Pathophysiology, emerging techniques for the assessment and novel treatment of aortic stenosis

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ABSTRACT

Our perspectives on aortic stenosis (AS) are changing. Evolving from the traditional thought of a passive degenerative disease, developing a greater understanding of the condition’s mechanistic underpinning has shifted the paradigm to an active disease process. This advancement from the ‘wear and tear’ model is a result of the growing economic and health burden of AS, particularly within industrialised countries, prompting further research. The pathophysiology of calcific AS (CAS) is complex, yet can be characterised similarly to that of atherosclerosis. Progressive remodelling involves lipid-protein complexes, with lipoprotein(a) being of particular interest for diagnostics and potential future treatment options. There is an unmet clinical need for asymptomatic patient management; no pharmacotherapies are proven to slow progression and intervention timing varies. Novel approaches are developing to address this through: (1) screening with circulating biomarkers; (2) development of drugs to slow disease progression and (3) early valve intervention guided by medical imaging. Existing biomarkers (troponin and brain natriuretic peptide) are non-specific, but cost-effective predictors of ventricular dysfunction. In addition, their integration with cardiovascular MRI can provide accurate risk stratification, aiding aortic valve replacement decision making. Currently, invasive intervention is the only treatment for AS. In comparison, the development of lipoprotein(a) lowering therapies could provide an alternative; slowing progression of CAS, preventing left ventricular dysfunction and reducing reliance on surgical intervention. The landscape of AS management is rapidly evolving. This review outlines current understanding of the pathophysiology of AS, its management and future perspectives for the condition’s assessment and treatment.

BACKGROUND

Aortic stenosis (AS) is the most prevalent acquired valvular heart disease. The condition’s incidence increases with age, affecting 2% of adults over 65 years old and rising to 10% in the eighth decade of life.1–3 Disease burden is set to increase due to an ageing population.1–4 AS has a subclinical period which is asymptomatic and does not increase mortality.3,5 However, the prognosis when symptoms arise is poor and untreated patients have an average survival rate of 2–3 years.6

The aetiology of AS can be classified into three groups: congenitally bicuspid aortic valve, inflammatory rheumatic heart disease and degenerative calcification. Chronic rheumatic fever can cause immunologically mediated scarring of the valve, however, its incidence has decreased in developed countries due to better treatment against group A streptococcus.1,7,8 Congenital bicuspid aortic valves have two cusps, impeding blood flow which can increase the risk of early-onset AS and calcification.9,10 It is calcific AS (CAS) which poses the greatest disease burden on developed countries due to its greater prevalence.1,10–12 Symptoms occur in CAS due to the calcification and thickening of the aortic valve reducing the flow of blood into the left ventricular (LV) outflow tract (figure 1).6 The symptoms of severe AS include angina, syncope and, ultimately, heart failure.3,13,14

The European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery Task Force have recently published guidance on the workup and treatment of AS.13 Challenges remain in the timing of surgical intervention, procedural risk, lack of medical treatment options and the unpredictable nature of AS deterioration.15 As a result of this, evolving data on the pathophysiology seeks to elucidate novel biomarkers and therapeutics to better patient outcomes. Furthermore, clinical trials such as the Early Valve Replacement guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) and The Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study aim to influence patient management through emerging imaging modalities, better patient stratification and early intervention.16–24
OUTLINE
This paper will focus on the cellular underpinnings of CAS and future perspectives for the condition’s management. In particular, it will highlight the pathophysiology of CAS, current management of the condition, the use of biomarkers and advanced imaging techniques aim to change the paradigm of AS management as pathway biomarkers for assessment; the use of cardiovascular MR imaging (CMR) for assessment and treatments targeting lipoprotein(a) (Lp(a)) to slow disease progression.

PATHOPHYSIOLOGY
Cellular pathology
The precise pathological mechanism behind the stenosis of the aortic valve remains unresolved. Nonetheless, advancements in technology and research have changed our insight. A once considered passive, degenerative process due to ageing is now understood to be active, similar in its molecular underpinning to atherosclerosis and its associated inflammatory response. As a result, the two conditions share common risk factors: old age, elevated Lp(a), hypertension, smoking, raised body mass index, hypercholesterolaemia and diabetes. Knowledge of this active pathophysiology has the potential to change the paradigm of AS management as pathway biomarkers and advanced imaging techniques aim to identify early signs of significant disease and Lp(a) lowering treatments have the potential to slow progression.

