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Chapter 1
Introduction and outline of the thesis

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Ventricular tachycardia ablation: indications and techniques
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Abstract

The growing role of catheter ablation for ventricular arrhythmias in patients with and without structural heart disease reflects the progress made in this field over the last decades. Due to the high ablation success for non scar-related VA catheter ablation has become a first line therapy for symptomatic idiopathic VT and PVCs or VA presumed to cause ventricular dysfunction. In patients with scar-related VT development of substrate based techniques, irrigated tip catheter ablation and the introduction of an percutaneous epicardial approach in selected patients has rendered many VT previously considered ‘unmappable’ approachable for ablation. Catheter ablation may be considered in post MI patients even after a first VA episode to prevent VT recurrences during follow-up or to avoid drug therapy, provided that the procedure can be performed safely. The underlying heart disease affects the substrate that determines VT characteristics. Better understanding of the VT substrate in different diseases and individual patients is important for the improvement of mapping and ablation strategies. Advances in substrate imaging technologies and their integration during ablation procedures may provide more insights into the substrates and may guide VT ablation in the future. Since treatment strategies and prognosis of scar-related and non scar-related VT differ, the distinction between these entities is of great relevance and may be enhanced by identification of the VT substrate during catheter mapping. Ablation failure is frequently due to the anatomical localization of the target site. However, evolving new catheter techniques and energy sources may overcome these limitations.
Introduction

Since the first report in 1959 of surgical ventriculoplasty abolishing recurrent ventricular tachycardia (VT) in a patient after myocardial infarction\(^1\) ablation of VT has evolved from surgical treatment to radiofrequency catheter ablation (RFCA). Over the last decennium indications have broadened and techniques have been developed resulting in an increasing use of RFCA for different types of VT.\(^2\)

Patients presenting with VT and underlying structural heart disease are at risk for sudden cardiac death (SCD).\(^3\) The use of implantable cardioverter defibrillators (ICDs) has resulted in a significant reduction in SCD in this patient population.\(^3\)\(^-\)\(^5\) ICDs effectively terminate VT but cannot prevent VT recurrence and after an initial episode of VT or ventricular fibrillation (VF) up to two thirds of patients receive one or more appropriate therapies within two years.\(^6\), \(^7\) An important number of VT termination requires shocks which have an significant impact on quality of life.\(^8\) In addition, in patients with heart failure ICD shocks are associated with an increased risk of death.\(^9\) Therapies that prevent episodes of VT are therefore warranted. RFCA can prevent VT recurrence, thereby decreasing the number of ICD shocks in patients with structural heart disease by modifying the VT substrate.\(^6\), \(^7\)

Ventricular arrhythmias (VA) that occur in the absence of structural heart disease are generally considered benign and are associated with a favorable prognosis.\(^10\) Distinction between patients with scar-related and idiopathic (non scar-related) VA is therefore of key relevance. However, a small number of patients presents with malignant VA without (todays) evidence of structural heart disease or scar and some patients have idiopathic VA that cause a potential reversible cardiomyopathy.\(^11\), \(^12\)

Since its first use in 1978 RFCA for idiopathic VA has been proven to be curative and safe and is now considered a first line therapy in highly symptomatic patients.\(^2\)

Even though RFCA for VT is recognized to be of value in structural heart disease, the appropriate patient selection, methods to use, optimal timing and best endpoint are still matter of debate. Individual patient factors and operator experience play an important role in risk-benefit considerations.
Mechanisms and substrates underlying ventricular arrhythmia

Scar-related reentrant ventricular tachycardia

Reentry is the prevailing mechanism for VT related to scar. The requirements for reentry to occur are areas of slow conduction, sites of fixed or functional conduction block and an initiating stimulus or sequence of stimuli.

The time that is needed for propagation through slow conduction areas allows for repolarization of the remaining parts of the circuit so that the reentrant wavefront does not encounter block during its progression.

Histological evaluation of slow conduction areas showed tracts of viable myocardial cells traversing areas of fibrous tissue. Several factors may contribute to the reduction in conduction velocity. Fibrosis between strands of viable cells functionally prolongs the pathway for impulse propagation. In addition, changes in cell coupling by a decreased number of gap-junctions and altered connexin expression may contribute to slow conduction on a cell to cell level.

Conduction velocity is also influenced by the direction of wave front propagation and architecture of fibrosis. Wavefront propagation perpendicular to fiber direction is slower than propagation parallel to the fiber direction.

Areas of fixed or functional conduction block influence reentrant circuit characteristics and form the borders of a protected channel or ‘isthmus’ of viable myocardial cells. Dense fibrosis and other unexcitable tissue like valve annuli and surgical scars may serve as areas of fixed conduction block. In contrast, functional block is not present during normal rhythm but can evolve due to change in refractoriness in response to a premature excitation and may be equally important defining the reentrant circuit isthmus. The 3-dimensional geometry of myocardial scar plays an important role in the formation of block and may even predict the location of potential reentry circuits.

The critical part of a reentry circuit is an area of slow conduction bordered by two lines of fixed or functional conduction block, the critical isthmus. Reentry is initiated by a premature excitation wavefront that enters this isthmus through its entrance and traverses it slowly. At the exit of the isthmus, often located at the border of the scar, the wavefront emerges to rapidly depolarize the remainder of the ventricles. The activation propagates along the border of the scar (the outer loop) to reactivate the excitable entrance of the circuit thereby closing the circle. (Figure 1) The dimensions of a reentry circuit are 3-dimensional and parts of the circuit may lay subendocardial, intramural and subepicardial, depending on the location and geometry of the structures causing conduction block.
Figure 1. Components of the reentrant circuit and corresponding response to entrainment mapping

Schematic of a scar-related reentrant circuit. The gray areas represent dense scar and white areas represent conducting myocardium. Numbers indicate different reentrant circuit sites encountered during mapping.

