Pathophysiology of Ventricular Tachycardia

Subjects: Physiology

Contributor: Matthew Leonard Repp , Ikeotunye Royal Chinyere

The use of catheter-based irreversible electroporation in clinical cardiac laboratories, termed pulsed-field ablation (PFA), is gaining international momentum among cardiac electrophysiology proceduralists for the non-thermal management of both atrial and ventricular tachyrhythmogenic substrates. One area of potential application for PFA is in the mitigation of ventricular tachycardia (VT) risk in the setting of ischemia-mediated myocardial fibrosis, as evidenced by recently published clinical case reports. The efficacy of tissue electroporation has been documented in other branches of science and medicine.

cardiac arrhythmia pulsed-field ablation catheter

1. Introduction

Ventricular tachycardia (VT) is a wide-complex tachyrhythm (QRS duration on surface electrocardiogram > 120 milliseconds) that disrupts normal sinus rhythm and may lead to hemodynamic instability. This arrhythmia originates from within the ventricles and can be clinically defined as ≥3 consecutive ventricular beats occurring at ≥100 beats per minute. VT is categorized by the duration of the episode and the QRS morphology. Based on duration, VT is divided into non-sustained VT and sustained VT. Non-sustained VT terminates spontaneously within 30 s, whereas sustained VT lasts longer than 30 s or requires termination due to hemodynamic instability in <30 s [1]. Based on QRS morphology, VT can be classified as monomorphic (mmVT) or polymorphic. On electrocardiographic assessment, mmVT consists of a singular, consistent QRS morphology with minimal beat-to-beat variation, while polymorphic VT depicts varying QRS morphologies beat-to-beat [1][2]. The most common cause of mmVT is structural sequelae from ischemic heart disease, but it may also arise from non-ischemic cardiomyopathies, iatrogenic etiologies, Purkinje system defects, or idiopathic etiologies [3]. Several causes of polymorphic VT exist, including R-on-T phenomenon, acute myocardial ischemia, congenital short QT syndrome, acquired long QT syndrome, catecholaminergic, torsade de pointes, bidirectional VT [4], and Brugada syndrome.

Pulsed-field ablation (PFA) is a tunable non-thermal ablative technique that, with the appropriate settings, is capable of inducing irreversible cell death via phospholipid bilayer electroporation in selective cardiac tissue populations with minimal damage to anatomically adjacent structures. This technique has recently been adapted to catheter-based technology to allow for clinical use in cardiac electrophysiology laboratories, though its use for research applications such as transmembrane transportation of relatively large macromolecules (ex.: plasmids) dates back to the early 1980s [5]. Furthermore, its use for clinical applications, such as selectively destroying malignant cells in oncology patients, dates back to the early 1990s [6]. PFA has demonstrated in pre-clinical [7] and non-randomized clinical [8] studies an acceptable degree of efficacy with respect to preventing atrial fibrillation

recurrence over a short interval (approximately 1 year) while also maintaining an exceptionally favorable safety profile through the avoidance of collateral damage typically observed with post-thermal catheter ablation techniques.

Recently published case reports have illuminated the potential for PFA utilization for substrate suppression in the setting of recurrent ventricular tachycardia secondary to multiple underlying etiologies [9][10][11][12][13]. These preliminary reports likely signal the beginning of an expansion of the clinical electrophysiologists' armamentarium to include a non-thermal catheter-based therapy in addition to the well-described catheter-based radiofrequency, cryoballoon, and laser options. As such, a careful review of the literature published to date is warranted in order to expedite regulatory approval in the United States of America [14], maximize the proportion of clinical decisions backed by evidence, and support the eventual generation of evidence- and consensus-based clinical guidelines for the use of PFA for ventricular tachyrhythms.

2. Pathophysiology of Ventricular Tachycardia

2.1. Etiologies Leading to Ventricular Tachycardia

2.1.1. Myocardial Infarction, Adverse Remodeling, and Re-Entry

Sustained mmVT is nearly exclusively found secondary to the adverse ventricular remodeling associated with acute- or chronic ischemic heart disease. Adverse ventricular remodeling is frequently observed months to years post-acute myocardial infarction without appropriate pharmacologic suppression, where previously healthy contractile myocytes become irreparably damaged and are eventually replaced by myofibroblast-mediated fibrous tissue [15][16]. Within this myocardial scar are bundles of stunned cardiomyocytes with poor intercellular coupling and subsequently exhibit delayed electrical conduction.

