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

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CHAPTER 1

General introduction, aim and outline of the thesis

Introduction

Ventricular tachycardia (VT) originating from the right ventricle (RV) can be idiopathic, due to RV cardiomyopathies of various underlying etiologies, including arrhythmogenic right ventricular cardiomyopathy (ARVC), cardiac sarcoidosis, (peri) myocarditis and other (rare) causes or the consequence of (repaired) congenital heart disease. This thesis focusses on ventricular arrhythmia due to RV cardiomyopathies. ARVC is a hereditary disease characterised by fibrofatty replacement of predominantly the RV myocardium, but can also affect the left ventricle (LV).[1-3] The disease was first described by Guy Fontaine, in 1977, in patients undergoing cardiac surgery for the treatment of RV VT.[3] In 1982, Frank Marcus and Guy Fontaine described the clinical characteristics of ARVC in a case series of 24 patients.[4]

The first disease manifestation can range from RV dysfunction, RV heart failure, ventricular arrhythmias (VA) to sudden cardiac death (SCD).[5] The diagnosis is based on the ARVC task force criteria including subsets of imaging and ECG criteria, tissue characteristics, family history and/or genetic mutations.[6] Early recognition and treatment of ARVC is important because ventricular tachycardia or SCD can be the first disease manifestation.[7] The diagnosis, however, remains challenging due to minimal structural abnormalities in the early stage of the disease, which makes it difficult to differentiate these patients from healthy individuals.[6, 8] Inflammatory diseases such as cardiac sarcoidosis can also be erroneously diagnosed as ARVC due to overlapping clinical presentation and low specificity of ARVC task force criteria.[9]

The majority of ARVC patients carry a class IV/V variant in desmosomal and some other ARVC associated genes. In a Dutch ARVC registry a pathogenic mutation was found in 58% of ARVC index patients and in 90% of familial cases.[10] Desmosomal genes are responsible for cell to cell linking proteins. Pathogenic mutation can lead to protein misfolding, resulting in less effective or dysfunctional proteins. The exact mechanism from pathogenic mutation to disease manifestation remains unclear. Of importance, not every subject with a pathogenic mutation develops signs and symptoms of ARVC. Additional factors are likely to play an important role in the development and progression of ARVC. One of these factors associated with disease progression is endurance training. Endurance training in ARVC patients has been associated with disease progression with earlier manifestation of VT and heart failure.[11-13]

Endurance training and arrhythmia

Endurance training can have a profound effect on the heart depending on the type of exercise. Strength training at a low percentage of maximal oxygen uptake can lead to concentric hypertrophy with a normal or slightly enlarged LV end diastolic diameter.

[14] Longstanding endurance training, for a long period at a high percentage of VO2 max, can lead to balanced biventricular dilatation and eccentric hypertrophy, with preservation of systolic and diastolic function and left atrial dilatation.[14-17] The largest increase in LV wall thickness and LV end diastolic diameter have been reported in endurance athletes with a combination of strength and endurance training such as rowing and cycling.[14, 18, 19] This physiological form of hypertrophy or athletes' heart is considered to be a normal and benign adaptation of the heart to athletic training.[15]

Although exercise-induced non-sustained VT in athletes are usually considered benign,[20] in some athletes performing exercise at high levels of dynamic and static demand, fatal arrhythmic events do occur.[21] In a Belgian cohort of high-level endurance athletes with VA of RV origin, a desmosomal gene mutation was found in only 13% of these endurance athletes.[22] These athletes may have a mutation not yet identified and/or may have RV scarring due to the longstanding endurance training. Imaging studies in intense endurance training have shown acute but reversible dysfunction of the right ventricle, while the left ventricle remained unaffected. The effect was more pronounced after longer endurance events.[23] It has therefore been hypothesized that repetitive training of long duration, without sufficient recovery until the next training, may lead to damage as a consequence of chronic pressure and/or volume overload in longstanding endurance training and may lead to pathological RV remodelling.[24]

Ventricular arrhythmia in de RV

VA in the RV can encompass premature ventricular contraction, but also life-threatening fast monomorphic VT and ventricular fibrillation. PVC and VT in structurally normal hearts are typically due to triggered activity, often originate from a focal source in the RVOT, and have a favourable prognosis.[25, 26]

In contrast, in patients with RV cardiomyopathy, scar-related re-entry is the dominant VT mechanism and can result in syncope or SCD.[7] Scar related re-entry VT is often confined to scar areas with conduction delay, unexcitable boundaries and unidirectional block. In infarcted myocardial tissue, it has been demonstrated that slow conduction is caused by a "zigzag" course of activation.[27]. The slow conduction areas are usually embedded in heterogeneous scar tissue or adjacent to anatomical unexcitable boundaries (e.g. valve annulus), and thereby protected from direct activation of adjacent myocardial tissue. The critical slow conducting pathway, between entrance and exit site, is called a VT- isthmus. The VT morphology depends on the VT exit site and the activation pattern of the RV and LV.

