Universiteit Leiden
The Netherlands

New insights on post-myocardial infarction ventricular tachycardia ablation: defining patient-tailored endpoints to improve outcome

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Citation

De Riva Silva, M. (2022, June 2). *New insights on post-myocardial infarction ventricular tachycardia ablation: defining patient-tailored endpoints to improve outcome*. Retrieved from https://hdl.handle.net/1887/3307420

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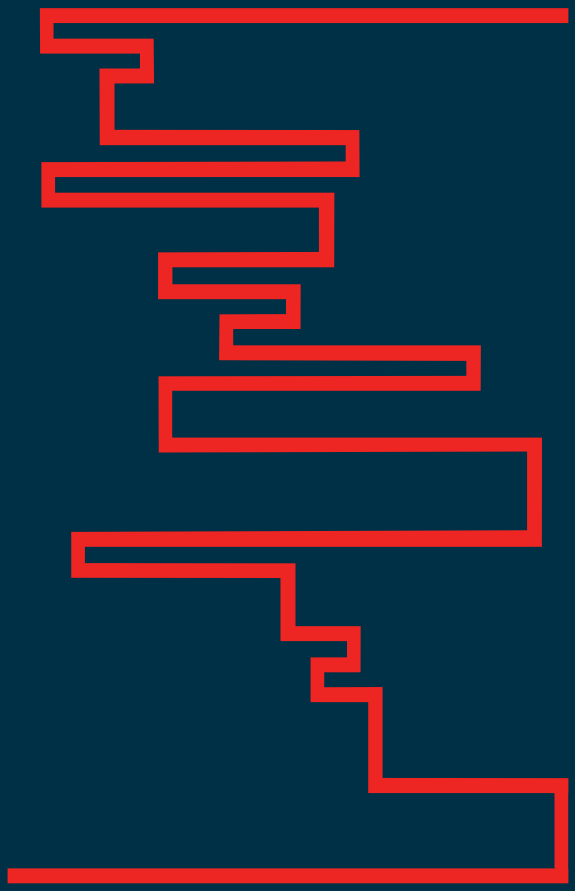

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M. de Riva Silva

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Cover design: Marta de Riva and Erwin Timmerman, inspired on the seminal work of Prof. Jacques de Bakker, Slow Conduction in the Infarcted Human Heart 'Zigzag' Course of Activation (Circulation 1993)
Layout and printing by Optima Grafische Communicatie (www.ogc.nl)
ISBN: 978-94-6361-708-6
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New insights on post-myocardial infarction ventricular tachycardia ablation: defining patient-tailored endpoints to improve outcome

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. dr. Ir. H. Bijl,
volgens besluit van het College voor Promoties
te verdedigen op 2 juni 2022
klokke 16.15 uur

door

Marta de Riva Silva
geboren te Segovia
in 1980

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Para Jose, por seguirme hasta aquí.

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1

General Introduction and Outline of Thesis

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Ventricular tachycardia after myocardial infarction

One to two percent of patients surviving an acute myocardial infarction (MI) develop monomorphic ventricular tachycardia (VT) over time, often more than a decade after the acute ischemic event.[1] Of importance, occurrence of VT may not only be a cause of disabling symptoms such as palpitations, dyspnea or syncope but it is also an important cause of sudden cardiac death (SCD) in this population.[2–4]

Implantable cardioverter defibrillators (ICDs) are effective in terminating VT and have demonstrated to increase survival in post-MI patients presenting with a cardiac arrest due to hemodynamically unstable VT or ventricular fibrillation (VF)[5–7]. However, it is important to highlight that ICDs do not prevent VT recurrence. Although the majority of VTs can be terminated by anti-tachycardia pacing (ATP) and therefore, some patients might be asymptomatic even if they suffer from recurrent VT, some VTs only terminate with ICD shocks, which can be a cause of pain and psychological distress and have even been associated with increased mortality[8–12]. In addition, some clinical presentations, such as VTs that do not terminate after multiple ICD interventions, slow VTs that are not recognized by the ICD or highly symptomatic VTs despite termination with ATP may require additional therapy to terminate VT and/or to avoid VT recurrence.

Treatment options in these scenarios are anti-arrhythmic drugs (AAD), catheter ablation and surgical ablation. Use of AAD is, however, often limited by their disappointing efficacy and their frequent side effects leading to drug discontinuation, and, surgical ablation, although potentially very effective, it is an invasive procedure associated with high morbidity.[13–15]

Catheter ablation has evolved into a very important therapy for VT after MI. In the last three decades, important progress in the understanding of the post-MI VT substrate and technological advancements have increased the efficacy and safety of the procedure. However, ablation still acutely fails in approximately 10% of the patients and VT recurs in 10 to 50% depending on baseline patient characteristics and follow-up time.[16–18]

Several crucial aspects which would likely contribute to improve ablation acute and long-term efficacy such us the deep comprehension of the VT substrate, the optimal ablation endpoints and the limitations of the technique remain unclear.

Mechanism and substrates for monomorphic ventricular tachycardia after myocardial infarction: implications for mapping and ablation

The majority of sustained VTs after MI are due to reentry involving areas of myocardial scar. In regions of scar, coupling of surviving myocardial bundles is reduced by interspersed fibrosis, diminished gap junction density and decreased connexin expression resulting in slow conduction and eventually in conduction block. Slow myocardial conduction through an isthmus protected by areas of dense fibrosis and/or valvular annuli acting as fixed conduction barriers or areas of functional conduction block only present at rapid rates, allows for initiation and maintenance of a stable re-entrant VT. [19–21]

Ablation in the setting of post-MI VT relies on the identification of the critical isthmus of the reentry circuit followed by transection of the isthmus, ideally with transmural and durable radiofrequency lesions. In patients presenting with hemodynamically stable VT, this can be best achieved through accurate characterization of the VT circuit by means of activation and entrainment mapping.[22] However, approximately 10% of patients currently referred for ablation are not inducible for any tachycardia during the procedure and up to 70% are inducible for one or more unstable VTs due to hemodynamic compromise requiring immediate interruption, transition to a different morphology or spontaneous termination.[16–18,23,24] In these scenarios, interrogation of multiple sites to define the re-entry circuit by analysis of the intracardiac activation sequence and/or the response to entrainment is not possible. In addition, scars frequently present a complex three-dimensional architecture, with multiple areas of slow conduction that may act as potential isthmuses for future VTs, even if they have not yet occurred spontaneously and are not inducible during the procedure.

Substrate-based VT ablation techniques have been developed with the main purpose of targeting areas of slow conduction within the scar area during stable sinus or paced rhythm. These sites represent putative surrogates of the VT isthmuses and are therefore critical sites to target when aiming to eliminate present and future VTs.[23,25–28]

The first step of all substrate-based ablation approaches consist on the delineation of the electroanatomical (EA) scar area by bipolar voltage mapping. Accurate identification of the scar area is important since, on one hand, it almost invariably contains at least parts of the VT circuit and, on the other hand, the surviving myocardium beyond the scar should be spared from ablation injury because it may contribute to cardiac function. Up to now, the majority of centers use an uniform cut-off of 1.5mV to discriminate scar from normal myocardium and a cut-off of 0.5mV to discern between dense scar and scar border zone. However, it is important to realize that these cut-off values were only validated by gross histopathology to detect the dense scar core.[23,29,30] Accordingly,

in patients with transmural infarctions, a cut-off of 1.5mV seems to precisely distinguish between the scar and preserved myocardium. However, this is not the case in patients with non-transmural infarctions, in whom high voltage signals generated by large surviving bundles of myocardium located in the sub-epicardium or surrounding the necrotic area may contaminate the local electrical activity leading to an underestimation of the scar area when an uniform cut-off of 1.5mV is applied.[31] In fact, a mismatch between the non-transmural infarct size defined by bipolar voltage mapping and contrast-enhanced magnetic resonance imaging (CE-MRI), the gold standard for fibrosis identification, has been observed.[32] In addition, termination of VT in areas with bipolar voltage larger than 1.5mV has been reported, further emphasizing the limitations of bipolar voltage mapping to detect the entire potential arrhythmogenic substrate in this patient population.[33] This is relevant since small non-transmural scars are currently increasingly encountered in patients who underwent reperfusion of the infarct related artery during the acute MI.[31] Mapping with multipolar catheters with small electrodes and narrow interelectrode spacing and ventricular pacing from multiple sites may help to separate local from far-field signals and to identify additional low-voltage areas not detected during sinus rhythm.[33,34] However, low voltage is not a synonym of arrhythmogenic substrate and ablation based only on electrogram amplitude may lead to damage of viable myocardium not involved in VT.

The second step of substrate mapping is therefore to identify electrograms consistent with slow conduction within the scar area that may be critical for VT circuits.[27,35] Isolated and late potentials have been demonstrated to be specific surrogates of VT isthmuses and, in accordance, late potential elimination has been associated with improved ablation outcomes.[36] However, although endocardial scar is almost invariably found in patients with old infarctions, in up to one third of post-MI patients, late potentials are not present.[26] These patients have typically small, non-dense scars which are associated with the presence of fast VTs.[26] Of note, for fast VTs, slow conduction and block might be functional, only present at fast rates, and hence, not detectable if mapping is performed during sinus rhythm or continuous pacing only.[21] In this setting, additional manoeuvres, such as RV extra-stimulation might be necessary to unmask areas of slow conduction responsible for VT.

Endpoints of post-MI VT ablation: non-inducibility and beyond

Since the advent of post-MI VT ablation, the response to programmed electrical stimulation (PES) at the end of the procedure has been used to assess the acute ablation result and to predict the mid-long term probability of VT recurrence.[37–40] Non-inducibility of VT after ablation has been associated with VT free survival in many studies.[16,41–43] However, using non-inducibility as a single ablation endpoint has limitations. In fact, there is a

significant number of patients who do not experience VT recurrence despite remaining inducible for VT at the end of the procedure and there is also an important number of patients who present VT recurrence despite being categorized as non-inducible after the last RF application. This might be explained by several factors. First, the definition of non-inducibility has not been uniformly applied and while some have used non-inducibility of the clinically documented VT or VTs with a similar CL to the clinical VT, others have used inducibility of any VT for definition.[16,36,37,39,40] This is important, since while persistent inducibility of the clinical VT or slow VTs with a CL similar to the (presumed-) clinical VT has clearly been associated with a high chance of VT recurrence, the impact of inducibility of non-clinical, particularly fast VTs remains unclear. Second, VT induction is a probabilistic phenomenon and, therefore, performing multiple evaluations over time likely increases the chance of induction.[44,45] In addition, the applied PES protocol, which should include the introduction of at least three extra-stimuli with short coupling intervals from multiple ventricular sites also influences the probability of induction, especially of fast VTs.[46–48] However, PES protocols are not uniformly and entirely performed after ablation in all EP laboratories, which affects the interpretation of the data.

As stated before, substrate-based ablation approaches were developed to allow targeting non-inducible and poorly tolerated VTs with the general aim of eliminating all potential arrhythmogenic areas during stable rhythm. Multiple endpoints for substrate ablation of scar-related VT have been proposed which could be divided into two groups; anatomical-based and EGM-based approaches. Anatomical approaches include performance of linear lesions, scar homogenization and core isolation.[23,25,49] EGM-based approaches target late and isolated potentials, all local abnormal ventricular activities or EGMS displaying slow-conduction characteristics during the applications of extra-stimuli (functional substrate ablation).[28,36,50] Although several of these approaches have shown to increase VT-free survival compared to ablation based on inducible VTs, to date no prospective comparison between the different techniques has been performed and therefore, the optimal substrate-based ablation endpoint for a given patient remains unknown.

AIM AND OUTLINE OF THE THESIS

The present thesis aims to provide new insights on catheter ablation of post-MI VT. Improved understanding of the underlying VT substrate in different types of MI, re-assessment of old and development of new physiologically meaningful ablation endpoints and recognition of the limitations of the technique will likely contribute to optimize procedural outcomes in the future.

In **chapter 2**, the value and limitations of the oldest and easiest-available mapping tool for VT, the 12-lead ECG, are extensively reviewed. The chapter is illustrated with several paradigmatic cases. **Chapter 3** analyzes the influence of individual patient characteristics and, in particular, of the left ventricular (LV) function, on the predictive value of non-inducibility after ablation for VT recurrence and cardiac mortality in the population currently referred for post-MI VT ablation. The objectives of **chapter 4** are to propose a new definition for fast VT based on the individual ventricular refractory period (VRP) and to assess the prognostic value of persistent inducibility after ablation of non-clinical VTs with a CL close to VRP in a mixed cohort of patients with ischemic and non-ischemic cardiomyopathy. In **chapter 5**, a systematic approach for post-MI VT substrate identification based on the analysis of electrograms within the scar area with RV extra-stimulation is proposed. In addition, the outcome of the procedure for the different infarct subtypes when using elimination of electrograms displaying functional slow conduction characteristics as ablation endpoint is analyzed. The prevalence of myocardial calcification and its impact in the acute and long-term outcome of endocardial ablation for post-MI VT is evaluated in **chapter 6**. Finally, a summary of the thesis, conclusions and future perspectives are provided in **chapter 7**.

REFERENCE LIST

1. Henkel DM, Witt BJ, Gersh BJ, Jacobsen SJ, Weston SA, Meverden RA, Roger VL. Ventricular arrhythmias after acute myocardial infarction: A 20-year community study. *Am Heart J* 2006;**151**:806–812.
2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Multicenter Automatic D. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N. Engl. J. Med. 2002. p. 877–883.
3. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
4. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Hafley G, Multicenter Unsustained T. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N. Engl. J. Med. 2000. p. 1937–1945.
5. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**:1576–1583.
6. Kuck KH, Cappato R, Siebels J, Ruppel R, Investigators C. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest - The Cardiac Arrest Study Hamburg (CASH). Circulation. 2000. p. 748–754.
7. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B, Investigators C. Canadian implantable defibrillator study (CIDS) - A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000. p. 1297–1302.
8. Andersen A, Damj T, Jb J, Ss P. Anxiety, depression, ventricular arrhythmias and mortality in patients with an implantable cardioverter defibrillator: 7 years' follow-up of the MIDAS cohort. Gen. Hosp. Psychiatry. Gen Hosp Psychiatry; 2020. https://pubmed.ncbi.nlm.nih.gov/32866884/ (10 January 2021)
9. Magyar-Russell M-R, Bd T, Jx C, T B, Ea K, Pp S, M MBB, E A, M R, N A, Je M, Rc Z. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: a systematic review. J. Psychosom. Res. J Psychosom Res; 2011. https://pubmed.ncbi.nlm.nih.gov/21911099/ (10 January 2021)
10. Broek K van den, Fb T, M H, M A, Ph van der V, J D. Emotional distress, positive affect, and mortality in patients with an implantable cardioverter defibrillator. Int. J. Cardiol. Int J Cardiol; 2013. https://pubmed.ncbi.nlm.nih.gov/21963213/ (11 October 2020)
11. Wilkoff B, Bd W, Rs S, Sl M, F L, Sw L, Um B-G, Ms W, Ic VG, Bm H, Ml B, Kk H. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J. Am. Coll. Cardiol. J Am Coll Cardiol; 2008. https://pubmed.ncbi.nlm.nih.gov/18687248/ (11 October 2020)
12. Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM, EMPIRIC Trial Investigators. A comparison of empiric to physician-tailored programming of implantable cardioverter-defibrillators: results from the prospective randomized multicenter EMPIRIC trial. *J Am Coll Cardiol* 2006;**48**:330–339.

13. Connolly S, P D, Rs R, M G, S B, Es F, K T, J C, M T, B C, Gc G, Sh H. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. JAMA; 2006. https://pubmed.ncbi.nlm.nih.gov/16403928/ (12 October 2020)
14. Kuhlkamp V, Mewis C, Mermi J, Bosch RF, Seipel L. Suppression of sustained ventricular tachyarrhythmias: A comparison of d,l-sotalol with no antiarrhythmic drug treatment. J. Am. Coll. Cardiol. 1999. p. 46–52.
15. Kienzle MG, Miller J, Falcone RA, Harken A, Josephson ME. Intraoperative endocardial mapping during sinus rhythm: relationship to site of origin of ventricular tachycardia. *Circulation* 1984;**70**:957–965.
16. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H, Multictr Thermocool VTAT. Irrigated Radiofrequency Catheter Ablation Guided by Electroanatomic Mapping for Recurrent Ventricular Tachycardia After Myocardial Infarction The Multicenter Thermocool Ventricular Tachycardia Ablation Trial. Circulation. 2008. p. 2773–2782.
17. Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin J-F, Thibault B, Rivard L, Gula L, Leong-Sit P, Essebag V, Nery PB, Tung SK, Raymond J-M, Sterns LD, Veenhuyzen GD, Healey JS, Redfearn D, Roux J-F, Tang ASL. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. *N Engl J Med* 2016;**375**:111–121.
18. Marchlinski FE, Haffajee CI, Beshai JF, Dickfeld T-ML, Gonzalez MD, Hsia HH, Schuger CD, Beckman KJ, Bogun FM, Pollak SJ, Bhandari AK. Long-Term Success of Irrigated Radiofrequency Catheter Ablation of Sustained Ventricular Tachycardia. *J Am Coll Cardiol* 2016;**67**:674–683.
19. Debakker JMT, Vancapelle FJL, Janse MJ, Tasseron S, Vermeulen JT, Dejonge N, Lahpor JR. SLOW CONDUCTION IN THE INFARCTED HUMAN HEART - ZIGZAG COURSE OF ACTIVATION. Circulation. 1993. p. 915–926.
20. Wit AL, Peters NS. The role of gap junctions in the arrhythmias of ischemia and infarction. *Heart Rhythm* 2012;**9**:308–311.
21. Anter E, Tschabrunn CM, Buxton AE, Josephson ME. High-Resolution Mapping of Postinfarction Reentrant Ventricular Tachycardia: Electrophysiological Characterization of the Circuit. *Circulation* 2016;**134**:314–327.
22. Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, Wiener I. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993;**88**:1647–1670.
23. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation. 2000. p. 1288–1296.
24. Di Biase L, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P, Trivedi C, Santangeli P, Bai R, Forleo G, Horton R, Bailey S, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Pelargonio G, Hongo RH, Beheiry S, Hao SC, Reddy M, Rossillo A, Themistoclakis S, Dello Russo A, Casella M, Tondo C, Natale A. Ablation of Stable VTs Versus Substrate Ablation in Ischemic Cardiomyopathy. *J Am Coll Cardiol* 2015;**66**:2872–2882.
25. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, Dello Russo A, Casella M, Mohanty S, Pump A, Hongo R, Beheiry S, Pelargonio G, Santarelli P, Zucchetti M, Horton R, Sanchez JE, Elayi CS, Lakkireddy D, Tondo C, Natale A. Endo-Epicardial Homogenization of the Scar Versus Limited Substrate Ablation for the Treatment of Electrical Storms in Patients With Ischemic Cardiomyopathy. J. Am. Coll. Cardiol. 2012. p. 132–141.

26. Tsiachris D, Silberbauer J, Maccabelli G, Oloriz T, Baratto F, Mizuno H, Bisceglia C, Vergara P, Marzi A, Sora N, Guarracini F, Radinovic A, Cireddu M, Sala S, Gulletta S, Paglino G, Mazzone P, Trevisi N, Della Bella P. Electroanatomical Voltage and Morphology Characteristics in Postinfarction Patients Undergoing Ventricular Tachycardia Ablation: Pragmatic Approach Favoring Late Potentials Abolition. *Circ Arrhythm Electrophysiol* 2015;**8**:863–873.
27. Bogun F, Good E, Reich S, Elmouchi D, Igic P, Lemola K, Tschopp D, Jongnarangsin K, Oral H, Chugh A, Pelosi F, Morady F. Isolated Potentials During Sinus Rhythm and Pace-Mapping Within Scars as Guides for Ablation of Post-Infarction Ventricular Tachycardia. *J Am Coll Cardiol* 2006;**47**:2013–2019.
28. Jaïs P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haïssaguerre M. Elimination of Local Abnormal Ventricular Activities: A New End Point for Substrate Modification in Patients With Scar-Related Ventricular Tachycardia. *Circulation* 2012;**125**:2184–2196.
29. Callans DJ, Ren J-F, Michele J, Marchlinski FE, Dillon SM. Electroanatomic Left Ventricular Mapping in the Porcine Model of Healed Anterior Myocardial Infarction: Correlation With Intracardiac Echocardiography and Pathological Analysis. *Circulation* 1999;**100**:1744–1750.
30. Wrobleski D, Houghtaling C, Josephson ME, Ruskin JN, Reddy VY. Use of Electrogram Characteristics During Sinus Rhythm to Delineate the Endocardial Scar in a Porcine Model of Healed Myocardial Infarction. *J Cardiovasc Electrophysiol* 2003;**14**:524–529.
31. Wijnmaalen AP, Schalij MJ, Thüsen JH von der, Klautz RJM, Zeppenfeld K. Early Reperfusion During Acute Myocardial Infarction Affects Ventricular Tachycardia Characteristics and the Chronic Electroanatomic and Histological Substrate. *Circulation* 2010;**121**:1887–1895.
32. Wijnmaalen AP, Geest RJ van der, Huls van Taxis CFB van, Siebelink H-MJ, Kroft LJM, Bax JJ, Reiber JHC, Schalij MJ, Zeppenfeld K. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. *Eur Heart J* 2011;**32**:104–114.
33. Tung R, Josephson ME, Bradfield JS, Shivkumar K. Directional Influences of Ventricular Activation on Myocardial Scar Characterization: Voltage Mapping With Multiple Wavefronts During Ventricular Tachycardia Ablation. *Circ Arrhythm Electrophysiol* 2016;**9**.
34. Berte B, Relan J, Sacher F, Pillois X, Appetiti A, Yamashita S, Mahida S, Casassus F, Hooks D, Sellal J-M, Amraoui S, Denis A, Derval N, Cochet H, Hocini M, Haïssaguerre M, Weerasooriya R, Jaïs P. Impact of Electrode Type on Mapping of Scar-Related VT: Mapping of Scar-Related VT. *J Cardiovasc Electrophysiol* 2015;**26**:1213–1223.
35. Jais P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haissaguerre M. Elimination of Local Abnormal Ventricular Activities A New End Point for Substrate Modification in Patients With Scar-Related Ventricular Tachycardia. Circulation. 2012. p. 2184–2196.
36. Silberbauer J, Oloriz T, Maccabelli G, Tsiachris D, Baratto F, Vergara P, Mizuno H, Bisceglia C, Marzi A, Sora N, Guarracini F, Radinovic A, Cireddu M, Sala S, Gulletta S, Paglino G, Mazzone P, Trevisi N, Bella PD. Noninducibility and Late Potential Abolition: A Novel Combined Prognostic Procedural

End Point for Catheter Ablation of Postinfarction Ventricular Tachycardia. *Circ Arrhythm Electrophysiol* 2014;**7**:424–435.

37. Rothman SA, Hsia HH, Cossú SF, Chmielewski IL, Buxton AE, Miller JM. Radiofrequency Catheter Ablation of Postinfarction Ventricular Tachycardia: Long-term Success and the Significance of Inducible Nonclinical Arrhythmias. *Circulation* 1997;**96**:3499–3508.
38. Tung R, Josephson ME, Reddy V, Reynolds MR, on behalf of the SMASH-VT Investigators. Influence of Clinical and Procedural Predictors on Ventricular Tachycardia Ablation Outcomes: An Analysis from The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia Trial (SMASH-VT). *J Cardiovasc Electrophysiol* 2010;
39. Kim YH, Sosa-Suarez G, Trouton TG, O'Nunain SS, Osswald S, McGovern BA, Ruskin JN, Garan H. Treatment of ventricular tachycardia by transcatheter radiofrequency ablation in patients with ischemic heart disease. *Circulation* 1994;**89**:1094–1102.
40. Segal OR, Chow AWC, Markides V, Schilling RJ, Peters NS, Davies DW. Long-term results after ablation of infarct-related ventricular tachycardia. *Heart Rhythm* 2005;**2**:474–482.
41. Ghanbari H, Baser K, Yokokawa M, Stevenson W, Della Bella P, Vergara P, Deneke T, Kuck K-H, Kottkamp H, Fei S, Morady F, Bogun F. Noninducibility in Postinfarction Ventricular Tachycardia as an End Point for Ventricular Tachycardia Ablation and Its Effects on Outcomes: A Meta-Analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:677–683.
42. Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P, Vergara P, Hindricks G, Arya A, Zeppenfeld K, Riva Silva M de, Daoud EG, Kumar S, Kuck K-H, Tilz R, Mathew S, Ghanbari H, Latchamsetty R, Morady F, Bogun FM. Predictive Value of Programmed Ventricular Stimulation After Catheter Ablation of Post-Infarction Ventricular Tachycardia. *J Am Coll Cardiol* 2015;**65**:1954–1959.
43. Della Bella P. Catheter ablation and antiarrhythmic drugs for haemodynamically tolerated post-infarction ventricular tachycardia. Long-term outcome in relation to acute electrophysiological findings. *Eur Heart J* 2002;**23**:414–424.
44. Kudenchuk PJ, Kron J, Walance CG, Cutler JE, Griffith KK, McAnulty JH. Day-to-day reproducibility of antiarrhythmic drug trials using programmed extrastimulus techniques for ventricular tachyarrhythmias associated with coronary artery disease. *Am J Cardiol* 1990;**66**:725–730.
45. McPherson CA, Rosenfeld LE, Batsford WP. Day-to-day reproducibility of responses to right ventricular programmed electrical stimulation: Implications for serial drug testing. *Am J Cardiol* 1985;**55**:689–695.
46. Mann DE, Luck JC, Griffin JC, Herre JM, Limacher MC, Magro SA, Robertson NW, Wyndham CRC. Induction of clinical ventricular tachycardia using programmed stimulation: Value of third and fourth extrastimuli. *Am J Cardiol* 1983;**52**:501–506.
47. Lin H-T, Mann DE, Luck JC, Krafchek J, Magro SA, Sakun V, Wyndham CRC. Prospective comparison of right and left ventricular stimulation for induction of sustained ventricular tachycardia. *Am J Cardiol* 1987;**59**:559–563.
48. Morady F, DiCarlo L, Winston S, Davis JC, Scheinman MM. A prospective comparison of triple extrastimuli and left ventricular stimulation in studies of ventricular tachycardia induction. *Circulation* 1984;**70**:52–57.
49. Tzou WS, Frankel DS, Hegeman T, Supple GE, Garcia FC, Santangeli P, Katz DF, Sauer WH, Marchlinski FE. Core Isolation of Critical Arrhythmia Elements for Treatment of Multiple Scar-Based Ventricular Tachycardias. *Circ Arrhythm Electrophysiol* 2015;**8**:353–361.
50. Porta-Sánchez A, Jackson N, Lukac P, Kristiansen SB, Nielsen JM, Gizurarson S, Massé S, Labos C, Viswanathan K, King B, Ha ACT, Downar E, Nanthakumar K. Multicenter Study of Ischemic

Ventricular Tachycardia Ablation With Decrement-Evoked Potential (DEEP) Mapping With Extra Stimulus. *JACC Clin Electrophysiol* 2018;**4**:307–315.

51. Sarkozy A, Tokuda M, Tedrow UB, Sieria J, Michaud GF, Couper GS, John R, Stevenson WG. Epicardial Ablation of Ventricular Tachycardia in Ischemic Heart Disease. *Circ Arrhythm Electrophysiol* 2013;**6**:1115–1122.
52. Piers SRD, Everaerts K, Geest RJ van der, Hazebroek MR, Siebelink H-M, Pison LAFG, Schalij MJ, Bekkers SCAM, Heymans S, Zeppenfeld K. Myocardial scar predicts monomorphic ventricular tachycardia but not polymorphic ventricular tachycardia or ventricular fibrillation in nonischemic dilated cardiomyopathy. *Heart Rhythm* 2015;**12**:2106–2114.
53. Piers SRD, Tao Q, Huls van Taxis CFB van, Schalij MJ, Geest RJ van der, Zeppenfeld K. Contrast-Enhanced MRI–Derived Scar Patterns and Associated Ventricular Tachycardias in Nonischemic Cardiomyopathy: Implications for the Ablation Strategy. *Circ Arrhythm Electrophysiol* 2013;**6**:875–883.

Part I

2

Twelve-lead ECG of ventricular tachycardia in structural heart disease

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Circulation: Arrhythmia & Electrophysiology 2015;8(4):951-962

INTRODUCTION

In patients with structural heart disease (SHD), defined by the presence of myocardial scarring either on cardiac imaging and/or electroanatomical (EAM) mapping, catheter ablation is increasingly employed for the treatment of ventricular tachycardia (VT).

With more detailed knowledge of potential substrates and anatomical structures involved in VT, not only the endocardium of the left (LV) and right ventricle (RV) but also more complex structures like the aortic root, the cardiac veins or the epicardium have become areas of interest for ablation.

Pre-procedural analysis of the clinically documented VT 12-lead electrocardiogram (ECG) is often used to predict the *VT site of origin* (SoO) and it is considered to be an important tool for planning the ablation, to estimate the probability of success and to recognize potential procedural limitations and related risks. These factors may have important implications for patient advice and decision making but also for the selection of a center capable to perform the expected procedure.

Since the majority of inducible VTs in patients with SHD are not hemodynamically tolerated[1-2], a detailed analysis of the VT 12-lead ECG of each induced VT may also be helpful. Combining the ECG with information of the scar size and distribution obtained from EAM during sinus rhythm or from pre-procedural imaging may direct mapping to the area of interest with the potential of increasing procedural success and to reduce procedural duration.

In this review we will focus on the reported evidence for the value of the 12-lead VT ECG as a “mapping tool” in patients with scar related VT and discuss its potential implications when combined with scar information from EAM or imaging.

VENTRICULAR TACHYCARDIA SITE OF ORIGIN

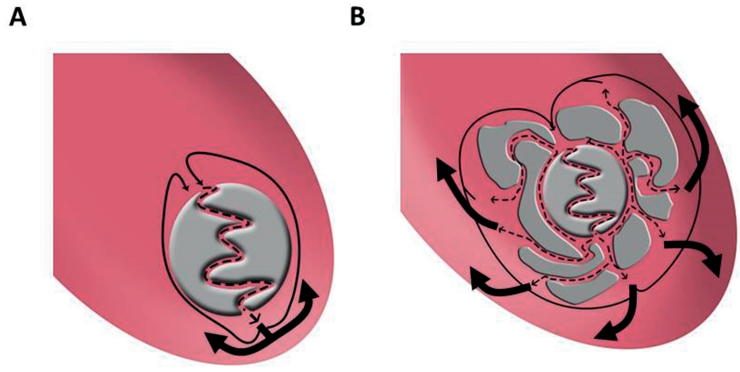
The mechanism of the majority of VTs in patients with structurally normal hearts is focal, and the 12-lead ECG can be very helpful to predict its SoO, since rapid activation of the normal myocardium from a focal source results in typical QRS patterns[3].

As a general rule, VTs originating from the structurally normal LV have a right bundle branch block (RBBB) morphology (defined as predominant R in lead V1) and VTs from the normal RV have a left bundle branch block (LBBB) morphology (defined as predomi-

nant S in lead V1). The precordial transition for RBBB VTs (first lead with a predominant S) changes from positive concordant for VTs originating from the base of the LV to progressively earlier transition in V2-V4 as the VT origin moves towards the apex of the ventricle. For LBBB VTs, VTs originating from the basoseptal area of the RV have an early transition (first lead with a predominant R) and the transition becomes progressively later as the VT origin moves towards the ventricular free wall. With regard to the frontal plane axis, VTs originating from the superior aspect of the ventricles show an inferior axis (predominant R in aVF), VTs from the inferior aspect of the ventricles a superior axis (predominant S in aVF), LV free wall VTs have typically a right axis (with a dominant S in I and aVL) and septal VTs typically a left axis (with a dominant R in I and aVL). Finally, septal VTs have a narrower QRS than VTs from the ventricular free wall.

In contrast to patients with structurally normal hearts, the majority of VTs in patients with SHD are due to scar related reentry. The SoO of a scar related reentrant VT has been differently defined as 1) the *"VT exit site"*, from which the *normal* myocardium is rapidly activated which corresponds to the scar border and coincides with the QRS onset on the surface ECG [4-7]; 2) the *"reentry circuit exit site"* from which the activation wavefront emerges from the critical slow conducting VT isthmus which may not necessarily correspond with the scar border and may precede the activation of the rapidly conducting myocardium with only little effect on the 12-lead ECG or 3) *'the target site for ablation"*, usually defined as the critical slow conducting VT isthmus, which is activated during diastole, thereby not contributing to the surface ECG at all[8].

Figure 1.



Panel A: Schematic representation of a VT reentry circuit. The reentry circuit exit site corresponds with the scar border zone. Rapid activation (indicated by large arrows) of the normal myocardium determines the VT QRS morphology. Pacing at the scar exit site will likely resemble the VT morphology.
Panel B: Schematic representation of a complex scar with one potential VT reentry circuit. The reentry circuit is located within the scar. The wave front emerges from the exit of the reentry circuit isthmus and propagates through multiple small pathways activating the remaining normal myocardium from different sites giving rise to a "fused" QRS complex. In this case, the VT morphology may not help to predict the scar exit site.

The 12-lead ECG morphology of a scar related reentrant VT depends mainly on the VT exit site, or the site(s) or the area(s) from which the normal myocardium is activated. Thus, only if the reentry circuit exit site coincides with the scar border, the 12-lead VT ECG may be helpful to directly guide to the area of interest for ablation **(Figure 1, see supplement Case 1)**.

Furthermore, the overall size and distribution of the scar and the size, distribution and properties of the remote myocardium determine the overall 12-lead VT ECG morphology. Therefore, in patients with large scars, the accuracy of the 12-lead ECG to localize the VT SoO may be limited also for tachycardias with a focal mechanism.

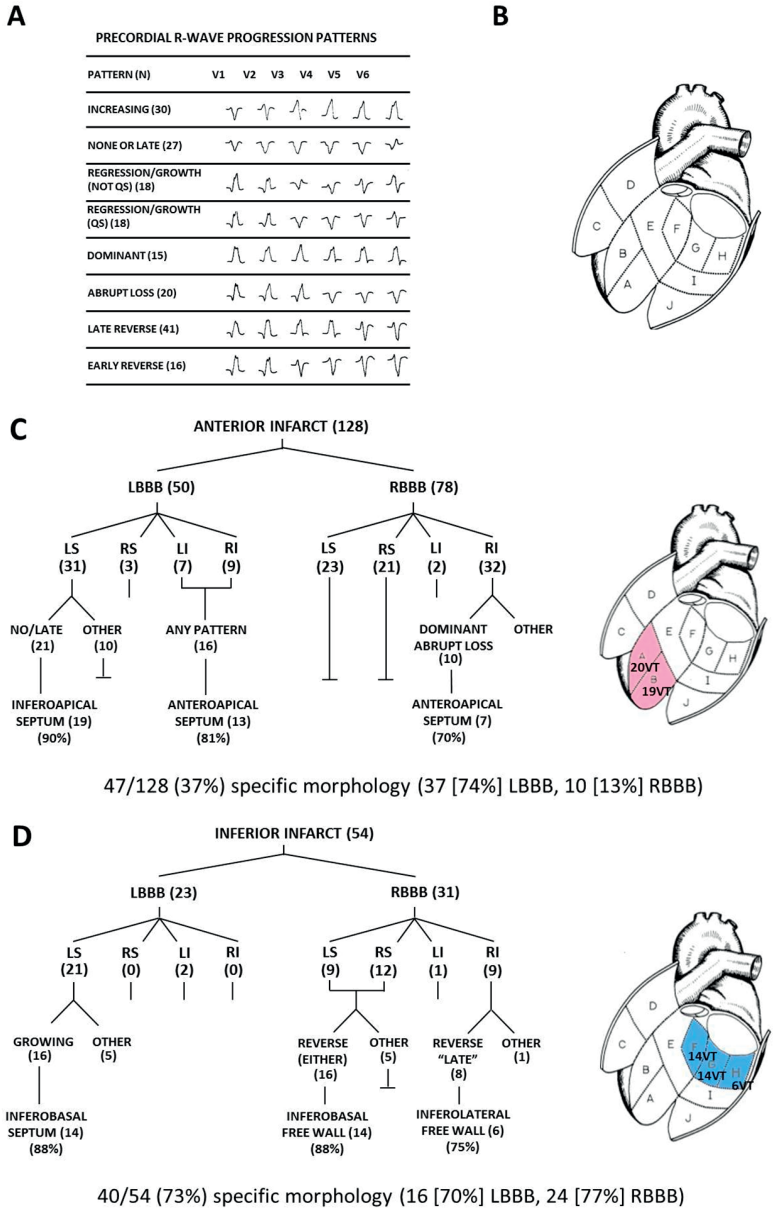
VALUE OF THE 12-LEAD ECG TO PREDICT THE ENDOCARDIAL VT SITE OF ORIGIN IN PATIENTS WITH PRIOR MYOCARDIAL INFARCTION

Site of origin as "exit site"

In the pioneering work of Miller et al.[4], the VT SoO was defined as the *earliest recorded activity on the second half of the diastole during endocardial VT activation mapping*. All 182 mapped VTs from 102 patients with single prior myocardial infarction (MI) had one endocardial site activated at least *40ms before the QRS onset*. Each 12 lead ECG of VT was categorized according to the location of the MI (anterior or inferior), the bundle branch block (BBB) type configuration, the frontal plane axis and one of 8 prespecified precordial R-wave progression patterns **(Figure 2A)**. A specific morphology of VT was defined as a characteristic morphology (based on the combination of these 4 factors) that was associated with one of 11 predefined LV regions based on fluoroscopy with a positive predictive value (PPV) greater than 70% **(Figure 2B).**

Of the 128 VTs in 73 patients with anterior MI, only 47 (37%) had such a specific morphology. Fifty VTs (39%) had a LBBB morphology, suggesting a septal VT exit site. Among the LBBB VTs, 37 (74%) had one of two identified specific patterns: 90% of the VTs with a left superior axis and a late or no transition were mapped to the inferoapical septum and the majority of VTs (81%) with inferior axis regardless of the precordial pattern were mapped to the anteroapical septum **(see supplement, Case 2).** Of the 78 VTs (61%) with a RBBB morphology, only 10 (13%) had a specific morphology: 7 out of 10 VTs (70%) which had a right inferior axis and either dominant or abrupt loss precordial pattern was also related to the anteroapical septum **(Figure 2C).**

Figure 2.



Algorithm proposed by Miller et al.[4] to predict the endocardial VT site of origin based on the 12-lead ECG VT morphology including BBB, axis and precordial transition pattern (Panel A) according to a 11 LV regions model (Panel B) in patients with anterior (Panel C) and inferior (Panel D) myocardial infarction. (Modified from Miller et al., Circulation 1988)
Regions of VT origin: A, inferoapical septum; B, anteroapical septum; C, anteroapical free wall; D, anterobasal free wall; E, anterobasal and mid septum; F, inferobasal septum; G, inferomedial free wall; H, inferolateral free wall; I, midinferior wall; J, inferoapical free wall; regions G and H together are the inferobasal free wall.
LBBB indicates left bundle branch block; RBBB, right bundle branch block; LS, left superior axis; RS, right superior axis; LI, left inferior axis; RI, right inferior axis.

For inferior MI the results were better. In 40 out of 54 VTs (73%) from 35 patients, a specific morphology could be identified. Of the 23 VTs (43%) with LBBB morphology, 88% of those with left superior axis and a growing precordial pattern were mapped to the inferobasal septum. Thirty-one VTs had RBBB morphology (57%) and of them, two specific morphologies could be determined: 14 out of 16 VTs (88%) with superior axis and either an early or late reverse precordial pattern were mapped to the inferobasal free wall whereas 8 out of 9 VTs (75%) **(see supplement, Case 3)**, with right inferior axis and a late reverse precordial pattern were mapped to the inferolateral wall **(Figure 2D).**

In this paper, an association between a specific 12-lead ECG VT morphology and one of the 11 predefined LV regions could only be found for 48% of the mapped VTs. Specific morphologies were more often identified in patients with inferior infarction and for VTs with LBBB morphology. In patients with anterior MI, only apicoseptal exit sites could be correctly identified.

The algorithm was developed before the advent of EAM and delayed enhancement MRI (DE-MRI) to delineate scar. Accordingly, it could not correct for variations in anterior and lateral scar extension which may explain the lack of additional identified specific patterns, in particular for RBBB VTs after anterior MI **(see supplement, Cases 4 and 5).** In contrast, scar extension in inferior MI may be less variable, as these scars are often restricted to the basal inferoseptal and posterior regions with the mitral annulus as one common boundary. The limited mapping density, with on average 9 catheter positions using a catheter with a 1cm tip electrode and an interelectrode spacing of 5 mm may have also reduced the accuracy of the algorithm. The broad definition of a VT exit site applied in this study may encompass VT exit sites from the scar border zone, VT reentrant circuit exit sites but also critical isthmus sites, which may further influence the predictive value of the algorithm for a specific location. Of note, the RV as potential site of origin was not included, which may contain reentry circuit and scar exit sites **(see supplement, Case 2)**

Based on the assumption that pacing at the VT endocardial exit site may generate a QRS morphology identical to the VT morphology, Kuchar et al.[5] proposed a different algorithm for localizing the VT SoO. They used ventricular pace-mapping as surrogate for a VT exit site. Ninety-three 12-lead ECGs recorded during pacing from different sites in 22 patients with single or multiple prior MI were analyzed and correlated to one of 24 LV regions based on fluoroscopy. Five paced QRS complex features could be related or were exclusive for a particular region:

1) A negative QRS in *precordial lead V1* was typical for septal sites, but never observed during pacing at lateral LV sites.

2) The QRS in *precordial lead V4* was never negative by pacing at the basal LV and never positive when pacing at apical regions.
3) A positive QRS in *lead I* was never observed when pacing from the lateral LV.
4) A predominant negative QRS in *lead aVL* was observed when pacing from the lateral LV and a predominant positive QRS in lead aVL when pacing from the septum.
5) A positive QRS in *lead II* was never observed during pacing from inferior sites.

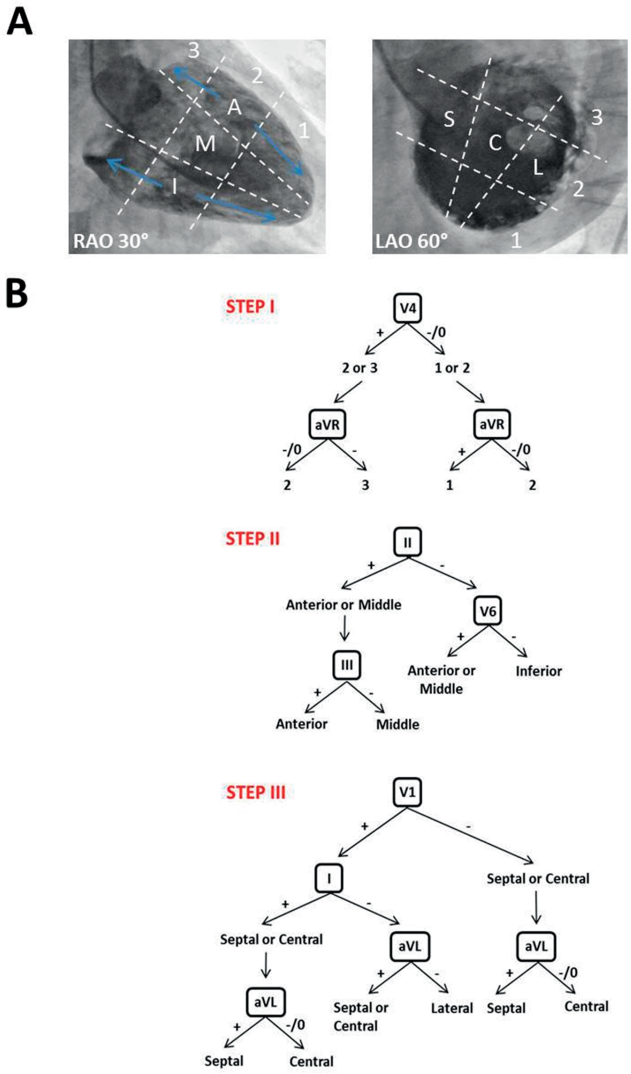
From these data an algorithm was derived and subsequently tested in 44 induced VTs from 42 additional patients in which the VT SoO could be determined by activation mapping **(Figure 3)**. Precise localization of the endocardial VT exit site using this algorithm was only possible for 39% of the VTs. The algorithm showed a high accuracy (80-90%) to distinguish between anterior, inferior, septal and lateral LV regions but was not useful to predict central and midventricular sites and only moderately successful in differentiating sites in the long axis of the ventricle (e.g. basal vs apical) (55-70%).

As for Miller's algorithm, the size and extension of the scar may significantly influence the accuracy of the algorithm to predict the VT SoO. Moreover, pacing at the scar border zone and at potential critical isthmus sites within the scar may not necessarily result in the same 12-lead ECG morphology with different stimulus to QRS intervals than the VT ECG. In particular for small scars, activation patterns during pacing may be different from the propagation during VT since reentry circuits may also be determined by areas of functional block only present during VT. In these cases a 12/12 lead pace-match of the VT ECG cannot be achieved. For large scars, De Chillou et al.[9] could recently demonstrate that the best match between the paced QRS morphology and the VT morphology could be obtained if pacing was performed at the VT exit region or towards the exit part of the critical VT isthmus. In contrast, pacing at the VT entrance region or at the entrance part of the critical VT isthmus resulted in a completely different QRS complex morphology due to the activation of the preserved myocardium in the opposite direction than during VT. Despite this limitation, careful comparison of the paced ECG morphologies with the VT ECG may still be very useful to determine the area of interest if combined with the EA scar information **(see supplement, Case 3)**. In addition, pacing at longer cycle length (CL) than VT CL may also significantly influence the 12-lead ECG. In the study by Kuchar, a fixed pacing rate of 400ms was used, which may also partly explain the low predictive value of the algorithm to precisely localize the VT SoO.

In 2007, Segal et al.[6] correlated 12 lead ECG characteristics during VT with VT exit site determined by non-contact mapping. VT ECGs were categorized according to BBB configuration, frontal plane axis and R-wave transition. The VT exit site was defined as the point from which the rapidly expanding systolic activation on the isopotential

map occurred synchronous or just before (up to 40ms) QRS onset and was allocated to 9 predefined LV segments based on the 3D reconstruction of the endocardial LV surface using the Ensite system (Ensite 3000, Endocardial Solutions, Inc., St. Paul, MN, USA).

Figure 3.



Algorithm proposed by Kuchar et al.[5] to predict the endocardial VT site of origin based on the 12-lead ECG VT morphology in patients with prior myocardial infarction. (Modified from Kuchar et al., J Am Coll Cardiol 1989)
Panel A: From two fluoroscopic projections (right anterior oblique [RAO] and left anterior oblique [LAO]) the LV endocardial surface is divided in 24 segments: 1, 2 and 3 indicate the apical, mid-ventricular and basal LV regions respectively; A, anterior; M, middle; I, inferior; S, septal; C, central and L, lateral.
Panel B: Proposed algorithm to identify the endocardial VT site of origin based on analysis of paced QRS in patients with myocardial infarction.

A total of 121 VTs from 51 patients with prior (single or multiple) MI were analyzed. All VT ECGs could be categorized in 10 ECG patterns, from which 8, accounting for 86 VTs (71%) had a PPV ≥70% for a predefined VT exit site region. Only the BBB morphology and the frontal plane axis were used in the construction of this algorithm since no consistent R-wave precordial transition pattern could be identified **(Table 1).** All LBBB VTs had a septal exit site and in contrast to Miller et al.'s, a PPV≥70% was more common for RBBB than for LBBB VTs (76% vs 43%). Rapid activation was often recorded from the mid LV regions which are less often involved in either anterior-apical or inferior-basal infarctions. VT exit sites were therefore likely to correspond with the true scar border zone.

Table 1. Algorithm proposed by Segal et al. to predict the endocardial VT site of origin according to a 9 LV regions model based on the 12-lead ECG VT morphology including BBB and frontal plane axis (Modified from Segal et al., J Cardiovasc Electrophysiol 2007)

	BBB	Axis	Exit	PPV%	Sensitivity%
1	RBBB	LS	Inferomedial/Inferobasal	100	100
2	RBBB	RS	Inferoapical	100	18
3	RBBB	RS	Inferoapical	77	59
4	RBBB	RI	Anteromedial	77	100
5	RBBB	LI	Anterobasal	100	100
6	LBBB	RS	Basoseptal	100	33
7	LBBB	LS	Medioseptal	100	35
8	LBBB	LS	Apicoseptal	22	100
9	LBBB	RI	Medioseptal	100	22

The application of distinct definitions for the VT SoO and the inclusion of different patient populations with different scar characteristics among studies (e.g. single prior MI in Miller's study, multiple prior MIs in Kuchar's and Segal's study) may also explain the inconsistent findings between algorithms.

