Quantitative assessment of left ventricular tissue relaxometry and dynamics in human heart transplant recipients in a Gold Standard comparison: a preliminary study

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Introduction: Orthotopic heart transplantation is regularly used as a final treatment for patients with severe heart failure. These patients need to be carefully monitored, as acute rejection of the graft can result in a loss of function. Histological reading of endomyocardial biopsy (EMB) remains the Gold Standard method for detection of rejection and monitoring of the immunosuppressive therapy, despite the invasiveness of the procedure. As an alternative, the measurement of T_2 relaxation times has been suggested for detection of graft rejection, as the T_2 values increase with inflammation [1]. While such T_2 measurements may provide information about regional changes in tissue characteristics, these are often accompanied or even preceded by more global alterations in myocardial motion patterns. In fact, transient changes in left ventricular twist mechanics as a function of rejection have been documented in earlier studies using invasive techniques in conjunction with x-ray measurements of radio opaque markers screwed into the epicardium [2]. However, a powerful alternative technique that is non-invasive and operates without ionizing radiation is myocardial tagging [3,4]. Because of the non-invasiveness of this technique, it has already been used to document the loss of function in cardiac graft rejection [5]: abnormalities could be detected in the circumferential strain values as rejection appears. As both myocardial tagging and T_2 mapping have proven to be highly reproducible [6,7], they lend themselves extremely well as a non-invasive, quantitative tool for longitudinal studies in heart transplant recipients who serve as their own controls. For these reasons, and since MRI can easily and safely be repeated, we investigated the feasibility of monitoring the evolution of graft rejection in heart transplant patients with T_2 mapping and MR myocardial tagging while biopsy served as the Gold Standard.

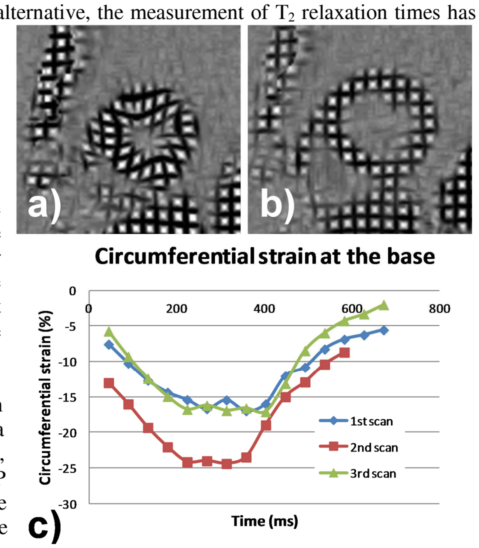

Figure 1. CSPAMM images and strain measurements. **a)** and **b)** Tagged images in a patient at end systole (a) and end diastole (b). **c)** Circumferential strain of a patient for all three scans obtained at the base of the left ventricle. The first curve in blue shows the strain measured during the first scan, with moderate rejection (grade 2R). The red curve represents the second scan after therapy. The biopsy found no rejection (grade 0R), which might explain the differences in strain values. The green curve shows the third scan in the same patient. The biopsy was performed 2 weeks later, showing moderate rejection (grade 2R).

Methods: Approval was obtained from the institutional review board. Four heart transplant recipients were each scanned 3 times over 6 months on three short-axis levels (basal, mid-ventricular and apical) using both a prototype navigator-gated ECG-triggered radial gradient-recalled-echo T_2 mapping [6] (resolution $1.17mm^2$, matrix 256^2, 20 lines per heartbeat, ECG trigger every 3 heartbeats) and a prototype slice-followed (SF) bSSFP breath-held CSPAMM tagging sequence [8] at 3T (MAGNETOM Verio, Siemens, Erlangen, Germany). Three T_2-map source images were acquired with T_2 preparation times of 0, 30 and 60 ms. The resulting T_2 maps were segmented according to AHA guidelines [9]. The SF CSPAMM acquisitions (resolution $3.6x1.2mm^2$, slice thickness 8mm, matrix 82x256, temporal resolution 45ms) were analyzed with Harmonic Phase Imaging [10] (HARP, v4.1, Diagnosoft Inc., Palo Alto, CA, USA) to obtain circumferential strain and rotation for all slices and scans. Myocardial biopsies [11] were obtained in each patient for Gold Standard comparison. Circumferential strain and T_2 values were compared over time and with the results from biopsy (rejection grade 0R-3R, with 0R being no rejection and 3R severe rejection). Student's t-tests were performed to ascertain whether there was a difference in T_2 as a function of time after transplantation.

