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Interdependent Relationship Between Atrial Fibrillation and Sinus Rhythm at the Hypothetical Interface of Atrial Fibrillation, Autonomic Tone, Sinoatrial Node and Inflammation : Analytical Review, Reconsiderations, Speculations and New Insights

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Abstract

Underlying mechanisms of atrial fibrillation occurrence and its self-extinguishing remain not completely investigated yet. The role of autonomic tone and sinoatrial node in the interplay between atrial fibrillation and sinus rhythm is also not fully understood. The influence of inflammation as a possible source of arrhythmia and likelihood of its pharmacologic treatment deserves special attention. These complex issues are important for better understanding of arrhythmogenesis and rhythm control. Conceptual reconsiderations through the new insights primarily on the hypothetic basis may delineate new therapeutic and preventive strategies. The aim of this analytical review was to reinforce the clinical and laboratory studies regarding the role of: 1) autonomic tone and sinoatrial node in restitution of sinus rhythm, 2) new concept of "vibrantly quiescent stroboscopic tuning" as a matured status of atrial fibrillation being prepared for its abruption by slight impulse, 3) inflammation in the interplay between atrial fibrillation and sinus rhythm, 4) anti-inflammation and anti-allergic therapy to prevent and to treat the arrhythmia.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in the world. This kind of arrhythmia being relatively benign is accompanied by some devastating symptoms and complications (impaired quality of life, thromboembolic stroke, congestive heart failure) which contribute substantially to cardiac morbidity and mortality. AF may manifest as an independent disorder (lone AF) but some valvular heart diseases, hypertension, myocardial infarction and cardiomyopathy potentially underlie the generation of AF.[1, 2] The electrophysiological substrate initiating and maintaining AF is very complex and evolves over time. "Capricious" arrhythmia was aptly termed by Wellens[3] as the last big hurdle in treating supraventricular tachycardia. Pharmacologic and non-pharmacologic treat-

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ment strategies are designed to control rate and rhythm and to provide any necessary support by antiarrhythmic drugs, diuretics, cardiac pacing, ablative therapy, cardioversion, etc. to improve the patients' condition. Depending on arrhythmia manifestation (paroxysmal, permanent, persistent, long lasting AF) different clinical approaches are used. Restoration of sinus rhythm in the early stages of this disorder is of paramount importance especially in the face of arrhythmia's progression from paroxysmal to permanent AF.

It is well known that paroxysmal or non-paroxysmal AF may terminate sporadically without any therapeutic help.[4-6] Spontaneous reversion of sinus rhythm in patients with recent onset of AF seems quite high in the absence of severe heart disease and symptoms of heart failure.[7] On the basis of this review we would like to focus attention on mechanisms both inducing and abrupting of AF, however predominantly discussing circumstances related to self-restitution of sinus rhythm. The understanding of the mechanisms of arrhythmia termination could potentially be as important as understanding of mechanisms of initiation.[8] The lack of knowledge is the impetus for the present analytical review and of subsequent hypothetical suggestions. Obviously, it is time to crystallize the criteria for anti-inflammation therapies especially in the early stages of paroxysmal AF, i.e. before the permanent AF is ingrained. Through insights it is desirable to seek for more lenient electrical therapies of paroxysmal AF rather than conventional cardioversion with relatively high energies. Innovative, though hypothetical approach likely will encourage an investigative strategy for restoration and maintenance of sinus rhythm.

Pathophysiology of the Arrhythmia

Numerous studies have addressed the complex pathophysiology of AF.[9, 10] A full understanding of the underlying mechanisms of human AF remains an ongoing challenge despite decades of basic and clinical research.[11] Arrhythmia is characterized by highly disorganized atrial electrical activity being irregular in regard of both rate and rhythm. AF is commonly associated with congestive heart failure and, in turn, congestive heart failure has been shown to be associated with atrial structural remodeling leading to fibrosis and intra-atrial conduction disturbances.[12, 13] Both mitral regurgitation and congestive heart failure produce structural remodeling and increased interstitial fibrosis resulting in AF.[1,2,11] Structural remodeling, in turn, is accompanied by contractile remodeling (loss of contractility) which leads to a reduced atrial transport function.[13] Furthermore, structural and electrical remodeling may produce differing atrial substrate with heterogeneity vulnerable to fibrillation.[14] Heterogeneity can arise from multiple factors that can be structural (e.g., gap junction disruption or fibrosis), functional (e.g., shortened action potential duration or decreased effective refractory periods), or both.[1,14] Different pathophysiological states and uderlying heart disease as a profibrillatory substrate can modify the electrical and structural properties of the atrium to increase AF susceptibility.[15] There is well-established link between cardiac inflammatory states and AF, predominantly paroxysmal.[16-18] It was shown that prednisone suppresses AF susceptibility and C-reactive protein in the canine sterile pericarditis.[19, 20] Methylprednisolone reduced AF recurrence and C-reactive protein levels in patients treated with propafenone after conversion of symptomatic, persistent AF,[19] while steroids have also been shown to reduce postoperative AF after coronary artery bypass grafting surgery.[21]

