Serial Myocardial Native T_1 Assessment for Prediction of LV Functional Recovery in Recent-Onset DCM: A Comparison with Histology

Brief title: Native T_1 for LV functional recovery in DCM

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Despite advances in heart failure therapies, the mortality rates of dilated cardiomyopathy (DCM) remain high and it is a leading cause of heart transplantation. Considering LV functional recovery is a pivotal process associated with better prognosis and a potential therapeutic target in DCM, a better understanding of myocardial tissue remodeling may be of great importance and inform a faster pathway for development of newer heart failure therapies.

Thirty patients (mean age; 49 years, 20 [67%] males) with recent-onset DCM and NYHA functional class ≥ II were enrolled onto a study protocol approved by our Institutional Review Board. A retrospective review of 14 patients with clinically ordered scans before and after optimal medical therapy and prospective data from 16 patients were analyzed in this study. A written informed consent or an opt-out informed consent was obtained from all study participants. All patients underwent CMR, coronary angiography and myocardial biopsy at baseline and follow-up CMR [11 months (IQR; 7-30)] after initiation of optimal medical therapy. Neuro-hormonal antagonists were introduced and up-titrated for every patient. No patients received ICD/CRT implantation before the follow-up imaging. Imaging was performed utilizing a 3T MR system incorporating cine MR, late gadolinium enhancement (LGE), and triple-slice T_1 mapping by MOLLI sequence. T_1 measurements were performed on the septal myocardium at the mid-ventricular level without LGE enhancement. LGE volume was measured using the full-width at half-maximum method. Biopsy samples were stained with picrosirius red to determine collagen volume fraction (CVF). A paired Student`s t-test or Wilcoxon sign-rank test were used, as appropriate, to compare continuous variables at baseline and follow-up. Pearson`s or Spearman`s correlation coefficient was used to examine possible relationships among LV function, histological CVF and CMR T_1 mapping findings. Intra- and inter-observer reliability of native T_1 measurements were assessed with the intraclass correlation coefficient (ICC). All tests

were 2-sided and p-values <0.05 were considered significant.

Figure 1A depicts representative cases with and without LV functional recovery. Native T_1 decreased from 1376 ± 55 ms to 1312 ± 78 ms after medical therapy (change of native T_1; -61 ± 60 ms, p<0.001), and 4/30 (13%) patients had no improvement at follow-up. The change of native T_1 after adjustment for baseline native T_1 moderately correlated with an absolute LVEF increase (r=-0.35, p=0.07) and relative percent decrease of indexed LVEDV (r=0.46, p=0.01) and LVESV (r=0.46, p=0.01) (**Figure 1B**). Each 5 percentage decrease in native T_1 was associated with a 12% and 17% reduction in indexed LVEDV and LVESV, respectively. The change of native T_1 was not associated with baseline native T_1, while it trended to be lower in patients with LGE (p=0.13). In addition, native T_1 and extracellular volume fraction (ECV) at baseline similarly and moderately correlated with absolute LVEF increase (r=-0.54, -0.52, respectively, both p<0.05) and relative percent decrease of indexed LVEDV (r=0.44, 0.42, respectively, both p<0.05) and LVESV (r=0.52, 0.51, respectively, both p<0.05), while histological CVF correlated with none of them (r=-0.31, 0.13, 0.26). LGE was observed in 19/30 (63%) patients. The extent of LGE, but not the presence or location of LGE, was associated with the prevalence of LV functional recovery (p=0.01). None of the 6 patients with LGE volume ≥5.0% had LV functional recovery. The ICCs for inter-observer and intra-observer measurements of native T_1 were 0.94 (95% CI: 0.88 to 0.97) and 0.97 (95% CI: 0.94 to 0.99), respectively.

