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CMR–Derived Extracellular Volume Fraction as a Marker for Myocardial Fibrosis

The Importance of Coexisting Myocardial Inflammation

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ABSTRACT

OBJECTIVES The aim of the present study was to evaluate whether extracellular volume fraction (ECV) can reliably inform on the extent of diffuse fibrosis in the simultaneous presence of myocardial inflammation, which has not been verified to date.

BACKGROUND Diffuse myocardial fibrosis is associated with unfavorable outcome in patients with cardiomyopathy, and is of prognostic relevance. Assessment of ECV bears promise for being a noninvasive surrogate parameter, but it may be altered by other pathologies.

METHODS In this prospective study, 107 consecutive patients with clinical suspicion of inflammatory cardiomyopathy were included. All patients underwent left ventricular (LV) endomyocardial biopsy (EMB) and cardiac magnetic resonance imaging on a 1.5-T scanner. T1 mapping was obtained with the modified Look-Locker inversion recovery sequence, and ECV was calculated.

RESULTS Myocardial inflammation was present in 66 patients. Patients with and without inflammation were of similar age and had comparable LV ejection fraction (37 ± 17% vs. 36 ± 18%; $p = 0.9$) and symptom duration (median 14 days [interquartile range: 5 to 36 days] vs. median 14 days [interquartile range: 7 to 30 days]; $p = 0.73$). Although LV collagen volume percentage was comparable between groups (inflammation 12.3 ± 17.8% vs. noninflammation 11.4 ± 7.9%; $p = 0.577$), ECV was significantly higher in patients with inflammation (0.37 ± 0.06%) than in those without inflammation (0.33 ± 0.08%; $p = 0.02$). Importantly, ECV adequately estimated the degree of LV fibrosis percentage only in patients without inflammation ($r = 0.72$; $p < 0.0001$) and not in those with inflammation ($r = 0.24$; $p = 0.06$).

CONCLUSIONS These findings prove the theoretical concept of ECV as an estimate for diffuse myocardial fibrosis, but only in the absence of significant myocardial inflammation. Assuming that various degrees of myocardial inflammation and fibrosis coexist in such a scenario, the measured ECV will reflect a sum of these different pathologies but will not inform solely on the extent of diffuse fibrosis. (J Am Coll Cardiol Img 2018;11:38–45) © 2018 by the American College of Cardiology Foundation.

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Fibrosis is a pathological endpoint of essentially any cardiovascular disease (1,2). Myocardial fibrosis (local or diffuse) contributes to the progression of heart failure and is linked to poor outcome in patients with cardiovascular disease (3-6). Whereas local fibrosis favors the occurrence of malignant arrhythmia, diffuse fibrotic remodeling of the extracellular matrix predominantly results in myocardial stiffening and heart failure symptoms (7,8). Its quantification could improve risk stratification in patients with structural heart disease. As such, therapies and strategies to reduce myocardial fibrotic burden have been proposed for a number of cardiac pathologies (9).

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Until recently, endomyocardial biopsy (EMB) was the only available method for quantifying the extent of diffuse myocardial fibrosis. With the advent of new imaging modalities such as cardiac magnetic resonance (CMR), native and post-contrast T1 mapping, and estimation of the extracellular volume fraction (ECV), a noninvasive alternative appears to have emerged. ECV, as derived from changes in T1 relaxation rate before and after contrast application in tissue and blood, enables the relative quantification of the extracellular matrix (10-13). Several studies, most of which included patients with left ventricular (LV) hypertrophy and aortic stenosis, demonstrated a correlation between ECV and myocardial fibrosis as quantified in EMB (14-18). Consequently, ECV is believed to be increased as a result of reactive diffuse myocardial fibrosis in multiple cardiac pathologies. However, ECV can also be altered by pathologies other than fibrosis that are associated with an expansion of the extracellular space, including enhanced intracapillary plasma volume, interstitial infiltration, or extracellular edema, each of which is present in the context of myocardial inflammation (4,19). This study aimed to evaluate whether ECV can reliably inform on the extent of diffuse myocardial fibrosis in the presence of myocardial inflammation, because this has not been verified to date.