The main explanation for our current disappointing ability to control AF is an incomplete understanding of the mechanism(s) underlying its maintenance, despite many years of research and speculation.[22, 23] Over the past 50 years, the multiple wavelet hypothesis with anisotropic spread of electrical excitation has been the dominant mechanistic model of AF.[23, 24] The hypothesis, first postulated by Moe et al.[25] states that AF is the result of randomly propagating multiple electrical wavelets (circuits) that interact in very complex ways, with local excitation limited by heterogeneous distribution of refractory periods throughout the atria. [22,25] These circuits collide, become extinguished and arise again .[18] According to the statement by Jalife et al.[26, 27] the maintenance of AF, whether paroxysmal or persistent, may depend on the periodic activity of one or a small number of rotors and meandering spirals in the posterior left atrium wall – pulmonary veins' region; these rotors activate the atria at exceedingly high frequencies resulting in fibrillatory conduction. In 2009

Yamabe et al.[28] have indicated that complex fractionated atrial electrograms reflecting the AF are influenced by: 1) focal discharges with their specific firing frequencies, 2) frequencies of wave brake and wave fusion, 3) fusion of the wave fronts into a new wave front, 4) radial spread of activation, 5) changes the wave front direction over 90°, 6) wave front split into independent wave fronts (mother rotor gives rise to daughter waveforms), 7) conduction velocity, 8) functional block.

Driving of the fibrillatory activity is usually sustained on self-perpetuation manner. Initiation of impulse by automaticity or by triggered activity as well as impulse initiation resulting from the reentry has been also suggested.[29] Reentry is not self-starter; it requires excitation of a site within the potential reentry matrix that is timed in the interval between the shortest and longest refractory periods in the matrix in order to initiate reentrant propagation.[30] It was shown, however, that a rapidly firing focal excitation may be located inside or close to pulmonary veins, vena cavae, coronary sinus, ligament of Marshall or in both atria.[12, 24, 25, 29,31] Zrenner et al.[32] have hypothesized that AF is maintained by two mixture mechanisms – focal and re-entrant activation. Furthemore, the triggers (or stretch-related triggers) and reentry may be amplified by the process of remodeling.[33] These mechanisms are likely responsible for initiation and/or perpetuation of vicious circle of AF – the milieu treated as "AF begets AF".[34] Finally, AF produces changes in atrial function and structure thus providing a progressive nature of this arrhythmia which over time ingrains irreversibly and reaches the clinical entity coined "domestication of AF".[13] Recently a novel and intriguing hypothesis of cardiac arrhythmia genesis has been proposed.[35, 36] According to the theory a bi-stable wave propagation and cardiac biexcitability may be responsible for arrhythmia (atrial or ventricular) induction and the development of sustained AF. Moreover, a weak but suprathreshold stimulus may induce a strong "all-or-none" response. [36]

Overall, this observational study demonstrate that etiological factors do change the essentially fundamental electroanatomical features of atrial myocardium by shifting and/or distortion of its cellular automaticity, refractoriness, conduction and intercellular relationship– whether temporarily (paroxysmal AF) or chronically (permanent AF) - finally resulting in a loss of atrial transport function.

The Influence of Autonomic Nervous System

According to the current opinion of cardiology the autonomic nervous system is a potentially potent modulator of the initiation and perpetuation of atrial fibrillation.[8, 10, 11] Complex interactions exist between the sympathetic and parasympathetic nervous system on the atrial electrophysiological properties.[8, 37] Heart rate variability analyses have shown that either sympathovagal imbalance or sympathovagal discharges precede the onset of paroxysmal AF.[38] In 1993-1996 Coumel [39,40] stated that electrophysiological characteristics of atrial cells (action potential duration and refractoriness, conduction speed) are modulated differently by vagal and sympathetic influences; the former tend to favor macroreentry phenomena, whereas the latter favor abnormal automaticity and triggered activity. It appears that the relative sympathovagal balance is as important, or more important, than the absolute sympathetic or parasympathetic tone;[37] this can result in regional shortening of the atrial refractory period, heterogeneity of atrial repolarization, and predisposition to induction of AF. [41, 42] Overall, the differences between the sympathetic and vagal effects on the tendency toward spiral wave break-up may explain the reason why adrenergically-mediated paroxysmal AF terminates spontaneously and vagally-mediated paroxysmal AF tends to be maintained.[43] Self-cardioversion of paroxysmal AF may occur through vigorous exercise, especially in athletes.[44, 45] Chen and Tan in 2007 [46] have postulated that modification of cardiac autonomic nervous system inputs might be effective in AF control.