There is limited data on the substrate and mechanisms of VT in RV cardiomyopathy compared to VT after myocardial infarction. In ARVC, the substrate is often located in low bipolar voltage areas close to the tricuspid valve.[4, 28] Low voltage areas are suggestive

of fat or fibrofatty replacement.[29] In patients selected for invasive treatment of VT, catheter mapping is performed to localize the critical VT substrate. The VT isthmus site can be identified by activation and entrainment mapping, with concealed fusion and a post pacing interval equal to the VT CL indicating reentrant circuit sites.[30] Mapping during VT is considered the gold standard for detection of the VT isthmus. However VT-mapping can only be performed for hemodynamically tolerated VT. In RV VT, this is often impossible due to the short cycle length and subsequently hemodynamically instability observed in 68% of the VTs.[31] Therefore a substrate-based ablation strategy in SR is required to identify areas related to VT based on electrogram characteristics.

Substrate identification by electroanatomical mapping

Three dimensional electroanatomical mapping (EAM) is routinely performed for substrate identification of all VT, hereby coupling recorded electrograms to an anatomical location. A 3 dimensional map is constructed, which contains all information on the local electrogram characteristics of the mapped endocardial or epicardial surface of the RV or LV. Substrate-based ablation tries to identify the arrhythmic substrate during SR or RV-pacing based EGM features. In patients with RV cardiomyopathy, the arrhythmogenic substrate may be confined to the epicardium and is usually more extensive than on the endocardium.[1, 32, 33] Different techniques have been described to identify potential VT substrates, all with their own advantage and disadvantages: including bipolar and unipolar voltage mapping, distinct abnormal electrogram features, combined with pace-mapping techniques, facilitated by CT-image integration.

Low amplitude bipolar or unipolar electograms allow detection of areas compatible with scar. Voltage mapping has been described of being superior to current image modalities like MRI to detect small RV scars.[34] The local bipolar voltage (BV) is calculated from the unipolar recordings of the tip and ring-electrode of the mapping catheters. A BV above 1,5 mV is considered normal.[35] Unipolar voltage (UV) is measured between the tip and the Wilson central terminal. Low endocardial UV at sites with normal endocardial BV may detect subepicardial scar which may have important clinical implications for substrate identification and ablation strategies.[36, 37] Previous studies have suggested 4.4 mV and 5.5 mV endocardial UV cutoff values to detect epicardial bipolar low voltage areas.[36, 37] Both studies lacked important epicardial fat information. The surface of the epicardial RV is covered by a thick fat layer, in particular towards the atrioventricular groove.[38-40] An thick epicardial fat layer can attenuate the epicardial BV and may thereby lead to overestimation of the epicardial scar.[41] CT scan derived fat thickness can be integrated in EAM system and can be useful to distinguish sites with low voltages due to scar from low voltage sites that may be at least partly due to a thick epicardial fat layer. Studies using the information from CT derived fat thickness to evaluate the performance of endocardial UV mapping to detect epicardial low BV areas are lacking.

Patients with RV cardiomyopathy often have large low-voltages areas but not all low-voltages areas are related to VT. During sinus rhythm VT isthmus sites often exhibit signs of local conduction delay (split or fragmented EGM, late potentials).[30] Especially isolated late potentials have been demonstrated to be a specific marker of VT circuits in post-infarct patients.[42, 43] A VT-ablation strategy that targets all areas with fragmented, split or late potentials (LAVA signals) has been described.[44] Complete LAVA eliminations was associated with good long term VT free survival in patients with structural heart disease.[44] Others have proposed to target all conducting channels entrances to eliminate the arrhythmogenic substrate.[33, 45]

In ARVC, 69-79% of the VT are due to scar-related re-entry confined to the epicardium.[30-32, 46] Intramural fat and fibrosis may result in prolonged transmural activation and in protected subepicardial areas which may facilitate re-entry VT. These areas with functional of fixed conduction block may be detectable during sinus rhythm. A delayed and altered epicardial RV activation in SR has been reported in ARVC patients compared to healthy control patients.[31] Transmural activation time in SR have not been studied in criterial VT isthmus sites in ARVC patients with predominantly hemodynamically non-tolerated VT.

