Substrate-Based Ablation versus Ablation guided by Activation and Entrainment Mapping for Ventricular Tachycardia: A Systematic Review and Meta-analysis

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Short title: Substrate vs. activation/entrainment guided VT ablation

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Abstract

Introduction: Substrate-based ablation for scar-related ventricular tachycardia (VT) has gained prominence, however there is limited data comparing it to ablation guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs. We compared the acute procedural efficacy and outcomes of predominantly substrate-based ablation versus ablation guided predominantly by activation and entrainment mapping.

Methods and Results: Database searches through April 2016 identified 6 eligible studies (enrolling 403 patients, with 1 randomized study) comparing the two strategies. The relative risk of VT recurrence at follow-up was assessed as the primary outcome using a random-effects meta-analysis. Secondary endpoints of acute success (based on non-inducibility of VT), procedural complications, and mortality were assessed using weighted mean difference with the random effects model. At a median follow up of 18 months, the relative risk (RR) of VT recurrence was not significantly different with substrate-based vs. activation/entrainment guided VT ablation (0.72, 95% confidence interval [CI] 0.44-1.18), $P=0.2$). Acute success (RR 1.02, 95% CI 0.95-1.1, $P=0.6$), procedural complications (RR 0.8, 95% CI 0.35-1.82, $P=0.5$) cardiovascular mortality and total mortality did not differ significantly (RR 0.83, 95% CI 0.38-1.79, $P=0.6$ and RR 0.76, 95% CI 0.36-1.59, $P=0.5$, respectively).

Conclusions: This meta-analysis demonstrates similar acute procedural efficacy, and complications, VT recurrence and mortality rates when comparing a predominantly

substrate-based ablation strategy to a strategy guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs.

Keywords: ventricular tachycardia; catheter ablation; substrate mapping; activation mapping; entrainment mapping; meta-analysis.

Introduction

Recurrent sustained monomorphic ventricular tachycardia (VT) is an important cause of morbidity from recurrent defibrillator shocks, and mortality in patients with structural heart disease.¹⁻³ Percutaneous catheter ablation as an adjunct to anti-arrhythmic drug therapy is superior to anti-arrhythmic drugs alone in preventing VT recurrences.^{4, 5} Catheter ablation can reduce the burden of defibrillator shocks, improve quality of life⁶ and can be life saving in VT storm.⁷

In structural heart disease, VT is usually due to scar-related reentry. If a reentrant VT is reproducibly inducible and hemodynamically tolerated, activation and entrainment mapping can be used to identify a critical reentry isthmus and ablate the VT.⁸ If VTs are not inducible or not hemodynamically tolerated, ablation can be guided by identification of VT substrate during stable sinus or a paced rhythm. Substrate-based approaches involve identification of low voltage areas consistent with scar and abnormal electrograms which represent surviving myocytes capable of supporting re-entrant VT circuits.^{9, 10} Although a combination of the two approaches is commonly employed during VT ablation, a number of studies have examined whether substrate-based ablation strategy is comparable to one guided predominantly by activation/entrainment mapping of inducible and hemodynamically tolerated VTs with variable results.¹¹⁻¹⁶ We therefore undertook a systematic review and meta-analysis of all studies that sought to compare the outcomes of a predominantly substrate-based VT ablation approach versus a strategy predominantly guided by activation and entrainment mapping of inducible and hemodynamically tolerated VTs.

Methods

Search Strategy

We searched major databases (Pubmed, Embase, Web of Science, Scopus, Cochrane Database) for published studies describing the outcomes of VT ablation using the broad search term of ‘ventricular’ and ‘ablation’ in either the title or the abstract (Supplemental Table 1). No limits of start date were applied. The search was conducted up through 24th April, 2016. Additionally, reference lists from review articles; guidelines and meta-analyses were manually searched for references otherwise not listed in the initial search. Abstracts from conference meetings were not included in the search strategy. All randomized controlled trials, case–control studies, cohort studies, and were reviewed (irrespective of journal ranking).

