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Endpoints for Ablation of Scar-Related Ventricular Tachycardia

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Introduction

The main goal of catheter ablation strategies for the treatment of scar-related ventricular tachycardia (VT) is the interruption of critical areas of slow conduction within the VT circuit(s) responsible the development and maintenance of VT(s).[1,2] Over the past decade, multiple clinical studies have demonstrated the benefit of catheter ablation in patients with drug-refractory scar-related VT, with a striking reduction in VT recurrences compared to standard medical therapy.[3,4] However, despite improvements in mapping and ablation techniques, the long-term freedom from recurrent VT remains suboptimal, with up to 50% of patients experiencing VT recurrence at long-term follow-up.[5] Identification of the optimal endpoints for VT ablation is crucial to improve the success rate of this procedure. The response to programmed electrical stimulation (PES) has been traditionally used to understand the mechanisms of arrhythmias, localize critical areas of slow conduction within the VT circuit, and predict the long-term outcomes.[1,2]

In patients with mappable VTs, analysis of the response to PES can reliably identify specific areas within the VT circuit, such as protected zones of slow conduction within the dense scar, as well as the entry and exit sites of the circuit. This information can be used to identify the critical isthmus of the reentrant circuit, and ablation at that site often results in acute termination of the VT and noninducibility. Accordingly, acute VT termination and noninducibility by PES represent classical endpoints for VT ablation; in particular, the latter is the only endpoint endorsed by the current practice guidelines.[1,2]

In recent years, the value of PES in guiding ablation therapy and predicting long-term arrhythmia-free survival has been questioned,[6,7] as it has become clear that the great majority of patients present with only hemodynamically unstable arrhythmias and have either multiple inducible VT morphologies (with unclear clinical significance) or no inducible VT prior to the procedure.[8-12] Furthermore, a direct association between VT noninducibility at the end of the procedure and long-term arrhythmia-free survival has been suggested but not uniformly demonstrated.[4,6,7,13,14] The increasing adoption of substrate-based ablation techniques, which target the putative VT(s) exit sites as defined by pace mapping techniques along the scar border, together with peculiar electrograms representing the hallmark of slow conduction (abnormal, split, and late electrograms),[15,16] has been paralleled by an increasing need for new ablation endpoints. Although PES has also been used as an endpoint in studies evaluating substrate-based ablation approaches, other procedural endpoints have been described to validate the completeness of linear lesions and the elimination of abnormal potentials within the scar. This chapter will

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summarize the state-of-the-art on procedural endpoints for catheter ablation of scar-related VT.

Invasive Programmed Electrical Stimulation

Noninducibility at invasive PES represents the most widely accepted endpoint for catheter ablation of scar-related VT and the only one endorsed by the most recent expert consensus documents on VT ablation.[1,2] From a physiological perspective, reproducible induction of VT by premature stimuli delivered within well-defined timing intervals is a hallmark of reentrant arrhythmias. In the setting of healed myocardial infarction, earlier experiences with PES reported a rate of VT inducibility up to 95% in patients with spontaneous episodes of sustained monomorphic VT, as opposed to nearly 0% of controls.[17-19] The major pitfall of these early studies, which is built in their pure observational design, was that the control arm almost uniformly included relatively healthy subjects, whereas patients with history of VT (and positive PES) had significant underlying cardiomyopathic substrates;[17-19] the lack of a homogeneous control arm of patients with similar cardiomyopathic substrates (and no history of VT) was a source of bias and led investigators to hypothesize that PES might be used to longitudinally predict arrhythmic events also in patients without history of VT. Subsequent prospective randomized trials have provided mixed results.[20,21] On the other hand, in patients who already had experienced a VT episode, such as those referred for catheter ablation, PES remains highly specific. Early experiences with catheter ablation of postinfarct VT reported a significant association between noninducibility at the end of the procedure and VT-free survival,[22-26] hence the adoption of noninducibility as a procedural endpoint (Table 30.1). The clinical evidence supporting noninducibility as a procedural endpoint for ablation of scar-related VT will be discussed in the following section.

Clinical Evidence

The bulk of the evidence on noninducibility as an endpoint for catheter ablation of scar-related VT derives from studies on patients with postinfarct VT (Table 30.2).[4-6,13,14,22,23,25,27-36] Remarkably, none of these studies was specifically designed to perform a formal longitudinal evaluation of noninducibility as a predictor of postablation recurrences; only 2 studies had a prospective, randomized design.[4,14] To better appraise the value of noninducibility as a predictor of ablation outcomes, we performed a pooled analysis of the available evidence using established methods.[37] Overall, a total of 1,401 patients with postinfarct VT and severe left ventricular dysfunction (average ejection fraction [EF] = 31% ± 3.5%) were included in the analysis. The acute procedural endpoint was noninducibility at PES, although the definition for noninducibility varied across the studies. In particular, 11 studies had noninducibility of any VT as the procedural endpoint,[13,14,23,25,29-31,33,34] 2 studies provided no definition of noninducibility,[4,38] and the remaining 7 studies had noninducibility of only clinical VT(s),[22,28] any mappable VT(s),[6,27,32] or VT(s) with cycle length close to the clinical VT.[5,36] The acute procedural endpoint was achieved in 64% of patients. After an average follow-up of 22.8 ± 13.7 months, a total of 493 (37%) patients experienced VT recurrence. To evaluate the impact of noninducibility on long-term VT-free survival, a weighted meta-regression analysis was performed, assigning weight to the individual studies based on the sample size. Notably, no significant association was found between rate of noninducibility at PES and VT recurrences at follow-up ($r = -0.0571$, $P = 0.821$) (Figure 30.1). The same results were found when restricting the analysis only to studies with noninducibility of any VT as an endpoint ($r = -0.103$, $P = 0.791$).[13,14,23,25,29-31,33,34] These results would support the notion that noninducibility at PES is not an optimal endpoint for catheter ablation of postinfarct VT. It is important to emphasize that the results of our meta-analysis could not be adjusted for several potential

Table 30.1 Endpoints for Ablation of Scar-Related VT

	Pros	Contras
Programmed stimulation		
Noninducibility of any VT at PES*	Established predictive value when performed from multiple sites (RV and LV) up to 3 extrastimuli.	Not useful for noninducible patients. Suboptimal negative predictive value. Unclear significance of inducible nonclinical VTs.
Noninducibility of any VT at NIPS (3–5 days postprocedure)	Improves predictive value when immediate postprocedural PES is negative or not feasible.	Impact of early ablation in patients with positive NIPS is still unknown.
Linear ablation lesions		
Failure to capture with high-output pacing along the ablation line	Allows for rapid assessment of continuity of ablation lesions.	Optimal pacing output unknown. No prospective validation. Block across the line not demonstrated.
Change in QRS morphology with pacing from each sides of the line	Allows for rapid assessment of block across the ablation line.	Distinction between block and severe conduction delay across the line is not possible. No prospective validation.
Conduction block across the line with pacing from each side of the line (activation mapping)	Allows for definite demonstration of block across the ablation line.	Need for multiple catheters. No prospective validation.
Ablation of abnormal EGMs (late potentials)		
Elimination of late potentials	Empirical ablation of all the putative VT circuits within the scar. Prospectively validated in observational studies.	Complete elimination often difficult to achieve. Late potentials not always present. Need for extensive ablation.
Failure to capture with high-output pacing	Allows for assessment of lesion completeness (especially when "elimination" is not achieved).	Time consuming. No prospective validation.
Isolation of the scar core with box lesions	Allows for elimination of all the potentials VT circuits with the least amount of ablation necessary.	No prospective validation.

