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Journal of Atrial Fibrillation

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Homogenization of Atrial Electrical Activities: Conceptual Restoration of Regional Electrophysiological Parameters to Deter Ischemia-Dependent Conflictogenic Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) as a severe arrhythmia is now spreading worldwide at overwhelmingly high rates, particularly in elderly patients. Despite new insights, the mechanisms underlying AF are not conclusively determined yet. Taking into account the ischemic origin of arrhythmia induction (according to the so-called conflictogenic atrial fibrillation, declared recently) restoration of regional electrophysiological parameters is essential in tackling AF. We hypothesized that some atrial electrophysiological parameters, preferably the effective refractory period, might need to be controlled to prevent AF. All the remaining parameters - conduction velocity, conduction time, recovery time, vulnerability, excitability, repolarization etc. being as if secondary and less important could be ignored. Homogenization of the milieu producing AF might be implemented, at least theoretically, through restoration of blood supply in ischemic areas and/or via attenuation of electrophysiological differences between conflicting regions by delivery of atrial sub-threshold non-captured pulse-trains. Adjunctive therapy by drugs containing vasodilatory features and affecting the effective refractory period appears to be fundamental. Thus, stabilization of disorganized atrial cellular activities likely may lead to the recovery of atrial excitable characteristics. Despite the lack of compelling evidence, the application of the concept may be helpful in order to search for more precise and more effective methods to favorably change the refractory period. Further studies are necessary to determine whether restoration or improvement of blood circulation of atrial wall is feasible. Based on such considerations a novel preventive AF strategies are to be designed.

Introduction and General Reflections

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, the occurrence of which increases with age. AF can be characterized as an arrhythmia comprising of well-organized atrial activation in chaotic fashion with ventricular irregularity, often accompanied by co-production of auto-aggressive thromboemboli. Introductory sentences emphasizing relatively high morbidity and mortality rates in patients suffering from AF are reiterated in a myriad of literature sources analyzing genesis, maintenance, perpetuation, complications, prevention and therapy of AF. In fact, AF is an incrementally challenging burden for patients, for society and for modern cardiology. The challenges we face today in dealing with AF are similar to the ones we faced years back in dealing with coronary artery disease.[1]

Key Words:

Conflictogenic atrial fibrillation, ischemia, effective refractory period, revascularization, electrophysiological tension, sub-threshold pacing

Disclosures:

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

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Unfortunately, no worldwide gold standard has been established yet with regard to uniform understanding of causal mechanisms of AF. It is still unclear whether AF is the only driver of the disease in a self-perpetuating process or a consequence of an underlying structural heart disease, or an arrhythmic manifestation of an independent "fibrotic atrial cardiomyopathy", or of the aging atria.[2] In spite of such uncertainty there is some progress in the complex and versatile management of arrhythmia – antiarrhythmic, anti-inflammation therapy, anticoagulation, pacemaking, ablation, cardioversion, defibrillation, surgery.[3-14] Currently the (not required) catheter ablation has become accepted as an effective mainstream therapy for treatment of drug-refractory symptomatic AF.[15] This method is a promising therapy for AF however the success is limited in part by uncertainty in the mechanisms that sustain AF.[16] Pulmonary vein isolation is now a routine procedure,[17] however at long term follow-up after successful ablation, no evidence of reverse remodeling of atrial substrate is seen, and some evidence of further substrate progression is noted.[18] Verma et al. have described that preexistent left atrial scarring in patients undergoing pulmonary vein isolation is an independent predictor of procedural failure.[19] Obviously, the therapeutic modalities alone or in combination give rise to the hope that this evil may not actually be incurable. Therapy modalities are evolving, however at a relatively slow pace. Nevertheless, it seems that in the meantime we still find ourselves only halfway to winning

this battle. Thus, it is reasonable to continue the research for more effective therapeutic and preventive methods for AF.

