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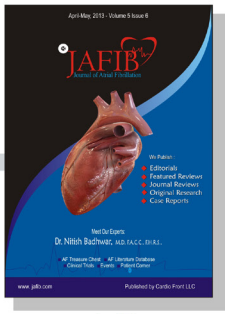

# Myocardial Ischemia as a Genuine Cause Responsible for the Organization and "Fertilization" of Conflictogenic Atrial Fibrillation:New Conceptual Insights into Arrhythmogenicity

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## Abstract

**Atrial fibrillation continues to be a challenging arrhythmia. There are some conventional, time-tested explanations of atrial fibrillation genesis, however some uncertainty of its complete understanding still exists. We focused on atrial ischemia which, hypothetically, could be responsible for manifestation of the arrhythmia, irrespective of the underlying heart disease. Evidences abounds that atrial fibrillation has an extremely strong association with nutritional/oxidative status of myocardium. This arrhythmia seemingly may stem from the electrophysiological differences taking place in the boundary areas. To validate such assumptions we have surveyed widely accepted theories based on clinical and experimental evidence. There was an attempt to integrate some well-known theoretical explanations (focal, multifocal, ectopic, reentrant activity, atrial remodeling, etc.) into a new conceptually systematized arrhythmogenesis. Confronting ischemic and non-ischemic atrial zones electrophysiologically on their borderlines presumably creates a substrate vulnerable to the development of atrial fibrillation. The behavior of these interrelated areas is likely ischemia-dependent; the separating borderline(s) may be treated as conflictogenic, releasing triggers/drivers to commence and to perpetuate the arrhythmia. Ischemically damaged and non-damaged myocardial areas likely participate in the relay-race carousel of arrhythmogenicity due to their mutual interactions, accompanied by the "fireworks" at the separating borderlines. It could be concluded that myocardial ischemia as a nonspecific proarrhythmic factor presumably plays a key role in the genesis and sustenance of atrial fibrillation. Theoretically the most important step in eradication of arrhythmogenic substrate might be an overall abolition of ischemia regardless of the characteristics of underlying heart disease. Innovative intellectual and explorative research is needed to render innocuous the ischemia that might help us win the century's cardioarrhythmological battle.**

## Introduction

Atrial fibrillation (AF) is a non-life-threatening arrhythmia however the scale of its damage to the population worldwide is huge. Despite some progress in research the results of pharmacologi-

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cal and non-pharmacological AF therapy do not satisfy the hopes of patients and clinicians. Regarding the overall complexity of AF this intrusive arrhythmia sometimes is called a "difficult puzzle".[1] Contemporary studies have pointed out tissue-level substrate for triggers of permanent AF.[2,3] Catheter or surgical ablation therapy is effective in patients with paroxysmal AF, but its efficacy to cure persistent AF is still under debate.[4-6] Electrical isolation of pulmonary vein (PV) continues to be the cornerstone of AF ablation today. [4, 7] Due to the lack of specificity it requires multiple procedures and the continuation of antiarrhythmic drug therapy.[6, 8-12] Irrespective of the target sites undertaken for the ablation of potential triggers (right atrium, left atrium, atrial roof, mitral isthmus, both atria, coronary sinus, myocardial sleeves of PVs, etc.) the success rate in restoration of sinus rhythm ranges from 16% to 63%,[13, 14] in rare cases – up to 80%.[4] Up to 74,5% of patients undergo a redo procedure and clinical results are not always reproducible.[15] Even ardent supporters do recognize the limitations of hypothesis of focal and multiple reentrant sources as if existing in the sleeves of PV.[8] Finally, it is still unclear whether reentrant or nonreentrant arrhythmia mechanism prevails and where the AF triggers actually do reside – in the left atrium, pulmonary veins[1, 15] or anywhere in the atria.