More recently, the University of Michigan's group[7] demonstrated that the value of the 12-lead VT ECG for localizing the VT exit site improves substantially when using an automated computerized algorithm. To create the algorithm, digitalized 12-lead ECGs of pace-maps from the scar area of 34 patients with prior MI and the locations of the pace-maps based on a 10 LV regions model were used. Subsequently, the training data containing only pace-maps was validated by using the 12-lead ECGs of 58 VTs from 33 post-MI patients in which the VT exit site was determined by pace-mapping. The accuracy of the algorithm for assigning both the 12-lead ECG of pace-maps from the training sample and the VTs of the testing sample to the correct anatomic region was ≈ 70% (in comparison to an estimated accuracy of 19% for Miller's et al. and 36% for Segal's et al. algorithms) with a spatial resolution of 15 cm^2. The accuracy of the algorithm varied

from region to region and in contrast to Miller's et al. it was higher for anterior infarcts and worse for apical regions (≈50%)**(Table 2)**.

Table 2 summarizes the proposed algorithms to identify the endocardial VT SoO in patients with prior MI.

First author and year of publication	Number of patients	Number of analyzed VTs	Number of VTs in which the algorithm could be applied	Number of VTs correctly localized by algorithm	VT Site of Origin definition	Method	Based on
Miller 1988	102	182	87 (48%)	73 (84%)	Exit site/ Ablation target site	Activation mapping	11-region LV model by fluoroscopy
Kuchar 1989	42	44	44 (100%)	17 (39%)	Exit site	Pace-mapping	24-region LV model by fluoroscopy
Segal 2007	51	121	86 (71%)	8/9 (89%)	Exit site	Non-contact mapping	9-region LV model by ENSITE system
Yokokawa 2012	33	58	58 (100%)	41 (71%)	Exit site	Pace-mapping	10-region LV model by CARTO system

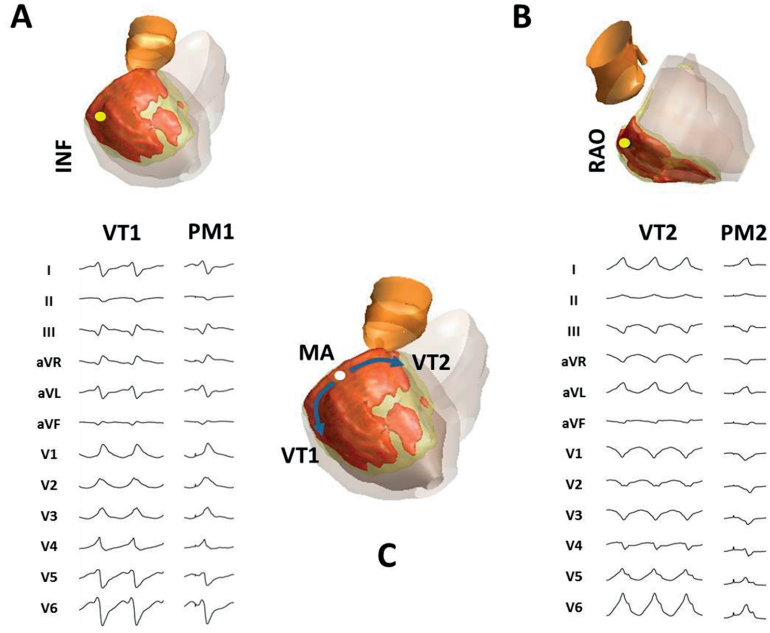
In all previously commented studies, the training cohort to create the algorithms differed from the validation cohort. This approach precludes correction for interindividual variations like LV and RV anatomy, rotation of the heart or lead placement[10], which may have also contributed to their limited accuracy to predict the VT SoO.

Site of origin as "target site for ablation"

Activation of the slow conducting critical isthmus does often not directly contribute to the 12-lead VT ECG. However, the combination of different 12-lead VT morphologies inducible in one patient may provide important, albeit indirect information for the location of an ablation target site. Wilber et al.[8] demonstrated that in patients with prior inferior MI inducible for two specific VT morphologies, one with LBBB and left superior axis and the other with RBBB and right superior axis, the critical isthmus site for both VTs can be located in the inferobasal LV, close to the mitral annulus. In this study, 4 out of 12 patients after inferior MI had these two inducible VT morphologies. In each of these 4 patients, participation of this "mitral isthmus" as critical slow conducting part of the reentrant circuit was demonstrated during both RBBB and LBBB tachycardias by entrainment mapping. A single RF application abolished both VT morphologies, suggesting that this critical site was shared by both VTs **(Figure 4).** Of interest, the BBB configuration and the frontal plane axis of the VTs were consistent among the 4 patients. However, some important differences in the precordial patterns were observed, sug-

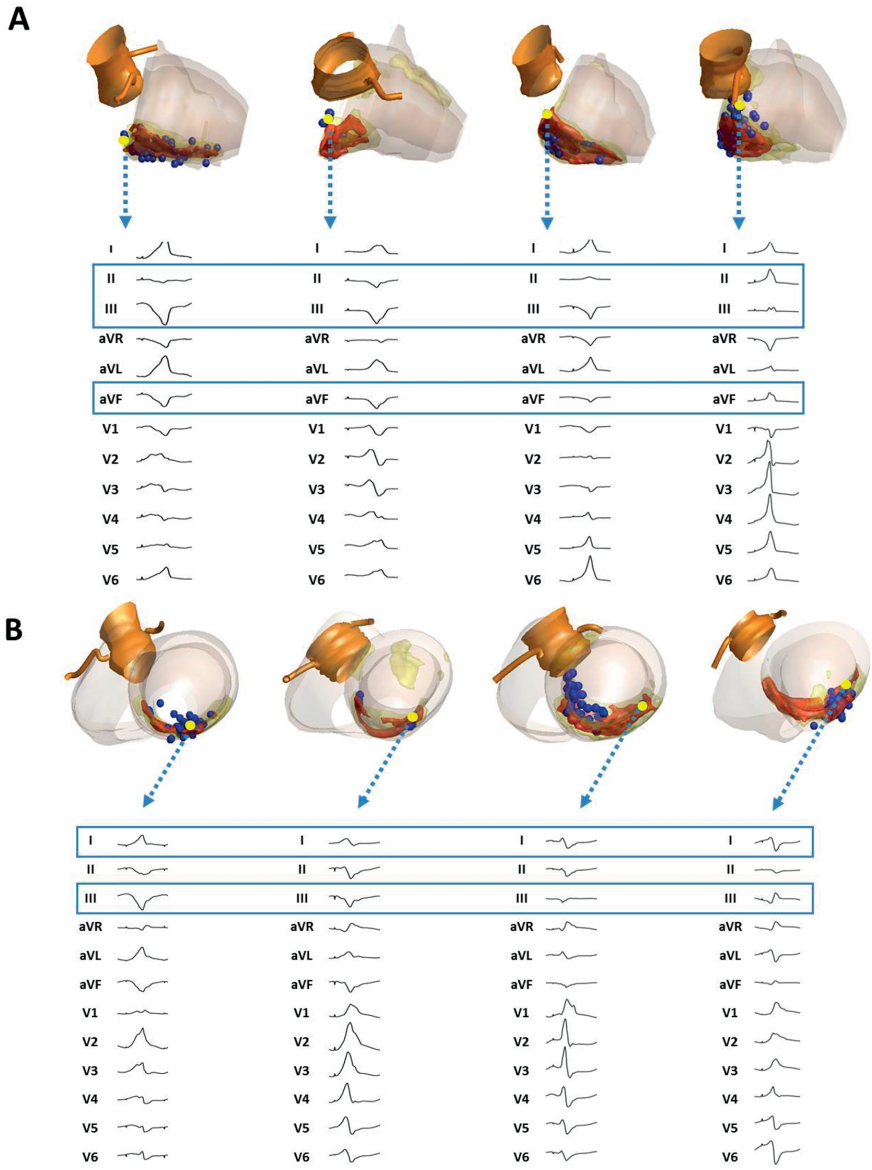
gesting that in particular, the precordial leads are more influenced by interindividual variations such as shape of the heart and scar distribution **(Figure 5).** With increasing septal scar extension, also LBBB VTs with early precordial transition and inferior axis can be related to a mitral isthmus reentry circuit **(see Figure 5, Patient 4)**. In addition, with more apical scar extension, the precordial transition of RBBB VTs to a dominant negative QRS complex may be observed in V4 despite a basolateral exit site **(see Figure 5, Patients 1 and 3)**.

Figure 4.
Mitral isthmus related VT.



DE-MRI derived 3D reconstruction of the scar of a patient after inferior MI. Orange indicates core scar and yellow, border zone based on signal intensity (SI). Two VT morphologies were induced.
Panel A: VT1: RBBB morphology, RS axis. Panel B: VT2: LBBB morphology, LS axis. The best pace-map (indicated by a yellow dot) for VT1 was found in the basolateral aspect of the scar (PM1, panel A). The best pace-map for VT2 was found in the basoseptal aspect of the scar (PM2, panel B). The successful ablation site for both VTs, located in the basal LV close to the mitral annulus (MA) is indicated with a white dot. The blue arrows indicate the assumed direction of the activation wavefront during VT1 and VT2, respectively.

Figure 5.



DE-MRI derived 3D reconstructions of scars of 4 patients with prior inferior MI are shown. Orange indicates core scar and yellow, border zone based on SI. The pacing site that corresponds to the displayed QRS paced morphologies are marked by yellow dots.

Panel A: paced 12-lead ECGs at the septal border of the inferior scar. All paced QRS had a LBBB morphology and monophasic R waves in I, V5 and V6. With higher septal scar extension, the frontal plane axis shifts gradually from left superior to left inferior axis.

Panel B: paced 12-lead ECGs at the lateral border of the inferior scar. All paced QRS had a RBBB morphology and a terminal S wave in V5 and V6. With higher lateral scar extension, the morphology of I changes from a monophasic R wave to a progressively pronounced terminal S wave and the morphology of III from a QS to a progressively higher amplitude of the terminal R wave.

VALUE OF THE 12-LEAD ECG TO PREDICT AN EPICARDIAL VERSUS AN ENDOCARDIAL LEFT VENTRICULAR VT SITE OF ORIGIN

Prior reports

Critical parts of the reentrant circuit that are located deep in the myocardium or at the subepicardium can often not be abolished by endocardial ablation. This is more common in patients with nonischemic cardiomyopathy (NICM), in which the VT substrate is frequently located intramurally or subepicardially, often requiring an epicardial or a combined endo-epicardial ablation to achieve procedural success[11-12].

DE-MRI performed prior to mapping and ablation can delineate the 3D scar geometry and its relationship to the endocardial and epicardial surfaces. Based on the MRI derived scar information, patients who may benefit from an endocardial, epicardial or combined approach can be selected[13]. However, currently MRI imaging in patients with implanted defibrillators is only available at selected centres. In addition, artifacts due to leads and pulse generators may hamper detailed analysis of, in particular, anterior basal segments[14]. EA voltage mapping may be an alternative to detect myocardial scar. However, endocardial bipolar voltage mapping is limited by the presence of endocardial viable myocardium in patients with mid-myocardial or subepicardial scars[15]. The value of endocardial unipolar voltage mapping to unmask epicardial scars has been recently suggested[16]. However, if compared with DE-MRI, unipolar endocardial voltage mapping has only a moderate sensitivity and specificity for detecting subepicardial scars[17].

Using the 12-lead ECG of the VT to determine the required access is appealing. Berruezo et al.[18] were the first proposing ECG criteria to distinguish an epicardial from an endocardial LV-VT SoO in a mixed group of patients with ischemic and NICM. All criteria are based on the assumption that ventricular activation originating from the epicardium is followed by a transmural activation delay until the subendocardial Purkinje system is reached. This propagation pattern will prolong the initial part of the QRS resulting in visible slurring and/or widening.

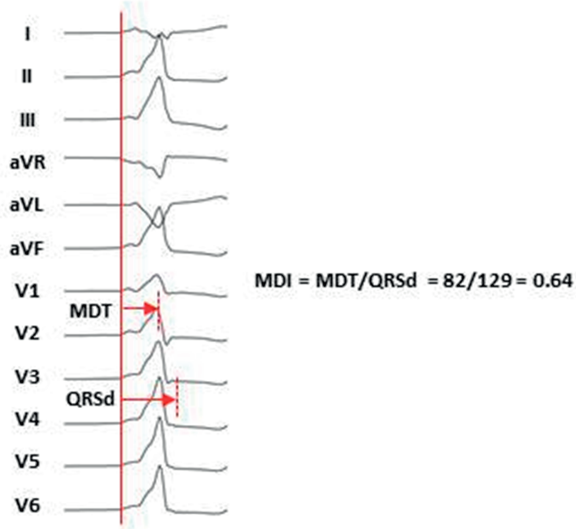
LBBB VTs were excluded from the initial analysis as these VTs were considered to originate from the interventricular septum.

A Pseudodelta wave (PDW) ≥ 34ms: interval from the earliest ventricular activation to the earliest rapid deflection in any precordial lead; an *Intrinsicoid deflection time (IDT) ≥ 85ms*: interval from the earliest ventricular activation to the peak of the R wave in V2 and a *shortest RS complex (SRS) ≥ 121ms*: interval from the earliest ventricular activation to the nadir of the first S wave in any precordial lead, predicted the failure of an

endocardial VT ablation with a high sensitivity and specificity in patients with SHD **(see supplement, Case 6).**

Following the same concept, Daniels et al.[19] could show that a *maximum deflection index (MDI) ≥55ms***,** defined as the interval from the earliest ventricular activation to the peak of the largest amplitude deflection in each precordial lead (taking the lead with the shortest time) divided by the QRS duration, identified an epicardial VT origin with a high sensitivity and specificity (>95%) in patients with idiopathic VTs with both RBBB and LBBB morphology **(Figure 6).**

Figure 6.



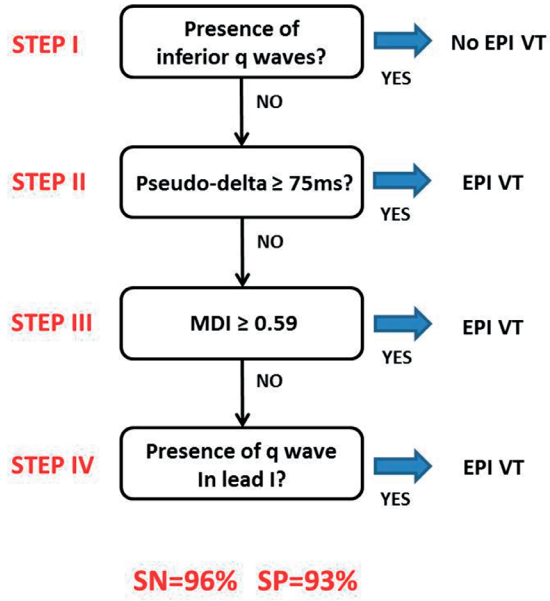
Determination of the MDI: the interval between the earliest ventricular activation and the maximum deflection in each precordial lead (taking the shortest interval) is divided by the QRS duration. A MDI ≥55ms had a high sensitivity and specificity to identify an epicardial VT origin in patients without structural heart disease. (Modified from Daniels et al., Circulation 2006)

Bazan et al.[20] reported that these previously suggested *interval criteria,* although useful to identify an epicardial LV-VT site of origin, did not perform uniformly for all LV regions. Additional site-specific *morphological criteria* were proposed based on the concept that the initial vector of impulse propagation from the epicardium towards the endocardium would result in the presence of an initial Q wave in the ECG leads reflecting the site of epicardial activation (or the absence of a Q wave in opposite leads). A Q wave in lead I for basal superior and apical superior VTs was associated with an epicardial site of origin. In addition, the absence of Q waves in any inferior leads for basal superior VT or a Q wave in inferior leads with VTs arising from the basal inferior and apical inferior LV also indicated an epicardial SoO.

Since the substrate for VTs in patients with NICM is often located in the basal LV, clustering around the mitral and aortic annulus, Vallès et al.[21], from the same group, evaluated the value of the previously proposed interval and morphological criteria to predict an epicardial VT origin from this specific LV region. Out of 24 VTs with RBBB morphology originated in the basal superior or lateral LV from 14 patients with NICM, 16 had an epicardial origin on the basis of entrainment and/or pace-mapping. Applying the interval ECG criteria, only a significantly longer duration of the QRS and a longer shortest RS complex were observed for epicardial compared to endocardial VTs. Of note, the presence of a Q wave in lead I had the highest individual sensitivity and specificity (88%) of all tested criteria. However, since a single criterion had a limited predictive value, a 4-step algorithm that included interval and morphological criteria was proposed reaching a high sensitivity and specificity for identifying an epicardial VT SoO from the basal or lateral LV in the preselected group of patients with NICM **(Figure 7).**

Recently, Yokokawa et al.[22] demonstrated that the accuracy of the 12-lead ECG for differentiating between endocardial and epicardial pace-map sites improved when applying a computerized algorithm compared to prior reported algorithms.

Figure 7.



Multistep algorithm to identify an epicardial left ventricular VT site of origin from the basal superior and lateral LV in patients with NICM. The cut-off values of the PDW and MDI were modified to increase its individual predictive value. (Modified from Vallès et al. Cir Arrhythm Electrophysiol 2010)

Limitations of the 12-lead ECG to predict an epicardial VT site of origin

The ECG criteria for identifying an epicardial LV VT SoO were derived from the analysis of pace-maps and a limited number of VTs from a population mainly comprised of patients without SHD or with NICM **(Table 3)**. Martinek et al.[23] showed that in post-MI patients, both the interval and the morphological ECG criteria failed to distinguish an epicardial from an endocardial LV VT SoO defined as the *successful ablation site*. Two factors may explain this finding. The presence of typical Q waves in the VT ECGs of patients with prior MI precludes the use of morphological ECG criteria and, when present in the precordial leads, Q waves may interfere with the measurement of all interval criteria **(see supplement, Case 6).** Perhaps even more importantly, the VT 12-lead ECG provides information about the VT exit site from the scar border, but successful ablation is often performed at other critical parts of the reentrant circuit. In particular, in patients with prior MI, both the presence of wall thinning and the subendocardial location of parts of the reentry circuit may allow successful ablation of VTs with an epicardial exit site from the endocardium. Accordingly, the number of VTs with an epicardial exit site may be underestimated.

Piers et al.[24] could recently demonstrate that when applied to clinically documented VTs (conventionally recorded with 25mm/s, 10mm/mV and measured with manual calipers) from patients with NICM, neither interval nor morphological ECG criteria could differentiate between an endocardial and an epicardial VT SoO defined as successful ablation site. For induced VTs (recorded on an electrophysiological recording system and measured with electronic calipers at 100mm/s), the interval criteria could distinguish between an endocardial and epicardial VT SoO for slow VTs but could also not reliably identify an epicardial VT origin in patients with fast VTs (CL≤350ms) or in patients off amiodarone. The absence of a clear isoelectric interval and/or the overlap of the QRS complex with the previous T wave during fast VTs may hamper an accurate identification of the QRS onset, which is mandatory for the measurement of all interval criteria. However, for induced VTs, the morphological criteria appeared to be not affected by the VT CL or amiodarone use. The latter confirms the findings from Vallès et al., who, as previously stated, has demonstrated that the presence of a Q wave in lead I had the highest individual accuracy for identifying an epicardial VT origin in patients with NICM **(Figure 8)**.

There are limited data on the value of the 12-lead VT ECG to predict an epicardial VT origin from the RV. Bazan et al.[25] analyzed 180 endocardial and 134 epicardial pace-maps from a group of 13 patients without structural heart disease (7/13) and RV cardiomyopathy (8/13). No interval criterion was able to distinguish an epicardial from an endocardial RV pace-map site in this population. Again, site-specific morphological criteria seemed to be useful for identifying an epicardial RV pace-map site. However, this finding was based on only 5 successfully ablated VTs from the epicardial RV.

Table 3. Proposed criteria to identify an epicardial left ventricular VT site of origin

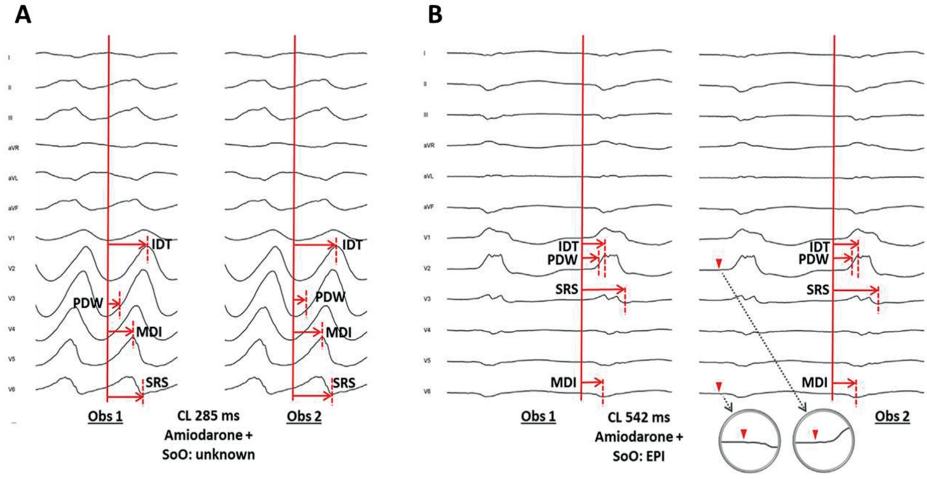
First author and year of publication	Population	Number of patients	Number of paced-maps/ VTs analyzed	Criteria	Sensitivity	Specificity
Berruezo 2004	Post-MI/ NICM	67	Not provided/69	Pseudodelta wave ≥ 34ms Intrinsicoid deflexion time ≥ 85ms Shortest RS interval ≥ 121ms	83% 87% 76%	95% 90% 85%
Daniels 2006	Idiopathic	12	0/12	Maximum deflexion index ≥ 0.55	100%	99%
Bazan 2007	Idiopathic/ NICM	28	636/19	Q wave in I: Basal superior LV Apical superior LV Q wave in inferior leads: Basal inferior LV Apical inferior LV	 86% 84% 74% 94%	 81% 78% 51% 61%

VALUE OF THE 12-LEAD ECG TO PREDICT THE UNDERLYING SUBSTRATE FOR VT

In patients with NICM, the VT 12-lead ECG morphology helps to predict the location and extension of the arrhythmogenic substrate, which may have implications for selecting the primary ablation approach (endocardial vs endo/epicardial) and for estimating the probability of procedural success and patient prognosis.

Piers et al.[17] demonstrated that 17 of 19 patients (89%) with NICM referred for VT ablation with DE-MRI integration had one of two typical scar patterns (basal anteroseptal or inferolateral). All but one patient had at least 1 of 3 characteristic VT ECG morphologies, diagnostic for one of these two typical scar locations. All patients with RBBB morphology, positive precordial concordance and inferior axis VTs or LBBB morphology, early precordial transition (≤V3) and inferior axis VTs had an anteroseptal scar whereas all patients with RBBB morphology, late precordial transition and right (superior or inferior) axis VTs had an inferolateral scar **(Figure 9)**. The majority of ablation target sites for patients with anteroseptal scars were located in the aortic root or in the basal anteroseptal LV endocardium **(see supplement, Case 7).** In these patients, if ablation via the coronary sinus and its branches fails, epicardial mapping and ablation using a conventional subxiphoid approach is unlikely to be appropriate due to the presence of the overlying left atrial appendage, coronary arteries and/or epicardial fat at the epicardial LV summit. On the contrary, in patients with inferolateral scars, the majority of ablation target sites could be reached from the LV epicardium. Epicardial mapping was not hampered by overlying structures like the left atrial appendage, a thick fat layer

Figure 8.



Reported interval and morphological ECG criteria for identifying a LV epicardial VT site of origin are assessed by two different observers for a fast (panel A) and a slow (panel B) VT. Of note, for the fast VT the QRS onset is defined differently, affecting the measurement of all the interval criteria. (Modified from Piers et al., Heart Rhythm 2014)

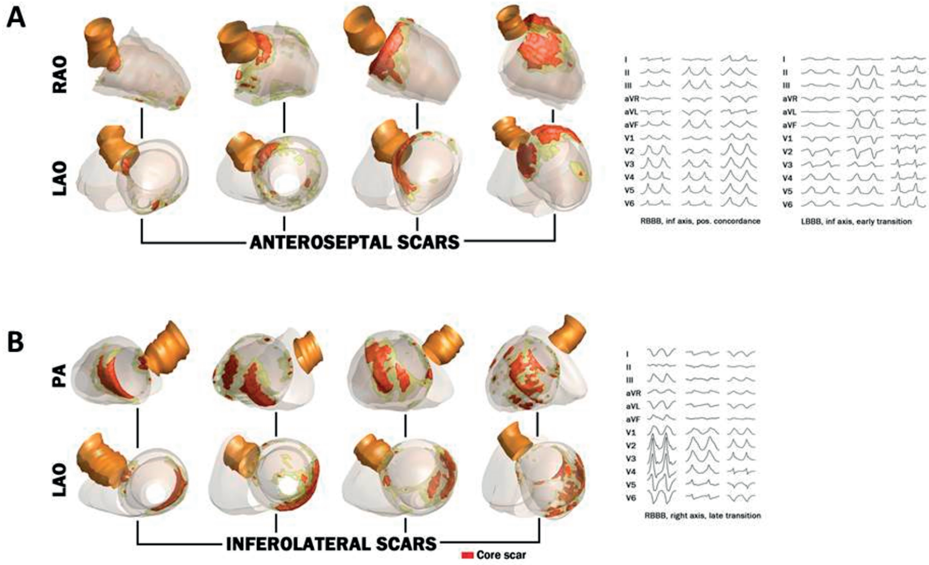
or coronary arteries in these patients; however RF delivery may need to be withheld if damage of the coronary arteries or the phrenic nerve cannot be excluded. Oloriz et al.[26] confirmed subsequently these findings in a larger cohort of patients.

As previously indicated, the VT substrate in patient with NICM is often located in the basal LV, around the valvular annuli with variable extension towards the LV apex. Out of 76 patients with NICM referred for VT ablation, Frankel et al.[27] identified 32 (42%) who had spontaneous or induced VTs with a morphology suggestive of an apical exit site. An *apical VT morphology* was defined as a VT with LBBB morphology and late precordial transition (≥V5) to a dominant positive QRS complex or with RBBB morphology and early precordial transition (≤V3) to a dominant negative QRS complex. Markedly, patients with apical VT morphologies had larger scar areas delineated by voltage mapping and a worse prognosis, with a higher likelihood of requiring heart transplant or left ventricular assist devices because of advanced heart failure.

Finally, data on the value of the 12-lead ECG for predicting the underlying substrate for VTs arising from the RV are scarce. Hoffmayer et al.[28] compared the 12-lead ECG morphology of VTs with LBBB and inferior axis from 42 patients with idiopathic RVOT VT and 16 with arrhythmogenic right ventricular cardiomyopathy (ARVC). Duration of the QRS in lead I ≥120ms, earliest onset of QRS in lead V1, presence of QRS notching in at least one lead and a precordial transition at V_5 or later were independent predictors of ARVC. Using these ECG features during VT and the presence/absence of negative T waves in

leads V1-V3 during sinus rhythm, the same authors constructed a risk score for ARVC[29]. A score ≥5 (maximum score 8 points) identified ARVC as underlying substrate for VT with a PPV of 100% and a negative PV of 91%.

Figure 9.



Typical scar patterns and associated 12-lead VT ECGs in non-ischemic cardiomyopathy (Modified from Piers et al., Circ Arrhythm Electrophysiol 2013)
DE-MRI derived 3D reconstructions of scars from patients with NICM are shown. Orange indicates core scar and yellow, border zone. Panel A: examples of typical basal anteroseptal scars and related 12-lead VT ECGs. Panel B: examples of typical inferolateral scars and related 12-lead VT ECGs.

SUMMARY

Several algorithms for identifying the *VT origin* based on the analysis of the 12-lead VT ECG have been suggested. These algorithms have applied different definitions for *VT site of origin* that include VT exit sites but also reentry circuit exit sites and isthmus sites. In addition, they have been validated by different mapping techniques encompassing activation and entrainment mapping, but also pace-mapping. None of the algorithms integrated information on the scar extension and distribution, which may increase the accuracy of the ECG to precisely predict the VT origin. A systematic re-evaluation of the value of the 12-lead ECG for VT ablation in the context of 3D EAM, scar imaging and changing ablation strategies with a shift from targeting clinical and induced VTs to substrate ablation approaches is needed.

REFERENCES

1. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H; Multicenter Thermocool VT Ablation Trial Investigators. Irrigated catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. *Circulation*. 2008;118:2773–2782.
2. Piers SR, Leong DP, van Huls van Taxis CF, Tayyebi M, Trines SA, Pijnappels DA, Delgado V, Schalij MJ, Zeppenfeld K. Outcome of ventricular tachycardia ablation in patients with nonischemic cardiomyopathy: the impact of noninducibility. *Circ Arrhythm Electrophysiol*. 2013;6:513-521.
3. Park KM, Kim YH, Marchlinski FE. Using the surface electrocardiogram to localize the origin of idiopathic ventricular tachycardia. *PACE*. 2012;35:1516-1527.
4. Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. *Circulation*. 1988;77:759-766.
5. Kuchar DL, Ruskin JN, Garan H. Electrocardiographic localization of the site of origin of ventricular tachycardia in patients with prior myocardial infarction. *J Am Coll Cardiol*. 1989;13:893-900.
6. Segal OR, Chow AWC, Wong T, Trevisi N, Lowe MD, Davies DW, Della Bella P, Packer DL, Peters NS. A novel algorithm for determining endocardial VT exit site from 12-lead surface ECG characteristics in human, infarct-related ventricular tachycardia. *J Cardiovasc Electrophysiol*. 2007;18:161-168.
7. Yokokawa M, Liu TY, Yoshida K, Scott C, Hero A, Good E, Morady F, Bogun F. Automated analysis of the 12-lead electrocardiogram to identify the exit site of postinfarction ventricular tachycardia. *Heart Rhythm*. 2012;9:330-334.
8. Wilber DJ, Kopp DE, Glascock DN, Kinder CA, Kall JG. Catheter ablation of the mitral isthmus for ventricular tachycardia associated with inferior infarction. *Circulation*. 1995;92:3481-3489.
9. De Chillou C, Groben L, Magnin-Poull I, Andronache M, Magdi Abbas MM, Zhang N, Abdelaal A, Ammar S, Sellal JM, Schwartz J, Brembilla-Perrot B, Aliot E, Marchlinski FE. Localizing the critical isthmus of postinfarct ventricular tachycardia: The value of pace-mapping during sinus rhythm. *Heart Rhythm*. 2014;11:175-181.
10. Anter E, Frankel DS, Marchlinski FE, Dixit S. Effect of electrocardiographic lead placement on localization of outflow tract tachycardias. *Heart Rhythm*. 2012;9:697-703.
11. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. *Circulation*. 2003;108:704-710.
12. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy. The importance of low-voltage scars. *J Am Coll Cardiol*. 2004;43:1834-42.
13. Andreu D, Ortiz-Pérez JT, Boussy T, Fernández-Armenta J, de Caralt TM, Prat-González S, Mont L, Brugada J, Berruezo A. Usefulness of contrast-enhanced cardiac magnetic resonance in identifying the ventricular arrhythmia substrate and the approach needed for ablation. *Eur Heart J*. 2014;35:1316-1326.
14. Dickfeld R, Tian J, Ahmad G, Jimenez A, Turgeman A, Kuk R, Peters M, Saliaris A, Saba M, Shorofsky S, Jeudy J. MRI-Guided ventricular tachycardia ablation: integration of late gadolinium-enhanced 3D scar in patients with implantable cardioverter-defibrillators. *Circ Arrhythm Electrophysiol*. 2011;4:172-184.

15. Piers SR, van Huls van Taxis CF, Tao Q, van der Geest RJ, Askar SF, Siebelink HM, Schalij MJ, Zeppenfeld K. Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging. *Eur Heart J*. 2013;34:586-596.
16. Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, Dixit S, Lin D, Tzou WS, Cooper JM, Verdino RJ, Callans DJ, Marchlinski FE. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2011;4:49-55.
17. Piers SRD, Tao Q, van Huls van Taxis CFB, Schalij MJ, van der Geest RJ, Zeppenfeld K. Contrast-enhanced MRI-derived scar patterns and associated ventricular tachycardias in nonischemic cardiomyopathy. Implications for ablation strategy. *Circ Arrhythm Electrophysiol*. 2013;6:875-883.
18. Berruezo A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic recognition of the epicardial origin of ventricular tachycardia. *Circulation*. 2004; 109:1842-1847.
19. Daniels DV, Lu YY, Morton JB, Santucci PA, Akar JG, Green A, Wilber DJ. Idiopathic epicardial left ventricular tachycardia originating remote from the sinus of Valsalva. Electrophysiological characteristics, catheter ablation, and identification from the 12-lead electrocardiogram. *Circulation*. 2006;113:1659-1666.
20. Bazan V, Gerstenfeld EP, Garcia FC, Bala R, Rivas N, Dixit S, Zado E, Callans DJ, Marchlinski FE. Site-specific twelve-lead ECG features to identify an epicardial origin for left ventricular tachycardia in the absence of myocardial infarction. *Heart Rhythm*. 2007; 4:1403-1410.
21. Vallès E, Bazan V, Marchlinski FE. ECG criteria to identify epicardial ventricular tachycardia in nonischemic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2010;3:63-71.
22. Yokokawa M, Yon Jung D, Joseph KK, Hero AO, Morady F, Bogun F. Computerized analysis of the 12-lead electrocardiogram to identify epicardial ventricular tachycardia exit sites. *Heart Rhythm*. 2014;11:1966-1973.
23. Martinek M, Stevenson WG, Inada K, Tokuda M, Tedrow UB. QRS characteristics fail to reliably identify ventricular tachycardias that require epicardial ablation in ischemic heart disease. *J Cardiovasc Electrophysiol*. 2012;23:188-193.
24. Piers SRD, de Riva Silva M, Kapel GFL, Trines SA, Schalij MJ, Zeppenfeld K. Endocardial or epicardial ventricular tachycardia in nonischemic cardiomyopathy?. The role of 12-lead ECG criteria in clinical practice. *Heart Rhythm*. 2014;11:1031-1039.
25. Bazan V, Bala R, Garcia FC, Sussman JS, Gerstenfeld EP, Dixit S, Callans DJ, Zado E, Marchlinski FE. Twelve-lead ECG features to identify ventricular tachycardia arising from the epicardial right ventricle. *Heart Rhythm*. 2006;3:1132-1139.
26. Oloriz T, Silberbauer J, Maccabelli G, Mizuno H, Baratto F, Kirubakaran S, Vergara P, Bisceglia C, Santagostino G, Marzi A, Sora N, Roque C, Guarracini F, Tsiachris D, Radinovic A, Cireddu M, Sala S, Gulletta S, Paglino G, Mazzone P, Trevisi N, Della Bella P. Catheter ablation of ventricular arrhythmia in nonischemic cardiomyopathy. Anterseptal versus inferolateral scar sub-types. *Circ Arrhythm Electrophysiol*. 2014;7:414-423.
27. Frankel DS, Tschabrunn CM, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical ventricular tachycardia morphology in left ventricular nonischemic cardiomyopathy predicts poor transplant-free survival. *Heart Rhythm*. 2013;10:621-626.
28. Hoffmayer KS, Machado ON, Marcus GM, Yang Y, Johnson CJ, Ermakov S, Vittinghoff E, Pandurangi U, Calkins H, Cannom D, Gear KC, Tichnell C, Park Y, Zareba W, Marcus FI, Scheinman MM. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right

ventricular cardiomyopathy and right ventricular outflow tract tachycardia. *J Am Coll Cardiol*. 2011;58:831-838.

29. Hoffmayer KS, Bhave PD, Marcus GM, James CA, Tichnell C, Chopra N, Moxey L, Krahn AD, Dixit S, Stevenson W, Calkins H, Badhwar N, Gerstenfeld EP, Scheinmann MM. An electrocardiographic scoring system for distinguishing right ventricular outflow tract arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy from idiopathic ventricular tachycardia. *Heart Rhythm*. 2013;10:477-482.

SUPPLEMENTARY CASE 1

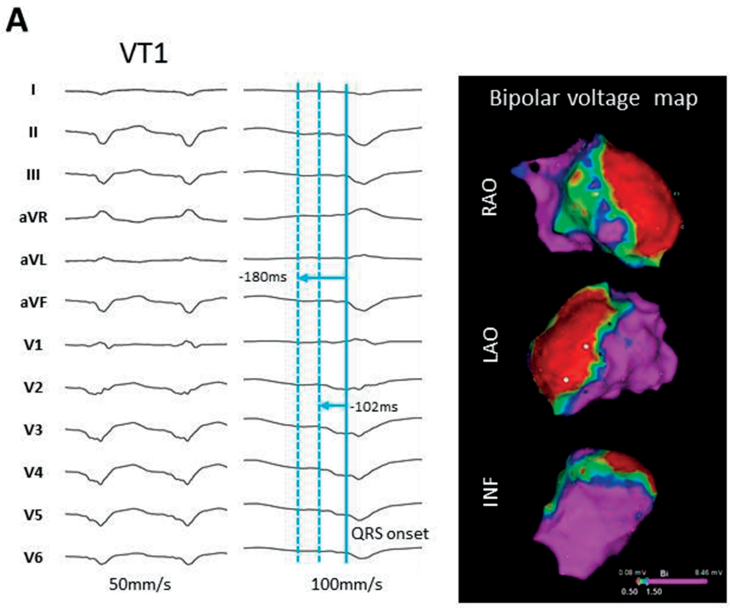
72 years male, 12 years after large anterior MI, clinical VTCL 548ms

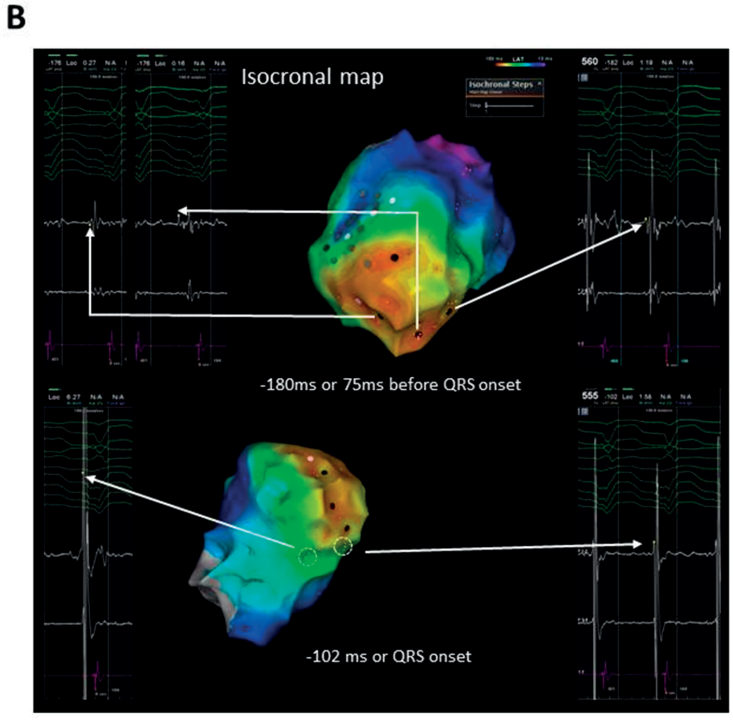
Panel A: The clinical VT (VT1) had RBBB morphology with early precordial transition (V2) and right superior axis. The RV apex (RVa) catheter served as a reference during VT activation mapping. RVa activation is indicated by a continuous blue line. On the ECG, the QRS onset is difficult to determine. Two potential onsets (102 and 180ms before RVa) are indicated with dashed blue lines. Electroanatomical (EA) endocardial bipolar voltage map of the LV in RAO, LAO and inferior views shows a large low voltage area in the anterior wall extending to the septum and lateral wall (voltages are color coded according to the bar).

Panel B: Activation map during VT1 (AP and inferior views) displayed as isochronal map. Black tags indicate LV sites activated 180ms before the RVa, which are located within the scar based on voltage mapping. Blue tags indicate LV sites activated 102ms before the RVa, which coincides with the most obvious QRS onset, and are located in normal voltage areas. These sites were considered as the probable VT exit site. However, entrainment mapping at these locations showed fusion and a post pacing interval (PPI) exceeding VTCL>70ms. During detailed endocardial mapping, no mid-diastolic activity or isthmus sites based on entrainment mapping could be identified. After endocardial ablation failure, an epicardial ablation approach was scheduled.

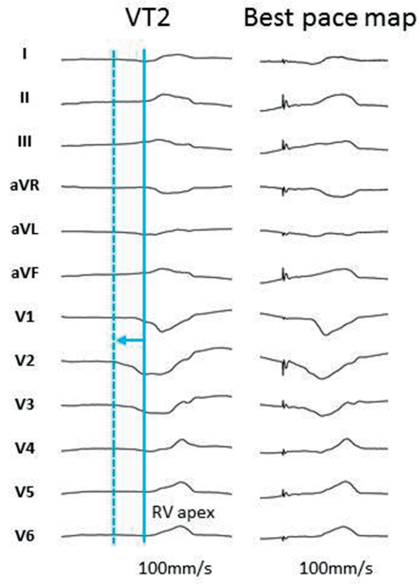
At the beginning of the second procedure, a different slow VT (VT2, panel C) with LBBB morphology, V4 transition and left inferior axis was induced. The RVa timing is indicated by a continuous blue line. The QRS onset is indicated by a dashed blue line. The best endocardial pace-map site for VT2 at the basoseptal border of the scar is indicated by a yellow tag (panel D, top). During activation mapping (panel D, bottom) activation of this site coincided with the QRS onset (indicated by a blue tag). However, entrainment mapping resulted in fusion with a PPI exceeding VTCL>70ms. Limited epicardial activation mapping was performed during VT2 (mapped area indicated by the dashed white line) (panel E). The direction of the activation wave front is indicated by a white arrow. The reentry circuit entrance site confirmed by entrainment mapping (indicated by a green dot) was found in the apicoseptal epicardial LV. Please note the very long electrogram-to-QRS onset interval at this site. With the first RF application at this position, VT2 slowed. The VT isthmus site (indicated by a white dot and confirmed by entrainment) was localized slightly superior. With a second RF application, VT terminated. The presumed reentry exit site is indicated by a yellow dot. Please note the long distance to the exit site from the scar, where the best endocardial pace-map was obtained.

The VT morphology is mainly dependent on the site(s) where the wavefront emerges from the scar border to activate the normal myocardium. If the reentry exit site and the exit site from the scar do not correspond, the accuracy of the 12-lead ECG to predict the VT origin is limited and may direct to wrong target areas.

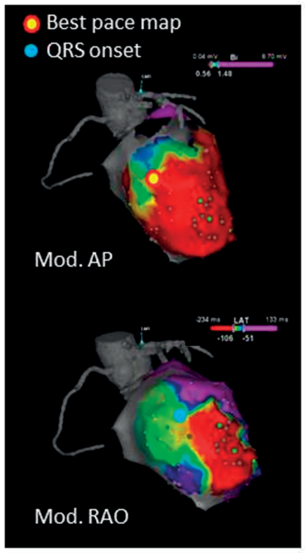

A
VT1
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
-180ms
-102ms
QRS onset
50mm/s
100mm/s
Bipolar voltage map
RAO
LAO
INF


B
Isocronal map
-180ms or 75ms before QRS onset
-102 ms or QRS onset

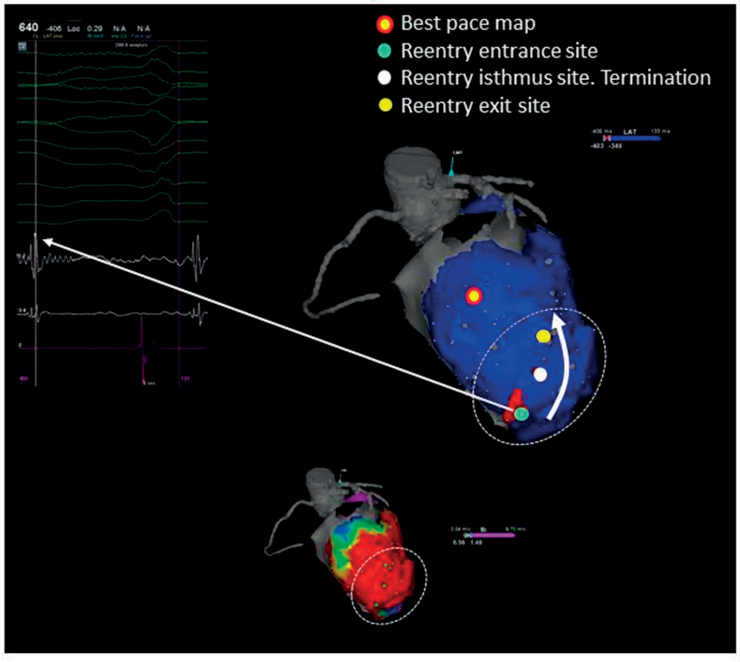
C


VT2
Best pace map
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
RV apex
100mm/s
100mm/s

D


Best pace map
QRS onset
Mod. AP
Mod. RAO

E


Best pace map
Reentry entrance site
Reentry isthmus site. Termination
Reentry exit site

SUPPLEMENTARY CASE 2

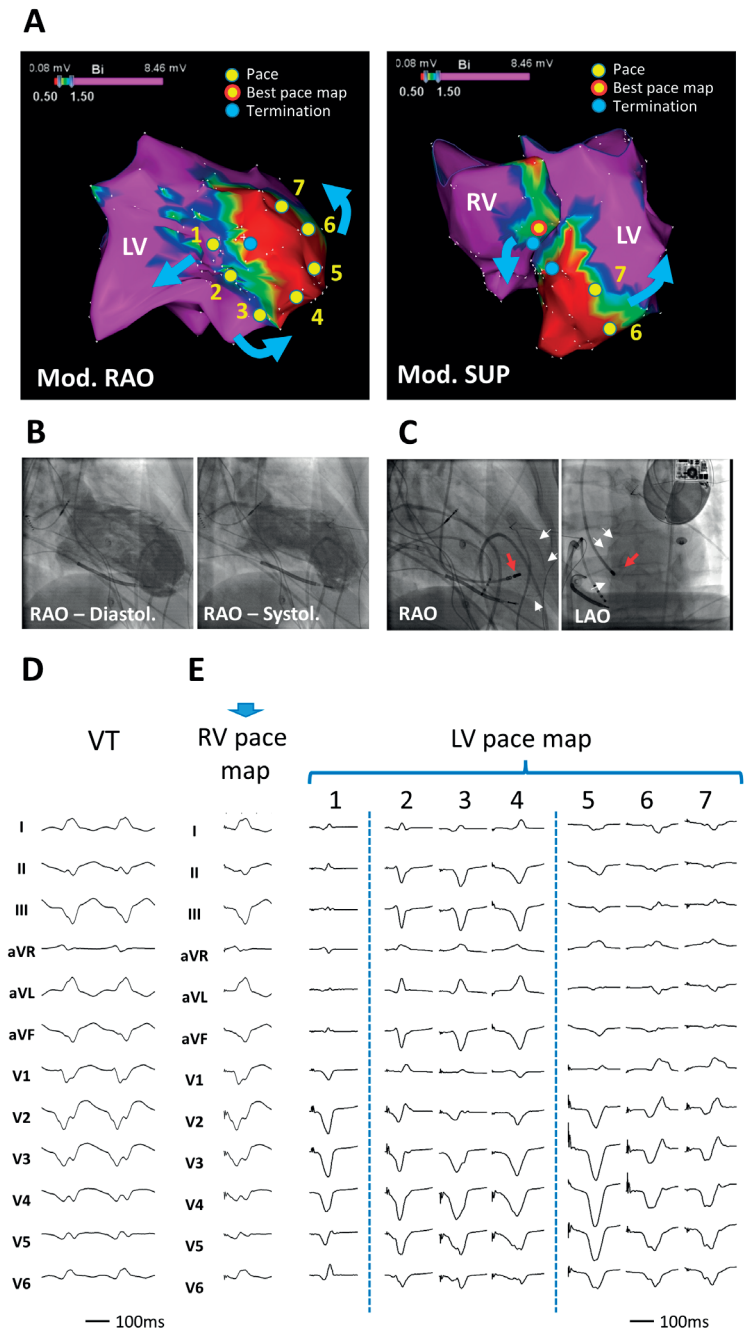
52 years male, 9 years after anterior MI, clinical VTCL 352ms

Panel A. Electroanatomical (EA) endocardial bipolar voltage map of the LV in a modified RAO view (left), and of the LV and RV in a modified superior view (right). Voltages are color coded according to the bar. Yellow tags indicate pacing sites around the EA scar; the numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel E). Best pace-map site and site of VT termination are indicated. Panel B: LV angiogram during diastole and systole showing a small apical aneurysm corresponding with the dense apical scar on EAM. Panel C: fluoroscopic views of the LV in RAO and LAO. Note the calcification of the aneurysm (white arrows). The position of the ablation catheter (red arrows) corresponds to the green tag, panel A.

