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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Treatment Challenges in Patients with Acute Heart Failure and Severe Aortic Valve Stenosis

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Abstract

Purpose of Review The goal of this paper is to describe the treatment challenges in patients with aortic stenosis in combination with a reduced left ventricular function.

Recent Findings Since the risk of mortality is increased in this patient population, transcatheter aortic valve implantation emerged as an important treatment option. Concomitant factors such as mitral regurgitation or coronary artery disease are important co-factors that need to be evaluated and taken into account for treatment decision.

Summary Treatment of the severe aortic stenosis is key in this complex setting. Since several co-factors may exist in addition to aortic stenosis, treatment needs to be decided by a Heart Team.

Keywords TAVI · Surgical aortic valve replacement · Heart failure · Treatment options · Reduced left ventricular ejection fraction

Introduction

Current ESC guidelines define heart failure (HF) as a clinical syndrome characterized by typical symptoms including breathlessness, ankle swelling, and fatigue and clinical signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral edema [1]. This definition of HF restricts itself to clinical symptoms without taking structural or functional cardiac abnormalities like reduced left ventricular ejection fraction (LVEF) or valvular heart disease, particularly severe aortic stenosis (AS) into account. Most clinical studies on medical treatment of HF in patients with reduced LVEF and no AS have shown a reduction in morbidity and mortality [1]. Data for patients with HF and preserved LVEF, especially in combination with AS, on mortality or morbidity are limited [1, 2]. The diagnosis of HF with preserved LVEF is more challenging and often overlaps with patients suffering from severe AS, since left ventricular walls are thicker and left ventricular filling pressures increase due to the "mechanical" barrier [1, 3•, 4]. In this article, we will focus on the treatment challenges in patients with severe AS and reduced LVEF. The new valvular heart disease guidelines from 2017 also included this aspect by providing a more accurate diagnostic pathway in patients with reduced LVEF using stress echocardiography to exclude pseudo-stenosis and evaluate LV contractile reserve [5].

Diagnosis of AS in Case of Concomitant Reduced LVEF

Echocardiography is the standard tool for evaluating the severity of AS. According to the ESC guidelines for valvular heart disease, there are different types of severe AS indicating the need for treatment [5].

High-gradient AS irrespective of LVEF and state of flow and low-gradient AS with an aortic valve area < 1.0 cm^2 constitute the classic AS that has a clear indication for aortic valve replacement when being symptomatic. Patients with low-flow low-gradient AS should be further classified in paradoxical low-flow low-gradient AS with normal LVEF (LVEF ≥ 50%), but reduced stroke volume index (≤ 35 ml/m^2) and classical low-flow low-gradient AS with reduced LVEF (< 50%) (Fig. 1). For these patients, a stepwise approach to further evaluate the severity of AS is needed. Low-dose dobutamine stress echocardiography is

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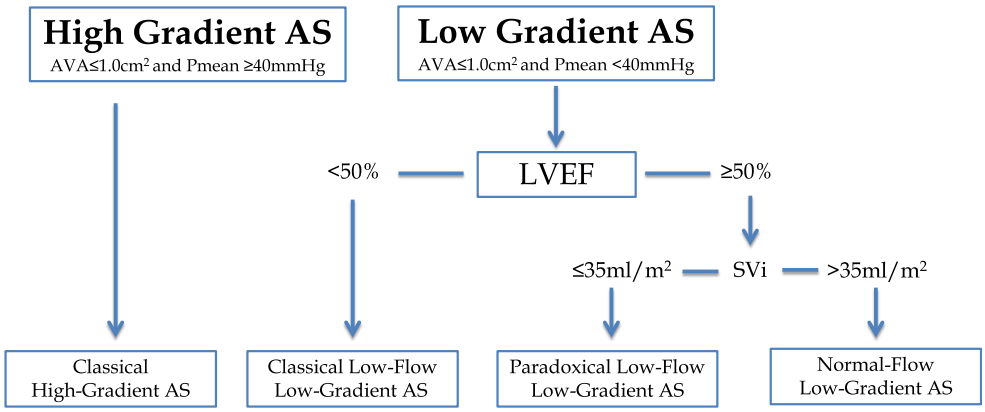

