Personal Perspectives of Mark E Josephson
Alfred Buxton, Hugh Calkins, David Callans, Philippa Hill, Demosthenes Katritsis, Frank Marchlinski, John Miller, Fred Morady, Edward Rowland, William Stevenson, Charles Swerdlow, Hein Wellens, Peter Zimetbaum, Douglas Zipes

Electrophysiological Testing for the Investigation of Bradycardias
Demosthenes G Katritsis and Mark E Josephson

Mahaim Accessory Pathways
Demosthenes G Katritsis, Hein J Wellens, Mark E Josephson

Dedicated to the Memory of
Mark E Josephson
1943–2017
The Heart Rhythm Society will host the brightest minds in cardiac pacing and electrophysiology this May in Chicago, IL. This renowned, global event will provide the latest science, best practices, and forums for peer-to-peer discussions and debate.

- 250+ Sessions
- 800+ Faculty
- 1,300+ Abstracts
- 12,000+ Attendees from 70+ Countries

Rahul Doshi MD, FHRS • Los Angeles, CA USA • Joined HRS in 2003
Lindsey Ward, BSN • Victoria, BC, Canada • Joined HRS in 2016

REGISTER TODAY AT HRSsessions.org
Aims and Scope
- Arhythmia & Electrophysiology Review aims to assist time-pressured physicians to keep abreast of key advances and opinion in the arrhythmia and electrophysiology sphere.
- Arhythmia & Electrophysiology Review comprises balanced and comprehensive articles written by leading authorities, addressing the most pertinent developments in the field.
- Arhythmia & Electrophysiology Review provides comprehensive updates on a range of salient issues to support physicians in continuously developing their knowledge and effectiveness in day-to-day clinical practice.
- The journal endeavours, through its timely teaching reviews, to support the continuous medical education of both specialist and general cardiologists, and disseminate knowledge of the field to the wider cardiovascular community.

Structure and Format
- Arhythmia & Electrophysiology Review is a tri-annual journal comprising review articles and editorials.
- The structure and degree of coverage assigned to each category of the journal is the decision of the Editor-in-Chief, with the support of the Section Editors and Editorial Board.
- Articles are fully referenced, providing a comprehensive review of existing knowledge and opinion.
- Each edition of Arhythmia & Electrophysiology Review is replicated in full online at www.AERjournal.com

Editorial Expertise
Arhythmia & Electrophysiology Review is supported by various levels of expertise:
- Overall direction from an Editor-in-Chief, supported by Section Editors and an Editorial Board comprising leading authorities from a variety of related disciplines.
- Invited contributors who are recognised authorities in their respective fields.
- Peer review – conducted by members of the journal’s Peer Review Board as well as other experts appointed for their experience and knowledge of a specific topic.
- An experienced team of Editors and Technical Editors.

Peer Review
- On submission, all articles are assessed by the Editor-in-Chief or Managing Editor to determine their suitability for inclusion.
- The Managing Editor, following consultation with the Editor-in-Chief, Section Editors and/or a member of the Editorial Board, sends the manuscript to members of the Peer Review Board, who are selected on the basis of their specialist knowledge in the relevant area.
- All peer review is conducted double-blind.
- Following review, manuscripts are either accepted without modification, accepted pending modification, in which case the manuscripts are returned to the author(s) to incorporate required changes, or rejected outright. The Editor-in-Chief reserves the right to accept or reject any proposed amendments.
- Once the authors have amended a manuscript in accordance with the reviewers’ comments, the manuscript is returned to the reviewers to ensure the revised version meets their quality expectations.
- Once approved, the manuscript is sent to the Editor-in-Chief for final approval prior to publication.

Submissions and Instructions to Authors
- Contributors are identified by the Editor-in-Chief with the support of the Section Editors and Managing Editor, and guidance from the Editorial Board.
- Following acceptance of an invitation, the author(s) and Managing Editor, in conjunction with the Editor-in-Chief, formalise the working title and scope of the article.
- Subsequently, the Managing Editor provides an ‘Instructions to Authors’ document and additional submission details.
- The journal is always keen to hear from leading authorities wishing to discuss potential submissions, and will give due consideration to any proposals. Please contact the Managing Editor for further details: managingeditor@radcliffecardiology.com. The ‘Instructions to Authors’ information is available for download at www.AERjournal.com

Reprints
All articles included in Arhythmia & Electrophysiology Review are available as reprints (minimum order 1,000). Please contact Liam O’Neill at liam.oneill@radcliffecardiology.com

Distribution and Readership
Arhythmia & Electrophysiology Review is distributed tri-annually through controlled circulation to general and specialist senior cardiovascular professionals in Europe. All manuscripts published in the journal are free-to-access online at www.AERjournal.com and www.radcliffecardiology.com

Abstracting and Indexing
Arhythmia & Electrophysiology Review is abstracted, indexed and listed in PubMed, Embase, Scopus, Google Scholar and Summon by Serial Solutions. All articles are published in full on PubMed Central one month after publication.

Copyright and Permission
Radcliffe Cardiology is the sole owner of all articles and other materials that appear in Arhythmia & Electrophysiology Review unless otherwise stated. Permission to reproduce an article, either in full or in part, should be sought from the journal’s Managing Editor.

Online

Also available at www.radcliffecardiology.com are other journals within Radcliffe Cardiology’s portfolio: Interventional Cardiology Review, Cardiac Failure Review, European Cardiology Review and US Cardiology Review.
EHRA 2017
18-21 June
Vienna, Austria

Connect

18 April 2017 - 18 May 2017 - Late Fee Registration
EHRA 2017 members save up to €220 on the congress registration

www.escardio.org/EUROPACE  #ehraeuropace

With the participation of the ESC Working Groups on e-Cardiology and Grown-up Congenital Heart Disease and in conjunction with the 41st Annual Meeting of the ESC Working Group on Cardiac Cellular Electrophysiology.
## Contents

**Foreword**

5  
Mark E Josephson The Elegance of Genius  
Demosthenes Katritsis, Editor-in-Chief  
Athens Euroclinic, Athens, Greece

### Guest Editorial

6  
Mark E Josephson: Characteristics of Leadership  
David Callans  
Section of Cardiac Electrophysiology, Division of Cardiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

9  
Mark E Josephson: Clinical Investigator  
John M Miller  
Indiana University School of Medicine; Indiana University Health, Indianapolis, USA

### Personal Perspective

13  
“What Would He Do Next?”  
Alfred Buxton  
Beth Israel Deaconess Medical Center, Boston, USA

14  
Getting to the Heart of the Matter  
Hugh Calkins  
John Hopkins Medical Institution, Baltimore, USA

15  
To Know Mark was to Love Him  
Philippa Hill  
Bruin Biometrics, Los Angeles, USA

17  
Mark E Josephson: A Tribute to His Work on Ventricular Arrhythmias  
Francis Marchlinski  
University of Pennsylvania Health System, Philadelphia, USA

18  
A Brash, Politically Incorrect, Opinionated and Brilliant Friend  
Fred Morady  
Cardiovascular Center, University of Michigan, Ann Arbor, USA

21  
Mark Josephson: Pioneer, Educator and Mentor to a Generation of Cardiac Electrophysiologists  
William G Stevenson  
Cardiac Arrhythmia Program, Brigham and Women’s Hospital, Harvard Medical School, Boston, USA

23  
Mark Josephson and the ICD: A Personal Perspective  
Charles D Swerdlow  
Cedars-Sinai Medical Center, Los Angeles, USA

24  
Mark E Josephson: The Boston Years  
Peter Zimetbaum  
Harvard Medical School; Beth Israel Deaconess Medical Center, Boston, USA

### Diagnostic Electrophysiology & Ablation

29  
Mahaim Accessory Pathways  
Demosthenes G Katritsis,1 Hein J Wellens,2 Mark E Josephson3  
1. Athens Euroclinic, Athens, Greece, 2. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA, 3. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA  

© RADCLIFFE CARDIOLOGY 2017
Mark E Josephson
The Elegance of Genius…

Three years ago I accepted an invitation by Mark Josephson to get attached to his Department as a part-time scientist, “in order to have fun” in his own words. Apart from being educated by his book and publications, I had in the past co-authored with him a number of papers that had provided a first-hand opportunity to appreciate his impressive mental capacity, and almost unlimited knowledge on arrhythmias. Living and working with him, however, was perhaps the most exciting experience in my whole professional life. Mark was not just an investigator, a clinician, a teacher, an electrophysiology and ablation expert, an inspiring chief. Mark was simply a genius. Anything else is an understatement, perhaps except from the fact that, in addition, he was also an incredibly honest, politically incorrect person of uncompromising intellectual dignity.

In this special issue of the journal, leaders who knew and had worked with Mark present their personal reflection on this giant in the field. Electrophysiologists of the world owe so much to this brilliant mind. He will live forever in every published paper that contains one figure with electrograms from the human heart. Mark the friend, however, will be deeply missed.

Demosthenes Katritsis,
Editor-in-Chief, Arrhythmia & Electrophysiology Review
Athens Euroclinic, Athens, Greece
Mark Josephson is without a doubt the most fascinating person I have ever met. I am proud to have had a close friendship with him and I miss him immensely. I have written in the past about his amazing academic contributions, but in a way I am relieved that this is not my topic today. I will instead talk about the unique aspects of his personality that allowed him to be a great leader in the field of electrophysiology and a powerful influence on the personal development of those of us who had the great good fortune of interacting with him closely.

