A case-based narrative review on the structural myocardial changes associated with systolic dysfunction in severe aortic stenosis

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ABSTRACT

Severe aortic stenosis (AS) is not a disease of the valve only, but one involving the myocardium. Left ventricular systolic dysfunction in severe AS is associated with worse outcomes, despite aortic valve replacement (AVR). This case-based narrative review aims to highlight both the macro- and microscopic structural features of the myocardium in severe classic AS, with a particular focus on differentiating the afterload mismatch group from those with true contractile dysfunction. Left ventricular systolic dysfunction is associated with maladaptive patterns of left ventricular hypertrophy, mid-wall interstitial fibrosis, subendocardial replacement fibrosis secondary to ischaemia and possibly, low-grade chronic inflammation, and myocardial oedema. The underlying molecular signals appear to establish an ongoing cycle of maladaptive remodelling, but the initiating triggers remain poorly understood. Furthermore, features that differentiate those with afterload mismatch from those with true contractile dysfunction have been poorly investigated and further prospective research would provide important insight that could translate to earlier detection of those who may benefit from AVR before irreversible myocardial damage ensues, improved decision-making around management of these patients and the development of novel therapeutic strategies. SA Heart® 2024;21:226-236

INTRODUCTION

Aortic stenosis (AS) is a disease of both the aortic valve and myocardium of the left ventricle (LV).[1,2] With a global prevalence of ± 18 million people, AS accounts for roughly 25% of all valvular heart disease and has a significant impact on patients' quality of lives.[2-4] The commonest causes for AS include rheumatic heart disease (RHD), calcific degenerative disease in the elderly and premature degeneration in congenital bicuspid aortic valves. Calcific degenerative disease in higher-income countries, has largely overtaken RHD as a cause for AS. In lower- and middle-income countries, however, RHD still predominates and remains an important cause for AS.[1-4] The only definitive therapy for AS is aortic valve replacement (AVR) which reverses the mechanical obstruction, in turn, reversing some of the adaptive myocardial changes e.g. left ventricular hypertrophy (LVH).[1,2,5] There are no definitive therapies available to address the impact on the myocardium itself and while it is well established that AVR reduces mortality in AS, the procedure itself is costly, invasive, reserved only for severe cases and carries a high surgical risk for those with left ventricular systolic dysfunction.[6-8]

Left ventricular systolic dysfunction is infrequently encountered in the setting of classic, severe AS.[6,9] The 2 described mechanisms underlying the systolic dysfunction include: (i) true myocardial contractile dysfunction, and (ii) afterload mismatch.[10-15] The current understanding is that for the former, there is irreversible myocardial damage that impedes improvement in post-operative systolic recovery while for the latter, intrinsic myocardial contractility is preserved therefore producing an often prompt, and drastic systolic improvement after AVR.[10-15] Understanding the differences between the drivers, morphological characteristics that signal a transition to decompensation / dysfunction, associated molecular pathways and outcomes for these 2 groups is important for predicting post-AVR responses and for the development of novel diagnostic and therapeutic strategies e.g. early biomarkers or gene / other molecular therapies.

This review aims to:

- Describe the existing literature on the macroscopic structural and haemodynamic features that are associated with left ventricular systolic dysfunction in classic severe AS using various cardiac imaging modalities.
- Understand the histological features and molecular pathways underlying these structural characteristics.
- Identify those features capable of differentiating the 2 broad mechanisms (as described) that lead to systolic dysfunction. The paper comprises 3 main sections based on broad themes derived from the literature; namely, LVH, myocardial fibrosis and myocardial inflammation and oedema.

CASE REPORTS

Two cases of severe AS with left ventricular systolic dysfunction are presented as an illustrative aid to the discussion.

Case 1

A 77-year-old woman presented with new onset pre-syncope, exertional dyspnoea (New York Heart Association class III) and exertional angina (Canadian Cardiovascular Society class II). Coronary angiogram showed unobstructed, normal coronary arteries. Severe AS and left ventricular systolic dysfunction was diagnosed on cardiac imaging. Transthoracic echocardiography showed an aortic valve area of 0.4cm^2, mean transvalvular pressure gradient of 60mmHg and a peak velocity of 5.2m/s. Using cardiac magnetic resonance (CMR) imaging, a volumetric assessment demonstrated a dilated, minimally hypertrophied LV with an indexed LV end-diastolic volume (LVEDVi) of 133ml/m^2, a posterior wall thickness (PWT) of 6mm and an indexed left ventricular mass (LVMi) of 96g/m^2 (Figure 1A). The global systolic function was severely impaired with a left ventricular ejection fraction (LVEF) of 21% (Figure 1A). On tissue characterisation, minimal myocardial fibrosis was detected using T1 mapping (Figure 1C) and late gadolinium enhancement (LGE) imaging (Figure 1E).

