Conquest of Ventricular Tachycardia: Insights Into Mechanisms, Innovations in Management

Contribution of Mark E. Josephson, MD, to Clinical Electrophysiology

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Cardiac Mapping in Ventricular Tachycardia

Mohammad Shenasa, MD

Cardiac mapping has always been an integral part of basic and clinical electrophysiology. Indeed, direct cardiac mapping with recording of local electrograms has been used since the early 19th century, well before intracardiac catheter mapping.[1,2] Walter H. Gaskell measured cardiac contraction to investigate the sequence of cardiac activation.[1] Thomas Lewis used direct electrogram mapping in a dog model with atrial and ventricular arrhythmias (Figure 1).[2] Intraoperative direct epicardial and endocardial mapping was later reported in patients with preexcitation syndromes and conduction disturbances, initially by the Amsterdam group[3]; however, systematic use of endocardial and epicardial mapping for ventricular tachycardia (VT) was pioneered by Josephson and colleagues at the University of Pennsylvania, although epicardial mapping was reported earlier by Fontaine et al.[4–8] These reports greatly improved our understanding of pathophysiology and mechanisms of VT initially in patients with coronary artery disease and previous myocardial infarction. Intraoperative endocardial mapping revealed that reentry circuits were often localized on the endocardial surface or subendocardially and that resection of those regions eliminated the substrate of VT.[9,10] These intraoperative studies led directly to the techniques we use in catheter ablation of VT today and has been applied to other VT substrates.

In modern interventional electrophysiology, cardiac mapping and imaging are integrated, and this merging is critical for success in complex ablation procedures. However, electrogram mapping remains an essential part of physiological understanding of the mechanism(s) of VT. The Penn group has set standards for electrogram characteristics, such as normal versus abnormal electrograms, amplitude, duration, ratio of amplitude to duration, and fractionation.

Thanks to the Philadelphia and Maastricht pioneers for their scientific achievements and paving the way for today's cardiac mapping and electrophysiology.

Surgical Therapy for VT

John Miller, MD

In the mid-1970s, the discipline of clinical cardiac electrophysiology was in its infancy but experiencing tremendous expansion of knowledge about arrhythmia diagnoses and mechanisms. With this came the hope that therapies for challenging rhythm disturbances, such as postinfarction VT, could be devised. When few other electrophysiologists had the interest or nerve to methodically study VT in man, Josephson et al[9,10] showed that postinfarct VT (1) was because of reentry, (2) occurred in a circuit that was in a fixed location, (3) was related to the region of the scar, and (4) tended to be on the endocardial surface. These facts were assembled into a strategy to treat the arrhythmia by surgically damaging or removing the tissue responsible for it. This involved opening a living patient's left ventricle (LV) at surgery, performing activation mapping during VT, and surgically removing those small portions of the endocardium.[11] Removal or resection of the endocardium (the Pennsylvania Peel) as determined by mapping was then undertaken, followed by attempts at reinitiating VT.

These studies went on to refine the nature of the postinfarct VT circuit: evidence accumulated that at least a critical portion of the circuit was usually superficial on the endocardial surface, in that (1) removal of small amounts of endocardial tissue (2–4 cm^2 and only 2 mm thick) at the edge of a scar or aneurysm as defined by mapping could eliminate VT inducibility; (2) focal pressure with the mapping electrode could slow or terminate VT; and (3) removal of tissue from which diastolic electrograms were recorded in VT (that correlated with late potentials during sinus rhythm) caused disappearance of these potentials when the (disconnected) tissue was set back in situ and recordings from the same sites were repeated (Figure 2).[12] Importantly, although the target tissue for surgical ablation contained diastolic potentials, not all diastolic potentials were involved in the VT circuit.

