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Introduction

Aortic valve stenosis is a degenerative disease affecting the elderly population, in which an active process of endothelial dysfunction, inflammation, oxidative stress, lipid deposition, extracellular matrix remodelling, and neoangiogenesis, lead to a progressive valvular calcification and fibrosis [1].

Current indications to treat severe aortic stenosis (AS) are mainly based on valvular parameters (peak velocity, mean gradient, estimated valve area, computed tomography-derived calcium score) combined with AS-related symptoms [2,3]. Left ventricular (LV) ejection fraction (EF) <50% is the only extra-valvular criterion used to give an indication for intervention [2]. Based on a pathophysiological model of cardiac damage (CD) related to aortic valve obstruction, G  n  reux et al. proposed a 5-stages echocardiographic classification: from the absence of cardiac damage (stage 0) to LV hypertrophic remodelling with systolic and/or diastolic dysfunction (stage 1), left atrial dilation and/or mitral regurgitation (stage 2), pulmonary hypertension (PH) and/or tricuspid regurgitation (stage 3) and, finally, to right ventricular dysfunction (RVD) (stage 4) [4]. This staging model demonstrated to have a progressive prognostic impact on all-cause mortality in a cohort of patients undergoing aortic valve replacement (AVR), surgical (SAVR), or transcatheter (TAVR), derived from PARTNER 2 trial [4]. The same evidence was shown in a population coming from two real-world registries [5], in which CD was associated with all-cause mortality and a composite outcome including all-cause mortality, stroke and cardiac-related hospitalisation, especially when PH, significant TR and/or RVD occurred [5]. Sex-specific differences in CD in patients undergoing TAVR have been investigated too [6]. Before TAVR, women were older and had higher surgical risk than men, but showed less comorbidities (chronic obstructive pulmonary disease, coronary and peripheral artery disease, history of previous myocardial infarction and cardiac surgery) [6]. CD staging was confirmed to stratify the prognosis irrespective of sex and the female sex resulted as an independent predictor of lower mortality in early stages (0,1,2), but not in the advanced one (3,4) [6].

From the first model to the validation of new staging systems

From the first model introduced by G  n  reux et al. [4] in 2017, new staging systems of AS-related CD have been proposed to improve and simplify patients' risk stratification.

Tastet et al. incorporated the global longitudinal strain (GLS) assessment in LV damage (stage 1) and added a moderate to severe low-flow state (assessed by the stroke volume index) in stage 4 [7]. This echocardiographic "modified" staging system was demonstrated to have a prognostic value in asymptomatic patients with moderate to severe AS [7,8].

Since CD stages 3 and 4 have been associated with excessive survival loss, an integrative staging system combining both echocardiography and right heart catheterisation has been proposed to allow for better individual risk stratification, especially when pulmonary vasculature damage and/or low-flow state is suspected. This model has been shown to be an independent predictor for all-cause death in a single-center cohort of patients with severe symptomatic AS undergoing TAVR, while the echocardiographic staging did not predict the outcome in the same population [9].

Gutierrez et al. simplified the echocardiographic staging in a 4-stage model, including LV-GLS and right ventricular-arterial coupling (RVAc – defined as tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) ratio) [10]. In a prospective cohort of patients undergoing TAVR, this model improved prognostic stratification compared to the system proposed by G  n  reux [4] underscoring the added value of GLS and RVAc [10].

Overcoming the concept of the physiopathological cascade: "Is the valve to blame?"

The first model of CD staging was born from the idea of a continuous process induced by the LV pressure–overload conditions expanding progressively upstream to the other cardiac chambers and to the pulmonary circulation. Thus, the staging originally represented a model of physiopathological cascade, in which CD was strictly related to the unfavourable anatomic and functional modifications induced by a severe AS. On the other hand, the same authors reported that, among patients with advanced stages, there was lower than expected proportion of patients with cumulated damage from earlier stages [4]. They hypothesised that the extension of CD may not be always sequential but may vary based on patient susceptibility/genetics [4].

Subsequent studies highlighted that patients in more advanced stages were older, had higher NYHA III-IV class probability, and had more significant comorbidities (coronary artery disease, chronic kidney disease, atrial fibrillation, history of previous myocardial infarction, stroke and

cardiac surgery) irrespective of the presence of symptoms [11]. To determine if CD was associated only with moderate and severe AS, Dahl et al. investigated the prevalence of and factors associated with CD in patients with mild AS [12]. The CD was highly associated with a number of comorbidities and no relationship was found between CD and the valvular hemodynamic status [12]. Finally, in the study cohort presented by Gutierrez et al., significant mitral regurgitation in the context of severe AS was reported to have more frequently a degenerative mechanism (88.6%) rather than functional [10]. This suggests that there is usually a common pathological valve deterioration rather than a cascade process from AS to left atrial damage and functional mitral regurgitation.

