Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The prevalence of AF increases dramatically with age and is seen in as high as 9% of individuals by the age of 80 years. In high-risk patients, the thromboembolic stroke risk can be as high as 9% per year and is associated with a 2-fold increase in mortality. Although the pathophysiological mechanism underlying the genesis of AF has been the focus of many studies, it remains only partially understood. Conventional theories focused on the presence of multiple re-entrant circuits originating in the atria that are asynchronous and conducted at various velocities through tissues with various refractory periods. Recently, rapidly firing atrial activity in the muscular sleeves at the pulmonary veins ostia or inside the pulmonary veins have been described as potential mechanism., AF results from a complex interaction between various initiating triggers and development of abnormal atrial tissue substrate. The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. To have effective surgical or catheter ablation of AF good understanding of the possible mechanism(s) is crucial. Once initiated, AF alters atrial electrical and structural properties that promote its maintenance and recurrence. The role of atrial remodeling (AR) in the development and maintenance of AF has been the subject of many animal and human studies over the past 10-15 years. This review will discuss the mechanisms of AR, the structural, electrophysiologic, and neurohormonal changes associated with AR and it is role in initiating and maintaining AF. We will also discuss briefly the role of inflammation in AR and AF initiation and maintenance, as well as, the possible therapeutic interventions to prevent AR, and hence AF, based on the current understanding of the interaction between AF and AR.

Abstract

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The prevalence of AF increases dramatically with age and is seen in as high as 9% of individuals by the age of 80 years. In high-risk patients, the thromboembolic stroke risk can be as high as 9% per year and is associated with a 2-fold increase in mortality. Although the pathophysiological mechanism underlying the genesis of AF has been the focus of many studies, it remains only partially understood. Conventional theories focused on the presence of multiple re-entrant circuits originating in the atria that are asynchronous and conducted at various velocities through tissues with various refractory periods. Recently, rapidly firing atrial activity in the muscular sleeves at the pulmonary veins ostia or inside the pulmonary veins have been described as potential mechanism., AF results from a complex interaction between various initiating triggers and development of abnormal atrial tissue substrate. The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. To have effective surgical or catheter ablation of AF good understanding of the possible mechanism(s) is crucial. Once initiated, AF alters atrial electrical and structural properties that promote its maintenance and recurrence. The role of atrial remodeling (AR) in the development and maintenance of AF has been the subject of many animal and human studies over the past 10-15 years. This review will discuss the mechanisms of AR, the structural, electrophysiologic, and neurohormonal changes associated with AR and it is role in initiating and maintaining AF. We will also discuss briefly the role of inflammation in AR and AF initiation and maintenance, as well as, the possible therapeutic interventions to prevent AR, and hence AF, based on the current understanding of the interaction between AF and AR.
various velocities through tissues with various refractory periods\(^2\).

Recently, rapidly firing atrial activity in the muscular sleeves at the pulmonary veins ostia or inside the pulmonary veins have been described as potential mechanism for AF.\(^3\) AF results from a complex interaction between various initiating triggers and development of abnormal atrial tissue substrate.\(^6\) The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. These changes further perpetuate the existence and maintenance of this arrhythmia (i.e., “atrial fibrillation begets atrial fibrillation”).\(^4\)

There has been an increase interest in AF surgical and catheter ablation in the past 15 years aiming to reduced its morbidity and mortality. However these procedures have limited success and are not without risk.

To have effective surgical or catheter ablation of AF good understanding of the possible mechanism(s) is crucial. Once initiated, AF alters atrial electrical and functional properties that promote its maintenance and recurrence. The role of atrial remodeling in the development and maintenance of AF has been the subject of many animal and human studies over the past 10-15 years. This review will discuss the mechanisms of atrial remodeling (AR), the structural, electrophysiologic, and neurohormonal changes associated with AR and it is role in initiating and maintaining AF. We will also discuss briefly the role of inflammation in AR and AF initiation and maintenance, as well as, the possible therapeutic interventions to prevent AR, and hence AF, based on the current understanding of the interaction between AF and AR.

**Atrial remodeling**

Atrial remodeling refers to structural and functional changes in the atrial myocytes in response to internal or external stimuli. Atrial remodeling may also be described as a time-dependent adaptive regulation of cardiac myocytes in order to maintain homeostasis against external stressors.\(^7\) The strength and the duration of exposure to the “stressors plays a major role in determining the extent of AR.\(^8\) Exposure to external stressors for a short period of time (<30 minutes) may lead to responses at the ionic/genomic level, which is usually reversible.\(^9\) Mid-term exposure (< or = 1 week)\(^10\) may result in changes at the cellular level which are usually reversible; however long-term exposure (>5 weeks)\(^11\) may result in changes at the cellular/ extracellular matrix level (e.g. apoptosis and fibrosis) and is usually irreversible.

Atrial remodeling may occur in response to tachycardia with high rates of cell depolarization as in patients with AF. In this case, AF is initially maintained by ectopic activity or single-circuit reentry in a given patient, but the high atrial rates induce spatially heterogeneous refractoriness abbreviation which creates conditions favorable to multiple-circuit reentry. This multiple reentry circuits reentry may then become the AF-maintaining mechanism. Thus, multiple-circuit reentry may be a final common pathway AF mechanism in many patients. Hence the term “AF begets AF”\(^4\).

