Myocardial Evaluation in Patients with Aortic Stenosis by Cardiac Computed Tomography

Beurteilung des Myokards bei Patienten mit Aortenstenose durch kardiale Computertomografie

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ABSTRACT

Background Aortic valve stenosis (AVS) is one of the most prevalent pathologies affecting the heart that can curtail expected survival and quality of life if not managed appropriately.
Current Status Cardiac computed tomography (CT) has long played a central role in this subset, mostly for severity assessment and for procedural planning. Although not as widely accepted as other imaging modalities for functional myocardial assessment [i. e., transthoracic echocardiogram (TTE), cardiac magnetic resonance (CMR)], this technique has recently increased its clinical application in this regard.
Future Outlook The ability to provide morphological, functional, tissue, and preprocedural information highlights the potential of the "all-in-one" concept of cardiac CT as a potential reality for the near future for AVS assessment. In this review article, we sought to analyze the current applications of cardiac CT that allow a full comprehensive evaluation of aortic valve disease.

Key Points:

- Noninvasive myocardial tissue characterization stopped being an exclusive feature of cardiac magnetic resonance.
- Emerging acquisition methods make cardiac CT an accurate and widely accessible imaging modality.
- Cardiac CT has the potential to become a "one-stop" exam for comprehensive aortic stenosis assessment.

Citation Format

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ZUSAMMENFASSUNG

Hintergrund Die Aortenklappenstenose (AVS) ist eine der häufigsten Erkrankungen des Herzens, die bei unzureichender Behandlung die Lebenserwartung und Lebensqualität beeinträchtigen kann.
Aktueller Stand Die kardiale Computertomografie (CT) spielt auf diesem Gebiet seit langem eine zentrale Rolle, vor allem zur Einschätzung des Schweregrads und zur Planung von Eingriffen. Obwohl diese Technik zur Beurteilung der Myokardfunktion nicht so weit verbreitet ist wie andere bildgebende Verfahren [z. B. transthorakales Echokardiogramm (TTE), kardiale Magnetresonanztomografie (CMR)], wird sie in letzter Zeit verstärkt in der klinischen Praxis eingesetzt.
Zukunftsperspektiven Die Fähigkeit, präoperationell Informationen über Morphologie, Funktion und das Gewebe zu liefern, unterstreicht das Fähigkeit der kardialen CT als „All-in-One"-Konzept, das zur Beurteilung der AVS möglicherweise in naher Zukunft realisiert wird. In diesem Übersichtsartikel haben wir versucht, die aktuellen Anwendungen der kardialen CT zu analysieren, die eine vollständige und umfassende Beurteilung der Erkrankungen der Aortenklappen ermöglichen.

Kernaussagen:

- Die nicht-invasive Charakterisierung des Myokardgewebes ist nicht mehr ausschließlich der kardialen Magnetresonanz vorbehalten.

- Neue Aquisitionsmethoden machen die kardiale CT zu einer genauen und allgemein zugänglichen Bildgebungsmodalität.
- Die kardiale CT hat das Potenzial, sich zu einer „One-Stop"-Untersuchung für eine umfassende Beurteilung der Aortenstenose zu entwickeln.

Introduction

Aortic valve stenosis (AVS) is the single most common adult heart valvular disease affecting over 5 % of those older than 65 years old. The relative frequency of AVS etiologies vary geographically, with rheumatic disease being the predominant cause in low-income countries, whereas degenerative fibrocalcific disease is dominant in North America and Europe [1–5]. In parallel to this development, there have been major advances in cardiac surgery and percutaneous valvular intervention thus allowing the possibility of successful intervention even in elderly, multimorbid patients [6–8]. However, despite successful intervention, many patients have worse outcomes compared to age- and sex-matched peers. Chronic biomechanical stress results in myocardial hypertrophy and progressive fibrosis due to the triggering of pro-inflammatory and fibrotic pathways leading to worsening diastolic and eventually systolic function [9–12].