There are complex relations between AF and autonomic tone that affect each other. [47] AF can itself change the autonomic tone or the sensitivity of atria to autonomic tone, possibly by alteration in autonomic nerve fibers located in the atria.[47, 48]

Self-Restitution of Sinus Rhythm

The ideal therapeutic goal for AF is the production and maintenance of sinus rhythm.[49] Sporadic abruption of AF and automatic reestablishment

of sinus rhythm (SR) often occurs in patients with paroxysmal AF and exceptionally with long lasting AF. The mechanisms and preconditions of arrhythmia transition to SR continue to be a considerable challenge. Obviously it is indiscernible and furtive action though an important shift is well documented by ECG and by better feeling of patient. Electrocardiographic patterns demonstrate sudden abruption of AF with ensuing SR.[5, 50] The transition duration is very short but the pre-abruption (preconditioning) likely is well prepared. We may speculate about the boundary conditions leading to the self-restitution of SR however it is worthy to explore the transitional zone (or transitional window) where the fundamental events take place. To compare, triggering extrasystole occurring during SR is sometimes crucial to start the arrhythmia. Similarly, the circumstances allowing the release of SR at the borderline of abruption of AF play a significant role. In other words, we talk about the substrate favorable to start the arrhythmia and the substrate which favors its abruption.

Nothing is generated spontaneously, unconditionally or unreasonably. Disengagement of sinoatrial node's (SAN) activity after a short or prolonged oppression by AF is presumably not accidental. Obviously, favorable conditions needed to mature for the reversion of SR. In 1993 Cotoi et al. [51] hypothesized that transition from AF to SR may manifest in two ways: 1) prolongation of atrial refractoriness reduces the wave fronts below a critical number and their collision terminates the arrhythmia 2) progressive shortening of refractoriness at a critical level with block and collision of wave fronts. According to Lovett and Ropella [52] conversion to SR is associated with a variety of time-frequency dynamics: both gradual and abrupt increases in coherence coincide with conversion. Deductively, the chaos and coherence collide as if fortuitously and finally converge into harmonic SR, orchestrating cardiac performance. It is quite reasonable to suggest that such a convergence occurs likely via concealed cardioversion of low or very low energy. Conceptually such kind of cardioversion (auto-cardioversion, intrinsic cardioversion) potentially may be implemented through the unique status – a phenomenon comparable with the vibrantly quiescent stroboscopic tuning (VQST). Hypothetically it stems from the pivoting activation – revolutions of the wave fronts. Such a mechanism often is termed as "circus movement", "circuitous wave front propagation", "reentry turnaround " , etc. [18, 53, 54] Fluctuating AF drivers-important contributors of arrhythmia (action potential duration, refractoriness and its dispersion, conduction velocity, volatile number of rotors , time-frequency characteristics of wavelets' and their break-ups, homogeneity of contractions of myocytes, etc.) are transformed into clinically favorable set of parameters mentioned, thereby creating positively vulnerable condition. Critical level of necessarily dynamic stability of VQST is presumably reached when ongoing highly dynamic instability of rotors (spiral waves) finally is preempted by some factors (antiarrhythmic drugs, restored balance of electrolytes, anti-inflammatory and/or anti-allergic therapy, regression of inflammation, cluster of mentioned tools or some unknown promotional and/or coincidental circumstances) leading toward the restoration of the order. This is not an endpoint, just the stabilization attempting the restitution of the previous qualitative and quantitative characteristics of automaticity, refractoriness, conduction, contractility, etc. - an extraordinary equilibrium amenable to convert into SR by lenient impetus. A bioelectrical phenomenon of VQST may eventually culminate with bridging the gap of dispersion (BGD) between above mentioned AF drivers. This bridging actually might be interpreted as a normalization ratio of AF drivers for proper "stroboscopic tuning". Finally, targeted criteria of VQST may precipitate through dynamic fluctuations of electrophysiological parameters participating in organization of AF. Unstable electrophysiological parameters (primarily the number of rotors) are likely swinging close to the clinically important point of VQST; significant decline actually determines unfavorable prognostic outcome. A pharmacologic manoeuvre is largely empirical containing uncertainty - whether the SR will be restored or not. Then the discharge(s) of autonomic tone, preferably of sympathetic one (or by activation of SAN, discussed below) as a favorable impact finally accomplishes the task – suppresses (neutralizes, extinguishes) the arrhythmia by intervening the VQST at its sensible phase. If it fails, stringent approach – electric cardioversion of high energy could be chosen. The success of external cardioversion actually means that serious structural changes have precipitated in the atrial myocardium, thus the crucial VQST state is unattainable by pretreatment.