Total Recall
Mark’s intellect seems to have been the driving force of much of his behaviour. His gifts were substantial. He apparently had a total recall memory on all sorts of topics, not only cardiac electrophysiology and electrocardiography, but details of individual patients, Patriots football, fine wine and much more internal medicine than I have ever mastered. He was in the habit of pretending that this was all completely natural, and that he “never read anything”. I knew that his depth and breadth of knowledge was acquired the old fashioned way, however, by intense study. In addition to recall, he had blazing analytical skills, which he applied, again, to any number of topics from complex intracardiac tracings to interpersonal relationships. We occasionally differed on the topic of whether or not someone was to be trusted, either intellectually or personally. I would come to my conclusions after much consideration, he after a millisecond. I would try to change his opinion on people, thinking that he must have overlooked a key element, but he never faltered. Without exception, when more information became available I would end up realising he had been right all along.

Encouraging Revolution
So, what would one set out to accomplish, equipped with such formidable skills? I often wonder what it must have felt like from Mark’s perspective – thinking so very quickly must have made the efforts of ‘neurotypicals’ seem agonisingly slow. It must have been clear to him that genius has the responsibility of encouraging revolution, and that is what he did. His overriding creative principles were to never accept the limitations of the present and to always question everything, even one’s own work. These forceful principles often made others uncomfortable – it was a very exacting, difficult way to think, requiring discipline and an intact ego structure. Some found his constant challenging and superior intellect difficult to bear. Nonetheless, these are the qualities that drove him to fundamentally change the practice of electrophysiology.

Mark’s time in the Public Health Service at Staten Island exposed him to intracardiac recording techniques, which at that time were used primarily for understanding abnormalities in the conduction system. It was revolutionary when Mark used these techniques to study ventricular tachycardia (VT), including stimulating and recording from the left ventricle during ongoing tachycardia. In a (distant) analogy, I remember being told by my young son’s hockey coach that we adults do everything we can to avoid ice, even when wearing study shoes. They were teaching our children how to do acrobatics on ice, despite wearing thin skates. In the same way, although almost everyone else in the world was deathly afraid of VT, Mark realised that the only way to understand this enemy well enough to devise therapy was to spend some time with it. From rigorous physiological investigation (anatomic and electrical substrate of VT, electrical stimulation during VT to determine the nature of the circuit) arose important therapeutic concepts: subendocardial resection, followed by catheter ablation of VT. This progression of physiology to therapeutic concept could only have been conceived by a quite limited number of investigators, but also required a great deal of work to bring to fruition. Mark and the all-star team he constructed, first at the University of Pennsylvania, then at Beth Israel Deaconess, provided the required mixture of creative spark and sweat equity.
Mark was always questioning, even some of the very concepts he had brought to life. He seemed to have taken responsibility for the intellectual dignity of our field (see Figure 1). He cautioned against blind acceptance of guideline-based patient care, particularly in the setting of primary prevention implantable defibrillator (ICD) therapy. This was not because he did not believe in this powerful technology, but because he wanted it to be better. He abhorred the loss of physiological basis for much of the current practice of interventional electrophysiology, particularly as applied to ablation of atrial fibrillation. He constantly strove to remind us that physiological understanding must precede therapy. He was righteously indignant about the casual relationship to truth that too many clinical research manuscripts appear to have. To the very end of his life, he was always questioning our fundamental concepts and improving on available techniques. In 2016 he wrote important manuscripts exposing some of our misconceptions about recording of intracardiac electrograms, particularly as this applies to VT substrate mapping and the nature of the VT circuit.

How did this all get translated on a personal level? You might expect that Mark’s fierce expectations would overwhelm all possibility for close relationships. That is in fact what I expected, as a beginning student of electrophysiology. At a time when his lectures were completely undecipherable to me, he was deeply interested in trying to bring me into his life and work. I remember hours in his Gladwyne house, sitting around a table with him drawing figures of the VT circuit (How is VT initiated? How do we understand the response to stimulation? Are the VT circuit barriers fixed or functional?) which certainly inspired an enthusiasm for learning, but was far above my ability to grasp. It reminds me of a quote from a famous long-distance runner, who was being interviewed about the arduous hours of training involved. At the end of the discussion, the interviewer asked with reverent appreciation for the human struggle of running “Is there anything I can do for you?” The runner answered “Run with me.” Mark did not need my meager input to understand the intricacies of mind experiments about the nature of the VT circuit, but it was lonely to think about it by himself (see Figure 2).

And so, I and many others benefitted greatly from his attempts. What were the rules of engagement? Never be anything less than completely honest. Always try your very hardest. It was nonsense to think that we could keep up with Mark and it would have been ridiculous for him to expect this. He was passionate about each of us becoming the best possible version of ourselves, both professionally and personally. What were the rewards? In addition to learning physiology in real time as it was being made from an expert teacher, the rewards for me included one of the most meaningful friendships of my adult life. I would have
Guest Editorial

walked through fire for Mark, and I knew he would have done the same and even more for me. He was fiercely loyal, incredibly honest and always seemed to make me feel like I was so much stronger/smarter/better than I really was (see Figure 3). I ache for the loss of his counsel and support.

Reaching Out

I was fortunate to have been close to him, but Mark was not about closing ranks to an inner sanctum. He was always reaching out, teaching, recruiting, encouraging. One of the enduring monuments to his love for teaching was the legacy of electrocardiography and intracardiac recording courses that he taught with his dear friend and kindred spirit Hein Wellens. Over 7,000 students participated in the rite of passage of interpreting tracings at the board over 35 years of courses throughout the world (see Figure 4). A remarkable number of these students admitted that they finally felt like a real cardiologist only after passing this milestone.

On 11 January 2017 we lost a transformative leader and a great friend. We have inherited what seems a tragically large responsibility to represent what Mark Josephson stood for, but we bear it with joy in dedication to his memory.

David J Callans
Section of Cardiac Electrophysiology, Division of Cardiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

Figure 4: Mark 'at the board' interpreting intracardiac electrograms with his first grandchild, who even at this tender age was an expert in distinguishing SVT mechanisms.
Mark E Josephson entered the world of clinical cardiac electrophysiology (EP) almost at its inception (1972); with so much to learn and so many directions one could take, he dived into the field with unbridled enthusiasm and an uncommon—perhaps almost unique—aptitude for asking questions and finding ways to answer them. Few aspects of EP escaped his indelible influence. In this short paper, I will attempt to touch on some of the high points of his astounding career as a clinical investigator.

The Electrocardiogram

In the entire realm of his work, Dr Josephson’s greatest love was the simple electrocardiogram (ECG). His discernment, based on the ECG, into the patient’s history and disease processes was legendary. Among the more important and insightful contributions he made to our understanding of heart disease and arrhythmias from the ECG are: observations of alternating preexcitation patterns in patients with Wolff-Parkinson-White (WPW) pattern who had more than one accessory atioventricular (AV) accessory pathway (AP),\(^1\) and a patient with 1:2 conduction AV using an AV pathway;\(^2\) the nature of electrocardiographic “left atrial enlargement”;\(^3\) multiple ECG manifestations of ventricular tachycardia (VT) in the same patient;\(^4,5\) use of the 12-lead ECG to localise exit sites of post-infarction VT\(^6,7\) and premature ventricular complexes;\(^8\) studies on electrical alternans in wide complex tachycardias;\(^9\) a highly useful method of distinguishing VT from supraventricular tachycardia (SVT) with aberration in left bundle branch block (LBBB) wide-QRS tachycardias;\(^10\) variations in the ECG expression of atrial flutter;\(^11\) differentiation of insertion sites of atriofascicular pathways;\(^12\) classification of which portion of which coronary artery was affected in myocardial infarction;\(^13,14\) features of the ECG in what appears to be right ventricular outflow tract ectopy and VT that correlate with difficult catheter ablation;\(^15\) distinction of the causes of T-wave inversion (post-pacing cardiac memory versus ischaemia);\(^16\) and whether LBBB was new or old (with implications for patients with chest pain and LBBB on ECG).\(^17\)

Throughout his career, Dr Josephson gave courses on ECG interpretation with his close friend Prof Hein Wellens; most EP fellows of the last 25 years have attended these legendary courses and come away with a new appreciation of this old tool and how much information can be extracted by masters such as Josephson and Wellens. In the later years of his career, he was invited along with Prof Wellens to provide a regular contribution to the prestigious journal *Heart Rhythm* – ‘Josephson and Wellens’ ECG Lessons: A Monthly Visit to the ‘12-Lead ECG’. Here, they retrieved some of the choice jewels from their treasures of ECGs obtained over the prior half-century, sharing their insights into how the ECG could yield important and often surprising information about the patient and their proper diagnosis and management. These pearls bear careful reading by the serious student of electrophysiology. Josephson was often heard to state something like the following: “The ECG never lies, but it doesn’t always tell you all it knows.”