Currently, myocardial remodeling due to AVS is a secondary indication when considering patients for intervention. Hemodynamic severity of the valve lesion and the presence of symptoms are the primary indications [13]. Whereas transthoracic echocardiogram (TTE) is the best imaging modality for the hemodynamic assessment of valve disease, cardiac magnetic resonance (CMR) additionally offers tissue characterization of the myocardium including the detection of focal and diffuse fibrosis [14]. However, several factors limit its widespread application in clinical practice, including access, cost, claustrophobia, and local expertise. In contrast, cardiac computed tomography (CCT) has become an essential modality mostly for the planning of structural valve intervention with recent advances that also include techniques allowing the evaluation of myocardial function and tissue characterization.

The aim of this review article is to provide a comprehensive review over the current role of CCT in myocardium evaluation in patients with AVS.

Aortic valve stenosis

AVS is defined as aortic valve thickening, usually with at least mild calcification and presence of antegrade velocity across an abnormal valve at least 2 m/s. Signs and symptoms are determined by valve anatomy, hemodynamics, and maladaptive cardiac remodeling.

The role of echocardiography

Echocardiography has a pivotal role in imaging assessment of patients with suspected AVS and is currently used for confirming the diagnosis, grading severity, assessing valve calcification, left ventricular (LV) function, and remodeling, detecting other valve disease or aortic pathology, and providing prognostic information [15, 16]. Moreover, it also provides key information analyzing the feasibility of potential invasive interventions and the likelihood of having a successful approach.

Current guidelines rely on three key parameters for severity assessment of AVS: mean pressure gradient, peak transvalvular velocity, and valve area. However, due to the frequent display of discordant results, additional parameters need to be taken into account (most of them echocardiographic) such as: LV ejection fraction, stroke volume, Doppler velocity index, LV hypertrophy, flow conditions, the adequacy of blood pressure control, aortic valve (AV) calcium score, and planimetry [17].

LV systolic function is a major prognostic determinant, and it has been traditionally assessed by LV ejection fraction (LVEF) quantification. However, this method has significant limitations, in particular the tracking of early functional changes in the remodeled LV where hypertrophy initially increases the LVEF at the expense of stroke volume. An alternative, the assessment of global longitudinal strain (GLS), which is the ratio or percentage of change in length over the original length, offers a stronger correlation with adverse remodeling and adverse cardiovascular events, even in patients with preserved LVEF [18], but has not yet been integrated in the clinical management pathway. In addition, strain imaging can also unveil features of concomitant dual pathologies, such as amyloid protein deposition [12].

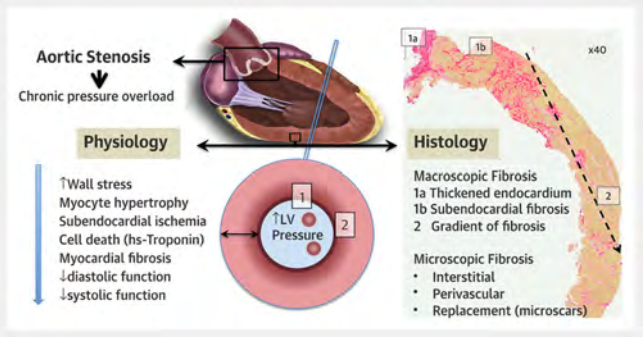
Transformational role of cardiac CT in aortic valve stenosis

CCT is a fundamental tool in VHD management. The strong correlation between calcium burden and aortic valve stenosis severity has resulted in aortic valve (AoV) calcium scores on non-contrast CCTs (with sex-specific cut-offs) being implemented in international guidelines. Particularly in patients with classic low-flow low-gradient AS with inconclusive low-dose dobutamine stress echocardiography and those with paradoxical low-flow low-gradient AS, AoV calcium scoring is recommended [13]. Combining this with angiographic evaluation allows not only precise geometric assessment of valve area using multiplanar reconstruction software [19, 20] but also newer approaches quantifying the fibrotic volume of the valve, which promises to be a more accurate measure of AS severity [21].

Furthermore, cardiac CT allows assessment of valve morphology, evaluation within the valve and root (i. e. coronary ostium height, annulus and leaflet dimensions, membranous septum length, calcium distribution within the valve), and appraisal of aortopathy and coronary artery disease, and provides unique information for procedural planning of a structural intervention (e. g., femoral or alternative access routes) as depicted in ▶ **Fig. 1** [13, 21]. Hybrid assessment with CT for the LVOT and echocardiography for flow may also optimize calculation of the AoV area by the continuity equation [22].

