Wave Tail Mapping to Guide Ablation Therapy for Ventricular Arrhythmias

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Depolarization Versus Repolarization as ventricular anti-arrhythmic strategy

The first two decades of cardiac electrophysiology involved investigating the role and targeting repolarization as antiarrhythmic strategy (Vaughan Williams, 1985). The mainstay antiarrhythmic treatments had been to lengthen repolarization, homogenize repolarization and modifying the excitable gap. Pharmacological strategies of Class 1 and 3 antiarrhythmic drugs utilize global therapeutic effects and is limited, as targeting selected target regions of arrhythmogenicity has not been possible due to unwarranted systemic effects on healthy myocardium. The systemic effect of prolonging repolarization and reducing excitability in unintended regions of the heart with antiarrhythmic drugs significantly increases the propensity for proarrhythmia. This has made exploiting phases of repolarization risky and unpredictable and has favored the EP community moving away from targeting activation and repolarization with drugs whenever feasible.

Catheter-based therapies have mainly targeted depolarization of tissue, in particular the delay in activation, allowing treatment to focused regions of disease or arrhythmogenicity. Cardiac mapping for VT therapy has focused on activation during VT or substrate-based approaches during sinus or paced rhythm has been the historical preferential tool for localizing VT ablation target. Techniques have been developed to locate prepotentials, Purkinje potentials, late activation as well as substrate methods such as local abnormal ventricular activity (LAVA) and decrement evoked potential (DeEP) mapping, all of those approaches rely on the depolarization wave front with no consideration of wave tail or repolarization of local tissue.

Compared to depolarization, cardiac repolarization and wave tail is temporally dispersed over a longer time: by a factor of at least 10-fold, and further heightened in the diseased myocardium. In fact, slow conduction or conduction block in diseased myocardium is largely
driven by prolonged repolarization and calcium-dependent conduction, wavefront wavetail interactions rather than reduced excitability alone (Auerbach, jalife 2011). Yet, clinical substrate mapping relies heavily on measuring depolarization and wavefront rather than the underlying primary wavefront wavetail interactions. Potassium channel function and their distribution heterogeneity has been demonstrated to be much more prevalent than heterogeneity in sodium channels in surviving myocardial tissues that support ventricular tachycardia in cardiomyopathy. Direct measures of repolarization differences may be therefore more reflective of primary disease than measuring local conduction delays. Heterogeneity in repolarization is more prevalent than depolarization and is a known greater driver of arrhythmogenicity (Baker, 2000; Akar 2000). Therefore, diseased myocardial tissue is more likely to manifest and be detectable during repolarization and behavior of the wave tail. There is emerging data that exists that targeting repolarization has mechanistically a more profound anti-arrhythmic impact. In this review, we revert back to the original direction described in the early stages cardiac electrophysiology of targeting repolarization, but now with the application of the role of targeted, catheter and substrate-based approaches.

**Repolarization as primary target in ventricular arrhythmogenesis**

It has clearly been established that repolarization heterogeneity and gradients are risk marker in VT/VF (Chauhan et al). Others (Akar et al 2003) have also demonstrated the role of transmural heterogeneities of repolarization with prolongation of midmyocardial (‘M’) cell action potential duration producing enhanced gradients and functional conduction block in the development of polymorphic VT. In this cardiomyopathic model using transmural optical mapping, it was the borderzone between M-cells and the subepicardial layer where the
repolarization gradient was most pronounced. As several ion channels are responsible for repolarization ($K^+$ channel types (Akar 2002) such as $I_{Ks}$, $I_{Kr}$, calcium channels (Banyasz et al) such as $I_{Ca-T}$, $I_{Ca-L}$ and $I_{lo}$) in contrast to depolarization (sodium channels), it is possible that repolarization abnormalities are more vulnerable to disease and may precede any manifestation of conduction delay. This infers that assessment may allow early diagnosis of at-risk patients. Also, repolarization metrics are more susceptible to changes in the rate of activation, and as described by Rosenbaum (Kaufman et al), T-wave alternans (TWA) precedes QRS alternans with increasing heart rate.

In addition, steep gradients of repolarization are known to be a predisposing factor for VAs. Repolarization gradients correlate with disease severity: Using ECG-I, epicardial spatial gradients in repolarization applying the inverse solution to unipoles have been observed in a variety of primary electrical disorders such as Long QT, Brugada and Early repolarization syndromes as well as pacemaker-induced cardiac memory; all of which have limited measures of depolarization abnormalities. Additionally, recent seminal work by Rivaud and Coronel (Rivaud et al., 2021) convincingly demonstrates sustained VT pivots around lines of repolarization gradients opening the door now for catheter-based therapy targeting cardiac repolarization abnormalities.

