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CLINICAL REVIEW

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Reflections on the early invasive clinical cardiac electrophysiology era through fifty manuscripts: 1967–1992

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Abstract

In 1967, researchers in The Netherlands and France independently reported a new technique, later called programmed electrical stimulation. The ability to reproducibly initiate and terminate arrhythmias heralded the beginning of invasive clinical cardiac electrophysiology as a medical discipline. Over the next fifty years, insights into the pathophysiologic basis of arrhythmias would transform the field into an interventional specialty with a tremendous armamentarium of procedures. In 2015, the variety and complexity of these procedures were major reasons that led to the recommendation for an increase in the training period from one year to two years. The purpose of this manuscript is to present fifty manuscripts from the early invasive clinical cardiac electrophysiology era, between 1967 and 1992, to serve as an educational resource for current and future electrophysiologists. It is our hope that reflection on the transition from a predominantly noninvasive discipline to one where procedures are commonly utilized will lead to more thoughtful patient care today and to inspiration for innovation tomorrow. In the words of the late Dr. Mark E. Josephson, "It is only by getting back to the basics that the field of electrophysiology will continue to grow instead of stagnate."

KEYWORDS

clinical cardiac electrophysiology, education, fellowship, history, training

1 | INTRODUCTION

In 1967, invasive clinical cardiac electrophysiology (EP) began.[1,2] The seminal event was the demonstration that arrhythmias could be initiated and terminated with programmed electrical stimulation. This led to refinement of theories regarding arrhythmia mechanisms, insight into the effects of the autonomic nervous system and medications on the electrical conduction system, and elucidation of the electrical substrate using catheter mapping.[3,4] Invasive studies advanced what was to that time a primarily noninvasive field.

In 2017, the specialty reached its 50th anniversary. The modern era is characterized by an emphasis on procedures. In fact, in 2015, the recommended training period increased from 1 to 2 years due to the increasing breadth and complexity of procedures.[5] With this evolution, the late Dr. Mark E. Josephson believed the field had lost focus on critical thinking regarding pathophysiology, lacked appreciation for the limitations of technology, and struggled to correctly interpret research.[6,7] He urged the field to recapture the spirit of the early invasive clinical cardiac EP era.

Our purpose was to provide a resource to reflect on a transitional period where invasive studies clarified theories previously derived

by mostly noninvasive methods. We present fifty manuscripts from the early invasive clinical cardiac EP era that laid the foundation for the modern interventional era. While there is no accepted time for the end of the "early" invasive clinical cardiac EP era, we chose 1992 as it was both the midpoint of the first fifty years and also the year the American Board of Internal Medicine introduced the first certification examination.[8] We focused on human clinical studies. Our sampling is subjective and cannot encompass all important manuscripts, but it includes many classic studies that are relevant today.

