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T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy

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Aim The aim of this study was to determine the value of extracellular volume fraction (ECV) for the non-invasive assessment of diffuse myocardial fibrosis (MF) in different stages of systolic left ventricular (LV) dysfunction in dilated cardiomyopathy (DCM) in comparison with endomyocardial biopsy.

Background Non-invasive ECV assessment using cardiovascular magnetic resonance (CMR) T1 mapping reflects diffuse MF in patients with severe DCM, but earlier stages of DCM with mild LV functional impairment have not been investigated yet.

Methods Forty-five subjects with mild functional impairment and LV dilation ['early DCM', ejection fraction (EF) 45–55%], 29 with LV dysfunction and volume dilatation ('DCM', EF <45%) and 56 healthy volunteers (controls) underwent standard CMR imaging, late gadolinium enhancement (LGE) and T1 mapping for the calculation of ECV. The collagen volume fraction (CVF) was quantified histologically from endomyocardial biopsies of 24 DCM patients out of the study cohort.

Results The ECV between 'early DCM' (25 ± 4%), 'DCM' (27 ± 4%), and controls (23 ± 3; $P < 0.05$ for all) differed significantly. There was a weak inverse correlation between ECV and EF ($r = -0.35$; $P < 0.01$). A strong correlation between ECV and CVF could be detected ($r = 0.85$; $P = 0.01$). The cut-off value for ECV to differentiate between healthy myocardium and DCM was 26% (specificity 91.1%, sensitivity 62.1%, area under the curve 0.8, $P < 0.0001$). ECV is already elevated at early stages of functional impairment, whereby an overlap between early DCM and controls is present. But 31% of the early DCM patients had an ECV fraction above the mean ± 2 SD ECV of controls.

Conclusions ECV measurement with CMR reflects myocardial collagen content in DCM. Therefore, CMR-based assessment of ECV may have the potential to serve as a non-invasive tool for the quantification of diffuse MF in order to monitor therapy response and aid risk stratification in different stages of DCM.

Keywords Cardiovascular magnetic resonance imaging • ECV • T1-mapping • DCM

Introduction

Myocardial fibrosis results in elevated right and left ventricular (RV and LV) myocardial stiffness and is closely related to clinically evident systolic and diastolic cardiac failure.[1,2] Recent reports identified myocardial fibrosis (MF) as a major independent predictor of adverse clinical outcomes in dilated cardiomyopathy (DCM) patients.[3,4] Diffuse interstitial fibrosis, i.e. represented by the

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accumulation of collagen within the extracellular myocardial space, can be frequently observed in histological specimen of DCM patients[5] and leads to irreversible replacement fibrosis.[6] Since MF is both a therapeutic target[7–10] and a prognostic index,[11] the measurement of diffuse MF may be crucial for the risk stratification of such patients. Currently, the determination of diffuse MF in DCM patients requires endomyocardial biopsy for evaluation by histopathology. However, endomyocardial biopsy is associated with some risk[12] and discomfort due to its invasive nature and the possibility of sampling errors. Therefore, a non-invasive method, which can reliably quantify MF, would be preferable.

Cardiovascular magnetic resonance (CMR) allows the assessment of myocardial function and anatomy with high spatial and temporal resolution and excellent intrinsic blood-to-tissue contrast. By using gadolinium contrast agents, late gadolinium enhancement (LGE) can be used as a surrogate of pronounced replacement fibrosis.[13] Recent studies[14–16] indicate that T1-mapping can be applied to quantify myocardial extracellular volume (ECV) with excellent inter- and intra-observer variabilities and could, therefore, be potentially employed for serial therapy follow-up monitoring in DCM patients.[17,18] New sequences allow the determination of tissue-specific T1 relaxation times of each myocardial voxel and the construction of high resolution T1 maps.[19]

While elevated levels of ECV can be detected in different forms of advanced cardiomyopathies, so far only sparse data exist on the degree of MF in patients with only mildly reduced LV ejection fraction (LVEF) and mild dilatation, who do not meet the criteria for DCM yet. Especially, in this clinically challenging borderline group with non-severely impaired LV function, an additional tissue biomarker could be of importance to help distinguish healthy subjects from already affected subclinical DCM patients.