Atrial remodeling may also occur in response to volume/pressure overload such as in heart failure syndromes. Specific stressors, such as diastolic dysfunction, ischemia, and valvular diseases, e.g. mitral stenosis and mitral regurgitation, impose excess pressure and/or volume load on the atrial myocytes, which responds with a range of adaptive, as well as maladaptive, processes.\(^7\) These processes include myocyte growth, hypertrophy, necrosis, and apoptosis, alterations in the composition of extracellular matrix, recalibration of energy production and expenditure, changes in the expression of cellular ionic channels and atrial hormones and reversal to a fetal gene program. These changes promote a cascade of reactions, which lead to AR with structural, functional, electrical, metabolic, and neurohormonal consequences.\(^7\)

**Structural and ultra-structural changes in atrial remodeling**

**Atrial structural and ultra-structural changes due to rapid atrial rates**

Rapid atrial rate is associated with structural and ultra-structural changes in both right and left atria. Starting with the structural changes; in clinical practice there is a clear relationship between...
AF and atrial dilatation. For many years atrial dilatation has been recognized as a predictive factor for the development of AF. On the other hand, atrial diameters have been shown to further increase when AF is present. Sanfillipo et al. demonstrated an increase in atrial diameters of almost 40% during a mean follow-up of 20.6 months in patients with AF and in the absence of structural heart disease. In addition, it has been demonstrated that atrial diameters may decrease after conversion of AF to sinus rhythm. Rapid atrial pacing for 6 weeks in healthy dogs was shown to result in progressive biatrial enlargement. Furthermore AF results in loss of atrial contraction and the recovery of this function may take weeks to months to be seen after cardioversion depending on the duration of the previous episode of AF.

In terms of atrial ultra-structural changes due to high atrial rates, chronic experimental AF leads to extensive changes in atrial ultra-structure. The nature and time course of these alterations have been elaborately investigated in goats by Ausma et al. in which after 9 to 23 weeks of artificially maintained AF, they found marked changes in atrial cellular substructures, including loss of myofibrils, accumulation of glycogen, changes in mitochondrial shape and size, fragmentation of sarcoplasmic reticulum, and dispersion of nuclear chromatin. These changes were present in up to 92% of studied atrial cells and are considered to be a sign of dedifferentiation rather than degeneration, that is, the cells seemed to have changed to a fetal phenotype.

There are few studies describing atrial ultra-structural changes in humans suffering AF. Bailey et al. reported the first study in which the atrial myocardium of living patients with AF was examined. They obtained atrial tissue from patients undergoing valve surgery for rheumatic valve disease. Of the 44 patients included, 32 were in AF, of whom 18 had AF for more than 5 years at the time of surgery. They observed that long-term AF was characterized by loss of muscle mass, which they described as diffuse atrophy. The presence of rheumatic heart disease, however, may have importantly influenced the structural abnormalities that were seen.

Mary-Rabine et al. described the relationship between atrial cellular electrophysiology, function, and ultra-structure in 121 patients undergoing cardiac surgery, of whom 23 had AF. Atrial biopsies obtained from patients with AF showed ultra-structural abnormalities such as loss of myofibrils and disorganization of sarcoplasmic reticulum. However, interpretation of these changes is difficult because AF was associated with higher patient age and atrial dilatation, factors independently associated with these structural changes.

Brundel et al. evaluated atrial tissue of patients with normal ventricular function undergoing coronary artery bypass grafting and compared patients with persistent AF, paroxysmal AF, and sinus rhythm. In patients with paroxysmal and persistent AF, contraction bands were observed, which were virtually absent in patients with sinus rhythm. In patients with AF, degenerative features such as clumping of nuclear chromatin and the presence of lysosome-like bodies were present. Furthermore, only in patients with persistent AF, were hibernating atrial myocytes found, characterized by glycogen accumulation and the dispersion of nuclear chromatin.

Apart from these intracellular changes, alterations in expression of atrial intercellular gap junctions have been described during AF. These gap junctions are responsible for the cell-to-cell propagation of electrical conduction and consist of 2 connexons, each formed by 6 proteins called connexins. In the heart, connexin 43 is the most abundant, whereas connexin 40 is mainly present in the atrium.

Whether AF-induced changes in these connexins play a significant role in atrial remodeling remains a subject of debate.

AF has been shown to be associated with a net increase or decrease in connexin 40 expression with redistribution to the lateral borders of the atrial myocytes. This may result in anisotropy and dispersion of atrial conduction, thus favoring an environment vulnerable to AF.

**Atrial structural and ultra-structural changes due to volume/pressure overload**
Atrial remodeling due heart failure or other causes of increased atrial volume /pressure overload is characterized primarily by biatrial dilatation, which is considered an important factor in the genesis of atrial arrhythmias in these patients. In the presence of acute or chronic stress or injury, the atria stretch and stiffen.\(^28,29\) Larger atrial size means that more circuits can be accommodated and that long-wavelength circuits that are too large for a normal atrium can be supported. Atrial dimensions are a particularly important determinant of the occurrence of multiple-circuit reentry.\(^30\) In canine models, Shi. et al.\(^31\) showed that five weeks of rapid ventricular pacing (220-240 beats per minute) resulted in an increase of 80.2% and 61.2% in left and right atrial diastolic area, respectively, as measured by transthoracic echocardiography. This biatrial dilatation was associated with a decrease in atrial contractile function, which was reflected by a decrease in left and right fractional area shortening of 41.8% and 33.7%, respectively. Similar results were obtained by Power et al.\(^32\) who found a 100% increase in diastolic left atrial cross-sectional area in sheep after 6 weeks of rapid ventricular pacing. In patients with diastolic dysfunction, there is also a clear relationship between the magnitude of diastolic dysfunction and left atrial diameter and volume which could explain the propensity to develop AF in patients with hypertension and diastolic dysfunction \(^33,34\).

Verheule et al.\(^36\) showed that chronic atrial dilatation in dogs due to experimental mitral regurgitation in the absence of overt CHF results in atrial fibrosis, signs of chronic inflammation, and increased accumulation of glycogen.

Aimé-Sempé et al.\(^37\) investigated human specimens of dilated right atrial myocardium and found signs of apoptosis and myolysis in patients with AF as well as in patients with a decreased left ventricular ejection fraction (LVEF) who were in sinus rhythm. These included a disrupted sarcomeric apparatus with replacement by glycogen granules, the presence of large Terminal deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling (TUNEL)-positive nuclei with condensed chromatin indicating the presence of DNA breakage and the decreased expression of antiapoptotic proteins.

