The role of myocardial fibrosis in determining the success rate of ablation for the treatment of atrial fibrillation

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Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia observed in clinical practice currently affecting 1-2% of the general population [1]. With an increasing lifespan its prevalence will also increase. Whilst technological advances have resulted in earlier and easier diagnosis of AF even outside of the hospital setting, the appropriate selection of patients for specific pharmacotherapy or electrophysiological ablation procedures has not seen similar improvement. For example, using the Kardia Band by AliveCor integrated with Apple's smart watch can give accurate electrocardiograms for the wearer, enabling early detection of asymptomatic AF [2-4]. This device has obtained regulatory approval in Europe and whilst this can allow us to detect AF reliably early on, it remains to be seen how such early diagnosis can improve prognosis.

Having thus improved the timely diagnosis of AF this places significant pressure on its treatment to reach the same standards with regards to both symptomatic and prognostic therapies. In the past, anti-arrhythmic drugs represented the only means of maintaining sinus rhythm. However, given their side-effects, especially with long-term use, and limited efficacy, interventional approaches such as percutaneous catheter ablation have become increasingly important [5]. Over the last 30 years, atrial fibrillation ablation has continued to develop, with its frequency and success steadily increasing[6, 7]. However, its widespread adoption has been limited by the frequent need for repeated ablation procedures in order to maintain sinus rhythm. Myocardial fibrosis (or scarring) has been suggested to play a key role in the need for re-ablation [8, 9] with patients who have increased atrial or ventricular scarring having poorer outcomes with ablation procedures. Characterization of myocardial tissue therefore both pre- and also potentially post-procedure is important as it could enable appropriate selection of patients who will be more likely to have a successful outcome from an ablation procedure. In this review we will discuss mechanistic pathophysiology of myocardial fibrosis in AF and how this could potentially help guide the success of atrial fibrillation ablation.

The bi-directional relationship between myocardial fibrosis and atrial fibrillation

AF is thought to be secondary to underlying heart disease in 70% of patients [10]. The extracellular matrix (ECM) is largely formed by myofibroblasts, which are flat spindle shaped cells that proliferate profoundly in pathological conditions [11, 12]. Tight connections between these fibroblasts form a multidimensional network that acts as a sensor of dynamic change within the myocardium [12]. Myofibroblasts exhibit different electrophysiological properties compared to surrounding cardiomyocytes. For example, they are non-excitable cells but can mediate current transfer between cardiomyocytes via gap junctions [12]. Increased collagen deposition in the ECM is important in the process of electrophysiological remodelling, leading to shortening of action potential durations, increased heterogeneity of conduction and repolarization, and spontaneous induction of phase 4 depolarization [10, 12]. Therefore, fibroblasts may be directly linked with not only triggered but also re-entrant arrhythmogenesis [13]. Myocardial diffuse fibrosis is identified as the excess deposition of extracellular matrix material, which mainly consists of the protein collagen, by myofibroblasts within the myocardial tissue. This would further alter the electrophysiological properties of the atrial myocardium, thereby increasing the propensity of AF development. Following on from myocardial diffuse interstitial fibrosis, myocyte necrosis ensues and the myocardium becomes scarred with a pathological and irreversible process of replacement fibrosis. Myocardial fibrosis is therefore a spectrum of disease with diffuse interstitial fibrosis on the one side progressing to focal replacement fibrosis on the other. Both have been linked to arrhythmogenesis and in this review the general term myocardial fibrosis will be used when referring to either of the patterns of fibrosis in patients with AF.

It is not just that myocardial fibrosis can promote AF, but AF can itself potentially promote atrial fibrosis [14, 15] causing a “chicken and egg” situation as sometimes it is unclear which is the cause and which is the result. The very rapid atrial rate and associated tachycardia in AF may

induce electrical remodelling, which is an attempt to adapt to new pathophysiological conditions [12]. The ECM undergoes alterations as fibrotic tissue replaces atrial cardiomyocytes by the release of pro-fibrotic factors, such as transforming growth factor -β1 (TGF) [16], platelet derived growth factor [17] and connective tissue growth factor [18]. Therefore, AF is not only a consequence, but also a cause of, fibrosis lending support to the commonly used medical aphorism "AF begets more AF", likely secondary to myocardial fibrosis [19]. Interestingly, permanent AF can downregulate angiotensin II type 1 receptors and upregulate angiotensin II [20]. Increased levels of angiotensin II may activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and increase the release of reactive oxygen species [21], in turn promoting fibrosis [22]. Similar mechanisms could exist in myocardial fibrosis-mediated ventricular fibrillation (VF) but are not as well established as atrial fibrosis-mediated AF. Although both share common signal transduction pathways, there are significant chamber-specific differences. Thus, the increase in TGF- β1 levels is higher in the atria than in the ventricles in transgenic mice with TGF- β1 overexpression [23]. Furthermore, atrial fibroblasts respond to greater extents to angiotensin II than ventricular fibroblasts [24]. It is therefore likely that fibrosis (with the exception perhaps of an acute myocardial infarction) is not localised but likely to affect both atria and ventricles. Therefore as atrial fibrosis can be more challenging to quantify many studies have used myocardial ventricular fibrosis as a surrogate marker [25].

