

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

Subothini Selvendran BSc (Hons)^{1*}, Nikhil Aggarwal BSc (Hons)^{1*}, Justin Li², Gary Tse MBBS, MPH, PhD, FESC, FACC³, Vassilios S Vassiliou MA, MBBS, MRCP, PhD, FHEA, FESC^{1,4}

Author Affiliations:

¹ Royal Brompton Hospital and Imperial College London, UK

² Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, SAR, P.R. China

³ Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China; Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China; School of Health Sciences, University of Manchester, United Kingdom (tseg@cuhk.edu.hk)

⁴ Norwich Medical School, University of East Anglia, Bob Champion Research & Education Building, James Watson Road, Norwich, UK; Royal Brompton Hospital and Imperial College London, UK

*SS and NA contributed equally

Corresponding Author

Dr Vassilios S Vassiliou

Norwich Medical School, University of East Anglia, Second Floor, Bob Champion Research & Education Building, James Watson Road, Norwich, UK

Email: v.vassiliou@rbht.nhs.uk

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-excitabile 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 conditions¹². The ECM undergoes alterations as fibrotic tissue replaces atrial cardiomyocytes by the release of pro-fibrotic factors, such as transforming growth factor β 1 (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- β 1 levels is higher in the atria than in the ventricles in transgenic mice with TGF- β 1 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 revolutionized 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 (\geq 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 \geq 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 success⁴⁵. One promising candidate is metalloproteinase-2 (MMP-2), which has been shown to predict AF recurrence rates after ablation procedures⁴⁶⁻⁴⁸. 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 period⁴⁶. 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 biosynthesis⁴⁹. It is upregulated during fibrogenesis and scar formation⁵⁰. Higher PIIINP levels over the first six months after ablation predicted recurrent AF⁵¹. Other biomarkers, such as metalloproteinase 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 analysis⁴⁷. 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 community¹². Ultimately, a clinical score to predict outcome based on different modalities, for example CMR and blood biomarkers, will prove useful for this purpose²⁶, similar to the scoring systems that exist for guiding selection of anticoagulants in AF⁵² or primary prevention for atrial arrhythmia, ventricular arrhythmia or stroke in cardiomyopathy.

Conflict of interest: No conflict of interest declared by any of the authors.

Funding: Assistant Professor Tse has received funding from the Croucher Foundation of Hong Kong and Dr Vassiliou has received funding from Rosetrees Charity Trust, London, UK.

References

1. Aggarwal N, Selvendran S, Raphael CE, Vassiliou V. Atrial Fibrillation in the Young: A Neurologist's Nightmare. *Neurology Research International* 2015;2015:9.
2. <https://www.alivecor.com/>.
3. Baquero GA, Banchs JE, Ahmed S, Naccarelli GV, Luck JC. Surface 12 lead electrocardiogram recordings using smart phone technology. *J Electrocardiol* Jan-Feb 2015;48:1-7.
4. Lown M, Yue A, Lewith G, Little P, Moore M. Screening for Atrial Fibrillation using Economical and accurate Technology (SAFETY)-a pilot study. *BMJ Open* Jan 13 2017;7:e013535.
5. A EDMF. Recurrent Atrial Fibrillation After Catheter Ablation: Considerations For Repeat Ablation And Strategies To Optimize Success. *J Atr Fibrillation* Jun-Jul 2016;9:1427.
6. D'Agostino RS, Jacobs JP, Badhwar V, Paone G, Rankin JS, Han JM, McDonald D, Shahian DM. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2016 Update on Outcomes and Quality. *Ann Thorac Surg* Jan 2016;101:24-32.
7. Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart* 2016.
8. Kottkamp H, Bender R, Berg J. Catheter Ablation of Atrial Fibrillation: How to Modify the Substrate? *Journal of the American College of Cardiology* 1/20/ 2015;65:196-206.
9. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S, Badger T, Burgon N, Haslam T, Kholmovski E, Macleod ROB, Marrouche N. Atrial Fibrosis Helps Select the Appropriate Patient and Strategy in Catheter Ablation of Atrial Fibrillation: A DE-MRI Guided Approach. *Journal of Cardiovascular Electrophysiology* 2011;22:16-22.
10. Burstein B, Nattel S. Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation. *Journal of the American College of Cardiology* 2/26/ 2008;51:802-809.