A disease of the valve and the myocardium

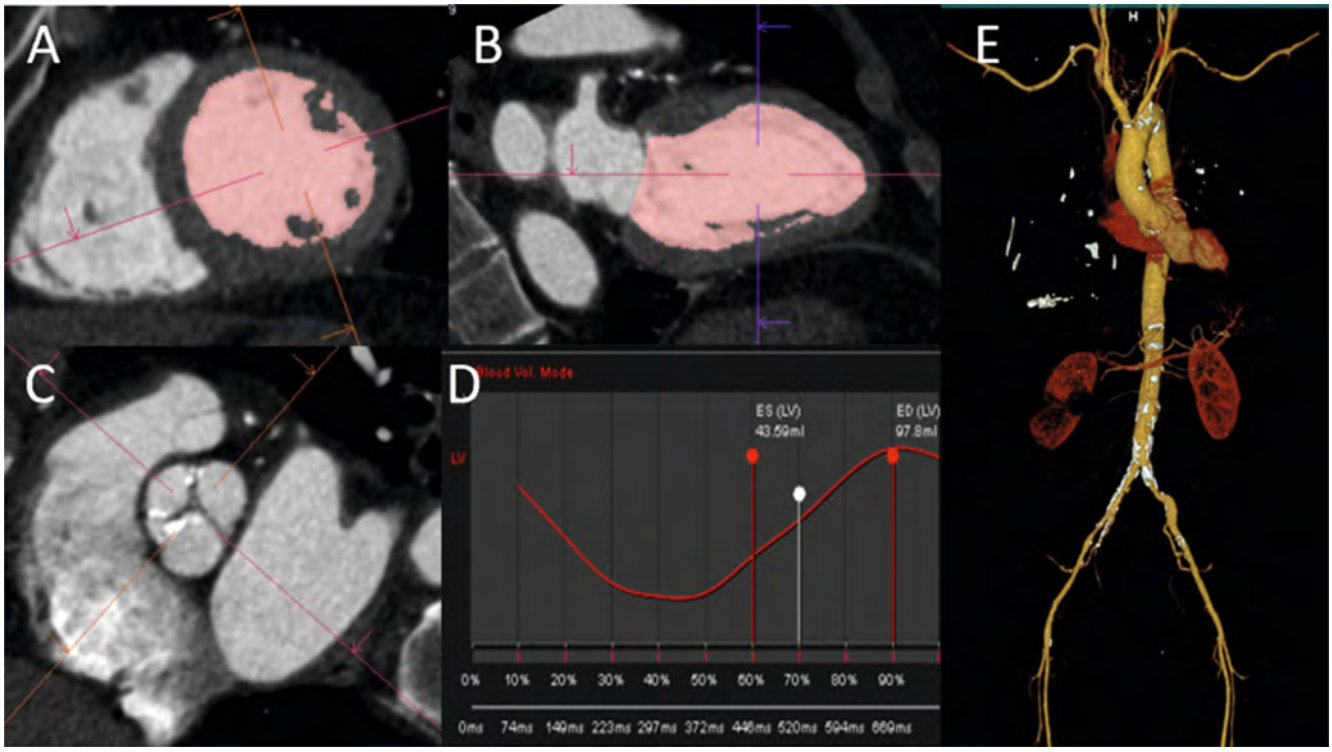
In AVS, patients' symptoms and outcome are determined not only by the severity of valve stenosis but also by the myocardial response to the excessive afterload [18–23]. A complex interplay of cellular (i. e., hypertrophy, cell death) and extra-cellular (i. e., microvascular ischemia, increased collagen synthesis and deposition) changes occurs simultaneously and culminates in myocardial fibrosis (MF) [24]. Histological assessment of this pro-fibrotic process has revealed a complex morphology and distribution with three main patterns: thickened endocardium with a massive fibrotic layer; a gradient from the subendocardium to the mid-myocardium with abundant microscopic scars; and diffuse interstitial fibrosis (see ▶ **Fig. 2**) [14]. The fibrotic gradient appears to be related to the capillary rarefaction towards the endocardial surface, responsible for microvascular ischemia, cell loss, and consequent replacement fibrosis [25, 26]. Furthermore, microscopic scars occur due to reactive responses of the mechanically stressed cardiomyocytes to chronic pressure overload, triggering fibroblasts for collagen deposition [23–28].



