Bioimpedance Spectroscopy Reveals Important Association of Fluid Status and T_1-Mapping by Cardiovascular Magnetic Resonance

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Background: Extracellular matrix expansion is a key pathophysiologic feature in heart failure and can be quantified noninvasively by cardiac magnetic resonance T_1-mapping. Free water within the interstitial space of the myocardium, however, may also alter T_1-mapping results.
Purpose: To investigate the association between systemic fluid status and T_1-mapping by cardiac magnetic resonance.
Study Type: Prospective, observational single-center study.
Population: Two-hundred eighty-five consecutive patients (44.4% female, 70.0 ± 14.9 years old) scheduled for cardiac MR due to various cardiac diseases.
Sequence and Field Strength: 1.5-T scanner (Avanto Fit, Siemens Healthineers, Erlangen, Germany). For T_1-mapping, electrocardiographically triggered modified-Look-Locker inversion (MOLLI) recovery sequence using a 5(3)3 prototype on a short-axis mid-cavity slice and with a four-chamber view was performed.
Assessments: MR parameters including native myocardial T_1-times using MOLLI and extracellular volume (MR-ECV) were assessed, and additionally, we performed bioimpedance analysis (BIA). Furthermore, demographic data and comorbidities were assessed.
Statistics: Wilcoxon's rank-sum test, chi-square tests, and for correlation analysis, Pearson's correlation coefficients were used. Regression analyses were performed to investigate the association between patients' fluid status and T_1-mapping results. A *P*-value <0.05 was considered statistically significant.
Results: The mixed cohort presented with a mean overhydration (OH) of +0.2 ± 2.4 liters, as determined by BIA. By MR, native T_1-times were 1038 ± 51 msec and MR-ECV was 31 ± 9%.
In the multivariable regression analysis, only OH was significantly associated with MR-ECV (adj. beta: 0.711; 95% CI: 0.28 to 1.14) along with male sex (adj. beta: 2.529; 95% CI: 0.51 to 4.55). In linear as well as multivariable analysis, only OH was significantly associated with native T_1 times (adj. beta: 3.750; 95% CI: 1.27 to 6.23).
Conclusion: T_1-times and MR-ECV were significantly associated with the degree of OH on BIA measurement. These effects were independent from age, sex, body mass index, and hematocrit. Patients' volume status may thus be an important factor when T_1-time and MR-ECV values are interpreted.
Level of Evidence: 2
Technical Efficacy Stage: 3

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Cardiac magnetic resonance imaging is increasingly used to characterize myocardial tissue.[1] In the 1990s, the implementation of contrast agents for the first time facilitated non-invasive visualization of myocardial scars, for example, after myocardial infarctions.[2] Late gadolinium enhancement (LGE) imaging is now a standard application in cardiac MR exams but is limited in assessing diffuse alterations of the extracellular matrix.[3] T_1-mapping overcomes this limitation as it allows for quantification of T_1-times of every voxel within a certain region of interest (ROI).[3] While native T_1-times provide information of both intra- and extracellular signals, correction for the hematocrit allows for quantification of extracellular volume (ECV).[3] Numerous studies have shown that T_1-mapping accurately estimates the extracellular space when validated against myocardial biopsies.[4–8] T_1-mapping has been implemented in routine practice in experienced centers and is used in a variety of cardiac disorders. Both diagnostic and prognostic utility have been reported for native T_1-mapping and MR-ECV.[3] The main driver for an increase in both native T_1-time and MR-ECV is believed to be accumulation of collagen in ischemic heart disease, valvular heart disease, and dilated cardiomyopathy[5,6,9] or—in acute myocardial infarction—by increase in ECV resulted from extravasation of blood albumin and loss of cell membrane integrity.[10] In contrast, disease-specific proteins or lipids may also alter T_1 signals and affect native T_1-times and/or MR-ECV.[3,11] Amyloid fibrils deposited in the extracellular space cause a considerable prolongation of native T_1-times and an increase in MR-ECV estimates,[11–13] while in Anderson Fabry's disease, intracellular sphingolipids lower T_1-times at normal MR-ECV values.[11] Myocarditis is a particularly important application of T_1-mapping, as an inflammatory state including myocardial edema alters T_1 signals.[3]

