

## Review Article

# Remodelling in atrial fibrillation: the impact of amiodarone

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### Abstract

Atrial fibrillation (AF) is a common heart rhythm disorder with a prevalence of up to 2.9% in the general population. Its mechanism involves a particular electrophysiological profile as well as structural and biohumoral changes that are often irreversible. With the recent advances in pharmacology, amiodarone remains the cornerstone for the treatment of AF. Although it is one of the most controversial anti-arrhythmic agents due to the multitude of side effects, it is further recognised as the most effective drug available for the conversion and maintenance of sinus rhythm in the case of significant left ventricular dysfunction or severe aortic stenosis. This quality is provided by its multivalent profile, with a complex electrophysiological activity overlapped with an anti-inflammatory and vasodilatory effect. This review aims to outline the main structural and functional changes in AF and the multisite impact of amiodarone on its treatment.

**Keywords:** atrial fibrillation, inflammation, remodelling, amiodarone, anti-arrhythmic

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The prevalence of atrial fibrillation (AF) in the general population is estimated to be around 0.5–1%. Some recent data indicate that the condition has doubled in prevalence in the last decade among European countries, with values of up to 2.9% in Sweden.<sup>1</sup>

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Although the interventional approach for the treatment of AF has had a great impact over the past two decades, the recent CABANA study did not reveal any general differences in terms of death, risk of stroke, haemorrhagic events or hospitalisation time between patients undergoing ablation and those with anti-arrhythmic drug therapy on an average of four years of follow up. An improvement was observed in quality of life and in people under the age of 65 years,<sup>2</sup> and ablation proved beneficial in patients with heart failure and left ventricular dysfunction. The results were similar to those of the CASTLE-AF trial.<sup>3</sup>

Amiodarone (AM) is an iodinated benzofuran derivative, developed in 1961 by a Belgian pharmaceutical company and originally marketed in Europe and South Asia as an anti-anginal agent due to its coronary vasodilator properties and its capacity to reduce myocardial oxygen demand. Some years later, in 1974, Mauricio Rosenbaum published the results of a study demonstrating the efficacy of AM for the treatment of supraventricular and ventricular arrhythmias.<sup>4</sup> This article opened up new horizons in cardiology practice, with AM today being one of the most prescribed anti-arrhythmic drugs worldwide, with more than three million annual prescriptions in the USA.

Over the decades, the multiple effects of AM have been reported. It possesses a complex electrophysiological profile, induces modulation of the inflammatory cascade, and not least, being a possible agent for reverse remodelling of the left atrium. These characteristics have successfully placed AM on top of the list as the most efficient anti-arrhythmic agent for both conversion and rhythm-control strategy for AF. Its safety profile recommends it as the only medication that can be used for the maintenance of sinus rhythm in patients with severe forms of systolic heart failure or aortic stenosis. This article reviews important elements of the pathophysiology of AF and the multilevel impact of AM on its treatment.

### Electrical remodelling in AF

AF is characterised by chaotic atrial electrical activity, which causes irregular and usually rapid ventricular contraction. It is initiated when ectopic excitation encounters a pathological substrate of AF. The left atrium and pulmonary veins in particular are responsible for over 90% of cases of AF, the role played by pulmonary veins being more important in the case of paroxysmal AF. These contain muscular beams originating from the left atrium with pace-maker ability, similar to cells in the sinus and atrioventricular nodules. Subsequently, the electrical pulse passes through the left atrium, with the generation of AF. In less than

10% of cases, other veins such as Marshall's vein, the inferior vena cava, upper vena cava, or even left atrial tissue may be the sources of AF. Exceptionally, the right atrium can be linked to AF.

Electrical remodelling is the first stage in the onset of arrhythmias. Changes in membrane potentials and in the physiology of ion channel activation lead to changes in atrial frequency. Metabolic processes induced by inflammation and reactive oxygen species cause changes in intracellular ion concentration, ion channel activity and phosphorylation. In terms of long-term alteration, we can talk about electrical remodelling of atrial tissue.