Study selection

Detailed inclusion criteria are outlined in Table 1. Studies were included if they:

- (i) enrolled patients with structural heart disease and VT referred for catheter ablation;
- (ii) had reported data on VT recurrence; (iii) compared the predominantly substrate-based ablation strategy in one arm with an ablation strategy predominantly guided by activation/entrainment mapping in the other study arm. Other exclusions are summarized in Table 1 and Figure 1. Case reports, reviews, meta-analyses and studies published in languages other than English were excluded.

Data extraction

Two investigators (SK, SB) independently screened all titles, abstracts and manually searched the full text versions of all relevant studies that fulfilled the inclusion criteria. Relevant data was extracted using a standardized form (Figure 1). Differences were resolved by consensus.

Primary and secondary outcomes

The primary outcome was VT recurrence during follow up. Secondary outcomes included acute procedural success (based on inducibility of VT at the end of the procedure), acute procedural complications, cardiovascular mortality and all cause mortality during follow-up, and ablation parameters such as radiofrequency ablation time and procedure duration.

Statistical analysis

Descriptive statistics are presented as means and standard deviations for continuous variables or number of cases and as percentages for dichotomous and categorical variables. Statistical analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using Review Manager (RevMan), version 5.3, the Cochrane Collaboration, 2014. Heterogeneity was assessed using the I^2 statistics, which is the proportion of total variation observed among the studies attributable to differences between studies rather than sampling error (chance).¹⁷ Data were summarized across treatment arms using the Mantel-Haenszel RR fixed effects model. We considered I^2 less than 25% as low and I^2 greater than 75% as high. The Random-Effects Model of DerSimonian and Laird was used if $I^2 > 25\%$.¹⁸ All analyses were performed using the

intention-to-treat principle. Publication bias was estimated visually by funnel plots.^{18, 19}

Results

Search results

The initial search yielded 9551 references. After exclusions summarized in Figure 1, the full text of 290 studies reporting outcomes of catheter ablation of VT were reviewed.

Only 6 studies directly compared a predominantly substrate-based ablation with a predominantly activation/entrainment guided ablation strategy (Figure 1). Notably, a number of studies described different substrate-based ablation strategies in the absence of a control group undergoing ablation predominantly guided by activation/entrainment mapping. Some examples of such studies were those by Soejima et al (pace mapping)²⁰, Tzou et al²¹ and Tilz et al (scar “core” isolation)²², Jais et al (elimination of late abnormal ventricular activities),²³ Vergara et al (late potential abolition),²⁴ Berruezo et al (scar dechanneling),²⁵ and Jackson et al (decremental evoked potential mapping).²⁶

A number of studies reported the use of hemodynamic support devices to facilitate detailed activation/entrainment but lacked a control group of patients undergoing ablation using a predominantly substrate-based ablation.^{27, 28} Majority of the studies were excluded as they used a combination of activation/entrainment and substrate mapping and lacked a direct comparison between the two strategies. There was no significant publication bias for the primary outcome as assessed by Funnel plots (Figures 2-6).

Study characteristics

Table 2 summarizes the characteristics of the included studies. Six studies were included with a total of 403 patients. Median follow-up duration was 18 months and mean sample size of each study was 33-35 patients. Mean age of the participants was 61-63 years with a mean left ventricular ejection fraction of 32-33%; 79-81% of patients had ischemic cardiomyopathy.