Case 2

A 62-year-old woman with a background history of hypertension and diabetes mellitus presented with syncopal episodes on exertion. Additionally, she reported a preceding history of worsening dyspnoea from New York Heart Association class I to III, over a 2- year period. Similarly to Case 1, severe AS and left ventricular systolic dysfunction was diagnosed on cardiac imaging. The aortic valve area measured 0.5cm^2 on transthoracic echocardiography, with a mean transvalvular pressure gradient of 69mmHg and a peak velocity of 5m/s. On CMR, the LV was non-dilated and hypertrophied with a LVEDVi of 81ml/m^2, PWT of 11mm and a LVMi of 103g/m^2 (Figure 1B). The global systolic function was mildly impaired with an LVEF of 41% (Figure 1B). The greater degree of LVH was accompanied by a greater degree of myocardial fibrosis (Figure 1D, 1F).

Left ventricular hypertrophy

The natural history of classic aortic stenosis is well described. The myocardial response to a rising afterload is concentric LVH, characterised by the parallel addition of sarcomeres within cardiomyocytes and a thickened LV.[6,7,9-12,14,16-21] In line with the law of Laplace, this thickening normalises wall stress and maintains an adequate LVEF, implying that the hypertrophy is initially adaptive and beneficial.[6,7,9,10,12,17-20] Should patients survive long term, persistence of the pressure overload eventually drives the ventricle into a state of decompensation and left ventricular dilation, which is considered the end-stage morphology of the disease.[17] Associations between LVH and left ventricular systolic dysfunction have been made; more specifically, that dysfunction may be associated with either inadequate LVH or excessive LVH.

Decade-old research has demonstrated an association between inadequate LVH and left ventricular systolic dysfunction.[22,23] This was observed in Case 1 above. Despite severe AS with high mean gradients, the LV wall thickness remained within normal limits with a marginal increase in LVMi (Figure 1A). As the afterload rises in AS, use of the preload reserve and an increase in myocardial contractility are required to maintain adequate pump performance.[19] Two hallmark studies by Carabello, et al. and Grossman, et al. discovered that AS patients with a decreased LVEF, tended to have lower wall thickness, lower left ventricular mass and higher wall tension, implying that there was insufficient LVH and by extension, a failure to normalise wall stress.[22,23] This finding is physiologically and logically supported, as the addition of sarcomeres ultimately translates to the addition of contractile apparatus. Insufficient LVH would fail to improve myocardial contractility and fail to normalise wall stress, and once preload reserve is exhausted, impairment in pump performance is an inevitable consequence. For some, the LVEF recovers once the loading conditions are reversed through AVR, implying that for these patients, the intrinsic myocardial contractility is preserved – a concept now accepted as afterload mismatch, i.e. a mismatch between the degree of afterload increase and compensatory LVH, putatively at fault for the dysfunction.[22,23] For others, the LVEF fails to recover, and this is attributed to irreversible, "true," contractile