CT image integration to visualize intramyocardial fat

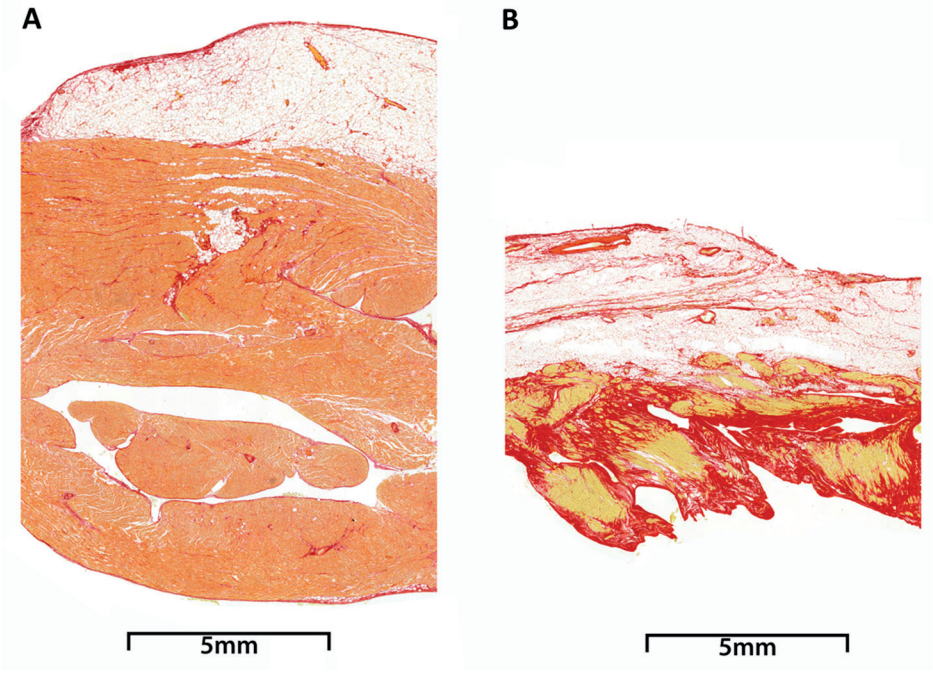
CT and MRI data can be loaded in the EAM system and may be helpful to identify potential arrhythmogenic substrates.[39, 47] ARVC is characterized by fibrofatty replacement of myocardium, progressing from the epicardium towards the endocardium (Figure 1).[4, 48, 49] Cardiac computed tomography (CT) allows identification of fat with high spatial resolution.[50-52] The overall percentage of intramyocardial fat within the RV free wall, quantified on CT, has been demonstrated to be higher in patients with ARVC compared to matched controls,[50] and local abnormal ventricular electrograms have been related to areas with a high percentage of intramyocardial fat.[53] High percentages of fat, however, may also be due to confluent areas of intramyocardial fat, which result in local abnormal low voltage electrograms without conduction delay, required for re-entry VT. Heterogeneous tissue provides the substrate for slow conduction facilitating re-entrant VT.[54] To date, no study has investigated the relation of conduction delay detected by EAM and the intermingling of fibrofatty tissue and normal myocardium, quantified on CT, at a specific location.

Treatment of VT

Treatment options for VT in ARVC are antiarrhythmic medication, catheter ablation or ICD implantation for those VT that are considered life-threatening. Abnormal sympathetic innervation has been described in ARVC, which may result in dispersion of repolarization and thereby contributing to pro-arrhythmogenicity.[56] Beta-blockers

may reduce arrhythmogenicity in ARVC.[56] Amiodarone is considered the most effective drug for preventing VA recurrence, but study results are contradictive.[57, 58] High doses of sotalol has been effective to suppress inducibility of VT but not to prevent spontaneous VTs during follow-up.[58] Flecainide in combination with sotalol or metoprolol may be an effective antiarrhythmic strategy.[59]

Figure 1. Histology of the RV myocardium in a patient with ARVC



Panel A. The myocardial slide shows a thick epicardial fat layer (white) with minimal fat infiltration between epicardial myocardial fibers in a patient without structural heart disease. Almost no fibrosis (red) is visible in the myocardium. Panel B. Histology of a patient with end stage ARVC. This myocardial slide shows a high percentage of fibrosis and fat infiltration between the remaining myocardium. Reprinted from Venlet et. al.[55]