In this study, we investigated whether T1 mapping could detect remodelling in DCM patients already at an early stage of the disease. To validate the non-invasive results, we further compared the calculated ECV with histological findings.

Methods

Study subjects

In total, 130 subjects were analysed: 56 healthy volunteers prospectively and 74 DCM patients retrospectively. The local ethics committee approved the study and all participants gave their consent to elicitation, analysis, and publication of the data sets.

Seventy-four consecutive patients with symptoms of heart failure underwent clinical examination, blood analysis, and echocardiography and received the suspected diagnosis DCM at the University Hospital Heidelberg between July 2011 and December 2012. For further evaluation CMR was performed in these patients.

Forty-five patients had at least a mildly increased end-diastolic diameter (LVEDD) or an elevated end-diastolic volume (LVEDV), but a preserved LVEF (EF 45–55%). Formally, these patients do not meet the current diagnostic criteria for DCM.[20] In the absence of other causes such as chronic lung diseases, anaemia, or ischaemic heart disease, we assumed that this 'borderline group' might have an early form of DCM, hereinafter referred to as 'early DCM'.

Twenty-nine patients had increased LVEDV and LVEDD compared with an age- and gender-matched reference group and a reduced LVEF (EF $\leq$45%; 'DCM').

Significant coronary artery disease was excluded by means of coronary angiography.

Fifty-six prospectively enrolled healthy volunteers (37 males) without systemic disease or history of cardiovascular events and with normal clinical examination served as a 'control', all underwent the following diagnostic procedures: 12 lead electrocardiogram (ECG), echocardiography oral glucose tolerance test and high-dose dobutamine stress CMR as well as subsequent contrast-enhanced CMR using a T1-weighted inversion recovery-prepared fast gradient echo sequence with an optimized inversion time 15 min after injection of a contrast agent revealed no pathological findings. Controls also showed no elevation of NT-pro-BNP as well as high-sensitive Troponin-T values.

Scan protocol

All exams were performed on a 1.5-Tesla scanner (Philips Achieva) with a 32-element cardiac receiver coil. Vector ECG-gated standard steady-state-free precession cine sequences were acquired in short axes covering the whole LV and in three long-axis views (two-, three-, four-chamber views). Late gadolinium enhancement images were acquired 15 min post-contrast injection employing a T1-weighted inversion recovery-prepared fast gradient echo sequence with an optimized inversion time. T1 maps were acquired pre- and 10 min post-gadolinium DTPA contrast (Magnevist 0.2 mmol/kg body weight) using a modified Look-Locker inversion recovery sequence[19] during breath-hold in end-expiration, producing 11 raw images with increasing inversion times (TI: 100–4400 ms) in a mid-ventricular short-axis view (TR/TE: 3.5/1.8 ms; flip angle: 35°). Blood samples for the determination of haematocrit (HCT) were taken within 24 h prior to the scan.

Data analysis

Cardiac volumes, EF, and myocardial mass in late diastole were measured from short-axis image stacks by manual delineation of endocardial and epicardial borders using a commercially available workstation (Philips Viewforum, Version 3.4, Best, The Netherlands).

Pre- and post-contrast T1 maps were generated using the open-source software tool 'MRmap',[21] with motion correction in the *x*-axis and *y*-axis conducted for each view manually and heart rate correction. All maps were analysed with OsiriX (v5.5.2 32 bit, PixmeoSarl). Myocardial T1-values were determined by drawing regions of interest in every single segment of the mid-ventricular slice according to the AHA 17-segment model. The global T1-value was calculated as a mean of all segments with respect to the segments area. T1 values for blood were gathered by manually drawing a region of interest in the LV cavity.