METHODS

PATIENT POPULATION. Patients with clinical suspicion of inflammatory cardiomyopathy were included from August 2012 until May 2015. Inclusion criteria were: 1) new onset or persisting symptoms suggestive of heart failure; and 2) suspicion of myocarditis according to previously published criteria (19-21). In all patients, coronary angiography was performed to exclude coronary artery disease. Furthermore, patients underwent LV EMB and CMR. Patients with contraindication to cardiac catheterization, EMB, or CMR were excluded.

Patients were divided into 2 groups according to immunohistological findings on EMB to separate patients with significant myocardial inflammation (≥14 leucocytes/mm^2, including ≥7 cells/mm^2 CD3-positive T lymphocytes, CD68-positive macrophages, and enhanced human leukocyte antigen class II expression in professional antigen-presenting immune cells) from patients with no relevant myocardial inflammation (<14 leucocytes/mm^2). This definition was in accordance with recent recommendations of the European Society of Cardiology (22). All subjects gave written informed consent before inclusion in the study, and the study was approved by the local ethics committee.

CORONARY ANGIOGRAPHY AND EMBs. Significant coronary artery disease (defined as stenosis >50% of vessel diameter) was excluded by coronary angiography. For EMB sampling, a myocardial biopsy forceps (Teleflex Medical Tuttlingen GmbH, Tuttlingen, Germany) was used. Five to 6 EMB samples were taken under fluoroscopic guidance from different locations within the LV.

EMB ANALYSIS. All histological and immunohistological analyses to diagnose myocardial inflammation were performed at the Department of Molecular Pathology, University Hospital Tuebingen (Tuebingen, Germany), as previously published (19). Paraffin-embedded EMB samples were stained with Masson's trichrome to reflect myocyte necrosis and interstitial fibrosis and analyzed by light microscopy (23). Fibrotic and artifact areas were digitally marked on stained EMB sections. The percentage area of fibrosis in each section was evaluated by dividing the sum of the fibrotic areas of the section by that of the total tissue area according to the following equation: collagen volume (%) / (100 − artificially blank areas [%]) × 100 = actual collagen volume (%) (24).

CMR IMAGE ACQUISITION. CMR was performed with a 1.5-T scanner and dedicated surface cardiac coils with 5 elements (Intera, Philips, Best, the Netherlands). Patients received a total of 0.15 mmol of gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) per kilogram of body weight intravenously. The sequence protocol was prefaced by survey images in coronal, sagittal, and transverse orientations. Retrospectively gated steady-state free precession cine images were acquired in vertical long-axis (VLA), horizontal long-axis (HLA), and short-axis (SA) orientations at 1.5-T (repetition time [TR] 3.4 ms,

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

ECV = extracellular volume fraction

EMB = endomyocardial biopsy

HLA = horizontal long axis

LV = left ventricular

SA = short axis

VLA = vertical long axis

echo time (TE): 1.7 ms, flip angle 60°, voxel size 1.25 × 1.25 × 8 mm^3). T1 mapping was obtained with a modified Look-Locker inversion recovery sequence with 3 single slices in VLA, HLA, and SA orientation native and 15 min after contrast. A modified Look-Locker inversion recovery sequence variant was used with 8 single-shot balanced steady-state free precession cine image readout trains (inversion, 3 readouts in consecutive RR intervals; reinversion, 5 consecutive readouts; "3[3]5" scheme), where the number in brackets denotes the number of empty RR intervals before reinversion (25). Typical sequence parameters were as follows for 1.5-T: TR 2.9 ms, 8 echoes (3-5 scheme), flip angle 50°, voxel size 1.19 × 1.19 × 10 mm^3, 13 startup cycles to approach steady state, and effective inversion times between 167 and 5,472 ms.

T2 mapping was performed before contrast injection in a single-slice, free-breathing, navigator-gated, multi-echo sequence in VLA, HLA, and SA orientations with the following parameters at 1.5-T: TR 1,052 ms, 9 echoes (echo time = 13.2, 17.6, 21.9, 26.3, 30.7, 35.1, 39.5, 43.9, and 48.3 ms), flip angle 90°, and voxel size 0.96 × 0.96 × 8 mm^3.