However, although factors that impact T_1 times on MR have extensively been studied previously,[3] it is currently unknown to what extent the systemic volume status—that may well affect extracellular water (ECW) content of the myocardium[3]—can alter myocardial T_1 signals. Early data indicate a relationship of volume overload and T_1-times in patients undergoing hemodialysis.[14] However, the impact of overhydration (OH) has not been systematically investigated in unselected patients undergoing cardiac MR. This, however, is an important question as it may shift the attention regarding the prognostic power of myocardial T_1 times from myocardial fibrosis alone to also the important clinical status of OH.

This study aimed to prospectively evaluate the influence of systemic volume status, assessed by bioimpedance analysis (BIA), on native T_1-times and ECV using a modified-Look-Locker inversion (MOLLI) recovery sequence.

Materials and Methods

Study Setting

This was a prospective, observational single-center study carried out at the Medical University of Vienna, a tertiary referral center for cardiovascular imaging. All patients gave written informed consent. An institutional review board approved the study protocol (EK 1318/2018). The study has been registered at ClinicalTrials.gov (NCT03372512). Consecutive patients referred to the MR laboratory, excluding acute myocarditis patients due to expected myocardial edema, were enrolled in the study. Also, we prespecified a subgroup of patients with storage disorders (cardiac amyloidosis [CA], Anderson Fabry's, and hemochromatosis) since in these conditions significant T_1 alterations are known to be present due to the underlying condition. Individuals presenting with overt cardiac decompensation were also excluded.

Clinical Definitions

At the time of cardiac MR, demographic data (age, sex, body mass index [BMI], and body surface area) and comorbidities were assessed. These included atrial fibrillation (documented episode during the previous 6 months), arterial hypertension (≥140/90 mmHg or antihypertensive treatment), hypercholesterolemia (total serum cholesterol 240 mg/dL or cholesterol-lowering medication), diabetes (fasting blood glucose level > 126 mg/dL or use of antidiabetic medication), coronary artery disease (CAD, coronary artery stenosis > 50% or fractional flow reserve < 0.8), previous percutaneous coronary intervention, and previous coronary artery bypass grafting. Previous myocardial infarction was defined by both history and cardiac MR. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease formula.[15]

Cardiac Magnetic Resonance Imaging

All exams were performed on a 1.5-T scanner (Avanto Fit, Siemens Healthcare GmbH, Erlangen, Germany) with protocols including LGE (0.1 mmol/kg gadobutrol [Gadovist®; Bayer Vital GmbH, Leverkusen, Germany]) if renal function was preserved (eGFR > 30 mL/min/1.73 m^2). Left and right atrial volumes were assessed using the biplane area-length method.[16] At the time of inserting the intravenous cannula, blood was drawn for hematocrit and serum creatinine level measurement. LGE was quantified on short-axis stacks using a semiautomatic approach by defining a threshold of 5 SDs above mean signal intensity of healthy myocardium (S.A. and A.K. with >5 years of experience; C.N. with 3 years of experience; C.D. and M.K. with 2 years of experience).[17]

T_1-mapping was performed using electrocardiographically triggered MOLLI based on a 5(3)3 prototype (5 acquisition heartbeats are followed by 3 recovery heartbeats and a further 3 acquisition heartbeats) on a short-axis mid-cavity slice and a four-chamber view. This approach included inline motion correction and inline calculation of the T_1 relaxation curve within one breath-hold. T_1 sequence parameters: starting inversion time (TI) = 120 msec, TI increment = 80 msec, reconstructed matrix size = 256 × 218, and acquired matrix size = 256 × 144 (phase encoding resolution = 66%, phase encoding field of view = 85%). T_1 maps were acquired both before and 15 minutes after contrast agent application. For post contrast T_1-mapping, a 4(1)3(1)2 prototype was used. ROIs were defined as left ventricular myocardium without LGE not detectable by visual assessment without areas of scar (S.A. and A.K. with >5 years of experience; C.N. with 3 years of experience; C.D. and M.K. with 2 years of experience). T_1 values (msec) of the blood pool were derived with sufficient distance to papillary muscles and the endomyocardial border (done by S.A. and A.K. with