▶ **Fig. 1** Comprehensive assessment of AS patient with computed CT. Caption: 83 y/o male with syncope and severe aortic stenosis by TTE (Vmáx: 4 m/s, mean gradient 43 mmHg). Patients underwent cardiac CT for an "all-in-one" morphological and functional assessment of valve disease. A. B. endocardial borders and LV volume quantification. C. LV volumes throughout the cardiac cycle; D: En face of tricuspid aortic valve E. Peripheral vascular access evaluation for TAVI planning.

Assessment of adverse myocardial remodeling with CMR

Although CMR is not used routinely for clinical evaluation of aortic valve severity in AS, it can provide reliable measurements of valvular severity by assessing peak velocity, aortic valve area, and flow. Being the gold standard for functional and volumetric assessment, CMR also offers accurate assessment of the remodeled heart in addition to advanced tissue characterization. CMR can qualitatively and quantitatively assess the complex myocardial fibrotic process secondary to chronic pressure overload, namely focal replacement and diffuse reactive fibrosis. Diffuse reactive fibrosis, appears to be an early response to chronic pressure afterload and results from the extracellular matrix (ECM) expansion and regresses after aortic valve replacement (AVR) accompanied by structural, functional, and biomarker improvement. Focal fibrosis may be captured by late gadolinium enhancement (LGE), which highlights differences



▶ **Fig. 2** Physiological and histological changes expected in severe AS patients. The chronic increased afterload in aortic stenosis elicits complex cellular and extracellular changes that progress towards myocardial fibrosis and impaired function. The excessive collagen deposition typically follows a gradient from the subendocardium to the mid-myocardium.

between normal and abnormal myocardium, but only identifies the tip of the iceberg (as the remote myocardium is fibrotic as well). Focal replacement fibrosis represents the irreversible loss of cardiomyocytes (i. e., scar). Therefore, a more advanced state can be identified by LGE and it persists after AVR [28–34]. In order to capture diffuse fibrosis, absolute quantification of the myocardial signal is obtained by native T1 mapping (which captures the signal from both the cell and the ECM) and the T1-derived extracellular volume fraction (ECV%). Both have been validated against histology [28]. Both LGE and ECV are independent predictors of adverse outcome after surgical and transcatheter intervention [35].

Emerging applications of cardiac CT

In the last decade, the utility of cardiac CT has broadened exponentially with promising new techniques that can complement clinical information to guide the current clinical pathway of patients with AS. Beyond anatomical pre-procedural assessment and evaluation of the coronaries, cardiac CT also allows accurate functional, volumetric assessment of the ventricle and the potential for myocardial tissue characterization.

Functional assessment

The isotropic sub-millimetric spatial resolution and the good contrast between the ventricular lumen and the myocardium make CT well suited to obtain valuable information on ventricular function, regional wall motion, and LV mass comparable to CMR [36]. Although this requires data acquisition across the cardiac cycle, the resultant radiation penalty can be minimized by using dose modulation techniques. Meta-analysis of 27 studies comparing transthoracic echocardiogram and CMR (15 vs. 12 studies) with 64-slice (or higher) CCT showed no difference between modalities on ejection fraction quantification [37]. Recently, in a small-comparative study in patients following transcatheter aortic valve replacement (TAVR), Szilveszter et al. found a good correlation between GLS by echocardiography of the LV and the left atrium (LA) with GLS by 256-slice CT ($r = 0.78$, $p < 0.05$ and $r = 0.87$, $p < 0.001$, respectively) [38]. Considering the growing evidence base regarding TTE and GLS as an early surrogate of worse prognosis, CCT (if proven widely applicable, robust, and standardized) emerges as an attractive tool with the ability to complement anatomical and functional assessment. However, larger volume multicentric studies are currently needed to confirm its applicability with respect to prognosis.

