Substrate identification and treatment of right ventricular tachycardia: scar patterns and novel mapping tools

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CHAPTER 7

Summary, conclusions and future perspectives

Summary and future perspectives

In the introduction section **(chapter 1)** background and aims of this thesis are summarized. Improved understanding and better identification of the VT substrate in patients with right ventricular VT may allow for improved risk stratification and treatment of VT in this patient population.

Exercise induced non-sustained VT are usually considered benign, however syncope and sudden death do occur in these patients. In a prior cohort study of high level endurance athletes with RV VT, an ARVC associated mutation was found in only 13% of the athletes. These patients may have a mutation not yet identified or may have RV scarring only due to longstanding endurance training, which has important prognostic implications. **Chapter 2** described a novel entity of fast re-entrant VT from an isolated subepicardial RV outflow tract (RVOT) scar in endurance athletes, for which we introduced the name 'exercise induced arrhythmogenic remodeling (EIAR)'. This scar pattern could be differentiated from a dominant peritricuspid scar pattern in patients with ARVC and inflammatory cardiomyopathy. None of 11 endurance athletes with an isolated RVOT scar fulfilled definitive criteria for ARVC or cardiac sarcoidosis and none had a pathogenic mutation in cardiomyopathy-related genes. All were longstanding endurance athletes with a median of 15 training hours per week. The endurance athletes could only be identified by electro-anatomical mapping (EAM) and not by ECG, echo or cardiovascular magnetic resonance imaging (CMR). Limited ablation rendered the majority of patients non-inducible at the end of the procedure with no VT recurrence during long-term follow-up. The distinct scar pattern in the epicardial RVOT and the absence of any genetic mutation suggests that EIAR is a distinct clinical entity, and not due to ARVC or cardiac sarcoidosis. In prior studies, transient RV dysfunction and elevated troponin levels have been described in athletes after an endurance race and these effects were more pronounced after the longest endurance events. Repetitive training of long duration without recovery may lead to pathological remodeling and ultimately arrhythmogenic scar. Although the exact mechanisms for the predilection for the anterior subepicardial RVOT remains unclear, it may be hypothesized that this region is more vulnerable to exercise-induced wall stress. Future studies are needed to identify those athletes at risk to develop this rare disease entity. Whole genome sequencing is required to evaluate if these patients have an inherited risk not yet identified. To understand the disease mechanism it's important to know whether asymptomatic endurance athletes without VT might have an epicardial RVOT scar without conduction delay. A prior study in 5011 asymptomatic endurance athletes, exercise-related PVCs and non-sustained VT were observed in 7% of the athletes and 68% are of RVOT origin. The common site of origin is striking suggesting that EIAR is potentially the most severe end of a spectrum of RVOT VA in endurance athletes.

Identification of the arrhythmic substrate in the RV during EAM is challenging due to multiple factors. The substrate is often confined to the epicardium and covered by a thick epicardial fat layer, especially towards the RV groove the predilection site of VT substrate in ARVC. Epicardial fat attenuates epicardial voltage often leading to overestimation of the scar. The presence of epicardial scar can be detected by low endocardial unipolar voltages during EAM. **Chapter 3** described the first study using CT-derived epicardial fat thickness information to analyze the optimal cutoff value for endocardial unipolar voltage mapping to detect epicardial scar in the RV in 33 consecutive patients with ARVC who underwent combined endocardial and epicardial mapping with CT integration. It was demonstrated that the optimal endocardial cutoff for identification of epicardial scar was 3.9 mV (sensitivity 60% and specificity 79%) in areas with <1 mm epicardial fat on CT. Abnormal electrograms (fragmented electrograms and late potentials) were typically located in areas with transmural scars. The optimal cutoff for the identification of these, clinically more relevant, abnormal epicardial electrogram was 3.7 mV (sensitivity 100%, specificity 67%). The combined use of both endocardial bipolar and unipolar voltage cutoffs resulted in the detection of all abnormal electrograms in areas <1 mm of fat. The current reported cutoff value of 3.9 mV had a substantial higher specificity (79%) compared to prior cutoff values, when calculated in the present study (cutoff 4.4 mV, specificity 75%; and 5.5 mV, specificity 56%). These two prior RV endocardial unipolar voltages cutoff studies lacked the important epicardial fat information, potentially resulting in overestimation of epicardial scar size and thereby resulting in a higher endocardial unipolar cutoff value for detection of epicardial scar. The newly proposed lower unipolar voltage cutoff value may prevent unnecessary epicardial access and related complications as bleeding, pericarditis and epicardial adhesions. Future studies are warranted to evaluate whether this unipolar voltage can diagnose ARVC in an early stage in particular in patients who are referred for catheter ablation of PVCs or VT and are considered to have idiopathic VA. Higher endocardial unipolar voltages were observed at point pairs with a thicker fat layer compared to point pairs with <1 mm of fat. Current reported cutoff values had a lower performance in areas >1 mm of fat probably due thicker fat layer and thicker RV wall towards the basal RV. Further research is required whether different cutoff values per region are required.