The details of the mapping and ablation strategy employed in the included studies are summarized in Tables 3 and Supplemental Table 2. Only one study was randomized and three studies had multicenter recruitment. The randomized study compared a strategy of ablation of only the hemodynamically stable VTs (clinical or a matching non-clinical VTs) against a strategy of endocardial and epicardial substrate ablation through the entire scar without *any* activation/entrainment mapping.¹¹

Four studies were retrospective, and two were prospective. Of the retrospective studies, three were observational studies that included consecutive patients ablated during the specified study period.^{16,14, 15} In these three observational studies, the mapping and ablation strategy was based on inducibility and hemodynamic tolerability of inducible VT at the beginning of the procedure. Patients who were inducible and had hemodynamically tolerable VTs that allowed mapping were assigned to the activation/entrainment arm whereas non-inducible patients or patients with hemodynamically non-tolerated VTs were assigned to the predominantly substrate-based ablation arm.¹⁴⁻¹⁶ One of the retrospective studies was a case-control design that compared consecutive patients undergoing activation and entrainment guided VT ablation facilitated by hemodynamic

support who were matched to a consecutive population of control patients who underwent substrate-based ablation only without hemodynamic support.¹³

One prospective, non-randomized study included two groups of patients who were ablated with a predominantly activation and entrainment guided ablation with additional limited substrate ablation targeting a putative VT isthmus who were then compared to the next set of consecutive patients who were treated with a strategy of extensive endocardial and epicardial substrate ablation without *any* attempts at activation/entrainment mapping.²⁹

Comparison of VT recurrence in follow-up

Compared to a predominantly activation/entrainment guided ablation strategy, a predominantly substrate-based ablation strategy had a similar risk of VT recurrence during follow-up (relative risk [RR] 0.72, 95% confidence interval [CI] 0.44-1.18), $P=0.19$). However there was moderate heterogeneity in the included studies ($I^2=66\%$; Figure 2). Subgroup analysis of ischemic versus non-ischemic cardiomyopathy was not possible due to lack of outcome data according to disease type.

Comparison of acute procedural outcomes

There was some variation in the definition of acute procedural success. Three studies defined acute procedural success as non-inducibility of any VT at the end of the procedure. Three studies used the following definitions: (i) inability to induce the VT recorded at beginning of the procedure (1 study);¹³ (ii) non-inducibility of clinical VT and any VT slower than the clinical VT at end of the procedure (1 study);¹⁶ (iii)

abolishment of targeted VTs defined as clinical VTs and other morphologies with similar or slower cycle lengths; also reported non inducibility (1 study).¹⁵ When a standard definition of non-inducibility of any VT was applied, such data were not available for 2 studies.^{15, 16} Due to the variability in the authors' definition of acute success, we chose to define acute success as the definition used by the authors in their study.

Compared to a predominantly activation/entrainment guided ablation strategy, a predominantly substrate-based ablation strategy had a similar acute success rates (RR 1.02, 95% CI 0.95-1.1, P=0.58) with minimal statistical heterogeneity ($I^2 = 5\%$; Figure 3). Acute procedural complications were also comparable between the two groups (RR = 0.8, 95% CI 0.35-1.82, P=0.59) with no statistical heterogeneity ($I^2 = 0\%$; Figure 4).

Cardiovascular mortality was similar between the two groups (RR 0.83, 95% CI 0.38-1.79 P=0.6; Figure 5A), however this information was available in only 4 of the 6 studies.^{11, 13, 14, 16} Finally, all cause mortality during follow-up was comparable (RR 0.76, 95% CI 0.36-1.59, P=0.47; statistical heterogeneity $I^2=3\%$; Figure 5B), but this information was available in only 3 of 6 studies.^{11, 13, 16}

Ablation time and procedure duration

Information about total RF ablation time was present in 3 studies.^{11, 13, 29} The other three studies specified the length of the ablation lines performed or the number of RF pulses delivered without reporting the mean duration of RF pulses.¹⁴⁻¹⁶ There was a trend toward longer RF ablation time with substrate-based versus activation/entrainment-guided ablation (P=0.14; Table 2). Information about total procedure duration was available in

all but one study. There were no significant differences in procedure duration between the two groups ($P=0.7$; Table 2).

