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Catheter Ablation of Ventricular Tachycardia: Lessons Learned from Past Clinical Trials and Implications for Future Clinical Trials

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Abstract

Catheter ablation of ventricular tachycardia (VT) has evolved in recent years, especially in patients with ischemic heart disease. Data from prospective studies show that VT catheter ablation reduces the risk of recurrent VT; however, there is paucity of data on the effect of VT catheter ablation on mortality and patient centered outcomes such as quality of life. Performing randomized clinical trials of VT catheter ablation can be fraught with challenges, and as a result, several prior trials of VT catheter ablation had to be stopped prematurely. The main challenges are inability to blind the patient to therapy to obtain a traditional control group, high cross-over rates between the two arms of the study, patient refusal to participate in trials in which they have an equal chance of receiving a “pill” versus an invasive procedure, heterogeneity of mapping and ablation techniques as well as catheters and equipment, rapid evolution of technology that may make findings of any long trial less relevant to clinical practice, lack of consensus on what constitutes acute procedural and long-term success, and presentation of patients to electrophysiologists late in the course of their disease. In this paper, a panel of experts on VT catheter ablation and/or clinical trials of VT catheter ablation review challenges faced in conducting prior trials of VT catheter ablation and offer

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potential solutions for those challenges. It is hoped that the proposed solutions will enhance the feasibility of randomized clinical trials of VT catheter ablation.

Keywords

Ventricular tachycardia; catheter ablation; implantable cardioverter-defibrillator; clinical trials; appropriate shock; anti-tachycardia pacing; mortality

Background

Sudden cardiac death (SCD) is an important public health problem with more than 200,000 cases occurring annually in the United States.[1, 2] Implantable cardioverter-defibrillators (ICDs) improve survival, but ICD shocks that terminate ventricular tachycardia (VT) are associated with higher mortality, which may be a reflection of ICD shocks being a marker of more advanced disease versus shocks causing a worse prognosis.[3,4] In addition, ICD shocks are associated with decreased functional status and quality of life.[5] Antiarrhythmic medications reduce ICD shocks but have high rates of side effects and discontinuations within 1 year of initiation.[6] Catheter ablation of ventricular tachycardia (VT) can decrease the number of episodes of VT and ICD shocks which could translate to an improvement in patient outcomes.[7–9]

The number of catheter ablation procedures for VT performed in the United States has increased over time.[10] Catheter ablation targets myocardial scar which is the typical substrate for reentrant ventricular arrhythmias.[11] Scar consists of a mixture of fibrosis and areas of surviving diseased myocardium, resulting in areas of protected slow conduction that can be the substrate for reentrant arrhythmias.[12] Monomorphic VT occurs when scar-mediated reentry utilizes a consistent breakout site.[13] The majority of patients with recurrent VT have ischemic heart disease and most VT ablation studies have targeted this population. Additional VT ablation targets, which are more common in non-ischemic cardiomyopathies, can be focal automatic or triggered VT, as well as VT from bundle branch or fascicular reentry.[14]

Randomized and non-randomized VT ablation studies have demonstrated that VT ablation is associated with a reduction in device treated ventricular arrhythmias.[15–17] However, ICD programming can also reduce shocks,[18] and prior VT ablation trials did not specify parameters for ICD programming, so the magnitude of the effect of VT ablation on shock reduction in patients with optimally programmed devices requires further evaluation.[19] Furthermore, the impact of VT ablation on clinical trajectory, quality of life, functional status, healthcare utilization, and mortality, remain unclear. Clinical trials are needed to explore the impact of the procedure on these important endpoints in addition to more traditional endpoints such as VT recurrence, VT burden, and ICD therapies.

