Translating Novel Imaging Technologies Into Clinical Applications

Risk Stratification in Patients With Aortic Stenosis Using Novel Imaging Approaches

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The prevalence of calcific aortic stenosis increases with age, occurring in 3% to 5% of individuals aged >75 years.1,2 The narrowing of the aortic valve is driven by a highly complex and intricately regulated process of inflammation, fibrosis, and calcification, which eventually results in leaflet immobility and the associated hemodynamic consequences.3 In response to the narrowed valve, left ventricular hypertrophy is initially adaptive to restore wall stress and cardiac performance. Ultimately, adverse events, such as symptoms, heart failure, and death, occur as the left ventricle decompensates. This transition from adaptation to decompensation is driven by progressive myocyte death and myocardial fibrosis.4,5 Therefore, it is important to consider aortic stenosis as a condition that affects both the valve and the myocardium.5,6 Indeed, contemporary guidelines recommend aortic valve replacement in patients with severe aortic stenosis and evidence of advanced ventricular decompensation, defined by either the presence of symptoms or an impaired systolic ejection fraction <50%.7,8

The current strategy relies heavily on the timely identification of symptoms. However, the poor prognosis associated with the development of angina, exertional dyspnea, and syncope first described by Ross and Braunwald4 in 1968 was based on younger patients with bicuspid or rheumatic disease (average age of 63 years at the time of death). Establishing symptoms in the more elderly population encountered in current clinical practice is more challenging because of their comorbidities and often sedentary lifestyles. Moreover, it is now widely recognized that left ventricular ejection fraction is not a sensitive marker of myocardial dysfunction,9,10 and impairment in ejection fraction is often a late manifestation that may not be reversible.11,12 Furthermore, there is an urgent need to improve our understanding of the pathogenesis of aortic stenosis, both with respect to the valve and myocardium, so that we can develop novel biomarkers and therapeutic targets for this common condition.

There is considerable interest in novel imaging techniques that can provide key insights into the pathogenesis of aortic stenosis and in improving risk stratification of patients. In this review, we will examine novel imaging biomarkers of the valve and myocardium, with a particular focus on those with prognostic value and potential of translating into clinical practice. Subsequently, we will discuss how we can integrate these techniques to improve the management of patients with aortic stenosis in the near future.

Aortic Valve Calcification as a Marker of Disease Progression and Adverse Prognosis

The risk factors associated with the establishment and incidence of aortic stenosis are remarkably similar to those of atherosclerosis. They include increasing age, smoking, and elevated cholesterol concentrations.13,14 Indeed, like atherosclerosis, early calcification in the valve seems closely related to lipid deposition and inflammation. However, once established, the subsequent progression of aortic valve narrowing seems to be dominated by a self-perpetuating cycle of calcium accumulation.15–17 As a consequence, disease progression and the development of cardiovascular events are more closely associated with markers of calcification rather than lipid or inflammation. For that reason, noninvasive assessments of aortic valve calcification have major potential in risk-stratifying patients and improving the patient management.

Assessing the Burden of Aortic Valve Calcification

The clinical importance of aortic valve calcification was first described more than a decade ago in a landmark study using echocardiography. In 128 asymptomatic patients with a peak aortic jet velocity of ≥4 m/s, moderate or severe aortic valve calcification on echocardiography (defined as aortic valve calcium scores of 3 and 4 on a 4-point ordinal scale) was a strong independent predictor of death or aortic valve replacement, outperforming conventional hemodynamic assessment on echocardiography.18 The value of this score with respect to disease progression and adverse cardiovascular events was subsequently demonstrated in patients with mild and moderate...
aortic stenosis. Unfortunately, this 4-point score remains semiquantitative and limited by poor interobserver agreement.

Electrocardiography-gated noncontrast computed tomography (CT) is able to provide more detailed information with respect to the density, volume, and mass of macroscopic calcium deposits within the aortic valve. CT calcium scoring of the valve is similar to the approach used in the coronary arteries and most commonly expressed as Agatston units (AU). Indeed, aortic valve CT calcium scoring demonstrates high intra, interobserver, and scan-rescan reproducibility (a limitation with the echocardiographic calcium score) and correlates well with the calcium weight of excised valves and other echocardiographic parameters of aortic stenosis severity. Interestingly, patients with more severe disease at baseline experienced more rapid progression of aortic valve calcification on CT (Figure 1B), and multiple studies have also demonstrated a strong relationship between baseline calcium scores and the rate of subsequent disease progression.

