Intensive research over the last few decades has seen significant advances in our understanding of the complex mechanisms underlying atrial fibrillation (AF). The epidemic of AF and related hospitalizations has been described as a ‘rising tide’ with estimates of the global AF burden showing no sign of retreat. There is urgency for effective translational programs in this field to facilitate more individualized and targeted therapy to modify the abnormal atrial substrate responsible for the perpetuation of this arrhythmia. In this review, we chose to focus on several novel aspects of AF pathogenesis whereby practical applications in clinical practice are currently available or potentially not too far away. Specifically, we explored the contribution of atrial fibrosis, epicardial adipose tissue, autonomic nervous system, hyper-coagulability, and focal drivers to adverse atrial remodelling and AF persistence. We also highlighted the potential practical means of monitoring and targeting these factors to achieve better outcomes in patients suffering from this debilitating illness. Emerging data also support a new paradigm for targeting AF substrate with aggressive risk factor management. Finally, multi-disciplinary integrated care approach has shown great promise in improving cardiovascular outcomes of patients with AF along with potential cost savings.

Keywords
Atrial fibrillation • Pathogenesis • Mechanisms • Substrate • Risk factor management • Integrated care

Introduction
The pathophysiologic mechanisms responsible for the development of atrial fibrillation (AF) are known to be complex and variable in different individuals suffering from this debilitating arrhythmia. Novel risk factors for AF have been identified over the last decade including obesity, pericardial fat, obstructive sleep apnoea, aortic stiffness, pre-hypertension, excessive endurance exercise, and new genetic variants. Several promising mechanistic links to AF have also emerged from recent studies regarding microRNAs, intracellular calcium homeostasis, heat shock proteins, and autonemics. Moreover, mapping studies have implicated the potential role of rotors and endo-epicardial dissociation as drivers and sustainers of AF. Understanding how these myriad of factors interact and contribute to the pathogenesis of AF in an individual remains a challenge in our bid to combat this arrhythmia. Catheter ablation strategies for treating AF have shown promising long-term results with declining complication rates. However, the attrition in success rates following such labour and resource intensive procedures is of great concern and highlights progression of the primary process with an evolving underlying substrate. To this end, there has been increased focus on thorough assessment of risk factors in affected individuals with an aim to prevent AF progression and complications. Importantly, recent studies have demonstrated that aggressive targeting of the risk factors responsible for abnormal atrial remodelling can reduce AF burden and improve ablation outcome. In this review, we focused on several novel aspects in the pathogenesis of AF whereby practical management or therapeutic options are currently available or potentially on the horizon.
Atrial fibrosis

Atrial fibrosis has been a common feature in remodelling due to various risk factors such as heart failure, hypertension, and obesity, contributing to the development of AF. Moreover, AF itself can also promote atrial fibrosis with recent experimental work showing increased endomyssial fibrosis especially in the epicardial layer. Direct histological evidence of increased atrial fibrosis and indirect evidence of reduced atrial voltage from electroanatomical mapping have been demonstrated in humans with heart failure, valvular heart disease, hypertension, obstructive sleep apnoea, advancing age, and ‘lone’ AF. A multitude of signalling pathways are involved in the pro-fibrotic process due to the underlying risk factors or AF itself, although current understanding of these complex pathways remains incomplete. The following are known to be involved: pro-inflammatory cytokines, oxidative stress, transforming growth factor-β, connective tissue growth factor, renin–angiotensin–aldosterone system, calcium-dependent proteases/phosphatases, extracellular matrix regulatory proteins, hypoxia-inducible factor-1α, and endothelin-1 system. Several interventional studies have shown that the atrial fibrosis can be attenuated or prevented in various experimental models with agents such as renin–angiotensin–aldosterone inhibition, HMG-CoA reductase inhibitor, n-3 polyunsaturated fatty acids, and anti-fibrotics including pirfenidone, tranilast, and relaxin. Perhaps, due to the historical lack of a non-invasive means of quantifying atrial fibrosis, these agents have not been studied in detail in the clinical setting.