2 | FIFTY MANUSCRIPTS

1. **"The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff-Parkinson-White Syndrome"** (Durrer et al,[9] 1967). Investigators in The Netherlands reported a new technique that would become known as programmed electrical stimulation in four patients with Wolff-Parkinson-White (WPW) syndrome. Introducing premature atrial complexes (PACs) and premature ventricular complexes (PVCs), they demonstrated the ability to reproducibly initiate and terminate supraventricular tachycardia (SVT), thereby characterizing the electrical properties of accessory pathways. Coumel et al, simultaneously and independently, reported similar findings in France.[10]
2. **"Successful surgical interruption of the bundle of Kent in a patient with Wolff-Parkinson-White syndrome"** (Cobb et al,[11] 1968). A case of incessant atrioventricular (AV) reentrant tachycardia that resulted in tachycardia related heart failure in a 32-year-old man was described. They detailed body surface mapping to localize the right ventricular insertion of the accessory pathway, isochronal epicardial mapping to pinpoint the accessory pathway at the time of cardiac surgery, and the first surgical transection of an accessory pathway. Later work by Guiraudon et al would set the stage for catheter ablation of WPW syndrome.[12-14]
3. **"Supraventricular tachycardia with left aberrant conduction due to retrograde invasion into the left bundle branch"** (Wellens and Durrer,[15] 1968). This was the first report in a human of simultaneous initiation of SVT and left bundle branch block (LBBB) with left bundle aberration perpetuated by retrograde invasion. It demonstrated that a critically timed PVC can "peel back" the refractoriness of the left bundle with subsequent transformation to a narrow QRS complex tachycardia at the same rate. This manuscript supported findings in dog experiments described in 1965 by Moe et al[16] The observations improved the understanding of the true nature of bundle branch "block."
4. **"Catheter technique for recording His bundle activity in man"** (Scherlag et al,[17] 1969). As an extension of their work in a canine model, investigators described a simple and safe method to record activity from the His bundle. This allowed further key investigations into the diagnosis of arrhythmia mechanisms. Measurement of the His bundle electrogram allowed determination of the level of heart block.[18] It also became instrumental in our ability to discriminate arrhythmia mechanism in the modern EP study.
5. **"Ventriculo-atrial conduction in man"** (Goldreyer and Bigger Jr.,[19] 1970). This manuscript focused on ventriculo-atrial (VA) conduction properties using programmed electrical stimulation and His bundle recordings. It confirmed a functional relationship between AV and VA conduction, VA conduction is usually longer than AV conduction, VA refractoriness exceeds AV refractoriness, and ventricular reentrant beats may be easily produced. Understanding VA relationships would later assist in the diagnosis and treatment of reciprocating tachycardias as well as pacemaker programming. Also, short-coupled introduced PVCs from the right ventricular outflow tract resulted in His bundle electrograms appearing after ventricular depolarization. This phenomenon implied retrograde block in the right bundle with intramyocardial conduction up the ventricular septum that is faster than intramyocardial conduction to the left bundle and up the His-Purkinje fibers.
6. **"Ventricular fibrillation: A possible mechanism of sudden death in patients with Wolff-Parkinson-White syndrome"** (Dreifus et al,[20] 1971). A case of rapidly conducted pre-excited atrial fibrillation (AF) in a patient with WPW syndrome that precipitated ventricular fibrillation (VF) was reported. The mechanism for sudden death was thereby postulated to be rapid conduction through the accessory pathway during the vulnerable period. Subsequent work by Wellens et al would demonstrate a correlation between the effective refractory period of the accessory pathway and the shortest R-R interval during AF.[21] Both observations are now fundamental to risk stratification for sudden death in WPW syndrome.
7. **"Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome"** (Moss and McDonald,[22] 1971). In a patient with long QT syndrome, left cervicothoracic sympathetic ganglionectomy shortened the QT interval and effectively corrected syncopal episodes due to VF. This was proof-of-concept of the sympathetic nervous system involvement in the mechanism of VF in long QT syndrome. Sympathetic blockade, through beta-blockers or left cardiac sympathetic denervation, subsequently emerged as the primary treatment strategies to prevent ventricular arrhythmias.[23]
8. **"Electrical stimulation of the heart in patients with ventricular tachycardia"** (Wellens et al,[24] 1972). Reproducible initiation and termination of ventricular tachycardia (VT) originating from the left ventricle following right ventricular premature extrastimuli in five patients, four of whom suffered prior myocardial infarctions, was described. The findings supported the necessary components to allow for reentry as a tachycardia mechanism. A systematic method for programmed electrical stimulation that became the foundation of catheter-based cardiac EP study was also described in this manuscript.
9. **"Ventricular fibrillation occurring on arousal from sleep by auditory stimuli"** (Wellens et al,[25] 1972). The first case of VF

triggered exclusively and reproducibly by sudden auditory stimuli, now known as congenital long QT syndrome type 2, was reported. Based on meticulous observations on electrocardiograms (ECGs) during events, the investigators correctly associated this condition with the known syndromes of prolonged QT intervals. The first report of long QT syndrome was described by Jervell and Lange-Nielsen in 1957.[26] While the pathophysiology was only later identified to involve a potassium channel mutation, they successfully treated the patient with propranolol and diphenylhydantoin. The former remains a cornerstone in the treatment of congenital long QT syndromes to this day.[26]