TABLE 1. Baseline Characteristics

Parameter	All Patients, $n = 284$	OH ≤ +0.3 liters, $n = 150$	OH > +0.3 liters, $n = 134$	*P*-Value
Age (years)	69.7 ± 14.9	69.1 ± 15.8	70.4 ± 13.7	0.897
Female (%)	44.4	57.9	42.1	0.123
MR indication				0.708
VHD (%)	48.9	53.2	46.8	
HF (%)	40.1	50.9	49.1	
CAD (%)	5.3	6.7	3.7	
Other (%)	5.6	5.3	6.0	
Hypertension (%)	79.5	76.4	83.2	0.229
Diabetes (%)	20.2	19.3	21.3	0.722
AFib (%)	45.3	42.2	48.9	0.337
Hyperlipidemia (%)	57.1	54.1	60.6	0.350
CAD (%)	34.5	34.0	35.1	0.865
Prev. MI (%)	7.9	8.4	7.3	0.768
Prev. PCI (%)	17.6	20.6	14.1	0.235
Prev. CABG (%)	5.5	3.7	7.5	0.241
Prev. valve surg. (%)	11.4	10.3	12.8	0.581
PAD (%)	11.1	8.6	14.0	0.227
Smoker (%)	8.8	11.4	5.6	0.205
NYHA				0.211
I–II (%)	47.9	52.5	41.9	
III–IV (%)	52.1	47.5	58.1	
BMI (kg/m^2)	26.5 ± 4.6	27.6 ± 4.6	25.4 ± 4.4	<0.001
BSA (m^2)	1.90 ± 0.23	1.92 ± 0.22	1.88 ± 0.23	0.169
Hemoglobin (mg/dL)	12.3 ± 2.1	12.5 ± 2.0	12.2 ± 2.1	0.196
Hematocrit (%)	36.8 ± 5.5	37.3 ± 5.3	36.3 ± 5.7	0.117
Sodium (mmol/L)	139.0 ± 3.4	139.0 ± 3.5	139.0 ± 3.5	0.851
Potassium (mmol/L)	4.3 ± 0.6	4.3 ± 0.5	4.4 ± 0.6	0.184
eGFR (ml/1.73 m^2/min)	60.5 ± 25.7	63.6 ± 24.8	57.1 ± 26.2	0.134
NT-proBNP (pg/mL)	3527 ± 6550	2276 ± 4046	4887 ± 8284	0.006
LVEDD (mm)	46.2 ± 7.4	46.6 ± 8.0	45.6 ± 6.6	0.364
LVEDV (mL)	157.2 ± 57.8	152.7 ± 60.5	162.7 ± 54.2	0.097
LVEF (%)	57.5 ± 14.3	59.4 ± 13.8	55.2 ± 14.7	0.023
RVEDD (mm)	39.3 ± 6.7	35.7 ± 6.7	40.0 ± 6.7	0.129
RVEDV (mL)	151.4 ± 49.8	145.6 ± 47.0	158.4 ± 52.3	0.082
RVEF (%)	51.8 ± 10.9	53.3 ± 9.8	55.2 ± 14.7	0.080
LA volume (mL)	105.8 ± 46.1	98.9 ± 38.4	114.6 ± 53.3	0.033

TABLE 1. Continued

Parameter	All Patients, $n = 284$	OH ≤ +0.3 liters, $n = 150$	OH > +0.3 liters, $n = 134$	*P*-Value
RA volume (mL)	101.4 ± 59.6	93.5 ± 59.7	111.5 ± 58.2	<0.001
IVS (mm)	12.7 ± 4.1	12.4 ± 4.2	13.2 ± 4.0	0.032
LV mass (g)	149.6 ± 59.5	142.6 ± 59.1	158.0 ± 59.0	0.038
Native T_1 myo (msec)	1037.5 ± 50.6	1027.1 ± 46.5	1049.3 ± 52.7	0.001
Native T_1 blood (msec)	1645.6 ± 117.6	1618.1 ± 109.9	1676.3 ± 118.7	<0.001
ECV (%)	30.6 ± 8.8	29.1 ± 7.3	32.2 ± 9.9	0.001

