INNOVATIONS IN VENTRICULAR TACHYCARDIA

RESEARCH ARTICLE

Catheter Ablation at the Forefront: The Tribulations of Clinical Trials

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ABSTRACT. Radiofrequency ablation (RFA) has become an essential component of ventricular tachycardia (VT) management. In the era of implantable cardioverter-defibrillators (ICDs), antiarrhythmic therapy and RFA are frequently required for patients with both primary prevention and secondary prevention indications for ICD implant. “VT ablation” encompasses ablation across a spectrum of various ventricular arrhythmias. In addition to ablation of monomorphic VT in the setting of structural heart disease, the evolving field also includes VT in structurally normal hearts (idiopathic VT), premature ventricular contractions (PVC) ablation (for symptoms and optimization of cardiomyopathy), and ablation of ventricular fibrillation via targeting of triggering PVCs. While these sub-categories of VT ablation represent significant advancement in the breadth of the field, the focus of this article is to review the evidence for catheter ablation of monomorphic VT in the setting of structural heart disease and to discuss future studies that are anticipated.

KEYWORDS. radiofrequency ablation, PAUSE-SCD, ventricular tachycardia.

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Introduction

Radiofrequency ablation (RFA) has become an essential component of ventricular tachycardia (VT) management. In the era of implantable cardioverter-defibrillators (ICDs),^{1–4} antiarrhythmic therapy and RFA are frequently required for patients with both primary prevention and secondary prevention indications for ICD implant. “VT ablation” encompasses ablation across a spectrum of various ventricular arrhythmias. In addition to ablation of monomorphic VT in the setting of structural heart disease, the evolving field also includes VT in structurally normal hearts (idiopathic VT), PVC ablation (for symptoms and optimization of cardiomyopathy), and ablation of ventricular fibrillation via targeting of triggering PVCs. While these sub-categories of VT ablation represent significant advancement in the breadth of the field, the focus of this article is to review the evidence for catheter ablation of monomorphic VT in the setting of structural heart disease and to discuss future studies that are anticipated.

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Current state

VT leading to ICD shocks is associated with significant decreased quality of life, worsening heart failure and increased mortality.^{4–6} While medical therapy with antiarrhythmic medications is traditionally prescribed as first-line therapy, the success rate of antiarrhythmics is modest and long-term use is often limited by significant side effects.⁷ Although the approach for scar-related VT ablation was initially developed to address VT after healed myocardial infarction, a greater proportion of patients referred have non-ischemic etiologies of structural heart disease. These conditions include myocarditis, hypertrophic cardiomyopathy, Chagas disease, sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy. A percutaneous epicardial approach developed by Sosa and colleagues¹⁰ has improved the ability to characterize the transmural predilection and extent of scarring and provides an additional therapeutic option for patients with failed endocardial ablation.⁸ While VT ablation was previously felt to be a high-risk and last-resort form of palliation, increasing experience has likely led to greater safety during the procedure. In a recent retrospective analysis assessing 9,699 discharge records, adverse event rates were seen in 8.5% and major adverse events in 3% with procedural death rates of 1.1%.⁹

VT RFA has consistently been shown to reduce VT recurrence and ICD shocks in the ischemic^{10–15} and non-ischemic population.^{16–18}

The majority of studies to date have been limited to single-center studies, registries, and small randomized trials. Early prospective registry data with currently available irrigated ablation technology such as the Multicenter Thermocool Ventricular Tachycardia Ablation Trial¹² suggested that early intervention was safe and effective. In this study, freedom from VT at 6 months was 53%, with a 3% procedural mortality and an associated mortality of 18% at 1 year in this patient population. The majority of earlier studies were conducted in post-myocardial infarction patients with nonischemic cardiomyopathy (NICM) patients excluded, and epicardial approaches were predominantly not undertaken.