Importantly, several studies have highlighted that reversing the risk factor contributing to AF development can reduce AF burden and possibly atrial fibrosis.

Recently, several groups have reported on the quantification of atrial fibrosis using late gadolinium-enhanced magnetic resonance imaging (LGE-MRI), although it has become apparent that LGE-MRI is a challenging imaging technique limited by variable image and analytical algorithms. Daccarett and coworkers demonstrated that the ‘computed tomography-derived pericardial fat volume predicted AF risk independent of other measures of adiposity.’ Similarly, Batal and coworkers demonstrated that the ‘computed tomography-derived posterior left atrial fat thickness’ was associated with AF burden, independent of left atrial area and body mass index. Further, Wong et al. reported that cardiac magnetic resonance-derived atrial pericardial fat was associated with the severity of AF and post ablation recurrence, which persisted after adjusting for body weight. Importantly, the association between pericardial fat with AF has been found to be independent of other measures of obesity. These studies provide the foundation for the hypothesis that the epicardial fat may exert a direct impact on the atrial substrate in obese subjects.

The development of the obese state has been shown to be associated with hypoxia of the expanding adipose tissue resulting in adipose tissue fibrosis and production of a myriad of adipokines including TGFβ superfamily. The paracrine effect of these adipokines is facilitated by the absence of fascial barriers between the epicardial fat and contiguous atrial musculature and the common vascular supply. Venteclcf et al. demonstrated the paracrine effects of epicardial fat in inducing atrial fibrosis by incubating secretome derived from human epicardial fat in a rat organo-culture model. In addition, epicardial fat has been shown to infiltrate the underlying myocardium in both large animal and human atria samples. It is likely that fatty infiltration could separate myocytes and result in conduction abnormalities in a fashion similar to microfibrosis. The combination of increased epicardial adiposity, atrial fibrosis, and altered three-dimensional atrial architecture could therefore be pro-fibrillatory with increased likelihood of conduction heterogeneity/anisotropy that may sustain re-entry, electrical dissociation, and wave breakthrough. Non-invasive atrial epicardial fat quantification has recently been validated using magnetic resonance imaging. This will facilitate further studies on the effect of epicardial fat on atrial remodelling and whether weight loss or other medical therapies can reverse the epicardial atrial fat burden and its consequences on the atrial substrate. Improved understanding of the biology of epicardial adipose tissue may lead to novel therapeutics targeting adipokines and more targeted ablative strategies.

Epicardial adipose tissue

There is emerging data to suggest that local epicardial fat depots have an important role in the development of the AF substrate. Several clinical studies have confirmed a relationship between epicardial fat and AF. The term ‘epicardial’ and ‘pericardial’ fat has been used inter-changeably but most studies have reported on the fat located in the pericardial sac. The Framingham Heart Study Offspring and Third Generation Cohorts reported that computed tomography-derived pericardial fat volume predicted AF risk independent of other measures of adiposity. Similarly, the Framingham Heart Study Offspring and Third Generation Cohorts reported that computed tomography-derived pericardial fat volume predicted AF risk independent of other measures of adiposity. These studies provide the foundation for the hypothesis that the epicardial fat may exert a direct impact on the atrial substrate in obese subjects.

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Autonomic atrial remodelling

The autonomic nervous system is intricately associated with the AF substrate as well as its initiation and persistence. This is not
surprising as the atria are innervated by both the parasympathetic and sympathetic components of the extrinsic ganglia, the complex neural ganglionated plexi (GP) network of the intrinsic ganglia as well as the mechano/baro/chemo-receptors within the heart and great vessels (Figure 1). For decades, both β-adrenergic and cholinergic stimulations have been used to induce AF in experimental studies. Similarly, changes in sympa-tho-vagal balance have been recorded during AF onset in both human and animal studies.62,63 Furthermore, autonomic atrial remodelling has been demonstrated in various experimental models. In brief, rapid rates of AF were found to lead to a heterogeneous increase in atrial sympathetic innervation.64 In the heart failure model, increased sympathetic/parasympathetic fibres and cardiac ganglia were seen in the posterior left atria and pulmonary veins contributing to AF maintenance.65 Increased parasympathetic tone with augmented baroreceptor responsiveness and increased cardiomyocyte sensitivity to cholinergic stimulation were seen with atrial dilatation and fibrosis following chronic endurance training to contribute to AF susceptibility.66 In a large animal model of obstructive sleep apnoea with negative tracheal pressure, enhanced vagal activation was found to contribute to shortening of atrial refractoriness and increased AF.67 The mechanisms by which these autonomic changes can promote and sustain AF are highly complex to involve enhanced automaticity, early/delayed after-depolarizations, and spatially heterogenous abbreviation of refractoriness, as detailed in a recent review by Chen et al.12