Fig. 1 Differentiation of aortic stenosis. *AS* aortic stenosis, *AVA* aortic valve area, Pmean mean pressure gradient, *LVEF* left ventricular ejection fraction, *SVi* stroke volume index

recommended to evaluate the contractile fractional flow reserve in patients with reduced LVEF. If fractional flow reserve is present and aortic valve area does not increase ≥ 0.2cm^2 and remains ≤ 1.0cm^2, a pseudo-severe AS due to the impaired LV function is excluded and treatment for AS is indicated [6]. In addition, fractional flow reserve (with an approximate increase of 20% in stroke volume) has prognostic implications and is associated with a better outcome [6, 7]. If fractional flow reserve is missing, a multislice computer tomography with calcium scoring of the aortic valve is recommended as the next step (see Fig. 2) [8–10].

In addition to the evaluation of AS severity, echocardiography is the main imaging modality to assess the LV. Echocardiographic evaluation of the LV should include LV function with stroke volume, LVEF, diastolic dysfunction, left atrial pressure, and pulmonary arterial pressure [4]. There is data showing a reduction in LVEF even before AS becomes severe and accelerates already after aortic valve area reached 1.2 cm^2 [11]. In addition, even a LVEF < 60% in the presence of moderate AS predicts a further deterioration of LVEF and appears to represent an abnormal LVEF in patients with AS [11].

Treatment of Patients with HF and AS

All patients with HF due to reduced LVEF should receive optimal medical treatment according to the guideline for HF [1]. Care must be taken using vasodilators (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor-neprilysin inhibitors, calcium channel blockers, hydralazine, and nitrates) in patients with severe AS in order to not cause hypotension or increase the gradient across the stenotic valve.

Medical therapy for AS cannot improve outcome compared with the natural history. Randomized trials have consistently shown that statins do not affect the progression of AS [12].

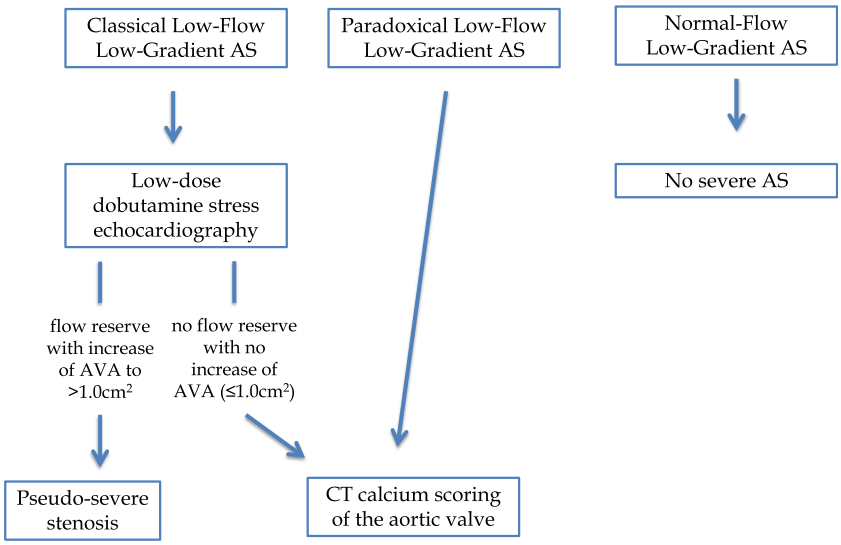

Fig. 2 Stepwise approach for further evaluation of aortic stenosis. *AS* aortic stenosis, *AVA* aortic valve area, *CT* computer tomography

Since progression of degenerative AS is an active process, sharing a number of similarities with atherosclerosis, treatment of atherosclerotic risk factors is strongly recommended following the guidelines of secondary prevention in atherosclerosis but without having an impact on the progression of AS [13].

