Mental Exit Block
Escaping the Pulmonary Veins in Search of New Approaches to Atrial Fibrillation Management

“The significant problems we face cannot be solved at the same level of thinking we were at when we created them.”
— Albert Einstein

The pulmonary vein (PV) has been a source of fascination for electrophysiologists ever since the landmark work of Haissaguerre et al first showed that the PVs were a common source of atrial fibrillation (AF) triggers. The distinct embryological origins of PV tissue were thought to predispose these sites to be repositories of ectopy and thereby AF. Initial therapeutic approaches reliant on targeting individual pulmonary vein triggers evolved to segmental pulmonary vein isolation and, at present, wide area antral isolation.2–4

Unfortunately, improvements in ablation efficacy have been only incremental. The first descriptions of PV isolation as ablative therapy for atrial fibrillation (AF) described success rates of 63%.5 This large failure rate was initially due to technical limitations, as acute successes in the laboratory often gave way to chronic reconnection at repeat procedures. In the current era, technology has begun to catch up with our intellectual understanding of AF. Tools like JET ventilation, force-sensing catheters, and newer electro-anatomic mapping systems have improved the ability to create durable isolation of the PVs. Yet even in the best of circumstances, in patients with paroxysmal AF and minimal comorbidities, the long-term freedom from reoccurrence after AF ablation approaches only about 80%.6 By comparison, other ablative procedures, such as typical isthmus dependent right atrial flutter or atrioventricular nodal reentrant tachycardias, have durable therapeutic success rates in excess of 95%.

This raises the question: Can we solve our ablative shortcomings simply by ablating more atrial tissue? This approach has been tried in numerous ways and in numerous trials. Effort has been expended to determine whether PV isolation alone, targeting additional atrial substrate, eliminating AF triggers, or some combination of the three is the ideal ablation approach for managing AF. Unfortunately, many of our efforts have been met with only modest gains in procedural efficacy and, in certain circumstances, increased risk of left atrial arrhythmia. This multitude of approaches reveals that we have yet to truly understand the disease process.

In the current issue of Circulation, Wijesurendra et al take a step toward understanding AF on a more basic level.7 In a thought-provoking article, this group demonstrates that some patients with paroxysmal AF have altered left ventricular (LV) myocardial energetics even in the absence of other comorbid diseases. Fifty-three patients with lone AF undergoing catheter ablation and 25 matched controls without AF had sequential studies of cardiac function with MRI (ejection fraction and peak systolic circumferential strain) and energetics with phosphorus-31 MR (ratio of...
phosphocreatine-to-adenosine triphosphate) spectroscopy. Subtle but significant LV dysfunction and abnormalities in ventricular energetics were observed in patients relative to controls at baseline. Although PV isolation effectively eliminated AF in all the patients in this study, the AF hearts continued to express an energetic profile consistent with a myopathic phenotype. The authors argue that a lack of myocardial energetic recovery and normalization is proof of causation, ie, an underlying myopathy was the genesis of the lone AF, rather than the AF being the genesis of the cardiomyopathy. At the moment, it is unclear whether this assertion is true, as additional studies will be required to validate this claim. However, what is more apparent from this type of biological investigation is that, in crafting our solutions and therapies for AF, we may not be able to rely entirely on ablation alone.

It has been well shown that fibrosis and scarring occurs in the atria of AF patients, and this is thought to contribute to the progression of disease. Yet we lack proven medical therapies to target this process. By way of contrast, in the realm of heart failure, the myopathic ventricular substrate has been well studied, and medical therapies have been designed to encourage healing and reverse remodeling. Why should the standard of care for a dilated and failing atrium lag so far behind that of a dilated and failing ventricle? Often the biology of AF is prodding us to think differently. In most patients, AF is the culmination of chronic diseases such as obesity, obstructive sleep apnea, and hypertension. These risk factors elevate the complexity of disease management because they change over time, and thus our targets for managing AF are ever moving. All too frequently, a medicine or therapy that was effective today is no longer effective tomorrow. When viewed in this fashion, the expectation that a one-time ablative intervention will provide a durable and long-lasting cure by itself may be unfair because the procedure can only focus on the arrhythmic substrate at one moment in time. Just as few physicians would expect a stent to protect a myocardial infarct from further damage, we may not be able to rely entirely on ablation alone.

Further biological studies may find that some of the answers to managing AF do not even lie within the heart. Apart from the cardiac substrate and cardiac triggers are autonomic and neural inputs that mediate profound effects on the initiation, termination, and maintenance of arrhythmia. In fact, some of the success of wide antral isolation of the PVs is thought to be through a combination of blocking the exit of PV signals and incidental targeting of the sites of autonomic input into the atria. A great deal of work remains to fully understand the neural physiology within the left and right atria and its bearing on AF. However, new therapies such as vagal stimulators are showing promise during development.

Although some aspects of our understanding of AF physiology are in their nascency, these undiscovered details may ultimately prove the most useful. Current therapeutic approaches to AF rely on coarse divisions such as presence or absence of symptoms or frequency of arrhythmia to inform clinical decision making. These broad labels fail to recognize the complex heterogeneity of AF in terms of both mechanisms and pathophysiology. It is likely that with an expanding fund of knowledge, there can be greater refinement and granularity when creating treatment plans on a more individualized basis. One can envision a scenario where genetic characterization may contribute greatly to this as individuals with a predisposition toward fibrosis may be started on anti-fibrotic agents whereas patients with a channel mutation driving atrial premature depolarizations may benefit from a targeted anti-arrhythmic medication.

This editorial highlights several emerging concepts in AF and potential targets for novel therapeutics. Although none of the ideas presented here appears poised to overtake AF ablation and PV isolation as the cornerstone of AF disease management, we can still improve. Although we have become increasingly skilled at treating the trigger sources of AF, we still do not fully understand the pathophysiologic substrate of a disease with multiple risk factors and polygenic contributors. Just as management of this disease will likely require a combination of therapeutic approaches, it is likely that we as cardiologists will have to think both inside and outside the PV to solve the mystery of AF.

DISCLOSURES
None.

AFFILIATIONS
From Division of Cardiovascular Medicine, Electrophysiology Section, University of Pennsylvania, Philadelphia, PA (M.C.H., D.J.C.).

FOOTNOTES
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REFERENCES


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Matthew C. Hyman and David J. Callans

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