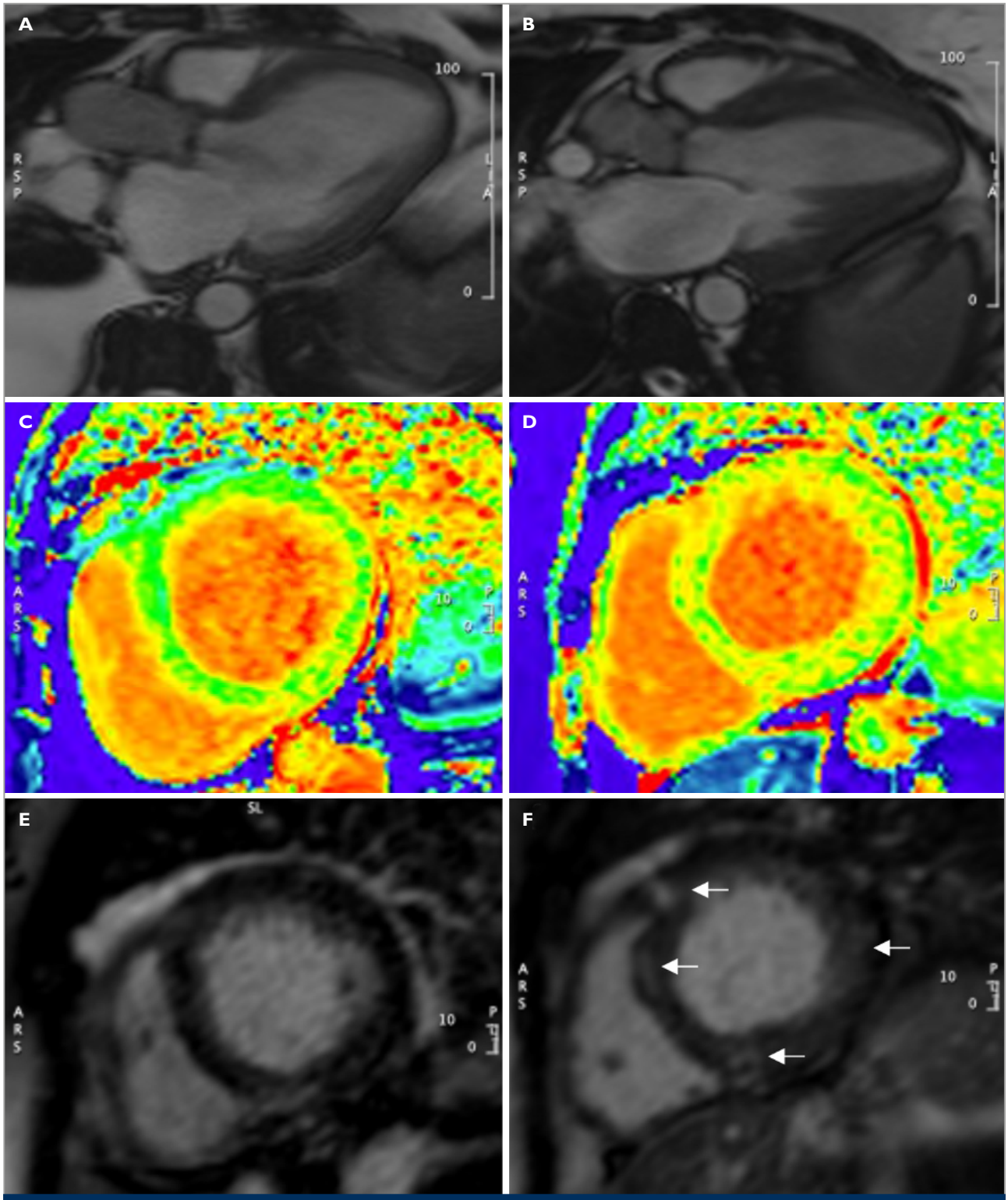

FIGURE 1: CMR images for CASE 1 (left) and CASE 2 (right).
A: End-diastolic cine image (long axis 3 chamber view) of Case 1. LVEF=21%, PWT=6mm, LVMi=96g/m2. B: End-diastolic cine image (long axis 3 chamber view) of Case 2. LVEF=41%, PWT=11mm, LVMi=103g/m^2. C: T1 map (basal short axis view) of Case 1. The global T1 time is within normal range for our magnetic field (1 030ms). D: T1 map (basal short axis view) of Case 2 showing diffuse areas with prolonged T1 time (yellow regions, exceeding 1 100ms). E: LGE image (basal short axis view) of Case 1 demonstrating minimal myocardial fibrosis. F: LGE image (basal short axis view) of Case 2 demonstrating midwall replacement fibrosis in the anterior septum, midwall replacement fibrosis at the RV insertion points and diffuse interstitial fibrosis in the posterolateral wall (indicated by the arrows).

LVEF: left ventricular ejection fraction, PWT: posterior wall thickness, LVMi: left ventricular mass indexed for body surface area, LGE: late gadolinium enhancement, RV: right ventricle.

impairment.[22,23] The factors driving these 2 groups down different pathways was not investigated further at the time, and with advancements in cardiac imaging, the association between left ventricular systolic dysfunction and excessive LVH has since emerged.

A relationship between left ventricular systolic dysfunction and excessive LVH is frequently described in more recent literature. With ongoing pressure-overload, the ventricle continues to hypertrophy. The accepted pathway for how this leads to systolic dysfunction is that the increased muscle mass, together with the increased work required to overcome the high afterload, increases the oxygen demand.[7,9,13,18,24-26] Evidence from perfusion imaging and histology based studies show that endothelial cell damage and capillary loss ensue, leading to impaired myocardial perfusion.[27-29] As the perfusion reserve is depleted, a supply / demand mismatch ensues, leading to ischaemia, cardiomyocyte death, and myocardial fibrosis.[7,9,13,18,24-26] The conclusion that this is the mechanism underlying left ventricular systolic dysfunction is supported by perfusion imaging studies that show an inverse correlation between myocardial perfusion reserve and impaired LV function.[27,29] There are, however, arguments against this theory.

Arguments against this include the observation that excessive LVH in systolic dysfunction is not always accompanied by excess fibrosis or worse function. As illustrated in 2 additional cases below, the degree of LVH is roughly 2-fold higher in Case 4 compared to Case 3, yet the degree of myocardial fibrosis is significantly lower (Figure 2). Secondly, the pattern of fibrosis in those with excessive LVH is not always subendocardial which is expected for ischaemia (Figure 2D). Thirdly, the correlation between the abovementioned histological findings and the degree of LVH was not evaluated in the aforementioned studies, nor the relationship between the degrees of LVH and systolic dysfunction.[27-29] Lastly, whether this theory applies solely to the true contractile dysfunction group, as eluded to in many of these studies, is unclear and cannot be confirmed with the available evidence.

As mentioned, the histological and perfusion imaging studies do not assess the statistical correlation between the degrees of LVH and systolic dysfunction. Similarly, studies using other imaging modalities such as transthoracic echocardiography and / or CMR, infrequently evaluate the correlation and those that do, have collectively, produced conflicting results.[7,13,14,25,30-36] One reason for these conflicting findings may be that most studies capture data that represents a single snapshot of a dynamic process and its evolving structural consequences. Secondly, most of these studies have been designed to evaluate those with severe AS and preserved systolic function. And thirdly, like most processes governed by nature, the underlying molecular pathways leading to LVH are several in number, are complex and dynamic with many signals that have yet to be discovered.