Figure 1  Autonomic nervous system and neuromodulation for atrial fibrillation. From Chen et al.12 showing the complex atrial autonomic innervation by both the sympathetic and parasympathetic components of the extrinsic ganglia, ganglionated plexi network of the intrinsic ganglia, and baroreceptors within the great vessels. Black dots indicate neuromodulation sites. VLCCN, ventral lateral cervical cardiac nerve; VMCCN, ventromedial cervical cardiac nerve. Original illustration by Ben Smith.
Various methods of autonomic nervous system modulation have been shown to ameliorate the atrial remodelling in experimental studies. In atrial tachypacing AF models, GP ablation, pharmacological autonomic blockade, high thoracic epidural anaesthesia to block cardiac sympathetics, and low-level vagosympathetic nerve stimulation were able to prevent abbreviation of atrial refractoriness and reduce AF inducibility.68–70 However, the same effects were not seen with renal sympathetic denervation (RSDN) except for slowing of ventricular rate during AF and reduced AF duration following atrial tachypacing.71 More recent high-density-mapping studies in the goat model of AF have demonstrated reduced AF complexity (reduced fibrillation waves and wave breakthroughs) together with reduced atrial sympathetic nerve sprouting and reduced fibrosis following RSDN.72 In a model of obstructive sleep apnoea, both negative tracheal pressure-induced atrial refractoriness shortening and blood pressure elevation were inhibited by RSDN.73 In separate studies, pharmacological autonomic blockade and GP ablation could reduce the AF inducibility due to acute obstructive sleep apnoea.74,75 In ambulatory dogs with pacing-induced heart failure, reduction in atrial arrhythmias was seen following cryo-ablation of the stellate ganglia.76 However, more recent studies demonstrated a paradoxical effect of GP ablation with reduced atrial refractoriness and increased AF inducibility at longer-term follow-up.77,78 This may explain the diverse outcome of GP ablation in human AF, although a recent randomized trial showed superior outcome when GP ablation was done in conjunction with pulmonary vein isolation for paroxysmal AF patients.79–81

More recently, RSDN has shown promising results in humans with one small randomized study demonstrating superior result with combined pulmonary vein isolation and RSDN to pulmonary vein isolation alone in patients with resistant hypertension and symptomatic AF.82 In this study, patients who underwent both interventions had significantly lower blood pressure profile and lower recurrence of AF at 12-month follow-up.82 It is very likely that the beneficial effect of additional RSDN is to a degree derived from improved blood pressure control given the findings that the greatest benefits were seen in those with severe drug-resistant hypertension and persistent AF.83 Importantly, mice overexpressing PAR-1 developed cardiac hypertrophy and dilated cardiomyopathy while its deficiency reduced both hypertrophy and cardiomyopathy due to ischaemia and reperfusion injury.84 Similarly, PAR-2 deficiency reduced both infarct size and inflammatory responses in ischaemia–reperfusion models.97 In humans, PAR-1 expression is elevated with ischaemic heart disease or heart failure.85 Protease-activated receptors are also involved in the pathogenesis of atherosclerosis. In transgenic mice with hypercoagulability, the atherosclerotic phenotype of ApoE knockout mice was strongly aggravated. This effect was fully prevented by the direct thrombin inhibitor, dabigatran.99

