

Extracellular remodeling in patients with wild-type amyloidosis consuming epigallocatechin-3-gallate: preliminary results of T1 mapping by cardiac magnetic resonance imaging in a small single center study

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Abstract

Objectives T1 mapping by cardiac magnetic resonance imaging (CMR) is able to determine the extracellular volume fraction. Wild-type transthyretin amyloidosis (WT-ATTR) is characterized by extracellular amyloid deposition in the heart. Recent reports indicated a reduction of left ventricular (LV) myocardial mass in WT-ATTR after consumption of epigallocatechin-3-gallate, the main catechin in green tea. It remained unclear, whether reduction of LV myocardial mass reflects decrease of amyloid load or progressive atrophy of cardiomyocytes.

Methods This study included 7 male patients with CMR repetitively performed before and 12 months after daily consumption of green tea extract (600 mg epigallocatechin-3-gallate). Short axis slices as well as 2-, 3-, and 4-chamber views were acquired using SSFP sequences. T1 mapping was created out of 11 mid-ventricular short axis views with increasing inversion times using a single breath-hold modified look-locker inversion recovery sequence before and 15 min after Gadolinium contrast administration.

Results After 12 months, a significant decrease of LV myocardial mass [198 (160; 212) vs. 180 (142; 204) g; $p < 0.05$] was observed. Moreover, a significant decrease of native [T1 1110 (1072; 1150) ms vs. 1080 (970; 1101), $p < 0.05$ or $p = 0.03$] was noticed. The calculated extracellular volume decreased in 5 patients (62.5 %) by 7 % and increased in 2 patients (37.5 %) by 9.5 %, in trend resulting in a (not significant) decrease of median ECV by 2.4 %. Left ventricular ejection fraction (LVEF) [57 (48; 65) vs. 55 (47; 64) %; $p = 0.3$] remained unchanged.

Conclusions This study provided further evidence of LV myocardial mass reduction in patients with WT-ATTR daily consuming green tea extract. Additionally, this study gave first insights into the histomorphological correlate of LV mass reduction using T1 mapping. LV mass reduction appeared to be rather due to a decrease of amyloid load than atrophy of cardiomyocytes.

Keywords Wild-type TTR amyloidosis · Cardiovascular magnetic resonance imaging · EGCG

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Introduction

Wild-type transthyretin amyloidosis (WT-ATTR) is an age-related type of amyloid disease characterized by extracellular deposition of wild-type transthyretin amyloid almost exclusively in the heart. Thus, patients primarily present with symptoms of heart failure [1, 2]. Up to now causative treatment options are lacking. Standard heart failure medication is not able to halt progression of the disease [3]. Tafamidis (Vyndaqel®), a stabilizer of the TTR tetramer [4], has been approved for treatment of stage 1 familial amyloid polyneuropathy in Germany in 2011 [5,

6]. However, the effect of tafamidis on TTR amyloid cardiomyopathy has not been elucidated yet.

In the past, *in vitro* experiments gave evidence that epigallocatechin-3-gallate (EGCG), the most abundant catechin in green tea, appeared to inhibit fibril formation of diverse amyloidogenic proteins [7–9]. This therapeutic effect was further confirmed in an animal study [10]. Moreover, a recent observational study from our group in patients with TTR-related cardiac amyloidosis demonstrated a reduction of left ventricular (LV) myocardial mass by approximately 10 % after daily consumption of 450 mg EGCG over a 1-year period [11]. However, the morphological correlate of LV myocardial mass reduction remained unknown since mass reduction could either be related to atrophy of cardiomyocytes or for reduction of amyloid load.

With respect to this, CMR tissue characterization offers a unique perspective for further clarification of the histological correlate resulting in decrease of LV myocardial mass: the emerging technique of T1 mapping allows a precise analysis of the myocardial interstitial space [12], including quantification of the extracellular volume (ECV) [13, 14] that expands due to edema, fibrosis or even amyloid deposition.

In this study, we sought to investigate the morphological correlate of LV myocardial mass reduction observed in a small group of WT-ATTR patients after consumption of EGCG by the use of the CMR T1 mapping technique. None of the study patients has been included in our previous study (11).