OH = overhydration; VHD = valvular heart disease; HF = heart failure; CAD = coronary artery disease; AFib = atrial fibrillation; prev. = previous; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; PAD = peripheral artery disease; NYHA = New York Heart Association functional class; BMI = body mass index; BSA = body surface area; eGFR = estimated glomerular filtration rate; LVEDD; left ventricular end-diastolic diameter; LV = left ventricular; EDD = end-diastolic diameter; EDV = end-diastolic volume; RV = right ventricular; LA = left atrial diameter; RA = right atrial diameter; IVS = interventricular septal thickness; ECV = extracellular volume.

>5 years of experience; C.N. with 3 years of experience; C.D. and M.K. with 2 years of experience). T_1 values from the short-axis and the four-chamber view were averaged.

MR-ECV was calculated using the formula[10]:

$$\text{MR}-\text{ECV} = (1-\text{hematocrit}) \times \frac{\left(\frac{1}{T_1\ \text{myo post}}\right) - \left(\frac{1}{T_1\ \text{myo pre}}\right)}{\left(\frac{1}{T_1\ \text{blood post}}\right) - \left(\frac{1}{T_1\ \text{blood pre}}\right)}$$

where "T_1 myo pre"/"T_1 blood pre" indicates myocardial/blood native T_1 times and "T_1 myo post"/"T_1 blood post" indicates T_1 times of myocardium/blood 15 minutes after contrast agent application.

For further MR analyses dedicated software (cmr42, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada) was used.

Bioimpedance Analysis

All patients underwent BIA assessment to determine and quantify their volume status and body composition directly before undergoing the cardiac MR examination. For this purpose, a body composition monitor (BCM, Fresenius Medical Care, Germany) was used. Patients were placed in supine position and electrodes were attached to the nondominant hand and ipsilateral foot. Based on a fluid model using body compartment resistance, ECW, intracellular water (ICW), and total body water (TBW) as well as adipose and lean tissue mass were measured.[18,19]

Extracellular fluid overload was then determined through a BIA algorithm.[20] First, normohydration status was calculated. Subsequently, tissue hydration status was determined as the difference between the actual ECV and the ideal normohydration volume. Fluid overload was calculated as an absolute value in liters and in percentage above the normal ECV. In addition to OH, this method allows for the assessment of ECW, ICW, and TBW.

Statistical Analysis

Demographic data are presented as mean ± SD or median (IQR) after checking for data normality. The cohort was divided into two groups according to the median of OH. Differences between groups were investigated using Wilcoxon's rank-sum test and chi-square tests as appropriate. For correlation analysis, Pearson's correlation coefficients were used. By univariate and multivariate linear regression analysis, the association of parameters assessed by BIA on native T_1-times and MR-ECV was investigated. Multiple regression analyses were run to determine the impact of BIA parameters on T_1-times and MR-ECV on top of laboratory and clinical parameters. A *P*-value <0.05 was considered statistically significant.

All statistical analyses were performed using SPSS Statistics (version 27) and STATA (version 13).

Results

Of the 295 screened patients (44.1% of females, 70 ± 15 years old), 5 (1.7%) declined participation, 4 (1.4%) patients aborted the MR exam due to claustrophobia, and 1 (0.3%) patient did not undergo MR due to a non-MRI compatible implant. Furthermore, in 32 (10.8%) patients, CA was detected whereas other storage disorders were not present. Patients with known storage disease at the time of referral were not included. The final cohort, hence, consisted of 285 patients (44.4% of females; 70 ± 15 years old), including 32 (11.3%) with CA. Referral diagnoses were 139 (48.9%) valvular heart disease, 114 (40.1%) heart failure (HF, including the 32 CA patients), 15 (5.3%) CAD, and 16 (5.6%) others.