Except nonclinical very fast (cycle length < 270 ms) VTs. EGMs = electrograms; LV = left ventricle; NIPS = noninvasive programmed stimulation; PES = programmed ventricular stimulation; RV = right ventricle; VT = ventricular tachycardia.

confounders, such as different periprocedural antiarrhythmic drug regimens (and adoption of preprocedural antiarrhythmic drug washout), different anesthesia protocols, and heterogeneous PES protocols. In this regard, only 1 study included also left ventricular (LV) stimulation;[13] in this particular study, noninducibility of any VT was shown a strong predictor of long-term success at multivariable analysis. LV stimulation has been demonstrated superior to right ventricular (RV) stimulation for the induction of clinical VT in patients with ischemic cardiomyopathy.[39-41]

In a recent study, Santangeli et al prospectively compared RV stimulation with LV stimulation within the scar (as defined by conventional voltage criteria at 3-dimensional electroanatomic mapping) in a series of 156 patients undergoing catheter ablation of postinfarction VT.[39] PES (drive trains of 600/500/400 ms with up to 3 extrastimuli) was carried out sequentially from the RV apex, outflow tract, and within the infarct scar defined with electroanatomic mapping. RV stimulation induced clinical VT(s) in 31% of cases, while stimulation within the scar achieved

Table 30.2 Summary of Clinical Studies Utilizing Noninducibility at PES as the Endpoint for Catheter Ablation of Postinfarct VT

Study name	Year	No. of Pts	EF, %	Endpoint	PES Protocol	Acute Endpoint	Follow-up, months	VT Recurrence
Morady et al[22]	1993	15	27	Noninducibility of clinical VT	600/400/350 ms, S4, 2 RV sites	80%	9	13%
Kim et al[31]	1994	21	32	Noninducibility of any VT	No information	29%	13	45%
Rothman et al[23]	1997	35	24	Noninducibility of any VT	600/400 ms, S4, 2 RV sites. Protocol repeated after 30 min waiting period	31%	14	31%
Stevenson et al[25]	1998	52	33	Noninducibility of any VT	600/400 ms, S4, 2 RV sites (only 1 site in 5 cases)	40%	18	31%
Ortiz et al[33]	1999	34	31	Noninducibility of any VT	600/400 ms, S4, 2 RV sites	67%	26	38%
El-Shalakany et al[30]	1999	15	26	Noninducibility of any VT	3 drive trains (NS), S4	93%	15	27%
Calkins et al[6]	2000	119	31	Noninducibility of any mappable VT	NS drive train(s), S4, 2 RV sites	89%	8	46%
O'Callaghan et al[38]	2001	55	32	No information	No information	–	39	NS
Borger et al[27]	2002	89	29	Noninducibility of any mappable VT	600/500/400 ms, S4, 2 RV sites	78%	34	23%
Della Bella et al[28]	2002	124	34	Noninducibility of clinical VT	600/500/400 ms, S4, 2 RV sites	73%	41	28%
O'Donnell et al[32]	2002	109	NR	Noninducibility of any VT with a CL>230 ms	600/400 ms, S6, one RV site (apex)	38%	61	23%
Segal et al[34]	2005	40	36	Noninducibility of any VT	600/400 ms, S4, 2 RV sites	60%	36	57%
Verma et al[74]	2005	46	NR	Noninducibility of any VT	600/400 ms, S4, 2 RV sites	NS	16	37%
Volkmer et al[36]	2006	47	30	Noninducibility of any VT with a CL within 30 ms of the clinical VT	NS drive train(s), S4, 2 RV sites	81%	25	25%
Stevenson et al[75]	2008	231	25	Noninducibility of any VT with a CL within 20 ms of the clinical VT. Faster VT(s) targeted at the discretion of the operator	600/400 ms, S4, 2 RV sites	49%	6	47%
Carbucicchio et al[13]	2008	95	36	Noninducibility of any VT	600/500/400 ms, S4, multiple RV/LV sites	65%	22	34%
Tanner et al[35]	2010	63	30	Noninducibility of any clinical VT and VT(s) slower than clinical VT	600/400 ms, S4, 2 RV sites	81%	12	49%
Kuck et al[4]	2010	52	34	No information	No information	52%	23	53%
Tung et al[14]	2010	54	31	Noninducibility of any VT	600/400 ms, S4, 2 RV sites	76%	24	15%
Dinov et al[29]	2012	102	32	Noninducibility of any VT	500/430/370/330 ms, S2, one RV site (apex)	76%	14	42%
Summary	**–**	**1401**	**–**	**–**	**–**	**64%**	**–**	**37%**

CL = cycle length; EF = left ventricular ejection fraction; LV = left ventricle; NS = not specified; PES = programmed electrical stimulation; Pts = patients; RV = right ventricle; S4 = three extrastimuli; S6 = five extrastimuli; VT = ventricular tachycardia.

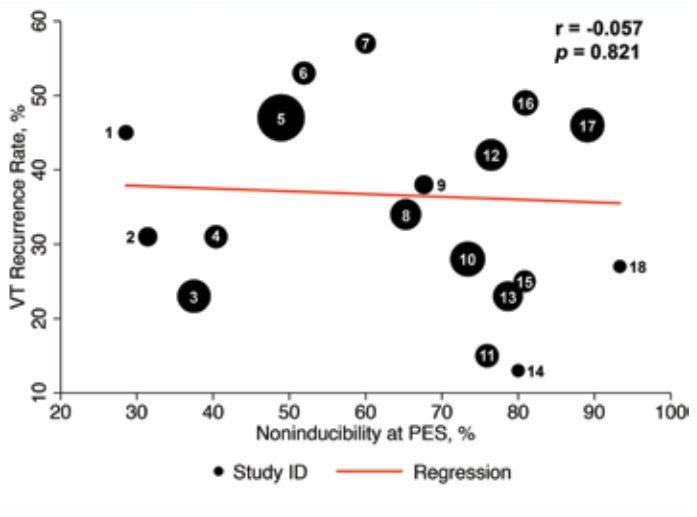

Figure 30.1 Evidence that noninducibility at PES is not a reliable endpoint for catheter ablation of postinfarct VT. The rates (*y*-axis) of VT recurrence at follow-up are plotted against the rate of VT noninducibility at the end of the procedure for each included study (*x*-axis). Weighted meta-regression analysis (**red line**) shows that increasing rates of VT non-inducibility are not correlated to an increase in long-term procedural success. Note: weights are based on study sample size. **Legend:** (1) Kim et al[31]; (2) Rothman et al[23]; (3) O'Donnell et al[32]; (4) Stevenson et al[25]; (5) Stevenson et al[5]; (6) Kuck et al[4]; (7) Segal et al[34]; (8) Carbucicchio et al[13]; (9) Ortiz et al[33]; (10) Della Bella et al[28]; (11) Tung et al[14]; (12) Dinov et al[29]; (13) Borger et al[27]; (14) Morady et al[22]; (15) Volkmer et al[36]; (16) Tanner et al[35]; (17) Calkins et al[6]; (18) El-Shalakany et al.[30]

the endpoint in 69% of cases (risk ratio [RR] = 2.20, 95% confidence interval [CI] 1.68 to 2.89, $P < 0.001$). Notably, 13 (8%) patients were inducible only from the scar.[39] It is important to emphasize that the relative merits of RV-only vs. LV stimulation according to different VT morphologies (LBBB versus RBBB VTs) were not assessed in this study; in our experience, scar-related LBBB VTs are more easily inducible from the RV, as opposed to RBBB VTs that are best induced with lateral LV stimulation. Nonetheless, the study by Santangeli et al highlights the importance of multiple site stimulation (including the LV) for the induction of VT in patients with ischemic cardiomyopathy.[39] It is conceivable that noninducibility of any VT achieved with a consistent stimulation protocol that includes triple extrastimuli from multiple RV and LV sites might provide incremental value in predicting long-term VT-free survival.