Further insights on the role of PARs on atrial structural remodelling could be gained from recent pilot experiments at the cellular and whole animal levels.100 In isolated rat cardiac fibroblasts, thrombin enhanced the phosphorylation of the pro-fibrotic signalling molecules Akt and Erk, and increased expression of TGFβ1 and the pro-inflammatory factor monocyte chemo-attractant protein-1. Thrombin also increased the incorporation of 3H-proline, suggesting enhanced collagen synthesis by fibroblasts. All these effects were attenuated by thrombin inhibition with dabigatran. In goats with persistent AF treated with nadroparin, targeting Factor Xa and thrombin, the complexity of the AF substrate was less pronounced than in control animals. In the treated animals, AF-induced α-smooth muscle expression was lower and endomyocardial fibrosis was less pronounced. These pilot studies strongly support the role of PAR activation by the activated coagulation cascade to the development of a substrate for AF as recently outlined in a separate
The hypothesis that the coagulation system is involved in the atrial remodelling system is also supported by a recent study whereby Factor Xa provoked pro-inflammatory responses and an upregulation of PAR receptors in human atrial tissues. These responses were aggravated by rapid pacing and could be prevented by a Factor Xa inhibitor. Hyper-coagulability may also contribute to AF initiation and progression by altering calcium handling. This was demonstrated in isolated rabbit pulmonary vein sleeves whereby thrombin-induced after-depolarizations and burst firing were inhibited by dabigatran.

Ischaemia may play an important role in the activation of the interstitial coagulation system. In ischaemic infarct border zones, Erlich et al. demonstrated upregulation of tissue factor on the myocyte surface resulting in interstitial fibrin deposition and interestingly, thrombin inhibition by hirudin could reduce the infarct size. Importantly, there is experimental evidence for atria supply–demand mismatch and ischaemia with increased atrial lactate production during acute AF. Further, high-energy phosphate concentrations are reduced after short period of AF and markers for ischemia are upregulated in fibrillating atria. Taken together, a significant activity of coagulation factors exists in the interstitial space and ischaemia during AF could activate the coagulation system leading to fibroblast activation, cellular hypertrophy, and atrial fibrosis to produce a substrate for AF. Therefore, anticoagulation therapy may confer atrial electrical and structural protective effects to reduce AF burden in addition to preventing thromboembolic complications.

AF mechanisms: insights from mapping studies

Early mapping studies have demonstrated complex electrical activations with re-entrant circuits during AF indicating a heterogeneous electrophysiological substrate. In 1998, Haissaguerre et al. reported on the spontaneous initiation of AF by ectopic focal activity in the pulmonary veins. Not only did this seminal finding provide the basis for pulmonary vein isolation as cornerstone of catheter ablation therapy, it has also fuelled a plethora of translational research on AF mechanisms. In a bid to improve outcome of catheter ablation in those with persistent AF, electrophysiologists have performed additional ablation based on substrate mapping guided by electrogram fractionation and sites with high dominant frequency. However, the temporal variability of AF electrograms together with the diverse underlying mechanisms and the inherent technical challenges with such mapping techniques have hampered the success of substrate-guided ablation approaches.