In a study of 15 patients with an atrial septal defect, who were in sinus rhythm and had a dilated RA, structural abnormalities including hypertrophy and cell degeneration were observed only in the presence of elevated RA pressures.\(^38\)

Also, ultra-structural changes in heart-failure-induced remodeling characterized by degenerative changes, including cellular edema, nuclear pyknosis, and contraction band necrosis leading to cell loss.\(^29\)

**Electrophysiological changes in atrial remodeling**

Electrophysiological studies comparing heart-failure-induced AR with atrial tachycardia-induced AR have shown significant differences in electrophysiological properties between these two types. These differences depend mostly on the changes in the ionic channels during the remodeling process.\(^7\)

**Atrial electrophysiological changes due to rapid atrial ratesy Vein**

Olsson et al.\(^39\) found short right atrial monophasic action potentials in patients immediately after conversion of AF to sinus rhythm.

Boutjdir et al.\(^40\) and Le Heuzey et al.\(^41\) found short atrial refractory periods with loss of physiological adaptation to high rates in atrial appendages of patients with chronic AF undergoing surgery.

In 1995, two independent studies showed changes in atrial electrophysiology as a consequence of AF. Wijffels et al\(^4\) demonstrated that repeated induction of AF in goats resulted in progressive duration of the induced paroxysms, together
they demonstrated a decrease of the mRNA expression of the L-type calcium channel a1c subunit, as well as Kv4.3 (encoding for Ito). Human studies also demonstrated a decrease in ICa,L and Ito in patients with AF undergoing cardiac surgery. The reduction in ICa,L may be explained by a decreased expression of the L-type calcium channel a1c subunit.

Brundel et al. reported a decreased protein expression of the L-type calcium channel, a finding that could not be confirmed by others. Reduced mRNA and/or protein concentrations of several potassium channels have also been reported.

Despite these findings, a pivotal role of atrial electrical remodeling in the progressive nature of clinical AF has never been proven. Furthermore, experimental atrial electrical remodeling is complete within hours to days, whereas the development of sustained AF generally takes at least 1 week. This indicates that other factors must be involved.

A study in thirty-five patients with a left-sided accessory pathway and without a prior history of AF where after successful ablation, the effective refractory periods (ERPs) and conduction times of the right atrium (RA), left atrium (LA), and the PVs were determined. Afterwards, AF was induced and maintained for a period of 15 min. Thereafter, the stimulation protocol was repeated. It was found that new-onset, short-lasting AF creates electrical characteristics similar to those of patients with AF. However, these alterations are pronounced in the PVs compared with the atria, indicating that “AF begets AF in the PVs”.

Electrophysiological changes due to volume/pressure overload AR

Increased ventricular and atrial pressures during the development of CHF may modulate atrial electrophysiology by causing myocardial stretch. This phenomenon is called mechanoelectric feedback or contraction-excitation coupling and has been demonstrated in animal studies as well as in humans.

In the setting of an acute rise in the atrial pressure, several studies have demonstrated changes in atrial refractoriness because of an acute rise in
atrial pressure. However, there is disagreement whether refractory periods shorten or prolong. In dogs, an acute rise in atrial pressure caused by (near) simultaneous atrioventricular (AV) pacing or by saline infusion resulted in prolongation of atrial effective refractory period (AERP). In contrast, Solti et al. reported a decrease of AERP along with an increase of atrial conduction times. Similarly, acute atrial volume overload in rabbits resulted in shortening of AERP and a decrease of atrial conduction velocity. Although the results of these studies are conflicting, all report an enhanced susceptibility to AF during an acute rise in atrial pressure.

The effects of chronic heart failure producing long-standing atrial hemodynamic overload on atrial electrophysiologic properties are even less well established. Li et al. evaluated the processes underlying the enhanced propensity of AF during the development of pacing-induced CHF in a dog model. They induced CHF by rapid ventricular pacing over 5 weeks. When compared with controls, the dogs with CHF had a dramatically increased duration of AF induced by burst pacing (535 ± 82 vs 8 ± 4 seconds). When comparing the AERP between the groups, at longer basic cycle lengths AERP was comparable between both groups, whereas at shorter cycle lengths, AERP was slightly longer in the CHF group. However, this prolongation of AERP is not likely responsible for the enhanced inducibility and sustenance of AF during CHF. Li et al. also observed a dispersion of atrial conduction in the CHF dogs, caused by extensive interstitial atrial fibrosis, resulting in an environment vulnerable to reentry. Comparable results were obtained in sheep with ventricular pacing–induced CHF. During 6 weeks of pacing left, but not right AERP was prolonged and the susceptibility to AF initially increased. However, the sheep became less susceptible to AF when induced, although the duration of AF, when induced, was longer.

Boyd et al. found no differences in the action potential duration and shape in the right atrium and only a slightly increased duration in the left atrium of cats with cardiomyopathy when compared with controls. Furthermore, the diseased atria had a substantially increased amount of excitable cells and showed structural abnormalities including fibrosis, cellular hypertrophy, and degeneration. In dogs with artificially induced right atrial enlargement caused by tricuspid regurgitation, they found no difference in the right atrial action potential, although the susceptibility and duration of AF was significantly increased when compared with controls. However, there was no spontaneously occurring AF.

On the other hand, Verheule et al. found prolonged atrial refractory periods but unchanged atrial conduction velocity in dogs 1 month after the induction of mitral regurgitation. Dogs with pacing-induced CHF had an enhanced inducibility of atrial tachycardia with foci located along the crista terminalis and pulmonary veins. The focal nature of specific types of AF recently has gained a lot of interest. These findings indicate that the development of CHF may evoke atrial foci, leading to AF.