Based on the experience on catheter ablation of postinfarct VT, noninducibility at PES has been used as an ablation endpoint across all the spectrum of scar-related VTs.[1,2] In patients with nonischemic substrates, few studies have evaluated the role of noninducibility as a predictor of survival free from recurrent VT after catheter ablation.[9,42,43] In a recent report, Piers et al determined the value of noninducibility at PES in a consecutive series of 45 patients with nonischemic cardiomyopathy (average EF = 44% ± 14%) and scar-related VT. In this study, PES consisted of 3 drive trains (600/500/400 ms) with 3 extrastimuli from at least 2 RV sites, and burst pacing. A total of 17 (38%) patients achieved noninducibility of any VT at the end of the procedure; other 17 (38%) patients had a partial procedural success, defined as elimination of the clinical VT and persistent inducibility of at least 1 nonclinical VT, and 11 (24%) patients had a failed ablation, defined as lack of elimination of the clinical VT. After a mean follow-up of 25 ± 15 months, VT recurred in 24 (53%) patients. Noncomplete procedural success (inducibility of any VT at the end of the procedure) was the strongest predictor of VT recurrence (hazard ratio = 8.20, 95% CI 2.37 to 28.43, $P = 0.001$).[42] These results would support the appropriateness of considering noninducibility as an endpoint also for catheter ablation of scar-related VT in the setting of nonischemic cardiomyopathy.

Areas of Uncertainty

Although a statistical association between lack of VT inducibility at the end of the procedure and long-term arrhythmia-free survival has been shown in multiple studies, this endpoint clearly has limitations. As mentioned, none of the studies

was specifically designed to test the value of noninducibility at PES in predicting VT recurrences after catheter ablation, and none had a prospective randomized design; this prevents an estimation of the real positive and negative predictive values of noninducibility.[44] PES often yields more VT morphologies than those clinically documented, with an average of 3 or 4 VTs per patient.[23,25] The clinical relevance of previously undocumented VTs is challenging to assess, and the current approach in most institutions is to target for ablation every inducible VT except very fast nonclinical VTs. There is some evidence that using a cycle length cutoff of 270 ms would distinguish between nonclinical VTs with no prognostic relevance and nonclinical VTs that should be targeted for ablation;[23] slow VTs also tend to recur more often as compared to very fast VTs. However, no cycle length cut-off value has ever been validated in adequately designed prospective studies. Lack of VT inducibility before ablation represents another limitation of PES; in recent studies, lack of VT inducibility was reported in up to 50% of patients referred for catheter ablation of scar-related VT.[12] Finally, the optimal time point when to perform PES after the ablation procedure is unknown.[45]

Noninvasive Programmed Electrical Stimulation

Our group has recently tested the hypothesis that repeat programmed stimulation a few days after the ablation procedure in subjects who were noninducible at the end of the procedure and/or without spontaneous early VT recurrence might provide additional prognostic information.[45] In a prospective study including 178 consecutive patients with VT and structural heart disease, Frankel et al performed NIPS from the right ventricular ICD lead (drive trains of 600/400 ms, up to 3 extrastimuli) in a total of 132 (74%) patients a mean of 3.1 ± 2.1 days after ablation. The remaining 46 patients did not undergo NIPS for different reasons, including unstable medical condition (N = 26), death prior to NIPS (N = 6), and physician or patient preference (N = 14). NIPS confirmed noninducibility of any VT in 45% of cases. Nonclinical VT was inducible in 37.1% of patients, and clinical VT in 18.2% of cases. The latter group was more likely to be treated with amiodarone (typically high dose of amiodarone), and more likely to have their amiodarone dose decreased or discontinued after ablation. Such a change in the dose of amiodarone immediately after the ablation procedure, together with differences in autonomic tone and/or degree of sedation or anesthesia, might have contributed to the higher likelihood of clinical VT induction with NIPS as compared to PES immediately after the procedure. After 1 year of follow-up, patients without any inducible VT at NIPS experienced the best outcome (85% VT-free survival). Patients with inducible clinical VT had markedly decreased VT-free survival (< 30%, P = 0.001 for comparison to no inducible VT); those with inducible nonclinical VT had intermediate VT-free survival (65%, P = 0.01 for comparison to no inducible VT) (Figure 30.2). These findings strongly suggest the adoption of noninducibility of clinical VT at NIPS a few days after the procedure as an endpoint for catheter ablation of scar-related VTs. Compared to PES immediately after the procedure, NIPS may have more predictive value, possibly due to the time-dependent interaction with antiarrhythmic drug discontinuation, changes in autonomic tone and/or degree of sedation/anesthesia, and ablation lesion maturation or regression due to the resolution of transient EP effects possibly due to edema. Whether early intervention with repeat ablation in patients with inducible clinical VT(s) at NIPS results in improved arrhythmia-free survival still requires confirmation.

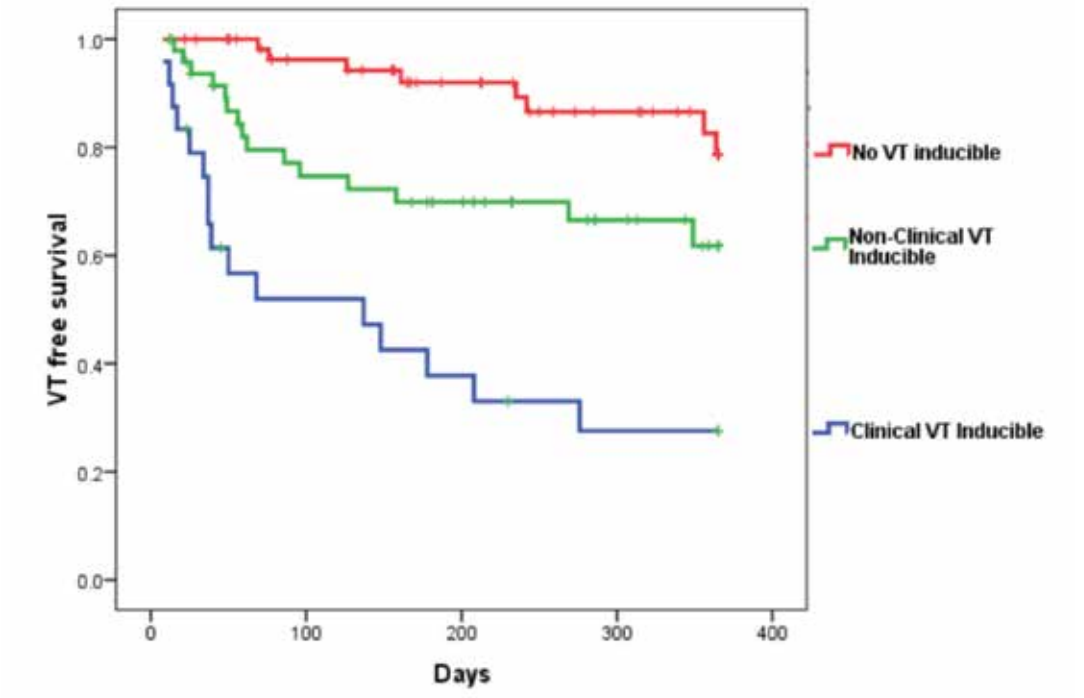

Figure 30.2 One-year outcome based on response to NIPS at 1–7 days after VT ablation. *Source:* Reproduced with permission from Frankel et al.