1. Exit site. The activation wavefront exits the scar to activate the remainder of the ventricles. During VT concealed entrainment, a difference between post pacing interval (PPI) and VT cycle length ≤30ms and a short stimulus to QRS interval (<30% of VT cycle length) are typically found at this site.

2. Critical isthmus. Protected area of slow conduction through the scar. Concealed entrainment, a difference between PPI and VT cycle length ≤30ms and an intermediate stimulus to QRS interval (31 – 50% of VT cycle length) are encountered at this site during VT.

3. Adjacent bystanders. Slow conducting areas in the scar not part of the reentry circuit under evaluation. Even though during VT concealed entrainment can be found the difference between PPI and VT cycle length is usually long (>30ms).

4. Entrance site. The activation wave front enters the circuit isthmus. Features: Concealed entrainment, a difference between PPI and VT cycle length ≤30ms and a long stimulus to QRS interval (51-70% of VT cycle length).

5. Outer loop. Rapid activation of the ventricular myocardium from exit toward entrance site. Mapping during VT reveals entrainment with QRS fusion.
Non scar-related idiopathic ventricular arrhythmia

Idiopathic VA is a term used for VA that is known to occur in the absence of clinically apparent structural heart disease. Most idiopathic VA have a focal origin in the ventricular outflowtracts (OT) making them susceptible to discrete radiofrequency ablation. The mechanism underlying focal repetitive monomorphic VT (RMVT) can be triggered activity or automaticity. Most focal VA respond to adenosine, verapamil or beta blockers, agents interfering with the cAMP mediated inward calcium current. In particular the specific effect of adenosine indicates that triggered activity induced by cAMP-mediated delayed afterdepolarizations is the major mechanism underlying these focal VA. More rarely the mechanism of focal VA may be automaticity provoked by adrenergic stimulation or arising from damaged Purkinje fibers.

Although most idiopathic VA have a focal origin it has been demonstrated that reentry is the underlying mechanism for a distinct subset of VT, idiopathic left ventricular tachycardia (ILVT), arising from the area of the left posterior or anterior fascicle. The mechanism of this verapamil sensitive form of VT, although not completely understood, may be intrafascicular reentry or involves abnormal Purkinje tissue in which slow conduction is dependent on the slow inward calcium current in partially depolarized cells.

Ablation of VT

Catheter ablation of VT aims to abolish the arrhythmic source in VT with a focal origin or to permanently interrupt the circuit in reentrant VT. The strategy for catheter mapping and ablation is determined by the type of VT and the location of the underlying substrate. The following section summarizes different mapping techniques and potential ablation target sites.

Ablation of Scar-related VT

Mapping during VT

When reentrant VT is stable and hemodynamically well tolerated point by point catheter mapping can be performed to identify the critical isthmus allowing for interrupting the circuit with a limited number of RF lesions during ongoing VT. The QRS of the VT begins when the excitation wavefront emerges from the exit of an isthmus often located at the scar border zone.

Thus the depolarization of the slow conducting isthmus occurs prior to QRS onset. Isthmus sites may be recognized by recording isolated low amplitude, presystolic or diastolic potentials (DP) during VT. These potentials are generated by the depolarization of isolated bundles of viable myocardial cells within the scar. DP are observed at 50% of isthmus sites.
and help to identify sites where RF ablation can terminate VT. However, DP are also seen in bystander areas outside the critical isthmus of the VT under evaluation. Isthmus and bystander sites can be discriminated by entrainment mapping or pacing from a remote site to dissociate the DP from the VT.

Entrainment mapping is used to distinguish different components of the reentry circuit. Pacing slightly faster than the VT continuously resets the reentry circuit. Interpretation of entrainment depends on the assumption that pacing does not alter the conduction through the circuit path or initiate another VT. At circuit isthmus sites, pacing entrains VT without changing the ventricular activation remote from the scar, producing entrainment with concealed fusion recognizable by the same paced QRS as recorded during VT. Entrainment with QRS fusion is observed when pacing is performed from sites outside the protected isthmus resulting in an altered ventricular activation and consequently a different QRS morphology than during VT.

At reentry circuit sites the post-pacing interval (PPI) is equal to the revolution time through the circuit, which is the tachycardia cycle length. The PPI increases with increasing distance and/or conduction time from the pacing site to the circuit. If the difference between PPI and VT cycle length is ≤30ms the pacing site is considered to be part of the reentry circuit. The electrogram (EGM) selected for measuring the PPI is important and should represent the local depolarization at the pacing site. The selection of farfield signals is a common reason for incorrect measurement of the PPI. The local signal is not visible during pacing and reappears when pacing is ceased. Farfield signals are usually not obscured by the stimulus artifact and may be recognized by the fact that they remain visible during pacing.

At reentry circuit isthmus sites the stimulus to QRS interval (S-QRS) equals the conduction time from the pacing site to the reentry circuit exit, and is short (e.g., < 30% of the tachycardia CL) near the exit region, and longer at sites proximal to the exit. At inner loop sites, the stimulus to QRS time may be longer than 70% of the VTCL. Outer loop sites are recognized from a PPI that approximates the VTCL, however at these sites QRS fusion occurs. (Figure 1)

VT unstable for mapping

Only one third of patients after myocardial infarction (MI) and less than 45% of patients with non-ischemic cardiomyopathy referred for ablation of VT are only inducible for VT stable for mapping during ongoing arrhythmia. The majority of patients has ‘unstable’ VTs that are either hemodynamically not tolerated or not reproducibly inducible. Furthermore, multiple morphologies of VT are frequently inducible while data from the spontaneous VT may only be available from ICD interrogation, preventing the definite identification of the clinical VT. Therefore the focus of VT ablation has shifted away from mapping of single VT reentry circuits during ongoing VT to a substrate based approach targeting broader regions
of scarred myocardium likely containing the critical part of the reentry circuit without the need for mapping during VT.