The clinical VT (Panel D) had LBBB morphology with late transition and left superior axis and a predicted apicoseptal SoO/exit site according to Miller[4], Kuchar[5] and Segal[6].

However, pacing from the LV could not reproduce the VT morphology. The best pace-map was recorded during pacing at the RV septum (panel A,E). Limited entrainment mapping (not shown) could confirm the apical LV as outer loop and the RV apical septum as reentry circuit exit site (RF at this site abolished VT) which coincided with the RV scar border zone. The VT reentry circuit involved the septum and perhaps the subepicardial LV. Please note the changes of the paced QRS from left superior to right superior axis with only little changes in the precordial lead transition if pacing sites move from septal to anterolateral. These small changes may be explained by the limited lateral and anterior scar extension.

In addition to prior algorithms it is important to consider the RV as VT SoO.

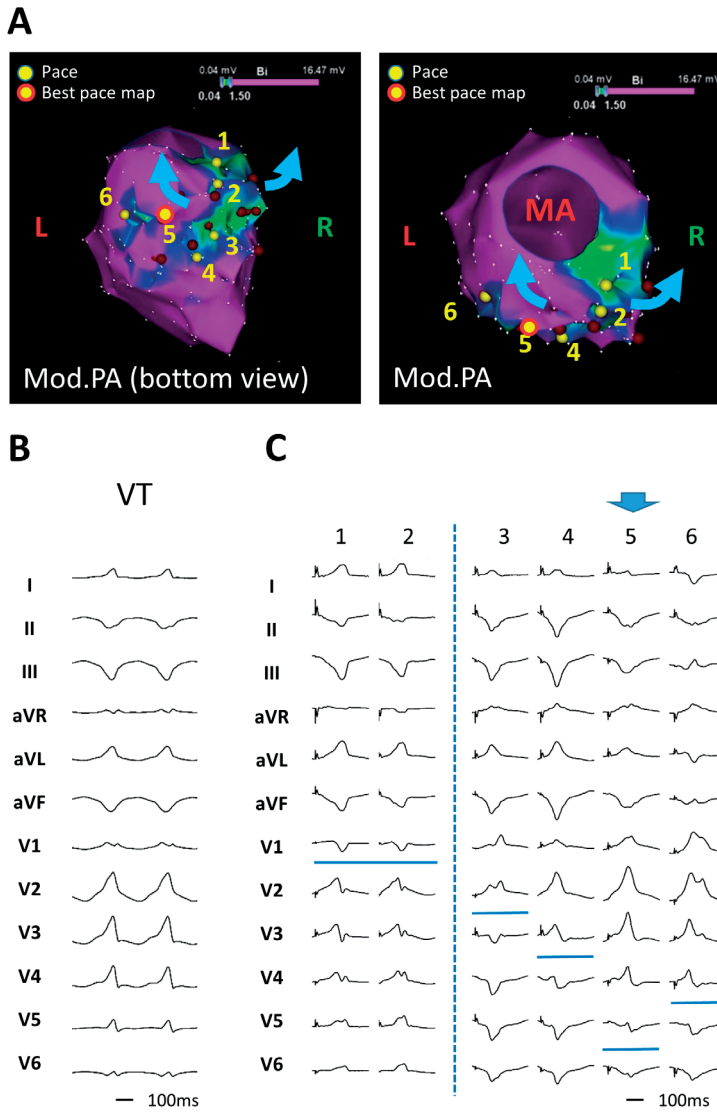

A
0.08 mV
Bi
8.46 mV
0.50 1.50
Pace
Best pace map
Termination
LV
1
2
3
4
5
6
7
Mod. RAO
RV
LV
Mod. SUP
B
RAO – Diastol.
RAO – Systol.
C
RAO
LAO
D
VT
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
100ms
E
RV pace map
LV pace map
1 2 3 4 5 6 7
100ms

SUPPLEMENTARY CASE 3

65 years male, 5 years after small inferior MI, clinical VTCL 320ms

Panel A. EA endocardial bipolar voltage map of the LV in a modified posterior view (PA) rotated to the bottom (left) and standard PA (right) view (color coding according to the bar). Tags represent catheter positions as indicated; numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel C).

The clinical VT (panel B) had RBBB morphology with late transition (V6) and left superior axis and a predicted inferobasal SoO by Miller[4] and Segal[6]. Despite the small EA scar the paced QRS morphology changed from LBBB with early transition (V2) and left superior axis at pacing site 2 (inferoseptal) to RBBB with transition at V3 and left superior axis at site 3 (basal inferior) and to RBBB with late transition (V5) and left superior axis at site 5. Site 5 was the best albeit not perfect pace-map site. During pacing within this small area, the propagation direction changed from septal, to apical to lateral (indicated by the blue arrows). Based on the careful analysis of the paced-ECG the assumed activation during VT occurred in an apical to basal direction followed by two wave fronts in a septal (towards 2) and lateral (towards 5) direction resulting in a “fused” QRS VT morphology not reproducible by pacing at either site. Indeed, ablation at the presumed isthmus site (and predicted site of origin), indicated by the white tag, abolished VT.


A
Pace
Best pace map
0.04 mV
Bi
16.47 mV
0.04 1.50
L
R
1
2
3
4
5
6
Mod.PA (bottom view)
MA
Mod.PA
B
VT
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
100ms
C
1
2
3
4
5
6
100ms

SUPPLEMENTARY CASE 4

69 years male, 17 years after small apical MI, clinical VTCL 375ms

Panel A. EA endocardial bipolar voltage map of the LV in modified anterior (AP), LAO and inferior views (color coded according to the bar) showing a very small dense apicoseptal scar with only little lateral involvement. Grey tags indicate sites with no capture at high output pacing.

The clinical VT (panel C) had RBBB morphology with early precordial transition and right superior axis and a predicted posterior-apical SoO by Segal[6] (not predictable by Miller[4] and Kuchar[5]).

The best pace-map was obtained at site 5 (corresponding catheter position using a transeptal approach on fluoroscopy provided in panel B, red arrows) and ablation adjacent to this point successfully terminated VT.

Please note that pacing at all scar border zone sites resulted in a RBBB morphology with early transition and a superior axis similar to VT (R/S transition is indicated as blue lines). The superior axis can be explained by an inferior-anterior activation of the normal myocardium from all scar border sites. However, subtle QRS axis changes from RS to LS as pacing sites move from right to left (best visible in lead aVL) can direct to the VT scar exit in small apical scars.

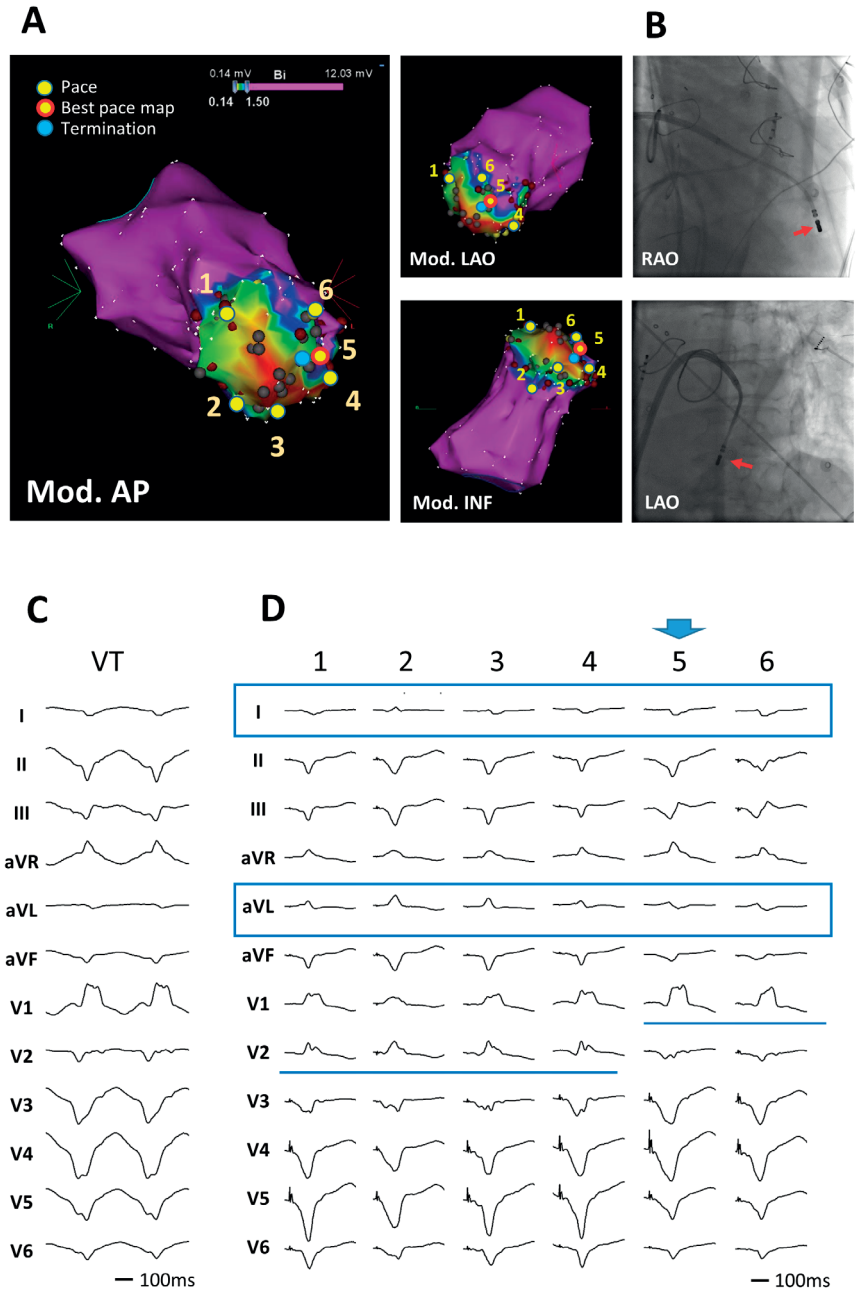

A
B
Pace
Best pace map
Termination
0.14 mV
Bi
12.03 mV
0.14
1.50
1
2
3
4
5
6
Mod. AP
Mod. LAO
RAO
Mod. INF
LAO
C
D
VT
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
100ms
1
2
3
4
5
6
100ms

Figure 1

SUPPLEMENTARY CASE 5

64 years male, 16 years after large anterior MI, clinical VTCL 440ms

Panel A. EA endocardial bipolar voltage map of the LV in modified RAO and LAO views (color coded according to the bar, grey tags indicate sites with no capture at high output pacing). Tags represent catheter positions as indicated; numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel C).

The clinical VT (panel C) had RBBB morphology with positive concordance and left inferior axis, which was rarely observed in Miller's[4] report (2 out of 78 RBBB VT from anterior infarctions) but had a predictable anterobasal SoO according to Kuchar[5] and Segal[6]. The best pace-map was obtained at the basal anterior EA scar border (site 2). Please note the abrupt change in the paced QRS morphology from a left inferior axis to a left superior axis with early precordial transition if pacing moved from the basoseptal EA scar border zone (site 1, corresponding catheter position on fluoroscopy, panel B, red arrows) to the mid-septal (site 3) border zone. The EA scar extension (dashed line, panel A) between these two sites may lead to different propagation wave fronts and abrupt changes in the paced QRS morphology. Please also note that pacing at mid anteroseptal sites (point 3 and 4) resulted in a RBBB morphology with early transition with left superior axis while pacing at mid lateral sites (point 9 and 10) had later transition and less superior axis. Unexpected ECG morphologies are likely related to the variation in scar distribution after anterior MI and may explain the limited predictive value of prior algorithms.

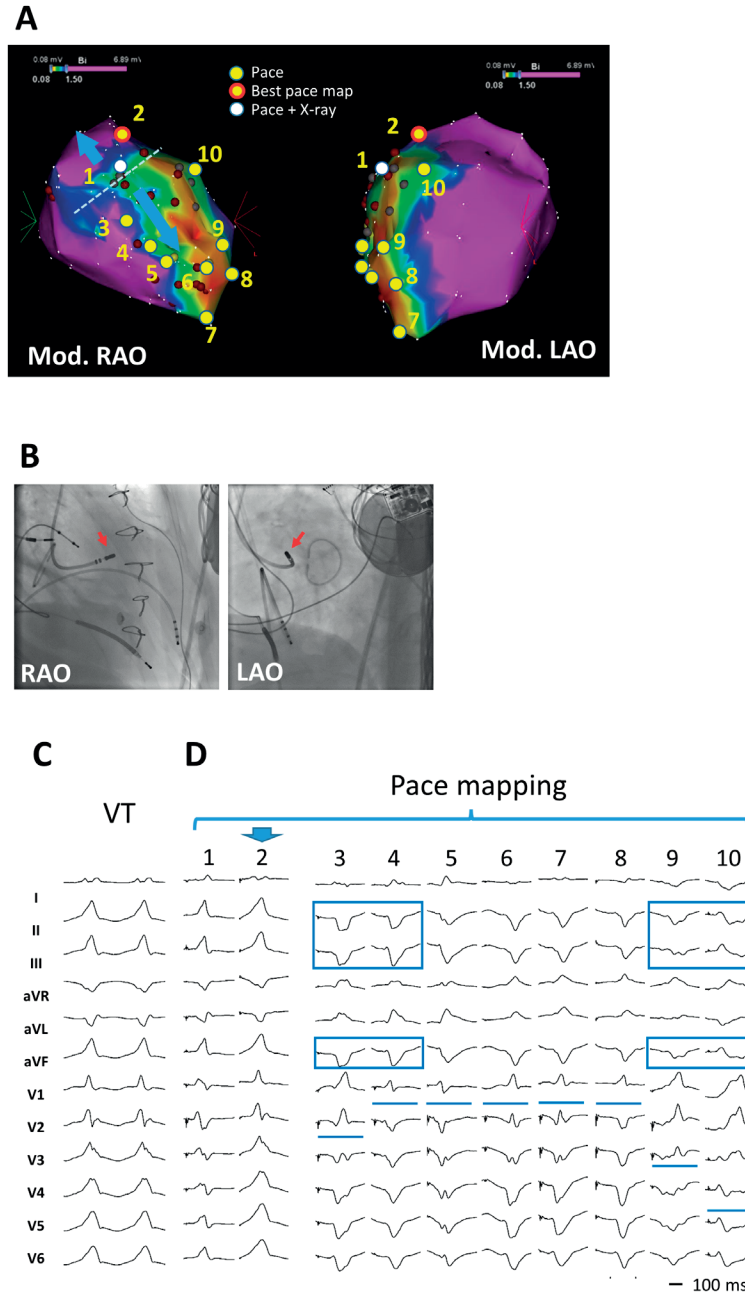

A
Pace
Best pace map
Pace + X-ray
Mod. RAO
Mod. LAO
B
RAO
LAO
C
VT
D
Pace mapping
1
2
3
4
5
6
7
8
9
10
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
100 ms

Figure 5

SUPPLEMENTARY CASE 6

73 years male, 16 years after inferolateral MI, epicardial ablation after endocardial ablation failure, clinical VTCL 630ms

Panel A. EA endocardial bipolar voltage map of the LV in modified left lateral and posterior views (color coded according to the bar, grey tags indicate sites with no capture at high output pacing). Tags represent catheter positions as indicated; position of the best endocardial pace-map on fluoroscopy in RAO and LAO view (red arrows). Numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel D).

Panel B. EA epicardial bipolar voltage map of the LV in the same modified left lateral and posterior views as panel A (color coded according to the bar, please note that for the epicardium, a bipolar cut off <1.8mV for abnormal voltage is applied[14], grey tags indicate sites with no capture at high output pacing). Tags represent catheter positions as indicated; position of the best epicardial pace-map after endocardial ablation failure on fluoroscopy in RAO and LAO view (red arrows). Numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel E).

The clinical VT had RBBB morphology, positive concordance, inferior axis, not classifiable by Miller[4] and with a predicted mid to basal anterior SoO according to Kuchar[5] and Segal[6] (panel C, left). The best, although not perfect endocardial pace-map was obtained at endocardial site 1 (panel A, D). After RF at the endocardium a similar VT remained inducible (VT´) with slightly shorter CL and subtle changes of the initial part of the VT QRS (panel C, right) suggesting an epicardial exit site.

ECG criteria for a potential epicardial site of origin (sweep speed 100mm/sec) were applied; Pseudodelta wave (PDW ≥ 34ms), Intrinsicoid deflection time inV2 (IDT ≥ 85), Shortest RS complex (SRS ≥ 121ms), Maximum deflection index (MDI ≥ 0.45). Despite a similar morphology, after endocardial ablation VT´ QRS was broader (251ms vs. 387ms after) and ECG parameters were strongly suggestive for an epicardial origin; PDW 65ms vs 198ms, IDT 112ms vs 252ms, SRS 182ms vs 322ms and MDI 0.39 vs 0.59 in VT before and after endocardial ablation. Notably, morphology criteria did not differentiate between endo and epicardial pacing sites (Q-waves), perhaps because of the transmural lateral scar.

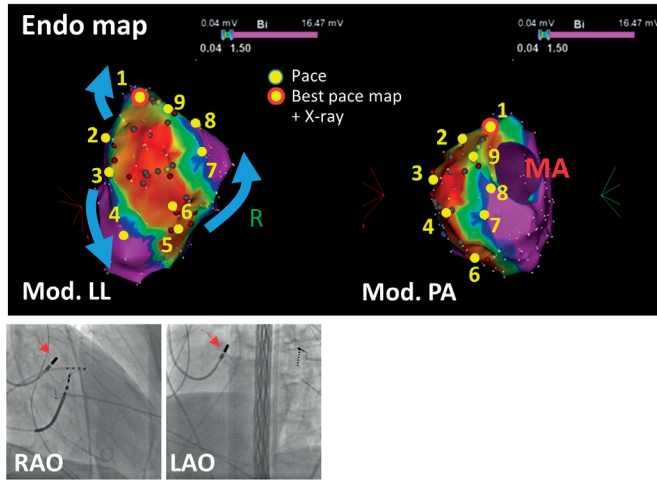
During epicardial mapping, the best pace-map for VT´ could be obtained at epicardial site 1 (epicardial catheter position on fluoroscopy opposite (slightly lateral) to the endocardial catheter position). With the catheter in place VT was re-induced and terminated

after 6 seconds RF. The change in QRS morphology after endocardial ablation may be explained by a shift in exit site from the endocardium to the epicardium.

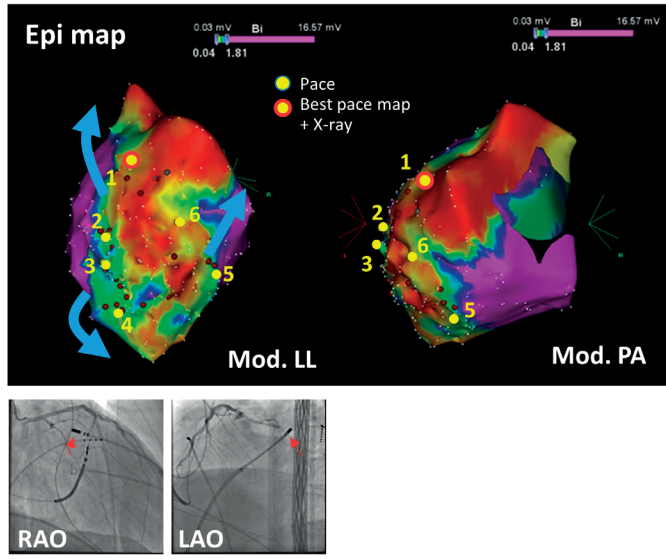
Voltage mapping showed a remarkable anterior scar extension, which explains the unusual 12 lead VT QRS morphology in a patient after inferolateral MI.

Please also note the abrupt change in the precordial leads between pacing site 4 and 5 from a RS in V1, negative concordant in the precordial leads to a RBBB, late transition morphology. These changes may be explained by the scar extension and transmurality as derived from endo and epicardial voltage mapping resulting in different wavefront propagation and QRS morphologies.

A


Endo map
0.04 mV
Bi
16.47 mV
0.04 1.50
Pace
Best pace map
+ X-ray
1
2
3
4
5
6
7
8
9
R
MA
Mod. LL
Mod. PA
RAO
LAO

B


Epi map
0.03 mV
Bi
16.57 mV
0.04 1.81
Pace
Best pace map
+ X-ray
1
2
3
4
5
6
Mod. LL
Mod. PA
RAO
LAO

SUPPLEMENTARY CASE 7

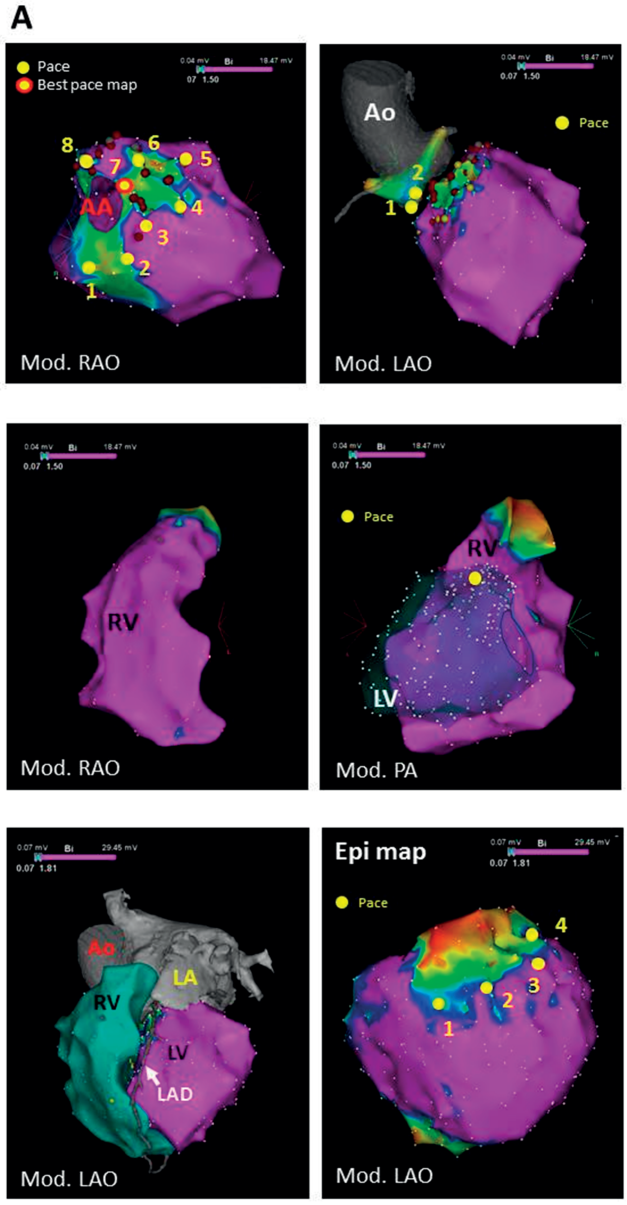
62 years male, NICM, clinical VTCL 405ms

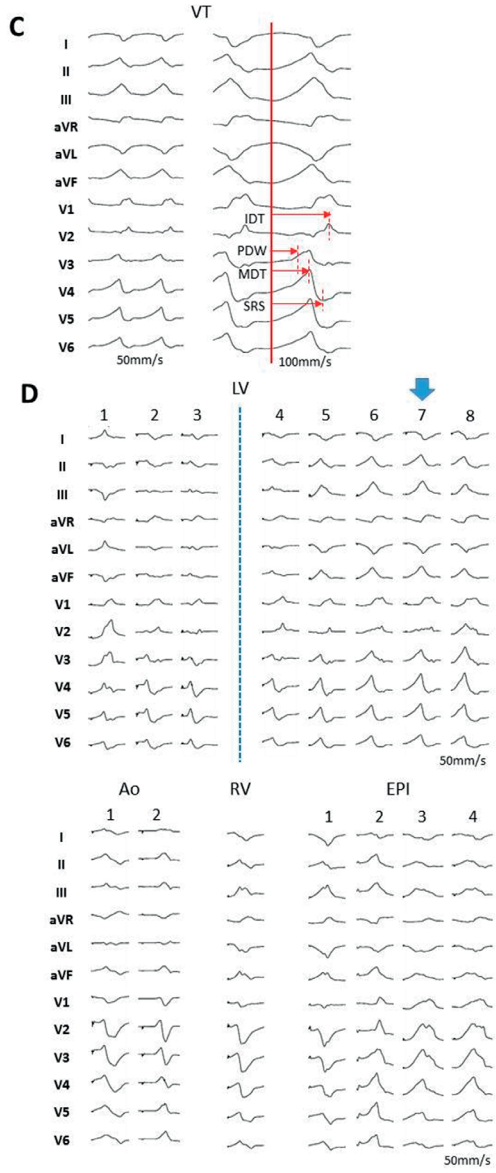
Panel A. EA endocardial bipolar voltage map of the LV in modified RAO and LAO views, the aorta (Ao) and the RV (modified RAO and posterior view[LV transparent]) (color coded according to the bar, grey tags indicate sites with no capture at high output pacing). Tags represent catheter positions as indicated; numbers correspond to the numbers of the paced 12 lead ECG morphologies (Panel D).

Panel B. EA epicardial bipolar voltage map in a modified LAO view (left) and integration of the CT derived anatomy of the aorta, left atrium and coronary arteries (LAD, left anterior descending coronary artery) with the endocardial EA maps (right, same modified LAO view).

The endocardial EA scar was confined to the basal anteroseptal LV, which is one of the typical scar patterns observed in NICM patients[27]. Image integration demonstrates that this particular area is not reachable from the epicardium. The epicardial low voltage area (ventricular electrograms annotated) is covered by the large left atrial appendage (LAA) and the fat overlying the LAD at the interventricular groove.

The clinical VT (Panel C, 50mm/sec [left]; 100mm/sec [right]) had a RBBB morphology with positive concordance and right inferior axis, suggesting an origin from the anterobasal LV, so called 'LV summit'. ECG parameters were indicative of an epicardial SoO (PDW 135ms (≥34ms), IDT 275ms (≥ 85), SRS 270ms (≥ 121ms) and MDI 0.56 (≥ 0.45)). The best although not perfect pace-map (no prolonged initial slurring in precordial lead V3) was obtained just beneath the aortic valve (panel D, endocardial site 7). Ablation at the endocardial LV basal anterolateral region could modify but not abolish the VT. Pace mapping neither at RV, CS or aortic cusp sites could resemble VT QRS. Although epicardial mapping was performed, neither pace-mapping nor activation mapping could identify a VT related site. Although no complication related to the epicardial access occurred in this patient, the 12 lead VT ECG morphology combined with the information from image integration after endocardial substrate mapping can predict a VT substrate not accessible from the epicardium.


A
Pace
Best pace map
8
7
6
5
AA
4
3
2
1
Mod. RAO
Ao
Pace
2
1
Mod. LAO
RV
Mod. RAO
Pace
RV
LV
Mod. PA
Ao
LA
RV
LV
LAD
Mod. LAO
Epi map
Pace
4
3
2
1
Mod. LAO


C
VT
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
IDT
PDW
MDT
SRS
50mm/s
100mm/s
D
LV
1 2 3 4 5 6 7 8
50mm/s
Ao
RV
EPI
1 2
1 2 3 4
50mm/s

Part II

3

Re-assessing non-inducibility as ablation endpoint of post-infarction ventricular tachycardia: The impact of left ventricular function

Marta de Riva, MD, Sebastiaan R.D. Piers, MD, PhD, Gijsbert F. Kapel, MD, PhD, Masaya Watanabe, MD, PhD, Jeroen Venlet, MD, Serge A. Trines, MD, PhD, Martin J. Schalij MD, PhD, Katja Zeppenfeld, MD, PhD

Circulation: Arrhythmia & Electrophysiology 2015;8(4):853-862

ABSTRACT

Background

Noninducibility is frequently used as procedural end point of ventricular tachycardia (VT) ablation after myocardial infarction. We investigated the influence of left ventricular (LV) function on the predictive value of noninducibility for VT recurrence and cardiac mortality.

Methods and Results

Ninety-one patients (82 men, 67±10 years) with post–myocardial infarction VT underwent ablation between 2009 and 2012. Fifty-nine (65%) had an LV ejection fraction (EF) >30% (mean 41±7) and 32 (35%) an LVEF≤30% (mean 20±5). Thirty patients (51%) with EF>30% and 13 (41%) with EF≤30% were noninducible after ablation (P=0.386). During a median follow-up of 23 (Q1–Q3 16–36) months, 35 patients (38%) experienced VT recurrences and 17 (18%) cardiac death. At 1 year follow-up, survival free from VT recurrence and cardiac death for patients with LVEF>30% was 80% (95% confidence interval [CI], 70–90) compared with 42% (95% CI, 33–51) for those with LVEF≤30% (P=0.001). Noninducible patients with LVEF>30% had a recurrence-free survival from cardiac death of 90% (95% CI, 71–100) compared with 65% (95% CI, 47–83) for inducible patients (P=0.015). In the subgroup of patients with LVEF≤30%, the survival free from VT recurrence and cardiac death was 31% (95% CI, 0%–60%) for noninducible compared with 39% (95% CI, 27–52) for those who remained inducible (P=0.842).

Conclusions

Noninducible patients with moderately depressed LV function have a favorable outcome compared with patients who remained inducible after ablation. On the contrary, patients with severely depressed LV function have a poor prognosis independent of the acute procedural outcome.

INTRODUCTION

In patients late after myocardial infarction (MI), noninducibility of any sustained monomorphic ventricular tachycardia (VT) with programmed electric stimulation (PES) after ablation has been associated with favorable long-term outcome (lower VT recurrence rate and mortality).1–5

Noninducibility is therefore currently used as procedural end point in many electrophysiology laboratories and the only endorsed by the current expert consensus.6 However, the predictive value of noninducibility for VT recurrence is limited because ≤30% of patients who are rendered noninducible experience VT recurrences and more than half of the patients who remain inducible for nonclinical VTs do not present recurrence on short-term follow-up.5

In line with prior recommendations, the majority of patients included in former studies of post-MI VT ablation had an advanced disease with poor left ventricular function, presenting with multiple VT episodes refractory to antiarrhythmic drugs (AAD), including amiodarone.1–5,7 More recently, ablation early in the course of the arrhythmic disease has been recommended based on 2 randomized trials.8,9

Because of the reported high recurrence rates, despite noninducibility, new ablation end points like elimination of late or abnormal potentials have been suggested for all patients with scar-related VT, irrespective of baseline patient characteristics and clinical presentation. Achieving these end points may require more invasive and extensive procedures likely to be associated with patient discomfort and procedure-related complications.10–12

We hypothesize that differences between patients, in particular in left ventricular (LV) function, may not only affect procedural and long-term outcome but also the optimal procedural end point for an individual patient.

The main objective of this study was to analyze the influence of individual patient characteristics on the predictive value of noninducibility for VT recurrence and cardiac mortality in the population currently referred for VT ablation after MI.

METHODS

Patient Population

The study population consisted of consecutive patients with prior MI and spontaneous symptomatic sustained monomorphic VT who underwent a first catheter ablation procedure at the Leiden University Medical Center between January 2009 and December 2012. Diagnosis of MI was based on the presence of wall motion abnormalities, nonreversible perfusion defects, and subendocardial or transmural late gadolinium enhancement areas in the perfusion territory of a significant stenotic coronary artery (>75%). Patients who underwent surgical ablation or presented with frequent premature ventricular contractions or nonsustained VT without documented spontaneous sustained VT were excluded. All patients provided informed consent and were treated according to the institutional clinical protocol.

Preprocedural Evaluation

Before the procedure, patients underwent a comprehensive clinical evaluation. VT clinical presentation was classified as electrical storm (≥3 implantable cardioverter defibrillator [ICD] shocks/24 h), incessant VT (recurrent sustained VT despite repeated intervention for termination), recurrent ICD therapies, VT below detection of ICD, and first episode of VT. A special effort was taken to obtain 12-lead documentation of the spontaneous VTs.

All patients underwent 2-dimensional and color Doppler echocardiography to assess LV ejection fraction (LVEF). LV end-diastolic and end-systolic volumes were obtained from the apical 2- and 4-chamber views and LVEF was calculated according to the biplane Simpson's method. Echocardiographic analyses were performed by an experienced observer blinded to all clinical and procedural data.

In 25 patients without ICD, contrast-enhanced MRI was performed. Seventy-nine patients (87%) underwent coronary angiography, and in 23 patients (25%), percutaneous coronary intervention was performed before catheter ablation.

Electrophysiological Study

Studies were performed in the fasting state under conscious sedation. In stable patients, all AAD with the exception of amiodarone (n=39, 43%) were discontinued for 5 half-lives before the study.

The PES protocol consisted of burst pacing and extrastimulation with 3 drive cycle lengths (CL; 600, 500, and 400ms) from at least 2 sites (right ventricular apex and right

ventricular outflow tract) with 1, 2, and 3 extrastimuli until 200 ms or refractoriness. Positive end point for stimulation was considered the induction of a sustained monomorphic VT lasting for >30 s or requiring termination because of hemodynamic instability. Induced VTs where classified as (1) clinical when there was a 12/12 electrocardiographic morphology match with a previously documented VT, (2) presumptive clinical when the CL was ±30 ms of an ICD recorded VT, or (3) nonclinical VT when the previous criteria were not fulfilled.

Electroanatomical Mapping and Catheter Ablation

The initial approach was endocardial in all but one patient (after 2 failed attempts of endocardial ablation in another center). If noninducibility could not be achieved from the endocardium and an epicardial site of origin was assumed based on endocardial activation and substrate mapping, epicardial mapping as secondary approach was considered depending on VT clinical presentation and patient preference. Electroanatomical LV mapping was performed through a retrograde aortic approach (n=88) or a combination of retrograde and transeptal approach (n=3) during sinus or paced rhythm (n=9). Bipolar voltage maps were created with a 3.5 mm irrigated-tip catheter with a 2-5-2 mm interelectrode spacing (NaviStar ThermoCool; Biosense Webster, Inc, Diamond Bar, CA) and the CARTO system. Electrograms were filtered at 30 to 400 Hz (bipolar) and 1 to 240 Hz (unipolar). The area with bipolar voltages under 0.5 mV was defined as dense scar. The area with bipolar voltages between 0.5 to 1.5mV was defined as scar border zone. Re-entry isthmus sites were identified with entrainment and activation mapping for stable VTs and with substrate mapping for unstable VTs. Potential ablation targets based on electrogram characteristics and pace mapping (≥10/12 morphology match with induced VT and stimulus-to-QRS delay > 40 ms) were tagged on the map. Once the area of interest was localized, VT was reinduced. Whenever possible, poorly tolerated VTs were at least briefly mapped during VT to either perform entrainment mapping or slow and terminate VT during radiofrequency application. Only areas specifically related to induced VTs based on entrainment and pace-mapping were targeted. Radiofrequency energy was delivered between 35 and 50 W with a temperature limit of 43°C and a flow rate of 20 to 30 mL/min until the capture threshold postablation was >10 mA/2 ms.

Procedural End Point

All clinical and nonclinical sustained monomorphic VTs were targeted for ablation. Only nonclinical fast VTs, defined as VTs with a VTCL close to ventricular refractory period, that were not reproducible inducible were considered to be of unknown clinical relevance and were not targeted. Safety was taken into major consideration; therefore, the procedure was stopped if multiple electric cardioversions were required or the patient had prolonged hemodynamic instability.

Acute Procedural Outcome

After the last radiofrequency application, the entire PES protocol was repeated. Complete acute success was defined as noninducibility of any sustained monomorphic VT; partial success as elimination of all clinically documented VTs but inducibility of any nonclinical VT independent from VTCL and morphology also including nontargeted fast VTs and failure as persistent inducibility of any clinical VT.

Postprocedural Management

An ICD was offered to all patients regardless of acute procedural outcome. Preablation AAD were maintained until the first follow-up visit. Thereafter, the AAD regimen was left at the discretion of the referring cardiologist

Follow-Up

Patients were followed at the outpatient clinic 3 and 6 months after the procedure and every 6 months afterward, including a careful history regarding symptoms for VT and ICD interrogation. For patients followed at other institutions and in case of death, the referring cardiologist or general physician was contacted for VT recurrence and cause of death. VT recurrence was defined as occurrence of any documented VT after ablation, independently of CL or clinical presentation. In-hospital recurrences were also included in the analysis. During follow-up, VT recurrence was classified as electrical storm (≥3 ICD shocks/24 h), incessant VT (recurrent sustained VT despite repeated intervention for termination), VT terminated by ICD shock, VT terminated by ATP, VT in monitor zone, or ECG-documented VT. A clinically relevant VT recurrence was defined as any VT that was treated with ICD shock or led to hospitalization, reablation, or modification of the antiarrhythmic therapy.

Statistical Analysis

Continuous variables are reported as mean±SD or medians with upper and lower quartiles (Q1–Q3). Categorical variables are presented as numbers and frequencies (%). Categorical variables were compared using the Chi-squared test or the Fisher exact test and continuous variables with the Student's t test or the Mann–Whitney U test when appropriate. The VT and ICD shock frequency before and after ablation and the CL of the spontaneous, remaining, and recurrent VTs were compared with the Wilcoxon signed-rank test. Freedom from VT recurrence and cardiac death was estimated by Kaplan–Meier method and compared by log-rank test between groups. Predictors of acute procedural outcome, VT recurrence, and mortality were assessed with univariate logistic regression and Cox regression analysis, respectively. For the regression analysis of predictors of mortality on follow-up, VT recurrence was treated as time-dependent variable. Independent predictors of acute procedural outcome and VT recurrence were

analyzed with multivariable models using a backward stepwise selection. Variables with a P value <0.10 were initially included. At each step, the least significant variable was removed from the model, until all variables reached a P value <0.20. All tests were 2-sided and a P value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

During the study period, 116 patients with prior MI and symptomatic ventricular arrhythmias were referred for ablation. Twenty patients (17%) with nonsustained VT and premature ventricular contractions, 4 (3%) who underwent surgical ablation, and 1 (1%) with pleomorphic VT at presentation were excluded. Finally, 91 patients (82 men, 67±10 years) with remote MI and history of spontaneous sustained monomorphic VT comprised the study population. Ten (11%) patients had previously undergone ≥1 failed endocardial VT ablation in another center. Fifty-seven patients (63%) had an ICD implanted before the procedure. Fifteen patients (17%) presented with electrical storm and 14 (15%) with incessant VT. Twenty-eight patients (31%) were referred for ablation after the first documented VT episode.

Fifty-nine patients (65%) had a moderately depressed LVEF (defined as LVEF>30%, mean 41±7) and 32 (35%) a severely depressed LVEF (defined as LVEF≤30%, mean 20±5). Patients with severely depressed LVEF were younger (64±13 versus 69±8 years-old, P=0.048) and had more frequently a history of an anterior MI (53% versus 29%, P=0.026), atrial fibrillation (47% versus 22%, P=0.018), heart failure hospitalizations (72% versus 29%, P<0.0001), ICD implantation before the procedure (84% versus 51%, P=0.002), a previous VT ablation in another center (22% versus 5%, P=0.030), and slower VTs at presentation (438±69 versus 353±77 ms, P<0.0001). Patients with LVEF>30% were more often referred for ablation after the first episode of a symptomatic VT (42% versus 9%, P=0.001). In most of these patients, the procedure was performed clinically, before ICD implantation. Baseline characteristics of the patients according to LVEF are displayed in **Table 1**.

Ablation Procedure

Eighty-five patients (93%) were either inducible (median 3 VTs per patient, Q1–Q3 2–5; mean CL 355±87 ms) or in VT at the beginning of the procedure. Clinical VTs were present or induced in 75 patients (82%). VT was classified as clinical based on the 12 lead-ECG in 60 patients (66%) and on ICD recordings in 15 (16%). Ten patients (11%) were only inducible for nonclinical VTs. Sixty-four (70%) had at least one hemodynamically unstable VT inducible.

Table 1. Baseline characteristics of the patients according to left ventricular ejection fraction

	All (n=91)	EF > 30% (n=59)	EF ≤ 30% (n=32)	P
Age, y	67 ± 10	69 ± 8	64 ± 13	P=0.048
Male sex	82 (90%)	53 (90%)	29 (91%)	P=1.000
Hypertension	41 (45%)	30 (51%)	11 (34%)	P=0.186
Diabetes mellitus	13 (14%)	8 (14%)	5(16%)	P=0.764
Hypercholesterolemia	32 (35%)	23 (39%)	9 (28%)	P=0.362
History of Stroke/TIA	8 (9%)	6 (10%)	2 (6%)	P=0.708
History of atrial fibrillation	28 (31%)	13 (22%)	15 (47%)	P=0.018
History of renal failure	29 (32%)	15 (25%)	14 (45%)	P=0.063
Prior admissions for heart failure	40 (44%)	17 (29%)	23 (72%)	P<0.0001
Anterior MI	34 (37%)	17 (29%)	17 (53%)	P=0.026
MI acute reperfusion	15 (16%)	10 (17%)	5 (16%)	p=1.000
Time since MI, y	19 ± 9	20 ± 9	18 ± 7	P=0.441
Prior CABG	37 (41%)	25 (42%)	12 (38%)	P=0.823
Prior PCI	36 (39%)	23 (39%)	13 (41%)	P=1.000
LV ejection fraction, %	34±12	41 ± 7	20 ± 5	P<0.0001
ICD before ablation	57 (63%)	30 (51%)	27 (84%)	P=0.002
Prior VT ablation	10 (11%)	3 (5%)	7 (22%)	P=0.030
Clinical VT mean CL, ms	382±84	353 ± 77	438 ± 69	P<0.0001
Medication at admission				
Statins	81 (89%)	53 (90%)	28 (88%)	P=0.737
Antialdosteronic	31 (34%)	20 (34%)	11 (34%)	P=1.000
ACE inhibitor/ARB	76 (84%)	51 (86%)	25 (78%)	P=0.378
Betablockers	69 (76%)	43 (73%)	26 (81%)	P=0.448
Amiodarone	39 (43%)	21 (36%)	18 (56%)	P=0.076
VT clinical presentation				
Electrical storm	15 (17%)	8 (14%)	7 (22%)	P=0.378
Incessant VT	14 (15%)	7 (12%)	7 (22%)	P=0.234
ICD therapies	24 (26%)	13 (22%)	11 (34%)	P=0.221
Below ICD detection	10 (11%)	6 (10%)	4 (13%)	P=0.737
First episode	28 (31%)	25 (42%)	3 (9%)	P=0.001

TIA indicates transitory ischemic attack; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LV, left ventricular; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; CL, cycle length; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

Compared with patients with LVEF>30%, patients with LVEF≤30% were inducible for a higher number of VTs (2.8±2.0 versus 5.0±2.9, P<0.0001), which were slower (mean CL 323±63 versus 409±97 ms, P<0.0001) and had more often left bundle branch block morphology (51% versus 78%, P=0.033). Procedural data according to LVEF are summarized in **Table 2**.

Table 2. Electrophysiological and procedural characteristics according to left ventricular ejection fraction

	All (n=91)	EF > 30% (n=59)	EF ≤ 30% (n=32)	P
Inducible before ablation	85 (93%)	54 (92%)	31 (97%)	P=0.419
Number of Induced VTs	3.6 ± 2.5	2.8 ± 2.0	5.0 ± 2.9	P<0.0001
Induced VT max CL, ms	418 ± 116	367 ± 86	507 ± 108	P<0.0001
Induced VT mean CL, ms	355 ± 87	323 ± 63	409 ± 97	P<0.0001
Induced VT min CL, ms	295 ± 79	282 ± 61	319 ± 101	P=0.036
HD unstable VT inducible	64 (70%)	39 (72%)	25 (81%)	P=0.443
LBBB VT inducible	55 (60%)	30 (51%)	25 (78%)	P=0.033
Epicardial mapping	7 (8%)	4 (7%)	3 (9%)	P=0.236
Complete success	43 (47%)	30 (51%)	13 (41%)	P=0.386
Partial success	44 (49%)	25 (42%)	19 (59%)	P=0.132
Remaining VT mean CL, ms	279 ± 59	275 ± 59	286 ± 59	P=0.531
Procedural duration, min	207 ± 92	202 ± 80	216 ± 113	P=0.516
Fluoroscopic time, min	38 ± 23	36 ± 21	41 ± 25	P=0.434
ICD after ablation	77 (85%)	47 (80%)	30 (94%)	P=0.126
Amiodarone post-ablation	44 (48%)	22 (37%)	22 (54%)	P=0.005

VT indicates ventricular tachycardia; CL, cycle length; LBBB, left bundle branch block; ICD, implantable cardioverter defibrillator.

All patients underwent endocardial mapping and ablation. In 8 of 52 patients (15%) who remained inducible after endocardial ablation, an epicardial approach was attempted. Of the 7 patients who finally underwent epicardial mapping (one was not successful because pericardial adherences) only in 4 epicardial radiofrequency was applied. Three patients were rendered noninducible and one remained inducible for nonclinical VTs only after combined endo-epicardial approach.

At the end of the procedure, all patients underwent PES. Complete acute success was achieved in 43 patients (47%) and partial in 44 (49%). Procedural failure occurred in 4 patients (4%). Of note, there was no difference between patients with severely and moderately depressed LV function regarding the acute procedural success rate (noninducibility was achieved in 30 patients [51%] with EF>30% versus 13 [41%] with EF≤30%; P=0.386).

The majority of inducible patients after ablation (41/48, 85%) had remaining VTs, which were faster than all spontaneous VTs (mean CL 280±59 versus 389±89 ms, P<0.0001), 35/48 patients (73%) had only VTs with a CL≤300 ms. Importantly, in 38 of 48 patients (79%), remaining fast VTs were not targeted because they were considered to be of unknown clinical relevance (mean CL 263±42 ms).

Complications

There was no procedure-related mortality. One patient with multiple ICD shocks and a basoseptal central isthmus site developed anticipated complete AV block after ablation. Ten patients had vascular access-related complications. None of them needed surgical intervention. Cardiac tamponade requiring percutaneous drainage after endocardial ablation occurred in one patient and late tamponade after an epicardial approach in one other patient. There was no difference in the occurrence of procedural-related complications according to baseline LVEF (EF>30%; 18% versus EF≤30%; 6%, P=0.129).

Predictors of Acute Outcome

Noncomplete acute success was associated with a higher number of induced VTs (odds ratio 1.42 per additional VT induced; 95% confidence interval [CI] 1.15–1.76; P=0.001) and the induction of faster (odds ratio 2.79 per 50 ms decrease in minimum VT CL; 95% CI 1.66–4.72; P<0.0001) and hemodynamically unstable VTs (odds ratio 6.55; 95% CI 2.11–20.32; P=0.001; **Figure 1**). On multivariate analysis, the number of induced VTs (odds ratio 1.23 per additional VT induced; 95% CI 1.00–1.57; P=0.047) and the CL of the fastest induced VT (odds ratio 2.78 per 50 ms decrease in minimum VT CL; 95% CI 1.60–4.76; P<0.0001) remained independently associated with the acute procedural outcome.

This was observed for both patient groups, those with LVEF>30% and LVEF≤30% with the exception of the number of induced VTs that was not associated with worse acute outcome for patients with LVEF≤30% (odds ratio 1.30 per additional VT induced; 95% CI 0.97–1.77; P=0.080).

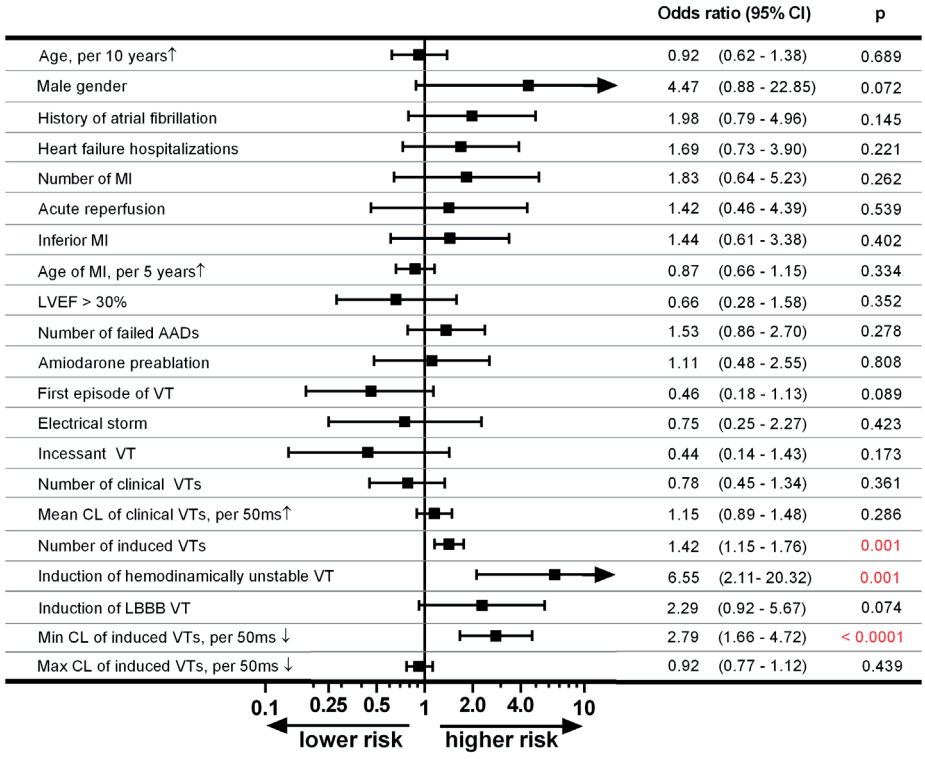
Postprocedural Management

Seventy-seven (85%) patients were discharged with an ICD. Fourteen (15%) patients refused ICD implantation. These patients were older (odds ratio 0.35 per 10 years increase; 95% CI 0.16–0.75; P=0.007), had better LVEF (odds ratio 0.69 per 5% increase EF; 95% CI 0.51–0.92; P=0.011, all but 2 EF>30%), and were more often noninducible after ablation (odds ratio 20.37; 95% CI 2.53–163.82; P=0.005). Seventy-two (79%) patients were discharged on AAD other than conventional β-blockers (44 [48%] on amiodarone and 28 [31%] on sotalol).