Endpoints for Substrate-Based Ablation

Up to two-thirds of patients referred for catheter ablation of scar-related VT present with only hemodynamically unstable arrhythmias that prevent mapping during prolonged periods of tachycardia.[1,5,46] Substrate-based ablation approaches have been developed to eliminate the requirement for mapping during VT and are based on the transection of the putative VT(s) exit sites and putative isthmuses within the dense scar,[3,46,47] together with elimination of abnormal electrograms that indicate areas of slow conduction (split and late potentials). Although noninducibility at PES has been adopted as the main endpoint also in studies evaluating substrate-based ablation approaches, novel procedural endpoints have been described to evaluate the completeness of linear lesions and the effective elimination of abnormal electrograms. The role of such novel endpoints will be reviewed in the following section.

Linear Ablation Lesions

The development of substrate-based linear ablation strategies was based on experience from surgical ablation of VT. In early studies, subendocardial resection was demonstrated highly effective in eliminating VT in up to 90% of cases, albeit with a high risk of periprocedural mortality.[48] Linear extension of surgical lesions outside the dense infarct scar to reach visible anatomical barriers (eg, mitral annulus) further improved the long-term arrhythmia-free survival.[49] In the effort to replicate the results of subendocardial resection with catheter-based techniques, our group has developed a substrate-based ablation strategy that includes contiguous linear lesions delivered from the dense infarct area (as defined by standard voltage criteria at 3D electroanatomic mapping) through the infarct border zone and connecting to anatomical barriers or normal myocardium. In the original description of the technique, linear lesions were placed using 3 main principles: (1) lesions were extended across the borders of the endocardium with abnormal

bipolar voltages (ie, ≤ 1.5 mV); (2) lesions extended from the dense scar (ie, < 0.5 mV) to areas demonstrating normal bipolar voltages (ie, > 1.5 mV) or to a valve continuity; and (3) lesions were crossed at the infarct border zone at sites where pace mapping approximated the QRS morphology of the VT (Figure 30.3).[46] Linear lesions are also commonly deployed to transect "channels" visualized after adjusting voltage cutoffs on color isopotential electroanatomic maps; these channels, particularly when associated with late potentials, have been correlated with VT isthmuses as defined by entrainment mapping.[50] Finally, a linear ablation strategy is often required for mappable VTs with a broad isthmus, as defined by entrainment mapping (Figure 30.4). In these cases, even if

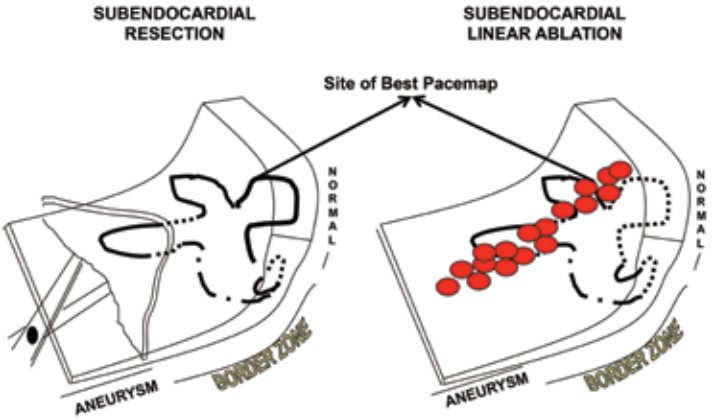

Figure 30.3 Schema of the catheter-based linear ablation strategy designed to replicate the experience with subendocardial resection. High-density bipolar voltage maps identifies the dense scar (< 0.5 mV), the border zone (between 0.5 mV and 1.5 mV), and normal myocardium (> 1.5 mV). Linear lesions guided by pace mapping extend from the dense scar to normal myocardium. *Source:* Reproduced with permission from Marchlinski et al.[46]

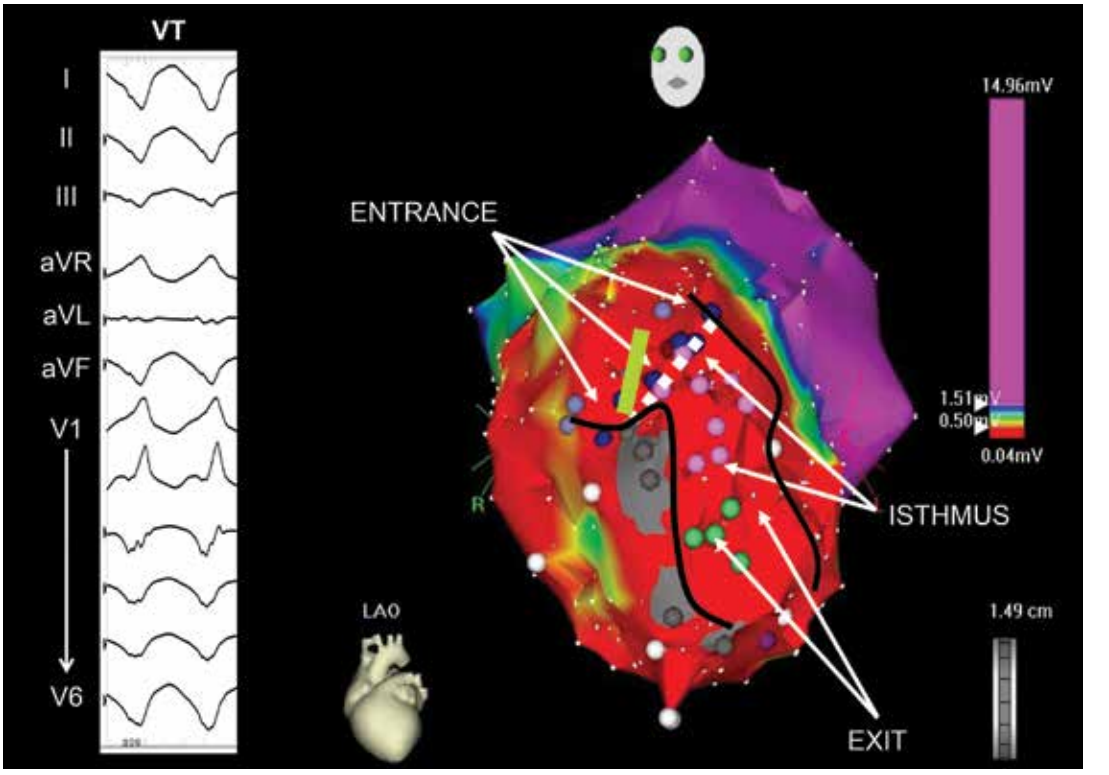

Figure 30.4 Example of a VT with a broad isthmus, as defined with entrainment mapping. Even if acute VT termination is achieved, ablation should be extended to cover the entire width of the isthmus in order to prevent VT recurrence. Verification of the completeness of the linear ablation and block across the line may be difficult unless the boundaries of the isthmus are fixed anatomically so that pacing techniques can be applied.