Materials and methods

Study subjects

The initial study cohort consists of 9 male WT-ATTR patients [72(70; 73) years, Table 1] with histologically proven TTR amyloid by endomyocardial biopsy (Congo red staining, immunohistochemistry) and exclusion of any TTR gene variant by moleculargenetical testing [11]. Patients were recruited between 2011 and 2012 at the Heidelberg Amyloidosis center. All patients had compensated heart failure for at least 4 months prior to study inclusion. Patients were observed over a period of 12 months while daily consuming four capsules of green tea extract (praevent® Loges, Dr. Loges & Co, Winsen/Luhe, Germany; 600 mg EGCG, extraction solvent ethyl acetate/ethanol/water). Detailed methodological aspects have been described previously [11]. The study was approved by the local ethics committee and has been performed in accordance with the ethical standards according to the declaration of Helsinki.

Laboratory testing

Blood samples were taken on the day of CMR examination for the determination of haematocrit (HCT), serum creatinine, serum albumin, troponin T and NT-proBNP. For NT-proBNP and troponin T determination electrochemiluminescence immunoassays (Elecsys-proBNP/troponin T, Roche Diagnostics, Mannheim, Germany) were used.

Echocardiography

Transthoracic echocardiograms were performed using commercially available ultrasound diagnostic systems (Vivid 7, GE Healthcare, Milwaukee, WI, USA) and examinations were analyzed offline on a commercially available workstation (Centricity Cardiology CA1000 2.0, GE Medical Systems, Milwaukee, WI, USA).

The LV cavity diameter was scaled in end diastole and end systole, thickness of interventricular septum (IVS) and posterior wall were measured in late diastole. M-mode imaging from the apical 4-chamber view was used to obtain mitral (MAPSE) and tricuspid annular plane systolic excursion (TAPSE). For measurements of the systolic velocity, pulsed-wave Doppler tissue imaging of the mitral annulus was performed.

CMR protocol

CMR assessment was performed before consumption of green tea extract and at the end of a 1-year period with daily intake of green tea extract. All CMR exams were performed on a 1.5-Tesla scanner (Philips Achieva, Best, The Netherlands) with a 32-element cardiac receiver coil as reported previously [11]. Vector ECG-gated standard steady state free precession (SSFP) cine sequences were acquired (a) in short axis planes covering the whole LV and (b) in three long axis views (2-, 3-, 4-chamber views).

For calculation of T1 mapping, 11 raw images with increasing inversion times (TI 100–4400 ms) were acquired before and 15 min after injection of 0.2 mmol per kg body weight gadolinium-diethylene triamine pentaacetic acid (DTPA) contrast agent (Magnevist®, Bayer Healthcare, Leverkusen, Germany) using a modified look-locker inversion recovery sequence (MOLLI) during breath-hold in expiration (TR/TE: 3.5/1.8 ms, flip angle 35°).

CMR data analysis

All CMR data analyses were performed independently by two experienced investigators (HS, FS) blinded to all clinical data. A commercially available workstation (Philips Viewforum, Version 3.4, Best, The Netherlands) was used. Mean values were reported in the manuscript.