Discussion

This systematic review and meta-analysis compared the acute procedural efficacy, complications and outcomes following percutaneous catheter ablation of VT using a predominantly substrate-based ablation strategy to a strategy guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs. Only a small number of studies (six of 290 studies reviewed) directly compared the two approaches and fulfilled inclusion criteria. The main findings were that outcomes were comparable between the two groups in terms of acute procedural success (non-inducibility of the targeted VT), procedural complications, VT recurrence during follow-up, and mortality. Moreover, no significant differences in procedural duration were found, although there was a trend toward reduction in RF ablation time in the activation/entrainment mapping group.

The VT ablation procedure has evolved remarkably over the past two decades. Earlier reports of percutaneous catheter ablation predominantly used activation³⁰ and/or entrainment mapping of VT to identify a critical VT isthmus that could be targeted with limited RF ablation.⁸ Such studies included only patients in whom VT was hemodynamically tolerated (or mappable), could be reproducibly initiated, and matched the morphology of the spontaneous VT (“clinical VT”). This approach remains attractive as short linear lesions transecting VT isthmii critical to targeted VTs could render such VTs non-inducible with limited ablation. There are a number of limitations of this

approach such as a critical dependence on inducibility and sustainability of VT to allow complete mapping. The VT needs to hemodynamic tolerated to allow mapping.

Moreover, patients with structural heart disease need to have sufficient cardiac reserve to permit long periods of mapping in VT. This approach also requires reproducible initiation of the targeted VT to allow entrainment maneuvers in order to identify VT isthmii.

Patients with structural heart disease often have multiple inducible VTs that may not necessarily be “clinical”, and may therefore interfere with mapping of the targeted VT.

VTs may be unmappable due to hemodynamic instability, or the patient may be non-inducible for *any* VT during the procedure. Furthermore, targeting only the mappable or clinical VT can result in recurrence of other non-targeted or non-clinical VTs.

As an adjunctive or an alternative approach, substrate-based ablation allows identification of abnormal substrate in stable sinus or paced rhythm and allows ablation of patients in whom VT is non-inducible or not hemodynamically tolerated to allow detailed activation/entrainment mapping. However, there are also a number of disadvantages of this approach. Low voltage regions consistent with scar may be large in patients with structural heart disease, not all abnormal electrograms may participate in VT circuits, and may be not specific to the mechanism of the targeted VTs. Thus a substrate-based ablation may increase mapping and procedure time and result in more extensive ablation due to lack of specificity of electrogram markers for VT circuits. Furthermore, the substrate mapping can be influenced by electrode mapping density,³¹ definitions of abnormal substrate and can vary between operators and centers (e.g. late abnormal ventricular activities²³ vs. late potential mapping²⁴ vs. scar channel identification²⁵) as can the approach to ablation (e.g. core isolation^{21, 22} vs. late potential

abolition²⁴ vs. scar dechanneling,²⁵ vs. scar homogenization^{11, 12}). Ablation endpoints can also be unclear with substrate-based ablation, for example non-inducibility of VT at the end of the procedure versus complete elimination of abnormal electrograms on remapping.

The relative advantages and disadvantages of each approach has prompted questions about the superiority of one predominant approach verses the other. A recent randomized study¹¹ and a non-randomized study,²⁹ however found that a purely substrate-based approach with extensive endocardial and epicardial RF ablation (scar homogenization) without *any* activation/entrainment mapping was superior to a strategy of limited ablation guided predominantly by activation/entrainment mapping of hemodynamically tolerated VTs. However, other prior non-randomized studies did not suggest such superiority.¹³⁻¹⁶ Hence we conducted a meta-analysis of the published literature to compare the outcomes using these two approaches to answer a highly clinically relevant question.

