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Destruction Of Medium Already Affected By Destructive Disorder: Fibrillating Atria Conceptually Need Therapeutic Help Rather Than Surgical Or Ablative Destruction

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Abstract

Atrial fibrillation (AF) as the most common supraventricular arrhythmia is scarcely amenable to contemporary treatment. Due to the diverse origin and variable clinical course of AF there is a broad spectrum of therapy options. However, optimal AF management has not become a gold standard yet. In general, the recurrence rate of AF is most often clinically unacceptable despite drug, surgical and/or ablation therapy. Substrate-based approach and ongoing ablation of atrial wall in its selected areas including the vicinity of pulmonary veins can be harmful. Applied physical factors do produce total disintegration of cardiomyocites – both intra- and inter-cellular damage which, in turn, leads to functional hypo-/inactivation of atria irrespective of whether the sinus rhythm is restored or not. In fact, iatrogenic phenomenon of ablation-induced atrial incompetence did emerge. Heterogeneity in clinical results reflects the uncertainty regarding the efficacy, risks and benefits of invasive AF therapy. In this regard the overall burden of AF may increase when using current therapy methods. Applicability of destructive techniques is yet to be fully elucidated and discussed. We hypothesize that currently used ablation and/or surgical techniques are potentially harmful since the success rates are likely achieved through violation of atrial myocardium. That is why a new and well-designed therapeutic strategy is needed. Invention of highly selective curative methods producing fibrillatory/electric blockage with concomitant saving of atrial transport function is to be encouraged.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac rhythm abnormality and one of the major causes of morbidity and mortality.[1] AF is characterized by functional cardiac deterioration and loss of atrial contraction.[2] It is evolutionary dynamic arrhythmia with capability of spontaneous termination especially in its initial stage. A major problem in the treatment of refractory AF is that it is not a single disease, but a wide spectrum of diseases with heterogeneity in clinical presentation and mechanisms, as well as therapeutic options and targets.[3] Current therapeutic approaches include antiarrhythmic drugs, anticoagulation, cardioversion, pacemaking, and constantly evolving techniques of catheter, surgical and hybrid ablation.[2-6] There is a great variance in AF treatment success rates. Aliot and Ruskin[3] have stressed that optimal tools are still lacking, patients may exhibit a delayed response to the ablation procedure, electrophysiological and clinical outcomes may not fully coincide and partial responses are very frequent, as is necessity for multiple procedures, which remains a frustrating problem. Overall, an assembly of AF treatment methods used to-date may be considered to provide relative therapeutic efficacy. Notwithstanding, growing efforts are dedicated to tackle AF.

Based on dissatisfaction of patients and clinicians some authors have indicated that contemporary interventional treatment of AF is a palliation than a true cure.[7] Hence, the therapeutic options are far from the gold standard of effective AF management. Salutary effects of modern AF treatment are well known and continuously analyzed. Similarly, treatment failures and/or adverse effects – AF recurrence, multiple repeat interventions, moderate and severe complications, etc. – are also well documented. We will briefly review the current state of AF management with subsequent focus on major problems and critical assessment of the destructive therapeutic approaches. Particular attention was paid to atrial hemodynamic input aftermath especially when sinus rhythm is restored.

Interventional Therapy Of AF

From a clinical point of view it is very important to effectively terminate and prevent AF. Pharmacologic approaches to rhythm control have repeatedly demonstrated high failure rates and suboptimal side effect profile.[8,9] Advances in contemporary treatment of the most stubborn arrhythmia – preferably ablation of pulmonary veins (PV) and adjacent structures – have improved clinical outcomes.[10-13] However, in order to reduce the recurrence

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rate, alternative locations or highly selected areas of the heart are often included for radiofrequency (RF) delivery and/or surgery, e.g. atrial roof, anterior or septal mitral isthmus, atrial areas represented by high-frequency complex fractionated electrograms, superior vena cava isolation, elimination of ganglia response, creation of long linear lesions (replicating the surgical maze procedure), ligament of Marschall ablation, left atrial appendage exclusion, empirical or individually tailored ablation sites, etc.[3, 4, 6, 14-16] Although catheter-based ablation has demonstrated good short-term success, mid-term results have revealed a significant recurrence rate.[5] Recently Hummel et al.[17] have pointed out that, despite high acute success rate, persistent and long-standing persistent AF often requires extensive and/or repeat RF ablation procedures. After a 12-month follow up, according to Mulder et al.[18] 56.2% of patients with persistent AF were free from arrhythmia however, long-term data have proven to be less encouraging.[19, 20] Meanwhile optimistic curative reports along with their promising results should be interpreted with caution.