Thus repolarization gradient mapping could be of relevance in mapping VT/VF substrate in ischemic, nonischemic cardiomyopathy and channelopathies where arrhythmia is often pleomorphic and there is otherwise paucity of fixed conduction corridors, depolarization abnormalities and late potentials are sparse in the mapped endocardium. Epicardial or intramural sites could also be better deciphered as inherently low frequency changes may be detectable from the epicardium.
**Anecdotal Evidence of wavetail wavefront interaction as ablation target**

Repolarization as a substrate mapping and ablation target in various disease states have been serendipitously accumulating and is the original motivation for this viewpoint. The literature supports variety of disease states where repolarization has been targeted for catheter-based therapy. Repolarization ablation targets has been used in Brugada, Early repolarization, ARVC and, more recently, ischemic cardiomyopathy.

*Brugada syndrome:* Brugada syndrome (BrS) is believed to be an example of the concept of repolarization dispersion (repolarization hypothesis). Phase II re-entry across the myocardial wall due to heterogenous loss of transient outward potassium current Ito-mediated epicardial action potential (AP) dome exaggerates differential repolarization currents between the epicardium and endocardium resulting in formation of gradients during both phase I and II of the AP facilitating the development of VAs. Szul and Antzelevitch (Szul et al, 2014) and Patocskai and Antzelevitch (Patocskai et al 2018) provided a compelling alternative explanation for the epicardial substrate abnormalities in BrS described by Nadananee, directly linking these as a consequence of repolarization, not depolarization. Using Pinacidil and ajmaline, two BrS models to mimic either gain of function of the I_{so} or I_{K-ATP} channels and loss of function of the I_{Ca} and I_{Na} channels, respectively, arrhythmogenic substrate was mapped from drug-infused RV tissue samples until PVCs, polymorphic VT and VF induced. Dynamic, low voltage, fractionated bipolar EGMs were generated in the presence of accentuated epicardial AP ‘spike-and-dome’ appearance and late potentials as a result of concealed phase 2 re-entry. Furthermore, bipolar EGM abnormalities could be reversed with normalization of the epicardial AP second upstroke. These findings strongly
support that fractionation of the epicardial EGMs are secondary to heightened AP notching and concealed phase 2 re-entry and not due to conduction slowing. Finally, abolishment the repolarization pattern rendering patients VT-free suggest that regions of repolarization abnormality could be potential targets for radiofrequency-based therapy. Presumably, ablation normalizes BrS pattern by removing the ‘critical substrate’: myocytes with accentuated AP notching and overall reducing the $I_{\text{to}}$ concentration. This also suggests that the targets identified by Nadamanee and Pappone are not only related to the repolarization duration gradient, but the phase and shape of AP are also important to examine within the substrate for ablation. Repolarization gradients can also occur between neighboring endocardial or epicardial surfaces and is also possible for the gradients to occur transmurally involving epicardial, mid-myocardial and endocardial surfaces.

*Long QT*: QT prolonging therapies and primary mutations in channels mediating repolarization currents underpin the electrophysiological basis of R from T complexes, Torsades de pointes (TdP) and subsequent polymorphic VT in long QT syndromes. Recently, Rivaud and Coronel (Rivaud et al., 2021) demonstrated in a sotalol-infused porcine Langendorff model, that TdP initiation was dependent on RT heterogeneity where the critical difference between the short RT and long RT was if this interval exceeded 69ms. Furthermore, the duration of the short RT could not exceed 331ms to trigger TdP. Following initiation, phase singularities were maintained by figure-of-8 re-entry anchored by a core functional line of block wandering along sites of repolarization gradients (border of short and long repolarization regions) depicted as double potentials. These findings support the notion that localization of repolarization gradients in long QT and other arrhythmogenic syndromes is a potential target of substrate modification with catheter ablation.
Arrhythmogenic right ventricular cardiomyopathy: Repolarization abnormalities may complement depolarization findings in ARVC, or may be used to identify early disease when typical arrhythmogenic regions of slow conduction are sparse. The role of repolarization mapping as an adjunct to depolarization mapping is emerging. The genesis of T-wave inversion in ARVC involves amplified AP gradients between the endocardium and epicardium leading to local spatial dispersion of repolarization. Detailed mapping was performed in 21 ARVC patients with analysis of the unipolar EGM repolarization parameters including the morphology and negative amplitude of the T-wave, Q-Tpeak interval and Tpeak-Tend intervals. Tpeak has been shown in experimental models to correspond to full repolarization (Antzelevitch et al., 2001). Epicardial negative T-wave area was significantly larger than healthy controls and these regions correlated strongly to typical abnormal substrate including critical VT sites as determined by activation and entrainment.