Although studies attempted to examine one approach compared to the other, there is an inevitable overlap between the ablation approaches that may explain the neutral result of this meta-analysis. Fundamentally, an isthmus identified using activation and entrainment mapping is also within the target area of abnormal substrate. Presently, many centers, including ours, employ a combination of both substrate mapping and a short period of activation/entrainment mapping to confirm or refute whether the proposed ablation site is located in close proximity to the putative isthmus.

A large majority of structural heart disease patients will have unmappable VT (>70%) and thus activation and entrainment mapping is not possible;³² in this regard the

strategy chosen is strongly influenced by individual patient characteristics and therefore a given patient may not be appropriate for both strategies. The current meta-analysis comprises only 6 studies, and this is reflective of the lack of well-designed clinical trials addressing our central proposition. These six studies comprise of a relatively small cohort with heterogeneity in both clinical phenotype (i.e. ischemic vs. non-ischemic cardiomyopathy) and procedural methodology; this limits the meaningful generalizability of this systematic review. However, an important question evoked from this analysis is the need for a randomized study that compares an approach of ablation guided by activation and entrainment mapping coupled with substrate-based ablation versus purely substrate-based ablation, specific to cardiomyopathy type. Whether a patient was assigned to the activation/entrainment arm versus the substrate ablation arm is also critically dependent on VT inducibility and tolerability that may vary on a daily basis depending on loading conditions, autonomic tone, and effects of anesthetic drugs.

The majority of the studies included in this meta-analysis were retrospective studies. Such studies are subject to selection bias in the technique that was used because some patients might be better treated with activation and entrainment mapping whilst others are better treated with a purely substrate-based approach. Furthermore, it is important to note that the experience, skill, and commitment to a comprehensive approach to either technique also might influence outcomes.

Conclusions

This meta-analysis found no difference in acute procedural success (non-inducibility of the targeted VT), procedural complications, VT recurrence or mortality when comparing

a strategy of predominantly substrate-based ablation versus a strategy predominantly guided by activation and entrainment mapping. The small number of available studies (and small patient population) and the inherent overlap between the ablation approaches may explain the neutral effect.

Author contributions

Saurabh Kumar: Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics, Data collection.

Samuel Baldinger: Critical revision of article, Approval of article, Data collection.

Jorge Romero: Critical revision of article, Approval of article, Statistics, Data collection.

Akira Fujii: Critical revision of article, Approval of article, Data collection.

Saagar Mahida: Critical revision of article, Approval of article, Data collection.

Usha B. Tedrow: Critical revision of article, Approval of article.

William G. Stevenson: Critical revision of article, Approval of article.

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Figures

Figure 1: Bibliographic Search Strategy

Figure 2: Comparison of VT recurrences between the predominantly substrate-based ablation strategy (Group A) versus a strategy guided predominantly by activation/entrainment mapping (Group B).

Study or Subgroup	Group A		Group B		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Bunch et al. 2012	9	18	6	13	16.3%	1.08 [0.51, 2.29]
Di Biase et al. 2012	8	43	23	49	17.2%	0.40 [0.20, 0.79]
Di Biase et al. 2015	9	58	29	60	17.8%	0.32 [0.17, 0.62]
Makimoto et al. 2015	15	50	15	35	19.3%	0.70 [0.40, 1.24]
Ventura et al. 2007	6	14	4	16	12.1%	1.71 [0.60, 4.86]
Volkmer et al. 2006	11	24	8	20	17.2%	1.15 [0.57, 2.29]
Total (95% CI)		207		193	100.0%	0.72 [0.44, 1.18]

Total events

58

85

Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 14.50$, $df = 5$ ($P = 0.01$); $I^2 = 66\%$

Test for overall effect: $Z = 1.30$ ($P = 0.19$)

Figure 3: Comparison of acute ablation success between the predominantly substrate-based ablation strategy (Group A) versus a strategy guided predominantly by activation/entrainment mapping (Group B).