11. Krenning G, Zeisberg EM, Kalluri R. The Origin of Fibroblasts and Mechanism of Cardiac Fibrosis. *Journal of cellular physiology* 2010;225:631-637.
12. Dzeshka MS, Lip GYH, Snezhitskiy V, Shantsila E. Cardiac Fibrosis in Patients With Atrial Fibrillation. *Mechanisms and Clinical Implications* 2015;66:943-959.
13. Tse G, Yeo JM. Conduction abnormalities and ventricular arrhythmogenesis: The roles of sodium channels and gap junctions. *Int J Cardiol Heart Vasc* 2015;9:75-82.
14. Tse G, Lai ET, Yeo JM, Yan BP. Electrophysiological mechanisms of Bayés syndrome: insights from clinical and mouse studies. *Front Physiol* 2016;7:188.
15. Tse G, Liu T, Li KH, Laxton V, Wong AO, Chan YW, Keung W, Chan CW, Li RA. Tachycardia-bradycardia syndrome: Electrophysiological mechanisms and future therapeutic approaches (Review). *Int J Mol Med Mar* 2017;39:519-526.
16. Behnes M, Hoffmann U, Lang S, Weiss C, Ahmad-Nejad P, Neumaier M, Borggrefe M, Brueckmann M. Transforming growth factor beta 1 (TGF-beta 1) in atrial fibrillation and acute congestive heart failure. *Clinical Research in Cardiology* 2011;100:335-342.
17. Liao C-h, Akazawa H, Tamagawa M, et al. Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. *The Journal of clinical investigation* 01/04/2010;120:242-253.
18. Ko W-C, Hong C-Y, Hou S-M, Lin C-H, Ong E-T, Lee C-F, Tsai C-T, Lai L-P. Elevated Expression of Connective Tissue Growth Factor in Human Atrial Fibrillation and Angiotensin II-Treated Cardiomyocytes. *Circulation Journal* 2011;75:1592-1600.
19. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;92:1954-1968.
20. Goette A, Arndt M, Röcken C, Spiess A, Staack T, Geller JC, Huth C, Ansoerge S, Klein HU, Lendeckel U. Regulation of Angiotensin II Receptor Subtypes During Atrial Fibrillation in Humans. *Circulation* 2000;101:2678-2681.
21. Kim YM, Guzik TJ, Zhang YH, Zhang MH, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. A Myocardial Nox2 Containing NAD(P)H Oxidase Contributes to Oxidative Stress in Human Atrial Fibrillation. *Circulation Research* 2005;97:629-636.
22. Tse G, Yan BP, Chan YW, Tian XY, Huang Y. Reactive oxygen species, endoplasmic reticulum stress and mitochondrial dysfunction: the link with cardiac arrhythmogenesis. *Front Physiol* 2016;7:313.
23. Rahmutula D, Marcus GM, Wilson EE, Ding C-H, Xiao Y, Paquet AC, Barbeau R, Barczak AJ, Erle DJ, Olgin JE. Molecular basis of selective atrial fibrosis due to overexpression of transforming growth factor- β 1. *Cardiovascular Research* 2013;99:769-779.
24. Burstein B, Libby E, Calderone A, Nattel S. Differential Behaviors of Atrial Versus Ventricular Fibroblasts. A Potential Role for Platelet-Derived Growth Factor in Atrial-Ventricular Remodeling Differences 2008;117:1630-1641.
25. Ling L-h, Kistler PM, Ellims AH, Iles LM, Lee G, Hughes GL, Kalman JM, Kaye DM, Taylor AJ. Diffuse Ventricular Fibrosis in Atrial Fibrillation. Noninvasive Evaluation and Relationships With Aging and Systolic Dysfunction 2012;60:2402-2408.
26. Begg GA, Holden AV, Lip GYH, Plein S, Tayebjee MH. Assessment of atrial fibrosis for the rhythm control of atrial fibrillation. *International Journal of Cardiology* 10/1/2016;220:155-161.
27. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement mri and atrial fibrillation catheter ablation: The decaaf study. *JAMA* 2014;311:498-506.
28. Dweck MR, Joshi S, Murigu T, Gulati A, Alpendurado F, Mohiaddin R, Pepper J, Pennell D, Newby D, Prasad S. 169 Mid-wall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *Heart* 2011;97:A94-A94.
29. Ismail TF, Jabbour A, Gulati A, et al. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart* 2014;100:1851-1858.
30. Gu J, Hu W, Liu X. The Value of Magnetic Resonance Imaging in Catheter Ablation of Atrial Fibrillation. *Clinical Cardiology* 2015;38:190-194.
31. Longobardo L, Todaro MC, Zito C, Piccione MC, Di Bella G, Oreto L, Khandheria BK, Carerj S. Role of imaging in assessment of atrial fibrosis in patients with atrial fibrillation: state-of-the-art review. *European Heart Journal - Cardiovascular Imaging* 2014;15:1-5.
32. Malcolm-Lawes LC, Juli C, Karim R, et al. Automated analysis of atrial late gadolinium enhancement imaging that correlates with endocardial voltage and clinical outcomes: A 2-center study. *Heart Rhythm* 2013;10:1184-1191.
33. McGann C, Akoum N, Patel A, et al. Atrial Fibrillation Ablation Outcome Is Predicted by Left Atrial Remodeling on MRI. *Circulation: Arrhythmia and Electrophysiology* 2014;7:23-30.