The process substratum is not yet fully elucidated, but certainly includes impairment of depolarisation and repolarisation. It has been shown that in AF, alternations in action potential duration (APD), measured by atrial pacing, occurred at lower cardiac frequencies of 100–120 beats/min, not being related to restitution of action potential duration. Spontaneous initiation of AF by ectopic beats was observed under these conditions. Paroxysmal oscillations of action potential (AP) are amplified prior to AF, while in healthy subjects AP alternans only occurs at very high frequencies at a cycle length of < 250 ms.<sup>5</sup>

Depolarisation involves complex electrophysiological changes in voltage-dependent Na (INa) current, L-type (ICal) calcium channels, and cardiac sodium–calcium exchanger type-1 (NCX1). Repolarisation requires transient-outward K<sup>+</sup> current (I<sub>to</sub>) activation, delayed-rectifier K<sup>+</sup> currents and, last but not least, Na<sup>+</sup>/K<sup>+</sup>-ATPase current (INaK). In association, AP duration and resting membrane potential are influenced by acetylcholine-activated K-rectifying currents.<sup>6</sup>

In cardiac myocytes, AM is capable of reducing cell inward-rectifier potassium current [I(K1)] and single I(K1) channel activity as a result of a direct blocking action caused by an interaction with a hydrophobic site within the membrane, inhibiting single I(K1) channel activity by prolonging the inter-beat interval.<sup>7</sup>

Two-pore-domain potassium (K2P) channels play an important role in the modulation of cellular excitability. They mediate background potassium currents, stabilising resting membrane potential and expediting action potential repolarisation. In patients with AF, the downregulation of atrial and ventricular K2P mRNA and protein levels was observed.<sup>8</sup>

AM is an inhibitor of cardiac K2P channels, which may induce prolongation of cardiac repolarisation and AP duration in patients with high individual plasma concentrations, possibly contributing to the anti-arrhythmic efficacy of the class III drug.<sup>9</sup>

Studies in animal models have shown reduced (INa) as a result of atrial tachycardia remodelling. These changes contribute to the slow atrial conduction observed in AF.<sup>10</sup> However there were no genomic changes in atrial INa.<sup>11</sup>

In AF, sodium channel density is approximately 16% lower than sinus rhythm, accompanied by a 26% decrease in Nav1.5, an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit. Conversely, there was a 26% increase in the INa strain in the atria of AF patients.<sup>12</sup>

AM preferentially inhibits the Na channels of the atrial myocardium to the detriment of the ventricle, this selectivity allowing the control of AF without affecting ventricular contractility.<sup>13</sup> Because of this property, it remains the only solution for the rhythm-control strategy in AF with major depression in chronic heart failure or severe aortic stenosis.<sup>14</sup>

As it can determine the decrease in AP V<sub>max</sub> and the conduction in the myocardial tissue whose excitability depends on the activation of fast-acting sodium channels, AM has an electrophysiological profile similar to lidocaine.<sup>15</sup>

In patients at risk for AF (e.g. heart failure, mitral stenosis), atrial myocyte Ical levels were lower compared to low-risk AF patients, this being secondary to the downregulation process.<sup>16</sup> Atrial remodelling of this arrhythmia causes instability of calcium homeostasis and contributes to the pro-arrhythmic phenomenon based on several cellular mechanisms: changes in Ca<sup>2+</sup> capture by ryanodine receptor (RyR2) gene defects, enhanced RyR2 phosphorylation, increased calcium–calmodulin-dependent protein kinase II (CaMKII) activity, intracellular calcium alternans, and by slowing electrical conduction and atrial interstitial fibrosis encountered in patients with heart failure and left atrial dilation.<sup>17</sup> During AF, elevated heart rate causes an increase in intracellular calcium accumulation, engaging homeostatic defence mechanisms against chronic Ca<sup>2+</sup> overload. Ical reduction decreases the Ca<sup>2+</sup> inward current, maintaining the AP plateau, shortening AP duration and thus promoting re-entry.<sup>18</sup>