Numerous molecular signals and pathways underlying LVH have been investigated. The molecular milieu clearly differs for those with and without associated left ventricular dysfunction. Beginning at a genetic level, intense genetic reprogramming has been observed in those with left ventricular dysfunction.[37] More specifically, the pattern of gene expression mirrors that of a foetal cardiomyocyte.[37] Downstream of the genetic reprogramming, altered calcium handling, G-protein signalling, reduced capillary density through upregulation of p53 and oxidative stress have been linked to impaired contractility and forward signalling for further LVH, thus establishing a maladaptive cycle.[21,38] Whether some patients are pre-destined for a maladaptive phenotype or whether there is a transition from an initially adaptive phenotype to a maladaptive one, remains unclear. Furthermore, molecular differences between those with afterload mismatch, true contractile dysfunction, and preserved contractile function, and whether one phenotype (afterload mismatch) progresses to another (true contractile dysfunction), have yet to be explored.

Myocardial fibrosis

Myocardial fibrosis, like LVH, is well described in severe AS. The earliest evidence of myocardial fibrosis in AS dates back more than 3 decades, when Krayenbuehl, et al., evaluated myocardial histology on tissue acquired from the anterolateral walls of patients undergoing diagnostic cardiac catheterisation.[39] Since then, several studies have performed similar investigations using basal left ventricular septal biopsies acquired during AVR.[12,14,36,40-47] With the help of Picrosirius Red, Masson Trichrome and Haemotoxylin and Eosin staining techniques, 2 patterns of myocardial fibrosis have been described; namely, diffuse interstitial fibrosis characterised by loose bands of collagen surrounding bundles of cardiomyocytes and replacement fibrosis, identified by dense, focal regions of collagen-containing tissue.[48] The former, has mostly been localised to the myocardial mid-wall and is thought to be a reactive process.[40,44,46,48] The latter, tends to localise within the subendocardium and progressively increases with cardiomyocyte degeneration.[40,43,44,46,48] These histological findings have been corroborated and further characterised through CMR imaging.