Quantification of fibrosis with imaging and relationship to ablation success

Advances in cardiac imaging have enabled not only characterization but also quantification of cardiac fibrosis non-invasively [26]. Echocardiography was the first investigation designed to screen for underlying cardiac pathologies that can influence the success or failure rates of ablation [26]. Some examples are left atrial dilatation, valvular heart disease or left ventricular systolic impairment [26]. Cardiovascular magnetic resonance (CMR) has revolutionalized this field as it can

non-invasively provide myocardial tissue characterization which can provide further prognostic information in a plethora of cardiac conditions [27-29]. CMR using late (delayed) gadolinium enhancement (LGE) can accurately quantify focal areas of atrial fibrotic tissue and scar burden. This is dependent on uptake of gadolinium by the cardiac tissue, and it is retained for longer periods in fibrotic cells compared to normal cells. Thus areas of damaged myocardium appear hyper-intense relative to the normal myocardium [30]. Indeed more fibrosis has been associated with increased recurrence following the ablation. This further supports the use of CMR in the prediction of AF recurrence rates after ablation [31].

Several studies have investigated the association between fibrosis assessed by CMR-LGE and ablation outcomes in the context of AF. The DECAAF study, a multicenter, prospective trial, revealed that atrial fibrosis estimated by CMR-LGE is independently associated with likelihood of recurrent arrhythmia after ablation [27]. This study proposed a 4-stage classification of left atrial (LA) fibrosis: Stage I (<10% of the LA wall), stage II (10-20%), stage III (20-30%) and stage IV (≥30%). The AF post-ablation recurrence rates correlated with the classification stage of fibrosis, with recurrence rates of 15%, 33%, 46% and 51% respectively at 325 days indicating a more than a threefold increase in recurrence risk in the group with higher fibrosis burden than the group with lower fibrosis burden [27]. A more recent study that followed up 50 patients post pulmonary vein isolation procedures demonstrated the patients who had AF recurrence had a mean 6.6% of atrial LGE scar compared to 3.5% in those who did not have a recurrence, further supporting that atrial scar is an independent factor for recurrence [32]. Moreover, an additional study confirmed higher atrial arrhythmia recurrence risk with higher burden of fibrosis ≥30% fibrosis (stage IV patients) on pre-ablation MRI scans over a one year follow-up period [33]. This study concluded that LA wall fibrosis scores below 30% carry almost a third of the risk of recurrence when compared to patients with more than 30% atrial scarring on the pre-procedural CMR, and provides therefore a pathway towards identification of patients who are far more likely to benefit from catheter ablation

procedures. In summary, there is emerging evidence to support use of CMR-LGE to quantify atrial fibrosis both pre- and post-operatively for prognostication and although 30% of atrial fibrosis has significantly worse recurrence than lower values, it should be remembered that there is no threshold in terms of fibrosis and AF recurrence but likely a linear relationship. Therefore one could expect the best results when there is no atrial fibrosis- something potentially explaining why ablation in paroxysmal AF is more successful than permanent AF [34].

The evaluation and risk stratification of fibrosis using LGE-MRI prior to ablation could be a personalized medical approach in the treatment of AF [35]. It is noted that while a pulmonary vein isolation (PVI) ablation strategy is effective for patients with LA fibrosis in stages I and II, PVI fails to provide optimal outcomes for patients with stage III and IV fibrotic remodeling. While non-PV triggers, such as foci arising from atrial chambers or other thoracic arteries, can lead to recurrent atrial tachy-arrhythmias, most recurrences are due to pulmonary vein reconnection [36]. Therefore, pre-procedure CMR can identify those patients who are unlikely to benefit from PVI but also those that could potentially require more extensive ablation during the first procedure in an attempt to minimize recurrence. Likewise, it is possible that patients with a very significant burden of fibrosis might be advised against ablation or quoted a very small percentage of success. CMR performed at 3 months post-ablation can be used to assess for the presence of continuous scar lesions and effective PVI [37]. Due to the poor results of PVI on patients with LA fibrosis in stages III and IV [9], it is recommended to consider posterior and septal wall debulking (i.e. the surgical removal of tissue) or a completely different treatment approach due to the high risk of recurrence [9, 33].