AM, but not its active metabolite desethylamiodarone, is a potent competitive verapamil-like inhibitor, blocking the calcium influx at Ca-dependent voltage channels. Some authors suggest that the acute effect of sino-atrial and atrioventricular node inhibition, vasodilation and negative inotropism may be attributable to the action of Ca<sup>2+</sup> channel blockers.<sup>19</sup>

In the myocardium, the connection through gap junctions is essential for controlling the electrical impulse. The structural remodelling of the myocardium is accompanied by gap junction remodelling with changes in signalling molecules. Changes in the topology of connexin (Cx) channels are attributed to electrical remodelling and contribute to impaired conduction and arrhythmogenic substrate generation. The most abundant gap junction protein in atrial myocytes is Cx43 and AF is associated with a low expression of this protein. Cx43 reduces susceptibility to AF and the downregulation of this Cx mediates the induction and maintenance of sympathetic AF.<sup>20</sup>

Previous studies have shown the importance of c-Jun N-terminal kinase (JNK), an enzyme from the mitogen-activated protein kinase family, which binds and phosphorylates c-Jun, a cellular transcription factor. JNK activation contributes to Cx43 reduction that promotes the development of AF.<sup>21</sup> Augmented JNK activation in aged atria downregulates Cx43 to impair cell–cell communication and enhance atrial arrhythmogenicity.<sup>22</sup>

There is no evidence of a relationship between AM administration and Cx43 levels in atrial myocytes. However, no uncoupling activity of Cx43 was observed<sup>23</sup> after AM therapy, and moreover, in the case of severe myocardial damage such as *Trypanosoma cruzi* infection, AM proved capable of fully restoring Cx43 distribution. Treated cultures displayed gap junction plaques comparable to those of uninfected controls, promoting cardiac cell recovery with gap junction and cytoskeleton reassembly.<sup>24</sup>

## Autonomic nervous system remodelling in AF

Autonomous cardiac innervation is extremely complex and plays an important role in triggering and maintaining AF. Sympathetic pathways start from the intermediolateral cords of the first five to six medullary thoracic segments. The post-ganglionic synapse is located in the cervical and dorsal nodes, from where

post-ganglionic fibres form upper, middle and lower cardiac nerves, which are responsible for the excitoconductor system and the contractile fibre innervation. Right sympathetic fibres are distributed mainly to the excitoconductor system with a more pronounced impact on heart rate, while left fibres predominantly are distributed to the contractile myocardium, playing an important role in contractility by amplifying its activity.

There is a permanent discharge of impulses by releasing epinephrine, acting on beta-1 receptors. Norepinephrine stimulates all myocardial properties and mobilises glycogen and macro-energetic phosphates, and increases membrane permeability for sodium and calcium, resulting in depolarisation. Therefore intracellular growth due to beta-adrenergic signals and spontaneous calcium release from the sarcoplasmic reticulum may have a pro-arrhythmic effect.<sup>25</sup> Increased regional innervation with an increased adrenergic nervous density was the first type of nervous remodelling associated with arrhythmias.<sup>26</sup>

AM also exerts an anti-adrenergic effect by inhibiting non-competitive  $\alpha$  and  $\beta_2$  receptors. This is an important aspect in the use of the intravenous formula, the initial effect being more prominent in terms of beta-blockade than the effect on potassium channels.<sup>27</sup> The mechanism of action differs from beta-blockers, as it does not effectively block these receptors but induces downregulation and reduces the binding capacity of beta-receptors with the regulatory unit: G-adenylate cyclase protein.<sup>28</sup> Therefore AM can be attributed to class II anti-arrhythmic drug properties: decreased sinus and NAV automatism as well as conduction speed (negative chronotropism and dromotropic effect).