VT Recurrence

During a median follow-up of 23 (Q1–Q3 16–36) months, 35 patients (38%) experienced any VT recurrence with a median time to recurrence of 133 (Q1–Q3 36–608) days (only one patient was lost for follow-up, all but 2 had a follow-up longer than 1 year, 9 patients died during the first year).

Figure 1.
Predictors of inducibility after ablation



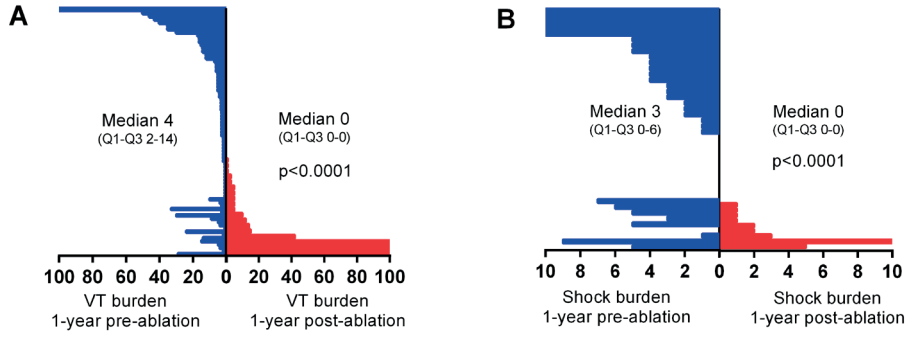
AAD indicates antiarrhythmic drugs; CL, cycle length; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; Max, maximum; MI, myocardial infarction; Min, minimum; and VT, ventricular tachycardia.

Patients with a LVEF>30% had a lower incidence of VT recurrence than patients with LVEF≤30% (34% versus 48%, hazard ratio [HR] 0.43; 95% CI 0.21–0.87; P=0.02).

The 1-year VT burden was reduced in the entire group from a median of 4 (Q1–Q3 2–14) episodes before ablation to a median of 0 (Q1–Q3 0–0) episodes after ablation (P<0.0001). Sixty-five of 79 (82%) patients with a follow-up longer than 1 year had a ≥75% reduction of the VT burden (**Figure 2A**). In patients with ICD before ablation, the frequency of shocks per year was reduced from a median of 3 (Q1–Q3 0–6) to a median of 0 (Q1–Q3 0–0) after ablation (P<0.0001; **Figure 2B**).

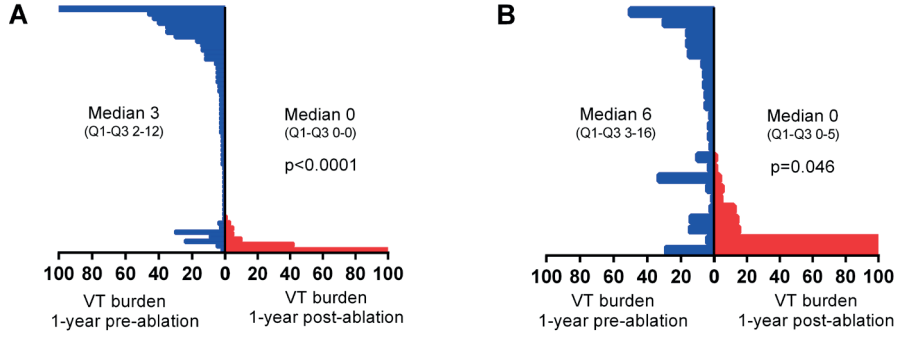
A significant reduction of the 1-year VT burden was observed in patients with both severely and moderately depressed LV function (**Figure 3**).

Figure 2.



A: One-year ventricular tachycardia (VT) burden before (blue lines) and after ablation (red lines) of 77 patients with follow-up longer than 1 year. The number of VT episodes is truncated at 100. **B:** One-year shock burden before (blue lines) and after ablation (red lines) in patients with prior ICD and follow-up longer than 1 year. The number of shocks is truncated at 10. IQR indicates interquartile range.

Figure 3.



One-year ventricular tachycardia (VT) burden before (blue lines) and after ablation (red lines) in patients with LVEF>30% (Panel A) and LVEF≤30% (Panel B). The number of VT episodes is truncated at 100.

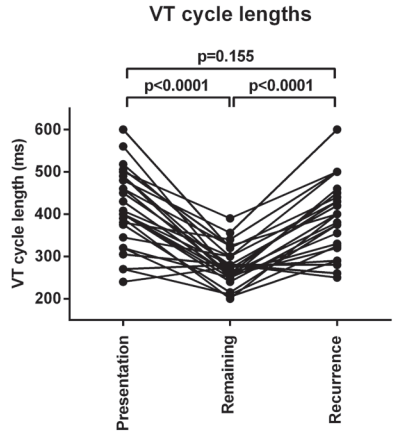
Mode and Predictors of VT Recurrence

Based on the provided definition, only 27 patients (29%) presented with clinically relevant VT recurrences (3 (3%) electrical storm, 5 (5%) incessant VT, 12 (13%) ≥ 1 ICD shock, 4 (4%) VT below detection of ICD, 3 (3%) frequent symptomatic ATP). Eight patients (9%) presented with sporadic ATP or asymptomatic self-terminating VTs in the monitor zone that did not require any intervention. Thirteen patients (42%) with LVEF≤30% presented with relevant VT recurrences compared with 14 (24%) with LVEF>30% (P=0.150). In 21 of 27 patients (81%) with relevant VT recurrences, these occurred during the first year of follow-up (18 (67%) in the first 6 months). No VT recurrence was documented in patients discharged without ICD.

Recurrent VTs were significantly slower than the remaining VTs in patients with non-complete acute procedural success (378±74 versus 285±63 ms; P<0.0001). In fact, in 23 of 28 patients (82%) with noncomplete acute success and recurrences on follow-up, the CL of the recurrent VT was at least 30 ms longer than the CL of the slowest remaining VT after ablation, suggesting that remaining fast VTs were not the cause of recurrence in these patients. **Figure 4** shows the CL of spontaneous, remaining, and recurrent VTs in individual patients with partial acute success and VT recurrence during follow-up.

On multivariate analysis, after adjusting for age, sex, hypertension, ejection fraction, history of atrial fibrillation, renal failure, history of heart failure hospitalizations, electrical storm, incessant VT at presentation, and amiodarone use after ablation, a higher number of induced VTs (HR 1.22 per additional VT induced; 95% CI 1.08–1.40; P=0.002) and inducibility after ablation (HR 2.49; 95% CI 2.49–5.61; P=0.028) were independently associated with VT recurrence for the entire population. Ablation after the first documented VT episode was independently associated with lower VT recurrence (HR 0.30; 95% CI 0.10–0.89; P=0.029).

Figure 4.



The cycle length of the spontaneous ventricular tachycardia (VT), slowest remaining VT after ablation, and recurrent VT from 28 patients with partial success and VT recurrence on follow-up are plotted.

Mortality on Follow-Up

Twenty-five patients (27%) died during follow-up with a median time to death of 442 days (IQR 245–655), and 17 (19%) died of cardiac causes. Patients with LVEF>30% had better prognosis with cardiac mortality of 10% compared with 35% for patients with LVEF≤30% over the follow-up period (HR 0.21; 95% CI 0.08–0.58; P=0.003). VT recurrence (HR 2.46; 95% CI 0.93–6.51; P=0.070) and inducibility after ablation (HR 0.8; 95% CI

0.31–2.10; P=0.647) were not associated with cardiac mortality for the entire population. The most frequent cause of death was terminal heart failure (n=15, 60%), in particular for patients with severely depressed LV function (n=9, 75%). In 3 patients, death was of arrhythmic/presumed arrhythmic origin (one 80-year-old patient with 45% LVEF and complete acute success without ICD died unwitnessed while sleeping, 2 patients with severely depressed LVEF (26 and 19%) died because of an electrical storm that was not targeted by ablation). Seven of 13 patients (54%) with EF>30% died from noncardiac causes compared with 1 of 12 with LVEF≤30% (P=0.073).

VT Recurrence and Cardiac Mortality According to LV Function, VT Inducibility, and Clinical Presentation

During follow-up, the combined end point of VT recurrence or cardiac death occurred in 24 of 59 patients with LVEF>30% (41%; 34% had VT recurrence, and 10% cardiac death) had VT recurrence and 38% cardiac death).

Patients with an LVEF>30% had a higher probability of survival free from VT recurrence and cardiac death compared with those with LVEF≤ 30% (81% [95% CI 71–91] versus 61% [95% CI 43–79] at 6 months and 80% [95% CI 70–90] versus 42% [95% CI 33–51] at 1 year follow-up, P=0.001; **Figure 5A**).

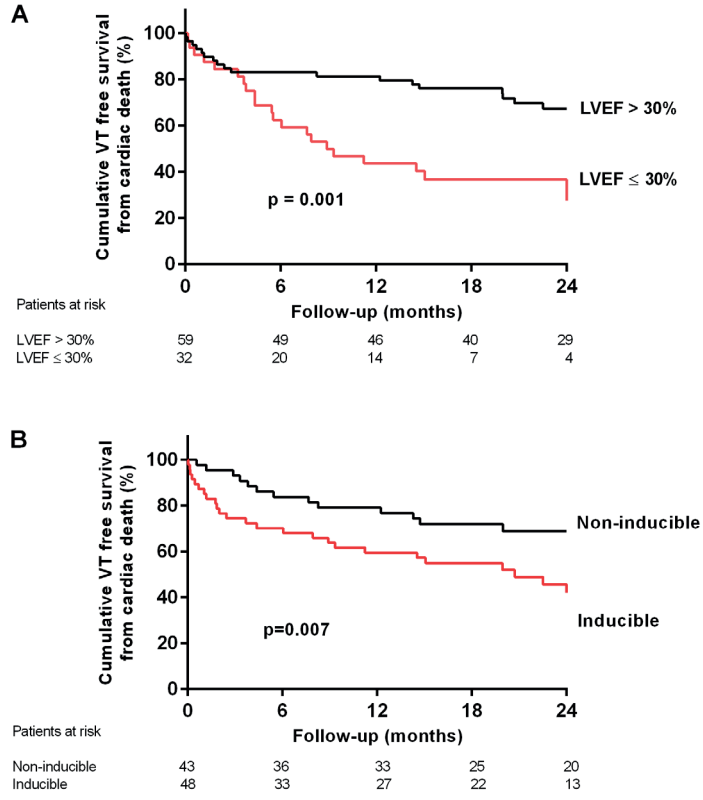
Survival free from VT recurrence and cardiac death was also higher for patients who were rendered noninducible compared with patients who remained inducible after ablation (81% [95% CI 69–93] versus 77% [95% CI 65–89] at 6 months and 68% [95% CI 54–82] versus 57% [95% CI 43–71] at 1 year follow-up: P=0.007; **Figure 5B**).

In the subgroup of patients with LVEF>30%, survival free from VT recurrence and cardiac death at 1 year follow-up was 90% (95% CI 71–100) for noninducible patients compared with 65% (95% CI 47–83) for those who remained inducible for any VT after ablation (P=0.015; **Figure 6**). This was mainly because of a higher incidence of VT recurrence in inducible patients. In fact, the probability of VT recurrence was higher in those who remained inducible after ablation (HR 4.26; 95% CI 1.54–11.78; P=0.005), whereas no significant difference was found in the incidence of cardiac death (HR 1.23; 95% CI 0.26–6.28; P=0.774). A higher number of induced VTs (HR 1.55 per additional VT induced; 95% CI 1.23–1.88; P<0.0001) was associated with VT recurrence in these patients with LVEF>30%, whereas ablation after the first documented VT episode was associated with lower VT recurrence (HR 0.25; 9 5% CI 0.08–0.74; P=0.012). No patient with LVEF>30% and who was rendered noninducible by ablation after the first symptomatic VT episode had VT recurrence or died of a cardiac cause during the first year of follow-up.

On the contrary, patients with LVEF≤30% had a poor prognosis that was independent from the acute outcome of the procedure. At 1 year follow-up, the cumulative incidence of VT free survival from cardiac death was 31% (95% CI 0–60) for noninducible patients compared with 39% (95% CI 27–52) for those who remained inducible after ablation (P=0.842).

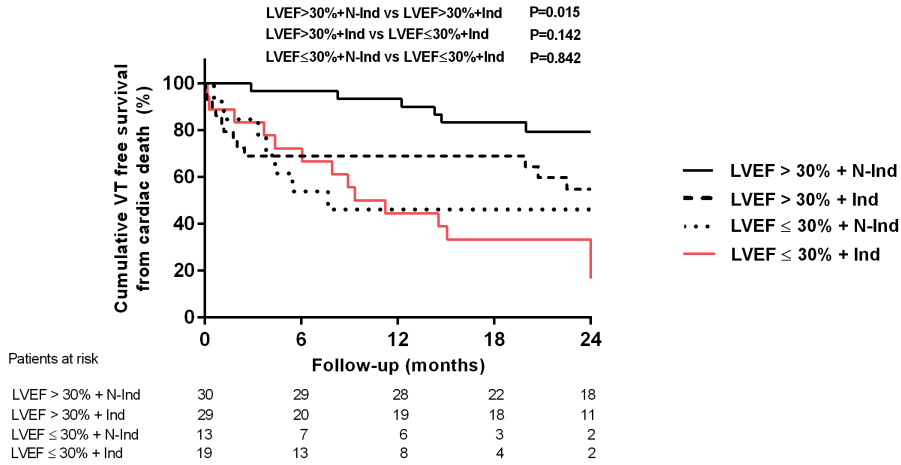
Noninducibility was neither associated with VT recurrence (HR 2.7; 95% CI 0.78–9.69; P=0.121) nor with cardiac mortality (HR 0.31; 95% CI 0.09–1.11; P=0.073) in this subgroup of patients. There was a nonsignificant trend to a higher number of inducible VTs in patients who experienced VT recurrence (HR 1.19 per additional VT induced; 95% CI 0.99–1.42; P=0.054). Ablation after the first VT episode was not associated with lower VT recurrence in these patients (HR 0.39; 95% CI 0.00–35.63; P=0.352).

Figure 5.



Ventricular tachycardia–free survival from cardiac death according to left ventricular ejection fraction (LVEF; A) and inducibility after ablation (B).

Figure 6.



Ventricular tachycardia (VT)–free survival from cardiac death according to left ventricular ejection fraction (LVEF) and inducibility after ablation.

DISCUSSION

The present study is the first to evaluate the influence of individual patient characteristics—in particular LV function—on the predictive value of noninducibility for VT recurrence and cardiac mortality in the population currently referred for VT ablation after MI.

The predictive value of noninducibility for VT recurrence and cardiac mortality was influenced by the baseline LVEF. At 1 year follow-up, only 10% of the patients with moderately depressed LV function that were rendered noninducible by ablation experienced VT recurrence or died from a cardiac cause compared with 35% of patients in whom noninducibility was not achieved. Furthermore, patients with LVEF>30% that were referred after the first documented episode of symptomatic VT and became noninducible by ablation had an excellent prognosis. No patient with these characteristics had VT recurrence or died from a cardiac cause during the first year of follow-up. On the contrary, patients with severely depressed LV function had a poor prognosis that was independent from the acute result of the procedure or the VT clinical presentation, mainly driven by heart failure–related death. In fact, >50% of the patients with LVEF<30% experienced VT recurrence or cardiac death or both during the first year of follow-up.

Prior Reports

A recent meta-analysis including 928 post-MI patients from 8 observational studies showed that lack of inducibility of any VT after ablation was associated with lower

VT/ventricular fibrillation recurrence and all-cause mortality during follow up and, therefore, proposes noninducibility as a reasonable end point for the procedure.5 This meta-analysis included, however, an unselected pool of patients that were referred for ablation over >20 years (1991–2011) and did not correct for individual patient characteristics that may per se influence outcome.

The recommendations and strategies of post-MI VT ablation have changed over time. In line with clinical guidelines, the majority of patients initially included in studies had an advanced disease, with poor LV function, symptomatic heart failure, and multiple VT episodes despite amiodarone.1–5,7,13 Since the publication of the last expert consensus, more patients with moderately depressed LV function after the first documented VT episode are referred for ablation.6 In this regard, our study is more representative of the current practice because it includes only patients treated after 2008, frequently referred after the first documented VT episode (31%) with a high prevalence of moderately depressed LV function (65%). The basal cardiac function and the stage of the arrhythmic disease may impact both the outcome and the appropriate end point of the ablation procedure for an individual patient.

Ablation Late in the Therapeutic Course of Disease

It has been shown that, in post-MI patients, the predictive value of PES to predict ventricular arrhythmic events depends on the basal cardiac function. In the MUST trial, the cause of death of inducible patients with LVEF>30% was arrhythmic in 61% of the cases. On the contrary, no difference in the incidence of arrhythmic death was observed between inducible and noninducible patients with LVEF<30%.14 In line with these results, in our study, noninducibility was not associated with lower VT recurrence and cardiac mortality in patients with severely depressed LV function. This finding might be explained by 2 factors. First, not all VTs have a fixed reentrant mechanism and, in particular, in patients with advanced cardiac remodeling and heart failure, other focal arrhythmic mechanisms not so accurate reproducible by PES and not so easily approachable by our current ablation techniques may play an important role.14 Secondary, in patients with poor LV function and end-stage heart failure, a high competing risk of nonarrhythmic cardiac death is present.15 In fact, the most prevalent cause of death in this population was terminal heart failure (75% of the cases).

Ablation Early in the Therapeutic Course of Disease

The evidence that supports the benefit of an early intervention in patients with post-MI VT is based on 2 recent randomized trials.8,9 However, in the VTACH trial, only patients with LVEF>30% had a significant higher survival free from VT/ventricular fibrillation after ablation.9 According to these results, in our study, 20% of the patients with moderately

depressed LV function had VT recurrence or died from a cardiac cause during the first year of follow-up compared with 58% of patients with severely depressed LV function in spite of a similar rate of acute procedural success.

Patients with LVEF>30% that where rendered noninducible by ablation had a good prognosis because only 10% experienced VT recurrence or cardiac death 1 year after ablation. In line with a recent publication, if these patients where referred for ablation after the first documented VT episode, the outcome was excellent.16 No patient fulfilling these criteria had events during the first year of follow-up, further supporting an early ablation in this patient population. Inducibility of any VT after ablation seems to be therefore a good predictor of VT recurrence in patients with moderately depressed LV function, and noninducibility might be a sufficient end point for the ablation procedure in these patients.

Patients with LVEF>30% in whom noninducibility was not achieved had a worse prognosis mainly related to a higher VT recurrence rate. If noninducibility is not achieved, analyzing and understanding the reasons for ablation failure is mandatory to select the appropriate next step for each individual patient (eventually epicardial).17 The clinical significance of nonclinical VTs, in particular fast and nonreproducible inducible VTs, remains still unclear. Prior studies, based on the analysis of ICD recordings, suggested that the cause of recurrence in patients with noncomplete acute success were nonclinical VTs that were either not targeted or not successfully abolished during ablation.1,2 In the present study, in 82% of patients with partial success and VT recurrence on follow-up, VTCL was at least 30 ms longer than remaining VTs, suggesting that these VTs were not the cause of recurrence. VT recurrence might be related to lesion healing but may also be caused by new reentry circuits, and inducibility of nonclinical fast VTs might just indicate a more complex arrhythmic substrate. These findings support the need for additional ablation end points based on substrate mapping and the development of new ablation tools able to perform deeper and long-lasting lesions for patients with moderately depressed LV function in whom noninducibility is not achieved.

Limitations

This study is limited by its observational nature. The reported acute and long-term outcomes after ablation come from a high-volume referral center and may therefore not apply for smaller less experienced centers. The antiarrhythmic regimen after ablation was left at the discretion of the referral physician, and this might have influenced the outcome of some patients. The number of patients with severely depressed LV function that were referred for ablation after the first episode of symptomatic VT was small, limiting its power to determine whether this factor was associated with better outcome.

To discern between remaining VTs after ablation and recurrent VTs on follow-up, only the CL of the VTs was taken into account. Routine analysis of ICD-stored VT electrogram morphology was not performed.

CONCLUSION

Patients with prior MI and moderately depressed LV function that are rendered noninducible by ablation, in particular if they are referred after the first episode of symptomatic VT, have an excellent prognosis. Therefore, in this population, an early intervention aiming noninducibility seems to be appropriate. On the contrary, patients with severely depressed LV function have a poor prognosis that is independent of the acute outcome of the procedure and is mainly driven by heart failure–related death. In this subgroup of patients, a more conservative approach, prioritizing symptoms relief, patient comfort, and safety might be preferable.

CLINICAL PERSPECTIVE

What is known

- In patients with prior MI, non-inducibility is frequently used as VT ablation endpoint.
- Non-inducibility has been associated with improved outcomes.

What the study adds

- The LV function has an important impact on the predictive value of non-inducibility for VT recurrence and cardiac mortality.
- Patients with moderately depressed LV function who are rendered uninducible by ablation have an excellent prognosis. Non-inducibility seems to be an appropriate ablation endpoint in this population.
- Patients with severely depressed LV function have a poor prognosis, independent of the acute result of the procedure, mainly due to heart failure related death. In these patients, a more conservative approach might be preferable.

REFERENCES

1. Rothman SA, Hsia HH, Cossú SF, Chmielewski IL, Buxton AD, Miller JM. Radiofrequency catheter ablation of postinfarction ventricular tachycardia; long-term success and the significance of inducible nonclinical arrhythmias. Circulation. 1997;96:3499-508.
2. Della Bella P, De Ponti R, Uriarte JAS, Tondo C, Klersy C, Carbucicchio C, Storti C, Riva S, Longobardi M. Catheter ablation and antiarrhythmic drugs for haemodinamically tolerated post-infarction ventricular tachycardia. Eur Heart J. 2001;23:414-424.
3. Della Bella P, Baratto F, Tsiachris D, Trevisi N, Vergara P, Bisceglia C, Petracca F, Carbucicchio C, Benussi S, Maisano F, Alfieri O, Pappalardo F, Zangrillo A, Maccabelli G. Management of ventricular tachycardia in the setting of a dedicated unit for the treatment of complex ventricular arrhythmias: long-term outcome after ablation. Circulation. 2013;127:1359-1368.
4. Dinov B, Fiedler L, Schönbauer R, Bollmann A, Rolf S, Piorkowski C, Hindricks G, Arya A. Outcomes in catheter ablation of ventricular tachycardia in dilated non-ischemic cardiomyopathy in comparison to ischemic cardiomyopathy: results from the prospective HEart Centre of Leipzig (HELP-VT) Study. Circulation. 2014;129(7):728-736.
5. Ghanbari H, Baser K, Yokokawa M, Stevenson M, Della Bella P, Vergara P, Deneke T, Kuck K-H, Kottkamp H, Fei She, Morady F, Bogun F. Noninducibility in postinfarction ventricular tachycardia as an endpoint for ventricular tachycardia ablation and its effects on outcomes: a meta-analysis. Circ Arrhyhtm Electrophysiol. 2014;7:677-683.
6. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jaïs P, Josephson ME, Kautzner J, Kay GN, Kuck KH, Lerman BB, Marchlinski F, Reddy V, Schalij MJ, Schilling R, Soejima K, Wilber D. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhyhtm. 2009;6:886-933.
7. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H; Multicenter Thermocool VT Ablation Trial Investigators. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation. 2008;118:2773–2782.
8. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med. 2007;357:2657-65.
9. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacrétaz E, Pitschner HF, Kautzner J, Schumacher B, Hansen PS; VTACH Study Group. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010;375:31-40.
10. Arenal A, Glez-Torrecilla E, Ortiz M, Villacastín J, Fdez-Portales J, Sousa E, del Castillo S, Perez de Isla L, Jiménez J, Almendral J. Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. J Am Coll Cardiol. 2003;41(1):81-92.
11. Silberbauer J, Oloriz T, Maccabelli G, Tsiachris D, Baratto F, Vergara P, Mizuno H, Bisceglia C, Marzi A, Sora N, Guarricini F, Radinovic A, Cireddu M, Sala S, Gulleta S, Paglino G, Mazzone P, Trevisi

N, Della Bella P. Non-inducibility and late potential abolition: a novel combined prognostic procedural endpoint for catheter ablation of post-infarction ventricular tachycardia. Circ Arrhythm Electrophysiol. 2014;7(3):424-435.

12. Jaïs P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haïssaguerre M. Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. Circulation. 2012;125:2184-2196.
13. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ. ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhyhtmias and the prevention of sudden cardiac death. A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2006;48(5):247-346.
14. Buxton AE, Lee KL, Hafley GE, Wyse DG, Fisher JD, Lehman MH, Pires LA, Gold MR, Packer DL, Josephson ME, Prytowsky EN, Talajic MR; MUSTT Investigators. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the multicenter unsustained tachycardia trial. Circulation. 2002;106:2466-2472.
15. Johnson CM, Pogwizd SM. Focal initiation of sustained and nonsustained ventricular tachycardia in a canine model of ischemic cardiomyopathy. J Cardiovasc Electrophysiol. 2012;23:543-552.
16. Dinov B, Arash A, Bertagnolli L, Schirripa V, Schoene K, Sommer P, Bollmann A, Rolf S, Hindricks G. Early referral for ablation of scar-related ventricular tachycardia is associated with improved acute and long-term outcome: results from the Heart Center of Leipzig Ventricular Tachycardia Registry. Circ Arrhythm Electrophysiol. 2014. Epub ahead of print.
17. Schmidt B, Chun KB, Baensch D, Antz M, Koektuerk B , Tilz RR, Metzner A, Ouyang F, Kuck KH. Catheter ablation for ventricular tachycardia after failed endocardial ablation: epicardial substrate or inappropiate endocardial ablation?. Heart Rhythm. 2010;7(12):1746-1752.

4

Fast non clinical ventricular tachycardia inducible after ablation in patients with structural heart disease: Definition and clinical implications

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Heart Rhythm 2018;15:668-676

ABSTRACT

Background

Noninducibility of ventricular tachycardia (VT) with an equal or longer cycle length (CL) than the clinical VT is considered the minimum ablation endpoint in patients with structural heart disease (SHD). Since their clinical relevance remains unclear, fast nonclinical VTs are often not targeted. However, an accepted definition for fast VT is lacking. The shortest possible CL of a monomorphic reentrant VT is determined by the ventricular refractory period (VRP).

Objectives

We propose a patient-specific definition for fast VT based on the individual VRP (fVT_{VRP}) and assess the prognostic significance of persistent inducibility after ablation of fVT_{VRP} for VT recurrence.

Methods

Out of 191 patients with prior myocardial infarction or with nonischemic cardiomyopathy undergoing VT ablation, 70 (63±13 years, 64% ischemic) remained inducible for a nonclinical VT and comprised the study population. A fVT_{VRP} was defined as any VT with CL $\leq VRP_{400}$ +30ms. Patients were followed for VT recurrence.

Results

After ablation, 30 patients (43%) remained inducible exclusively for fVT_{VRP} and 40 (57%) for any slower VT. Patients with only fVT_{VRP} had a 3-year VT free-survival of 64% (CI95%:46-82%) compared to 27% (CI95%:14-48%) for patients with any slower remaining VT (P=0.013). Inducibility of only fVT_{VRP} was independently associated with lower VT recurrence (HR 0.38, CI95%:0.19-0.86; P=0.019). Within 36 patients inducible for any fVT_{VRP}, only one recurred with a fVT_{VRP}.

Conclusion

In patients with SHD, inducibility of exclusively fVT_{VRP} after ablation is associated with low VT recurrence.

INTRODUCTION

Noninducibility of the (presumed) clinical ventricular tachycardia (VT) is considered the minimum endpoint for radiofrequency catheter ablation (RFCA) in patients with structural heart disease (SHD)[1]. Since the clinical relevance of induced nonclinical fast VTs remains controversial[2-8], many laboratories only target VT with equal or longer cycle length (CL) than clinical VT but not fast remaining VTs (1). A major limitation for data comparison is the lack of an accepted definition for fast VT.

It is generally accepted that the majority of VTs in patients with SHD are caused by reentry facilitated by areas of slow conduction and fixed or functional conduction (pseudo-) block within the scar[9, 10]. Substrate-based ablation approaches target abnormal electrograms consistent with slow conduction during sinus rhythm assuming that all induced VTs depend on slow conducting regions[11-14]. However, fast nonclinical VTs may remain inducible even after complete ablation of the electroanatomical substrate[13, 14].

As the wavelength, the product of the myocardial conduction velocity and refractory period determines the shortest possible CL of a reentrant arrhythmia, Monomorphic VTs with a CL close to ventricular refractory period (VRP) may have a distinct underlying substrate, may require different induction protocols and may occur less often spontaneously.

The objectives of our study were 1) to propose a definition for fast VT based on the individual VRP (fVT_{VRP}) and 2) to assess the prognostic value of persistent inducibility of nonclinical fVT_{VRP} based on our proposed definition in patients with SHD.

METHODS

Study population

Consecutive patients referred for ablation of monomorphic VT after prior myocardial infarction (MI) or with nonischemic cardiomyopathy (NICM) to the Leiden University Medical Centre between January 2009 and December 2013 (post MI patients) and between January 2007 and December 2013 (NICM patients) and with partial success as acute procedural outcome were included. Partial success was defined as elimination of all clinical VTs but persistent inducibility of ≥1 nonclinical monomorphic VT.

All patients were treated according to our standard clinical protocol and provided informed consent. The Dutch Central Committee on Human-related Research (CCMO)

permits use of anonymous data without prior approval of an Institutional Review Board if the data are obtained for patient care and if the data do not contain identifiers that could be traced back to the individual patient.

Electrophysiological study

Before the procedure, antiarrhythmic drugs (AADs) except for amiodarone were discontinued. The programmed electrical stimulation (PES) protocol consisted of burst pacing and stimulation with 3 basic CLs (S1, 600, 500 and 400ms) and 1 to 3 extrastimuli (S2-S4) down to 200ms or refractoriness, from RV apex and RV outflow tract. A stimulus strength of twice the diastolic threshold was used for stimulation and a pause of 3 seconds between trains of ventricular pacing was applied. The first extrastimulus (S2) from the RV apex was used to determine the individual VRP for 2 drive CLs of 400 and 600ms: starting with a coupling interval (CI) of 350ms, S2 CI was decreased by 10ms until VRP was reached. Positive PES endpoint was the induction of a sustained monomorphic VT lasting >30 seconds or requiring termination because of hemodynamic instability. Induced VTs were classified as: clinical, in case of 12/12 lead electrocardiographic (ECG) match and a difference in VTCL ≤30ms with a previously documented VT, presumptive clinical, when VTCL was ±30ms of an ICD recorded VT, or nonclinical, when the previous criteria were not fulfilled.

Based on individual VRP at a drive CL of 400ms (VRP_{400}), VTs were defined as fast if VTCL was ≤VRP_{400} +30ms (fVT_{VRP}). This was based on the consideration that the possible shortest CL of a reentrant VT is determined by VRP in conjunction with the myocardial conduction velocity;[15] theoretically, no reentrant VT can have a shorter CL than the minimal VRP for a given situation. As the individual VRP may show variations (depending among others on the autonomic balance) we used VRP +30ms for the definition of fVT_{VRP}, which is in line with prior reports allowing a range of VTCL ±30ms for the definition of presumed clinical VT[5, 8, 16].

To evaluate the underlying VT mechanism, an attempt was made to entrain and terminate the VT by pacing unless VT was polymorphic.

Electroanatomical mapping and catheter ablation

Electroanatomical LV endocardial mapping was performed in all patients. Epicardial mapping was performed through a subxiphoid puncture if appropriate[5, 17]. Voltage maps were created with a 3.5mm irrigated-tip catheter (NaviStar ThermoCool; Biosense Webster, Inc., Diamond Bar, CA, USA) and the CARTO system. Electrograms were filtered at 30 to 400 Hz (bipolar) and 1 to 240 Hz (unipolar). The areas with bipolar voltage ≤0.5mV and 0.5-1.5mV were defined as dense scar and scar border zone respectively.

EGMs consistent with the presence of local slow conduction were tagged in the map (fragmented, late potentials [onset after QRS, separated by an isoelectric segment from the far-field signal >20ms). Reentry isthmus sites were identified with the combination of entrainment-, activation- and pace- mapping for stable VTs. For unstable VTs, re-entry isthmus sites were identified based on the combination of EGM characteristics and pace-mapping (morphologhy match with an induced VT ≥10/12 and stimulus-to-QRS delay >40ms). In addition, all late and prolonged, fragmented potentials were targeted, independently of their relation to an induced VT.[5, 8] RF energy was delivered at 35-50W (maximum temperature, 43°C; flow rate, 20-30ml/min) until pacing with 10mA and 2ms stimulus failed to capture.

Procedural endpoint

All clinical VTs were targeted for ablation. Nonclinical VTs were also targeted with the exception of VTs with CL close to the VRP which were considered of unknown clinical relevance. The procedure was stopped when multiple electrical cardioversions for non-clinical VTs were required or no additional substrate for VTs could be identified.

Group definition

After ablation, the entire PES protocol was repeated. Patients were divided into 2 groups according to the CL of remaining nonclinical VTs: "FVT_{VRP} group" consisting of patients in whom only fVT_{VRP} were inducible after ablation and "Non-fVT_{VRP} group" in whom at least one slower VT remained inducible.

Post-procedural management and follow-up

Implantable cardioverter defibrillator (ICD) implantation was offered to all patients. All ICDs were programmed with the slowest VT detection zone at ≥10 bpm below the slowest clinical or induced VT (VT1). The programming of detection time/number of intervals for the VT1 zone was left at the discretion of the operator, tailored normally to the hemodynamic tolerance to prior documented VTs. In the VF zone (and if programmed, in the fast VT [VT2] zone) a detection time of 2.5 seconds or 18 of 24 intervals was programmed. Patients were followed at the outpatient clinic 3 months after RFCA and every 6 months thereafter or in case of ICD therapies or symptoms suggesting VT. For the analysis, the maximum follow-up period was set at 3 years to avoid the influence of disease progression on the occurrence of new arrhythmic events.

Endpoint definition

VT recurrence was considered as any VT treated by the ICD or registered in the monitor zone lasting>30 seconds. In patients without ICD, recurrence was defined as any VT >30 seconds documented on 12-lead ECG or 24-hour Holter. VT recurrence was further cat-

egorized in (1) any VT recurrence, regardless of VTCL and (2) fVT_{VRP} recurrence according to the definition.

Statistical analysis

Continuous variables are reported as mean±SD or medians with interquartile ranges (IQR) and compared using Student t-test or Mann–Whitney *U* test. Categorical variables are presented as numbers and percentages(%) and compared using Chi-squared test or Fisher exact test. Continuous paired variables were compared with Wilcoxon signed rank test. To estimate and compare freedom from VT recurrence between groups, Gray's test was performed to take competing risk of death into account. Predictors of VT recurrence were assessed by Fine-Gray subdistribution hazard model, considering all-cause death as competing risk. Independent predictors of VT recurrence were analysed with multivariable models using a backward stepwise selection. Variables with a p value ≤0.10 were initially included. At each step the least significant variable was removed from the model, until all variables reached a p value <0.20. All tests were 2-sided and a p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients

Baseline characteristics and procedural outcome of the entire 191 patients are shown in **Supplementary Table 1**. Of these patients, 70 (45 post-MI [64%] and 25 NICM [36%], 63±13 years, 89% male, LVEF 35±12%) with partial procedural success comprised the study population. Based on the CL of remaining VTs after ablation, 30 patients (43%) with only fVT_{VRP} constituted the "fVT_{VRP} group" and 40 patients (57%) with any slower VT the "non-fVT_{VRP} group". Six patients in non-fVT_{VRP} group remained also inducible for fVT_{VRP}.

Compared to the patients in fVT_{VRP} group, those in non-fVT_{VRP} group had lower LVEF (31±11% vs. 39±11%; P=0.007), had more frequently impaired renal function (58% vs. 10%; P<0.001), slower VTs at presentation (clinical VTCL 413±84ms vs. 344 ± 73ms; P <0.001) and were more often on amiodarone at admission (70% vs. 23%; P <0.001). Baseline characteristics of the patients are displayed in **Table 1.**

Electrophysiological study and catheter ablation

Electrophysiological parameters and procedural data are shown in **Supplementary Table 2**.

Table 1. Baseline clinical characteristics

	All (n=70)	FVT_{VRP} (n=30)	Non-fVT_{VRP} (n=40)	P
Age, years	63±13	60±15	65±12	0.159
Male sex	62 (89%)	28 (93%)	34 (85%)	0.278
Underlying disease				
Prior MI	45(64%)	21(70%)	24(60%)	0.386
NICM	25(36%)	9(30%)	16(40%)	0.386
LVEF, %	35±12	39±11	31±11	0.007
Prior admission for heart failure	29(41%)	10(33%)	19(48%)	0.234
Hypertension	22(31%)	7(23%)	15(38%)	0.206
Diabetes Mellitus	5(7%)	4(13%)	1(3%)	0.082
History of atrial flutter/fibrillation	23(33%)	9(30%)	14(35%)	0.659
Renal failure	26(37%)	3(10%)	23(58%)	<0.001
ICD before ablation	54(77%)	21(70%)	33(83%)	0.218
Prior VT ablation	15(21%)	6(20%)	9(23%)	0.801
Clinical VT CL, ms	384±86	344±73	413±84	<0.001
VT clinical presentation				
Electrical storm*	11(16%)	2(7%)	9(23%)	0.072
Incessant VT	11(16%)	3(10%)	8(20%)	0.255
ICD shocks	36(51%)	15(50%)	21(53%)	0.836
Below ICD detection	10(14%)	4(13%)	6(15%)	0.844
First episode	17(24%)	10(33%)	7(18%)	0.126
Failed AADs before ablation				
Amiodarone	35(50%)	7(23%)	28(70%)	<0.001
Sotalol	25(36%)	13(40%)	12(30%)	0.249
Class 1 AAD	7 10%)	3(10%)	4(10%)	1.000

VT indicates ventricular tachycardia; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; CL, cycle length and AAD, anti-arrhythmic drug. *Electrical storm: ≥3 ICD shocks within 24 hours.

VRP at a drive CLs of 600 and 400ms were comparable between fVT_{VRP} and non-fVT_{VRP} groups (260±31ms and 226±23ms vs. 267±23ms and 234±26ms; P=0.387 and P=0.236 respectively).

Patients in non-fVT_{VRP} group were inducible for a larger number of distinct VTs (median 4 [IQR 3-6] vs. 3 [IQR 2-5]; P=0.005) which were slower (mean VTCL 370±61ms vs. 286±53ms; P <0.001) and had more often a left bundle branch block morphology (80% vs. 53%; P=0.017).

Characteristics of remaining VTs

After ablation, a total of 87 nonclinical VTs (median 1 VT per patient [IQR 1-1]) remained inducible. Remaining VTCL was 230±24ms in fVT_{VRP} and 310±41ms in non-fVT_{VRP} groups. With regard to the induction protocol for post-RFCA remaining VTs, more often triple extrastimuli (94% VTs in fVT_{VRP} vs. 72% in non-fVT_{VRP} group, P=0.01) and the shorter CIs of the extrastimuli (224±30ms in fVT_{VRP} vs. 257±28ms in non-fVT_{VRP} group; P <0.001) were required in the fVT_{VRP} group. An attempt of rapid pacing for entrainment and VT termination was performed in 80 (92%) of 87 remaining VTs, resulting in successful VT termination in 36 VTs (45%; 12 (39%) in fVT_{VRP} vs. 24 VTs (49%) in non-fVT_{VRP} group; P=0.368). Details of the induction mode and response to overdrive pacing of remaining VTs are shown in **Supplementary Table 3**.

Post-procedural management

All but one patient were discharged with an ICD. In the majority, AAD regimen remained unchanged after ablation. Thirty-four patients (49%) were discharged on amiodarone, 18 on sotalol (26%) and 6 (9%) on a class I AAD. Patients in non-fVT_{VRP} group were more often discharged on amiodarone (27 patients [68%] vs. 7 [23%] in fVT_{VRP} group; P <0.001)

Impact of remaining VT cycle length on the incidence and characteristics of recurrent VTs

During a median follow-up of 31 months (IQR 16-36), 36 patients (51%) had VT recurrence (median time to recurrence 61 days (IQR 30-407)). Only one patient was lost to follow-up.

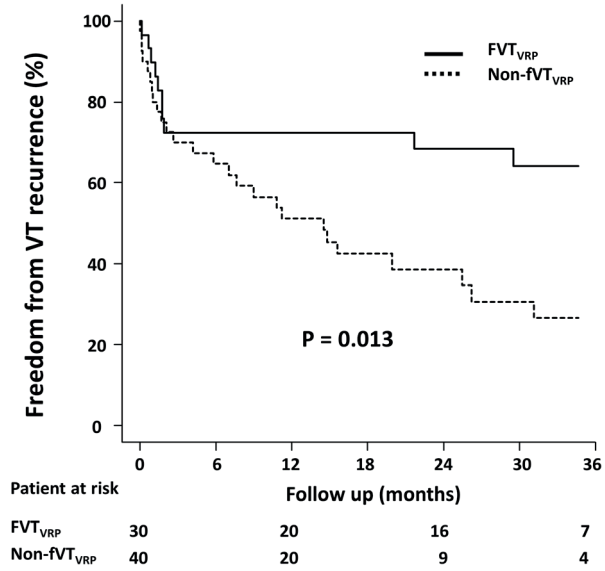
Compared to non-fVT_{VRP} group, patients in fVT_{VRP} group had a significantly lower incidence of VT recurrence (10 [33%] vs. 26 patients [65%], HR 0.40: CI95% 0.18-0.80; P=0.01). Patients in fVT_{VRP} group had a 3-year VT recurrence-free survival of 64% (CI95% 46-82%) compared to 27% (CI 95% 14-48%) for those in non- fVT_{VRP} group (P=0.013) **(Figure 1)**.

The predictive value of inducibility of only fast VT_{VRP} for absence of VT recurrence was 90% in our population. If a fixed arbitrary value for the definition of fast VT was used (VT CL ≤ 250ms), the predictive value for absence of VT recurrence decreased to 84%. This difference did not reach, however, statistical significance, probably because of the limited number of patients included in the study (P=0.257).

Since patients in the non-fVT_{VRP} group were more often on amiodarone at the time of the procedure, which may have had an effect both in the induced VTCL but also in the outcome after ablation, we performed a subanalysis including only patients off amiodarone. This analysis showed a similar trend of lower VT recurrence in the fVT_{VRP} group (3-year

VT free survival 63% [95% CI 38-79%] in fVT_{VRP} group vs 20% (95% CI 1-54%) in non-fVTgroup; P=0.12). Recurrent VTs were significantly slower than remaining VTs in both groups (remaining VTCL and VTCL of first recurrent VT were 235±28ms vs. 311±61ms in fVT_{VRP} and 303±41ms vs. 381±74ms in non-fVT_{VRP} group; both P <0.001). However, there was no significant difference between the clinical VTCL before RFCA and the recurred VTCL (349±80ms vs. 311±61ms in fVT_{VRP} and 399±84ms vs. 381±74 ms in non-fVT_{VRP} group; P=0.54 and 0.755, respectively). In **Figure 2**, the CLs of clinical, remaining and first recurrent VT for each individual patient who had VT recurrence in fVT_{VRP} **(A)** and non-fVT_{VRP} group **(B)** are depicted.

Figure 1.
VT-free survival according to groups



fVT_{VRP} indicates fast ventricular tachycadia based on the individual ventricular refractory period; VT ventricular tachycardia.

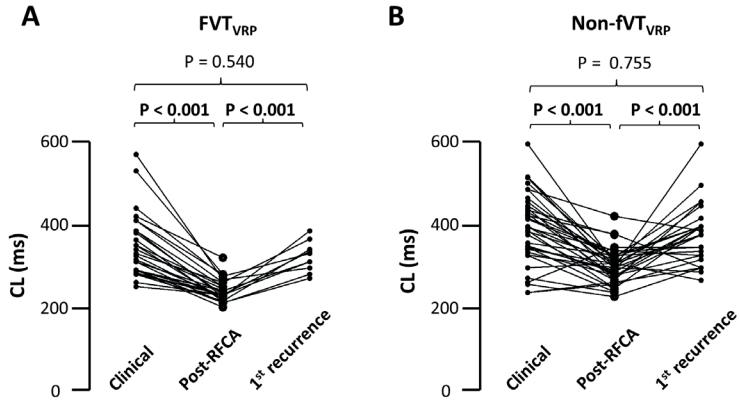
Predictors of VT recurrence

On multivariate analysis, inducibility of only fVT_{VRP} after ablation was independently associated with lower VT recurrence (HR 0.38: CI95% 0.19–0.86; P=0.019) **(Figure 3)**.

Recurrence and new occurrence of fVT_{VRP}s after ablation

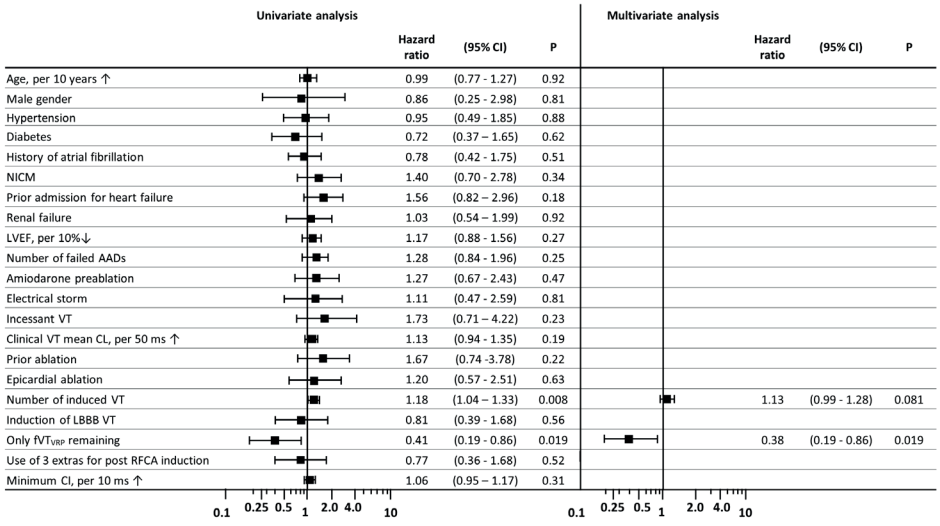
Among 36 patients in whom ≥1 fVT_{VRP} was inducible after RFCA (including 6 patients in non-fVT_{VRP} group), only one patient recurred with a fVT_{VRP} 2 months after the procedure. Three additional patients in non-fVT_{VRP} group experienced a fVT_{VRP} which was not induced during the procedure 4 days, 4 and 28 months after ablation. **Figure 4** shows the survival curve free from fVT_{VRP} for both groups. See **Supplementary Figure 1** for details.

Figure 2.



Cycle length of clinical, remaining VT (Post-RFCA) and recurrent VT at first recurrent event (1st Recurrence) in fVT$_{VRP}$ (left panel) and non-fVT$_{VRP}$ groups (right panel).
CL indicates cycle length; fVT$_{VRP}$, fast ventricular tachycadia based on the individual ventricular refractory period; RFCA, radiofrequency catheter ablation.

