**Novel therapeutic concepts**

**Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy**

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The atrial structure/substrate of patients with atrial fibrillation (AF) and clinically similar characteristics can present very differently, and also the 'phenotype' (i.e. paroxysmal, persistent, and long standing persistent) of the arrhythmia cannot comprehensively explain these differences. It was unclear why some patients stay in paroxysmal AF for decades, whereas other patients with the same characteristics progress to persistent AF within a few months. In this review, evidence is described that AF patients without apparent structural heart disease have a chronic fibrotic bi-atrial substrate. There is also evidence from intraoperatively obtained specimen analysis, post-mortem autopsy findings, electroanatomic mapping studies, and delayed enhancement-MRI investigations that a higher mean value of fibrosis is detected in patients with persistent vs. paroxysmal AF but that the variability in the extend of fibrosis is always very high with part of paroxysmal AF patients having massive fibrosis and part of persistent AF patients showing mild fibrosis. In addition, patients undergoing ablation very early after the first AF episodes show already significant fibrosis. These data do not support a causal relationship that AF (significantly) produces fibrosis in the sense of 'AF begets AF' instead of being a consequence of the fibrotic process. In patients with mitral stenosis, evidence for reverse atrial remodelling after commissurotomy was reported, however, in patients with 'lone' AF, the atrial substrate progressed after successful AF elimination indicating towards the independent/progressive disease process of an underlying structural atrial disease called fibrotic atrial cardiomyopathy. Other 'conventional wisdoms' also need to be re-considered including the aetiological role of age and arterial hypertension for human structural atrial remodelling.

**Keywords**
Atrial fibrillation • Fibrosis • Cardiomyopathy • Substrate • Pathophysiology

**Different substrates for atrial fibrillation**

The observation of tachycardia-induced experimental electrical remodelling providing the prerequisites for atrial fibrillation (AF) to persist led to the landmark concept of 'AF begets AF'. However, the underlying pathophysiological process of human structural atrial remodelling remained less completely understood.

The atria of patients with AF and clinically similar characteristics can present very differently during electroanatomic mapping. Interestingly, even patients with the worst (bi-)atrial substrate may present with paroxysmal (instead of persistent) AF. Left atrial size, underlying heart disease, age, and 'phenotype' (i.e. paroxysmal, persistent, and long-standing persistent) of the arrhythmia alone cannot explain these differences. Some patients with no or limited heart disease stay in paroxysmal AF for decades or 'forever', whereas some patients with the same clinical characteristics progress to persistent AF directly or within weeks or months (Figure 1). The experimental concepts of atrial remodelling induced by the arrhythmia itself cannot conclusively explain these differences.

The clinical and pathophysiological differentiation between patients where the PV trigger in paroxysmal 'focal' AF is the only driver of the disease in a self-perpetuating process and patients with substrate-based AF as a consequence of, e.g. mitral stenosis with a significantly enlarged left atrium seems clear. In addition, there is now increasing evidence that even in patients with so-called lone or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM). Different expressions can be found from mild (FACM I), moderate (FACM II) to excessive fibrosis (FACM III), and wide clinical variations from asymptomatic to multiple arrhythmic manifestations (including AF, left and/or right atrial re-entrant tachycardia, sinus, and/or AV node disease). Furthermore, the seemingly clear role of co-existing structural cardiovascular

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diseases (e.g. hypertension) and also the role of age for human structural atrial remodelling need to be re-analysed.

Atrial structural remodelling and atrial arrhythmias

The presence of interstitial (micro-)fibrosis leading to changes in cellular coupling results in spatial ‘non-uniform anisotropic’ impulse propagation and is a potential cause of atrial activation abnormalities that may underlie the initiation and perpetuation of re-entrant arrhythmias including fibrillation. Importantly, the arrhythmogenic conduction events were described to occur within very small areas, e.g. re-entrant circuits were found as small as 0.6 × 2.6 mm in human atrial bundles. Accordingly, increased fibrosis as a structural correlate of AF has been reported in humans using intra-operatively obtained specimen. Cardiac atrial and/or ventricular fibrosis is characterized by excessive accumulation of collagenous material in the extracellular space. Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities in an experimental model and is now used in clinical electrophysiological studies for substrate description. Alternatively, the utility of delayed enhancement (DE) — magnetic resonance imaging (MRI) was described in detecting, quantifying and localizing atrial fibrosis including four categories of structural changes (‘Utah stages I–IV’)