CT calcium scoring of the aortic valve holds potential as an alternative assessment of aortic stenosis severity. Indeed, CT assessment holds several potential advantages over and above echocardiography, as it is independent from flow, geometric assumptions, and the presence of other cardiovascular conditions, such as hypertension and mitral regurgitation. Until recently, we lacked appropriate thresholds to differentiate patients with severe and nonsevere disease, thereby limiting the clinical utility of this technique.

These thresholds were recently proposed in a multicenter study involving >600 patients with at least moderate aortic stenosis and preserved ejection fraction who had undergone both CT and echocardiography. Using sex-specific thresholds (men, ≥2065 AU or ≥476 AU/cm² when indexed to aortic annular area and women, ≥1274 AU or ≥292 AU/cm²), aortic valve CT calcium score defined severe aortic stenosis with high accuracy (sensitivity, ≥86% and specificity, ≥79%). Moreover, the prognostic effect of these calcium score thresholds was subsequently demonstrated in subsequent studies.

Figure 1. A, ¹⁸F-Fluoride (¹⁸F-NaF; a marker of novel calcification) activity increased markedly with severity of aortic stenosis (AS). Conversely, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG; a marker of inflammation) activity had a more modest association with AS severity. This supports the notion that calcification rather than inflammation predominates in the valve, particularly in the later stages of the disease. Fused positron emission tomography (PET)/computed tomography (CT) scans demonstrated a significant difference in tracer activity (top right: ¹⁸F-NaF and bottom: ¹⁸F-FDG) on coaxial views of the aortic valves in patients with mild and severe AS. White and yellow/red areas depict calcium deposits and PET tracer activity, respectively. Results presented in box and whiskers plot (Tukey): the central box represented the interquartile range of tissue-to-background ratios (TBR) with the median indicated by the dark line. The whiskers extended to the most extreme values within the 1.5 interquartile ranges. Reprinted from Dweck et al with permission of the publisher. Copyright © 2011, Wolters Kluwer Health. B, Aortic valve calcification can be quantified accurately on CT (right). Consistent with PET data, the progression of aortic valve calcification on CT was associated with severity of AS. Patients with severe AS experienced increased progression of aortic valve calcification compared with those with mild or moderate disease. Results presented in box and whiskers plot: the central box represented the interquartile range, with the mean and median indicated by the dark and dotted lines, respectively. The whiskers indicated the 5th and 95th percentiles. Reprinted from Nguyen et al with permission of the publisher. Copyright © 2015, BMJ Publishing Group.
demonstrated, with severe aortic valve calcification demonstrating a strong association with increased all-cause mortality, over and above traditional predictors of outcome in aortic stenosis (Figure 2). Of note, aortic valve replacement was an independent predictor of improved survival in patients with severe aortic valve calcification but not in those with nonsevere disease.25

Furthermore, aortic valve CT calcium score is of particular clinical relevance in patients with discordant small aortic valve area and low mean pressure gradient where the true severity of the disease remains uncertain. This commonly affects up to a third of patients with moderate or severe disease and can be because of either low flow states (as a consequence of a depressed left ventricular ejection fraction or a small ventricle) or inaccuracies in echocardiographic measurements coupled with inconsistent thresholds in current guidelines.27,28 Indeed, when the above sex-specific calcium score thresholds were applied to patients with discordant echocardiographic measures of severity, approximately half were classified as moderate aortic stenosis and the remaining patients as severe disease, underlining the disparate nature of this patient population.29 Although further validation is required in other cohorts, aortic valve CT calcium score holds great promise because of its diagnostic and prognostic effect.