The aortic valve has three leaflets, each leaflet consisting of a three-layer, extracellular matrix structure covered by an endothelial layer (figure 2). The ventricularis layer (on the ventricular side) is rich in circumferentially aligned elastin fibres which allow for flexibility. On the aortic side, the fibrosa layer consists of collagen and fibroblasts. Between these, the spongiosa layer provides lubrication due to its high proteoglycan content. Cumulatively, all layers amalgamate to resist mechanical stress during the cardiac cycle.

Although the fibrosa is the main load-bearing structure, it is also the most susceptible to fibrocalcification. Valve interstitial cells (VICs) form the largest proportion of cells within the valve and their function is to maintain valvular structure. Pathologically, this cell type is pivotal in understanding the progression of calcification, particularly the cell phenotype within the fibrosa.

On a cellular level, CAS progression can be divided into two phases: initiation and propagation (figure 2). The initiation stage is analogous to that found in atherosclerosis. Initial endothelial insult results in the infiltration of low-density lipoproteins (LDLs) and Lp(a) into the valve, depositing within the fibrosa. Haemodynamic stress exerted during aortic cusp movement is the likely cause of endothelial damage; the altered blood flow through bicuspid valves intensifies this stress. Following this, reactive oxygen species modify the lipids into oxidised LDLs (OxLDLs). OxLDLs stimulate the extravasation of monocytes into the valve interstitium which consequently differentiate into macrophages. At this stage, the inflammatory cascade initiates; macrophages capture the OxLDLs to form foam cells, enhancing the influx of immune cells through a greater expression of adhesion molecules E-selectin and intercellular adhesion molecule 1, thus perpetuating the cycle.

Furthermore, Lp(a) acts as a carrier for oxidised phospholipids, potentiating inflammatory pathways. The activated macrophages release proinflammatory cytokines: interleukin 1 beta (IL-1β), interleukin 6 (IL-6), receptor activator of nuclear factor kappa-B ligand (RANKL) and tumour necrosis factor alpha (TNF-α) which activates nuclear factor-κB (NF-κB). This recruits T lymphocytes, promotes extracellular matrix remodelling leading to fibrosis and activates VICs, propagating CAS.

The propagation phase of CAS is characterised by repeated fibrosis and calcification. Inflammation activated VICs induce fibrosis by the secretion of matrix metalloproteinases through a myofibroblastic phenotype. This scarring tissue acts as a nidus for calcification in which inflammation-induced apoptosis of VICs leads to diffuse microcalcification through the release of apoptotic bodies. Microcalcification is potentiated by the release of calcifying microvesicles by VICs and macrophages. Following this, VICs drive macrocalcification by switching to an osteoblast-like phenotype, promoted by the dysregulation of osteogenic mediators such as bone morphogenetic protein 2 and NOTCH1.

Lp(a) has also been shown to stimulate VIC differentiation. The multifactorial nature of CAS progression is demonstrated as both Lp(a) levels and NOTCH1 function are influenced by genetic variance. As the disease progresses, stiffening of the valve prompts further apoptosis, resulting in the calcific mechanisms superseding the immunological pathway in propagating CAS. Furthermore, morphological differences of the aortic valve become more apparent.
Valvular heart disease

Morphological pathology
The macroscopic manifestations of CAS, as a result of cellular pathological processes, affect the aortic valve and surrounding myocardium (Figure 2). Initially, valve disease is difficult to detect. This subclinical phase, aortic sclerosis, involves valve thickening without impeding blood flow.\(^{49,50}\) Within 7 years, 10% of these patients would progress to CAS,\(^{50,51}\) distinguished by restricted valve motion and haemodynamic obstruction.\(^5\) The degree of calcium deposition is visualised by CT, although clinical severity is more frequently determined with echocardiograms assessing valve narrowing.\(^{15,52}\)

Valvular narrowing increases myocardial burden, precipitating morphological maladaptation. Frank-Starling forces demonstrate that stenosis increases after load and subsequently, greater ventricular pressures are needed to maintain cardiac output.\(^{53}\) As a result, there is compensatory concentric hypertrophy of the