The cohort presented with +0.2 ± 2.4 liters OH, equivalent to 1.0 ± 12.4 OH%, 18.7 ± 0.2 liters ECW, 23.4 ± 0.4 liters ICW, and 41.6 ± 0.6 liters TBW. Table 1 displays baseline characteristics stratified by the median OH of +0.3 liters (IQR: −1.0 to 1.5 liters).

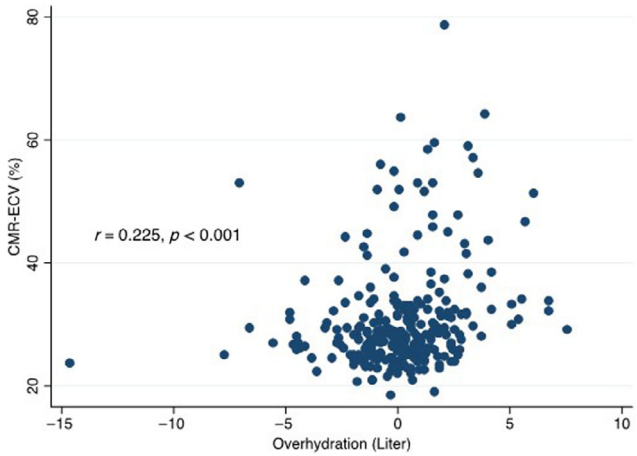

FIGURE 1: Correlation between overhydration by bioimpedance analysis and extracellular volume on cardiovascular magnetic resonance imaging.

TABLE 2. Linear Regression Analysis for Extracellular Volume by Cardiovascular Magnetic Resonance Imaging

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	0.004	−0.06 to 0.73	0.901
Sex	2.763	0.75 to 4.78	0.007
Heart rate	0.004	−0.02 to 0.02	0.723
BMI	−0.251	−0.47 to −0.03	0.025
BSA	−2.041	−6.68 to 2.60	0.387
Hematocrit	0.180	−0.03 to 3.88	0.090
OH	0.827	0.41 to 1.25	<0.001
Multivariable			
Sex	2.529	0.51 to 4.55	0.014
BMI	−0.188	−0.41 to 0.03	0.093
OH	0.711	0.28 to 1.14	0.001

BMI = body mass index; BSA = body surface area; OH = overhydration.

TABLE 3. Linear Regression Analysis for Extracellular Volume by Cardiovascular Magnetic Resonance Imaging in Women

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	−0.05	−0.16 to 0.06	0.345
Heart rate	0.06	−0.01 to 0.03	0.575
BMI	−0.25	−0.51 to 0.07	0.056
BSA	−5.54	−13.0 to 1.93	0.145
Hematocrit	−0.25	−0.70 to 0.20	0.271
OH	1.00	0.30 to 1.70	0.006
Multivariable			
OH	1.00	0.30 to 1.70	0.006

BMI = body mass index; BSA = body surface area; OH = overhydration.

TABLE 4. Linear Regression Analysis for Extracellular Volume by Cardiovascular Magnetic Resonance Imaging in Men

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	−0.05	−0.16 to 0.06	0.345
Heart rate	0.05	−0.11 to 0.12	0.934
BMI	−0.26	−0.63 to 0.10	0.159
BSA	−4.85	−12.7 to 3.0	0.225
Hematocrit	−0.12	−0.44 to 0.20	0.460
OH	0.69	0.144 to 1.24	0.014
Multivariable			
OH	0.69	0.144 to 1.24	0.014

BMI = body mass index; BSA = body surface area; OH = overhydration.

Patients with an OH over the median of the cohort had significantly lower BMI (25.4 ± 4.4 vs. 27.6 ± 4.6) whereas no significant differences were observed with regard to all other baseline parameters (Table 1). There was no significant difference in renal function between groups (eGFR: 57.1 ± 26.2 vs. 63.6 ± 24.8 mL/min/1.73 cm^2, $P = 0.134$).