Study or Subgroup	Group A		Group B		Weight	Risk Ratio		Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Bunch et al. 2012	12	18	10	12	7.1%	0.80 [0.53, 1.21]		
Di Biase et al. 2012	43	43	49	49	27.2%	1.00 [0.96, 1.04]		
Di Biase et al. 2015	58	58	60	60	35.0%	1.00 [0.97, 1.03]		
Makimoto et al. 2015	37	48	22	35	15.0%	1.23 [0.91, 1.65]		
Ventura et al. 2007	9	14	11	16	6.0%	0.94 [0.56, 1.56]		
Volkmer et al. 2006	17	21	17	22	9.8%	1.05 [0.77, 1.42]		
Total (95% CI)		202		194	100.0%	1.02 [0.95, 1.10]		
Total events	176		169					
Heterogeneity: $\text{Chi}^2 = 5.29$, $\text{df} = 5$ ($P = 0.38$); $I^2 = 5\%$								
Test for overall effect: $Z = 0.56$ ($P = 0.58$)

Figure 4: Comparison of acute complications between the predominantly substrate-based ablation strategy (Group A) versus a strategy guided predominantly by activation/entrainment mapping (Group B).

Study or Subgroup	Group A		Group B		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Bunch et al. 2012	3	18	4	13	41.7%	0.54 [0.15, 2.02]	
Di Biase et al. 2012	0	43	0	49		Not estimable	
Di Biase et al. 2015	3	58	3	60	26.5%	1.03 [0.22, 4.92]	
Makimoto et al. 2015	0	50	0	35		Not estimable	
Ventura et al. 2007	0	14	1	16	12.6%	0.38 [0.02, 8.59]	
Volkmer et al. 2006	3	25	2	22	19.1%	1.32 [0.24, 7.19]	
Total (95% CI)		208		195	100.0%	0.80 [0.35, 1.82]	
Total events	9		10				
Heterogeneity: $\chi^2 = 1.00$, $df = 3$ ($P = 0.80$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.53$ ($P = 0.59$)							

Figure 5A: Comparison of cardiovascular mortality between the predominantly substrate-based ablation strategy (Group A) versus a strategy guided predominantly by activation/entrainment mapping (Group B).

Study or Subgroup	Group A		Group B		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bunch et al. 2012	4	18	1	13	9.0%	2.89 [0.36, 22.94]	
Di Biase et al. 2012	0	0	0	0		Not estimable	
Di Biase et al. 2015	3	60	5	58	39.2%	0.58 [0.15, 2.32]	
Makimoto et al. 2015	2	50	3	35	27.2%	0.47 [0.08, 2.65]	
Ventura et al. 2007	0	0	0	0		Not estimable	
Volkmer et al. 2006	3	25	3	22	24.6%	0.88 [0.20, 3.92]	
Total (95% CI)	153	128	100.0%			0.83 [0.38, 1.79]	
Total events	12	12					
Heterogeneity: $\text{Chi}^2 = 2.08$, $\text{df} = 3$ ($P = 0.56$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.47$ ($P = 0.64$)

Figure 5B: Comparison of all cause mortality between the predominantly substrate-based ablation strategy (Group A) versus a strategy guided predominantly by activation/entrainment mapping (Group B).

Study or Subgroup	Group A		Group B		Weight	Risk Ratio		Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Bunch et al. 2012	4	18	1	13	8.0%	2.89 [0.36, 22.94]		
Di Biase et al. 2012	0	43	0	49		Not estimable		
Di Biase et al. 2015	5	60	9	58	62.8%	0.54 [0.19, 1.51]		
Makimoto et al. 2015	0	0	0	0		Not estimable		
Ventura et al. 2007	0	0	0	0		Not estimable		
Volkmer et al. 2006	3	25	4	22	29.2%	0.66 [0.17, 2.63]		
Total (95% CI)		146		142	100.0%	0.76 [0.36, 1.59]		
Total events	12		14					
Heterogeneity: $\chi^2 = 2.07$, $df = 2$ ($P = 0.36$); $I^2 = 3\%$								
Test for overall effect: $Z = 0.73$ ($P = 0.47$)