10. **"The electrophysiologic demonstration of atrial ectopic tachycardia in man"** (Goldreyer et al,[27] 1973). Observations that would become the foundation for diagnosing atrial tachycardia were described. These included a lack of dependence on the AV node; identical morphologies between the initiating p-wave and other p-waves of the SVT; "warm up" phenomenon; resetting of the atrial cycle length with timed PACs; failure of introduced PACs to initiate or terminate the SVT; and failure of atrial overdrive pacing to interrupt the SVT. In 2007, sensitivity to adenosine was demonstrated to be associated with automaticity and triggered activity, whereas lack of sensitivity suggested reentry.[28]
11. **"Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia"** (Denes et al,[29] 1973). This report was the first to suggest reentry using dual AV nodal pathways as the basis for paroxysmal SVT in two patients with normal PR intervals and narrow QRS complexes. Investigators demonstrated different conduction times and refractory periods in the two AV nodal pathways. Sudden increases in the A_2-H_2 intervals during programmed atrial stimulation suggested block in the antegrade fast pathway and "jump" to the antegrade slow pathway. Availability of retrograde fast pathway conduction was suggested by echo beats. Establishing the mechanism of this arrhythmia was the foundation for subsequent efforts to achieve cure. Eventually, catheter ablation of the slow AV nodal pathway was established as the procedure of choice when medications are ineffective or undesirable, with a near 100% success rate and low risk for heart block.[30]
12. **"Demonstration of re-entry within the His-Purkinje system in man"** (Akhtar et al,[31] 1974). Reentry within the bundle branches was postulated to be due to retrograde block within the right bundle branch and retrograde activation of the His bundle via the left bundle branch followed by antegrade conduction through the right bundle branch. The primary observation was that additional ventricular depolarizations occurred with critical prolongation of VH intervals within a narrow range of V_1-V_2 intervals during programmed ventricular stimulation. These extra beats would become known as bundle branch reentry. Elucidation of the mechanism of this phenomenon eventually led to cure of this arrhythmia via ablation of the right bundle.[32]
13. **"Unusual properties of accessory pathways"** (Zipes et al,[33] 1974). In five patients, the complexities and variations of AV accessory pathways was revealed. In a 29-year-old man with a retrograde conducting AV accessory pathway and SVT with LBBB aberrancy, introduction of His-refractory PVCs during SVT was described for the first time. Both advancement of subsequent atrial depolarizations and SVT termination without conduction to the atrium were depicted. Using this technique, the "preexcitation index" was later developed to predict the location of accessory pathways.[34]
14. **"Patterns of ventriculo-atrial conduction in the Wolff-Parkinson-White syndrome"** (Wellens and Durrer,[35] 1974). EP study results examining VA conduction patterns in 36 patients with manifest ventricular preexcitation were presented. The investigators elegantly described the predominant possibilities of VA conduction patterns in the presence of an accessory pathway and concluded that the absence of increase in VA conduction time with increasingly premature ventricular extrastimuli signified conduction over an accessory pathway. Jackman et al would build upon these observations over left-sided pathways utilizing multi-electrode catheters in the coronary sinus.[36] These insights would prove instrumental in the catheter ablation era via both the retrograde aortic and transseptal approaches for left-sided pathways.[13,14,37]
15. **"The role of an accessory atrioventricular pathway in reciprocal tachycardia: Observations in patients with and without the Wolff-Parkinson-White syndrome"** (Wellens and Durrer,[38] 1975). Differentiating mechanisms of SVT is a requisite skill for the invasive clinical cardiac electrophysiologist. To distinguish orthodromic AV reentrant tachycardia from AVNRT, the sensitivity and specificity of observations during EP studies were derived from 125 patients with and without WPW syndrome. They also correlated intracardiac findings with the 12-lead surface ECG and suggested a stimulation protocol for analyzing patients with SVT. In subsequent years, additional diagnostic observations and the advent of catheter ablation were added to the foundation provided by this study to increase the ability to establish definitive diagnoses in SVTs.[39]
16. **"Bidirectional tachycardia in a child: A study using His bundle electrography"** (Reid et al,[40] 1975). The mechanism of bidirectional tachycardia was controversial at the time. In a 6-year-old girl with a structurally normal heart and absence of other potential precipitating factors, EP study diagnosed VT based on the absence of His bundle potentials preceding ventricular depolarizations. Importantly, VT was induced with both rapid atrial pacing and isoprenaline. This was the first accepted case of catecholaminergic polymorphic VT. A large series would not be published until two decades later.[41]
17. **"Entrainment and interruption of atrial flutter with atrial pacing: Studies in man following open heart surgery"** (Waldo et al[42] 1977). Entrainment, considered among the most elegant and ingenious concepts in EP, was introduced. Rapid pacing was performed using epicardial wires in 30 patients with classical atrial flutter following cardiac surgery. This resulted in "entrainment", or acceleration of the native tachycardia. With cessation

of pacing at these rates, the tachycardia resumed. When the pacing rate was increased to a critical value, the flutter wave morphology changed and the arrhythmia terminated. Concepts introduced here extended to other reentrant arrhythmias.[43] Defining arrhythmic mechanisms had further therapeutic implications in the ablation era. For example, achieving "bidirectional block" was first noted during ablation across the cavotricuspid isthmus for typical atrial flutter.[44]

