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. In the 1990s, the implementation of contrast agents for the first time facilitated non-invasive visualization of myocardial scars, for example, after myocardial infarctions. 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. T1-mapping overcomes this limitation as it allows for quantification of T1-times of every voxel within a certain region of interest (ROI). While native T1-times provide information of both intracellular and extracellular signals, correction for the hematocrit allows for quantification of extracellular volume (ECV). Numerous studies have shown that T1-mapping accurately estimates the extracellular space when validated against myocardial biopsies. T1-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 T1-mapping and MR-ECV. The main driver for an increase in both native T1-time and MR-ECV is believed to be accumulation of collagen in ischemic heart disease, valvular heart disease, and dilated cardiomyopathy or—in acute myocardial infarction—by increase in ECV resulted from extravasation of blood albumin and loss of cell membrane integrity. In contrast, disease-specific proteins or lipids may also alter T1 signals and affect native T1-times and/or MR-ECV. Amyloid fibrils deposited in the extracellular space cause a considerable prolongation of native T1-times and an increase in MR-ECV estimates, while in Anderson Fabry’s disease, intracellular sphingolipids lower T1-times at normal MR-ECV values. Myocarditis is a particularly important application of T1-mapping, as an inflammatory state including myocardial edema alters T1 signals.

However, although factors that impact T1 times on MR have extensively been studied previously, it is currently unknown to what extent the systemic volume status—that may well affect extracellular water (ECW) content of the myocardium—can alter myocardial T1 signals. Early data indicate a relationship of volume overload and T1-times in patients undergoing hemodialysis. 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 T1 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 T1-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 T1 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.

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 m²). Left and right atrial volumes were assessed using the biplaner area-length method. 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). T1-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 T1 relaxation curve within one breath-hold. T1 sequence parameters: starting inversion time (TI) = 120 msec, TI increment = 80 msec, reconstructed matrix size = 256 x 218, and acquired matrix size = 256 x 144 (phase encoding resolution = 66%, phase encoding field of view = 85%). T1 maps were acquired both before and 15 minutes after contrast agent application. For post contrast T1-mapping, a 4(13)(12) 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). T1 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...
| 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/m²)          | 26.5 ± 4.6            | 27.6 ± 4.6                | 25.4 ± 4.4                | <0.001  |
| BSA (m²)             | 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 m²/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   |
First, normohydration status was calculated. Normohydration was defined by the following parameters: extracellular volume (ECV) equivalent to 1.0 liters, intracellular water (ICW), and total body water (TBW). 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 T₁-times and MR-ECV was investigated. Multiple regression analyses were run to determine the impact of BIA parameters on T₁-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. Referential 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).

### 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 T₁ myo (msec) | 1037.5 ± 50.6 | 1027.1 ± 46.5 | 1049.3 ± 52.7 | 0.001 |
| Native T₁ 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; RV = right ventricle; LA = left atrial diameter; RA = right atrial diameter; IVS = interventricular septal thickness; ECV = extracellular volume.
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 cm², 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 T₁-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 1. 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 2. 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.

### FIGURE 1: Correlation between overhydration by bioimpedance analysis and extracellular volume on cardiovascular magnetic resonance imaging.
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).
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} \((r = 0.235, P < 0.001)\) and native T1-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 T1-times_{without_Amyloid} on a univariate level, only hematocrit remained significantly associated with native T1-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 T1-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**

T1-mapping is increasingly used for noninvasive myocardial tissue characterization. Several methods currently exist, with the majority based on MOLLI recovery, as performed in the present study. T1-mapping has shown to be of diagnostic value in CA where native T1-times and MR-ECV values are markedly elevated. Also, T1-mapping outperformed T2-weighted edema sequences and LGE in the diagnosis of acute myocarditis and appears to predict prognosis in individuals with suspected myocarditis. Recently, T1-mapping was identified as a prognostic imaging marker in other conditions including nonischemic cardiomyopathy, aortic stenosis, HF with preserved ejection fraction, and mixed cohorts. While conflicting data have been reported whether T1-mapping provides incremental value over established clinical parameters, its value among imaging variables is well established.

While accumulation of collagen, amyloid, iron deposits, and sphingolipids are known to alter T1 signals, 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 T1 signals. Global T1-values for the myocardium cannot distinguish between the individual components of myocardial space—both on a cellular and interstitial level. Data from studies investigating T1-mapping in patients with acute myocarditis show altered T1-signals in areas of focal edema as visualized by LGE imaging. 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. A previous study on hemodialysis patients suggested an association of systemic volume load and native T1-times, 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. These findings underline the potential importance of the presence of “free” myocardial water when interpreting T1-mapping results. It is necessary to clarify such a potential interaction, as clinical applications of T1-mapping will broaden and will, more and more, be used for the monitoring of disease progression as well as therapy.

This study demonstrated that OH has an incremental influence on both native T1-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, hepatopugal reflux, congestion on chest radiographs, or jugular venous distension. It is difficult to integrate our findings in previous T1-mapping trial results, due to limited reporting in previous trials. Of note, the prognostic impact of T1-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 and HF with preserved ejection fraction. Hence, the fluid status in these patients may be partly...
responsible for the dismal prognosis in patients with elevated T1 as well as MR-ECV values. These results suggest that the individual patient’s volume status plays an important role when interpreting T1-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. Our findings highlight the interplay between fluid status and T1-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 T2-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
T1 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 be an important factor when T1 time and MR-ECV values are interpreted.

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