Whilst CMR-LGE is ideal for analyzing focal areas of cardiac replacement fibrosis, more recent techniques using T1 mapping are more commonly used to evaluate diffuse fibrosis [38]. A recent study investigated the impact of diffuse atrial fibrosis detected by T1 mapping on the post-AF ablation clinical outcome [39]. It found a post-contrast atrial T1 time of >230ms was associated

with an 85% single procedure success rate after AF ablation [39]. This technique of identifying diffuse interstitial fibrosis has been very welcomed in the imaging community as it has the potential to image "early" myocardial fibrosis. This form of early fibrosis could be potentially reversible and therefore scanning the patients following the ablation can allow us to see whether the diffuse fibrosis has stabilised, progressed or even regressed. Certainly if it has stabilised or regressed this would be a better situation, or if it has progressed we will know at least that the patients will be more at risk of a recurrence and ensure closer monitoring [26,30].

Targeting fibrosis in ablation using electro-anatomical voltage mapping

Patients with identified fibrosis undergoing catheter ablation have been associated with an increased likelihood of arrhythmia recurrence [40]. Electro-anatomic voltage mapping (EAVM) can provide information on local voltage abnormalities to accurately identify myocardial fibrosis [41]. It can characterize the underlying atrial substrate and identify areas injured by previous ablation [42]. A number of studies have demonstrated accurate identification of ventricular fibrosis using specific voltage cut-off values, however the values for atrial fibrosis are less well defined [40]. By using EAVM in combination with CMR, it was recently shown that areas of dense fibrosis have smaller voltages than those of patchy fibrosis (0.63mV vs. 0.86mV) [43]. These findings are supported by those of another study, which demonstrated an association between areas with increased fibrosis identified by CMR-LGE and lower voltages (0.7 mV) in the left atrium of AF patients [44]. Moreover, a voltage cut-off of 0.27 mV was suggested as a good value for delineating scars in AF with sensitivity of 90% and specificity of 83%) [41]. It should be noted that several factors can affect accurate voltage measurements, such as contact between the myocardium and the mapping catheter, the orientation of the catheter, underlying atrial rhythm, and the electrode size [26]. Nevertheless, identification of low voltage areas has promise in guiding AF ablation.

Blood markers of fibrosis in predicting ablation success

Recent research efforts have focused on elucidating the roles of inflammatory pathways in atrial fibrillation. As such, systemic inflammatory markers may provide utility in predicting AF ablation success [45]. One promising candidate is metalloproteinase-2 (MMP-2), which has been shown to predict AF recurrence rates after ablation procedures [46-48]. A study involving 50 patients with symptomatic AF showed that baseline serum MMP-2 was significantly higher in patients with AF recurrence than in patients who remained in sinus rhythm over a 14-month post-ablation period [46]. The ability of this marker to predict AF recurrence rates has been confirmed in two other studies [47, 48]. Another promising marker is the amino terminal peptide of type III procollagen (PIIINP), which is generated during collagen type III biosynthesis [49]. It is upregulated during fibrogenesis and scar formation [50]. Higher PIIINP levels over the first six months after ablation predicted recurrent AF [51]. Other biomarkers, such as metallopeptidase inhibitor 2 (TIMP2), galectin-3 (Gal-3) and transforming growth factor beta (TGFβ) have also been examined for their ability to predict AF recurrence, but these failed to predict AF recurrent post-ablation in multivariate Cox regression analysis [47]. The use of biomarkers in clinical practice is likely to increase significantly in the next few years, especially if they can associate with success of recurrence before or after the procedure.

Conclusion

With an ageing population and increasing prevalence and burden of AF, the role of AF ablation is likely to increase. However, it is possible that personalised/precision medicine will improve our selection of patients for this procedure and therefore tailor to the individual patients- by offering a simple procedure to those with low or no fibrosis, offering a more complex procedure to those with moderate fibrosis and even declining the procedure to those with very high burden of fibrosis who would be unlikely to benefit from it. Definite guidelines using the

presence of fibrosis will need to be developed and are likely to also include the use of biomarkers of fibrosis, as this would be simpler, cheaper and more reproducible than CMR which would also be well-received by the electrophysiological community[12]. Ultimately, a clinical score to predict outcome based on different modalities, for example CMR and blood biomarkers, will prove useful for this purpose [26], similar to the scoring systems that exist for guiding selection of anticoagulants in AF [52] or primary prevention for atrial arrhythmia, ventricular arrhythmia or stroke in cardiomyopathy .

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