AF is sometimes characterized as the electrical equivalent of coronary artery disease, which occurs due to mechanical obstruction or functional stenosis of coronary arteries.[1] In contrast, AF induced alterations in coronary blood flow result in symptoms of myocardial ischemia in patients with AF,[20] while the termination of arrhythmia has an opposite effect.[21] Even in the absence of coronary artery disease, patients with AF frequently present with angina-like chest pain and transient ischemia-type ST-segment depression.[20] At large the ischemic etiological factor results in the change of the fundamental features of atrial myocardium by shifting of its refractoriness, automaticity, conduction velocity, excitability, vulnerability etc., whether temporarily (paroxysmal AF) or permanently. Reportedly, hypoxemia and oxidative stress associated with obstructive sleep apnea increase the recurrence of AF.[22] Regarding these observations the ischemia seems to be essential for AF occurrence.

According to fundamental cardiac electrophysiology, ventricular myocardium becomes arrhythmogenic during the phase 1b interval of ischemia.[23,24] In one of the most comprehensive studies by Coronel et al.[25] it was postulated that with regional ischemia some important electrolyte imbalances and metabolic changes are confined to the poorly perfused tissue that is electrically coupled with normal myocardium at the ischemic border where injury currents flow between regions. Border zone interactions are important to arrhythmias because the relationship between source charge generation and downstream sink charge requirements modulate membrane depolarization and repolarization, and they also dictate success or failure of action potential propagation.[26]

Recently, based on literature data, we hypothesized that there is a strong interrelationship between myocardial ischemia and interstitial atrial fibrosis, i.e., the fibrosis is stipulated/influenced by ischemia and vice versa.[27] In brief, mutual interdependence might be formulated as "fibrosis-related ischemia" or "ischemia-related fibrosis". It was revealed, at least hypothetically, that ischemia is a key etiological factor of AF genesis irrespective of the underlying heart disease. From this point of view other syndromes associated with accessory pathways or those of genetic origin are to be excluded. According to the new hypothetical doctrine, ischemia as a primary cause results in atrial fibrosis. Then the progressing fibrotic process accompanied by anatomical constraints induces detrimental conditions for arterial microcirculation which, in turn, activates fibrosis. Thus, a vicious circle is launched. Fibrosis also may be initiated by inflammation or by overstretching of the atrial wall in cases of myocarditis, vasculitis or valvular heart disease. Joint action of ischemia and fibrosis leads to the production of a structurally inhomogeneous region with specific electrophysiological parameters which differ from those inherently dominating a healthy myocardium. Thus, at least two regions – ischemic and non-ischemic - arises along with their own electrophysiological parameters. As a result of the electrophysiological tension (polarization) occurring in between neighboring areas, an arrhythmia may finally evolve. In other words, the tension emanating from the aforementioned differences might be treated as a fundamentally potential precursor of AF initiation. From an electroanatomic point of view, an arrhythmogenic substrate is likely located in/within the borderlines of conflicting areas i.e., within the surrounding rim (penumbral zone, demarcation line). Sub-threshold electrophysiological tension between areas of "strained relations" may evoke no arrhythmogenicity therefore providing peaceful coexistence until the threshold of tension is reached. Ischemia as a parent element of the arrhythmogenic substrate actually circumscribes corresponding ischemically injured region(s) thus creating favorable conditions for the secondary element to occur – electrophysiological differences and polarization. Circumferential borderlines likely have irregularly-shaped geometry (including ramifications) corresponding to the specific arterial network. Some influence on the behavior of AF may depend on the amount of tissue involved, i.e. the size, and the depth of the ischemic region (subendocardial, subpericardial, intramural, transmural) and the dimensional proportions of conflicting areas. Along with ischemic expansion the healthy myocardial area likely shrinks and therefore AF gradually assumes more grave features. One may consider that conceptually the higher the degree of ischemia the higher the chances for AF manifestation. Based on this postulation, this hypothesis was given the name of "ischemia-dependent conflictogenic atrial fibrillation". This concept has not been analyzed or corroborated by independent sources yet and fortunately not dismissed either. In all likelihood the utility of the concept containing mild speculations will be weighed by the future.

