# RETROSPECTIVE-GATING MYOCARDIAL T1 MAPPING IN RATS WITH DOXORUBICIN CARDIOMYOPATHY

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**Abstract**: In vivo $T_1$ mapping of rat myocardium can be challenging given to the high heart and respiratory rate and small size of the heart. We propose a new method for in vivo $T_1$ estimation based on retrospectively gated inversion-recovery fast low-angle shot (IR FLASH) pulse sequence. The method was tested on an animal model of dilated cardiomyopathy. The T1 estimates were mostly in line with the effects of doxorubicin and estradiol described in literature.

**Keywords**: $T_1$ mapping, CMR, doxorubicin, dilated cardiomyopathy, postprocessing gating

## 1. INTRODUCTION

The longitudinal relaxation time $T_1$ of a tissue indicates how fast protons recover after an excitation radio-frequency pulse. The $T_1$ value within the myocardium is altered in various disease states due to increased water content or other changes of the local molecular environment. Changes in both native $T_1$ and $T_1$ following administration of gadolinium (Gd) based contrast agents are considered important biomarkers [1]. Nevertheless, in vivo imaging of animal models can be challenging due to a rapid heart beat and respiration and due to a small size of the heart. Fairly few methods have been introduced for in vivo $T_1$ mapping of myocardium in small animal models. They are based on the Look-Locker inversion recovery acquisition [3, 2] and the variable-flip-angle method [4]. The disadvantage of the Look-Locker inversion recovery methods is their dependence on a good quality of the ECG related to their prospective-gating character. The variable-flip-angle methods can use retrospective gating which avoids deterioration due to noisy ECG, however they suffer from long acquisition time and they are sensitive to the imperfections of the excitation radio-frequency pulse[4, 5]. In this contribution, a new method for $T_1$ quantification is proposed which provides advantages of both retrospective gating and fast acquisition time. It is based on inversion recovery fast low-angle shot (IR FLASH) pulse sequence.

The method was applied and validated in a doxorubicin study. Doxorubicin cardiomyopathy is a serious adverse effect occurring when doxorubicin is used as a chemotherapeutic agent in oncology. It is manifested as diffuse myocardial fibrosis which is known to affect native and post contrast $T_1$ [1].

## 2. METHODS

### 2.1. $T_1$ MAPPING

The acquisition method is based on the IR FLASH pulse sequence. Nonselective adiabatic inversion pulse is applied immediately after a respiration trigger. It is followed by 1000 FLASH excitation/acquisition cycles (TR=4 ms). Every second TR cycle has a zero-size phase encoding pulse and is used as a navigator. Phase encoding of the remaining TR cycles is fixed to the same value corresponding to the given IR pulse. Hence, the number of IR pulses corresponds to the number of phase

encoding steps (here 128). The repetition time of IR pulses is 5000 ms. The acquisition time of the sequence is approximately 11 minutes. [6]

Following the acquisition, images for various TI values are reconstructed (implemeted in Matlab, Mathworks, Natick, MA, USA). From the mean values of each navigator echo, a heart-motion signal is created for each phase-encoding step. It is then band-pass filtered to discard frequency bands out of the presumed heart rate. This quasi-harmonic heart-motion signal is then used for determination of the phase of the cardiac cycle. Only echoes acquired at local maxima and minima of the heart-motion signal are selected, representing two heart-cycle phases – systole and diastole. The echoes of maxima and minima are then linked together to form k-space data for both local maxima and minima and for each TI interval. An image is then reconstructed with TI being the mean TI of all phase-encoding-step echoes. By visual inspection, diastolic phase images (corresponding to local optima or minima of the heart-motion signal depending on TI and its location on the global $T_1$ recovery curve) are selected and images degraded by respiratory-motion are discarded. For our setup, this resulted in 10-20 images with different TI values (200 – 4000 ms). These image sets are then used for pixel-by-pixel $T_1$ estimation according to [6]:

$$S_\theta(TI) = k\rho(1 - 2 \cdot e^{-\frac{TI}{T_1}}), \tag{1}$$

where $S_\theta$(TI) is the acquired signal and $\theta = \{k\rho, T_1\}$. To obtain $\theta$, least-square approximator using Equation 1 is applied (as implemented in the Matlab Optimization Toolbox).