ECV values were created according to the following formula:

$$\mathrm{ECV} = (1 - \mathrm{HCT}) \frac{\left(\frac{1}{T1_{\mathrm{myo}_{\mathrm{post}}}} - \frac{1}{T1_{\mathrm{myo}_{\mathrm{pre}}}}\right)}{\left(\frac{1}{T1_{\mathrm{blood}_{\mathrm{post}}}} - \frac{1}{T1_{\mathrm{blood}_{\mathrm{pre}}}}\right)}.$$

Histological analysis

DCM patients underwent diagnostic coronary angiography for excluding a significant coronary artery disease maximum 30 days prior the magnetic resonance examination. Two to eight endomyocardial biopsy specimens were taken from the left ($n = 16$) or right ($n = 8$) ventricle from 24 patients ('early DCM': $n = 9$, 'DCM': $n = 15$) during X-ray catheterization with a 7F biopsy catheter (Maslanka GmbH, Tuttlingen, Germany) for clinical reasons. Samples were fixed in formalin, embedded in paraffin, stained with Acid Fuchsin Orange-G (AFOG) obtaining contrast between fibrotic tissue and myocardium, and digitized in $\times$20 magnification using

a ScanScope CS capture device (Aperio; Vista, CA, USA). The amount of collagenous tissue was calculated using an automated image analysis system (Image Pro Discovery Version 5.1.1.0.18, 2002–04 Media Cybernetics, Bethesda, MD, USA). Subendocardial areas were manually excluded as described in Flett *et al.*, 2010.[22] Collagen volume fraction (CVF) was assessed as a percentage of the entire endomyocardium. CVF values for all single specimens were averaged for each patient.

Statistical analysis

Analyses were performed using SPSS (Version 20.0, IBM Corp.). Statistical significance was defined for *P*-values <0.05. Groups were compared using unpaired Student's *t*-test or, if multiple groups were compared, one-way analysis of variance (ANOVA) with the Student–Newman–Keuls *post hoc* test. Pearson's correlation coefficient was used to correlate ECV with CVF. Receiver operating characteristic (ROC) analysis was done according to the method of DeLong *et al.*, whereas 'control' was considered negative, 'early DCM' or 'DCM' was considered positive.

Results

Complete CMR data sets could be obtained from all study patients. There was no statistically significant difference regarding age (*Table 1*) between the three groups (52 ± 9 vs. 55 ± 16 vs. 58 ± 12 years; P = ns). LVEF differed between controls, 'early DCM' and 'DCM' (62 ± 3 vs. 52 ± 5 vs. 31 ± 10%, respectively; $P < 0.01$).

NT-pro-BNP was higher in DCM patients, compared with controls and higher in 'DCM' compared with 'early DCM' (controls: 61 ± 37 ng/L vs. 'early DCM': 690 ± 1094 ng/L vs. 'DCM': 2516 ± 3193 ng/L; $P = 0.001$). There was no significant difference in blood HCT between the three groups (42 ± 3 vs. 41 ± 4 vs. 40 ± 5%; $P = 0.1$).

T1 relaxation times

While no significant difference between 'early DCM' and controls for native (1019 ± 47 vs. 1020 ± 40 ms; $P = 0.9$) or post-contrast myocardial T1 relaxation times (431 ± 40 vs. 442 ± 43 ms; $P = 0.2$) could be observed, T1 from 'DCM' and controls differed significantly in both native (1056 ± 62 vs. 1020 ± 40 ms; $P = 0.001$) and post-contrast situations (420 ± 45 vs. 442 ± 43 ms; $P = 0.035$).

ECV comparison

ECV values between the groups 'early DCM', 'DCM', and controls (25 ± 4 vs. 27 ± 4 vs. 23 ± 3%) were significantly different (all $P \leq 0.02$, *Figure 1*). There was a weak inverse correlation between ECV and LVEF ($r = -0.346$; $P < 0.01$), but not between ECV and myocardial mass ($r = -0.07$; $P = 0.9$) or between ECV and LVEDV ($r = -0.23$; $P = 0.8$).