18. **"Longitudinal dissociation in the His bundle: Bundle branch block due to asynchronous conduction within the His bundle in man"** (Narula,[45] 1977). This report complemented a prior histology study James and Sherf.[46] Fibers within the His bundle were demonstrated to be destined to form the left and right bundle branches. Normalization of the QRS complex with distal His bundle pacing in left bundle branch "block" was shown. It strengthened the concept that bundle branch block is often due to differences in conduction velocities between the bundles, rather than transmission failure. These insights have continued relevance into recent investigations of permanent His bundle pacing, introduced in 2000 by Deshmukh et al[47]
19. **"The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex"** (Wellens et al[48] 1978). ECG findings to differentiate the origin of a wide QRS complex tachycardia helped lay the foundation for a thought process to approach this differential diagnosis. Features examined included the role of AV dissociation, QRS width, RR interval regularity, QRS axis, monophasic or biphasic right bundle branch block (RBBB) morphology in V_1, and qR or QS morphology in V_6 in the presence of LBBB. Such exercises are instrumental in formulating treatment plans, including preprocedural preparations when invasive EP study and catheter ablation are contemplated. The importance of distinguishing ECG artifact from VT to avoid unnecessary and potentially harmful treatments would later be emphasized by Knight et al[49]
20. **"Recurrent sustained ventricular tachycardia: 1. Mechanisms. and 2. Endocardial mapping"** (Josephson et al,[50,51] 1978). These paired papers defined reentry as the mechanism of reproducible, sustained VT. Part 1 defined the process of programmed ventricular extrastimuli for initiation and termination of VT. Part 2 described the novel technique of endocardial catheter based ventricular mapping and its utility in determining sites of VT origin. Though regarded as cavalier by many in the cardiology community, these investigators at the University of Pennsylvania discovered insights into the pathophysiology of VT without procedural complications. This work guided endocardial surgical resection for VT, and would become the basis for modern catheter-based mapping and ablation.[52]
21. **"Continuous local electrical activity: A mechanism of recurrent ventricular tachycardia"** (Josephson et al,[53] 1978). Progressive fractionation of electrograms during programmed ventricular stimulation in three patients with structurally abnormal hearts was described. For the first time, continuous electrical activity was demonstrated at the onset of and during sustained VT. This manuscript described why these findings helped to define the site of origin and reentrant mechanism of sustained VT. This work was instrumental in building our understanding of VT substrate and, in later years, catheter ablation techniques.[54] Current exploration of VT treatment using noninvasive substrate-based techniques are also grounded in early observations such as these.[55]
22. **"Atrial induction of ventricular tachycardia: Reentry vs triggered automaticity"** (Zipes et al,[56] 1979). This series was the first report of idiopathic fascicular VT. Three patients had RBBB and left anterior fascicular block QRS morphology that suggested localization to the "posteroinferior left ventricle", although the mechanism could not be definitively defined. During VT, dissociation of His electrograms and ventricular depolarizations were observed in two patients and negative HV intervals were seen in the third. Suppression with propranolol was successful and among the recommended medical options until catheter ablation targeting the Purkinje network was developed.[57]
23. **"Paroxysmal nonreentrant tachycardias due to simultaneous conduction in dual atrioventricular nodal pathways"** (Csapo,[58] 1979). This report described the first case of dual AV nodal nonreentrant tachycardia whereby sinus impulses result in dual antegrade conduction to the ventricles, or "double fire", via dual AV nodal pathways. Characteristics that continue to stand today were described and an elegant model of AV nodal conduction was depicted. Although not common, this arrhythmia is important to recognize given frequent misdiagnosis, poor response to medications, the potential to incite cardiomyopathy, and high cure rate with slow pathway ablation.[59]
24. **"Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings"** (Mirowski et al,[60] 1980). Development of the implantable cardioverter-defibrillator (ICD) was far from inevitable when this proof-of-concept paper was published. Defibrillation had been understood for decades, but designing a device in a self-contained package small enough to be implanted posed a technical challenge. These investigators presented three patients with recurrent ventricular arrhythmias who were implanted with an abdominal generator connected to an endovascular coil in the superior vena cava and an epicardial defibrillator patch placed via thoracotomy. Further improvements led to a device that could be implanted transvenously technique, as first reported in 1998 by Saksena and Parsonnet.[61]
25. **"Lyme carditis: Cardiac abnormalities of Lyme Disease"** (Steere et al,[62] 1980). Investigators described 20 patients with Lyme disease who had various and fluctuating degrees of AV block. Intracardiac recordings proved block at the AV nodal level. PR intervals of 300 milliseconds or greater were found to be at greater risk of higher grade heart block. Almost all patients demonstrated complete resolution and none required permanent pacing. This work detailed the natural history of Lyme carditis and established the principle of waiting enough time

