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Review Article

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Atrial Fibrillation Ablation: When and Why?

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Abstract

Ablation of Atrial Fibrillation (AF) has quickly become an alternative strategy to impact the adverse symptoms and outcomes associated with or caused by AF. Early reports in 1998 demonstrated spontaneous initiation of AF by ectopic beats originating in the Pulmonary Veins (PVs) followed rapidly by showing that Radio Frequency (RF) circumferential ablation around the orifices of the PVs could "electrically disconnect" the PVs from the Left Atria (LA). This resulted in the explosive growth utilizing this procedure for AF Ablation (AFA) across a wide demographic spectrum of recipients. Foreseeable healthy debates have surfaced as to who best benefits and who may actually suffer complications or harm from AFA utilizing present techniques. Disagreement also persists as to whether AFA fundamentally and universally reduces stroke, death, hospitalization or does it initiate a more nuanced set of outcomes. The present effort asks the simple question: Has AFA matured to the point of requisite explicative review? Is it time now to peel back the layers and identify which cohort will be optimally served by AFA and perhaps which ones need demonstration of benefit? The present brief review suggests that prudent employment of AFA must now identify disparities in the variables reflected in these cohort outcomes. This will enable judgment in the use of AFA and the achievement of optimal outcomes.

Introduction

Every new technology, device, or laboratory value that propels the treatment, or enhances understanding of disease demands that the community of health care practitioners exploit judgment as to their use. In fact, "A basis of this profession is clinical judgment". It lies at the heart of the doctor's connoisseurship, expertise and skills, being almost as important as the technical ability to carry out the procedure itself [1]. It is the delightful and fulfilling privilege of assisting others that calls into need the exercise and substantive employment of judgment. The current effort is to focus our concerns on the need for pragmatic decision making in the choice whether or not to ablate Atrial Fibrillation (AF). Thus, this is a review of the challenges, the successes and nuanced issues regarding Atrial Fibrillation Ablation (AFA), hoping to assist the clinician's perspective supporting optimal judgment to obtain similar outcomes.

Ablation of AF, similar to other medical advancements leapt onto the stage in near whirlwind fashion [2]. Early reports in 1998 demonstrated spontaneous initiation of AF by ectopic beats originating in the pulmonary veins (PVs) Rapid advances soon followed showing that circumferential Radio Frequency (RF) ablation around the orifices of the PVs could "electrically disconnect" the PVs from the Left Atria (LA) demonstrated directly by entrance blocking of the propagating stimulus from the LA into the PVs [2,3]. This provided hope to the myriad of patients who could not tolerate the multiple cocktails of drugs used for AF or for whom these pharmacological agents were routinely unsuccessful in controlling the AF. There was also subgroup analysis from the AFFIRM trial that suggested a trend toward increased mortality in those 65 or older who were maintained in Sinus Rhythm (SR) requiring the use of such medications [4]. But a sober assessment of AFA supplanted the initial unrestrained wave of enthusiasm as mixed outcomes suggested that a more detailed understanding of AFA was needed to optimize its utilization.

European guidelines as of 2016 suggest that AFA done as Pulmonary Vein Isolation (PVI) was recommended for drug refractory symptomatic AF or in patients who were intolerant or unwilling to take such pharmacological therapy [4]. Given such preconditions, these pronouncements admittedly provided practitioners expanded options as to assess whether their patients individually might benefit from AFA-PVI. Predictably, a foreseeable "pushing the envelope" subjected multiple cohorts including the elderly with chronic or persistent AF to a procedure that was not absent inherent risk [5]. Furthermore, outcomes for the elderly with persistent AF were often clearly inferior to results obtained from younger patients with the paroxysmal form of the dysrhythmia [6-8]. Thus, 77-year-old individuals with persistent or permanent AF who are symptomatic but minimally so, were considered by some to not constitute the ideal subgroup for procedural success [5]. However, a growing body of literature suggested to some that benefits were

still obtainable in this subset of patients with complication rates comparable to younger patients [6]. But there are more subtle and less well understood variables that impact mortality with AF and thus likely also influence AFA success [9]. Ongoing concerns for the practicing clinician are to understand who best fits the profile of a patient likely to benefit from RF-based AFA and how does one define AFA success?

Which Atrial Fibrillation is Being Ablated?