The presence of non-conductive tissue with spatially distributed pockets of conductive myocardium that have impaired repolarization creates a substrate for re-entry [17][18][19]. The criteria for anatomic re-entry are satisfied, namely, a fixed anatomic obstacle mediated by the focus of scar tissue, a circuit-like excitation wavefront pathway through impaired bundles, and unidirectional conduction block facilitated by locally prolonged repolarization in the setting of globally heterogenous repolarization [20]. A myocardial scar provides a fixed arrhythmogenic substrate and a single ventricular focus that consequentially favors mmVT pathophysiology [3].

In the acute phase of myocardial ischemia, transient sub-clinical ischemia and/or therapeutic reperfusion in acute coronary syndrome (ACS) can cause regional variations in myocyte membrane voltage stability. This instability can lead to ectopic depolarizations or increased automaticity described as R-on-T, Ashman phenomenon, or long-short coupling. These irregular, unregulated focal depolarizations can act as a nidus for triggered activity and initiate hemodynamically significant ventricular arrhythmias [21]. Although VT from ACS is predominately polymorphic, early studies have described an increased risk of mmVT with superimposed acute ischemia on a healed myocardial scar [22][23].

2.1.2. Congenital and Acquired Cardiomyopathies

The incidence of mmVT is certainly higher in ischemic cardiomyopathy relative to non-ischemic; however, cases have been reported [24]. Akin to scar formation from myocardial infarction, inflammatory and degenerative processes can also lead to fibrotic tissue replacement of previously healthy myocytes, thus predisposing to the re-entrant form of VT. Causes of non-ischemic cardiomyopathy are vast and include familial cardiomyopathies such as arrhythmogenic right ventricular cardiomyopathy and non-compaction, autoimmune conditions such as cardiac sarcoidosis and cardiac amyloidosis, or infectious etiologies such as untreated Chagas disease and chronic viral myocarditis. Patients with established non-ischemic cardiomyopathies exhibit a surprisingly high incidence of mmVT via scar-related re-entry mechanisms, as evidenced by the seminal study from Marchlinski et al. [25].

2.1.3. Iatrogenic Causes

Congenital heart disease (CHD) that is incompatible with life and consequently requires surgical repair increases the risk for life-threatening arrhythmias. The majority of VT in CHD occurs predominantly by re-entry mechanisms and is quintessentially illustrated in early-to-middle-aged adults with repaired tetralogy of Fallot (rTOF). Well-defined anatomic isthmuses bordered by regions of unexcitable tissue are created by the numerous suture lines created by the congenital heart surgeons to the anatomical barriers and slowed conduction necessary for re-entry circuits [26]. The arrhythmogenic substrates in rTOF include postsurgical scars following right ventricular outflow tract incisions, valve annuli, and patches [27]. In addition to the expected post-operative surgical scarring, patients with CHD can also develop VT due to adverse ventricular remodeling from impaired function, increased workload, or subsequent conduction system destruction.

2.1.4. Purkinje System Disease

Bundle-branch re-entrant VT (BBR-VT) accounts for approximately 8% of sustained mmVTs [28] and can involve the right/left bundle, their branches, or the His bundle. Bundle-branch diseases, notably left-bundle branch blocks (LBBBs), facilitate interventricular conduction delays, which lead to ventricular contraction desynchrony and, if sufficiently severe, chronic, or hemodynamically significant, can lead to myocardial fibrosis via activation of the renin–angiotensin–aldosterone axis due to impaired perfusion of the periphery. The diffuse scar tissue deposition from this systemic process can provide an arrhythmogenic substrate for the formation of re-entrant circuits. These abnormalities disrupt the intrinsic cardiac conduction system, further increasing the likelihood of ventricular arrhythmias, including mmVT.

2.1.5. Idiopathic Ventricular Tachycardia

Idiopathic VT is a small subset of tachyarrhythmias that occurs in patients without structural heart disease. The VT focus can be located anywhere in the heart but predominantly arises from the right ventricular outflow tract (RVOT) and, less commonly, from the left ventricular outflow tract [29]. RVOT-VT is frequently precipitated by high adrenergic states such as exercise, intense emotions, and illness [30]. Individuals affected by idiopathic VT are typically female, young, and healthy and thus require a thorough diagnostic workup for other causes and then for

underlying heart disease. Unlike other causes of VT, this type is relatively benign given its transient nature in otherwise unremarkable cardiac systems and thus is associated with a low risk of sudden cardiac death [31].