for conduction recovery as a key treatment strategy. In 1986, Reznick et al would demonstrate the supra-Hisian nature of AV block with EP testing in a patient with Lyme carditis and a spirochete isolated from myocardial biopsy.[63]

26. **"Sustained ventricular tachycardia: Role of the 12-lead electrocardiogram in localizing site of origin"** (Josephson et al,[64] 1981). Investigators correlated the QRS morphology of the 12-lead ECG of 41 distinct VTs in 34 patients with their site of origin as determined by endocardial catheter mapping. Validation of the origin of the VT was subsequently obtained in 20 of these patients who underwent surgical correction with intraoperative mapping. Activation mapping is now common practice in VT ablation.[54]
27. **"Amiodarone: Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation"** (Heger et al,[65] 1981). Amiodarone, at the time, was not approved for use in the United States and American physicians obtained it from other countries. This study was the first substantial series to describe the effectiveness and adverse event profile of oral amiodarone in the treatment of ventricular arrhythmias in structural heart disease over a mean follow-up of one year. This data assisted in paving the way towards approval by the Food and Drug Administration. It remains the most effective antiarrhythmic medication for VT suppression to this day.[66]
28. **"Sequence of retrograde atrial activation in patients with dual atrioventricular nodal pathways"** (Sung et al,[67] 1981). Investigators sought to characterize the retrograde activation sequence in subjects with both antegrade and retrograde dual AV nodal physiology using four catheters placed throughout the right atrium and coronary sinus. Shifting of the earliest retrograde atrial activation from the His bundle catheter during fast pathway conduction to the proximal coronary sinus electrode during slow pathway conduction was observed, suggested posterior breakthrough of the slow pathway. Later, surgical mapping by McGuire et al demonstrated different AV nodal inputs, highlighting the existence of heterogeneity in AVNRT.[68,69] These studies defined the anatomical regions for catheter ablation.[30]
29. **"Sudden death in hypertrophic cardiomyopathy: A profile of 78 patients"** (Maron et al,[70] 1982). Elevated sudden cardiac death risk in hypertrophic cardiomyopathy was known by the early 1980s. This series was the first to systematically analyze clinical predictors. A case-control study was performed of 78 patients with and 76 patients without sudden death. Most patients were younger at time of death. In 39%, death occurred during strenuous exertion; remarkable considering the low proportion engaged in such activities. Sudden death during exertion provided an early basis for the recommendation to abstain from competitive sports. In 2007, a multi-center study of ICD use continued to demonstrate the difficulty of sudden death risk stratification based on non-invasive features in most with hypertrophic cardiomyopathy.[71]
30. **"Right ventricular dysplasia: A report of 24 adult cases"** (Marcus et al,[72] 1982). Patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy, most with VT, were assembled in this series that outlined demographic, clinical, radiological and electrophysiological characteristics. In addition to evidence of RV enlargement, common findings included anterior precordial T wave inversions, postexcitation (epsilon) waves and VT of LBBB morphology that was induced during EP testing in all but 1 patient. Also insightful was a thorough discussion on strategies to differentiate this condition from other congenital heart defects and idiopathic VTs which may present with similar findings. Many observations would later become featured in proposed criteria to establish this diagnosis.[73]
31. **"Ventricular activation during ventricular endocardial pacing. II. Role of pace-mapping to localize origin of ventricular tachycardia"** (Josephson et al,[74] 1982). Investigators induced VT in 12 patients and performed endocardial activation mapping to identify the site of origin. They then performed endocardial pacing at different sites to compare the QRS morphology to that of the clinical VT. Pacing at the origin of tachycardia frequently replicated the clinical QRS morphology, whereas pacing elsewhere yielded differing morphologies. Pace mapping was thus introduced as a complementary method to activation mapping in localizing VT. It has become an important component of "substrate modification" methods for VT ablation, introduced by Marchlinski et al in 2000.[75]
32. **"Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias"** (Scheinman et al,[76] 1982). Extending their work from the animal laboratory, investigators at the University of California at San Francisco described direct current shock ablation of the AV junction with pacemaker placement in five patients with medically-refractory AF or SVT. Earlier that year, Gallagher et al at Duke University reported similar findings.[77] Demonstrating the feasibility of catheter ablation, it heralded the seismic shift of ablation for arrhythmias from an open-chest procedure in the operating room by surgeons to a closed-chest procedure in the EP laboratory by electrophysiologists.
33. **"Adenosine: Electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia"** (DiMarco et al,[78] 1983). The effects of adenosine in humans with SVT had not previously been described. Intravenous adenosine administration suppressed sinus node activity and prolonged AV node conduction, but had no effect on antegrade accessory pathway conduction in patients with WPW syndrome. This study was instrumental in establishing 6 mg as the starting dose for termination of SVT. Also notable in patients with atrial flutter and "intra-atrial reentry," lack of slowing of the atrial cycle length but worsening AV block revealed the diagnostic utility in macroreentrant atrial tachycardias.
34. **"Risk stratification and survival after myocardial infarction"** (The Multicenter Postinfarction Research Group,[79] 1983). A cohort of 866 patients was assessed by symptoms, physical exam,