The optimal timing of VT RFA is not well established, although current consensus guidelines support the use of ablation as an upfront approach as an alternative to antiarrhythmic therapy with a medication such as amiodarone.¹⁹ In the real world, many patients undergo VT RFA after admission for recurrent ICD therapies despite antiarrhythmics and electrical storm. Prophylactic VT ablation has been shown to prevent ICD therapies in the post-infarction setting in two randomized multicenter trials, the Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT)²⁰ and the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH).¹⁰ While SMASH-VT showed a significant reduction in ICD shocks in patients who received ICD for secondary prevention, the VTACH trial¹⁰ demonstrated similar benefit from ablation before ICD implantation in patients with tolerated VT.

Several single-center retrospective reports strongly suggest that earlier intervention may translate into improved clinical outcomes, highlighting the promising role of upfront ablation. Frankel et al.²¹ showed that earlier referral for ablation led to an improved 1-year survival free of VT. Hayashi and colleagues²² in a retrospective study demonstrated improved event-free survival after prophylactic VT ablation in a primary prevention population. Dinov et al.²³ demonstrated that early referral for VT ablation was associated with improved acute and long-term freedom from VT recurrence. In this study, VT recurrence was 37.3% if ablation was performed within 30 days of the first arrhythmic event, versus 61.9% in patients who had ablation >30 days to 1 year after the first event.

While the SMASH VT and VTACH trial were not powered to evaluate mortality benefit from catheter ablation, a 2011 meta-analysis²⁴ of four studies demonstrated a 35% reduction in VT and a non-significant trend towards reduced mortality with ablation with a relative risk of 0.76 (0.41–1.38; $p = 0.37$). The largest multicenter retrospective study to date by the International VT Ablation Center Collaborative Group reported a 70% freedom from VT at 1 year in patients with ischemic cardiomyopathy and non-ischemic etiologies.²⁵ Importantly, this analysis of 2,061 patients showed a consistent association between recurrent VT after catheter ablation and mortality, independent of ejection fraction and heart failure severity.²⁵ Greater differences in

mortality between patients who underwent successful ablation and those with recurrence were observed in sicker patients, suggesting the absence of a U-shaped curve with catheter ablation. Additional retrospective data suggest a mortality benefit from catheter ablation similar to rates seen in patients receiving ICD without any therapy for spontaneous VT.²⁶

Clinical Trials

Realistically, large prospective randomized trials comparing VT ablation with medical therapy are exceedingly difficult to recruit for given the fact that a large percentage of patients with VT present with electrical storm, at which point electing for medical therapy may not be a viable option. Studies that evaluate early intervention after an index event have the greatest potential to recruit patients before the VT burden becomes too high that it precludes randomization. However, patients with limited VT burden are frequently not referred by general cardiologists for consideration of ablation, as the prevailing view in the community is that the procedure is a palliative option of last resort.

Additionally, due to the tertiary nature of specialized VT ablation centers and the urgent nature of ICD shocks, significant referral pressures and biases frequently limit the ability to enroll patients into a randomization scheme. Many patients referred are highly selected and arrive with preconceived expectations or preferences that do not favor initiation or continuation of medical therapy. For these reasons, many well-conceived prospective multicenter randomized trials have closed due to slow enrollment. These trials include CEASE VT, ASPIRE, and most recently STAR VT.

The STAR-VT trial (Substrate Targeted Ablation using the Safire Flex Catheter Ablation System for the Reduction of Ventricular Tachycardia) is a prospective, multicenter, randomized controlled trial conducted in the United States and Europe, evaluating early intervention for spontaneous VT or inducible VT in patients with primary prevention indication for ICD implantation. The hypothesis is that an early scar-based VT ablation results in superior clinical outcomes than routine drug therapy with an acceptable safety profile. Importantly, non-ischemic etiologies will be included, and the ejection fraction cut-off is <50%. The inclusion of inducible VT after implantation of an ICD (St. Jude, Minneapolis, MN) with diagnostic electrophysiologic study or non-invasive programmed stimulation is a unique aspect to the study that will increase eligibility for randomization. Patients will be enrolled within 90 days of ICD implant.