**Substrate mapping**

Substrate based mapping and ablation techniques use local EGM characteristics obtained during stable sinus rhythm (SR) or paced rhythm to identify myocardial scar and areas of abnormal electrical conduction. The reduction of myocytes in scar areas reduces the amplitude of recorded EGMs, allowing areas of scar to be recognized from the peak to peak EGM voltage. Animal studies to validate the method were performed in a model of homogeneous dense, infarct scar surrounded by a small scar border zone. It has been shown that a value of ≤1.5mV peak to peak bipolar EGM voltage best demarcated infarct scar areas. In addition, more than 95% of EGMs in normal human ventricles have a voltage of ≥1.55mV. Areas with low voltage EGM can be visualized in 3-dimensional anatomical maps by colour-coding peak-to-peak EGM voltage (voltagemaps). (Figure 2A-C) Ablation of the entire low voltage area or its circumference is usually not feasible. Therefore additional criteria to further select ablation targets within the scar have been applied.

EGM characteristics obtained during SR can be suggestive for potential reentry circuit sites. Slow and heterogeneous conduction through the scar area may result in broadening and fractionation of the local EGM. Longer duration (>40ms) and fractionated (>4 deflections) EGM have been associated with successful ablation sites for VT after myocardial infarction. Similar to diastolic potentials that precede the QRS complex during VT, isolated late potentials that follow the QRS during SR may indicate the presence of slow conducting channels and can be considered as target sites for ablation. Late potentials may be better recognized during right ventricle (RV) apex pacing in selected patients. (Figure 2C)

Conducting channels within dense fibrosis may have larger voltage amplitudes than the surrounding non-conducting areas. Lowering the voltage criteria for the colour coding of dense scar may allow for the identification of these channels.

**Pacemapping**

Pacemapping can be employed to identify potential VT exit and isthmus sites at the border of the scar during SR. By pacing along the scar-borderzone regions can be identified where the paced 12-lead ECG QRS morphology resembles the VT QRS morphology. Pacing sites with a matching QRS morphology are likely to be near the exit of the reentry circuit. During pacemapping a stimulus-to-QRS (S-QRS) delay of ≥40ms indicates slow conduction away from the pacing site. (Figure 2C) A paced QRS matching the VT QRS in combination with a long S-QRS interval is consistent with a potential VT isthmus site. Pacing performed at a site more proximal in the circuit may however result in a different QRS morphology since the activation sequence following the stimulus may be opposite to that of the tachycardia.
Figure 2. Image integration of electroanatomical voltage mapping and CE-MRI derived data on anatomy and scar characteristics (for figure in color see page: 252)
Example of a patient presenting with VT due to non-ischemic cardiomyopathy in whom combined endocardial and epicardial catheter ablation was performed using image integration of CE-MRI derived data sets and electroanatomical substrate mapping techniques during sinus rhythm.
A and C. Successful integration of the CE-MRI derived LV and aortic cusp anatomy with the LV endocardial electroanatomical voltage map (EAVM) (voltages>1.5mV defined as normal and color coded in purple) using the left main coronary artery (LM) as a single landmark for registration.
B. The fluoroscopy image shows contrast injection through the ablation catheter (MAP) to confirm its position in the LM. Other catheters shown are located at the right ventricular apex (RVa), coronary sinus (CS) and a pigtail catheter in the pericardial space.
Pacing within the scar may further be used to identify area with electrically unexcitable scar (EUS), defined as sites with a unipolar pacing threshold of ≥10mA at 2ms pulse width. Areas of EUS and anatomical boundaries such as valve annuli may form regions of fixed conduction block bordering the VT reentry circuit isthmus; targeting these isthmuses by connecting the anatomical boundaries to EUS or the areas of EUS by linear RF lesions can abolish VT.17, 38

Linear ablation lines along the scar border in the region of a presumed exit site or through an identified isthmus performed during SR can be also effective in controlling VT. Additional ablation lesions connecting to dense scar areas or anatomical boundaries or perpendicular to the scar border into the scar have also been applied.32, 34, 38

Substrate mapping can also be combined with limited mapping during VT, allowing for identification of the regions of interest during stable SR first. After VT induction evaluation of VT EGMs, entrainment mapping, and ablation can be restricted to predefined regions and may be feasible also for poorly tolerated VT.32

Non-contact mapping

Unstable VTs can be mapped as well using multielectrode mapping arrays that sample and mathematically reconstruct virtual EGMs from multiple distant sites simultaneously. These
Figure 3. Integration of electroanatomical activation mapping and MSCT derived anatomy during epicardial ablation (for figure in color see page: 253)

Example of a patient presenting with frequent highly symptomatic non-sustained idiopathic VT in whom combined endo- and epicardial electroanatomical mapping and ablation was performed facilitated by integration of CT derived anatomy.

A. 12-lead QRS of the non-sustained VT.

B. Endocardial activation mapping showing limited maps of the aortic cusps (AoSV), great cardiac vein (GCV), right ventricular outflowtract (RVOT) and left ventricle (LV). Earliest local activation time (LAT) was recorded in the GCV but ablation at this site was not successful. C. A limited epicardial activation map overlaying the endocardial maps; epicardial LAT during VT is earlier than the earliest LAT in the GCV.

D. Short axis slice of contrast enhanced multislice computed tomography scan (CT) showing the left and right ventricles (LV and RV) and pericardial fat in the interventricular groove and RV lateral wall.

E and H. Different views of CT derived anatomy showing the proximal aorta, left main coronary artery and pulmonary artery with overlaying CT derived mesh of the epicardial surface. Color
Non contact mapping may be able to identify the VT exit site in >90% of VTs and some diastolic activity in two-thirds of VTs. However, a complete diastolic pathway could only be identified in 21% of patients in one study.

**Intramural and Epicardial Circuits**

Although parts of scar-related reentry circuits are usually located subendocardially, circuits may extend deep into the myocardium. Inability to define an adequate endocardial ablation target where catheter ablation can interrupt the reentry circuit is an important cause for ablation failure. Ablation using open, irrigated tip catheters increases lesion size and may therefore be more effective targeting circuits extending deep into the myocardial wall.