Assessing Activity of Aortic Valve Calcification

Positron emission tomography (PET) is a functional imaging technique that, in theory, can measure the activity of any biological process in the body if an appropriate radioactive tracer is available. Recently, the novel application of hybrid PET/CT imaging has been used to study patients with aortic stenosis, providing unique and important insights into its pathophysiology.20

18F-Fluoride is a PET tracer that is believed to act as a marker of newly developing calcium in the vasculature. It preferentially binds to these regions of newly developing microcalcification because of the high surface area of nanocrystalline hydroxyapatite crystals compared with established macroscopic calcium deposits, where much of the calcium is internalized and unavailable for binding.30 In the valve, 18F-fluoride also acts as a marker of calcification activity, demonstrating a close association with alkaline phosphatase staining on excised valves.31 In a recent prospective study of 121 patients with aortic sclerosis and stenosis, we have established excellent reproducibility for the quantification of PET activity in the aortic valve and demonstrated a progressive increase in calcification activity with severity of aortic stenosis32 (Figure 1A). Moreover, a close association was observed between the baseline 18F-fluoride activity and disease progression as assessed by both CT and echocardiography.33 Interestingly, the distribution of 18F-fluoride activity was often distinct from the macroscopic calcium deposits on CT and over time, novel calcification developed in these regions of increased PET activity (Figure 3). We think that 18F-fluoride PET will be of particular use in the research arena where the immediate readout of disease activity will facilitate rapid assessment of the efficacy of novel therapies. Indeed, 18F-fluoride PET is already being used as an end point in just such a study targeting calcium metabolism in patients with aortic stenosis (ClinicalTrials.gov NCT0213206).

The utility of 18F-fluorodeoxyglucose has also been investigated in aortic stenosis.31,32 In aortic and carotid atheroma, this glucose analogue acts as a marker of valvular and vascular inflammation on the basis that macrophages have increased metabolic requirements compared with surrounding cells. Its mechanism of action in the valve is less clear given the presence of multiple other cells with increased glucose requirements.33 Nevertheless, 18F-fluorodeoxyglucose activity was higher in patients with aortic stenosis compared with controls and increased modestly with disease activity (Figure 1A). Further work is required to establish the exact mechanism of action of this tracer in the valve and to overcome the problems posed by its uptake in the adjacent myocardium.

Myocardial Fibrosis as a Prognostic Marker
The increased afterload associated with aortic stenosis triggers a hypertrophic response in the left ventricle. Although initially adaptive, patients ultimately progress to heart failure and other adverse cardiovascular events.6,34 This transition from adaptation to decompensation is mediated by progressive cell death and 2 predominant forms of myocardial fibrosis.35,36 Replacement fibrosis occurs later as the disease advances, and it is characterized by a more focal distribution corresponding to areas of myocyte loss. On the other hand, interstitial fibrosis is diffusely distributed, reflecting the more uniform and progressive nature of the condition.36 Both represent potential imaging targets and hold promise as objective biomarkers of left

Figure 2. Patients with severe aortic valve calcification based on absolute aortic valve calcium score (A) or aortic valve calcification density (aortic valve calcium score indexed to aortic annular area; B) had increased all-cause mortality compared with those with nonsevere aortic valve calcification. Prognostic value remained significant after adjusting for age, sex, New York Heart Association ≥3, diabetes mellitus, coronary artery disease, indexed aortic valve area, mean pressure gradient, and systolic ejection fraction. Reprinted from Clavel et al26 with permission of the publisher. Copyright © 2014, Elsevier.
Assessing Burden of Myocardial Fibrosis

Myocardial biopsy remains the gold standard for validating myocardial fibrosis, but it is invasive, susceptible to sampling errors and unable to assess the fibrotic burden of the whole heart. Multiparametric cardiovascular magnetic resonance is currently the only imaging modality that offers a direct, whole-heart assessment of myocardial fibrosis.37 To date, 2 approaches are used: late gadolinium enhancement, for direct visualization and quantification of focal replacement fibrosis, and novel myocardial T1 mapping, for assessing more diffuse patterns of interstitial fibrosis.

Late gadolinium enhancement requires the administration of extracellular gadolinium-based contrast agents. After intravenous injection, gadolinium diffuses into the extracellular space. As a result of redistribution and renal excretion, the blood concentration of gadolinium falls and the contrast is washed out from the extracellular space into the blood pool. In the normal myocardium, contrast concentration in the extracellular space equilibrates rapidly with the blood pool. Conversely, in regions of myocardial fibrosis, the extracellular space is expanded as a consequence of excessive collagen deposition. As a result, gadolinium accumulates in these regions and contrast wash out is delayed, thereby producing differences in signal intensities between normal and abnormal myocardium. Focal regions of replacement fibrosis (frequently in the midwall of the myocardium) therefore seem white in contrast to the surrounding normal myocardium that is black.36,38,39 Of note, this distinctive pattern of midwall fibrosis must be differentiated from late gadolinium enhancement because of previous myocardial infarction, which is also common in patients with aortic stenosis. Late gadolinium enhancement because of a previous myocardial infarction typically involves the subendocardium and then it extends transmurally toward the epicardium. Unlike midwall myocardial fibrosis, regions of myocardial infarction correspond to specific epicardial coronary distribution.39

