Left Ventricular Remodeling in Degenerative Aortic Valve Stenosis

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Abstract: Aortic stenosis was once considered a pure isolated valve obstacle challenging left ventricle driving force of contraction and flow generation. Left ventricular (LV) adaptation was merely interpreted as a uniform hypertrophic response to increased afterload. However, in these last 2 decades cardiac imaging research and some histopathology correlation studies brought insight towards the complex interaction between the vasculature, the valve and the myocardium. Verily, LV remodeling in this setting is a complex multidetermined process that goes further beyond myocardial hypertrophy. Ultrastructural changes involving both diffuse and replacement fibrosis of the myocardium take part and might explain the transition of clinical phenotypes with distinct prognosis, from compensated hypertrophy to LV maladaptive dysfunction and heart failure. Presently, the combined appropriate use of echocardiography and cardiac magnetic resonance may better assess the global LV

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afterload, hypertrophy and geometric remodeling, global and regional LV function, beyond ejection fraction, and structural changes that include the fibrotic burden of the myocardium. As a whole these may not only better stratify individual risk of disease progression but also identify patients benefiting from earlier valve intervention. In this paper, we review the maladaptive response of the LV to chronic pressure overload, describing the different signaling pathways and mechanisms that underly both hypertrophy and remodeling. Histomorphology changes in this setting are described and we try to make sense of the use of new imaging tools for LV characterization. (Curr Probl Cardiol 2021;46:100801.)

Introduction

Degenerative aortic valve stenosis (AS) is the most common acquired valvular disease in western countries, where it is an important cause of morbidity and mortality in middle aged and elderly adults. Between 2% and 4% of the adult population is affected and in people older than 65 years of age, the annual incidence of severe disease is estimated to be between 4% and 7%, numbers that are bound to increase.[1,2]

AS disease progression is a result of LV remodeling, triggered by stenosis, and seems to be multifactorial. In fact, patients with comparable grades of AS may have markedly different patterns of LV hypertrophy, which appears to be influenced by age, gender and genetic background, in addition to comorbidities such as hypertension, reduced vascular bed compliance, diabetes and neurohormonal activation.[3,4]

LV remodeling is believed to begin as a compensatory process to maintain wall stress. In this pathological state, however, it soon becomes maladaptive and leads to a progressive impairment of diastolic relaxation and systolic contractile function.[5] These maladaptive changes do not necessarily reverse after surgical aortic valve replacement (AVR) and negatively impact periprocedural outcomes and survival.[6-8]

This indicates that, ideally, an accurate measure of LV remodeling should be included in clinical decision making when selecting patients for surgery. For this purpose, myocardial biopsy remains the gold standard, being able to evaluate the morphological hallmarks of LV remodeling, such as cardiomyocyte degeneration and myocardial fibrosis.[4,8,9]

However, obtaining a biopsy is an invasive procedure, associated with significant complications. It is also susceptible to sampling bias and unable to assess the fibrotic burden of the whole heart, which is thought to be widespread in patients with AS.[4,10] Furthermore, it only allows for a single snapshot of what is presumed to be a dynamic process and cannot capture the functional implications of remodeling on LV function. Thus, it is impractical for risk assessment purposes and follow-up and is not routinely used in clinical practice.[11]

Because of these reasons, there is great interest in the development and use of noninvasive imaging modalities for the study of the myocardium. Cardiac magnetic resonance imaging (MRI) has been shown to be an appropriate phenotyping tool in this setting, combining the functional evaluation that biopsies cannot provide with a detailed structural characterization of the global structure of the heart.[12]

Aortic valve disease severity continues to be mainly assessed by transthoracic echocardiography and distinct phenotypes of the disease, with uneven prognosis, are defined from the combination of echocardiography derived indexes such as flow, transvalvular gradients and valvular-arterial impedance, reflecting global LV afterload.[13] Moreover, current guidelines place an emphasis on LV ejection fraction when selecting asymptomatic patients for intervention. Unfortunately, this measure has been shown to be a bad predictor of postoperatory LV ejection fraction and mass regression in AS patients submitted to AVR. In fact, it does not accurately predict cardiovascular events and mortality after intervention and is unrelated to the burden of myocardial fibrosis.[4,5,10]

MRI has been shown to be a more reproducible tool for morphofunctional LV assessment, while also providing standard clinical measures of LV mass, volume and ejection fraction.[13] Eventually, it should be able to identify patients with advanced LV remodeling, regardless of LV ejection fraction, better predicting prognosis and selecting patients for an earlier intervention.[4,5,14]

In this paper, we review the maladaptive response of the LV to chronic pressure overload, describing the different signaling pathways and mechanisms that underly both hypertrophy and remodeling. Histomorphology changes in this setting are described and we try to make sense of the use of new imaging tools for LV characterization.

Left Ventricular Hypertrophy in Aortic Stenosis

In patients with AS, the presence of a persistent obstacle to LV systolic ejection leads inexorably to a chronic increase in pressure and

hemodynamic load. The LV usually responds with cardiomyocyte and muscle fiber hypertrophy; the new fibers are preferentially disposed in parallel contractile units.[6]

These changes can be observed macroscopically as concentric remodeling – a gradual increase in wall thickness and reduction of cavity volume, usually accompanied by an increase in LV mass. In the short term, these changes are adaptative and allow for a reduction in wall stress and preservation of inotropic capacity, allowing the cardiac output to match the increased afterload.[15]

LV adaptation to chronic pressure overload is more complex than a simple, mechanistic process and is a clearly distinct phenomenon from the physiological hypertrophy seen during childhood, pregnancy or sustained exercise. The adult heart is composed of highly specialized cardiomyocytes embedded in a stroma and/or extracellular matrix (ECM), lymphoid and undifferentiated multipotent mesenchymal cells.[16]

Although classically described as being accompanied by an increase in mass, this is not always the case for LV remodeling in the context of AS. In fact, the correlation of hypertrophy with the degree of valve stenosis seems to be weak at best – ultrasound studies have demonstrated that between 10% and 20% of patients with AS do not have LVH, and others that over 10% of patients with asymptomatic severe AS had inappropriate high LV mass.[17,18,19]

Classically, in clinical practice, the adaptation of the LV to chronic pressure overload and AS is defined by LV mass, cavity dimensions and wall thicknesses, evaluated by M-mode echocardiography. Using this technique, 4 patterns have been defined: normal ventricular geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. This said, it challenged the paradigm that hypertrophy is needed to maintain wall stress and contractility as there is no direct correlation between those patterns, LV ejection fraction and symptoms.[4,19,20]

More recent cardiac MRI studies have built up on this, describing 6 patterns of ventricular adaptations: normal ventricular geometry, concentric remodeling, asymmetric remodeling, concentric hypertrophy, asymmetric hypertrophy and LV decompensation. Asymmetric patterns appear to be more common in older patients and those with previous history of hypertension. LV decompensation, instead of eccentric hypertrophy, appears in patients with LV dilatation, increased mass, normal geometry and reduced ejection fraction. These studies highlight the lack of relationship between the degree of stenosis and hypertrophy. Furthermore, a reduced ejection fraction was shown not to be exclusive to the LV decompensation pattern.[3]

Several distinct factors can affect the LV response in patients with AS. LV remodeling in AS is largely dependent on the combined effect of valvular disease, decreased arterial distensibility and hypertension. It has been shown that AS patients with significantly reduced arterial compliance and resulting hypertension are particularly prone to the development symptoms of AS and reduced exercise capacity, as well as LV systolic and diastolic dysfunction, independently of the severity of valve disease and LV ejection fraction.[21,22,23]