Overview of Completed VT Ablation Trials

Few randomized controlled VT ablation trials have been completed and published. The Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study and the

Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) study were randomized trials of VT ablation versus no ablation in ischemic cardiomyopathy patients at the time of secondary prevention ICD implantation.[17,20] The primary end-point of the VTACH trial was time to first recurrence of VT, which was longer (18.6 months) in the 52 ablation patients compared with the 55 control patients (5.9 months) (p=0.051).[20] Survival free from appropriate ICD therapy was the primary endpoint in SMASH-VT, which randomized 128 patients 1:1 to ablation versus control. The number of appropriate ICD therapies was lower in the ablation arm (12%) than the control arm (33%) (hazard ratio 0.35, 95% CI 0.15–0.78, p-value=0.007).[17]

The Catheter Ablation for VT in Patients with an Implantable Cardioverter Defibrillator (CALYSPO) pilot trial was a randomized controlled trial of early catheter ablation in 27 patients. This was a feasibility trial which demonstrated that most patients are being referred for VT ablation late in their disease process, after failing one or more antiarrhythmic medications, and the recurrence of VT (52%) and mortality (15% at 6 months) were high, irrespective of the treatment arm.[21] None of these trials had sufficient power to assess the impact of ablation on mortality.

Complexities of Completing Clinical Trials of VT Ablation

Performing a randomized VT ablation trial is associated with complexities; some pertain to all studies comparing a procedure versus no procedure, and some are unique to VT ablation.

Comparing a procedure versus no procedure

All trials comparing an interventional procedure to no procedure share some complexities. Generally, it is not possible to execute a double blind trial, and it can be very challenging to execute a single blind study with a sham procedure. There are prominent examples of recent randomized trials with a “sham” procedure arm, which were negative despite encouraging unblinded results (pacemaker for vasovagal syncope[22] and renal denervation[23]). This underscores the significance of the “placebo effect” with procedures, particularly for outcomes that are difficult to assess objectively, such as quality of life. Cross-over from the conservative management arm, usually pharmacologic therapy, to the interventional arm is a frequent problem, especially in unblinded studies.

Patient recruitment can also be challenging, as patients may be reluctant to agree to participate in a trial in which there is an equal chance of receiving a medication versus undergoing an invasive procedure with known potential complications. However, this was not observed in the CALYPSO pilot trial in which patient refusal to participate in the trial was relatively low. In CALYPSO, the opposite scenario was a barrier, as patients were referred to a VT ablation specialist expecting a procedure and were reluctant to be randomized to a medication. Physicians also have biases, which influence their decision to enroll patients in a trial that randomizes to procedure versus no procedure.

Standardization of Procedures and Tools

There are multiple techniques for catheter ablation of VT. Some centers target predominantly “clinical VTs”, while others target all monomorphic VTs, or the substrate causing VTs without focusing on VT morphologies.

VT ablation is a heterogeneous procedure making it difficult to study. There are many approaches to VT ablation that can be used alone or in combination. Activation mapping and entrainment mapping can be performed for inducible VTs that are hemodynamically tolerated. These methods can identify the critical isthmus in a re-entrant VT or the focus of a triggered VT. Substrate modification selecting ablation targets based on findings in sinus, including late potentials, or paced rhythm can be performed in patients in whom the clinical VT is not inducible at the time of catheter ablation or is not hemodynamically tolerated.[24] Even the procedure for substrate modification of abnormal potentials is not uniform; some ablationists focus on elimination of local abnormal ventricular activities (LAVA)[25], while others seek to eradicate late potentials, which also have variable definitions.[26,27] Furthermore, the characterization of these abnormal potentials varies based even on the type of catheter that is used.

In some cases, mechanical circulatory support is used to allow for activation mapping and entrainment while in VT. Variation in patient selection and mapping and ablation techniques contributes to variability in the procedural success.[28] The three largest prospective studies of VT ablation have reported the absence of all inducible VTs in 40–75% of patients and inability to induce the “clinical VT” in 72%–93% of patients.[7,8,29]

Although an endocardial only VT approach is the standard initial approach in patients with coronary artery disease, some experienced centers opt for an upfront combined endocardial/epicardial approach (based on small observational studies) in certain clinical situations.[30,31] For example, a study comparing limited substrate ablation and extensive combined endocardial/epicardial scar homogenization demonstrated that although all patients in both groups achieved the acute procedural endpoint of complete non-inducibility, the scar homogenization group that included more epicardial ablation had significantly less recurrent VT.[30] Therefore, a key challenge to studying the efficacy of VT ablation is identifying and standardizing a procedural approach that can be protocolized and widely used across all study sites.