Chapter 4 described the usage of tissue heterogeneity on CT to identify the VT substrate. CT heterogeneity is a measure for the complexity of local tissue transition from fat to myocardium in Hounsfield units per millimeter (HU/mm). It was hypothesized that a homogeneous areas with (fibro)fatty replacement (probably not related to VT) results in a low CT heterogeneity, while heterogeneous areas with (fibro)fatty replacement interspersed by layers of viable myocardium (potentially related to VT) would result in a high CT heterogeneity. Late potentials (LP, late activated areas) detected by EAM were used as marker for sites potentially related to VT. Seventeen patients with ARVC and 9

EIAR patients underwent endocardial and epicardial mapping prior to VT-ablation. In ARVC, CT heterogeneity was higher at sites with LP compared to normal points and scar points without late potentials. With the optimal CT heterogeneity cutoff value (25 HU/mm), LP could be accurately differentiated from normal points and scar points without late potentials. One prior study has analyzed electrograms at sites with intramyocardial fat, but not tissue heterogeneity, in 16 ARVC patients. In the present study, local CT heterogeneity allowed a more accurate identification of LP sites compared to local intramyocardial fat percentage. This supports the hypothesis that tissue heterogeneity on CT may be a more reliable marker for the arrhythmogenic substrates in ARVC than the percentage of intramyocardial fat. CT heterogeneity could play a role to guide substrate based VT ablation. Future research may evaluate if CT heterogeneity can be used for non-invasive risk stratification for ventricular arrhythmia in ARVC patients.

The overall median CT heterogeneity of the RV free wall was higher in ARVC compared to EIAR and control patients. The optimal overall CT heterogeneity to differentiate between ARVC and controls was 15 HU/mm (sensitivity 100%, specificity 82%) and between ARVC and EIAR 21 HU/mm (sensitivity 65%, specificity 89%), respectively. CT heterogeneity had a better sensitivity compared to intramyocardial fat percentage suggesting that tissue heterogeneity may be a more specific feature of pathological infiltration. CT scans are not part of ARVC Task Force criteria but outperformed echo and CMR in the current study suggesting that CT heterogeneity may be of significant value for diagnosing ARVC. Further research may aim to analyze the value of RV tissue heterogeneity on CT for diagnosing patients with an early stage of ARVC and to analyze whether CT may be incorporated in the Task Force criteria in the future.

Intramural scar may prevent direct endocardial to epicardial activation. The protected epicardium may facilitate re-entry VT. It was the aim of **Chapter 5** to systematically investigate the transmural activation interval (TAI) during sinus rhythm at VT related sites in patients with ARVC and EIAR and predominantly hemodynamically non-tolerated VT. TAI was defined as the first endocardial bipolar sharp peak deflection to the first epicardial sharp peak deflection. Maximal activation interval (MAI) was the first endocardial bipolar sharp peak deflection to the last epicardial sharp peak deflection. Nineteen patients (63% ARVC and 37% EIAR) with simultaneous endocardial-epicardial mapping for VT were enrolled. An optimal TAI cutoff of 17 ms could accurately differentiate epicardial VT related sites form all other sites (AUC 0.81, sensitivity 75%, specificity 84%). The median MAI was also significantly longer at epicardial VT related sites compared to other scar sites with an optimal cutoff of 45ms (AUC 0.81, sensitivity 77%, specificity 80%). A critical prolonged TAI and MAI could identify sites that are related to VT and had a higher diagnostic accuracy compared to conventional substrate mapping based on bipolar and unipolar voltages and epicardial electrogram duration (AUC 0.51-0.73).

It is noteworthy that the epicardial electrogram duration was normal at the majority of VT-related sites and therefore did not allow to distinguish between VT-related sites and other scar sites. These findings suggest that areas without evident subepicardial inlayer conduction delay during sinus rhythm can still be critical for VT that depends on intramural activation delay. Together, these findings support the concept that the epicardial substrates are likely to sustain VT if protected from rapid and direct activation from the opposing endocardium.

Automatic electrogram annotation is increasingly used for 3D high density mapping. This opens the possibility to directly visualize transmural activation time and guide VT-mapping and ablation. Future prospective studies are warranted to test TAI and MAI during VT-ablation.

Chapter 6 is a multicenter study comparing antiarrhythmic drugs (AAD) versus VT-ablation strategies in ARVC patients for the prevention of VT. In this retrospective study, 110 patients with ARVC and a presentation of >3 VT episodes were included. Of all 110 patients, 77 (70%) were initially treated with AAD while 32 (29%) underwent direct VT-ablation. VT free survival at three years was comparable in both groups (VT-ablation: 35%, AAD medication: 28%). Of the 77 patients initially treated with AAD, 43 (56%) underwent VT-ablation after AAD failure. In the VT-ablation group endocardial/epicardial ablation was used in 53% of the patients and was associated with lower VT recurrence (combined endocardial/epicardial vs endocardial only: 71% vs 47% VT free survival after 3 years, P=0.05). There was no difference in mortality or transplantation in the ablation versus medication group. This study was consistent with previous studies in ARVC patients with a high risk of VT recurrence despite AAD and/or VT-ablation and a superior VT free survival in patient undergoing combined endocardial/ epicardial approach versus endocardial only. The treatment strategy with AAD or VT-ablation was left at the discretion of the treating physician and will probably have resulted in selection bias. Future randomized control trials are required to determine the optimal timing and treatment strategy (anti-arhythmic drugs and endocardial/epicardial VT-ablation) for VT in patients with ARVC.

Conclusion

This thesis aims to improve the understanding and identification of the VT substrate in patients with RV VT. An isolated epicardial RVOT scar is described in high level endurance athletes. Novel parameters such as endocardial unipolar voltage, transmural activation time and CT heterogeneity may help to guide substrate mapping and ablation. Implementing these techniques in current clinical practice may improve the identification and treatment of VT substrates in RV cardiomyopathies.