Atrial remodelling in conditions predisposing to atrial fibrillation

John et al. described electroanatomic remodelling of the left and right atria in 24 patients with rheumatic mitral stenosis undergoing mitral commissurotomy. Importantly, patients were excluded if they had any suggestion of atrial arrhythmia/AF or other structural heart disease besides mitral stenosis. In comparison with 24 control patients, the patients with mitral stenosis showed—beyond left atrial enlargement—a significantly reduced biatrial voltage (left atrium 1.8 ± 0.6 vs. 3.6 ± 0.6 mV, right atrium 1.9 ± 0.6 vs. 3.3 ± 0.5 mV), reduced conduction velocity, and prolonged effective refractory periods. These abnormalities may clearly play a role in the increased propensity to AF in patients with mitral stenosis. Indeed, patients with mitral stenosis were more susceptible to induction of AF with extrastimulus provocation. Similar left atrial remodelling was described in patients with haemodynamically significant atrial septal defects (but no AF) compared with control patients including significantly reduced left atrial voltage. Hypertension is another common co-existing factor which is described to be associated with AF. Medi et al. described results from electroanatomic mapping and reported right atrial changes in 10 patients with systemic hypertension plus left ventricular hypertrophy (but no AF) compared with 10 control patients. In patients with chronically treated hypertension, a significant slowing of conduction velocity was described. Furthermore, sustained AF was induced in 30% of hypertension patients but no controls.
the structural changes in hypertensive patients observed in this study were less pronounced (compared with the changes in patients with mitral stenosis or atrial septal defect). Importantly, the mean right atrial voltage as a surrogate for the structural (i.e. fibrotic) atrial remodelling was identical in the hypertension and control groups (2.2 ± 0.5 vs. 2.2 ± 0.3 mV).

**A chronic bi-atrial substrate in patients with paroxysmal ‘lone’ atrial fibrillation**

The evidence for a chronic and substantial atrial substrate in patients with lone AF is substantiated by an investigation of extracellular matrix proteins in left atrial tissue of patients with ‘lone’ AF (n = 56), with AF plus mitral valve disease (n = 46), and with sinus rhythm (n = 16). Left atrial tissue was obtained from atriotomy during cardiac surgery. The association of human AF with fibrosis was shown with collagen concentrations being significantly increased in patients with AF compared with those in sinus rhythm. Importantly, collagen I—which is the major collagenous product of cardiac fibroblasts—was enhanced in ‘lone’ AF patients even to a similar extent compared with AF in patients with severe mitral valve disease (Figure 3).

Stiles et al. investigated 25 patients (53 ± 8 years) with ‘lone’ AF during an electrophysiological study after at least 7 days in sinus rhythm and found slower conduction velocity, longer effective refractory periods, and importantly—significantly lower voltages (left atrium 1.7 ± 0.7 vs. 3.3 ± 0.7 mV, right atrium 1.7 ± 0.4 vs. 2.9 ± 0.4 mV) compared with control patients without AF. These findings confirm a substantial chronic structural bi-atrial substrate since the electrical remodelling is reversible within a few days. It might be that not all patients with paroxysmal ‘lone’ AF have an (underdetected) chronic substrate, but many more then assumed (Figure 4).

The findings of a chronic substrate in patients with paroxysmal ‘lone’ AF were recently extended in a DE-MRI study of the left atrial substrate. In that study, 40 of 333 included patients met criteria for ‘lone’ AF. The majority of these ‘lone’ AF patients showed a mild or even moderate degree of left atrial fibrosis, thereby compatible with mild/moderate and/or early forms of FACM I/II.