acute VT termination is achieved, ablation should be extended to cover the entire width of the isthmus in order to prevent VT recurrence. Typically, linear lesions are deployed with sequential point-by-point ablation. The effectiveness of each ablation lesion is assessed monitoring multiple parameters, including adequate tissue-catheter contact validated with fluoroscopy and intracardiac echocardiography (ICE), and impedance drop with the endpoint of achieving a decrease of at least 15 Ohms. Once a linear lesion has been deployed, it is important to assess for completeness (Table 30.2); unfortunately, there is no established method to confirm block across a linear lesion in the setting of VT ablation, although some criteria have been suggested.[51] In theory, when an ablation line is complete, high-output pacing along the line should result in complete lack of excitability, similar to what has been reported in the context of catheter ablation of atrial fibrillation.[52] However, unlike for atrial fibrillation ablation where the tissue targeted is typically healthy and with low baseline pacing threshold, in the setting of scar-related VT the tissue targeted for ablation has already high baseline pacing thresholds. Based on previous clinical experiences, most investigators use a current output of 10 mA and a pulse width of 2 ms to confirm unexcitability,[53] although capture within the dense scar can still be achieved using higher pulse strengths.[54] Therefore, the optimal pacing output to confirm electrical unexcitability after ablation is still undefined. Electrophysiological criteria for confirmation of block across a line of ablation have not been established. Recently, Bala et al from our group described a novel endpoint for confirmation of block across a linear ablation lesion, namely, the change in QRS morphology with pacing at a protected isthmus.[51] The index case was a 44-year-old male patient with history of tetralogy of Fallot and scar-related VT, which was documented to be clockwise macroreentry below the pulmonic valve by means of entrainment maneuvers (Figure 30.5). The exit site of the VT was under the pulmonic valve on the posterior aspect of the conal septum; the isthmus site was the conal free wall of the RVOT. A single radiofrequency lesion delivered at the isthmus site terminated the VT; after ablation, pace mapping proximal to the isthmus site resulted in a dramatic change in the QRS morphology, with a superior axis that no longer matched the clinical VT but matched the pace map obtained from the conal free wall prior to ablation. In this case, the change in pace maps pre- and postablation demonstrated that a line of block (or much slower conduction) had been created with ablation, therefore resulting in a different exit out of the scar from the pacing site (Figure 30.5).[51] This report highlights how demonstration of block across a linear ablation can be rapidly assessed with pace mapping techniques; however, as mentioned, this technique does not allow for distinction between complete block and extreme delay created by the ablation. The ultimate demonstration of block across a linear lesion can be achieved with activation mapping techniques with pacing from each side of the ablation line. Activation mapping requires at least 2 catheters, and demonstration of block should be ideally achieved with a detailed activation map with pacing from the proximal side of the ablation line (close to the entrance of the VT circuit) at different cycle lengths. Block is demonstrated when the distal side of the line (close to the exit of the VT circuit) is activated later than the outer loop and the putative VT exit site at the border zone of the scar (Figure 30.6). Bidirectional block might be confirmed with pacing from the distal aspect of the line, and this is particularly important when bidirectional revolution across an isthmus has been clinically documented. A classical example of this phenomenon is the combination of a VT with a left bundle branch block configuration with a left superior axis (septal exit) and a VT with a right bundle branch block configuration and a right superior axis (lateral exit) in the setting of an inferior myocardial infarction. In this case, linear ablation at the "mitral isthmus" is

necessary to eliminate both VTs,[49,55] and demonstration of bidirectional conduction block across the ablation line is important. Another technique to approximate block across a linear lesion is to analyze the activation delay to a site immediately distal (closer to the VT exit) to the ablation line when pacing proximal to the line (closer to the VT entrance). Although no absolute timing value can be used as a proof of conduction block, a conduction time across the line longer than the VT cycle length can be used as a reasonable surrogate for complete (unidirectional) block (Figure 30.6). In conclusion, in the setting of scar-related VT the completeness of a linear ablation lesion with demonstration of conduction block can be achieved with activation mapping techniques; whether systematic confirmation of block results in improved long-term VT-free survival warrants further prospective investigation.

Ablation of Late Potentials

Regions with delayed and fragmented conduction bordering on scar tissue[46,56,57] and islets of surviving myocytes within otherwise dense scar[8,46,56,57] have all been demonstrated to be essential components of circuits underlying reentrant ventricular arrhythmias. Substrate mapping has been extensively used to characterize the electrical correlates of such arrhythmogenic substrates, such as abnormal fractionated and late electrograms.[8,56] Fragmented electrograms can be recorded throughout the scar and are not specific

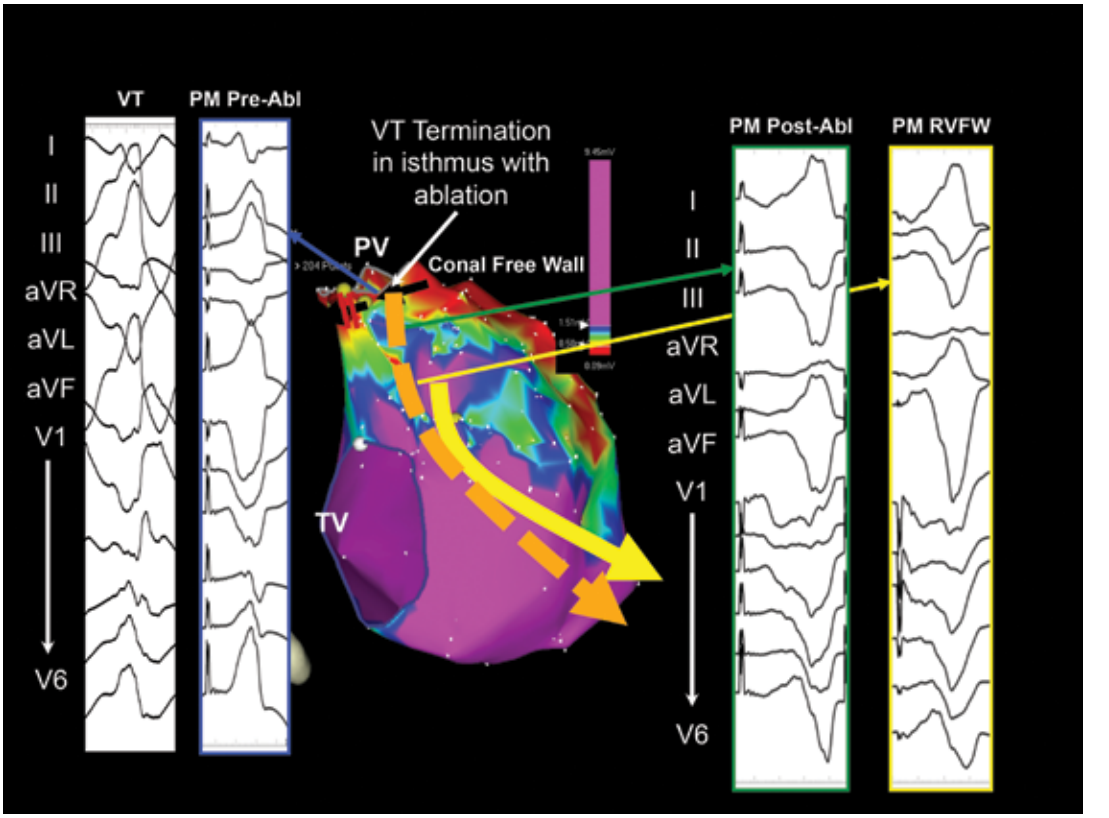

Figure 30.5 High-density voltage map of the right ventricle in a patient with tetralogy of Fallot and scar-related ventricular tachycardia (VT). A large area of scar extends from the pulmonic valve (PV) to the conal free wall. Pace maps before ablation (PM Pre-Abl) from the conal free wall under the pulmonic valve (**blue panel**) and in the right ventricular free wall (RVFW) adjacent to the tricuspid valve (TV) (**yellow panel**) are shown. After termination of VT in the isthmus, a pace map proximal to the site of ablation (PM Post-Abl, **green panel**) is consistent with a change in QRS morphology matching the pace map from the RVFW preablation. This finding suggests that linear block (or severe conduction delay) has been achieved with radiofrequency application. *Source:* Modified from Bala et al.[51]

