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

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**Samenvatting en Toekomstigeperspectief**  
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## SUMMARY AND FUTURE PERSPECTIVES

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

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

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

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

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

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

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

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

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

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

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



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