Early in their experience, although the success rate with anterior infarction was good (88%), it was only 60% with inferior infarction.[13] After carefully analyzing the results of

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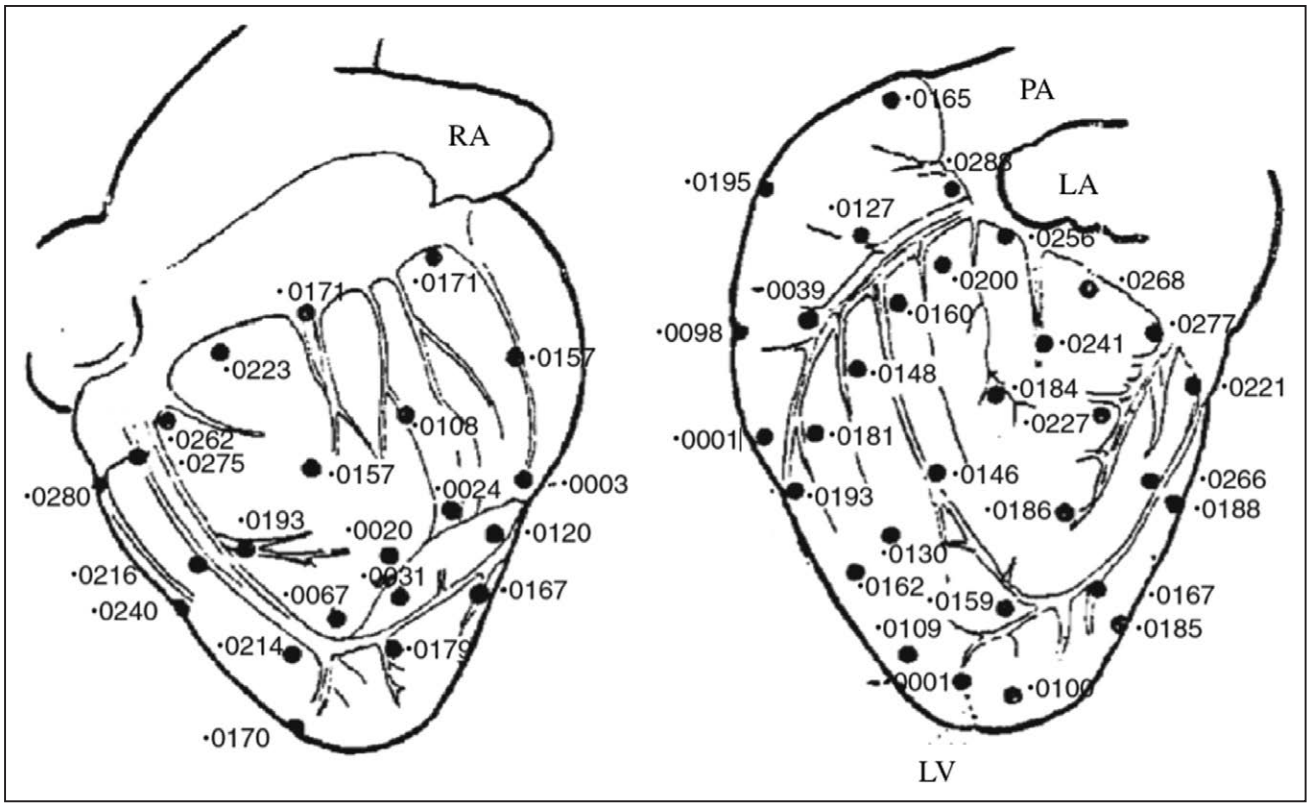

Figure 1. Thomas Lewis's activation map for direct electrogram recording in a dog heart.[2] DBL indicates descending branch of left (coronary artery); DBR, descending branch of right (coronary artery); IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; and SVC, superior vena cava.

mapping, they hypothesized that reentry occurred around the inferior scar (instead of at its edge), incorporating a surviving isthmus of muscle between scar and mitral annulus. The surgeon did not typically remove scar at this basal location out of concern for disrupting mitral valve function, and thus, the critical isthmus often escaped the surgical process, resulting in persistence of VT in many patients. Freezing this area with a cryoprobe resulted in a dramatic improvement in surgical success (Figure 3).[14]

Dr Josephson's bold, innovative work in devising a surgical solution for an otherwise almost hopeless arrhythmia has been a landmark development in cardiac electrophysiology. Although surgery is rarely used to treat VT in current practice, the principles on which surgical therapy was based, and lessons learned in the operating room, are the foundation for much of the current ablative strategies.