CMR IMAGE ANALYSES. Image analysis was performed on dedicated cardiac magnetic resonance imaging evaluation software (cmr42, version 5.1.0, Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada). Parametric maps depicting the relaxation times were calculated and generated for visualization purposes with dedicated software (MapMaker, version 1.1.2, Medis Medical Imaging Systems, Leiden, the Netherlands). Cardiac function was analyzed by the Simpson method, with endocardial contours drawn in the end-systolic and end-diastolic phase and determination of the end-diastolic and end-systolic volume for the calculation of ejection fraction.

For analyses of mapping sequences, a rigid motion correction was performed by drawing myocardial regions of interest on the different images with the different inversion times, covering the entire myocardium on that slice. Special caution was taken to exclude partial volume effects from the surrounding tissue (i.e., blood, liver, lung, and epicardial fat). Regions of late enhancement were included to the extent they were in the corresponding slice. A curve fit was performed by the software algorithm, and T1 and T2 times were assessed. Special caution was taken to ensure that only compact myocardial pixels were measured, sparing the epicardial and endocardial border zones to minimize partial volume artifacts, which can occur even after motion correction. The same caution was taken concerning the blood pool region of interest for the ECV calculation.

ECV was then calculated using the following formula:

$$ECV = (1 - Hct) \cdot \frac{\left(\frac{1}{T1\ myocardium\ post\ contrast} - \frac{1}{T1\ myocardium\ native}\right)}{\left(\frac{1}{T1\ blood\ post\ contrast} - \frac{1}{T1\ blood\ native}\right)}$$

Each motion-corrected series was analyzed for correct image alignment and then transformed in a parameter map. For the analyses of T1, ECV, and T2 values, the mean of the myocardial values determined in the VLA, HLA, and SA orientations was used.

STATISTICAL ANALYSIS. Kolmogorov-Smirnov testing was performed for assessment of data distribution. Continuous variables of the patient population are presented as mean ± SD if normally distributed or as median and interquartile range if non-normally distributed. Categorical variables are expressed as frequencies and percentages. Continuous variables were compared between groups by the Student *t* test or Mann-Whitney *U* test as appropriate; categorical variables were compared with the chi-square test. The association between LV myocardial fibrosis percentage and parameters of CMR imaging and myocardial inflammation was assessed by Spearman correlation analysis. Two-sided p values <0.05 were considered statistically significant for all statistical procedures used. Statistical analyses were performed by SPSS version 21 (SPSS, Inc., Chicago, Illinois) and GraphPad Prism version 5.0b (GraphPad Software, San Diego, California).

RESULTS

BASELINE CHARACTERISTICS. In this prospective study, 107 consecutive patients with clinical suspicion of inflammatory cardiomyopathy were included. Baseline characteristics are summarized in Table 1. Myocardial inflammation was present in 66 patients, and 41 patients exhibited no significant inflammation on EMB. Patients in both groups reported a median duration of symptoms of 14 days before hospital admission. Patients with and without inflammation were of similar age (45 ± 15 years vs. 45 ± 14 years; p = 1.0) with no differences in symptoms or pathological blood results. Cardiovascular risk factor profile was similar between the 2 groups apart from the frequency of diabetes mellitus (20% vs. 5% in non-inflammation vs. inflammation population, respectively; p = 0.02). Referring to EMB, the final diagnosis in patients with significant inflammation was chronic myocarditis in 63 patients and acute myocarditis in 63 patients. In those without significant inflammation, dilative cardiomyopathy was

diagnosed in 27 patients, hypertrophic cardiomyopathy in 2, healed myocarditis in 3, latent virus genome presence in absence of inflammation in 7, and amyloidosis in 1 patient.