Table 1 Patient characteristics

| | Study inclusion | 1-year follow-up | <i>p</i> |
|---------------------------------|------------------|------------------|----------|
| Age (years) | 72 (70;73) | 73 (71;74) | ns |
| Height (cm) | 178 (173;183) | 178 (173;183) | ns |
| Weight (kg) | 80 (79;89) | 85 (78;90) | ns |
| mBMI (kg/m ²)*(g/L) | 1115 (1046;1342) | 1188 (1072;1267) | ns |
| Serum albumin (g/L) | 44.7 (44.5;46.6) | 44.6 (44.5;46.0) | ns |
| Troponin T (μg/L) | 31 (14;36) | 26 (20;39) | ns |
| NT-proBNP (ng/L) | 2313 (763;5664) | 3920 (2079;6437) | ns |
| eGFR (mL/min) | 68.5 (64.1;75.1) | 72.8 (61;77.6) | ns |
| Heart rate (min ⁻¹) | 73 (63;80) | 70 (64;73) | ns |
| Systolic blood pressure (mmHg) | 140 (100;150) | 130 (120;140) | ns |
| Diastolic blood pressure (mmHg) | 80 (65;90) | 80 (75;80) | ns |
| NYHA class | NYHA class | | |
| I | 2 (29 %) | 1 (14 %) | ns |
| II | 2 (29 %) | 3 (43 %) | |
| III | 3 (43 %) | 3 (43 %) | |
| Cardiac magnetic resonance | | | |
| Myocardial mass (g) | 179 (150;214) | 166 (126;207) | 0.046 |
| Native <i>T1</i> (ms) | 1110 (1042;1174) | 1080 (970;1120) | 0.031 |
| Post-contrast <i>T1</i> (ms) | 179 (150;214) | 166 (126;207) | ns |
| ECV (%) | 42.9 (36.0;47.3) | 41.9 (38.4;44.4) | ns |
| LGE | | | |
| Diffuse | 3 (43 %) | 3 (43 %) | ns |
| Patchy | 4 (57 %) | 4 (57 %) | |
| Subendocardial | 3 (43 %) | 3 (43 %) | |
| Subepicardial | 5 (71 %) | 5 (71 %) | |
| Echocardiography | | | |
| <i>E/A</i> ratio | 1.15 (0.67;1.53) | 1.5 (0.96;2.0) | ns |
| <i>E/E'</i> ratio | 9 (7; 15) | 10 (7; 21) | |
| ECG findings | | | |
| RBBB | 2 (29 %) | 2 (29 %) | ns |
| LBBB | 2 (29 %) | 2 (29 %) | |
| LAHB | 3 (43 %) | 3 (43 %) | |
| Sinus rhythm | 4 (57 %) | 4 (57 %) | |
| Atrial fibrillation | 3 (43 %) | 3 (43 %) | |
| Sokolow–Lyon index (mV) | 1.5 (0.9;2.2) | 1.7 (1.0;2.1) | |

Continuous data are expressed median (interquartile range) discrete data as absolute numbers (percentage) *mBMI* modified body mass index (BMI*plasma albumin), *eGFR* estimated glomerular filtration rate, *ECV* extracellular volume, *LGE* late Gadolinium enhancement, *ECG* electrocardiogram, *RBBB* right bundle branch block, *LBBB* left bundle branch block, *LAHB* left anterior hemiblock, *E* early ventricular filling velocity, *A* atrial ventricular filling velocity, *E'* early diastolic velocity

Analyses included assessment of end-systolic and end-diastolic volumes and LV ejection fraction (LVEF). LV myocardial mass was measured in short axis image stacks of late diastole by manual delineation of endocardial and epicardial borders excluding papillary muscles. Mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were obtained in 4-chamber views by measuring the distance traveled by the lateral annulus from end diastole to end systole.

Pre- and post-contrast *T1* mappings with motion correction in *x*- and *y*-axis were generated using the open-source software tool “MRmap”. All maps were analyzed with OsiriX (v5.5.2 32 bit, PixmeoSarl). Myocardial *T1* values were determined by tracing endocardial and

epicardial borders manually and *T1* values for blood were gathered by manually drawing a region of interest (ROI) in the LV cavity.

ECV values were created according to the following formula:

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

Statistical analysis

Analyses were performed using SPSS (Version 20.0, IBM Corp.). Statistical significance was defined for

p values <0.05. Differences between the non-parametric, continuous parameters assessed at study inclusion and at 12-month follow-up were compared by the Wilcoxon matched-pairs signed rank test. Continuous data were expressed as median (interquartile range). Categorical variables were expressed as absolute numbers (percent).

Results

Complete CMR datasets were obtained from seven study patients; one patient did not receive Gadolinium contrast agent due to markedly reduced renal function (MDRD < 30 ml/min × 1.73 m²); another dataset was excluded due to poor image quality. Three patients had a history of mild arterial hypertension, but normotensive blood pressure due to medical treatment. One patient had a moderate aortic stenosis. None of the patients received pacemaker or ICD prior to study inclusion or during follow-up. Clinical characteristics are given in detail in Table 1. Mean time from first diagnosis of amyloid disease to assessment by CMR was 16 ± 27 months.

