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Universiteit Leiden



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Title: Understanding ventricular tachycardia : towards individualized substrate-based therapy

Issue Date: 2016-01-28

Chapter 1

General Introduction and Outline of Thesis

GENERAL INTRODUCTION AND OUTLINE OF THESIS

Background

Although important scientific advances have shed some light onto the substrate and mechanisms of ventricular arrhythmias in patients with structural heart disease, many aspects remain incompletely understood. Meanwhile, a pragmatic approach has been adopted, employing implantable cardioverter defibrillators (ICDs) to reduce sudden cardiac death in patients who survived cardiac arrest due to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF),¹⁻³ and in selected patients who are considered to be at high risk for sudden cardiac death.⁴⁻⁶ ICDs can usually effectively terminate ventricular arrhythmias and have thus saved numerous lives, but it is important to realize that they do not prevent the occurrence of arrhythmias. ICD shocks are associated with significant morbidity and even with increased mortality,⁷ although there may not be a *causal* relation with the latter.^{8,9} Therapies to control recurring ventricular arrhythmias and ICD shocks, such as anti-arrhythmic drugs and endocardial or epicardial catheter ablation, have thus become even more important and indispensable in the era of ICDs.

In the past, catheter ablation was only applied in patients with hemodynamically stable VT.¹⁰ The development of substrate and pace mapping has allowed catheter ablation of hemodynamically unstable VTs,¹¹ which are inducible in the majority of patients with prior myocardial infarction¹² or nonischemic cardiomyopathy (NICM).¹³ Catheter ablation is typically performed in patients with recurrent VT despite anti-arrhythmic drugs, but is also recommended in patients who do not prefer or tolerate anti-arrhythmic drugs¹⁴ and may even be applied after a first episode of VT in patients after myocardial infarction, as a direct adjunct to ICD implantation for secondary prevention to prevent future appropriate ICD shocks.^{15,16} Despite these recommendations and potential applications, the vast majority of clinicians restrict VT ablation to patients who experience multiple ICD shocks or electrical storm,¹⁷ suggesting that *'there is a need to catch up with current recommendations'*.¹⁸ One potential reason for the poor implementation rate of VT ablation may be the disappointing long-term outcomes, with 6 month recurrence rates of 47% in one large multicenter study in patients with VT after myocardial infarction,¹² and 12-month recurrence rates of 43% and 59% in patients after infarction and with NICM, respectively, in a large tertiary care facility.¹⁹ Notably, although VT ablation may not completely prevent VT recurrence in around 50% of patients, the 6-month VT burden is reduced by $\geq 75\%$ in approximately 67% of patients.¹² It is unclear whether, and to what extent, the high VT recurrence rates are attributable to not identified or not reachable substrates, imperfect ablation, lesion recovery, arrhythmogenic substrates that evolve over time, progressive heart failure, or other factors.

The key to more effective primary and secondary preventive therapies for ventricular arrhythmias may be improved understanding of different types of ventricular arrhyth-

mias, and of its underlying substrate and mechanisms. Improved understanding may lead both to more accurate risk stratification and to development of more effective, individualized and substrate-based therapies.

Myocardial Fibrosis and Monomorphic Ventricular Tachycardia

In patients with prior myocardial infarction and other causes of replacement fibrosis (e.g., laminopathy²⁰, myocarditis^{21,22}), surviving bundles of myocytes may be located within regions of fibrosis, resulting in slow conduction.^{23,24} Classically, slow conduction in fibrotic regions has been attributed to increased path length (so-called *zig-zag* course of activation²³), but there is also emerging evidence for functional components, which may be unmasked by premature stimulation.²⁵ The presence of inexcitable barriers, slow conduction and unidirectional conduction block may allow for stable re-entrant activation through a central slow-conducting critical isthmus, which manifests as VT. For hemodynamically stable VTs, activation and entrainment mapping can be performed to identify the slow-conducting critical isthmus during ongoing arrhythmia, so that the arrhythmia can be slowed and terminated by ablation.²⁶⁻²⁸ In case of hemodynamically unstable VT, substrate mapping and ablation are typically performed to localize and eliminate the slow-conducting isthmuses during stable rhythm, thereby preventing VT recurrence.^{11,29-31}

Nonischemic scars are different from post-infarct scars as they exhibit less late potentials³² and are frequently located intramurally or subepicardially,³² limiting the efficacy of endocardial VT ablation. Epicardial mapping and ablation may therefore be required to abolish VT.^{33,34} Substrate mapping may however be hampered at the epicardium by interposed epicardial adipose tissue, which is typically not only present in the atrioventricular and interventricular grooves, but also at the acute margin and in other areas.^{35,36} In patients undergoing catheter ablation for ventricular arrhythmias, on average 25% of the epicardial surface is covered by >4 mm of fat.³⁶ The integration of CT-derived fat thickness during VT ablation procedures has demonstrated that fat reduces bipolar electrogram amplitudes,^{35,36} thereby preventing accurate delineation of scar regions. The combined integration of both CT and LGE-MRI may compensate for this limitation, allowing distinguishing between scar, viable myocardium and epicardial fat.