AF as the most frequent cardiac arrhythmia is associated with almost all cardiac disorders. [16] Initially we have focused on atrial myocardial infarction as an extreme condition creating the substrate for the arrhythmias. It seems at least hypothetically that myocardial ischemia irrespective of the antecedent heart disease is perhaps the only significant contributory factor being responsible fundamentally and entirely in organizing the substrate of arrhythmogenicity. An elegant experimental study by Nishida et al. with their meaningful insights demonstrates that chronic atrial ischemia/infarction provides favorable conditions for both spontaneous ectopy and sustained reentry.[17] Clinical observations also show the outbreak of various arrhythmias including fibrillation (atrial or ventricular) appearing on the ischemic basis.[17-20] Interestingly, AF itself diminishes coronary flow reserve, especially in the subendocardial layer.[21, 22] In general, cardiac ischemia causes complex interactions between ionic, metabolic and neurohumoral factors with deleterious effects on cardiac cellular electrophysiology.[23] It could be considered that not only ischemia, but some other organic cardiac/atrial disorders evoking atrial architectural changes - valvular or nonvalvular such as, atrial chronic overstretch, atrial sarcoidosis, amyloidosis, inflammatory vicinity (myocarditis, coronary vasculitis), etc.[24-26] - may result in AF primarily via indispensable ischemic component of the milieu. Therefore, myocardial ischemia might be considered as a favorable proarrhythmic and profibrillatory substrate. We will attempt to compile and collate the well-known evidence in order to support this viewpoint. The review of the literature sources will serve as a baseline on which a supplementary hypothesis of conceptually systematized arrhythmogenicity will be built. Finally, the goal of this article is the hypothetical attempt to dismantle the mechanisms originating and maintaining the AF.

## Arterial Vascularization of the Atria and Ischemic Consequences

The atrial arterial network in humans is extremely variable, however there are two widely recognized coronary atrial branches participating in the blood supply: the sinus node and the atrioventricular node arteries .[27] Also an artery with a specific name – Kugel's artery - provides an additional though unstable direct arterial anastomosis in 6% of the hearts.[27, 28] Sinoatrial node is supplied by the right coronary artery more frequently than by the left one.[29]

Let's look at the contributing factors influencing the impairment of arterial blood flow. Three major circumstances are responsible for the initiation and advance of atrial fibrosis: ischemia-, inflammation-, and stretch-related vicinity.[7, 17-19, 30-32] Occlusion of the sinus node artery may evoke a nodal rhythm with premature atrial beats and AF .[18] Atrial ischemia and sinus node ischemia in particular, may be involved in the pathogenesis of AF .[30] The development of AF is usually associated with inferior wall myocardial infarction (also involving an atrial wall) because of right coronary artery occlusion.[23] The pathological study by Steiner et al. has shown that AF may be initiated due to hypoxia and the degenerative changes of the pulmonary myocardial sleeves .Some inflammatory diseases – myocarditis, coronary vasculitis – are often accompanied by atrial arrhythmias and AF.[26, 31] Reportedly, both factors

– ischemia including vasospasm and inflammation take place in acute myocardial infarction complicated with arrhythmias.[32,33] At large atrial infarction is concurrent with AF.[17, 19, 23] It is known that amyloidosis sets the stage of the favorable morphological substrate for AF with subsequent impairment of left atrial systolic function .[24, 25, 34, 35]