We found that 26/30 (87%) patients showed a decrease in native T_1 between baseline and follow-up, and patients with a greater reduction in native T_1 displayed greater improvements in LVEF and more substantial reductions of indexed LVEDV and LVESV. In a study by Díez et al., some angiotensin receptor blockers (ARBs), such as losartan, induced regression of myocardial

fibrosis in hypertensive patients.[1] Thus, these differences might be partially explained by regression of diffuse myocardial fibrosis after medical therapy. Actually, 82% (9/11) of patients receiving follow-up ECV assessment showed a decrease in ECV between baseline and follow-up, with an absolute ECV decrease of -2.3%. Studies have demonstrated that DCM is associated with microvascular dysfunction, which correlates with the degree of LV function. There is a close association between elevated native T_1 and myocardial ischemia in patients with coronary artery disease.[2] A decrease in native T_1 might also reflect improved microvascular dysfunction. Further studies are needed to confirm what a decrease in native T_1 after medical therapy means and how best to use it in clinical practice. Given the high reproducibility of T_1 assessment, serial native T_1 assessment would enable the cardiologist to adopt a more tailored approach, allowing closer follow-up and more rapid escalation of therapy for patients at higher risk for progressive LV dilatation and LVEF decline and vice versa for those at lower risk.

References

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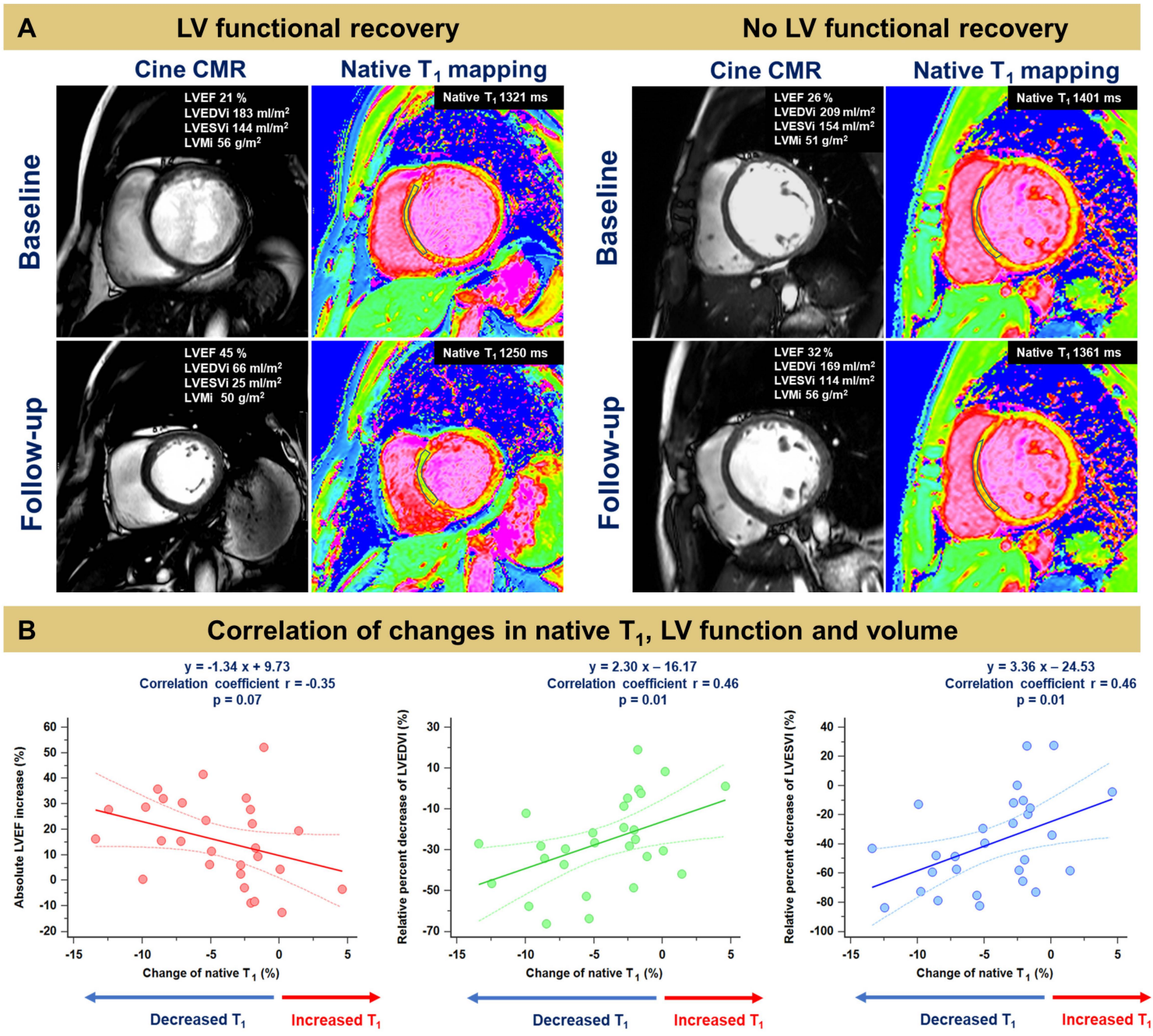
Figure legend

