Understanding ventricular tachycardia : towards individualized substrate-based therapy

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Chapter 12

Summary, conclusions and future perspectives:

Towards more effective, individualized substrate-based therapies for ventricular arrhythmias

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In the general introduction of this thesis (**chapter 1**) it is stated that improved understanding of different types of ventricular arrhythmias, underlying substrates and mechanisms is the key to more accurate risk stratification and development of more effective, individualized and substrate-based therapies.

Part I of this thesis focuses on image integration during VT ablation. The reported applications, potential advantages and limitations are reviewed in **chapter 2**. Imaging modalities that have been applied include multidetector computed tomography (MDCT), late gadolinium enhancement magnetic resonance imaging (LGE-MRI), intracardiac echocardiography (ICE) and nuclear imaging modalities. The majority of studies have focused on the integration of MDCT and LGE-MRI in post-myocardial infarction patients; MDCT because of its relatively high spatial resolution, and LGE-MRI as current non-invasive gold standard for visualization of fibrosis. To date, image integration has been used to uncover and delineate the arrhythmogenic substrate,[1-10] to guide the procedural strategy,[11,12] to avoid ablation in close proximity of coronary arteries,[13,14] to visualize epicardial fat tissue[9,13] and to analyze ablation lesions.[15,16] Although image integration has provided important insights into the substrate for VT, to date it has not been demonstrated that it is cost-effective, reduces total radiation exposure, shortens procedure and mapping time and, most importantly, improves the safety and acute and long-term outcome after VT ablation. Prospective randomized studies comparing imaging-guided VT ablation with standard VT ablation in the setting of different cardiac diseases are required to determine whether this promising technology translates into improved results.

Substrate mapping is indispensable during VT ablation, mainly due to the frequent inducibility of hemodynamic unstable VT. At the epicardium substrate mapping may be hampered by fat tissue, which attenuates bipolar electrogram amplitudes,[13,17] and as a result, it may be difficult to differentiate between scar, myocardium and epicardial fat. Previous studies have demonstrated the feasibility and accuracy of integration of MRI-derived scar data with endocardial electroanatomical maps,[2,7,10,16] and of MDCT-derived epicardial fat with epicardial electroanatomical maps.[13,17] In **chapter 3**, these image integration techniques are combined in a series of 10 patients with NICM who underwent endocardial and epicardial VT ablation. It is demonstrated that bipolar voltage ≤1.81mV and unipolar voltage ≤7.95mV are the optimal cutoff values to distinguish scar from viable myocardium in epicardial regions devoid of fat. However, both bipolar and unipolar voltages are reduced by epicardial fat. Specific electrogram morphologies were not affected by fat, but were present at only one quarter of all scar sites. An algorithm

was constructed to improve differentiation between scar, viable myocardium and fat. These findings provide important insights into epicardial substrate mapping in patients with NICM, which is essential for successful VT ablation.

Chapter 4 describes typical scar patterns and associated VT morphologies in a series of 19 consecutive patients with NICM who underwent VT ablation. In 17 of 19 patients, either a basal anteroseptal or inferolateral scar was observed. Both scar patterns were associated with specific VT 12-lead ECG morphologies. In the 9 patients with anteroseptal scar-related VT, the ablation target sites were mainly located in the aortic root and/or anteroseptal LV endocardium, and in only one case at the epicardium. Of the 8 patients with inferolateral scar-related VT however, 5 had epicardial ablation target sites. The anteroseptal LV is usually difficult to reach during epicardial VT ablation due to the proximal coronary arteries, epicardial fat and the left atrial appendage.[13,18] Epicardial access to the inferolateral LV is typically not or only partly limited by epicardial fat, although the coronary arteries and the variable course of the phrenic nerve need to be considered. These findings are likely to be important for clinicians who consider epicardial VT ablation in patients with NICM. After publication of this study, other investigators have replicated and extended our findings in a larger patient cohort, demonstrating that patients with predominant anteroseptal scar types are at higher risk for VT recurrence during follow-up.[19]