The ideal therapeutic goal for AF is the maintenance of sinus rhythm to preserve the atrial transport function. Theoretically it could be implemented as long as atrial fibrosis has not ingrained completely and irreversibly. Homogenization of the milieu producing AF might be achieved through restoration of blood supply in ischemic areas and/or via attenuation of the electrophysiological differences between conflicting regions. Whether these two fundamental prerequisites act in consort to successfully harmonize atrial performance is still the key question. According to universally recognized axiom, every unfavorable inhomogeneity of the atria – whether ischemic, electrical, structural or mixed – needs to be homogenized, (i.e. transformed into previous state), if possible, in order to fulfill the expectations of any clinical benefit.

Simultaneous annihilation of ischemia and electrophysiological polarization may elicit a favorable atrial response and act as a deterrent tool for the prevention of AF. To achieve the goal it could be reasonable to focus on potential therapeutic and preventive scenarios: 1) diagnostic identification of ischemic regions of atrial wall and subsequent amelioration of blood supply, 2) verification of electrophysiological properties and their differences in conflicting areas (preferably in ischemic ones) and search for tools and methods to affect the electrophysiological parameters by equalizing/unifying the effective refractory period (ERP), conduction velocity, activation time, repolarization time, etc. Importantly, the primary strategic goal of this article is an attempt at the stewardship of ischemia-related inhomogeneity thereby anticipating that inhomogeneity will likely be homogenized. Reestablishment of good blood flow presumably might result in automatic mitigation of the inter-regional electrophysiological differences, while bleaching out of the latter would mean that the ischemic problems remain unsolved.

Identification of Atrial Ischemic Regions

As mentioned above, it is becoming increasingly clear that ischemia plays a key role in the organization and perpetuation of AF and this viewpoint is supported by many other investigators.[28-31] It is therefore important to identify and verify the region(s) with poor blood supply. Obviously, it presents an enormous challenge since

we deal with peculiarities of arterial vascularization of the atria. The atrial arterial network in humans is extremely variable[32-34] and the blood supply mainly depends on microvascular network. The sinus node and the sinoatrial region are, in 55% of patients, perfused by an atrial branch from the proximal part of the right coronary artery.[8] In 45% of the cases this region is perfused by a proximal branch of the circumflex coronary artery.[35] A proximal occlusion of the right coronary artery or the circumflex coronary artery may therefore lead to ischemia of the sinus node and surrounding atrium.[8] The diameter of human atrial microvessels is approximately 103±2 μm,[34] therefore conventional angiographic visualization is scarcely feasible.

In 2010 Smit et al. investigated myocardial perfusion by single-photon emission computed tomography in patients suffering from AF.[36] Authors emphasized the need for new non-invasive techniques to adequately assess the coronary artery disease in AF patients. Apart from the conventional percutaneous angiography[37] there are several non-invasive diagnostic methods for the detection and stratification of myocardial ischemia.[38-41] Unfortunately, these methods exclusively serve the evaluation of ventricular circulatory status and coronary artery disease in general. Therefore, the results of such explorative data cannot be utilized to evaluate atrial vascular status – detection, localization and quantification of perfusion defects. Obviously, to reveal the atrial regions marked with poor blood circulation and to determine the extent and severity of ischemia more precise improvements of diagnostic tools and accuracy are needed.

Revascularization Peculiarities of Atrial Myocardium

Multiple stenotic obstacles (intravascular atheromatous-related or extra-vascular fibrotic matrix-related) within small vessels actually induce the restrictions in blood flow. To the best of our knowledge, there have been no atrial revascularization attempts reported. Thrombolysis, angioplasty, stenting, endarterectomy or any other kind of intervention into atrial arteries actually appears to be beyond imagination. The role of direct mechanical affection to the obstacles particularly in diffuse coronary artery disease is still ill-defined. The challenge also is to find a way to precisely install the vessels running to the ischemic area(s) in order to restore the blood circulation. Fibrosis dispersion in the end stage of atrial disease with its classical atrial remodeling leads to persistent AF.[42-43] Revascularization afterwards is actually impossible and no longer helpful perhaps except for atrial or heart transplantation.