Is mild-to-moderate left atrial fibrosis necessary on top of PV triggers for AF to sustain for hours or days? Clinically, the time relationship of the trigger initiating AF and the substrate taking over for maintaining AF is largely unknown. Evidence for short trigger activity came from a study investigating a surgical left atrial linear lesion concept targeting at the prevention of anatomic left atrial re-entry without PV isolation in patients with paroxysmal and persistent AF. After a mean follow-up of 3.6 years, atrial ectopy, atrial runs,
and re-occurrence of AF episodes were analysed by 7-day-ECGs in 30 patients. Overall, 87% of the patients were free from AF. However, atrial ectopy was present in all patients and atrial runs in 83% of the patients with a median of 9 runs per patient/week (range, 1–321). Importantly, the median duration of the atrial runs as a surrogate for the duration of PV trigger activity measured only 1.2 s (range, 0.7–25). This may indicate that a chronic atrial substrate is indeed necessary for even relatively short episodes of AF to sustain.

More atrial substrate in patients with persistent vs. paroxysmal atrial fibrillation? Fibrotic changes as cause for or consequence of atrial fibrillation?

If the clinical AF episodes were the critical stimulus for the development of structural (fibrotic) remodelling, then there should be a step-wise increase with longer history and/or longer episodes of AF (higher cumulative AF burden), and especially a clear increase in fibrosis when patients with paroxysmal and persistent AF are compared. However, this does not seem to be the case.

Differences in patients with paroxysmal and persistent AF were analysed in the study with left atriotomy specimen obtained during cardiac surgery.\(^7\) Importantly, there was a similar degree of enhanced collagen expression in paroxysmal and persistent AF (Figure 5). While there was a tendency of an increased mean fibrosis level in patients with persistent AF vs. paroxysmal AF, the variation within the two groups was clearly very high and a statistical difference in fibrosis extent, therefore, could not be demonstrated.

Figure 4  Electroanatomic left atrial voltage mapping in two patients with paroxysmal ‘lone’ atrial fibrillation. (A) The patient had a long history of paroxysmal atrial fibrillation of 12 years, however, the duration of the atrial fibrillation episodes remained very short and the voltage map still shows no evidence at all of fibrosis. These fibrosis-free maps are found in our experience in < 10% of patients with paroxysmal ‘lone’ atrial fibrillation. (B) This patient had a very short history of PAF of only 7 months. Since the patient was extremely symptomatic, an overall cumulative frequency of 10–12 atrial fibrillation episodes could be estimated. However, the fibrotic atrial cardiomyopathy process was already substantial with moderate fibrosis at the time of the clinical advent of paroxysmal atrial fibrillation. Projections from anterior and posterior are given. Voltages of mapping points > 2.5 mV are annotated purple (normal voltage), voltages < 0.5 mV are indicated red (severely reduced voltage). LPV and RPV, left and right pulmonary veins.

Figure 5  Collagen I expression in human atrial tissue from patients with sinus rhythm, ‘lone’ paroxysmal atrial fibrillation and persistent (CAF) atrial fibrillation, and in patients with mitral valve disease plus sinus rhythm, paroxysmal atrial fibrillation, and CAF, respectively. Note, the overlapping wide variation/range of collagen I in patients with paroxysmal atrial fibrillation and CAF, with some paroxysmal atrial fibrillation patients having excessive fibrosis (asterisks) and some CAF patients having mild fibrosis (double asterisks) (modified from Boldt et al.\(^7\)).

Platonov et al.\(^{18}\) confirmed and extended the results from Boldt et al. by investigating structural abnormalities in post-mortem autopsy atrial specimen from 30 patients in three age-matched groups of patients without AF history, with paroxysmal AF, or with permanent AF. Atrial tissue samples were collected from the right atrium, Bachmann’s bundle, and from the posterior left atrial wall.
Patients with any history of AF had a three- to five-fold greater extend of fibrosis compared with patients without AF history. A comparison revealed a greater extent of fibrosis in patients with permanent AF compared with patients with paroxysmal AF. However, these differences were statistically significant in the left atrial tissue specimen only at the superior PV level, whereas no significant differences between patients with paroxysmal and permanent AF were found in the posterior left atrial wall and at the inferior PV level.\textsuperscript{18} Importantly, the variation in the data obtained from the posterior level between patients with paroxysmal and permanent AF were very high. In addition, the extent of fibrosis showed no clear correlation with the duration of AF history.

