) Normal-flow, low-gradient AS with preserved ejection fraction [valve area <1.0 cm^2, mean gradient <40mmHg, ejection fraction ≥50%, SVi >35mL/m2]. These patients will in general have only moderate aortic stenosis.

Finally, valve area may be ≥1.0 cm^2 with a peak velocity higher than 4 m/s and mean gradient ≥40 mmHg in the pres¬ence of a high transvalvular flow. This may be due to concomitant AR or shunt lesions. Although valve area may not indicate severe AS, haemodynamics remain consistent with severe LV pressure overload and therefore severe aortic valve disease. For clinical decision-making, reversible causes of increased flow in case of high cardiac output (fever, anaemia, hyperthyroidism, etc.) must be excluded.

Exercise stress testing. It may be used in apparently asymptomatic patients to unmask symptoms or demonstrate limited exercise capacity or an abnormal blood pressure response[1,2]. It should be absolutely avoided in symptomatic patients.

Computed tomography (CT). It may be used in cases with suspected aortic root disease, especially at patients with a bicuspid valve. Evaluation of aortic dimensions at several levels is necessary for clinical decision making and surgical planning. Also, CT may be helpful when the severity of the stenosis is in doubt, particularly in those with low-flow, low-gradient AS[1,2].

Cardiac catheterization. It is now recommended only when noninvasive tests are inconclusive, when clinical and echocardiographic findings are discrepant, and for coronary angiography before surgical intervention[1,2].

Cardiac magnetic resonance (CMR). It is useful for evaluation of LV volume, function, and mass[1,2]. CMR is used in assessing aortic dimensions in patients with a bicuspid valve. It is also practical for assesing myocardial fibrosis and can be used instead of CT for evaluation of valve morphology, vascular anatomy, and annular dimensions in preparation for transcatheter aortic valve replacement. But, it should be avoided in assessment of transvalvular velocities.

Disease Course

Asymptomatic patients

The rate of progression of AS is highly variable and difficult to predict. The factors associated with more rapid hemodynamic progression included older age, more severe leaflet calcification, renal insufficiency, hypertension, obesity, metabolic syndrome, smoking and hyperlipidemia[1,2,6,8,9].

Asymptomatic patients with moderate to severe AS have excellent prognosis[1,2,22]. Several predictors of symptoms onset at patients with asymptomatic severe AS are abnormal exercise test, elevated BNP, moderate to severe valve calcification, very high aortic velocity (>5 or 5.5 m/sec), rapid increase in aortic velocity, increased hypertrophic LV remodeling, reduced LV longitudinal systolic strain, myocardial fibrosis and pulmonary hypertension. The strongest predictor of progression to symptoms is the Doppler aortic jet velocity[1,2,19,21,23,24].

Exercise testing monitored by a physician should be applied in adults with severe AS when symptom status is unclear, and patients who develop symptoms or exhibit a decrease in blood pressure with exertion should be considered to have symptomatic disease. An elevated BNP level may be helpful when symptoms are equivocal or when stenosis severity is only moderate, but the role of BNP monitoring in the evaluation of disease progression has not been fully defined[1,2].

Generally, repeat echocardiographic imaging is performed every 6 to 12 months for severe AS, every 1 to 2 years for moderate AS, and every 3 to 5 years for mild AS, unless a change in signs or symptoms prompts repeat imaging sooner[1,2].

Symptomatic patients

Once even mild symptoms are present, survival is poor unless outflow obstruction is relieved. The average survival without aortic valve replacement (AVR) is only 1 to 3 years after

symptom onset[1,2,25-28]. Also, the outlook is poorest when the left ventricle has failed and the cardiac output and transvalvular gradient are both low. The risk of sudden death is high with symptomatic severe AS, so these patients should be promptly referred for AVR. In patients who do not undergo AVR, recurrent hospitalizations for angina and decompensated heart failure are common, associated with significant consumption of health care resources [1,2,25-28].