Patients with dilated atria have been shown to have a shorter atrial action potential with lower amplitude than patients in whom the atria have normal dimensions. However, this finding may partly be due to the presence of AF in 25% of patients with the dilated atria, which apart from underlying heart disease, shortens AERP. In contrast, Calkins et al. found no change in AERP during simultaneous AV pacing. However, an acute increase of the atrial pressure by two simultaneous AV beats resulted in a shortening of AERP. These results were not influenced by the presence or absence of autonomic blockade.

In addition, chronic hemodynamic load may lead to changes in atrial electrophysiology. Patients with AF and mitral valve regurgitation were shown to have an increased AERP. This prolongation was not related to arrhythmia history, that is, patients with chronic or paroxysmal AF and mitral regurgitation also had longer AERP than patients suffering the same arrhythmia without valve disease.

Sparks et al. investigated the effect of VVI pacing in patients during sinus rhythm in the presence of an AV block. Chronic AV dissociation also resulted in prolongation of AERP and an impairment of left atrial contractility, processes which were reversible after reestablishing AV synchrony by DDD pacing. Experimental CHF in dogs decreases the densities of atrial ICaL, Ito, and IKs.
The net result of the decrease of repolarizing potassium currents and the decrease of depolarizing calcium current results in a slight prolongation of the atrial refractory period and action potential, but only at higher rates. Furthermore, the Na+/Ca+ exchanger current increases, which may promote delayed afterdepolarization induced ectopic activity and indirectly influence atrial refractoriness. Le Grand et al. found a decrease in ICaL in humans with dilated atria whereas others found no change. In addition, reported changes in Ito and other potassium currents are conflicting. Some authors have reported an increase; others have found a decrease of Ito in dilated atria. In addition, the inward rectifier current IK1 was found to be reduced or unchanged. The discrepancies of these findings may be explained by the variety of underlying cardiac disease, use of medication, and the presence of AF.

**Neurohormonal disturbances in atrial remodeling**

In addition to the role in the electrophysiologic and hemodynamic function of the heart, the atria also have an endocrinologic function.

AR is associated with neurohormonal changes that include increase in angiotensin II (Ang-II), aldosterone, transforming growth factor-beta1, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and sympathetic hyperinnervation.

The neurohormonal changes resulted from rapid atrial rates and volume/pressure overload will be elaborated below.

**Neurohormonal disturbances due to rapid atrial rates**

High atrial rates are associated with increase plasma levels of atrial natriuretic peptide (ANP). ANP is elevated not only in the acute phase but also when the arrhythmia is chronic. ANP is secreted by right and left atria, has diuretic effects, reduces peripheral vascular resistance, reduces the sympathetic tone, and suppresses the renin-angiotensin-aldosterone axis. Therefore ANP reduces the preload and protects the atria from hemodynamic overload. The exact mechanism by which an atrial arrhythmia results in secretion of ANP is unknown, although it has been demonstrated that atrial stretch is an important factor.

Atrial remodeling due to rapid atrial rates, at least in part, depends on angiotensin II–dependent pathways. Angiotensin II is a potent promoter of fibrosis, leading to cardiac fibroblast proliferation and, thus may play an important role in the formation of a substrate vulnerable to AF.

Angiotensin II acts by binding to two discrete receptor subtypes, angiotensin type I (AT1R) and type II (AT2R) receptors. The signaling cascades coupled to AT1Rs and AT2Rs are distinct and often have opposing actions. AT1Rs mediate the profibrotic effects of angiotensin II by stimulating fibroblast proliferation, cardiomyocyte hypertrophy, and apoptosis. AT1R signaling through the Shc/Grb2/SOS adapter-protein complex activates the small GTPase protein Ras, which initiates mitogen-activated protein kinase phosphorylation cascades that are centrally involved in remodeling. AT1R activation stimulates phospholipase C. Phospholipase C breaks down membrane phosphoinositols: phosphatidylinositol bisphosphate (PIP2) into diacylglycerol and inositol 1,4,5-trisphosphate (IP3). Diacylglycerol activates protein kinase C, and IP3 causes intracellular Ca++ release, both of which promote remodeling. Signal transduction also occurs through the JAK/STAT pathway, activating transcription factors such as activator protein-1 and nuclear factor-B. AT2R activation inhibits mitogen-activated protein kinases via dephosphorylating actions of phosphotyrosine phosphatase and protein phosphatase 2A and produces anti-proliferative and survival-promoting effects that oppose AT1R-mediated changes.

Angiotensin II mediates cardiac fibrosis in a variety of cardiac pathologies, including hypertensive heart disease, CHF, myocardial infarction, and cardiomyopathy. Transgenic mice with cardiac-restricted ACE overexpression show marked atrial dilation with focal fibrosis and AF. Aldosterone promotes fibrosis through its action on cardiac fibroblasts and matrix metalloproteinases (MMPs). Thus, the neurohormonal changes have an important role in the genesis and the progression of AR, which lead to the development and maintenance of AF.
Neurohormonal disturbances due to volume/pressure overload

Natriuretic peptides defend against excess salt and water retention, inhibit vasoconstrictor peptides, promote vascular relaxation, and inhibit the sympathetic neural system. These neurohormones have been shown to be important markers in the assessment of clinical severity and prognosis of CHF. Patients with CHF have high plasma concentrations of both ANP and BNP. These concentrations are associated with the degree of left ventricular dysfunction and may raise a factor 30 in patients with New York Heart Association Class IV CHF. ANP is mainly secreted from the cardiac atria but during CHF, a proportion is also produced in the ventricles. Several experimental pacing–induced CHF studies have demonstrated an increase in circulating ANP and BNP during the development of CHF.

Mechanical stretch of atria is the strongest stimulator for ANP secretion, which is augmented by endothelin and inhibited by nitric oxide (NO). However, longstanding AF in severe LV dysfunction and development of atrial fibrosis can cause depletion of ANP stores.

AR is associated with increase BNP level. The association between BNP and LA volume in predicting AF was demonstrated in post-thoracotomy patients where patients with larger LA volume and higher BNP levels had higher incidence of post-operative AF.