A significant correlation between MR-ECV and OH ($r = 0.225$, $P < 0.001$; Fig. 1) as well as ECW ($r = 0.167$; $P = 0.005$) was found, but not between MR-ECV and TBW ($r = 0.092$, $P = 0.129$) or ICW ($r = 0.047$,). Native T_1-times also significantly correlated with OH ($r = 0.175$, $P = 0.003$), but not with ECW, ICW, or TBW ($r = 0.041$, $P = 0.428$; $r = -0.027$, $P = 0.725$ and $r = -0.008$, $P = 0.924$, respectively). Hematocrit was not significantly correlated with OH ($r = -0.028$, $P = 0.674$), but with ICW and TBW ($r = 0.139$, $P = 0.038$ and $r = 0.147$, $P = 0.038$, respectively).

TABLE 5. Linear Regression Analysis for Extracellular Volume by Cardiovascular Magnetic Resonance, Excluding Patients with Cardiac Amyloidosis

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	−0.01	−0.03 to 0.04	0.869
Male sex	0.93	−0.07 to 1.94	0.069
Heart rate	0.01	−0.01 to 0.01	0.262
BMI	−0.05	−0.15 to 0.06	0.378
BSA	−0.01	−2.24 to 2.22	0.995
Hematocrit	−0.30	−0.41 to −0.19	<0.001
OH	0.40	0.19 to 0.61	<0.001
Multivariable			
Hematocrit	−0.29	−0.40 to −0.18	<0.001
OH	0.32	0.11 to 0.53	0.003

BMI = body mass index; BSA = body surface area; OH = overhydration.

TABLE 6. Linear Regression Analysis for Native T_1 Time by Cardiovascular Magnetic Resonance Imaging

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	0.234	−0.17 to 0.63	0.251
Sex	2.154	−9.77 to 14.08	0.723
Heart rate	0.043	−0.07 to 1.16	0.462
BMI	−1.195	−2.45 to 0.06	0.062
BSA	−20.821	−46.91 to 5.27	0.117
Hematocrit	−0.008	−1.19 to 1.17	0.990
OH	3.750	1.27 to 6.23	0.003
Multivariable			
OH	3.750	1.27 to 6.23	0.003

BMI = body mass index; BSA = body surface area; OH = overhydration.

TABLE 7. Linear Regression Analysis for Native T_1 Time by Cardiovascular Magnetic Resonance Imaging in Women

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	−0.12	−0.79 to 0.55	0.717
Heart rate	0.03	−0.08 to 0.15	0.566
BMI	−0.86	−2.51 to 0.79	0.307
BSA	−28.3	−75.32 to 18.7	0.236
Hematocrit	−2.80	−5.53 to 0.06	0.045
OH	2.62	0.92 to 7.17	0.032
Multivariable			
Hematocrit	−2.74	−5.48 to 0.06	0.051
OH	2.43	0.87 to 8.21	0.039

BMI = body mass index; BSA = body surface area; OH = overhydration.

TABLE 8. Linear Regression Analysis for Native T_1 Time by Cardiovascular Magnetic Resonance Imaging in Men

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	0.47	−0.05 to 0.98	0.074
Heart rate	0.31	−0.31 to 0.94	0.323
BMI	−1.63	−3.62 to 0.35	0.106
BSA	−48.8	−91.47 to 6.15	0.025
Hematocrit	−0.97	−2.79 to 0.84	0.291
OH	4.10	1.16 to 7.03	0.006
Multivariable			
BSA	−41.4	−83.8 to 0.96	0.056
OH	3.70	0.76 to 6.63	0.014

BMI = body mass index; BSA = body surface area; OH = overhydration.

By linear regression, male sex ($P = 0.007$) and BMI ($P = 0.025$) were associated with MR-ECV but not with native T_1-time ($P = 0.723$ and $P = 0.062$, respectively). In addition, OH was significantly related with both MR-ECV and native T_1-time ($P < 0.001$ and $P = 0.003$, respectively). By multivariate regression analysis, OH remained independently associated with MR-ECV and native T_1-time (Tables 2–9).