Sustained Monomorphic VT in Coronary Artery Disease

David Callans, MD

It seems impossible to imagine that the nature of VT in the setting of healed infarction was not clarified until the late 1970s. The electrophysiological mechanism and the cause of slow conduction (largely thought secondary to slow fibers in the field of infarction) were largely determined through the investigation of Josephson and coworkers. In the first of the iconic *Circulation* manuscripts comprising a manifesto on VT, 5 important physiological points were established: (1) VT was reproducible, initiated, and terminated with programmed electric stimulation (more than rapid pacing); (2) there was an inverse relationship between the extrastimulus coupling interval and onset of the first VT complex; (3) site dependence of initiation and termination was observed; (4) there was lack of involvement of proximal His Purkinje system; and (5) the VT circuit was small in size because the atrial overdrive pacing could capture the entire QRS without termination.[10] These observations were compatible with a reentrant mechanism (the final planks in the platform would eventually be continuous activity[15] and the response to stimulation during VT[16,17]) in a relatively small circuit that did not involve the proximal His Purkinje system.

LV mapping during sinus rhythm revealed the electrophysiological nature of slow conduction in the area of the healed infarct. Bipolar recordings were often low amplitude, late (compared with the surface QRS offset), and fractionated.[18] This correlated well with histological examination of the infarcted surgical specimen showing muscle bundles with reasonably intact cellular electrophysiology separated from adjacent bundles by fibrous scar.[19] This was the cause of slow conduction in the infarct that allowed for reentry. This realization, as well as catheter and intraoperative mapping during VT, established the obligate relationship of the VT circuit to the infarct substrate. This in turn led to successful surgical intervention for VT with subendocardial resection.[7] The results of this experience are remarkable, particularly in the context of the VT-free survival rates with catheter ablation. In