**Epicardial ablation**

In an important number of patients with scar-related VT RV or left ventricular (LV) endocardial ablation may however be insufficient despite the use of irrigated tip catheters. In these patients, part of the reentry circuit may be located at the subepicardium and a transcutaneous epicardial ablation approach should be considered. The necessity of an epicardial ablation may be different according to the underlying disease causing the substrate for VT. The VT surface ECG can be helpful in identifying VT of epicardial origin prior to the procedure. The time needed for the activation wave front to initially traverse the myocardial wall may result in a prolonged initial component of the VT QRS that may be suggestive of an epicardial origin.

Access to the pericardial space can be obtained by a subxyphoid pericardial puncture. If adhesions from prior cardiac surgery or pericarditis limit the access, a surgical approach via a subxyphoid pericardial window may allow at least limited pericardial mapping and ablation.

Epicardial substrate and VT mapping approaches are similar to those employed during endocardial mapping. Epicardial fat however can limit the feasibility of voltage, pace
and entrainment mapping due to the local reduction of the bipolar amplitude and a higher stimulation threshold or no capture of the myocardium covered by fat. In addition, epicardial fat (>5mm) can prevent effective ablation lesion formation in the underlying myocardium.\textsuperscript{46, 47} (Figure 3) The real time integration of CT derived coronary anatomy and fat distribution to aid RFCA is further studied in chapter 6. RFCA in the vicinity of coronary arteries or the phrenic nerve should be avoided. Coronary arteries may be visualised by coronary angiogram or by integration of pre-acquired multislice CT imaging; a distance of >5mm between the ablation catheter and the coronary artery during RF delivery is recommended.\textsuperscript{2, 46, 48} (Figure 2 and 3) The course of the phrenic nerve traversing the lateral LV pericardium can be identified by diaphragmatic stimulation during pacing.\textsuperscript{49}

The results of epicardial ablation after failed endocardial ablation in selected patients is encouraging; however data are derived from experienced centers and may not be applicable to less experienced operators.\textsuperscript{2}

**Substrate imaging**

Most of 3-dimensional electroanatomical mapping systems allow for the integration of pre-acquired cardiac images with electroanatomical voltagemaps. Currently, different imaging modalities are used to facilitate substrate mapping and ablation. Integration with pre-acquired Multislice computed tomography (MSCT) images can facilitate real-time visualization of the proximal coronary arteries and the distribution of epicardial fat during epicardial mapping and ablation.\textsuperscript{48, 50} (Figure 2 and 3)

Information derived from imaging modalities like positron emission tomography (PET) CT and contrast enhanced magnetic resonance imaging (CE-MRI) that provide not only anatomical data but potential information on VT substrate may be of complementary value before and during ablation procedures.

PET can detect non-viable myocardial scar and the combination with CT may accurately delineate location and extend of scar. The integration of PET/CT derived data with electroanatomical mapping has shown to be feasible and accurate. Potential advantages of these techniques are limitation of procedure and fluoroscopy times, the identification of false positive low voltage areas, due to poor catheter contact, and perhaps the identification of viable channels through the scar.\textsuperscript{51} However, the substrate information provided by PET represents local glucose metabolism and does not visualize fibrosis. Furthermore, despite the high spatial resolution of CT the resolution of PET is relatively poor thereby limiting the visualization of smaller viable channels within the scar.

CE-MRI allows for the visualisation of the three-dimensional geometry of myocardial fibrosis and is the gold standard for the detection of subendocardial and non-transmural scar.\textsuperscript{52, 53} In patients with non ischemic cardiomyopathy (NICM) CE-MRI can sensitively detect intramural and epicardial scars, which might help to choose the appropriate mapping strategy (endocardial, epicardial or combined).\textsuperscript{54-56} (Figure 2B) In addition, CE-MRI
can characterize scar heterogeneity based on signal intensity (SI) the extend of which has been associated with spontaneous VT. Furthermore, animal studies have shown that the detailed scar geometry as assessed by in vitro CE-MRI can predict the location of VT reentry circuits.19, 58 Real time integration of CE-MRI derived scar information with electroanatomical mapping may allow for visualisation of intramural or epicardial scars and scar characteristics during the procedure and facilitate mapping and catheterablation.54, 55, 59 (Figure 2A) (This topic is further studied in chapter 5)

In the process of merging imaging derived data sets with electroanatomical maps anatomical landmarks are of key importance. Several studies have used the combination of the LV apex, mitral annulus and the aorta for registration.51, 54, 55, 59 Others have used the ostium of the left main coronary artery located by contrast injection which has the potential to preclude rotation errors.48, 55 (Figures 2 and 3) Whether integration of CE-MRI or PET/CT derived information with electroanatomical mapping during ablation procedures translates in to improved outcome needs further evaluation.

Ablation of Focal VT

The activation wavefront of focal arrhythmias spreads radially from the source to depolarize the ventricles creating monomorphic VT or premature ventricular contractions (PVC).

Most focal VA are hemodynamically well tolerated allowing for point by point mapping and evaluation of the recorded local unipolar and bipolar EGM. Unipolar EGMs provide information about the direction of the activation wavefront: an initial positive deflection of the unipolar EGM indicates propagation towards the catheter and has a high negative predictive value for a successful ablation site in focal VA. As the wavefront reaches the electrode and propagates away, the deflection turns negative. When the catheter is located at the focal source the wavefront propagates away producing a monophasic QS configuration. (Figure 4) However, unipolar EGMs provide information about a relatively large area and contain important far field signals. In contrast, in bipolar EGMs the far field signal is subtracted out thereby providing information about the local electrical activity, but do not contain information about the direction of the wavefront. Currently, most ablation procedures for focal arrhythmias are guided by local activation time defined by the initial peak of the bipolar EGM or the rapid negative deflection of the unipolar EGM and in addition by an unipolar QS configuration.60 (Figure 4) Targeting the arrhythmia focus based on local activation time is successful in >85% of patients.61 However, additional mapping criteria that can increase mapping resolution may be helpful to enhance effectiveness and limit the number of required radiofrequency lesions. Reversed polarity of adjacent bipolar EGMs has shown to be useful in ablation of atrial
fibrillation, chapter 3 further studies the use of this mapping criterion for idiopathic RVOT VA.62 (Figure 4)