Figure 3.
Predictors of VT recurrence

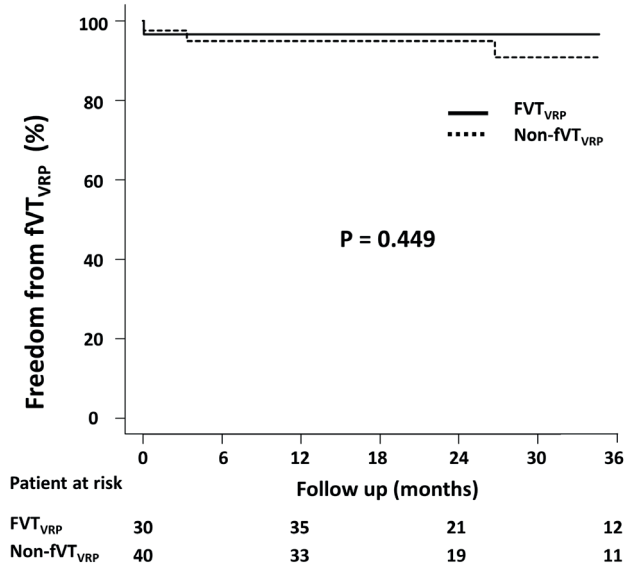


NICM indicates nonischemic cardiomyopathy; LVEF, left ventricular ejection fraction; AAD, anti-arrhythmic drug; and LBBB, left bundle branch block.

Complications

There was no procedure-related mortality. Four patients had complications of the vascular access. One patient with a basoseptal central isthmus developed predicted complete atrioventricular block after ablation. Pericardial bleeding requiring percutaneous drainage occurred in 2 of 19 patients undergoing pericardial access.

Figure 4.
FVT_{VRP} free survival according to groups



fVT_{VRP} indicates fast ventricular tachycadia based on the individual ventricular refractory period; VT ventricular tachycardia.

Mortality

Thirteen patients died during follow-up (4 [13%] in fVT_{VRP} and 9 [23%]) in non-fVT_{VRP} group; P=0.329). Cardiac death occurred in 9 patients (70%). No patient died suddenly. Heart failure was the leading cause of death in both groups (3 and 4 patients in fVT_{VRP} and non-fVT_{VRP} group, respectively). There was no difference in the incidence of cardiac death between groups (HR 1.53: 95% CI 0.40–7.24: P=0.543).

DISCUSSION

In the present study, we propose a patient-specific definition for 'fast VT' based on the individual ventricular refractory period (fVT_{VRP}) and evaluate the clinical relevance of persistent inducibility of nonclinical 'fVT_{VRP}' after ablation.

Patients with SHD who remained exclusively inducible for fVT_{VRP}, defined as a VT with CL ≤ individual VRP_{400} (+30ms) had a better VT-free survival compared to patients who remained inducible for any slower nonclinical VT. Inducibility of only fVT_{VRP} was associated with lower VT recurrence on multivariate analysis after adjusting for confounding factors. These nonclinical fVT_{VRP} were typically inducible with multiple short coupled

extrastimuli and occurred rarely spontaneously questioning the need for targeting them by ablation.

A proposal for an individualized definition of fast VT

The prognostic impact of inducibility of previously undocumented VTs after ablation, in particular of fast VTs, remains unclear[2-8]. Accordingly, many electrophysiology laboratories employ noninducibility of VTs with similar or longer CL than clinical VT as one procedural endpoint and accept persistent inducibility of faster VTs[1]. However, an important limitation for data comparison and endpoint recommendation is that a CL cutoff value to define a fast VT has not been established. Previously applied arbitrary definitions are based on ICD zones rates (typically<320ms)[18], hemodynamic tolerance, indeterminate VT-QRS morphology (former ventricular flutter) or comparison with the CL of clinically documented VTs[2].

The most common mechanism of VT in patients with SHD is reentry facilitated by slow conducting regions and fixed or functional conduction (-pseudo)block within scar tissue[9, 10]. This has been demonstrated by activation and entrainment mapping for slow tolerated VTs[19]. Substrate-based ablation approaches targeting electrograms consistent with slow conduction or poor coupling during sinus rhythm are based on the assumption that all induced VTs are dependent on regions of slow conduction[11-13]. However, fast VTs may remain inducible even after complete scar homogenization suggesting the presence of a different underlying substrate[13, 14].

In our study, we have defined fast VT for an individual patient (fVT_{VRP}) as a VT with a CL close to the VRP measured with a CL of 400ms, which derived from the rationale that the possible shortest CL of a reentrant VT is regulated by VRP in conjunction with the myocardial conduction velocity[15]. Determination of the VRP at the RV apex with a CL of 400ms cannot account for regional variations and the potential shortening of VRP at shorter CL. However, despite the complexity of rate-dependency and regional differences in VRP, our suggested cut-off may be clinically useful as an easily applicable surrogate for the shortest CL of inducible VT in an individual patient.

Clinical relevance of persistent inducibility of fVT_{VRP}. Do they need to be targeted?

Current expert consensus on VT ablation recommends elimination of clinical VT as the minimum endpoint for scar-related VT ablation[1]. However, spontaneous occurrence of non-targeted nonclinical VTs has been reported[7, 8]. In addition, persistent inducibility of any VT has been associated with an increased risk of VT recurrence favouring non-inducibility of any VT as ablation endpoint[5, 20]. Of note, highly variable acute success

results have been reported across studies (noninducibility of any VT in 38-77%) despite similar recurrence rates during follow-up (34-53%[2-4, 8, 13, 21]. This may be partly explained by the variation of PES protocols which are not standardized and not always (entirely) performed after ablation. Particularly, fast VT induction may depend on the application of the entire protocol including triple extrastimuli down to the refractory period. Of importance, in our study, triple extrastimulation and short coupled extrastimuli (mean CL: 224±30ms) were required for fVT_{VRP} induction in the majority of the patients. In addition, although a large range of remaining VTCL has been reported in patients with partial success (230-545ms)[7], data on its impact on VT recurrence are scarce.

To the best of our knowledge, our study is the first to systematically evaluate the influence of remaining VTCL on VT recurrence in patients in whom clinical VTs have been successfully abolished by ablation. Patients who remained exclusively inducible for fVT_{VRP} had a lower incidence of VT recurrence compared to those inducible for any slower VT. Patients with remaining slower VTs had lower LVEF, more often an impaired renal function, were more often on amiodarone and had a higher number of induced VTs, probably representing a more diseased population. However, inducibility of only fVT_{VRP} remained associated with lower VT recurrence after adjusting for baseline patient characteristics. Of importance, 3-year VT-free survival in patients rendered noninducible for any VT (complete success group) was comparable with those in fVT_{VRP} group (74%, CI95% 58-84% vs. 63%, CI95% 47-78%; P=0.156).

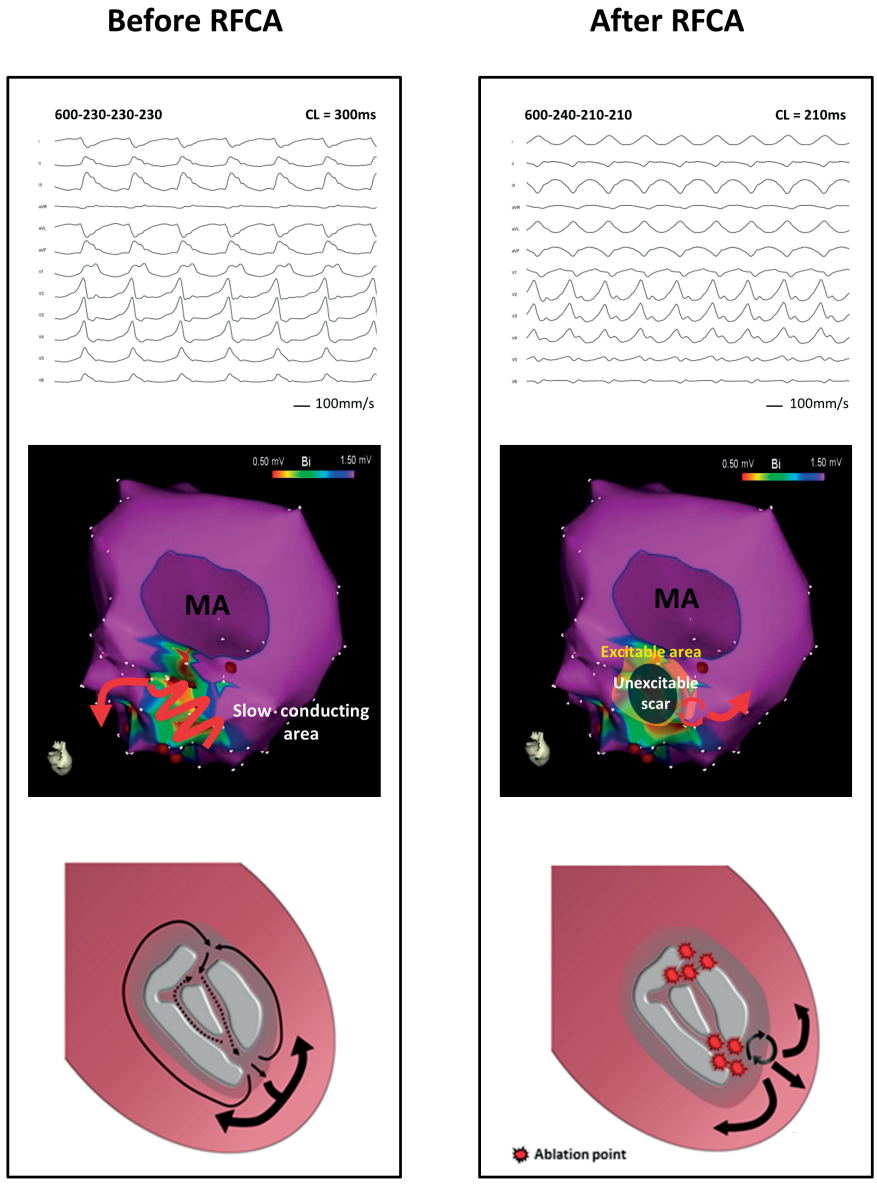
In addition, fVT_{VRP} occurred rarely spontaneously. No clinical VT before ablation fulfilled the criteria for fVT_{VRP} and only 4 out of 70 patients (6%) had a spontaneous fVT_{VRP} after the procedure. Of note, only 5 of the 70 patients (7%) were on an AAD at VT recurrence that was not present during VT induction and may therefore have prolonged the CL of the recurrent VT.

Our findings suggest that induction of fVT_{VRP} after ablation may not be prognostically relevant, questioning the need for targeting them by ablation. Prospective studies to confirm our hypothesis are warranted.

Potential underlying mechanisms and substrate for fVT_{VRP}

FVT_{VRP} have a CL close to the individual VRP, induction requires the application of multiple short coupled extrastimuli and they are typically inducible after slow conducting areas within the scar have been ablated. These fVT_{VRP} may have a different underlying substrate than macroreentrant VTs with an area of slow conduction identifiable during VT or stable sinus rhythm (**Figure 5**).

Figure 5.



Representative case of a patient with a prior inferoposterior MI. VT 12-lead ECGs (top), LV endocardial bipolar voltage maps (middle) in posteroanterior view color-coded according to the bar and schematic representations of the presumed VT mechanisms (bottom) before (left panel) and after RFCA (right panel) are shown. Before ablation, the clinical VT (CL=300ms, left top) was induced with triple extrastimulation. Ablation on the exit site of the slow conducting area terminated the VT (left middle, bottom). After rendering the scar core unexcitable (dark grey area, right middle) by RF, a nonclinical fVT_{VRP} (CL=210ms, VRP_{400}=200, right top) was induced with triple extrastimulation but shorter coupling intervals. According to its morphology, the fVT_{VRP} exit site was assumed at the septal edge of the scar (right middle). The myocardium in the scar border zone (grey shaded area) remained excitable and may have been involved in the maintenance of a small reentrant circuit giving rise to the fast fVT_{VRP} (right bottom). MA indicates mitral annulus; PA, posteroanterior

Functional reentry is a mechanism of reentrant excitation with an unexcitable gap in its center, and could represent itself as a scroll wave in the affected ventricles. Although this concept is often used to explain the mechanism of meandering reentrant circuits giving rise to fibrillatory activity, the presence of more stationary, yet functional, reentrant circuits have been demonstrated in a prior experimental study[22] and in human ventricle[23] and atria, where its source was localized near fibrotic areas. In addition, a scroll wave as source of monomorphic VT has been case reported[24]. Even after eliminating slow conducting regions, the border to normal myocardium may still serve as a source for scroll wave stabilization, thereby creating the conditions favoring monomorphic VT in which the CL would indeed be determined by VRP. More experimental approaches, including animal experiments, might be needed to elucidate the potential substrate and mechanism for fVT_{VRP}.

Limitations

The main limitation of this study is its retrospective observational nature. The VRP for definition of fVT_{VRP} was always determined from the RV apex at a basic drive CL of 400ms. We can therefore not exclude that regional variations in the VRP (RV vs LV ERP, VRP in infarcted vs non-infarcted myocardium) as well as variations in the VRP related to the VTCL (namely during fast VTs, the VRP is expected to be shorter) could have impacted our results. Inducibility of fVT_{VRP} in the non-fVT_{VRP} group might be underestimated because reinduction was stopped when any sustained VT was induced with less aggressive induction protocols. Reproducibility of fVT_{VRP} induction after ablation was generally not performed. The anti-arrhythmic regimen after ablation was left at the discretion of the referring cardiologist and it might have influenced the incidence of VT recurrence in some patients.

CONCLUSION

In patients with SHD, inducibility after ablation of only fVT_{VRP} is associated with low VT recurrence during follow-up. In addition, fVT_{VRP} occur rarely spontaneously. These findings suggest that eliminating these VTs might not be required, questioning noninducibility of any VT as a prognostically relevant ablation endpoint.

REFERENCES

1. Aliot EM, Stevenson WG, Almendral-Garrote JM, et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart rhythm : the official journal of the Heart Rhythm Society Jun 2009;6:886-933.
2. Stevenson WG, Wilber DJ, Natale A, et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation Dec 16 2008;118:2773-2782.
3. Della Bella P, Baratto F, Tsiachris D, et al. Management of ventricular tachycardia in the setting of a dedicated unit for the treatment of complex ventricular arrhythmias: long-term outcome after ablation. Circulation Apr 02 2013;127:1359-1368.
4. Yokokawa M, Kim HM, Baser K, et al. Predictive value of programmed ventricular stimulation after catheter ablation of post-infarction ventricular tachycardia. Journal of the American College of Cardiology May 12 2015;65:1954-1959.
5. Piers SR, Leong DP, van Huls van Taxis CF, Tayyebi M, Trines SA, Pijnappels DA, Delgado V, Schalij MJ, Zeppenfeld K. Outcome of ventricular tachycardia ablation in patients with nonischemic cardiomyopathy: the impact of noninducibility. Circulation Arrhythmia and electrophysiology Jun 2013;6:513-521.
6. Dinov B, Fiedler L, Schonbauer R, Bollmann A, Rolf S, Piorkowski C, Hindricks G, Arya A. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy: results from the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation Feb 18 2014;129:728-736.
7. Rothman SA, Hsia HH, Cossu SF, Chmielewski IL, Buxton AE, Miller JM. Radiofrequency catheter ablation of postinfarction ventricular tachycardia: long-term success and the significance of inducible nonclinical arrhythmias. Circulation Nov 18 1997;96:3499-3508.
8. de Riva M, Piers SR, Kapel GF, Watanabe M, Venlet J, Trines SA, Schalij MJ, Zeppenfeld K. Reassessing noninducibility as ablation endpoint of post-infarction ventricular tachycardia: the impact of left ventricular function. Circulation Arrhythmia and electrophysiology Aug 2015;8:853-862.
9. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N, Lahpor JR. Slow conduction in the infarcted human heart. 'Zigzag' course of activation. Circulation Sep 1993;88:915-926.
10. Anter E, Tschabrunn CM, Buxton AE, Josephson ME. High-Resolution Mapping of Postinfarction Reentrant Ventricular Tachycardia: Electrophysiological Characterization of the Circuit. Circulation Jul 26 2016;134:314-327.
11. Arenal A, Glez-Torrecilla E, Ortiz M, Villacastin J, Fdez-Portales J, Sousa E, del Castillo S, Perez de Isla L, Jimenez J, Almendral J. Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. Journal of the American College of Cardiology Jan 01 2003;41:81-92.
12. Bogun F, Good E, Reich S, Elmouchi D, Igic P, Lemola K, Tschopp D, Jongnarangsin K, Oral H, Chugh A, Pelosi F, Morady F. Isolated potentials during sinus rhythm and pace-mapping within scars as guides for ablation of post-infarction ventricular tachycardia. Journal of the American College of Cardiology May 16 2006;47:2013-2019.

13. Jais P, Maury P, Khairy P, et al. Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. Circulation May 8 2012;125:2184-2196.
14. Vergara P, Trevisi N, Ricco A, Petracca F, Baratto F, Cireddu M, Bisceglia C, Maccabelli G, Della Bella P. Late potentials abolition as an additional technique for reduction of arrhythmia recurrence in scar related ventricular tachycardia ablation. Journal of cardiovascular electrophysiology Jun 2012;23:621-627.
15. Rensma PL, Allessie MA, Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circulation research Feb 1988;62:395-410.
16. Frankel DS, Mountantonakis SE, Zado ES, et al. Noninvasive programmed ventricular stimulation early after ventricular tachycardia ablation to predict risk of late recurrence. Journal of the American College of Cardiology Apr 24 2012;59:1529-1535.
17. Sosa E, Scanavacca M, d'Avila A, Oliveira F, Ramires JA. Nonsurgical transthoracic epicardial catheter ablation to treat recurrent ventricular tachycardia occurring late after myocardial infarction. Journal of the American College of Cardiology May 2000;35:1442-1449.
18. Kumar S, Sivagangabalan G, Choi MC, Eipper V, Thiagalingam A, Kovoor P. Long-term outcomes of inducible very fast ventricular tachycardia (cycle length 200-250 ms) in patients with ischemic cardiomyopathy. Journal of cardiovascular electrophysiology Mar 2010;21:262-269.
19. Stevenson WG, Friedman PL, Sager PT, Saxon LA, Kocovic D, Harada T, Wiener I, Khan H. Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping. Journal of the American College of Cardiology May 1997;29:1180-1189.
20. Ghanbari H, Baser K, Yokokawa M, Stevenson W, Della Bella P, Vergara P, Deneke T, Kuck KH, Kottkamp H, Fei S, Morady F, Bogun F. Noninducibility in postinfarction ventricular tachycardia as an end point for ventricular tachycardia ablation and its effects on outcomes: a meta-analysis. Circulation Arrhythmia and electrophysiology Aug 2014;7:677-683.
21. Dinov B, Arya A, Schratter A, Schirripa V, Fiedler L, Sommer P, Bollmann A, Rolf S, Piorkowski C, Hindricks G. Catheter ablation of ventricular tachycardia and mortality in patients with nonischemic dilated cardiomyopathy: can noninducibility after ablation be a predictor for reduced mortality? Circulation Arrhythmia and electrophysiology Jun 2015;8:598-605.
22. Davidenko JM, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. Nature Jan 23 1992;355:349-351.
23. Nair K, Umapathy K, Farid T, Masse S, Mueller E, Sivanandan RV, Poku K, Rao V, Nair V, Butany J, Ideker RE, Nanthakumar K. Intramural activation during early human ventricular fibrillation. Circulation Arrhythmia and electrophysiology Oct 2011;4:692-703.
24. Hayase J, Tung R, Narayan SM, Krummen DE. A case of a human ventricular fibrillation rotor localized to ablation sites for scar-mediated monomorphic ventricular tachycardia. Heart rhythm : the official journal of the Heart Rhythm Society Dec 2013;10:1913-1916.
25. Kienzle MG, Doherty JU, Cassidy D, Buxton AE, Marchlinski FE, Waxman HL, Josephson ME. Electrophysiologic sequale of chronic myocardial infarction local refractoriness and electrocardiographic characteristics of the left ventricle. Am J Cardiol Jul 1986;58:63-69.

Supplementary table 1. Baseline characteristics and procedural outcome of the entire population

	All
	(n=191)
Age, years	64±13
Male sex	161 (84%)
LVEF, %	37 ± 13
Prior admission for heart failure	72 (38%)
Hypertension	81 (42%)
Diabetes Mellitus	28 (15%)
History of atrial flutter/fibrillation	60 (31%)
Renal failure	61 (32%)
ICD before ablation	124 (65%)
Prior VT ablation	34 (18%)
Clinical VT CL, ms	371 ± 81
VT clinical presentation	
Electrical storm*	23 (12%)
Incessant VT	27 (14%)
Failed AADs before ablation	
Amiodarone	78 (41%)
Sotalol	53 (28%)
Class 1 AAD	14 (7%)
Epicardial ablation	56 (49%)
Fluoro time, min	38 ± 20
Procedure time, min	213 ± 85
Acute procedural outcome	
Complete success	77 (40%)
Partial success	70 (37%)
Failure	31 (16%)
Undetermined	13 (7%)

MI indicates myocardial infarction; NICM, non-ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; CL, cycle length and AAD, anti-arrhythmic drug *Acute procedural outcome was undetermined because of incomplete PES after RFCA

Supplementary table 2. Electrophysiological and procedural characteristics

	All (n=70)	FVT_{VRP} (n=30)	Non-fVT_{VRP} (n=40)	P
Amiodarone during the procedure	34 (49%)	7 (23%)	27 (68%)	<0.001
VRP drive CL 600ms	264 ± 27	260 ± 31	267 ± 23	0.387
VRP drive CL 400ms	230 ± 25	226 ± 23	234 ± 26	**0.236**
Number of induced VTs	4 (3-5)	3 (2-5)	4 (3-6)	0.005
Induced VT max CL, ms	423 ± 126	356 ± 97	469 ± 124	<0.001
Induced VT min CL, ms	262 ± 43	237 ± 40	281 ± 36	<0.001
Induced VT mean CL, ms	335 ± 71	286 ± 53	370 ± 61	<0.001
Induction of clinical/presumptive clinical VT	65 (94%)	26 (87%)	39 (98%)	0.082
Epicardial ablation	20 (29%)	4(13%)	4(13%)	0.242
Procedure time	204 ± 69	196 ± 60	209 ± 76	0.476
Fluoroscopy time	37 ± 17	34 ± 12	40 ± 20	0.165
Number of remaining VTs	1 (1-1)	1 (1-1)	1 (1-2)	0.100
Remaining VT max CL, ms	271 ± 49	232 ± 25	319 ± 39	<0.001
Remaining VT min CL, ms	282 ± 55	230 ± 26	302 ± 40	<0.001
fVT_{VRP} remaining	36 (51%)	30 (100%)	6 (15%)	<0.001

VT indicates ventricular tachycardia; VRP, ventricular refractory period; max, maximum; CL, cycle length and min, minimum.

Supplementary table 3. Mode of induction and termination of remaining VTs

	All (n=70)	FVT_{VRP} (n=30)	Non-fVT_{VRP} (n=40)	P
Number of remaining VTs	87	34	53	
Mode of induction				
Spontaneous or catheter manipulation	5 (6%)	1 (3%)	4 (8%)	0.368
Single or double extrastimuli	12 (14%)	1 (3%)	11 (21%)	0.010
Triple extrastimuli	70 (80%)	32 (94%)	38 (72%)	0.010
Min coupling interval for induction	244 ± 33	224 ± 30	257 ± 28	<0.001
Mode of termination				
Spontaneous termination	2 (2%)	1 (3%)	1 (2%)	0.690
Immediate ECV due to unstable HD	5 (6%)	2 (6%)	3 (6%)	0.949
Rapid pacing attempt	80 (92%)	31 (91%)	49 (92%)	0.831
Success	36 (45%)	12 (39%)	24 (49%)	0.368
Failure	44 (55%)	19 (61%)	25 (51%)	0.368

VT indicates ventricular tachycardia; ECV, electrical cardioversion and HD, hemodynamic

5

Targeting the hidden substrate unmasked by right ventricular extrastimulation improves ventricular tachycardia ablation outcome after myocardial infarction.

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JACC: Clinical Electrophysiology 2018;4:316-327

ABSTRACT

Background

In patients with small or non-transmural scars after myocardial infarction (MI), part of the ventricular tachycardia (VT) substrate might be functional and, in addition, masked by high voltage far-field signals arising from adjacent normal myocardium.

Objectives

To determine whether ablation of hidden substrate unmasked by right ventricular extra-stimulation (RVE) improves ablation outcome

Methods and Results

In sixty consecutive patients, systematic analysis of electrograms recorded from the presumed infarct area was performed during sinus rhythm, RV pacing at 500ms and during a short coupled RV extrastimulus. Sites showing low voltage, near-field potentials *wit*h evoked conduction delay in response to RVE were targeted. In 37 patients (62%), ablation target sites located in areas with normal voltage during sinus rhythm were unmasked by RVE (hidden substrate group). These patients had better LV function (36±11% vs. 26±12%; P=0.003), smaller electroanatomical scars (<1.5mV) and smaller dense scars (<0.5mV) (median 59 and 14 vs. 82 and 44 cm^2; P=0.044 and P=0.003) than those in whom no hidden substrate was identified (overt substrate group). During a median follow-up of 16 months, 13 patients (22%) had VT recurrence. Patients with hidden substrate had a lower incidence of VT recurrence (12 month VT-free survival 89% vs 50% in patients with overt substrate; P=0.005). Compared to a historical cohort of 90 post-MI patients matched for LV function and electroanatomical scar area, in whom no RVE was performed, patients in the hidden substrate group had a higher 1-year VT free survival (89% vs 73%; P= 0.039).

Conclusion

Hidden substrate ablation unmasked by RVE improves ablation outcome in post-MI patients with small or non-transmural scars.

INTRODUCTION

Substrate-based ablation for post-myocardial infarction (MI) ventricular tachycardia (VT) relies on: 1) delineation of low bipolar voltage (BV) areas (<1.5mV) by electroanatomical (EA) mapping and 2) identification of electrograms (EGMs) consistent with slow conduction or conduction block within low-voltage areas during sinus rhythm (SR).(1,2) Mapping accuracy to detect scar might, however, be limited by the current use of ablation catheters with large electrodes and wide inter-electrode spacing leading to far field contamination of local EGMs.(3) This phenomenon might be particularly relevant in patients with smaller and subendocardial scars, in whom parts of the arrhythmogenic substrate may be obscured by high-voltage far-field signals arising from adjacent normal myocardium. Of note, this scar pattern is often encountered in contemporary patients undergoing early reperfusion therapy, associated with fast and poorly tolerated VT.(4,5) The inability of BV mapping during SR to delineate non-transmural scars has been demonstrated by head-to-head comparison of voltage maps with contrast-enhanced magnetic resonance imaging (CE-MRI).(5) Changing the activation wavefront by continuous ventricular pacing may identify low-voltage areas that are not evident during SR.(6) However, using EGM amplitude as only guide may lead to unnecessary ablation with potential damage of viable myocardium contributing to cardiac function. Critical sites for VT should exhibit additional electrophysiological characteristics, most importantly functional conduction delay or conduction block.

We hypothesized that: 1) systematic evaluation of EGMs located in the infarct area during right ventricular extrastimulation (RVE) can identify scar areas with functional conduction delay or block as substrate for VT that are not evident during SR and 2) ablation targeting this hidden, functional substrate may improve ablation outcome in post-MI patients.

METHODS

Between October 2013 and February 2016, consecutive post-MI patients referred for VT ablation to the Leiden University Medical Center were prospectively included. All patients were treated according to the institutional clinical protocol and provided pre-procedural informed consent.

Preprocedural evaluation

Patients underwent a comprehensive clinical evaluation including review of all medical records. Data on past ischemic events, acute reperfusion therapy, prior revascularizа-

tion, spontaneous ventricular arrhythmias, implantable cardioverter-defibrillator (ICD) interrogation reports and failed anti-arrhythmic drugs (AAD) were collected. All patients underwent coronary angiography or non-invasive stress testing to detect ischemia. Coronary angiograms were reviewed to determine the area supplied by the infarct-related artery. Wall motion abnormalities and left ventricular (LV) function were derived from echocardiograms. If possible, CE-MRI was performed for scar delineation (Supplementary Methods 1).(7) Patients scheduled for epicardial ablation underwent ECG-gated cardiac computed tomographic imaging for procedural integration.(8) Before ablation, all AAD with the exception of amiodarone were discontinued.

Ablation procedure

Prior to ablation, programmed electrical stimulation (PES) was performed (4 drive cycle lengths [S1, CL: 600, 500, 400 and 350ms], 1-4 ventricular extrastimuli [S2, ≥200ms] from 2 RV sites and ≥1 LV site). Positive endpoint of stimulation was induction of sustained VT lasting > 30s or requiring termination because of hemodynamic compromise. Fast VT was defined as a VT with CL ≤ventricular refractory period (VRP) + 30ms. (9)

Electroanatomical mapping

All patients underwent LV endocardial mapping. Additional RV and/or epicardial mapping was performed if appropriate. BV maps were created with a 3.5mm irrigated-tip catheter (NaviStar ThermoCool; Biosense Webster, Inc, Diamond Bar, CA) and the CARTO 3 system. Standard cut-off values of 1.5mV for scar, 0.5mV for dense scar and 0.5-1.5mV for border-zone were applied. A patchy scar pattern was defined as two low-voltage areas separated by areas of preserved voltage. (4) CE-MRI derived scars were integrated with EA maps as previously described. (7)

Electrogram analysis

Bipolar EGMs were filtered at 30-500Hz and displayed at a gain of 0.072 mV/cm and a sweep speed of 200mm/s on the Prucka EP system. With the mapping catheter in a stable position, EGMs were systematically analysed during SR, RV pacing at a fixed rate of 500ms and during the application of a single RV extrastimulus (RVe) with a coupling interval of 50ms above the VRP. Care was taken to cover the presumed infarct area as derived from imaging data (echocardiogram and CE-MRI) and review of coronary angiogram, regardless of local EGM amplitude or morphology during SR.

During SR, the peak-to-peak EGM amplitude was automatically determined by the CARTO 3 system. If during RV pacing, the local EGM showed two distinct components, a low-frequency potential consistent with far-field EGM and a single or multicomponent high-frequency potential consistent with near-field EGM, the amplitude of the near-field

was manually measured on the EP system using electronic callipers. Subsequently, EGM duration, measured as the interval between the earliest and the last sharp deflections,(2) during the pacing train and the RVE was compared. Sites exhibiting low-amplitude (<1.5mV) near-field potentials with conduction delay >10ms or block in response to RVE were categorized as Evoked Delayed Potentials (EDP) and annotated on the map (**Figure 1**).

Ablation

Substrate modification aiming EDP elimination was performed. Late potentials (LP, onset after QRS, separated by an isoelectric segment from the far-field signal >20ms) during SR or RV pacing without additional conduction delay during RVE were not targeted. Radiofrequency (RF) energy was delivered (45-50W, temperature limit 43°C, flow rate 20-30 ml/min) until stimulation with high output pacing (10 mA, 2ms) failed to capture. After the last RF application, a re-map including RVE was performed and the entire induction protocol was repeated. Fast VTs with a CL close to VRP were considered clinically not relevant and not targeted. If any other sustained monomorphic VT remained inducible, additional mapping and ablation was performed until no further substrate could be identified.

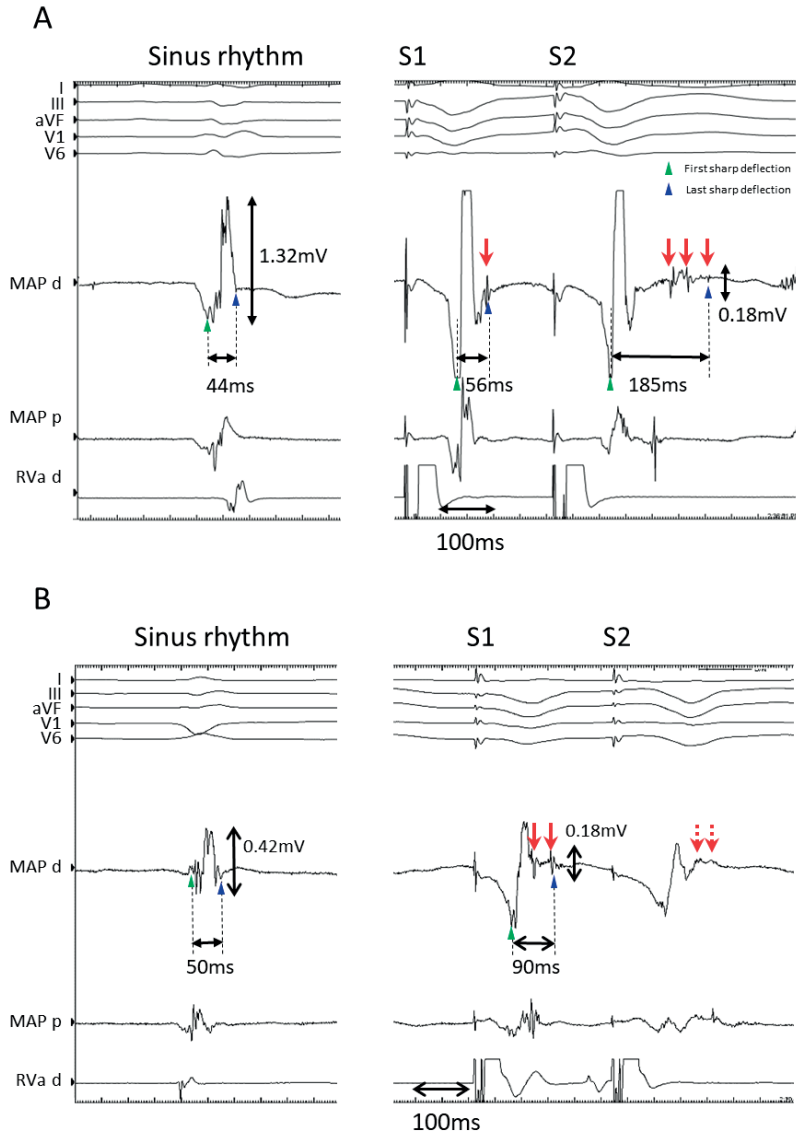
Post-procedural management and follow-up

Patients underwent routine echocardiogram to exclude pericardial effusion and assess post-ablation LV function. ICD implantation was offered to those without a device before ablation. Pre-procedural AADs were continued until the first follow-up visit. Patients were followed at 3 months post-ablation and every 6 months thereafter. VT recurrence was defined as occurrence of any VT requiring ICD therapy, recorded within the ICD monitor zone lasting >30s or documented on 12-lead ECG.

Long-term outcome comparison with historical group

For long-term outcome comparison, a historical cohort of consecutive ischemic patients who underwent VT ablation in the same institution between 2009 and 2012 was used. In this period, RVE for substrate identification was not performed and ablation target sites were selected based on a combination of activation and entrainment mapping, pace-mapping and substrate mapping (identification of fragmented EGMs and LPs during SR). All procedures in the historical and present study group were performed by the same operator, using irrigated-tip ablation catheters and the CARTO system.

Figure 1.
EGM response to RV extra-stimulation



(A) *Evoked delayed potential* (EDP). EGM with borderline amplitude during SR (left). During RV pacing (S1), a low-amplitude high-frequency potential (red arrow) separates from the far-field high-voltage signal (centre). This second component further delays and splits into multiple components during an extrastimulus (S2) (right). (B) EDP. Low-voltage, fragmented EGM during SR (left). Two high-frequency delayed potentials (red arrows) are observed during S1 (centre) which disappeared during S2 (right, dashed red lines). (C) Negative response to RVE. Low-voltage abnormal signal during SR (left). During S1, a high-frequency potential (red arrow) occurred after the far-field signal (centre), which showed no additional conduction delay after S2 (right). (D) EDP. Normal EGM (amplitude and morphology) during SR (left). Low-voltage near-field potential separated from the far-field signal (S1), delaying and splitting in multiple components (S2) (right). (E) Negative response to RVE. Fragmented low-voltage EGM during SR (left). Local conduction delay during S1 (centre) but without further prolongation after S2. All EGM durations measured from first to last sharp deflection irrespective of number of components.

Figure 1.
EGM response to RV extra-stimulation

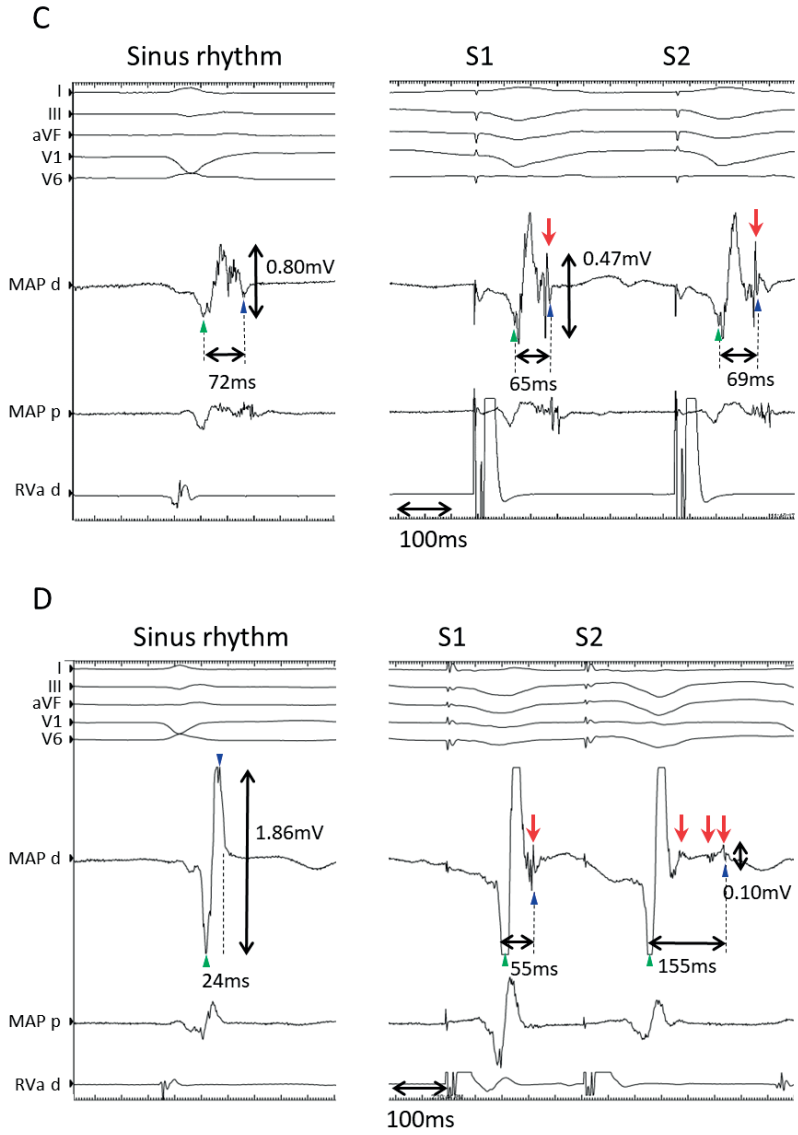


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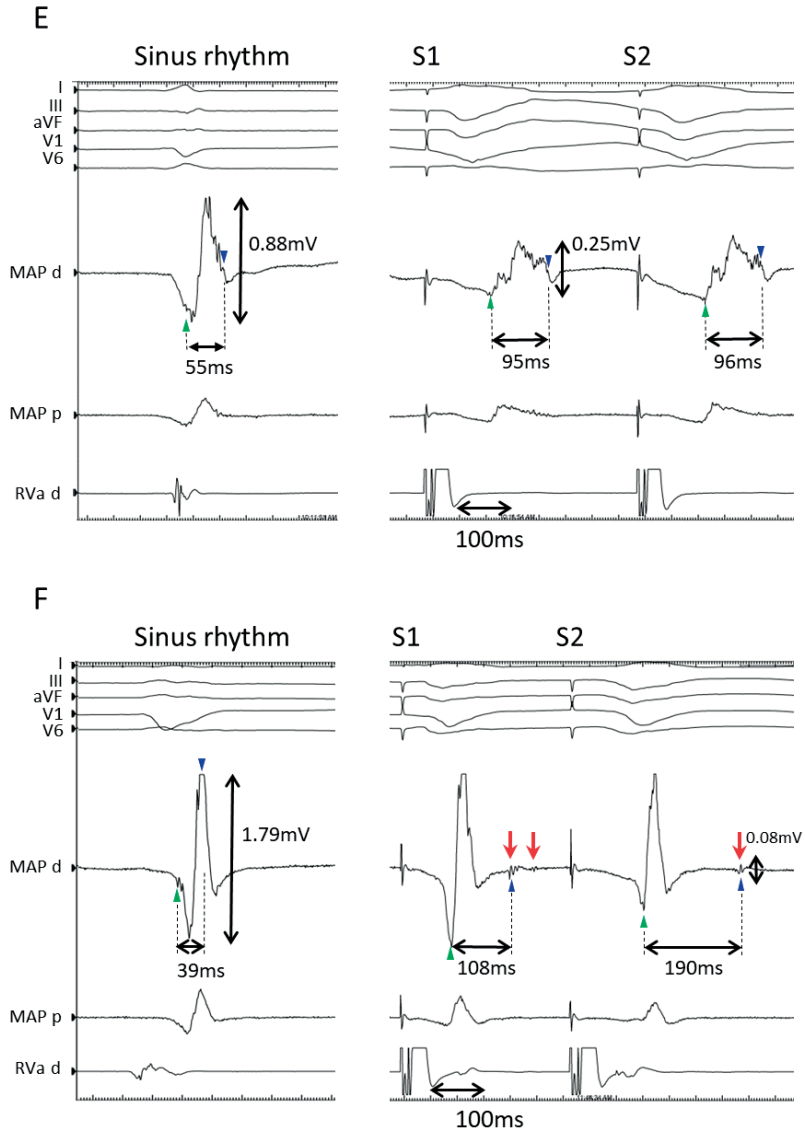
Figure 1.
EGM response to RV extra-stimulation



(A) *Evoked delayed potential* (EDP). EGM with borderline amplitude during SR (left). During RV pacing (S1), a low-amplitude high-frequency potential (red arrow) separates from the far-field high-voltage signal (centre). This second component further delays and splits into multiple components during an extrastimulus (S2) (right). (B) EDP. Low-voltage, fragmented EGM during SR (left). Two high-frequency delayed potentials (red arrows) are observed during S1 (centre) which disappeared during S2 (right, dashed red lines). (C) Negative response to RVE. Low-voltage abnormal signal during SR (left). During S1, a high-frequency potential (red arrow) occurred after the far-field signal (centre), which showed no additional conduction delay after S2 (right). (D) EDP. Normal EGM (amplitude and morphology) during SR (left). Low-voltage near-field potential separated from the far-field signal (S1), delaying and splitting in multiple components (S2) (right). (E) Negative response to RVE. Fragmented low-voltage EGM during SR (left). Local conduction delay during S1 (centre) but without further prolongation after S2. All EGM durations measured from first to last sharp deflection irrespective of number of components.

Statistical analysis

Continuous variables are reported as mean±SD or medians with interquartile range (IQR) and compared with the Student's t or the Mann-Whitney U test when appropriate. Categorical variables are expressed as numbers and percentages (%) and compared with the Chi-squared or the Fisher exact test. Freedom from VT recurrence was estimated by Kaplan-Meier method and compared with log-rank test between groups. Cox proportional regression analysis was performed to detect any significant predictor of VT recurrence (reported as the hazard ratio [HR] with a 95% confidence interval [CI]). All tests were 2-sided and a P value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients

During the study period, 62 post-MI patients underwent VT ablation. Two patients with poor hemodynamics in whom the complete pacing protocol could not be performed were excluded. The remaining 60 patients (49 men, 67 ± 8 years, LV ejection fraction (EF) 33 ± 12%) comprised the study population. Baseline characteristics are displayed in **Table 1**. In **Supplementary Table 1**, baseline characteristics of the historical cohort are shown.

PES, electroanatomical mapping and electrogram analysis

Fifty-five patients (92%) were inducible for a median of 3 VTs (IQR 1-4). LV endocardial mapping was performed in all and epicardial and endocardial RV mapping in 6 (12%) and 13 (22%) patients, respectively. Procedural characteristics of the study patients and historical group are shown in **Table 2 and Supplementary Table 2,** respectively.

A total of 2858 bipolar EGMs (median 45 per patient, IQR 27-62) in the presumed infarct area were analysed during SR, RV pacing and RVE. Of these, 1367 (48%) were located in the EA dense scar and 867 (30%) in the border-zone. The remaining 624 EGMs (22%) were located in normal BV areas. During RVE, 930 EGMs (33%) were classified as EDPs (810 (87%) showed EGM prolongation >10ms (median 31ms, IQR 20-46) and 120 (13%) block). Of importance, 184 of 930 EDPs (20%) were located in sites with normal voltage during SR. Details of EGM analyses are displayed in **Table 3**.

Seven patients (12%) underwent integration of CE-MRI derived scars with EA maps. In these patients, a total of 391 EGMs were analysed with RVE and 91 (23%) were categorized as EDPs. Of importance, 34/91 EDPs (37%) were located in areas with normal

BV. However, according to the CE-MRI, 31/34 (91%) were located within the scar and of interest, 22 of 31 (71%) in an area of non-transmural scar.

Table 1. Baseline characteristics of the patients according to left ventricular ejection fraction

	All (n=60)	Hidden Substrate (n=37)	Overt Substrate (n=23)	*P-value*
Age, years	68 ± 8	69 ± 8	66 ± 7	0.237
Male	49 (82%)	31 (84%)	18 (78%)	0.734
Hypertension	19 (32%)	12 (32%)	7 (30%)	1.000
Diabetes Mellitus	10 (17%)	7 (19%)	3 (13%)	0.727
Prior stroke/TIA	5 (8%)	3 (8%)	2 (9%)	1.000
Atrial fibrillation	15 (25%)	11 (30%)	4 (17%)	0.366
Heart failure	24 (40%)	10 (27%)	14 (61%)	0.014
Renal failure	18 (30%)	9 (24%)	9 (39%)	0.177
Inferior MI	36 (60%)	25 (68%)	11 (48%)	0.419
Time since MI, year	19 ± 8	21 ± 9	17 ± 7	0.096
MI acute reperfusion	12 (20%)	7 (19%)	5 (22%)	1.000
Prior CABG	18 (30%)	15 (41%)	3 (13%)	0.041
Prior PCI	24 (40%)	13 (35%)	11 (48%)	0.419
LV ejection fraction, %	33 ± 12	36 ± 11	26 ± 12	0.003
ICD before ablation	50 (83%)	28 (76%)	22 (96%)	0.073
Prior VT ablation	14 (23%)	9 (24%)	5 (22%)	1.000
Clinical VT CL, ms	417 ± 102	404 ± 96	437 ± 109	0.224
Medication at admission				
Statins	53 (88%)	31 (84%)	22 (96%)	0.233
Antialdosteronic	17 (28%)	5 (14%)	12 (52%)	0.003
ACE-I/ARB	46 (77%)	26 (70%)	20 (87%)	0.211
Betablockers	48 (80%)	30 (81%)	18 (78%)	1.000
Amiodarone	22 (37%)	13 (35%)	9 (39%)	0.788
VT clinical presentation				
Electrical storm	7 (12%)	4 (11%)	3 (13%)	1.000
Incessant VT	5 (8%)	2 (5%)	3 (13%)	0.362
ICD therapies	15 (25%)	10 (27%)	5 (22%)	0.764
Below ICD detection	24 (40%)	13 (35%)	11 (48%)	0.419
First episode without ICD	9 (15%)	8 (22%)	1 (4%)	0.134

Values are reported as mean ± standard deviation or n (%). TIA indicates transitory ischemic attack; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI: percutaneous coronary intervention; LV, left ventricle; ICD, implantable cardiac defibrillator; VT, ventricular tachycardia; CL, cycle length; ACE-I, angiotensin-converting-enzyme inhibitor and ARB, angiotensin receptor blocker.

Table 2. Procedural characteristics

	All (n=60)	Hidden substrate (n=37)	Overt substrate (n=23)	*P-value*
Inducible before RFCA	55 (92%)	36 (97%)	19 (83%)	0.066
Number of induced VTs	3 (1–4)	2 (1–4)	3 (1–4)	0.963
Induced VT max CL, ms	420 ± 103	411 ± 112	438 ± 85	0.354
Induced VT min CL, ms	304 ± 78	293 ± 58	325 ± 105	0.230
LV bipolar scar area, cm^2	64 (41–87)	59 (34–79)	82 (47–106)	0.044
LV dense scar area, cm^2	25 (6–44)	14 (5–32)	44 (24–62)	0.003
LV border zone area, cm^2	34 (23–47)	33 (21–51)	37 (25–47)	0.662
Dense scar area/total LV area, %	10 (3-17)	7 (3-7)	15 (9-15)	0.003
Epicardial mapping	6 (10%)	2 (5%)	4 (17%)	0.027
Procedural duration, min	173 (150–205)	175 (151–205)	167 (150–230)	0.982
Fluoroscopic time, min	39 (33–47)	38 (35–47)	39 (28–48)	0.814
Radiofrequency time, min	15 (10-21)	15 (11-21)	13 (9-21)	0.626
ICD after RFCA	53 (88%)	31 (84%)	22 (96%)	0.233
AADs at discharge				
Amiodarone	23 (38%)	14 (38%)	9 (39%)	1.000
Sotalol	12 (20%)	7 (19%)	5 (22%)	1.000
Class I	1 (2%)	1 (3%)	0 (0%)	1.000

Values are reported as mean ± standard deviation, median and IQR or n (%). RFCA indicates radiofrequency catheter ablation and AAD, antiarrhythmic drugs. Other abbreviations as in Table 1.