A couple of anecdotes are worth sharing here. In preparing our 1988 paper on correlation of the 12-lead ECG with ‘site of origin’ of VT, some of the ECGs had been recorded as a long continuous strip from which I had to cut several complexes of individual leads and affix them to paper in a standard 12-lead ECG format. In one case, I had inadvertently mounted a lead V5 upside down; as I was reviewing a stack of these ECGs with Dr Josephson, he immediately noted the error. I was of course very embarrassed and apologetic but he was not as bothered by it as I was, knowing what it should look like. He could also name from which patient most of the ECGs came. In another instance, during a regular Monday ECG conference in a darkened room, a fellow was squirming uncomfortably at the front of the room trying to analyse an ECG projected on the screen that showed an atrial bradycardia, incomplete right bundle branch block and mild right ventricular hypertrophy. At that moment, Dr Josephson burst into the room looking for one of the other fellows; he glanced at the ECG on the screen and blurted out the diagnosis (sinus venosus atrial septal...
whether the atrium was a necessary component in AV nodal reentry.19

extensively throughout his career. The first of these studies investigated

nodal reentrant tachycardia (AVNRT), on which he published

much was still unknown). Among his favourite arrhythmias was AV

his understanding of this family of arrhythmias was (as well as how

author – he showed even this early in his career (1978) how extensive

his command of the ECG. Although most cardiologists interpret the ECG

well, and some even interpret it expertly, Dr Josephson interpreted

and understood the ECG deeply, as do but a few others.

Supraventricular Arrhythmias

Dr Josephson started his investigative career with supraventricular

arrhythmias such as SVT and atrial fibrillation (AF) and flutter. In a
general overview on paroxysmal SVT18 – on which he was the sole

author – he showed even this early in his career (1978) how extensive

his understanding of this family of arrhythmias was (as well as how

much was still unknown). Among his favourite arrhythmias was AV

nodal reentrant tachycardia (AVNRT), on which he published

extensively throughout his career. The first of these studies investigated

whether the atrium was a necessary component in AV nodal reentry.19

Following this were investigations into upper and lower common

pathways between the tachycardia circuit and atrium (above) and His

bundle (below);20,21 using the ∆HA interval (HA during SVT versus HA
during ventricular pacing;23,24 the origin of accelerated junctional rhythm
during slow pathway ablation for AVNRT;22 that standard slow pathway
ablation of AVNRT suffices in patients with earliest retrograde activation in the coronary sinus;26 the unusual rhythm disturbance of
1:2 AV conduction during sinus rhythm coexisting with typical AV
nodal reentry (which many thought impossible);27 and his final major
work on AVNRT, in which he matter-of-factly corrected some of his
own prior work in the light of newer evidence.28 Dr Josephson also
added to knowledge and practice in a paper on selection of sites for
ablation of APs in WPW, in particular using the unipolar electrogram;29
the previously-noted atriofascicular AP insertion study;30 and several
papers investigating AF. These included evaluating the success of AF
ablation by pulmonary vein (PV) isolation when entrance block into,
and exit block out of, the PV were obtained,30,31 as well as correlating
acute PV reconnection after ablation with poorer outcomes;32 a case
in which AF was contained within a PV after isolation,33 and pointing
out the frequency of aortic wall injury during AF ablation procedures.34

From the start of his career to its end, despite his plethora of other
investigative interests, his attention was never very far from SVTs.

Ventricular Tachycardia

The area of clinical investigation for which Dr Josephson is most
renowned is VT. In the 1970s, post-infarction VT was a major problem
without a good solution. Antiarrhythmic drugs were palliative at best,
and neither catheter ablation nor implantable defibrillators had been
developed. Dr Josephson believed that effective treatment might hinge
on a better understanding of the nature of the arrhythmia – which at that
time was poor. He and his colleagues began a series of investigations
that not only changed many aspects of the care of patients with VT, but
eventually those with many other types of arrhythmias (to which the
principles learned in VT investigation could be applied). The first studies
he published in this area were an astounding series of four landmark
papers, appearing in Circulation over a span of 13 months.4,35–37 This was
a planned series (the first is entitled ‘Recurrent Sustained Ventricular
Tachycardia. 1. Mechanisms’) setting forth the state of the art at that
time, and showing that:

- VT in this setting was due to reentry;
- Reentry occurred on the endocardium;
- Reentry did not involve the proximal His-Purkinje system; and
- Reentry occurred in a relatively small area.
These findings led directly to surgical treatment of VT by excising endocardial tissue proven to be essential for ongoing arrhythmia; finally, a cure for VT was possible. A series of papers followed this providing further insights into the behaviour of VT.45-47 – where circuits were, patterns of activation during VT, what accounted for multiple QRS morphologies of VT, observations about “dead-end” conduction pathways with 2:1 conduction during VT – and led to innovations in technique, resulting in improved outcomes.48 This, in turn, paved the way for subsequent work in catheter ablation of VT, in which Dr Josephson was an active investigator.49 Additional investigations involved the aforementioned use of the ECG during VT to localise exit sites from circuits,6,7 pace-mapping to corroborate activation mapping;41,42 and one of his favourite studies, the effect of endocardial tissue resection on electrograms at sites of reentry.46 In this study, a multipolar electrode array was positioned on a portion of endocardium to which VT had been mapped during the procedure; recordings were made during sinus rhythm (and usually also VT), the endocardium was then removed by undermining with scissors; and finally, the array was placed back in the same position where recordings were repeated during sinus rhythm (see Figure 1). This showed that endocardial late potentials (recorded after the end of the QRS complex) that correlated with mid-diastolic potentials during VT were located on the endocardial surface (present prior to resection, absent after), and that the larger signals seen during the QRS complex were recorded from deeper layers, with their amplitudes decreased by endocardial scar (see Figure 2). He also participated in studies of VT in the absence of structural heart disease67 as well as in the setting of congenital heart disease (repaired tetralogy of Fallot, Ebstein anomaly).48,49 One of his last battles against VT was in the form of prophylactic catheter ablation of VT to try to prevent shocks from implanted defibrillators;50 he always believed prevention was a better strategy than rescue (analogy: preventing injury by preventing a motor vehicle accident, versus rescue by airbag, so this study was a natural fit for him.

Mechanisms and Tools of Investigation

Dr Josephson was known for his earnest search for a more thorough understanding of the mechanisms of arrhythmias, strongly believing that correct therapy depended on knowing the correct diagnosis. While this seems self-evident, some electrophysiologists still perform catheter ablation procedures based on a presumption of a diagnosis and mechanism (reentry versus automaticity, for instance), rather than taking the extra few seconds or minutes needed to prove the case. A long and ultimately unsuccessful procedure can result from a strategy of presumption, if incorrect. Dr Josephson penned two perspective papers entitled “Electrophysiology at a Crossroads”51,52 that set forth his reservations about how EP practices had evolved from mechanism-and evidence-based care to what was expedient and economically driven; these are required reading in many training programmes.

Dr Josephson’s research into mechanisms of arrhythmias was spread throughout his career, starting with a publication on the effects of lidocaine in man.53 A few years later, the previously-mentioned work on mechanisms of VT appeared as the first of many regarding this arrhythmia. Following this were papers describing continuous electrical activity during VT;54 the mechanism of ventricular fibrillation;55 structure and ultrastructure of surgically-removed specimens from VT patients;66 and the meaning of endocardial late potentials.57 A series of monumental papers on resetting and entrainment of arrhythmias began in 198566 and continued for a decade thereafter, including resetting response patterns;59,60 resetting in the presence of fusion;61 comparing results of single-beat resetting versus entrainment;62 predictability of overdrive pacing to terminate VT;68 and investigation as to whether functional or fixed lines of conduction block are present in VT.64 The lessons learned from these studies provide substantial help in some cases of complex reentry, which are increasingly encountered after ablation of AF. Dr Josephson provided a lucid explanation of the mechanism of the rare but important disorder known as paroxysmal AV block.62 He also contributed to the development of the first electroanatomical mapping system.65

Dr Josephson participated in investigations into drug therapy of arrhythmias and the adverse effects of these drugs; cardiovascular genetics; animal models of arrhythmias; heart failure; valvular heart disease; device-based therapy of atrial and ventricular arrhythmias; clinical trials in arrhythmia therapy; and healthcare economics.

Conclusion

The panoply of contributions by Dr Josephson to our understanding of cardiac arrhythmias is far too broad to recount in a short paper. Even in failing health in his last two years here, he continued to develop new ideas about ways to investigate arrhythmias. His contributions to the field are large, both in number and impact; practically every procedure that a practicing electrophysiologist does on any given day has been influenced by Dr Josephson’s work. These accomplishments were of course important to him; far more important were his relationships with his family, colleagues and trainees. Ever the advocate and friend, he never saw himself as too important or busy to help someone understand a difficult point, or offer patient care or career advice when asked. A good clinical investigator does good work; an exceptional investigator inspires those with whom he works to launch out onto their own investigative paths. Dr Josephson was clearly among the exceptional. Thus it is that, through his students – who he taught how to think and ask questions – his work continues.