Delayed enhancement by cardiac CT

Although noninvasive myocardial tissue characterization was once exclusively assessed by CMR, CCT has recently emerged as an attractive alternative, especially for myocardial fibrosis. Both gadolinium and iodine-based contrast agents are extracellular, extravascular contrast agents with a similar volume of distribution and contrast kinetics, thus allowing comparable myocardial characterization with CMR and CT not only on delayed enhancement (DE) imaging but also in first-pass perfusion [39–41]. Furthermore, the linear relationship between iodine and tissue signal is a more straightforward (linear) relationship than the effect of gadolinium on protons (including effects of fast intracellular water exchange) [42].

In ischemic cardiomyopathy, the volume of distribution of contrast agent is increased due to ruptured cell membranes of the necrotic myocytes in the acute stage, whereas in the chronic phase, iodine accumulation will also be increased in the infarcted segments due to the replacement of necrotic cells by collagen-rich scar tissue [40]. Compared to CMR, this modality offers excellent agreement for the identification of infarct region and size with reported sensitivities and specificities of 98 % and 94 %, respectively [43]. The hyper-enhanced areas on delayed image acquisitions are not exclusive to ischemic cardiomyopathy. Indeed, DE on CT has already been shown to be diagnostically useful for different pathologies such as sarcoidosis, hypertrophic cardiomyopathy, and amyloidosis [44–46]. However, this modality cannot be used to assess the early stages of maladaptive remodeling secondary to AVS characterized by diffuse fibrotic process, making visual assessment difficult to depict disperse increase of extracellular volume. Further acquisitions, namely assessment of extracellular volume fraction, emerged to rectify these inherent qualitative and quantitative limitations of DE sequences,

Extracellular volume fraction based on cardiac CT

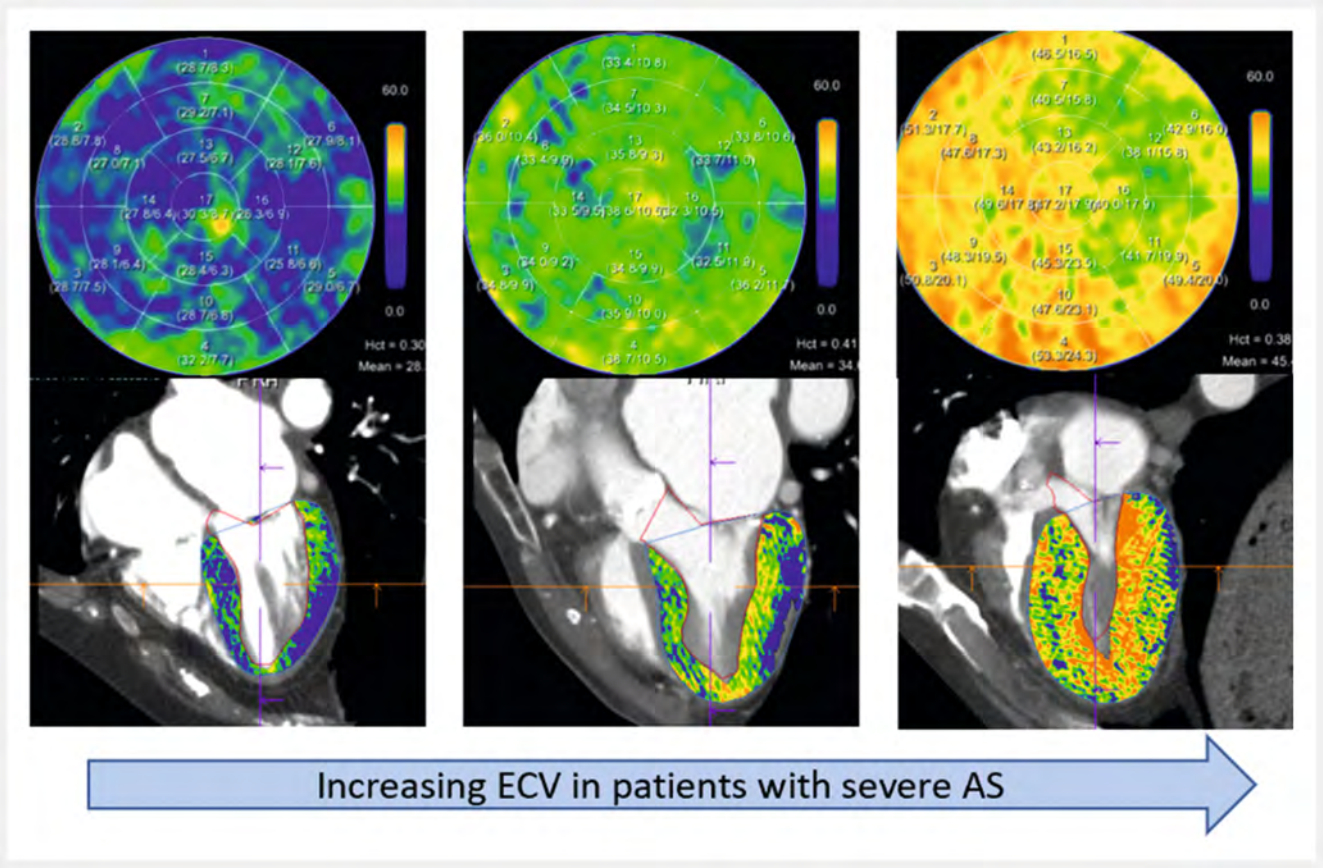
Extracellular volume quantification based on CT (CTECV) requires a baseline and a delayed post-contrast scan acquired at least 3 minutes after contrast injection [47, 48]. At the time of the delayed scan, a condition of pseudo-equilibrium is established between contrast in the blood pool and in the myocardium, which is a prerequisite for accurate ECV quantification. Currently, there are 2 established distinct methods to calculate ECV, determined by the scanner detector: single- or dual-energy. The single-energy (SE) approach determines contrast media distribution and hence ECV based on the change of CT attenuation between the pre-contrast and LE images. The formula used for ECV calculation is as follows:

