Comparison of the region-based and pixel-wise methods for cardiac T2* analysis in 50 transfusion-dependent Thai Thalassemia patients

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Introduction: Cardiac T2* measurement is currently a crucial tool for clinicians to monitor myocardial iron overload in Thalassemia patients [1]. Since cardiac related mortality is the leading cause of death in patients with transfusion-dependent thalassemia, there has been an urgent need to develop and validate the T2* measurement worldwide. The measurement can be separated into the acquisition and analysis parts. The recent acquisition method, namely the black- and bright-blood techniques, provides more precise and reliable measurement with less motion artifact and mis-spatial-registration with in a single breath hold time [2]. Such the improvement makes the point-by-point (Pixel-Wise: PW) analysis feasible to implement providing more important information about the T2* distribution and heterogeneity, which are not available in the previous averaging (Region-Based: RB) analysis. These two techniques are often in good agreement [3] but may deviate when susceptibility artifacts project into the interventricular septum. RB techniques typically include these artifacts while PW approaches can identify and exclude them [3]. Currently both RB and PW methods have been widely utilized for routine clinical evaluation and international multi-center clinical trials on iron chelation therapy, nevertheless, the intra- and inter-observer variabilities have not been well studied. We hypothesized that PW techniques would outperform RB approaches, particularly if median T2* value were used in place of the arithmetic mean of the PW distributions.

Materials and Methods: Fifty thalassemia major patients (24 males and 26 females, age 17.5 ± 5.9 years) who received regular transfusion and iron chelation therapy as well as aged ≥ 10 years with serum ferritin levels > 1000 ng/ml were enrolled for the study. The images were acquired on a 1.5T Philips Achieva XR system using a cardiac phased-array coil. Short axis bright- and black-blood sequences were acquired and analyzed using the RB and PW methods. An in-house software developed with MATLAB software tool was implemented for the analysis. Regions were defined, manually, using the whole septum (WS) as in the conventional RB method (WS-RB) or partial septum (PS) utilizing color-map information for the PW method to avoid region of susceptibility and motion artifact. From the same PS region, results were reported by mean (PS-PW) and median (MPS-PW). Intra- and Inter-observer variability was investigated on all data set by two independent observers blinded to the result. Bland-Altman plot was employed to analyze the agreement between two different T2* data sets. Bias was assessed using one-sample t-test and coefficient of variation (CV). The Kolmogorov-Smirnov test was used to test of standard normal distribution of T2* values from PW method. A measurement of the skewness (asymmetry of the data around the sample mean) and kurtosis (a measure of the effect of outlier to a distribution) were examined on the T2* distributions calculated from the PW method.

Results: An example of cardiac images with T2* color-map from PW method obtained from a thalassemia patient was displayed on Figure 1 for both the bright- and black-blood images (upper and lower rows, respectively). Figure 2 shows an example of cardiac images and T2* color-map overlaid with ROIs from WS (the green lines) and PS (the blue lines) regions. All T2* value distributions from the PS regions of all patients on both scanning techniques were not normally distributed according to the Kolmogorov-Smirnov test at the 5% significant level. Additionally, the means of skewness and kurtosis of the T2* in the PS region of the bright-blood technique were 1.1 ± 0.9 and 3.0 ± 4.5, respectively as well as 0.48 ± 0.54 and 0.55 ± 1.96 for the black-blood technique. These data suggest that the distribution of T2* values tend to skew to the right on both techniques and were more outlier-prone on the bright- than the black-blood technique. The T2* values from the PS-PW and MPS-PW methods were comparable to the conventional WS-RB method on both scanning techniques. When comparing the inter-observer variability from the WS-RB to the PS-PW method, the CV of the PS-PW method was equivalent (4.5% vs 4.7%, p = NS) for the bright-blood technique (Figure 3), but 31% lower (4.0% vs 2.8%, p=0.21) for the black-blood technique. The proposed MPS-PW method performed even better with respect to the conventional WS-RB method, decreasing inter-observer CV by 24% (4.5% vs 3.5%, p=0.08) and 42% (4.0% vs 2.4%, p=0.02), respectively. Intra-observer reproducibility followed the same trend.