When mapping during arrhythmia is not feasible due to infrequent occurrence of the arrhythmia pacemapping may be an alternative mapping strategy. Pacemapping compares the 12-lead surface ECG QRS morphology while pacing at a particular site to the morphology of the spontaneous arrhythmia. A good match or ‘pacemap’ however might have an inferior mapping resolution as compared to mapping of local activation time.63

Idiopathic VA usually originate from the ventricular outflow tract region that includes a number of anatomical structures confined to a limited 3-dimensional space. Prior to the ablation procedure the surface ECG QRS morphology may already indicate the site of origin.22, 43, 64 In > 80% of idiopathic VT the RVOT is the site of origin. However, focal VT can also
originate from the pulmonary artery, the parahisian region, the left ventricular outflow tract (LVOT), the mitral annulus, aortic sinuses of Valsalva and the epicardium (in particular in the proximity of the venous system) requiring a transvenous or trans-pericardial approach.43

In addition, VA arising from the papillary muscle or the Purkinjesystem are described. Ablation of PVC’s originating form the purkinje system may be effectively abolished by targeting sharp purkinje potentials preceding the local EGM during arrhythmia and local activation during SR.11, 65

**New technologies**
The reason for VA ablation failure and recurrence after ablation is often unclear. One important cause for may be insufficient lesion formation due to poor catheter contact, which might be improved by the use of real time ablation tip contact force measurement.66 Effective ablation of deep septal reentry circuits or intramural circuits and focal sources that are not abolished from the endo- or epicardium may require deeper ablation lesions. In animal studies enhancement of ablation lesions was demonstrated by using bipolar ablation between two catheters on either side of the interventricular septum or by the use of intramural needle ablation.67, 68

**Specific Substrates**

**Ischemic Cardiomyopathy**
The incidence of VT in patients late after myocardial infarction (MI) is 1-2%, often occurring after an interval of several years.2 Most research on VT reentry circuits and catheter ablation of VT was performed in animal models of MI and in patients after MI.

**Substrate**
The substrate of VT after MI is determined by the geometry of myocardial fibrosis which is influenced by the extent of irreversible injury and surviving myocyte bundles. During MI the injury develops as a wave front beginning in the subendocardial myocardium progressing towards the subepicardium.59 Scar size and geometry are among others determined by the duration of coronary artery occlusion. Timely reperfusion of the infarct related artery terminates the wave front of necrosis resulting in non-transmural necrosis whereas late reperfusion or permanent coronary occlusion may result in a uniform transmural necrosis.70 Infarct size is also influenced by collateral perfusion during the acute MI71, which may be present in variable degrees in humans. The finding that in post MI patients the endocardial scar area as defined by voltagemapping is generally larger than the epicardial scar47 is consistent with the ‘wave front’ theory.
Much of our understanding of the VT substrate after MI is based first on animal models of a chronically occluded coronary artery which typically results in a dense scar with only a small scar borderzone; and secondly on interaoperative mapping studies in post-MI patients with a chronically occluded artery and typically aneurism formation. However, currently early reperfusion strategies have become the standard treatment of acute MI. Whether early reperfusion affects electroanatomical scars and impacts late VT characteristics is studied in chapter 4 and 9.72

Outcome

Early single-center studies reported acute ablation success rates of up to 90% abolishing the targeted or clinical VT. Recurrence rates were 26-37 % over a follow-up of 34-41 months.73,74 In these studies only selected patients with drug refractory, monomorphic, hemodynamically tolerated and reproducibly inducible VTs were included and mapping and ablation was performed using standard RF catheters. Due to the formation of larger and deeper lesions cooled or irrigated RF ablation has proved to be more effective for terminating scar-related VT compared with standard RF and is now preferred for ablation of scar related VT.

In the first multicenter study, which evaluated the efficacy and safety of irrigated tip catheter ablation only stable VTs were targeted in 146 patients; all mappable VT’s were successfully ablated in 75% of patients. The 1-year recurrence rate was 56%; however a major reduction of VT frequency was observed in most patients. Importantly in 40% of patients fast VTs (<300ms) could be induced that were not targeted.75

The high incidence of VT unstable for mapping during ongoing tachycardia has lead to the development of substrate based ablation approaches. In small single-center studies including 9-40 post MI patients all inducible VTs were treated by using additional substrate based criteria to identify ablation target areas. In these series linear RF lesions were applied. In 45-47% of patients no monomorphic VT was inducible after the procedure. The recurrence rate was 25-38% during 8- 10 months follow-up and was higher if VT was still inducible after the procedure or if a VT isthmus could not be identified.32,34

The current status and outcome of VT-ablation in post MI patients is probably best reflected by two recently conducted multi-center trails. The Multicenter Thermocool Ventricular Tachycardia Ablation Trail reported on 231 patientes from 18 centers and the Euro-VT-study on 63 patients from 8 centers.25,76 Both trails included patients with recurrent or incessant VT for ablation with irrigated open tip catheters using substrate and entrainment mapping facilitated by a 3-D electroanatomical mapping system. The mean number of inducible VTs was 3±2 per patient and unmappable VTs were present in 69 and 63% of patients.25,76

In the Thermocool study ablation abolished at least one VT in 81% and all VTs in 49% of patients. During a follow-up period of 6 months 51% of patients experienced a recurrent VT. However, the frequency of VT episodes was reduced by ≥75% in 67% of patients. The periprocedural mortality rate was 3%, mainly attributable to uncontrollable arrhythmia.25
In the Euro-VT study ablation was acutely successful in 81% of patients. During 12 months follow-up 37% of successfully ablated and 49% of all patients experienced a VT recurrence. One patient experienced a major complication in this study.76

In a subgroup of patients presenting with incessant VT or VT storm catheter ablation can be life saving. Acute termination of VT can be achieved in 89% of patients, with a VT recurrence rate of 34% in 22 months as reported by Carbucicchio et al.77

An epicardial ablation approach to control recurrent VT seems to be less frequently needed in post MI patients as compared to patients with NICM. Surgical mapping studies have demonstrated that only a minority of VT reentry circuits was located in the subepicardium, in particular in patients after inferior MI.20 In a large observational study epicardial ablation was performed in only 7% of 278 ablation procedures for post MI VT.42 However, a significant number of these patients has undergone coronary artery bypass graft (CABG) surgery in the past which has perhaps restricted the epicardial ablation approach.