The complex electrophysiological action of this drug is also accompanied by the anti-arrhythmic effect via other mechanisms, incompletely elucidated, such as the interference with the action of thyroid hormones (inhibition of their action at the cardiac level) in the modulation of the effects of the autonomic nervous system.<sup>29</sup>

### Structural atrial remodelling in AF

Rapid and irregular atrial activation leads to severe systolic dysfunction of the atrium, completely reversible only in the case of short periods of AF. For paroxysmal AF, complete atrial functional recovery occurs after two to three days, while for persistent AF, the effective atrial refractory period normalises over days, and atrial activation returns to baseline within a few weeks. As for contractile function, its normalisation can last for weeks or even months.<sup>30</sup> In AF, left atrial (LA) dilation is generally present, being related to both the severity and underlying disease leading to the onset of arrhythmia.<sup>31</sup> LA dilation was highlighted as a precursor of AF in the Framingham Heart Study and the Cardiovascular Health Study.<sup>32</sup>

In the case of conversion to sinus rhythm, by either pharmacological or electrical cardioversion, or through radiofrequency ablation, LA size may be a prognostic marker for its recurrence. Dilated LA is a risk factor for the recurrence of AF post-ablation, being associated with significant remodelling and it consequently limits the efficacy of ablation.<sup>33</sup> Atrial remodelling, especially interstitial fibrosis, is an important factor in the AF substrate.<sup>34</sup> The mechanism is not fully known and the signalling molecules that lead to structural changes may vary from one patient to another.

There are multiple pro-fibrotic factors in AF (angiotensin II, TGF- $\beta$ 1, platelet-derived growth factor, endothelin 1, etc.) that can act independently or synergistically, therefore enhancing the fibrotic process.<sup>35</sup> Although the administration of AM is incriminated for the generation of a pro-fibrotic effect in the pulmonary parenchyma,<sup>36</sup> there are no studies confirming such an effect in the atrial myocardium. Chronic administration of AM does not influence ventricular remodelling after myocardial infarction. It does not alter myocardial dimensions, vascular density or interstitial fibrosis, with no changes in the structure or function of the left ventricle.<sup>37</sup>

Nearly all AF patients undergoing pharmacological cardioversion with AM show a recovery of the bilateral atrial mechanical function in approximately 24 hours, reaching normal function within seven days post-conversion.<sup>38</sup> Compared to propafenone, in AM-treated patients, LA fractional shortening and total atrial fraction were significantly higher and showed lower LA stunning.<sup>39</sup>

### Inflammation in AF

Several inflammatory markers are associated with AF. Whether we are talking about an increase in fibrinogen expression, tissue factor production by monocytes, destruction or endothelial activation, or interleukin synthesis, these are all mechanisms where inflammation is associated with pro-thrombotic status, modifying the impact, clinical presentation and prognosis in AF.

The association between C-reactive protein (CRP) and AF has long been debated, the direct relationship still being controversial. In the Copenhagen City Heart Study, the authors highlighted that elevated plasma CRPs were robustly associated with increased risk of AF; however, genetically elevated CRP levels were not. This leads to the conclusion that elevated plasma CRP per se does not increase the risk for AF.<sup>40</sup> However, the intracytoplasmic presence of CRP was found in the atrial cardiomyocytes from patients with paroxysmal AF, in a significantly higher percentage compared to the control group. Therefore it can be concluded that local inflammation assessed by atrial tissue localisation of CRP is more likely to be involved in paroxysmal rather than persistent AF.<sup>41</sup>

Following conversion to sinus rhythm, CRP levels are independent predictors of AF recurrence in patients with persistent or paroxysmal AF, which can be helpful for prediction of the recurrence of AF. A positive high-sensitivity CRP test result at baseline can predict a 73% chance of AF recurrence in the six to 12 months following cardioversion.<sup>42</sup>

Interleukin-2 (IL-2) serum levels in new-onset AF have been related to pharmaceutical cardioversion outcomes. Elevated levels of this pro-inflammatory non-vascular cytokine were an independent predictor for the recurrence of AF after catheter ablation.<sup>43</sup> In a similar manner, patients who developed AF immediately (within 24 hours) after coronary artery bypass grafting (CABG) had significantly higher IL-2 levels compared to patients without paroxysmal AF.<sup>44</sup>

TNF- $\alpha$  (tumour necrosis factor alpha) increases IL-6 and IL-1 levels, inducing a decrease in cardiac contractile proteins such as  $\alpha$ -myosin heavy chain and cardiac  $\alpha$ -actin, both of which have a detrimental role in atrial and ventricular cardiomyocyte function. In an animal experimental trial, a single dose of TNF- $\alpha$  was sufficient to induce persistent AF without any

significant change in cardiac size or overall cardiac function.