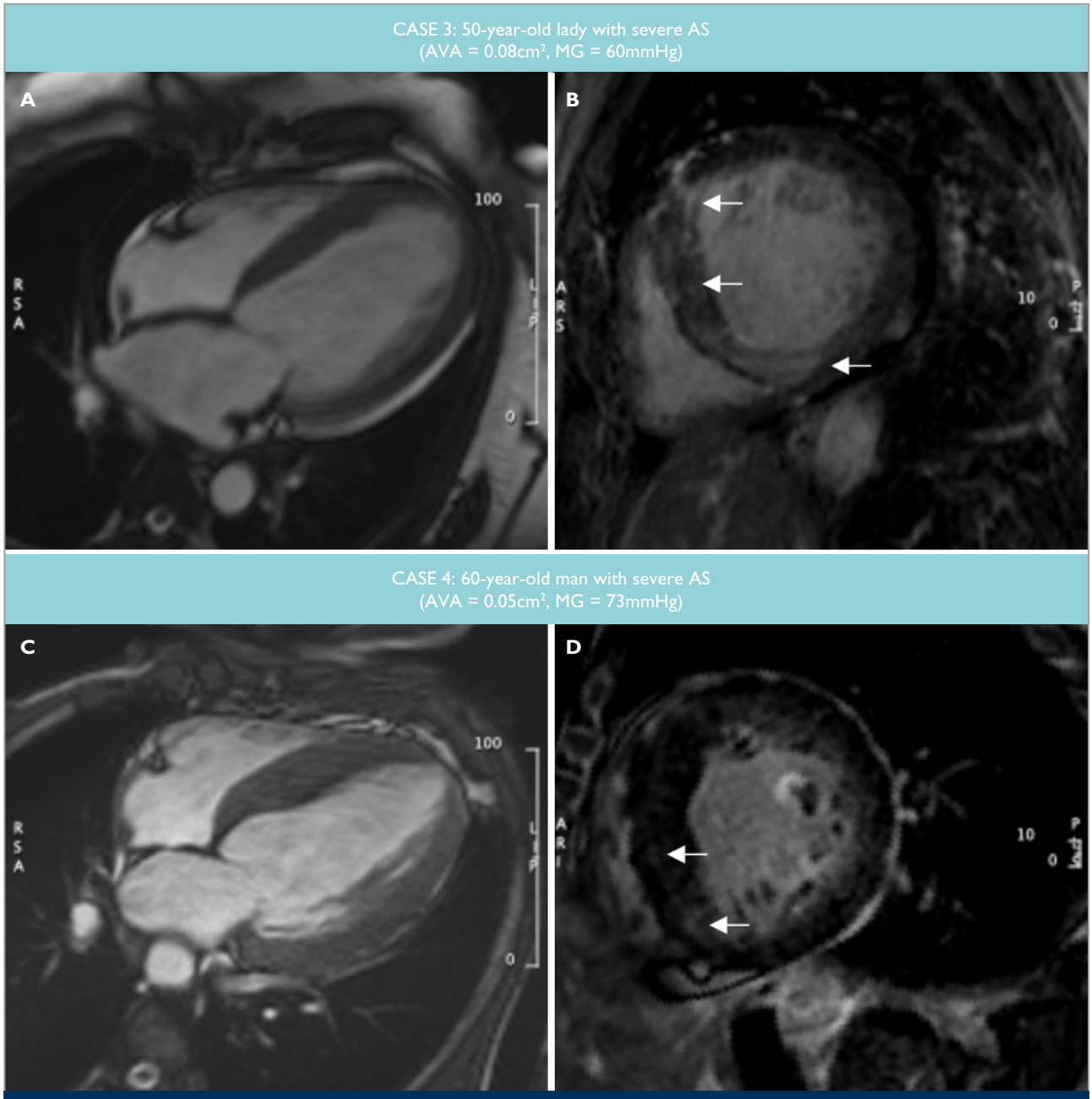

FIGURE 2: CMR images of 2 cases demonstrating variable patterns and degrees of LVH and fibrosis.
A: End-diastolic cine image (long axis 4 chamber view) of Case 3. LVEF=28%, lateral LV wall thickness=6mm, LVMi=125g/m². B: The corresponding LGE image (mid-ventricular short axis view) of Case 3. Arrows indicate midwall replacement fibrosis in the anterior septum and inferior RV insertion point as well as extensive diffuse interstitial fibrosis along the entire septum. C: End-diastolic cine image (long axis 4 chamber view) of Case 4. LVEF=37%, lateral LV wall thickness=14mm, LVMi=237g/m². D: The corresponding LGE image (mid-ventricular short axis view) of Case 4. Arrows indicate a small region of replacement fibrosis in the inferior RV insertion point and diffuse interstitial fibrosis in the septum. The degree of fibrosis, despite excessive LVH, is lower compared to Case 3.

AVA: aortic valve area, MG: mean gradient (transvalvular pressure gradient).

Cardiac magnetic resonance imaging offers a non-invasive approach for the detection of myocardial fibrosis.[49] While endomyocardial biopsy / histopathology remains the gold standard for fibrosis assessment, CMR offers the added benefit of characterising the entire myocardium rather than a single region / segment.[41,43] Delayed contrast imaging / late gadolinium enhancement (LGE) and T1 mapping / extracellular volume (ECV) have been used to identify focal replacement and diffuse interstitial fibrosis respectively.[43,44,47] Using these techniques, a variable pattern of AHA segment involvement has been shown.

Furthermore, there appears to be a predilection for the mid-wall followed by the subendocardium in a non-infarct pattern (spanning different coronary territories and present in those with angiographically proven normal coronary arteries), and a decreasing gradient of fibrosis from base to apex.[32,40,41,43,45,50] Both histology and CMR suggest that a relationship between myocardial fibrosis and left ventricular systolic dysfunction exists.

It is widely accepted that myocardial fibrosis, in classic severe AS, is associated with left ventricular systolic dysfunction and a worse prognosis despite AVR. To our knowledge, no evidence currently exists on how the pattern, distribution and quantity of fibrosis differs between those with afterload mismatch and true contractile dysfunction. Furthermore, no myocardial fibrosis quantity / cut-off exists for predicting left ventricular systolic dysfunction, functional recovery after AVR and / or long-term prognosis. There are several reasons for this. Firstly, most CMR studies exclude those with left ventricular systolic dysfunction. In 2 studies that investigated a wider AS cohort which includes a proportion of cases with left ventricular systolic dysfunction, the fibrotic burden was shown to be higher in those with dysfunction compared to those with normally functioning ventricles.[40,44] Neither of the studies, however, were designed to specifically interrogate those with left ventricular systolic dysfunction therefore limiting their statistical power to detect true differences between those with and without dysfunction. Secondly, while CMR can detect fibrosis, its ability to quantify it proves challenging. Some studies show a good correlation between their CMR based fibrosis quantification and the gold standard technique i.e. biopsy / histology.[40,41,43-47] The techniques used for fibrosis quantification, however, vary. For example, some centres use a manual method for LGE quantification while others use a semi-automated method with varying standard deviations for fibrosis identification and quantification.[32,41] This brings into question the true correlation between CMR based fibrosis quantification and histology. Not only does this hinder the agreement of a quantitative fibrosis cut-off that serves as a reliable predictor of outcomes but also, poses a challenge in terms of comparability across studies.