**Early ablation for VT**

Recent studies indicate that there might be a role of early catheter ablation after a first episode of VT in post-MI patients concomitant with ICD implantation.

The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trial included 128 post MI patients with a planned or recent ICD implantation for secondary prevention for hemodynamically intolerated VT, syncope with inducible VT during EP study or VF. Patients were randomized to implantation of ICD alone or ICD implantation with adjunctive catheter ablation of VT using a substrate based approach.6 During 22.5 months follow-up 12% of patients in the ablation group and 33% of patients in the control group experienced at least one appropriate ICD therapy, a reduction of 65%. Catheter ablation led to a 73% reduction in ICD shocks. Of interest, there was a trend towards a reduced mortality in the ablation group versus the control group (9% vs. 17%).6

In the multicenter Ventricular Tachycardia Ablation in Addition to Implantable Defibrillators in Coronary Heart Diseasese (VTACH) trial 107 post MI patients presenting with stable VT and reduced LV ejection fraction were randomized to ICD alone or ICD with adjunctive catheter ablation. Mean follow-up was 22.5 months. The median time to first episode of VT or VF was significantly prolonged in the ablation group. The median number of appropriate ICD therapies was reduced by 93% per patient per year.7

No procedure related death was reported in both studies. Non-fatal, procedure related complications occurred in 4.7% and 3.8% of patients, respectively.6,7 Based on these findings an early use of catheter ablation may be considered in selected patients who receive and ICD as alternative to drug therapy, provided that the procedure can be performed safely.

A recent meta-analysis including 5 studies with a total of 457 participants, 58% treated with adjunctive catheter ablation, showed a 35% reduction in the number of patients with VT recurrence after adjunctive catheter ablation during 6 - 22.5 months of follow-up. No
significant difference in mortality was observed. Further controlled trails with longer follow-up are warranted to evaluate the effect of early catheter ablation on mortality.

**Substrate in Dilated Cardiomyopathy.**

Even though uncommon, VT also occurs in patients with DCM. The mechanism of VT in DCM is scar-related reentry in 80% of patients, with the remainder being due to bundle branch reentry or a focal origin. At necropsy only 14% of patients with DCM have grossly visible left ventricular scars, in the majority of patients however interstitial or replacement fibrosis is found at histological evaluation. A CE-MRI study performed in patients with clinically defined DCM reported on subendocardial scar in 13% and midwall scar in 28% of patients. No delayed enhancement at all was found in 59% perhaps because of the inability of CE-MRI to detect microscopic interstitial fibrosis. Of interest, the presence of scar detected with CE-MRI and increasing scar thickness have been associated with VT inducibility in DCM patients. Accordingly, evidence of scar is often present in patients who undergo catheter ablation for VT. Areas of endocardial abnormal EGMs as depicted by voltagemapping are relatively small, commonly <25% of the endocardial surface. In patients who underwent epicardial voltage mapping the electroanatomical scar tends to be larger on the epicardial surface. Scar areas are commonly found at the basal LV with a predilection at the inferolateral LV wall both endo- and epicardially. Epicardial EGMs in low voltage areas are characterised by low amplitude (<1.0mV) and long duration (>80ms). Late potentials, that likely reflect areas of slow conduction in a fixed substrate, however may be observed less frequently in DCM patients than in post MI patients. (Figure 2C) The latter finding may suggest that in DCM patients’ functional block, rather than isthmuses bordered by fixed lines of block are important for the occurrence of reentry circuits. This is in line with findings from de Bakker et al. who found short and long strands of fibrous tissue running parallel to the myocardial fiber orientation in human hearts after transplantation for DCM. In these samples activation delay and EGM fractionation was caused by discontinuous and circuitious conduction through zones of patchy fibrosis, which plays an important role for non-uniform anisotropy.

**Catheter ablation**

Data on catheter ablation for VT in DCM are derived from small single-center studies performed in selected groups of patients. The success of endocardial ablation may be disappointing; acute complete success rates of 27% and 33% have been reported, with a VT recurrence rate of 58% and 47%, respectively in two different series. However, after endocardial ablation failure an epicardial approach might be effective. Eighteen of 22 patients who underwent endo- and epicardial catheter ablation after a previous endocardial ablation failure were rendered non-inducible at the end of the procedure. During 18 months follow-up 71% of patients were free of VT recurrence.
RV scar related VT

Patients with scar-related right ventricular tachycardia (VT) are at risk for VT recurrence and sudden cardiac death. An important cause of RV scar is arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a progressive and most likely genetic disease. However, in more than 50% of affected patients no familial occurrence or disease-specific genetic mutations are found; therefore, diagnosis of ARVC/D is based on criteria proposed by a generally accepted consensus report by an international task force (TF). ARVC/D is histologically characterized by loss of right ventricular myocytes, which may be due to impaired function of the cell adherence complex in combination with mechanical stress, resulting in myocardial cell death with replacement by fibro-fatty tissue. This process begins in the subepicardium and progresses towards the subendocardium.