Fibrosis as a primary cause associated with increased collagen depositions (excessive extracellular matrix), amyloid deposits (nidi) and sarcoid granulomas as well usually form the pathological conditions[36-41] leading presumably to the micro-angioarchitectural alteration. Consequently, the detrimental blood supply is likely also related to the extravascular pressure/siege/strangulation (impact of fibrosis, amyloids, sarcoid granulomas or inflammatory infiltrates) onto the vasculature – the coronary arterial tree, finally resulting in regional or global ischemia. Obviously, atherosclerosis being associated with aging is responsible for the production of the pathologic intimal thickening/lesions and, in fact, constructs intravascular stenotic obstacles/restrictions or occlusion resulting in reduced blood supply of atrial myocardium. Atrial dilatation and patchy fibrosis ranging from scattered foci to diffuse involvement, including evidence of destruction of the sinoatrial node, are commonly present when AF is associated with structural heart disease.[41-43] Chronic atrial overstretch related to the hemodynamic overload (in cases of valvular heart disease) apparently evokes architectonic abnormalities of arterial network - elongation of coronary arteries with their lumen narrowing and/or rough deformation of the coronary articulation concomitant with the impairment of arterial circulation.Deductively, the low-flow ischemia may be attributed to the attenuation of viable myocites and to their degenerative degradation. Hypoperfusion also being a favorable arrhythmogenic substrate may trigger arrhythmias in both atrial and ventricular levels.[44] Paradoxically and importantly, similar or identical fibrotic changes are induced by atrial fibrillation per se, i.e., AF itself promotes atrial fibrosis and structural remodeling.[45-48] This notion suggests the presence of reciprocal/mutual relationship which leads to the understanding that actually we deal with the classic phenomenon of a vicious circle: ischemia generates fibrosis and vice versa. Arguably, there is a close relationship between patchy/diffuse fibrosis and patchy, non-uniform/disseminated ischemia and conversely. In fact, these processes are inseparable. The coalescence of the tissue-level substrate with the vessel-level one leads to the formation of physical conglomerate(s), finally resulting in permanent and potentially irreversible arrhythmia. One may speculate that so called lone AF[49] occurring ostensibly without underlying heart disease actually is not alone but is related, at least hypothetically, to the transient regional/ focal atrial ischemia; the onset of AF paroxysm may be provoked by ischemia exacerbation thus intermittently activating vigilant triggers.

## Pivotal Role of Closely Juxtaposed Regions – Non-Ischemic, Ischemic and/or Ischemic Penubra

It could be considered that AF triggers and AF drivers most likely are located in the myocardial conflict zone represented by the borderline (norm-pathology boundary) separating the ischemic (ischemically injured myocardium) and non-ischemic areas or ischemic and sub-ischemic (less ischemic) areas – in between the territories with different degree of ischemia. In a sense, this line represents the meeting point(s)/flank(s) of electrically normal heart (atria) and electrically abnormal one. Presumably, zigzagging borderlines – the invisible rim around the ischemic areas - are extended across the atria thus dividing both atria into several ischemic and non-ischemic micro- or macro-regions. Hypothetically, one of these most active borderlines serves as a substrate for the generation of AF drivers (mother rotors), while all the rest are places where the main wavefront splits into wavelets (daughter wavelets).

Noteworthy, ischemia-induced cellular electrophysiological abnormalities – the increase of the cellular excitability and emergence of the "injury currents" (an intercellular current flow between the ischemic region and the surrounding normal myocardial cells) were demonstrated experimentally in the border zone of myocardial ischemia .[50, 51] This is related to a reduction in $Ca^{2+}$ transient amplitude and slower $Ca^{2+}$ removal as well as to reduced density of K+ currents and the changes in Ca+-dependent ionic currents.[33] Coexistence of slightly antagonistic neighboring zones may create some disparity of electrophysiological parameters resulting in subtle electrophysiological tension /

stress (or electrophysiological polarization) thus forming a substrate for the manifestation of arrhythmias. Hypothetically, it may be considered that the existence of some critical threshold of tension below which no arrhythmia outbreak can be expected. Sub-threshold electrophysiological tension between viable (non-necrotic) myocites and the healthy ones is perhaps in close relationship with the so-called "silent" myocardial ischemia/infarction which is not accompanied by atrial or ventricular arrhythmias [52-56] – an example of benign/peaceful coexistence of different regions. Thus, certain antagonistic interrelationship is observed between these two adjacent zones. Their presence results in the occurrence of different or slightly different and importantly peculiar electrophysiological characteristics – dispersion of refractoriness, spatial heterogeneity of refractoriness, atrial conduction velocity, changes in action potential duration, changes of excitability, susceptibility and their recovery, etc. Taken together these alternating electrophysiological properties are estimated in the global atrial scale in terms of electrophysiological instability, anisotropy, heterogeneity, spatial inhomogeneity, atrial vulnerability, etc. [23, 57, 58] The differences of these parameters in specific atrial regions presumably are insignificant, however potentially important to release AF trigger(s). In other words, the contiguous non-uniform confronting zones alongside with electrophysiologically invisible borderlines provide the vulnerability for arrhythmia firing. Greater odds of AF occurrence are likely proportional to the degree of electrophysiological tension. Smooth advance of atherosclerotic intimal changes within the atrial arterial network likely evokes no arrhythmogenic risk until regional or global asymmetry of blood supply and corresponding electrophysiological threshold of tension is reached; the threshold and the range of its fluctuation is scarcely identifiable (detectable or measurable). Supposedly, wide interindividual variability of threshold variations may occur. Before the advent of ischemic manifestations normal electrophysiological functioning of atrial myocardium is stored and altogether – myocites and the sinoatrial node "live in peace and harmony". Therefore, AF conceptually is a result of lifelong accumulation of arterial atherosclerosis. Hopefully there is an individual myocardial susceptibility/resistance to the provocative ischemia and its individual tolerance.