**Figure 2** Invasive and non-invasive mapping for rotors in atrial fibrillation. (A) From Narayan et al. showing fluoroscopy image of bi-atrial mapping using 64-electrode basket catheter and (B) two consecutive left atrial clockwise rotations (white arrows) in the activation maps. (C) Non-invasive mapping using ECVue vest (252 body surface electrodes, CardiolInsight Technologies Inc, Cleveland, OH, USA) is combined with CT thorax to help map epicardial activations during atrial fibrillation. (D) Here, two consecutive counterclockwise rotor activities are depicted near the right pulmonary veins ostia from Haissaguerre et al.
More recently, the focus in the field has shifted to identification and ablation of rotors which can be defined as highly localized drivers or organized sources of re-entrant tachycardia and fibrillation that may be critical to AF sustenance with phase mapping using endocardial high-density 64-electrode basket catheter (Figure 2). Narayan and colleagues have demonstrated superior 3-year outcome with additional ablation of rotors and focal sources to conventional wide area circumferential pulmonary vein isolation alone. Furthermore, Haissaguerre and co-workers were able to acutely terminate 75% of persistent AF following ablation of re-entrant and breakthrough drivers guided by phase mapping of AF recorded from non-invasive array of 252 body surface electrodes and thoracic computed tomography for bi-atrial geometric localization (Figure 2). Of note, one of the key electrophysiological characteristics of such drivers remains contentious with some purporting rotors to be highly stable for thousands of cycles and others finding them largely transient and unstable from both phase mapping and direct contact activation mapping. In addition, alternative rotor mapping method is being investigated in humans using Shannon entropy of bipolar electrogram which has been shown to be consistent in localizing rotor pivot zone. Mechanistically, endo-epicardial electrical dissociation between the complex three-dimensional myocardial bundle architecture in the atria rather than ectopic focal discharges has been found to be largely responsible for some of these ‘drivers’. Specifically, atrial bundle re-arrangement has been found to underlie anisotropy of conduction and endo-epicardial electrical dissociation. The availability of new clinical mapping system with mini-basket mapping catheter may provide the opportunity for higher fidelity studies critical for mapping AF. Taken together, advancement in mapping studies has unveiled novel insights regarding the electrophysiological mechanisms driving AF. Undoubtedly, further studies are required to strengthen our understanding of the complex electrical activation patterns during AF to facilitate more targeted ablative approach.

Towards individualized mechanistic-based atrial fibrillation management

Conventional treatment paradigm for AF has focused on rate and rhythm control with appropriate anticoagulation therapy for prevention of thromboembolic complications according to the individual’s risk profile. Current rhythm control strategies with anti-arrhythmic drugs are limited by the lack of atrial-specific agents, modest efficacy, and significant toxicities including risk of pro-arrhythmia. Alternatively, catheter ablation is now a widely accepted procedure, especially for patients with symptomatic AF despite anti-arrhythmic drug therapy. However, despite improving safety and success rates, the outcomes remain suboptimal for

Figure 3 Individualized mechanistic-based atrial fibrillation management. Various non-invasive substrate based atrial mapping can help to improve phenotyping of AF patients. These may include: (A) atrial pericardial adipose tissue assessment using CMR from Mahajan et al. (B) atrial fibrosis detection using LGE-CMR from Daccarett et al. (C) non-invasive mapping of AF rotors from Haissaguerre et al. (D) assessment of pro-coagulation state; (E) assessment of sympathetic tone from measurement of subcutaneous nerve activity from Robinson et al.
those with persistent AF and follow-up studies have shown attri-
tion over time with need for repeat procedures. As such, spe-
cific mechanistic-based therapeutic options are urgently needed to
modify the complex interactions between triggers and substrate
maintaining AF in a given individual. The novel pathogenic insights
highlighted in this focused review on AF mechanisms will help to
overcome some of the practical challenges towards individualized
mechanistic-based management of AF.

Defining the individualized atrial fibrillation substrate
For decades, the key factors guiding the clinical management of AF
are based on symptom severity and chronicity of the arrhythmia.
There is a need to better define the AF substrate in an individual be-
"Beyond such primitive notions given the diverse mechanistic processes
that could be involved. Several less invasive diagnostic options are
now available to improve phenotyping of AF individuals, although
more work is needed to further ascertain their accuracy and repro-
ducibility. As illustrated in Figure 3, LGE-MRI may prove to be a use-
ful non-invasive tool to quantify the degree of atrial fibrosis.
Likewise, MRI or computed tomography scans can be utilized to de-
lineate the epicardial fat burden. Also, non-invasive body surface
mapping has been shown to be feasible in defining the atrial electric-
al substrate from recent report. Measurement of subcutaneous
nerve activity of the thorax using bipolar electrodes is under inves-
tigation for determining the contribution of sympathetic tone to ar-
rhythmogenesis. It remains to be determined how measurement
of procoagulant factors can add to the overall quest to better define
the AF substrate to guide more targeted therapy.