TABLE 9. Linear Regression Analysis for Native T_1 Time by Cardiovascular Magnetic Resonance Imaging Excluding Patients with Cardiac Amyloidosis

	Regression Coefficient	95% CI	*P*-Value
Univariable			
Age	0.33	−0.02 to 0.69	0.066
Male sex	−3.3	−14.2 to 7.6	0.553
Heart rate	0.05	−0.05 to 0.15	0.358
BMI	−0.34	−1.49 to 0.81	0.560
BSA	−21.5	−45.4 to 2.4	0.078
Hematocrit	−2.74	−3.69 to −1.16	<0.001
OH	2.44	0.15 to 4.74	0.037
Multivariable			
Hematocrit	−2.39	−3.66 to −1.12	<0.001
OH	1.01	−1.42 to 3.42	0.416

BMI = body mass index; BSA = body surface area; OH = overhydration.

In the prespecified subgroup ($n = 252$) excluding patients with CA ($n = 32$), major findings were identical as in the entire cohort. OH was significantly related with MR-ECV$_{_without_Amyloid}$ ($r = 0.233$, $P < 0.001$) and native T_1-times$_{_without_Amyloid}$ ($r = 0.131$, $P = 0.037$). By linear regression analysis, OH and hematocrit were the only factors listed in Table 5 influencing MR-ECV$_{_without_Amyloid}$, both remained significantly associated in the multivariate analysis. However, while OH was significantly related with native T_1-times$_{_without_Amyloid}$ on a univariate level, only hematocrit remained significantly associated with native T_1-times$_{_without_Amyloid}$ (see Tables 5 and 9).

When repeating regression analyses for male and female subjects separately, the same results were observed (see Tables 3, 4, 7, and 9).

In the multiple regression analysis including native T_1-times and hematocrit, OH was still significantly associated with MR-ECV ($P = 0.001$). These results were reproduced when excluding patients with CA ($P = 0.002$).

Discussion

T_1-mapping is increasingly used for noninvasive myocardial tissue characterization.[21] Several methods currently exist, with the majority based on MOLLI recovery, as performed in the present study. T_1-mapping has shown to be of diagnostic value in CA where native T_1-times and MR-ECV values are markedly elevated.[11,22] Also, T_1-mapping outperformed T_2-weighted edema sequences and LGE in the diagnosis of acute myocarditis[23] and appears to predict prognosis in individuals with suspected myocarditis.[24] Recently, T_1-mapping was identified as prognostic imaging marker in other conditions including nonischemic cardiomyopathy,[25] aortic stenosis,[26] HF with preserved ejection fraction,[27] and mixed cohorts.[4,28] While conflicting data have been reported whether T_1-mapping provides incremental value over established clinical parameters, its value among imaging variables is well established.[3,4]

While accumulation of collagen, amyloid, iron deposits, and sphingolipids are known to alter T_1 signals,[11] the impact of volume overload is currently unknown (see Fig. 2), although previously reported studies have shown an influence of myocardial edema after myocardial infarction on T_1 signals.[29] Global T_1-values for the myocardium cannot distinguish between the individual components of myocardial space—both on a cellular and interstitial level. Data from studies investigating T_1-mapping in patients with acute myocarditis show altered T_1-signals in areas of focal edema as visualized by LGE imaging.[23] Interestingly, in a biopsy study of patients with suspected myocarditis, MR-ECV accurately estimated the degree of myocardial fibrosis only in areas without active inflammation.[30] A previous study on hemodialysis patients suggested an association of systemic volume load and native T_1-times,[14] another study by Nitsche et al was able to show a significant association between increased MR-ECV and OH in patients with severe aortic stenosis and could show a prognostic impact on the outcome.[31] These findings underline the potential importance of the presence of "free" myocardial water when interpreting T_1-mapping results. It is necessary to clarify such a potential interaction, as clinical applications of T_1-mapping will broaden and will, more and more, be used for the monitoring of disease progression as well as therapy.[3]

This study demonstrated that OH has an incremental influence on both native T_1-times and MR-ECV and is not a surrogate parameter for volume dilution resulting in a lower hematocrit, hence altering MR-ECV calculation.