Most likely the phenomenon of virtual VQST can be represented by set(s) of appropriate fluctuations of the oscillatory frequencies in cascades, every one of which is suitable for successful completion - restoration of SR. Due to the alterations of autonomic tone and following discordant contractions of neighboring myocites part of atrial cells are stretched, some of them are overstretched and some under-stretched. This leads to the differences in length of myocites, to the differences in depolarization and conduction velocity and these alternating differences are involved into harmonization of the complex interrelations of components representing the status of VQST. Due to internal preparations - apparently it takes time - the rhythm is not restored rapidly. Obviously, the autonomic tone (sympathovagal delicate imbalance evoked by vigorous exercise, as mentioned above) may positively influence the process in the end stage of arrhythmia extinguishing. We have observed several patients suffering from paroxysmal AF who have benefited from slight physical activity (after antiarrhythmic drug intake) and this maneuver has encouraged the restoration of SR with significant shortening of restoration time in comparison to the resting state (unpublished data).

Speculative Role of the Sinoatrial Node and Virtual Electrodes

Self-restitution of SR in paroxysmal AF may be accomplished by a similar hypothetical scenario of VQST without medication or other help. It is likely that natural conditions may occur for the emergence of VQST with subsequent self-extinguishing of AF and with possible participation of sympathetic tone. Is there any encrypted role of the SAN? That is the question. Unfortunately the behavior of this node – whether passive or active – is still unclear. From the hierarchic standpoint the significance of the SAN's role (despite coexistence of sick sinus syndrome) might not be ignored. The participation of a biological pacemaker (as a parent regulatory element) in the undermining of AF at least theoretically is quite reasonable because the "capricious" arrhythmia cannot retreat voluntarily. Hypothetically it may be speculated that SAN might be involved in the process of SR restoration but hidden from our view. With the progression of SAN's dysfunction along with the fibrosis of atrial myocardium the hierarchic role of this node attenuates gradually yielding its positions to the arrhythmia. When permanent AF ingrains the influence of the SAN's hegemony dissipates irreversibly. The depicted scenario actually contains the synthesis of explanation - well known and hypothetically supplemented – to penetrate into the vexed issues.

SR may be restored by the pharmacologic or electrical cardioversion but the latter one requires relatively high energy – up to 300 J.[18] A low-voltage multiple shock therapy was attempted to delivery in order to infiltrate the excitable gap of reentry and to disrupt the circuit(s) maintaining AF;[55] success rate was 100% on rabbit heart preparations. A single low-voltage shock is unlikely to be effective because its ability to activate the gap depends on the timing of its delivery;[56] delivery of a train of several low-voltage pulses is the logical alternative because it offers independence of the therapy outcome from the phase of reentrant wave. Recent elegant experimental studies by Pumir, Fenton et al. [57, 58]have promised a more lenient approach. The authors argue that conventional cardioversion attempts to reset all electrical activity in the atria and requires the use of large (> 5 V/cm) electric field gradients. These high energies cause pain and trauma to the patient, damage the myocardium and reduce battery life in implanted devices. Authors have developed a new strategy – low-energy anti-fibrillation pacing. The method employs a series of low-amplitude pulsed electric fields to overdrive AF and thereby terminate it. According to the explanation of the researchers, after delivery of electrical pulse virtual electrodes may arise at the interfaces separating regions with different conductivities. These sites may be macroscopic, such as blood vessels or ischemic regions, or smaller-scale discontinuities, including areas of fibrosis or abrupt changes in fiber direction. Virtual electrodes may become a secondary source (i.e. a site of wave emission), depending on the extent of the conductivity discontinuity and the electric field strength. The authors have concluded that AF in vitro and in vivo experiments can be terminated by a new pacing mode with only 13% of the energy required for cardioversion. This theory has improved our understanding of the mechanisms of AF termination, providing the opportunity for novel therapeutic targets and rhythm control strategies.