### 2.2. Study design and MR protocol

The doxorubicin study included eighteen female Wistar healthy rats (250-300 g) divided into two groups. The first group of animals (N=9) received a weekly dose of doxorubicin (2.5 mg/kg/week) intraperitoneally for six weeks. The second group (N=9) received the same dose of doxorubicin and moreover a dose of estradiol (agofolin, 5$\mu$g/week per toto) subcutaneously. In both groups the age of the animals was 10 weeks when the administration was started. Animals were scheduled to undergo MRI examinations at baseline and then again 18 weeks after weekly receipt of doxorubicin (and estradiol). Rats were anesthetized with isoflurane and placed on a surface coil with heart centered on the coil. A respiratory sensor and a rectal temperature probe (SA Instruments, Stony Brook, NY, USA) were applied for monitoring of the animal's state. The body temperature was kept at 36.5$\pm$1.5°C throughout the experiment. All experiments were in accordance with national legislature.

All imaging was performed on a 9.4T NMR system (Bruker-Biospec 94/30 USR). FLASH IntraGate was used for scout imaging. Three sets of anatomical images in long axis, short axis and four-chamber view were acquired. Images for $T_1$ mapping were acquired using the retrospectively gated IR FLASH sequence described above. The slice was positioned in the middle of the left ventricle in the short axis view. The field of view was 4$\times$4 cm – 6$\times$6 cm, depending on the size and position of the heart, the slice thickness was 1.0 mm. A bolus of Gd-based contrast agent Magnevist (Bayer HealthCare Pharmaceuticals Inc., Berlin, Germany) was administrated intravenously via the tail vein (dose a 0.02 mmol/kg of body weight) followed by 0.2 mL of saline per toto. Approximately thirty minutes after the contrast injection images for post contrast $T_1$ mapping were obtained using the same sequence.

### 2.3. Statistical analysis

For statistical analysis a region of interest (ROI) was drawn manually for each $T_1$ map in the left ventricle wall as shown in Figure 1. The results are expressed as mean value $\pm$ standard deviation in Table 1. During the experiment eight rats had died due to the doxorubicin treatment. One rat was excluded from the experiment due to artifacts from an incorrectly placed identification microchip.

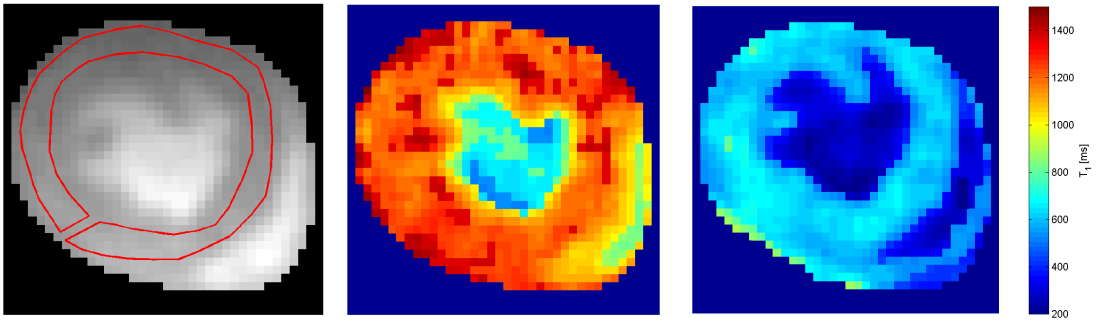


**Figure 1:** Left: A mean image from all the TI images of rat number 04 examined on the 18th week after the doxorubicin treatment. Center: A native (pre contrast) $T_1$ map. Right: A post contrast $T_1$ map.