ICDs can terminate VT or ventricular fibrillation but cannot prevent the occurrence of arrhythmia. In a follow-up study in ARVC patients with ICD, appropriate therapy was high despite antiarrhythmic medication or beta-blockers in 83% of the patients with ICD therapy.[60]

A number of studies have reported promising results of VT-ablation with significant reduction of VT burden during follow-up.[28, 61, 62] Combined endocardial and epicardial ablation was more efficacious than endocardial ablation alone.[33, 46, 63] Studies comparing antiarrhythmic medication and VT-ablation are missing.

Aim and outline of this thesis

The present thesis aims to improve the understanding and identification of the VT substrate in patients with right ventricular VT. Better understanding may allow improved risk stratification and treatment of VT in this patient population. **Chapter 2** aims to evaluate whether RV electroanatomical scar patterns related to VTs can distinguish endurance athletes with VT from ARVC and post-inflammatory cardiomyopathies. Epicardial voltages are attenuated by epicardial fat thickness. **Chapter 3** aims to improve endocardial unipolar voltage mapping to detect epicardial scar using CT derived fat thickness. An endocardial unipolar voltage cutoff to detect, potentially more relevant, abnormal epicardial electrograms was investigated. In RV cardiomyopathies, intramural scar may prevent rapid and direct endocardial to epicardial activation. This activation delay may facilitate subepicardial VT circuits. **Chapter 4** investigates the association between transmural activation delay during sinus rhythm, and VT-related sites. The hallmark of ARVC is fibrofatty replacement starting at the epicardium**. Chapter 5** investigates whether RV tissue heterogeneity on CT is associated with conduction delay in ARVC and if overall tissue heterogeneity can be used to distinguish ARVC from endurance athletes with VT and healthy control patients. **Chapter 6** is a multicenter study comparing AAD versus VT-ablation strategies to prevent VT recurrence in ARVC patients. Finally, a **s**ummary, conclusions and future perspectives are provided in **Chapter 7.**

Reference list

1. Te Riele, A.S., et al., *Mutation-positive arrhythmogenic right ventricular dysplasia/ cardiomyopathy: the triangle of dysplasia displaced.* J Cardiovasc Electrophysiol, 2013. **24**(12): p. 1311-20.
2. Sen-Chowdhry, S., et al., *Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment.* Annu Rev Med, 2010. **61**: p. 233-53.
3. Fontaine, G., et al., *Reentrant arrhythmias.* Lancaster: MTP, 1977.
4. Marcus, F.I., et al., *Right ventricular dysplasia: a report of 24 adult cases.* Circulation, 1982. **65**(2): p. 384-98.
5. Corrado, D., et al., *Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases.* Am J Med, 1990. **89**(5): p. 588-96.
6. Marcus, F.I., et al., *Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria.* Eur Heart J, 2010. **31**(7): p. 806-14.
7. Dalal, D., et al., *Arrhythmogenic right ventricular dysplasia: a United States experience.* Circulation, 2005. **112**(25): p. 3823-32.
8. Quarta, G., et al., *Familial evaluation in arrhythmogenic right ventricular cardiomyopathy: impact of genetics and revised task force criteria.* Circulation, 2011. **123**(23): p. 2701-9.
9. Philips, B., et al., *Arrhythmogenic right ventricular dysplasia/cardiomyopathy and cardiac sarcoidosis: distinguishing features when the diagnosis is unclear.* Circ Arrhythm Electrophysiol, 2014. **7**(2): p. 230-6.
10. Cox, M.G., et al., *Arrhythmogenic right ventricular dysplasia/cardiomyopathy: pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study.* Circulation, 2011. **123**(23): p. 2690-700.
11. Kirchhof, P., et al., *Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice.* Circulation, 2006. **114**(17): p. 1799-806.
12. James, C.A., et al., *Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers.* J Am Coll Cardiol, 2013. **62**(14): p. 1290-1297.
13. Ruwald, A.C., et al., *Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy.* Eur Heart J, 2015. **36**(27): p. 1735-43.
14. Pluim, B.M., et al., *The athlete's heart. A meta-analysis of cardiac structure and function.* Circulation, 2000. **101**(3): p. 336-44.
15. Maron, B.J., *Sudden death in young athletes.* N Engl J Med, 2003. **349**(11): p. 1064-75.
16. Scharhag, J., et al., *Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging.* J Am Coll Cardiol, 2002. **40**(10): p. 1856-63.
17. Scharf, M., et al., *Atrial and ventricular functional and structural adaptations of the heart in elite triathletes assessed with cardiac MR imaging.* Radiology, 2010. **257**(1): p. 71-9.
18. Pelliccia, A., et al., *The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes.* N Engl J Med, 1991. **324**(5): p. 295-301.
19. Pelliccia, A., et al., *Physiologic left ventricular cavity dilatation in elite athletes.* Ann Intern Med, 1999. **130**(1): p. 23-31.