Chapter 5 analyzes the scar characteristics at critical isthmus sites of VTs in patients after myocardial infarction or with nonischemic cardiomyopathy (NICM), aiming to improve our understanding of the substrate for VT, and to analyze the value of MRI-based areas of interest to guide VT ablation. Analysis of scar features at critical VT isthmus sites revealed that critical isthmus sites are characterized by relatively high scar transmurality and signal intensity, compared to the average values for the entire scar, which was particularly evident for the central isthmus sites. The vast majority of critical isthmus sites were located within close proximity (i.e., 5 mm) of >75% transmural scar, and the transition between core and border zone. It is concluded that MRI-derived scar features may be used to guide VT ablation. Other investigations also suggest an association between scar transmurality and electrogram prolongation[7,9,20,21] and VT isthmuses.[21] The relation between scar transmurality and VT in NICM patients is further supported by the study described in chapter 10, which demonstrated that the area of 50-75% scar transmurality carried important prognostic information in patients with NICM undergoing ICD implantation.

Overall, the integration of CT- and MRI-derived data has led to important insights into the substrate for sustained monomorphic VT. Practically, integration of MRI-derived data helps to identify and delineate the substrate, and to lead to areas that contain parts of the reentry circuit. Novel MRI techniques such as T1 mapping, which allows calculation of exact extracellular volumes, and wideband inversion pulses, which allows acquisi-

tion of high-quality contrast-enhanced MRI images in patients with devices,[22,23] may be applied to further enhance the added value of MRI during VT ablation procedures. Ultimately, randomized controlled trials need to be performed to assess the effect of MRI integration on procedural duration, complications and outcomes.

In **part II** of this thesis, the substrate, mechanisms and treatment for different types of ventricular arrhythmias are analyzed in patients with ischemic and nonischemic heart disease.

Chapter 6 focuses on the identification of VTs with an epicardial site of origin in patients with NICM. Although several investigators have previously reported that 12-lead ECG criteria allow differentiation between endocardial and epicardial VTs,[24-26] the ECG criteria were only evaluated on electrophysiology recording systems with electronic calipers at a sweep speed of 100 mm/s. To guide pre-procedural planning, the ECG criteria would however have to be applied to standard 25mm/s 12-lead ECGs of clinically documented VTs. The current study analyzed the value of ECG criteria for identification of VTs with an epicardial site of origin in 36 patients who underwent combined endocardial and epicardial VT ablation. When applied to standard 25mm/s 12-lead ECGs, none of the criteria could accurately differentiate between endocardial or epicardial VTs. When applied to 100mm/s tracings, part of the ECG criteria could distinguish epicardial from endocardial VTs, but only in slow VTs and in patients on amiodarone. The latter may be explained by the fact that the majority of ECG criteria rely on accurate identification of the QRS onset, which may be difficult to define in fast VTs in patients off amiodarone. These data suggest that when applied to standard 12-lead ECGs, the ECG criteria do not allow identification of patients who are likely to benefit from a primary epicardial ablation approach. LGE-MRI-derived substrate features may be more reliable to guide the procedural strategy in patients undergoing VT ablation.[11]

If epicardial mapping and ablation are performed, post-procedural pericarditic chest pain and pericarditic ECG changes may occur. In **chapter 7** we analyzed the effect of intrapericardial and systemic steroids on post-procedural pericarditic chest pain and ECG changes in a series of 85 patients who underwent epicardial mapping and ablation for VT. Over the years, the post-procedural management has evolved from no steroids, to systemic steroids, and finally to intrapericardial steroids. Pericarditic chest pain occurred in 59%, 43% and 21% of patients, respectively (overall p=0.017; no steroids vs intrapericardial steroids, p=0.006), and ECG changes in 41%, 30% and 37%, respectively (overall p=0.72), suggesting that intrapericardial steroids may reduce pericarditic chest pain, but not ECG changes after epicardial mapping and ablation. Although not randomly allocated, therapies were applied unselectively in consecutive patients, and the observed effects were large, suggesting a true beneficial effect of intrapericardial

steroids on pericarditic chest pain after epicardial mapping and ablation. A randomized study would however be required to definitively prove its efficacy.

