The Tribulations of Atrial Fibrillation Ablation Trialists

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Pulmonary vein isolation (PVI) with catheter ablation has been demonstrated to be an effective method for controlling atrial fibrillation (AF) in most patients. It is assumed that complete isolation is required for effective treatment and clinical failure is because of electric reconnection of a pulmonary vein (PV). On rare occasions, some electrophysiologists have seen conversion of AF to sinus rhythm with continued fibrillation seen within the PV further supporting this theory (Figure). Aside from anecdotal evidence, the data from observational PV remapping studies and repeat ablations that describe exclusively reisolating veins as the only intervention resulting in a successful outcome after an initial failure further collaborate the importance of complete PVI.1

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Still, although PVI has been recommended to be the cornerstone of AF ablation, there has never been a randomized trial that compares PVI with purposeful incomplete PVI as a procedural end point. At first consideration, it may seem obvious that complete PVI should be required as part of an ablation strategy as agreed on by expert consensus.2 However, studies targeting only non-PV triggers and/or non-PV rotors reporting success have raised questions of the central role complete PVI has.3 In addition, chronic PV reconnection is common, and thus, it is assumed that there exists a certain portion of patients who have unintentional incomplete PVI because of this phenomenon, yet still may not have recurrence of AF.

This is the reasoning behind the Gap-AF study in this issue of Circulation: Arrhythmia and Electrophysiology.4 This randomized, multicenter trial set out to understand whether an upfront approach of complete PVI (group B) is superior to intentionally allowing for electric reconnection (group A). Two hundred thirty-three patients with drug refractory, symptomatic, paroxysmal AF were enrolled. The primary end point was recurrent AF within 3 months, which was observed in 69.1% (62.2% of group B and 79.2% of group A patients [P<0.001]). Repeat invasive PV mapping at 3 months performed in 103 group A and 93 group B patients revealed conduction gaps in 92 (89.3%) and 65 (69.9%) patients, respectively. The authors assert that these data prove that complete PV isolation is superior to incomplete based on improvement in AF recurrence at 3 months.

Does the Gap-AF Trial Settle Controversy Regarding the Primacy of PVI?

There are 2 end points in Gap-AF that the authors use to support PVI as the superior strategy: improvement in freedom from AF recurrence at 3 months and improvement in durable PVI at repeat invasive study. Although there is a statistically significant improvement in 3-month freedom from recurrence, this metric is a curious end point (although probably chosen to facilitate return for repeat invasive study), as this time period is typically considered the blanking period. Though early AF recurrence is not a favorable sign, recurrence within 3 months is multifactorial and does not necessarily indicate long-term failure.5 Of note, there is an unusually high rate of early recurrence in this study—even if only the optimal strategy is considered, 62% had early recurrence. Two recent studies using regular irrigated radiofrequency observed early recurrence in 33.5% (in the control arm)6 and 46% (among the paroxysmal group).7 Das et al7 presented a small study using force-sensing catheters that demonstrated an early recurrence rate of 43%.

Gap-AF demonstrated an increased (but disappointing) incidence of durable PVI in group B patients. However, several previous studies seem to contradict the intuitive conclusion that durable PVI correlates with intermediate term freedom from AF recurrence. Cappato et al,8 in an early study (using nonirrigated RF ablation), found that PV reconnection was common, but of 17 patients without recurrent AF, 14 had PV reconnection. Pratola et al9 studied a small but distinctive group of 20 patients with acute procedural success and a minimum of 2.5 years freedom from recurrent AF. They frequently observed PV reconnection in these patients and no difference in PV reconnection compared with patients who had repeat study for clinical recurrence of AF. Finally, Jiang et al10 demonstrated 90% PV reconnection in patients who had acutely successful ablation procedures and 12 months freedom from recurrent AF.

What could possibly account for freedom from AF without durable PVI? Sometimes it seems that even if all PVs are not isolated, the triggering PV is; these patients can have long periods of freedom from AF, only to recur when the contralateral vein pair learns how to make trouble. In addition, autonomic and rotor hypotheses of AF do not require PVI for success. To be sure, we are not advocating against durable PVI, just questioning the “mission accomplished” message of the current work.

Aside from understanding the mechanism of AF and targeting this mechanism with precision, we also need to focus on...
understanding how our ablation lesions can become permanent before we can compare any strategy that depends on this. If we are to compare complete PVI with incomplete PVI, then there must be a reliable rate of durable PVI. Otherwise, the comparison is unintentional incomplete PVI versus intentional incomplete PVI, and differences will be difficult to detect.