Treatment

Studies revealed that medical treatment has no influence on disease progression and aortic valve replacement (AVR) is superior to medical therapy at patients with severe symptomatic AS [1,2,29-61]. It is of mutual importance that patients report promptly the development of any symptoms possibly related to AS as the risk of sudden death increases dramatically once symptoms are present. In asymptomatic patients with AS of any degree, evaluation and treatment for conventional cardiovascular risk factors is recommended in accordance with established guidelines.
Hypertension treatment reduces ventricular afterload and hypetrophic LV remodeling. Also, vasodilation is accompanied by increases in stroke volume, even in patients with severe AS[1,2].
Because the renin-angiotensin system is upregulated in the valve and ventricle of patients with AS, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may preferentially considered[1,2].
Coronary artery disease and statin prescribtion should be guided according to the primary and secondary preventio guidelines and not be infleunced by the presence of AS[1,2].
Atrial fibrillation (AF) or atrial flutter are frequent at patients with AS, especially with concomitatnt mitral valve disease. As the loss of the left atrial „buster pump“ during AF affects LV filling and may cause sudden fall in cardiac output and serious hypotension, clinicans must choose between the two treatment strategies, rate and rhytm control. In patients with chronic stable HF diuretics may reduce congestion and provide some symptomatic relief prior to valve replacement. Patients with acute decompensated HF may benefit from medical therapy as a bridge to definitive therapy with valve replacement. Nitroprusside has been used during hemodynamic monitoring in the intensive care unit to unload the left heart, reduce congestion, and improve forward flow. Similarly, phosphodiesterase type 5 inhibition has been shown to provide acute improvements in pulmonary and systemic hemodynamics resulting in biventricular unloading [1,2]. These medications may improve the patient's hemodynamic status, allowing the AVR procedure to be performed more safely.

Symptomatic severe aortic stenosis

Intervention is indicated[1,2] in symptomatic patients with severe, high-gradient aortic stenosis (mean gradient ≥40 mmHg or peak velocity ≥4.0 m/s) (Class I, Level B).
Intervention is indicated in symptomatic patients with severe low-flow, low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction and evidence of flow (contractile) reserve excluding pseudosevere aortic stenosis (Class I, Level C).
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation of severe aortic stenosis (Class IIa, Level C).
Intervention should be considered in symptomatic patients with low-flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis (Class IIa, Level C).

Choice of intervention in symptomatic severe aortic stenosis

Surgical aortic valve replacement (SAVR) is recommended (1,2) in patients at low surgical risk and no other risk factors (frailty, porcelain aorta, sequelae of chest radiation, older age, previous cardiac surgery, chest deformations, etc) (Class I, Level C).
Transcatheter aortic valve implantation (TAVI) is recommended in patients who are not suitable for SAVR as assessed by the Heart Team (Class I, Level B). It offers a less invasive option for the treatment of severe AS, with evidence supporting TAVI compared with medical therapy in inoperable patients and superior with surgical aortic valve replacement (SAVR) in high-risk patients.
Balloon aortic valvotomy (BAV) may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery (Class IIb, Level C).
BAV may be considered as a diagnostic means in patients with severe aortic stenosis or other potential causes for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, pre-renal insufficiency or other organ dysfunction that may be reversible with balloon aortic valvotomy when performed in centres that can escalate to TAVI (Class IIb, Level C).

Asymptopmatic severe aortic stenosis

SAVR is indicated[1,2] in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) not due to another cause (Class I, Level C).
SAVR is indicated in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing symptoms on exercise clearly related to aortic stenosis (Class I, Level C). SAVR should be considered in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing a decrease in blood pressure below baseline (Class IIa, Level C).
SAVR should be considered in asymptomatic patients with normal ejection fraction and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present (Class IIa, Level C):

• Very severe aortic stenosis defined by a Vmax >5.5 m/s
• Severe valve calcification and a rate of Vmax progression ≥0.3 m/s/year
• Markedly elevated BNP levels (>threefold age- and sex-corrected normal range) confirmed by repeated measurements without other explanations
• Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation.

Other indications for intervention

SAVR is indicated [1,2] in patients with severe aortic stenosis undergoing CABG or surgery of the ascending aorta or of another valve (Class I, Level C).
SAVR should be considered in patients with moderate aortic stenosis undergoing CABG or surgery of the ascending aorta or of another valve after Heart Team decision (Class IIa, Level C).

Conclusion

Severe AS is the most common form of valve heart disease. AVR is primary recommended when the aortic valve is severely stenotic and the patient is symptomatic. Most asymptomatic patients with severe AS should be managed conservatively, with close monitoring to detect new onset of symptoms, except those with systolic LV dysfunction, an abnormal exercise test, very severe aortic stenosis, severe valve calcification, markedly elevated cardiac biomarkers and severe pulmonary hypertension without other explanation. TAVI offers a less invasive option for the treatment of severe AS, with evidence supporting TAVI compared with medical therapy in inoperable patients and superior with SAVR in high-risk patients.

Author contributions:

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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