Aortic Valve Replacement

As stated above, there is no specific medical treatment available for AS, only HF can be addressed with optimal medical therapy according to current guidelines. Therefore, aortic valve replacement is the primary therapeutic option in patients with severe AS and impaired LVEF to reduce mortality, improve clinical symptoms and to allow for the recovery of left ventricular function [14–18]. The choice of treatment (transcatheter aortic valve implantation [TAVI] vs. surgical aortic valve replacement [SAVR]) should take into account the individual patient characteristics and the individual risk of surgery and should be assessed by the local Heart Team together with the patient.

Surgical Aortic Valve Replacement

Even with steadily increasing new data available for TAVI, SAVR remains the first choice in younger or low-risk patients [5]. In these patients, SAVR achieves excellent results with low rates of operative mortality, paravalvular aortic regurgitation, and new pacemaker implantation [19–22]. In addition, good long-term results for up to 25 years are well documented [22–26]. The risk of complications after SAVR depends on numerous factors including patient comorbidities, e.g., reduced LVEF, additional coronary artery disease, or chronic lung disease increasing mortality [27–29]. In the past, surgery was denied in 33% of elderly patients with severe, symptomatic AS, because of a high operative risk [30].

A dobutamine stress echocardiography is particularly important in patients considered for SAVR, since the absence of an increase in stroke volume during stress testing indicates an inadequate LV contractile reserve and has been associated with worse prognosis after SAVR [6].

Transcatheter Aortic Valve Implantation

TAVI is nowadays the standard treatment of surgical high-risk and moderate-risk patients with symptomatic severe AS [5, 14, 31]. Higher rates of paravalvular regurgitation and higher risk for permanent pacemaker implantation compared with SAVR are known, but the avoidance of a heart lung machine and cardioplegia seems to be more important in higher or intermediate risk patients [14, 32–35]. Especially patients with reduced LVEF and other comorbidities (e.g., coronary artery disease, pulmonary hypertension, COPD, chronic renal failure) are more preferred for a transcatheter treatment since mortality risk increases [36–39]. In contrast to the data from SAVR treated patients, the absence of contractile reserve was not associated with any negative effect on clinical outcomes or LVEF changes at follow-up [15].

Balloon Aortic Valvuloplasty

Balloon aortic valvuloplasty (BAV) was first performed by Alain Cribier in 1986 [40]. He provided data on BAV in ten patients in 1992 [41]. In the era of TAVI, BAV has limited indications. According to current guidelines, BAV "may be considered as a bridge to SAVR or TAVI in hemodynamically unstable or symptomatic patients who require urgent major non-cardiac surgery" (class of recommendation IIb) [5]. Furthermore, "BAV may be considered as a diagnostic means in patients with severe AS 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 BAV when performed in centers that can escalate to TAVI" (class IIb) [5]. Nowadays, BAV procedures are performed mostly in patients with cardiogenic shock [42]. Even in successful urgent BAVs, morbidity and mortality in patients with cardiogenic shock remain high with almost 50% mortality at 30 days and 70% at 1 year [42, 43]. Furthermore, mean aortic valve area remains low at 0.8 ± 0.2 cm^2, corresponding to severe AS in the majority of patients despite successful BAV [42–44]. In addition, there is also a risk for the occurrence of aortic regurgitation after BAV, which is known to increase all-cause mortality [45]. Therefore, in the era of TAVI, BAV should only be considered for a very limited number of patients. In our opinion, the best indication for performing a BAV is for patients with a symptomatic severe AS and a concomitant septic focus that needs to be operated to reduce operative mortality or ongoing infection with high risk for endocarditis if performing a TAVI or SAVR.

Coronary Artery Disease

The incidence of coronary artery disease (CAD) in patients with AS ranges from 30 to 65% [46, 47]. Ischemic cardiomyopathy in addition to AS can worsen HF. Careful evaluation of the severity of CAD is important, when severe AS is coexisting. Decision for a surgical or interventional treatment strategy should be discussed individually for each patient and must take patient comorbidities, coronary anatomy, and anatomy of the aortic valve into account.