Although predominantly found in the RV, dysplasia can also involve the LV. Areas of scar as identified by electroanatomical voltage mapping are commonly localized adjacent to the lateral tricuspid annulus, the RVOT, and RV apex. Macroreentrant circuits tend to be clustered around the tricuspid annulus and RVOT and focal activation patterns, perhaps the endocardial breakthrough of an epicardial reentry circuit, have been observed at the RV free wall.

Other diseases like post inflammatory myopathy or sarcoidosis can mimic ARVC/D. In sarcoidosis active granulomatous inflammation can be replaced by fibrosis thereby providing the substrate for reentrant VT. Catheter mapping may reveal low voltage areas in both the RV and LV.

Subtle or early forms of RV fibrosis as substrate for RV tachycardia may only be detected by electroanatomical mapping which may have important prognostic and therapeutic implications by excluding an idiopathic VA.

Outcome

Prior to the widespread use of substrate based ablation techniques two series reported acute ablation success rates, defined as non-inducibility at the end of the procedure, of 46 and 45% using conventional mapping techniques. The two year VT recurrence rate was 71 and 41% respectively. The concept of substrate mapping and ablation including the application of linear lesions to encircle or connect scars facilitated by 3-dimensional mapping systems has evolved over the last decennium. Three more recently conducted studies using a substrate based approach reported much higher acute success rates (74-88%). Long term success rates varied between 53, 76 and 89% of patients who were free of VT recurrence after 36, 26 and 27 months, respectively.

Results of RFCA of scar-related VT due to sarcoidosis seem to be disappointing. In one small series reporting on 8 patients VT remained inducible at the end of the ablation procedure in 7 (88%) patients and during follow-up 6 (77%) patients experienced recurrent VT.
Both ARVC/D and sarcoidosis are progressive diseases and VT recurrence rates may also be due to further development of substrate over time.

However, similar to DCM patients with ARVC/D have more extensive epicardial scar. A combined endo- and epicardial approach after prior endocardial ablation can be highly effective in abolishing VTs in selected patients and might improve long-term results. Eighty-five percent of patients were non-inducible for VT after ablation and 77% were free of recurrence during 18 months follow-up in one series.93

Factors influencing outcome of scar-related VT from the RV including subtle scars only detected by electroanatomical mapping is further evaluated in chapter 8.

VT after cardiac surgery

Catheter ablation can be an effective treatment option for scar-related VT occurring after surgical intervention. Surgical scars or patch material may contribute to the substrate for VT late after repair of congenital heart disease, valve surgery or ventricular reconstructive surgery for heart failure.

Small series of patients who underwent RFCA for recurrent VT after corrected congenital heart disease (CHD), the majority after repair of tetralogy of Fallot have been reported.17, 94 Ablation guided by mapping during VT can be successful in selected patients who present with stable VT with recurrence rates of up to 40% in 3.8 years.94 However, the majority of patients after repair of CHD has fast VTs that require a substrate based ablation approach. Electroanatomical mapping performed during SR can identify unexcitable surgical scars, patch material and anatomical boundaries such as valve annuli that anatomically define the critical isthmus for VT. Transecting these isthmuses with linear RFCA lesions resulted in 91% freedom of VT recurrence after a follow-up of 30 months in one series.17

VT after aortic or mitral valve surgery in the absence of prior myocardial infarction is rare. In a small series of 20 patients 14(70%) had VT due to scar-related reentry, the majority having scars adjacent to the replaced valve annulus. Ablation abolished 98% of inducible VT and 11(55%) patients remained free of recurrence during a 2.1 year follow-up.95

Catheter ablation of VT occurring after surgical ventricular restoration for heart failure in ischemic cardiomyopathy is studied in chapter 10.

Idiopathic VT

Despite a good prognosis idiopathic VA can cause severe symptoms including palpitations, chest pain, syncope and fatigue.22 Catheter ablation for idiopathic VA is associated with a high success rate, 76-100% of patients are without arrhythmia at the end of the procedure and the recurrence rate is very low.22, 43, 60, 61, 63

Perhaps due to chronic hemodynamical effects frequent premature ventricular contractions (PVC) may affect the ventricular function. One study following patients with frequent PVCs and normal cardiac function for 4 years showed a modest but significant decline in LV
ejection fraction in 5% of patients. Single center studies have reported on mild to severe reduced LV ejection fraction and increased ventricular dimensions associated with frequent PVCs in selected patients. These detrimental effects of PVCs seem to be reversible after suppression of PVCs by medication or successful catheter ablation. In a recent observational study of 174 patients referred for catheter ablation of PVCs the only independent predictor for LV dysfunction at presentation was PVC burden. The best cut-off was 24% PVCs in 24 hours but some patients with >10% PVCs may also be at risk. However, the clinical relevance of frequent PVCs in asymptomatic patients without LV dysfunction in the unselected general population is not fully understood and a benefit of “preventive” RFCA in these patients has not been proven. Whether subclinical LV dysfunction undetected by normal imaging techniques may be already present in patients with frequent PVCs as compared to normal control patients is studied in chapter 7.

It has been demonstrated that the short coupled variant of PVCs originating from the purkinje system or from the outflow tracts can induce episodes of polymorphic VT and VF. These PVCs can be targeted for ablation to prevent VA episodes. Longer coupling intervals in benign RVOT PVC/VT as compared to those associated with malignant polymorphic VT and idiopathic VF have been reported. However, in the largest series including 16 patients with polymorphic VT or VF originating from the RV outflow tract, the frequency of isolated PVCs and their coupling intervals were not different to those observed in 85 patients with idiopathic monomorphic RV tachycardia. Ablation targeting the initiating PVCs prevented recurrence of VF during a follow-up of 54 months.