Concerning the area size, ischemia may encompass different territories which may be circumscribed not only by the borderlines as such, but also by the transitional/intermediate strips with their different width and depth. These juxtaposed marginal boundaries likely compose the sensitive and irritable rim which hides "volcanic" proarrhythmic activity. The peculiarities of the frontier environment via unique electrophysiological parameters may contribute to the character of AF (paroxysmal, long-lasting, etc.). Such an electroanatomic segmentation/compartmentalization of the regions finally results in transformation of the corresponding territories which gradually acquire different electrical, functional, structural and contractile status known as the remodeling process.

## Discreet Coin of new Definitions and Importance of Blood Flow Restoration

It is well known that the Frank-Starling mechanism conceptually regulates cardiac mechanical performance. Similarly, a new hypothetical definition might evolve: it can be stated that the AF occurrence may increase in response to an increase in the ischemic and ensuing electrophysiological differences in between segmented non-uniform atrial areas. Deductively, elimination of AF triggers actually may be accomplished through the elimination of regional ischemic differences. However, the question is: why the electrical isolation of PV's is still effective in some patients? There is a suspicion that myocardial sleeves of PV's do represent an area of increased reflexogenic activity. Destruction of these localities seems to resemble the removal of spurious/misleading pathways or foci. Most likely this procedure could induce depressive antiarrhythmic effect – a favorable disbalance of autonomic tone with subsequent regional vasodilatation resulting in ischemia annihilation, unfortunately often transient and unstable.

In order to properly validate and characterize the suggested hypothetical assumptions a new definition might be proposed, e.g. ischemia-dependent conflictogenic atrial fibrillation (IDCAF). This term concentrates the essence of the AF occurrence on the regional ischemic basis. Actually it means that electrophysiological differences de-

rive from the ischemic one; the endpoint of these antagonistic differences as the result of conflict, in fact is the manifestation of the arrhythmia - premature beats, AF, etc. Thus, it seems reasonable that for the mitigation or elimination of such unfavorable circumstances the only therapeutic recommendation might be the restoration, equalization and normalization of global blood supply of the atria. It can be supposed that periodic recovery or normalization of the blood's flow balance between ischemic and non-ischemic zones may provide the spontaneous termination of AF and/or facilitation of the abruption of AF by drug therapy. Also it might be suspected that some antiarrhythmic drugs along with their direct impact may selectively improve the macro- and microcirculation within the ischemic area(s). Restored homogeneous blood circulation presumably leads to disarrangement of clinically unfavorable vulnerability of the substrate predominantly in the initial stages of the arrhythmia. Currently such an approach might be treated as a purely theoretical one, since the vessels of very small caliber are not amenable to the modern revascularization surgery or to the remote intravascular manipulations. Normalized blood flow as a precondition may presumably promote the primary prevention of AF paroxysm. Unfortunately our assumptions cannot explain the effectiveness of cardiac defibrillation. This therapeutic procedure scarcely abolishes the regional ischemic differences unless indirectly via shocking stress by forced violation of myocardium, thus temporary increasing/maximizing the threshold of electrophysiological tension/polarization.