A significant, albeit weak correlation between ECV and NT-pro-BNP could be observed ($r = 0.358$; $P = 0.01$). ECV levels in different NYHA classes did not differ significant (NYHA I: 27 ± 4%, NYHA II: 26 ± 3%, NYHA III: 26 ± 4%; $P = 0.5$).

Reproducibility analysis of T1 mapping

Inter-observer and intra-observer variability was analysed in a subset of subjects ($n = 10$). For T1 values inter-observer mean differences were 8.2 ms in native and 4.3 ms in post-contrast scans. Mean intra-observer differences were 5.9 ms for native and 2.3 ms for post-contrast T1 values. ECV values had inter-observer mean differences of 0.4% and intra-observer mean differences of 0.2%. The mean time needed for creation and analysis of the T1 and ECV maps was 8 ± 3 min.

Table 1 Patient characteristics and results

	Controls	Early DCM	DCM	*P* (ANOVA)
Male/female	37 (66%)/19 (34%)	27 (59%)/18 (41%)	20 (69%)/9 (31%)	
Age (years)	52 ± 9	55 ± 16	58 ± 12	n.s.
LVEF (%)	62 ± 3	52 ± 5	31 ± 10	0.0001
EDV (mL)	157 ± 35	192 ± 42	277 ± 91	0.0001
EDV/BSA (mL/m^2)	86 ± 15	100 ± 20	142 ± 41	0.0001
ESV (mL)	56 ± 18	91 ± 25	195 ± 88	0.0001
ESV/BSA (mL/ m^2)	31 ± 9	49 ± 12	103 ± 45	0.0001
Stroke volume (mL)	102 ± 21	100 ± 23	82 ± 25	0.0001
Mass (g)	77 ± 24	90 ± 33	125 ± 39	0.0001
Myocardial native T1 (ms)	1020 ± 40	1019 ± 47	1056 ± 62	0.01
Myocardial post-contrast T1 (ms)	442 ± 43	431 ± 40	420 ± 45	0.03
Native T1 blood (ms)	1558 ± 79	1600 ± 124	1596 ± 130	n.s.
Post-contrast T1 blood (ms)	262 ± 38	265 ± 40	265 ± 39	n.s.
ECV (%)	23 ± 3	25 ± 4	27 ± 4	0.0001
CVF (%)		10 ± 9	23 ± 15	
HCT (%)	42 ± 3	41 ± 4	40 ± 5	n.s.
NT pro-BNP (ng/L)	61 ± 38	690 ± 1094	2615 ± 3193	0.0001
Presence of LGE	0	15 (33%)	14 (48%)	

Continuous data were expressed as mean ± SD, categorical variables as absolute numbers and percentages.

Histological validation

All specimens could be analysed sufficiently. The fraction of fibrotic tissue was significantly higher in 'DCM' compared with 'early DCM' (23 ± 15 vs. 10 ± 9%; $P = 0.001$).

A strong correlation between ECV and corresponding CVF could be detected ($r = 0.85$; $P = 0.01$; *Figure 3*), even in subsection analysis of the two groups separately (*Figure 4*).