The development of atrial fibrosis during CHF is angiotensin-mediated. In dogs subjected to rapid ventricular pacing, administration of enalapril resulted in attenuation of pacing-induced changes in angiotensin II concentrations, atrial fibrosis, and impairment of atrial contractility.

No direct effect of ACE inhibiting drugs or angiotensin II blockers on atrial refractoriness have been established in patients. However, potential benefits of these drugs in arrhythmia burden in patients with CHF have been reported. Administration of the ACE inhibitor trandolapril reduced the incidence of AF in patients with systolic dysfunction after myocardial infarction. Data from heart failure trials indicate that treatment with an ACE inhibitor or angiotensin II blocker reduces the risk of developing AF in patients with left ventricular dysfunction. Furthermore, these effects have been shown to be independent of changes in blood pressure.

The role of systematic inflammation in atrial remodeling and AF initiation and perpetration

Recent studies have indicated that inflammation might play a significant role in the initiation, maintenance, and perpetuation of AF. Inflammatory cells have been demonstrated to infiltrate atrial tissue of patients with AF. Inflammatory markers such as C-reactive protein (CRP), tumour necrosis facort, interleukin and cytokines have been shown to be elevated in patients with AF. Elevation of CRP and IL-6 might also contribute to generation and perpetuation of AF, as evidenced by marked inflammatory infiltrates, myocyte necrosis, and fibrosis found in atrial biopsies of patients with lone AF. Complement activation has also been described in a cohort of patients with AF without other associated inflammatory diseases. It has been suggested in a population-based cohort of 1,011 patients who were followed up to 4 years, that in the absence of high baseline complement component levels (C3 and C4) a high baseline CRP level is not significantly associated with a high incidence of AF.

The exact mechanism of inflammation leading to tissue remodeling in AF patients is unclear and warrants further research. It is thought that AF leads to myocyte calcium overload, promoting atrial myocyte apoptosis. C-reactive protein might then act as an opsonin that binds to atrial myocytes, inducing local inflammation and complement activation. Tissue damage then ensues and fibrosis sets in. Specifically, in the presence of Ca++ ions, CRP binds to phosphatidylcholine. Long-chain acylcarnitines and lysophosphatidylcholines are generated from phosphatidylcholine and can further contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in sarco- meres. This can eventually lead to the maintenance of AF.
The inflammatory cascade and catecholamine surge associated with surgery might play a prominent role in initiating atrial tachyarrhythmias after cardiac surgery. It has been reported to occur in up to 40% of patients undergoing cardiac bypass surgery (CABG) or up to 50% of patients undergoing cardiac valvular surgery.\textsuperscript{3,4} After cardiac surgery, the complement system is activated and pro-inflammatory cytokines are released. Bruins et al.\textsuperscript{128} found that IL-6 rises initially and peaks at 6 h after surgery and a second phase occurs in which CRP levels peak on post-operative day 2, with complement-CRP complexes peaking on postoperative day 2 or 3. The incidence of atrial arrhythmias follows a similar pattern and peaks on post-operative day 2 or 3.\textsuperscript{4,127,133,134} Another study correlated leukocytosis to an increased incidence in AF in post-operative cardiovascular patients.\textsuperscript{132}

Burzotta et al.\textsuperscript{135} discovered that the development of postoperative AF was linked to 174G/C polymorphism of the IL-6 promoter gene. In this particular study of 110 patients undergoing CABG, genetic analysis revealed that the GG genotype was associated with higher IL-6 plasma levels and subsequently, a greater inflammatory burden. Similarly Gaudino et al.\textsuperscript{136} established a genetic link between inflammation and AF and found that the GG genotype was an independent predictor of postoperative AF.

The notion that the inflammatory process plays a role in AF has garnered much attention in many recent studies and is now a well-established connection. Many clinicians now consider inflammation to be an independent risk factor for the initiation and maintenance of AF.\textsuperscript{123} Studies are currently underway in an attempt to attenuate the inflammatory burden in patients with AF by novel therapeutic interventions.

Agents with potential anti-inflammatory effects such as ACEI, statins, steroids, omega 3 fatty acids, and vitamin C have increasingly recognizable roles in prevention of AF. This will be discussed in the next section.

**Potential therapeutic interventions to prevent or reverse AR**

Reversal of AR is possible, especially if it is in an early stage. The earlier the restoration of sinus rhythm by medication, electrical cardioversion, catheter ablation or even surgery, the better the outcome, in term of reverse remodeling.

**Phrenic Nerve Injury during Adjunctive Procedures Atrial Fibrillation**

Phrenic stimulation as well as injury may occur during device implantation. This may be particularly relevant with epicardial device implantation and combined pacing and ablation procedures in patients with a Mustard/Senning procedure with congenital d-transposition of the great arteries.\textsuperscript{52-54}

**Medical interventions**

**The angiotensin converting enzyme inhibitors (ACEI) and the angiotensin receptor blockers (ARBs)**

The ACEI and ARBs are antihypertensive medications which may improve LV systolic and diastolic function; and have beneficial effects on AR.\textsuperscript{137} However, it appears that altering renin-angiotensin-aldosterone system has strong effects on AR, which extends beyond their beneficial effects on blood pressure regulation. AR structural remodeling appeared reversible with quinapril, which occurs in parallel with an improvement in arterial stiffness but independent of blood pressure changes.\textsuperscript{138} Angiotensin-converting enzyme inhibition has been shown to have important beneficial effects on electrical remodeling\textsuperscript{139,140} atrial stretch,\textsuperscript{138,141} interstitial fibrosis\textsuperscript{142-144} and inflammation.\textsuperscript{144-146} ACEI has been shown to prevent first and recurrent AF in patients with hypertension.\textsuperscript{122} and LV dysfunction.\textsuperscript{120-122,147,148} Patients with persistent AF who were treated with amiodarone plus irbesartan had a lower rate of recurrence of AF than did patients treated with amiodarone alone.\textsuperscript{149} A number of large clinical trials have shown a beneficial impact of ACE inhibition on AF, however, the AF was not the primary end point in these studies.\textsuperscript{122,148,150-156} The meta-analysis of 11 studies, which included 56,308 patients, were identified: 4 in heart failure, 3 in hypertension, 2 in patients following cardioversion for AF, and 2 in patients following myocardial infarction. Overall, ACEIs and ARBs reduced the relative risk of AF by 28% (95% confidence interval [CI] 15% to 40%, p = 0.0002). Reduction in AF was similar between the
two classes of drugs (ACEI: 28%, p = 0.01; ARB: 29%, p = 0.00002) and was greatest in patients with heart failure (relative risk reduction [RRR] = 44%, p = 0.007). Overall, there was no significant reduction in AF in patients with hypertension (RRR = 12%, p = 0.4), although one trial found a significant 29% reduction in patients with left ventricular (LV) hypertrophy.157