Tables

Table 1: Study selection criteria

Selection criteria	Inclusion criteria for Studies	Exclusion criteria for Studies
Population	>3 patients with structural heart disease undergoing catheter ablation of sustained ventricular tachycardia (VT)	Studies pertaining to ex- or in vivo models or computer simulation, animals, children, patients with congenital heart disease, idiopathic ventricular arrhythmias, exclusive reports on bundle branch re-entry or premature ventricular contractions (including triggered ventricular fibrillation).
Intervention	Invasive management with percutaneous catheter ablation using radiofrequency energy comparing a substrate-based ablation strategy versus a strategy guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs.	Medical therapy, percutaneous catheter based fulguration or electroporation, primary surgical ablation, alternative ablation modalities not involving percutaneous catheter ablation such as transcoronary ethanol ablation, autonomic modulation, renal denervation, studies describing only one type of substrate based ablation with the absence of a comparative control group undergoing ablation guided predominantly by activation/entrainment mapping, studies describing a combination of

		activation/entrainment mapping and substrate-based ablation, studies describing ablation of inducible and hemodynamically tolerated VTs facilitated by hemodynamic support with the absence of a comparative control group
Study design	Observational (retrospective or prospective) or case-control studies of >3 patients, randomized clinical trials reporting VT recurrence outcomes	Studies not published in English, single patient case reports, editorials, meta-analyses, statements, conference abstracts.

Table 2: Summary of Baseline characteristics

	Predominantly Substrate- based ablation	Ablation guided predominantly by activation/entrainment mapping
Number of studies	6	6
Number of multi-center studies	3	3
Number of randomized studies	1	1
Retrospective design	4	4
Total number of patients	208	195
Number of patients per study, mean $\pm$ SD (median, minimum- maximum)	35 $\pm$ 19 (34, 14-58)	33 $\pm$ 19 (29, 13-60)
Age, mean, SD, years	63 $\pm$ 5	61 $\pm$ 5
Male gender, % mean	85	87
Left ventricular ejection fraction, % (mean $\pm$ SD)	33 $\pm$ 10	32 $\pm$ 10

Percentage of patients with ischemic cardiomyopathy, % mean	81	79
Radiofrequency ablation time, mean, (median, minimum-maximum), minutes ^a	58.4 (68, 33.2-74)	33.9 (35, 27.6-39)
Procedure time, mean, (median, minimum-maximum), hours ^b	5.1 (4.6, 4.2-7.1)	5.4 (5, 3.6-7.1)
Follow up, median (minimum-maximum)	18 (9-59)	18 (9-64)

^ainformation available for 3 of 6 studies, P=0.14 for comparison between two groups; ^binformation available for 5 of 6 studies, P=0.7 for comparison between two groups.

Abbreviations: SD-standard deviation.

Table 3: Inclusion criteria, study groups and study design of the included studies.

Study name	Inclusion criteria	Groups	Study Design
		Predominantly substrate-based ablation	Ablation guided predominantly by activation/entrainment mapping
Volkmer et al 2006 ¹⁶	Consecutive patients with clinically sustained, hemodynamically tolerated monomorphic VT occurring remote post MI (>3 months)	Patients in whom a complete VT map was not possible because of catheter-induced mechanical block or because the induced VT was unmappable due to hemodynamic deterioration during VT.	<p>Incessant or inducible VT that is hemodynamically tolerated permitting construction of VT circuit using a 3D mapping system</p> <p>Retrospective, observational, non-randomized, single center study.</p> <p>Differentiation into two groups based on pre-ablation VT induction and initial attempts at mapping under conscious sedation.</p>