Figure 2  Schematic diagram portraying the pathophysiology of CAS. (A) Diagram showing the histological structure of the aortic valve. Initial endothelial damage promotes the uptake of LDLs which in turn activate an inflammatory cascade leading to subsequent calcification. Of note is the abundance of pathological processes occurring within the fibrosa microenvironment. The two stages of CAS progression are initiation and propagation. Initiation is associated with inflammation, mediated by immune cells, whereas propagation involves fibrocalcification. (B) On a local, valvular level, morphological change is visualised by calcium deposits narrowing the valve. (C) As a result of valvular narrowing, Doppler velocities increase leading to maladaptive ventricular remodelling. Image from Lung and Vahanian.\(^{32}\) Ang II, angiotensin II; BMP-2, bone morphogenic protein 2; CAS, calcific aortic stenosis; LDL, low-density lipoprotein; Lrp5: low-density lipoprotein receptor-related protein 5; TGF-β: transforming growth factor beta; TNF-α: tumour necrosis factor alpha.
LV myocardium. Hypertrophy itself can be maladaptive, contributing to diastolic dysfunction. Chronically, this mechanism decompensates due to fibrosis and myocyte death. Dilation of the myocardium results in systolic dysfunction and heart failure, which is the main driver of adverse outcomes. The dilated heart can be visualised by multiple imaging modalities however CMR imaging can identify the underlying fibrosis at an earlier stage.

CURRENT MANAGEMENT

AS is detected following a physical examination. The clinical signs include a slow rising pulse, palpable precordial thrill, narrow pulse pressure, ejection-systolic murmur radiating to the carotids, soft second heart sound due to valve restriction and a fourth heart sound. Currently, transthoracic echocardiography remains the initial imaging modality to assess valve morphology and haemodynamics. Following diagnosis, patients are stratified based on symptom status, valvular anatomy and haemodynamics. Severe AS is defined by an aortic valve area (AVA) ≤1 cm² (or indexed AVA of ≤0.6 cm² m²), peak transvalvular velocity ≥4.0 m/s, mean pressure gradient ≥40 mm Hg and velocity time integral of <0.25. Severity guides intervention timing, valve replacement being the gold standard in symptomatic patients. Transcatheter aortic valve implantation is preferred in high-risk patients over surgery and its indications are expanding.

However, limitations around the timing of intervention arise; the balance between early intervention risk and irreversible cardiac damage is difficult to evaluate within current diagnostic parameters. Compounding this is the lack of robust evidence in treating severe asymptomatic AS. As a result, standard recommendations are passive and suggest watchful waiting. Interpretation of symptom severity is challenging in an elderly, comorbid, sedentary population and the rapid deterioration of symptomatic AS necessitates the need for advanced assessment techniques. Current research is ongoing assessing evaluating earlier valve intervention in the asymptomatic patient.

AHA and ESC guidelines currently do not recommend intervention in patients with moderate AS but it can be considered if the patient is undergoing CABG or surgical intervention on the ascending aorta or another valve. Large cohort studies do, however, show that moderate AS is not a benign condition and that these patients have poor survival rates and that AVR in this population group is associated with better outcomes. Further randomised controlled trials (RCTs) are required to guide future recommendations. The PROGRESS and Evolut EXPAND TAVR II Pivotal trials are aiming to evaluate the efficacy and safety of TAVR in moderate AS and the TIAMAR and TAVR UNLOAD studies are also investigating intervention in patients with concomitant moderate mitral regurgitation and heart failure, respectively.

EMERGING ASSESSMENT TECHNIQUES

Biomarkers

A range of CAS biomarkers have been identified with the potential to monitor asymptomatic patients and predict postprocedural outcomes. BNP and highly sensitive troponin I (hsTnI) hold promise due to their accessibility, simple analysis and cost-effectiveness.