RESULTS OF EMB AND CMR IMAGING. According to grouping of the cohort, patients without significant inflammation had lower numbers of CD3-positive T lymphocytes and CD68-positive macrophages on EMB samples than patients with significant inflammation (Table 2). LV collagen volume percentage was comparable between groups (inflammation 12.3 ± 17.8% vs. noninflammation 11.4 ± 7.9%; p = 0.58). On CMR imaging, there were no differences in LV ejection fraction between groups (median 42% [interquartile range: 24% to 51%] for inflammation vs. 36% [interquartile range: 18% to 33%] for noninflammation; p = 0.46). Patients without inflammation exhibited significantly lower values for native T1 mapping (1,075 ± 55 ms vs. 1,109 ± 63 ms; p = 0.009), ECV (33.2 ± 8.1% vs. 36.7 ± 5.8%; p = 0.02), and T2 mapping (58.9 ± 6.0 ms vs. 62.3 ± 4.6 ms; p = 0.002) (Table 2). Figure 1 illustrates increased values of ECV in the context of marked fibrosis as opposed to lower ECV in the context of very subtle diffuse fibrosis in patients without inflammation, as well as high ECV with mild fibrosis but significant inflammation.

CORRELATION ANALYSES. ECV correlated with the degree of LV myocardial fibrosis percentage only in patients without inflammation (r = 0.72; p < 0.0001), not in those with inflammation (r = 0.24; p = 0.06) (Figure 2). Among patients with inflammation, the sum of myocardial fibrosis percentage and number of CD68-positive infiltrating cells correlated weakly but significantly with ECV (r = 0.34; p = 0.003). Likewise, in the inflammation cohort, ECV correlated with results from T2 mapping (r = 0.41; p < 0.001). When the cohort of patients with inflammation was divided into tertiles according to CD68 cell count, a significant association between ECV and fibrosis was found in the lowest tertile only (r = 0.48, p = 0.04 in the lowest tertile; r = 0.38, p = 0.07 in the mid tertile; and r = −0.19, p = 0.41 in the highest tertile). When the patient cohort was grouped according to T2 mapping values with a cutoff of 59 ms, 43 patients demonstrated values ≤59 ms and 64 had values >59 ms. ECV correlated significantly with fibrosis in the T2 ≤ 59 ms group (r = 0.6; p < 0.001) but less so in the T2 > 59 ms group (r = 0.4; p < 0.001).

TABLE 1 Patient Characteristics

	All Patients (n = 107)	No Inflammation (n = 41)	Inflammation (n = 66)	p Value for Group 1 vs. 2
Age, yrs	45 ± 15	45 ± 14	45 ± 15	1.00
Female	30	32	29	0.80
Duration of symptoms, days	14 (6–30)	14 (7–30)	14 (5–37)	0.70
Symptoms				
Dyspnea	59	68	55	0.20
Fatigue	44	49	41	0.40
Peripheral edema	13	17	11	0.40
Angina	25	17	30	0.10
Chest pain	38	46	33	0.20
Pathological blood results				
Elevated troponin (>14 pg/l)	74	75	73	0.80
Elevated creatine kinase-MB (>0.41 µmol/ls)	24	15	30	0.06
Elevated C-reactive protein (>5 mg/l)	61	51	67	0.13
NT-proBNP (pg/ml)	767 (263–2,726)	760 (249–4,474)	767 (256–2,059)	0.72
Cardiovascular risk factors				
Hypertension	57	61	54	0.40
Smoker	36	32	38	0.50
Diabetes mellitus	10	20	5	0.02
Hyperlipoproteinemia	32	32	32	1.00

Values are mean ± SD, %, or median (interquartile range).
IQR = interquartile range; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

DISCUSSION

To the best of our knowledge, this is the first study to assess the impact of coexisting inflammation on ECV as an estimate of diffuse myocardial fibrosis using EMB as the reference standard. We showed that ECV represents an adequate estimate of diffuse myocardial fibrosis in patients with no myocardial inflammation, whereas this association was markedly confounded in the presence of relevant myocardial inflammation.