Patients with clinically overt decompensation were excluded from this study. However, fluid overload represents a dynamic continuum and may be present even in the absence of typical clinical signs such as pronounced leg edema, hepatojugular reflux, congestion on chest radiographs, or jugular venous distension.[32] It is difficult to integrate our findings in previous T_1-mapping trial results, due to limited reporting in previous trials. Of note, the prognostic impact of T_1-mapping has been described in cohorts where signs of fluid overload have been shown to greatly impact prognosis, such as in HF with reduced ejection fraction[33,34] and HF with preserved ejection fraction.[33,34] Hence, the fluid status in these patients may be partly

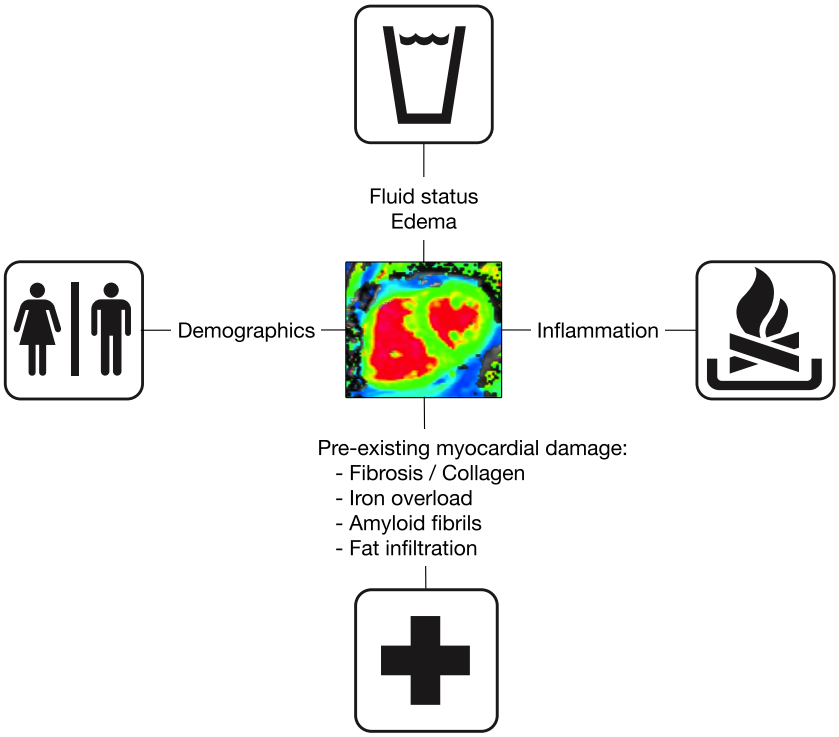

FIGURE 2: T_1-mapping by cardiovascular magnetic resonance imaging reflects all components within a given region of interest. Longitudinal relaxation is influenced by demographics (age and sex) and interstitial and/or intracellular accumulation of collagen/ other proteins, iron, amyloid, or fat, inflammatory cells, and free water.

responsible for the dismal prognosis in patients with elevated T_1 as well as MR-ECV values.

These results suggest that the individual patient's volume status plays an important role when interpreting T_1-mapping results. While there is no linear relationship between fluid status assessed by BIA, the significant influence of the individual hydration status on mapping results should prompt further investigations.

Limitations

While a selection bias must be taken into account due to the single-center character as well as the preselected subject collective as well as an information bias due to single field strength, this study followed the identical protocol in both cardiac MR as well as BIA settings throughout the entire study. However, since no comparison with healthy subjects was performed, a bias cannot be excluded. Although validated in several clinical scenarios, BIA is relying on several mathematical assumptions, potentially introducing errors as previously summarized.[35] Our findings highlight the interplay between fluid status and T_1-mapping findings; however, the overall poor correlation between ECV and OH has to be mentioned, additionally, its clinical relevance has yet to be determined. Also, the study lacks T_2-mapping data. Furthermore, an average value using one short-axis and one four-chamber view was created potentially creating altered average results, especially in the presence of diffuse myocardial disease.

Conclusions

T_1 time and MR-ECV are associated with the degree of OH on BIA measurement. These effects were independent from age, sex, BMI, and hematocrit. Patients' volume status may thus to be an important factor when T_1 time and MR-ECV values are interpreted.

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