34. Mohanty S, Mohanty P, Di Biase L, et al. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. *Europace* Dec 29 2016.
35. Fabritz L, Guasch E, Antoniades C, et al. Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol* 04/print 2016;13:230-237.
36. Zhao Y, Di Biase L, Trivedi C, et al. Importance of non-pulmonary vein triggers ablation to achieve long-term freedom from paroxysmal atrial fibrillation in patients with low ejection fraction. *Heart Rhythm* 2016;13:141-149.
37. Cochet H, Salel M, Clement-Guinaudeau S, Corneloup O, Montaudon M, Laurent F. Atrial scar on late gadolinium-enhanced imaging to predict electrical reconnection after pulmonary vein isolation for atrial fibrillation. *Journal of Cardiovascular Magnetic Resonance* 2016;18:P201.
38. Jellis CL, Kwon DH. Myocardial T1 mapping: modalities and clinical applications. *Cardiovascular Diagnosis and Therapy* 09/02/received 09/13/accepted 2014;4:126-137.
39. Ling L-h, McLellan AJA, Taylor AJ, et al. Magnetic resonance post-contrast T1 mapping in the human atrium: Validation and impact on clinical outcome after catheter ablation for atrial fibrillation. *Heart Rhythm* 9// 2014;11:1551-1559.
40. Letsas KP, Efremidis M, Sgouros NP, Vlachos K, Asvestas D, Sideris A. Catheter ablation of persistent atrial fibrillation: The importance of substrate modification. *World Journal of Cardiology* 03/26 10/25/received 12/26/revised 01/18/accepted 2015;7:111-118.
41. Kapa S, Desjardins B, Callans DJ, Marchlinski FE, Dixit S. Contact Electroanatomic Mapping Derived Voltage Criteria for Characterizing Left Atrial Scar in Patients Undergoing Ablation for Atrial Fibrillation. *Journal of Cardiovascular Electrophysiology* 2014;25:1044-1052.
42. Harrison JL, Jensen HK, Peel SA, et al. Cardiac magnetic resonance and electroanatomical mapping of acute and chronic atrial ablation injury: a histological validation study. *European Heart Journal* 2014;35:1486-1495.
43. Jadidi AS, Cochet H, Shah AJ, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. *J Am Coll Cardiol* Aug 27 2013;62:802-812.
44. Spragg DD, Khurram I, Zimmerman SL, Yarmohammadi H, Barcelon B, Needleman M, Edwards D, Marine JE, Calkins H, Nazarian S. Initial experience with magnetic resonance imaging of atrial scar and co-registration with electroanatomic voltage mapping during atrial fibrillation: Success and limitations. *Heart Rhythm* 2012;9:2003-2009.
45. Vilchez JA, Roldán V, Hernández-Romero D, Valdés M, Lip GYH, Marín F. Biomarkers in atrial fibrillation: an overview. *International journal of clinical practice* 2014;68:434-443.
