Diffusion tensor cardiovascular magnetic resonance

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ABSTRACT

Cardiac structure and function are complex and inter-related. Current in vivo techniques assess the heart on a macroscopic scale, but a novel technique called diffusion tensor cardiovascular magnetic resonance (DT-CMR) can now assess the cardiac microstructure non-invasively. It provides information on the helical arrangement of cardiomyocytes that drives torsion and offers dynamic assessment of the sheetlets (aggregated cardiomyocytes) that rotate through the cardiac cycle to facilitate wall thickening. Through diffusion biomarkers, the expansion and organisation of the underlying myocardium can be described. DT-CMR has already identified novel microstructural abnormalities in cardiomyopathy, and ischaemic and congenital heart disease. This new knowledge supports the potential of DT-CMR to improve diagnostics and prognostication in various cardiac diseases.

INTRODUCTION

Cardiovascular magnetic resonance is a versatile imaging tool that offers a variety of methods of cardiac phenotyping. It is the gold standard for ventricular volumetric assessment, can assess cardiac perfusion and has the unique ability to characterise the myocardium, for example, discriminating fibrosis.^{1–3} Recent developments have led to an exciting new technique called diffusion tensor cardiovascular magnetic resonance (DT-CMR), which is the only method currently available to non-invasively assess the microstructure of the myocardium. Information about myocardial organisation, myocyte packing as well as cardiomyocyte and sheetlet (aggregated cardiomyocytes) orientation can be obtained.^{4–6} Consequently, CMR is now able to provide information on the myocardium on a scale ranging from microns to centimetres and therefore offers a deeper understanding of how the heart works in both health and disease. This review introduces DT-CMR and how preclinical and initial patient studies may shape potential future clinical application.

DIFFUSION TECHNIQUE

DT-CMR exploits the interaction between water and the myocardium. The pattern of free diffusion of water, in which molecules may diffuse out in all directions, can be depicted as a sphere. However, in heart diffusion, it is restricted by myocardial components such as cardiomyocytes, capillaries and the collagenous matrix. To assess this diffusion, images are acquired with and without diffusion weighting, which is applied through use of diffusion gradients. Weighting is described by a factor, called the b value, which incorporates the gradient

duration, amplitude and temporal separation of the gradient pulses.^{7,8} When diffusion weighting is applied in the presence of diffusion, signal loss occurs due to a loss in the phase coherence of spins. The measured signal attenuation is fitted on a voxel basis to derive diffusion parameter maps. For each voxel of the image, DT-CMR assumes that the restrained diffusion can be pictorially demonstrated by an ellipsoid shape and mathematically described by a tensor.⁹ In order to gather enough information to fill the tensor and depict the ellipsoid diffusion, it is measured in at least six different directions. The tensor gives information about how freely water can diffuse in the myocardium via mean diffusivity (MD). Typical values are in the region of $0.8\text{--}1.5 \times 10^{-3} \text{ mm}^2/\text{s}$.^{4,10–16} The degree of diffusion restriction (how much the diffusion sphere is compressed into an ellipsoid) is described by fractional anisotropy (FA) and reflects the underlying organisation of the myocardium. FA uses a scale of 0 (highly disorganised) to 1 (extremely linearly organised). Reported values range from 0.36 to 0.61.^{10–16} The diffusion ellipsoid itself has an axis system and the orientations of the principal, secondary and tertiary axes of the ellipsoid are termed E1, E2 and E3. E1 is projected on the circumferential-longitudinal plane of the left ventricle (LV) and the angle between E1 and the circumference is called E1A. E2 is projected onto the cross-myocyte plane and the angle between this and the radial direction is E2A. The orientation of the third axis of the ellipsoid is E3 and its direction is perpendicular to E2.

RELATING DIFFUSION FINDINGS TO CARDIAC MICROSTRUCTURE

E1A is also known as helix angle (HA) and has been histologically proven to align with cardiomyocyte orientation in several preclinical studies.^{4,6,17,18} In this article, the term cardiomyocyte is preferred over myofibre or fibre to retain the distinction between cardiac and skeletal muscle. DT-CMR is capable of detecting the transmural variation in HA, as shown in [figure 1A](#). Both dissection and various histological techniques have revealed that cardiomyocytes take a left-handed helical course at the epicardium, progress through a circumferential alignment in the mesocardium and then a right-handed helix in the endocardium.^{19,20} A secondary level of cardiomyocyte organisation exists. Groups of 4–12 cardiomyocytes aggregate together and are termed sheetlets. Sheetlets are surrounded by the perimysial collagen and separated by cleavage planes ([figure 1C and G](#)).^{21,22} Preclinical histology work has shown that E2A aligns with sheetlet orientation.^{6,23,24} Some groups use E3 as an index of sheetlet orientation.²⁵

To summarise, the key DT-CMR parameters are

- Mean diffusivity: myocardial packing.

