Left Atrial Fibrosis by Late Gadolinium Enhancement Cardiovascular Magnetic Resonance Predicts Recurrence of Atrial Fibrillation After Pulmonary Vein Isolation Do You See What I See?

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Atrial fibrillation (AF) is the most common sustained arrhythmia with 3 to 6 million currently afflicted and the prevalence expected to double by 2050. AF carries an increased risk of cardiovascular morbidity and mortality driven largely by increased risk of stroke and congestive heart failure. Management of AF represents a significant and growing healthcare burden, with an estimated cost of $6.65 billion in 2005 and likely doubling by 2020.

The advent of catheter-based therapies for rhythm management of AF has revolutionized the electrophysiological field and provides a less invasive approach similar to the surgical Maze procedure goals. Pulmonary vein isolation (PVI), the most commonly used catheter-based technique, aims to electrically isolate the pulmonary veins, a major source of ectopy and provides a less invasive approach similar to the surgical Maze procedure. With the abundance of imaging already in use for these patients, there is great interest in identifying imaging-based biomarkers that predict long-term procedural success.

During the past decade, late gadolinium enhancement (LGE-CMR) has emerged as a well-established method for accurate and sensitive detection of left ventricular fibrosis in coronary artery disease and cardiomyopathies. Higher spatial resolution LGE-CMR was subsequently extended to identifying scarring/fibrosis in the wall of the LA and pulmonary vein ablation catheter after PVI. Studies suggest that quantification of post-PVI LA or pulmonary vein scarring may play a role in determining the risk of AF recurrence. Despite the obvious excitement of these findings, several challenges have emerged in the application of LGE-CMR to LA and PV tissue characterization. First is an issue of spatial resolution. The walls of the LA and PV are relatively thin (1–2 mm) and thus susceptible to partial volume effect from surrounding tissue (ie, blood, esophagus). This may lead to falsely characterizing adjacent areas of the LA and PV walls with LGE or fibrotic. Higher field strength and higher spatial resolution imaging have helped to address these issues, but challenges persist. Second, adjusting for cardiac motion is important for high-quality images of small, mobile structures. Imaging during atrial diastole, when atrial motion is at a minimum, may reduce cardiac motion–related artifact. Although electrocardiographic gating may be sufficient for patients in sinus

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rhythm, imaging in patients with AF is far more challenging. Respiratory motion artifacts, another bugaboo, can be addressed with either breath holding or respiratory gating. Finally, the quantitative analysis of LA and PV LGE remains a great challenge. Visual inspection for LGE remains the most common clinical approach, but lacks reproducibility. Grayscale signal intensity scaling or thresholding has helped improve reproducibility for the assessment of left ventricular scar/fibrosis.\textsuperscript{13} Thresholding often uses a semiautomated approach, which asks the user to define the region-of-interest, and then, through either user-determined cutoffs or pixel signal intensity histogram-derived cutoffs, automatically determines the number of pixels with a signal intensity above/below the cutoff value. By nature, this limits human visual error and is inherently more reproducible. However, grayscale thresholding is more susceptible to errors from imaging artifacts and noise and thus can often misrepresent the amount of scarring or fibrosis in a structure.\textsuperscript{14} Imaging a thin structure such as the LA wall, more prone to local artifact and noise, poses a challenge to current thresholding methods and thus remains to be well validated. Despite these challenges, visualization of postablation burns/scars of the LA and PVs is possible with adequate training, although the optimal method is not yet defined.\textsuperscript{15}

More recently, interest has migrated to using LGE-CMR to detect fibrosis of the LA that predates PVI, representing both the underlying AF substrate and as a marker of response to ensuing ablation therapy.\textsuperscript{16} The noninvasive identification of noniatrogenic or intrinsic LA fibrosis, although exciting, is an entirely different beast. Whereas ablation sites possess bright scar tissue (a healed burn) depicted by LGE-CMR, intrinsic fibrosis is much more subtle. Histopathologic studies suggest that atrial fibrosis exists and represents a degenerative process depicted by interstitial changes clearly appreciated by microscopy and staining.\textsuperscript{17}

