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Multimodality Imaging Markers of Adverse Myocardial Remodelling in Aortic Stenosis

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Unstructured Abstract

Aortic stenosis (AS) causes left ventricular remodeling (hypertrophy, remodeling, fibrosis) and other cardiac changes (left atrial dilatation, pulmonary artery and right ventricular changes). These, and whether they are reversible (reverse remodeling), are major determinants of timing and outcome from transcatheter or surgical aortic valve replacement. Cardiac changes in response to AS afterload can either be adaptive and reversible, or maladaptive and irreversible where they may convey residual risk after intervention. Structural and hemodynamic assessment of AS therefore needs to evaluate more than the valve and in particular the myocardial remodeling response. Imaging plays a key role in this. This review assesses how multimodality imaging evaluates AS myocardial hypertrophy and its components (cellular hypertrophy, fibrosis, microvascular changes and additional features such as cardiac amyloid) both before and after intervention and seeks to highlight how care and outcomes in AS could be improved.

Key words: Aortic Stenosis, aortic valve replacement, myocardial hypertrophy, myocardial fibrosis.

Abbreviations and Acronyms

AS = aortic stenosis

ATTR = transthyretin amyloidosis

AVR = aortic valve replacement

ECV = extracellular volume fraction

hsTnT = high sensitivity Troponin T

LGE = late gadolinium enhancement

LV = left ventricle / ventricular

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

LVMi = indexed left ventricular mass

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

Introduction

Valvular heart disease affects 1 in 2 of the elderly (1), with aortic stenosis (AS) affecting >3% of those over 75. In AS, progressive valve narrowing increasing LV pressures and reduces coronary perfusion pressure so the LV responds, first with adaptive hypertrophy to maintain wall stress, later maladaptive changes including inappropriate hypertrophy, fibrosis, dilatation and impairment (Figure 1). These ventricular responses vary between individuals, as does the degree they are tolerated over time. As the ventricular responses become inadequate, additional upstream (atrial dilation, atrial fibrillation, mitral regurgitation, pulmonary pressure elevation, right ventricular impairment and tricuspid regurgitation) (2) or downstream effects are induced – with an increasingly vulnerable, less adaptable systemic circulation. The results are symptoms (breathlessness, chest pain and syncope), and eventually death through heart failure or arrhythmia (3). Treatment is valve replacement (AVR) by either surgery (SAVR) or transcatheter aortic valve replacement (TAVR), and current guidelines use valve severity, symptoms and reduced LVEF as primary gatekeepers to intervention (4,5).

Better timing of intervention may improve outcomes. Intervening too early brings forward procedural risk (a low risk patient will have 1-2% mortality and a 5-10% risk of infection, re-operation or pacemaker implantation), in some cases unnecessarily and starts the accrual of new risk (anticoagulation, endocarditis, valve failure). Watchful waiting risks pre-procedure sudden death or decompensation and the conversion of (routine) elective surgery in stable patients to salvage surgery in decompensation. In addition, irreversible myocardial (and other cardiovascular) changes may accumulate, conferring residual risk to patients after AVR. Although AVR is guideline driven, there is heterogeneity of interpretation globally. Strategies appear to give different results. For example in one study, earlier intervention (not waiting for overt symptoms) halved 3-year mortality AVR [9% vs 17.9%] (6), but a recent

meta-analysis (excluded symptomatic patients) found the case for early intervention was far from certain (7).

It is at this point that the problems with AS become apparent: The literature is vast. Key features such as LVH, symptoms, remodeling and valve stenosis are poorly standardized, have wide measurement error and our concepts are frequently simplistic. A whole-system approach is not taken: valve narrowing is only one of a range of insults, others including high afterload from hypertension and vascular stiffness, myocardial ischemia, comorbidities and sex difference in remodeling. Valve narrowing is the *insult* but it is the ventricular response that determines whether the insult is tolerated, the urgency of intervention and, potentially, any response to mitigate residual post intervention risk. Key concepts, such as LVH are simplistic – the myocardium consists of cells, vasculature and interstitium, all of which change. Therefore the hunt is on for imaging biomarkers that can be used to predict adverse remodelling at earlier stages – whether this can lead to improved outcomes remains unknown and will require future trials. The current report reviews the use of multimodality imaging of the myocardial response to AS in the above context to improve patient care (2).

Aortic Stenosis – the Valve, the Vasculature and the Myocardium

This review focuses on the myocardial response in AS, but it is important to highlight the interplay of valve, vascular and myocardium. The insult arises from progressive valvular stenosis, but it is the combined afterload from the valve and the vascular with its resultant myocardial response – initially adaptive then maladaptive – that determines disease progression, symptoms and outcome.

The Aortic Valve

Stages of AS range from patients at risk of AS (stage A) or with progressive hemodynamic obstruction (stage B) to severe asymptomatic (stage C; subdivided into C1 with normal LVEF and C2 with LVEF<50%) and symptomatic AS (stage D), and are defined by valve

anatomy, valve hemodynamics (with normal flow [D1], low flow due to LV systolic dysfunction [D2] or a low stroke volume [D3]) (5).

The Vasculature

These stages reflect the time integral of the combined afterload of the narrowing valve and the vasculature, itself composed of aortic stiffness and arterial hypertension (8). Global afterload can be captured by valvular-arterial impedance, and high impedance is associated with worse survival in severe symptomatic (in particular low-flow, low-gradient AS with preserved LVEF) and moderate to severe asymptomatic AS (9).

The Myocardium – AS Cardiomyopathy

Myocardial changes play a key role in functional deterioration, symptoms and outcome .