Any type of myocardial revascularization is based on improvement in the delivery of oxygenated blood to the ischemic area. The conventional methods of increasing ventricular (not atrial) myocardial perfusion include percutaneous transluminal coronary angioplasty and coronary artery bypass grafting surgery,[44] a small vessel disease is not amenable to these therapeutic methods. To create myocardial neovascularization as well as stimulating further angiogenesis a method of transmyocardial revascularization (TMR) was developed.[44,45] For this purpose either a carbon dioxide laser or Holmium:YAG laser is used.[46-48] There is an outstanding report[47] demonstrating the effectiveness of TMR used as adjunctive to the coronary artery bypass grafting; a significant lower incidence of postoperative AF was observed regardless of revascularization of ventricular myocardium, not atrial. Even though TMR may lead to a decrease in angina and improved exercise tolerance[46] the short-term and long-term outcomes indicate that usefulness of TMR needs further research.[48] Literature sources lack to indicate the usefulness of neovascularization by TMR on the atrial level. It is still unclear whether the doubtful clinical benefit of the TMR might outweigh the consequences of myocardial damage induced by a laser beam. In this context further studies are warranted to delineate the possible beneficial mechanisms of the procedure.

Experimentally it was found that isolated human coronary arterioles demonstrate endotellium-dependent dilatation in response to some drugs.[34] Beta-blockers may improve atrial blood supply by their vasodilatory impact and appear to effectively prevent occurrence of AF, especially in patients with systolic heart failure.[49] Their antiarrhythmic and anti-ischemic role or both have not been clearly defined yet, at least in relation to AF prevention. Some authors have indicated that the recurrence rate of AF is known to be high, even under beta-blocker prophylaxis.[50] However, the beta-blocker therapy prolongs atrial cell ERP[50] thus favoring antiarrhythmic background. Noteworthy amiodarone, class III antiarrhythmic agent also extends atrial ERP, prolongs the duration of action potential and depresses conduction velocity thereby possessing the efficacy in prevention and termination of AF.[52,53] The ERP has been identified as the most vulnerable parameter and therefore a correct therapeutic approach could be based on drugs being able to prolong the refractoriness.[54] The significance of the ERP is discussed below.

Atrial Pacing and AF Protective Effects

It is assumed that better organization of atrial activation and the correction of electrophysiological states could be implemented by means of antiarrhythmic pacing.[55,56] Different atrial pacing modes and a number of pacing algorithms have been suggested for the prevention of AF.[56-60] Conventional overdrive atrial pacing is supported by both electrical and mechanical theory in preventing the onset of AF,[61] atrial pacing prevents potential triggers for AF such as bradycardic episodes and ectopic atrial beats, and atrial pacing avoids the atrial stretch caused by increased atrial pressure that is associated with atrioventricular dyssynchrony. Specifically, continuous atrial overdrive pacing does not prevent new-onset AF and is poorly tolerated.[62,63]

For the prevention of atrial tachyarrhythmias Becker et al. have stressed the rationale of the selection of pacing locations and the number of pacing sites.[55] It was hypothetically supposed that pacing, particularly delivered at multi-sites, may homogenize electrical conduction properties of the atrium and promote sinus rhythm.[62] Studies of biatrial and multisite pacing have been shown to decrease atrial activation time.[61] Distal coronary sinus pacing has been proven to suppress atrial premature beats from inducing AF by limiting their prematurity at the triangle Koch, which is a region of local conduction delay and re-entry.[64] However some multicenter studies failed to show any AF preventive benefit compared with single-site or no pacing, therefore the use of alternative site pacing should be considered unproven and experimental.[61,62,65] At large, studies of preventive algorithms have yielded mixed results, further clouding the role of pacing algorithms themselves.[60,61,65-67]