| | baseline | | 18th week | | |
|---|---|---|---|---|---|
| Rat No. | native $T_1$ | post contrast $T_1$ | native $T_1$ | post contrast $T_1$ | estradiol |
| 01 | 1242 ± 60 | 1125 ± 60 | 1380 ± 45 | 749 ±35 | 1 |
| 02 | 1263 ± 30 | 986 ± 67 | 1438 ±141 | - | 1 |
| 03 | 1157 ± 84 | 1010 ± 79 | 1372 ± 56 | 795 ±130 | 1 |
| 04 | 1180 ± 39 | 988 ± 45 | 1235 ± 72 | 612 ± 60 | 1 |
| 05 | 1158 ± 51 | 1081 ± 53 | 1216 ±111 | 1108 ±314 | 0 |
| 06 | 1200 ± 13 | 986 ± 52 | 1460 ± 78 | 1088 ± 45 | 0 |
| 07 | 1212 ±113 | 887 ± 82 | 1207 ± 82 | 911 ± 70 | 0 |
| 08 | 1317 ±158 | 1036 ± 214 | 1307 ± 54 | 1062 ± 58 | 0 |
| 09 | 1180 ± 39 | 988 ± 45 | 1244 ± 72 | 1125 ±165 | 0 |

**Table 1:** Outcomes of the $T_1$ estimation for the nine rats at the baseline and at the 18th week after receipt of weekly dose of DOX. In the column "estradiol" the receipt of estradiol is determined, number 1 marks rat with estradiol dosages. All $T_1$ values are in ms.

For rat number 02 at examination after 18 weeks of treatment, the contrast agent administration was not successful, so only a native $T_1$ is stated for this case.

The mean values were imported to the Satistica software (Dell software, Tulsa, Oklahoma, USA). The data were not normally distributed thus the non-parametric tests were applied. All analyzes that examined changes before and after the contrast agent bolus and before and after the doxorubicin treatment were evaluated using Wilcoxon matched pairs test. To asses the effects of estradiol administration on native and post contrast $T_1$, the Mann-Whitney U test was performed.

## 3. RESULTS

Figure 1 shows the example of $T_1$ maps estimated by our method. In Table 1 the ROI mean value for each animal is stated. At baseline (before the doxorubicin treatment), the $T_1$ estimates of all animals were similar and both the native and post contrast $T_1$ were consistent. The mean value of native and post contrast $T_1$ at baseline overall both groups was 1212±53 ms and 1009±67 ms respectively. We