Because of this lack of lesion durability, Gap-AF does not actually prove that complete PVI is superior to incomplete PVI for treating AF. The trial proved that complete PVI as the intended ablation strategy is better than a strategy of purposely having incomplete PVI. Because the long-term reconnection rate is so high in both groups, it is impossible to conclude that the PVI itself is the reason for the difference in success rates. In fact, the “success” rate of patients assigned to group B who actually achieved durable PVI was 43%. Even if we assume that all 24 patients in the complete PVI group who refused repeat invasive study were AF free and had complete durable PVI, the 3-month success rate associated with permanent PVI in this group is still < 70%. This means that additional ablation would be needed in almost a third of patients with paroxysmal AF. As expected, this success rate is higher than the 20% of patients without complete PVI who maintained sinus rhythm; however, this means that 1 in 5 patients will receive at least some unnecessary ablation while attempting to achieve PVI that is not required for successful treatment. This may include unnecessary ablation over the esophagus and near the phrenic nerve. Conversely, the failure rates are not similar in those patients who did not achieve PVI regardless of initial assignment (62% versus 80%). We need to understand the mechanisms for AF in these patients to guide ablation, otherwise we are ablating atrial tissue arbitrarily and unknowingly subjecting our patients to unnecessary risks.

Learning While Burning

The Gap-AF trial reveals the challenges of conducting a study evaluating ablative treatments of AF without regard to underlying arrhythmia mechanisms. Any trial focused purely on anatomic ablation strategies without an evaluation of the arrhythmia mechanism being targeted ignores the diagnostic basis of clinical cardiac electrophysiology. However, because we do not fully understand all of the mechanisms for AF in all patients and PVI has become the mainstay of AF ablation, it must be and is an accepted approach. For instance, there would be no basis for a trial evaluating slow pathway modification in all patients with undifferentiated regular supraventricular tachycardia (SVT). Some or most of those patients would certainly benefit from this strategy—those with atioventricular nodal reentrant tachycardia (AVNRT) as the arrhythmia mechanism. Yet all other patients with a different mechanism for their tachyarrhythmia, such as those with atioventricular reciprocating tachycardia, will have recurrence. There is a distinct possibility that this fictitious trial would prove that slow pathway modification is superior to medications because the majority of patients enrolled had AVNRT, the arrhythmia mechanism that is successfully treated with slow pathway modification. Thankfully, we have been able to understand the mechanisms behind SVT, and thus, we can perform a diagnostic electrophysiological study before selecting an appropriate target for ablation, rather than empirically choosing sites.
that will only likely be effective. Unlike those with a well-understood arrhythmia mechanism like AVNRT, patients with AF represent a heterogeneous group that may include those with non-PV sources of AF and those with arrhythmogenic tissue at the left atrium–PV junction that is successfully, yet unknowingly, ablated without completed PVI. The issue at hand for any useful clinical trial comparing different strategies for treating AF then becomes an issue of understanding the true underlying mechanism of the arrhythmia. For example, if a younger patient has SVT because of a concealed bypass tract as the mechanism for the initiation and maintenance of AF, then inclusion of this patient is inappropriate for a trial comparing different strategies focused on PV ablation.

Years from now, perhaps we will look back on the clinical trials that examined purely anatomic strategies for ablation of AF, like Gap-AF, in the same way that we would consider the example of the SVT ablation trial. Instead of comparing marginally effective empirical strategies that depend on unreliable lesion durability, we will have learned to focus on understanding an individual’s specific anatomy and physiology to design an appropriate ablation strategy for that specific patient. A pure anatomic approach for the treatment of arrhythmias, without consideration to mechanisms, completes our transition from true electrophysiologists to “ablationists” as fearfully described by Josephson11 a decade ago.

Moving Target of Science and Technology in Cardiac Electrophysiology

Planning, executing, and analyzing a clinical trial evaluating a complex disease such as AF with all the issues inherent with an ablation procedure is challenging enough, but we must also contend with a trial’s relevance after it has been completed. The technology for ablation is so rapidly developing that any clinical trial that would be considered today may use strategies that are obsolete by the completion of the trial. In Gap-AF, some of the more recent advances we have made for improving PVI were not used. These include proven ablation techniques such as force-sensing catheters and automated lesion assignment based on catheter stability.12 If an ablation trial uses outdated technology and techniques by the time it is reported, the application of its results to clinical practice is in question. In fact, one may consider the relatively low success rate seen in the standard PVI group and wonder if a greater difference would be observed if newer techniques and ablation strategy was used.

The authors of Gap-AF4 are to be commended for their commitment to science, despite the obstacles described above. It can be confidently stated that our current practice of AF ablation is not well informed by randomized clinical trials. Their research has not only confirmed expert consensus but also may open the door to future scientific advances and improved understanding of ablation.

Regardless of whether or not PVI is assumed to be a critical component of AF ablation, Gap-AF contributes to our understanding, as little as it may be, of AF mechanisms. It is because of this level of scientific rigor and equipoise in clinical trials that make them worthwhile, despite the obstacles that researchers face. At some point, we will feel as confident as we do when treating AF as we do with our treatment of SVT and can look to the scientific basis built by clinician scientists evaluating proposed arrhythmia mechanisms in the face of all of the trials and tribulations we encounter.

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References


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