## Incorporation of the Arrhythmogenicity into Ischemic Entity

Universally accepted mechanisms of induction, maintenance and perpetuation of AF are based mostly on hypothetical assumptions, simulation studies, experimental and clinical observations. However, there is general agreement that genesis and maintenance of AF requires complex interaction between trigger, perpetuator, and vulnerable atrial substrate. Important contributors to AF are shortened refractory period, regional variations of refractoriness (dispersion of repolarization) and conduction velocity, and increased ectopic or reentrant activity.[6, 62, 63] Profound historical analysis of AF by Jalife[6] highlighted the most important issues, controversies, and advances that have driven the field of investigation into AF mechanisms at any given time during the last ~ 100 years. In this elegant review we can find very important data regarding long competition of theories of AF genesis (focal, ectopic activity, reentry, circus movement, meandering spiral waves, scroll waves, multiple wavelets, vortices, turbulent activity, rotors, mother rotors, daughter rotors, etc.) postulated by prominent cardiologists and electrophysiologists – Lewis, Moe, Haissaquerre, Wiener, Rosenblueth, Allessie and many others .[47, 63-68] According to Jalife,[69] it is conceivable that electrical impulses from the ectopic focus (e.g., localized in pulmonary vein inlets) may induce chaotic activation of the atria due to interaction with anatomical and/or functional barriers that leads to fragmentation of the depolarization front (daughter wavelets). Similarly, the spiral waves and scroll waves emitted by the rotor propagate through the cardiac muscle and interact with anatomical and functional obstacles, leading to fragmentation and new wavelet formation.[70] Moe[66] described the substrate of AF as a continuous activation of the atrial myocardium by several reentry circles that are not anatomically fixed, but spread and mingle in a seemingly chaotic pattern. The theoretical length of each reentry circle gives an expression of the minimal circumference and each depolarization must travel to avoid that the electrical impulse reaches its origin before this is again excitable; when refractoriness is short and conduction velocity is low, wavelength is also short.[62, 66, 71] Thus, several reentry circles may exist simultaneously in the atria.[62] Five or six reentry circles are associated with the stable AF, while a situation with fewer reentrant circles either converts to sinus rhythm, or degenerates into more reentry circles. [47, 63] Reportedly, there are different number of propagating wavelets and rotors participating in AF and giving rise to the turbulent atrial activity. Some authors indicate single or small number of high-frequency sources, [72-74] 4-6 wavelets [75, 76] and even 23-40 multiple circulating waves for arrhythmia sustenance.[77] It is widely known that rotors may be responsible for the perpetuation of AF.[6, 66, 69, 70] The periodicity of rotations depends on wavelength (action potential duration), refractory period and conduction velocity, and these parameters are unstable,

they shift in response to tempo of the electrical and structural remodeling.[74, 78] There are methodological difficulties in determining wavelength however some authors through indirect methods have established that it ranges from 5-7 cm up to 12-13 cm.[74, 79, 80] Direct measurements from a computer model showed the wavelength of 5 cm. [71] Electrical remodeling primarily shortens the refractory period and the action potential duration, while structural remodeling impedes propagation and hence decreases conduction velocity,[74] electrical and structural remodeling both decrease the wavelength, thus potentially perpetuating AF.

