JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 8, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.06.1172

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Atrial Fibrillation Ablation

Translating Basic Mechanistic Insights to the Patient

Kunihiro Nishida, MD,*† Tomás Datino, MD,‡ Laurent Macle, MD,* Stanley Nattel, MD*

ABSTRACT

Atrial fibrillation (AF) ablation is widely performed and is progressively supplanting drug therapy. Catheter-based AF ablation modalities have evolved progressively in parallel to our understanding of underlying mechanisms. Initial attempts to mimic the surgical maze procedure, which were based on the multiple wavelet model, failed because of adverse outcomes and insufficient effectiveness. A major advance was the targeting of pulmonary veins, which is highly effective for paroxysmal AF. Active research on the underlying mechanisms continues. The main challenge is reconnection, but procedures to minimize this are being developed. Ablation procedures for persistent AF are presently limited by suboptimal success rates and long-term disease progression that causes recurrences. Basic research into the underlying mechanisms has led to promising driver mechanism-directed clinical approaches along with pathways toward the prevention of atrial remodeling. Here, we review the role of basic research in the development of presently used AF-ablation procedures and look toward future contributions in improving outcomes. (J Am Coll Cardiol 2014;64:823–31) © 2014 by the American College of Cardiology Foundation.

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, has complex underlying mechanisms (1). The incidence and prevalence of AF are increasing as the population ages (2). By the mid-1990s, ablation had revolutionized the therapy of most cardiac arrhythmias, with the notable exceptions of AF and ventricular tachycardias (3). The subsequent development of successful AF ablation procedures has dramatically changed AF management, but many limitations remain (4). The evolution of AF ablation has been marked by dynamic feedback between basic science concepts and clinical observations, each at various times contributing to advances in the other (**Fig. 1**). This paper reviews the fundamental science related to AF ablation, discussing the basic knowledge that led to advances in ablation procedures, findings emanating from clinical observations that forced a return to the bench to reconsider basic mechanisms, and present challenges to ablation success that require further improvements in our understanding of underlying mechanisms (**Central Illustration**).

BASIC RESEARCH AND THE EARLIEST AF ABLATION PROCEDURES

Multiple basic mechanisms (**Fig. 2**) were recognized as potential contributors to AF in the early 20th century (1,5). However, following Gordon Moe's classic work (6), the multiple wavelet hypothesis (**Fig. 2A**) predominated. The multiple wavelet hypothesis provided a quantitative framework for Garrey's much earlier idea (5) that the persistence of fibrillation depends on a critical mass of tissue large enough to support multiple re-entrant waves that prevent simultaneous termination of all underlying re-entrant activity. Translation of this paradigm (**Fig. 1A**) to humans led to the development of the surgical maze

From the *Research Center, Montreal Heart Institute and Université de Montréal, Montreal, Quebec, Canada; †Second Department of Internal Medicine, University of Toyama, Toyama, Japan; and the ‡Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain. Funding for this work was provided by the Canadian Institutes of Health Research (grant 6957) and Heart and Stroke Foundation of Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Nishida and Datino contributed equally to this work.

Manuscript received May 27, 2014; revised manuscript received June 26, 2014, accepted June 27, 2014.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CFAE = complex fractionated atrial electrogram

DF = dominant frequency (of fast-Fourier transformed signals)

ERP = effective refractory period

GP = ganglionated plexus

LA = left atrium/atrial

PV = pulmonary vein

PVI = pulmonary vein isolation

procedure (7) (**Fig. 1B**), arguably the single most successful nonpharmacological approach to sinus rhythm maintenance for AF ("arguably" because the quoted success rates for the maze procedure are on the basis of symptomatic recurrences, and many AF recurrences are asymptomatic). The first catheter-based ablation approaches for AF (**Fig. 1C**) were designed to mimic the surgical cut-and-sew maze procedure (8–10). This first phase of AF ablation largely failed because right atrial-directed ablations were generally insufficient to control the arrhythmia, transmural linear lesions proved very difficult to achieve, and left atrial (LA) procedures were associated with an unacceptable risk of major complications, particularly stroke (10).