Table 3. Electrogram characteristics

	All (n=2858)	Evoked Delayed Potentials (n=930)	Other EGM (n=1928)	*P-value*
EGM location				0.094
Dense scar (<0.5mV)	1367 (48%)	469 (50%)	898 (47%)	
Border zone (0.5–1.49mV)	867 (30%)	277 (30%)	590 (31%)	
Normal voltage area (≥1.5mV)	624 (22%)	184 (20%)	440 (22%)	
EGM characteristics during SR				
Amplitude, mV	0.52 (0.03–25.61)	0.49 (0.04–6.69)	0.54 (0.03–25.61)	0.026
Duration, ms	69 (15–422)	75 (21–288)	65 (15–422)	<0.001
EGM characteristics during RV pacing				
Near-field amplitude (if present), mV	0.09 (0.03–0.93)	0.09 (0.03–0.93)	0.10 (0.04–0.39)	0.486
Duration, ms during S1	70 (19–450)	86 (29–450)	64 (19–308)	<0.001
Duration, ms during S2	79 (11–589)	112 (27–589)	69 (11–296)	<0.001
EGM prolongation from S1 to S2, ms	7 (0–364)	31 (10–364)	4 (0–85)*	<0.001

Values are reported as median and range or n (%). EGM indicates electrogram and RV, right ventricle. EGMs with near-field low voltage signals *and* conduction delay >10ms or conduction block in response to RV extrastimulation were categorized as evoked delayed potentials. *EGM with conduction delay or block by RVE with BV>1.5mV were not considered EDP.

Group definition

Thirty-seven patients (62%) in whom EDPs were identified in areas with normal BV during SR constituted the "*hidden substrate group*". The remaining 23 patients (38%), in whom either no EDP was identified (4/23 [17%]) or only within the EA scar area (19/23 [83%]), conformed the "*overt substrate group*" (**Figure 2**). Patients in the overt substrate group had lower LVEF (26±12% vs. 36±11%; P=0.003), larger scars and dense scars (median 82 [IQR 47-106] and 44 [IQR 24-62]cm^2 vs. 59 [34-79] and 14 [5-32]cm^2; P=0.044 and P=0.003 respectively) and more frequently heart failure (14 (61%) vs 10 (27%); P=0.014). Of note, patients in the hidden substrate group had more often undergone CABG (15 (41%) vs. 3 (13%); P=0.041).

Ablation

The median time of RF was 15 minutes (IQR 10-21). After EDP elimination, 40 patients (67%) did not require any additional ablation. In 14 patients (23%), remaining induced VTs were successfully abolished based on activation, entrainment and/or pace-mapping. Six patients (10%) remained inducible for any targeted VT at the end of the procedure.

Complications

One patient with prior CABG underwent surgical adhesiolysis for epicardial access, which was complicated by a bypass occlusion. The patient died 24h despite surgical revascularization due to a vasoplegic syndrome. Pericardial bleeding requiring percutaneous drainage occurred in 2 patients

Post-procedural management

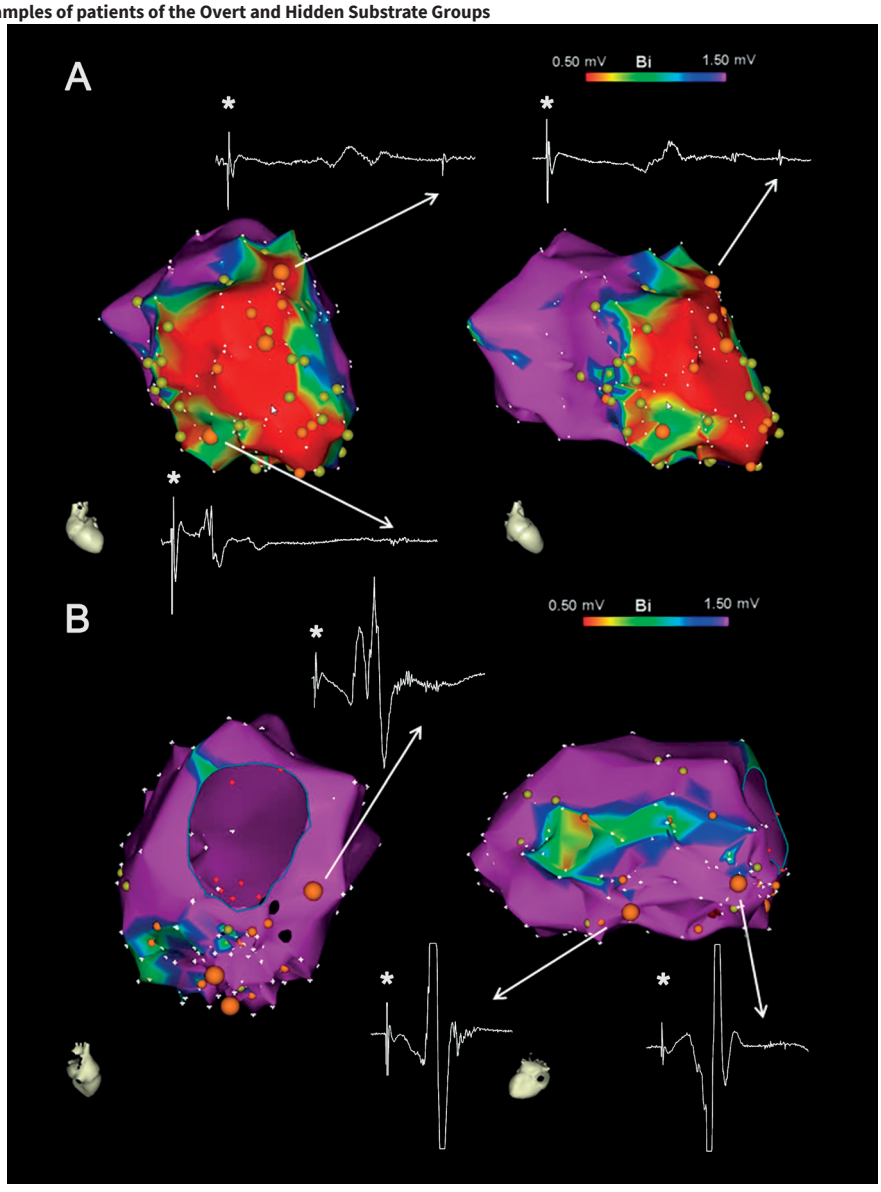
No patient had deterioration of LV function on post-procedural echocardiogram. Fifty-three patients (88%) were discharged with an ICD. Seven patients (12%) refused ICD implantation (all non-inducible after ablation and LVEF≥ 35%). Thirty-three patients were discharged on AADs (21 patients (57%) in the hidden substrate group vs 12 (52%) in the overt substrate group; P=0.793). In total, 22 patients (38%) were discharged on amiodarone, 12 (20%) on sotalol and 1 (2%) on the combination of amiodarone with mexiletine.

Follow-up

During a median follow-up of 16 months (IQR 8-23), 13 patients (22%) experienced VT recurrence (median time to recurrence 150 days). Patients in the hidden substrate group had a higher 12-month VT free survival (89% [95% CI 78-100] vs 50% [95% CI 24-76] in the overt substrate group; P=0.005) (**Figure 3**). Five patients died after a median of 205 days (3/5 of cardiac causes) and 2 patients received a Left Ventricular Assist Device 12 days and 17 months after ablation. At last follow-up, 35 patients (58%) were on AADs (18

patients (49%) in the hidden substrate group vs 17 (74%) in the overt substrate group; P=0.065).

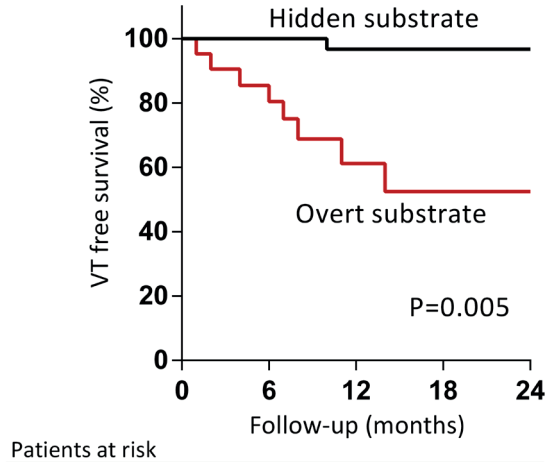
Figure 2.
Examples of patients of the Overt and Hidden Substrate Groups



BV maps and local EGMs during RVE (S2) from patients of the overt substrate group (A) and the hidden substrate group (B). BV is color-coded according to bar. Sites with *"evoked delayed potentials" (EDP)* are marked by orange tags. Other pacing sites are marked by yellow tags. Panel A: BV maps in anteroposterior (left) and right anterior oblique (right) views. All EDPs are confined to the low-voltage area. Panel B: BV maps in posterior and inferolateral views. EDPs are also located in areas with normal voltage and unmasked by RVE.

Univariate Cox regression analysis showed that the absence of a hidden substrate (HR 4.63; CI 95% 1.41-15.15: P=0.011), a higher number of induced VTs (HR 1.24 per additional VT; 95% CI 1.01-1.52: P=0.039) and a larger bipolar scar area (HR 1.02 per cm^2; 95% CI 1.0-1.03: P=0.007) were associated with higher incidence of VT recurrence (**Supplementary Table 3**).

Figure 3.



Patients at risk					
Hidden	37	32	25	12	7
Overt	23	15	7	3	0

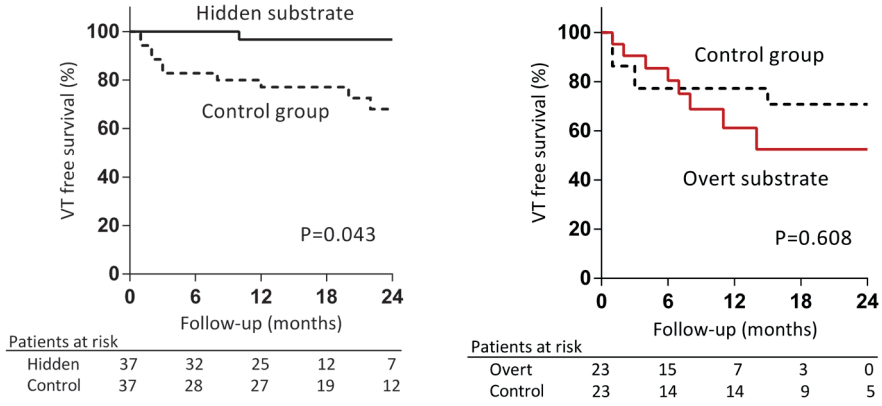
Ventricular tachycardia-free survival in hidden vs. overt substrate groups

Long-term outcome comparison with historical group

Patients from the hidden and overt substrate groups differed in baseline characteristics known to impact the incidence of VT recurrence (LVEF, scar area).(10,11) Therefore, long-term ablation outcome for each group was compared with a LV function and bipolar scar area matched cohort of patients from the historical group who underwent ablation without RVE for substrate identification.

Patients in the overt substrate group had a similar incidence of VT recurrence than patients in the matched historical cohort (12-month VT free survival 66% [95% CI 46-86] vs. 65% [95% CI 45-85]; P=0.608). On the contrary, patients in the hidden substrate group had a better VT-free survival than patients in the matched historical cohort (12-month VT free survival 89% [95% CI 79-99] vs. 73% [95% CI 59-87]; P=0.039), suggesting that substrate identification and ablation based on RVE might be particularly beneficial in post-MI patients with moderately depressed LV function and small and non-transmural scars (**Figure 4**).

Figure 4.



Ventricular tachycardia-free survival in hidden substrate (A) and overt substrate groups (B) vs. LV ejection fraction and bipolar scar area matched historical controls

DISCUSSION

In the present study, we demonstrate that in patients undergoing ablation for post-MI VT, systematic evaluation of EGMs recorded from the presumed infarct area during RVE can unmask areas of scar with functional conduction delay or block. These areas with *evoked delayed potentials* as potential substrate for VT cannot be detected if mapping is performed during SR or continuous RV pacing only. Patients in whom EDP were recorded within normal EA voltage areas had a relatively preserved LV function and small and patchy scars. These hidden substrates were particularly located in areas of non-transmural scar with viable subepicardial myocardium on CE-MRI. The latter can result in “pseudo” normal BV during SR and is important to consider in contemporary patients with acute reperfusion therapy and after prior CABG. Of importance, compared to a LV function and scar area matched historical cohort of post-MI patients in whom substrate identification based on RVE was not performed, patients undergoing ablation of unmasked *hidden substrate* had better VT-free survival after ablation.

Substrate-based ablation for post-MI VT

Substrate-based ablation approaches have been developed for targeting unstable or non-inducible VTs, circumstances that affect 70% and 10% of patients currently referred for ablation of post-MI VT.(10,12) Although substrate-based ablation is superior to ablation limited to clinical or hemodynamically stable VTs, (13) the reported VT recurrence rates after substrate modification remain high (32%-47%). (12,14,15) It has been suggested that the scar size impacts the long-term outcome after ablation. In a prior cohort

of post-MI patients who underwent substrate modification targeting LPs during continuous RV pacing, the presence of a dense scar area >25cm^2 was independently associated with a higher incidence of VT recurrence. Of interest, although patients with small scars (<25cm^2) and slow VTs (CL >350ms) had an excellent prognosis, patients with small scars *and* fast VTs (CL<350ms) had higher recurrence rates, comparable to those with large scars *and* slow VTs (CL >350ms). (12) These findings suggest that, in patients with small scars and a substrate for faster VT, substrate identification during SR or RV pacing might not be sufficient.

Substrate mapping: Delineation of scar area

The cornerstone of substrate-based VT ablation is the delineation of the EA scar using standard BV cut-off values of 1.5mV and 0.5mV for scar and dense scar. (1) Mapping accuracy to detect scar might, however, be hampered by far-field contamination of local low-voltage signals. This might be particularly relevant in the presence of non-transmural scars, typically encountered in patients undergoing acute reperfusion of the infarct related artery (4) or with well-developed collaterals. In these patients, subepicardial viable myocardium overlying the subendocardial scar may generate high voltage far-field signals leading to underestimation of the scar area.(16) Accordingly, a mismatch between non-transmural scar size delineated by voltage mapping and CE-MRI has been demonstrated. (17) In addition, VT termination by ablation beyond the EA scar area has been reported, further emphazising the limitation of BV mapping during SR to identify the entire arrhythmogenic scar. (6) In our study, patients in whom additional areas of scar with local conduction delay were unmasked by RVE had smaller EA scars with either no dense scar (n=2) or only small dense scar areas (involving a median of 7% of the total LV area), suggesting the presence of a non-transmural scar. In fact, in those patients who underwent CE-MRI scar integration with EA maps, 71% of sites showing hidden substrate for VT were located in areas of non-transmural scar. This finding could not be explained by a higher acute revascularization rate in our cohort, which was low in both groups. However, significantly more patients in the hidden substrate group had undergone CABG which may have contributed to improved epicardial collateral coronary flow and the non-transmurality of the scar. The use of narrow-spaced, multipolar catheters and voltage mapping performed during pacing from multiple sites may help to identify additional low-voltage areas not detected during SR. (3,6) However, whether small, narrow-spaced electrodes reduce far-field contamination from the subepicardium for small and patchy scars is unknown. Similarly, whether the change of activation sequence at a fixed CL is sufficient to change the temporal relation between epicardial and subendocardial activation at the recording site in small scars with little activation delay at lower pacing rates, needs further evaluation. In addition, ablation only guided by EGM voltage may lead to unnecessary damage of functional myocardium not involved in VT.

Substrate mapping: Identification of slow conduction

Post-MI VTs are typically due to re-entry facilitated by slow conduction and fixed or functional conduction (pseudo-)block within the scar. (18) Accordingly, substrate-based ablation also relies on identification of EGMs consistent with slow conduction during SR that may be critical for VT circuits. Elimination of all EGMs with late or isolated components within the scar has been associated with improved ablation outcome. (15) However, in particular for fast VTs, slow conduction and block might be functional, only occurring at fast rates and short couplings intervals and hence, not detectable if mapping is performed during SR or continuous RV pacing only.(18,19) In a prior series, up to 33% of 100 post-MI patients referred for ablation did not have LPs. Of note, patients without LPs had typically smaller and less-dense scars. (15) Ablation of all EGMs poorly coupled to the rest of the myocardium (local abnormal ventricular activities [LAVAs]) has also been proposed. (14) The definition of LAVA includes, however, a broad spectrum of signals with low and high voltage sharp components occurring at any time before, during or after the far-field EGM. These EGMs might therefore be recorded in large areas. In addition, although in the work by Jais et al. the application of extrastimuli was used in some cases to detect LAVAs, neither the electrophysiological characteristics of LAVAs (e.g systematic evaluation of the response to RVE) nor their potential involvement in VT circuits was s studied systematically.-Of importance, in a recent study validated by simultaneous intraoperative activation mapping, EGMs with decremental conduction properties were more specifically associated with the diastolic VT pathway than LPs. (20) In our study, we restricted ablation to those EGMS exhibiting functional conduction delay or block during RVE (EDPs) aiming to reduce RF applications and to minimize the risk of damaging viable myocardium, in particular at those sites exhibiting normal BV during SR. Of note, LPs which did not delay further or block in response to RVE, indicating a fixed late activated area within the scar were not targeted. This approach translated into a median RF time of only 15 minutes, which is significantly shorter than reported for other substrate-based ablation strategies (**Supplementary Table 4**). Of note, the RF time was not different among groups despite the significant difference in scar size, suggesting that the size of the area exhibiting EDPs might be independent of the total scar size. Using EGM response to RVE for guiding substrate modification does not only increase the likelihood to identify relevant VT related sites, but also helped to identify ablation targets beyond the low BV area in 62% of the patients without prolonging the procedural time. Of importance, the identification an ablation of the hidden substrate in these patients with small and non-trasmural scars resulted in a lower incidence of VT recurrence on follow-up. On the contrary, patients with larger dense scars and overt slow conducting areas identified during SR did not benefit from additional substrate identification by RVE. In a recent small and heterogeneous group of patients undergoing ablation for scar-related VT, the value of the application of a double ventricular

extrastimulus for identifying additional slow conducting areas has been reported. (21) However, in contrast to our study, only sites with abnormal EGMs and particular characteristics (> 3 deflections, duration <133ms) were analysed, leading to underdetection of sites with functional delay hidden by normal EGMs (**Figure 1D**). The impact of this strategy on VT recurrence during follow-up was not reported.

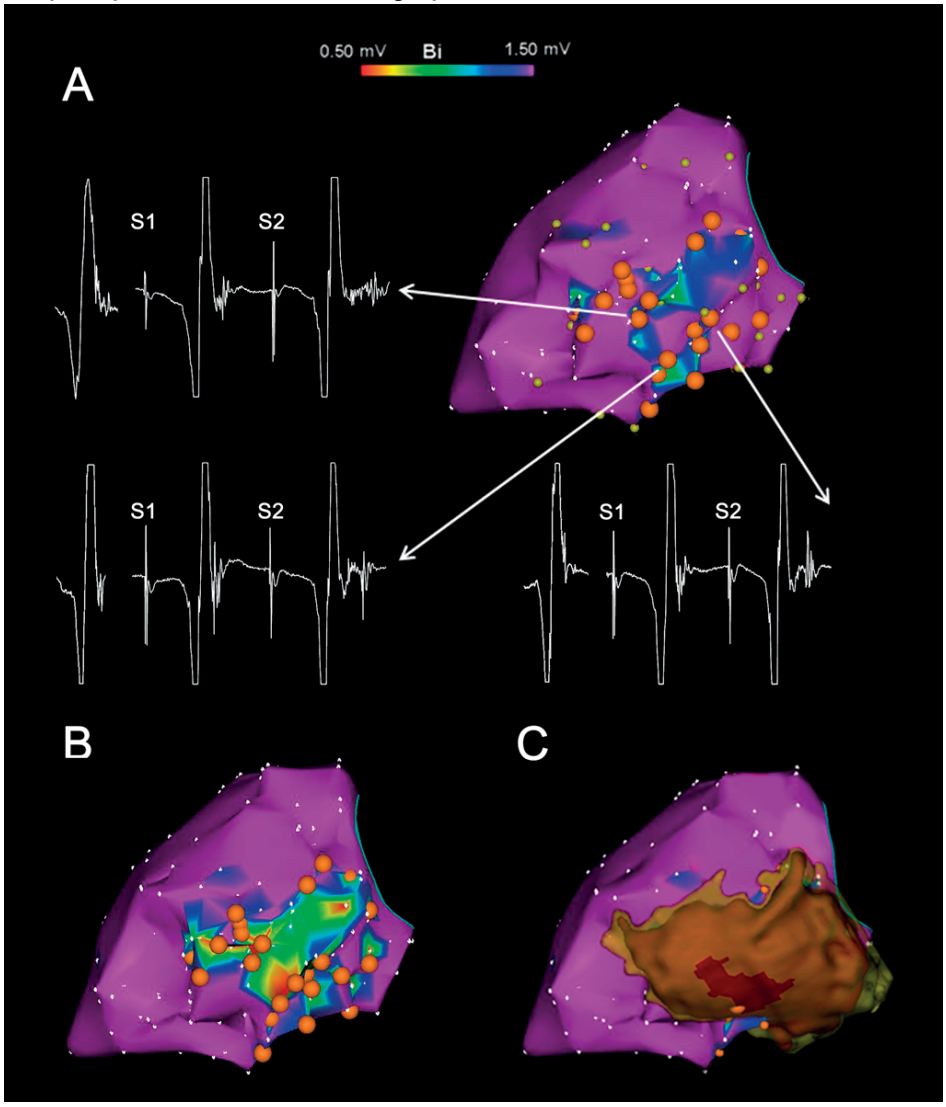
Limitations

The major limitation of the study is its observational nature. Outcome comparison was performed with a historical cohort and although known determinants of VT recurrence (LV function, scar area) were matched, other uncontrolled factors may have influenced outcome. All procedures were performed by an experienced operator in a high volume centre which limits the generalization of the ablation results. Multipolar mapping catheters with small and narrow-spaced electrodes which may have improved far-field from near-field discrimination during SR were not used. Ventricular extrastimuli were always applied from the RV apex. Pacing from multiple sites (including LV) might have allowed identification of additional areas with EDPs. However, we expect the influence of the pacing site, especially for small scars, to be limited due to rapid activation of normal myocardium from the pacing site to the scar border. In addition, pacing from multiple LV sites would require an additional LV access and would likely prolong the procedure.

CONCLUSIONS

In patients with small and non-transmural scars after MI, systematic use of RVE during substrate mapping allows identification of areas of scar with functional conduction delay or block as substrate for VT that are not detectable if mapping is performed during SR or continuous RV pacing only. Ablation of this hidden substrate unmasked by RVE is associated with improved long-term procedural outcome.

Central Illustration.
Example of a patient from the hidden substrate group



A: BV map (color-coded according to bar, left lateral view) showing a small lateral scar with no dense scar. Three EGMs recorded during SR and their response to RV pacing (S1) and RVE (S2) are shown. All three EGMs had normal amplitude. A high-frequency near-field potential is visible at the end of the far-field during SR. During RVE, conduction delay of the near-field is shown. These *Evoked Delayed Potentials* (EDPs) were targeted by ablation. Orange tags indicate EDPs. Other pacing sites are marked by yellow tags. **B:** Electroanatomical map corrected for the BV of the near-field EGM shows a better correlation with the CE-MRI segmented scar(C). **C:** 3D CE-MRI derived scar as registered with the voltage map. Scar border zone is displayed in yellow, scar core in brown and scar core with 100% transmurality in red. Note that EDPs outside the EA low BV area are located in areas of non-transmural scar.

REFERENCES

1. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation 2000;101:1288-96.
2. Zeppenfeld K, Kies P, Wijffels MC, Bootsma M, van Erven L, Schalij MJ. Identification of successful catheter ablation sites in patients with ventricular tachycardia based on electrogram characteristics during sinus rhythm. Heart rhythm 2005;2:940-50.
3. Berte B, Relan J, Sacher F et al. Impact of electrode type on mapping of scar-related VT. Journal of cardiovascular electrophysiology 2015.
4. Wijnmaalen AP, Schalij MJ, von der Thusen JH, Klautz RJ, Zeppenfeld K. Early reperfusion during acute myocardial infarction affects ventricular tachycardia characteristics and the chronic electroanatomic and histological substrate. Circulation 2010;121:1887-95.
5. Piers SR, Wijnmaalen AP, Borleffs CJ et al. Early reperfusion therapy affects inducibility, cycle length, and occurrence of ventricular tachycardia late after myocardial infarction. Circulation Arrhythmia and electrophysiology 2011;4:195-201.
6. Tung R, Josephson ME, Bradfield JS, Shivkumar K. Directional Influences of Ventricular Activation on Myocardial Scar Characterization: Voltage Mapping With Multiple Wavefronts During Ventricular Tachycardia Ablation. Circulation Arrhythmia and electrophysiology 2016;9.
7. Piers SR, Tao Q, de Riva Silva M et al. CMR-based identification of critical isthmus sites of ischemic and nonischemic ventricular tachycardia. JACC Cardiovascular imaging 2014;7:774-84.
8. van Huls van Taxis CF, Wijnmaalen AP, Piers SR, van der Geest RJ, Schalij MJ, Zeppenfeld K. Real-time integration of MDCT-derived coronary anatomy and epicardial fat: impact on epicardial electroanatomic mapping and ablation for ventricular arrhythmias. JACC Cardiovascular imaging 2013;6:42-52.
9. Watanabe M, de Riva M, Piers SRD et al. Fast nonclinical ventricular tachycardia inducible after ablation in patients with structural heart disease: Definition and clinical implications. Heart rhythm 2018.
10. de Riva M, Piers SR, Kapel GF et al. Reassessing noninducibility as ablation endpoint of post-infarction ventricular tachycardia: the impact of left ventricular function. Circulation Arrhythmia and electrophysiology 2015;8:853-62.
11. Arenal A, Hernandez J, Calvo D et al. Safety, long-term results, and predictors of recurrence after complete endocardial ventricular tachycardia substrate ablation in patients with previous myocardial infarction. The American journal of cardiology 2013;111:499-505.
12. Stevenson WG, Wilber DJ, Natale A et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation 2008;118:2773-82.
13. Di Biase L, Burkhardt JD, Lakkireddy D et al. Ablation of Stable VTs Versus Substrate Ablation in Ischemic Cardiomyopathy: The VISTA Randomized Multicenter Trial. Journal of the American College of Cardiology 2015;66:2872-2882.
14. Jais P, Maury P, Khairy P et al. Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. Circulation 2012;125:2184-96.
15. Tsiachris D, Silberbauer J, Maccabelli G et al. Electroanatomical voltage and morphology characteristics in postinfarction patients undergoing ventricular tachycardia ablation: pragmatic

approach favoring late potentials abolition. Circulation Arrhythmia and electrophysiology 2015;8:863-73.

16. Berte B, Sacher F, Cochet H et al. Postmyocarditis ventricular tachycardia in patients with epicardial-only scar: a specific entity requiring a specific approach. Journal of cardiovascular electrophysiology 2015;26:42-50.
17. Wijnmaalen AP, van der Geest RJ, van Huls van Taxis CF et al. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. European heart journal 2011;32:104-14.
18. Anter E, Tschabrunn CM, Buxton AE, Josephson ME. High-Resolution Mapping of Postinfarction Reentrant Ventricular Tachycardia: Electrophysiological Characterization of the Circuit. Circulation 2016;134:314-27.
19. Kawara T, Derksen R, de Groot JR et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. Circulation 2001;104:3069-75.
20. pacing site, especially for small scars, to be limited due to rapid activation of normal myocardium from the pacing site to the scar border. In addition, pacing from multiple LV sites would require an additional LV access and would likely prolong the procedure.

SUPPLEMENTARY METHODS

CE-MRI acquisition and processing

CE-MRI was performed on a 1.5-T Gyroscan ACS-NT/Intera or on a 3.0-T Ingenia MR system (Philips Medical Systems, Best, the Netherlands). A standardized clinical protocol was followed including cine MRI in long (2- and 4-chamber views) and short axis. Contrast enhanced images were acquired 15 min after bolus injection of gadolinium. The heart was either imaged in 1 or 2 breath-holds with 20 to 24 imaging levels in short and long axis views or with 20 to 26 imaging levels in the short axis view in one or two three-dimensional stacks, each stack acquired within one breathhold. Using in-house-developed MASS software (research version 3-1-2017; Medis; Leiden University Medical Center, Leiden, the Netherlands), the centreline of the left main, right coronary artery and the luminal boundary of the proximal aorta were manually defined. In the CE short-axis images, the endocardial and epicardial contours were semi-automatically detected. Scar was defined as myocardium with SI ≥35% of maximal myocardial SI, and was subdivided into core scar (≥50% of maximal SI) and border zone (35 to 50% of maximal SI). The LV anatomy, defined by the endocardial and epicardial contours was converted into 3D meshes using MASS software package. The scar anatomy was visualized as a 3D structure created with the MASS software. All meshes were imported into the Carto 3 system using CartoMerge image integration software (Biosense Webster Inc., Diamond Bar, California). After the procedure, all mapping points, including those categorized as EDPs, were projected onto the LGE MRI images using MASS software. For EDPs located within the CE-MRI derived scar, local transmurality of the scar was visually assessed.

Supplementary table 1: Baseline characteristics of the entire population

	All (n=150)	Historical group (n=90)	Study group (n=60)	*P-value*
Age, years	68 ± 9	68 ± 10	68 ± 8	0.907
Male	130 (87%)	81 (90%)	49 (82%)	0.151
Hypertension	60 (40%)	41 (46%)	19 (32%)	0.125
Diabetes Mellitus	23 (15%)	13 (14%)	10 (17%)	0.818
Prior stroke/TIA	13 (9%)	8 (9%)	5 (8%)	1.000
Atrial fibrillation	43 (29%)	28 (31%)	15 (25%)	0.465
Heart failure	63 (42%)	39 (43%)	24 (40%)	0.737
Renal failure	47 (31%)	29 (32%)	18 (30%)	0.858
Inferior MI	92 (61%)	57 (63%)	36 (60%)	0.864
Time since MI, year	19 ± 8	19 ± 9	19 ± 8	0.886
MI acute reperfusion	27 (18%)	15 (17%)	12 (20%)	0.667
Prior CABG	55 (37%)	37 (41%)	18 (30%)	0.226
Prior PCI	59 (39%)	35 (39%)	24 (40%)	1.000
LV ejection fraction, %	33 ± 12	34 ± 12	33 ± 12	0.632
ICD before ablation	106 (71%)	56 (62%)	50 (83%)	0.006
Prior VT ablation	24 (16%)	10 (11%)	14 (23%)	0.068
Clinical VT CL, ms	401 ± 93	391 ± 86	417 ± 102	0.101
Medication at admission				
Statins	133 (89%)	80 (89%)	53 (88%)	1.000
Antialdosteronic	48 (32%)	31 (34%)	17 (28%)	0.478
ACE-I/ARB	121 (81%)	75 (83%)	46 (77%)	0.399
Betablockers	116 (77%)	68 (76%)	48 (80%)	0.557
Amiodarone	60 (40%)	38 (42%)	22 (37%)	0.610
VT clinical presentation				
Electrical storm	22 (15%)	15 (17%)	7 (12%)	0.484
Incessant VT	19 (13%)	14 (16%)	5 (8%)	0.220
ICD therapies	38 (25%)	23 (26%)	15 (25%)	1.000
Below ICD detection	34 (23%)	10 (11%)	24 (40%)	<0.0001
First episode without ICD	37 (25%)	28 (31%)	9 (15%)	0.033

Values are reported as mean ± standard deviation or n (%). Abbreviations as in table 1.

Supplementary table 2: Procedural characteristics of the entire population

	All (n=150)	Historical group (n=90)	Study group (n=60)	*P-value*
Inducible before RFCA	139 (93%)	84 (93%)	55 (92%)	0.755
Number of induced VTs	3 (2–5)	3 (2–5)	3 (1–4)	0.129
Induced VT max CL, ms	420 ± 113	418 ± 117	420 ± 103	0.902
Induced VT min CL, ms	298 ± 78	295 ± 80	304 ± 78	0.511
LV bipolar scar area, cm^2	65 (41–87)	65 (41–88)	64 (41–87)	0.754
LV dense scar area, cm^2	24 (7–44)	23 (10–43)	25 (6–44)	0.661
LV border zone area, cm^2	35 (22–49)	36 (23–51)	34 (23–47)	0.743
Epicardial mapping	12 (8%)	6 (7%)	6 (10%)	0.544
Procedural duration, min	180 (150-225)	190 (145-235)	173 (150-205)	0.309
Fluoroscopic time, min	35 (24–48)	32 (23–48)	39 (33–47)	0.029
Radiofrequency time, min	15 (10-21)	15 (9-22)	15 (10-21)	0.997
Complications	19 (13%)	11 (12%)	8 (13%)	1.000
ICD after RFCA	129 (86%)	76 (84%)	53 (88%)	0.634
AADs at discharge				
Amiodarone	66 (44%)	43 (48%)	23 (38%)	0.314
Sotalol	41 (27%)	29 (32%)	12 (20%)	0.134
Class I	1 (1%)	0 (0%)	1 (2%)	0.400

Values are reported as mean ± standard deviation, median and IQR or n (%). Abbreviations as in table 3.

Supplementary table 3: Cox regression analysis for predictors of VT recurrence in the study group

	Hazard Ratio	95% CI	*P-value*
Absence of hidden substrate	4.63	1.41-15.15	0.011
Number of induced VTs (per VT)	1.24	1.01-1.52	0.039
LV ejection fraction per 1% increase	0.96	0.92-1.01	0.112
Bipolar scar area (per cm^2)	1.02	1.0-1.03	0.007
Non-inducibility after RFCA	0.87	0.28-2.65	0.799

CI indicates confidence interval. Rest of the abbreviations as in prior tables

Supplementary table 4:

First author and year of publication	Number of post-MI patients	Substrate ablation technique	Procedural time min	RF time min
Jaïs P. et al 2012(15)	56	LAVA elimination	148±73	23±11
Di Biase L. et al 2012(14)	92	Scar homogenization	288±90	74±21
Berruezo A. et al 2015(21)	75	Scar dechanneling	227±69	28±16
Tsiachris D. et al 2015(16)	100	Late potential abolition	243.1±72.4	28.9±14.7
Tzou W. et al 2015(22)	32	Core isolation	326±121	111±91
De Riva. et al 2017	60	EDP ablation	173 (150-205)	15 (10-21)

SUPPLEMENTARY REFERENCES

21. Berruezo, A., et al., *Scar dechanneling: new method for scar-related left ventricular tachycardia substrate ablation.* Circ Arrhythm Electrophysiol, 2015. **8**(2): p. 326-36.
22. Tzou, W.S., et al., *Core isolation of critical arrhythmia elements for treatment of multiple scar-based ventricular tachycardias.* Circ Arrhythm Electrophysiol, 2015. **8**(2): p. 353-61.

6

Myocardial calcification is associated with endocardial ablation failure of post-myocardial infarction ventricular tachycardia

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Europace. 2021;23:1275-1284

ABSTRACT

Background

In patients with post-myocardial infarction (MI) ventricular tachycardia (VT), the presence of myocardial calcification (MC) may prevent heating of a subepicardial VT substrate contributing to endocardial ablation failure.

Objectives

The aims of this study were to assess the prevalence of MC in patients with post-MI VT and evaluate the impact of MC on outcome after endocardial ablation.

Methods and Results

In 158 patients, presence of MC was retrospectively assessed on fluoroscopy recordings in 7 standard projections obtained during pre-procedural coronary angiograms. MC, defined as a distinct radiopaque area that moved synchronously with the cardiac contraction was detected in 30 patients (19%). After endocardial ablation, only 6 patients (20%) with MC were rendered non-inducible compared to 56 (44%) without MC (P=0.033) and of importance, 8 (27%) remained inducible for the clinical VT (compared to 9 (6%) patients without MC; P=0.003) requiring therapy escalation. After a median follow-up of 31 months, 61 patients (39%) had VT recurrence and 47 (30%) died. Patients with MC had a lower survival free from the composite endpoint of VT recurrence or therapy escalation at 24-month follow-up (26% vs. 59%; P=0.003). Presence of MC (HR 1.69; P=0.046), a lower LV ejection fraction (HR 1.03 per 1% decrease; P=0.017) and non-complete procedural success (HR 2.42; P=0.002) were independently associated with a higher incidence of VT recurrence or therapy escalation.

Conclusion

MC was present in 19% of post-MI patients referred for VT ablation and was associated with a high incidence of endocardial ablation failure.

INTRODUCTION

Catheter ablation is an effective therapy for preventing ventricular tachycardia (VT) recurrence in patients with prior myocardial infarction (MI). However, despite improvement in the understanding of the VT substrate and technical developments, 10% of patients remain inducible for clinically relevant VTs at the end of the procedure and up to 50% of the patients experience VT recurrence at 6-month follow-up.(1) It has been suggested that both acute procedural failure and VT recurrence after endocardial ablation may be due to epicardial VT circuits that cannot be interrupted from the endocardium.(2) However, less than one third of patients with post-MI VT in whom a first-line endo-epicardial approach was performed had an epicardial ablation target site.(3) In addition, in a majority of patients with post-MI VT, at least part of the epicardial substrate located in areas of wall thinning could be abolished by endocardial ablation.(4) Considering the reported 4-7% additional risk of complications and the significant patient discomfort related to epicardial mapping and ablation (5,6), non-invasive identification of post-MI patients who may benefit from a primary epicardial approach is desirable.(7-9)

MI leading to myocyte necrosis is the most frequent cause of dystrophic myocardial calcification (MC).(10) Although its real prevalence is unknown, significant MC defined as thin curvilinear radiopaque areas were seen in thorax radiographies of up to 8% of patients with MI older than 6 years, frequently associated with the presence of apical aneurysms.(11,12) We hypothesized that in patients with prior MI, MC protecting a sub-epicardial VT substrate from thermal injury may be one potential cause of endocardial ablation failure despite the presence of wall thinning.

The aims of our study were: 1) to assess the prevalence of MC in a consecutive cohort of patients referred for ablation of post-MI VT and 2) to evaluate the impact of the presence of MC on the acute and long-term outcome of post-MI endocardial VT ablation.

METHODS

Consecutive patients with prior MI referred for ablation of scar-related VT to the Leiden University Medical Center between January 2009 and February 2016 were included. The diagnosis of MI was based on the presence of wall motion abnormalities, non-reversible perfusion defects and/or subendocardial or transmural late gadolinium enhancement areas in the perfusion territory of a significant stenotic coronary artery (>75 %). All patients were treated according to the clinical protocol and provided informed consent for the procedure. The research protocol was accepted by the Institutional Review Board.

Assessment of myocardial calcification

Fluoroscopy recordings in 7 standard projections obtained during pre-procedural coronary angiography (n=132) and/or during the ablation procedure (n=26) were retrospectively analysed for the presence of MC by two experienced cardiologists (J.M.M. and M.R.) blinded to the patient clinical characteristics and ablation outcome. MC was defined as the presence of a distinct and curvilinear radiopaque area that moved synchronously with the cardiac contraction. Calcifications corresponding to the valvular annuli or to the trajectory of an epicardial coronary artery were excluded.

In a subgroup of patients (n=18), presence of MC was also visually assessed on ECG-gated cardiac computed tomography (CT).

Assessment of infarct transmurality

As previously described,(8) an infarction was classified as transmural when the late gadolinium enhanced area extended to >75% of the wall thickness on contrast-enhanced magnetic resonance imaging (CE-MRI), a region of wall thinning ≤5mm was detected on cardiac CT and/or an area of thinned (≤6mm), hyperechogenic and aki/dyskinetic myocardium was observed on echocardiogram. See Supplementary Methods for details.

Ablation procedure

Electrophysiological study

Programmed electrical stimulation was conducted (3-4 drive cycle lengths (CL) [600, 500, 400, 350ms], 3-4 extra's [≥200ms] from 2 right ventricular (RV) and ≥1 left ventricular (LV) site). Positive endpoint of stimulation was induction of a sustained monomorphic VT lasting >30s or requiring termination because of hemodynamic compromise. Induced VTs were regarded (presumed-) clinical if the 12-lead ECG matched that of a spontaneous documented VT or the VTCL was ±30ms of the CL of the implantable cardioverter defibrillator (ICD)-recorded VT.

Substrate mapping and ablation

The initial ablation approach was endocardial in all cases with the exception of 3 patients who had failed ≥1 endocardial ablation attempts in another centre and in whom an epicardial VT origin was suspected by the referring electrophysiologist.

A LV endocardial bipolar voltage map was constructed during stable rhythm using a 3.5mm irrigated-tip catheter (NaviStar ThermoCool or Thermocool Smarttouch SF; Biosense Webster, Inc, Diamond Bar, CA) and the CARTO 3 system. Standard voltage cut-off values of 1.5mV and 0.5mv were used to define scar and dense scar. From 2009 to 2013, all patients underwent substrate-based ablation which was based on elimination of late

potentials and fragmented electrograms (EGMs). Pace-mapping was used to identify VT exit sites. Since October 2013, a systematic pacing protocol was used for substrate identification.(12) In brief, EGMs located in the presumed infarct area, as derived from cardiac imaging and coronary anatomy, independently of their voltage or morphology during sinus rhythm, were analysed during RV pacing at a fixed rate of 500ms and during the application of a short-coupled RV extra-stimulus. Sites showing low voltage, near-field potentials which delayed >10ms or blocked in response to RV extra-stimulation were categorized as *evoked delayed potentials* (EDP) and targeted for ablation. In addition, during the whole study period, if the patient was in VT at the beginning of the procedure, if a hemodynamic stable VT remained inducible after substrate modification or it was repeatedly induced during catheter manipulation, activation and entrainment mapping were performed with the aim of identifying the VT critical isthmus and terminating the VT during ablation.

Radiofrequency (RF) energy was delivered (45-50W, temperature limit 43°C, flow rate 15-30 ml/min, 60-120 seconds, CF>9gr) until stimulation with high output pacing (10 mA, 2ms) failed to capture.

Acute outcome definition

After the last RF application, a re-map was systematically performed (including RV extra-stimulation since October 2013) and the entire induction protocol was repeated. Complete acute success was defined as non-inducibility of any VT, partial success as elimination of the clinical VT but persistent inducibility of any non-clinical VT and procedural failure as persistent inducibility of clinical VT after ablation. Fast non-clinical VTs with a CL close to ventricular refractory period (fast VT_{VERP}) were considered of unknown clinical relevance and not targeted. Accordingly, induction of only fast VT_{VERP} was defined as acute clinical success.(13)

Management after endocardial ablation

After endocardial ablation failure, an epicardial ablation attempt was offered to all patients with the exception of those with prior cardiac surgery. In those patients, “escalation” of anti-arrhythmic drugs (AAD) was the next attempt to control VT, including sotalol with a dose of ≥160mg per day, initiation or increase of the dose of amiodarone or combination of amiodarone with a class I AAD. In patients who did not use amiodarone before ablation, amiodarone was started at a dose of 400mg three times per day for one week, followed by a dose of 400mg per day for one week and 200 mg per day thereafter. In patients receiving amiodarone 200mg per day at the time of ablation, the dose was increased to 300-400mg per day (after one week re-loading dose of 400mg three times a day) or mexiletine (600mg per day) was added. *Therapy escalation* after endocardial

ablation was defined as either escalation of anti-arrhythmic drugs or performance of a successful epicardial or surgical ablation. In the remaining patients, pre-procedural AAD were continued until the first follow-up visit. ICD implantation was offered to all patients without a device before ablation.

Follow-up after hospital discharge and study endpoints

Patients were followed 3 months after ablation and every 6 months thereafter. After acute endocardial ablation success, in the absence of VT recurrence at first follow-up visit, discontinuation of AAD was recommended. For patients followed at other institutions or in case of death, the referring cardiologist or the general physician was contacted for VT recurrence and cause of death.

Endpoints of the study were: 1) VT recurrence, defined as occurrence of any VT requiring ICD therapy, recorded within the ICD monitor zone lasting >30s or documented on 12-lead ECG and 2) Composite endpoint including VT recurrence or need of therapy escalation for controlling the clinical VT.

Statistical analysis

Continuous variables are reported as mean±SD or medians with interquartile range and compared with the Student's t or the Mann-Whitney U test when appropriate. Categorical variables are expressed as numbers and percentages (%) and compared with the Chi-squared or the Fisher exact test. Freedom from the composite endpoint of VT recurrence or escalation of therapy was estimated by Kaplan-Meier method and compared with log-rank test between groups. Predictors of acute procedural outcome and VT recurrence were assessed with univariate logistic regression and Cox regression analysis respectively. Independent predictors of acute ablation failure and VT recurrence or therapy escalation were analysed with multivariable models using a backward stepwise selection. Variables with a p value < 0.10 were initially included. At each step the least significant variable was removed from the model, until all variables reached a p value <0.20. All tests were 2-sided and a P value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 23.0 (SPSS Inc, Chicago, IL).

RESULTS

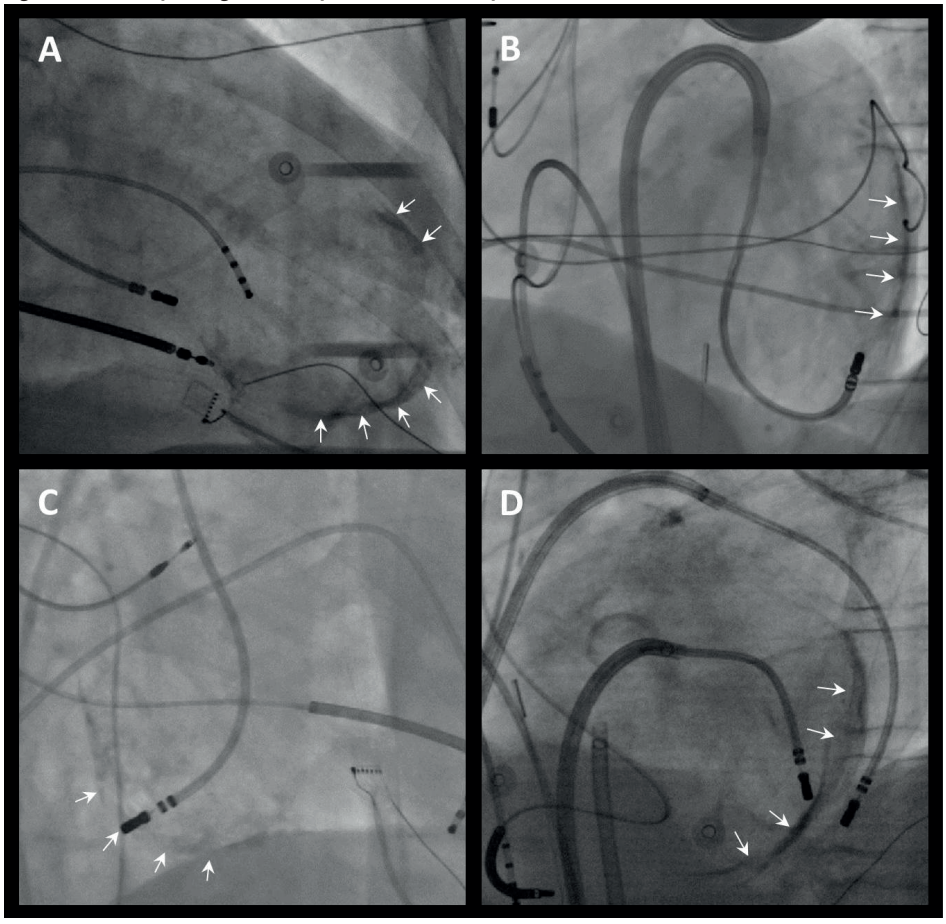
Patients

During the study period, 168 patients underwent ablation for post-MI VT in our centre. Ten patients in whom cine-fluoroscopy recordings were not available or had insufficient

quality for the assessment of MC were excluded. Finally, 158 patients (68±9 years, 87% men, LV ejection fraction 33±12%) constituted the study population.

In 30 patients (19%), an area of MC was detected on cine-fluoroscopy which corresponded in all cases with the infarcted area on echocardiogram. (**Figure 1**) In 5 of them, a cardiac CT was available which confirmed the presence of MC in all. (**Supplementary Figure 1**) Of note, no patient without MC on CT (n=13) had MC on fluoroscopy.