Normal aging, diabetes, renal disease and atherosclerosis may all interfere with global afterload through a decreased arterial distensibility.[24] However, this is not always the case, as multivariate analysis has revealed that age was only weakly associated with LVH in women and not at all in men.[25] Gender differences do not end there: in pressure overload states, such as hypertension and AS, many studies have reported different LV remodeling in males and females with similar LV mass indexes. A higher prevalence of LVH has been reported in postmenopausal women.[26] These distinctive remodeling responses may be explained by the effect of sex hormones on the myocardium, as there is evidence of the presence of estrogen and androgen receptors in cardiomyocytes. In fact, estrogens appear to have antiproliferative effects on cardiac fibroblasts and vascular smooth-muscle cells.[27,28]

Specific data addressing the effect of renal function on LV mass in patients with AS are scarce but more recent evidence demonstrated that even early and mild renal impairment was independently associated with excessive and inappropriate LVH in moderate and severe AS.[29] Additionally, it has been shown in groups of hypertensive patients that any change in glomerular filtration rate leads to an increase in LV mass independent of hemodynamic overload.[30]

Patients with AS and moderate chronic kidney disease exhibit a higher baseline LV mass and show less evident LV hypertrophy regression after AVR compared to those with normal renal function. This is not affected by uncontrolled hypertension and whether prosthesis-patient mismatch was present at the follow-up.[30] The underlying mechanism seems to be related to a progressive sodium retention and associated changes in renin-angiotensin-aldosterone system and concomitant sympathetic overactivity.[26]

Diabetes has been shown to be an independent risk factor for the progression of calcification and aortic valve stenosis, also exacerbating atherosclerotic disease and arterial stiffening.[31,32] A Japanese study highlighted the role of diabetes as an independent risk factor for reduced LV mass regression in 183 patients submitted to either surgical or

transcatheter aortic valve intervention.[33] Later publications built on these findings, showing that both diabetes and metabolic syndrome were associated with a higher preoperative LV mass, concentric remodeling and hypertrophy in patients with severe symptomatic AS and preserved LV ejection fraction. This might be explained by insulin resistance, the activation of the renin-angiotensin system, chronic inflammation and also sympathetic activation.[34]

Furthermore, there is evidence that the hyperglycemic state of diabetes may directly interfere with the remodeling process, through the promotion of myocardial fibrosis, aggravated by intramyocardial vascular deposition of advanced glycation end-point products, and also by increasing oxidative stress, which contributes to increased cellular death.[35]

In prognostic terms, several studies have brought to attention the negative impact of maladaptive LV remodeling on the survival of AS patients, leading to an increased risk of cardiovascular events in patients with LVH.[5,19] Advanced hypertrophic growth leads to a depression in LV contractility. In a prospective cohort of patients with isolated AS, increased LV mass, by itself, was strongly associated with systolic dysfunction and heart failure, regardless of the severity of the obstruction. This finding was confirmed on a single center observational study with more than 3000 patients submitted to AVR, that showed a decreased long-term survival in patients with severe preoperative LVH.[36]

The concept of excessive LVH is defined as an observed-to-predicted LV mass ration greater than 128% for a given hemodynamic load, gender and height. This happens in over 10% of patients with asymptomatic severe aortic stenosis and seems to be linked to a worse clinical prognosis. Excessive LVH is more frequent in severe vs mild and moderate AS and is related to higher risk of adverse CV events both before and after AVR in severe AS.[18]

Several studies have also suggested that AS patients with concentric LV geometry, showing an increase in relative wall thickness without overt LVH, have a particularly poor prognosis.[37] The archetypal patient shows a paradoxical preserved ejection fraction, low-flow, low-gradient, AS phenotype, which is characterized by more pronounced LV remodeling with a restrictive physiology.[38]

Interestingly, some AS patients lack LVH. This seems counterintuitive, even going against the known physiology of the disease. These patients do not have a worse prognosis, even after AVR. In another study, postoperative deaths occurred exclusively in patients with elevated relative LV wall thickness at baseline, irrespective of LVH;[17] similarly, another publication showed that a significant survival benefit occurred in

AS patients with preserved ejection fraction and lacking an increase in LV mass and concentric remodeling before surgery.[39]

Classically, it was thought that the increase in wall stress that characterizes AS lead to a compensatory hypertrophic response of the LV, that in chronicity became mal-adaptative. In fact, it was a long-held belief that patients could progress from a normal LV systolic function with high pressure gradients to a phenotype of impaired LV function, reduced flow and low gradients, accompanying the underlying chronic, remodeling process.[4] However, it is gradually becoming apparent that both the initiation and inhibition of cardiac hypertrophy encompass multiple distinct signaling pathways from the beginning of pressure overload setting that are unrelated to the severity of the stenosis, supporting the multifactorial nature of LV remodeling.[5,6]

Rather than "*pointing hypertrophy as a step in the development of heart failure, since it is followed by a period of broken compensation that commonly takes place slowly and results from degeneration and weakening of the heart muscle*" (Sir William Osler in "*The Principles and Practice of Medicine*") LV remodeling and transition of phenotypes do not seem to be a completely straightforward process.

Beyond Hypertrophic Growth

As previously perceived, LV adaptation to chronic pressure overload in patients with AS is a complex process and LVH is a simplistic concept. The normal myocardium consists of differentiated cardiomyocytes and stroma formed by the ECM components, tissue fluid and multipotent mesenchymal cells, all of which change in disease states.[37] ECM provides a structural basis for myocyte organization, prevents muscle fiber slippage and overstretching, being important for the transmission of contractile force and electrical signals.[40] Besides, ECM remodeling and cell to ECM interaction are essential biological processes, both in normal physiology and after myocardial injury.[41] The balance between myocyte growth and death governs the process of age-related fibrotic remodeling, and disruption of this equilibrium by conditions such as pressure or volume overload can lead to increased myocyte death and fibrosis.[42]

Beyond mechanical stress from pressure overload in AS, several stimuli modulate cardiomyocyte response through adrenergic, angiotensin, growth factors and cytokine receptors, with distinct signaling pathways such as protein kinase A and C, calcineurin, Akt-3 phosphoinositol and transcription factors. Fetal gene re-expression (natriuretic peptides, beta-myosin heavy chain, alpha-actin), alpha-myosin heavy chain and sarco-

endoplasmatic reticulum Ca-ATPase down-regulation expression and change in energy substrate use are present in this setting.[6,41] Not less important for the LV maladaptive response in AS, running with cardiomyocyte hypertrophy, increased protein synthesis and energetic demands without concomitant increase in coronary microvascular network, is mitochondrial dysfunction, through the same activated signaling pathways. This has an effect on cardiomyocyte viability through a range of effects that include transition to a more glycolytic metabolism, loss of ATP synthesis and increased ATP hydrolysis, formation of reactive oxygen species and release of proapoptotic proteins.[43] In the meantime, the increased LV wall thickness (concentric remodeling/hypertrophy), despite lowering average mural systolic and diastolic pressure, has the detrimental side effect of an exacerbated asymmetry in regional wall tension distribution.[6] Vascular endothelial cells dysfunction has also been described in pressure overload hearts and it may represent a crucial step in insufficient capillary growth, which does not keep up with myocyte hypertrophy.[44] In this way there is progressive nonuniform distribution of myocardial blood flow, with predominant subendocardial compromise of coronary flow reserve.[45] All these changes pave the way for progressive cardiomyocyte loss.

Both necrosis and apoptosis are believed to take place during the LV response to AS, the former occurring to a greater extent.[46] As more recent evidence suggests that necrosis either results from a series of programmed events, both processes may represent different manifestations of a common mechanism termed necroptosis. In the same way the common paradigm that apoptosis but not necrosis is antiphogistic and tolerogenic, that is, taking place with no inflammation and with immunological tolerance, is not strict.[47] Actually, animal studies and small human investigations suggest that persistent innate inflammation underlies myocardial remodeling in pressure overload conditions. This encompasses cytokine overproduction and both resident and recruited macrophage activity, whose myocardial density is increased.[6,41,46] Still, it is incompletely known if inflammation is exclusively coupled to necroptosis or mediated by independent triggers and signaling pathways. Either way and interestingly myocardial cytokine levels, a surrogate marker of inflammation, are often higher in patients with elevated afterload and preserved LV function, as opposed to those with reduced ejection fraction.[48] This could have an impact in understanding and eventually targeting therapeutics in LV remodeling in AS, as it might be supposed that inflammation precedes LV function deterioration.