Results: All scans were successful and well tolerated by the patients. In the patients without rejection (grade 0R), T_2 values were similar to those previously reported in healthy volunteers [4] (T_2=42.7±4.0ms). A significant elevation in the myocardial T_2 value was observed in a case of moderate rejection by biopsy (grade 2R): T_2 values increased by 28% from 34.8±1.2ms at baseline without rejection to 44.8±2.2ms with moderate rejection in the apical slice ($p<0.002$). Strain measurements showed similar results to those commonly found in healthy volunteers (mean maximal strain value 15±4.4% in patients versus 16.4±3.2% in healthy volunteers [6]). One patient showed differences in strain values after therapy (figure 1.c)) (from grade 2R for the first scan in blue to 0R for the second in red). Rotation measurements demonstrated counterclockwise rotation at the base and clockwise rotation in the apex, as has been observed in healthy volunteers, too [6].

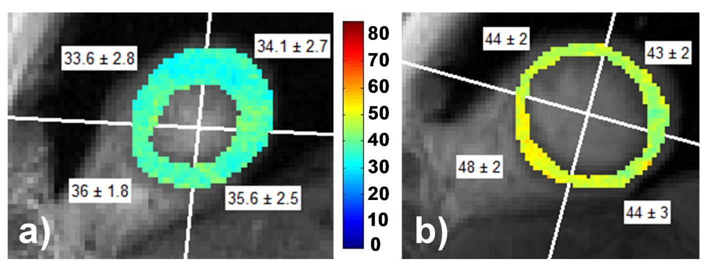

Figure 2. Example of a segmented T_2map in a patient in an apical slice. The color bar indicates the T_2 values in ms. **a)** T_2 map with no rejection by EMB, the T_2 values are homogenous, although a bit lower than what can usually be found in healthy adults. **b)** Second scan in the same patient. The T_2 values are significantly increased with moderate rejection (grade 2R) on EMB.

Discussion and conclusion: This preliminary study demonstrates that it is feasible to evaluate and follow the T_2 relaxation time and dynamics of the left ventricle in heart transplant patients over time. Monitoring the evolution of the T_2 values and the strain measurements allows us to generate patient-specific reference values, and alterations thereof on an individual basis. This may ultimately help to avoid biopsy and to better monitor and guide therapy with the goal of adjusting the dosage of immunosuppressive drugs for each individual patient. Although no major difference in circumferential strain was detected, all patients showed strain values that suggest normal contractility of the left ventricle. More patient scans will be needed to define the link and the temporal relationship between strain values and rejection by biopsy. In general, probing local tissue properties and local myocardial mechanics may lead to complementary regional information that is not easily obtained with biopsy, which suffers from a sampling problem. Thus, the combination of T_2 mapping and measures of myocardial mechanics may provide a unique opportunity for probing the health of a transplanted heart over time.

References: **1.** Marie et al., JACC 2001 1;37(3):825-31, **2.** Ingels et al., Circulation. 1980 61(5):966-72, **3.** Zerhouni EA et al., Rad 1988; 169:59-63, **4.** Axel L et al., Rad 1989;171:841-845, **5.** Donofrio et al., Am J Physiol. 1999; 277(5 Pt 2):R1481-7, **6.** Swoboda et al., JMRI 2014, **7.** van Heeswijk et al., JACCCardiovImag 2012; 5(12):1231, **8.** Feliciano et al., ISMRM 2013, **9.** Cerqueira et al.; Circulation 2002;105:539, **10.** Osman NF et al., MRM 1999; 42:1042-1060, **11.** Tan et al., ArchPatholLabMed. 2007 131(8):1169-91.