Accumulating evidence suggests that myocardial fibrosis is associated with nearly all forms of heart disease (1,2). Estimating myocardial fibrosis could

TABLE 2 Results of CMR Imaging and EMB

	All Patients	No Inflammation	Inflammation	p Value for Group 1 vs. 2
CMR results				
LV ejection fraction, %	38 (21–51)	36 (18–53)	42 (24–51)	0.47
Native T1, ms	1,098 ± 63	1,075 ± 55	1,109 ± 63	0.009
ECV, %	35.3 ± 7.0	33.2 ± 8.1	36.7 ± 5.8	0.02
T2, ms	61.0 ± 5.4	58.9 ± 6.0	62.3 ± 4.6	0.002
Results of EMB				
CD3+ cell count	9.2 ± 10.6	3.1 ± 2.5	13.0 ± 111.9	<0.001
CD68+ cell count	23.5 ± 16.8	11.8 ± 6.2	30.9 ± 17.2	<0.001
LV myocardial fibrosis percentage, %	12.1 ± 7.2	11.4 ± 6.9	12.3 ± 7.8	0.58

Values are median (interquartile range) or mean ± SD.
CMR = cardiac magnetic resonance; ECV = extracellular volume; EMB = endomyocardial biopsy; LV = left ventricle.

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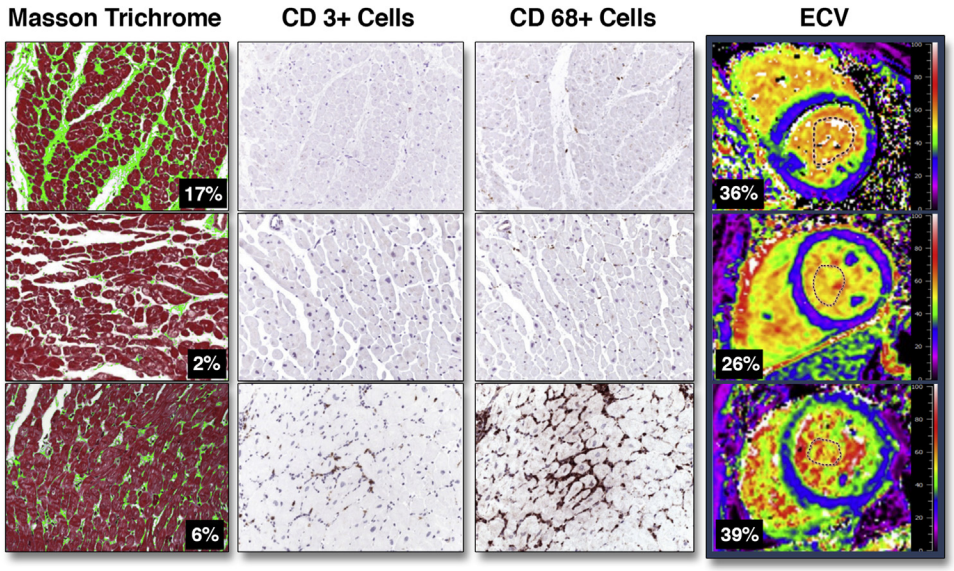
FIGURE 1 Relation of Different Degrees of Inflammation and Fibrosis to ECV



Exemplary results of myocardial fibrosis percentage **(first column)**, endomyocardial biopsy staining for CD3-positive cells **(second column)** and CD68-positive cells **(third column)**, and extracellular volume fraction (ECV) maps on cardiac magnetic resonance **(last column)**. **(Top)** Patient with high myocardial fibrosis percentage **(green marked area)**, no inflammation (CD3/68 stain), and high ECV. **(Middle)** Patient with almost no myocardial fibrosis, no relevant inflammation, and low ECV. **(Bottom)** Patient with low left ventricular myocardial fibrosis but significant inflammation and high ECV.