One of the most important hallmark feature of LV remodeling in chronic pressure overload of AS is the deposition and accumulation of excessive ECM. The deposition of surplus material that corresponds to fibrosis is actually a final common tissue change upon injury, unspecific to the heart, usually following the critical phases of necroptosis, inflammation and proliferation of nonmyocytes.[49] In this process fibroblasts play a major role after converting themselves to their activated form, often known as myofibroblasts. These cells secrete elevated levels of ECM proteins to promote a profibrotic environment, essential component of the wound-healing process.[16]

Inflammatory cells and myofibroblasts are each involved in the initiation and formation of a functional reparative unit, "secretome," that emerges at the site of cardiomyocyte loss to regulate matrix turnover. Myofibroblast origin in this setting is still debatable and mounting evidence suggests that they derive from proliferation and activation of resident fibroblast. However, numerous additional precursors have been proposed, namely endothelial and epicardial cells, hematopoietic bone marrow-derived cells, perivascular cells and fibrocytes, via epithelial and endothelial-mesenchymal transitions.[16,40] Mechanical, paracrine humoral and metabolic factors might participate in myofibroblast activation through numerous signaling pathways (beta-adrenergic receptor, activin receptor like kinase, ALK 5, type 1 angiotensin II receptor, AT1R, endothelin receptor, transient receptor potential channel and integrins), whose scientific interest is obvious as potential therapeutic targets.[16] AT1R, in particular, mediates many of the effects of angiotensin II in fibroblast, including cell proliferation, migration and ECM protein synthesis. It is though that angiotensin II is also involved with transforming-growth-factor beta signaling (TGF-), both in cardiomyocytes and myofibroblasts, with previous evidence of the presence of a crosstalk between both cell types.[50,51] and also autocrine effects of these mediators on myofibroblast cell surface. AT1R activation induces the expression of TGF- and this is possibly required for angiotensin II to induce both cardiomyocyte hypertrophy and deposition of matrix proteins (including fibronectin, fibrillar collagen type I and III, and proteoglycans) with inhibition of matrix degradation, that is, promoting fibrosis.[52,53] In addition, qualitative changes are also present in ECM composition and fibrillogenesis: higher noncollagen protein turnover when compared to collagen production, increased proportion of type I collagen (up to 90% of the total collagen content) and changes in collagen postprocessing cross-link and phosphorylation.[40] Lysyl oxidase increased activity and tissue transglutaminase are plausible enzymatic mechanisms behind these changes, with possible direct

regulation of myofibroblast activity and matrix metalloproteinases and/or tissue inhibitor of metalloproteinases balance.[54] Interestingly, soluble signals locally generated in the ECM remodeling process are capable of traversing the interstitial space to distant sites. This was initially shown after acute myocardial infarction in nonischemic areas, but is a recognized mechanism explaining augmented synthesis of collagen by interstitial and adventitial fibroblasts in remote "healthy" areas of the myocardium in several disease settings.[40]

It has been previously recognized that profound diastolic functional abnormalities may arise from altered loading conditions without concomitant structural or biochemical changes in interstitial myocardial collagen, significant myocardial ischemia or ventricular hypertrophy. These may actually be entirely reversible once the primordial stimulus is removed.[55] On the contrary, considerable evidence indicates that chronic, unremitting stress, as occurs in AS, may lead to systolic dysfunction[56 57] and an association between ventricular hypertrophy and increased cardiac mortality was established in the Framingham Heart Study.[58] However, and as previously mentioned (see above, *left ventricular hypertrophy*) this observation is strictly correlative and no mechanistic link can be inferred. Moreover, an inverse relation between LV ejection fraction and myocyte degeneration and fibrosis was previously noted, not only suggesting that cell loss and ECM change contribute to the progression of LV systolic dysfunction,[59] but also favoring that the behavior of the different structures of the myocardium influences systolic and diastolic function in a distinct mode.[26] In fact, myocardial fibrosis is an independent and predictive risk factor for heart failure development and post-AVR cardiovascular events in patients with aortic stenosis.[60,61,62,63] Modified calcium handling, metabolic and electrical myocardial remodeling, diminished sarcomeric contractile efficacy per unit of volume and reduced LV compliance are possible consequences of changes in ECM composition with ensuing fibrosis. Myocardial stiffness and reduced LV compliance, in particular, appears not to be influenced by LV mass or muscle fiber size, but by the presence of massive interstitial fibrosis superimposed on small ventricles with concentric hypertrophy.[64] With worsening diastolic dysfunction, LV end-diastolic pressure rises, reducing coronary perfusion pressure and exacerbating ischemia in a LV wall with increased oxygen demand. This further perpetuates cardiomyocyte loss and ECM remodeling with fibrosis, being the mechanism that suggests that LV fibrosis is the primary cause of diastolic dysfunction and clinical progression, from compensated LV hypertrophy up to heart failure phenotype.[65,66]

All these mechanisms and signaling pathways in the cardiomyocyte may eventually explain maladaptive features of LV hypertrophy in AS patients, clearly distinct from physiological hypertrophy. In physiological forms of cardiomyocyte and/or myocardial growth, only direct mechanotransduction routes and the PI3K lipid kinase-Akt serine and/or threonine kinase pathway are activated, by growth factors and/or hormones, such as insulin-like growth factor-1, with normal fetal gene expression, leading to LV eccentric remodeling. This involves replication of cardiomyocyte sarcomeres both in-parallel and in-series, normal cardiomyocyte energetics and normal or increased microvascular density, with an overall amplified systolic myocardial performance. Neither necroptosis nor ECM remodeling with associated fibrosis take place.[6]

Lessons From Histomorphology

Cardiomyocytes are postmitotic cells with an extreme differentiation towards protein synthesis and assembly, geared towards cytoskeletal microtubular interaction and the optimization of energy use. This commitment is essential for building up the sarcomere, a complex organic functional unit, and it is the probable reason for the inability of adult cardiomyocytes to undergo mitosis and respond with hyperplasia to the pressure overload, namely in the context of AS.[6]

Myocardial growth is accomplished through augmented sarcomerogenesis without accompanying cell division, resulting in an increased contractile strength.

As mentioned above, structural adaptation to pressure overload goes further than simple cardiomyocyte hypertrophy, however. In the normal heart, fibroblasts are the predominant cell type, exceeding myocytes in number but not in volume. These cells provide a 3D mechanical scaffold that supports the contractile activity of myocytes and synthetize the ECM, regulating its composition.[67]

The ECM is made of different types of collagen, fibronectin, glycosaminoglycans, growth factors and proteases. When activated following injury, fibroblasts differentiate into myofibroblasts. These are not commonly found in healthy hearts, and are responsible for ECM remodeling, partly through the secretion of growth factors and proteases.[68]

Pathology findings in endomyocardial biopsy specimens from patients with AS reflect global myocardial remodeling, including cardiomyocyte hypertrophy and changes in the ECM composition.

Our knowledge of the pathological findings in the myocardium of AS patients is derived mainly from biopsy specimens of the left ventricular

basal septum, obtained by myectomy performed during surgical AVR in patients with severe AS. This additional procedure has been shown to reduce the risk of persistent sub-aortic stenosis in patients with severe AS showing an asymmetric basal septal hypertrophy with bulging, present in up to 10% of the cases.[69] Left ventricular septal myectomy is also carried out as a primary procedure to reduce outflow tract obstruction in patients with obstructive hypertrophic cardiomyopathy (HCM). Myocardial biopsies may also be performed only for diagnostic purposes, such as the identification of rare metabolic or infiltrative storage diseases with a hypertrophic phenotype and specific therapeutic targets.