The tools for VT ablation, like the strategies, are heterogeneous. There are currently three electroanatomic mapping systems for VT ablation: Ensite NaVx (St. Jude Medical) CARTO (Biosense Webster), and RHYTHMIA (Boston Scientific). Although the NaviStar Thermo-cool catheter (Biosense Webster) is the only FDA approved catheter for VT ablation, a wide variety of ablation catheters (approved for ablation of other arrhythmias) are used off-label in clinical practice. Many newer catheter technologies including force sensing,[32,33] infusion needle tip,[34] and flexible tip technology have been developed since the FDA approved the NaviStar Thermo-cool catheter in 2006. The lack of FDA approval of other frequently used catheters is likely related to a lack of industry resources for these studies and IDE applications rather than safety or efficacy concerns. This represents an important challenge for VT ablation trials as heterogeneous catheter and mapping system combinations introduce

sources of bias among centers and may impact outcomes and interpretability of study results. Conversely, limiting procedural tools to a single mapping system and ablation catheter has the potential to limit a randomized trial in a number of key ways. First, enrollment may be adversely impacted as perceived advantages associated with newer technologies may cause VT electrophysiologists to hesitate to enroll patients in a trial using an older FDA approved technology or even a newer technology with perceived limitations. Second, exclusive use of an older (potentially inferior) technology may lead to an underestimation of the potential for VT ablation to improve clinical outcomes and may make the findings of the trial irrelevant to future clinical practice.

A study of VT ablation requires a uniform procedural endpoint and definition of acute procedural success to ensure uniform procedural quality. However, there is still no widely agreed upon definition of acute procedural success.[35] Multiple recent observational studies have demonstrated that non-inducibility of any VT is associated with a reduction in recurrent VT and mortality.[36,37] Importantly, it appears that patients rendered completely non-inducible with regards to all VTs fare better than patients who receive successful ablation of a “clinical VT” but are left with “non-clinical VTs.”[36,37] One recent observational study demonstrated that successful ablation of late potentials was associated with a reduction in VT and cardiac death even among patients who were rendered completely non-inducible at the end of the VT ablation.[38]

Thus, mounting evidence suggests that more extensive ablation with the acute procedural endpoint of complete non-inducibility may be associated with a reduction in recurrent VT. As such, some argue that complete non-inducibility should be the acute procedural endpoint for any prospective trial of VT ablation. It remains unclear whether additional ablation seeking to achieve scar homogenization, or targeted to eliminate selected substrate (e.g. ablation of late potentials), should be required. The interpretation of non-inducibility is further complicated by lack of a uniform protocol for attempted induction of VT among centers with differences not only in the number of extrastimuli and drive train cycle length, but stimulation sites and use of beta-adrenergic stimulation. Furthermore, implementing a uniform, rigorous stimulation protocol at the end of a VT ablation procedure may not be feasible, as it raises concerns about the safety of applying this protocol at the conclusion of a long and complicated ablation case, especially in patients with more advanced structural heart disease.

Barriers to Enrollment—Patient enrollment in randomized trials of VT ablation has been problematic for a variety of reasons. Longstanding referral patterns are a key limiting factor. In the US, 29% of all ICDs are implanted by non-electrophysiologists[39] who do not perform VT ablation. Many electrophysiologists who implant ICDs do not practice at large centers where VT ablation is commonly performed. Thus many providers who longitudinally follow ICD patients may not consider ablation until late in the course of the disease. As a result, patients tend to be referred for VT ablation as a “last resort” approach after the patient has failed multiple anti-arrhythmic drugs.[37] These referral patterns are unfavorable for enrollment in VT ablation trials because (1) other options for control of VT, including antiarrhythmic agents such as amiodarone, have been exhausted, (2) patients often have end stage cardiovascular disease that increases procedural risk and is associated with arrhythmias

that may be less amenable to successful treatment with ablation or (3) patients and their referring providers often expect or prefer VT ablation and are unwilling to consider randomization.