Although the '*grass may appear greener*' on the opposite (i.e., epicardial) side of the wall during endocardial mapping (Tung et al.³⁷), not all patients with NICM have VTs originating from the epicardium³⁴ and as a consequence, pericardial puncture and its associated risks (including RV perforation, severe pericardial bleeding, coronary stenosis and occlusion, and liver injury³⁸) are not required in all patients with NICM. Also, even if the arrhythmogenic substrate is located subepicardially, it may not be amenable to epicardial ablation because of overlying coronary arteries and/or epicardial fat.³⁶ Patients with isolated septal substrates are unlikely to benefit from epicardial ablation.³⁹

Pre-procedural imaging studies, scar patterns, and associated VT morphologies may be very helpful to identify patients who are not expected to benefit from epicardial VT ablation.

During VT ablation procedures, the slow-conducting critical isthmuses that cause VT are typically located in or adjacent to regions with low bipolar voltage based on electro-anatomical mapping studies,^{11,29-34,40,41} and in or adjacent to regions with late gadolinium enhancement (LGE) on MRI based on image integration studies,⁴²⁻⁴⁶ which are both considered to be indicative of focal myocardial fibrosis, based on histological correlation studies.⁴⁷⁻⁴⁹ There is however limited data on more specific features of the area harboring critical isthmuses of VT. Some evidence suggests that fibrosis density may play a role,⁵⁰ and that higher scar transmuralty is related to slow conduction.^{43,50,51} Improved insights into LGE characteristics at critical isthmuses may improve our understanding of VT and the integration of LGE-MRI-derived data may be of significant added value during catheter ablation procedures if MRI-derived features can lead to critical isthmus sites, in particular in the setting of hemodynamically unstable VT,¹² inducibility of multiple VTs,¹² intramural re-entry circuits^{52,53} and epicardial fat overlying the area of interest.^{35,36} Finally, LGE-MRI characteristics at critical isthmus sites may facilitate improved risk stratification for VT in broader populations and in particular in patients with non-myocardial infarction scars in the future. The potential benefits of image integration during VT ablation are discussed in more detail in Chapter 2.

From Substrate and VT Features to Therapy and Outcome

The 12-lead ECG of epicardial VTs has been reported to exhibit specific features that may be useful for identification of VTs with an epicardial origin,⁵⁴⁻⁵⁹ and for guidance of the procedural strategy (i.e., endocardial, epicardial, or both). Based on these ECG features, specific criteria have been developed, which all indicate either the initial direction of the activation wave front from epicardium to endocardium (e.g., initial Q-waves in the inferior leads in VTs with a superior axis), or a delayed and slurred onset of the QRS-complex in the precordial leads consistent with late activation of the endocardially located conduction system (e.g. pseudodelta wave, intrinsicoid deflection time in lead V2).⁵⁴⁻⁵⁹ The ECG criteria have however previously only been analyzed during pacing and in induced VTs, using electronic calipers at a sweep speed of 200 mm/second on electrophysiology recording systems. To guide the procedural strategy and to select patients that need an epicardial approach, the criteria should be derived from regular 25 mm/second ECGs of clinically documented VTs. The accuracy of the criteria in this setting is unclear.

If epicardial mapping and ablation are performed, post-procedural pericarditic chest pain,^{38,60} atrial fibrillation⁶¹ and adhesions⁶² may occur. Animal experiments demonstrated that intrapericardial installation of triamcinolone can reduce the development of adhesions.⁶² In humans, the effects of intrapericardial triamcinolone or systemic steroids

on pericarditic chest pain and on ECG changes after epicardial mapping has never been investigated.

After VT ablation, programmed electrical stimulation is typically performed to assess for inducibility of clinical and non-clinical VTs. The value of programmed electrical stimulation (PES) after ablation as a procedural endpoint is however unclear in patients with NICM; it has mainly been analyzed in patients after myocardial infarction.^{63,64} Patients after infarction do however have a different substrate, higher acute success rates and lower VT recurrence rates.^{32,63} Moreover, even in patients after infarction data are inconsistent, possibly due to differences in induction protocols, incomplete application of protocols but also changes in VT ablation populations over time.^{12,25,63-65} The predictive value of PES as a procedural endpoint in NICM has only been analyzed in two small studies.^{32,66} Also, VT ablation is now more frequently performed in patients without an ICD and off amiodarone, and fast hemodynamically unstable VTs are typically inducible, with uncertain clinical significance. Novel substrate-based endpoints have been proposed as an alternative to post-ablation PES,^{25,67} but are arbitrarily defined and to date, their independent predictive value for long-term outcomes has not been reported.

Post-infarct scar features such as transmuralities are known to be influenced by reperfusion therapy,⁶⁸ which may have important implications for VT. In patients undergoing VT ablation, it has recently been demonstrated that reperfused patients had non-transmural, patchy scars that were associated with faster VTs, whereas non-reperfused patients typically had more transmural, confluent scars that were associated with slower VTs.⁶⁹ The effect of reperfusion therapy on VT characteristics has not yet been analyzed in a broader population of patients at risk for VT after myocardial infarction.