There is little data regarding the histological evaluation of myectomy specimens, and most of it originates in small studies. These have found no morphological differences between cardiac hypertrophy in the setting of different overload conditions, such as AS and HCM.[70,71,72]

Hypertrophic cardiomyocytes have traditionally been defined as those showing a cellular transverse diameter greater than 20μm, measured at the mid cell level, an hypereosinophilic cytoplasm, prominent functional units, and hyperchromatic nuclei (Fig 1A and B).

According to the literature, histology remains the key for the diagnosis of HCM. Myocyte hypertrophy and disarray, along with interstitial fibrosis are considered the pathological hallmarks of the disease.[73] Disarray is defined as a haphazard alignment of adjacent myocytes, with crisscrossing and branching myofibrils, and it is found only focally and not through the entire myocardium.[74-76] It was thought to be pathognomonic to HCM, but that has been shown to not be the case, as this pattern occurs in hearts with both congenital and acquired conditions, such as AS, and even being commonly found in specific sites of healthy hearts, namely in the subaortic septal region, right ventricular free wall, ventricular apices and LV-right ventricular junctions[77,78] (Fig 1C).

Diffuse endocardial thickening is also a common, nonspecific, finding in AS patients and is related to collagen and elastin deposition in areas of imposed shear stress, such as the basal interventricular septum (Fig 1F and G).

It is possible that there is a close relation between endocardial thickness and the gradient of whole myocardium fibrosis. Morphometry studies have shown that in patients with pressure overload conditions, such as AS, fibrosis, measured as a percentage of the observed tissue, is significantly higher in the subendocardium than in the subepicardium. This does not occur in patients with volume overload, who show no difference in the amount of fibrosis in the different myocardial layers.[10,79] Supply-demand mismatch at the innermost part of the myocardium could be a possible contributing factor for this interesting finding.

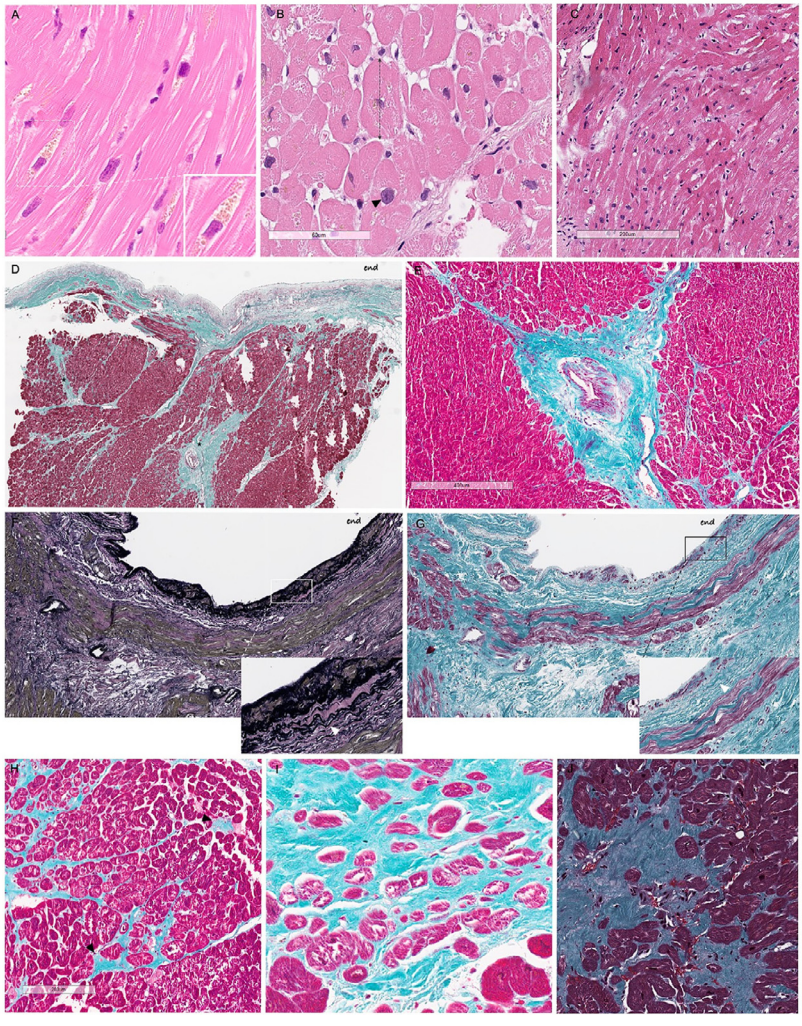

FIG 1. Histomorphology patterns from septal endomyocardial biopsies in patients with severe aortic stenosis. (A) Syncytium-like arrangement of cardiac myocytes in a patient with severe aortic stenosis and myocardial hypertrophy (Hematoxylin-eosin x 200). Intracellular perinuclear yellow-brown pigment (detail) corresponds to lipofuscin, an ageing related aggregate of oxidized proteins. (B) Detailed view of cardiomyocyte hypertrophy in cross-section with hyperchromatic nuclei (arrowhead) and hypereosinophilic cytoplasm. Adequate measurement of diameter (—) is to be performed in the center cell plane (a cross-section encompassing the nucleus) (Hematoxylin-eosin x 100). (C) Cardiomyocyte disarray, storiform pattern. Cellular interlacing, whirling, or herringbone patterns typically define this nonspecific finding Hematoxylin-eosin x 40). Several features might compromise its accurate diagnosis: there are 4 main histological types; 3-dimensional architecture affects fiber disposition and the plane of histological sectioning; it may occur in normal hearts, particularly at septal right and left ventricle fiber junction, as well as in conditions that result in increased myocardial mechanical stretch.[72] Although not pathognomonic, other pathology changes, such as cardiomyocyte nuclear enlargement with pleomorphism,

Excessive deposition of collagen in ECM remodeling had been traditionally categorized as reactive and replacement fibrosis. Reactive type is interstitial and diffuse. It follows an increase in myofibroblast activity and collagen deposition at the early stages of AS. It is not related to cardiomyocyte cell death and has been demonstrated to be reversible after AVR.[49] Net accumulation of collagen in reactive fibrosis starts at the skeletal scaffold of the myocardium, with progressive thickening of both endomysium and perimysium. With time there is expansion of the interstitium, seen on histology as bands of collagen in the intercellular space between cardiomyocytes (Fig 1H). Reactive fibrosis is also characterized by the deposition of thick collagen fibers around intramyocardial coronary arteries and arterioles and medial hypertrophy of these vessels.[40,80] This contributes to the architectural distortion of the myocardium, with streaky fibrosis appearing as a consequence of outward radiating collagen fibers from perivascular locations (Fig 1D and E).[80] Coalescent areas of interstitial fibrosis are sometimes described as myocardial microscars, usually more prevalent at the subendocardium.[79] With time and increasing fibrosis, cardiomyocytes may become ensnared by the fibrillar collagen that is generated by adjacent myofibroblasts and atrophy (Fig 1I), leading to reduced myocardial workload. This leads to a considerable