Recently, Teh et al.\textsuperscript{17} described electroanatomic remodelling of the left atrium in paroxysmal (n = 17) and persistent (n = 14) AF patients without structural heart disease compared with control patients (n = 15). Again, a lower voltage in the AF patients was found compared with the control patients. The mean left atrial voltage difference between patients with paroxysmal and persistent AF even reached a low statistical difference, however, in half of the left atrial areas that were investigated, this difference was not statistically significant.

Oakes et al.\textsuperscript{19} reported on the DE-MRI quantification of left atrial structural remodelling in 81 patients with AF. Mild enhancement was found in 43 patients, 28 of these (65%) had paroxysmal AF. However, 15 of these patients (35%) still had only mild enhancement but were already in persistent AF. Furthermore, from the 30 patients with moderate enhancement, 43% still presented with paroxysmal and 57% with persistent AF, respectively, again indicating towards the high variability of structural remodelling in patients with paroxysmal and persistent AF.

**Atrial fibrillation and the association to age and other co-existing cardiovascular diseases**

From an epidemiological point of view, human ageing certainly is associated with an increased likelihood of developing AF.\textsuperscript{20} However, a potential causative aetiological relationship of human age and development of AF is far less well established. Indeed, data on qualitative and quantitative analyses of bi-atrial human tissue from patients with non-valvular AF are scarce. In the human autopsy investigation, Platonov et al.\textsuperscript{18} reported on the association between structural changes in the human atria, age, and history of AF. In contradiction to the ‘conventional wisdom’ about the association between human age and atrial fibrosis, Platonov et al. were not able to detect any correlation between patient age and increase in fibrosis extent. Furthermore, atrial samples from age-matched arrhythmia-free patients contained ‘negligibly’ low amounts of fibrofatty tissue, even in very old patients. These autopsy results match well with data from an electroanatomic mapping study investigating the impact of age on left and right atrial voltage.\textsuperscript{21} In that study, the mean bipolar voltage in young patients ≤40 years was somewhat higher compared with older patients; however, there were hardly any differences in the age group 51–60 compared with 61–70 and beyond 70 years. Furthermore, age was also equally distributed in the four DE-MRI fibrosis grade groups (mean age 69 years in the total non-lone AF group, 68 years in the Utah I group, 66 years in the Utah II group, 68 years in the Utah III group, and 70 years in the Utah IV group, respectively).\textsuperscript{16}

Similar to the assumed aetiopathogenetic association of human age and AF, co-existing cardiovascular diseases (e.g. hypertension) are also thought to play an important aetiological role in the development of AF. Mahnkopf et al.\textsuperscript{16} compared the left atrial structural changes using DE-MRI in patients with ‘lone’ AF (n = 40) vs. those with ‘classical’ comorbidities (n = 293). Importantly, the degree of left atrial structural remodelling was found to be completely independent of co-morbidities. Furthermore, the distribution of groups Utah I–IV showed no significant differences between patients with lone AF and non-lone AF. For example, fibrosis grade Utah II was found in 65 vs. 64% of lone AF and non-lone AF patients, and fibrosis grade Utah III in 23 vs. 23% of lone AF and non-lone AF patients, respectively.\textsuperscript{16} In addition, co-existing cardiovascular diseases were equally distributed in the four fibrosis grade groups, e.g. hypertension in 66% of patients of the total non-lone AF group, in 76% of the Utah I group, in 67% of the Utah II group, in 61% of the Utah III group, and in 68% of the Utah IV group, respectively. These data thereby confirm the autopsy study data, where the co-morbidity status expressed in the CHA\textsubscript{2}-DS\textsubscript{2}-VASc score measured 3.8 ± 1.8 in patients with AF vs. 4.3 ± 1.9 in patients without AF.\textsuperscript{18} These data also confirm results from electroanatomic mapping, where no atrial voltage differences could be detected in patients with (arhythmia free) hypertension patients vs. control patients.\textsuperscript{13}

**Evidence for reverse human atrial structural remodelling?**

John et al.\textsuperscript{22} investigated the potential for reverse human atrial remodelling in 21 patients undergoing mitral commissurotomy for treatment of severe mitral stenosis. Bi-atrial voltage mapping was performed before and after commissurotomy—and in 14 patients, right atrial mapping was repeated after ≥6 months. Importantly, a further significant increase in atrial voltage was demonstrated late after interventional treatment from 1.8 ± 0.7 to 2.8 ± 0.6 mV. Therefore, late after reversal of chronic stretch, a progressive improvement in bipolar voltage could be shown indicating the potential for reverse human atrial remodelling.