2.2. Molecular Mechanisms of Monomorphic Ventricular Re-Entry

2.2.1. Calcium Handling

Under optimal cardiomyocyte conditions, a sodium influx-mediated membrane action potential initiates the opening of voltage-gated L-type Ca^{2+} channels (LTCCs), leading to Ca^{2+} release from the sarcoplasmic reticulum (SR), facilitating allosteric manipulation of thin filament regulatory proteins and actin–myosin cross-bridge cycling. LTCCs play a vital role in maintaining membrane depolarization throughout the plateau phase of the action potential. For this reason, the L-type calcium current ($I_{Ca,L}$) is crucial for preserving optimal action potential duration (APD) and illustrates why any alternations in $I_{Ca,L}$ kinetics carry a high arrhythmogenic potential.

2.2.2. Action Potential Prolongation and Repolarization Heterogeneity

In structural heart disease, a myriad of compensatory and pathophysiologic electrophysiological alterations ensue, precipitating a persistent proarrhythmic state. Ischemia-mediated calcium dysregulation (via sarco-endoplasmic reticulum adenosine triphosphate-ase expression downregulation and allosteric inhibition in addition to uncontrolled calcium sparks from failing ryanodine receptor clusters) and impaired potassium efflux [18] can directly lead to apoptosis via caspase activation or can lead to an impaired resting membrane potential and subsequent cell death. These two electrolyte abnormalities increase APD and ultimately exacerbate the repolarization reserve to depletion. Under conditions of acute metabolic stress, this low reserve state can lead to electrical alternans and, subsequently, mechanical alternans [32] as well as increase the likelihood of re-entrant arrhythmia via furthering the global cardiac repolarization heterogeneity.

This dispersion of repolarization can allow early afterdepolarizations, occurring during phases two or three of the cardiac action potential near the absolute refractory period, or the higher risk delayed afterdepolarizations occurring during phase four in the relative refractory period, to perturb the systems sufficiently to activate a dormant re-entrant system.

2.2.3. Dysregulated Na^+ Handling

The rapid upstroke of phase one in the cardiomyocyte action potential is primarily attributed to the influx of sodium ions (Na^+) through the sodium current (I_{Na}), making it predominantly responsible for tissue conduction velocity. In myocytes battered by local hypoxia and impaired membrane voltage regulation, the properties of the I_{Na} fail to completely inactivate and/or close throughout the action potential, resulting in late I_{Na}. This late depolarizing current has been demonstrated to be induced by the Ca^{2+}/calmodulin-dependent protein kinase II pathways, which are activated in the presence of structural heart disease to facilitate salvaging cardiac function via calcium desensitization [33]. The heightened intracellular Na^+ concentration subsequently triggers an additional increase in

cytosolic Ca^{2+} levels via membrane-bound Na^{+}-Ca^{2+} exchangers. These mechanisms collectively contribute to APD dispersion and elevated arrhythmogenic risk [18].