In response to afterload, early changes are benign and physiologically appropriate with myocardial cellular hypertrophy, intracellular changes (e.g. titin isoform switch and hypophosphorylation) and proportionate extracellular matrix expansion to maintain wall stress (10,11). Reduced capillary density, compensatory vasodilation and impaired myocardial blood flow accompany increasing LVH (12), so even if myocytes were infinitely adaptable, compensation through adaptation cannot be indefinite. Furthermore, afterload of AS is proximal to the coronary origins, adding to reduction of microvascular function. Hence, increasingly maladaptive changes occur with microvascular ischemia, cell death by apoptosis or autophagy, and alterations of extracellular matrix components (ratio of collagen I and III, collagen phosphorylation and cross-linking). Eventually these changes result in the development of irreversible microscars particularly in the sub-endocardium with a gradient from the inner to the outer third of the myocardium (Figure 1) (13-15), and interfibre and perivascular fibrosis throughout the myocardium. These result in an increasingly precarious circulation, with loss of normal physiological adaptive capability to stressors like exercise, posture, arrhythmia with increasing risk of irreversible feedback loops and sudden death. The theoretical impetus for early AVR is therefore to avoid irreversible changes; this paradigm

requires imaging (or blood) biomarkers capable of heralding the transition from adaptive to maladaptive myocardial remodeling would allow more timely intervention, thus optimizing the chances for normalization myocardium and improved postoperative outcomes – randomized controlled trials are required to test this.

Left Ventricular Geometry and Sex Dimorphism

AS triggers altered global LV geometry (radius and wall thickness, or mass volume ratio) (16). Four pattern are conventionally described based on either wall to cavity dimensions or LV volume and mass (17): normal geometry, remodeling, concentric hypertrophy and eccentric hypertrophy (Figure 3). There is marked sex dimorphism in the remodeling response (18,19) with men having higher indexed LV mass, lower LVEF, and increased myocardial stiffness (20), and women more concentric remodeling with higher relative wall thickness and LVEF, but the scale of the differences is being increasingly recognized with apparently more maladaptive myocardial response to AS in men (Figure 3)(21).

Left Ventricular Hypertrophy and Co-morbidities

Classically, LVH has been seen as the key response to increasing afterload and LV intra-cavity pressure in order to maintain normal wall stress. This response is however not consistent (10-20% of patients with severe AS display no LVH) and only weakly correlates with the degree of apparent valve stenosis on single timepoint imaging – this "paucihypertropy" may in fact be a maladaptive response. Arterial hypertension is common in calcific AS, depending on age - e.g. affecting 72% of patients aged 67±10 in the SEAS trial (22). Hypertension increases global afterload, hypertrophic remodeling, interstitial fibrosis and LV dysfunction, thereby heralding worse outcome. Uncontrolled hypertension confounds assessment and may cause underestimation of AS-severity; the markers of AS severity should thus be interpreted with caution in hypertensive patients and be re-evaluated when the patient is in a normotensive state (23). Furthermore, reverse remodelling after AVR can be attenuated by untreated/uncontrolled hypertension and increased vascular stiffness.

Other factors affecting the magnitude of hypertrophic response are age, metabolic syndrome and obesity (24), angiotensin enzyme polymorphism, arterial hypertension and cardiac amyloidosis *(see below)*.

Myocardial changes After Valve Replacement – Reverse Remodeling

The extent of myocardial reverse remodeling after reduction of afterload by AVR is linked to outcome but remains incompletely understood. A full exploration should ideally assess pre-intervention temporal changes over months to years and assess both the effectiveness of the intervention (change in afterload – hypertension and valve gradient, extent of baseline changes, aortic regurgitation, other interventions, as well as sex and survival bias) and myocardial characteristics (biomarkers, hypertrophy, scar, other features).

Normalization of Left ventricular function

After intervention, LV function normalizes. At baseline, there are more abnormalities in MAPSE, peak longitudinal strain (LS) and strain rate compared to EF. Post-AVR these also improve more, suggesting these are more sensitive markers of LV function (25,26). Changes can be early, but most improvement takes 6 months (27).

Left Ventricular Hypertrophy Regression

Following SAVR or TAVR, LV mass (LVM) regresses fastest in the first 6 to 12 months – achieving 20-30% LVM reduction at 1 year, associated with improved LV systolic function (20,28). A systematic review by Douglas et al showed that SAVR and TAVR were hemodynamically comparable with higher incidence of patient-prosthesis-mismatch in the SAVR cohorts offset by higher incidence of paravalvular leak in TAVR cohorts, but that LV mass regression was double at 1-year in the SAVR cohorts (22% vs 11%) (29). There is some evidence that initial LVH regression can be fast (PARTNER A)(72), and there may be different temporal patterns depending on burden of comorbidities, vascular stiffness and hemodynamic performance of the prosthesis type (30,31). Diastolic dysfunction (relaxation)

improves later (~3 years) with further regression of LVH out to 10 years dependent on baseline hypertrophy and co-existent arterial hypertension (32) with other factors likely to play a role as well (initial gradients, subsequent valve type, patient prosthetic mismatch, degree of post procedure aortic regurgitation) (33).

Multimodality Imaging Approaches

Clinical assessment – remembering to think of AS, detecting a murmur, assessing symptoms and their likely explanation in context, is the gatekeeper to further testing. It can be difficult, especially in the elderly and comorbid patient (4). LVH and strain pattern on EKG and cardiac biomarkers (brain natriuretic peptides and troponins), as prognostic markers shape investigation urgency (34), but the key diagnostic tool is imaging using echocardiography. Other modalities (cardiovascular magnetic resonance [CMR], nuclear and computed tomography [CT] offer additional insights (35), and should be considered if echocardiography is not able to obtain the required data or when there is a disagreement between AVA and gradients. Aortic valve calcium quantification by CT as well as volume, function, aortic flow quantification and tissue characterization by CMR are particularly helpful.

Echocardiography

Echocardiography allows anatomical, functional and hemodynamic assessment of valve, ventricle and upstream structures (Figure 2). Valve obstruction is measured using Doppler and flow-derived parameters (peak velocity, mean gradient, effective orifice area and dimensionless velocity index); these parameters are prognostic, but have been reviewed in details elsewhere (3). Assessment of ventricular performance begins with the ejection fraction (LVEF) – LV impairment is a strong adverse prognostic marker and sufficiently reliably measured that it forms part of guidelines: impaired systolic function (LVEF<50%) is, even in asymptomatic patients, a class I indication for AVR. LVEF is an excellent marker of

advanced LV impairment but it remains normal until late in the course of the disease (Central Illustration), with increased LVH and LV remodeling. A reduced stroke volume has added value; in the setting of preserved LVEF it can reflect a small LV cavity due to LVH with high afterload (elevated vascular impedance) and compounded by long axis dysfunction (36). Other valvular pathologies, atrial fibrillation and right ventricular dysfunction can also contribute to low flow states and need to be identified for optimal management.