$$ECV = (1 - Haematocrit) \times \frac{\Delta HU\ myo}{\Delta HU\ blood}$$

Dual-energy detector scans enable the reconstruction of iodine maps from LE scans for calculation of the ECV using the following formula, without the need of a baseline scan:

$$ECV = (1 - Haematocrit) \times \frac{Iodine\ myo}{Iodine\ blood}$$

Post-acquisition, ECV can be calculated based on a region of interest (ROI), or three-dimensional (3D) analysis can be performed for the whole heart by matching a heart model (blood pool) generated from the respective coronary CTA data. The LV heart model, automatically determined from the coronary CTA data, is overlaid onto the respective ECV volume data. Results can be displayed and numerically exported using standard 17-segment polar maps as depicted in ▶ **Fig. 3**.



▶ **Fig. 3** Increased extracellular volume in three patients with severe AS. Caption: A. Normal ECV; B. Mildly increased ECV due to diffuse fibrosis; C. Highly increased ECV due to dual pathology of AS and cardiac amyloidosis.

In clinical use, extracellular volume fraction based on CCT quantification based on cardiac CT has been significantly correlated with adverse outcomes in severe AS patients. Scully et al. prospectively enrolled 132 elderly patients exclusively with severe AS undergoing TAVR and demonstrated that ECV by CT was strongly associated with all-cause mortality over a median follow-up of 28 months [Hazard Ratio (HR):1.246, p = 0.004], with a doubling of the mortality risk for each 2 % increase in ECV [49]. These findings were further supported in a retrospectively enrolled cohort of 95 consecutive patients with severe AS undergoing TAVR, where ECV based on CT was the single independent predictor on multivariable Cox regression analysis (HR: 1.25; p < 0.001) for the composite endpoint of all-cause mortality and heart failure hospitalization [50]. Furthermore, Tamarappo et al. demonstrated the value of CT-derived ECV in 150 patients with low-flow low-gradient AS that underwent TAVR (HR:1.04, p = 0.01) with respect to predicting the composite endpoint of all-cause mortality and heart failure hospitalization over a median follow-up of 13.9 months [51].

Patients with severe AS often have coexistent cardiac amyloidosis (CA) with a reported prevalence of 1 in every 7 elderly patients undergoing TAVR. The hallmark deposition of misfolded proteins within the myocardium further increases the ECV which can also be readily identified by cardiac CT [52–54]. The presence of a dual pathology indicates a worse prognosis of heart failure. Therefore, early identification is important since there are novel therapeutic options that are capable of improving outcome, especially at early stages [55–57].