Funding—Funding for trials of VT ablation is problematic. VT ablation utilizes advanced technologies that government and non-profit funders expect will be supported by industry. Generally, industry sponsored studies include only the sponsor's products. For example, the currently enrolling STAR-VT trial (Sponsor: St. Jude Medical) requires participants to be implanted with a St. Jude Medical ICD and investigators to use catheters and mapping systems made by St Jude Medical. A single sponsor trial may be associated with a variety of issues as detailed above. The optimal funding strategy may involve partnerships between non-industry funding (e.g. National Institutes of Health) and multiple industry sponsors. Despite these obstacles, there are several ongoing randomized controlled studies investigating timing of ablation and/or comparing ablation versus antiarrhythmic therapy (Table 1).[40]

Endpoints for Use in Clinical Trials of VT Ablation

Published data on VT ablation are insufficient for patient centered discussions regarding whether or not to pursue VT ablation. Physicians are able to counsel patients that ablation could reduce VT recurrence and perhaps by association improve quality of life.[15–17] However, physicians are unable to fully inform patients about the impact of VT ablation on quality and longevity of life owing to the paucity of data on these issues. Non-traditional endpoints, such as clinical trajectory, quality of life, functional status, healthcare utilization, are affected by subject crossover, so a time to first event analysis may partially mitigate this issue.

In this era of patient-centered care, VT ablation trials should capture information on disease burden and impact on patient well-being through quality of life questionnaires. Incident hospitalizations and total number of hospital days should be compared among treatment groups.

The impact of VT ablation on mortality is a key unanswered question. If financially feasible, a trial powered to assess the impact of VT ablation on mortality should be performed. However, VT ablation need not be associated with a mortality reduction in order to be considered a first or second line therapy.

Gaps in Knowledge about VT Catheter Ablation

Although several studies have provided helpful information about VT catheter ablation, many questions remain unanswered. The following are critical questions that may be addressed by ongoing trials:

1. Does VT catheter ablation result in fewer VT recurrences and appropriate ICD therapies compared with antiarrhythmic pharmacologic therapy?
    - VANISH and STAR VT were designed with primary endpoints to address this question.

2. Does VT catheter ablation reduce mortality compared with medical therapy?
   - VANISH and AVATAR have mortality as secondary endpoints, but these trials are not powered to answer this question.
3. Does VT catheter ablation affect incidence or severity of heart failure?
   - PARTITA has a primary endpoint focused on worsening heart failure.
4. Does VT ablation improve patient quality of life?
   - AVATAR has a quality of life endpoint as a secondary endpoint, but this study may not be adequately powered to address quality of life.
5. How does VT ablation influence heath care resource utilization? Is the procedure cost-effective?
   - AVATAR has health care utilization as a secondary endpoint, but again may not adequately powered to address this issue.
6. Are there patients with significant structural heart disease, who have experienced sustained VT in whom catheter ablation of VT should be recommended without implantation of an ICD?
   - INTERVENE is exploring this question with all-cause 2 year mortality as the primary endpoint.

Other important gaps in knowledge and questions that are not being addressed by ongoing trials include:

1. What is the optimal timing of VT ablation, including consideration for ablation at the time of ICD implantation and after the occurrence of appropriate ICD therapies?
2. What impact does the severity of underlying disease or left ventricular dysfunction have on the outcome of VT ablation?
3. Which procedural techniques and tools for VT catheter ablation are best in non-ischemic versus ischemic VT?
4. Are ventricular size and function affected by VT ablation?
5. How can complications of VT catheter ablation be minimized?
6. Are there patient subgroups in whom VT catheter ablation is particularly effective? Cost effective? Futile? Harmful?
7. What are the effects of comorbid diseases on the effectiveness and cost effectiveness of VT catheter ablation?

8. What is the role of prophylactic ablation at the time of primary and secondary ICD implantation?

It is important to recognize that most VT ablation studies have enrolled only patients with coronary artery disease. Patients with VT due to nonischemic cardiomyopathies have different arrhythmia substrate locations and ablation outcomes. Studies of VT ablation in this distinct group of patients are needed.