Atrial Refractoriness as an Exceptional Electrophysiological Parameter

Further insights into atrial electrophysiological features may be helpful in tackling AF. Holmqvist et al.[68] have considered that alterations in atrial electrophysiology are common in the early stages of AF, which may indicate that these changes play a key role in AF

development. Recently Teh et al.[18] have stressed that AF patients demonstrate an abnormal substrate characterized by reduction in voltage, conduction slowing, and increased signal complexity. Botto et al. have postulated that the most important atrial parameter related to AF-induced electrical remodeling is the ERP.[69] Both experimental and clinical studies have substantiated that an increase in the dispersion of refractoriness favors the occurrence of AF.[71-73] According to Carnes et al. the earliest observed change in AF is an abbreviation of the atrial ERP.[73] Sato et al.[74] have observed that atrial ERP increases just after conversion of AF to sinus rhythm. Similarly, atrial electrical remodeling occurs when AF is sustained, leading to a shortening of ERP and slowing of conduction velocity that promotes AF.[43,51,62] In 1998 Fareh et al. have reported that in dogs premature extrastimuli induce AF predominantly at sites with short ERP.[70] Also the presence of short ERP and short action potential facilitate the induction of AF.[75] On the contrary, AF alters atrial electrophysiology and produce ultrastructural abnormalities to favor its own maintenance.[42] Finally, atrial activation increases the spatial variability in AF cycle length[76] which is an index of atrial refractoriness.[77] Overall, the prolonged ERP is predictive of stable sinus rhythm.[78] Deductively, subtle control of the refractoriness makes the atrium less vulnerable to AF. Hence, it is possible that when ERP is restored properly all the remaining electrophysiological parameters (conduction velocity, potential duration, potential duration, vulnerability, excitability, etc.) may regain their previously inherent values automatically.

This suggests that ERP represents the most important electrophysiological parameter, apparently being directly involved in AF mechanisms. It could be considered that some drugs (beta-blockers or others) may change the ERP in different ways when affecting different atrial regions. Preventive drug therapy may be insufficient to control AF occurrence even when highly selected antiarrhythmic drugs are prescribed. It might be related to the inadequate/non-uniform ERP response in specific atrial regions. That is why we observe different clinical results with medication – sometimes effective AF prevention but sometimes manifestation of proarrhythmias. In other words, drugs may fail to increase the tension threshold of existing electrophysiological parameters, at least hypothetically, in-between conflicting regions. Thus, simultaneous unification of ERP duration in corresponding atrial regions appears to be problematic.

Promising Atrial Sub-Threshold Conditioning Pacing

There are reports demonstrating that single sub-threshold conditioning pulses and/or pulse-trains may favorably affect atrial refractory period.[79,78] Gang et al.[81] have declared that sub-threshold pulses are able to terminate reciprocating tachycardia. Ultra-rapid sub-threshold pacing may also provide a safe and effective termination of AV node reentrant tachycardia with the electrode located either in the right atrial sites or in coronary sinus.[82,83] It was pointed out that sub-threshold pacing is only effective when applied adjacent to critical components of the reentrant circuit.[83] Sub-threshold conditioning stimuli have been shown to be effective in the prevention or termination of ventricular tachycardias, but this possibility is constrained by the spatial limitations of the technique[84] effectiveness of such a sham pacing is explained by the ability of lengthening the ventricular ERP. Some beneficial effects may provide hybrid efforts joining the positive sides of antiarrhythmic, and vasodilatory drugs and with sub-threshold atrial pacing - preferably applying conditioning pulse-trains. However, the latter pacing modality has not been clinically approved yet thus more detailed studies are necessary for its technical and methodological effectiveness. Finally, much remains to be done in order to establish which region – whether ischemic, non-ischemic or both – is to be preferentially paced to achieve appreciable clinical benefit.

Conclusions:

Homogenization of atrial electrical activity might be achieved hypothetically via normalization of global atrial blood supply or by sub-threshold atrial conditioning pacing. Despite the lack of compelling evidence, further application of the concept may be helpful in the search for more effective methods to influence atrial refractory period. Some initiatives could be undertaken to test hybrid atrial conditioning pacing by pulse-trains and by vasodilatory drugs containing the capability to increase atrial effective refractory period. There is a pressing need for further studies to determine whether restoration or improvement of blood circulation of the atrial wall is even feasible. Taking into account the ischemic origin and background to atrial fibrillation, new strategies of arrhythmia prevention need to be devised.

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