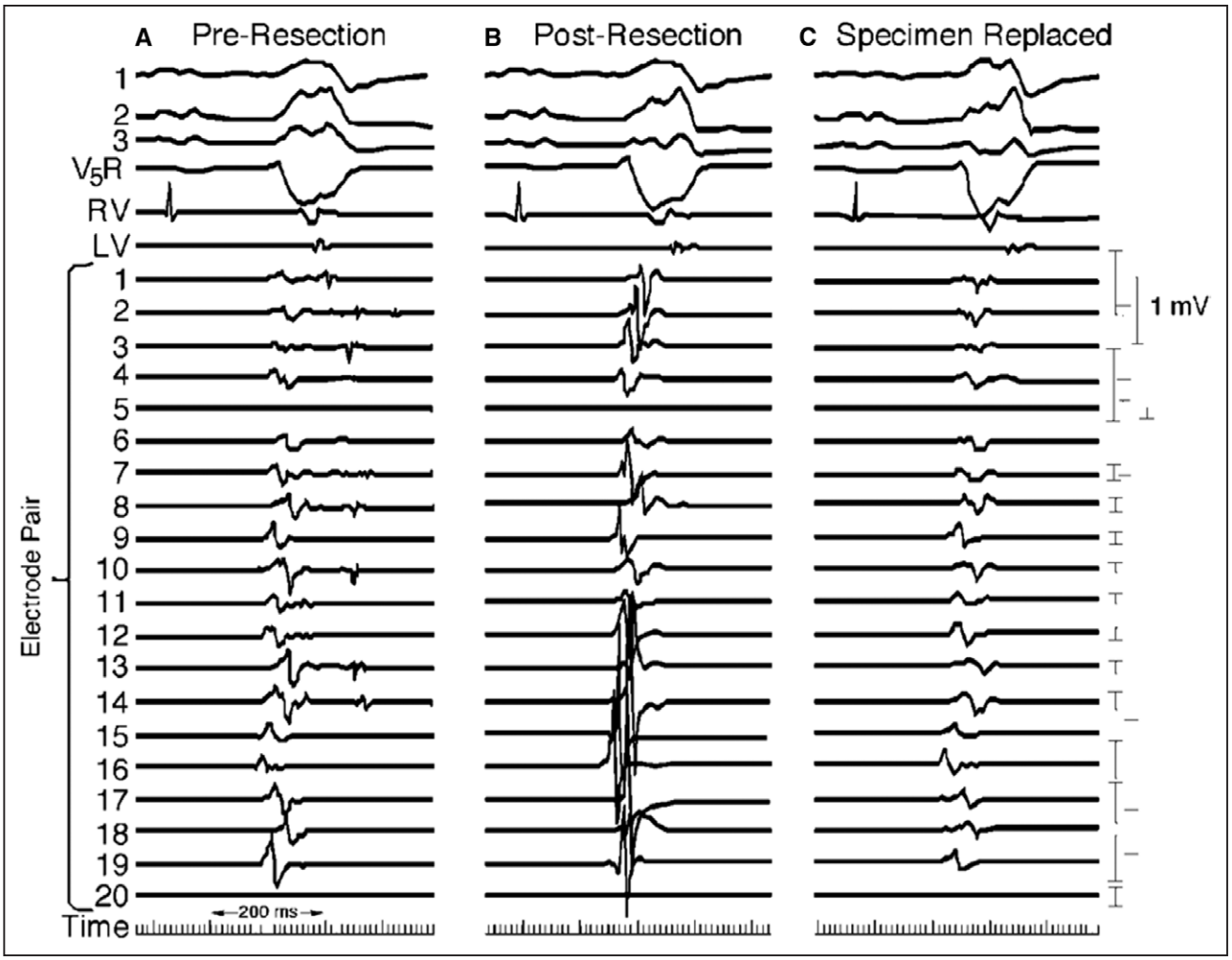

Figure 2. Bipolar recordings made from the infarct area a recording array with 1 cm interelectrode spacing before (**A**) and after (**B**) subendocardial resection and with the resected specimen replaced (**C**). The electrograms in **A** are markedly abnormal, with low amplitude, late and fractionated components; these abnormal components are not present after resection. After the resected specimen is replaced (**C**), the amplitude of the array recordings again resemble the main electrograms (without the fractionated and late components) observed in **A**. This observation demonstrates that slow conduction (marked by fractionated and late electrograms) is caused by the infarct substrate; resection removed the substrate for slow conduction and prevented ventricular tachycardia (VT). LV indicates left ventricle; and RV, right ventricle. Reprinted from Miller et al.[12]

this initial series, 28 patients (only 4 of whom were on antiarrhythmic drugs) were completely free from VT recurrence over a mean follow-up of 13.5±6 months.

The observations from mapping and the responses to stimulation during VT led to the development of strategies for catheter ablation of VT. Entrainment mapping was based on the physiology of the reentrant circuit initially described in the Mechanisms paper,[10] field tested by Stevenson et al.[20] Substrate mapping naturally followed from attempts to recapitulate the surgical experience,[21] as well as observations about electrogram characteristics that might mark VT circuit locations (Figure 2).[12] Mark Josephson engineered a true proof-of-concept randomized trial of ablation, the SMASH-VT trial (Substrate Mapping and Ablation in Sinus Rhythm to Halt VT), demonstrating for the first time that largely substrate-based ablation could prevent recurrent VT.[22]

The timeline represents decades of work, which continues at the time of this writing. Recent insightful investigations include a detailed analysis of the recording strategies central to voltage mapping[23] and using a new mapping technology to stare into the soul of the VT circuit.[24] The logical progression is pure Josephson: understand physiology, make thoughtful hypotheses augmented by colleagues in basic science, and prove these hypotheses with insightful clinical research. We are greatly in his debt!