References

1. Al-Khatib, S.M.; Stevenson, W.G.; Ackerman, M.J.; Bryant, W.J.; Callans, D.J.; Curtis, A.B.; Deal, B.J.; Dickfeld, T.; Field, M.E.; Fonarow, G.C.; et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J. Am. Coll. Cardiol. 2018, 72, e91–e220, Erratum in J. Am. Coll. Cardiol. 2018, 72, 1760.
2. Buxton, A.E.; Calkins, H.; Callans, D.J.; DiMarco, J.P.; Fisher, J.D.; Greene, H.L.; Haines, D.E.; Hayes, D.L.; Heidenreich, P.A.; Miller, J.M.; et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). J. Am. Coll. Cardiol. 2006, 48, 2360–2396.
3. Stevenson, W.G.; Soejima, K. Catheter ablation for ventricular tachycardia. Circulation 2007, 115, 2750–2760.
4. Ransom, J.L.; Wong, K.C.; Kircher, J.; Usry, C.; Larson, C. Bidirectional Ventricular Tachycardia in a Young Female: A Case of Andersen-Tawil Syndrome. Mil. Med. 2023, 188, e412–e416.
5. Neumann, E.; Schaefer-Ridder, M.; Wang, Y.; Hofschneider, P.H. Gene transfer into mouse lyoma cells by electroporation in high electric fields. EMBO J. 1982, 1, 841–845.
6. Dev, S.B.; Hofmann, G.A. Electrochemotherapy--a novel method of cancer treatment. Cancer Treat. Rev. 1994, 20, 105–115.
7. Yavin, H.D.; Higuchi, K.; Younis, A.; Anter, E. Lattice-tip catheter for single-shot pulmonary vein isolation with pulsed field ablation. J. Interv. Card. Electrophysiol. 2023, 66, 1741–1748.
8. Verma, A.; Haines, D.E.; Boersma, L.V.; Sood, N.; Natale, A.; Marchlinski, F.E.; Calkins, H.; Sanders, P.; Packer, D.L.; Kuck, K.H.; et al. Pulsed Field Ablation for the Treatment of Atrial Fibrillation: PULSED AF Pivotal Trial. Circulation 2023, 147, 1422–1432.
9. Ouss, A.; van Stratum, L.; van der Voort, P.; Dekker, L. First in human pulsed field ablation to treat scar-related ventricular tachycardia in ischemic heart disease: A case report. J. Interv. Card. Electrophysiol. 2022, 66, 509–510.

10. Martin, C.A.; Zaw, M.T.; Jackson, N.; Morris, D.; Costanzo, P. First worldwide use of pulsed-field ablation for ventricular tachycardia ablation via a retrograde approach. J. Cardiovasc. Electrophysiol. 2023, 34, 1772–1775.
11. Lozano-Granero, C.; Hirokami, J.; Franco, E.; Tohoku, S.; Matía-Francés, R.; Schmidt, B.; Hernández-Madrid, A.; Zamorano Gómez, J.L.; Moreno, J.; Chun, J. Case Series of Ventricular Tachycardia Ablation With Pulsed-Field Ablation: Pushing Technology Further (Into the Ventricle). JACC Clin. Electrophysiol. 2023, 9, 1990–1994.
12. Krause, U.; Bergau, L.; Zabel, M.; Müller, M.J.; Paul, T. Flowerpower: Pulsed field ablation of ventricular tachycardia in a patient with Ebstein's anomaly. Eur. Heart J. Case Rep. 2023, 7, ytad093.
13. Adragão, P.; Matos, D.; Carmo, P.; Costa, F.M.; Ramos, S. Pulsed-field ablation vs radiofrequency ablation for ventricular tachycardia: First in-human case of histologic lesion analysis. Heart Rhythm. 2023, 20, 1395–1398.
14. Ekanem, E.; Reddy, V.Y.; Schmidt, B.; Reichlin, T.; Neven, K.; Metzner, A.; Hansen, J.; Blaauw, Y.; Maury, P.; Arentz, T.; et al. Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF). Europace 2022, 24, 1256–1266.
15. Dhanjal, T.S.; Lellouche, N.; von Ruhland, C.J.; Abehsira, G.; Edwards, D.H.; Dubois-Randé, J.L.; Moschonas, K.; Teiger, E.; Williams, A.J.; George, C.H. Massive Accumulation of Myofibroblasts in the Critical Isthmus Is Associated With Ventricular Tachycardia Inducibility in Post-Infarct Swine Heart. JACC Clin. Electrophysiol. 2017, 3, 703–714.
16. D'Souza, K.M.; Biwer, L.A.; Madhavpeddi, L.; Ramaiah, P.; Shahid, W.; Hale, T.M. Persistent change in cardiac fibroblast physiology after transient ACE inhibition. Am. J. Physiol. Heart Circ. Physiol. 2015, 309, H1346–H1353.
17. Chinyere, I.R.; Moukabary, T.; Hutchinson, M.D.; Lancaster, J.J.; Juneman, E.; Goldman, S. Progression of infarct-mediated arrhythmogenesis in a rodent model of heart failure. Am. J. Physiol. Heart Circ. Physiol. 2021, 320, H108–H116.
18. Chinyere, I.R.; Hutchinson, M.; Moukabary, T.; Lancaster, J.; Goldman, S.; Juneman, E. Monophasic action potential amplitude for substrate mapping. Am. J. Physiol. Heart Circ. Physiol. 2019, 317, H667–H673.
19. Chinyere, I.R.; Hutchinson, M.; Moukabary, T.; Koevary, J.W.; Juneman, E.; Goldman, S.; Lancaster, J.J. Modulating the Infarcted Ventricle's Refractoriness with an Epicardial Biomaterial. J. Investig. Med. 2021, 69, 364–370.
20. Ciaccio, E.J.; Coromilas, J.; Ashikaga, H.; Cervantes, D.O.; Wit, A.L.; Peters, N.S.; McVeigh, E.R.; Garan, H. Reprint of 'Model of unidirectional block formation leading to reentrant ventricular