20. Verdile, L., et al., *Clinical significance of exercise-induced ventricular tachyarrhythmias in trained athletes without cardiovascular abnormalities.* Heart Rhythm, 2015. **12**(1): p. 78-85.
21. Heidbuchel, H., et al., *High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification.* Eur Heart J, 2003. **24**(16): p. 1473-80.
22. La Gerche, A., et al., *Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin.* Heart, 2010. **96**(16): p. 1268-74.
23. La Gerche, A., et al., *Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes.* Eur Heart J, 2012. **33**(8): p. 998-1006.
24. Heidbuchel, H., D.L. Prior, and A. La Gerche, *Ventricular arrhythmias associated with long-term endurance sports: what is the evidence?* Br J Sports Med, 2012. **46 Suppl 1**: p. i44-50.
25. Aquaro, G.D., et al., *Cardiac magnetic resonance predicts outcome in patients with premature ventricular complexes of left bundle branch block morphology.* J Am Coll Cardiol, 2010. **56**(15): p. 1235-43.
26. Lerman, B.B., *Mechanism, diagnosis, and treatment of outflow tract tachycardia.* Nat Rev Cardiol, 2015. **12**(10): p. 597-608.
27. de Bakker, J.M., et al., *Slow conduction in the infarcted human heart. 'Zigzag' course of activation.* Circulation, 1993. **88**(3): p. 915-26.
28. Marchlinski, F.E., et al., *Electroanatomic substrate and outcome of catheter ablative therapy for ventricular tachycardia in setting of right ventricular cardiomyopathy.* Circulation, 2004. **110**(16): p. 2293-8.
29. Corrado, D., et al., *Three-dimensional electroanatomical voltage mapping and histologic evaluation of myocardial substrate in right ventricular outflow tract tachycardia.* J Am Coll Cardiol, 2008. **51**(7): p. 731-9.
30. Garcia, F.C., et al., *Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia.* Circulation, 2009. **120**(5): p. 366-75.
31. Haqqani, H.M., et al., *Layered activation of epicardial scar in arrhythmogenic right ventricular dysplasia: possible substrate for confined epicardial circuits.* Circ Arrhythm Electrophysiol, 2012. **5**(4): p. 796-803.
32. Jiang, R., et al., *Spatial and transmural properties of the reentrant ventricular tachycardia circuit in arrhythmogenic right ventricular cardiomyopathy: Simultaneous epicardial and endocardial recordings.* Heart Rhythm, 2021. **18**(6): p. 916-925.
33. Berruezo, A., et al., *Safety, long-term outcomes and predictors of recurrence after first-line combined endoepicardial ventricular tachycardia substrate ablation in arrhythmogenic cardiomyopathy. Impact of arrhythmic substrate distribution pattern. A prospective multicentre study.* Europace, 2017. **19**(4): p. 607-616.
34. Marra, M.P., et al., *Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance.* Circ Arrhythm Electrophysiol, 2012. **5**(1): p. 91-100.
35. Marchlinski, F.E., et al., *Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy.* Circulation, 2000. **101**(11): p. 1288-96.
36. Polin, G.M., et al., *Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia.* Heart Rhythm, 2011. **8**(1): p. 76-83.