Several variables must be addressed in attempting to identify and characterize success in AFA. For starters there must be recognition that AF cannot be considered in isolation but must be contextually placed within its pathophysiologic environment. For example, evidence has surfaced that AF behaves differently in Heart Failure with preserved Ejection Fraction (HFpEF) in comparison to HF with reduced EF (HFrEF) and thus, ejection performance significantly influence outcomes [9]. A larger dependence on left ventricular filling from the contributing atrial contraction in the presence of diastolic stiffening, dysfunction and restrictive physiology may make the outcome of AF in HFpEF more detrimental [10]. Given that AF and HFpEF are frequent co-existing pathological conditions their commonly shared etiologies and comorbidities influencing occurrence overlap [10]. These include Obstructive Sleep Apnea (OSA), pulmonary and renal chronic age-related abnormalities, obesity and especially aging [11]. But HFpEF with permanent AF now is considered a distinct phenotype with a poorer prognosis [10]. This detrimental outcome is thought to represent the effect of subtle but progressive path histological changes in the atrial tissue such as that reported as a consequence of the duration of AF [12]. Here fibrotic changes quantified from atrial samples taken at the time of surgery showed a progression in the extent of fibrosis from an average 5% in those with SR to a cumulative 35% average fibrosis of the atrial tissue seen in those with chronic AF [12]. These acquired histological changes join electrical remodeling in addition to neurohormonal changes [13]. Each variable individually and or collectively may thus characterize and then define a general continuum of pathological progression within the substrate atrial tissue itself [12].

Using this information, a logical hypothesis is that each co-morbidity and its ultimate derivative impact on atrial tissue will exert influence on AF development. Each condition (i.e. OSA, age, obesity etc) associated with AF development either alone or in combination may alter the phenotypic destiny, causing structural and then functional changes within the atrial tissue. Could not such structural and functional disparities also reasonably impact the outcomes for AFA? Atrial fibrosis found by Gramley et al may have other triggers independent of or amplified by AF duration [12]. In fact, there is a recognized discordance between the duration of AF and the burden or extent of atrial fibrosis [14]. But what specifically causes fibrosis in the atria, both the right and left, that is a contributing factor to the development and sustaining of AF? Here data is unclear [15]. Metalloproteinase and their inhibitors may be potent actors in cardiac fibrosis, inflammatory control and remodeling changing cardiac performance as a consequence of altering substrate [16,17]. Some of these elements (i.e. extent fibrosis, inflammation) are acquired and others inherited, but detailed information regarding which ones belong to which category remain elusive. In HFpEF the expressive levels of each are cumulatively coupled to their impact on the inherent atrial tissue activity [10]. The impact of the altered cardiac phenotype may then be intrinsically linked to responsiveness to pharmacology or AFA outcomes and even mortality. It seems logical that this altered tissue histology and both the mechanical and electrical performance may then relate to the ultimate success or failure of AFA? [12,13,15].

Similarly, AFA for reduced ventricular performance (i.e. HFrEF) may represent yet another distinct grouping of disparate mortality outcomes within the granularity of AF phenotypes. Such a paradigm linking alterations of structure and performance, specifically related to quantifying fibrosis within the atria is gradually gaining traction [14,15]. Is it a consistent association impacting AFA outcomes? Almost assuredly so if one examines the conclusions of Kottkamp et al [14,15]. If so, predictors of AFA success might optimally first identify and address these distinct elements (characterizing structure and function, e.g. specifically atrial fibrosis) in separate cohorts representing differential AF progression. These elements may not only identify different cohorts, but cellular and/or molecular drivers of myocardial remodeling within disparate HF phenotypes may actually mechanistically underwrite their outcomes [18-20]. And do such characteristic changes in substrate influence dissimilar mortality outcomes in AF with and without HFpEF as opposed to other AF states? It could now be argued that therapeutic AFA absent consideration of these variables (especially extent of fibrosis) might be ill-advised? Failure to understand who is really likely to benefit may actually undermine accurate 'risk-benefit' assessment hindering clinical judgment [6,9,10]. And it is now apparent that too extensive the fibrosis after AFA renders the atria injured with reduced atrial performance and a higher likelihood of AF recurrence after AFA [21-23]. Accordingly reports suggest that identifying and isolating atrial fibrosis within the upper cardiac chambers is essential for effective or successful ablative strategies and outcomes [14,15,24]. And perhaps now is the time to ask what defines success in AFA? The current goal is to eliminate AF but data suggests that symptoms of recurrent AF in patients are less troublesome after AFA, and this may be a different but no less valid component of success of AFA [25].