It is estimated that CMR is not suitable in 10 % of patients, mainly due to claustrophobia and artifacts. The wider accessibility of CT-derived ECV, in addition to faster acquisitions (currently completed in 3 minutes), high-resolution 3 D ECV volumes, and the fact that this imaging modality already takes part in the current management pathway in a considerable proportion of patients with severe aortic valve disease, makes this technique an attractive alternative to CMR for additional information on myocardial assessment in patients with valvular heart disease [58].

Challenges to implementation

Wider application of cardiac CT is still limited by the inherent radiation exposure that can reach up to 5 and 8 mSv for volumetric assessment (dual- and single-source scanner, respectively) and an additional 2.3 mSv for the ECV quantification [49, 59]. However, most severe aortic stenosis patients are older individuals whose long-term toxic exposure to radiation might be less of an issue. In addition, cardiac CT is already in the clinical pathway for most of these patients. While functional assessment would only be a sporadically useful tool for those with prior unclear LVEF evaluation, routine use of CTECV could potentially be of great value.

However, this remains speculative while cost-effectiveness studies are still lacking.

As described above, CTECV is conceptionally easy, straightforward to implement, does not require additional contrast administration at a cost of limited additional radiation. The current challenges to wider clinical implementation are analogous to ECV based on CMR field and are three-fold. First, the evidence base for CTECV needs to grow with further protocol and post-processing refinements and standardization, cross-vendor validation, wider application across health and disease, multi-center outcome cohort validation, and use in clinical trials. Second, CT hardware and software vendors are currently in various stages of development of CTECV products, and wider access to post-processing software is essential for broader use. Finally, the cardiac CT community needs to recognize the utility of myocardial tissue characterization based on CT as the field moves beyond coronary artery imaging. Clinical validation, the growing evidence base, and products from CT vendors will facilitate this.

Future outlook

The introduction of photon-counting detector CT (PCCT) allows direct conversion of X-ray photons to electrical signals, providing an increased contrast-to-noise ratio, improved spatial resolution, reduced electronic noise, and the ability to acquire spectral data during each scan [60–64]. These unique characteristics make it an attractive modality to further improve myocardial tissue characterization with CT by direct computation of delayed enhancement from the late enhancement (LE) scan [62]. Although the sample size was small and it was a single-center study, Mergen et al. introduced PCD-CT for valvular disease assessment, highlighting its ability to accurately assess ECV quantification and distribution in a cohort of severe AS patients [30].

Finally, these patients frequently have significant coronary artery disease that must be excluded by invasive coronary angiography prior to intervention. Coronary computed tomography angiography (CCTA) has already shown its excellent sensitivity for the exclusion of coronary artery disease (CAD). Promising results regarding the potential role of functional CAD assessment by CT (CT-FFR) in these patients have recently emerged [65]. Although prospective validation is still lacking, this might correspond to the last step for establishing CT as an ultimate “all-in-one” exam for these patients. Furthermore, CCT play an important role in those with incongruent echo measurements or a low-flow low-gradient phenotype that requires further evaluation. CCT can now reliably characterize myocardial tissue, depicting signs of maladaptive remodeling or patterns of increased ECV, providing prognostic stratification and potentially tailoring therapeutic management towards frequently encountered pathologies concomitantly present in AVS patients. In the future, this can potentially replace the need for CMR, thereby omitting one additional imaging exam for these often elderly and frail patients.

Conclusion

In patients with AVS, cardiac CT has long played a central role in procedural planning. The assessment of myocardial health can provide valuable prognostic stratification. Noninvasive tracking of extracellular components highlights the pathophysiological transition from adaptive to maladaptive remodeling with the potential to enhance the clinical management pathway that currently does not include the myocardial burden as a criterium for intervention, besides impaired ejection fraction that can be a sign that is too late. In the future, CT could become a tool for monitoring the response to extracellular modulating therapies (anti-fibrotic, anti-amyloid) in the search for new individualized heart failure therapies[3].

Conflict of Interest

The authors declare that they have no conflict of interest.

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