Lastly, although Dr Josephson made many new discoveries and devised new therapies in his investigative career, some of the conclusions he made from these studies turned out to be less than completely correct; he was big enough to own up to these and criticise his own prior work. A pioneer in any field, like an explorer in new territory, occasionally goes down a seemingly promising path that eventually leads nowhere. Far more often than not, however, Dr Josephson led us down a path of new discovery and we find, in
looking back, that the "hits" far outnumbered the "misses". It is difficult to imagine where our knowledge about arrhythmias would be, and how we would be practicing EP today, were it not for the contributions of this one man. His legacy as a pioneer in our field is secure.
“What Would He Do Next?”

I met Mark Josephson in 1973 when he came to the Hospital of the University of Pennsylvania (HUP) as a cardiology fellow. He had just completed 2 years at the US Public Health Service Hospital on Staten Island where he began his career in clinical electrophysiology. I was beginning medical internship at the same time. Even though Mark was among the most junior members of the cardiopulmonary division he quickly became one of the leaders, both by force of his personality, as well as a remarkable series of observations encompassing broad areas of clinical electrophysiology, including supraventricular (SVT) and ventricular tachycardias (VT). In the 1970s at our clinical cardiology conferences, Mark and colleagues described exciting new observations almost on a weekly basis. These observations formed the basis for much of the practice of clinical electrophysiology, not only in that decade, but to the present time. For myself, as someone interested in asking questions, this was an incredibly stimulating environment, and Mark was a most exciting mentor and role model.

Subsequently, from 1979 to 1981 when I served my electrophysiology fellowship, the work of the EP lab continued to expand. During this time surgical therapy for ventricular tachycardia was growing enormously, and both patients and electrophysiologists came to HUP from all over the US and abroad. The mantra of Mark, which carried over to the entire lab, was to study everyone possible, and enroll everyone possible into a research protocol. These were times before catheter ablation existed: therapeutic efforts were aimed at appropriate drug choices, based on physiology as we then understood it. Direct EP therapy was limited to the operating room for patients with VT as well as SVT – we routinely operated on patients with Wolff-Parkinson-White syndrome. Mark loved studying patients with SVT, and used these cases to expand and refine our understanding of the underlying physiology.

Two major changes took place in clinical electrophysiology in the 1980s: the introduction of the implantable cardioverter-defibrillator (ICD) and the introduction of catheter ablation (initially using direct current shock, then radiofrequency energy). Characteristically, Mark was initially skeptical of each, before embracing them, and utilising them fully and skillfully. Nevertheless, a common theme drove him crazy about each of these therapeutic modalities: indiscriminate, unphysiological use. Regarding the ICD, he felt that it is often used inappropriately, without regard to the individual patient’s overall clinical situation – he was staunchly against blind adherence to practice guidelines, without attempts to comprehend individual patients’ arrhythmic tendencies and mechanisms (i.e., underutilization of diagnostic electrophysiological studies). Second, he both practiced and preached against empiric catheter ablation without first exploring a patient’s physiology. That is, he did not believe in “Learning While Burning”. Rather, his philosophy could probably be expressed as “Learn Before You Burn”.

I spent about 22 years training under, and then working alongside, Mark. I also spent 18 years working at institutions separate from Mark. I think his influence on me (and I suspect this is true for most of the many others who trained under him) can best be summed up in this way: regardless of his physical presence, I have never done an EP study or ablation without him at my side, thinking, “What would he do next?” Almost every time I care for a patient, I think, “What would he do?” For me, this will never end. What greater tribute could there be for a physician, electrophysiologist and teacher. I am extremely grateful for the time we had together. I will miss him sorely.

Alfred Buxton
Beth Israel Deaconess Medical Center, Boston, USA

DOI: 10.15420/aer.2017.6.1:PP1

ARRHYTHMIA & ELECTROPHYSIOLOGY REVIEW
Getting to the Heart of the Matter

I have always held Mark Josephson in the highest of regard. He was a true giant in the field. As an electrophysiology fellow I read his famous text book on electrophysiology from cover to cover. I first met Mark when I was a junior faculty member at the University of Michigan. I was assigned the high honour of picking him up at the airport. He showed enormous interest in me and in the research projects I was working on. Ever since then I have looked forward to reading his articles and catching up with him at medical meetings. A particularly memorable meeting was at the South African Heart Association meeting. Mark and Joan had just returned from a high-end game park and were in tremendous spirits. Beth and I shared a wonderful bus ride with them to the conference. One of Mark’s most important qualities was that he always said exactly what he thought about a given topic. Whether it was the indiscriminate use of ICDs or the less than perfect results of AF ablation you could count on Mark to get to the heart of the matter. He was also an outstanding speaker.

I am sorry that my fellowship predated his ECG meetings. I am sure I would have learned a lot if I had been lucky enough to attend one of these courses.

To Know Mark was to Love Him

I was fortunate to work for Dr Josephson at the Beth Israel Hospital in Boston as my first job in the US after leaving the UK. My interview with Mark was a taste of the man – his flair for the dramatic, the need to shock you and see your response. But more importantly his kindness. My friendship with this amazing man endured from that first meeting. I learned so much more about him over the next few years – we shared laughs, a love of Motown music and more importantly the love of learning in the challenging world of electrophysiology. A lot of fellows came through the labs and to my great amusement one of the greatest compliments in a true MEJ back-handed manner when a fellow got the answer wrong he would look at me with a wry grin and say to them, "Even she knows the answer to that" – me, a mere cardiac technician. What a compliment from the man himself. It didn’t matter who you were, what level in the hierarchy you were, as long as you showed passion and enthusiasm.

To know Mark was to love him, and I’m honoured to be part of the group of people who can say they knew him.

Hugh Calkins
John Hopkins Medical Institution, Baltimore, USA

Philippa Hill
Bruin Biometrics, Los Angeles, USA
Dr Josephson was passionate about the study of ventricular arrhythmias and bold in his pioneering approach to their evaluation and management. Programmed right ventricular stimulation to test for antiarrhythmic drug efficacy was already pushing the risk limits for the invasive management of cardiac arrhythmias in the 1970s.

**Catheter-based Mapping to Characterise Ventricular Tachycardia**

Catheter-based mapping of the left ventricle (LV) to characterise the substrate and origin of ventricular tachycardia (VT) was thought to involve a much greater level of risk and therefore not to be pursued. Mark proved the naysayers wrong with his careful and methodical approach to evaluating the LV endocardium.

What made these early efforts even more remarkable was that left ventricular mapping was performed with a nonsteerable, quadripolar catheter. Sampling each of the ‘12 Josephson endocardial sites’ with the catheter tip localisation guided only by fluoroscopy was frequently a daunting task but always accomplished. Abnormal, late, split and fractionated electrograms, diastolic activation and continuous electrical activity would become part of the electrophysiology lexicon in describing the VT substrate and circuit.1–3

This early work also revealed the subendocardium to be a critical component of most post-MI VTs. This would lead to the surgical ‘peeling’ of the subendocardial layer of infarcted myocardium extending from the edge of the more densely scarred aneurysm to eliminate VT.4-5 The ‘Pennsylvania Peel’ was established as the surgical technique to cure infarct-related VT.

**Championing the Diagnostic Value of the 12-lead ECG**

Throughout his efforts to understand the physiological mechanisms related to the initiation and maintenance of VT, Dr Josephson also continued to champion the role of the lowly but critically important 12-lead ECG in helping us pinpoint the origin of VT.

I always refer those interested in the subject to Mark’s epic work published in *Circulation* in 1981.6 The paper had 11 figures, each with multiple 12-lead ECGs, helping the reader understand how the 12-lead ECG QRS pattern could help regionalise the area of interest to focus more detailed mapping.

A year later, Mark also detailed the role of pace mapping in patients with VT, making observations that have stood the test of time.7 He pointed out that long activation times from the site of earliest activation during VT (isthmus sites) were mimicked by the long stimulus to QRS interval during pace mapping and that the production of grossly disparate 12-lead ECG patterns was frequently observed during pacing from closely adjacent areas within the scar. Years later, other investigators would echo the value of his early observations and emphasise their importance in localising the best sites for VT ablation.8,9

**Resetting with Fusion – the Hallmark of Reentry**

In the mid-1980s Mark worked with a young trainee in his lab at that time, Dr Jesus Almendral from Madrid. They introduced extrastimuli during VT to characterise the resetting response of scar-related VT.10,11 The ability to reset the VT after surface electrocardiogram (ECG) or intracardiac recordings had already indicated onset of activation (resetting with fusion) represents the hallmark of reentry.12 The list of accomplishments and key observations goes on and on.
During his more than 45 year of working on ventricular arrhythmias the ground-breaking efforts which improved our understanding of ventricular arrhythmia pathogenesis and treatment would number in the hundreds; all seminal in nature, clearly described and moving the needle of care worldwide.

An Inspirational Mentor
Perhaps, gifts of equal value to his enormous scientific legacy, were his ability to inspire and his skill in mentoring. Mark both inspired us and indicated that we had the responsibility to join him in the effort to inch the field forward. He taught us to challenge accepted treatment strategies that were based on opinion and dogma but not sound physiological principles. He encouraged us to be skeptical of technology or treatment trends that avoided physiological confirmation in their development and use. He was selfless with his time, always accessible and enthusiastically supportive but always challenging us to get it right. We had a ‘hotline’ to Mark over the last 25 years, which linked us immediately to him for academic discussion, challenge and advice, no matter what the geographical or institutional differences. This hotline has been sadly disconnected and he is very much missed. We find solace in knowing that he blazed the path, showed us the way and served as a role model for how things should be done. We will follow in his footsteps and tip our academic hats to our friend and mentor as we continue the important effort to inch the study of ventricular arrhythmias forward.