abnormal small intramural coronary arteries (intimal and medial smooth muscle cell hyperplasia) (detailed in E) and interstitial adiposity, follow the presence of disarray in patients with HCM, and are not common in biopsy samples from patients with AS. Thereto disarray tends to be quantitively mild, dispersed and not positively related to segmental LV thickness in conditions other than HCM.[71,136] (D) Severe perivascular fibrosis (Masson's trichrome x20) (end:endocardium). (E) Intramural dysplastic vessel with media thickening and narrowing of the lumen (Masson's trichrome x100). (F) Subendocardial fibroelastosis in a patient with severe AS, put in evidence by elastic van Gieson's stain (x100, enhanced dark elastic fibers - arrowhead). This predominantly occurs in overload conditions other than in primary muscle disease (hypertensive heart disease, subaortic septal bulge). (G) Abundant collagen fibers at subendocardial level at the same tissue sample as in F (Masson's trichrome x100). (H) Detailed visualization of collagen fibers amid cardiomyocytes, explaining extracellular volume expansion (compare with Panel A and B, where cardiomyocytes are fit together with no expansion of intercellular spaces). Coalescent areas of interstitial fibrosis may be described as microscars (arrowhead) (Masson's trichrome x 100). (I) Detailed view of encased cardiomyocytes within collagen bundles, with reduced cell diameters reflecting progressive cell atrophy (compare with individual cell diameter in B). (Masson's trichrome x 200). # A special note should be given concerning histochemistry for ECM characterization. Masson's trichrome is more specific for collagen fibers and does not significantly stain other components of the ECM. On the contrary, Picrosirius red, an alternative stain for ECM, also stains other components such as fibronectin. In this way, quantification of myocardial fibrosis is usually overrated in endomyocardial biopsies studies with Picrosirius red staining.[137] (J) Large areas of collagen deposition devoid of cardiomyocytes may be identified as replacement/reparative fibrosis in patients with severe AS (Masson's trichrome x 200). Ultrastructurally the meshwork of collagen fibers is said to be distinct from reactive fibrosis as thick collagen fibers run perpendicular to muscle fibers.[80] (Color version of figure is available online.)

increase in diastolic stiffness, culminating in the restriction of length-dependent myocardial force generation.[49,80]

Since this type of fibrosis is a reactive rather than a reparative process, pressure overload removal would in theory reverse pathophysiology and restore both diastolic and systolic integrity. Cardiomyocyte atrophy (but not death) should also, in theory, be reversible.

The other side of the coin is replacement or reparative fibrosis, which also seems to occur in AS patients, but in more severe cases and later in the course of the disease. It is related to cardiomyocyte cell death and thus irreversible (Fig 1J). Reparative fibrosis in the context of AS is indistinguishable from that which occurs in other contexts, such as ischemic and nonischemic cardiomyopathies. The sequential relation between reactive and replacement fibrosis which we have described lacks confirmation. However, it has recently been shown that patients with advanced AS undergoing AVR have a combined histologic pattern of both replacement and diffuse reactive fibrosis.[79]

Besides these 2 well established patterns of fibrosis, some authors have proposed new ones according to specific functional consequences or arrhythmogenic potential.[81] In spite of this, they seem to represent different combinations of replacement and reactive fibrosis, and thus identifying them appears to be of limited clinical value.

As detailed in the next section, myocardial texture and functional changes, including noninvasive assessment of both types of fibrosis, may be characterized by the combination of several imaging modalities.

Although not a pattern of fibrosis per se, cardiac senile amyloidosis (CA) should still be mentioned in this section, as it contributes to an increase in ECM in a significant portion of mostly elderly AS patients. In autopsy studies, wild-type senile transthyretin amyloid deposits are found in up to 15% of patients with AS, with a higher prevalence in elderly, male, symptomatic patients with low-flow states and sub-normal LV ejection fraction.[82-84] Thus, Congo Red staining for amyloid should be performed routinely on all surgical myectomy specimens in patients with >65 years old, particularly in those with LV hypertrophy and AS.[70,85]

Advanced Imaging for a Left Ventricular Disease

Transthoracic echocardiography remains the keystone modality for the characterization of aortic valve disease severity, hemodynamic consequences and LV remodeling and adaptation to pressure overload condition. Parameters describing aortic valve severity (peak velocity and mean transvalvular gradient) are heavily flow dependent and these should be

always fully integrated in a comprehensive echo-based assessment. This modality may additionally provide information concerning global LV afterload, resulting jointly by fixed valve stenosis, decreased systemic arterial compliance and/or increased vascular resistance.[38] Valvuloarterial impedance (Zva) measurement takes into account mean pressure gradient, systolic arterial pressure and body surface area indexed flow to estimate global hemodynamic load, being a strong predictor of LV dysfunction and outcome in AS patients.[86,87]

Beyond LV mass estimation and relative wall thickness, which stem from "old" m-mode measurements extrapolation and oversimplification, LV remodeling is scarcely characterized by echocardiography. Small old studies performed before the clinical routine use of cardiac MRI quantitatively assessed myocardial reflectivity properties by ultrasonic integrated backscatter (IBS) signal. This has been not only related to myocardium collagen content, but also to its intrinsic contractility, when analyzed throughout the cardiac cycle.[88,89] This measure of myocardial acoustic impedance has also been identified as a possible discriminator for LV systolic impairment is patients with severe AS, with significant change in patients with LV mass regression after AVR.[90] However, impedance quantification is highly laborious and dependent on acquisition settings with vendor and/or machine specific variabilities. Moreover, it seems poorly correlated with histology in patients with less than extensive grades of myocardial fibrosis,[91] with paucity of data supporting its clinical use.

LV ejection fraction as a measure of LV systolic function is limited as it is largely dependent on loading (pressure and volume) conditions, particularly relevant in patients with significant valve lesions. Beyond that, concentric remodeling with increased wall thickness and reduced cavity diameter, typical of stenotic lesions, may run with LV EF preservation in spite of reduced myofibers shortening.[92] As a volume-based parameter it does not account for the complexity of multi-layered derived myocardial mechanics, which by itself is dependent on compensation processes limiting remodeling and maintaining volumes.[93]

Normal flow, high gradient severe AS often coexist with reduced ejection fraction. In these patients myocardial function is globally preserved and usually there is LV ejection fraction recovery after aortic valve intervention, as a purely "*afterload mismatch*" definition. A proportion of patients, contrariwise, present with low-flow, low-gradient and preserved LV ejection fraction disease. This nonclassical form seems more like a separate entity characterized by progressive maladaptive remodeling rather than an end-stage high gradient disease.[94] Either way, both

phenotypes have dismal prognosis if left untreated.[95] In fact, comparative studies evaluating the prognostic value of preoperative LV ejection fraction have shown that this is an inaccurate marker for both postoperative LV ejection fraction and LV mass regression. Besides and as an isolated marker it scantly predicts postintervention clinical events. As a consequence, asymptomatic patients may be referred for intervention in a late-stage phase once LV ejection fraction is compromised, as its impairment may follow already established adverse LV remodeling. In this same view, normal LV ejection fraction before intervention does not warrant adequate reverse remodeling and better clinical outcomes after treatment.[4]

Myocardial deformation imaging may be superior in detecting subtle LV sub-clinical dysfunction. Longitudinal deformation has been identified as an independent mortality and clinical events predictor in asymptomatic patients.[14,96] In a registry with more than 200 asymptomatic patients, global longitudinal strain (with a cut-off value of -18%) was an independent predictor for development of symptoms and surgical referral through a mean follow-up period of 12 months.[97] For asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction, a longitudinal strain cut-off value of -14.7% was a good discriminator of global mortality in a recent metanalysis (2.5 times risk of mortality during a near 2-year follow-up period).[98]

As above mentioned, LV hypertrophy is the adaptative response to chronic rise in intracavitary pressure as occurs in AS. As previously demonstrated, LV ejection fraction might be maintained with both longitudinal and circumferential strain reductions as long as there is progressive increase in wall thickness.[92] However, LV contractility is a complex process that stems from the interaction of distinct myocardial layers´ deformation, each of them with different responses to chronic pressure overload conditions.[99] In fact longitudinal strain is the most vulnerable component of LV mechanics and in an early stage of disease its impairment may be compensated by an augmented circumferential function, which in itself seems to contribute more to LV ejection fraction than longitudinal deformation.[92,93] One other component of deformation changes that occurs in pressure overload conditions is also related to differential myocardial layer affection. As subendocardial ischemia has long been recognized as an early sign of myocardial suffering from pressure overload caused by AS,[100] explaining longitudinal strain affection, this is possibly related to increased LV twist in these patients. This is caused by the dynamic interaction between oppositely oriented subepicardial and subendocardial fiber helices. With predominant subendocardial affection,

meaning less basal rotational counteraction, there will be an increased subepicardial arm of force, with more apical rotation and twist. These parameters were positively correlated to aortic valve jet velocity and mean gradient, albeit declining with increasing LV hypertrophy and dilatation, regressing after AVR, as previously shown[101,102] (Fig 2). Accordingly, diastolic rotational properties in this setting are also modified. Delayed and reduced early LV untwisting but higher peak diastolic untwisting velocity have also been noted. These findings may not only derive from subendocardial ischemia affecting the active part of relaxation, but also to increased store of potential energy that will be later released.[102]