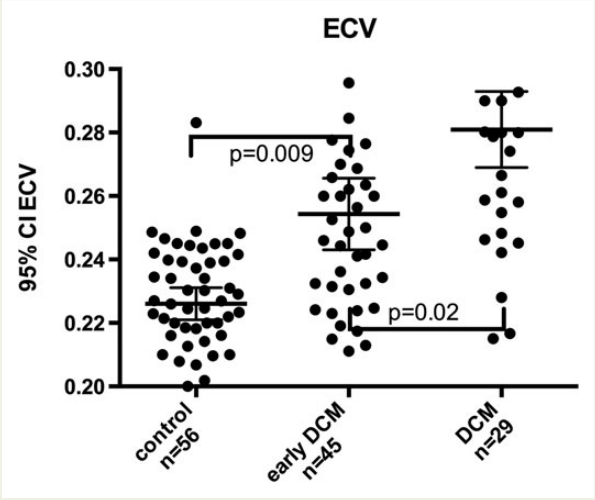

Figure 1: Different levels of calculated ECV fraction in DCM patients and controls—ECV fraction (in percentage) in controls ($n = 56$), patients with early DCM (LVEF >45%, $n = 45$), and patients with DCM (LVEF <45%, $n = 29$). ECV, extracellular volume; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction.

Multivariate regression analysis revealed ECV ($P = 0.0001$) as the only independent predictor for CVF among LVEF ($P = 0.52$), myocardial mass ($P = 0.60$), and LVEDV ($P = 0.90$).

Discrimination of DCM

ROC analysis of our data recommended an ECV fraction of 26% as the best cut-off for the distinction between controls and 'DCM' [specificity 91.1%, sensitivity 62.1%; $P < 0.0001$, area under the curve (AUC) = 0.80, *Figure 5*] and an ECV fraction of 24% as the best cut-off for the distinction between controls and 'early DCM' (specificity 77%, sensitivity 62%; $P < 0.0001$, AUC = 0.75). Already 31% of all 'early DCM' patients had an ECV fraction above the mean ± 2 SD ECV of controls.

Discussion

In our report, we investigated for the first time non-invasive ECV T1 mapping in patients with different severity stages of DCM in comparison with a thoroughly characterized age-matched reference population and further correlated the ECV values with histological findings as assessed by endomyocardial biopsy.

We could show that (i) diffuse MF was already present in early stages of DCM, respectively, patients with mild functional impairment and dilatation and (ii) that these early myocardial texture abnormalities could be detected non-invasively by T1 mapping using ECV measurements. Furthermore, ECV levels correlated significantly with the amount of fibrotic tissue as determined by endomyocardial biopsy, even when different groups of severity were compared separately. Representative examples of ECV maps and corresponding biopsies are shown in *Figure 2*.

The diagnosis of DCM is primarily based on the presence of reduced myocardial function (measured by LVEF <45–50% or fractional

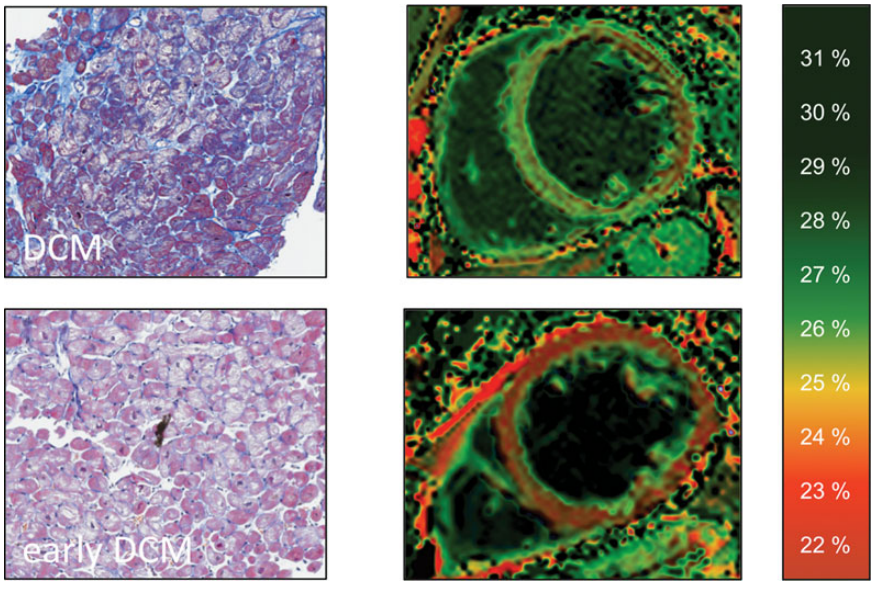

Figure 2: Representative examples of ECV maps and histologies—AFOG-stained histologies and corresponding ECV maps of patients with early DCM and DCM and the used ECV colour-scale. AFOG, alpha fuchsin orange-G; DCM, dilated cardiomyopathy; ECV, extracellular volume.