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- ▶ Fractional anisotropy: myocardial organisation.
- ▶ Helix angle: cardiomyocyte orientation.
- ▶ E2A: sheetlet orientation.

RELATING THE MICROSTRUCTURE TO CARDIAC FUNCTION

While histology is the current gold standard for assessing the myocardial microstructure, it is limited by being a static technique that is unable to give dynamic information about myocardial mechanics. DT-CMR can overcome this hurdle and is able to assess changes in the microstructure at various timepoints through the cardiac cycle. An *in vivo*, *in situ*, *ex vivo* and histology porcine study demonstrated that while there are only limited changes in HA between diastole and systole, there are significant changes in E2A through the cardiac cycle (figure 1).⁶ Sheetlets are aligned more parallel to the LV epicardial wall in diastole (low E2A) but reorient to a more wall-perpendicular arrangement in systole (high E2A). The degree of rotation between systole and diastole is known as 'sheetlet mobility'. This is usually about 25°–45°. ^{6 15 26} The dynamic nature of sheetlets is important in explaining how cardiomyocyte thickening of only 8% translates into LV wall thickening of 40%. ^{6 20 27}

The helical arrangement is also important for cardiac function. ^{28 29} The left-handed epicardial cardiomyocytes drive clockwise rotation at the base and anticlockwise rotation at the apex. The larger radius of the epicardial wall dominates the forces generated by the opposite helical arrangement of the endocardium. These opposing rotations result in torsion; the wringing motion that in conjunction with wall thickening and LV shortening aids ejection of blood from the heart in systole. The subsequent recoil and unwinding are important for passive LV filling during diastole. Thus, there are important links between the cardiac microstructure and cardiac function, which DT-CMR is helping elucidate.

DT-CMR FINDINGS IN CARDIAC DISEASE

Cardiomyopathy

DT-CMR has demonstrated novel pathophysiological insight into microstructural dysfunction in patients with cardiomyopathy. In hypertrophic cardiomyopathy (HCM), diastolic E2A was significantly elevated compared with healthy controls (47° vs 24°, $p < 0.001$), indicating that sheetlets were stuck in a predominantly systolic orientation with failure of diastolic relaxation. ^{6 26} This is in keeping with the disease-causing sarcomeric mutations of HCM that result in increased myofilament sensitivity to calcium, elevated cardiomyocyte tension and impaired diastolic relaxation. Furthermore, DT-CMR may offer a non-invasive method to detect myocardial disorganisation known as disarray. ^{30 31} This abnormality is considered a marker of HCM and has been associated with sudden cardiac death (SCD), especially in the young. ³² Small studies have suggested that disarray may be detectable using the parameter FA which was reduced in the hypertrophied septum compared with the lateral wall in patients with HCM and also reduced compared with controls. ^{33 34} DT-CMR may potentially provide the first *in vivo* option to detect this histological marker that is typically identified at autopsy. Myocardial fibrosis in HCM predicts adverse outcomes including heart failure events, SCD and all-cause mortality. ^{35 36} MD has been shown to map the extent of both focal and interstitial fibrosis and correlates with CMR measures of fibrosis in HCM. ³⁷ Together, these studies show that DT-CMR has the potential to assess the microscopic changes that occur in HCM and may help identify those patients who succumb to the adverse outcomes in this condition.

DT-CMR has also been applied in dilated cardiomyopathy (DCM). ^{6 38} No significant difference was found in MD between patients with DCM and controls. However, FA was reduced in the DCM cohort, but only in diastole. ³⁸ In a different DCM study, the most striking abnormality detected was impaired sheetlet mobility. ⁶ However, very differently to the patients with HCM, E2A was reduced in systole (40° vs 60°, $p < 0.001$), indicating sheetlets were stuck in a more diastolic orientation and fail to reorient as expected. ⁶ In a subsequent study, recovered patients with DCM with entirely normalised LV size and function showed residual impairment of sheetlet mobility. ³⁹ This suggests that DT-CMR may offer a role in discriminating remission from recovery in DCM.