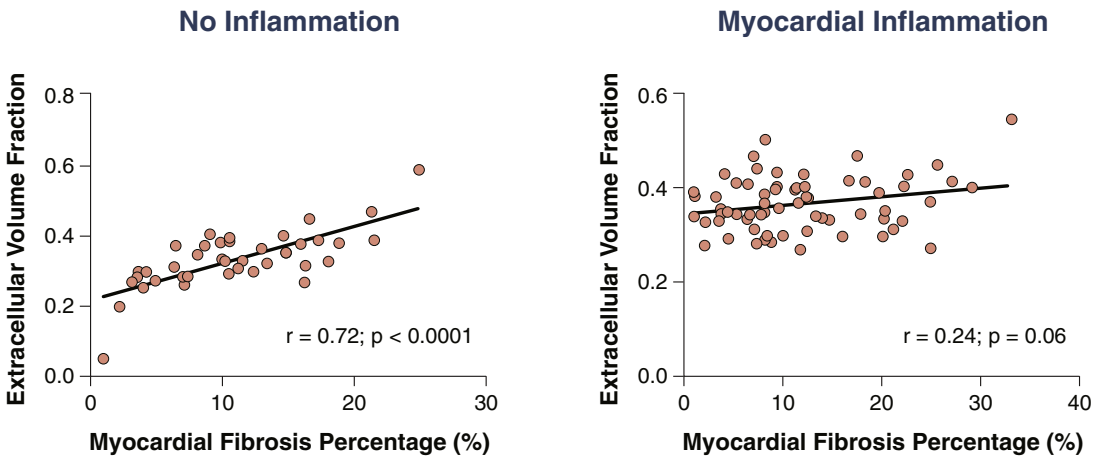
improve risk stratification in patients with structural heart disease and could serve as a surrogate outcome measure for antifibrotic therapies in the future. However, monitoring cardiac fibrosis remains a major challenge in the clinical setting. Thus far, the primary and reference standard for the quantification of diffuse myocardial fibrosis is EMB, which is a highly invasive procedure. Alternatively, several circulating biomarkers have been suggested as potential estimates of diffuse myocardial fibrosis, but adequate validation of these is still pending (3). With the advent of CMR-based techniques, notably T1 mapping and calculation of ECV, promising tools for the estimation of diffuse myocardial fibrosis have emerged (10-13,26-28).

ECV is defined as a coefficient of the changes in T1 in tissue and blood before and after contrast injection. As such, ECV should be most suited to provide information on extracellular/interstitial pathologies, because it should reduce some of the confounding factors of intracellular pathology compared with native T1 mapping (12,13). Also, as opposed to post-contrast T1 measurements, ECV is less susceptible to variations in clearance of contrast from blood and differences between contrast agent relaxivity and magnetic field strength (12,13). These theoretical considerations are supported by a comparative analysis of native T1, post-contract T1, and ECV as estimates for myocardial fibrosis, in which ECV emerged as the best estimate of collagen volume fraction on EMB (pooled r = 0.85) (12). However, most studies included patients with aortic stenosis (15,16,18), in which other confounding pathologies are less likely. This is of relevance because ECV does not measure collagen volume faction itself but is also affected by extracellular edema and hyperemia, both of which are seen in myocardial inflammation.

Therefore, the presence of inflammation might prohibit the use of ECV as a surrogate for collagen volume fraction. This is of particular importance in patients with dilative cardiomyopathy, in whom myocardial inflammation is a common finding on EMB (29).

When assessing ECV in cardiomyopathy with versus without inflammation, ECV appears to represent a mélange of 2 pathologies: fibrosis and inflammation. ECV is a measure of the entire extracellular space (intravascular and predominantly the interstitial space), and it embodies a reliable estimate for fibrosis only in the absence of inflammation.

FIGURE 2 Correlation of Extracellular Volume Fraction and Extent of Fibrosis in Patients With and Without Inflammation



Correlations between myocardial fibrosis percentage and extracellular volume fraction in patients without inflammation **(left)** and with inflammation **(right)**.

If additional inflammation exists in the myocardium, ECV will represent both. The association of T2 times and ECV in patients with EMB-proven inflammation supports this hypothesis, because inflammation goes along with myocardial edema and enhanced capillary plasma flow. This is also supported by the weak but significant association between ECV and the sum of collagen volume fraction and the number of CD68-positive infiltrating inflammatory cells in patients with inflammation. In our study, an association between fibrosis and ECV could be shown in patients exhibiting only a minor extent of inflammation. This implies that ECV can function as a reasonable estimate of diffuse myocardial fibrosis as long as the confounding effect of myocardial inflammation is minor.

The findings in the noninflammatory group are in keeping with previous reports on cardiomyopathy patients (14,30), but the association between ECV and fibrosis is weaker than what has been described for patients with aortic stenosis (15,16,18). A potential explanation is that even in absence of leucocyte infiltration and overt inflammation, edema might be present in noninflammatory cardiomyopathy as well. Microvascular dysfunction as a cause for repetitive ischemia has been described in a variety of studies in patients with noninflammatory cardiomyopathies. Therefore, even when EMB does not show inflammation, some degree of edema secondary to microvascular dysfunction could attenuate the use of ECV as a measure for fibrosis in cardiomyopathy patients (31).