Figure 3  Diagram illustrating the morphological pathology and use of multiple markers within the pathological timeline of CAS. Morphological change is demonstrated by myocardial remodelling. Hypertrophy is followed by fibrosis which leads to the decompensatory dilation of the heart, visualised through imaging modalities. Specific markers include the CMR techniques of T1 mapping, which can quantitatively analyse diffuse fibrosis and late gadolinium enhancement. The red arrow illustrates an area of irreversible, replacement myocardial fibrosis. Both troponin and BNP are non-specific biomarkers for the assessment of CAS. Troponin detects myocyte injury and fibrosis. Whereas BNP measures the degree of ventricular stretch as a result of the fluid overload exhibited in heart failure. Image adapted from Everett et al. BNP, brain natriuretic peptide; CAS, calcific aortic stenosis; CMR, cardiovascular MR.
BNP is a hormone secreted in response to cardiomyocyte stretch commonly used to assess heart failure severity. With regard to AS, BNP can approximate the point of ventricular dysfunction, thus predicting symptom-free survival and improving interventional timing. The ESC guidelines suggest considering valve replacement in asymptomatic patients with a BNP of over three times the normal. However, the attributed recommendation class of IIb indicates the need for more RCTs. Nonetheless, a recent systematic review of 21 biomarker studies associated BNP level rise with all-cause mortality. Importantly, BNP was the strongest predictor, with risk of death more than doubling. Due to the overlap in mechanisms behind BNP release, it is non-specific for AS in isolation. As a result, an approach with multiple biomarkers may provide better insight.

Troponin acts as a surrogate for myocardial damage. Mechanistically, it is associated with maladaptive remodelling and fibrosis within AS. Currently, it is the preferred marker for assessing acute coronary syndromes, increasing its accessibility and cost-effectiveness. In a systematic review of AS biomarkers, elevated troponin predicted increased risk of death. However, three studies did not find significance; and the negative finding was supported by a large (n=708) retrospective cohort study. This variance further demonstrates the need for RCTs to determine causality and reduce our reliance on observational biomarker studies. A multimarker approach would likely increase the specificity of prognosis. EVOLVED, a multicentre RCT, seeks to evaluate these limitations by screening asymptomatic patients with hsTnI. Measurements of hsTnI are more sensitive than BNP as it identifies low-level myocyte death. Moreover, prior to early valve replacement, CMR is used to assess myocardial fibrosis as a surrogate of myocardial strain.

**Imaging modalities**

AS is a disease with isolated valvular and subsequent global myocardial dysfunction. CMR can quantify both parameters with a high degree of specificity, allowing for enhanced risk stratification and treatment timing optimisation. Myocardial fibrosis with cardiac biopsy is not routinely assessed due to the complication rates and sampling error. As the gold standard in measuring ventricular function, CMR’s growing use in the non-invasive tissue characterisation of AS gives it the potential to revolutionise management especially in the asymptomatic population.

Aortic compliance and flow are CMR markers which can predict morbidity in patients with AS. Arterial load consists of resistive load and pulsatile load, the latter determined by arterial wave reflections and arterial stiffness. In addition to the increased ventricular pressures exerted due to valvular stenosis, increased arterial load can further drive maladaptive remodelling and decompensation. In particular, greater magnitudes of wave reflections and reduced arterial compliance are associated with decompensation and a poorer clinical course following valve replacement. Measurements of LV blood flow kinetic energy have also been associated with ventricular remodelling and an inverse correlation to exercise capacity. The ability of CMR to assess these components can lead to greater risk stratification and prediction of clinical outcomes, guiding management prior to and following treatment. Although these findings are derived from small sample sizes, larger clinical studies are

Figure 4  (A) Three-chamber cine demonstrating restrictive aortic valve at peak systole with a dephasing artefact at the level of accelerated flow through the restrictive aortic valve. (B, C) T1-mapping and extracellular volume (ECV) mapping demonstrating a rise in ECV with increased afterload associated fibrotic changes. (D) Late gadolinium enhancement imaging shows no evidence of any ischaemic scar. (E, F) Four-dimensional flow mapping demonstrating in 3D the peak velocity (red zones) in 3D and in two orthogonal planes (F). The peak velocity was 4.3 m/s, which is consistent with severe AS. 3D, three dimensions; AS, aortic stenosis.
warranted to evaluate the prognostic capabilities of CMR and to therapeutically target these biomarkers to improve patient quality of life.