Figure 1. Fluoroscopic images of MC in patients referred for post-MI VT ablation



In panels A, B and C, a large apical calcified aneurysm (right anterior oblique (RAO) view), a lateral MC (left anterior oblique (LAO) view) and an infero-posterior calcified aneurysm (RAO view) are respectively shown. In panel D, a large infero-lateral MC (LAO view) is shown. Note the presence of two ablation catheters at the endocardial and epicardial side of the MC. MC are indicated by white arrows.

The rate of acute reperfusion during the index MI (10 vs. 20%; P=0.294), the baseline LV ejection fraction (31±12 vs. 34±12; P=0.214), the time from the acute MI (median 21 vs. 19 years; P=0.438), the prevalence of renal failure (37 vs. 33%; P=0.832) and the rate of amiodarone use before ablation (47 vs. 41%; P=0.546) were similar in patients with and without MC. Patients with MC were younger (64±11 vs. 69±8 years in patients without MC; P=0.019), had experienced more often an anterior MI (63% vs. 36%; P=0.008) and had undergone more often a prior VT ablation attempt (27% vs. 11%; P=0.038). Baseline characteristics are displayed in **table 1**.

Table 1. Baseline clinical characteristics

	All patients (n=158)	MC (n=30)	No MC (n=128)	*P-value*
Age, years	68±9	64±11	69±8	0.019
Male, n (%)	137 (87)	26 (87)	111 (87)	1.000
Diabetes, n (%)	24 (15)	7 (23)	17 (13)	0.169
Anterior MI, n (%)	66 (42)	19 (63)	46 (36)	0.008
Acute reperfusion, n (%)	29 (18)	3 (10)	26 (20)	0.294
Time since MI	19 (13-26)	21 (15-26)	19 (13-26)	0.438
Atrial fibrillation, n (%)	47 (30)	9 (30)	38 (30)	1.000
Heart failure, n (%)	72 (46)	13 (43)	59 (46)	0.841
Renal failure, n (%)	53 (34)	11 (37)	42 (33)	0.832
CABG, n (%)	60 (38)	9 (30)	51 (40)	0.405
Prior VT ablation, n (%)	22 (14)	8 (27%)	14 (11%)	0.038
LVEF, n (%)	33±12	31±12	34±12	0.214
Clinical VT CL, ms	401±93	420±97	396±91	0.200
Electrical storm, n (%)	27 (17)	5 (17)	22 (17)	1.000
Incessant VT, n (%)	18 (11)	4 (13)	14 (11)	0.750
ICD before ablation, n (%)	110 (70%)	23 (77%)	87 (68%)	0.388
AADs pre-ablation				
Amiodarone, n (%)	66 (42)	14 (47)	52 (41)	0.546
Sotalol, n (%)	38 (24)	7 (23)	31 (24)	1.000

Values are reported as mean ± standard deviation, median and IQR or n (%). MC indicates myocardial calcification; MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; CL, cycle length; ICD, implantable cardioverter defibrillator and AADs, anti-arrhythmic drugs.

Procedural data and acute outcome after endocardial ablation

Patients with MC had a comparable endocardial electroanatomical scar area (71 vs. 62cm^2; P=0.105) but with a larger dense scar component than those without MC (median 31 vs. 21cm^2; P=0.005). Procedural details are shown in **table 2**. In addition to substrate modification, at least one stable VT was mapped and eventually terminated by RF in 110 patients (70%).

Table 2. Procedural characteristics and acute outcome after endocardial ablation

	All patients (n=158)	MC (n=30)	No MC (n=128)	P value
Number of induced VTs	3 (2-5)	3 (2-5)	3 (2-5)	0.753
Induced VT max CL, ms	420±110	433±114	417±110	0.500
Bipolar scar area, cm^2	64 (42-86)	71 (50-94)	62 (39-86)	0.105
Dense scar area, cm^2	24 (78-43)	31 (22-60)	21 (6-42)	0.005
Border zone area, cm^2	35 (22-49)	31 (27-47)	36 (22-50)	0.849
Procedural time, min	192±68	197±61	191±70	0.697
RF time, min	17±10	18±10	17±11	0.570
Acute outcome (n=156)				
Complete success, n (%)	62 (40)	6 (20)	56 (44)	0.033
Partial success, n (%)	78 (50)	14 (52)	63 (49)	1.000
Failure, n (%)	16 (10)	8 (26)	9 (7)	0.003
ICD after ablation, n (%)	136 (86)	29 (97)	107 (84)	0.079
AADs at discharge				
Amiodarone, n (%)	74 (47)	17 (57)	57 (46)	0.310
Sotalol, n (%)	41 (26)	9 (30)	32 (25)	0.644
Mexiletine, n (%)	1 (1)	1 (3)	0 (0)	0.190

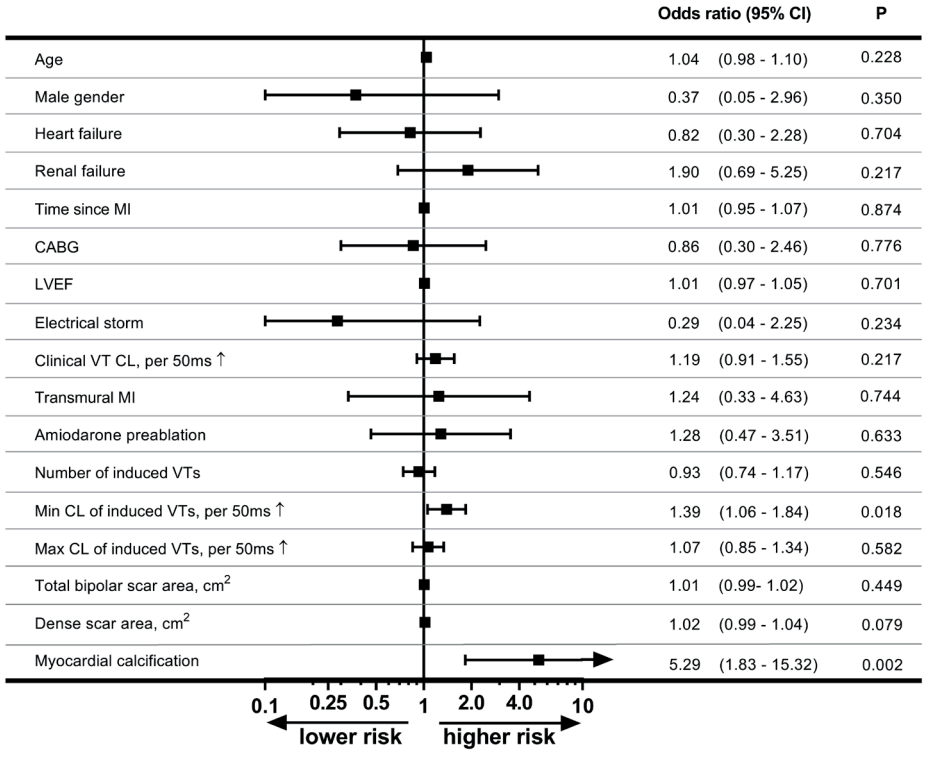
Values are reported as mean ± standard deviation, median and IQR or n (%). RF indicates radiofrequency. Other abbreviations as in table 1.

Acute complete and partial procedural success were achieved in 6 (20%) and 14 (52%) patients with MC (10/14 remained inducible only for fast VT_{VERP}) and in 56 (44%) and 63 (49%) patients without MC (P=0.033 and P=1.000, respectively; 32/63 remained inducible only for fast VT_{VERP}). In 8/30 patients with MC (27%), endocardial ablation failed to eliminate the (presumed-) clinical VT despite extensive activation and entrainment mapping and ablation with high power (50W), long duration applications (120 sec). Critical VT sites were located in areas of calcification in 6 of them (the remaining 2 patients were only inducible for hemodynamically unstable VTs, preventing exact delineation of VT circuits). Of importance, in 5 of these 6 patients, RF applications led to late VT termination but persistent inducibility after extensive ablation, supporting that the critical part of the VT isthmus had been correctly identified but could not be sufficiently abolished. In additional two patients with MC, inducibility at the end of the procedure could not be tested (in one patient ventricular fibrillation was repeatedly induced, in the other patient several cardioversions were necessary to terminate a hemodynamically unstable VT before RF). On the contrary, only 9 patients (7%) without MC remained inducible for the (presumed-) clinical VT after ablation (P=0.003).

Predictors of acute endocardial ablation failure

In univariate logistic regression analysis, presence of MC and induction for slower VTs were associated with acute ablation failure. In multivariate analysis, both (presence of MC: odds ratio 6.898; CI 95% 2.209-21.544; P=0.001 and induction of slower VTs: odds ratio 1.442 per 50ms increase in minimum VTCL; CI 95% 1.084-1.920; P=0.012), remained independently associated with the acute outcome after adjusting for the size of the dense scar area. Of importance, beyond MC, no other pre-procedural factor was found to be associated with acute ablation failure. **Figure 2**

Figure 2. Predictors of acute endocardial ablation failure



CABG indicates coronary artery bypass; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; CL, cycle length; Min, minimum and Max, maximum.

Complications

One patient with prior CABG and recurrent non-tolerated VTs underwent surgical adhesiolysis prior to epicardial ablation after 3 unsuccessful endocardial attempts in another center which was complicated by a bypass occlusion. Despite urgent revascularization, the patient died within 24 hours due to a vasoplegic shock. One patient developed an

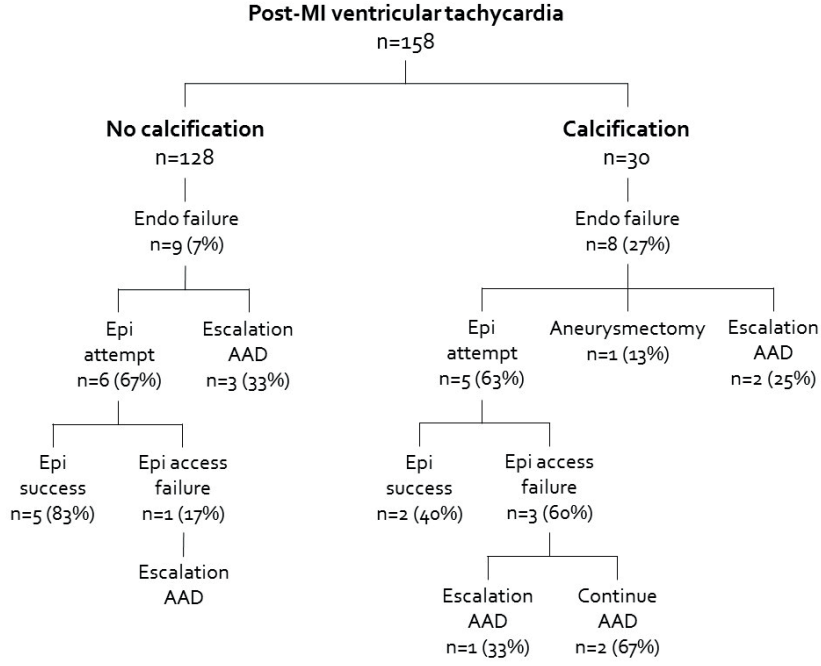
anticipated complete atrioventricular block after ablation of a VT with a basoseptal critical isthmus. Pericardial bleeding with percutaneous drainage occurred in 4 patients.

Management after endocardial ablation

Patients with MC

After endocardial ablation failure, a percutaneous epicardial approach was attempted in 5 of the 8 patients. In 2 of 5 patients, epicardial access and ablation were successful. However, in 3 of the 5, epicardial access was not possible due to the presence of pericardial adhesions. These 3 patients were discharged with AADs (including the combination of amiodarone and mexiletine) (Supplementary Figure 2) One additional patient with an apical aneurysm and a prior valve-sparing replacement of the ascending aorta underwent a surgical aneurysmectomy with concomitant epicardial cryo-ablation. In the remaining 2 patients, AADs were escalated (one refused epicardial ablation, one had prior CABG). After a (partially-) successful endocardial ablation, 22 patients (73%) continued the pre-procedural AADs. (**Figure 3**)

Figure 3. Flow-chart showing the treatment strategy after endocardial ablation failure in patients with and without MC.



Patients without MC

An epicardial ablation attempt was performed in 6 of 9 patients after endocardial ablation failure which was successful in all but one. In this patient, epicardial ablation was prevented by the presence of pericardial adhesions at the area of interest and AADs were escalated. (Figure 2) In the remaining 3 patients (all with prior CABG), AADs were escalated. After a (partially-) successful endocardial ablation, 116 patients (85%) were discharged without modification of the pre-procedural AADs and in 3 patients AAD were initiated for other indications.

At discharge

In total, 136 patients were discharged with an ICD (86%, 97% of patients with MC vs. 84% of patients without; P=0.079) and 115 on AADs (73%, 87% of patients with MC vs. 70% of patients without; P=0.069). Seventy-three patients (43%) were on amiodarone, 41 on sotalol (26%) and one patient on the combination of amiodarone and mexiletine.

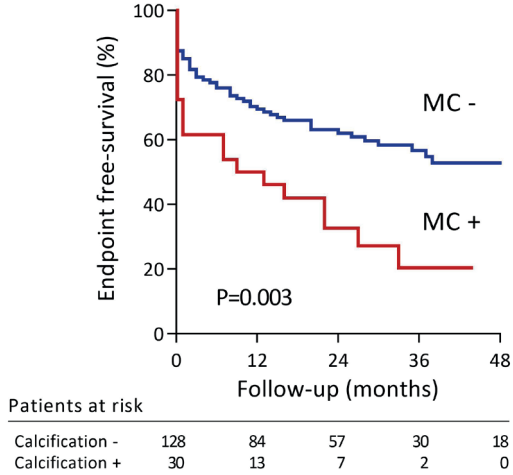
Follow-up after admission for endocardial ablation

In total, 18 patients underwent escalation of therapy after endocardial ablation (6/30 patients (20%) with MC and 12/128 patients (9%) without MC). In 10 patients, AADs were escalated, 7 patients underwent successful epicardial ablation and in one patient, surgical removal of the VT substrate was performed. One patient with MC was lost to follow-up. After a median of 31 months (20-47), 61 patients (39%) had VT recurrence (13 patients with MC [43%] and 48 patients without [38%]; P=0.529, 7/17 patients [41%] with endocardial failure vs. 52/138 [38%] with endocardial success; P=0.779). Forty-seven patients died (30%; 8 patients with MC [27%] and 39 patients without [30%]; P=0.826), 2 patients underwent left ventricular assist device implantation and one patient was transplanted.

After endocardial ablation, patients with MC showed a lower 2-year survival free from the combined endpoint of VT recurrence or need of therapy escalation to control the clinical VT than patients without MC (26% [95% CI 8-44] vs. 59% [95% CI 50-68] in patients without MC; P=0.003). (**Figure 4**)

On multivariate Cox-regression analysis, presence of MC (HR 1.86; CI 95% 1.11-3.10; P=0.018), a lower LV ejection fraction (HR 1.03 per 1% decrease; CI 95% 1.01-1.05; P=0.008) and a higher number of induced VTs (HR 1.12; CI 95% 1.03-1.22; P=0.008) were independently associated with a higher incidence of the composite endpoint of VT recurrence or need of therapy escalation to control the clinical VT. (**Table 3**)

Figure 4. Combined endpoint (VT recurrence or therapy escalation) free survival in patient with vs. without MC.



MC indicates myocardial calcification. Therapy escalation included escalation of AADs, epicardial ablation or surgical ablation.

Table 3. Cox regression analysis for predictors of the combined endpoint of VT recurrence or escalation of therapy.

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Age (per year)	0.99 (0.97-1.01)	0.389		
LVEF (per 1% decrease)	1.04 (1.01-1.05)	0.001	1.03 (1.01-1.05)	0.008
Myocardial calcification	2.04 (1.23-3.38)	0.006	1.86 (1.11-3.10)	0.018
Dense scar area (per $1cm^{2)}$	1.01 (1.00-1.02)	0.003		
Number of induced VTs	1.16 (1.07-1.26)	0.001	1.12 (1.03-1.22)	0.008

Escalation of therapy includes escalation of AADs, epicardial ablation or surgical ablation. Abbreviations as in tables 1 and 2.

Impact of infarct transmurality on acute and long-term outcome after endocardial ablation

A transmural scar was detected in 32 of 36 patients (89%) in whom a CE-MRI was available for analysis and in 89 of 116 patients (77%) in whom scar transmurality was assessed either on CT or on echocardiogram. There were no differences between patients with or without transmural scar nor in the acute neither in the long-term outcome after endocardial ablation (**Table 4**). In 6 patients (4%), no imaging modality of appropriate quality was available for the assessment of scar transmurality.

Table 4. Acute and long-term outcome after endocardial ablation in patients with vs. without transmural scar

	Transmural scar (n=119)	Non-transmural scar (n=31)	*P-value*
Acute outcome (n=150)			
Complete success, n (%)	45 (38)	14 (45)	0.537
Partial success, n (%)	60 (50)	14 (45)	0.688
Failure, n (%)	14 (12)	3 (10)	1.000
24-month endpoint free survival*	52% (95%CI 43-61)	52% (95%CI 33-71)	0.560

*Endpoint includes VT recurrence or escalation of therapy

DISCUSSION

This study systematically evaluated the presence of MC in a cohort of patients with post-MI VT and investigated the impact of MC on acute outcome and long-term results of endocardial ablation. The prevalence of MC assessed on easily available pre-procedural coronary angiograms was 19%. Of note, endocardial ablation failed to eliminate the clinical VT that motivated the procedure in one third of the patients with MC. Subsequently, percutaneous epicardial access was not possible in two third of these patients because of the presence of unexpected pericardial adhesions or due to prior cardiac surgery. At 2-year follow-up, only 26% of patients with MC were free of VT recurrence in the absence of therapy escalation (including percutaneous or epicardial ablation and/or escalation of AADs) compared to 59% of patients without MC. Presence of MC was associated with a lower VT-free survival in the absence of therapy escalation independently of LV ejection fraction, the size of the dense scar area and the number of induced VTs during the procedure.

Post-infarction MC: pathophysiology, prevalence and diagnosis

MI leading to myocyte necrosis is the most common cause of dystrophic MC, this is, calcification occurring in the absence of elevated calcium levels.(10) The process of dystrophic calcification consists ultimately in the formation of calcium phosphate microcrystals that can accumulate both intra and extracellularly.(14) Autopsy studies reporting on the prevalence of MC in patients with prior MI are lacking. However, MC defined as the presence of thin and curvilinear radiopaque areas located at the periphery of the infarcted area was observed in radiographic examinations of up to 8% of patients with MIs older than 6 years.(11) In our study, we detected MC in 19% of patients with post-MI VT. This almost 3-fold higher prevalence of MC than previously reported might be at least partially explained by the different imaging technique that we used for assessment. Fluoroscopic evaluation of the thorax allows for identifying the synchronous motion of the calcium with the beating heart. In addition, the use of sev-

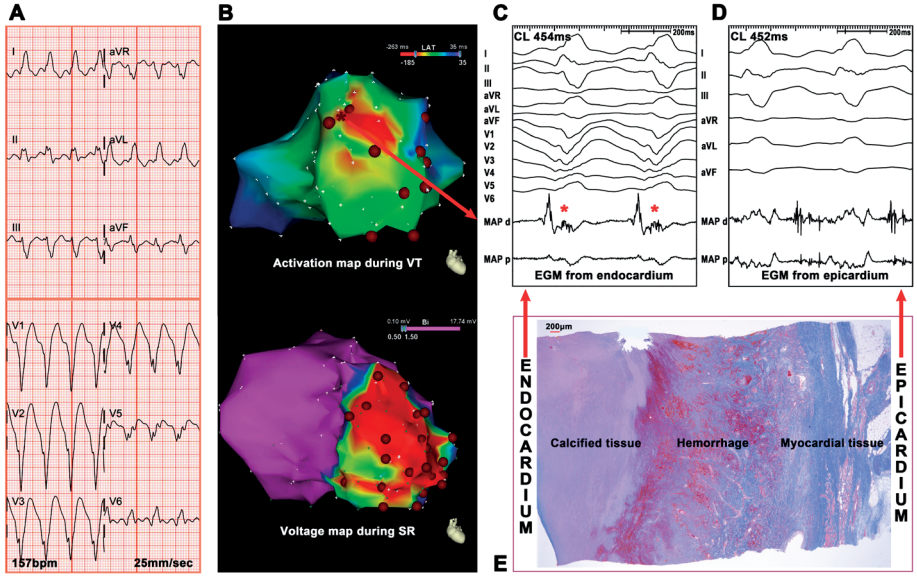
eral complementary fluoroscopic projections, may bring MCs to a heart border-forming location, both improving the sensitivity to detect MC.(12) Whether the selected group of patients with post-MI VT present more often MC than the general post-MI population remains unknown. Recently, a much higher prevalence of 70% of very small MC has been reported from high resolution CT scans. The median volume was only 0.89ml, which may be difficult to detect by standard angiograms and CT scans.(15) ECG-gated cardiac CT is the gold standard for diagnosis, localization and characterization of calcifications in the heart.(16) However, in our study, full agreement on detection/exclusion of MC was found in 18 patients in whom CT *and* cine-fluoroscopy recordings were available for evaluation. In line with prior descriptions, MC was more often observed in patients with anterior MIs. The pathophysiological reason for this location predilection is, however, unknown. Of note, the age of the infarction was not different among patients with and without MC, questioning the assumption that development of MC is a progressive, time-dependent process.

Post-infarction MC: impact on VT catheter ablation

Acute ablation failure, defined as persistent inducibility of the clinically documented arrhythmia at the end of the procedure, has been reported to occur in ≈10% of patients with post-MI VT.(1,17) Of importance, acute ablation failure has been associated not only with high VT recurrence rates of up to 80% at medium-term follow-up but also with occurrence of sudden cardiac death despite the presence of an ICD in patients referred for ablation in the context of an electrical storm.(18) Therefore, current expert consensus on VT ablation recommends elimination of the clinical VT as the minimum endpoint of scar-related VT ablation.(19) One of the potential causes of endocardial ablation failure is the persistence of an epicardial substrate for VT that cannot be eliminated from the endocardium. However, only 14 of 43 (33%) ischemic patients presenting with an electrical storm who underwent systematic epicardial mapping had any epicardial low voltage or abnormal EGM as target for ablation.(3) In addition, considering 1) the association of very low voltage areas and wall thinning, 2) the colocalization of VT related sites and LAVAs with areas of wall thinning (20) and 3) the expected lesion depth with high power (50W) long duration (120s) applications, endocardial ablation failure for post-MI VT substrates remains poorly understood. Even if a subepicardial substrate is critical for VT, it should be possible to abolish the substrate from the endocardium provided that no insulating factors prevent transmurality. Indeed, in up to 84% of patients with post-MI VT undergoing endo-epicardial mapping, at least part of the epicardial LAVAs located in areas of wall thinning as detected by cardiac CT could be abolished by endocardial ablation.(4) In our study, almost one third of the patients with MC compared to less than 10% of patients without MC remained inducible for the clinical VT after endocardial ablation and only 26% of the patients with MC remained free from VT without therapy

escalation on long term follow-up. We speculate that during endocardial ablation, the lower thermal conductivity of calcified myocardium (0.32±0.03 W/m/°C, assuming it to be similar to the bone cortex) compared to the non-calcified myocardium (0.49±0.04 W/m/°C) may protect a surviving layer of epicardium from tissue heating and subsequently, from thermal injury despite the presence of wall thinning.(21) See **Figure 5,** panel E. Of note, percutaneous epicardial access failed in 3 of the 5 patients (60%) with MC in whom it was attempted due to the presence of pericardial adhesions, which is a much higher rate of failure than previously reported in patients with no prior pericarditis or cardiac surgery (2%).(22) Perhaps an inflammatory reaction at the time of the acute infarction may facilitate both formation of MC and pericardial adhesions. Taking into account the potential serious complications associated with epicardial access, mapping and ablation, it is important to identify more specifically post-MI patients who may benefit from a primary endo-epicardial ablation approach. . Although based on our

Figure 5



Representative example of a 53 year-old patient with an anterior calcified MI and prior valve-sparing replacement of the ascending aorta who was admitted with incessant VT. Panel A: the clinical VT is shown (157bpm, left bundle branch block morphology, V6 transition, left superior axis). Panel B, above: LV endocardial activation map during VT in antero-posterior view. No mid-diastolic activity was identified at the endocardium. An entrance site was found at the septal border of the scar (see correspondent electrogram in Panel C). Ablation at this site did not terminate the VT. Panel B, below: LV endocardial bipolar voltage map during sinus rhythm in antero-posterior view. A large part of the scar was unexcitable and despite RF with high power, the VT remained inducible The patient underwent subsequently intraoperative mapping prior to aneurysmectomy. At the epicardial side of the aneurysm, continuous diastolic activity was recorded during VT (see correspondent electrogram in Panel D). Ablation at this site terminated the VT within 5 seconds. In Panel E, a transmural biopsy taken from the site of ablation success is shown. Note the calcification at the endocardial side protecting a layer of viable myocardium at the epicardial side. VT indicates ventricular tachycardia; SR, sinus rhythm and EGM, electrogram.

results, pre-procedural identification of MC helps to non-invasively identify patients with a high chance of endocardial ablation failure, due to the high rate of unsuccessful percutaneous epicardial access, other therapies (including surgery) might be needed in these patients for arrhythmia control.

It has been reported that patients with transmural infarctions defined on routine pre-procedural imaging had higher VT recurrence rates after endocardial ablation and a high prevalence of epicardial substrate for VT, that, when targeted, led to improvement of ablation outcome.(8) Following the same criteria for definition on pre-procedural imaging, patients with transmural infarctions in our cohort had neither higher rates of endocardial ablation failure nor higher VT recurrence rates without escalation of therapy than patients with no transmural infarctions. This difference might be partially explained by the lower prevalence of non-transmural infarctions in our cohort (19% compared to 38%), if the previously according criteria are applied. However, the prevalence of MC in the previous cohort has not been reported and its potential impact on endocardial ablation is unknown. Additionally, animal and human studies have shown that BV <0.5mV are usually recorded at sites with high scar transmurality, which, if localized, may not be detected by all image modalities.(23,24)

CONCLUSIONS

Myocardial calcification was present in 19% of post-MI patients referred for ablation of recurrent sustained VT. The presence of myocardial calcification was associated with high rates of endocardial ablation failure and VT recurrence if no other therapies were applied for arrhythmia control. MC may prevent deep and transmural lesions as a potential explanation for the observed association.

Limitations

This study included a relatively small number of patients and has the intrinsic limitations of an observational retrospective analysis. Our results should therefore be confirmed in a larger prospective cohort. Presence of MC was analyzed on fluoroscopy and not systematically on cardiac CT. Therefore, the prevalence of MC (especially of small calcifications) might have been underestimated. All procedures were performed by an experienced operator in a high volume centre which might limit the generalization of the ablation results. The anti-arrhythmic regimen after ablation was left at the discretion of the referral physician and this might have influenced the outcome of some patients. Currently, discontinuation of AADs is encouraged in patients who are rendered not inducible by ablation or remain inducible for only fast VT_{VERP}.

REFERENCES

1. Marchlinski FE, Haffajee CI, Beshai JF, Dickfeld TM, Gonzalez MD, Hsia HH et al. Long-Term Success of Irrigated Radiofrequency Catheter Ablation of Sustained Ventricular Tachycardia: Post-Approval THERMOCOOL VT Trial. J Am Coll Cardiol 2016;67:674-683.
2. Sarkozy A, Tokuda M, Tedrow UB, Sieria J, Michaud GF, Couper GS et al. Epicardial ablation of ventricular tachycardia in ischemic heart disease. Circ Arrhythm Electrophysiol 2013;6:1115-22.
3. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C et al. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. Journal of the American College of Cardiology 2012;60:132-41.
4. Komatsu Y, Daly M, Sacher F, Cochet H, Denis A, Derval N et al. Endocardial ablation to eliminate epicardial arrhythmia substrate in scar-related ventricular tachycardia. J Am Coll Cardiol 2014;63:1416-26.
5. Sacher F, Roberts-Thomson K, Maury P, Tedrow U, Nault I, Steven D et al. Epicardial ventricular tachycardia ablation a multicenter safety study. J Am Coll Cardiol 2010;55:2366-72.
6. Della Bella P, Brugada J, Zeppenfeld K, Merino J, Neuzil P, Maury P et al. Epicardial ablation for ventricular tachycardia: a European multicenter study. Circ Arrhythm Electrophysiol 2011;4:653-9.
7. Arenal A, Perez-David E, Avila P, Fernández-Portales J, Crisóstomo V, Báez C et al. Noninvasive identification of epicardial ventricular tachycardia substrate by magnetic resonance-based signal intensity mapping. Heart Rhythm 2014;11:1456-64.
8. Acosta J, Fernandez-Armenta J, Penela D, Andreu D, Borras R, Vassanelli F et al. Infarct transmurality as a criterion for first-line endo-epicardial substrate-guided ventricular tachycardia ablation in ischemic cardiomyopathy. Heart Rhythm 2016;13:85-95.
9. Soto-Iglesias D, Acosta J, Penela D, Fernández-Armenta J, Cabrera M, Martínez M et al. Image-based criteria to identify the presence of epicardial arrhythmogenic substrate in patients with transmural myocardial infarction. Heart Rhythm 2018;15:814-821.
10. Nance JW, Jr., Crane GM, Halushka MK, Fishman EK, Zimmerman SL. Myocardial calcifications: pathophysiology, etiologies, differential diagnoses, and imaging findings. J Cardiovasc Comput Tomogr 2015;9:58-67.
11. Freundlich IM, Lind TA. Calcification of the heart and great vessels. CRC Crit Rev Clin Radiol Nucl Med 1975;6:171-216.
12. Gowda RM, Boxt LM. Calcifications of the heart. Radiol Clin North Am 2004;42:603-17, vi-vii.
13. Watanabe M, de Riva M, Piers SRD, Dekkers OM, Ebert M, Venlet J et al. Fast nonclinical ventricular tachycardia inducible after ablation in patients with structural heart disease: Definition and clinical implications. Heart Rhythm 2018;15:668-676.
14. Cotran Ra. Pathologic basis of disease, 2015.
15. Alyesh DM, Siontis KC, Sharaf Dabbagh G, Yokokawa M, Njeim M, Patel S et al. Postinfarction Myocardial Calcifications on Cardiac Computed Tomography. Circulation Arrhythmia and electrophysiology 2019;12:e007023.
16. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P et al. CCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear

Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology 2010;56:1864-94.

17. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation 2008;118:2773-82.
18. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G et al. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. Circulation 2008;117:462-9.
19. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart rhythm 2009;6:886-933.
20. Komatsu Y, Cochet H, Jadidi A, Sacher F, Shah A, Derval N et al. Regional myocardial wall thinning at multidetector computed tomography correlates to arrhythmogenic substrate in postinfarction ventricular tachycardia: assessment of structural and electrical substrate. Circ Arrhythm Electrophysiol 2013;6:342-50.
21. PA H, F DG, C B et al. IT'IS database for thermal and electromagnetic parameters of biological tissues. Version 4.0.
22. Li A, Buch E, Boyle NG, Shivkumar K, Bradfield JS. Incidence and significance of adhesions encountered during epicardial mapping and ablation of ventricular tachycardia in patients with no history of prior cardiac surgery or pericarditis. Heart Rhythm 2018;15:65-74.
23. Wijnmaalen AP, van der Geest RJ, van Huls van Taxis, Siebelink HM, Kroft LJ, Bax JJ CF et al. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. Eur Heart J 2011;32:104-14.
24. Reddy VY, Malchano ZJ, Holmvang G, Reddy VY, Malchano ZJ, Holmvang G et al. Integration of cardiac magnetic resonance imaging with three-dimensional electroanatomic mapping to guide left ventricular catheter manipulation: feasibility in a porcine model of healed myocardial infarction. J Am Coll Cardiol 2004;44:2202-13.

SUPPLEMENTARY METHODS

Assessment of infarct transmurality

Contrast enhanced magnetic resonance imaging

With the patient in the supine position, CE-MRI was performed on a 1.5-T Gyroscan ACS-NT/Intera or on a 3.0-T Ingenia MR system (Philips Medical Systems, Best, the Netherlands). Images were obtained during breath-holds of approximately 15 seconds using vector electrocardiographic gating. A standardized protocol was followed including cine sequences in long (2- and 4-chamber views) and short axis covering the entire LV. CE images were acquired 15 min after injection of a gadolinium bolus. The heart was either imaged during one breath-hold with 20 to 24 imaging levels (depending on heart size) in the short axis view, or with 20 to 26 imaging levels in the short axis view in one or two three-dimensional stacks, each stack acquired within one breathhold. All CE images were analysed by an experienced cardiologist. A scar was defined as transmural if the hyperenhanced area extended ≥75% in the radial direction between the endocardial and epicardial borders. A non-transmural scar was defined as the presence of hyperenhancement extending between 25 and 75% of the wall thickness.(23)

Echocardiogram

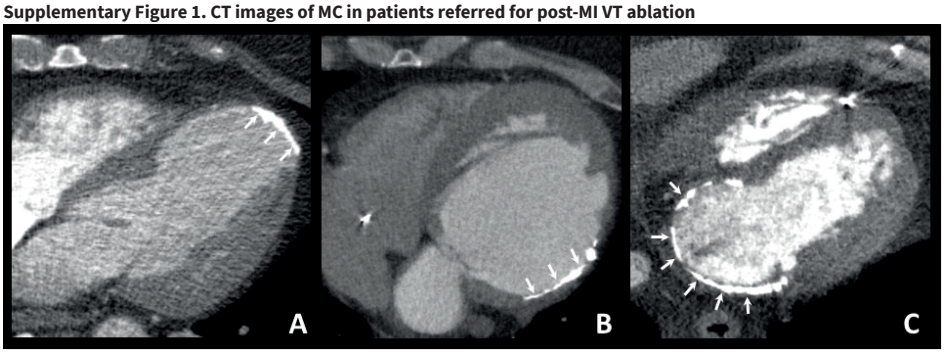
Prior to the procedure, all patients underwent a two-dimensional and color Doppler transthoracic echocardiogram. Images were obtained at rest from the standard parasternal (long- and short-axis), apical (2- and 4-chamber) and subcostal views. Images were analysed offline using EchoPAC (version BT13, GE Medical Systems, Horten, Norway). LV end-diastolic and end-systolic volumes were measured in the apical 2- and 4-chamber views and LVEF was calculated according to the biplane Simpson's method. For the assessment of regional LV function, the LV was divided into 16 segments and according to endocardial motion and systolic wall thickening, each segment was scored as normal (=1), hypokinetic (=2), akinetic (=3) or dyskinetic (=4). As previously reported, it was considered that an abnormal contracting LV segment (score 2-4) had lost the majority of its viable myocardium and therefore, the scar was classified as transmural when 1) the end-diastolic wall thickness was reduced ≤6mm and 2) an abnormal increase in acoustic reflectance was observed.(25,26)

Computed tomography

Contrast ECG-gated cardiac CT was performed on a 64-detector CT scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) or on a 320-detector CT scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan). One hour before the scan, a single dose of metoprolol (25 to 150mg) was administered to patients with a heart rate ≥60 bpm if no contraindications were present. First, a low-dose non-contrast enhanced

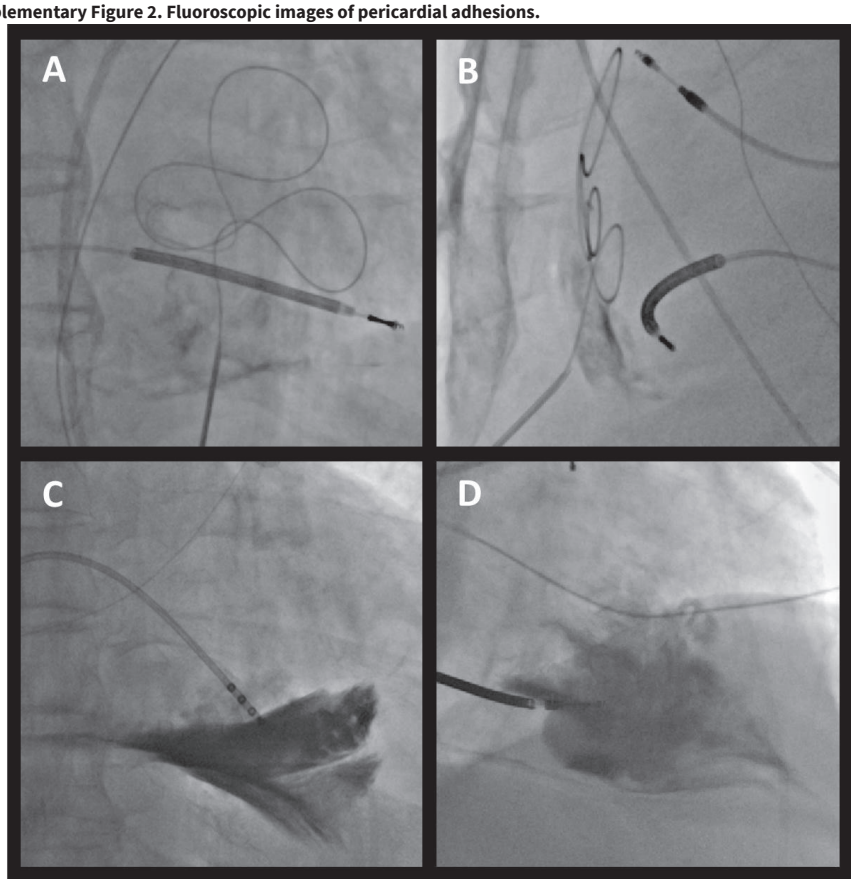
scan of the heart was performed with slice thickness of 3mm. Subsequently, a bolus of a non-ionic contrast (Iomeron 400; Bracco, Milan, Italy; 60-110ml, flow rate 5-6ml/s) was administered. Image acquisition was completed within a single breath hold of 10 seconds with retrospective (64-detector scanner) or prospective (320-detector scanner) ECG gating. The presence of myocardial calcification was visually assessed in both non-contrast and contrast images. In addition, wall thickness was measured between the endocardial and epicardial borders. A scar was classified as transmural when the wall thickness was ≤5mm. (20)

Supplementary Figure 1. CT images of MC in patients referred for post-MI VT ablation



In panels A, B and C, an anterior, a lateral and an infero-posterior area of MC in a long-axis view are respectively shown. MC are indicated by white arrows.

Supplementary Figure 2. Fluoroscopic images of pericardial adhesions.



Panels A and B: antero-posterior and lateral views showing the guide wire used to gain epicardial access that buckles when it cannot be advanced freely in the epicardial space. Panels C and D: RAO images showing contrast retained within the pericardial adhesions.

SUPPLEMENTARY REFERENCES

25. Cwajg JM, Cwajg E, Nagueh SF, He ZX, Qureshi U, Olmos LI et al. End-diastolic wall thickness as a predictor of recovery of function in myocardial hibernation: relation to rest-redistribution T1-201 tomography and dobutamine stress echocardiography. Journal of the American College of Cardiology 2000;35:1152-61.
26. Faletra F, Crivellaro W, Pirelli S Parodi O, De Chiara F, Cipriani M et al. Value of transthoracic two-dimensional echocardiography in predicting viability in patients with healed Q-wave anterior wall myocardial infarction. The American journal of cardiology 1995;76:1002-6.

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Summary and future perspectives
Samenvatting en Toekomstigeperspectief
Acknowledgements
List of publications
Curriculum vitae

SUMMARY AND FUTURE PERSPECTIVES

The aim of this thesis was to provide new insights on catheter ablation of VT in patients with prior MI. Improved understanding of the VT substrate in different types of MI, and in particular, in contemporary non-transmural reperfused infarctions, a critical re-assessment of the value of non-inducibility as ablation endpoint and the development of new physiologically meaningful endpoints for substrate modification will hopefully contribute to optimize procedural outcomes in this patient population. In addition, recognition of the limitations of the technique will aid in patient selection and will help to consider alternative treatment options in some individuals.

In **chapter 2**, the value and limitations of the VT 12-lead electrocardiogram (ECG) to predict the VT site of origin in patients with structural heart disease (SHD) is reviewed. Catheter ablation is increasingly employed for the treatment of VT in SHD.[1,2] With more detailed knowledge about the potential anatomical structures and substrates involved in VT, not only the LV and right ventricular endocardium but also more complex structures like the aortic root, the cardiac veins and the epicardium have become areas of interest for ablation.[2–4] The clinically documented VT 12-lead ECG can help to predict the VT site of origin and, for this reason, it is frequently used to select the ablation approach, to estimate the probability of ablation success and to evaluate the risks associated with the procedure. Several algorithms have been proposed for identifying the VT site of origin based on the analysis of the VT 12-lead ECG.[5–8] These algorithms, however, have applied different definitions for VT site of origin, including VT exit and isthmus sites, have been tested in different patient populations (i.e. ischemic cardiomyopathy, non-ischemic cardiomyopathy) and have been validated with different mapping techniques including activation and entrainment mapping but also pace-mapping. Last, none of the algorithms have integrated imaging or mapping-derived information regarding the scar extension and distribution which may likely increase the ECG accuracy to precisely predict the VT origin. A systematic reevaluation of the value of the VT ECG for predicting the VT origin in the context of 3D electroanatomical mapping and scar imaging is needed.

Part II of this thesis focuses on the evaluation of ablation endpoints for post-MI VT. The value of non-inducibility of VT after ablation in patients with ischemic heart disease is re-assessed and the impact on outcome of a new substrate mapping and ablation strategy – functional substrate mapping – is evaluated. Finally, the prevalence and the impact of myocardial calcification (MC) on the efficacy of endocardial ablation is studied.

In **chapter 3**, the impact of individual patient characteristics, and in particular, of the LV function on the predictive value of non-inducibility after ablation for VT recurrence

and cardiac mortality is assessed. Out of 92 post-MI patients undergoing ablation for monomorphic sustained VT, 59 (65%) had a LV ejection fraction (LVEF) >30% and 32 (35%) had a LVEF ≤30%. After ablation, no differences in the rate of non-inducibility was observed among patients with LVEF below and above 30%. However, at one year follow-up, patients with LVEF ≤30% had a poorer prognosis, with a survival rate free of VT of only 42% (compared to 80% in patients with LVEF>30%). Of importance, non-inducibility was a good predictor for VT recurrence and cardiac mortality in patients with LVEF>30% but not in patients with LVEF≤30, which is in line with the results of a previous randomized trial.[9] Only 10% of patients with a LVEF>30% who were rendered non-inducible by ablation experienced VT recurrence or cardiac mortality one year after the procedure, compared to 65% of those in whom non-inducibility was not achieved. The worse outcome of patients who remained inducible for VT was mainly due to VT recurrence, highlighting the need for additional ablation endpoints based on substrate mapping and the development of new ablation tools to perform deeper and long-lasting lesions in these patients. On the contrary, patients with severely reduced LV function had a bad prognosis independently of the acute procedural result in terms of inducibility, which was mainly driven by heart-failure related death. This finding suggests that in this group of patients, a more conservative approach, prioritizing ablation of the clinically documented VT for reducing patient symptoms might be preferrable. After our study, a retrospective analysis of 1064 patients with post-MI VT showed that non-inducibility after ablation was associated with lower mortality on follow-up.[10] However, in this study, the LV function was not included as one of the factors related to outcome in multivariate analysis. Prospective, longitudinal studies with the prespecified endpoint of non-inducibility are warranted to confirm our results.

In patients with structural heart disease, the prognostic significance of induction of fast non-clinical VTs after ablation remains unclear. Accordingly, many electrophysiology laboratories use non-inducibility of VTs with similar or longer cycle length (CL) than the clinically documented VT as one ablation endpoint but accept persistent inducibility of faster VTs at the end of the procedure, strategy that was supported by the HRS/EHRA expert consensus on VT ablation from 2009.[11] However, a standard widely accepted CL to define fast VT is lacking, which justifies, at least in part, the similar reported long-term outcome after ablation despite the very variable reported rates of acute non-inducibility among studies[1,2,12–14]. In **chapter 4,** we propose a new patient-specific definition for fast VT based on the individual ventricular refractory period (fVT_{VRP}) and assess the prognostic significance of persistent inducibility after ablation of fVT_{VRP} for VT recurrence. Seventy patients with SHD (45 post-MI, 65%) who remained inducible only for non-clinical VTs after ablation were included. A VT was defined as a fast VT (fVT_{VRP}) when the VTCL was ≤VRP determined with a basic drive CL of 400ms. The hypothesis behind this

proposed definition was that the possible shortest CL of a reentrant VT is determined by the VRP and the myocardial conduction velocity. Therefore, theoretically, no reentrant VT could have a shorter CL than the VRP for a given situation. To account for changes in the VRP derived from, among others, changes in the autonomic balance, we accepted a difference of maximum 30ms for the definition of fVT_{VRP}. After ablation, 30 (43%) patients remained inducible exclusively for fVT_{VRP} and 40 (57%) patients for any slower VT (with or without concomitant fVT_{VRP}). Induction of fVT_{VRP} often required the introduction of short-coupled triple extra-stimuli, which due to the heterogeneous application of stimulation protocols among EP laboratories, may justify the wide differences in the reported post-procedural non-inducibility. After a median of 2,5 years follow-up, patients with only fVT_{VRP} had a higher rate of survival free of VT (74% vs. 63% for patients with any slower VT remaining). Although patients with slower VTs seemed to represent a more diseased population (with a lower LVEF and more often impaired renal function among other differences), inducibility of fVT_{VRP} remained associated with lower VT recurrence also after adjusting for patient and procedural characteristics. In addition, fVT_{VRP} occurred rarely spontaneously. In fact, no documented VT before the procedure fulfilled the criteria for a fVT_{VRP} and only 4 (6%) patients presented with a fVT_{VRP} during follow-up after ablation. All these findings support that induction of fVT_{VRP} after ablation may not be prognostically relevant and question the need of targeting these VTs by ablation. However, as stated before, prospective studies with pre-specified endpoints regarding VT inducibility are needed to confirm our hypothesis.

Substrate-based approaches have been developed to allow targeting unstable and non-inducible VTs, circumstances that affect approximately 70% and 10% of post-MI patients currently referred for ablation.[1,12,15] In addition, substrate ablation has been shown to be superior to ablation limited to stable VTs in ischemic patients and has therefore become regular practice in the majority of the EP laboratories.[16] These ablation techniques rely on two pillars: first, on the delineation of the scar area by means of bipolar voltage mapping and second, on the identification of electrograms consistent with slow conduction as surrogates of VT isthmuses. In general, a standard cut-off value of 1.5mV is used to differentiate scar from normal tissue.[17] However, mapping accuracy to detect scar using this single cut-off can be limited by far-field contamination of the local electrical activity. This phenomenon is especially relevant in contemporary patients with small non-transmural infarctions after acute reperfusion of the infarct-related artery.[18] In these patients, large far-field signals arising from a surviving subepicardial myocardial layer or from the surrounding healthy myocardium can obscure part of the arrhythmogenic substrate.[19] In **chapter 5**, we study 60 consecutive patients referred for ablation of post-MI VT. In these patients, we systematically analyzed all electrograms in the scar area with RV extra-stimulation. The area of interest for pacing was defined based on the presumed

infarct area derived from imaging (echocardiogram, cardiac magnetic resonance when available) and the distribution of the MI-related artery. Near-field electrograms exhibiting local delay >10ms or block during RV extra-stimulation were categorized as evoked delayed potentials (functional VT substrate) and targeted for ablation. In 37 (62%) patients, evoked delayed potentials outside the area with voltage <1.5mV were revealed during RV pacing (hereafter refer as "hidden substrate group"). These patients had better LV function and smaller less dense scars than patients in whom all ablation targets were contained within the low voltage area (hereafter refer as "overt substrate group"). During a follow-up of 1.5 years, 22% of the patients had VT recurrence. Not surprisingly, patients with hidden functional substrate had a lower rate of VT recurrence than patients with overt substrate. However, of importance, when compared with a historical cohort of patients matched for LVEF and electroanatomical scar area, patients in whom the hidden functional substrate was ablated had a higher survival free of VT at 1 year follow-up (89% vs. 73%). This findings support the use of pacing maneuvers in addition to voltage mapping to detect the entire arrhythmogenic substrate in patients with post-MI scars. Simultaneously with our work, two other small retrospective studies demonstrated the value of RV extra-stimulation for unmasking the VT substrate in patients with prior MI[20] and in a heterogenous group of patients with scar-related VT[21,22]. In a group of post-MI patients in whom a CE-MRI was available for integration during electroanatomical mapping, we recently showed that a bipolar voltage cut-off value of 3mV better distinguish between scar and normal myocardium if the LVEF was preserved.[23] Therefore, we have modified our protocol and we now limit the are of interest for RV extrastimulation to that with a BV <3mV. Currently we are conducting a multicentre international registry including patients with post-MI VT who underwent identification and ablation of the functional substrate, which will hopefully allow us to confirm our initial results in a larger and prospective patient population.

