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Myocardial T1 Measurement Predicts Beneficial LV Remodeling after Long Term Heart Failure Therapy

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Abstract

Objective—We assessed the hypothesis that interstitial myocardial fibrosis measured by cardiac magnetic resonance imaging (CMR) predicts left ventricular (LV) beneficial remodeling in non-ischemic dilated cardiomyopathy (NIDCM) after heart failure (HF) treatment including mineralocorticoid receptor antagonists (MRA).

Background—The myocardial longitudinal relaxation time (T1) on CMR, can quantify myocardial fibrosis in the presence or absence of visually detectable late gadolinium (Gd) enhancement (LGE) MRA treatment produces beneficial remodeling in NIDCM.

Methods—Twelve patients with NIDCM, on stable beta blocker and angiotensin converting-enzyme inhibitor/angiotensin receptor blocking therapy, were studied before and after 6–29 months of MRA, with CMR assessment of LV structure, function, and T1 from standard Look-Locker sequences ($T1_{LL}$).

Results—All patients had depressed cardiac function, dilated left ventricles and no visual LGE. After adding MRA to HF treatment, the LV ejection fraction increased and the LV end-systolic volume index (LVESVI (LVESV/m2)) decreased in all patients ($p<0.0001$). This this was inversely proportional to the baseline myocardial $T1_{LL}$ ($r=-0.65$, $P=0.02$).

Conclusion—Myocardial $T1_{LL}$, in the absence of visually detectable LGE, was quantitatively related to the degree of beneficial LV remodeling achieved in response to adding MRA to a HF regimen.

Keywords

cardiac magnetic resonance imaging; myocardial fibrosis; heart failure

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INTRODUCTION

Nonischemic dilated cardiomyopathy (NIDCM) is characterized by left ventricular (LV) dilation, systolic dysfunction, and myocardial fibrosis [1], which is associated with worse clinical status and poor prognosis[2]. Mineralocorticoid receptor antagonism (MRA) reduces morbidity and/or mortality in ischemic and nonischemic cardiomyopathies [3]. Cardiac magnetic resonance imaging (CMR), using gadolinium (Gd) contrast, is used to visually detect late Gd enhancement (LGE) and myocardial fibrosis. T1, the exponential time constant for CMR longitudinal relaxation, provides a quantitative measurement proportional to the fibrosis burden, detecting fibrosis even when the myocardium appears visually normal (LGE absent)[4]. We examined the hypothesis that myocardial T1 predicts the degree of beneficial reverse remodeling achieved by HF therapy including MRA.

METHODS

Study Design and Participants

Twelve newly diagnosed NIDCM patients underwent CMR studies before and after adding MRA to a standard HF regimen. 590 clinic visits with a diagnosis of HF were reviewed for inclusion/exclusion criteria, and 16 patients were enrolled in the study. The inclusion criteria were: age >18, NYHA Functional Class II-IV HF, echocardiographic LV ejection fraction (LVEF) of < 35%, and serum potassium below 5.0 mmol/L. Exclusion criteria were: 1) presence of or indication for cardioverter-defibrillator (ICD), 2) prior myocardial infarction on ECG, 3) stress test positive for myocardial ischemia or infarction, or 4) angiographic coronary artery disease with 50% or greater stenosis in a major epicardial artery. Further exclusion criteria included reversible causes of LV dysfunction such as myocarditis, post-partum cardiomyopathy and alcoholic cardiomyopathy, severe chronic obstructive airway disease, creatinine > 2.5 mg/dL or estimated glomerular filtration rate (eGFR) < 30 ml/min/m2 (contraindication for Gd), uncontrolled atrial fibrillation, current MRA therapy, and physician preference. Of 16 enrolled, 4 did not complete the protocol because of normal LVEF on CMR (1), bronchoconstriction with adenosine (1), patient withdrawal (1) and placement of an ICD for primary prevention (1), leaving a group of 12 subjects (8 male, 4 female). Beta-adrenergic blocking (BB) drugs and an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocking (ARB) drug were uptitrated to stable and maximally tolerated doses for at least 3 months prior to the initial CMR study. The study was approved by our IRB, and the patients gave informed consent.

Cardiac MR Imaging and T1 Analysis

CMR was performed using a 1.5-T Siemens Magnetom Avanto scanner (Erlangen, Germany), with a previously published protocol [5]. The post-contrast myocardial T1 was calculated using a TI “scout” or Look-Locker (LL) inversion recovery sequence acquired in a single mid ventricular, short axis imaging plane with progressively longer TI times. Post contrast T1 times, termed “T1 Look Locker” ($T1_{LL}$), were determined using MRMAP v 1.4 software [6] based on a 3-parameter Levenberg-Marquardt curve fitting [7]. Individual pixels were manually selected in the interventricular septum, extending from the inferior to the superior right ventricular (RV) insertions, to minimize artifact secondary to cardiac motion,

and to avoid the RV and LV blood pool signal (Supplementary Figure 1). Pixels were analyzed for $T1_{LL}$; 12–24 measurements were made depending on wall thickness, and the results were averaged. The $T1_{LL}$ results were highly reproducible and are shown in the on-line supplementary material.