46. Okumura Y, Watanabe I, Nakai T, Ohkubo K, Kofune T, Kofune M, Nagashima K, Mano H, Sonoda K, Kasamaki Y, Hirayama A. Impact of Biomarkers of Inflammation and Extracellular Matrix Turnover on the Outcome of Atrial Fibrillation Ablation: Importance of Matrix Metalloproteinase-2 as a Predictor of Atrial Fibrillation Recurrence. *Journal of Cardiovascular Electrophysiology* 2011;22:987-993.
47. Kimura T, Takatsuki S, Inagawa K, Katsumata Y, Nishiyama T, Nishiyama N, Fukumoto K, Aizawa Y, Tanimoto Y, Tanimoto K, Fukuda K. Serum inflammation markers predicting successful initial catheter ablation for atrial fibrillation. *Heart Lung Circ* Jul 2014;23:636-643.
48. Sasaki N, Okumura Y, Watanabe I, Mano H, Nagashima K, Sonoda K, Kogawa R, Ohkubo K, Nakai T, Hirayama A. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. *Journal of Interventional Cardiac Electrophysiology* 2014// 2014;39:241-249.
49. Rosenberg MA, Maziarz M, Tan AY, Glazer NL, Zieman SJ, Kizer JR, Ix JH, Djousse L, Siscovick DS, Heckbert SR, Mukamal KJ. Circulating fibrosis biomarkers and risk of atrial fibrillation: The Cardiovascular Health Study (CHS). *Am Heart J* May 2014;167:723-728 e722.
50. Kawamura M, Munetsugu Y, Kawasaki S, Onishi K, Onuma Y, Kikuchi M, Tanno K, Kobayashi Y. Type III procollagen-N-peptide as a predictor of persistent atrial fibrillation recurrence after cardioversion. *EP Europace* 2012;14:1719-1725.
51. Richter B, Gwechenberger M, Socas A, et al. Time course of markers of tissue repair after ablation of atrial fibrillation and their relation to left atrial structural changes and clinical ablation outcome. *Int J Cardiol* Oct 20 2011;152:231-236.

52. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* Feb 2010;137:263-272.

Additional references

- 1 www.alivecor.com.
- 2 Chan P-H, Wong C-K, Pun L, *et al*. Head-to-Head Comparison of the AliveCor Heart Monitor and Microlife WatchBP Office AFIB for Atrial Fibrillation Screening in a Primary Care Setting. *Circulation* 2017;135:110–2. doi:10.1161/CIRCULATIONAHA.116.024439
- 3 Ling L-H, Kistler PM, Ellims AH, *et al*. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol* 2012;60:2402–8. doi:10.1016/j.jacc.2012.07.065
- 4 Dweck MR, Joshi S, Murigu T, *et al*. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2011;58:1271–9. doi:10.1016/j.jacc.2011.03.064
- 5 Ismail TF, Jabbour A, Gulati A, *et al*. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart* 2014;100:1851–8. doi:10.1136/heartjnl-2013-305471
- 6 Mohanty S, Mohanty P, Di Biase L, *et al*. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. *Europace* Published Online First: 29 December 2016. doi:10.1093/europace/euw338