shortening of <25%) and volume dilation (as measured by LVEDV >117% of the predicted value corrected for age and body surface area) in the absence of ischaemic heart disease.[23,24] In clinical practice, the diagnosis of DCM at an early stage with only mildly reduced LVEF and slightly elevated LVEDV is challenging. Patients in this borderline group with preserved LVEF do not meet the criteria for DCM, but might benefit from anti-fibrotic medication, if MF is already present.

Therefore, T1 mapping with its possibility to quantify MF could not only provide additional information but also evolve as a supplementary imaging biomarker facilitating clinical work.

While elevated ECV levels have been demonstrated before in advanced stages of DCM,[25,26] aortic stenosis,[27] HCM,[22] and congenital heart disease,[15] only scarce data exist on the early stages, namely initial forms of DCM. As for late-stage DCM, our results are in agreement with previous findings, demonstrating elevated ECV levels. In addition, our study revealed that the expansion of myocardial extracellular space might already occur at earlier stages of the disease, potentially before LV function decreases significantly. T1 values as well as ECV values for normal and affected myocardium in our study differed from values reported in previous reports by other centres. A possible explanation might be a variation across different magnetic resonance imaging (MRI) scanners. T1 errors up to 14% between two scanners with the same field strength provided by different vendors were reported lately.[28]

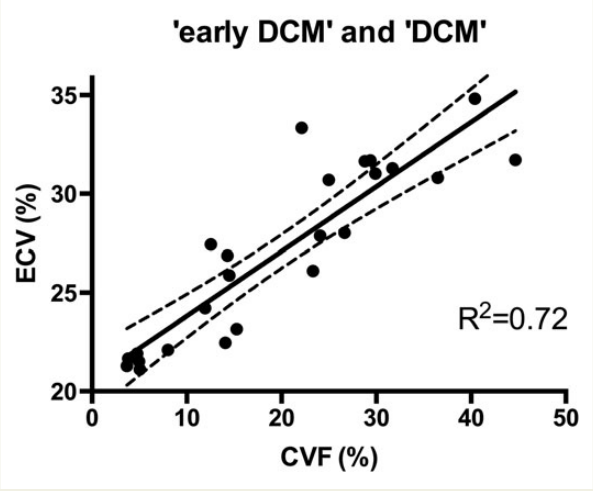

Figure 3: Correlation between CMR findings and histologies—Correlation between ECV as assessed from T1 maps and CVF as assessed from myocardial biopsies. CVF, collagen volume fraction; ECV, extracellular volume.

Dysfunctional myofibroblasts produce elevated levels of collagen, which eventually results in diffuse MF. The induction of cardiac fibroblast growth and differentiation might be triggered by raised plasma concentrations of angiotensin II and/or aldosterone.[6] Furthermore, increased LV pre-load is related to cardiomyocyte growth, which in turn can induce fibrocyte proliferation. Even though the exact pathophysiological mechanisms are still unclear, diffuse MF appears to be detectable non-invasively at early stages of myocardial dysfunction and could potentially serve as a novel biomarker in subclinical DCM and a novel marker for monitoring early therapy response.

ROC analysis of our study cohort (*Figure 5*) suggested that an ECV fraction of >26% could serve as an optimal cut-off value between controls and 'DCM' with an acceptable specificity of 91%. Owing to variations in ECV values among different MRI scanners as described above, this cut-off value might not be valid for other systems. The cut-off value to differentiate between controls and 'early DCM', determined by ROC analysis, was 24%. Unfortunately, due to the low sensitivity of 62% and the low specificity of 77%, this cut-off does not seem to be suitable for clinical practice to distinguish between healthy myocardium and 'early DCM'.