Focal midwall myocardial fibrosis has been demonstrated in 19% to 62% of patients with aortic stenosis,40–43 and it is associated with impaired cardiac function and adverse cardiovascular events.42,44,45 In 143 patients with moderate to severe aortic stenosis, focal midwall fibrosis was an independent predictor of cardiovascular and all-cause mortality. Although patients without myocardial fibrosis had extremely good prognosis, those with midwall fibrosis had more than an 8-fold increase in all-cause mortality despite similar severity of aortic stenosis (Figure 4). Of note, the prognosis worsened with
an increasing burden of fibrosis. Similar findings were also observed in patients after aortic valve replacement. Mid-wall fibrosis was associated with adverse ventricular remodeling, incomplete left ventricular functional recovery, and worse cardiovascular outcomes after aortic valve replacement. Recently, midwall fibrosis on cardiovascular magnetic resonance provided further validation for other biomarkers of left ventricular decompensation. In separate studies, high sensitivity cardiac troponin I concentrations and electrocardiographic left ventricular hypertrophy and strain pattern not only demonstrated a close association with the presence of midwall late gadolinium enhancement but also provided incremental prognostic information in asymptomatic patients with aortic stenosis. These data provide increasing support that midwall fibrosis is a marker of left ventricular decompensation in aortic stenosis, and several on-going prospective studies will confirm the prognostic value of this technique (ClinicalTrials.gov NCT01755936, NCT01658345, and NCT02174471), which can prove useful in identifying patients who may benefit from early aortic valve replacement.

Unlike focal replacement fibrosis that is believed to be irreversible, there is increasing interest in diffuse interstitial fibrosis as a potential treatment target. Late gadolinium enhancement relies on a difference in signal intensity between normal and focal regions of myocardial fibrosis. It is therefore not an optimal technique for assessing interstitial fibrosis, which is more uniformly distributed and does not provide the necessary signal contrast for visualization. Instead, myocardial T1 mapping has emerged as a novel cardiovascular magnetic resonance technique to assess this form of diffuse fibrosis. T1 mapping improves myocardial characterization by its ability to quantify signal intensity for each voxel in the myocardium, generating a parametric T1 map (Figure 5). Indeed, the role of myocardial T1 mapping has been well studied in aortic stenosis, with many studies demonstrating a correlation between this marker of diffuse fibrosis and aortic stenosis severity, left ventricular mass, and cardiac performance. To date four different T1 mapping approaches have been investigated and validated against the extent of myocardial fibrosis on histology. Each has its own potential advantages and limitations (Figure 5). In our experience, extracellular volume fraction, which corrects for blood pool and the plasma gadolinium volume of distribution, offers the best reproducibility (including scan-rescan repeatability) and the ability to differentiate patients from healthy volunteers. Furthermore, increasing extracellular volume fraction values were associated with worse diastolic function. Yet even with this parameter, we have observed a substantial overlap in extracellular volume fraction values between patients with aortic stenosis and healthy volunteers, highlighting a potential limitation of myocardial T1 mapping as a diagnostic marker or clinical decision making tool. This has also been observed in other studies. Although the prognostic value of extracellular volume fraction has been demonstrated in other patient

![Late gadolinium enhancement](image1.png)

![Native T1 Map](image2.png)

![Post contrast T1 Map](image3.png)

**Figure 5.** To date, there are 4 different myocardial T1 mapping techniques used to assess diffuse interstitial fibrosis. Each technique has its own unique merits and limitations. In aortic stenosis, extracellular volume fraction seems to be the most promising technique in assessing diffuse fibrosis. Extracellular volume fraction demonstrates excellent scan-rescan reproducibility, which is necessary when assessing change related to treatment response and disease progression.
populations, similar outcome data are currently lacking in aortic stenosis, but results from the above-mentioned studies may provide further insights in the near future. Despite its potential limitations, myocardial T1 mapping may still be useful in assessing treatment responses and disease progression because of its low scan-rescan variability and greater sensitivity.