All this recent evidence supports the idea that the CD stages represent individual risk categories rather than phases of a continuous physiopathological cascade, in which CD is only related to the aortic valve disease.

The clinical impact of staging cardiac damage

Current guidelines are limited to the presence of symptoms and LVEF <50% to give indications for AVR [2]. A recent systematic review and meta-analysis compared an early AVR (SAVR or TAVR) strategy vs clinical surveillance in asymptomatic severe AS including four randomised controlled trails (RECOVERY, AVATAR, EVOLVeD, EARLY-TAVR) for a total of 1427 patients, followed-up for an average of 4.1 years [13]. An early AVR procedure demonstrated a benefit in terms of heart failure (HF) hospitalisation, unplanned cardiovascular or HF hospitalisation and stroke, but not for all-cause mortality and cardiovascular

mortality [13]. Future publications are announced to determine if CD affected the outcomes in both strategies.

A meta-analysis including studies with patients across the spectrum of AS undergoing AVR reconstructed survival curves dividing the cohort per stage and separating patients with symptomatic severe AS vs asymptomatic moderate/severe AS [11]. Two interesting evidences emerged from this work: a) corresponding stages kept their prognostic value independent from the presence of symptoms and b) 60% of the patients with asymptomatic moderate to severe AS had a CD stage prior to AVR ≥ 2 , which was associated with a higher mortality [11]. This analysis pointed out a clear lack of specificity and sensitivity of giving indication for AVR solely on the basis of the presence of symptoms.

Starting from this evidence, an algorithm for AS treatment according to valvular disease severity, presence of symptoms, and stage of CD is proposed in Figure 1. Patients with symptomatic severe AS have a class I indication for AVR irrespective of the presence of CD according to the European guidelines [2]. Patients with asymptomatic severe AS may benefit from an “early” AVR, especially when a CD stage ≥ 2 is present. Personalised invasive treatments for moderate AS associated with CD are currently under investigation (PROGRESS and EXPANDR-TAVR II trials).

The staging model has also been proposed to guide the decision between SAVR and TAVR in symptomatic severe AS [14]. The percutaneous approach may be preferable in the case of advanced CD (stage ≥ 3) due to the fourfold higher risk of RVD following SAVR compared to TAVR, which is associated with an increased risk of

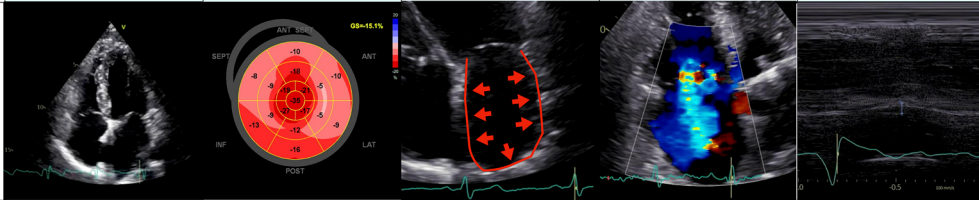
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Grading/staging AS	No cardiac damage	LV damage	LA/MV damage	PC and/or TV damage	RV damage and/or low-flow state
					
Moderate AS		Under investigation: PROGRESS, EXPAND-TAVR II			
Severe asymptomatic AS	AVATAR, EARLY TAVR, EVOLVeD, RECOVERY: benefit in HF hospitalization, unplanned CV or HF hospitalization and stroke				
Severe symptomatic AS	Class I indication for AVR				

Figure 1. Proposed algorithm for aortic stenosis treatment according to valvular disease severity, presence of symptoms, and stage of cardiac damage. AS: aortic stenosis; AVR: aortic valve replacement; CV: cardiovascular; HF: heart failure; LA: left atrial; LV: left ventricular; MV: mitral valve; PC: pulmonary circulation; RV: right ventricular; TV: tricuspid damage.

PROGRESS - NCT04889872 at Clinical Trials.gov, EXPAND-TAVR-II: NCT05149755, AVATAR: NCT02436655, EARLY-TAVR: NCT03042104, EVOLVeD: NCT03094143, RECOVERY: NCT01161732.

mortality [15]. The appropriateness of this choice may also impact on healthcare system costs [16,17].

Staging CD has also been demonstrated to predict the risk of developing significant conduction disorders (left bundle-branch block and high-degree atrioventricular block), which are among the common complications after TAVR, as well as the need for permanent pacemaker implantation after the procedure [18,19].

Conclusions

Current guidelines to treat severe AS rely only on the presence of symptoms and a reduced LVEF, which are often late findings [2,20]. Several pieces of evidence highlights a clear lack of specificity and sensitivity of giving indication for AVR following these criteria. The idea of extending our focus from the sole aortic valve to a comprehensive assessment of all the cardiac structures through a staging model has gained large evidence for patients' prognostic stratification. These stages are emerging as individual risk categories more than part of a continuous physiopathological process and may guide the decision for an AVR in asymptomatic severe AS and moderate AS.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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