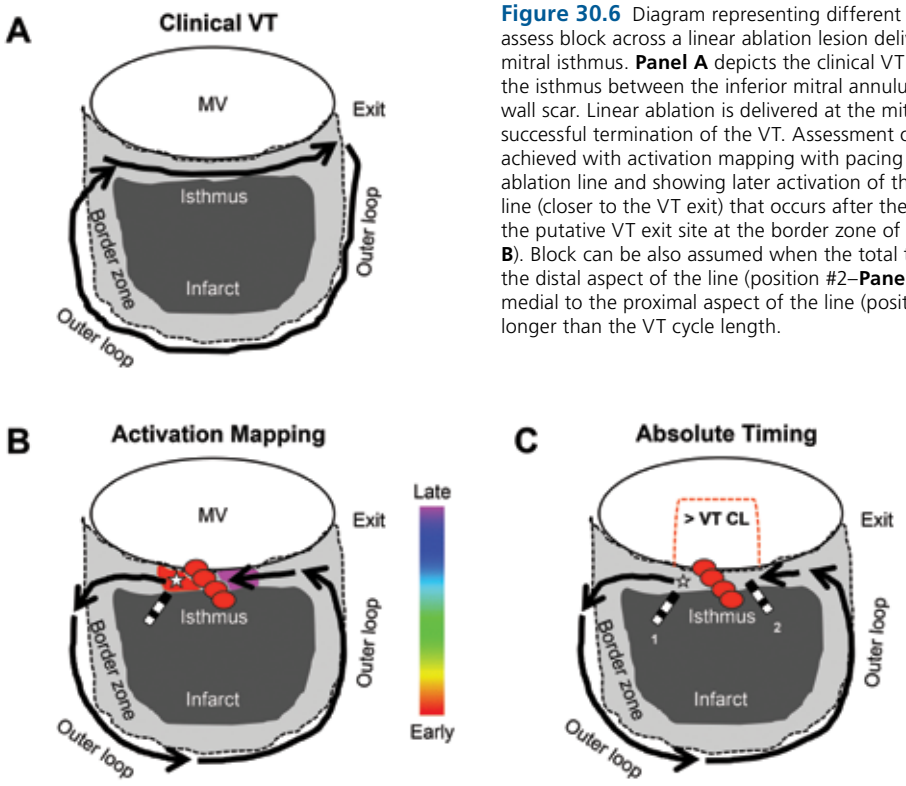

Figure 30.6 Diagram representing different techniques to assess block across a linear ablation lesion delivered at the mitral isthmus. **Panel A** depicts the clinical VT circuit utilizing the isthmus between the inferior mitral annulus and the inferior wall scar. Linear ablation is delivered at the mitral isthmus with successful termination of the VT. Assessment of block can be achieved with activation mapping with pacing medial to the ablation line and showing later activation of the distal side of the line (closer to the VT exit) that occurs after the outer loop and the putative VT exit site at the border zone of the scar (**Panel B**). Block can be also assumed when the total timing to activate the distal aspect of the line (position #2–**Panel C**) when pacing medial to the proximal aspect of the line (position #1–**Panel C**) is longer than the VT cycle length.

for VT circuit components, whereas isolated and late potentials have been demonstrated to be relatively specific markers for VT circuits.[15,16,50] In a seminal study, Miller and colleagues demonstrated disappearance of late potentials after successful subendocardial resection.[15] More recently, Bogun et al reported a high degree of correlation between presence of late potentials in sinus rhythm and VT isthmuses confirmed by entrainment mapping.[16] Presence of late potentials has also been longitudinally correlated with occurrence of spontaneous sustained ventricular arrhythmias in substrates different from coronary artery disease, such as in arrhythmogenic right ventricular cardiomyopathy.[58] Due to the demonstrated critical role of late potentials in reentrant VT circuits, many institutions have incorporated ablation of late potentials in their substrate-modification approach, resulting in a substantial improvement in VT-free survival (see also chapter 22).[12,59,60] Studies evaluating the role of late potential ablation in scar-related VT adopted heterogeneous procedural endpoints to ensure completeness of ablation, ranging from complete elimination of late potentials to failure to capture with high-output pacing (or a combination of the two criteria).[12,59,60] It is important to emphasize that the definitions of late potentials were not consistent among different studies, and late potentials were assessed predominantly in sinus rhythm.[12,59,60] Earlier works suggest that RV pacing might allow detection of late potentials in more patients as compared to sinus rhythm.[8] In addition, with currently available ablation tools, complete abolition of late potentials is not always achievable.[12,60] In a prospective study, Vergara et al reported complete elimination of late potentials in 42/50 (84%) patients with scar-related VT undergoing a substrate-based ablation strategy targeting only late potentials. Similar results have been reported by Jaïs et al, who targeted high-frequency late potentials

(so-called local abnormal ventricular activities [LAVA]) in a group of 67 patients with VT and structural heart disease. In this study, LAVA were successfully eliminated only in 47 (70%) patients.[60] Of note, the reasons for incomplete elimination of late potentials were not addressed in these studies.[12,60] In a prospective multicenter trial, Di Biase et al adopted a combination of late potential elimination and high-output pacing (20 mA output, pulse duration of 10 ms) to confirm effective ablation.[59] High-output pacing is particularly valuable in areas where late potentials are persistently recorded despite extensive ablation. In these situations, lack of (global) capture might be explained by either far-field recording or by local capture with exit block and suggest that one can discontinue radiofrequency application. Of note, late potential activation maps appear to suggest sequential activation from the border of the scar and through well-defined channels.[9,61] By targeting the earliest late potential, one may eliminate a series of important late potentials that may be critical for supporting a reentrant circuit.

One of the main limitations of late potential ablation relate to the likely bystander nature of many late potentials,[62,63] which are empirically targeted for ablation without any clinical benefit and with potential risk of complications. This is especially common in inferior infarctions where large areas of myocardium can be activated "late" in the normal process of activation in sinus rhythm. Targeting these sites may not be necessary. Further studies are warranted to better understand the clinical relevance and relation to clinical arrhythmias of late potentials recorded within the scar, in order to target for ablation only the electrograms that are relevant to the development of VT. The second major limitation is related to the site-dependent nature of pacing required to bring out late potentials. Identifying best site(s) based on scar location and/or VT morphology has not been established. The number of pacing sites that are required to optimally define clinically relevant late activation has also not been determined. Thirdly, the optimum recording technique to identify late potentials and their elimination with ablation related to electrode size requires further study. Finally, the need for additional remapping to establish total elimination of late potentials from different pacing sites still needs to be determined.

Box Lesion Set with Loss of Excitability in the Core

The concept of box lesion to isolate critical arrhythmogenic areas within the dense scar has been recently developed by our group as a novel approach for substrate modification. The physiological rationale underlying this approach is based on previous clinical evidences demonstrating that zones of slow conduction critical for VT maintenance are frequently located within the dense scar.[8,53,64,65] Hsia et al characterized the location, dimensions, and characteristics of the reentrant circuit in a group of 26 patients with scar-related VT.[66] Entrainment mapping was performed in 53 VTs, of which 19 entrance, 37 isthmus, 48 exit, and 32 outer loop sites were identified. Entrance and central isthmus sites were located in the dense scar in 84% of cases, whereas exit or outer loop sites were more likely located within the border zone.[66] In the same study, Hsia et al pointed out the relevance of corridors of consecutive low-voltage electrograms bounded by electrically unexcitable scar identified during sinus rhythm mapping, so called "channels," that were found in 18/32 (56%) VTs and were associated with VT termination during ablation in 16/18 (89%) cases.[66] Mountantonakis et al reviewed the relationship between channels at high-density voltage map and VT isthmuses in a series of 24 patients with postinfarction cardiomyopathy.[50] In this study, only 30% of channels that could be identified with voltage mapping contained a VT isthmus, and only 44% of mappable VTs were associated with an identifiable channel. Of note, the presence of late potentials