Resetting and Entrainment in VT

Jesus Almendral, MD

Resetting and entrainment of tachycardias are essentially similar, in that both phenomena result from an interaction of paced wave fronts with an ongoing tachycardia. They were studied in depth during VT by Josephson and his group.[16,17,25–35] The recognition of resetting during a regular rhythm is simple: the delivery of one extrastimulus that captures locally results in a relative pause that is different (usually less) than fully compensatory.[16] This occurs because the wave front generated by the pacing stimulus has interacted with the intrinsic rhythm. In order for this to occur, the wave front must be critically timed to encounter the circuit's excitable gap. The barriers for

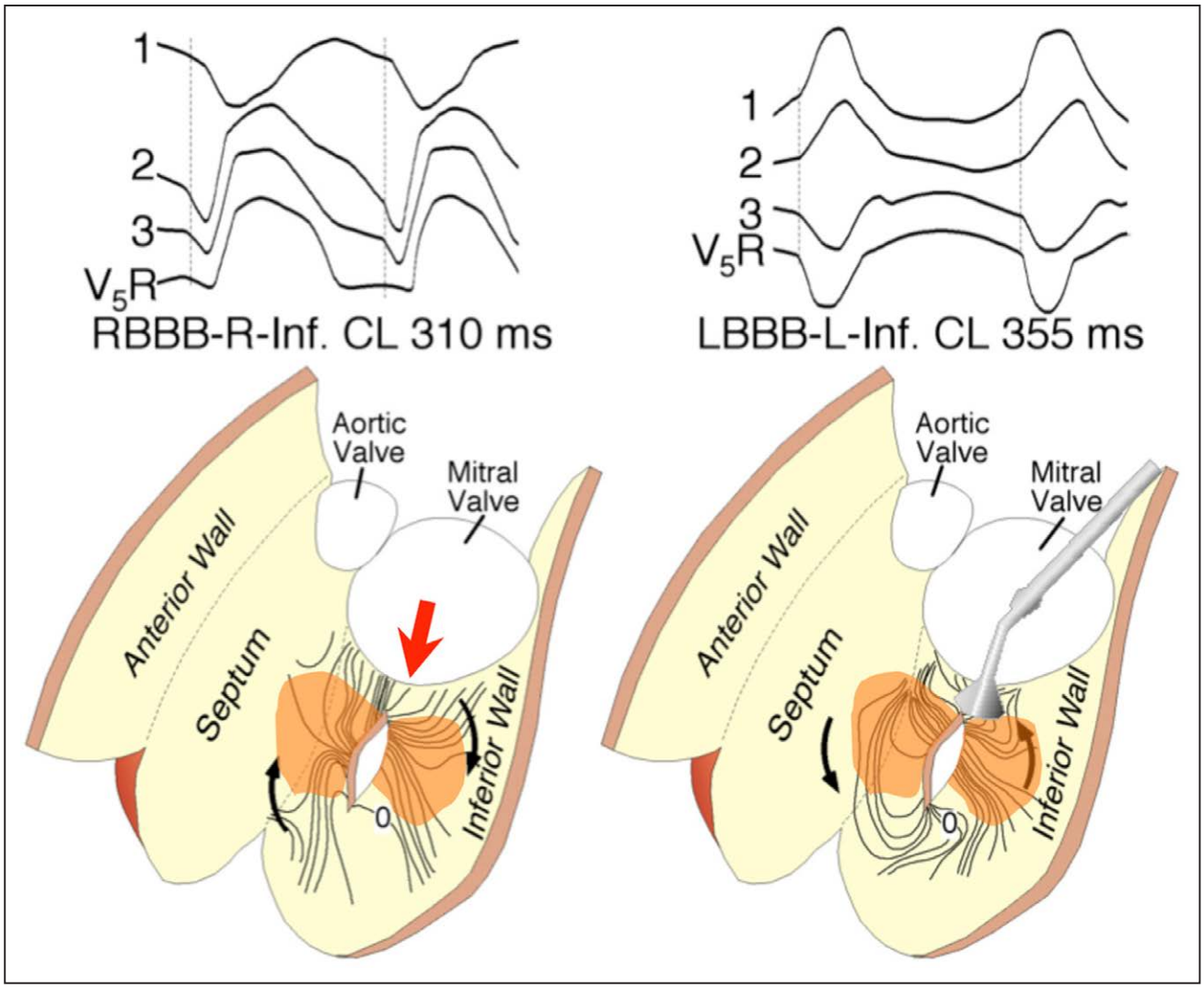

Figure 3. Two ventricular tachycardia (VT) morphologies of VT arising from an inferior myocardial infarction (MI) are shown; corresponding endocardial activation maps are displayed (**bottom**). Mapping demonstrates a clockwise rotation for the right bundle VT and a counterclockwise rotation in the same circuit for the left bundle VT; the 0 isochrone marks the QRS onset. The red arrow (**lower left**) shows the annular isthmus essential to propagation in both VTs. Orange areas indicate where endocardial resection was performed, sparing the annular isthmus area to avoid damage to mitral valve function, which is treated with cryoablation. inf indicates inferior; LBBB, left bundle branch block; and RBBB, right bundle branch block.

this to occur include local refractoriness and transit time from the stimulation site to the circuit. In an early study, resetting could be elicited by a single right extrastimulus in 47 out of 78 (60%) VT in 53 patients.