Myocardial infarction

Structural changes occur in the acute myocardial infarct (MI) zone, where myocardial necrosis, oedema and wall thinning predominate, but over a longer period of time remote changes also occur as the LV remodels through dilatation, hypertrophy and altered ventricular architecture. ^{40 41} Several studies demonstrate increased MD and reduced FA in the acute infarct zone compared with the remote zone, in keeping with expanded disorganised ischaemic myocardium. ^{42–45} A human study of acute infarction has shown a reduction in the right-handed cardiomyocytes that usually populate the endocardium and are the first to be affected by an ischaemic insult. ⁴⁵ A further longitudinal study comparing acute and chronic DT-CMR in the remote zone of patients with MI showed a correlation between the percentage increase in right-handed cardiomyocytes and the increase in wall thickening, suggesting an adaptive remodelling response. ⁴⁶

DT-CMR has also shown potential in delineating infarct scar by measuring a metric of 'myofibre curvature' called propagation angle (PA). ^{47 48} A threshold of PA greater than 4° was the most accurate marker of infarct size, having the strongest correlation with gadolinium determined infarct size, as well as being associated with abnormal electroanatomic mapping voltages (figure 2). These studies indicate that DT-CMR has potential roles in managing infarction-related complications, such as predicting adverse remodelling and guiding ablation of scar-related arrhythmias.

Congenital heart disease

The helical arrangement of cardiomyocytes is typically preserved throughout mammalian species. ¹⁹ However, DT-CMR has demonstrated that there is gross derangement of cardiomyocyte organisation in situs inversus totalis (SIT). ⁴⁹ Figure 3 shows that in SIT patients' hearts display the expected helical arrangement is inverted at the base, progresses through a mid-ventricular transition zone and becomes more like a situs solitus heart at the apex. These structural changes were associated with a significant reduction of absolute torsion in the SIT group. The transition zone wall thickening and LV shortening were also reduced compared with situs solitus hearts.

In a different report, DT-CMR has shown predominance of longitudinal and oblique fibres in the systemic right ventricle of a patient with transposition of the great arteries corrected by arterial switch. These changes were thought to be an adaptive response to the systemic pressure and load being applied to a right ventricle. ⁵⁰

These findings indicate that there is greater disruption to cardiac structure in congenital disease than previously appreciated and the role of the microstructure needs to be further

Figure 1 Heart has a primary helical organisation and secondary sheetlet structures. (A) Diffusion tensor cardiovascular magnetic resonance (DT-CMR) imaging of the transmural variation of helix angle (HA), where blue represents left-handed cardiomyocytes (negative helix angles), yellow are circumferential cardiomyocytes (near zero HA) and red are right-handed cardiomyocytes (positive HA). A zoomed view is shown in (B). (C, G) Histology of sheetlets in diastole and systole, respectively. The orientation of the sheetlets relative to the left ventricle (LV) epicardial wall is summarised by the sheetlet angle. This is low in diastole and high in systole (C–J). At both timepoints, the helix angle (shown by the sticks, going from blue to red) does not change substantially, but there is a significant increase in sheetlet angle. Reproduced from Nielles-Vallespin *et al.*⁶

Figure 2 Diffusion tensor cardiovascular magnetic resonance (DT-CMR) can delineate myocardial infarction through use of the propagation angle (PA). DT-CMR can delineate the extent of a myocardial infarction. Areas with a PA of greater than 4° correlate with infarct size, both by the CMR gold standard of late gadolinium imaging and also electroanatomical mapping. Reproduced from Mekkaoui *et al.*⁴⁸

investigated, particularly in the context of identifying which patients go on to develop heart failure.