Assessing Activity of Myocardial Fibrosis

Similar to the relationship between 18F-fluoride PET and CT calcium scoring, a marker of fibrosis activity would complement current assessments of fibrosis burden by cardiovascular magnetic resonance. 18F-Fluciclatide is a PET tracer that has a high affinity for extracellular integrin receptors, which are upregulated in regions of myocardial infarction, and the potential of this radioactive tracer as marker of fibrosis activity in aortic stenosis is currently being investigated (ClinicalTrials.gov NCT01837160). Other metabolic markers of fibrosis and cell death are in development and might similarly provide useful information with respect to disease activity in the myocardium.

Assessing the Functional Consequences of Myocardial Fibrosis

Although impaired left ventricular systolic ejection fraction is the conventional marker of global systolic dysfunction and a current indication for aortic valve replacement, it is a late manifestation of ventricular decompensation and myocardial fibrosis. In fact, left ventricular ejection fraction in aortic stenosis can overestimate myocardial function in the presence of advanced concentric hypertrophy because of increased myocardial wall thickness and reduced ventricular volumes. By contrast, novel myocardial deformation imaging (strain and strain rate imaging) using speckle tracking echocardiography has been proposed as an alternative and a more sensitive approach of assessing intrinsic myocardial contractility. In particular, longitudinal deformation (motion from base to apex) assessed using 2-dimensional (2D; and more recently 3D) speckle tracking echocardiography has demonstrated incremental prognostic value in patients with aortic stenosis. In a recent study involving 104 asymptomatic patients with severe aortic stenosis and preserved left ventricular ejection fraction, both 2D and 3D global longitudinal strain was associated with increased adverse events, but the latter provided a higher accuracy in predicting adverse events (Figure 6). Future studies will be needed to confirm the emerging role of 3D speckle tracking echocardiography and to investigate how this functional parameter relates to and might complement direct assessment of myocardial fibrosis using cardiovascular magnetic resonance.

Future Role of Modern Imaging Techniques in Aortic Stenosis

Currently, the assessment and management of patients with aortic stenosis rely heavily on hemodynamic assessments by echocardiography. While echocardiography will remain...
the mainstay of imaging in aortic stenosis, modern noninvasive imaging provides important complementary information that has the potential to inform how we manage our patients.

Aortic valve CT calcium score will likely emerge as an alternative method for assessing the severity of aortic stenosis, particularly in evaluating disease progression and when echocardiographic measurements are discordant. PET imaging may have the potential of refining the prediction of disease progression offered by CT and for rapidly assessing the efficacy of novel therapeutic strategies. As aortic stenosis progresses in the later stages, the detection of replacement fibrosis by cardiovascular magnetic resonance as an objective marker of left ventricular decompensation will help guide the optimum timing of aortic valve replacement.

Although we are progressing in the early stages of this journey, an integrated multimodality approach of assessing the valve and myocardium in aortic stenosis may ultimately facilitate a stratified-medicine approach to the management of patients with aortic stenosis (Figure 7).

Conclusions

Aortic valve CT calcium scoring, PET/CT, cardiovascular magnetic resonance, and echocardiographic strain analyses are novel imaging techniques that have not only advanced our understanding of the natural history of aortic stenosis but also improved our ability to risk stratify patients with this condition. In combination, they offer the ability to predict adverse events related to the valve and the myocardium. Future prospective studies and clinical trials are now needed to investigate their clinical utility and whether their potential might translate into improved patient care.

Figure 7. Echocardiography will remain the mainstay of imaging in the initial assessment. Aortic valve computed tomography (CT) calcium score is an alternative method in assessing aortic stenosis severity, particularly in patients with discordant echocardiographic findings. In the early stages of aortic stenosis, hybrid positron emission tomography (PET)/CT may complement assessment of disease progression by aortic valve CT calcium score and to monitor efficacy of novel anticalcification therapies. In the later stages, the focus shifts to the myocardium with the aim of identifying patients with myocardial fibrosis using cardiovascular magnetic resonance, to help guide the timing of aortic valve replacement (AVR). LGE indicates late gadolinium enhancement.

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Disclosures

None.

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