No changes in NYHA class and renal function calculated by modified diet in renal disease [MDRD; 69 (64; 75) vs. 73 (61; 77) ml/min × 1.73 m²; *p* = 0.9] were observed after 12 months. Median NT-proBNP plasma levels [2313 (763; 5864) vs. 3920 (2079; 6436) ng/ml; *p* = 0.11] and NYHA functional class remained unchanged and no hospitalization for heart failure was observed during the study period.

Detailed data for all the seven study patients at the beginning and the end of the observation period are given in Table 2 (Supplemental material).

Morphological and functional CMR analysis

After 12 months, a significant decrease of median LV myocardial mass by 6 % was observed in these patients [198 (160; 212) vs. 180 (142; 204) g; *p* = 0.03; Fig. 1]. Overall, in 5 (71 %) patients LV myocardial mass decreased during 1 year of green tea consumption, in 1 (14 %) patient LV myocardial mass remained unchanged. Only 1 (14 %) patient presented as a non-responder with increase of LV myocardial mass. LV ejection fraction [57 (48; 65) vs. 55 (47; 64) %; *p* = 0.3], right ventricular longitudinal function [TAPSE: 15.0 (8.8; 16) vs. 12.5 (10.3; 15.8) mm; *p* = 0.7] and LV longitudinal function [MAPSE: 6.5 (5.0; 8.8) vs. 5.5 (3.3; 6.0) mm; *p* = 0.06] remained unchanged during the observation period.

Tissue characterization by T1 mapping

Native T1 time decreased in 6 (86 %) patients after 12 months of green tea consumption resulting in a median

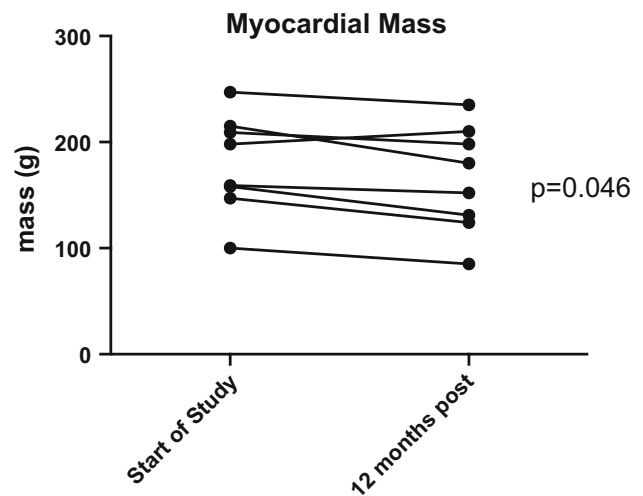


Fig. 1 Comparison of LV myocardial mass of the study patients at the beginning and after 12 months of green tea extract consumption

decrease of 4 % [1110 (1072; 1150) vs. 1080 (971; 1101), *p* < 0.05; Fig. 2]. Moreover, post-contrast T1 time remained unchanged [347 (324; 396) vs. 356 (294; 394) ms; *p* = 0.8]. The calculated ECV decreased in 5 patients (62.5 %) by 7 % and increased in 2 patients (37.5 %) by 9.5 %. One of those patients with increase of ECV (+17 %) presented with a decrease of LV myocardial mass (−16 %), while in the other one an increase of ECV by 2 % was accompanied by an increase of LV myocardial mass by 6 %. In total, a trend for lower median ECV was observed (42 vs. 41 %) after consumption of green tea for 12 months, but statistical significance was not reached in this small patient population (*p* = 0.47).

The inter-observer mean differences in T1 determination were 9.3 ms in native, 5.6 ms in post-contrast scans and

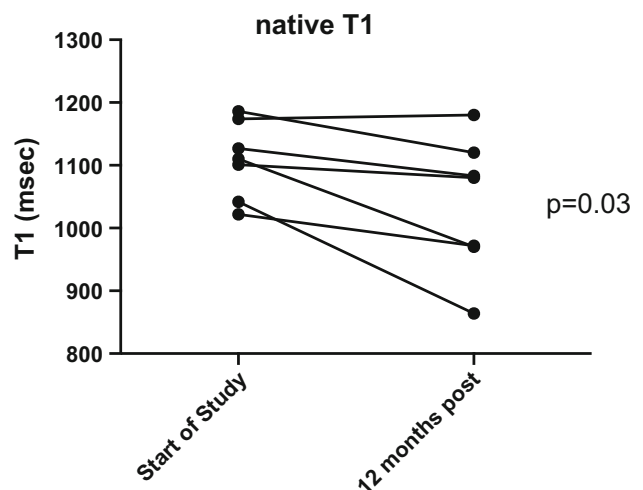


Fig. 2 Comparison of native T1 of the study patients at the beginning and after 12 months of green tea extract consumption

0.5 % in ECV calculation. Mean intra-observer differences were 6.5 ms for native, 4.7 ms for post-contrast T1 values and 0.3 % for ECV values (Figs. 3, 4).