Most of the above questions can be best addressed in the context of randomized clinical trials; however, the best design for such trials is yet to be determined. Some questions can be best answered in the context of a registry, and professional societies may be able to play an important role in supporting VT ablation registries. Information that can be learned form a registry include the characteristics of patients undergoing this procedure in clinical practice, which catheters and ablation devices are being used, how the outcomes of this procedure differ between routine clinical practice and clinical trials, the outcomes of subgroups of patients not enrolled or not well represented in clinical trials, patterns of antiarrhythmic medication use pre- and post-VT ablation and anticoagulation post-VT ablation, durability of outcomes, the incidence of infrequent and/or late-manifesting complications, and health care resource utilization pre- and post-VT ablation. Registries are good at defining basic demographic issues, the incidence of early complications, and procedural success among patients currently being offered VT ablation in clinical practice. The International VT Ablation Center Collaborative Group is an example of the valuable contributions that multicenter observational data can provide.[37] However, it is important to recognize the limitations of registries that include the difficulty to obtain detailed long-term outcome data and selection bias

Future Clinical Trial Design: Proposing Solutions

Although the successful completion of randomized clinical trials of VT ablation is fraught with challenges, lessons learned from previous studies should inform the design of future clinical trials. As mentioned previously, one potential challenge is patient refusal to participate in a randomized clinical trial which involves a “pill” vs. an invasive procedure. However, this was not the case in the CALYPSO trial in which only 18 (8%) patients of the 216, who failed screening did so because of refusal to participate in the trial. This observation was likely due to the investigators’ commitment to the trial and their taking time to educate patients about uncertainties surrounding ablation vs. antiarrhythmic medication in treating VT. The low recruitment in CALYPSO was due to the inability to identify patients for participation in the trial early enough in their disease state.

Clinical trials should use a consistent definition of procedural success. The PARTITA and STAR-VT trials define procedural success as the prevention of inducibility of any monomorphic VT and the elimination of late potentials. Some argue that although the use of multiple technologies (many of which are not FDA approved) in a randomized trial may be associated with a number of additional regulatory hurdles, it would likely improve enrollment and possibly generalizability. However, trials should strongly encourage (but not mandate) the use of uniform techniques and catheters to ensure data are comparable and interpretable.

An aforementioned potential challenge to completing VT ablation trials is the high rate of use of pre-enrollment antiarrhythmic medications, which was an exclusion criterion in several studies. This could be mitigated either by making the eligibility criteria of the trials more inclusive or by capturing patients when they first present with appropriate ICD therapies or even earlier when they undergo ICD implantation. This is for example the case in the PARTITA and the STAR-VT trials. The advantage of this approach is that it offers the ability to explore the natural arrhythmia history following ICD implantation. Capturing patients soon after appropriate ICD therapies could be achieved by using central remote monitoring databases and/or by engaging the health care providers who are managing the implantable device follow-up. Heart failure specialists practicing in the community who are likely to see many of these patients could be engaged to identify and refer patients.

One possible approach to the completion of VT ablation clinical trials that may address the concern regarding the lack of relevance of trials' findings to current clinical practice if the trial takes long to complete is improving efficiencies. This could be potentially accomplished by adopting a "pragmatic" study design in which patient screening and enrollment and data collection could be achieved by leveraging national registries like the NCDR ICD Registry. This approach would be similar to the use of the NCDR CathPCI Registry for the Study of Access site For Enhancement of Percutaneous Coronary Intervention for Women (SAFE PCI) trial.[41] Another promising approach is to form a network of experts who are interested in VT ablation and committed to completing trials successfully.

Conclusion

Catheter ablation for VT decreases recurrences of VT and ICD shocks and has the potential to improve other outcomes such as mortality and quality of life. Limited data from randomized, controlled clinical trials have been published on the topic, although there are several ongoing trials. There are several barriers to VT ablation trials especially focused around patient identification and enrollment at the optimal time during the course of their disease and the heterogeneity of the procedural techniques. These barriers need to be addressed to ultimately determine the optimal role for VT ablation in the management of this increasing population of patients. Developing a network of experts interested in VT ablation clinical trials may further improve the feasibility of such trials.