Predicting and Defining Successful Ablation

The above statement suggests a second but inherently related issue of how success is specifically articulated for AFA. Explaining to patients that paroxysmal AF, where the AFA success is defined as between 60-80%, must be contrasted against the effectiveness of PVI in those with persistent and long-standing persistent AF [26,27]. This latter group has reported AFA success rates noted to be as low as 21% [26,27]. The proposed explanation is that the cardiac tissue, the organ and its performance, the substrate itself is inherently different between paroxysmal versus chronic or persistent AF [28]. Here again the above-noted paradigm may hold value. Traditional explanations have been that persistent AF has multiple sites of the dysrhythmia including all four PVs and their antrum [28]. Thus, PVI of a single vein area in this setting is predictably unsuccessful. Further, in this explanation there is believed to be a fundamental alteration in the etiology of permanent AF itself making it inherently distinct from the paroxysmal form [4,29]. Such chronic AF may also impact mortality in this more conventional view [30-32]. These changes include variable autonomic system contribution, increased rotor activity, macro re-entry circuits and ectopic foci that are proposed as progressive but distinct modifications in the behavior and triggering of AF when persistent or

permanent [32-34]. In other words, the duration of AF engenders changes in both structure and function [30,32].

But such explanations using a metric "time in AF" may in reality have only minor or limited value for predicting mortality. Duration of AF does not account for the growing body of evidence suggesting variables other than extent or length of AF intervals are important, if not actually pivotal, in determining outcomes [10,14,15,35]. Here it is critical to separate associated co-morbidities from actual mechanistic drivers of AF. The agreed upon co-morbid conditions of OSA, diabetes and obesity along with age very likely are important predictors of mortality, but these are not equivalently weighted risk factors for either AF development or subsequent mortality in each individual patient [9-11,35]. They are almost certainly not the mechanistic underpinnings of the dysrhythmia. And once again we encounter a fundamental paradigm within biology that expresses itself in a multitude of nuanced circumstances. Living tissue reacts to an incredibly diverse array of injury with a rather stereotypic almost mundane response. The relevant response here is fibrosis. Fibrosis is a fundamental corrective reply to injury throughout the disparate organ systems; myocardial atrial tissue is no different. As noted fibrotic extent, severity and burden have surfaced as the primary inducers of AF [14,15,20]. It has become apparent that as clinicians there is also a need to understand and address the central role that fibrosis plays in best forecasting outcomes of success for AFA. This effort has begun and has started to illuminate specific cohorts with the greatest likelihood of fibrotic transformation to myocardial tissue translating into the greatest incidence of AF [18-20,24,36,37]. Traditionally, "time in AF", paroxysmal versus permanent or persistent typified the variable most valued in forecasting successful AFA. This was thought important because the adage "AF begets AF" implied that it was the AF itself that initiated and caused the fibrotic transformation [15,37]. It now seems that data taken from Wijffels et al was misinterpreted as the chicken preceded the egg, and only now is atrial tissue with fibrosis thought to be an inherently fertile environment for developing AF [15,38]. But does duration of AF mechanistically endorse changes in mortality for different AF cohorts? Or are other variables equally or superiorly predictive? Explaining disparities in AF-related mortality may be dependent on subtleties that invoke both duration of AF as well as the "newly appreciated" inherent atrial fibrotic burden. And does AFA success influence mortality independent of co-morbidities? It remains unclear whether success in AFA directly influences mortality or are these other elements associated with AF noted previously disparately influential. Some feel that the actual complete elimination of AF is uncommon after AFA [39]. Yet, as noted, even the recurrence of AF after ablation may not trouble the patient with the same intensity of symptoms as before the procedure [25]. This suggests that yet another cohort outcome may be identified, with a less limited effective definition of AFA success as compared to traditional definitions using complete freedom from recurrence [25,40-42]. But conceptually, by whatever definition used, does successful AFA influence mortality associated with AF?