Pursuing more specific atrial fibrillation therapies
Improved phenotyping of AF patients through improved definition
of the underlying substrate may allow for more specific AF therapies
(Figure 3). These may range from upstream therapy with targeting of
the pro-fibrotic signalling pathways through renin–angiotensin–
aldosterone inhibition or anti-fibrotic compounds to more targeted
ablative strategy as guided by areas with AF drivers or high epicardial
fat burden. Other novel-targeted approaches will include neuromo-
dulation strategies to modify the cardiac autonomies and more spe-
cific agents to treat the hyper-coagulable state that can promote
adverse remodelling. All the above options are potentially feasible
and further studies are needed to quantify their effects on the atrial
substrate using novel mapping and imaging techniques as described
in the previous section.

Targeting the substrate with aggressive risk factor
management
The notion that AF is a progressive disease, which is compounded
by ongoing remodelling consequent to the various underlying risk
factors, calls for early and aggressive risk factor intervention.
There is a need to actively identify the risk factors that may contri-
"In a prospective, randomized, and
controlled trial, we have shown that weight reduction with intensive
risk factor management could result in beneficial cardiac remodel-
ling and reduced AF burden and severity in overweight or obese

Figure 4 Aggressive risk factor management. Adapted from Pathak et al. BMI, body mass index; LDL, low-density lipoprotein; TG, triglyceride;
BP, blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, AH1, apnoea–hyponoea index; CPAP, continuous positive airway pressure.
patients with symptomatic AF. The LEGACY study further consolidated the long-term benefits of weight reduction, demonstrating a dose-dependent improvement in AF free survival. Similarly, aggressive risk factor management strategy has been shown to improve the long-term arrhythmia-free survival following catheter ablation for AF in conjunction with improved metabolic status in those with body mass index $\geq 27$ kg/m$^2$ at study baseline. Aggressive risk factor management comprised of 3-monthly clinic visits to facilitate the following goals (Figure 4): weight loss of at least 10%, frequent moderate intensity exercise up to 250 min/week, lipid management with LDL cholesterol $< 100$ mg/dl, glycaemic control with HbA1c $\leq 6.5\%$, blood pressure target of $< 130/80$ mmHg, continuous positive airway pressure therapy if overnight polysomnography showed apnoea–hyponoea index $> 30$/h or $> 20$/h in the presence of resistant hypertension or daytime somnolence, complete smoking cessation, and alcohol consumption to $< 30$ g/week or abstinence.

Rationale for integrated chronic care approach for atrial fibrillation

Ongoing research has unravelled many new insights regarding the pathogenesis of AF, further highlighting the complexity and heterogeneity of the disease. Atrial fibrillation management has thus become a complex process requiring focus on the rhythm and symptom management, prevention of thromboembolic complications, treatment of underlying heart disease and aggressive targeting of modifiable cardiovascular risk factors. As such, adherence to recommended management guidelines remains suboptimal, resulting in unnecessary cardiovascular morbidity and mortality. Indeed, the trend of increasing hospitalizations due to AF and high mortality in AF individuals remains a great concern. Recent work has highlighted that software supported integrated care in terms of a nurse-led, guideline-based, and specialized AF outpatient clinic could reduce cardiovascular hospitalizations and death in patients with AF together with improved guidelines adherence in comparison to routine care. This model of integrated care exemplifies a comprehensive approach through integration of multi-disciplinary teams wherein allied health professionals provide patient education and care coordination, while the supervising physician focuses on the medical care (Figure 5). Such redesign in health care does not imply greater expenditure since this integrated approach has been shown to be a cost-effective management strategy.

Conclusions

Advances in our understanding of the pathogenesis of AF have matured significantly to allow for improved phenotyping of AF individuals beyond mere categorizing of AF based on its chronicity. The
ultimate goal of targeting the specific individualized substrate must be accompanied by aggressive risk factor management and a multidisciplinary integrated chronic care approach to achieve optimal adherence to guidelines and improved outcomes.

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