Keeping in mind the hierarchic (hegemonic) position of the SAN we may hypothesize that the above mentioned pacing modality might be replaced, at least theoretically, by the intrinsic activity of SAN which may create specific conditions, including the uprising of virtual electrodes, etc. with the capability of termination of AF. This may happen at least while the SAN is robust and well functioning. The odds of AF abruption presumably may decrease with the gradual slow of SR, i.e. with the appearance of signs of the sick sinus syndrome. However, no traces of SAN activity within transitional zone are left on the ECG. The energy required for cardioversion by SAN hypothetically could be amplified by virtual electrodes (if they do exist). Theoretically such a scenario might be suspected in patients with tachy-brady syndrome accompanied by intermittent activation of SAN which is interrelated with the autonomic nervous system to a certain extent.

The Role of Inflammation

A multifactorial background usually predisposes the interplay between the sporadic onset of AF and its self-termination. Even the so called "lone paroxysmal AF" (without distinct underlying heart disease) likely occurs under certain circumstances however the specific cause for the manifestation of the paroxysm remains conjectural. Increasing attention has been focused on the potential factors including inflammation on the manifestation of lone AF. The inflammation as a causative factor of the recurrent AF and its possible treatment with specific anti-inflammatory drugs emerged as a new hope. Though the association between inflammation and AF undoubtedly is present however such an association does not equate to causative.[59] In 2008 Boos and Lip [60] on the basis of right atrial biopsies have established that 67% of patients with lone AF showed evidence of right atrial myocarditis. In dogs exposed to chronic mitral regurgitation the left atrial size was found increased along with the signs of chronic inflammation and fiber separation.[14] Clinical observations have demonstrated that a combination of conventional antiarrhythmic medication with an anti-inflammatory agent, in greater scale clinical trials of patients with paroxysmal AF is rather effective .[20] Recent experimental studies by Kume et al.[62] have shown that inflammatory profibrotic processes are involved in the pathogenesis of AF. Inflammatory infiltrates are often found in the atria of patients with atrial dilatation; an increased C-reactive protein predicts the development of AF or relapse after cardioversion.[16] Plasma concentration of both C-reactive protein and interleukin-6 are elevated in AF.[61] The inflammation containing allergic component (evoking local edema, etc.) may be helpful in explanation of both – initiation and termination of AF. Roving, spreading or disseminating interstitial and cellular edema (in the atrial myocardium, within SAN or in the vicinity of SAN) may induce the extrasystole and the arrhythmia as well, while the SAN itself also may be activated by the same inflammatory (irritative) factors leading to the evoked participation of the SAN in SR restoration. A rapidly changing focal or multifocal edema of allergic origin may stipulate the sporadic and unpredictable interplay between AF and SR. Occasional "targeted" activity of the SAN also may likely be related to the exacerbation of the inflammation. Consequently, it may be considered that rare episodes of AF relapse or long periods of remission could be determined by low-grade of subclinical smouldering of the process. In some cases hidden inflammation also may take place.

With the emphasis on the significance of inflammation the aphorism "AF begets AF" could be enriched by "Paroxysmal AF begets anti-inflammatory and/or anti-allergic drugs" to stress the importance of prevention or mitigation of the arrhythmia. Inflammation suppression by medication might be argued in early stages of paroxysmal AF, i.e. before the "domestication" of AF.

As mentioned above inflammation of any origin is universally accompanied by tissue fibrosis or microfibrosis. Such intra-atrial substrate changes eventually pave the way for the perpetuation of AF.

Conclusions

Conceptual explanation of atrial fibrillation abruption and subsequent self- restitution of sinus rhythm along with an active participation of autonomic tone and/or sinoatrial node cannot be taken as evidence of a lack of confirmative data. We believe that a natural response of autonomic

nervous system to the arrhythmia may contribute to the process of SR restoration. We cannot strongly argue, however the concept comparable to the vibrantly quiescent stroboscopic tuning may be helpful for the explanation of complex interactions leading toward establishing of sinus rhythm. To evaluate an inflammation-dependant atrial fibrillation further clinical and laboratory studies are needed. It seems intuitive that a favorable response to anti-inflammation and/or anti-allergic therapy might positively influence either the development of or the self-termination of paroxysmal AF or both.

Disclosures

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

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