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Table 1

Ongoing randomized VT ablation trials

Trial Title	**Ventricular Tachycardia Ablation versus Enhanced Drug Therapy**	**Does Timing of VT Ablation Affect Prognosis in Patients with an Implantable Cardioverter-Defibrillator?**	**Anti-arrhythmic Therapy vs. Catheter Ablation as First Line Treatment for AICD Shock Prevention**	**Substrate Targeted Ablation Using the Cool Flex Irrigated Catheter Ablation System for the Reduction of Ventricular Tachycardia**	**Indian Trial of Endocardial Ventricular Substrate Ablation to Prevent Recurrent VT Events**
Acronym	VANISH	PARTITA	AVATAR	STAR VT	INTERVENE
Clinicaltrials.gov identifier	NCT00905853	NCT01547208	NCT02114528	NCT02130765	NCT02301390
Description	Compare ablation vs antiarrhythmic (amiodarone +/− mexiletine) for drug refractory VT in post-MI patients	Two part study. Part A: monitor all patients to assess whether NSVT or ATP is predictive of ICD shocks. Part B among patients with an ICD shock in Part A: compare ablation vs medical therapy	Single center catheter ablation vs antiarrhythmic for appropriate ICD therapy	Substrate catheter ablation vs medical therapy	Compare ablation vs amiodarone in post-MI patients unable to afford an ICD
Estimated Enrollment	260	590	40	1453	136
Study Start Date	May-09	Sep-12	Jun-14	Jul-14	Oct-09
Estimated Primary Completion Date	Nov-15	Sep-18	Dec-16	Jul-20	Dec-16
Primary Endpoint	1) Appropriate ICD shocks (5 years) 2) VT storm (5 years) 3) Death (5 years)	1) First appropriate ICD shock 2) Number of patients with worse CHF hosptializations or death (2 years)	1) Appropriate ICD therapy (after 30 day treatment period)	1) Number of ICD shocks (appropriate and inappropriate)	1) All-cause mortality (2 years) 2) All-cause mortality, cardiac arrest, and sustained VT
Secondary Endpoints	1) All cause mortality (5 years)	1) Cardiac death (2 years) 2) Electrical storm recurrences (2 years) 3) VT recurrences (2 years)	1) Composite safety endpoint: procedural complications; antiarrhythmic drug use, side effects, and discontinuation; death 2) Slow VT below detection threshold leading to hospitalization or requiring ablation 3) Mortality 4) Quality of life score 5) Health care resource utilization	1) Number of cardiovascular hospitalizations and CV related ER visits	
Inclusion Criteria	Prior MI, ICD in-situ,	Part A: ICD in-situ	ICD, CAD with prior	ISt. Jude ICD or CRT-D	History of MI (≥1

Trial Title	**Ventricular Tachycardia Ablation versus Enhanced Drug Therapy**	**Does Timing of VT Ablation Affect Prognosis in Patients with an Implantable Cardioverter-Defibrillator?**	**Anti-arrhythmic Therapy vs. Catheter Ablation as First Line Treatment for AICD Shock Prevention**	**Substrate Targeted Ablation Using the Cool Flex Irrigated Catheter Ablation System for the Reduction of Ventricular Tachycardia**	**Indian Trial of Endocardial Ventricular Substrate Ablation to Prevent Recurrent VT Events**
	VT within 3 months (3 episodes ATP, 1 ICD shock, sustained VT below detection on ECG, 3 episodes VT in 24 hours), failed 1st line antiarrhythmic	Part B: ICD in-situ and s/p ICD shock in Part A	MI, appropriate ICD therapy (>3 ATP or >/= 1 appropriate shock)	(within 90 days of enrollment), history of spontaneous monomorphic VT or inducible VT during EP study	month), patient unable to afford an ICD and has planned treatment with amiodarone