tachycardia in the infarct border zone of postinfarction canine hearts'. Comput. Biol. Med. 2015, 65, 256–266.

21. Morton, M.B.; Morton, J.B.; Mond, H.G. Aberrant Ventricular Conduction: Revisiting an Old Concept. Heart Lung Circ. 2023, 32, 555–566.
22. Furukawa, T.; Moroe, K.; Mayrovitz, H.N.; Sampsell, R.; Furukawa, N.; Myerburg, R.J. Arrhythmogenic effects of graded coronary blood flow reductions superimposed on prior myocardial infarction in dogs. Circulation 1991, 84, 368–377.
23. Stambler, B.S.; Akosah, K.O.; Mohanty, P.K.; Wood, M.A.; Ellenbogen, K.A. Myocardial ischemia and induction of sustained ventricular tachyarrhythmias: Evaluation using dobutamine stress echocardiography-electrophysiologic testing. J. Cardiovasc. Electrophysiol. 2004, 15, 901–907.
24. De Potter, T.; Balt, J.C.; Boersma, L.; Sacher, F.; Neuzil, P.; Reddy, V.; Grigorov, I.; Verma, A. First-in-Human Experience With Ultra-Low Temperature Cryoablation for Monomorphic Ventricular Tachycardia. JACC Clin. Electrophysiol. 2023, 9, 686–691.
25. Hsia, H.H.; Callans, D.J.; Marchlinski, F.E. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. Circulation 2003, 108, 704–710.
26. Caldaroni, F.; Lo Rito, M.; Chessa, M.; Varrica, A.; Micheletti, A.; Pappone, C.; Giamberti, A. Surgical ablation of ventricular tachycardia in patients with repaired tetralogy of Fallot†. Eur. J. Cardiothorac. Surg. 2019, 55, 845–850.
27. Kapel, G.F.; Sacher, F.; Dekkers, O.M.; Watanabe, M.; Blom, N.A.; Thambo, J.B.; Derval, N.; Schalij, M.J.; Jalal, Z.; Wijnmaalen, A.P.; et al. Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired Tetralogy of Fallot. Eur. Heart J. 2017, 38, 268–276.
28. Mizusawa, Y.; Sakurada, H.; Nishizaki, M.; Ueda-Tatsumoto, A.; Fukamizu, S.; Hiraoka, M. Characteristics of bundle branch reentrant ventricular tachycardia with a right bundle branch block configuration: Feasibility of atrial pacing. Europace 2009, 11, 1208–1213.
29. Badhwar, N.; Scheinman, M.M. Idiopathic ventricular tachycardia: Diagnosis and management. Curr. Probl. Cardiol. 2007, 32, 7–43.
30. Ward, R.C.; van Zyl, M.; DeSimone, C.V. Idiopathic Ventricular Tachycardia. J. Clin. Med. 2023, 12, 930.
31. Buxton, A.E.; Waxman, H.L.; Marchlinski, F.E.; Simson, M.B.; Cassidy, D.; Josephson, M.E. Right ventricular tachycardia: Clinical and electrophysiologic characteristics. Circulation 1983, 68, 917–927.

32. Chinyere, I.R.; Moukabary, T.; Goldman, S.; Juneman, E. Electrical and mechanical alternans during ventricular tachycardia with moderate chronic heart failure. J. Electrocardiol. 2018, 51, 33–37.
33. Liu, X.; Ren, L.; Yu, S.; Li, G.; He, P.; Yang, Q.; Wei, X.; Thai, P.N.; Wu, L.; Huo, Y. Late sodium current in synergism with Ca2+/calmodulin-dependent protein kinase II contributes to β-adrenergic activation-induced atrial fibrillation. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2023, 378, 20220163.

Retrieved from https://encyclopedia.pub/entry/history/show/121904