The pathology of CAS fibrosis can be visualised using late gadolinium enhancement (LGE) and T1 mapping (figure 3). LGE involves the accumulation of gadolinium chelate within an expanded extracellular matrix, qualitatively detecting replacement fibrosis. Multiple studies support LGE’s prognostic capabilities in AS. In addition, the emergence of quantitatively assessing CMR maps on a voxel by voxel basis and quantifies fibrosis by measuring T1 relaxation time. The strength of T1 mapping is its ability to detect early AS pathology prior to decompensation; there is potential to accurately monitor patients and intervene to prior to fibrosis. Standardised protocols have redressed initial concerns with result reproducibility, however, limitations due to variance between patients still exist. As a result, the ongoing EVOLVED trial will test the clinical efficacy of CMR and provide insight into potential thresholds for T1 mapping. Moreover, a greater understanding of early patient stratification will assist in developing targeted novel therapeutics for CAS.

**NOVEL TREATMENTS**

There are no efficacious pharmacological treatments proven to slow CAS progression. However, multiple therapeutics have been repurposed or developed to decrease mortality without the associated complications of valve replacement (table 1). Novel treatments targeting Lp(a) show promise due to the molecule’s known structure and role in CAS pathophysiology; associated genetics and role as a monitorable biomarker (figure 5).

Elevated Lp(a) potentiates the atherosclerotic process of CAS, with an approximated one billion people having high levels. Furthermore, the identified polymorphism rs1045872 in genetically susceptible patients supports the causal role of Lp(a) concentration on
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calcification progression.\textsuperscript{47} Genetics also provides a platform from which screening and quantification of circulating Lp(a) could stratify at-risk patients for medical intervention.\textsuperscript{33} 96 97 The viability of genetic screening is simplified as Lp(a) is the only monogenic risk factor for AS.\textsuperscript{41} Following potential screening, lipoprotein apheresis is the current treatment for raised Lp(a). However, its clinical viability is limited to severe dyslipidaemia due to its costs and inherent extracorporeal risks.\textsuperscript{89} 91 98 Consequently, the development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and RNA-based antisense oligonucleotides (ASOs), as Lp(a) lowering therapies, is necessitated (figure 5). Although unable to reverse CAS, these drugs aim to slow disease progression by targeting the initiation phase.\textsuperscript{29} As a result, it is hypothesised that their use is most effective in mild-moderate AS,\textsuperscript{99} a population with no current therapeutics of significant benefit.

PCSK9 inhibitors function to lower LDL and Lp(a) through upregulation of LDL receptors on hepatocytes, preventing the progression of CAS pathology.\textsuperscript{88} 100 In comparison, ASOs use RNA to target apolipoprotein(a) overexpression, reducing Lp(a). Both drug classes are supported by robust RCTs showing an ability to decrease Lp(a)\textsuperscript{93} 101 102 and a study is ongoing to test PCSK9 inhibitors’ effect on CAS.\textsuperscript{103} ASOs may prove to be superior for populations with genetic overexpression and very high Lp(a) levels.\textsuperscript{104} This is, in part, due to ASOs greater ability to reduce Lp(a): a 99% decrease in comparison to 25% with PCSK9 inhibitors.\textsuperscript{89} Within a wider population, this increased effect of ASOs may also prove beneficial.\textsuperscript{104} In addition to this, the failure of statins to affect CAS outcome suggests therapeutics targeting LDLs are less effective than anticipated.\textsuperscript{105} 106 Nevertheless, large RCTs testing the clinical efficacy of these drugs on the progression of CAS are warranted. This, coupled with improved in vitro techniques to understand the disease’s pathophysiology and develop advanced treatments,\textsuperscript{33} will validate the use of pharmacotherapies in addressing the burden of AS.

CONCLUSION
Our perspectives are shifting from passive monitoring to active management for the assessment and treatment of those with AS. Insight into the two stages of CAS, initiation and propagation, have proven to be invaluable, providing novel management options. Of particular interest is Lp(a), which can play a multifaceted role in genetic screening, biomarker measurement and targeted treatment. Further studies into cellular pathology are warranted to contextualise current research and identify additional biomarkers, increasing the specificity of a multimarker screening approach. In addition to this, asymptomatic management has the potential to be revolutionised through the use of therapeutics to slow disease progression and CMR to guide early valve replacement. Validation of advanced patient stratification and diagnostic workup could propagate the widespread adoption of personalised AS therapy. Although many pharmacotherapies have exhibited potential, an increase in the number of prospective RCTs, with the larger cohort sizes of retrospective studies, is necessary to validate their clinical efficacy in reducing CAS burden.
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