In patients with AF, an ACE-dependent increase in the amounts of activated Erk1/Erk2 in atrial interstitial cells was noted.164 The effectiveness of angiotensin blocker to reverse AR and suppress AF lies in its ability to modulate the Ang-II–activated Erk1/Erk2 proteins, thereby effectively inhibiting interstitial fibrosis.119, 139, 140

Animal studies showed that the use of angiotensin blockers can mitigate increase in interstitial fibrosis and LA pressure; reduce myolysis, loss of contractile proteins, and LA dysfunction; and shorten the duration of AF.119, 139, 140 Administration of the angiotensin-converting enzyme (ACE) inhibitor captopril attenuated shortening of AERP after 3 hours of rapid atrial pacing in dogs.139 In the TRACE (Trandolapril Cardiac Evaluation) trial,2.8% of patients in the trandolapril arm developed AF versus 5.3% (p _ 0.05) in the placebo arm; similarly, patients randomized to enalapril in SOLVD (Studies Of Left Ventricular Dysfunction) [121] had a 78% relative risk reduction in developing AF (P Value0.0001).

There are a few studies linking reduction in AF with an administration of an ARB. In one prospective study, addition of irbesartan to amiodarone resulted in lower recurrence of AF after DCCV in patients with normal ejection fraction (79.52% vs. 55.91%, p _ 0.007)148 Subset analysis of Val-HeFT (the Valsartan Heart Failure Trial)250 and (Candesartan in Heart Failure)148 showed a reduction in the incidence of AF in patients receiving ARBs compared with placebo. Current evidence does not support the administration of statins and ACEIs /ARBs for the sole purpose of preventing AF, because many of the current published reports available were retrospective and observational in nature, with limited sample size.123

Aldosterone receptor antagonists

Aldosterone receptor antagonists, such as spironolactone and eplerenone, appear to have a beneficial impact in modifying the extracellular matrix, especially in terms of collagen deposition and fibrosis. Spironolactone has been shown to reverse the effects of AR by reducing atrial hyperexcitability,108 inhibition of vascular Ang-I/Ang-II conversion,108 and attenuation of atrial fibrillation.159-161

In animal models, Milliez et al.160 demonstrated that spironolactone attenuated atrial fibrillation, caused by chronic CHF in rats, more than did lisinopril and atenolol. The role of spironolactone and eplerenone on arrhythmia prevention was inferred from the RALES (Randomized ALdactone Evaluation Study),161 and EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study).162 trials where patients treated with these drugs had lower rates of sudden cardiac deaths. No studies have been done to assess the direct effects of aldosterone antagonists on AF prevention and treatment.

Beta blockers

The effect of beta-blockers on AR and AF suppression has not been well studied. Metoprolol and carvedilol can attenuate LV remodeling.163-165 In a double-blind, placebo-controlled study in 394 patients with persistent AF who underwent cardioversion, metoprolol CR/XL was effective in preventing relapse into atrial fibrillation or flutter.166

Statins

Statins are highly effective and widely used lipid-lowering agents in clinical practice but they also display a number of pleiotropic properties beyond cholesterol lowering. These pleiotropic effects include anti-inflammatory, antioxidant, atrial remodeling attenuation, ion channel stabilization, and autonomic nervous system regulation.167

In animal and human studies and in human studies168-171 Simvastatin has been shown to reduce the propensity to AF possibly through its antioxidant effects.166,168

Two studies have evaluated the role of statin treatment in animal models of HF. Firstly, Shiroshita-Takeshita et al.168 demonstrated that simvastatin effectively attenuates atrial structural remodeling.
and AF promotion in a dog model of tachycardio-
myopathy. Furthermore, Okazaki et al.\textsuperscript{172} showed
that atorvastatin attenuates atrial oxidative stress
and prevents atrial electrical and structural remodel-
ing in rat hypertensive HF induced by chronic inhibi-
tion of NO synthesis.

During the past few years, the association between
statin use and development of AF has been exam-
ined in different clinical settings.\textsuperscript{167,173,174} Recent
meta-analysis by Liu et al.\textsuperscript{167} on this issue showed
different results between randomized clinical trials
(RCTs) and observational studies, suggesting that
statins maybe effective in AF prevention, especially
in postoperative patients. Therefore, larger RCTs
with longer follow-up periods and more sensitive
methods of AF detection are urgently needed. Re-
cently, a review by Abi Nasr et al.\textsuperscript{175} provided an
overview of the evidence regarding AF management
in elderly patients with CHF. The authors discussed
treatments for the underlying disease, prevention of
thromboembolism, rate or rhythm control, as well
as nonpharmacological therapy that may be effec-
tive in some patients. In their review, they noted the
possible role of statins in maintaining sinus rhythm
in persistent lone-AF patients.

A post-hoc analysis from the Sudden Cardiac Death
in Heart Failure Trial (SCDHeFT)\textsuperscript{176} also demon-
strated similar findings. After adjusting for several
confounding factors, statin use was independently
associated with a significant reduction (28\%) in the
relative risk of AF or atrial flutter during a follow-
up period of 45.5 months.