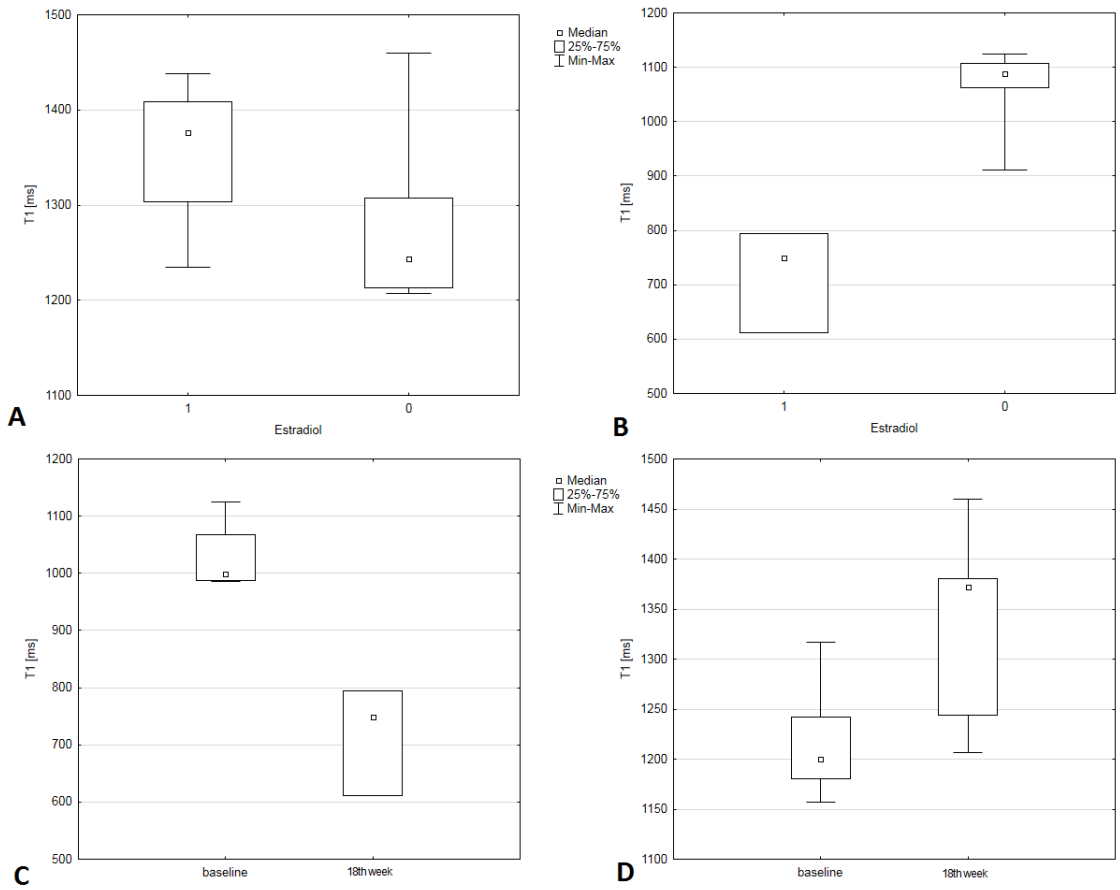


**Figure 2:** A: Box and whiskers plot by group for the native $T_1$ at the 18th week, p=0.2. B: Box and whiskers plot by group for the post contrast $T_1$ at the 18th week, p=0.02. C: Box and whiskers plot for the group with estradiol administration, post contrast $T_1$ at the baseline and at the 18th week, p=0.054. D: Box and whiskers plot for both groups, native $T_1$ at the baseline and at the 18th week, p=0.01.

observed a statistically significant decrease in the $T_1$ value after the contrast agent was administrated (p=0.004). There was no significant change between the group with estradiol administration and without in the native $T_1$ at the 18th week as seen in Figure 2 A. Given that fact we evaluated the changes in native $T_1$ for the whole population. Relative to the baseline, there was an increase of the native $T_1$ at the 18th week (p=0.01) (Figure 2 D). As shown in Figure 2 B, we observed a significant difference between groups with and without estradiol in the post contrast $T_1$ at the 18th week (p=0.02). In the group with estradiol treatment the post contrast $T_1$ decreased at the 18th week when collated with the baseline (p=0.054) as seen in Figure 2 C. We observed a significant increase in the post contrast $T_1$ between the baseline and the measurement at the 18th week (p=0.01).

## 4. DISCUSSION AND CONCLUSIONS

In this work, a fast IR FLASH method with retrospective gating for in vivo $T_1$ mapping of rat myocardium was introduced and tested on a rat doxorubicin study. The observed increase in native $T_1$ due to doxorubicin treatment is in line with literature [7]. This increase can be explained by increased water content and increased concentration of collagen macromolecules in diffuse myocardial fibrosis [1]. Also the observed decrease of post contrast $T_1$ in the group with estradiol dosage (although not

significant) is in accordance to literature and can be explained by elevated extracellular space in a fibrotic tissue, hence higher content of extravased contrast agent leading to a more pronounced shortening of $T_1$. The significant increase of the post contrast $T_1$ in the group without estradiol dosage was not expected. This might be due to unknown biological effects which could be revealed by histology (which was missing in this study). Another reason could be insufficient accuracy and precision of our $T_1$ estimation method in combination with a small number of the animals in the study. One source of errors was the inconsistency in the time between the contrast agent administration and acquisition for T1-quantification image data (the deviation of about 5 minutes).

Our hypothesis is that the administration of estradiol is affecting the effect of doxorubicin treatment and is increasing the cardiotoxicity. The significant difference at post contrast $T_1$ between group with estradiol administration and without supports this hypothesis. However, no histopathology analysis was conducted to confirm this theory.

To draw stronger conclusions, more animals will be included in the study. In addition, the pulse sequence will be further modified to acquire a navigator signal following each excitation. This will enable us to double the TI sampling and hence increase the robustness of the estimation algorithm.

## ACKNOWLEDGEMENT

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