Diastolic assessment and myocardial deformation detects earlier changes in function (37,38). Deformation can be measured in a variety of ways include long axis annular excursion, mid-wall fractional shortening, myocardial systolic and diastolic velocities, and global longitudinal strain using speckle tracking. Strain abnormalities follow a disease specific pattern, starting sub-endocardially, becoming mid-wall then transmural in advance disease where they are prognostic (39). Apical twist and torsion increase with progressive AS (40), and regress after AVR (39) – may serve as a compensatory mechanism for reduced longitudinal function. Worsening of myocardial mechanics indices reflect aggregates of several myocardial insults including intrinsic myocyte dysfunction, fibrosis or ischemia and change early in the disease. Historically measurement of strain had high inter-vendor variability, but this has been addressed by standardization task force recommendation (41).

Cardiovascular Magnetic Resonance (CMR)

CMR as the reference standard for quantifying LV volumes, mass and systolic function allows a more accurate three-dimensional assessment of geometric changes, particularly in patients with poor echocardiographic windows. It can quantify flow, which may have advantages over echocardiography for regurgitation (42), and myocardial deformation where temporal resolution is not important. Furthermore, strain analysis by CMR is now feasible on standard CMR cine SSFP images using feature-tracking, which has been shown to be robust and was validated again CMR tagging (43).

The key strength however is myocardial tissue characterization, in particular the late gadolinium enhancement technique (LGE) to detect scar – focal fibrosis – which is coming to the fore as an independent prognostic marker in AS (44,45). In addition, diffuse fibrosis, edema and cardiac amyloid deposition are now detectable using multi-parametric mapping. T1 mapping allows derivation of the extracellular volume fraction (ECV), which reflects interstitial expansion and its reciprocal (1-ECV=ICV), the cell volume fraction (mainly myocyte), reflecting cell hypertrophy (21,46). ECV and ICV as a percentage can also be expressed as volumes by multiplying by myocardial volume. With this armamentarium, we can now better interrogate the biology of LVH (10,47).

Furthermore, new sequence developments in CMR allow detection of subtle subendocardial scar (with dark blood LGE) (48), myocardial blood flow (12,49), and myocardial edema (50). Quantification of myocardial perfusion reserve (MPR) by adenosine stress perfusion has been investigated: Ahn et al found angina to be related to impaired coronary microvascular function and LVH (12). The PRIMID-AS study showed MPR was associated with symptom-onset in initially asymptomatic patients, but was not superior to symptom-limited exercise testing (49). New fully-quantitative perfusion techniques such as perfusion mapping may offer greater insights into the pathophysiology of myocardial remodelling in AS.

CMR also offers additional insights into the reverse remodelling response after AVR: Early mass regression is greater when there is more LVH, and when scar is absent (51). LVM can be further split into matrix and cellular compartments using T1 mapping: Early ECV data interrogating LVM regression at 6 months post-AVR noted cellular regression without significant extracellular matrix changes (52) but more recent data (the RELIEF-AS Study) shows that by 1 year that a 19% LVM regression is comprised of a 16% reduction in matrix volume and (still greater) 22% reduction in cell volume (meaning that the ECV increases). Scar by LGE however is irreversible (47). This is important as it appears both myocardial compartments are plastic, providing scar is absent, a result that has been reproduced by other

groups (53). Finally, T2 may be elevated and fall after AVR suggesting myocardial edema and low-grade inflammation may be present (50).

Computed Tomography

Cardiac computed tomography (CT) is established for the work-up and pre-procedural planning prior to TAVR, combining accurate anatomical assessment with patient ease (well-tolerated even in the very elderly). Quantification of aortic valve calcium has been shown in multicentre studies to be reproducible and offers prognostic value above and beyond echocardiographic indices of AS severity (54,55). CT can also provide useful 3D information to more precisely measure the left ventricular outflow tract and aortic valve calcium score (which can improve assessment of AS severity in some cases), can help characterize anatomy of aortic valve (number of leaflets; patterns of calcification) aortic root, and allow evaluation of the vascular access root in the same scan.

Nuclear Imaging

Nuclear scintigraphy until recently has not played a significant role – theoretical concerns about vasodilator stress in AS mean that invasive coronary angiography had been the mainstay of pre-operative work-up, although adenosine is actually well tolerated. Recently, the recognition of transthyretin cardiac amyloidosis (ATTR) as an important myocardial dual pathology in the over 75s, has led to the increased use of bone scintigraphy, which has an exquisite diagnostic accuracy for the non-invasive diagnosis of ATTR (56). Positron emission tomography (PET) imaging allows assessments of disease activity in the heart, but requires hybrid imaging with either CT or MRI to provide additional anatomical information. Hybrid PET-CT imaging is widely used to study the heart and large arteries, in particular myocardial perfusion and viability assessments in patients with ischemic heart disease, whereas the use of PET-MRI is very limited due to high cost and access. Other use include cardiac metabolism using ^{11}C-labeled fatty acids, myocardial viability using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) or cardiovascular inflammation using FDG with dedicated

high-fat-no-carbohydrate dietary preparation. These and other potential PET tracers have been reviewed elsewhere, but the potential use of ^{18}F-fluoride–PET-CT imaging as a marker of aortic valve disease activity in AS is promising and prospective studies are underway to assess whether it can improve prediction of risk and response to therapy (57).

Predictors of Outcome

Upstream effects – left atria dilatation, pulmonary hypertension and RV impairment

Atrial dilatation has long been known to be adverse, as are other features (28). High pulmonary artery pressure is often but not always be associated with adverse outcome (58) and can be reversible with intervention – reversal being associated with improved outcomes (59), but severe pulmonary pulmonary hypertension (PASP>60mmHg) is associated with both short-term and long-term outcomes (60). Right ventricular per se impairment is also an adverse marker, with recovery after TAVR better than SAVR, although it is not clear whether this is due to post-SAVR tethering (potentially more benign) or adverse impact of on-pump cardiopulmonary bypass (potentially more adverse) on the right ventricle (61). Furthermore, it is important to highlight that pulmonary hypertension cannot be understood without concomitant evaluation of RV function. Right ventricular-pulmonary arterial coupling is therefore more meaningful than either parameter alone (62).