Recently, the combination of LV strain assessment throughout the cardiac cycle and noninvasively estimated LV pressure was proposed as a measure of instantaneous power, integrated over time to obtain myocardial work. In severe AS, however, LV systolic pressure does not equal noninvasive measurement of systolic blood pressure and it should be corrected with the addition of Doppler-derived mean aortic gradient. Even so, this evaluation may be of particular value as it distinguishes if global longitudinal strain reduction is due to reduced contractility (reflected as reduced myocardial work) or increased afterload (reflected as increased myocardial work).[103,104]

As a whole, deformation imaging assessing myocardial mechanics may shed light on the pathophysiology of patients with AS, namely on compensatory mechanisms preventing LV ejection fraction deterioration until late stages of the disease. Still being indirect parameters, whose changes might reflect different stages of myocardial remodeling, their routine use may identify patients with subclinical LV dysfunction, benefiting from earlier referral and intervention.

More recently, global impact of severe symptomatic aortic valve stenosis on the heart was categorized according to distinct echocardiographic parameters (LV mass and ejection fraction, filling pressure estimation, left atrial volume and mitral regurgitation, atrial fibrillation, pulmonary hypertension, tricuspid valve disease and right ventricular dysfunction).[105] This 4-stage system does not specifically account for LV remodeling or adaptation, except for LV mass estimation, but reflects a practical bedside approach for prognosis definition in what concerns global mortality, hospital admission and stroke incidence, after STS and fragility scores adjustment. Nevertheless, one could suppose that echocardiographic stage definition starting at LV dysfunction and going through upstream affection up to right ventricular dysfunction follows previous mal-adaptative LV remodeling and myocardial ultrastructural changes.

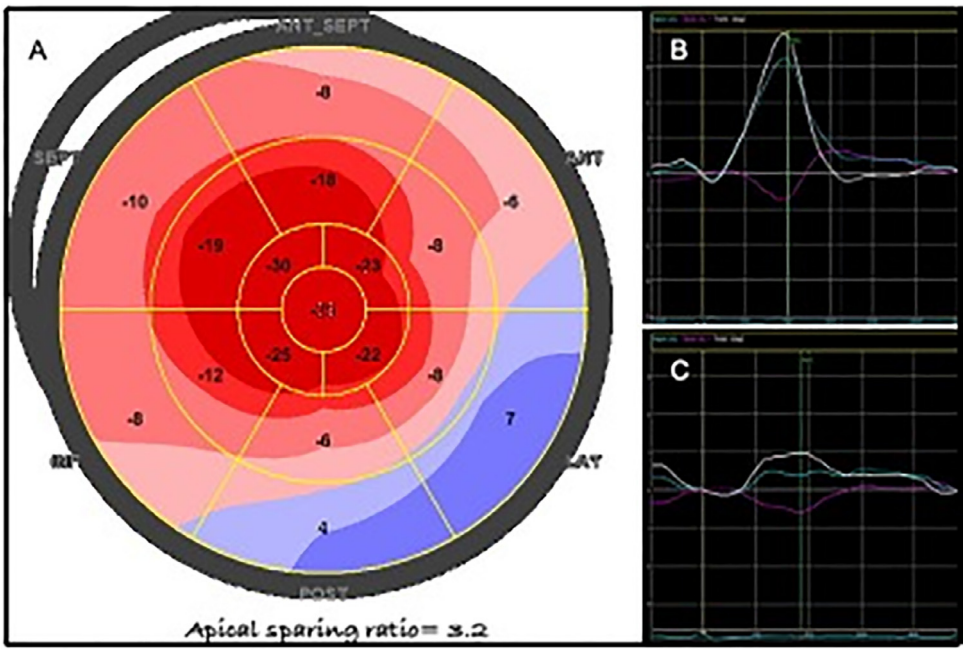

FIG 2. Examples of echocardiographic deformation imaging in patients with severe aortic stenosis. Panel A – Reduced global LV longitudinal strain with typical apical sparing pattern, as defined by *average apical LS / average basal LS + average mid LS > 1*, in a patient whose both cardiac magnetic resonance and histological analysis at myectomy specimen were not in favor for the presence of amyloid. Panel B/C – Basal and apical rotation/twist curves in the same patient, before (B) and after (C) AVR.

The incorporation of deformation imaging, namely global longitudinal LV strain, in this novel staging classification, as proposed by Vollema et al, may actually detect more individuals with advanced LV damage, providing incremental prognostic value over the original classification.[106]

As already mentioned, distinct outcomes of patients with AS, even among those with preserved ejection fraction and across the same echocardiographic based definition phenotypes, are mainly related to the complex interaction between myocyte injury, necroptosis, ECM remodeling and fibrosis. Particular attention was devoted to myocardial fibrosis, not only due to the fact that it may be adequately characterized by routine available noninvasive imaging tools, but also because it seems an important driver of LV decompensation leading to heart failure development, similarly to what occurs in other myocardial disease settings.[107] In this way, cardiac MRI may provide information towards myocardial composition as a primordial soft tissue characterization imaging tool. In a single radiation-free examination, joint information on myocardial fibrosis and extracellular matrix composition, LV mass, geometric remodeling and function can be provided. Just like for echocardiography, deformation assessment may also be assessed at MRI study by new tools such as tissue tracking, with already demonstrated value towards the prediction of reverse remodeling after surgical AVR.[108]

Late enhancement-based imaging relies on T1-value shortening in places where gadolinium containing contrast media accumulate. These extracellular agents are not normally retained in intact myocardium, being distributed in the interstitial and/or extracellular spaces of the heart within few minutes after intravenous administration, with a homogenous and fast wash-out time. Whereas contrast uptake depends on the tissue perfusion properties, with some interference from heart rate, blood hematocrit and glomerular filtration rate, contrast retention and wash-out rates mainly depend on the amount of extracellular space.[109] Indeed, areas of necrosis and fibrosis are generally more hydrated, containing greater extracellular space than normal tissue, which is responsible for higher concentration of gadolinium and high signal on postcontrast T1-weighed images.[110] As replacement or reparative fibrosis occurs after myocyte necroptosis, this could be identified by LGE in some of the patients with severe aortic stenosis. Actually, LGE in patterns that range from subendocardial infarct type scars to patchy focal and linear midwall noninfarct type fibrosis, with predominance towards left ventricular basal segments, have been demonstrated in 19 to 62% of the patients at preoperative magnetic resonance studies.[111-113]

Previous studies have found good correlations between the amount of myocardial fibrosis at histopathology and LGE, namely between interstitial fibrosis and the percentage of LGE.[63] However, much weaker correlations have been subsequently described for the histological validation of LGE and this could be explained by several reasons. First, LGE reflects the presence of focal replacement fibrosis, which by itself, as previously mentioned, is histologically distinct from reactive, diffuse, interstitial fibrosis. A straightforward relation between reactive and replacement fibrosis would also have to be established, particularly at specific myocardial locations, for this to be true. Second, histological analysis provided by biopsy does not capture the global myocardial involvement and structural changes, only possible at autopsy studies. Furthermore, regional myocardial *in vivo* sampling is both dependent on the site and type of biopsy. Basal anteroseptal specimens either gathered for diagnostic or therapeutic purposes, at concomitant myectomy procedures performed during surgical AVR, may well overestimate structural myocardial changes occurring in this setting. As basal LV segments are theoretically more prone to endocavitary pressure overload and hence to mechanically induced cardiomyocyte stress and ECM remodeling, one might suppose that myocardial changes and fibrosis would be more prominent at this location. Additionally, myocardial samples obtained from needle aspiration instead of excisional biopsies from surgical scalpels might skip important information concerning subendo to midmyocardium fibrosis gradient. As previously demonstrated, there is a decreasing collagen gradient from subendocardium towards deeper myocardial layers and this could be of pathophysiological relevance.[114-116] At needle aspiration biopsies endocardium identification is often missed, which hampers sample orientation, adequate description of fibrosis patterns and possible correlation to noninvasive MRI myocardial characterization.