If AF itself were the stimulus for the development of this fibrotic substrate in patients without structural heart disease, it could be hypothesized that this substrate was reversed after successful AF elimination. Teh et al.\textsuperscript{23} performed right atrial electroanatomic maps in 11 control patients and 11 ‘lone’ AF patients undergoing catheter ablation at baseline plus ≥6 months following successful elimination of AF. The substrate did not appear to reverse after successful ablation of AF. In contrast, there was a progressive substrate remodelling 6–14 months after successful catheter ablation with further decrease in atrial bipolar voltage and further prolongation of regional refractoriness.

**Fibrotic atrial cardiomyopathy: diagnosis, causality, and implications for ablation**

Electroanatomic mapping and DE-MRI are potential clinical diagnostic tools. Electroanatomic mapping, however, has all limitations of...
Invasive procedures and does not allow diagnostic follow-up investigations. In contrast, the potential of DE-MRI for detecting and quantifying atrial fibrosis looks attractive as a non-invasive, repeatable diagnostic tool. Recently, pre-operatively elevated serum markers of collagen synthesis (PICP) have been reported to be associated with post-surgical AF. Furthermore, a linear correlation between PICP and left atrial fibrosis was described. This raises the potential option of identifying subclinical FACM in general before the advent of AF. Overall, the definition and the understanding of the term ‘lone’ AF needs to be modified in the future. FACM to date is difficult to detect by conventional means but constitutes a substantial and chronic structural atrial disease posing the patient to the risk of developing AF and other manifestations.

Genetics seem to play a key role in FACM. A familiar aggregation of lone AF in young persons has been described recently. Frequently, a familiar appearance of clinical findings indicating towards FACM can be observed. However, genetic analyses of specific subgroups of AF so far are limited. Besides the key player genetics, additional pathophysiological aspects might include an inflammatory process as indicated by studies from Frustaci et al. on biopsy findings in patients with lone AF, Chung et al. on C-reactive protein elevation in patients with atrial arrhythmias, and findings on the role of steroids to prevent AF recurrences after ablation.

In patients with ‘pure’ focal AF (i.e. without atrial fibrosis), PV isolation can be considered a curative treatment option. In patients with the potentially progressive disease FACM, where AF is a manifestation of a structural atrial disease, catheter ablation can also effectively treat AF but ablation cannot be considered curative. Verma et al. reported that pre-existent left atrial scarring in patients undergoing ablation was an independent predictor of procedural failure, which was confirmed in DE-MRI studies. Progressive atrial remodelling after ablation in FACM cases may explain late recurrences despite durable PV isolation and development of ‘new’ arrhythmias. In addition, the association of left atrial fibrosis and the risk of stroke in patients with AF will need to be considered for oral anticoagulation strategies in the future.

**Fibrotic atrial cardiomyopathy: summary and outlook**

There is substantial evidence that the majority of patients without apparent structural heart disease (so-called ‘lone’ AF) has a chronic fibrotic bi-atrial substrate. A higher mean value of fibrosis is detected in patients with persistent vs. paroxysmal AF. A higher mean value of fibrosis is detected in patients with persistent vs. paroxysmal AF. However, the variability in the extend of fibrosis in patients with...
paroxysmal and persistent AF is very high with part of paroxysmal AF patients having massive fibrosis as well as part of persistent AF patients showing mild fibrosis.15,17,18 Thus, these data do not support a causal relationship that AF (significantly) produces fibrosis in the sense of ‘AF begets AF’ instead of being a consequence of the fibrotic process in FACM (Figure 6). There are obviously patients with ‘lone’ AF, where the substrate is already very advanced with massive bi-atrial fibrosis before the advent of AF.3 Accordingly, no clear correlation could be demonstrated between the extent of fibrosis and the duration of AF history.16,18 The analysed studies with different methodologies are very consistent, however, the relatively small size of some of these studies necessitates confirmation and extension in future trials.