The recent work by the experienced Utah group of McGann et al\textsuperscript{18} in this issue of \textit{Circulation: Arrhythmia and Electrophysiology} extends their previously published methodology of grayscale signal intensity LA LGE quantification to 386 patients before their first PVI. Composite data for each subject’s LA are categorized using the previously defined Utah structural remodeling (SRM) stages of LA wall LGE as stage I (<10% LA wall LGE), stage II (10%–20%), stage III (21%–30%), and stage IV (>30%). After a 90-day blanking period, patients were closely followed up with 8-day Holter monitoring at 3, 6, and 12 months. Subjects with Utah stage IV (>30% LA LGE) had a 71% chance of recurrent AF at 1 year. AF subjects with LGE-CMR Utah stages I, II, and III had similar levels of 1-year success. In principle, their results are intuitive and raise interest in the use of CMR as a preprocedural risk assessment tool. Intrinsic fibrosis may play a role in the genesis of AF and greater quantities, whether they are a function of aging, comorbidity, or genetics, may be a barrier to restoring sinus rhythm. Supportive of this concept are their correlations of LA LGE quantity with LA volume and the presence of persistent AF. Despite this initial optimism, there are concerns. The Kaplan–Meier rates of AF recurrence for Utah stages I, II, and III cluster together, suggesting a threshold relationship rather than a linear correlation between AF recurrence and LGE quantity. Although those with stage IV have a low rate of 1-year maintenance of sinus rhythm, they only represent 11% of the entire cohort. LA LGE-CMR scanning of all pre-PVI patients would thus lead to potential withholding PVI therapy for only a small minority of patients. The images presented in Figure 1A do not provide overwhelming confidence in the presence of LA wall LGE, despite the post-thresholding depiction shown in Figure 1C and 1D. Some of what is depicted as fibrosis may be artifact from the partial volume effect of enhanced surrounding tissue and blood pool as the line thickness circumscribing the LA in Figure 1B appears to be thicker than the LA wall. Nevertheless, an important component of their study is the histopathologic correlation of LA LGE and histological collagen on biopsy in 10 subjects.

The details of the grayscale signal intensity thresholding used to identify LGE amount are also important to discuss and was previously published by Oakes et al.\textsuperscript{16} On paper, this seems straightforward, but one needs to be prepared for some serious time commitment to postprocess each study. Lacking is information on how much time is required for each analysis. McGann et al\textsuperscript{18} do report on the reproducibility of the analysis, which seems good, but they do not report on the reproducibility of the acquisition (potentially a more important factor when trying to reproduce these findings at other centers and other CMR vendors). Conceptually the approach seems convoluted as each slice is treated as a separate pixel distribution with a different threshold chosen for each slice based on the slice-by-slice pixel distribution analysis, so no uniform threshold is chosen for an individual patient. A multicenter, multivendor LA LGE study suggests that alternative strategies may be preferred.\textsuperscript{15}

Finally, we urge caution when adopting a complex method such as this for routine clinical use. Three fundamental questions must be more definitively addressed before widespread application: (1) does the LA LGE grayscale threshold truly reflect LA fibrosis? Despite the correlation seen in both electroanatomic voltage maps\textsuperscript{16} and the 10 biopsies provided in the study by McGann et al,\textsuperscript{18} more precise histopathologic correlation should be pursued; (2) is there a simpler/more reproducible means to derive similar predictive insights? LA volume is certainly more easily obtained/measured (by CMR, echocardiography, or computed tomography) and may have equal predictive power\textsuperscript{19,20}; and (3) is there a threshold effect, and if so, what is the threshold? The 10% increments in the Utah classification seem somewhat arbitrary.

The power of CMR to comprehensively assess anatomy, function, and tissue character has led to its widespread use for a variety of clinical disorders. McGann et al\textsuperscript{18} are congratulated on paving the way for future research in this exciting area that potentially affects the growing ever increasing AF population. The ability of CMR to measure atrial anatomy and function, extent of fibrosis, and other tissue-characterizing methods, such as T1 mapping, seems too powerful to ignore and may also lead to new paradigms in which patients at high risk for developing AF are identified for primary prevention intervention. Despite the promise, however, until we no longer need to ask the question, “Do you see what I see?”, much work remains ahead!
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