Holter electrocardiography and radionuclide ventriculography. Mortality was measured after an average follow-up of almost two years. The findings validated the utility of depressed left ventricular ejection fraction, frequent ventricular ectopy, New York Heart Association class, and rales in predicting mortality. Concepts of risk stratification outlined by this manuscript remain valid to this day and led to the Multicenter Automatic Defibrillator Implantation Trial, the first primary prevention randomized controlled trial for ICDs in ischemic cardiomyopathy.[80]

35. **"Endocardial activation of left bundle branch block"** (Vassallo et al,[81] 1984). Intracardiac activation mapping of the ventricles in sinus rhythm revealed the heterogeneous nature of LBBB and the relation to underlying substrate. Demonstration of delay in the left ventricle eventually led to the hypothesis that treatment of LBBB-associated cardiomyopathy through "resynchronization" may improve cardiac function. In 1994, Cazeau et al published the first case of cardiac resynchronization therapy with a four chamber pacemaker created from a dual-chamber pacemaker generator and two Y-connectors.[82] Further observations have supported the emerging concept of LBBB-induced cardiomyopathy as a distinct clinical entity.[83,84]
36. **"A classification of antiarrhythmic actions reassessed after a decade of new drugs"** (Vaughan Williams,[85] 1984). The Vaughan Williams classification, first proposed in 1970, was reappraised after the development of additional antiarrhythmic drugs. The four-class system divided drugs by their primary mechanism of action and is the only widely used system. This classification remains popular due to its relative simplicity.[86] Nevertheless, new drugs should not be assumed to have similar safety and effectiveness as others in their class as no drug has a single effect.
37. **"Adenosine-sensitive ventricular tachycardia: Evidence suggesting cyclic AMP-mediated triggered activity"** (Lerman et al,[87] 1986). The mechanism of idiopathic LBBB morphology VT was elucidated in 4 subjects. Arrhythmias were suppressed with adenosine, verapamil, vagal maneuvers, and beta-blockers. Similar responses were not observed in 14 control patients with structural heart disease and re-entrant VT. These findings supported that the mechanism was cyclic AMP-mediated triggered activity through either direct modulation of calcium channels or indirect inhibition of cellular cyclic AMP production. Idiopathic PVCs would have added interest with the first description of PVC-induced cardiomyopathy in 2000 by Chugh et al[88]
38. **"Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction"** (Denniss et al,[89] 1986). The protocol for programmed electrical stimulation and significance of inducible ventricular arrhythmias was in evolution.[90] Programmed ventricular stimulation was performed in 403 patients who were 7 to 28 days after myocardial infarction. Freedom from cardiac death or nonfatal VT/VF was assessed after two years and found to be lower for patients with inducible VT, when compared to patients with inducible VF and no inducible arrhythmias. That inducible monomorphic VT, and not VF, has predictive value in sudden cardiac death risk stratification remains an important tenet to modern assessment for ICDs. In addition, the presence of late potentials on signal-averaged electrocardiography was associated with inducible VT and adverse outcomes. These observations led to the concept of targeting local late potentials during substrate-based VT ablation.[54]
39. **"Endocardial catheter mapping in patients in sinus rhythm: Relationship to underlying heart disease and ventricular arrhythmias"** (Cassidy et al,[91] 1986). Differences in endocardial mapping during sinus rhythm in those with ischemic vs nonischemic heart disease were detailed in this study. As those with nonischemic etiology were more likely to have normal endocardial electrograms, the VT substrate was surmised to be epicardial. In 1996, percutaneous epicardial catheter mapping was first described by Sosa et al in Brazil in three patients with Chagas disease and VT.[92] This ultimately led to the pioneering efforts of epicardial mapping and catheter ablation of VT in idiopathic nonischemic cardiomyopathy by Soejima et al in 2004.[93]
40. **"High frequency alternating current ablation of an accessory pathway in humans"** (Borggrefe et al,[94] 1987). Catheter ablation using direct current was limited by variable success, high recurrence, and significant complications. This report described a 40-year-old man with WPW syndrome via a right-sided accessory pathway who had failed direct current ablation and opted to undergo repeat ablation with alternating current. Using an irrigated catheter, a single lesion delivered at 50 watts for 10 seconds during SVT resulted in SVT termination and elimination of pre-excitation. This demonstrated proof-of-concept of alternating current, or radiofrequency, energy to cure arrhythmias. Alternating current continues to be the most widespread energy used for catheter ablation.
41. **"Idiopathic ventricular fibrillation: Inducibility and beneficial effects of class I antiarrhythmic agents"** (Belhassen et al,[95] 1987). The EP characteristics of idiopathic VF were poorly defined prior to this case series. Five survivors of cardiac arrest were included after organic heart disease had been ruled out. All five patients had inducible VF with single or double extrastimulus testing that was suppressed with disopyramide or quinidine. All remained free of recurrent VF over follow-up periods of 12 to 93 months. Since this publication, idiopathic VF has been refined as more specific entities, such as Brugada syndrome and catecholaminergic polymorphic VT, have been identified. Thus, many such syndromes are no longer "idiopathic". The observation that introduced PVCs initiated VF also provided the basis for the hypothesis that catheter ablation of spontaneous triggering PVCs could decrease recurrent episodes.[96]
42. **"Resetting of ventricular tachycardia: Implications for localizing the area of slow conduction"** (Stevenson et al,[97] 1988). This study built upon their first report of entrainment with concealed fusion in VT.[98] Endocardial mapping was used in seven patients