Discussion

This is the first study using repetitive CMR scans with T1 mapping in a small cohort of patients with WT-ATTR. This study provided first insights into the potential role of serial CMR assessments and the histomorphological correlate of LV myocardial mass reduction that has recently been reported after daily consumption of green tea for 1 year [11]. According to the present data, it appears that a decrease of LV myocardial mass might rather be caused by reduction of amyloid load than hypertrophy or atrophy of cardiomyocytes as a decrease of ECV was observed in the vast majority of patients. A trend for lower median ECV after green tea consumption was observed, however, no statistical significance was reached in this small study cohort of seven patients.

In general, hereditary ATTR amyloidosis is claimed to be a rare disease with an incidence of 0.1–1 patients per 1,000,000 inhabitants. Pre-mortem diagnosis of WT-ATTR amyloidosis is infrequent, but appears to be an underestimated cause of left ventricular hypertrophy. It is assumed that approximately in 0.5–1 % of patients above 60 years of age ATTR amyloid deposition will be present [15]. Although survival of patients with WT-ATTR is much better than survival of patients with light-chain amyloidosis [16, 17], the clinical course of the disease is (slowly)

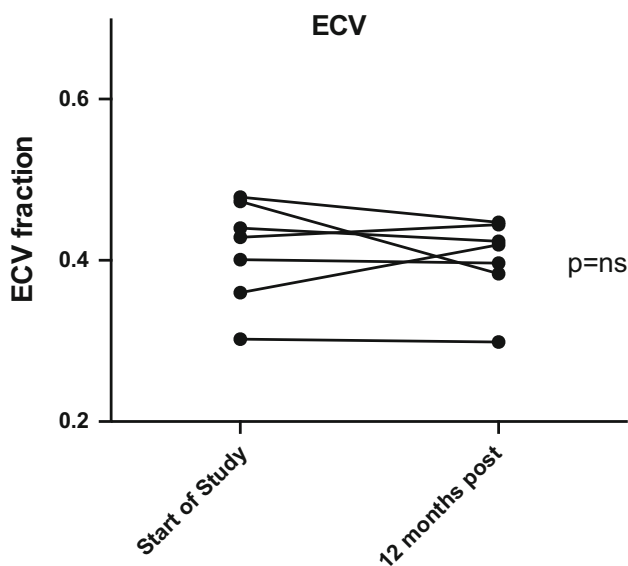


Fig. 3 Comparison of extracellular volume (ECV) of the study patients at the beginning and after 12 months of green tea extract consumption