A new staging classification based on the extent of upstream cardiac damage associated with AS in patients from the PARTNER B trial (n=1661) (2): no extra-valvular cardiac damage (Stage 0), left ventricular damage (Stage 1), left atrial or mitral valve damage (Stage 2), pulmonary vasculature or tricuspid valve damage (Stage 3), or right ventricular damage (Stage 4). Stages were associated with progressively increased 1-year mortality (Stages 0-4 respectively: 4.4%, 9.2%, 14.4%, 21.3% and 24.5% P_{trend} <0.0001) and post intervention mortality (HR 1.46 per stage $P < 0.0001$).

Left Ventricular Hypertrophy and Geometry

LVH at baseline, whether measured by electrocardiographic (LVH with strain) or imaging is associated early and late adverse outcome particularly when excessive (63). LVM regression is a marker of good outcome together with age, NYHA functional class, arterial hypertension, reduced EF, and high pre-operative LVM (64). Several studies have suggested that concentric LV geometry (i.e. increasing relative wall thickness but no overt LVH) has a particularly poor prognosis in AS: Duncan et al (n=964, severe AS) propensity-matched concentric geometry patient to patients with nonconcentric geometry, and identified an increased in-hospital mortality, cardiac morbidity, and prolonged intubation in patients with concentric geometry (65).

Left Ventricular Diastolic Function

One of the earliest functional effects of progressive LVH and myocardial fibrosis (focal and diffuse) in AS is worsening of diastolic function. Although a sensitive marker of myocardial changes, it has found a specific role in the management of patients with severe AS, predominantly because there is a lack of prospective outcome data supporting its routine use. Reviewed in greater detail by others (66), key changes include: Diastolic dysfunction at baseline is associated with increased mortality and diastolic dysfunction; it worsens with progressive myocardial remodelling prior to AVR and gradually, but not totally improves with reverse remodelling after AVR.

Left Ventricular Systolic Function

The ejection fraction as a predictor is known, although little effort is taken to determine the relative contribution of EF related to other processes (such as infarction). For advanced features, *mitral annular velocity (S')* ≤ 4.5cm/s is linked to symptom onset, AVR need and cardiac death in patients with asymptomatic severe AS and preserved LVEF (67). Peak systolic mitral annular velocities improve early post TAVR and by 6 months after SAVR and TAVR (68,69). Other *myocardial deformation* parameters are impaired in AS and correlate with AS severity with reduced strain and strain rate predicting clinical events in

asymptomatic AS (70). GLS improves both after TAVR and SAVR (25,27), as early as prior to discharge in TAVR (26). In a recent individual participant data meta-analysis (10 studies, n=1,067, asymptomatic severe AS, LVEF>50%), Magne et al demonstrated that GLS performed well in the prediction of death (area under the curve: 0.68) with the best cut-off value being 14.7% (sensitivity, 60%; specificity, 70%) (71). Baseline GLS has also been shown to be the strongest predictor of LVM regression in a cohort of severe AS patients post SAVR (72); in low-flow low-gradient AS, baseline GLS not LVEF was independently associated to GLS improvement at 12 months after TAVR (73).

Focal Myocardial Fibrosis By Late Gadolinium Enhancement

LGE is established as the gold standard for focal scar assessment in both ischemic and non-ischemic heart diseases and is reproducible in multi-center trials. LGE patterns in AS range from subendocardial infarction-pattern to patchy focal, and linear non-infarct LGE (Figure 4). Several groups have investigated LGE in AS (Table 3): Prevalence of LGE in severe AS ranges from 27% to 51% (44,45,74), is associated with more severe valvular stenosis (74) and worse systolic and diastolic function (75), correlates with histology (13,75) and appears to be fixed at 9 and 12 months post SAVR (37,47). In mild AS, LGE accumulates over time slowly (with minimal annual change), but faster in moderate and severe AS (53) with an apparent acceleration trajectory for both scar number and extent. After AVR, de-novo LGE may occur in between 5 and 18% of patients (76,77) but myocardial vulnerability during surgery is not yet well understood. Single center studies suggested that an LGE mortality association (45) for both non-infarct and infarct-pattern LGE (78). In a large multi-center study, the British Society of CMR Valve consortium (n=674, severe AS; 399 SAVR / 275 TAVR) showed that LGE was present in half patients (18% infarct-pattern; 33% non-infarct) highlighting a 22% mortality at 3.6 years (21.5%; 13% post-SAVR, 34% post-TAVR). LGE independently predicted all-cause (26% vs 13%; $p<0.001$) and cardiovascular mortality (15%

vs 4.8%; p<0.001), regardless of intervention. Every 1% increase in scar was associated with 11% higher all-cause mortality and 8% higher cardiovascular mortality hazard (44). The next step is to determine whether early intervention guided by LGE improves survival; the EVOLVED-AS (NCT03094143) is currently under way to assess early intervention in asymptomatic patients with LGE. LGE quantification is not without challenges; there is no Societal or International consensus on which LGE quantification method to use in AS. Although the full-width-half-max methodology has been shown to be most reproducible for LGE of 'scar' of both non-ischemic and chronic infarct etiology (79,80), we have found that full-width-half-max and standard deviation threshold methods delivered equivalent results.

Diffuse Myocardial Fibrosis By T1 Mapping

Diffuse myocardial fibrosis is an attractive biomarker, because it may precede irreversible focal fibrosis (11). Diffuse fibrosis at the time of surgery predicts symptomatic and LV function improvement (81). ECV, its imaging surrogate has therefore potential (82). Early histological validation in small validation cohorts was strong (82) but more recent studies have found much weaker correlations between ECV and histology (13,83); this discrepancy is likely due to technical aspects of the methodology – fibrosis in AS follows a subendocardial gradient of distributions; i.e. T1 mapping misses fibrosis in less severe fibrosis where the gradient has not yet reached the mid-myocardium (13). Native T1, which captures both cellular and extracellular changes, has also been validated and tracks AS severity. ECV is higher in AS than in controls and correlates with functional capacity at baseline. In the PRIMID-AS study (n=170, asymptomatic moderate to severe AS), neither LGE nor ECV were associated with the primary outcome of symptom onset requiring AVR, MACE or cardiovascular death (49). Mortality data is only available from one single center study, where BSA-indexed extracellular volume (called iECV here) when used together with LGE to categorize patients (normal myocardium vs elevated iECV vs replacement fibrosis),

there was stepwise increase in unadjusted mortality across groups (46). Multicenter ECV outcome studies are under way.