These results are similar to a study by Hanna et
al.\textsuperscript{177} which reported the result of a registry of 25,268
patients with reduced left ventricular ejection frac-
tion (LFEF $<$OR $=$ 40\%), that demonstrated a 31 \%
reduction in the odds of AF prevalence with statin.
Recently also, another observational study by Ada-
bag et al.\textsuperscript{178} added new evidence to this issue. There
are three large ongoing RCTs (GISSI-HF, CORONA
and UNIVERSE)\textsuperscript{179} which hopefully will provide us
more clear data with respect to the role of statins in
AF prevention in patients with HF.

Vitamin C

Vitamin C is a potent water-soluble antioxidant\textsuperscript{180,181}
which has been recently shown to ameliorate electric-
cal remodeling in animal studies and to decrease
the incidence of postoperative AF in patients un-
dergoing cardiac surgery.\textsuperscript{182}

It was demonstrated that Vitamin C exerts favour-
able electrophysiological effects, ameliorating the
shortening of the AERP. Furthermore, Vitamin C
inhibits nitrotyrosine formation in the atrial tis-
sue, indicating an effective antioxidant action. In
a pilot study, the investigators showed that oral
administration of vitamin C significantly reduces
the incidence of postoperative AF in patients un-
dergoing coronary artery bypass graft surgery
(CABG).\textsuperscript{182}

A small study in 44 patients who underwent suc-
cessful electrical cardioversion of persistent AF
with one to one randomization to either oral Vi-
tamin C administration or no additional therapy,
the AF recurred one week after the successful car-
dioversion in 4.5\% of patients in the Vitamin C
group compared to 36.3\% in the control group (P
value 0.024). Compared to baseline values, inflam-
matory indices decreased significantly in the Vi-
tamin C group but not in the control group. CRP
and fibrinogen levels were higher in patients who
relapsed into AF compared to patients who main-
tained sinus rhythm.\textsuperscript{183} So the role of vitamin C
in prevention and treatment of patients with AF
is still unclear and needs further RCTs to evaluate
the issue.

Glucocorticoids

Most of the initial studies involving glucocorti-
coid therapy in AF were conducted in patients un-
dergoing cardiovascular surgery, and the results
were equivocal. Early studies by Chaney et al.\textsuperscript{184}
did not find any significant benefit of steroid ad-
mistration to patients undergoing coronary ar-
tery bypass graft surgery (CABG); however, Yared
et al.\textsuperscript{185} in a study of 216 patients undergoing car-
diothoracic surgery, found that dexamethasone
administration perioperatively decreased the in-
cidence of post-operative AF in the first few days
after surgery. Inflammatory markers (i.e., CRP, IL-
6, and so forth) were not measured in this study.
Yared et al.\textsuperscript{186} reported on the outcome of 78 pa-
tients undergoing combined CABG and valve
surgery who were randomized to receive either
dexamethasone or placebo before surgery. In this
study, dexamethasone did not affect the incidence of perioperative AF. However, it did modulate the release of several inflammatory and acute-phase response mediators that are associated with adverse outcomes. Most recently, a group from Finland showed in a prospective, randomized, double-blind study, that the use of 100 mg cortisone, given intravenously immediately before cardiac surgery and continued for 3 consecutive days, significantly decreased the incidence of AF after cardiac surgery by 15%.187

In a prospective trial which examined the effects of adding methylprednisolone to propafenone in AF patients undergoing pharmacological cardioversion to assess the recurrence rate, the methylprednisolone-treated group experienced an 80% decrease in CRP levels (p < 0.001) within the first month, which was maintained throughout the duration of the study. This corresponded to a reduction of AF recurrence from 50% in the placebo group to 9.6% in the methylprednisolone group (p < 0.001).188

 Unsaturated Fatty Acids (UFAs)

(Fish oil, and omega-3 fatty acids in particular, have been found to reduce plasma levels of triglycerides and increase levels of high-density lipoprotein in patients with marked hypertriglyceridemia, and a pharmaceutical-grade preparation has recently received approval from the US Food and Drug Administration to market for this purpose.189 However, in both bench research studies and clinical trials, evidence for clinically significant antiarrhythmic properties has also been detected in association with omega-3 fatty acid intake.189

The consumption of fish and fish oils appears in some large-scale clinical trials to have beneficial effects on survival, particularly or at least in ischemic substrates and in populations without high ambient consumption of fish intake.190,191

Clinical data supporting antiarrhythmic properties of fish oils have also been obtained from studies examining surrogate markers of lethal sustained ventricular arrhythmias, such as incidence of premature ventricular complexes, and from other arrhythmias, such as atrial tachycardia and atrial fibrillation.189

In a double-blind, placebo-controlled study in 65 patients with cardiac arrhythmias but without evidence of CAD or heart failure, the incidences of atrial and ventricular premature complexes, coupled, and triplets were reduced over a 6-month period among those randomized to treatment with 3 g/day of fish oil providing 1 g of omega-3 fatty acids, compared with those randomized to 3 g/day of olive oil as a placebo.192 Similarly, in a study in 40 patients with dual-chamber pacemakers who had paroxysmal atrial tachyarrhythmia recorded at periodic monitoring, treatment with 1 g/day of omega-3 fatty acids for 4 months significantly reduced the number of atrial tachyarrhythmia episodes by 59% (p = 0.037) and the burden by 67% (p = 0.029) without change in device programming or pharmacologic therapy.193 During the 4-month follow-up after discontinuation of the omega-3 fatty acid therapy, both the number of episodes and burden of duration increased to levels comparable to pre-treatment values.