Discussion and Conclusion: Reproducibility measurements for WS-RB methods were comparable to previously published results, with inter-observer CV of 4.0% vs 4.1% for black blood and 4.5% vs 7.8% for white blood [4]. The improved bright-blood result in the study could be attributed to the optimal scanning parameters, improved image quality, or better observer training as recently shown [5]. Reproducibility was significantly improved (31%) in the black blood images when PW methods were employed. The lower CV most likely results from exclusion of high T2* values caused by the partial volume effect of blood and myocardium signal at the edge of myocardium (the bright green region in Figure 2C, F). Such a reduction can be achieved due to the prior knowledge of T2* distribution (from the PW method) employed to guide the ROI drawing (the PS region), but such information was not available in the RB method so the analyses have to done from the WS region, instead. Such a lower of reproducibility of the PW to RB method also had been reported on a T2* liver study [6]. Although the PS region can be used to reduce the partial volume effect on the T2* values, the CV in the bright-blood technique was no better than conventional RB techniques. Such the higher CV could be due to the spurious T2* values inside the interventricular septum caused by the flow artifact inherited from the technique (as clearly shown in Figure 1C as the green or yellow dots inside the interventricular septum). Such spurious values cause the mean T2* values to be more outlier-prone which can be reduced by using the median of the T2* distribution as in the PS-MPS method. In summary, the CV of the inter-observer from the proposed MPS-PW method was lower, as compared to the conventional WS-RB method, by 24% and 42% in the bright- and black-blood techniques, respectively. The intra-observer studies in this study also presented the same trend as in the inter-observer studies. The MPS-PW method, therefore, provided lower observer variability as compared to the conventional WS-RB or PS-PW methods.
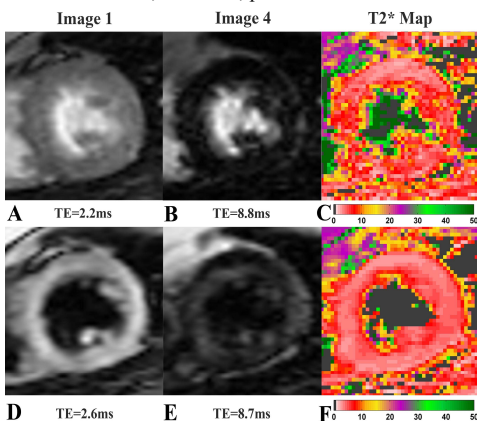

Figure 1. Example of cardiac images and T2* color-map from a severe iron overload Thalassemia patient.
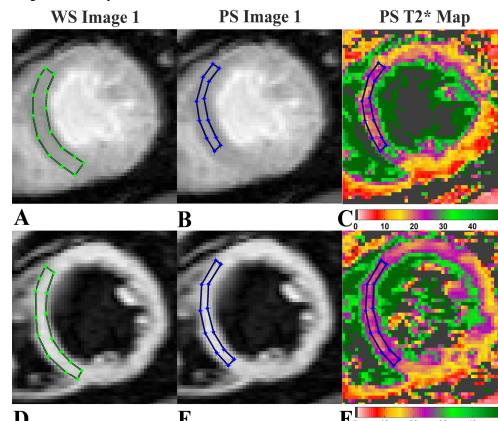
Figure 2. Cardiac images and T2* color-map with ROIs of the WS (the green lines) and PS (the blue lines) regions
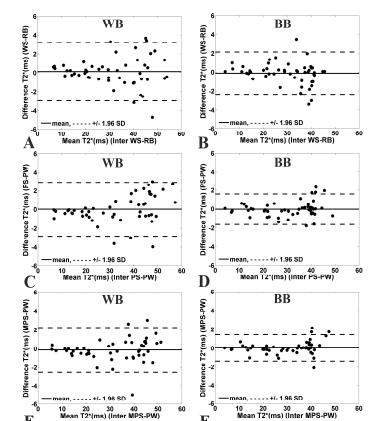
Figure 3. Bland-Altman plots of T2* values assess inter-study reproducibility.

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