For myocardial fibrosis to be useful as a predictor of outcomes / prognosis, a quantitative cut-off is necessary for 2 reasons. Firstly, the evidence shows that not all those with left ventricular systolic dysfunction and myocardial fibrosis are destined for a poor prognosis. For example, despite significant diffuse interstitial fibrosis and replacement fibrosis (Figure 1D, 1F) in Case 2, the LVEF recovered to 55% within 3 months after AVR. Secondly, most CMR based studies that identified myocardial fibrosis in severe AS were performed in cohorts with preserved left ventricular systolic function (LVEF >50%). This illustrates the fact that myocardial fibrosis is not a structural feature unique to those with a reduced LVEF or perhaps, highlights the notion that LVEF is a late marker of systolic dysfunction. Speckle-tracking echocardiography and strain analysis show that despite a normal LVEF, there is still a subtle degree of systolic dysfunction in both those with and without myocardial fibrosis.[14,32,42,43] In 2 studies by Hoffman, et al. and Weideman, et al., strain was demonstrably worse in the basal segments where the fibrotic burden was found to be highest thus strengthening the association between myocardial fibrosis and left ventricular systolic dysfunction. In these studies and several others, recovery after AVR tends to be worst in those with the highest fibrotic burden.[31,42]

This contrasts with our local experience where the degree of functional recovery is not always related to the degree of LVH or myocardial fibrosis. For example, in Case 3 where the fibrotic burden was significantly high, the LVEF showed improvement from 28% - 41% after AVR (Figure 2). In Case 4, however, despite a low fibrotic burden, the LVEF failed to recover after AVR (Figure 2). This highlights the fact that the LV response to severe AS and AVR is complex and remains incompletely understood. In addition to these clinical imaging limitations, a knowledge gap also exists in understanding the molecular pathways driving myocardial fibrosis in severe AS.

Signalling from transforming growth factor beta 1 (TGF-ß1) and angiotensin II are considered central components in the development of fibrosis.[51] Their triggering events, however, remain poorly understood. Evidence from stress-perfusion imaging has demonstrated an important inverse association between myocardial perfusion reserve and myocardial fibrosis suggesting a role for ischaemia as a fibrotic trigger.[27,29] The segmental correlation between myocardial hypoperfusion and myocardial fibrosis however, was not reported in these studies and interestingly, a midwall distribution of fibrosis emerged as the predominant pattern.[27,29] This is counter-intuitive as it is well-established that the subendocardial layer of the myocardium remains the most vulnerable to ischaemia-related injury. A limitation highlighted by Steadman, et al., is that this association was illustrated using cross-sectional data thus challenging the true establishment of a temporal relationship between the 2 observations.[29]

An association between AS and cardiac amyloidosis (CA) exists.[52-57] As for the association between myocardial hypo-

perfusion and fibrosis, the temporal or causative relationship between severe AS and CA is unknown.[55] Whether a causative relationship even exists between the 2 conditions remains debatable. The transthyretin (ATTR) subtype accounts for the majority of CA cases in those with severe AS.[52-57] This subtype is known to affect the elderly. Likewise, those with co-existing CA and severe AS are usually over the age of 65.[52-57] Their association therefore, may be an epidemiological chance finding. Nonetheless, it is noteworthy that histological studies consistently show that the extracellular space of the myocardium in CA is shared by both amyloid proteins and fibrosis.[58-60] In a study on CA by Pucci, et al., 100% of endomyocardial biopsies showed interstitial fibrosis as well as subendocardial replacement fibrosis.[58] The prevalence of CA in severe AS varies (4% - 16%) but is exceeded by the prevalence of myocardial fibrosis in AS.[52-57] Therefore, while CA may account for fibrosis in some cases of AS, several other triggers for the fibrosis must also exist.

Other triggers for fibrosis in AS, besides ischaemia and CA, may include haemodynamic / mechanical and / or inflammatory stimuli. The culprit cells responsible for myocardial fibrosis are cardiac fibroblasts; cells that are derived mainly from the epicardium during foetal development and considered quiescent in the healthy adult heart.[51,62,63] During the neonatal period, cardiac fibroblasts undergo population expansion in response to the high left ventricular pressures, a haemodynamic feature that is associated with severe AS and left ventricular systolic dysfunction.[62] This haemodynamic trigger, coupled with TGF-ß1 signalling, may play an important role in inducing fibroblast re-activation and proliferation, and ultimately, promoting fibrosis development. An important source of TGF-ß1 secretion are macrophages and other immune cells.[51] Albeit of low intensity, induction of the inflammatory system through cardiomyocyte signalling, oxidative stress and angiotensin II signalling has been described in several in vivo models of pressure overload.[51] This highlights the importance of considering the impact of inflammation in the development of left ventricular systolic dysfunction in severe AS.

Myocardial inflammation and oedema

Myocardial inflammation and oedema are rarely described in the context of AS pathophysiology. Prior to advanced cardiac imaging, histological studies contributed the most insight into the myocardial structure of AS patients. In addition to cardiomyocyte hypertrophy and myocardial fibrosis, cardiomyocyte degeneration through ubiquitin-related autophagy, oncosis and apoptosis was also observed in cases of left ventricular systolic dysfunction.[39,41,46,47,61] Evidence of myocardial inflammation, on the other hand, was rarely evaluated and / or reported.[39,41,46,47,61] The exception was a study by Hein, et al., where a nearly 3-fold increase in leukocytes, lymphocytes and macrophages was observed in the interstitial space, leading the group to speculate about low grade inflammation potentially contributing towards left ventricular systolic dysfunction.[61] Until recent advancements in CMR techniques that allow for non-invasive myocardial oedema evaluation, this idea was not probed much further in the clinical setting.