With a target of over 500 patients randomized 1:1 to ablation with a novel open-irrigated ablation catheter (FlexAbility, St. Jude Medical, Minneapolis, MN) or standard medical therapy, an additional registry will be maintained for patients that are non-inducible for monomorphic VT at the time of ICD implantation. (Figure 2). The primary endpoint is freedom from ICD shocks with secondary endpoints evaluation shock burden, rehospitalization, quality of life, and mortality. In comparison to other randomized VT ablation trials, STAR VT was aimed at

evaluating the role of prophylactic ablation in a broader population outside of ischemic cardiomyopathy and earlier in the course of management with the inclusion of primary prevention at high risk for VT. Due to slow enrollment, with a low proportion of patients enrolled relative to the numbers screened, this study was halted this past month (Figure 1).

Currently, the PARTITA and VANISH trials (clinicaltrials.gov) are among the most successful trials that are currently ongoing in Italy and Canada, respectively. The PARTITA protocol, led by Paolo Della Bella, aims to assess whether the timing of VT ablation (immediate vs deferred) affects prognosis in patients with ICD. With an estimated enrollment of 590 patients, this study will evaluate a primary endpoint that includes time to first appropriate ICD shock, worsening heart failure, and mortality. The VT Ablation versus Enhanced Drug Therapy (VANISH) study completed enrollment in November 2015 with an estimated 260 patients with ischemic cardiomyopathy that were randomized to ablation or intensification of amiodarone for recurrent VT. We anxiously await the results of this important clinical trial this year.

As the majority of VT ablation reported experiences have been centered around the US and Europe, the role of catheter ablation in Asia is less well understood. With a population that is 4-5x the number at risk as the US, clinical trials in China, Korea, and Japan have the potential to overcome recruitment barriers. Additionally, there are financial and cultural barriers to ICD penetration in these countries, which creates an opportunity to gain more clarity on the magnitude of therapeutic benefit for both VT ablation with and without background ICD therapy.

The Pan-Asia United States Prevention of Sudden Cardiac Death (PAUSE-SCD) was initiated to assess the role of

preemptive VT ablation in patients with primary and secondary indications for ICD. Like STAR-VT, patients that are inducible for monomorphic VT at the time of ICD implantation are considered to be higher risk for recurrent VT and eligible for randomization. Importantly, patients with ARVC, dilated cardiomyopathy, and ischemic cardiomyopathy with EF <50% will be included for a 1:1 randomization of ICD implantation with optimal medical therapy versus ICD implantation with adjunctive catheter ablation. The procedural approach will consist of high density multielectrode mapping with entrainment and activation mapping of tolerated VTs. For untolerated VTs, regions of isochronal crowding with pacemap matches with scar (<1.5 mV) will be targeted primarily, with secondary targets of local abnormal ventricular electrogram. With a target enrollment of 120 patients at 8 centers across Asia (China, Japan, and Korea), the primary endpoint will be ICD therapy with secondary endpoints that include hospitalization and mortality at 2 years (Figure 2).

Summary

Retrospective studies and a limited number of prospective studies to date have established VT ablation as an important therapeutic modality for management of VT in patients with structural heart disease and previous ICD implant. However, prospective studies are necessary to determine the optimal timing of VT ablation and the potential impact that it may have on mortality by reducing ICD shocks.

Numerous international multi-center ablation trials have been closed due to slow enrollment that results from referral and selection bias at specialized tertiary centers. The paucity of randomized clinical trials is currently impeding the growth of this evolving field.

Comparisons of VT Trials

Figure 1: Comparisons of ventricular tachycardia trials.

Figure 2: PAUSE-SCD Protocol.

Ongoing multi-center trials PARTITA, VANISH, and PAUSE-SCD have placed VT ablation at the forefront of clinical investigation and has promise to further advance the field on a global level.

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