within the channel increased the specificity for VT isthmuses defined by entrainment to 85%.[50] As mentioned, late potentials have shown relatively specific markers for VT circuits[15,16,50] and are currently targeted by most investigators throughout the scar, resulting in extensive ablation.[12,59,60] In an effort to limit the number of lesions required to target all the areas critical for VT(s) maintenance within the dense scar (eg, putative VT channels and late potentials), the box-type lesion set has been developed, with the procedural endpoint of electrical unexcitability within the scar core. The box-type substrate ablation is a stepwise approach that starts with identification of the "area of interest" within the dense scar that is related to the patient's clinical and/or induced VT(s) based on conventional criteria, including voltage channels, sites with late potentials, sites with good pace maps and long stimulus-to-QRS (S-QRS) intervals, or sites with entrainment with concealed fusion (when possible). Once identified, the "area of interest" is boxed by linear ablation lesions delivered at the edge between the dense scar (< 0.5 mV) and the border zone (between 0.5 mV and 1.5 mV) (Figure 30.7). The box lesion will typically encompass a well-defined area of interest of about 6–12 cm^2. At the end of the box lesion set, loss of capture within the boxed area is confirmed with high-output pacing (up to 50 mA output and 10 ms pulse width) from multiple regions within the ablation set. If such endpoint is not achieved, the lesion set is carefully remapped for potential gaps and further ablation is delivered until complete isolation of the boxed area is achieved. When complete isolation is not achieved, the core of

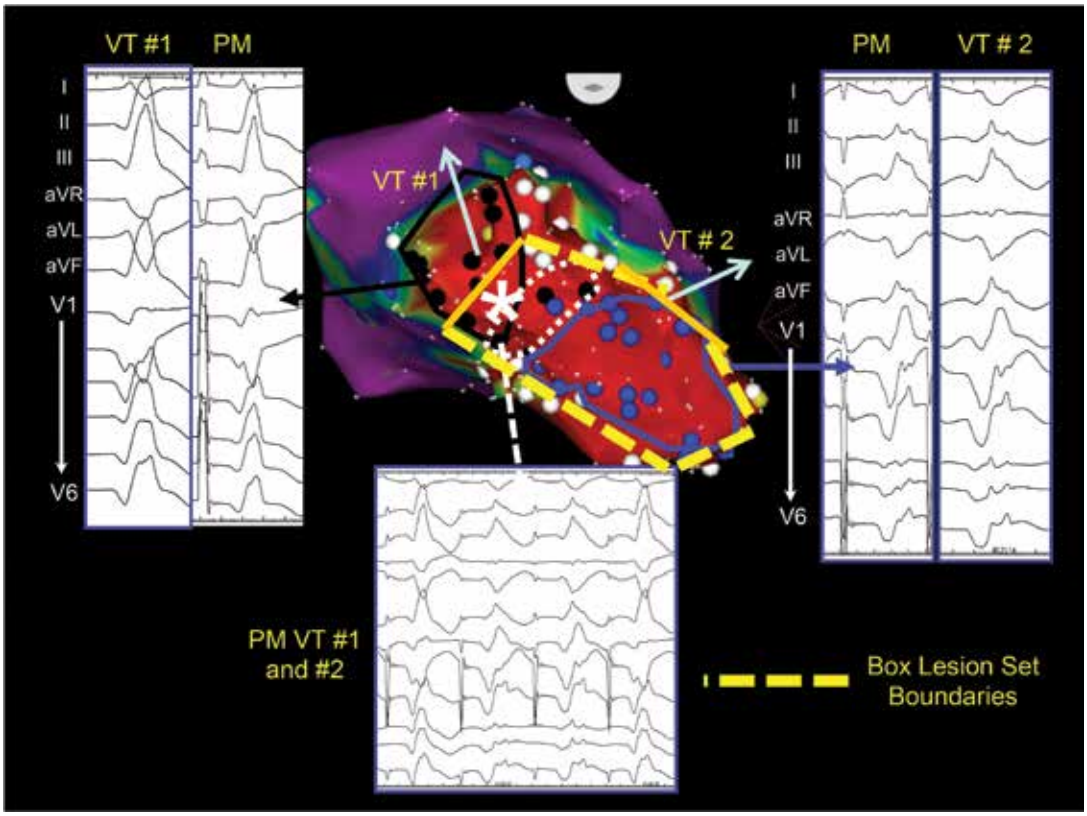

Figure 30.7 Example of elimination of all the potentials VT circuits by completing fixed anatomic boundaries in the core of the VT substrate. Pace mapping is used to define the anatomic boundary (**dashed lines**) in a patient with apical infarction and recurrent VT. At the end of the ablation set that connected anatomic boundaries (**solid lines**), electrical unexcitability within the boxed area was verified with high-output pacing (up to 50 mA output) (see text for details).

the box is assessed and additional lesions are placed inside the box to eliminate any remaining late or split electrograms. It is not expected that this isolation is transmural in nature in many patients. We suspect that isolation of the endocardial aspect of the region of interest can be achieved if an intramural dense scar forms an effective barrier to endocardial to epicardial conduction. This is consistent with the compartmentalization of RV endocardial from LV endocardial scar documented in patients with midmyocardial septal scar in the setting of nonischemic cardiomyopathy. This new substrate-based approach certainly minimizes the amount of ablation necessary to eliminate all the potential VT circuits within the dense scar and is based on a strong physiological rationale. Whether the box lesion set translates into improved arrhythmia-free survivals requires further prospective investigation.

Online Imaging for Direct Visualization of Lesions Formation

Although the selection of the ablation targets should always rely on information derived from established electrophysiological maneuvers and analysis of electrograms, direct visualization of lesion formation might provide valuable information on the adequacy and completeness of the lesions. At the University of Pennsylvania, online imaging with ICE is performed routinely to monitor tissue-catheter contact, catheter stability, and lesion formation during ablation of scar-related VT (Figure 30.8). In a preclinical study, Ren et al correlated the ICE imaging of intramural swelling during radiofrequency delivery with lesion size at pathological analysis in a swine model of chronic myocardial infarction,[67] thus providing a strong rationale for real-time ICE monitoring of lesion formation. The use of other imaging modalities, such as cardiac magnetic resonance (CMR), is still at the investigational stages, although early experiences have shown promising results.[68-70] Interstitial edema and tissue swelling occur during the acute phase of radiofrequency delivery; T2-weighted CMR imaging has been demonstrated able to identify hyperintense myocardial areas correlating with lesion size on pathology.[68,69] Such tissue modifications occur within the first 2 minutes from radiofrequency delivery, and persist for up to 12 hours postablation. In addition, T2-weighted imaging has been suggested useful to detect gaps between contiguous ablation lesions with a good degree of correlation with pathology (Figure 30.9).[70] Noncontrast T1-weighted sequences have also been used to monitor lesion formation, although the spatial resolution and contrast appears worse than T2-weighted sequences.[70] Gadolinium contrast-enhanced sequences represent the gold standard for noninvasive visualization of