Thus, current T1 mapping techniques might appear to be insufficient to serve as a tool for early disease detection in individuals. Nevertheless, with respect to the correlation between ECV and CVF, T1 mapping might therefore be helpful in deciding, whether a patient might benefit from anti-fibrotic medication or not.

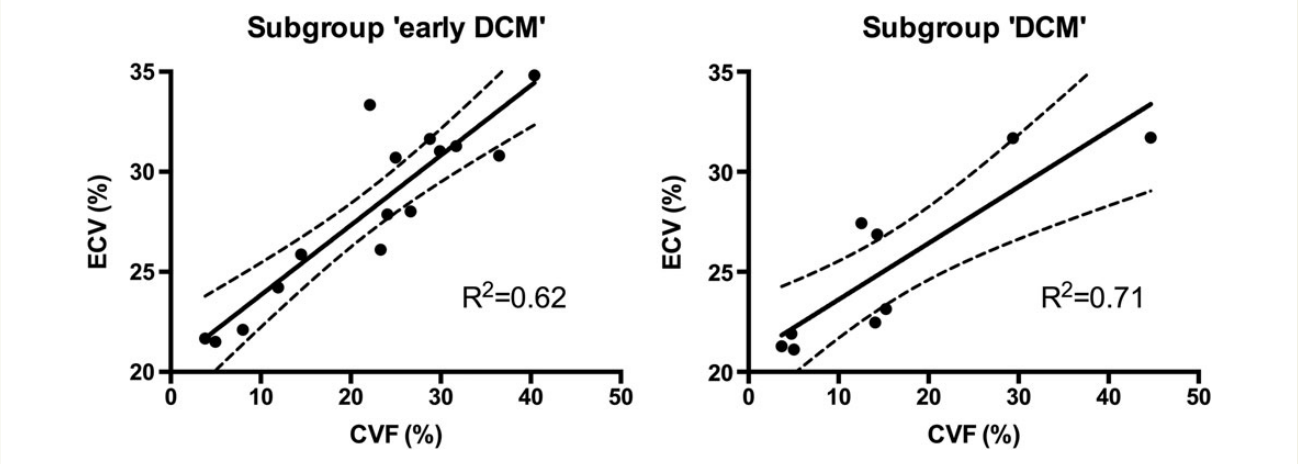

Figure 4: Correlation between CMR findings and histologies—Correlation between ECV and CVF in different groups of severity. CVF, collagen volume fraction; ECV, extracellular volume.

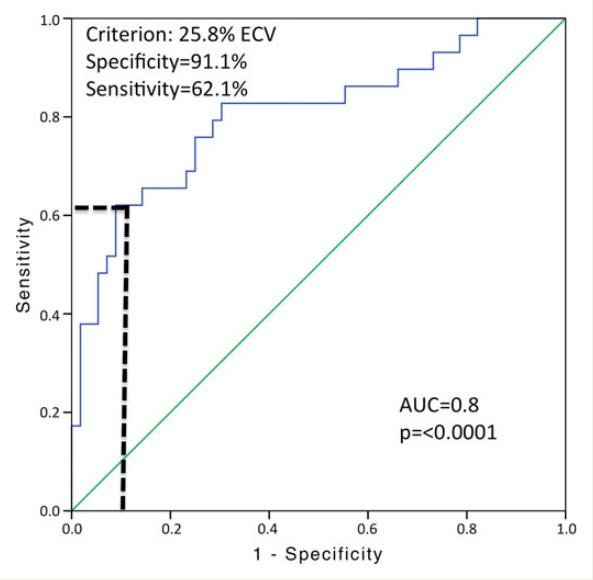

Figure 5: ROC analysis—ROC curve with 56 healthy subjects and 29 patients with DCM.