Figure 1: Changes in myocardial native T_1, LV function and volume after optimal medical therapy: (A) A 49-year-old male with idiopathic dilated cardiomyopathy. Cine MR showed severely reduced LVEF with severe LV cavity dilatation, while native T_1 and ECV mapping demonstrated high normal native T_1 of 1321 ms and slightly increased ECV of 34%, with a small amount of LGE in the inferior wall (ECV and LGE figures not provided). After medical therapy, this case revealed improved LVEF accompanied by a decrease in LV cavity size. Also, there was a significant decrease in native T_1 (-5.4%) at the follow-up scan (left panels). A 30-year-old male with toxic or idiopathic dilated cardiomyopathy. The native T_1 and ECV examples corresponded to 1401 ms and 38%, both of which were significantly elevated despite no LGE on LGE CMR (ECV and LGE figures not provided). Follow-up native T_1 mapping demonstrated only a small reduction in native T_1 (-2.8%), and no LV functional recovery was observed (right panels). (B) Correlation of changes in myocardial native T_1, LV function and volume.

ECV; extracellular volume fraction, LGE; late gadolinium enhancement, LVEDV; left ventricular end-diastolic volume, LVEF; left ventricular ejection fraction, LVESV; left ventricular end-systolic volume


A
LV functional recovery
No LV functional recovery
Cine CMR
Native T1 mapping
Cine CMR
Native T1 mapping
Baseline
Follow-up
Baseline
Follow-up
LVEF 21 %
LVEDVi 183 ml/m²
LVESVi 144 ml/m²
LVMi 56 g/m²
Native T1 1321 ms
LVEF 45 %
LVEDVi 66 ml/m²
LVESVi 25 ml/m²
LVMi 50 g/m²
Native T1 1250 ms
LVEF 26 %
LVEDVi 209 ml/m²
LVESVi 154 ml/m²
LVMi 51 g/m²
Native T1 1401 ms
LVEF 32 %
LVEDVi 169 ml/m²
LVESVi 114 ml/m²
LVMi 56 g/m²
Native T1 1361 ms
B
Correlation of changes in native T1, LV function and volume
y = -1.34 x + 9.73
Correlation coefficient r = -0.35
p = 0.07
Absolute LVEF increase (%)
Change of native T1 (%)
Decreased T1
Increased T1
y = 2.30 x – 16.17
Correlation coefficient r = 0.46
p = 0.01
Relative percent decrease of LVEDVI (%)
Change of native T1 (%)
Decreased T1
Increased T1
y = 3.36 x – 24.53
Correlation coefficient r = 0.46
p = 0.01
Relative percent decrease of LVESVI (%)
Change of native T1 (%)
Decreased T1
Increased T1