More recent technological developments in MRI tissue characterization provide further in-depth knowledge upon myocardial remodeling in this setting. T1 mapping techniques rely on the exact T1 estimation of the tissue and this will be increased with diffuse extracellular matrix expansion as seen in infiltrative and reactive interstitial fibrosis.[117] As opposed to LGE, which is characterized by gadolinium accumulation in areas of extensive fibrotic deposition, native T1 will change according to increased interstitial space between myocytes. As any change in the proportion of myocardial components will affect this parameter, well ahead cardiomyocyte death and replacement, its measurement has proven utility for infiltrative disorders, early disease stages[12] and heart valve diseases.[118] In a study with moderate and severe aortic stenosis Bull et al

found a significant correlation between native T1 values and collagen volume fraction at histochemistry as assessed in a small number of patients by automated quantification. Myocardial T1 values were also significantly higher for patients with severe symptomatic aortic stenosis when compared with those with asymptomatic and moderate disease.[119] Either way, single native T1 myocardial values may vary across vendor specific protocols and scanner field strengths, being gender and age dependent with regional asymmetries across LV segments.[120,121] Not less important, significant overlap exists between T1 values of normal and diseased myocardium, which restricts diagnostic assumptions, especially in asymptomatic patients with severe disease. Furthermore, there is some debate around the influence of intravascular volume in native T1 values. In spite of reduced capillary density and microvascular ischemia typical of pressure overload conditions, it was recently suggested that these conditions run with coronary vasodilatation and increased intravascular volume, eventually contributing to increased native T1.[122] Lastly and as said, myocardial infiltration such as occurs in amyloidosis, which may often co-exist in older patients with severe aortic stenosis, is responsible for particular high T1 myocardial values,[123] and this does not represent increased collagen interstitial deposition.

Postcontrast T1 mapping derived measures of partition coefficient and extracellular volume (ECV) fraction allow for the quantification of diffuse fibrosis according to the amount of gadolinium distribution in the myocardium. In theory these could be more sensitive to extracellular space expansion as native T1 values may vary due to both intracellular and extracellular compartment changes. As they are calculated from the ratio of change in myocardial T1 in relation to pre- and postcontrast blood-pool T1, they are less prone to both acquisition technique and post-processing confounding variables and errors, enabling less variability among studies and higher diagnostic accuracy across specific vendor protocols and MRI machines.[117,12]

Decreased postcontrast T1 values were previously associated with increased amounts of collagen volume fraction measured in endomyocardial biopsies[124] and ECV may be interpreted as an imaging surrogate marker of diffuse fibrosis. Actually, its reciprocal represents the myocardial cell volume fraction, reflecting cardiomyocyte mass and hypertrophy. In this way, combined pre- and postcontrast T1 mapping assessment may better describe cellular and extracellular compartment's changes across different clinical scenarios. In a study by Chin et al ECV measurements in patients with aortic stenosis, in particular when indexed to LV end-diastolic myocardial volume and body surface area, which takes

geometric remodeling into account, have shown good correlation to histological diffuse fibrotic burden. A clear stepwise relationship to distinct clinical and imaging measures of LV decompensation was also demonstrated, with less overlap between values across distinct disease states. Both indexes of focal and diffuse fibrosis were univariate predictors of outcome.[125] Moreover, mid-wall LGE happened to be present in patients with significantly higher values of indexed ECV, a fact that may shed a glimpse towards our understanding over myocardial tissue remodeling throughout time and in accordance to progressive severity of aortic valve stenosis.

In a comprehensive pathology study in patients with severe aortic stenosis, a structure-functional correlation confirmed that clinical transition to heart failure, hemodynamic deterioration and LV ejection fraction compromise was related to progressive myocardial fibrosis and cardiomyocyte degeneration.[65] Another multimodality imaging correlation study found that myocardial fibrosis at histology correlated well with echocardiographic markers of longitudinal systolic function but not with LV ejection fraction or aortic valve area. Importantly, the absence of fibrosis had significant impact in clinical functional improvement after AVR. The degree of late enhancement in patients with preoperative myocardial replacement fibrosis, which was also demonstrated to progressively increase in asymptomatic patients while waiting for intervention, remained unchanged after intervention, implying that AVR failed to reduce the degree of replacement fibrosis.[7,126] Last decade investigations went further ahead, trying to establish the relation between myocardial replacement fibrosis as assessed by noninvasive preoperative cardiac MRI LGE and clinical outcomes in patients with severe aortic stenosis. A 2019 metanalysis, involving 1300 patients followed over a mean period of 2.8 years, demonstrated that preoperative LGE was consistently, strongly and significantly associated with clinical outcomes. Almost one-half of the patients had LGE, with predominant nonischemic pattern, and this triples all-cause and cardiovascular mortality, independently contributing to their poorer long-term prognosis.[127] Accordingly, and as previously suggested it might be assumed that surgery is often tardily offered for optimal long-term outcomes in patients with severe AS and conventional indications for intervention.[60,62] This is particularly relevant as there is no significant correlation between these and the presence of LGE, namely between LV ejection fraction and LGE. Moreover, early mass regression after AVR is greater for patients with higher preoperative LV mass and when myocardial scar is absent,[128] allowing to presume that both cardiomyocyte and ECM compartments are plastic components of

myocardial tissue. Actually, it was already shown that despite being arrested by AVR, progressive focal myocardial scarring, as assessed by LGE, does not regress after intervention.[126] On the contrary, Treibel et al put in evidence that ECV fraction unexpectedly increased at the first year after aortic valve intervention in a cohort of 116 patients with severe symptomatic AS. As proposed, this could represent differential reverse remodeling across distinct tissue compartments. Faster regression of cellular hypertrophy when compared with diffuse fibrosis would explain proportional increments in ECM components after surgery[129] (Fig. 3 and 4).

Prospective outcome data in what concerns diffuse myocardial fibrosis in AS patients, as assessed by pre- and postcontrast mapping techniques, are much less robust than for replacement fibrosis and LGE, being limited to single center studies. Previous investigations showed that ECV fraction may predict outcomes as least as strongly as LV ejection fraction and that both native T1 and ECV are correlated with prognostic markers such as Nt-pro-BNP.[130,129] However intravascular compartment expansion is also responsible for changes in T1, and thus ECV values. As the severity of coronary microvascular dysfunction is related to the severity of aortic valve stenosis and diastolic perfusion time rather than to LV mass,[131] both T1 and ECV values should be interpreted with caution as surrogate markers of diffuse myocardial fibrosis, ECM changes and prognosis in this setting. Actually, in the PRIMID-AS (Prognostic Importance of Microvascular Dysfunction in Aortic Stenosis) study neither LGE nor ECV were associated with the primary outcomes of symptom onset requiring AVR, major adverse cardiovascular events or cardiovascular death in asymptomatic moderate to severe AS patients.[132] Contrariwise a 2020 prospective multicenter study following 440 AS patients through a median period of 3.8 years after AVR, found that diffuse myocardial fibrosis quantified by cardiac MRI T1 mapping is an independent predictor of all-cause mortality. Both the total volume and the percentage of diffuse fibrosis, as respectively assessed by indexed ECV and ECV%, were independently associated with clinical and imaging measures of LV decompensation.[133]