The proposed pathophysiological mechanisms include the increase in serum transforming growth factor beta levels, which supports the overexpression of MMP-2 (matrix metalloproteinases) and decreases the expression of Cx40, decapentaplegic homolog 3 (SMAD-3) and phospho-SMAD3 growth, activating fibroblasts and myofibroblasts, and finally generating fibrosis and inducing arrhythmogenic substrates.<sup>45</sup>

Serum TNF- $\alpha$  levels and mRNA expression of TNF- $\alpha$  were increased in the left atria of patients with AF; higher in permanent AF compared to paroxysmal AF, and associated with LA diameter.<sup>46</sup> However, TNF- $\alpha$  levels did not prove useful in predicting the risk of developing AF or AF recurrence. Although treatment with infliximab, a TNF- $\alpha$  inhibitor, may improve pre-existing LA abnormalities in patients with rheumatoid arthritis,<sup>47</sup> there is no evidence of protection against AF. On the contrary, infusion of this product is associated with the occurrence of ventricular or supraventricular rhythm disorders.<sup>48</sup>

Concerning AM, experimental studies, most of them performed on animal models or on *in vitro* cell cultures, have revealed new valences of this drug regarding its anti-inflammatory effect. The administration of AM has been shown to ameliorate glutathione depression by increasing the activity of some catalases, glutathione s-transferase enzymes and enhancing myeloperoxidase activity; all these anti-inflammatory mechanisms can lead to an anti-oxidative effect. AM reduces the activation and mobilisation of neutrophils. It may limit the activation of human T cells by inhibiting (in a dose-dependent manner) the production of cytokines, including IL-4, IL-2, TNF- $\alpha$  and interferon-gamma.<sup>49</sup>

Impairment of left ventricular function, irrespective of aetiology, is commonly associated with the onset of AF. AM is one of the few anti-arrhythmic drugs that can be used with beneficial results for an ejection fraction of less than 40%. In an animal model, treatment with AM can decrease plasma IL-6 levels in viral myocarditis,<sup>50</sup> and it is even able to prevent remodelling of the left ventricle, improving cardiac function in some cases of dilative cardiomyopathy.<sup>51</sup>

Although serum concentrations of AM and its metabolites are not routinely used in medical practice, the anti-inflammatory effects of AM appear to be dose dependent. In patients with dilative cardiomyopathy, lower serum AM levels (1–10  $\mu\text{mol/l}$ ) inhibited the production of TNF- $\alpha$  by human monocytes, molecules with a detrimental role in both heart failure and AF.<sup>52</sup> On the other hand, high serum AM levels (10–25  $\mu\text{mol/l}$ ) stimulated IL-6 production in cultured human thyrocytes, while 1- $\mu\text{mol/l}$  concentrations significantly decreased the levels of this cytokine.<sup>53</sup>

The production of monocyte cytokines and chemokines stimulated by CRP is also influenced by AM in a dose-dependent manner. At low concentrations (1–10  $\mu\text{mol/l}$ ), it has a beneficial effect, whereas higher levels (25–50  $\mu\text{mol/l}$ ) stimulate the synthesis of these pro-inflammatory molecules, most likely by the cytotoxic effect of AM on monocytes.<sup>51</sup>

Different AM doses may give rise to different results, requiring a more accurate outline of therapeutic serum levels to avoid its numerous adverse effects and to achieve a maximum anti-arrhythmic effect. However, its highly particular metabolism is well known, with unpredictable desethylamidarone levels, the main AM metabolite, with specific pharmacological properties.

This makes it difficult to create a mathematical model for the prediction of beneficial effects and adverse reactions.

## Stress activation in AF

AF may be detected in the setting of an acute stressor, such as surgery, medical illness or even heavy alcohol consumption ('holiday heart syndrome'). It remains unclear whether AF detected in these circumstances is secondary to a reversible trigger or it is simply paroxysmal AF.