Left Ventricular Remodelling In Challenging Patient Scenarios

Normal and Abnormal Flow States

Classic low-flow low-gradient AS with preserved LVEF, characterized by severe concentric remodeling, high wall thickness, small LV volumes and low indexed stroke volume and mean gradients, has more impaired LV longitudinal strain (84) and is at the highest risk of mortality and adverse events (85). Despite high surgical risk, AVR is associated with survival benefit. The challenges and prognostic implications of low-flow low-gradient AS with preserved LV have been discussed elsewhere (85), and are beyond the scope of this review.

Dual pathology – AS-Amyloid

AS and TTR amyloidosis (formerly senile amyloidosis) are mainly diseases of the elderly so are likely to co-exist (Figure 5). Indeed, AS-amyloid prevalence in severe AS patients referred for CMR is 8% (86), 6% in SAVR patients (87) and 13-16% (1 in 7) in (older) TAVR patients (88,89). Implications are two-fold: first, ATTR in patients with moderate AS may mimic severe AS (with low-flow, low-gradient) causing misdiagnosis; second, ATTR may be a disease modifier, leading to a more severe phenotype with more heart failure, arrhythmia, and higher mortality. With major therapies currently available and pending licenses, much further work in this area is needed.

Emerging Modalities

Exercise Echocardiography and Cardio-Pulmonary Exercise Testing

Exercise stress echocardiography in asymptomatic severe AS provides prognostic value over exercise testing alone (90), offering dynamic evaluation of transvalvular pressures, myocardial contraction and pulmonary pressures and providing deep insights into AS consequences and reserves (91). Cardiopulmonary exercise testing provides additional

objective measure of exercise tolerance and is feasible and reproducible in AS (92). In a recent study, over half of "asymptomatic" AS patients had reduced VO_2 peak and a VO_2 peak <85% was associated with lower event free survival (93); incorporation into a stress echocardiography protocol may benefit severe AS patients under watchful waiting.

The Myocardium by Cardiac CT

Cardiac CT can assess myocardial volumes, mass and function by LVEF (94) and strain (95). New biomarkers are emerging including CT stress myocardial perfusion, myocardial fat, focal scar and ECV by CT (ECV_{CT}; details in supplement). ECV_{CT} showed significant correlation with both histological measures of fibrosis ($r = 0.71$, $p < 0.001$) and ECV_{CMR} ($r=0.73$) (96), and is able to discriminate between patients with definite cardiac amyloid and those with AS. ECV_{CT} may be particular attractive in TAVR patients, as many undergo pre-procedural CT, and the 1 in 7 prevalence of AS-amyloid in TAVR patients, this may be shown to have early clinical utility.

Translation of Imaging Biomarkers in AS into Clinical Practice

Pathophysiological insights from multi-modality imaging are changing how we classify, risk assess and may determine timing for intervention in the future. But in order to move to an imaging-led, "myocentric" approach to the treatment of AS, large outcomes-driven randomized controlled trials are required. The EVOLVED-AS study (NCT03094143) represents the first randomized controlled trial of its kind to test whether identification of an imaging biomarker, in the absence of symptoms, would be enough of a trigger for AV intervention. Therefore, whether an imaging led approach could translate into better patient outcomes vs. conventional standard of care (watchful waiting) remains to be seen.

Conclusion

Outcome in aortic stenosis is driven by the myocardial remodeling response prior to and after intervention. Multimodality imaging of the stenotic insult, the vascular load and the myocardial response are crucial to develop a better understanding of the different phenotypes of this remodeling. Underlying pathways include myocardial hypertrophy, microvascular dysfunction and fibrosis. To improve outcome for patients, assessment of these new parameters needs to become robust to translate into clinical practice and need to be integrated into a wider assessment using clinical, ECG, exercise and biomarker assessment.

REFERENCES:

1. d'Arcy JL, Coffey S, Loudon MA et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J 2016;37:3515-3522.
2. Genereux P, Pibarot P, Redfors B et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J 2017;38:3351-3358.
3. Rosenhek R, Zilberszac R, Schemper M et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151-6.
4. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-2791.
5. Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252-289.
6. Nagao K, Taniguchi T, Morimoto T et al. Acute Heart Failure in Patients With Severe Aortic Stenosis- Insights From the CURRENT AS Registry. Circ J 2018;82:874-885.
7. Lim WY, Ramasamy A, Lloyd G, Bhattacharyya S. Meta-analysis of the impact of intervention versus symptom-driven management in asymptomatic severe aortic stenosis. Heart 2017;103:268-272.
8. Lancellotti P, Donal E, Magne J et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364-71.
9. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol 2009;54:1003-11.
10. Treibel TA, Kozor R, Menacho K et al. Left Ventricular Hypertrophy Revisited: Cell and Matrix Expansion Have Disease-Specific Relationships. Circulation 2017;136:2519-2521.
11. Schwarz F, Flameng W, Schaper J, Hehrlein F. Correlation between myocardial structure and diastolic properties of the heart in chronic aortic valve disease: effects of corrective surgery. Am J Cardiol 1978;42:895-903.
12. Ahn JH, Kim SM, Park SJ et al. Coronary Microvascular Dysfunction as a Mechanism of Angina in Severe AS: Prospective Adenosine-Stress CMR Study. J Am Coll Cardiol 2016;67:1412-22.
13. Treibel TA, Lopez B, Gonzalez A et al. Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients. Eur Heart J 2018;39:699-709.
14. Schwarz F, Flameng W, Schaper J et al. Myocardial structure and function in patients with aortic valve disease and their relation to postoperative results. Am J Cardiol 1978;41:661-9.
15. Cheitlin MD, Cheitlin MD, Robinowitz M et al. The distribution of fibrosis in the left ventricle in congenital aortic stenosis and coarctation of the aorta. Circulation 1980;62:823-830.
16. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 2000;102:470-9.
17. Ganau A, Devereux RB, Roman MJ et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992;19:1550-8.
18. Carroll JD, Carroll EP, Feldman T et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 1992;86:1099-107.