The mechanisms of recurrent arrhythmias are variable but frequently involve gaps, recovered conduction, or incompletely ablated tissue along ablation lines.[21] According to Pappone and Santinelli[22] it is conceivable that long linear lesions create new fixed obstacles to propagation, with eventual discontinuities representing an ideal substrate for large gap-related reentrant circuits. That is why the need for multiple ablations as well as reinterventions is common[6, 7, 23, 24] In cases of transvenous catheter ablation failure, occasionally surgical AF ablation is performed.[4] Unfortunately, no reverse atrial remodeling is observed in some surgical-based ablation groups even in patients with sinus rhythm.[25] Taken together, controversies in ablation of AF strategy still exist.[3]

Relatively rare, but severe complications (ostial PV stenosis, esophageal fistulae etc.) sometimes occur in patients who underwent attempts of RF ablation.[26-28] The risk of silent or subclinical complications associated with ablation procedures and long-term impact of ablation on left atrial mechanical function have not yet been fully determined.[3] Importantly, invasive percutaneous techniques and extensive surgical maze procedure as well as hybrid approaches may induce atrial hypocontractility.[29]

As more data accrue in favor of AF surgical and catheter ablation strategy,[23] conflicting reports regarding the efficacy, risks and benefits of interventional therapy still perpetuate.[7, 24] Although no strong evidence exists in favor of prevention or reduction of AF paroxysms using the modern destructive techniques, it is still considered that contemporary therapies may prevent arrhythmic outbreaks more or less effectively just in the early stages of atrial disease, preferably in patients suffering from paroxysmal AF.

General Cognitive Characteristics Of AF

Arrhythmia may be characterized as a disorder containing both well-organized and grossly disorganized (chaotic, degenerative) cardiac entities. It is believed that in many cases the natural history of AF involves evolution from paroxysmal to persistent to permanent forms through the influence of atrial remodeling caused by the arrhythmia itself and/or progression of underlying heart disease.[30, 31] The most frequent pathological observations in AF are atrial fibrosis and loss of atrial muscle mass.[32-34] Structural remodeling is accompanied by contractile remodeling which leads to a reduced atrial transport function.[35, 36] Hemodynamic impairment may be induced not only by the classical fibrillatory substrate, i.e. due to atrial intramural anatomopathological changes, but also by arrhythmia per se. According to some investigators, atrial mechanical dysfunction could largely be attributed to the structural abnormalities that are known to originate from atrial arrhythmia.[37]

In a normal functional syncytium, electrical impulses propagate freely between cells in every direction, so that the atrial myocardium functions as a single contractile unit.[38, 39] Apparently this unit is disintegrated a priori (due to advance of underlying heart disease) or later on when AF "takes the floor" with subsequent aggravation of cardiological situation by arrhythmia per se. To date, the pathophysiological mechanisms responsible for the development of AF are still not fully understood, although a heterogeneous model based on the interaction of multiple substrates and triggers is commonly accepted.[40] Shortening of the cardiac action potential (as a substrate for reentry wavelets), prolongation of the effective refractory period and disturbances in ionic currents are recognized as key causative to the development of AF.[41-44] Conflictogenic electrophysiological mechanisms originating at the borderlines of ischemic and non-ischemic regions may play a significant role in AF incitement.[45, 46] Furthermore, it is still unclear whether predominantly microscopic or macroscopic substrate (condensed, arborized, disseminated or mixed) drives the arrhythmia.