Atrial Fibrillation Ablation: Seminal Points

This fundamental question of whether AFA done to suppress AF reduces associated mortality is nuanced. Recent evidence by Yang et al. demonstrated using a Korean National Health Insurance Service database on more than 194,000 patients that AFA was associated with an all-cause death rate of 1.0 event rate (100 Person-years) versus 3.6 event rate (100 person-years) P value <0.001 [43]. This is a registry or database retrospective analysis of outcomes and thus must be interpreted within the well-described limitations inherent in attempting to infer causal relationships based on a retrospective registry [44]. This includes errors in coding or data entry specific to this study that limit conclusions to associations absent causality [43,44]. The CASTLE-AF trial demonstrated a 46% lower rate of death from any cause among those randomly assigned to catheter ablation versus those who received medical therapy [45]. However, review of CASTLE-AF delineated numerous shortcomings of the trial including randomization of 397 patients with predetermined definitional "symptomatic AF" who had HFrEF (<35%). Criticism was correctly focused on the source of dyspnea; comparing those with HF and whether AF contributed to dyspnea in this group of HF patients [39]. Further, the comparative groups did not actually reflect acceptable randomization as the non-ablative group was significantly more likely to have ischemic heart disease and diabetes and be treated with digitalis. This meant that the non-ablation group were at higher baseline risk of a primary study endpoint even before receiving their assigned therapy [39,46]. CASTLE-AF also provided unbalanced incomplete intention to treat data within the two groups that likely altered the sensitivity analysis of this study [39]. Thus, in similar fashion to the previous report by Yang et al, many relegated CASTLE-AF's findings to hypothesis generating only [39]. Finally, the CABANA trial randomized 2204 patients with atrial fibrillation using catheter ablation, compared against medical therapy to assess the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest. Catheter-based AFA was not associated with superior outcomes as there was no significant disparity between catheter-based AFA and medical therapy (8.0% vs 9.2%, respectively; hazard ratio, 0.86) [47]. The mortality benefit of RF-catheter-based AFA thus remains unclear. But there is an eerie sense of having traveled previously down a similar road. Most will remember the near conclusive hypothesis that suppression of premature heartbeats after myocardial ischemic injury was beneficial since presence of such extra systoles were known to adversely impact mortality. Only later was it found via the Cardiac Arrhythmia Suppression Trial (CAST) that the primary positive determinant of survival was not found in the pharmacological suppression of extra systoles. This type of suppression was associated with increased mortality [48]. CAST revealed a flaw in the hypothesis of pharmacological dysrhythmia suppression. This may be similar to the afore mentioned subgroup analysis from the AFFIRM trial that suggested a trend toward increased mortality in those 65 or older who were maintained in sinus rhythm (SR) requiring the use of such medications [4]. But CABANA may suggest that eliminating the dysrhythmia, either by catheter or drug, (like CAST), is not the relevant endpoint [47]. Instead, like CAST, the determinative element may be the substrate, i.e. its fibrotic burden and rate of fibrotic accumulation in the myocardium.

Do the AFFIRM trial subgroup data justify AFA in the elderly who are bothered by symptoms or who may be at undue risk due to use of rhythm controlling pharmaceuticals? [4]. Alternatively, might catheter-based RF ablation across all identifiable cohorts ignore disparities in outcomes reflective of more powerful predictors than AF, or AF duration? It is tempting to consider that a 77-year-old patient, with a body mass index of 43, hypertensive, with type 2 diabetes mellitus and stage 3 chronic kidney disease will have less risk with AFA than long-term rhythm-specific Drug therapy targeting AF. But is this true? And if her symptoms are not that severe in

AF with a controlled rate, does this further alter the decision-making process? Her AFA outcomes are clearly inferior to a younger patient with paroxysmal AF absent some or all of these listed co-morbidities. But does this alone justify taking a mildly symptomatic 77-year-old for AFA or using a beta blocker or amiodarone to suppress AF? Definitive understanding and outcome-driven conclusions remain unclear, but almost certainly the judgment of seasoned clinicians will use these and other variables to arrive at an optimal strategy for management of "this patients" AF.

A Healthy Debate

Current guidelines for use of AFA in treating this dysrhythmia are a thoughtful set of interpretive proposals covering a fast-moving field [49]. The authors believe there is strong evidence that AF ablation improves quality of life, (QOL), and purport that there is reasonable evidence that AFA improves ventricular function in those patients with AF who have HF. Here is room for reasonable debate on each of these tentative if not early conclusions. Additionally, many have strongly suggested that mortality benefit is as of yet unproven [39]. As noted above, debate as to whether AFA is superior to pharmacological suppression of AF immediately wanders into concerns found in subgroup analysis in the AFFIRM trial versus safety of AFA in the elderly [4,5]. But debate remains as it should, focused on who (i.e. which subgroup) best harvests the benefits from AFA (mortality and/or QOL) rather than its inherent universal appeal or value. The guideline authors suggest that the impact of AF control with ablation on other endpoints, including stroke risk, dementia, and mortality, will require further study [49]. The practical concern for many non-electrophysiologists who make up the majority of referrals for AFA still must ponder the circumstances favorable for this procedure. Gaps in our collective knowledge coupled with disparate expert conclusions drawn from limited and properly performed trials have created an environment challenging to those attempting to understand when and how to optimally utilize AFA.

The proper application for AFA remains to be determined. There will be enhancement of outcomes based on technical improvements but much of the real-world benefit brought to patients will be accomplished when clinicians understand who most likely will be helped, hurt or left without measurable gain. In many ways it reflects the evolution in maturity and skill seen in a young surgeon. Early in training the young man or woman speaks of or hears frequently about the need for "great hands". This is soon replaced by comments on their requisite "intraoperative skill". It is only as they gain experience that they finally realize that it is the hard-won modicum called wisdom yielding judgment that supplants technique and that the best surgeons are those best exemplifying this asset. It is this multidimensional asset, judgment that will allow the optimal utilization of AFA and give patients a better future.

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