19. Aurigemma GP, Gaasch WH. Gender differences in older patients with pressure-overload hypertrophy of the left ventricle. Cardiology 1995;86:310-7.
20. Dobson LE, Fairbairn TA, Musa TA et al. Sex-related differences in left ventricular remodeling in severe aortic stenosis and reverse remodeling after aortic valve replacement: A cardiovascular magnetic resonance study. Am Heart J 2016;175:101-11.
21. Treibel TA, Kozor R, Fontana M et al. Sex Dimorphism in the Myocardial Response to Aortic Stenosis. JACC Cardiovasc Imaging 2017.
22. Rossebo AB, Pedersen TR, Boman K et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343-56.
23. Kadem L, Dumesnil JG, Rieu R, Durand LG, Garcia D, Pibarot P. Impact of systemic hypertension on the assessment of aortic stenosis. Heart 2005;91:354-61.
24. Lindman BR, Arnold SV, Madrazo JA et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. Circ Heart Fail 2011;4:286-92.
25. Kempny A, Diller GP, Kaleschke G et al. Longitudinal left ventricular 2D strain is superior to ejection fraction in predicting myocardial recovery and symptomatic improvement after aortic valve implantation. Int J Cardiol 2013;167:2239-43.
26. Lozano Granero VC, Fernandez Santos S, Fernandez-Golfin C et al. Immediate improvement of left ventricular mechanics following transcatheter aortic valve replacement. Cardiol J 2018.
27. Rost C, Korder S, Wasmeier G et al. Sequential changes in myocardial function after valve replacement for aortic stenosis by speckle tracking echocardiography. Eur J Echocardiogr 2010;11:584-9.
28. Beach JM, Mihaljevic T, Rajeswaran J et al. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. J Thorac Cardiovasc Surg 2014;147:362-369 e8.
29. Kim SJ, Samad Z, Bloomfield GS, Douglas PS. A critical review of hemodynamic changes and left ventricular remodeling after surgical aortic valve replacement and percutaneous aortic valve replacement. Am Heart J 2014;168:150-9 e1-7.
30. Douglas PS, Hahn RT, Pibarot P et al. Hemodynamic outcomes of transcatheter aortic valve replacement and medical management in severe, inoperable aortic stenosis: a longitudinal echocardiographic study of cohort B of the PARTNER trial. J Am Soc Echocardiogr 2015;28:210-7 e1-9.
31. Lindman BR, Stewart WJ, Pibarot P et al. Early regression of severe left ventricular hypertrophy after transcatheter aortic valve replacement is associated with decreased hospitalizations. JACC Cardiovasc Interv 2014;7:662-73.
32. Lund O, Emmertsen K, Dorup I, Jensen FT, Flo C. Regression of left ventricular hypertrophy during 10 years after valve replacement for aortic stenosis is related to the preoperative risk profile. Eur Heart J 2003;24:1437-46.
33. Magalhaes MA, Koifman E, Torguson R et al. Outcome of Left-Sided Cardiac Remodeling in Severe Aortic Stenosis Patients Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol 2015;116:595-603.
34. Chin CW, Messika-Zeitoun D, Shah AS et al. A clinical risk score of myocardial fibrosis predicts adverse outcomes in aortic stenosis. Eur Heart J 2016;37:713-23.
35. Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for Multimodality Imaging in Valvular Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society,

Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;70:1647-1672.
36. Rusinaru D, Bohbot Y, Ringle A, Marechaux S, Diouf M, Tribouilloy C. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Eur Heart J 2018;39:1992-1999.
37. Weidemann F, Herrmann S, Stork S et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009;120:577-84.
38. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195-202.
39. Delgado V, Tops LF, van Bommel RJ et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30:3037-47.
40. van Dalen BM, Tzikas A, Soliman OI et al. Left ventricular twist and untwist in aortic stenosis. Int J Cardiol 2011;148:319-24.
41. D'Hooge J, Barbosa D, Gao H et al. Two-dimensional speckle tracking echocardiography: standardization efforts based on synthetic ultrasound data. Eur Heart J Cardiovasc Imaging 2016;17:693-701.
42. Myerson SG, d'Arcy J, Mohiaddin R et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. Circulation 2012;126:1452-60.
43. Hwang JW, Kim SM, Park SJ et al. Assessment of reverse remodeling predicted by myocardial deformation on tissue tracking in patients with severe aortic stenosis: a cardiovascular magnetic resonance imaging study. J Cardiovasc Magn Reson 2017;19:80.
44. Musa TA, Treibel TA, Vassiliou VS et al. Myocardial Scar and Mortality in Severe Aortic Stenosis: Data from the BSCMR Valve Consortium. Circulation 2018.
45. Barone-Rochette G, Pierard S, De Meester de Ravenstein C et al. Prognostic Significance of LGE by CMR in Aortic Stenosis Patients Undergoing Valve Replacement. J Am Coll Cardiol 2014;64:144-54.
46. Chin CW, Everett RJ, Kwiecinski J et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. JACC Cardiovasc Imaging 2016.
47. Treibel TA, Kozor R, Schofield R et al. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. J Am Coll Cardiol 2018;71:860-871.
48. Kellman P, Xue H, Olivieri LJ et al. Dark blood late enhancement imaging. J Cardiovasc Magn Reson 2016;18:77.
49. Singh A, Greenwood JP, Berry C et al. Comparison of exercise testing and CMR measured myocardial perfusion reserve for predicting outcome in asymptomatic aortic stenosis: the PRognostic Importance of MIcrovascular Dysfunction in Aortic Stenosis (PRIMID AS) Study. Eur Heart J 2017;38:1222-1229.
50. Gastl M, Behm P, Haberkorn S et al. Role of T2 mapping in left ventricular reverse remodeling after TAVR. Int J Cardiol 2018;266:262-268.
51. Dobson LE, Musa TA, Uddin A et al. Acute Reverse Remodelling After Transcatheter Aortic Valve Implantation: A Link Between Myocardial Fibrosis and Left Ventricular Mass Regression. Can J Cardiol 2016;32:1411-1418.
52. Flett AS, Sado DM, Quarta G et al. Diffuse myocardial fibrosis in severe aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2012;13:819-26.