Many observations demonstrate that AF triggers reside predominantly in PVs (their muscle sleeves and antra), therefore these locations are currently incriminated as being responsible for AF.[10, 12, 19, 20, 27] Consequently clinicians have focused on PVs by ablating their ostia and by performing wide circumferential linear injuries around the PVs.[13, 47] Nevertheless, it appeared that isolation of PVs alone is not enough to achieve the goal. Thus, along with the previously used techniques concomitant ablation lines were applied in the atria including hybrid methods.[4, 16] Such an evolution of therapies accompanied by undesirable AF recurrences has indirectly revealed the presence of a patchy picture of AF substrate which: 1) resides in several anatomical sites, 2) migrates, 3) reappears, 4) disseminates in a form of multifocal ectopy. In other words, we face true uncertainty – unstable and unreliable location of the substrate and its unpredictable behavior. Every AF-related substrate, wherever it is located, actually posses the ability to release the triggers and drivers – fibrillatory waves, wave-fronts, reentrant waves, meandering reentrant wavelets, spiral waves, rotors, complex fractionated potentials, etc.[17, 22, 40]

Destructive Nature Of Therapy And Its Clinical Consequences

Invasive AF therapy, although gaining wide popularity, boomerangs and results in severe complications and unacceptably high AF recurrence rate which leads to the negative cardiac performance. In some cases post-ablation patients do experience severely impaired left atrial transport function.[48] Obviously it depends on the scale of damaged atrial myocardium undergoing destructive maneuvers. The original Cox maze surgical procedure is reported to result in decreased left atrium size and diminished left atrial function.[49] Lemola and colleagues[50] have announced that restoration of sinus rhythm by left atrial circumferential ablation results in partial return of left atrial function in patients with chronic AF; however, in patients with paroxysmal AF this curative procedure results in decreased left atrial function. Large multicentre randomized, prospective study PRAGUE-12 has revealed that patients with paroxysmal and persistent AF obviously did not benefit from the intraoperative ablation procedure.[25] Wylie et al.[51] have concluded that catheter ablation of AF is associated with a decline in left atrium systolic function that is strongly correlated with the volume of ablation-

induced scar; newer ablation techniques generally involve destruction of larger volume of atrial tissue.

Worth to mention, surgical scarring and fibrosis, in addition to probable atrial myopathy potentially contribute to arrhythmia recurrences.[52] Scar related or iatrogenic arrhythmias, preferably atrial tachycardias, have been reported after either surgical or catheter ablation of AF.[53]

Clearly, primarily destructed myocardium (already induced by the existent underlying heart disease - ischemic, valvular or other) is injured supplementary by thermal ablation and/or surgical maneuvers. According to Anter et al.[54] ablative procedures are associated with new scar formation, paradoxically augmenting interstitial fibrosis; this effect can potentially perpetuate the progression of AF. In other words, already present diffuse fibrosis is enriched by iatrogenic scarring resulting in an avalanche of fibrotic proliferation which eventually may become immune to any treatment. Thus, the resulting complex lesions (co-existing initial i.e, underlying heart disease-related fibrosis along with aftermath scarring) compound and/or overlap, which may generate new cardioarrhythmological status with ensuing serious clinical problems.

Such major, though controlled, invasion – surgical or ablation lesions – certainly results in ambiguous clinical consequences. First of all, it produces electrical isolation (whether partial or complete) of AF substrate and prevents AF paroxysms, unfortunately providing unstable, transient, mid-term elimination of arrhythmia. Secondly, it results in disabling of myocites; ablation maneuver causes attenuation and/or incapability of considerable amount of atrial myocardium that becomes not fully excitable. Finally, it leads to significant reduction in contractile function of atrial myocites. Atrial ablation with ligation of the left atrial appendage reduces atrial function relative to normal controls in sinus rhythm.[55] Other concerns regarding extensive ablation strategies include risk of collateral damage to surrounding structures (circumflex coronary artery, phrenic nerve, etc.) with negative long-term impact on atrial transport function and coronary sinus patency.[56] Surgical compartmentalization of the atria (i.e., maze procedure) in up to a third of the patients may lack atrial contractile function despite being in sinus rhythm.[57]