Statistical Analysis

Data are presented as mean values (±SD) and normalized for body surface area where applicable. LV volumes and myocardial $T1_{LL}$ before and after adding MRA treatment were compared using the Wilcoxon signed-rank one-sample paired test. The relationships between myocardial $T1_{LL}$ and LV beneficial remodeling were expressed using linear regression analysis. Statistical analyses were performed in R (R Development Core Team, Vienna, Austria). Statistical significance was judged to be two-tailed P 0.05. Graphs were produced using Graphpad Prism (GraphPad Software Inc, La Jolla California USA, www.graphpad.com).

RESULTS

Clinical data (Table 1)

The patients' mean age was 48 years (range 27– 63 years), and the mean duration of HF was 19 (17) months, based on symptoms (range 3–57 months). The mean baseline LVEF was severely depressed, averaging 22 (7)%, with LV dilatation and reduced LV stroke volumes compared to normative data [8]. Eleven patients received spironolactone, and one received eplerenone (due to spironolactone intolerance). Repeat CMR studies were performed after 51(29) weeks of treatment (range 25–120, median 32).

Relation of baseline $T1_{LL}$ to LV remodeling

The mean LVEF improved significantly from 22% at baseline to 47% following the addition of MRA (P=0.007) (Table 2).

The percent decrease in LVESVI (beneficial remodeling) following MRA was related inversely to the $T1_{LL}$ on the baseline CMR (r=−0.65, P=0.02) (Figure).

The patients with longer baseline $T1_{LL}$ (consistent with less interstitial fibrosis) had greater decreases in LVESVI. Conversely, the patients with shorter baseline $T1_{LL}$ had lesser decreases in LVESVI. In spite of the significant beneficial remodeling, the myocardial $T1_{LL}$ was not modified by HF treatment, and was not significantly different from baseline (P=0.44).

DISCUSSION

This study showed that $T1_{LL}$ on CMR has utility for identifying dilated cardiomyopathies with the least fibrosis and the greatest potential for beneficial LV remodeling in response to anti-failure therapy that included MRA. We believe this is the first demonstration linking the therapeutic response to HF therapy with the findings of interstitial fibrosis on CMR.

The contrast agent, Gd, shortens the relaxation time of adjacent protons (and thus T1) in proportion to the tissue Gd concentration [9], is detectable as LGE on CMR [2], and is strongly associated with worse clinical status and poor outcomes [2]. In contrast, diffuse interstitial fibrosis is more difficult to detect and quantify. The $T1_{LL}$ technique we employed detects interstitial fibrosis even where LGE is not visually detected [4]. In patients with shorter $T1_{LL}$ (more fibrosis), there was less beneficial remodeling, as shown by smaller decreases in LVESVI. Conversely, patients with longer $T1_{LL}$ (less fibrosis), had a greater degree of beneficial remodeling, shown by greater decreases in LVESVI. This finding expands upon prior work showing the lack of myocardial LGE is an independent predictor of LV beneficial remodeling [10]. To our knowledge, the present study uniquely identifies the $T1_{LL}$ measurement, in the absence of visually detectable LGE, as an additional, quantitative predictor of LV remodeling by MRA. This finding may have significant prognostic value since more than half of NIDCM patients enrolled in imaging studies do not have LGE [10, 11]. We speculate that interstitial fibrosis may precede the development of overt LGE. As noted, our patients had no LGE, and the mean duration of HF symptoms at enrollment was 19 months (range 3–57), suggesting a relatively short duration of HF and greater potential for benefitting from anti-failure therapy that included MRA. Because of the relatively small patient population, this should currently be considered an hypothesis generating study.

Strengths and Limitations

The patient population was small, but the associations between $T1_{LL}$ and LV remodeling are based on physiologically plausible mechanisms. With the high precision of CMR, fewer patients are needed to establish a finding than with echocardiography [12]. Further, our results were aligned with previously reported systolic HF studies demonstrating beneficial remodeling in response to MRA [13].

The $T1_{LL}$ values were derived from conventional LL sequences available at the time of this study. Modified LL sequences (MOLLI) are now available and minimize cardiac and respiratory motion, but comparisons of LL and MOLLI demonstrate good agreement, supporting the applicability of our results [14]. We minimized cardiac and respiratory motion registration errors by measuring $T1_{LL}$ in the interventricular septum, with manual motion correction as needed. The Gd dose and injection-to-T1 acquisition time were tightly controlled. With this attention to detail, our results had excellent intra-observer reproducibility (see on line supplement).