There is limited data on the outcome after VT ablation in patients with NICM, and in particular on the value of programmed electrical stimulation to assess the acute procedural outcome. **Chapter 8** describes and analyzes the acute and long-term outcomes after VT ablation in a contemporary series of 45 patients with NICM. At the end of the procedure, a programmed electrical stimulation protocol was consistently applied and completed in all patients to assess the acute procedural outcome. Complete success was achieved in 38% of patients, partial success in another 38% and failure in 24%. Although 53% of patients had VT during an average of two years follow-up, the 6-month VT burden was reduced by ≥ 75% in 79% of patients. Non-complete success was the strongest predictor of VT recurrence, with recurrences in only 18% after complete success, compared with 77% after partial success and 73% after procedural failure. Importantly, the inducibility of non-clinical, usually fast VTs after successful ablation of the clinical VT was associated with high recurrence rates, and should therefore not be regarded as a non-specific finding. This does however not necessarily imply that fast, nonclinical VTs should always be targeted – persistent inducibility of fast VTs may also be a marker for a more complex or functionally determined arrhythmogenic substrate, which may be less amenable to VT ablation. Further studies are needed to assess whether targeting of these nonclinical, usually rapid VTs improves long-term outcomes after ablation. More generally, it is unclear whether and to what extent high VT recurrence rates are attributable to the timing of the procedure, not identified or not reachable substrates, insufficient lesion formation or lesion recovery, arrhythmogenic substrates that evolve over time, progressive heart failure, or other factors that are currently poorly understood. Future observational and experimental studies should aim to assess the effects of these and other factors (e.g., early referral, procedural strategy, ablation techniques, optimization of medical and device therapy) on procedural outcome.

Chapter 9 evaluates the impact of early reperfusion therapy on the inducibility and cycle length of VTs, and on the occurrence of VTs late after myocardial infarction. In a prior study in patients who were referred for treatment of VT, spontaneous and induced VTs were faster in reperfused patients, who typically had a patchy electroanatomic scar pattern, as opposed to a more confluent scar pattern in nonreperfused patients.[27] The present study aimed to analyze the effects of reperfusion therapy on ventricular arrhythmias in a large cohort of 506 post-infarction patients who underwent an electrophysiology study before ICD implantation for primary or secondary prevention. Inducibility of VT was comparable between primary prevention patients with and without reperfusion therapy (56% and 58%, respectively), but higher in secondary prevention patients without reperfusion therapy compared to those who had underwent reperfusion therapy (79% versus 56%, respectively, p=0.001). The absence of reperfusion therapy

was independently associated with a slower CL of induced VTs. In primary prevention patients, nonreperfused patients had a more than twofold increased risk for appropriate ICD therapy during follow-up. Thus, the application of reperfusion therapies at the time of acute myocardial infarction is an important determinant of the occurrence and characteristics of late ventricular arrhythmias. These findings improve our understanding of contemporary changes in arrhythmogenic substrates due to the widespread application of reperfusion therapies for acute myocardial infarction. Whether these changes are (partly) attributable to scar transmurality, which is associated with VT (chapter 5) and in general larger in nonreperfused patients, remains to be elucidated.