Indications

Evidence for a benefit of catheter ablation for the treatment of VA is mainly based on uncontrolled trails, single center experience and experts opinion. For patient with structural heart disease the current guidelines of the American College of Cardiology(ACC)/American Heart Association(AHA)/European Society of Cardiology(ESC) state that catheter ablation can be beneficial as a palliative and adjunctive therapy to ICD implantation in patients who receive multiple ICD shocks due to drug refractory sustained VT (Class I, level of evidence C), for incessant VT after failed drug therapy (Class IIa) and in patients with bundle branch reentry (Class I, C). Ablation can be useful in patients with otherwise low risk of SCD, like patients without structural heart disease with idiopathic VA, who present with sustained VT (Class I), symptomatic nonsustained VT (Class IIa) or symptomatic PVCs (Class IIa) for which drug therapy is ineffective, not tolerated or not desired. For patients with prior MI, but relatively preserved left ventricular (LV) ejection fraction (>40%), curative ablation may be considered in lieu of ICD therapy (Class IIb). In patients with congenital heart disease presenting with monomorphic VT ablation is even recommended prior to ICD therapy (Class
Ablation of ectopic foci that trigger recurrent polymorphic VT is an acceptable strategy for controlling electrical storm (Class IIb).\textsuperscript{100}

In the recently published expert consensus document the European Heart Rhythm Association (ERHA) and the Heart Rhythm Society (HRS) recommend to consider ablation for recurrent monomorphic VT in post MI patients with an LVEF >30% as alternative to amiodarone, in post MI patients with LV ejection fraction >35%, even if they have not failed drug therapy and in patients with VA presumed to cause ventricular dysfunction.\textsuperscript{2}

Catheter ablation is contra-indicated for NSVT/PVC that are asymptomatic and not suspected to cause ventricular dysfunction and for VT due to transient and reversible causes. Endocardial catheter ablation is furthermore contraindicated in the presence of a mobile ventricular thrombus for the risk of embolization.\textsuperscript{2}

Individual patient characteristics, available facilities and technical expertise may determine the possible risks and benefits of the ablation procedure and should therefore be taken into consideration when selecting patients for catheter ablation of VT.

**Aim and outline of the thesis**

The growing role of catheter ablation for ventricular arrhythmias in patients with and without structural heart disease reflects the progress in this field over the last decades. The aim of the current thesis was to study the determinants for the substrate causing VT, the VT characteristics and outcome specifically after invasive treatment and to develop techniques that facilitate and thereby potentially improve outcome after catheter ablation.

In **part I** determinants of the VA substrate and techniques for substrate identification are studied in patients referred for catheter ablation of VA.

In patients presenting with VA the discrimination between scar-related reentry and an idiopathic focus as underlying mechanism is guiding for further evaluation and treatment. **Chapter 2** studies the diagnostic value of the VA 12-lead surface ECG to determine the presence or absence of myocardial scar underlying the arrhythmia. In this chapter a simple stepwise algorithm based on surface ECG characteristics is developed to aid clinical decision making in patients presenting with VA. Even though non scar-related idiopathic VA is generally considered benign, catheter ablation can be indicated in symptomatic patients. During ablation in otherwise healthy myocardium it is desirable to limit the number of lesions to the minimum. In **chapter 3** catheter mapping is used to evaluate reversed polarity as an additional mapping criterion to improve the determination of successful ablation sites for idiopathic RVOT VA.

Post MI scar is the substrate in the majority of patients presenting with clinically significant scar related VT. Early reperfusion as standard treatment of the acute MI has been
developed over the last decennia. Chapter 4 describes the affect of early reperfusion on the substrate of VT as determined by electroanatomical mapping and histology and on VT characteristics. Substrate based methods for catheter ablation of VT, rely on delineation of scar by electroanatomical catheter mapping. CE-MRI can be used to visualize the three-dimensional geometry of myocardial fibrosis and is the gold standard for the detection of nontransmural scar. Chapter 5 focuses on the feasibility of integrating these two modalities to facilitate catheter ablation and evaluates additional value of the use of CE-MRI in a head to head comparison.

Over the last years percutaneous epicardial approach in selected patients has rendered many VT previously considered ‘unmappable’ approachable for ablation. The determination of VT substrate by electroanatomical mapping and catheter ablation is limited by the presence of epicardial fat and coronary arteries. In chapter 6 the use of CT derived information to determine fat distribution and coronary artery anatomy during epicardial catheter ablation procedures is studied.

After determination of VA substrate, catheter ablation has the potential to abolish the substrate, reentry circuit or arrhythmogenic focus, for VA. In addition differences in VA substrate between patients may impact clinical outcome. The focus of Part II is on the outcome in different ventricular tachycardia substrates.

Non scar-related VA are generally considered benign and in the majority of patients with frequent VA the LV ejection fraction is normal. Reversible deterioration of LV ejection fraction due to, perhaps hemodynamical effects, of frequent PVCs have been described in a limited number of patients. Chapter 7 assesses the effect of non scar related frequent PVCs on RV and LV function in patients with preserved LVEF. In addition, the effect of successful RFCA of frequent PVCs on LV and RV function is evaluated.

In contrast to non scar-related VA, patients with scar-related VA may be at risk for sudden cardiac death. Chapter 8 studies determinants of outcome in scar-related VA originating from the right ventricle. Baseline characteristics, diagnosis and acute ablation success are related to VT recurrence during follow-up.

Chapter 9 aims to extend the findings demonstrated in chapter 4 in a larger population of post MI patients who underwent electrophysiological evaluation prior to implantation of an ICD. The effect of early reperfusion during acute MI on inducibility of VT, characteristics of VT and VT recurrence during long-term follow-up is evaluated.

Chapter 10 addresses the substrate, VT characteristics, catheter ablation and VT recurrence in the, until now underexposed, subgroup of patients who present with VT after surgical ventricular restoration for heartfailure after MI.
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Ablation using one catheter may be successful in treating certain arrhythmias. Following an initial catheterization, a second may be used. The approach in these cases is often localized, focusing on areas of scar tissue. Treatment may include the use of radiofrequency ablation (RFCA) to target regions of myocardial tissue derived from scar. Additionally, anatomical structures such as fat and connective tissue may need to be considered in the treatment plan. The goal is to achieve a successful ablation, avoiding re-entrant tachycardia. Results can vary, with some studies showing high success rates over months or even years.