Combined SAVR and coronary artery bypass grafting carries a higher risk than isolated SAVR [48, 49]. Also,

percutaneous treatment of CAD and TAVI has been shown to be feasible [50, 51]. Especially in elderly patients undergoing TAVI for severe AS, complete revascularization seems not to be necessary for satisfying midterm outcome [52]. Mortality after TAVI is closely related to the complexity of CAD represented by the Syntax Score. Patients with a Syntax Score > 22 seem to benefit from coronary revascularization, since residual Syntax Score lower than 8 reduces 1-year mortality [53]. Early and midterm outcomes in a propensity score matched cohort showing comparable results for patients treated by TAVI and staged or concomitant coronary intervention with surgical treatment by SAVR and concomitant coronary bypass graft operation [54].

Randomized controlled trials are needed to confirm these results. However, current guidelines recommend to treat CAD if a stenosis > 70% is present in a proximal segment. It should be performed in a stepwise approach before TAVI, since coronary access can be limited afterwards. There are different TAVI prostheses available. Some overlap the coronary arteries and decrease percutaneous coronary intervention success rates [55, 56]. Decision for the type of TAVI prosthesis needs to take the presence of CAD into account.

Concomitant Other Valvular Heart Disease

Concomitant mitral valve regurgitation (MR) or tricuspid valve regurgitation (TR) are frequently associated with AS, especially in patients with reduced LVEF [57–59]. Degenerative as well functional MR may be present. In the special patient population with reduced LVEF, dilatation of the LV occurs and can result in additional functional MR [57]. Significant (moderate-to-severe) MR is found in about 15% of patients undergoing TAVI [60]. Severe MR is recognized as an independent predictor of mortality at 30 days and 1 year in patients undergoing TAVI [61]. The impact on MR following TAVR is controversial and not well defined. About 50% of patients are known to experience an improvement in functional MR [61]. For patients undergoing SAVR, there is a general consensus that in the presence of severe MR (especially degenerative MR), a combined correction of both valves is indicated [5]. But there is no data on severe MR left untreated at the time of SAVR, since this data has never been investigated in randomized controlled trials. For functional MR in the setting of severe AS, data remain controversial, since additional mitral valve surgery increases mortality compared with isolated SAVR [62–65]. After SAVR, a decrease in functional MR severity is commonly seen [66–68]. But there is also lack of improvement in about 50% of patients, which is similar to data of patients receiving TAVI [69, 70]. Although there are several predictive factors (e.g., persistent atrial fibrillation, pulmonary hypertension, large atrial size) known for the lack of improvement of MR after SAVR and TAVR, a definite conclusion for correction of MR during SAVR is unknown [60]. It still seems to be justified to operate severe functional MR during SAVR since MR severity may also have a negative impact on outcome after SAVR [54, 63, 71–73].

In chronic stages of heart failure, not only functional MR may be present but also functional TR is frequently seen. This is due to the pathomechanism of elevated pulmonary pressure leading to right ventricular dilation and distortion of the tricuspid annulus creating tricuspid regurgitation [74]. TR can also be taken as a marker of advanced HF and is known for poor outcomes in patients undergoing TAVI [75, 76]. Surgical data indicate annuloplasty for severe TR during left-sided surgery to achieve right ventricular reverse remodeling [5, 77, 78]. Percutaneous tricuspid valve intervention is not established yet, but may become a viable option in future.

There are various advantages and disadvantages in patients with concomitant MR and/or TR undergoing SAVR or TAVI. For patients undergoing SAVR, additional correcting of MR and/or TR in the same operation is favored. But this will result in longer procedure times and higher mortality rates [63–65]. For patients with severe AS and functional MR, a stepwise therapy may be performed with treating AS first and re-evaluate LVEF and functional MR and/or TR. If no improvement is seen, a second procedure with other interventional devices may be performed. This stepwise approach is not appropriate for surgical procedures. There is data on concomitant interventional aortic and mitral procedures, but prognostic data of the combined approach are insufficient and controversial. Therefore, randomized trials are needed, before general recommendations can be made [79].