Cardiac magnetic resonance imaging, in addition to fibrosis assessment, offers other tools capable of detecting myocardial inflammation and oedema. These include short tau inversion recovery (STIR) imaging and native T1 / T2 mapping techniques.[49,64-66] In 2 tissue characterisation studies that report prolonged native T1 time for severe AS, an inverse relationship between the native T1 and left ventricular systolic function is also demonstrated.[68,69] In both studies, the prolonged T1 time is attributed to the development of myocardial fibrosis.[68,69] Native T1 mapping, however, is not specific to fibrotic detection and may be influenced by increased water content, i.e. oedema.[49,64-66,70] From most papers that report a prolonged native T1 time secondary to fibrosis, information on how oedema is ruled out as a cause for the prolonged T1 is not available.[47,50,68,69] And, for the remainder, fibrosis is concluded as the cause based on concurrent histological evidence of fibrosis from endomyocardial biopsy.[45-47] Amongst these, however, the majority describe a weak or moderate correlation between histology and native T1 and only one demonstrates a strong correlation.[40,45,47] T2 mapping performed in parallel with T1 mapping often serves as a useful arbiter for confirming the presence of oedema in cases where the T1 time is prolonged.

Although T2 mapping is specific for oedema detection, its likelihood of detecting oedema in severe AS may be low. T2 mapping for Cases 1 and 2 showed normal T2 times of 49ms and 50ms, respectively (Figure 3A, 3C). Oedema, in these cases, may not necessarily be ruled out as the sensitivity for oedema detection is lower than its specificity. Additionally, studies showing the high sensitivity of T2 mapping are related to acute inflammation e.g. acute myocarditis or acute myocardial infarction.[66,67] For chronic oedema, on the other hand, the sensitivity of the test decreases to roughly 70% thus introducing the likelihood of missing oedema in the context of severe AS where inflammation is more likely a chronic process.[66] Another consideration for the normal T2 time observed is potential pseudo-normalisation of T2 relaxation by the co-