As for cardiac MRI and gadolinium, myocardial fibrosis may also be assessed with cardiac Computed Tomography (CT) and the use of iodine, an extracellular, extravascular contrast agent that lingers in extracellular water of scar areas, due to a higher volume of distribution and changed, slower kinetics. Myocardial ECV by CT was already validated in humans against the gold standard – endomyocardial biopsy, with good correlation to cardiac MRI ECV values. It involves a low dose radiation protocol

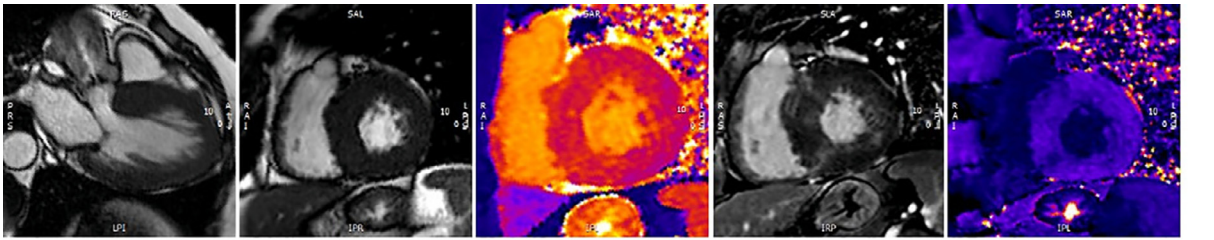

FIG 3. Example of a comprehensive cardiac MRI study focusing LV hypertrophy and remodeling in patients with aortic valve stenosis.

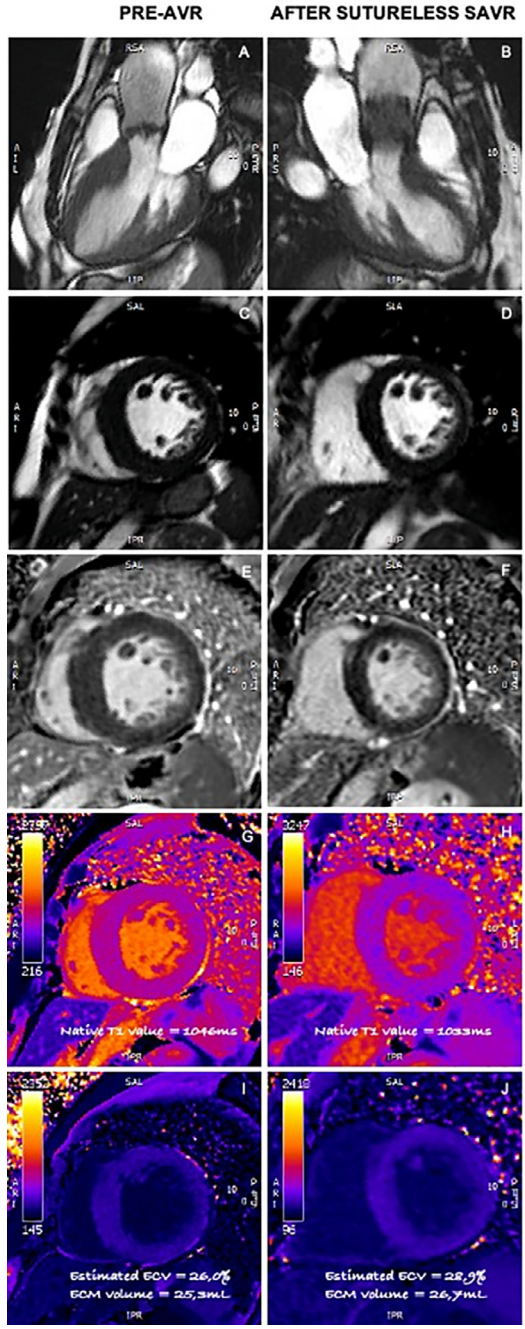

FIG 4. Global LV characterization before and after surgical AVR in a symptomatic patient with severe aortic stenosis. Panel A/B/C/D – *Cine-SSFP* long and short-axis images before and after

with additional baseline and one 3-5-minute postcontrast acquisition, beyond conventional angiographic acquisition for cardiac targeted studies. In this way it might represent an attractive modality for ECV myocardial quantification in AS patients being referred for cardiac CT studies, as part of routine imaging planning for transcatheter AVR.[134,135]

Conclusions

Aortic stenosis is a complex heart valve disease, challenging the mechanisms of LV response to a pressure overload scenario. In what concerns clinical management, diagnostic approach should necessarily include an integrated evaluation of the valve, the vasculature and the ventricle. Actually, it is the adaptation of the LV to this afterload condition that defines whether and until when it is tolerated, the urgency of intervention and the postinterventional outcome.

Valve narrowing is one of the insults that drives LV response. As seen, LV remodeling is not uniform and factors such as arterial hypertension and other comorbidities, vascular stiffness, myocardial ischemia and gender may be important modulators. Nevertheless, contemporary use of echocardiography and cardiac MRI in combination may better assess the afterload conditions, global and regional LV function beyond ejection fraction and myocardial structural changes. A comprehensive MRI protocol involving pre- and postcontrast mapping sequences and LGE may adequately provide information towards the fibrotic burden of the whole LV, assessing, with histopathology correlation, both interstitial and/or diffuse and replacement and/or focal type of fibrosis. As a research tool at longitudinal evaluations, it may further characterize ECM changes occurring both before and after valve intervention, going along with metabolic, vascular and functional LV remodeling. Deformation imaging is really opening up clues to define the evolving functional phenotype which may accompany the adverse structural changes.

AVR. Panel E/F – Late gadolinium enhancement images at the same LV level. Panel G/H – Precontrast T1 mapping at mid LV level. Panel F/G – Postcontrast T1 mapping at mid LV level. *ECV is calculated as: ECV= (1-hematocrit) x [ΔR1myocardium] / [ΔR1blood pool]; ΔR1 being the difference in relaxation rates (1/T1) before and after contrast. Total LV ECM and cell volumes are calculated from the product of LV myocardial volume (LV mass divided by myocardium specific gravity – 1.05g/mL) and ECV or (1-ECV), respectively. LGE mass remains the same at the sixth month after AVR in spite of increased percentage as LV mass regressed (quantification using a 5-SD threshold). A proportional higher reduction in myocardial cell volume is responsible for the increase in ECV after AVR (increased ECM volume). ECM, extracellular matrix; ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; SSFP, steady state free precession.*

However, there is paucity of data specifically addressing the relation between interstitial and replacement fibrosis as possible sequential or distinct structural events involved in the development of the heart failure phenotype. In symptomatic AS patients there is also a wide range of diffuse myocardial fibrosis, which suggests that symptom development may not be due to fibrosis alone. Moreover, it is not defined if strain measurement, or its correction for the afterload (myocardial work), is capable to predict the presence of myocyte hypertrophy vs diffuse myocardial fibrosis. Likewise, the relation between regional deformation impairment and focal fibrosis needs to be demonstrated in this setting.

As a whole, a holistic multi-imaging approach that goes further beyond valve obstruction evaluation and that includes overall pressure overload estimation, degree of LV hypertrophy, fibrotic burden and hemodynamic consequences, may help to predict symptom progression and better stratify prognosis in individual patients. This is particularly relevant as the results of both surgical and percutaneous aortic valve intervention continue to evolve and improve. The use of noninvasive markers of LV subclinical decompensation may ultimately better select patients benefiting from earlier valve intervention, before irreversible myocardial injury. Future development of medical therapies targeting ECM remodeling may be also eventually determined.

Authors' Contributions

João Abecasis, Conceptualization, Investigation, Writing – original draft. Daniel Gomes Pinto, writing – review and editing. Sância Ramos, Supervision, writing – review and editing. Pier Giorgio Masci, writing – review and editing. Nuno Cardim, writing – review and editing Victor Gil, Supervision, writing – review and editing. Ana Félix, writing – review and editing.

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