Francis Marchlinski
University of Pennsylvania Health System, Philadelphia, USA


DOI: 10.15420/aer.2017.6.1:PP4
A Brash, Politically Incorrect, Opinionated and Brilliant Friend

I met Mark for the first time over 30 years ago. I had completed my training only 1–2 years earlier and was amazed to discover that Mark was only a few years older than me. At that point, I had published one or two clinical research studies dealing with electrophysiology issues, whereas Mark already had established himself as a prolific investigator and a leader in the field of clinical cardiac electrophysiology. Hardly a month would go by without another study from Mark and his group at the University of Pennsylvania appearing in Circulation. His status as a pioneer in the field is undisputed. It is incredible to think back to how his early work shook up the cardiology community. I have a distinct memory of a debate that Mark had with a prominent icon in the field of electrocardiography and arrhythmia management at a national American Heart Association meeting in the late 1970s. Mark was quite literally and shockingly accused of advocating torture when he defended the practice of programmed ventricular stimulation to induce ventricular tachycardia. Perhaps to the dismay of this ‘expert’, Mark’s pioneering efforts were quickly adopted into standard clinical practice, as have many of his other contributions to the field.

Although Mark tragically is no longer with us, my strong memories of this brash, politically incorrect, opinionated and brilliant friend remain embedded in my mind.

A Gifted Teacher

Few in the medical world get to be a household name in their specialty. Some achieve it through an eponymous syndrome or the invention of a classic operational procedure. Mark Josephson’s name was known to throughout the world of cardiac electrophysiology, and through most of cardiology, because he was central to virtually all aspects of the modern investigation and management of cardiac arrhythmias from its beginning in the 1970s. Since those early days Mark Josephson’s name was on numerous classic scientific papers, conferences were incomplete without his presence, and any discussion on the mechanism of most arrhythmias had to encompass Mark’s contribution to our better understanding. A week spent with him in the hospital during his meetings and rounds was an education in a determination to be the best. Even a day spent at the courses where Mark held court was something of a rite of passage. Here one could glimpse his determination, an inquisitive mind backed up by huge experience and learning.

Asking colleagues their memories of Mark produced “gifted teacher” as the most common reply – of that there can be no doubt. His deductive skills, emphasising the importance of the ECG and using other information, especially intracardiac electrograms, to confirm these deductions was the cornerstone of much of his teaching. At times it was harsh, but it was never any more demanding of others than the demands he made of himself. Like all highly intelligent individuals he was never hide-bound by rules or received wisdom. Evidence and deductive reasoning were necessary to prove the point. Much of this extended to his life outside medicine. Playing golf with Mark was always an interesting and entertaining experience, where passion, determination and enthusiasm were not inhibited by a rule book!

All those involved in or affected by heart rhythm abnormalities whether clinical staff, patients or administrators owe Mark Josephson a huge debt of gratitude.
I first met Mark Josephson in the early 1980s at his conference in Philadelphia, which I attended as a trainee. He was an inspiring figure, with his incisive commentary and enthusiasm for the field. It was there that I first heard Al Waldo explain entrainment, which he illustrated by drawing diagrams on a large flip chart. The discussion was spirited! Mark brought people together, then pushed them with intellectual rigour. He used this approach with everyone from medical students to senior investigators. He routinely challenged conventional thinking, pushing the field forward.

From a review of Mark’s publications one would appreciate only part of his impact on the field. He was a tireless and inspiring teacher in the clinic, on the wards, in the electrophysiology laboratory, and in countless conferences and scientific meetings. His passion for electrocardiography and electrophysiology inspired more than a generation of physicians and investigators who can be found in academic institutions and clinics around the world. He was a mentor and friend to those who trained under him, as well as to those who did not have that opportunity but sought his advice. He will be greatly missed.

William G Stevenson
Cardiac Arrhythmia Program, Brigham and Women’s Hospital; Harvard Medical School, Boston, USA


DOI: 10.15420/aer.2017.6.1:PP7
Mark Josephson and the ICD: A Personal Perspective

Mark Josephson dedicated his career to the prevention of premature sudden cardiac death (SCD). Toward that goal, he was an early adopter of the implantable cardioverter defibrillator (ICD) and indefatigable advocate for better ICD technology, both as a clinical tool and as living laboratory to study SCD in ambulatory patients. With characteristic intellectual integrity and analytical rigour, he sought an honest and balanced appraisal of the life-saving benefits and serious complications of this unique therapy.

Balanced Evaluation of the ICD

Although better known for his transformative contributions to arrhythmia mechanisms, mapping and ablation, Dr Josephson participated in investigational studies of the first implantable defibrillator and served as a principal investigator for the MUSTT (Multicenter Unsustained Tachycardia Trial) foundational trial of primary-prevention ICD therapy. In one of the first systematic analyses of ICD far-field electrograms (EGMs), he stressed morphological disparities between spontaneous and induced VT; and he actively encouraged research to predict spontaneous VT in ambulatory patients based on ICD EGMs.

As enthusiasm for ICDs began to soar in the mid-1990s, Dr Josephson provided a vital, clear-thinking counterbalance. He emphasised the role of preventive, ablative therapy, both in conjunction with interruptive ICD therapy to reduce shocks and as a curative alternative in patients with single-vessel coronary disease and haemodynamically stable VT. Dr Josephson spotlighted critical issues related to overestimating the benefits of ICD therapy and under-appreciating its limitations: early observational studies used appropriate ICD therapy as a surrogate for prevention of SCD. With his mentees Joseph Germano and Roderick Tung, Dr Josephson played a vital role in exposing this fallacy by highlighting the reasons for this difference in event rates, unnecessary appropriate ICD therapy for self-terminating VT and device proarrhythmia, both of which were confirmed in subsequent studies.

Honesty with Evidence – Honesty with Patients

Dr Josephson sought to apply rigorous evidence to clinical care, yet he retained a deeply human connection to his patients at risk for SCD. He interpreted practice guidelines through their stated intent, to assist in clinical decision-making; he was deeply troubled by the trend to accept guidelines as canonical dictums that absolved physicians of cognitive responsibilities; and he discriminated unambiguously between those based on valid evidence and those he judged to be based on inconsistent evidence, omission of relevant evidence or incorrect interpretation of evidence. In this context, he contributed to an incisive critique of the inconclusive and statistically flawed evidence for primary-prevention ICDs in patients with nonischaemic cardiomyopathy, a critique supported by the recent Danish ICD Study in Patients with Dilated Cardiomyopathy (DANISH). He questioned the wisdom of some primary-prevention guidelines that required implanting 15 to 20 ICDs to save one life; and he consistently supported research to improve risk stratification. He emphasised that competing comorbidities and advanced age precluded ICDs from prolonging life in some guideline-indicated patients, even if their ICDs prevented SCD. In this context, Dr Tung penned a critical admonition with Dr Josephson as senior author:

“With modern medicine, less emphasis has been placed on the physician-patient dialogue where concerns and expectations are freely exchanged. Physicians should understand that choosing longevity with potential tradeoffs in device-related complications and quality of life is a personal decision that must be individually tailored to patient preference. … It is ethically imperative that we are honest with the data, so that we can be honest with our patients.”
An Inspirational Teacher

I first met Dr Josephson when he visited my fellowship programme, but I didn’t really get to know Mark until 2004, when he asked me to teach interpretation of ICD EGMs at the ‘How to Approach Complex Arrhythmias’ course he gave with Hein Wellens. Twice a year, for the next 12 years, I did my best to honour his implicit mandate – to develop a systematic approach to ICD EGMs that complemented the systematic approach to ECGs he taught with Hein. By serendipity, I had a ringside seat to master teachers in action. I studied how, beyond Mark’s occasional frustration with fools, he provided strategic and strategically timed clues when a student struggled with a tracing; invariably, these clues framed the solution, yet required students to complete the analysis and thus permitted them to walk away with a sense of mastery. At each course, I sat humbled by the blinding speed and penetrating power of Mark’s reasoning, the depth and ken of his analyses; I marvelled at the casual elegance with which he unravelled the intricate stories concealed within complex arrhythmias; and I witnessed his lucid expositions inspire students – including me – to seek out the stories hidden in our own patients’ tracings.

Mark was devoted to his gracious and inspirational wife Joan. They were inseparable, and she attended every course. Each Sunday morning, I drank coffee with Joan as she recounted stories of Mark’s deep personal investment in his fellows and his loving devotion as a father. I showed her the latest pictures of my two sons, and she offered practical and insightful parenting advice.

Over years, Mark became my friend and mentor. In that process, surpassing even his encyclopaedic knowledge and towering intellect, Mark’s humanity and moral compass became my greatest teacher. For me, his integrity, empathy and compassion continue to shine like a beacon, illuminating my path.