Overall, ECV does not appear to be of much help in fibrosis quantification if inflammation is not excluded. Unfortunately, clinical manifestation and conventional assessment do not differ between dilative cardiomyopathy patients with versus without inflammation. T2 mapping techniques might help to select cardiomyopathy patients with inflammation, in whom ECV does not reliably inform on diffuse myocardial fibrosis. T2 is increased in the presence of edema and can thereby detect significant inflammation (19,25). Such an approach is supported by the observation that in patients with a T2 cutoff value of ≤59 ms, the association between ECV and fibrosis was found to be better than in the group with T2 >59 ms. However, the fact that infiltrating cell count on EMB was found to be the much better selection criterion illustrates the limitations of T2 mapping in such a setting. Ideally, a combination of T2 and ECV would allow estimation of the inflammatory and the fibrotic component of ECV; however, this would require sophisticated weighting of the 2 values, which is complicated by the fact that interaction of pathologies remains uncertain and a nonlinear relation has to be assumed.

Of note, coexisting inflammation and diffuse fibrosis must also be considered in systemic inflammatory diseases that affect the heart, such as systemic lupus, rheumatoid arthritis, or systemic sclerosis. Several studies have demonstrated increased T1 values and ECV in these patients compared with control subjects. According to the

discussion above, this does not enable differentiation of the chronic effects of cardiac remodeling (fibrotic component) from disease activity (edema component) in these scenarios (32-34). Given the close association between inflammatory processes and the development of diffuse fibrosis, T1 and ECV might be well suited as predictors of outcome (27,35) but might be less suitable to monitor the effects of treatments that target one or the other.

STUDY LIMITATIONS. The most important limitation of any study validating CMR results against results of myocardial biopsies is caused by some uncertainty as to what degree EMB specimens are reliable representatives of the total myocardium. EMB specimens will always represent exemplary parts of the myocardium only. Therefore, assessment of collagen volume fraction relies on the assumption that pathologies are diffuse and homogenous, not regional or patchy. Second, we did not perform T1 maps that covered the entire LV myocardium. Although variations between slices were subtle in our experience, the addition of more slices could have made the results more robust.

Lastly, the semiautomated digital marking of the fibrotic areas on EMB specimens requires some manual correction by the investigator, which could introduce some subjectivity. However, all EMB specimens and collagen volume fraction calculations were performed by 1 experienced investigator.

CONCLUSIONS

These findings confirm the theoretical concept of using ECV as an estimate for myocardial fibrosis, but ECV cannot function as its direct measure, for it is only accurate in the absence of other pathologies, specifically myocardial inflammation that involves an expansion of the extracellular space because of other mechanisms. This includes enhanced intracapillary plasma volume, interstitial infiltration, or myocardial edema, each of which is present in the context of myocardial inflammation. Assuming that various degrees of myocardial inflammation and fibrosis coexist in such a scenario, the measured ECV will reflect a sum of these different pathologies but will not inform solely on the extent of myocardial fibrosis. This should be taken into account when using ECV as a surrogate parameter of diffuse myocardial fibrosis for prediction of outcome, monitoring of disease progression, or even as a measure of therapeutic success, which is of particular importance in patients with cardiomyopathies, in whom myocardial inflammation is a frequent finding on EMB.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ECV is a promising method to calculate the extent of diffuse myocardial fibrosis and possibly to predict outcome; however, it is not specific for fibrosis, and confounding pathologies, notably inflammation, can influence ECV. This should be considered when ECV is applied in patients with potentially coexisting inflammation.

TRANSLATIONAL OUTLOOK: Further studies evaluating whether and how T2 mapping can be applied in this scenario to exclude the confounding factors would be desirable. The availability of a reliable tool for the estimation of diffuse myocardial fibrosis bares the hope of predicting outcome, monitoring treatment effects, and serving as a surrogate endpoint in clinical trials.

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