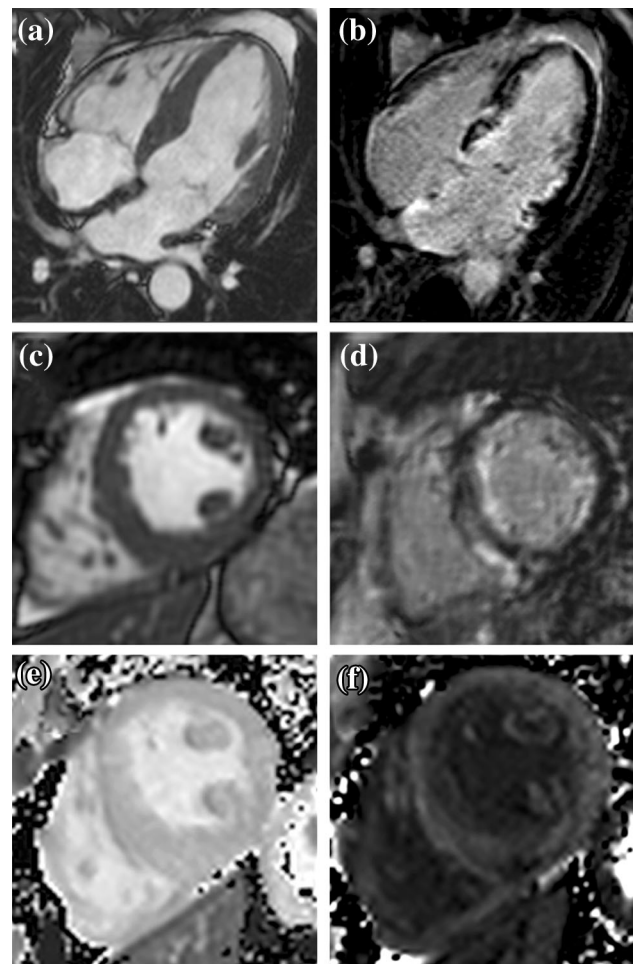


Fig. 4 Representative images of **a** SSFP Cine 4 chamber view **b** LGE 4 chamber view, **c** SSFP Cine short axis, **d** LGE short axis, **e** native T1 mapping, and **f** post-contrast T1 mapping

progressive. Recently, an 8 % increase of LV myocardial mass has been described within 12 months [18]. Additionally, TRACS data indicated a decrease of LV ejection fraction by 3.2 % for every 6 months increment [19]. Moreover, causative treatment approaches are lacking in WT-ATTR as common heart failure treatment is neither able to stop amyloid deposition nor to disaggregate amyloid fibrils.

Promising in vitro results [8, 9] and the letter by Hunstein [20] prompted us to evaluate the effect of EGCG on TTR amyloid. Later on a reduction of LV wall thickness was observed retrospectively in a larger cohort of patients with light-chain amyloidosis [21]. Recently, we reported on a decrease of LV myocardial mass in ATTR patients after consumption of green tea for 12 months [11].

Our present study, although obtained in a very small cohort, is well in line with previous reports. It supports the potential effects of green tea on the clinical course of WT-ATTR as again a decrease of LV myocardial mass was

observed in this cohort with WT-ATTR. Only one patient presented as a non-responder regarding reduction of LV myocardial mass. A potential explanation might be an irregular or incorrect intake of GT capsules or a very advanced amyloid disease. Additionally, excessively high levels of NT-proBNP and ECV were observed in this patient.

Focusing on the potential histological correlates of LV myocardial mass reduction, T1 mapping by CMR offers a unique diagnostic tool for a more specific analysis of myocardial tissue by analyzing signals from intra- and extracellular space separately. Thus, the technique might help to differentiate, whether the changes in LV myocardial mass are caused by progressive atrophy of cardiomyocytes or by decrease of extracellular amyloid load. While the native *T1* time represents a combination of cellular and interstitial information [22], the relative changes of *T1* time of the myocardium and of the blood pool after administration of Gadolinium indicate the extracellular volume fraction as a percentage of the whole myocardium [23–25]. The usefulness of CMR extracellular volume quantification has recently been demonstrated for early diagnosis [22, 26, 27] and prognosis [28] in different forms of cardiac amyloidosis. However, its potential role for monitoring of treatment effects in cardiac amyloidosis is lacking. In contrast to the well-established late gadolinium enhancement that can solely be analyzed semi-quantitatively, T1 mapping allows quantitative analysis of the myocardial tissue composition.

According to the preliminary results of the present study, reduction of LV myocardial mass observed in WT-ATTR patients after 12 months of green tea consumption appears to be associated with a decrease of cardiac amyloid burden. Tissue characterization by T1 mapping might be a promising tool and even more sensitive biomarker for monitoring of pharmaceutical treatment effects as compared with functional parameters of MAPSE, TAPSE or even LV ejection fraction, respectively. Almost all of the patients with LV myocardial mass reduction after 12 months of green tea intake presented with decrease of ECV. As the changes in general are small in present patients the results are prone to errors. This might potentially explain the mismatch between reduction of LV myocardial mass and increase of ECV as observed in a single patient of the present study. The potential reasons for this mismatch are manifold. First, image quality was suboptimal. Moreover, the patient's comorbidities including moderate aortic stenosis and arterial hypertension are associated with myocardial fibrosis that impacts native and post-contrast *T1* times and finally results in increase of ECV [29, 30]. Additionally, body composition and renal function have been reported to impact post-contrast *T1* time [12]. However, this appears to be highly unlikely as only a minimal change

of body weight (1 %) and glomerular filtration rate (7 %) was observed in this particular patient. Post-contrast *T1* time was notably low (240 ms) in comparison to the remaining patients. Thus, T1 mapping and ECV calculation might be of limited value in this case.