Physiological state and primary characteristics of healthy cardiomyocite include: automaticity, contractility, conductivity and excitability. With the destruction of the cell these functions, including contractility, are lost.[58] Destruction per se actually eliminates both the structure and the function of the cardiac cell. Again, contractility can be compromised by abnormal scarring, pathological stretching or thickening of cardiac muscle fibers.[58]

The sum of all damaged myocardial cells presumably may be impressive. Shah et al. have pointed out that the volume of tissue ablated to treat AF, particularly its resistant forms, is highest for any cardiac arrhythmia so far.[59] Rough invasion with partial or complete destruction of myocites may result in regional and/or diffuse hypo-/akinesis. Confirmation of the presence of electrical silence within the targeted region is a criterion of destructional efficacy.[29] The latter report contains fundamental information which reflects the essence of destructive consequences. Thus, therapeutically "renovated" complex fibrous texture complicates clinical course of AF instead of facilitating it. It is likely that this is the phenomenon of ablation-induced atrial incompetence. Emergence of a new structural and functional condition with the sinus rhythm but without accompanying myocardial contractility may be treated as ornamentally imitative. Thus, such aggressive procedures do have potentially adverse effects that offset some of the benefits. Of course, the electrocardiographically sham sinus rhythm lacking atrial systolic support is likely a better clinical entity than, e.g. tachyarrhythmia. Obviously the hemodynamic benefit is improved by restoration of sinus rhythm, however simultaneously achieved hemodynamic augmentation is probably annihilated by the ablation/surgical harm.

Clearly we are close to the fundamental understanding that fibrillating atria requires therapeutic help instead of harsh destruction. According to some investigators[60] preventing atrial remodeling (so-called upstream therapy) could suppress the development and progression of the AF substrate. Thus, the strategy of "destructive therapeutic" solutions is to be reconsidered with critical assessment. It is desirable to create alternative and harmless therapeutic methods to save myocardial viability with simultaneous prevention of AF recurrence. This analytical review, containing mild speculations, suggests that selective "hunting" of AF triggers, drivers and/or fibrillatory waves (wavelets, meandering waves, reentry waves, rotors, high frequency fractionated potentials etc.) by pharmacological means is more attractive in comparison to alternative approaches. Undoubtedly, debate on these issues is highly desirable.

Ongoing Discussion On Destructive Issues

There are some unanswered issues associated with clinical outcomes that provide contemporary interventional methods of AF management. It is widely acknowledged that recovery of atrial mechanical function is a major goal in AF therapy.[61] So-called radicalism – tissue disruption by ablational or surgical hyperactivity - may be treated as "artificial crippling of the heart" or iatrogenic harm resulting in hemodynamic compromise via partial loss of atrial kick. Ironically, ablation lines sometimes are named "curative lesions".[4]

RF energy, for example, produces tissue ablation depths of 3 to 4 mm[5] while surgical incisions create lines of transmural necrosis.[62] As a result, loss of active atrial contraction can be detrimental with haemodynamic and thromboembolic consequences.[61] The more of atrial myocardium is isolated, such as with the box lesion, the higher is the chance for AF to be terminated; however the chance of the atrial transport function being recovered is less.[63]

In general, invasive techniques evoke appreciable cytocidal effect. Thus, silent or semi-silent encircled/isolated areas with restricted functional activity (e.g. regional or even global atrial hypokinesis or akinesis) may occur. In contrast, Sacher et al.[61] have shown that chronic AF ablation restores and maintains sinus rhythm and restores active atrial contraction. These authors declared that superior atrial function is observed using the catheter-based procedure compared to the surgery and it is related to a less traumatic approach tailored to the patients' arrhythmias avoiding unnecessary lesions.

The majority of the healing response of cardiac tissue to thermal injury is completed approximately 2 to 4 weeks after RF application.[64, 65] However, atrial blanking period introduced intentionally and allowing postablational rhythm stabilization lasts 3 months[3, 47, 66] instead of a couple or several weeks. Such inconsistency reflects the presence of uncertainty and the shortage of convincing evidence in clinical outcomes. Again, it may be considered that ablation and/or surgical therapy represents empirical derangement of natural course of arrhythmia by restoration of sinus rhythm temporarily and/or accidentally with the signs of fortuitously salutary effects. In general the ablation procedure may contribute to favorable normalization of arrhythmia by its converting into more or less benign clinical course,

but probably not into complete recovery of the patient. Of course, complete recovery is largely restricted by underlying heart disease and/or aging.

