Introduction

Contrasting with rheumatic valvular heart disease (VHD), the incidence of degenerative VHD has significantly increased in industrialised countries. This is mainly driven by the increase in life expectancy reflected by the one in eight patients over the age of 75 with at least moderate disease.[1-5] In parallel to this development, there have been major advances in cardiac surgery and percutaneous valvular intervention opening the prospect of successful intervention even in elderly, multi-morbid patients.[6-8] However, despite successful intervention, many patients have worse outcomes compared to age- and sex-matched peers. Chronic biomechanical stress due to decades for worsening VHD (until the threshold of intervention is achieved) triggers pro-inflammatory and pro-fibrotic pathways resulting in myocardial hypertrophy and fibrosis with worsening diastolic and eventually impaired systolic function, and eventually worsening prognosis.[9-12]

Currently, myocardial remodelling due to VHD is a secondary indication when considering patients for intervention; severity of the valve lesion and the presence of symptoms are the primary indications.[13] Whereas transthoracic echocardiogram (TTE) offers the best imaging modality for the haemodynamic assessment of valve disease, cardiac magnetic resonance (CMR) offers additionally 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 planning structural valve intervention with recent advances also including techniques allowing evaluation of the myocardial function and tissue characterisation.

The aim of this review article is to provide a comprehensive review over the current role of cardiac CT on the myocardium evaluation in patients with VHD, specifically focussing

on aortic stenosis (AS) where transcatheter aortic valve intervention (TAVI) routinely uses CCT) and has driven the advances in the field of AS.

Aortic stenosis

The role echocardiography

Echocardiography has a pivotal role in imaging assessment of patients with suspected VHD, and is currently used for confirming the diagnosis, grading severity, assessing valve calcification, left ventricular (LV) function and remodelling, detecting other valve disease or aortic pathology and providing prognostic information.[15,16] Moreover, it also provides key information analysing 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 aortic stenosis: 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 planimmetry.[17]

LV systolic function is a major prognostic determinant, and it has been assessed by LV ejection fraction (LVEF), but LVEF has significant limitations: in particular tracking early functional changes in the remodelled LV where hypertrophy initial increases EF at the expense of stroke volume. An alternative, the assessment of global longitudinal strain, offers stronger correlation with adverse remodelling and adverse cardiovascular events, even in patients with preserved LV ejection fraction,[18] but has not yet been integrated in the clinical management pathway of patients with severe AS. Strain imaging emerges as a promising

tool to identify patients at increased risk of adverse prognosis, and can also highlight concomitant dual pathologies, such as amyloid deposition.[12]

Transformational role of cardiac CT in aortic stenosis

Cardiac CT is a fundamental tool in VHD management. The strong correlation between calcium burden and aortic valve stenosis severity has resulted in AoV calcium scores on non-contrast CTs (with sex-specific cut-offs) to be implemented in international guidelines. Particularly in patients with classical 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. 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), 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). [13,21] Hybrid assessment with CT for the LVOT and echocardiography for flow may also optimise calculation of the AoV area by the continuity equation.[22]

A disease of the valve and the myocardium

In AS, 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

ischaemia, increased collagen synthesis and deposition) changes occur simultaneously and culminate 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 figure 1).[14] The fibrotic gradient appears to be related to the capillary rarefaction towards the endocardial surface, responsible for microvascular ischaemia, cell loss and consequent replacement fibrosis.[25,26] Furthermore, microscopic scars result due to reactive responses of the mechanically stressed cardiomyocytes to chronic pressure overload, triggering fibroblasts for collagen deposition.[23-28]

Assessment of adverse myocardial remodelling with CMR

Although cardiac magnetic resonance (CMR) is not used routinely for clinical evaluation of aortic valve severity in AS, CMR can provide reliable measurements of valvular severity by assessing peak velocity, aortic valve area and flow, the latter particularly useful in those with discordant findings and mixed significant valve disease. Being the gold standard for functional and volumetric assessment, CMR also offers not only accurate assessment of the remodelled heart but also advanced tissue characterisation, which have been shown to be prognostic. CMR can qualitatively and quantitatively assess the complex myocardial fibrosis 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 between normal and abnormal

myocardium, but thereby 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) hence 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 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 trancatheter intervention. [35]

Emerging applications of cardiac CT

In the last decade, the utility of cardiac CT has exponentially broadened with promising new techniques that can complement the 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 structural, functional and volumetric assessment of the ventricle and the potential for myocardial tissue characterization.

