Is Otsu Thresholding the Answer to Reproducible Quantification of Left Atrial Scar from Late Gadolinium-Enhancement MRI?

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September 11, 2020

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Word count: 997

Grant Support: This work was supported in part by funding from the National Institutes of Health (R01HL116895, R01HL138578, R21EB024315, R21AG055954, R01HL151079, R01HL151079) and American Heart Association (19IPLOI34760317)

None of the authors have relationships with industry related to this study

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults[1]. Catheter ablation targeting the pulmonary veins and other atrial sites has emerged as the best intervention for restoring and maintaining sinus rhythm; however, 1-year success rates are only 60-70% or even lower for more persistent types of AF[2,3]. These statistics highlight an unmet clinical need to avoid an unnecessary procedure for expected non-responders (30-40%) or consider a more extensive ablative or surgical approach. Potential predictors of AF recurrence post-ablation derived from standard clinical and imaging metrics have proven to be of limited use. Left atrial (LA) fibrosis is more promising, because fibrosis plays a central role in the development of an arrhythmogenic substrate for AF and may be a marker for more extensive disease that is less amenable to standard pulmonary vein isolation (PVI)[4-8]. In fact, LA fibrosis assessed with 3D LA late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR)[9], pioneered by the Utah group, has shown promise for predicting AF recurrence post-ablation[10-16]. However, LA fibrosis quantification has garnered skepticism from the field because it has not been independently reproduced. This lack of reproducibility stems from two fundamental methodologic deficiencies of (1) data acquisition limitations: inadequate spatial resolution (1.5 mm x 1.5 mm x 2.5 to 5 mm)[9,17-21], contrast-to-noise ratio, and lengthy scan time (11-15 min), and (2) unreliable image analysis techniques: no robust method for quantifying of fibrosis in the thin (˜ 2 mm) LA wall. These deficiencies preclude widespread adoption of LA fibrosis quantification in clinical practice.

Currently, there is no standardized method for quantifying LA fibrosis or scar from LGE images. Existing analysis tools include standard deviation (SD) above the mean LA wall signal[11,22], SD above the blood pool (BP)[23,24], image intensity ratio (IIR)[19,20], and visual assessment[9,25]. Regrettably, the performance of these threshold-based methods varies among different groups and lacks independent evaluation. In this issue, Kamali et. al. conducted a study to identify which LA scar quantification methods is most reproducible. They do this by quantifying LA scar using different quantification methods from two post-ablation LGE CMR scans performed three months apart, while assuming that LA scarring remains the same between those two time points. The authors performed a retrospective study of patients who underwent AF radiofrequency ablation between May 2007 to August 2017, and found 45 patients who underwent consecutive post-ablation LGE CMR scans 3 months apart, first scan 120 $\pm$ 65 days post-ablation and the second scan 162 $\pm$ 98 days post first scan. They used a previously published pulse sequence[26] to acquire their LGE images that had a voxel size of 1.25 mm x 1.25 x 2.5 mm and was interpolated to 0.625 mm x 0.625 mm x 1.25 mm. Full LA segmentation from the LGE imaging was performed by trained raters using previously published methods[26,27]. From the LA wall intensities, outliers were removed, and the histograms were normalized with intensity values ranging from 0 to 1.

To determine areas of scar, the researchers performed four different methods: (1) simple thresholding (from 60^{th} to 90^{th} percentile), (2) Otsu thresholding[28,29], (3) 3.3 SD above mean BP[30], and (4) IIR > 1.61[20]. The authors studied two methods that used LA wall intensity (simple thresholding and Otsu thresholding) and two methods that used BP normalization (SD above BP and IIR). LA wall segmentation was registered between the first and second scan. After registration, a cut-off distance of 1.25 mm was used for comparing scar and healthy tissue voxels and Dice Similarity Coefficient (DSC) was computed to determine the level of agreement.

The authors determined that the normalized histograms for LA wall intensity was very closely correlated between the first and second scans, regardless of scanner's magnetic field strength. They calculated DSC for the different scan quantification methods and found the following results: Otsu thresholding = 71.3 $\pm$ 8.3, 3.3 SD above BP mean = 57.8 $\pm$ 21.2, and IIR > 1.61 = 45.8 $\pm$ 29.5, indicating that Otsu thresholding was significantly better than BP based methods. In addition, for all scanner type based groups, DSC for the intensity distribution was mostly flat until the 70th percentile and then increased progressively for higher deciles. Based on their results, the authors concluded three main points. First, they determined that for RF ablation, atrial scar quantification is highly reproducible from one scan to the next over a three-month span. Second, they found the reproducibility of LGE CMR for thresholds less than the 70th percentile of the wall intensity distribution is no better than the reproducibility of a random distribution. And finally, LA wall intensity-based quantification methods are more reproducible than BP based methods.

While this study systematically compared four different methods for quantification of LA scar, there are several limitations that warrant further discussion. First, the small sample size of 45 patients limits statistical significance. Second, several patients were excluded because of poor image quality, which brings into question a bias in patient selection. There are numerous factors that may influence LA intensity based thresholding, including spatial resolution, appropriate inversion time to null the normal myocardium, and image artifacts induced by cardiac and respiratory motion. Variations in such factors are likely to influence LA scar quantification. Third, the two post-ablation CMR exams were approximately 3 months apart, and there is a possibility of remodeling in both scarred and normal wall between those time points. Thus, readers ought to interpret reproducibility results with these caveats.

Is Otsu thresholding capable of producing a moderate DSC of 71.3 the answer to reproducible quantification of left atrial scar from LGE MRI? It is our opinion that the search must continue to establish more reproducible analysis methods, perhaps involving artificial intelligence. In conclusion, the study by Kamali et. al. is a strong reminder that LA scar or fibrosis quantification is an active area of research that warrants further investigation. If a robust LA fibrosis or scar quantification method is established, then it will be extremely beneficial for future studies to understand AF and its treatment to improve patient outcomes.

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