Charles D Swerdlow
Cedars-Sinai Medical Center, Los Angeles, USA


DOI: 10.15420/aer.2017.6.1:PP8
Mark E Josephson: The Boston Years

Mark Josephson came to Beth Israel Hospital from the University of Pennsylvania in 1992, having firmly established a reputation as a master clinician, scientist and educator. He had built one of the premier electrophysiology (EP) services in the world in Pennsylvania and had become Chief of Cardiology there by the age of 35. In those days, Beth Israel was well known for its interventional cardiology and cardiac imaging but had not yet committed to the development of a modern EP section. The buzz surrounding Mark’s arrival predicted an outspoken, larger than life and irreverent character who would profoundly change the place.

Intellectual Excitement

That turned out to be an understatement. As a Beth Israel resident at the time, I can remember his chagrin and frustration as he realised how behind we were. Perhaps it was the need to catch us up or just his irrepressible passion for EP, but he brought an intellectual excitement to the Division of Cardiovascular Medicine that was electric. From the start he was everywhere – teaching at the bedside, in ECG conference and in the laboratory. He insisted on the education of everyone from lab technicians and nurses to housestaff, fellows and cardiology attendings. No one got a pass – not even the then chief of cardiology, whom he quizzed on the details of reentry during his first cardiology grand rounds.

In short order, EP began to rival interventional cardiology for fellowship applicants, fellows were talking about arrhythmia mechanisms on rounds, and old attendings were embracing new ways of managing arrhythmias. In fact, at age 80, Paul Zoll stood next to Mark in the EP lab as he performed the first ventricular tachycardia (VT) ablation at Beth Israel on a patient of Paul’s whose VT was no longer suppressed on medication.

A Valued Mentor

For me personally, Mark was the best doctor I had – and have – ever worked with. He’s a big part of the reason that I’ve spent 25 years – the entirety of my career – here at Beth Israel Deaconess Medical Center (BIDMC). And I’m not alone in having considered Mark a valued mentor and friend. A few years ago, we held a symposium called ‘The Josephson Scholars – Four Decades of Clinical EP’, and nearly 200 of his mentees and their mentees came to Boston from across the country and around the world. Mark often proudly referred to his “academic children and grandchildren,” and he received much recognition for his role as mentor, including the American Heart Association’s prestigious Eugene Braunwald Academic Mentorship Award. Upon getting the award, Mark reflected that mentoring is about more than helping people advance professionally: “You have to love people; you have to care about people and want to see them grow and be happy.”

Tough Love

His style was very much tough love, however; his approach to life was to question, to debate, to agree to disagree. Mark started the practice and we continue it of meeting early every morning as an EP service and review the cases for the day and the patients on the ward service. The fellows quickly learn to bring all the tracings and be ready to interpret them with both a diagnosis and an explanation of the physiology. This morning meeting ritual is about education and clinical excellence. It keeps us honest in our approach to patient care, allows us to teach one another, creates a cohesive service and, in effect, creates a family. It embodies all the principles Mark stood for as an academic physician. It is one of the places where Mark shared his brilliance with us and helped us learn to think more deeply and rigorously. It is no surprise that many EP programmes in Boston and, I suspect, wherever his former fellows have landed now have similar morning meetings.
Ultimately Mark’s commitment to the care of patients, the education of young doctors, and the pursuit of academic excellence resulted in his selection as Chief of Cardiovascular Medicine in 2001, a position he held until 2016.

**An Enduring Legacy**
Mark’s spirit will live on at the BIDMC in countless ways – but two enduring symbols have been created; the first is the Joan and Mark Josephson scholar award – a three-year award given to a faculty member committed to the principles of humanism in medicine. The second is the first chair in cardiac electrophysiology at Harvard Medical School called the Josephson–Ben Haim Chair in Cardiac Electrophysiology. Mark was very proud of this honour and gratified to know that the future occupants of this chair would have his legacy to uphold and continue to ensure a vibrant environment for the training of young physicians and the relentless pursuit of innovation.

Peter Zimetbaum
Harvard Medical School; Beth Israel Deaconess Medical Center, Boston, USA

DOI: 10.15420/aer.2017.6.1:PP9
A Brilliant Pioneer and Leader

Mark Josephson was a leader, not just a leader, but a brilliant pioneer leader breaking new ground in multiple areas of electrophysiology, including research, patient care and teaching. We were friends since his early days at Penn Medicine, Philadelphia, when he was working with Len Horowitz as his collaborator. I watched his maturation and contributions over the next 40 years in all three areas. His textbook is one of a kind: a single authored electrophysiology teaching gem that will never be duplicated. His teaching seminars with Hein Wellens, known for the Socratic method initiated by Pick and Langendorf many years ago, will also never be replicated. Mark’s most recent contributions to teaching have been a plea – a demand, really – to harken back to our roots as electrophysiologists, to teach and learn physiology, not just implantation or ablation procedures. I couldn’t agree more.

So often our attributes become our failings, and Mark’s was his outspokenness. He never said things in a mean or vindictive manner, but always spoke his mind on a particular issue. Those colleagues fortunate enough to have known Mark had a friend in their corner for life. Those learners privileged to have taken his course or read his book had a teacher they will never forget.

Mark has left a legacy that will guide our specialty for many years to come.

DOI: 10.15420/aer.2017.6.1:PP10

Shared Moments

Professor Wellens has written memorials about Mark Josephson for Heart Rhythm and European Heart Journal and has also prepared a book about the Josephson school.

“I remember many moments from the 40 years that Mark and I worked together. This is one from a drink together after a long day of giving a course.”

— Hein Wellens —
University of Maastricht, the Netherlands

DOI: 10.15420/aer.2017.6.1:PP11
In patients with syncope or episodes of palpitations and heart disease, an electrophysiology study (EPS) may be of value by means of potential induction of sustained ventricular tachyarrhythmias.1,2 Programmed ventricular stimulation may be useful in the context of risk stratification of ischaemic patients with left ventricular ejection fraction (LVEF) 30–40 %, and there has been some evidence that it might also be of predictive value in revascularised patients with ST-segment elevation myocardial infarction and LVEF ≤30 %.3,4 In patients investigated for bradycardias, either due to sinus node or atrioventricular (AV) conduction disturbances, the role of EPS is not well defined. Most of the time, the criteria used for indications of permanent pacing are symptoms and electrocardiographic findings. However, there are certain occasions on which an EPS is mandatory either for the establishment of diagnosis or for appropriate implementation of prophylactic pacing.

Sinus Bradycardia
Early studies on limited patient cohorts had suggested that corrected sinus node recovery time (c-SNRT) may be useful in predicting the development of syncope and the need of permanent pacing in patients with bradycardia. A marked prolongation of the c-SNRT and an absent or blunted response to atropine and exercise suggest impaired sinus node function.5 However, a wide range of ‘normal’ c-SNRTs has been published, and it seems that only very prolonged c-SNRTs (>800 ms) have reasonable predictive ability.4 When considering conventional upper limits, such as 500–550 ms, the sensitivity of the test in asymptomatic patients with dizziness or no symptoms who will need a pacemaker in the future is only 50–65 %.6 The sinoatrial conduction time (SACT) is an insensitive indicator, being prolonged in only 40 % of our patients with clinical findings of sinus node dysfunction.7 The ACCF/AHA/HRS 2012 Guidelines on Device-based Therapy recommend EP testing in patients with syncope of unexplained origin for the detection of clinically significant abnormalities of sinus node function (IIa-C indication for permanent pacing),8 whereas the ESC 2013 Guidelines on Pacing and Cardiac Resynchronization Pacing do not consider the value of EPS established in this setting.9

AV Conduction Disturbances

Diagnosis
The ECG appearance of first- or second-degree block may be due to junctional (His bundle) extrasystoles that are concealed (not conducted to the atria or ventricles), but render a portion of the conduction system refractory to propagation of a sinus beat. The observance of junctional premature depolarisations on the surface ECG suggests that concealed His bundle extrasystoles are responsible for the apparent A-V block, but a His-bundle recording is the only method of positive identification (see Figure 1).

Anatomic Site of Block
High-grade block can occur anywhere in the AV conduction system, and the width of the QRS complex and the configuration of conducted beats and/or escape beats are of only limited value in localising the site of block. A narrow QRS complex is most compatible with an AV nodal or infra-His problem, and a wide QRS complex is most compatible with an infra-His problem; however, a wide QRS complex certainly may occur with A-V nodal or infra-His disease in the presence of coexistent bundle branch block.10 Approximately 70 % of type II blocks (i.e. consecutive, non-conducted P waves without changes in the PR interval) are associated with bundle branch block, whereas 30 % are associated with a narrow QRS complex, and are therefore within the His bundle.11 All type II blocks are infranodal, i.e. below the AV node or N zone, but not all infranodal blocks are type II blocks.12 Although 2:1 or higher degrees of block (e.g. 3:1 and 4:1) have traditionally been classified as type II block, the site of those blocks cannot be reliably determined by the surface ECG. A 2:1 block in the context of bundle branch block does not necessarily indicate infranodal block, since in 15–20 % of patients the block is in the AV node. Thus pacing may not be required in asymptomatic patients with this pattern and an EPS may be useful (see Table 1). Symptomatic patients with type I block and a bundle branch block should also be considered for an EPS to determine the site of block. Multiple levels of A-V block spontaneously or during pacing may also coexist in the same patient, and they can produce a confusing ECG picture that is extraordinarily difficult to
Specific loss-of-function SCN5A mutations demonstrate varied competing gating effects that reduce sodium current density and enhance slow inactivation with selective slowing of conduction velocity, in a way that may result in isolated progressive conduction system disease without provoking tachyarrhythmias. Initial EPS in mutation carriers with AV block revealed prolonged HV but normal A-H intervals, thus suggesting infra-Hisian block, but progressive AV block due to SCN5A mutations can be both supra- and infra-Hisian. Thus, an EPS may be useful in this setting. Several different types of muscular dystrophies, such as Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy (Erb’s muscular dystrophy), myotonic dystrophy type 1 (Steinert’s disease) and desmin-related myopathy, are also associated with progressive conduction defects. An EPS may identify patients in need of permanent pacing, and improve survival of these patients.