53. Everett RJ, Tastet L, Clavel MA et al. Progression of Hypertrophy and Myocardial Fibrosis in Aortic Stenosis: A Multicenter Cardiac Magnetic Resonance Study. Circ Cardiovasc Imaging 2018;11:e007451.
54. Pawade T, Clavel MA, Tribouilloy C et al. Computed Tomography Aortic Valve Calcium Scoring in Patients With Aortic Stenosis. Circ Cardiovasc Imaging 2018;11:e007146.
55. Clavel MA, Pibarot P, Messika-Zeitoun D et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. J Am Coll Cardiol 2014;64:1202-13.
56. Gillmore JD, Maurer MS, Falk RH et al. Non-Biopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016.
57. Robson PM, Dey D, Newby DE et al. MR/PET Imaging of the Cardiovascular System. JACC Cardiovasc Imaging 2017;10:1165-1179.
58. Levy F, Bohbot Y, Sanhadji K et al. Impact of pulmonary hypertension on long-term outcome in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2018;19:553-561.
59. Alushi B, Beckhoff F, Leistner D et al. Pulmonary Hypertension in Patients With Severe Aortic Stenosis: Prognostic Impact After Transcatheter Aortic Valve Replacement: Pulmonary Hypertension in Patients Undergoing TAVR. JACC Cardiovasc Imaging 2018.
60. Tang M, Liu X, Lin C et al. Meta-Analysis of Outcomes and Evolution of Pulmonary Hypertension Before and After Transcatheter Aortic Valve Implantation. Am J Cardiol 2017;119:91-99.
61. Ren B, Spitzer E, Geleijnse ML et al. Right ventricular systolic function in patients undergoing transcatheter aortic valve implantation: A systematic review and meta-analysis. Int J Cardiol 2018;257:40-45.
62. Sultan I, Cardounel A, Abdelkarim I et al. Right ventricle to pulmonary artery coupling in patients undergoing transcatheter aortic valve implantation. Heart 2018.
63. Cioffi G, Faggiano P, Vizzardi E et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart 2011;97:301-7.
64. Gaudino M, Alessandrini F, Glieca F et al. Survival after aortic valve replacement for aortic stenosis: does left ventricular mass regression have a clinical correlate? Eur Heart J 2005;26:51-7.
65. Duncan AI, Lowe BS, Garcia MJ et al. Influence of concentric left ventricular remodeling on early mortality after aortic valve replacement. Ann Thorac Surg 2008;85:2030-9.
66. Kampaktsis PN, Kokkinidis DG, Wong SC, Vavuranakis M, Skubas NJ, Devereux RB. The role and clinical implications of diastolic dysfunction in aortic stenosis. Heart 2017;103:1481-1487.
67. Lancellotti P, Moonen M, Magne J et al. Prognostic effect of long-axis left ventricular dysfunction and B-type natriuretic peptide levels in asymptomatic aortic stenosis. Am J Cardiol 2010;105:383-8.
68. Galema TW, Yap SC, Soliman OI et al. Recovery of long-axis left ventricular function after aortic valve replacement in patients with severe aortic stenosis. Echocardiography 2010;27:1177-81.
69. Nieh CC, Teo AY, Soo WM, Lee GK, Singh D, Poh KK. Improvement in left ventricular function assessed by tissue Doppler imaging after aortic valve replacement for severe aortic stenosis. Singapore Med J 2015;56:672-6.
70. Delgado V, Tops LF, van Bommel RJ et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30:3037-47.

71. Magne J, Cosyns B, Popescu BA et al. Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis: An Individual Participant Data Meta-Analysis. JACC Cardiovasc Imaging 2019;12:84-92.
72. Poulin F, Carasso S, Horlick EM et al. Recovery of left ventricular mechanics after transcatheter aortic valve implantation: effects of baseline ventricular function and postprocedural aortic regurgitation. J Am Soc Echocardiogr 2014;27:1133-42.
73. Kamperidis V, Joyce E, Debonnaire P et al. Left ventricular functional recovery and remodeling in low-flow low-gradient severe aortic stenosis after transcatheter aortic valve implantation. J Am Soc Echocardiogr 2014;27:817-25.
74. Debl K, Djavidani B, Buchner S et al. Delayed hyperenhancement in magnetic resonance imaging of left ventricular hypertrophy caused by aortic stenosis and hypertrophic cardiomyopathy: visualisation of focal fibrosis. Heart 2006;92:1447-51.
75. Lee SP, Park SJ, Kim YJ et al. Early detection of subclinical ventricular deterioration in aortic stenosis with cardiovascular magnetic resonance and echocardiography. J Cardiovasc Magn Reson 2013;15:72.
76. Kim WK, Rolf A, Liebetrau C et al. Detection of myocardial injury by CMR after transcatheter aortic valve replacement. J Am Coll Cardiol 2014;64:349-57.
77. Dobson LE, Musa TA, Uddin A et al. Post-procedural myocardial infarction following surgical aortic valve replacement and transcatheter aortic valve implantation. EuroIntervention 2017;13:e153-e160.
78. Dweck MR, Joshi S, Murigu T et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271-9.
79. Flett AS, Hasleton J, Cook C et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 2011;4:150-6.
80. Mikami Y, Kolman L, Joncas SX et al. Accuracy and reproducibility of semi-automated late gadolinium enhancement quantification techniques in patients with hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2014;16:85.
81. Milano AD, Faggian G, Dodonov M et al. Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. The Journal of Thoracic and Cardiovascular Surgery 2012.
82. Flett AS, Hayward MP, Ashworth MT et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138-44.
83. Child N, Suna G, Dabir D et al. Comparison of MOLLI, shMOLLLI, and SASHA in discrimination between health and disease and relationship with histologically derived collagen volume fraction. Eur Heart J Cardiovasc Imaging 2018;19:768-776.
84. Adda J, Mielot C, Giorgi R et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 2012;5:27-35.
85. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1845-53.
86. Cavalcante JL, Rijal S, Abdelkarim I et al. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 2017;19:98.
87. Treibel TA, Fontana M, Gilbertson JA et al. Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. Circ Cardiovasc Imaging 2016;9.