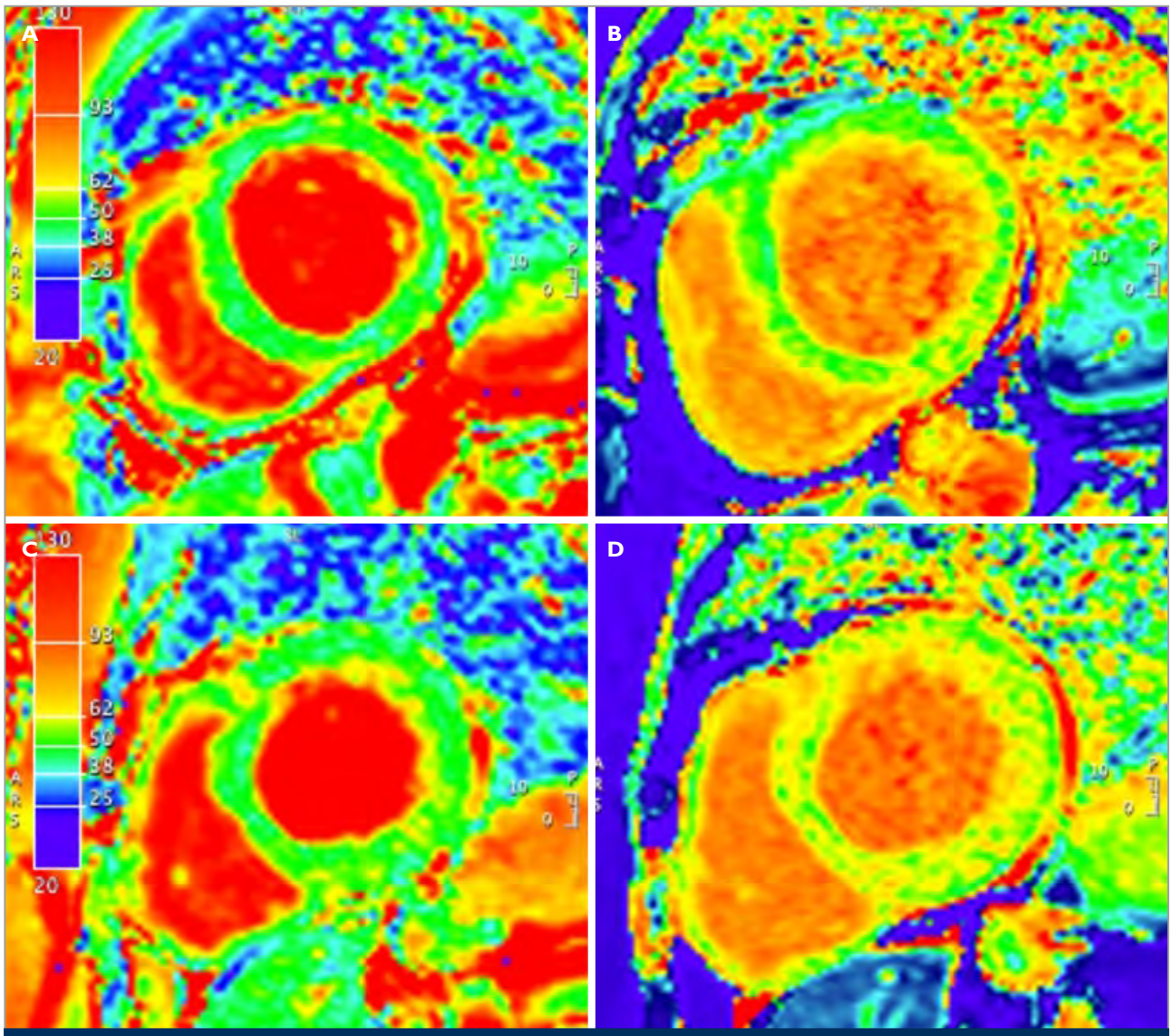

FIGURE 3: T1 and T2 mapping images for CASE 1 (top) and CASE 2 (bottom).
A: T2 map of Case 1 (basal short axis view). Global T2 time is normal (49ms). B: T1 map of Case 1 (basal short axis view). Global T1 time is normal (1 030ms). C: T2 map of Case 2 (basal short axis view). The global T2 time is normal (50ms). D: T1 map of Case 2 (basal short axis view). The global T1 time is markedly prolonged (1 134ms) indicating the presence of diffuse interstitial fibrosis. Despite this finding, the global T2 time remains normal.

existence of myocardial oedema and fibrosis. A recently performed in vivo study by Lee, et al., shows that that myocardial fibrosis in both aged and pressure overloaded mice, is associated with a relative decrease in T2 relaxation compared to their young and healthy counterparts without fibrosis.[71] It is then plausible that the co-existence of myocardial fibrosis and inflammation may falsely normalise the T2 time since it is an averaged measure. This observation has not yet been validated in human studies. Nonetheless, other evidence argues that myocardial inflammation may still form an important component in the pathophysiology of severe AS and LV systolic dysfunction.

The few studies that do report T2 mapping in severe AS, show prolonged T2 relaxation time for AS compared to healthy volunteers.[50,72,73] In one of these studies, prolonged T2 time correlates inversely with the mean transvalvular pressure gradient and in another, with the LVEF.[50,73] These findings suggest that a relationship may exist between inflammation, disease severity and impaired pump performance. This is further consolidated by modern molecular research studies. Tools such as immunohistochemistry and single cell RNA sequencing demonstrate a pro-inflammatory state in patients with severe AS and systolic dysfunction, as well as clusters of immune cells with altered cell signalling in the myocardium.[42,74] While inflammation

and oedema have not been as well characterised as LVH or fibrosis, the existing evidence suggests that further investigation in this regard, is warranted.

Limitations in existing knowledge

Histopathology, cardiac imaging and other basic science investigations have provided valuable insight into the macro- and microscopic myocardial features associated with left ventricular systolic dysfunction in severe AS. In addition, they have allowed for several key areas requiring further investigation, to be identified.

Firstly, most studies have been designed to interrogate the severe AS group with preserved left ventricular systolic function, thus limiting their ability to identify significant clinical characteristics, triggers, thresholds and early features that mark the transition to dysfunction. For example, both inadequate, and excessive LVH have been associated with systolic dysfunction, but a threshold wall thickness or critical left ventricular mass has yet to be investigated, a criterion that might offer clinical use in early decision-making for AVR. Secondly, there is a great paucity in imaging data for the afterload mismatch group and consequently, limited evidence available to understand how this group differs in terms of LVH and / or the type, degree and distribution of myocardial fibrosis. Besides a lack of imaging data for this group, there is also limited evidence on the underlying molecular environment / pathways associated with afterload mismatch. Finally, whether afterload mismatch and true contractile dysfunction are separate entities or form part of a single spectrum has yet to be considered and investigated.

Future prospective longitudinal studies specifically designed to interrogate those with severe AS and systolic dysfunction are needed. Investigating and comparing patients with afterload mismatch to those with true contractile dysfunction would offer important insights into the mechanistic intricacies underlying the dysfunction.

CONCLUSION

Left ventricular systolic dysfunction in severe AS is associated with worse morbidity and mortality both pre- and post-AVR. In this review, evidence from histopathology, cardiac imaging and molecular tools, e.g., enzyme-linked immunoassays for TGF-ß1 detection, was used to understand some of the pathophysiological processes underlying left ventricular systolic dysfunction. The relationship between left ventricular systolic dysfunction and LVH, myocardial fibrosis and myocardial inflammation / oedema has been highlighted. Although this is an important starting point, several gaps in the knowledge remain, including the triggers, structural myocardial features and molecular pathways that differentiate the afterload mismatch group from the true contractile dysfunction group. Furthermore, whether afterload mismatch and true contractile dysfunction are 2 separate scenarios, or whether they fall on a spectrum with one another, remains unknown. Future longitudinal, prospective studies that are better designed to specifically evaluate those with severe AS and left ventricular systolic dysfunction are needed.

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