LV Recovery After Aortic Valve Replacement

There is good data on recovery of LVEF after TAVI and SAVR. Data from the PARTNER trial showed a significant improvement in LVEF from 36 to 49% after TAVI and from 38 to 50% after SAVR [18]. This is in line with other randomized studies and registries showing a significant improvement in LV function after TAVI and SAVR [16–18, 80, 81]. Since AS leads to cardiac damage, it is not surprising that improvement after aortic valve replacement occurs [3•]. At this point in time, there is no indication for aortic valve replacement in patients with only moderate AS and decreased LVEF. The ongoing UNLOAD trial will enroll and randomize patients with moderate AS, but decreased LVEF in addition to optimal medical treatment for heart failure vs. optimal medical treatment alone and will help to understand the importance of AS on LV damage and LV recovery in patients with moderate AS [82].

Since LV recovery after aortic valve replacement is known, this brings up a discussion in patients with severely reduced LVEF and severe AS. Typically, patients with severe reduced

LVEF have an indication for an implantable cardioverter-defibrillator. Since treatment of the AS will improve LVEF, these patients need a close follow-up and a re-evaluation of the LVEF before implanting a cardioverter-defibrillator.

Cardiogenic Shock or Decompensated HF Due to AS

Patients in cardiogenic shock due to decompensated severe AS have a reduced cardiac output. SAVR for these patients has a poor prognosis and an extremely high risk [83]. Acute decompensation due to AS has an increased 5-year mortality compared with patients with no HF or chronic HF, even if undergoing aortic valve replacement [84••]. TAVI therapy in patients with acute decompensated AS is associated with a 30-day mortality comparable with elective TAVI procedures, while in patients with cardiogenic shock due to decompensated AS, TAVI is associated with a high 30% mortality rate, but an acceptable 59% 1-year survival rate confirming TAVI as a viable treatment option for these patients [85•, 86].

But there are further challenges in this special situation of emergency procedures for acute treatment of decompensated severe AS. For example, anticoagulation regimes cannot be paused prior to the procedure as performed for elective procedures, which might increase the risk of bleeding. In addition, missing information about concomitant factors like additional valvular heart disease or CAD may aggravate the procedural risk in an emergency situation. The presence of a porcelain aorta (especially important for surgical procedures with high incidence of thromboembolization, stroke, and aortic injury), which might be unknown at the beginning of the operation, is also an important factor. Furthermore, the size of the aortic annulus is most commonly unknown in an emergency case and fluoroscopy and transesophageal echocardiography are needed to measure annular dimensions and to decide about the size of TAVI prosthesis. In addition, important information like left ventricular outflow tract calcification or annulus calcification is missing and may increase the procedural risk.

Conclusion

There are several treatment challenges that need to be taken into account when patients with AS and HF are to be treated. Diagnostics in patients with reduced LVEF are important to rule out pseudo-stenosis. After diagnosis of a severe AS, aortic valve replacement should not be delayed since cardiac damage and mortality increases over time, no medical treatment exists, and LV recovery is known. Decision for the best treatment must be evaluated by an institutional Heart Team consisting of heart surgeons, interventional cardiologists, heart failure specialists, and anesthesiologists. Lower LVEF increases mortality for SAVR and TAVI; therefore, less invasive interventional procedures such as TAVI show advantages compared with SAVR, especially in patients with comorbidities. Additional factors such as CAD or concomitant mitral and/or tricuspid regurgitation, which are common in patients with reduced LV function, need to be discussed for each patient individually.

Compliance with Ethical Standards

Conflict of Interest Tobias Schmidt has received lecture honoraria from Medtronic and Edwards, as well as travel expenses from Edwards LifeSciences, Medtronic, and Boston Scientific.

Christian Frerker has received lecture honoraria and travel expenses from Medtronic, Edwards Lifesciences, Boston Scientific, and Abbott Vascular.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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