with VT to identify sites of slow conduction that participated in tachycardia. By delivering ablative shocks at or near these sites, VT was either abolished or significantly altered in configuration and cycle length. This was proof-of-concept that the critical circuit in VT could be identified and treated with catheter ablation. Subsequently, a follow-up study was performed where different reentry circuit sites in VT were characterized through endocardial mapping and became the current conceptual model for reentrant scar-based VT.[99]

43. **"Atriofascicular connection or a nodoventricular Mahaim fiber? Electrophysiologic elucidation of the pathway and associated reentrant circuit"** (Tchou et al,[100] 1988). At the time, accessory pathways with antegrade decremental properties, or Mahaim behavior, were believed to be "nodoventricular". Right bundle branch recordings were used to localize the distal insertion of the fiber to the right bundle branch. Ability to pre-excite the ventricle with introduction of late right atrial stimuli during tachycardia, when penetration of the AV nodal was not likely, proved lack of AV nodal involvement of the upper portion of the circuit. Defining the circuit would be instrumental for selecting targets for curative ablation.[101,102]
44. **"The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia"** (Fujimura et al,[103] 1989). Indications for permanent pacemakers were undergoing refinement and the utility of EP study in the setting of syncope and transient bradyarrhythmia was unknown. This study evaluated 21 patients who presented with syncope and a transient bradyarrhythmias. Abnormal EP study findings were demonstrated in only 3 of 8 patients with sinus pauses and 2 of 13 patients with AV block. The limitation of invasive EP testing in this setting was thereby demonstrated.
45. **"The ESVEM trial: Electrophysiologic study vs electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachyarrhythmias"** (The ESVEM Investigators,[104] 1989). Prior to the widespread use of ICDs, antiarrhythmic drugs were the primary treatment for ventricular arrhythmias. This design paper set the stage for a trial that would assess not only the optimal method for determining antiarrhythmic effectiveness, but also comparison of seven different antiarrhythmic drugs. Two major results came from the ESVEM trial. First, antiarrhythmic drug recommendations based on results from EP study and Holter monitoring strategies demonstrated similar rates of arrhythmia recurrence and death.[105] Second, sotalol was observed to be the most effective of the seven studies drugs and, with amiodarone, continues to be a major adjunctive treatment for ventricular arrhythmias.[106]
46. **"The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure"** (Cox et al,[107] 1991). The first patients to undergo the "maze" procedure were treated at Barnes Hospital. This was the first procedure designed with the intent to correct the three stated primary sequelae of AF: (i) irregular heartbeat, (ii) compromised hemodynamics, and (iii) vulnerability to thromboembolism. Interestingly, pulmonary vein isolation was performed due to the belief that the discontinuity of the posterior left atrium predisposed to macroreentry. In 1998, Haïssaguerre et al reported that pulmonary veins were involved in most with paroxysmal AF as the source of ectopic triggers, thereby paving the way for catheter-based treatment.[108] Pulmonary vein isolation alone presently remains the primary electrical endpoint for ablation, even in persistent AF.[109]