**Prediction of High-Grade AV Block**

**H-V Intervals**

Bifascicular block, specifically right bundle branch block (RBBB) with left-axis deviation, is the most common ECG pattern preceding complete heart block in adults. Early studies on patients with bifascicular or trifascicular block have reported an overall incidence of progression to complete heart block of approximately 1–2% per year. Patients with syncope, in particular, may have a 17% cumulative incidence of complete AV block within the next 5 years. The evaluation of the patient with bundle branch block or fascicular block necessarily involves testing the integrity of the remaining fascicle, and the simplest method of assessing this His–Purkinje reserve is the measurement of basal H-V intervals (normal <55 msec). In the presence of bundle branch block, with or without additional fascicular block, the H-V interval should be normal as long as conduction is unimpaired in the remaining fascicle. Most patients developing complete infra-His block have prolonged H-V intervals (>70 ms), and prolongation of the HV interval by ≥13 ms is strongly associated with AV block following transcatheter aortic valve replacement. Thus, analysis of H-V intervals was the factor initially evaluated as a predictor of subsequent heart block. However, an H-V interval >70 ms may not independently predict development of complete heart block, and approximately 50% of patients with RBBB and left anterior hemiblock, and 75% of patients with left bundle branch block (LBBB) have prolonged H-V intervals. This finding alone, therefore, is nonspecific as a predictor of the development of high-grade heart block, because the incidence of heart block is low, yet the presence of prolonged H-V interval is great. In our experience, approximately 70% of patients with H-V intervals ≥100 msec, develop second- or third-degree infra-His block within the next two years. However, H-V intervals in excess of 100 msec are uncommon. Thus, such marked H-V prolongation, although highly predictive, is insensitive.
Diagnostic Electrophysiology & Ablation

Figure 3: Prolonged P-R Interval with a Normal H-V Interval

The P-R interval is 290 msec, and the QRS complex is prolonged with a pattern of right bundle branch block and left anterior fascicular block. The H-V interval is normal at 45 msec, but the A-H interval is prolonged at 210 msec. Reproduced with kind permission from Josephson, 2016. 

Figure 4: Normal H-V Interval in Left Bundle Branch Despite P-R Prolongation and Marked QRS Complex Widening

The P-R interval is 230 msec and QRS complex 210 msec, yet the H-V interval is normal (50 msec). The P-R prolongation is due to A-V nodal delay (A-H interval = 150 msec). Reproduced with kind permission from Josephson, 2016.

Of note, the surface ECG may not allow accurate assessment of the H-V interval. Although a short P-R interval (i.e. ≤160 msec) makes a markedly prolonged H-V interval (i.e. ≥100 msec) unlikely, and a P-R interval of >300 msec almost always means at least some AV nodal conduction abnormality, intermediate values do not correlate with the H-V interval (see Figure 2). In the presence of RBBB and left anterior hemiblock or LBBB with or without left anterior hemiblock, a normal P-R interval can easily ‘conceal’ a significantly prolonged H-V interval, and a prolonged P-R interval can be the result of a prolonged A-H interval only (see Figure 3). Most patients who have LBBB have prolonged H-V intervals, regardless of the length of the accompanying P-R interval. Conversely, a long P-R interval does not automatically mean a long H-V interval (see Figure 4).

Pharmacological Challenge

The administration of pharmacological agents known to impair His–Purkinje conduction (e.g. procainamide) may unmask poor His–Purkinje system reserve. In normal persons as well as in most persons with moderately prolonged (55–80 msec) H-V intervals, procainamide typically produces a 10–20 % increase in the H-V interval. An increase of greater magnitude, including (a) doubling of the H-V interval, (b) a resultant H-V interval exceeding 100 msec, or (c) the precipitation of second- or third-degree infra-His block, all represent evidence of propensity for spontaneous infra-His block (see Figures 5 and 6). However, the incidence of provocation of AV block by procainamide is low, and the test may be useful in cases with borderline prolongation of the H-V interval but its diagnostic yield is rather limited.

Other drugs may also be used in order to provide additional information about the His-Purkinje reserve. If the conduction improves with atropine or exercise, or worsens with carotid sinus massage, the block is in the AV node. If the conduction worsens with atropine or exercise or improves with carotid sinus massage, the block is in His or bundle branches. The value of adenosine or ATP testing for induction of asystole due to latent sinus nodal disease AV block in patients investigated for unexplained syncope is not established, and these drugs have little or no effect on the His-Purkinje system. However, there has been evidence that induction of cardiac pauses (due to AV block or sinoatrial block >10 sec by an IV bolus of 20 mg ATP) indicates the need for DDD pacing in patients with unexplained syncope. Adenosine may also be used although its effects are not identical to those of ATP.

Atrial Pacing

The use of atrial pacing to stress the His–Purkinje system may provide further information beyond that of the basal H-V interval. Most normal patients will not exhibit second- or third-degree infra-His block at any time during incremental pacing, particularly at rates less than 150 bpm.
Physiologically, this occurs because the shortening of His–Purkinje refractoriness had decreased paced cycle lengths or because A-V nodal block developed at shorter paced cycle lengths, which thus protects the His–Purkinje system, even H-V prolongation during atrial pacing at rates less than 150 bpm. Second- or third-degree block within the His–Purkinje system in the absence of a changing A-H interval at paced cycle lengths of 400 msec or greater is abnormal and suggests a high risk for A-V block (see Figure 7). In patients who develop block distal to the His bundle induced by atrial pacing at rates of 150 bpm or less, there is a 33% progression to high-grade A-V block within the next 3 years. However, data on this procedure, in order to guide the decision for permanent pacing, are limited.

Table 1 presents current recommendations of learned societies for the utility of EPS in the selection of patients with AV conduction disturbances for permanent pacing. In Table 2 we have summarised all
Table 2: indications for Electrophysiology Study of Atrialventricular Block

1. Suspicion of concealed AV junctional extrasystoles
2. Asymptomatic type I second degree AV block with bundle branch block
3. Asymptomatic second degree AV block with bundle branch block
4. Questionable diagnosis of type II block with a narrow QRS complex
5. Suspicion of bradycardia-dependent (phase 4) infranodal block
6. Transient second degree AV block with bundle branch block in patients with inferior myocardial infarction where the site of block is suspected to be in the His-Purkinje system rather than the AV node
7. Third degree AV block with a fast ventricular rate
8. Progression of conduction disease due to neuromuscular disorders or suspected SCOSA mutations

indicators of EPS for diagnostic purposes in patients with apparent or suspected AV conduction abnormalities.

Conclusion

In sinus bradycardia the role of EPS is not established. In AV conduction disturbances, there are certain occasions in which an EPS is necessary for the appropriate diagnosis, and allows both the avoidance of unnecessary permanent pacing and the appropriate implementation of prophylactic pacing.

Clinical Perspective

• The value of electrophysiology studies in patients with sinus bradycardia is not established. A marked prolongation of the corrected sinus node recovery time (>800 ms) is a highly predictive but insensitive sign for sick sinus syndrome.

• In patients with atrioventricular node conduction disturbances an electrophysiology study may be necessary to define the site of block.

• An H-V interval >70 ms is a nonspecific predictor of development of high-grade atrioventricular block. An H-V interval >100 ms is highly predictive but insensitive.

• Adenosine triphosphate/adenosine, procainamide and atrial pacing have a rather limited diagnostic yield in patients with AV conduction disturbances.
Mahaim Accessory Pathways

Demosthenes G Katritsis,1 Hein J Wellens,2 Mark E Josephson3

1. Athens Euroclinic, Athens, Greece, 2. Cardiovascular Research Institute, Maastricht, the Netherlands, 3. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

Abstract
The term Mahaim conduction is conventionally used to describe decrementally conducting connections between the right atrium or the AV node and the right ventricle in or close to the right bundle branch. Although such pathways are rare, their unique properties make their diagnosis and treatment cumbersome. In this article we review the published evidence, and discuss the electrocardiographic and electrophysiological characteristics as well as the anatomy and origin of these fibres.