The above mentioned mechanisms of AF genesis are consistent with the conceptual assumptions related to the atrial segmentation into ischemic and non-ischemic regions, thus resulting in electrophysiological disintegration of atria. Ischemia-dependent atrial electrophysiological behavior may be incorporated into the scenario depicted as IDCAF. Theoretically the sheer number of rotors, daughter rotors, wavelets and wavelength(s) are unstable and situation-dependent. As noted above, each borderline separating different atrial areas is not capable of producing/releasing the triggers. The main (dominant) borderline initially plays a key role in emanating focal/multifocal/reentrant triggers for AF. Obviously, this line – insidious arrhythmogenic substrate - contains the greatest potential of trigger(s) activity. All remaining borderlines being less important serve as a functional obstacle(s)/hurdle(s) where the rotors split into wavelets, daughter wavelets, i.e. into secondary, tertiary, etc. wavefronts. Here the wavelets most likely breakthrough, traverse, split, fragment, multiply, anchor, abrupt, die and/or extinguish. However, over time the role of the main borderline is taken over by the borderline(s) theretofore being less active or dormant/inactive; this may occur when the threshold of electrophysiological tension between conflicting areas is reached. So, all borderlines may demonstrate their activity in alternating manner and sooner or later become interchangeable. As a result of such uncontrolled game, the total chaos (bioelectrical instability, high-frequency oscillation activity, etc.) gradually and finally ingrains. Due to the mutual interactions, ischemically damaged and non-damaged myocardium do participate fundamentally in the relay-race carousel of arrhythmogenicity accompanied by the "fireworks" at the separating borderlines. Any rotational direction of the driver – clockwise or counter-clockwise - is feasible. Regarding the localization, the size and geometric configuration of the ischemic region, the ectopic/reentrant pulses may propagate also centrifugally and/or centripetally. Most likely reentrant pulses move centrifugally inducing AF, while ectopic one – centripetally, thus evoking premature/extrasystolic beats. Different consequences may be expected in respect to which territory is traversed first (whether ischemic or non-ischemic) by the pulse emitted in the vulnerable substrate. It must be emphasized that the triggering pulse meets different, volatile and strongly defined medium – alternating environments with distinct electrophysiological characteristics being intersected by functional barriers. Taking into account the influence of gross structure and atrial myoarchitecture to the character of AF[81, 82] some different clinical manifestations of arrhythmia may occur and it could be related to the anatomical site of the vulnerable substrate – subendocardial, intramural, subepicardial, transmural. Finally, dislocation or migration of the separating borderlines also may take place and may influence the outbreak of AF, especially when the ischemic territory shrinks or expands. In any case, these peculiarities may act in concert with the previously declared phenomenon comparable with the vibrantly quiescent stroboscopic tuning. [83] As long as AF is initiated by the principal borderline the arrhythmia is more amenable to the therapy (drugs, DC shock, ablation), however due to the development of alternating activities of the rest borderlines' arrhythmia becomes less controllable and finally uncontrollable. Most likely the dynamics of arrhythmia control is related to the parallel ongoing process of fibrotic changes with the advance of atrial remodeling.

Of course, AF remains multiethiological. However, the hypothetical presumptions presented here might be helpful to assert the processes taking place in the chain of the onset, maintenance and termination of AF. Hypothetically the ischemia is a mainstay and crucial contributing factor. However, there is a lack of convincing data to strongly argue the suggested approach. In the broad sense, the knowledge that different number of ischemic areas and their borderlines exist along with unstable number of rotors, wavelets, reentrant circles with their complex interactions might better explain the intrusive phenomenon of AF.

Analogical ischemia-based argumentation may be helpful in elucidating the pathogenesis of ventricular arrhythmias including fibrillation (except of syndromes' associated with accessory conduction pathways or genetic origin).

## Conclusions

The understanding of pathogenesis of atrial fibrillation continues to evolve.Based on the survey of currently applied theories and reconsiderations it may be concluded that, regardless of the character of cardiac disorder, the ischemic factor is relevant and possibly responsible for the genesis and perpetuation of atrial fibrillation. Due to the electrophysiological differences (antagonistic tension, stress, polarization) occurring in between ischemic and non-ischemic atrial areas a vulnerable arrhythmogenic substrate most likely is created along the separating borderlines. The dominant borderline apparently may be involved in releasing of triggers/drivers of arrhythmia while the rest may be treated as functional obstacles/hurdles participating in the relay-race carousel of arrhythmogenicity. In time, along with the atrial remodeling all borderlines become functionally interchangeable, the chaos gradually ingrains and finally arrhythmia tends to become irreversible. Much innovative intellectual and explorative research work is to be done to overcome the difficulties in restoration of blood flow of ischemic areas where circulative problems are mostly concentrated in the microvasculary, pre-capillary or capillary level. Thus, further studies might be focused on reunification of ischemic areas or annihilation of ischemic asymmetry in order to rebuild global electrical and electrophysiological stability.

## Disclosures

No disclosures relevant to this article were made by the author.

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