THE ROLE OF PULMONARY VEINS AND OTHER KEY ANATOMICAL STRUCTURES

A key discovery in the development of AF ablation was the recognition by Haissaguerre et al. (11) of the role of pulmonary vein (PV) cardiomyocyte sleeves in AF, which led to a variety of PV-directed ablation approaches (**Fig. 1D**). Because the mechanisms for PV participation in AF were unclear, investigators began to address them (**Fig. 1E**). Initially, the role of the PVs was attributed to well-localized, spontaneous focal ectopic driver activity, which was supported by observations of dramatic resolution of AF with local radiofrequency (RF) energy application in a PV. However, it soon became apparent that AF tended to recur because other sources in the same and other PVs emerged, and pulmonary vein isolation (PVI) rapidly replaced focal ablation (12). Basic studies had identified spontaneous PV activity in the early 1980s, but the firing rate was slow and unlikely to contribute to AF (13).

Following the report by Haissaguerre et al. (11), basic scientists noted rapid arrhythmic activity in rabbit PVs (14) and provided evidence of Ca^{2+} mishandling in canine PVs (15). However, other observations in dogs failed to support the idea that normal PV sleeve cardiomyocytes spontaneously generate rapid focal activity (16–18). Moreover, PV cardiomyocytes displayed action potential (AP) properties (short AP duration and decreased phase 0 upstroke velocity) that reduce refractoriness and conduction velocity, potentially promoting re-entry (17). In addition, structural properties of PV cardiomyocyte sleeves, including longitudinal dissociation and abrupt shifts in fiber orientation, also favored local conduction slowing, block, and re-entry (19,20). A mathematical model incorporating realistic PV cellular electrophysiology and coupling properties suggested that there was enhanced vulnerability to local re-entry (21). This model was recently corroborated in the clinical electrophysiology laboratory (22). Present evidence suggests that multiple features of the PV cardiomyocyte sleeve predispose it to either focal or re-entrant activity, with discrete roles in AF initiation and maintenance in specific patient populations (23).

PVI was soon noted to be much more effective for paroxysmal than persistent AF (24). Subsequent work showed that non-PV sources become more important as AF becomes more persistent (25). Similarly, in animal models of persistent AF, the PVs play a limited role in AF maintenance (26). To deal more effectively with persistent AF, investigators sought other key anatomical structures and mechanisms involved in AF maintenance. Multiple linear lesions were found to suppress AF induced by vagal stimulation (27) and long-term rapid atrial pacing, with (28) or without (29) associated mitral regurgitation in dogs.

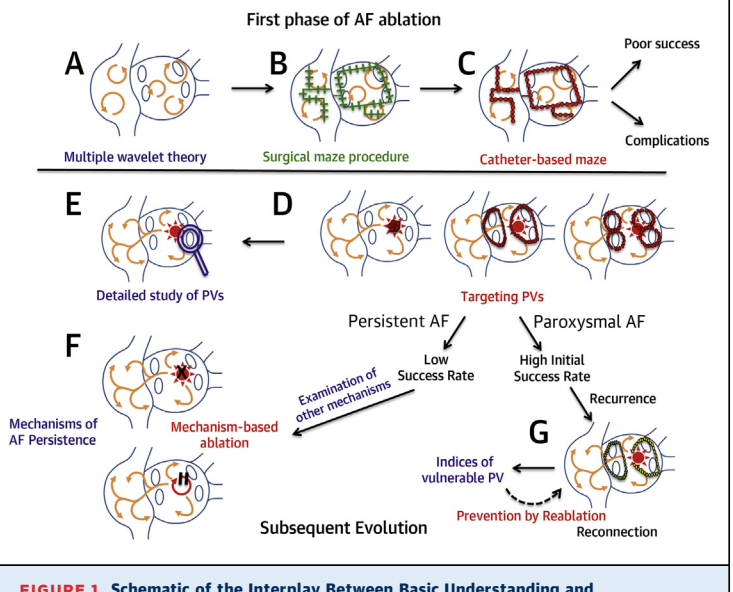

FIGURE 1 Schematic of the Interplay Between Basic Understanding and Clinical Approaches

The multiple wavelet theory of atrial fibrillation (AF) **(A)** led to the highly-successful surgical maze procedure **(B)**. However, attempts at mimicking the surgical maze by catheter ablation largely failed **(C)**. Clinical identification of the key role played by the pulmonary veins (PVs) led to the first truly successful ablation procedures for AF **(D)** and to basic studies of the underlying mechanisms **(E)**. Limited success of PV ablation for persistent AF led to a detailed examination of other mechanisms and mechanism-targeted procedures **(F)**. Clinical ablation procedures are labeled in **red**, basic research contributions are in **blue**.