[26] However, when 2 extrastimuli were introduced in a manner that only the second could interact with the circuit, the incidence of resetting increased to 79% (31 out of 39 patients with VT). In contrast to single or double stimulus during VT, entrainment involves continuous resetting of the reset circuit,[35] and as such, each paced wave front interacts with the previously reset circuit. As a consequence, the observed responses do not necessarily indicate the intrinsic characteristics of the circuit. The criteria for recognizing resetting and entrainment have been previously reported. Resetting and entrainment with the above criteria will differentiate focal from reentrant mechanism.[36–39] However, it is important to realize that entrainment can occur in the absence of any of the described criteria for its recognition.[39] In particular, concealed entrainment satisfies none of the classic criteria for entrainment.[39,40]

The presence of fusion during resetting or entrainment, demonstrated on either the surface ECG or intracardiac recordings, is the hallmark of reentry.[35] In addition,

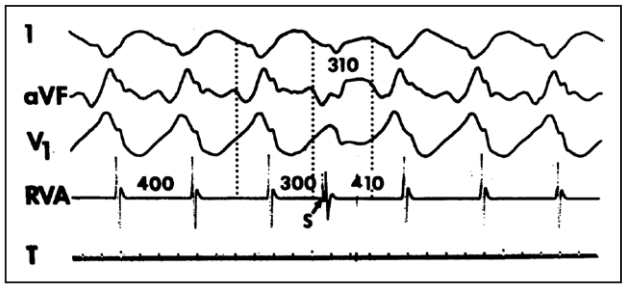

Figure 4. Prestimulus fusion. Note that the extrastimulus is delivered after the ventricular tachycardia (VT) QRS onset, but results in VT resetting. See text for details. Adapted from Josephson et al[35] with permission of the publisher. Copyright © 2017, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

prestimulus fusion was described[17,35] as a situation where an extrastimulus delivered after the onset of the ongoing VT QRS resulted in resetting (Figure 4).[35] In this case, the ongoing VT contributes to the QRS because it had already begun when the extrastimulus was delivered. The extrastimulus captures locally and contributes to the ventricular activation because it modifies the QRS morphology. Thus, the QRS is the result of 2 wave fronts, that is, it is fused.