TECHNICAL LIMITATIONS

DT-CMR is a novel tool that still has limitations.⁵¹ Both spatial and angular resolution could be improved. Currently, resolution is typically in the region of $2.8 \times 2.8 \times 8$ mm, affording 2–4 voxels across a typical LV wall.^{6 52} Within each voxel, there are many thousands of cardiomyocytes, so DT-CMR cardiomyocyte and sheetlet orientations represent average values for each voxel of the images. Submillimetre diffusion tensor imaging is possible, but this is reserved for ex vivo studies.^{25 53 54}

There are two main sequence types used to obtain DT-CMR images with the key difference relating to the time over which the diffusion is measured.^{14 16} A key effect of the different diffusion times is variability in FA and MD values; shorter diffusion

times result in higher MD and lower FA values.^{14 16 55} The spin echo technique measures diffusion over 30–40 ms and requires motion compensation technology, which may be less reliable in the erratic motion during diastole.^{16 52 56} The second technique is stimulated echo acquisition mode (STEAM), and this circumvents bulk motion artefact by measuring diffusion over a whole cardiac cycle so the heart returns to its original position at the end of the diffusion period.⁵⁷ The disadvantages of this approach include a strict requirement for a regular heart beat and the effects of myocardial deformation (strain) on the measured diffusion parameters.⁵⁸ Compression of the myocardium during the cardiac cycle can overestimate how much diffusion has taken place and vice versa. While it is accepted that strain is a confounder, its effects are limited and ex vivo DT-CMR parameters are closer to the raw STEAM values than when strain correction algorithms are applied.⁵⁹ Different scanners, scanning protocols and DT-CMR sequences exist, and there is a drive to establish standardisation between techniques and centres. Currently, scans still require approximately at least 6 breath-holds per slice. Data are typically processed post acquisition with no instant feedback on data quality, which may lead to extra images being acquired. Consequently, it may take in the region of 10–15 min for a single LV slice at both cardiac phases. As with any novel technique, there is much progress to be made to adapt DT-CMR from its current state into a mainstream clinical imaging sequence that is routinely acquired.

CONCLUSION

DT-CMR is a powerful new tool that provides microstructural information in vivo, without the need for invasive procedures or radiation exposure. Recent DT-CMR studies have improved our understanding of cardiac function in health and identified several novel abnormalities across various cardiac conditions. While not yet ready for widespread clinical use, evidence is building that

Main messages

- Diffusion tensor cardiovascular magnetic resonance is a novel non-invasive technique that assesses myocardial microstructure in vivo.
- The helical arrangement of cardiomyocytes is preserved through mammalian species but is grossly deranged in congenital heart disease.
- Sheetlet reorientation from wall-parallel to wall-perpendicular is integral to normal left ventricle wall thickening but is impaired in hypertrophic and dilated cardiomyopathy.
- Mean diffusivity and fractional anisotropy identify abnormally expanded and disorganised myocardium in hypertrophic cardiomyopathy and myocardial infarction.

Current research questions

- Is there a relationship between the different genotypes and microstructural phenotypes in cardiomyopathies?
- Can diffusion tensor cardiovascular magnetic resonance (DT-CMR) predict which dilated cardiomyopathy patients will recover?
- Could DT-CMR parameters identify which hypertrophic cardiomyopathy patients are at risk of sudden death?
- Can DT-CMR predict which myocardial infarction patients will adversely remodel?

Figure 3 Helical arrangement is grossly disturbed in situs inversus totalis. The typically preserved helical arrangement of cardiomyocytes is shown in the top row. Helix angles progress from negative at the epicardium through to positive at the endocardium. In situs inversus totalis (middle and bottom rows), this pattern is inverted at the base, but then trends towards a situs solitus arrangement at the apex. There is a mid-ventricular transition zone. adapted from Khalique *et al*, 2018.³⁹

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Self-assessment questions

1. Diffusion tensor cardiovascular magnetic resonance is a histologically validated technique.
2. Cardiomyocytes have a left-handed helical arrangement in the epicardium and right-handed helical arrangement in the endocardium.
3. Sheetlets are aggregated cardiomyocytes that reorient from wall-parallel in diastole to wall-perpendicular in systole.
4. Sheetlets exhibit failure of systolic relaxation in hypertrophic cardiomyopathy.
5. Mean diffusivity and fractional anisotropy both rise in the acute infarct zone.

DT-CMR shows promise in key areas such as identifying disarray pre-mortem in HCM to aid SCD risk stratification, differentiating causes of LV hypertrophy, predicting adverse outcomes such as negative remodelling and arrhythmias post MI, and discriminating patients with congenital heart disease that may go on to develop heart failure.

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Answers

1. True
2. True
3. True
4. False
5. False