88. Scully PR, Treibel TA, Fontana M et al. Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2018;71:463-464.
89. Castano A, Narotsky DL, Hamid N et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879-2887.
90. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005;112:I377-82.
91. Lancellotti P, Magne J, Donal E et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation 2012;126:851-9.
92. Dhoble A, Sarano ME, Kopecky SL, Thomas RJ, Hayes CL, Allison TG. Safety of symptom-limited cardiopulmonary exercise testing in patients with aortic stenosis. Am J Med 2012;125:704-8.
93. Domanski O, Richardson M, Coisne A et al. Cardiopulmonary exercise testing is a better outcome predictor than exercise echocardiography in asymptomatic aortic stenosis. Int J Cardiol 2017;227:908-914.
94. Wang R, Meinel FG, Schoepf UJ, Canstein C, Spearman JV, De Cecco CN. Performance of Automated Software in the Assessment of Segmental Left Ventricular Function in Cardiac CT: Comparison with Cardiac Magnetic Resonance. Eur Radiol 2015;25:3560-6.
95. Marwan M, Ammon F, Bittner D et al. CT-derived left ventricular global strain in aortic valve stenosis patients: A comparative analysis pre and post transcatheter aortic valve implantation. J Cardiovasc Comput Tomogr 2018;12:240-244.
96. Bandula S, White SK, Flett AS et al. Measurement of myocardial extracellular volume fraction by using equilibrium contrast-enhanced CT: validation against histologic findings. Radiology 2013;269:396-403.

FIGURE LEGENDS:

FIGURE 1: Pathophysiology Of Myocardial Fibrosis In Aortic Stenosis

Aortic valve stenosis results in chronic pressure overload. To maintain wall stress myocyte hypertrophy occurs. Eventually, subendocardial ischaemia causes myocyte cell death and myocardial fibrosis. These result in initially diastolic then systolic dysfunction. Histopathologically, myocardial fibrosis (seen in red on Picrosirus red staining) is accompanied with thickened endocardium (1a), is predominantly subendocardially (1b) and display a decreasing gradient towards the mid myocardium (2). Microscopically, interstitial, perivascular and microscars of replacement fibrosis are seen.

FIGURE 2: Assessment of Aortic Stenosis Severity and Function by Echocardiography

Assessment of aortic stenosis (AS) by transthoracic echocardiography (Case 1, A-D; Case 2 E-H) showing images of the parasternal long axis (A+E), aortic valve continuous Doppler trace (B+F), apical four chamber (C+G) and map of global longitudinal strain (D+H). Severity of the valvular stenosis is greater in case 2 (peak velocity 5.07 vs 4.17m/s), and although systolic function is preserved, strain imaging reveals significant reduction in global longitudinal strain (11.7% vs 15.1%).

FIGURE 3: Sex Dimorphism in Pattern of Remodeling in Aortic Stenosis

Cardiovascular magnetic resonance (CMR) found marked sex differences in left ventricular remodeling ($\chi^2 = 34$, $p<0.001$), which were not apparent by 2D-echocardiography ($\chi^2 = 2.7$, $p=0.4$). Patients were categorized into four pattern of LV geometric adaption: “normal geometry”, “concentric remodeling”, “concentric hypertrophy” and “eccentric hypertrophy”. For CMR, categories were defined by BSA-indexed LV mass, indexed LV end-diastolic volume and mass-volume ratio. For 2D-echocardiography, categories were defined by BSA-indexed LV mass, end-diastolic cavity dimension and relative wall thickness. *Adapted from Treibel et al JACC Imaging 2017.*

FIGURE 4: Late gadolinium enhancement and Outcome in Aortic Stenosis

A-D. Late gadolinium enhancement (LGE) images in a mid-ventricular short axis showing an example without LGE (A), patchy non-ischemia LGE in the mid inferolateral segment as well as more subtle LGE in the inferoseptum and right ventricular insertion points (B), near circumferential endocardial and papillary muscle LGE (C), and transmural LGE of a full-thickness myocardial infarct (D).
E. Kaplan Meier survival plot showing all-cause mortality in all patient with severe aortic stenosis (n=674) by pattern of late gadolinium enhancement (no LGE, infarct LGE, non-infarct LGE; both *p<0.001*). The plot is summarizing 6-year follow-up data. Adapted from *Musa TA et al Circulation 2018*.

FIGURE 5: Amyloid-Aortic Stenosis Dual Pathology

Multi-modality imaging of patient with amyloid-AS. Although the echocardiogram showed left ventricular hypertrophy (A), this was attributed to the myocardial response to severe valve gradients (B) due to a heavily calcified tricuspid aortic valve (C). Strain imaging showed a characteristic apical staring (D). DPD scintigraphy showed Perugini Grade 2 cardiac uptake (E). Cardiac magnetic resonance showed transmural late gadolinium enhancement with higher signal from the myocardium then the blood pool (F), and elevated native myocardial ECV (G). Diagnosis was confirmed as transthyretin amyloidosis on cardiac biopsy (H).

Central Illustration: Imaging Parameters and Remodeling in Aortic Stenosis

Myocardial remodeling in aortic stenosis (AS) is complex. Worsening valve stenosis is accompanied by compensatory increase in left ventricular mass (LVM). This results in a slight increase in left ventricular ejection fraction (LVEF) due to the remodeling response and progressive worsening of diastolic function and global longitudinal strain (GLS). The LVM is comprised of cell and matrix compartments, which increase proportionally with LV hypertrophy. Eventually focal, irreversible scars develop which accumulate subendocardially and eventually lead to overt systolic impairment and development of symptoms. Both are class one indications for aortic valve replacement (AVR). The impetus for finding biomarkers to time earlier AVR is that the presence of irreversible scar results in residual risk of heart failure, arrhythmia and death even after successful AVR.