In summary, Josephson and his group studied resetting and entrainment during VT and described fundamental differences between these 2 phenomena, despite their essential similarities.

Use of the ECG to Localize VT

Frank Marchlinski, MD

The ability to use the 12-lead ECG recorded during VT to regionalize the VT origin was first described by Mark Josephson in 1981.[41] The paper in *Circulation* is epic in nature, with 15 pages in length and 11 multicomponent figures. Each figure shows one to five 12-lead ECG patterns during VT and identifies to the corresponding region of the VT circuit on the cardiac silhouette based on the 12-lead pattern. The gold standard in this report used for VT localization was detailed activation mapping during VT. Specific rules based on the 12-lead ECG pattern were described in patients with prior myocardial infarction. In a landmark follow-up article 7 years later, investigators attempted to identify the origin of the VT based on the 12-lead ECG during VT but were blinded to the mapping results.[42] One hundred and eighty-two VTs were evaluated in 108 patients with prior infarction. Using ECG information recorded during VT, including the configuration of the QRS complex in V1, the frontal plane axis, and the precordial QRS transition, the 4 investigators were asked to identify the region of origin. The LV was divided into 10 distinct anatomic regions. Importantly, the 4 investigators demonstrated a 93% concordance in assigning the VT to a specific anatomic region.

Of note, the VT QRS morphology in the setting of structural heart disease identifies the exit region of the VT circuit but does not identify the VT isthmus. Nevertheless, the use of the 12-lead ECG became the gold standard for identifying a region of interest at which to begin more detailed mapping to identify isthmus sites that might be appropriate for ablation in scar-related VT.

The 2 aforementioned articles on the use of the 12-lead ECG to identify the origin of VT would serve as the platform for a plethora of key articles that document the role of the 12-lead ECG in VT localization. We now use the 12-lead ECG recorded during VT to help identify an epicardial origin in the setting of a nonischemic cardiomyopathy. Delayed activation in the initial portion of the QRS at epicardial sites away from the Purkinje system and Q waves, where they are not anticipated, particularly in lead 1 in the setting of a basal lateral LV scar, are useful clues suggesting an epicardial origin.[43–45] The 12-lead ECG has also become an important tool for precisely localizing VT in the absence of structural heart disease. Algorithms for distinguishing idiopathic VT from the free wall versus septal aspects of the right ventricular outflow tract and distinguishing septal right ventricular outflow tract versus aortic root origin have been described.[46–51] The 12-lead ECG pattern associated with idiopathic VT from LV summit sites, mitral annular and LV epicardium sites in proximity to the distal great cardiac vein, the anterior interventricular vein, and the middle cardiac vein have all been also described in detail.[52–54] More recently, the 12-lead ECG patterns for triggers for ventricular fibrillation from the right ventricular and LV papillary muscles and right ventricular moderator band have been described.[55,56] We express a debt of gratitude to Dr Josephson who established the fundamental principles for analyzing the humble 12-lead ECG and unleashing its power for VT localization.

Clinical Trials Designed by Mark E. Josephson and His Colleagues

Alfred Buxton, MD

Over the course of his career, Mark Josephson directly participated in 23 multicenter trials. When one considers that his curriculum vitae lists over 500 original publications, this constitutes a fairly small representation of his overall contribution to medicine. He had a major role in the design and execution of 4 major trials: the MUSTT (Multicenter Unsustained Tachycardia Trial),[57,58] the SMASH-VT,[22] the FRACTAL (Fibrillation Registry Assessing Costs, Therapies, Adverse Events, and Lifestyle),[59] and the M-PATHY (Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy).[60]

What accounts for this relatively small involvement in multicenter studies, now considered almost mandatory for establishing and altering practice guidelines? There are several reasons. First, Mark Josephson's primary love and interest was in physiology and mechanisms of arrhythmias. It is extremely difficult to execute physiological investigations in patients. It is more difficult to expect multiple centers to adhere to detailed, exhaustive study protocols. Pragmatically, designing and executing multicenter clinical trials demands compromise. Mark hated to compromise when it came to study design and execution.