In **chapter 6**, the prevalence of myocardial calcification (MC) and its impact on the acute outcome and long-term results of endocardial ablation in patients with post-MI VT is assessed. In 30 (19%) out of 158 consecutive patients with prior MI undergoing VT ablation, MC was detected on fluoroscopy during pre-procedural coronary angiograms and/or during the ablation procedure. Patients with MC were younger, had typically anterior infarctions and larger dense scar areas compared to patients without MC. Of importance, and despite extensive ablation with high-power long-duration applications, endocardial ablation acutely failed to eliminate the clinical VT that motivated the procedure in one third of the patients with MC but only in 7% of patients without MC. After endocardial ablation failure, a percutaneous epicardial ablation approach was attempted in 5 of 8 patients. However, in 3 of 5, epicardial access was not possible due to the presence of pericardial adhesions. During a follow-up of 2 years, patients with MC who did not

undergo any escalation of therapy after endocardial ablation, including escalation of AADs, epicardial or surgical ablation, had a poor prognosis with a VT free-survival of only 26%. Our observation support that in patients with old infarctions, MC may act as insulator preventing thermal injury of a subepicardial myocardial layer involved in VT during endocardial ablation. Additional therapies including escalation of AADs and epicardial ablation, but also surgical ablation taking into account the high prevalence of pericardial adhesions observed, might be necessary for obtaining arrhythmia control in these patients. Our study concerned a relatively small number of patients and therefore, it may be considered as a hypothesis-generating study that should be confirmed in a larger prospective cohort.

REFERENCES

1. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H, Multictr Thermocool VTAT. Irrigated Radiofrequency Catheter Ablation Guided by Electroanatomic Mapping for Recurrent Ventricular Tachycardia After Myocardial Infarction The Multicenter Thermocool Ventricular Tachycardia Ablation Trial. Circulation. 2008. p. 2773–2782.
2. Piers SRD, Leong DP, Taxis CFB van H van, Tayyebi M, Trines SA, Pijnappels DA, Delgado V, Schalij MJ, Zeppenfeld K. Outcome of Ventricular Tachycardia Ablation in Patients With Nonischemic Cardiomyopathy: The Impact of Noninducibility. *Circ Arrhythm Electrophysiol* 2013;**6**:513–521.
3. Piers SRD, Tao Q, Huls van Taxis CFB van, Schalij MJ, Geest RJ van der, Zeppenfeld K. Contrast-Enhanced MRI–Derived Scar Patterns and Associated Ventricular Tachycardias in Nonischemic Cardiomyopathy: Implications for the Ablation Strategy. *Circ Arrhythm Electrophysiol* 2013;**6**:875–883.
4. Sarkozy A, Tokuda M, Tedrow UB, Sieria J, Michaud GF, Couper GS, John R, Stevenson WG. Epicardial Ablation of Ventricular Tachycardia in Ischemic Heart Disease. *Circ Arrhythm Electrophysiol* 2013;**6**:1115–1122.
5. Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. *Circulation* 1988;**77**:759–766.
6. Kuchar DL, Ruskin JN, Garan H. Electrocardiographic localization of the site of origin of ventricular tachycardia in patients with prior myocardial infarction. *J Am Coll Cardiol* 1989;**13**:893–900.
7. Vallès E, Bazan V, Marchlinski FE. ECG Criteria to Identify Epicardial Ventricular Tachycardia in Nonischemic Cardiomyopathy. *Circ Arrhythm Electrophysiol* 2010;**3**:63–71.
8. Berruezo A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic Recognition of the Epicardial Origin of Ventricular Tachycardias. *Circulation* 2004;**109**:1842–1847.
9. Kuck K-H, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, Pitschner H-F, Kautzner J, Schumacher B, Hansen PS, Grp VS. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010. p. 31–40.
10. Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P, Vergara P, Hindricks G, Arya A, Zeppenfeld K, Riva Silva M de, Daoud EG, Kumar S, Kuck K-H, Tilz R, Mathew S, Ghanbari H, Latchamsetty R, Morady F, Bogun FM. Predictive Value of Programmed Ventricular Stimulation After Catheter Ablation of Post-Infarction Ventricular Tachycardia. *J Am Coll Cardiol* 2015;**65**:1954–1959.
11. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jaïs P, Josephson ME, Kautzner J, Kay GN, Kuck K-H, Lerman BB, Marchlinski F, Reddy V, Schalij M-J, Schilling R, Soejima K, Wilber D. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias. *Heart Rhythm* 2009;**6**:886–933.
12. Riva M de, Piers SRD, Kapel GFL, Watanabe M, Venlet J, Trines SA, Schalij MJ, Zeppenfeld K. Reassessing Noninducibility as Ablation Endpoint of Post-Infarction Ventricular Tachycardia: The Impact of Left Ventricular Function. *Circ Arrhythm Electrophysiol* 2015;**8**:853–862.
13. Jaïs P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haïssaguerre M. Elimination of Local Abnormal Ventricular Activities: A New End Point for Substrate

Modification in Patients With Scar-Related Ventricular Tachycardia. *Circulation* 2012;**125**:2184–2196.

14. Dinov B, Fiedler L, Schoenbauer R, Bollmann A, Rolf S, Piorkowski C, Hindricks G, Arya A. Outcomes in Catheter Ablation of Ventricular Tachycardia in Dilated Nonischemic Cardiomyopathy Compared With Ischemic Cardiomyopathy Results From the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation. 2014. p. 728–736.
15. Marchlinski FE, Haffajee CI, Beshai JF, Dickfeld T-ML, Gonzalez MD, Hsia HH, Schuger CD, Beckman KJ, Bogun FM, Pollak SJ, Bhandari AK. Long-Term Success of Irrigated Radiofrequency Catheter Ablation of Sustained Ventricular Tachycardia. *J Am Coll Cardiol* 2016;**67**:674–683.
16. Di Biase L, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P, Trivedi C, Santangeli P, Bai R, Forleo G, Horton R, Bailey S, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Pelargonio G, Hongo RH, Beheiry S, Hao SC, Reddy M, Rossillo A, Themistoclakis S, Dello Russo A, Casella M, Tondo C, Natale A. Ablation of Stable VTs Versus Substrate Ablation in Ischemic Cardiomyopathy. *J Am Coll Cardiol* 2015;**66**:2872–2882.
17. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation. 2000. p. 1288–1296.
18. Wijnmaalen AP, Schalij MJ, Thüsen JH von der, Klautz RJM, Zeppenfeld K. Early Reperfusion During Acute Myocardial Infarction Affects Ventricular Tachycardia Characteristics and the Chronic Electroanatomic and Histological Substrate. *Circulation* 2010;**121**:1887–1895.
19. Wijnmaalen AP, Geest RJ van der, Huls van Taxis CFB van, Siebelink H-MJ, Kroft LJM, Bax JJ, Reiber JHC, Schalij MJ, Zeppenfeld K. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. *Eur Heart J* 2011;**32**:104–114.
20. Porta-Sánchez A, Jackson N, Lukac P, Kristiansen SB, Nielsen JM, Gizurarson S, Massé S, Labos C, Viswanathan K, King B, Ha ACT, Downar E, Nanthakumar K. Multicenter Study of Ischemic Ventricular Tachycardia Ablation With Decrement-Evoked Potential (DEEP) Mapping With Extra Stimulus. *JACC Clin Electrophysiol* 2018;**4**:307–315.
21. Acosta J, Andreu D, Penela D, Cabrera M, Carlosena A, Korshunov V, Vassanelli F, Borras R, Martínez M, Fernández-Armenta J, Linhart M, Tolosana JM, Mont L, Berruezo A. Elucidation of hidden slow conduction by double ventricular extrastimuli: a method for further arrhythmic substrate identification in ventricular tachycardia ablation procedures. *EP Eur* 2018;**20**:337–346.
22. Acosta J, Soto-Iglesias D, Jáuregui B, Armenta JF, Penela D, Frutos-López M, Arana-Rueda E, Pedrote A, Mont L, Berruezo A. Long-term outcomes of ventricular tachycardia substrate ablation incorporating hidden slow conduction analysis. *Heart Rhythm* 2020;**17**:1696–1703.
23. Sramko M, Abdel-Kafi S, Geest RJ van der, Riva M de, Glashan CA, Lamb HJ, Zeppenfeld K. New Adjusted Cutoffs for “Normal” Endocardial Voltages in Patients With Post-Infarct LV Remodeling. *JACC Clin Electrophysiol* 2019;**5**:1115–1126.

SAMENVATTING EN TOEKOEMSTPERSPECTIEF

Het doel van dit proefschrift is om nieuwe inzichten te verschaffen in katheterablatie van ventriculaire tachycardiën (VT) bij patiënten met een eerder myocardinfarct (MI). Meer begrip van het substraat voor VT in verschillende typen MI en de ontwikkeling van nieuwe meer fysiologische eindpunten voor substraatmodificatie kunnen bijdragen aan verbeterde uitkomst van ablatie in deze populatie. Dit geld in het bijzonder voor de hedendaagse niet-transmurale littekens laat na primaire reperfusie van het acute MI. Hiernaast zal de herkenning van beperkingen van de huidige techniek leiden tot betere selectie van patiënten voor deze behandeling en het tijdig overwegen van alternatieve mogelijkheden.

Hoofdstuk 2 is een review van de waarde en beperkingen van het 12-afleidingen elektrocardiogram (ECG) om de oorsprong van VT in patiënten met structurele hartafwijkingen (SHA) te voorspellen. Katheterablatie wordt toenemend gebruikt voor de behandeling van VT in patiënten met SHA.[1,2] Door gedetailleerdere kennis over de mogelijke anatomische structuren en verschillende substraten van VT zijn naast het linker- en rechter kamer endocard ook complexere structuren als de aortawortel en het epicard mogelijke ablatie targets geworden.[2–4] Het ECG van de klinisch gedocumenteerde VT kan de anatomische oorsprong van de VT voorspellen. Het ECG wordt daarom gebruikt voor het selecteren van de benadering tijdens ablatie en het inschatten van de slagingskans en risico's van de procedure. Verschillende algoritmes zijn beschreven voor het identificeren van de anatomische oorsprong van VT gebaseerd op het ECG.[5–8] Hierbij zijn echter verschillende definities van de anatomische oorsprong gebruikt (VT isthmus- en exit-sites) en zijn deze getest in verschillende populaties (post-MI, niet-ischemische cardiomyopathie) en gevalideerd met verschillende kathetermapping technieken (activatie- en entrainmentmapping maar ook pacemapping). Ondanks dat informatie over de afmeting en distributie van het litteken in het hart, op basis van beeldvorming of kathetermapping, waarschijnlijk de precisie van het voorspellen van VT-origine met behulp van het ECG vergroot heeft geen van de huidig beschreven algoritmes dit geïncorporeerd. Een systematische herevaluatie van de waarde van het VT ECG voor het voorspellen van de anatomische VT-origine in de context van 3D electroanatomische mapping en beeldvorming van myocard litteken is daarom van belang.

Deel II van dit proefschrift richt zich op de evaluatie van eindpunten van ablatie van post-MI VT. De waarde van niet-induceerbaarheid van VT na ablatie in patiënten met ischemische hartziekte wordt herbeoordeeld en de uitkomst van een nieuwe substraat mapping- en ablatie strategie - functioneel substraat mapping – wordt geëvalueerd.

Verder wordt de prevalentie en impact van myocardiale calcificatie (MC) op de effectiviteit van endocardiale ablatie bestudeerd.

In **hoofdstuk 3** wordt de impact van patiënteigenschappen, in het bijzonder de linker ventrikel (LV) functie, op de voorspellende waarde van niet-induceerbaarheid na ablatie voor het opnieuw optreden van VT en voor cardiale mortaliteit bestudeerd. Van 92 post-MI patiënten die ablatie voor monomorfe aanhoudende VT ondergingen hadden 59 (65%) een LV ejectie fractie (LVEF) >30% en 32 (35%) een LVEF ≤30%. Er waren geen verschillen in het aantal patiënten dat niet-induceerbaar was na ablatie in patiënten met LVEF hoger of lager dan 30%. Na 1 jaar hadden patiënten met een LVEF≤30% echter een slechtere prognose met een overleving vrij van VT van slechts 42% (vergeleken met 80% in de patiënten met een LVEF>30%). Niet induceerbaarheid was een goede voorspeller voor het opnieuw optreden van VT en van cardiale mortaliteit in patiënten met LVEF>30% maar niet die met LVEF≤30%. Dit is in lijn met de resultaten van een eerdere gerandomiseerde studie.[9] Slechts 10% van de patiënten met LVEF>30% die niet-induceerbaar waren door ablatie hadden een herhaalde VT over overleden door cardiale oorzaken in het eerste jaar na de ablatie. Bij patiënten bij wie niet-induceerbaarheid niet werd bereikt was dit 65%. De slechtere uitkomst van patiënten die induceerbaar bleven berustte met name op herhaling van VT. Dit benadrukt de noodzaak voor aanvullende eindpunten voor ablatie gebaseerd op substraat mapping en de ontwikkeling van nieuwe ablatietechnieken om diepere en duurzamere laesies te creëren in deze patiënten. De patiënten met een sterk verminderde LV functie hadden een slechte prognose onafhankelijk van het directe resultaat van de ablatieprocedure. Dit werd voornamelijk veroorzaakt door hartfalen gerelateerd overlijden. Deze bevinding suggereert dat in deze patiënten een, meer conservatieve, benadering die gericht is op het behandelen van de symptomen van patiënt door het benaderen van de klinisch gedocumenteerde VT de voorkeur verdient. Na publicatie van onze studie toonde een andere retrospectieve analyse van 1046 patiënten met VT na MI dat niet-induceerbaarheid geassocieerd was met lagere mortaliteit in de periode na ablatie.[10] Echter in deze studie werd de LV functie niet meegenomen als een van de factoren die aan mortaliteit werden gecorreleerd. Prospectieve studies met een duidelijk van tevoren gespecificeerd eindpunt zijn nodig om onze bevindingen te staven.

Het prognostische belang van snelle niet-klinische VT na ablatie in patiënten met SHA is onduidelijk. In veel elektrofysiologie laboratoria wordt daarom niet-induceerbaarheid van VT met een vergelijkbare of langere cycluslengte (CL) als een eindpunt van ablatie gebruikt. In deze gevallen wordt induceerbaarheid van snellere VT aan het einde van de behandeling geaccepteerd. Deze benadering wordt gesteund in het HRS/EHRA expert consensus over VT ablatie uit 2009.[11] Een standard en breed geaccepteerde definitie van

fast VT op basis van CL is er echter op dit moment niet. Dit verklaart, in ieder geval deels, de vergelijkbare uitkomsten na ablatie ondanks de grote variatie in gerapporteerde niet-induceerbaarheid aan het einde van de procedure.[1,2,12–14] In **hoofdstuk 4** wordt een nieuwe, patiënt specifieke, definitie voor snelle VT gebaseerd op de individuele ventriculaire refractaire periode (fVT_{VRP}) voorgesteld en de prognostische waarde van persisterende induceerbaarheid van fVT_{VRP} voor opnieuw optreden van VT na de behandeling geëvalueerd. Zeventig patiënten met SHA (45 post-MI, 65%) die slechts induceerbaar waren voor niet-klinische VTs na ablatie werden geïncludeerd. De afkapwaarde voor fVT_{VRP} werd gesteld op een CL korter dan de VRP bepaald met een basis pacing frequentie van 400ms. De onderliggende hypothese voor deze voorgestelde definitie is dat de kortst mogelijke CL van een re-entry VT wordt bepaald door de VRP en de geleidingssnelheid in het ventrikel myocard. In theorie zou geen re-entry VT een kortere CL kunnen hebben dan de VRP. Omdat de VRP kan variëren, bijvoorbeeld door veranderingen in autonome balans, werd voor de definitie van fVT_{VRP} een maximaal verschil van 30ms ten opzichte van de VRP geaccepteerd. Dertig patiënten (43%) bleven na ablatie alleen induceerbaar voor fVT_{VRP} en bij 40 (57%) bleven ook tragere VT opwekbaar. fVT_{VRP} werd vaak geïnduceerd met behulp van drie kort-gekoppelde extrastimuli. Dit zou, door de heterogeniteit van inductie protocollen in verschillende elektrofysiologie laboratoria, de belangrijke gepubliceerde verschillen in post-procedurele niet-induceerbaarheid kunnen verklaren. Na een mediane follow-up van 2,5 jaar hadden patiënten met alleen fVT_{VRP} betere overleving vrij van VT (74% in vergelijking met 63% van de patiënten met ook tragere induceerbare VT). Hoewel patiënten met tragere VT zieker waren (onder andere met lagere LVEF en vaker nierfalen) bleef induceerbaarheid voor fVT_{VRP} geassocieerd met lagere kans op herhaalde VT ook na correctie voor patiënt- en procedurele variabelen. Verder trad fVT_{VRP} zelden spontaan op. Geen enkele voor de ablatie gedocumenteerde VT voldeed aan de criteria van fVT_{VRP} en slechts 4 (6%) van de patiënten presenteerde met fVT_{VRP} in het vervolg na ablatie. Al deze bevindingen ondersteunen de gedachte dat inductie van fVT_{VRP} na ablatie niet van prognostische betekenis is en plaatsen vraagtekens bij het nut van het benaderen van deze VT tijdens ablatie. Zoals eerder opgemerkt zijn er echter prospectieve studies met van tevoren gespecificeerde eindpunten met betrekking tot induceerbaarheid van VT nodig om deze hypothese te bevestigen.

Op substraat gebaseerde benaderingen zijn ontwikkeld om onstabiele en niet-induceerbare VT met ablatie te behandelen. Het gaat om respectievelijk 70% en 10% van de post-MI patiënten die verwezen worden voor ablatie. [1,12,15] Hierna is aangetoond dat substraat gebaseerde ablatie beter is dan ablatie die slechts stabiel mapbare VT benaderd in ischemische cardiomyopathie. Substraat ablatie is daarom reguliere praktijk geworden in de meeste elektrofysiologie laboratoria.[16] Deze ablatietechniek steunt op 2 pilaren: de

eerste is het in kaart brengen van het litteken gebied door middel van bipolair voltage mapping, de tweede is de identificatie van elektrogrammen die passen bij lokale trage geleiding mogelijk passend bij VT re-entry isthmus locaties. Over het algemeen word een afkapwaarde van 1,5mV gebruikt om litteken weefsel te onderscheiden van normaal myocard.[17] In het lokaal gemeten electrogram kan de potentiaal gegenereerd in het litteken worden overschaduwd door het 'far-field' electrogram van dieper of verder weg gelegen weefsel dat tegelijk wordt geactiveerd. Dit fenomeen is met name relevant bij hedendaagse patiënten die zich presenteren met VT bij een niet-transmuraal litteken na primair gereperfundeerd infarct.[18] In deze patiënten kan het signaal van het aritmogene substraat worden verborgen door het grote farfield signaal van het overlevende subepicardium of het omliggende gezonde myocard.[19]

In **hoofdstuk 5** bestuderen we 60 opeenvolgende patiënten die verwezen werden voor de ablatie van post-MI VT. In deze patiënten werden alle electrogrammen systematisch geëvalueerd tijdens RV extra-stimulus pacing. Het gebied dat specifiek werd geanalyseerd was het deel van het hart waar het eerdere MI was doorgemaakt. Dit werd gebaseerd op beeldvorming (echocardiogram, cardiale MRI wanneer deze voor handen was) en het beloop van de infarct gerelateerde coronairarterie. Near-field electrogrammen met een lokale geleidingsvertraging >10ms of geleidingsblok tijdens RV extra-stimulus pacing werden gemarkeerd als 'uitgelokt vertraagde potentialen' (functioneel VT-substraat) en benaderd met ablatie. Uitgelokt vertraagde potentialen op locaties met voltage >1,5mV werden gevonden in zevenendertig (62%) patiënten (hierna de "verborgen substraat" groep). Patiënten in deze groep hadden een betere LV-functie en kleinere littekengebieden dan patiënten bij wie al het te benaderen substraat binnen het <1,5mV gebied werd gevonden (hierna de ("het openlijke substraat" groep). Gedurende een vervolg periode van 1,5 jaar had 22% herhaalde VT. Patiënten in de verborgen substraat groep hadden een minder vaak VT tijdens vervolg dan patiënten met een openlijk substraat. Van belang is echter dat in vergelijking met een historisch cohort van patiënten met een vergelijkbare LVEF en afmeting van het electroanatomische littekengebied patiënten bij wie het verborgen substraat geableerd was een betere overleving vrij van VT hadden na 1 jaar (89% vs. 73%). Dit ondersteund het gebruik van pacing manoeuvres naast voltage mapping om het gehele aritmogene substraat te detecteren in patiënten met post-MI littekens. Twee andere kleine retrospectieve studies die gelijktijdig met de onze werden gepubliceerd toonden ook aan dat RV extrastimulus pacing het verborgen substraat kan identificeren. Een van deze studies werd verricht in post-MI patienten[20] en de andere in een meer heterogene groep van patiënten met litteken-gerelateerde VT[21,22]. In een groep post-MI patiënten bij wie een LGE-MRI beschikbaar was voor integratie met electroanomisch mapping hebben wij recent aangetoond dat een voltage afkapwaarde van 3mV beter kan onderscheiden tussen litteken en normaal myocard wanneer de LV functie

behouden is.[23] Wij hebben daarom ons protocol aangepast en beperken het gebied dat met behulp van RV extrastimulus pacing wordt geëvalueerd tot dat met een bipolair voltage <3mV. Op dit moment verrichten we een internationale multicenter registry van post-MI patiënten die VT-ablatie ondergaan met identificatie van functioneel substraat. Wij hopen dat dit onze initiële bevindingen kan bevestigen in een grotere en prospectieve populatie.

In **hoofdstuk 6** wordt de prevalentie van myocardiale calcificatie (MC) en de invloed hiervan op de uitkomst en lange termijn resultaten van endocardiale ablatie in post-MI patiënten geanalyseerd. In een groep van 158 opeenvolgende post-MI patiënten die een VT-ablatie ondergingen werd de aanwezigheid van MC beoordeeld op basis van fluoroscopie bij coronairangiogram en/of preprocedurele CT-scans. Bij 30 (19%) patiënten werd MC vastgesteld. Patiënten met MC waren jonger, hadden doorgaans een voorwandinfarct en hadden grotere gebieden van dicht littekenweefsel. Endocardiale ablatie faalde om de klinische VT te elimineren in een derde van de patiënten met MC en slechts in 7% van de patiënten zonder MC, ondanks uitvoerige ablatie met hoge power en lange applicaties. Na falen van endocardiale ablatie werd een percutane epicardiale benadering gepoogd in 5 van de 8 patiënten. In 3 van de 5 werd echter geen epicardiale toegang verkregen door de aanwezigheid van pericard verklevingen. De patiënten met MC die geen escalatie van antiaritmische therapie ondergingen (andere medicatie, epicardiale of chirurgische ablatie) hadden een slechte prognose met een VT vrije overleving van slechts 26% in 2 jaar. Deze bevindingen ondersteunen de gedachte dat bij patiënten met een oud infarct MC kan voorkomen dat de hitte energie van ablatie de subepicardiale laag van het myocard bereikt tijdens endocardiale ablatie. Aanvullende therapie, zoals escalatie van medicatie en epicardiale ablatie maar ook chirurgische ablatie kunnen noodzakelijk zijn om VT effectief te behandelen in deze populatie. Onze studie betrof slechts een relatief klein patiënten aantal en moet daarom als hypothese genererend worden beschouwd. Prospectieve studies in een groter cohort moeten deze bevindingen bevestigen.

REFERENTIES

1. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H, Multictr Thermocool VTAT. Irrigated Radiofrequency Catheter Ablation Guided by Electroanatomic Mapping for Recurrent Ventricular Tachycardia After Myocardial Infarction The Multicenter Thermocool Ventricular Tachycardia Ablation Trial. Circulation. 2008. p. 2773–2782.
2. Piers SRD, Leong DP, Taxis CFB van H van, Tayyebi M, Trines SA, Pijnappels DA, Delgado V, Schalij MJ, Zeppenfeld K. Outcome of Ventricular Tachycardia Ablation in Patients With Nonischemic Cardiomyopathy: The Impact of Noninducibility. *Circ Arrhythm Electrophysiol* 2013;**6**:513–521.
3. Piers SRD, Tao Q, Huls van Taxis CFB van, Schalij MJ, Geest RJ van der, Zeppenfeld K. Contrast-Enhanced MRI–Derived Scar Patterns and Associated Ventricular Tachycardias in Nonischemic Cardiomyopathy: Implications for the Ablation Strategy. *Circ Arrhythm Electrophysiol* 2013;**6**:875–883.
4. Sarkozy A, Tokuda M, Tedrow UB, Sieria J, Michaud GF, Couper GS, John R, Stevenson WG. Epicardial Ablation of Ventricular Tachycardia in Ischemic Heart Disease. *Circ Arrhythm Electrophysiol* 2013;**6**:1115–1122.
5. Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. *Circulation* 1988;**77**:759–766.
6. Kuchar DL, Ruskin JN, Garan H. Electrocardiographic localization of the site of origin of ventricular tachycardia in patients with prior myocardial infarction. *J Am Coll Cardiol* 1989;**13**:893–900.
7. Vallès E, Bazan V, Marchlinski FE. ECG Criteria to Identify Epicardial Ventricular Tachycardia in Nonischemic Cardiomyopathy. *Circ Arrhythm Electrophysiol* 2010;**3**:63–71.
8. Berruezo A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic Recognition of the Epicardial Origin of Ventricular Tachycardias. *Circulation* 2004;**109**:1842–1847.
9. Kuck K-H, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, Pitschner H-F, Kautzner J, Schumacher B, Hansen PS, Grp VS. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010. p. 31–40.
10. Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P, Vergara P, Hindricks G, Arya A, Zeppenfeld K, Riva Silva M de, Daoud EG, Kumar S, Kuck K-H, Tilz R, Mathew S, Ghanbari H, Latchamsetty R, Morady F, Bogun FM. Predictive Value of Programmed Ventricular Stimulation After Catheter Ablation of Post-Infarction Ventricular Tachycardia. *J Am Coll Cardiol* 2015;**65**:1954–1959.
11. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jaïs P, Josephson ME, Kautzner J, Kay GN, Kuck K-H, Lerman BB, Marchlinski F, Reddy V, Schalij M-J, Schilling R, Soejima K, Wilber D. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias. *Heart Rhythm* 2009;**6**:886–933.
12. Riva M de, Piers SRD, Kapel GFL, Watanabe M, Venlet J, Trines SA, Schalij MJ, Zeppenfeld K. Reassessing Noninducibility as Ablation Endpoint of Post-Infarction Ventricular Tachycardia: The Impact of Left Ventricular Function. *Circ Arrhythm Electrophysiol* 2015;**8**:853–862.
13. Jaïs P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haïssaguerre M. Elimination of Local Abnormal Ventricular Activities: A New End Point for Substrate

Modification in Patients With Scar-Related Ventricular Tachycardia. *Circulation* 2012;**125**:2184–2196.

14. Dinov B, Fiedler L, Schoenbauer R, Bollmann A, Rolf S, Piorkowski C, Hindricks G, Arya A. Outcomes in Catheter Ablation of Ventricular Tachycardia in Dilated Nonischemic Cardiomyopathy Compared With Ischemic Cardiomyopathy Results From the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation. 2014. p. 728–736.
15. Marchlinski FE, Haffajee CI, Beshai JF, Dickfeld T-ML, Gonzalez MD, Hsia HH, Schuger CD, Beckman KJ, Bogun FM, Pollak SJ, Bhandari AK. Long-Term Success of Irrigated Radiofrequency Catheter Ablation of Sustained Ventricular Tachycardia. *J Am Coll Cardiol* 2016;**67**:674–683.
16. Di Biase L, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P, Trivedi C, Santangeli P, Bai R, Forleo G, Horton R, Bailey S, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Pelargonio G, Hongo RH, Beheiry S, Hao SC, Reddy M, Rossillo A, Themistoclakis S, Dello Russo A, Casella M, Tondo C, Natale A. Ablation of Stable VTs Versus Substrate Ablation in Ischemic Cardiomyopathy. *J Am Coll Cardiol* 2015;**66**:2872–2882.
17. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation. 2000. p. 1288–1296.
18. Wijnmaalen AP, Schalij MJ, Thüsen JH von der, Klautz RJM, Zeppenfeld K. Early Reperfusion During Acute Myocardial Infarction Affects Ventricular Tachycardia Characteristics and the Chronic Electroanatomic and Histological Substrate. *Circulation* 2010;**121**:1887–1895.
19. Wijnmaalen AP, Geest RJ van der, Huls van Taxis CFB van, Siebelink H-MJ, Kroft LJM, Bax JJ, Reiber JHC, Schalij MJ, Zeppenfeld K. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. *Eur Heart J* 2011;**32**:104–114.
20. Porta-Sánchez A, Jackson N, Lukac P, Kristiansen SB, Nielsen JM, Gizurarson S, Massé S, Labos C, Viswanathan K, King B, Ha ACT, Downar E, Nanthakumar K. Multicenter Study of Ischemic Ventricular Tachycardia Ablation With Decrement-Evoked Potential (DEEP) Mapping With Extra Stimulus. *JACC Clin Electrophysiol* 2018;**4**:307–315.
21. Acosta J, Andreu D, Penela D, Cabrera M, Carlosena A, Korshunov V, Vassanelli F, Borras R, Martínez M, Fernández-Armenta J, Linhart M, Tolosana JM, Mont L, Berruezo A. Elucidation of hidden slow conduction by double ventricular extrastimuli: a method for further arrhythmic substrate identification in ventricular tachycardia ablation procedures. *EP Eur* 2018;**20**:337–346.
22. Acosta J, Soto-Iglesias D, Jáuregui B, Armenta JF, Penela D, Frutos-López M, Arana-Rueda E, Pedrote A, Mont L, Berruezo A. Long-term outcomes of ventricular tachycardia substrate ablation incorporating hidden slow conduction analysis. *Heart Rhythm* 2020;**17**:1696–1703.
23. Sramko M, Abdel-Kafi S, Geest RJ van der, Riva M de, Glashan CA, Lamb HJ, Zeppenfeld K. New Adjusted Cutoffs for “Normal” Endocardial Voltages in Patients With Post-Infarct LV Remodeling. *JACC Clin Electrophysiol* 2019;**5**:1115–1126.

ACKNOWLEDGMENTS

Many have contributed in different ways to make this thesis possible. I would like to thank especially:

Prof. dr. Katja Zeppenfeld for her big support throughout these years. Her high research and clinical standards motivates me to be better every day. Prof. dr. Martin Schalij for giving me the opportunity to develop my carrier at the LUMC. Dr. Hadrian Wijnmaalen, for being the best colleague one could wish. Dr. Serge Trines, for the many things I learnt from him and for all the nice non-work related conversations. All the clinical and research fellows who I have worked with both in research and at the EP lab. Especially, Dr. Sebastiaan Piers, with whom I started my first research project and Dr. Micaela Ebert, for the wonderful time in and outside the lab.

My parents, from whom I inherited the respect for the patients, the hard-working spirit and the passion for this beautiful profession.

Ale, Berta, Carlos and Chevi, my family in Leiden.

Jose, Juan and María, because they are the joy of my life.

LIST OF PUBLICATIONS

1. **Contemporary patients with congenital heart disease: uniform atrial tachycardia substrates allow for clear ablation endpoints with improved long-term outcome.**
   Brouwer C, Hebe J, Lukac P, Nürnberg JH, Cosedis Nielsen J, de Riva Silva M, Blom N, Hazekamp M, Zeppenfeld K.
   Circ Arrhythm Electrophysiol. 2021 Sep;14(9):e009695. doi: 10.1161/CIRCEP.120.009695

2. **Accuracy of electroanatomical mapping-guided cardiac radiotherapy for ventricular tachycardia: pitfalls and solutions.**
   Abdel-Kafi S, Sramko M, Omara S, de Riva M, Cvek J, Peichl P, Kautzner J, Zeppenfeld K.
   Europace. 2021;23:1989-1997.

3. **Predicting early reconnection after cryoballoon ablation with procedural and biophysical parameters.**
   Keçe F, de Riva M, Alizdeh Dehnavi R, Wijnmaalen AP, Mertens BJ, Schalij MJ, Zeppenfeld K, Trines SA.
   Heart Rhythm O2. 2021;2:290-297

4. **The Prognostic Value of J-wave Pattern for Recurrence of Ventricular Tachycardia after Catheter Ablation in Patients with Myocardial Infarction.**
   Naruse Y, De Riva M, Watanabe M. Wijnmaalen AP, Venlet J, Timmer M, Schalij M, Zeppenfeld K.
   Pacing Clin Electrophysiol. 2021;44:657-666

5. **Myocardial calcification is associated with endocardial ablation failure of post-myocardial infarction ventricular tachycardia.**
   De Riva M, Naruse Y, Ebert M, Watanabe M, Scholte AJ, Wijnmaalen AP, PhD, Trines SA, Schalij MJ, Montero-Cabezas, Zeppenfeld K.
   Europace. 2021;23:1275-1284

6. **An accessory pathway with automaticity and bidirectional conductive capacity.**
   Bruydonckx L, de Riva M, Blom NA, Bertels RA.
   Europace. 2021 Jan 4;euaa379.doi:10.1093/europace/euaa379.

7. **Broad complex tachycardia; never judge a book by its cover.**
   Regeer MV, Tops LF, de Riva M
   Neth Heart J. 2020 Oct 2. doi: 10.1007/s12471-020-01495-x

8. **Parameters associated with ventricular arrhythmias in mitral valve prolapse with significant regurgitation.**
   van Wijngaarden AL, de Riva M, Hiemstra YL, van der Bijl P, Fortuni F, Bax JJ, Delgado V, Ajmone Marsan N.
   Heart. 2021;107:411-418

9. **High prevalence and prognostic impact of pathogenic mutations in patients with dilated cardiomyopathy referred for ventricular tachycardia ablation**
   Ebert, M, Wijnmaalen AP, de Riva M, Trines S, Androulakis A, Glashan CA, van Tintelen JP, PhD, Jongbloed JD, Schalij MJ, Zeppenfeld K.
   JACC Clin Electrophysiol. 2020 Sep;6(9):1103-1114.

10. **RV tissue heterogeneity on CT: A novel tool to identify the VT substrate in ARVC.**
    Venlet J, Tao Q, de Graaf MA, Glashan CA, de Riva Silva M, van der Geest RJ, Scholte AJ, Piers SRD, Zeppenfeld K.
    JACC Clin Electrophysiol. 2020 Sep;6(9):1073-1085

11. **The harm of delayed diagnosis of arrhythmogenic cardiac sarcoidosis: a case series**
    Hoogendoorn J, Ninaber MK, Piers SRD, de Riva M, Grauss RW, Bogun FM, Zeppenfeld K. *Europace. 2020 Sep 1;22(9):1376-1383*

12. **Arrhythmia exacerbation after post-Infarction ventricular tachycardia ablation: prevalence and prognostic significance**
    Siontis KC, Kim HM, Vergara P, Peretto G, Do DH, de Riva M, Lam A, Qian P, Yokokawa M, Jongnarangsin K, Latchamsetty R, Jais P, Sacher F, Tedrow U, Shivkumar K, Zeppenfeld K, Della Bella P, Stevenson WG, Morady F, Bogun FM.
    Europace. 2020 Nov 1;22(11):1680-1687

13. **Integration of electroanatomical mapping with imaging to guide radiotherapy of VT substrates with high accuracy**
    Abdel-Kafi S, de Ridder M, de Riva M, van der Geest RJ, Rasch C, Zeppenfeld K.
    JACC Clin Electrophysiol. 2020 Jul;6(7):874-876

14. **Electroanatomical voltage mapping to distinguish right-sided cardiac sarcoidosis from arrhythmogenic right ventricular cardiomyopathy**
    Hoogendoorn J, Sramko M, Venlet J, Siontis KC, Kumar S, Singh R, Nakajima I, Piers SRD, de Riva Silva M, Glashan C, Crawford T, Tedrow UB, Stevenson WG, Bogun F, Zeppenfeld K.
    JACC Clin Electrophysiol. 2020 Jun;6(6):696-707

15. **New Adjusted Cutoffs for "Normal" Endocardial Voltages in Patients With Post-Infarct LV Remodeling.**
    Sramko M, Abdel-Kafi S, van der Geest RJ, de Riva M, Glashan CA, Lamb HJ, Zeppenfeld K.
    JACC Clin Electrophysiol. 2019;5(10):1115-1126.

16. **Effect of Non-fluoroscopic Catheter Tracking on Radiation Exposure during Pulmonary Vein Isolation: Comparison of Four ablation systems.**
    Naruse Y, Kece F, de Riva M, Watanabe M, Wijnmaalen AP, Dehnavi RA, Schalij MJ, Zeppenfeld K, Trines SA.
    J Atr Fibrillation. 2018;11 (3):2068. doi: 10.4022/jafib.2068.

17. **Entropy as a Novel Measure of Myocardial Tissue Heterogeneity for Prediction of Ventricular Arrhythmias and Mortality in Post-Infarct Patients.**
    Androulakis AFA, Zeppenfeld K, Paiman EHM, Piers SRD, Wijnmaalen AP, Siebelink HJ, Sramko M, Lamb HJ, van der Geest RJ, de Riva M, Tao Q.
    JACC Clin Electrophysiol. 2019 Apr;5(4):480-489.

18. **Incidence and Clinical Significance of Cerebral Embolism During Atrial Fibrillation Ablation With Duty-Cycled Phased-Radiofrequency Versus Cooled-Radiofrequency: A Randomized Controlled Trial.**
    Keçe F, Bruggemans EF, de Riva M, Alizadeh Dehnavi R, Wijnmaalen AP, Meulman TJ, Brugman JA, Rooijmans AM, van Buchem MA, Middelkoop HA, Eikenboom J, Schalij MJ, Zeppenfeld K, Trines SA. *JACC Clin Electrophysiol. 2019 Mar;5(3):318-326.*

19. **Optimizing ablation duration using dormant conduction to reveal incomplete isolation with the second generation cryoballoon: A randomized controlled trial.**
    Keçe F, de Riva M, Naruse Y, Alizadeh Dehnavi R, Wijnmaalen AP, Schalij MJ, Zeppenfeld K, Trines SA. *J Cardiovasc Electrophysiol. 2019 Jun;30(6):902-909.*

20. **Impact of left atrial box surface ratio on the recurrence after ablation for persistent atrial fibrillation.**
Keçe F, Scholte AJ, de Riva M, Naruse Y, Watanabe M, Alizadeh Dehnavi R, Schalij MJ, Zeppenfeld K, Trines SA.
Pacing Clin Electrophysiol. 2019 Feb;42(2):208-215.

21. **Noninvasive identification of ventricular tachycardia-related anatomical isthmuses in repaired Tetralogy of Fallot: what is the role of the 12-lead ventricular tachycardia electrocardiogram?.**
Brouwer C, Kapel GFL, Jongbloed MRM, Schalij MJ, de Riva Silva M, Zeppenfeld K.
JACC Clin Electrophysiol. 2018;4:1308-1318.

22. **Slow conducting electroanatomic isthmuses: an important link between QRS duration and ventricular tachycardia in Tetralogy of Fallot.**
Kapel GFL, Brouwer C, Jalal Z, Sacher F, Venlet J, Schalij MJ, Thambo JB, Jongbloed MRM, Blom NA, de Riva M, Zeppenfeld K.
JACC Clin Electrophysiol. 2018;4:781-793.

23. **Targeting the hidden substrate unmasked by right ventricular extrastimulation improves ventricular tachycardia ablation outcome after myocardial infarction.**
De Riva M, Naruse Y, Ebert M, Androulakis AFA, Tao Q, Watanabe M, Wijnmaalen AP, Venlet J, Brouwer C, Trines SA, Schalij MJ, Zeppenfeld K.
JACC Clin Electrophysiol. 2018;4:316-327.

24. **Whole human heart histology to validate electroanatomical voltage mapping in patients with nonischaemic cardiomyopathy and ventricular tachycardia.**
Glashan CA, Androulakis AFA, Tao Q, Gashan RN, Wisse LJ, Ebert M, de Ruiter MC, van Meer BJ, Brouwer C, Dekkers OM, Pijnappels DA, de Bakker JMT, de Riva M, Piers SRD, Zeppenfeld K.
Eur Heart J. 2018;39:2867-2875.

25. **Fast nonclinical ventricular tachycardia inducible after ablation in patients with structural heart disease: definition and clinical implications.**
De Riva M Watanabe M, Piers SRD, Dekkers OM, Ebert M, Venlet J, Trines SA, Schalij MJ, Pijnappels DA, Zeppenfeld K.
Heart Rhythm. 2018;15:668-676.

26. **Unipolar endocardial voltage mapping in the right ventricle: optimal cutoff value correcting for computed tomography-derived epicardial fat thickness and their clinical value for substrate delineation.**
    Venlet J, Piers SRD, Kapel GFL, de Riva M, Pauli PFG, van der Geest RJ, Zeppenfeld K.
    Circ Arrhythm Electrophysiol. 2017;10. Pii:e005175

27. **Isolated subepicardial right ventricular outflow tract scar in athletes with ventricular tachycardia.**
    Venlet J, Piers SR, Jongbloed JD, Androulakis AF, Naruse Y, den Uijl DW, Kapel GF, de Riva M, van Tintelen JP, Barge-Schaapveld DQ, Schalij M, Zeppenfeld K.
    J Am Coll Cardiol. 2017;69(5):497-507.

28. **Prognostic impact of the timing of recurrence of infarct-related ventricular tachycardia after catheter ablation.**
    Siontis KC, Kim HM, Stevenson WG, Fujii A, Bella PD, Vergara P, Shivkumar K, Tung R, Do DH, Daoud EG, Okabe T, Zeppenfeld K, Riva Silva M, Hindricks G, Arya A, Weber A, Kuck KH, Metzner A, Mathew S, Riedi J, Yokokawa M, Jongnarangsin K, Latchamsetty R, Morady F, Bogun FM.
    Circ Arrhythm Electrophysiol. 2016;9(12). pii:e004432.

29. **QRS prolongation after premature stimulation is associated with polymorphic ventricular tachycardia in nonischemic cardiomyopathy: results from the Leiden nonischemic cardiomyopathy study.**
    Piers SR, Askar SF, Venlet J, Androulakis AF, Kapel GF, de Riva Silva M, Jongbloed JJ, van Tintelen JP, Schalij MJ, Pijnappels DA, Zeppenfeld K.
    Heart Rhythm. 2016;13(4):860-869.

30. **Fatigue as presenting symptom and a high burden of premature ventricular contractions are independently associated with increased ventricular wall stress in patients with normal left ventricular function.**
    Van Huls van Taxis CF, Piers SR, de Riva Silva M, Dekkers OM, Pijnappels DA, Schalij MJ, Wijnmaalen AP, Zeppenfeld K.
    Circ Arrhythm Electrophysiol. 2015;8(6):1452-1459.

31. **Twelve-lead ECG of ventricular tachycardia in structural heart disease.**
    De Riva M, Watanabe M, Zeppenfeld K.
    Circ Arrhythm Electrophysiol. 2015;8(4):951-962.

32. **Re-assessing non-inducibility as ablation endpoint of post-infarction ventricular tachycardia: the impact of left ventricular function.**
De Riva M, Piers SR, Kapel GF, Watanabe M, Venlet J, Triens SA, Schalij MJ, Zeppenfeld K.
Circ Arrhythm Electrophysiol 2015;8(4):853-862.

33. **Incidence and predictors of dormant conduction after cryoballoon ablation incorporating a 30-min waiting period.**
Compier MG, De Riva M, Dyrda K, Zeppenfeld K, Schalij MJ, Trines SA.
Europace. 2015;17(9):1383-1390.

34. **Predictive value of programmed electrical stimulation after catheter ablation of post-infarction ventricular tachycardia.**
Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P, Vergara P, Hindricks G, Arya A, Zeppenfeld K, de Riva Silva M, Daoud EG, Kumar S, Kuck KH, Tilz R, Mathew S, Ghanbari H, Latchamsetty R, Morady F, Bogun FM.
J Am Coll Cardiol. 2015;65(18):1954-1959.

35. **An easy-to-use, operator-independent, clinical model to predict the left vs. right ventricular outflow tract origin of ventricular arrhythmias.**
Penela D, De Riva M, Hercku C, Catto V, Pala S, Fernández-Armenta J, Acosta J, Cipolletta L, Andreu D, Borras R, Rios J, Mont L, Brugada J, Carbuccichio C, Zeppenfeld K, Berruezo A.
Europace. 2015;17(7):1122-1128.

36. **Value of intraoperative electrical parameters obtained during implantation of cardiac resynchronization therapy devices for the prediction of reverse remodeling.**
De Riva-Silva M, López-Gil M, Salgado-Aranda R, Fontenla-Cerezuela A, Salguero-Bodes R, Arribas-Ynsaurriaga F.
Rev Esp Cardiol. 2014;67(10):855-857.

37. **CMR-based identification of critical isthmus sites of ischemic and nonischemic ventricular tachycardia.**
Piers SR, Tao Q, de Riva Silva M, Siebelink HM, Schalij MJ, van der Geest RJ, Zeppenfeld K.
JACC Cardiovasc Imaging. 2014;7(8):774-784.

38. **Delayed positive response to a flecainide test in a patient with suspected Brugada syndrome: a worrisome finding.**
De Riva-Silva M, Montero-Cabezas JM, Fontenla-Cerezuela A, Salguero-Bodes R, López-Gil M, Arribas-Ynsaurriaga F.
Rev Esp Cardiol. 2014;67(8):674-675.

39. **Endocardial or epicardial ventricular tachycardia in nonischemic cardiomyopathy?. The role of 12-lead ECG criteria in clinical practice.**
Piers SR, Silva M de R, Kapel GF, Trines SA, Schalij MJ, Zeppenfeld K.
Heart Rhythm. 2014;11(6):1031-1039.

40. **Usefulness of exercise test in cardiac resynchronization therapy follow-up.**
De Riva-Silva M, López Gil M, Fontenla-Cerezuela A, Salgado-Aranda R, Salguero-Bodes R, Arribas-Ynsaurriaga F.
Rev Esp Cardiol. 2013;66(11):912-913.

41. **1:1 atrial flutter after vernakalant administration for atrial fibrillation cardioversion.**
De Riva-Silva M, Montero-Cabezas JM, Salgado-Aranda R, López-Gil M, Fontenla-Cerezuela A, Arribas-Ynsaurriaga F.
Rev Esp Cardiol. 2012;65(11):1062-1064.

42. **An uncommon complication of an aortic root aneurysm.**
Montero Cabezas JM, de Riva Silva M, Martín Asenjo R, Hernández Hernández F.
Clin Res Cardiol. 2013;102(1):81-83.

43. **Single and inappropriate shock delivered out of tachycardia: device dysfunction?.**
Fontenla A, Carrero D, Salguero R, López-Gil M, De Riva M, Arribas F.
Pacing Clin Electrophysiol. 2012;35(7):884-886.

CURRICULUM VITAE

Marta de Riva Silva was born on November 25 1980 in Segovia (Spain). After graduating *cum laude* in secondary school in Segovia, she started her studies of Medicine at Universidad Autonoma de Madrid where she graduated in 2004. In 2005, she successfully passed the M.I.R exam classifying as number 46 out of more than 10.000 applicants. In 2005, she joined the cardiology training program at the Doce de Octubre University Hospital (Complutense University of Madrid) where she became a cardiologist in May 2010. Between May 2010 and June 2012, she followed the clinical electrophysiology fellowship program at the Doce de Octubre University Hospital. In 2011, she successfully underwent the EHRA (European Heart Rhythm Association) exams of cardiac pacing and clinical electrophysiology. In 2012, she won the EHRA grant for a one-year training fellowship in advanced cardiac electrophysiology which she underwent at the LUMC under the supervision of prof. dr. Katja Zeppenfeld. After completing this year of fellowship, she obtained a position as a staff member of the cardiology department at the LUMC, where she still works. Since her arrival at the LUMC in July 2012, Marta has been active in research in the field of invasive cardiac electrophysiology with national and international collaborations. The main interest of her research has been the invasive treatment of ventricular arrhythmias in the setting of ischemic cardiomyopathy, which is the focus of this thesis. The results of her research have been presented in different international conferences. In addition, she has participated in research projects on catheter ablation of atrial fibrillation, catheter ablation of idiopathic ventricular arrhythmias and ventricular arrhythmias related to structural heart disease other than ischemic cardiomyopathy and catheter ablation of atrial and ventricular arrhythmias in adults with repaired congenital heart disease. In the last years, Marta has also been highly involved in post-graduate education in invasive electrophysiology. Between 2017 and 2020 she was one of the members of the EHRA education committee being the co-director of the EHRA course on advanced clinical electrophysiology with focus on ventricular tachycardia ablation in its editions of 2018, 2019 and 2020.