Ventura et al 2008 ¹⁵	Sustained monomorphic VT prior MI documented by 12 lead ECG or ICD. No evidence of VT storm, valvular heart disease, NYHA class IV, LV thrombus, or cardiac surgery in prior 3 months	Hemodynamically non-tolerated VT	Hemodynamically tolerated VT	Retrospective, observational, non- randomized, single center study. Differentiation into two groups based on hemodynamic tolerability of VT.
Bunch et al 2012 ¹³	Drug refractory hemodynamically unstable VT; significant SHD with an LVEF ≤40% or ARVC; at least 1 shock and failed at least 1 AAD	Substrate based ablation not assisted by pVAD	Activation/entrainment facilitated by a pVAD	Retrospective, case-control, multi-center study. Consecutive patients undergoing pVAD-assisted ablation matched with consecutive patients undergoing non-pVAD assisted ablation over the same time period. Matching performed by age (within 5 yrs), LVEF (within 5%), NYHA (within 1 class), diabetes mellitus, irrigated ablation, medical therapy before and after procedure, and AAD

				by investigators blinded to outcome data
Makimoto et al 2012 ¹⁴	Consecutive patients with drug refractory VT having experienced at least 1 episode of sustained monomorphic VT	Patients with hemodynamically unstable VT, non clinical VT inducible during baseline induction, or if the induced VT did not persist long enough to perform activation/entrainment mapping	Patients with hemodynamically stable VT permitting mapping in VT	Retrospective, observational, non-randomized, single center, study. Consecutive patients undergoing VT ablation over a time period included. Differentiation into two groups based on pre-ablation VT induction.
Di Biase et al 2012 ²⁹	Consecutive patients with ischemic cardiomyopathy and electrical storm who did not	Patients undergoing ablation through entire scar endocardially	Patients undergoing limited endocardial ablation to critical	Prospective, non-randomized, multi-centre, observational study. Consecutive patients treated with limited endocardial ablation

	have: severe renal insufficiency, mobile left ventricle thrombus, unstable angina, severe aortic stenosis and end-stage heart failure (New York Heart Association functional class IV with a limited survival expectation at 12 months), previous coronary artery bypass graft, age $\leq$ 18 years, and prior failed ventricular arrhythmia ablations	and/or epicardially at sites of abnormal electrograms (“endo/epicardial scar homogenization”) with no activation or entrainment criteria applied. Epicardium mapped in all patients, ablation performed only in scar and/or regions of “abnormal” electrograms	regions identified by activation or entrainment mapping (when VT was hemodynamically tolerated) or exit region identified by pace mapping (when VT not hemodynamically tolerated). Epicardial ablation only if persistent inducibility after endocardial ablation.	were compared to the next set of consecutive patients treated with “endo/epicardial scar homogenization”
Di Biase et al 2015 ¹¹	Patients with ischemic cardiomyopathy with an ICD	Same as above.	Same as above, however only “clinical”	Prospective, randomized, multicenter study. Patients randomized to two different

who had recurrent	VTs and	mapping and ablation strategies.
hemodynamically stable	hemodynamically	
monomorphic VTs that were	stable, mappable “non-	
symptomatic or required ICD	clinical” VTs targeted if	
therapies despite AADs.	they had morphology	
Excluded patients with VT that	similar to the clinical	
presented with syncope, loss of	one.	
consciousness, or cardiac arrest;		
age <18 years; severe renal		
insufficiency; LV thrombus,		
unstable angina, severe aortic		
stenosis, end-stage heart failure		
with limited life expectancy,		
and prior failed VT ablation.		

Abbreviations: AAD-anti-arrhythmic drug; ARVC-arrhythmogenic right ventricular dysplasia; ICD-implanted cardioverter-defibrillator; LV-left ventricular; LVEF-left ventricular ejection fraction; MI-myocardial infarction; NYHA-New York Heart Association Class, pVAD-peripherally inserted ventricular assist device; SHD-structural heart disease, VT-ventricular tachycardia, yrs-years.

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