37. Tokuda, M., et al., *Direct comparison of adjacent endocardial and epicardial electrograms: implications for substrate mapping.* J Am Heart Assoc, 2013. **2**(5): p. e000215.
38. Schejbal, V., *[Epicardial fatty tissue of the right ventricle--morphology, morphometry and functional significance].* Pneumologie, 1989. **43**(9): p. 490-9.
39. van Huls van Taxis, C.F., et al., *Real-time integration of MDCT-derived coronary anatomy and epicardial fat: impact on epicardial electroanatomic mapping and ablation for ventricular arrhythmias.* JACC Cardiovasc Imaging, 2013. **6**(1): p. 42-52.
40. Burke, A.P., et al., *Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium: are they different diseases?* Circulation, 1998. **97**(16): p. 1571-80.
41. Piers, S.R., et al., *Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischaemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging.* Eur Heart J, 2013. **34**(8): p. 586-96.
42. Arenal, A., et al., *Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease.* J Am Coll Cardiol, 2003. **41**(1): p. 81-92.
43. Mountantonakis, S.E., et al., *Relationship between voltage map "channels" and the location of critical isthmus sites in patients with post-infarction cardiomyopathy and ventricular tachycardia.* J Am Coll Cardiol, 2013. **61**(20): p. 2088-95.
44. Jaïs, P., et al., *Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia.* Circulation, 2012. **125**(18): p. 2184-96.
45. Fernández-Armenta, J., et al., *Sinus rhythm detection of conducting channels and ventricular tachycardia isthmus in arrhythmogenic right ventricular cardiomyopathy.* Heart Rhythm, 2014. **11**(5): p. 747-54.
46. Philips, B., et al., *Outcomes and ventricular tachycardia recurrence characteristics after epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/ cardiomyopathy.* Heart Rhythm, 2015. **12**(4): p. 716-25.
47. Piers, S.R., et al., *Contrast-enhanced MRI-derived scar patterns and associated ventricular tachycardias in nonischemic cardiomyopathy: implications for the ablation strategy.* Circ Arrhythm Electrophysiol, 2013. **6**(5): p. 875-83.
48. Thiene, G., et al., *Right ventricular cardiomyopathy and sudden death in young people.* N Engl J Med, 1988. **318**(3): p. 129-33.
49. Basso, C., et al., *Arrhythmogenic right ventricular cardiomyopathy.* Lancet, 2009. **373**(9671): p. 1289-300.
50. Cochet, H., et al., *Automated Quantification of Right Ventricular Fat at Contrast-enhanced Cardiac Multidetector CT in Arrhythmogenic Right Ventricular Cardiomyopathy.* Radiology, 2015. **275**(3): p. 683-91.
51. Kimura, F., et al., *Helical CT features of arrhythmogenic right ventricular cardiomyopathy.* Radiographics, 2002. **22**(5): p. 1111-24.
52. Tada, H., et al., *Usefulness of electron-beam computed tomography in arrhythmogenic right ventricular dysplasia. Relationship to electrophysiological abnormalities and left ventricular involvement.* Circulation, 1996. **94**(3): p. 437-44.
53. Komatsu, Y., et al., *Relationship between MDCT-imaged myocardial fat and ventricular tachycardia substrate in arrhythmogenic right ventricular cardiomyopathy.* J Am Heart Assoc, 2014. **3**(4).

54. Perez-David, E., et al., *Noninvasive identification of ventricular tachycardia-related conducting channels using contrast-enhanced magnetic resonance imaging in patients with chronic myocardial infarction: comparison of signal intensity scar mapping and endocardial voltage mapping.* J Am Coll Cardiol, 2011. **57**(2): p. 184-94.
55. Venlet, J., et al., *RV Tissue Heterogeneity on CT: A Novel Tool to Identify the VT Substrate in ARVC.* JACC Clin Electrophysiol, 2020. **6**(9): p. 1073-1085.
56. Wichter, T., et al., *Abnormalities of cardiac sympathetic innervation in arrhythmogenic right ventricular cardiomyopathy : quantitative assessment of presynaptic norepinephrine reuptake and postsynaptic beta-adrenergic receptor density with positron emission tomography.* Circulation, 2000. **101**(13): p. 1552-8.
57. Marcus, G.M., et al., *Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry.* J Am Coll Cardiol, 2009. **54**(7): p. 609-15.
58. Wichter, T., et al., *Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia.* Circulation, 1992. **86**(1): p. 29-37.
59. Ermakov, S., et al., *Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy.* Heart Rhythm, 2017. **14**(4): p. 564-569.
60. Corrado, D., et al., *Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia.* Circulation, 2003. **108**(25): p. 3084-91.
61. Verma, A., et al., *Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia.* Circulation, 2005. **111**(24): p. 3209-16.
62. Dalal, D., et al., *Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy.* J Am Coll Cardiol, 2007. **50**(5): p. 432-40.
63. Santangeli, P., et al., *Long-Term Outcome With Catheter Ablation of Ventricular Tachycardia in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy.* Circ Arrhythm Electrophysiol, 2015. **8**(6): p. 1413-21.