Native *T1* time is independent of these factors and thus might be more reliable in some conditions. In contrast, native *T1* reflects composition of the extra- and intracellular space and thus might not be a sufficient and specific biomarker indicating amyloid burden exclusively localized extracellularly. Future (in an optimal way placebo controlled) studies need to focus on long-term observation and the correlation of histopathological findings (e.g. amount of amyloid) and T1 mapping parameters (e.g. native *T1*, ECV).

Limitations

We are fully aware of the limitations of the present study. However, this is the first report on the potential role of repetitive T1 mapping by cardiac MRI for assessment of response to treatment. First, this study is limited by the small number of patients and by its lack of a control group. WT-ATTR is an orphan disease with a limited number of diagnosed patients available for clinical trials. Additionally, there is a widespread knowledge of the results of Prof. Hunstein's experiment among patients with different types of amyloidosis. Green tea extract is available as over the counter supplements and reveals an excellent safety profile. This results in a very low acceptance to renounce on the use of a potential beneficial effect of green tea in the absence of any specific treatment approach for WT-ATTR up to now. Due to novelty of T1 mapping, we also were not able to create a control group from retrospective data. Currently, T1 mapping is an experimental tool and no general consensus concerning sequence and post-processing methods was made. Consistent normal values for *T1* relaxation times or ECV values are lacking, most likely due to variability among different MRI scanner types.

Second, the observation period of 1 year is relatively short. It needs to be demonstrated that changes of ECV might be more pronounced with longer follow-up. Nevertheless, lack of increase of LV myocardial mass during follow-up of 1 year potentially indicates any positive effect when compared to non-interventional reports in cardiac ATTR [18, 19].

Thirdly, we are familiar with the complexity and the potential sources of error of T1 mapping measurements and their related calculations. Nevertheless, a low inter-study variability and an excellent reproducibility were recently reported, when using the same MRI scanner and the same protocol [31, 32]. Regrettably, up to now, no data exist on

the consistency of T1 and ECV values in normal healthy volunteers reassessed after 1 year. Unfortunately, we were not able to obtain these data due to a recent exchange of the MRI scanner at our department. Moreover, technical limitations included that T1 mapping was only created in a mid-ventricular short axis, representing only 6 segments of the AHA 16-segment model. Though amyloid deposition is a global process, regional differences in T1 values or ECV cannot be fully excluded. The heterogeneity of amyloid deposition might even impact ECV measurements, even if the scans were performed in the same region and multiple measurements of ECV were performed.

Fourth, the clinical benefit of green tea consumption would be strengthened by demonstration of an increase of the individual exercise capacity. Unfortunately, cardiopulmonary exercise testing or 6 min walk test has not been performed in this study that was primarily focused on imaging aspects. However, none of the study subjects worsened regarding left ventricular function or NYHA functional class during the study period. No hospitalization for heart failure became necessary.

Conclusions

In summary, the present study confirms LV myocardial mass reduction in patients with cardiac TTR amyloidosis in a small, but more uniform cohort of patients with WT-ATTR daily consuming green tea. Moreover, this preliminary proof of principle data—although not statistically significant and limited by the low number of patients—gave first evidence that the decrease of LV myocardial mass could potentially rather be caused by reduction of the amyloid load than atrophy of cardiomyocytes. Thus, this study stimulates future research focused on the potential role of T1 mapping for monitoring of progression of amyloid deposition or even treatment effects. Further multi-center (in an optimal way placebo controlled) studies with longer follow-up in a larger patient cohorts are urgently needed to draw final conclusions from the present hypothesis generating study.

Conflict of interest AVK received financial support for research from Dr. Loges & Co GmbH, Winsen/Luhe Germany. All other authors state that they have no conflict of interest regarding this manuscript.

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