47. **"Mortality and morbidity in patients receiving encainide, flecainide or placebo"** (Echt et al,[110] 1991). Frequent PVCs had long been known to predict mortality following myocardial infarction. Antiarrhythmic drugs that suppressed PVCs were often used empirically to mitigate this risk. The Cardiac Arrhythmia Suppression Trial was a multicenter, randomized, placebo controlled study that tested this hypothesis. The trial was terminated early due to higher mortality in the antiarrhythmic arm. Following an open-label trial of one of these agents, patients who showed successful PVC suppression were randomized to either the effective drug or placebo. This study demonstrated the critical role served by randomized placebo controlled trials in testing the veracity of our clinical practices, even those that seem intuitive or obvious at face value.
48. **"Atrial fibrillation as an independent risk factor for stroke: The Framingham Study"** (Wolf et al,[111] 1991). Although AF had a known association with stoke, it was unclear whether it served as an independent risk factor or rather as a "marker" of stoke stemming from its relation to other known risk factors. This study analyzed 5070 subjects without cardiac disease on enrollment during 34 years of follow-up. Subjects were assessed biennially for stroke and AF, as well as other forms of heart disease. The results indicated AF indeed conferred increased stroke risk and this attributable risk increased with age. These observations ultimately led to the recommendation for oral anticoagulation for thromboembolic prophylaxis. A seminal review paper published in 1996 by Blackshear and Odell demonstrated that 91% of left atrial thrombi in nonrheumatic AF were confined to the appendage.[112] This data supported the development of percutaneous left atrial appendage occlusion, first reported in 2002 by Sievert et al[113]
49. **"Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy"** (Grogan et al,[114] 1992). This series of 10 patients with tachycardia-induced cardiomyopathy secondary to rapid AF was the first to measure left ventricular ejection fraction by echocardiography in patients presenting with this clinical scenario. Although five were in sinus rhythm and five were in AF at follow-up, all had heart rates of 80 beats per minute or lower and left ventricular ejection fractions of 40% or greater. Thus, the interaction between AF and heart failure was clarified. Although AF was largely considered benign, epidemiologic evidence eventually refuted this belief.[115] More recently, aggressive measures to maintain sinus rhythm with pulmonary vein isolation, compared to continued medical management, demonstrated both improvement in left ventricular ejection fraction

and reduction in mortality.[116] Earlier intervention may result in lower downstream arrhythmia burden.[117] However, the optimal treatment pathways for these patients still require much investigation.[118]

50. **"Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome: A multicenter report"** (Brugada and Brugada,[119] 1992). This was the first report of a constellation that would become known as Brugada syndrome. Eight patients with syncope, RBBB, persistent ST-segment elevation in leads V1-V3, and sudden cardiac death due to sustained polymorphic VT were described. Also suggested were a genetic link, predisposition to VT during fever, and treatment with ICDs. In 1998, *SCN5A* mutations were reported in three families with autosomal dominant transmission, thereby establishing a genetic basis for this condition.[120] Brugada syndrome and early repolarization syndrome are now considered related entities known as J-Wave syndromes.[121]

3 | CONCLUSIONS

As invasive clinical cardiac EP begins its second half-century, it is critical for trainees and practicing electrophysiologists to appreciate the foundation that transformed clinical cardiac EP from the noninvasive to the invasive era. Training programs should incorporate historical manuscripts to enhance the understanding of junctures in our specialty that heralded the forging of paths that have brought us to the present.

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CONFLICT OF INTEREST

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