Keywords
Mahaim; accessory, pathway

In 1941, Mahaim and Winston described the histology of anomalous connections that arise from the AV node and insert into the right ventricle.1 This was the first description of nodoventricular or so-called Mahaim accessory pathways. Accessory pathways with decremental conduction properties that connected the atrium to the right bundle branch (RBB) were subsequently mapped mainly at the lateral aspect of the tricuspid annulus, and thus the term atriofascicular was also adopted.2-4 We know now that decrementally conducting connections can be between the right atrium or the AV node and the right ventricle in or close to the RBB.5-7 Thus, although they are anatomically distinct from the initially described nodoventricular pathway, they present with similar electrocardiographic and electrophysiological characteristics and the term ‘Mahaim’ has been adopted to describe pathways with the following features:

- Baseline normal QRS or different degrees of manifest pre-excitation with left bundle branch block morphology;
- Programmed atrial pacing leading to obvious manifest pre-excitation following an increase in A-V interval along with shortening of H-V interval at shorter pacing cycle lengths; and
- Right bundle electrogram preceding His bundle activation during anterograde pre-excitation and supraventricular tachycardia (SVT).

Although such pathways are rare, their unique properties as well as the still unanswered questions about their true nature, make them particularly interesting from an electrophysiological point of view.8

Electrocardiographic Features

ECG During Sinus Rhythm
During sinus rhythm overt pre-excitation is usually absent (see Figure 1). Only subtle ECG abnormalities, such as an R5 pattern in lead III, absence of septal Q waves in leads I and V6, and terminal QRS slurring or notchting, suggest the presence of Mahaim conduction.9,10 However, patients with short, rapidly conducting fibres may have typical pre-excitation.10

ECG during tachycardia
Although, typically, antidromic atrioventricular reentrant tachycardia over a Mahaim fibre has a left bundle branch (LBBB) morphology (see Figure 2), various QRS patterns and axis may occur (see Figure 3).4,9 It seems that these pathways insert into or near the RBB, and variations in the frontal plane axis can be explained by the location of the exit of the RBB and a variable degree of fusion of ventricular activation between anterograde conduction over the pathway and, following retrograde invasion into the RBB, partial anterograde left ventricular activation over the left-sided conduction system, especially the anterior fascicle (see Figure 4). The various QRS patterns and rate changes seen during the change from short to long V-A tachycardia can be explained by the mode of retrograde conduction over the bundle branch system.6,7

Electrophysiological Properties

Nodoventricular or Atiofascicular?
Although the first case of this arrhythmia was studied electrophysiologically by Wellens and published in 1971, and considered to be based on a nodo-ventricular pathway,11 with the advent of surgical and then catheter ablation in the 1980s, it was discovered that most fibres with Mahaim conduction characteristics originated at the lateral aspect of the tricuspid annulus, and the term atriofascicular pathway was adopted.2,5,12-17 However, postero septal locations could also be found.2-4 and true nodoventricular fibres have been identified (see Figure 5).11,14,15 In addition, some of these pathways, so-called ‘short’ as opposed to ‘long’ Mahaims, may insert at the ventricle near rather than in the RBB.3,5-7 Thus, pathways with Mahaim characteristics can be atriofascicular, atrioventricular, nodofascicular and nodoventricular, depending on their variable proximal and distal insertions.

Origin
The electrocardiographic properties of Mahaim pathways are not uniform, and this may reflect the diversity of the limited histology findings.1,5,16 It seems that most, but not all, of these pathways represent duplications of the AV nodal conducting system and contain nodal
Figure 1: ECG during Sinus Rhythm and Atrial Pacing Demonstrating Characteristics of Mahaim Conduction

Figure 2: Induction of Tachycardia by Atrial (left panel) and Ventricular Pacing (right panel)

Figure 3: 12-lead ECG of Three Different Patients with Antidromic Tachycardia

Figure 4: Change in QRS Morphology from Short to Long V-A Atioventricular Re-entrant Tachycardia

Catheter Ablation

Mahaim pathways are typically decremental and conducting only anterogradely. However, retrogradely conducting nodoventricular pathways have been described. Whether such pathways are classified as “true” Mahaims is a matter of terminology rather than essence. Catheter ablation is accomplished by identifying the proximal tissue, and their association with the R3-2Q mutation in PRKAG2 has been considered as an indication that this gene is involved in the development of the cardiac conduction system. They may display spontaneous or post-ablation automaticity, may respond to adenosine but not to verapamil, and their properties may depend on their location and insertion site.

Catheter Ablation

Mahaim pathways are typically decremental and conducting only anterogradely. However, retrogradely conducting nodoventricular pathways have been described. Whether such pathways are classified as “true” Mahaims is a matter of terminology rather than essence. Catheter ablation is accomplished by identifying the proximal tissue, and their association with the R3-2Q mutation in PRKAG2 has been considered as an indication that this gene is involved in the development of the cardiac conduction system. They may display spontaneous or post-ablation automaticity, may respond to adenosine but not to verapamil, and their properties may depend on their location and insertion site.

From left to right: superior, horizontal and normal frontal plane QRS axis ablated from the same sector of the tricuspid annulus (site of ablation between 7 o’clock and 3 o’clock). Reproduced from Sternick et al, 2014, with kind permission.

A: During short V-A AVRT (tachycardia cycle length 300 ms), there is also anterograde activation over the left anterior fascicle to produce a fused QRS complex with a normal axis. B: With retrograde right bundle branch block, anterograde conduction over the left anterior fascicle is no longer possible and conduction to the left ventricle proceeds only via the right free wall. Therefore, the long V-A AVRT (tachycardia cycle length 350 ms) has a leftward axis. During the change from short V-A AVRT to long V-A AVRT, the QRS width also increases from 120 to 150 ms. A: atrial electrogram; AF: anterior fascicle; AVN: atrioventricular node; AVRT: atrioventricular reentrant tachycardia; CSp: proximal coronary sinus catheter; HBE: His bundle catheter; HRA: high right atrium catheter; LBB: left bundle branch catheter; M: Mahaim potential; PF: posterior fascicle; RB: right bundle potential; RVA: right ventricular apex catheter; V-H: ventriculo-His interval. Reproduced from Gandhavadi et al, 2013, with kind permission.
and distal insertions and, ideally, the recording of a proximal pathway potential at the tricuspid annulus or a distal one on the right ventricular free wall (see Figure 6).Pathway potential recording may be facilitated during atrial pacing. Since most of the Mahaims are mapped on the lateral tricuspid annulus or right free wall underneath the valve, the use of supportive long sheaths that stabilise the ablating catheter may be very helpful.

Rare true nodoventricular pathways may also be ablated with preservation of AV nodal conduction.

Conclusion

Mahaim pathways are decrementally conducting connections between the right atrium or the AV node and the right ventricle in or close to the right bundle branch. They can be atriofascicular, atrioventricular, nodoaortic, and nodoventricular, depending on their variable proximal and distal insertions. Catheter ablation is accomplished by identifying the proximal and distal insertions and, ideally, the recording of a proximal pathway potential at the tricuspid annulus or a distal one on the right ventricular free wall.

Clinical Perspective

- Mahaim pathways are decrementally conducting connections between the right atrium or the AV node and the right ventricle in or close to the right bundle branch.
- The baseline QRS is normal or displays different degrees of manifest pre-excitation with left bundle branch block morphology.
- Programmed atrial pacing leads to obvious manifest pre-excitation following an increase in A-V interval along with shortening of H-V interval at shorter pacing cycle lengths, and right bundle electrogram preceding his bundle activation during antegrade pre-excitation and reentrant tachycardia.
- Catheter ablation is accomplished by identifying the proximal and distal insertions and, ideally, the recording of a proximal pathway potential at the tricuspid annulus or a distal one on the right ventricular free wall.
Diagnostic Electrophysiology & Ablation


Elleröggen KA, Rogers R, Old W. Pharmacological characterization of conduction over a Mahaim fiber.


Giazitzoglou E, Katritsis DG. Wide-QRS tachycardia inducible by both atrial and ventricular pacing. *Hellenic J Cardiol* 2008;49:446–50. PMID: 19110934

A simply phenomenal course! My knowledge has improved tremendously...shedding a new light and bringing us out of the dark ages of the pure angiogram.

Dr. Surendra Avula  Christ Medical Centre, Illinois.

facebook.com/simpleeducation.co
Twitter @EducationSimple

The best outcome for your patient may just take a Moment.

At SIMPLE education unique educational Moments have been created giving access to the latest case studies, webinars, reviews, and publications. SIMPLE can also provide all course information and online post-course content from the SIMPLE education essential guides.

SIMPLE education essential guides are established as the premier global courses in the latest state-of-the-art interventional cardiology. Featuring some of the world’s leading consultant cardiologists, the online post-course Moments access enables you to experience all the learning resources, including video content from the course talks and live case transmissions.

SIMPLE education – Providing access to invaluable knowledge and insight from leading cardiologists.

- Dynamic content from leading cardiologists
- Live Case Transmissions
- Speakers’ Slide Decks
- On-demand web interface
- Course Certification
- Radcliffe Cardiology Journals

Take a look around our Courses, Moments and Webinars at www.simpleeducation.co
ESC CONGRESS
BARCELONA 2017
26 – 30 August
Where the world of cardiology comes together

SAVE ON REGISTRATION
Early registration deadline - 31 May
Late registration deadline - 31 July

Become an ESC Professional Member & save €125 more
+ benefit from a dedicated Members’ Lounge
and exclusive networking opportunities