In human AF, endoplasmic reticulum (ER) stress can be associated with autophagy and cardiomyocyte remodelling. Patients with persistent AF showed an accumulation of autophagosomes and autolysosomes and the presence of myolysis, which is absent in patients in sinus rhythm. The attenuation of ER stress results in the conservation of contractile protein expression, relieving autophagy and protecting from cardiac remodelling.<sup>54</sup>

JNK is a well-characterised stress-response kinase that is activated in response to various cellular stresses such as ischaemia, inflammatory cytokines and aging. The activation of JNK2, a major isoform in the heart, causes abnormal intracellular Ca<sup>2+</sup> waves and diastolic sarcoplasmic reticulum (SR) Ca<sup>2+</sup> leak, triggering a pro-arrhythmic effect. Recently, it has been demonstrated that JKN2 activation upregulates the expression in the aged atrium of CaMKII delta. The latter is a well-known cardiac pro-arrhythmic molecule that phosphorylates Ca<sup>2+</sup>-handling proteins, including phospholamban, Ca<sup>2+</sup>-releasing ryanodine receptors, inositol 1,4,5-trisphosphate receptors and L-type Ca<sup>2+</sup> channels, thereby playing a crucial role in the excitation–contraction coupling in the normal heart and enhanced arrhythmogenicity in pathological cardiac remodelling. JNK2-driven CaMKII activation can be described as a novel mode of kinase cross-talk and a causal factor in AF remodelling.<sup>55,56</sup>

Heavy episodic drinking is a well-known independent risk factor for cardiac arrhythmias, most frequently for AF. Alcohol activates stress-response kinase JNK, which leads to SR Ca<sup>2+</sup> mishandling with changes in cardiac contractile function, enhancing atrial arrhythmogenicity.<sup>57</sup>

Treatment with AM inhibited the JNK signalling pathway and reduced the activation of JNK on human T cells.<sup>58</sup> Despite the fact that the activation of T cells plays an important role in the pathogenesis of AF, there is a need for studies on atrial myocytes, as the modulation of JNK and CaMKII activity may contribute to the success of AM in maintenance of sinus rhythm.

## The use of AM in patients with AF

AF is a global epidemic, with significant and progressive effects on estimated disability and mortality. Because ablation therapy is not accessible worldwide, mainly due to high costs of periprocedural complications, anti-arrhythmic therapy remains the cornerstone in rhythm-control strategy. AM, with its multiple extra-cardiac adverse effects, is the most efficient anti-arrhythmic drug. Oral pre-treatment with AM for one month before cardioversion improved the reversion rate: 88 versus 56–65% without pre-treatment in patients with persistent AF.<sup>59</sup> AM has emerged as the most effective agent to prevent the relapse of AF after electrical cardioversion, with up to 69% of patients remaining in sinus rhythm after one year; however as many as



25% of AM-treated patients are forced to discontinue treatment due to its side effects.

As an alternative, short-burst therapy with oral AM appears to significantly improve six-week and six-month sinus rhythm maintenance rates following cardioversion, without exposing patients to the adverse effects of long-term AM therapy.<sup>60</sup> In patients regaining sinus rhythm after the first episode of persistent AF, three months of AM therapy after reversion is a reasonable option for rhythm control, with significantly lower recurrences after 18 months.<sup>61</sup>

The superior efficacy of this drug is partially overshadowed by the adverse effects that occur in 15 to 50% of cases, from the first year of treatment to prolonged treatment. Cardiac, pulmonary, thyroid and hepatic side effects are well known. For safe use, the following are recommended: semi-annual thyroid function and transaminase tests, an annual chest X-ray, as well as an annual ECG in all AM patients.<sup>62</sup>

## Conclusions

Once installed, AF can induce irreversible electrophysiological, histopathological or immunological changes. With the pharmacological advances of the last decades, despite its adverse reactions, AM is one of the most commonly used antiarrhythmic agents. It remains the most effective medication for the maintenance of sinus rhythm in patients with AF and the most used drug for pharmacological cardioversion. This is due to its multivalent profile, with a complex electrophysiological activity combined with an anti-inflammatory and vasodilatory effect.

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