Risk of atrial fibrillation was also inversely associated with fish intake in a prospective population-based cohort of 4,815 adults aged ≥65 years.194 A total of 980 cases of incident atrial fibrillation were diagnosed from hospital discharge records and annual ECGs at 12-year follow-up. A 28% lower risk of atrial fibrillation was associated with consumption of tuna or other broiled or baked fish 1 to 4 times weekly compared with intakes of <1 time monthly. Risk was 31% lower when fish was consumed ≥5 times weekly. Adjusting for a history of, or the presence of, MI or congestive heart failure did not change the results. This study also confirmed a significant relation between plasma phospholipid EPA and DHA concentrations and consumption of tuna or other broiled or baked fish. In contrast, consumption of fried fish or fish sandwiches did not significantly influence risk of atrial fibrillation nor did it relate to plasma phospholipid concentration of EPA and DHA. An additional trial in atrial fibrillation is ongoing.195

The incidence of atrial fibrillation has also been reported to be reduced by fish oils when used following coronary artery bypass surgery.196 In a prospective study, 160 patients were randomized to receive polyunsaturated fatty acids (2 g/day) or placebo control, starting 5 days before surgery and continuing until hospital discharge [196]. The incidence of atrial fibrillation was 33.3% in the control
group and 15.2% in the fish oil group (p = 0.013), and hospital stay was 1 day shorter in the fish oil group (p = 0.017).

There are several mechanisms through which n-3 FA could prevent arrhythmias. The n-3 FA is incorporated into myocyte membranes and may influence ion channel function. N-3 FA inhibits voltage-gated sodium channels in cardiomyocytes, resulting in a longer relative refractory period and an increased voltage required for depolarization which reduces heart rate. N-3 FA also maintains the integrity of L-type calcium channels, preventing cytosolic calcium overload during periods of ischemic stress. On other hand n-3 FA improves left ventricular efficiency and reduces blood pressure which could indirectly decrease heart rate.

**Other medications**

At interest in reverse remodeling has resulted in the development of new medications, one of which is Omapatrilat, a vasopeptidase inhibitor. In a canine model of tachycardia-induced congestive heart failure, chronic treatment with omapatrilat maintained myocardial ATP, the high-energy currency, and protected adenylate and creatine kinase phosphotransfer capacity. Omapatrilat-induced bioenergetic protection was associated with maintained atrial and ventricular structural integrity, albeit without full recovery of the creatine phosphate pool.

Alagebrium chloride (ALT-711) is a novel compound that breaks glucose crosslinks and may improve ventricular and arterial compliance. In 23 patients with diastolic heart failure, sixteen weeks of treatment with alagebrium (ALT 17) resulted in a decrease in left ventricular mass and improvements in left ventricular diastolic filling and quality of life in patient with diastolic HF. Alagebrium also improved total arterial compliance in older humans with vascular stiffening. Whether ALT-711 has the potential of reversing AR and reducing vulnerability to AF induced by arterial stiffness requires further investigation.

**Electrical cardioversion**

Conversion of AF to sinus rhythm, whether by electrical cardioversion or radiofrequency ablation, has been shown to reduce LA size and improve LA function. Reversal of electrical remodeling can usually be rapidly achieved, but vulnerability to the recurrence of AF depends on the amount of atrial fibrosis and the size of the LA. Normalization of atrial structure and function generally lags behind the reversal of electrical remodeling.

**AF catheter ablation**

In 57 consecutive patients with symptomatic drug-refractory AF, radiofrequency ablation reverted 39 (68%) to sinus rhythm. This was accompanied by a significant reduction in LA antero-posterior dimension (4.5 ± 0.3 cm vs. follow-up 4.2 ± 0.2 cm, p < 0.01), and LA volume (59 ± 12 ml vs. follow-up 50 ± 11 ml, p < 0.01) at 3 months follow-up. In contrast, patients who remained in AF after catheter ablation had increased LA size at 3 months follow-up (4.5 ± 0.3 cm to 4.8 ± 0.3 cm, p < 0.05; 63 ± 7 ml to 68 ± 8 ml, p < 0.05). In a cohort study of 251 consecutive patients with paroxysmal (n=179) or permanent (n=72) AF who underwent circumferential PV ablation, Paponi et al. reported no significant relationship between ablation success and clinical variables such as age, AF duration, presence of heart disease, or ejection fraction. Also the LA size did not seem to influence the outcome in paroxysmal AF patients, whereas in patients with permanent AF the likelihood for ablation failure was increased in the presence of LA dilation. They concluded that the fact that their technique was able to eradicate AF, regardless of its duration or the presence of structural heart disease, suggests that AF-induced atrial electrical remodeling may be reversible after the elimination of the focal source or arrhythmogenic substrate.

Catheter ablation of AF may also results in recovery of sinus node function in patients with persistent AF with prolonged sinus pauses.

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Catheter ablation of AF may also result in recovery of sinus node function in patients with persistent AF with prolonged sinus pauses.213

Cardiac surgery and surgical AF ablation

Mitral valve surgery for valvular stenosis or regurgitation can relieve LA pressure and volume overload with reduction of LA size and improved LA function.208 AF patients who underwent LA resection together with mitral valve surgery had lower AF recurrence after 3 months when compared to those who did not have LA resection.214 Further reduction in LA size was seen in those who remained in sinus rhythm when compared to those who had persistent or recurrent AF.214 Successful surgical ablation of AF (Maze procedure) has been shown to reduce neurohormonal activation as evidenced by a decrease in ANP, BNP, and angiotensin II.215,216 MAZE III procedure has been demonstrated to reduce LA size and improve LA transport function and LV diastolic function.217

Conclusions

AR is an important and increasingly recognizable factor in the development and maintenance of AF. It is likely that AR is playing an integral part in the cascade of the events that lead to AF development.

Understanding of AR mechanisms may help in the management and hopefully prevention of AF. The extent of AF burden reduction and other adverse clinical outcomes with prevention and reversal of AR remains to be proven. The measures to prevent or reverse AR at its early stages need to be studied further with large CRT. If proven successful these measures may result in significant reduction in the AF burden and its major impact on public health care.

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