Functional assessment

The isotropic sub-millimetric spatial resolution, and good contrast between ventricular lumen and 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 minimised by using dose modulation techniques. Meta-analysis of 27 studies comparing transthoracic echocardiogram and CMR (15 vs 12 studies) with 64-slice (or higher) cardiac CT showed no difference between modalities on ejection fraction quantification.[37] Recently, in a small-comparative study in patients following TAVI, Szilveszter et al. yielded a good

correlation between speckle-tracking echocardiography of the LV and the left atrium (LA) against global longitudinal strain (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 on transthoracic echocardiography and GLS as an early surrogate of worse prognosis even in asymptomatic patients and those with preserved overall systolic function, cardiac CT (if proven widely applicable, robust and standardised) emerges as an attractive all-in-one tool complementing anatomical and functional assessment, particular in elderly TAVI patients where echocardiographic windows are often challenging and radiation dose less of an issue than in younger patients. However, larger volume multicentric studies are currently lacking to confirm the utility on prognosis assessment using this technique.

Late enhancement by cardiac CT

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

In ischaemic 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 chronic phase, iodine accumulation will also be increased in the infarcted segments due to 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 ischaemic cardiomyopathy. Indeed, DE by CT has already yielded diagnostic utility of different pathologies such as sarcoidosis, hypertrophic cardiomyopathy and amyloidosis.[44-46] However, this modality lacks applicability in more diffuse disease processes, where DE imaging, which relies on the visual comparison of fibrotic versus normal remote myocardium, does not work. DE can therefore easily miss early stages of myocardial involvement and often overlooks the expansion of extracellular matrix, typical of diffuse fibrosis in pathologies like aortic stenosis.

Extracellular volume fraction by cardiac CT

Extracellular volume quantification by CT 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-equilibirum is established between contrast in the blood pool and in the myocardium, which is a requisite 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 derives contrast media distribution and hence ECV by the change of CT attenuation between the pre-contrast and LE images. The formula used for ECV calculation is as follows:

$$ECV(SE) = (1-hematocrit) \times \Delta HU_{myo} / \Delta HU_{blood}$$

Dual-energy (DE) detector scans enables the reconstruction of iodine maps from LE cans for calculation of the ECV by the following formula, without the need of a baseline scan:

$$ECV(DE) = (1-hematocrit) \times [Iodine_{myo}] / [Iodine_{blood}]$$

Post acquisition, ECV can be calculated on a region of interest (ROI) basis 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.

Clinical utility of extracellular volume fraction by cardiac CTECV quantification by cardiac CT has been significantly correlated with adverse outcomes in severe AS patients. Scully et al. prospectively enrolled 132 elderly patients with sole severe AS undergoing TAVI 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 in 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 TAVI, where ECV by 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 hospitalisation.[50] Furthermore, Tamarappo et al. demonstrated the value of ECV by CT in 150 patients with low-flow low-gradient AS that underwent TAVI (HR:1.04, p=0.01) also in predicting the composite endpoint off all-cause mortality and heart failure hospitalisation over a median follow-up of 13.9 months.[51]

Patients with severe AS often have coexistent cardiac amyloidosis (CA) with a reported prevalence in up to every 1 in 7 elderly patients that undergoes TAVI. 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 dual pathology confers worse prognosis heart failure and urges the clinicians for early identification considering the advent of novel therapeutic options 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 artefacts. The wider accessibility of ECV by CT technique, in addition to lower costs, faster acquisitions (currently completed in 3 minutes), high-resolution 3D 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 over CMR for additional information on myocardial assessment on patients with valvular heart disease.[58]

Challenges to implementation

As described above, ECV_{CT} is conceptionally easy, straight-forward to implement, and does not require additional contrast administration and limited additional radiation. The current challenges to wider clinical implementation are analogous to the ECV_{CMR} field and are three-fold. First, the evidence base for ECV_{CT} needs to grow with further protocol and post-processing refinements and standardisation, cross-vendor validation, wider application across health and disease, multi-centre outcome cohort validation and use in clinical trials. Second, CT hardware and software vendors are currently in various stages of development of ECV_{CT} products, and wider access to post processing software is essential for wonder take up. Finally, the cardiac CT community needs to recognise the utility of myocardial tissue characterisation by CT as the field moves beyond coronary artery imaging. Clinical validation, the growing evidence base and products by 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.[59-64] 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.[61] Bearing in mind the small sample size and its single centre nature, Mergen et al. introduced PCD-CT on valvular disease assessment, highlighting its ability to accurately assess ECV quantification and distribution in a cohort of severe AS patients.[30]

Conclusion

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

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