Ventricular Arrhythmias: Are All the Same?

Importantly, patients with prior infarction and NICM are not only at risk for monomorphic VT, but also for potentially fatal polymorphic VT and VF.^{70,71} Myocardial scar on LGE-MRI has been identified as an important novel predictor of sudden cardiac death, appropriate ICD therapy and combined arrhythmic endpoints in patients after infarction and in NICM.⁷²⁻⁷⁸ In the setting of NICM, the absence of LGE on MRI has been associated with (very) low arrhythmic event rates,^{73,75,77} which has led to questions regarding the benefit of ICD implantation in these patients. However, none of these studies has analyzed the predictive value of LGE for monomorphic VT and polymorphic VT/VF separately. Based on LGE-MRI studies in patients with and without inducible VT,⁷⁹ and on LGE-MRI integration during VT ablation procedures,⁴² monomorphic VT is expected to be related to regions of LGE on MRI. It is unclear whether LGE on MRI also contributes to the initiation and/or maintenance of polymorphic VT/VF.

Polymorphic VT and VF have been attributed to different causes, such as conduction and repolarization abnormalities and electrolyte imbalances.⁸⁰⁻⁸³ For example, progres-

sive activation delay after premature stimulation was associated with a history of VF in the setting of various nonischemic heart diseases.⁸³ More specifically, the increase in RV intracardiac electrogram duration was larger in patients with prior VF than in those without VF, and the premature stimulus coupling intervals at which the electrogram durations started to increase were longer. There are limited data on the underlying substrate and mechanisms of this electrophysiological phenomenon. An *in vitro* study has found tissue discontinuities as a cause for abnormal conduction velocity restitution,⁸⁴ studies in Langendorff-perfused mouse hearts have demonstrated that reduced sodium channel expression and severely reduced Cx43 expression can affect conduction velocity restitution,⁸⁵ and finally, two studies in 5-6 explanted hearts from patients with end-stage heart failure have demonstrated conduction abnormalities to occur in regions with long fibrotic strands.^{82,86} The underlying substrate and mechanisms of activation delay after premature stimulation have however never been studied in humans with NICM before end-stage heart failure developed.

AIM AND OUTLINE OF THESIS

The present thesis aims to contribute to an improved understanding of different types of ventricular arrhythmias, in both ischemic and nonischemic heart disease. An improved understanding is mandatory for the development of novel, more effective, individualized and substrate-based therapies in the future.

In **part I**, it is demonstrated how image integration strategies can provide insights into the substrate for monomorphic VT in patients with ischemic and nonischemic heart disease. **Chapter 2** provides a detailed overview of the current literature on this topic. Computed tomography-derived epicardial fat thickness and MRI-derived scars are integrated with epicardial substrate maps in **chapter 3** in order to obtain insights into the effects of scar, viable myocardium and epicardial fat on bipolar and unipolar voltages and on electrogram characteristics during epicardial substrate mapping. **Chapter 4** analyzes typical MRI-derived scar patterns in patients with nonischemic cardiomyopathy, the associated 12-lead ECG morphologies of VTs, and their potential use to assess the need for epicardial VT ablation. Specific MRI-derived scar characteristics at electroanatomical mapping-based critical isthmus sites of monomorphic VTs are analyzed in **chapter 5**. These scar characteristics may be used to restrict VT substrate mapping and ablation to limited MRI-identified areas that are likely to contain the critical isthmus for VT.

In **part II**, additional strategies are used to improve our understanding of sustained monomorphic VT and of polymorphic VT and VF. Previously proposed 12-lead ECG criteria to identify an epicardial origin of VTs in nonischemic cardiomyopathy are analyzed in **chapter 6**. The study focuses on the effect of amiodarone and VT cycle length on the

reliability of ECG criteria, and more importantly, on its value in clinical practice. If epicardial substrate mapping and VT ablation are performed, patients may experience post-procedural pericarditic chest pain and pericarditic ECG changes. **Chapter 7** analyzes the effects of systemic and intrapericardial steroids on these adverse procedural effects. The outcomes of VT ablation and the predictive value of post-ablation programmed electrical stimulation are analyzed in **chapter 8**, with a special emphasis on the predictive value of persistent inducibility of non-clinical VTs for VT recurrence during follow-up. In **chapter 9**, it is demonstrated how early reperfusion therapy may have an important impact on monomorphic VTs late after myocardial infarction. The last two chapters will focus on distinct substrates for different types of arrhythmias in nonischemic cardiomyopathy. In **chapter 10**, the predictive value of the presence and extent of MRI-based myocardial scar for monomorphic VT and for polymorphic VT and VF is analyzed. Several mechanisms have been proposed as potential causes for polymorphic VT and VF. In **chapter 11**, it is demonstrated how activation delay after premature stimulation can be quantified simply by measuring the QRS duration during a standard electrophysiological study, and how it relates to inducible polymorphic VT and to underlying fibrosis in endomyocardial biopsy specimens. Finally, a summary, conclusions and future perspectives are provided in **chapter 12**.

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