Other ‘conventional wisdoms’ also need to be re-considered. In the autopsy investigation specifically addressing the role of age, no correlation at all could be detected between patient age and fibrosis extent.19 Instead, the clinical manifestation of FACM with cardiac arrhythmias in most patients occurs in advanced ages (>60 years) and less frequently in younger ages. In the same line, the degree of left atrial structural remodelling was found to be independent of co-morbidities (e.g. hypertension, diabetes) in DE-MRI and autopsy studies.16,18 Given these results that age and ‘classical’ co-morbidities have no association with the extent of atrial fibrosis, these data all indicate that the chronic bi-atrial substrate of patients with AF is the result of a specific FACM. Further striking evidence for the existence of FACM in patients with ‘lone’ AF comes from electroanatomic mapping studies on the reversibility of human atrial structural remodelling.20,21 In patients with mitral stenosis, there was clear evidence for reverse atrial remodelling after commissurotomy. However, in patients with ‘lone’ AF, the atrial substrate progressed despite successful AF elimination indicating towards the independent and potentially progressive disease process of FACM.

Different expressions of the FACM disease exist from mild-to-severe fibrosis (FACM I–II), and with wide clinical variations from asymptomatic cases to cases with multiple arrhythmic manifestations, atrial mechanical dysfunction as well as thromboembolic complications.2 Clinically, the co-existence of sick sinus node plus paroxysmal AF (‘bradycardia–tachycardia–syndrome’) is the most frequent FACM manifestation combination.3,11 Recently, localized electrical ‘rotors’ have been described as prevalent sustaining mechanisms of human AF, and catheter ablation at patient-specific sources improved clinical outcome.4 It might be speculated that these patient-specific sources correlate with areas of atrial fibrosis where the site-specific micro-architecture of connective tissue fibres and the remaining myocardial fibres allows re-entrant/rotor activation to occur and to sustain. The combination of localizing atrial fibrosis plus mapping of specific functional areas allowing re-entrant/rotor activation may hold promise for catheter-based AF substrate modification in the future.

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References
Epicardial Wolff–Parkinson–White ablation

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A 45-year-old female patient without structural heart disease was referred for redo Wolff–Parkinson–White (WPW) ablation after an unsuccessful endocardial procedure. The refractory period of the accessory pathway had been measured at 230 ms and antiarrhythmic treatment with flecainide was unsuccessful.

(1) The surface electrogram shows the largest negative Δ-wave in lead III.

(2) During endocardial mapping of the ventricular insertion the earliest activation was found near the coronary sinus ostium (x); however, radiofrequency application was not successful. Note the morphology of the unipolar signal (Abl uni) with an initially positive small spike (red arrow) resulting from epi-endocardial activation followed by the broad negative ventricular activation signal.

(3) Epicardial mapping via subxiphoidal access showed the earliest signal (XX) opposite to the endocardial site (X). The distance between the two locations was 1.5 cm. Note the morphology with an entirely negative small pathway spike (red arrow) followed by the broad negative ventricular activation signal. Irrigated radiofrequency ablation was successful after 25 s and increase of power from 20 to 30 W.

Epicardial access can be necessary, if the largest negative Δ-wave is in lead III on the surface ECG. The morphology of the unipolar signal indicates the true epicardial origin of the ventricular pathway insertion. Success can be observed even after delayed response to RF delivery.

In Panel 1: ECG, electrocardiogram; LAO, left anterior oblique; Abl, ablation electrode; CS, coronary sinus; CSp, coronary sinus electrode proximal; Csd, coronary sinus electrode distal; RV, right ventricular electrode; LAT, local activation time measured relative to onset of QRS signals on surface ECG. The local activation time is measured conventionally (middle) and visualized in a coloured Carto-3D map (red earliest).