The origin of the MUSTT trial was due entirely to Mark. He repeatedly asked what our group at the University of Pennsylvania was doing about nonsustained VT. After >6 months of hearing this question raised at our daily meetings, I finally initiated design of the trial, and then with the intimate support of the other principal investigators (especially John Fisher, Eric Prystowsky, and Kerry Lee), under Mark's guidance, we successfully obtained National Heart, Lung, and Blood Institute funding. I have no doubt that Mark was supportive of the trial design because it was an attempt to ask physiological questions about the then current practice in electrophysiology. Since the late 1970s, Mark had said, "If we can induce it, you will have it…." None of us, especially Mark, was interested in performing a trial to determine whether one type of therapy or another improved survival of patients at risk for sudden death. Rather, this was a trial that questioned whether the then current practice (performing programmed stimulation in patients with nonsustained VT and reduced ejection fraction) resulted in improved survival. We also wanted to understand what were the chances of sustained

VT or cardiac arrest occurring in patients in whom sustained VT was induced but had never experienced a spontaneous sustained ventricular arrhythmia. Thus, this trial reflected many aspects of Mark's career: questioning current practices, trying to better understand physiology, and the prognostic implications of programmed stimulation.

Likewise, Mark originally conceived the SMASH-VT Trial to further understand our approach to VT or ventricular fibrillation occurring after myocardial infarction, an enduring interest of his. The concept behind the trial also reveals his longstanding aim to specifically treat VT or ventricular fibrillation, rather than using shotgun approaches, such as empirical pharmacological antiarrhythmic therapy or the implantable cardioverter-defibrillator (ICD). Although often labeled as anti-ICD, Mark was one of the earliest adapters of the ICD and was not in any way anti-ICD. In fact, early on, he sought to encourage incorporation of novel pacing modalities to improve the efficacy of the ICD and avoid shocks, a prescient move. He was steadfast in his opposition to indiscriminate, nonphysiological use of implantable devices and drugs. The outcome of this trial (showing significant reduction in subsequent ICD therapy in patients treated with catheter ablation) is likely due in part to Mark's skills in the clinical electrophysiology laboratory. Mark could not only manipulate catheters with a high degree of skill, but his ability to interpret intracardiac electrograms on the fly while in the laboratory was unparalleled.

I think the best way to characterize Mark Josephson's approach to multicenter clinical trials is that he was selective, participating when he felt there were important physiological questions being addressed; criticizing vigorously when he felt there were critical faults in the fundamental questions asked or trial design. He used clinical trials not to promote his own career, but rather to further the careers of younger colleagues. Thus, his relation to clinical trials mirrors his overall career in cardiac electrophysiology.

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KEY WORDS: cardiac mapping ■ clinical trials on ventricular tachycardia ■ ventricular tachycardia ablation ■ ventricular tachycardia mechanisms ■ ventricular tachycardia surgery

IN MEMORIAM

Mark E. Josephson, MD, died on January 11, 2017, after a long battle with cancer. Dr Josephson was a towering figure in cardiac electrophysiology whose careful investigations in the clinical electrophysiology laboratory and operating room shaped the field. Countless students and colleagues have been the beneficiaries of his unbridled enthusiasm for teaching at the bedside, in the laboratory, and at countless conferences spanning decades. He was a mentor and source of inspiration to a generation of cardiac electrophysiologists. He will be greatly missed.

Conquest of Ventricular Tachycardia: Insights Into Mechanisms, Innovations in Management: Contribution of Mark E. Josephson, MD, to Clinical Electrophysiology

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