T1 mapping potentially provides three evaluable parameters: native T1, post-contrast T1 and HCT-corrected ECV.[29] Most of the clinical studies so far focused on post-contrast T1. Unfortunately, a large range of factors influence post-contrast T1 measurements, e.g. contrast agent dose and relaxivity, renal function and time delay between gadolinium administration and T1 measurements. Considering the relative changes of T1 in the blood and the myocardium before and after contrast administration, as done in ECV mapping, this technique minimizes most of the aforementioned influences. Recent studies found that native myocardial T1 could be used to discriminate between healthy and affected myocardium.[30] Our study confirms these findings for late-stage DCM, whereas early-stage DCM differed from controls in ECV but not in native T1.

Our results from histological examination confirm findings from both human[22,31–33] and animal[34] studies indicating that ECV reflects the degree of MF. Miller *et al.* showed a similar correlation between ECV and CVF in histological whole-heart studies of explanted DCM hearts after transplantation.[35] Since ECV measurements are non-invasive, one might speculate that this technique could potentially allow for non-hazardous follow-up of DCM patients. This would enable improved clinical monitoring of the effect of novel medical therapies on myocardial function and would advance clinical risk stratification.

Up to now, progression and treatment of DCM, including ICD implantation, was primarily linked to the patients' LVEF. Affecting the myocardial conductivity,[36,37] the proportion of MF could be entrenched as an additional criterion. The amount of focal fibrosis detected by LGE is of increasing importance for the prediction of arrhythmic events in DCM. The role of diffuse fibrosis has yet to be investigated.

Methodologically, ECV measurements give a good estimate on the main characteristic of fibrosis, but, due to image resolution, the technique is not able to distinguish between the different subtypes of fibrosis, i.e. epimysial, perimysial, or subendocardial. Thus, it should be kept in mind that ECV measurements from T1-mapping only provide an estimate of the global amount of MF present in the heart without considering fibrosis qualitatively.

Envisioning the future establishment of non-invasive imaging tissue characterization, further research is needed with respect to the influence of ECV on future clinical outcome and prognosis to prove the clinical value and significance of this promising technique.

Limitations

At present, due to the novelty of the technique, no general consensus exists on methodological issues such as the optimal sequence, the best scan protocol, contrast protocol, and the most appropriate post-processing method. This underlies again the need for a multicentre approach with unified techniques and post-processing analysis methods.

In the current study, different DCM aetiologies were allowed for further assessment of diffuse MF, which was the primary aim of the study, therefore, we did not differentiate between DCM subgroups.

Even though it is probably safe to assume that MF is a global process in DCM affecting the whole myocardium, biopsy specimens reflect only a few myocardial sections in locations that cannot be accurately assigned. For this reason, CVF values based on myocardial biopsy specimens are less robust than those obtained from whole-heart autopsy studies.[35] Additionally, endomyocardial biopsies represent only the subendocardial part of the myocardium, while T1 mapping represents the whole myocardial wall. Nevertheless, at least a relative, although not absolute connection between subendocardial fibrosis and the amount of fibrotic tissue in the whole myocardium might be plausible with respect to the global character of the disease. This might explain the absolute differences between single ECV and CVF measurements, whereas ECV values were ~20% higher than CVF values.

Furthermore, eight endomyocardial biopsies in this study were taken from the right ventricle and thus might be inaccurate. Finally, we only created maps out of one slice, the mid-ventricular short axis. Further studies should regard all segments of the AHA 17 segment model.

Conclusions

DCM patients revealed elevated levels of ECV reflecting diffuse MF. Even at an early stage of the disease when LVEF was only mildly reduced, ECV values were already elevated, at least in part. However, the overlap in ECV between controls and early DCM indicates, that at this stage, T1 mapping does not allow a reliable differentiation in individuals between healthy and affected myocardium yet. T1 mapping-based ECV could serve as a novel non-invasive CMR imaging biomarker and may be employed for clinical therapy monitoring as well as for risk stratification in DCM patients in the future.

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