Not only in patients after myocardial infarction, but also in NICM patients accurate prediction of arrhythmic events is desirable, and would allow preventive treatment in those who are at risk. Prior studies have typically aimed to identify predictors for appropriate ICD therapy, sudden cardiac death, all-cause mortality or combined endpoints. Different types of ventricular arrhythmias may however have different underlying substrates and related predictors. Sustained monomorphic VT in NICM is considered to be the manifestation of a stable reentry circuit, whereas polymorphic VT and VF are thought to be related to one or more unstable reentry circuits or rotors. **Chapter 10** aimed to analyze the impact of myocardial scar on the occurrence and type of ventricular arrhythmia in patients with NICM, and to assess the predictive value of specific patterns of fibrosis for monomorphic VT. At the Maastricht en Leiden University Medical Centers, LGE-MRI was performed before ICD implantation in 87 patients with NICM. The presence, characteristics and extent of myocardial scar were assessed on LGE-MRI images. ICD recordings and 12-lead ECGs were reviewed to determine the occurrence and type of ventricular arrhythmia during follow-up. Importantly, the presence of myocardial scar predicted monomorphic VT, but not polymorphic VT/VF. The risk for monomorphic VT was particularly high when the LGE extent was ≥ 7.2 grams, whereas patients with < 7.2 grams LGE were at low risk for monomorphic VT, but remained at risk for potentially fatal polymorphic VT/VF. Features that were associated with high risk for monomorphic VT were core extent, location in basal segments and area with 51-75% transmurality. Thus, the current study demonstrates that patients at risk for monomorphic VT can be identified by LGE-MRI, which may have important implications for risk stratification and therapeutic interventions in patients with NIDCM. If patients at risk for polymorphic VT/VF can also be more accurately identified in the future, a randomized controlled trial should be performed to reassess the benefit of ICD implantation on all-cause mortality, quality of life and costs in patients who are considered at low risk for both monomorphic VT and polymorphic VT/VF.

Chapter 11 focuses on the substrate and mechanisms of polymorphic VT/VF in NICM. In order to improve our understanding of the substrate and mechanisms of ventricular arrhythmias in NICM, we designed and initialized the Leiden Nonischemic Cardiomy-

opathy Study in 2011. In this prospective cohort study patients are comprehensively analyzed by LGE-MRI, echocardiography, 24-hour Holter monitoring, exercise testing, blood sampling, an invasive electrophysiological study, endomyocardial biopsy, an MIBG scan and genetic analysis of 55 cardiomyopathy-related genes. The first results of this study are presented in chapter 11, which focuses on the substrate and mechanisms of polymorphic VT and VF. Prediction of these arrhythmias is challenged due to various potential causes, ranging from conduction and repolarization abnormalities to electrolyte imbalances.[28-31] One phenomenon that has been related to VF in patients with NICM is progressive activation delay after premature stimulation.[30] In the current study, we measured the paced QRS duration after premature stimulation as a simple marker of activation delay after premature stimulation in 40 patients with NICM and 20 healthy controls. The QRS duration started to increase at longer coupling intervals in NICM compared with controls, and the maximum increase was larger. In patients with NICM, the local refractory period at the pacing site was frequently shorter than the maximal paced QRS duration, which allowed to pace and capture within the previous QRS complex, with the potential to initiate a second, different activation wave front. This phenomenon was related to the inducibility of polymorphic VT and was associated with long thick strands of fibrosis in biopsy specimens. This study suggest that progressive activation delay may be quantified by measuring the QRS duration during a standard electrophysiological study, and that activation delay correlates with electrical instability. A future research project within the Leiden Nonischemic Cardiomyopathy Study aims to analyze whether progressive activation delay after premature stimulation predicts spontaneous polymorphic VT and VF during follow-up.

CONCLUSIONS

In patients undergoing VT ablation, image integration improves preprocedural planning, substrate identification and delineation, and can guide to areas containing critical isthmus sites. In patients with prior myocardial infarction or NICM, the presence, extent and features of myocardial scar determine the occurrence and characteristics of monomorphic VT. Progressive activation delay after premature stimulation is associated with the inducibility of polymorphic VT in NICM.

The studies described in this thesis contribute to an improved understanding of the substrate and mechanisms of ventricular arrhythmias in ischemic and nonischemic heart disease, which is the most important prerequisite for the development of effective, individualized and substrate-based therapies for ventricular arrhythmias in the future.

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