By killing intermingled atrial myocites we believe ostensibly that clinical course of AF is corrected beneficially. Unfortunately, every destroyed and inactivated myocardial cell is converted into nonfunctional state. As mentioned above, extensive destruction of AF substrate may be compared to the cytocidal effect, usually declared as creation of conduction block, reentrant block, blockade of wave fronts, etc. To compare, destruction of cardiac cell is to be treated as too stringent of an action; an old adage "Primum non nocere" reminds us to manage cardiomyocites with care and with everlasting responsibility. To continue this philosophy other old Latin dictum that echoes through ages might be modified, refreshed and revitalized with appropriate linguistic "choreography": Killing of oncological cell opus divinum est, while saving of cardiac one - opus divinissimum est. If such statement were accepted as "dogma non fantasia" probably it might create breakthrough concepts in the professional minds. Meanwhile, however, the intensity of clinical implementation of curative methods devastating atrial myocardium might be slowed down up to the level defined as "Andante non troppo" (ita.). Apparently herein is a natural niche to insert worthy aphorism: "Burn not your house to rid it of the mouse."

By analogy, in patients suffering from Parkinson's disease and by application of well-known "cut-and-sew" technique a conjecturably impressive clinical result might be achieved – transversal injuries of skeletal muscle will extinguish its tremor. Like a grim premonition - hypothetical treatment scenario by multiple transects of all tremulous muscles will result in the entire loss of their contractile activity and likely with zero recurrence rate. However, such a marginal activity likely raises doubts whether the patient may recover or whether it results in his/her incapability. In other words, the functional endpoints aftermath probably transforms into irreversible condition. Finally, clinical vetting of extremely aggressive method is scarcely available. Such a collage of two different clinical pathologies and their "destructive therapies" is to be treated as speculative, however worthy of reconsideration of therapeutic consequences. To surmise, perhaps atrial fibrillation represents some kind of atrial Parkinsonism. Certain suspicion may arise especially when facing the fact that autonomic ganglion ablation is receiving increasing recognition.[6, 67] Extracardiac and intracardiac autonomic regulatory factors are in close relationship with hierarchical organization of cardiac activity.[68-70] Some authors showed that atrial sympathetic hyperinnervation occurs in persistent AF patients and tachycardia-remodeled dogs.[71, 72] According to some researchers, in patients with paroxysmal AF vagal denervation can result in about 100% success.[73] By the way, it is currently believed that Parkinson's disease is due to degenerative process independently involving multiple areas of the central and peripheral nervous system including peripheral components of the autonomic tone.[74, 75] Complex aging-like process probably is the last but not least causative ingredient to commence the arrhythmia. Reports about the manifestation of AF in transplanted hearts as if negate the allusion to the potential relationship of arrhythmia with Parkinson's disease. This allusion, however, may be supported by the report of Baretti et al.[76] They stressed that arrhythmia in transplantation group of patients' is more related to cardiac graft failure rather than any other reason.

The mechanism of AF is very complex and even somewhat mysterious.[77] Conclusively, better understanding of the cardiac and non-cardiac diseases is very important because AF develops multifactorially in association with underlying systemic pathophysiologies.[77]

Conclusion:

The management of patients suffering from atrial fibrillation is often challenging. Radical interventional destruction of arrhythmia's substrate is potentially risky due to direct harm caused to myocardium. Adverse response to the delivery of thermal and/ or surgical factors is reflected by depressed atrial functional activity. Contemporary ablative AF therapy approaches along with their positive effects result in loss of atrial kick that appreciably compromises cardiac performance. New conceptual approaches to more effective arrhythmia control with concomitant cardioprotection - saving of myocardial viability and preservation of atrial circulatory support might be created.

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