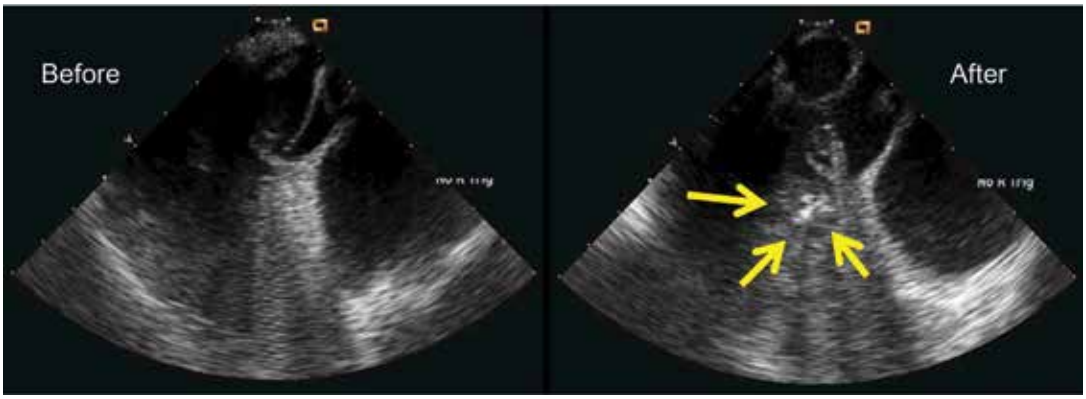

Figure 30.8 Intraprocedural imaging of lesion formation with intracardiac echocardiography (ICE). Effective lesion formation is associated with increased echogenicity of the myocardium, which has been shown to correlate with lesion size at pathology in preclinical studies.[67]

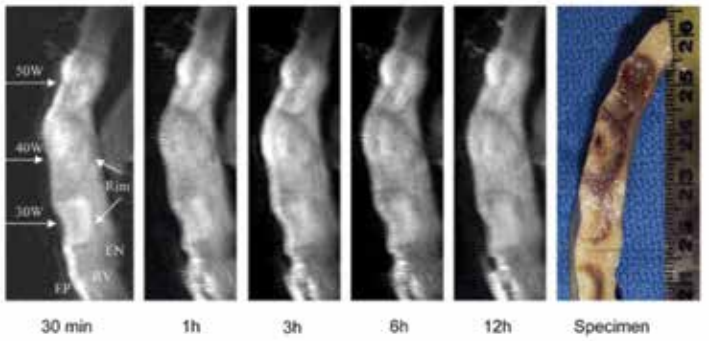

Figure 30.9 Evolution of ablation lesions with T2-weighted MRI imaging. Lesions at MRI demonstrate good correlation with pathology. *Source:* From Dickfeld et al[70] with permission.

ablation lesions; preliminary reports suggest that a good correlation with pathological analysis can be achieved by imaging intermediate late enhancement patterns, as early as 1 minute after contrast injection.[71] On the other hand, due to the relatively long half-life of elimination of gadolinium (1–2 hours) together with the maximum dose limit that can be safely administered in a single patient, gadolinium contrast-enhanced CMR appears less useful for serial assessment of lesion formation.[71] Other tools to allow direct imaging of scar architecture and lesion formation are in the active phase of development; among these, a novel endoscopic catheter (IRIS® cardiac ablation catheter; Voyage Medical Inc., Redwood City, CA) has undergone preclinical evaluation in an ovine model of myocardial infarction.[72] The catheter integrates an open-irrigated ablation platform with a high-resolution flexible fiberscope and allows for accurate distinction of the infarct architecture and ablation lesions, with a good correlation with bipolar voltage map (Figure 30.10). Although promising, the value and safety of this technology deserves clinical validation in humans.

Conclusion

Since its first introduction into clinical practice in 1983,[73] catheter ablation VT has become an established treatment strategy for scar-related VT with outstanding improvements in techniques and results. However, despite such advances the

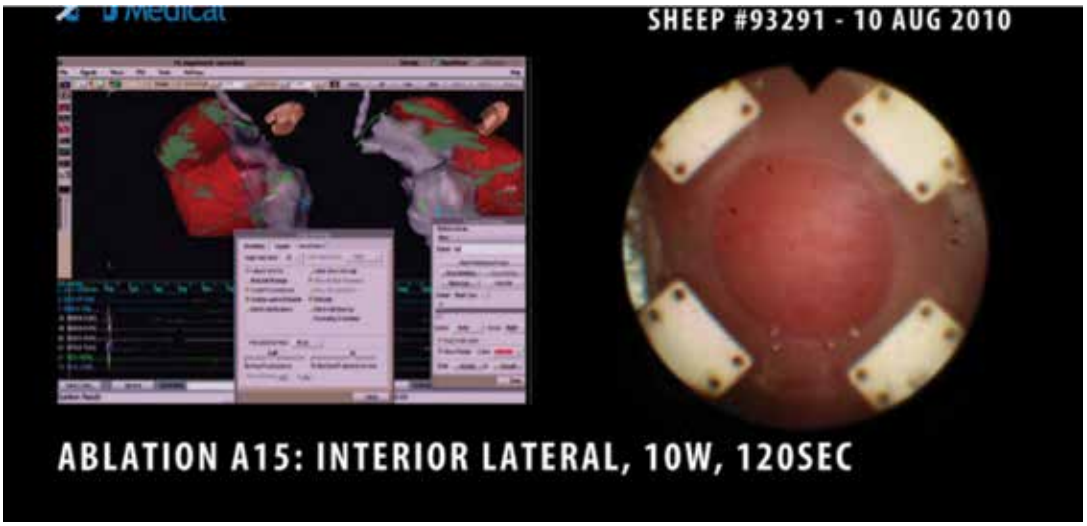

Figure 30.10 Example of direct endocardial visualization with the use of the IRIS® ablation catheter (Voyage Medical Inc.). The integrated high-resolution flexible fiberscope allows for accurate distinction of the infarct architecture, with a good correlation with bipolar voltage map. *Source:* From Betensky et al.[72] Image courtesy of Dr. Edward Gerstenfeld.

long-term outcomes still remain suboptimal. Thus far, the best ablative strategy and optimal procedural endpoints are undefined, and no randomized data are available comparing different ablation approaches and/or procedural endpoints. Traditionally, noninducibility at PES has been used as an endpoint for catheter ablation of scar-related VT, although with heterogeneous definitions and stimulation protocols among different studies. Notwithstanding the limitations inherent to the published studies, a pooled analysis of the available evidence does not support the adoption of noninducibility as the only endpoint for catheter ablation of scar-related VT and highlights the importance of evaluating novel endpoints in order to improve the ablation outcomes. Observational data suggest that incorporating left ventricular stimulation immediately postablation and repeat programmed stimulation from the ICD (NIPS) a few days after the procedure may provide incremental predictive value for assessing ablation efficacy.

The benefit of early intervention based on the results of NIPS warrants further investigation. In recent years, the increasing adoption of substrate-based ablation techniques has been paralleled by an increasing need for new ablation endpoints to validate the completeness of linear lesions and the elimination of abnormal potentials within the scar. Failure to capture with high-output pacing along the ablation line, changes in QRS morphology with pacing from each side of the line, and activation mapping to confirm conduction block across the line have all been used to demonstrate completeness of a linear ablation lesion. Presence of low-amplitude, isolated late potentials within the scar during sinus rhythm has been correlated to VT reentry circuits in multiple studies. Accordingly, ablation of late potentials has been incorporated in the substrate ablation approaches of most institutions. Studies evaluating the role of late potential ablation in scar-related VT adopted heterogeneous procedural endpoints to ensure completeness of ablation, ranging from complete elimination of late potentials to failure to capture with high-output pacing (or a combination of the two criteria). At the University of Pennsylvania, the "box lesion set" has been recently developed in the effort to minimize the amount of ablation necessary to eliminate all the potential arrhythmogenic areas within the scar. The endpoint of such an approach is electrical isolation of the dense scar core contained in the boxed lesion and is verified with high-output pacing from multiple sites within the boxed area. The benefit of the box lesion set in terms of arrhythmia-free survival requires prospective investigation. Finally, direct visualization of lesion formation with noninvasive imaging techniques (CMR) or using dedicated ablation catheters integrated with high-resolution fiberscopes has shown promising results in preclinical models and warrants appropriate validation in human studies if they can be used as adequate ablation endpoint for lesion continuity and possibly depth.

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