The extracellular volume (ECV) index incorporates the post-contrast T1 for estimating myocardial fibrosis. We did not calculate ECV because a pre-contrast T1 time was not then in our protocol. It should be noted that significant literature supports the validity of both post-contrast T1 and ECV as quantitative measures of fibrosis. [4],[15] Thus, based on our results, we conclude that $T1_{LL}$ identifies patients with the greatest potential for beneficial LV remodeling, and such an evaluation may be therapeutically useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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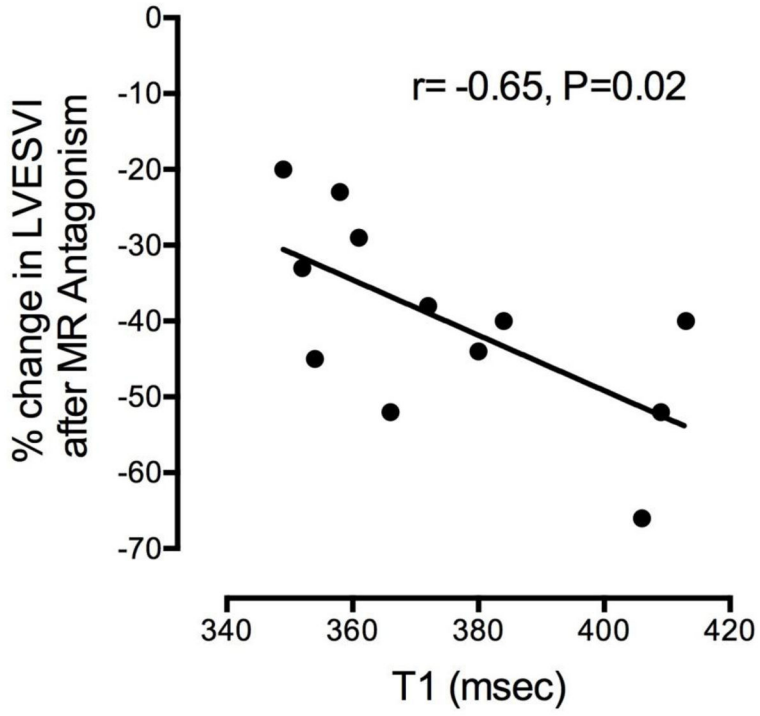

Figure 1.

Figure. Relation between LVESVI after adding MR antagonist and baseline T1. (Please see text for details and Table 2 for abbreviations).

Table 1

Patient Characteristics at Baseline CMR and Medications.

	Mean (SD)
Age yrs	48 (11)
Sex (M/F) (N)	8/4
SBP mmHg	123 (18)
DBP mmHg	69 (12)
HR bpm	65 (10)
Weeks on Medications preceding study 1:	
ACE-I/ARB	22 (19)
BB	22 (19)
MRA	
Spironolactone 25 mg daily (N)	5
Spironolactone 50 mg daily (N)	6
Eplerenone 50 mg daily (N)	1

SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocking drug; BB=beta-adrenergic blocking drug; MRA=mineralocorticoid receptor antagonist.

Table 2

Patient Parameters Before and After MRA Treatment.

	N	Baseline	After MRA	Difference	P
EF (%)	12	22 (7)	47 (7)	25 (11)	<0.001
LVEDV (mL)	12	173.6 (37.5)	153.3 (45.5)	−20.4 (13.7)	0.001
LVEDVI (mL/m2)	12	83.5 (14.7)	73.7 (19.4)	−9.8 (6.7)	0.001
LVESV (mL)	12	135 (29.1)	82 (29.1)	−53 (17.1)	<0.001
LVESVI (mL/m2)	12	65.3 (13.9)	39.2 (12.6)	−26.1 (10.1)	<0.001
LVSV (mL)	12	38.6 (16.2)	71.4 (20.8)	32.8 (18.3)	<0.001
LVSVI (mL/m2)	12	18.1 (6.7)	34.5 (9.5)	16.3 (10.5)	<0.001
LVM (g)	12	173.2 (41.3)	158.8 (36.7)	−14.33 (14.3)	0.005
LVMI (g/m2)	12	82.1 (11.7)	74.3 (9.7)	−7.7 (8.7)	0.002
T1 (ms)	12	375 (23)	381 (42)	6 (37)	0.435

EF = Ejection Fraction

LVEDV(I) =Left Ventricular End Diastolic Volume (Indexed for BSA)

LVESV(I) =Left Ventricular End Systolic Volume (Indexed for BSA)

LVM(I) =Left Ventricular Mass (indexed for BSA)

LVSV(I) = Left Ventricular Stroke Volume (Indexed for BSA)

MRA = mineralocorticoid antagonists

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