Ischemic and non-ischemic cardiomyopathies: Repolarization mapping and as an ablation target in ischemic or cardiomyopathic hearts is an attractive mechanistic strategy. Our group (Downar et al., 2021) has recently demonstrated the utility of high-density, simultaneous unipolar EGM mapping in an early ischemia model to define the mechanism of spontaneous PVCs being linked to transmural re-entry. Studies have shown that LV remodeling in failing human myocardium results in prolongation of APD and refractory periods, APD alternans and heterogeneous prolongation of APD. In humans, intramural repolarization gradients have not previously been evaluated due to the obvious limitation of instrumentation of this region and interpretation of low frequency content signatures of repolarization. Furthermore, cut sections of human heart with optical mapping to identify M cells have not been able to prove this concept. We have previously
evaluated M cells using an intact human heart model with multiple plunge needles and not identified M cells. We recently developed omnipolar mapping that provides local assessment of repolarization in addition to depolarization. In addition to traditional activation-recovery interval (ARI)-based repolarization mapping, future work from our centre will assess if optically validated omnipolar-ARI repolarization assessment can be used to accurately identify VT vulnerable regions and guide targeted catheter ablation and reduce arrhythmia burden.

In healthy heart, repolarization in epicardium, is on a different time course compared to the endocardium. This minimises the transmural dispersion in repolarization time. Both endocardial and epicardial ARI get locally prolonged in borderzone and dense scar irrespective of scar location, with greater proportional lengthening of ARI in the epicardium than endocardium (Srinivasan et al 2019). This minimizes the transmural dispersion of repolarization in scarred regions, possibly to compensate for further reduction in conduction velocity in epicardium from greater proportional downregulation of Cx43 in the epicardium (Peters et al). When opposing endocardial and epicardial scar patterns are congruent, the transmural dispersion of repolarization appears to diminish. Some degree of transmural dispersion of repolarization is preserved when either endocardial or epicardial scar is opposite normal paced tissue.

In models of healed ischemic scar with VT, ARI is prolonged and there is dynamic spatial dispersion of repolarization in critical isthmus sites. Srinivasan and colleagues (Srinivasan et al, 2021) used the Wyatt method to automate repolarization time color maps. The repolarization time (RT) was defined as activation time maximum negative dV/dt to the upslope of the unipolar EGM T-wave (whether negative or positive). An additional “dynamic” protocol was added to sinus rhythm substrate-based mapping with a single sensed extrastimulus form the RV apex. Maps were
created in 20 patients and compared to isthmus sites as defined by activation/entrainment (70%) or pacemap mapping. RT was most prolonged in dense scar (voltage <0.5 mV), progressively shortening in borderzone scar and normal voltage. RT was further exaggerated when only utilizing the single extrastimulus maps where it was most prolonged in dense scar. Furthermore, RT was significantly longer in regions of LPs, and, again amplified by the extrastimulus protocol. Spatial dispersion of repolarization was significantly prolonged in critical isthmus sites when stressing the substrate with the extrastimulus protocol. Importantly in that study no difference in repolarization was seen in critical sites when mapping only in sinus rhythm. These data promote the concept that critical isthmus sites harbour the cellular constituents for heterogenous dynamic refractory properties and low-voltage corridors susceptible to unidirectional block facilitating re-entry.

Recently, Callans and Donahue (Callans et al) describe repolarization heterogeneity in human post-infarct VT with significantly shorter ARIs in isthmus-proven sites, supporting experimental studies demonstrating spatial dispersion of refractoriness in non-infarct conditions. In 6 patients undergoing clinically-indicated VT ablation, critical circuit sites were demonstrated with gold standard entrainment or pacemap matching with a long stimulus-to-QRS using point-by-point mapping. Unipolar EGMs were bandpass filtered at 2 to 240Hz, ARI as a surrogate of local action potential duration (Millar et al, 1985) was measured from maximum negative dV/dt of activation to the either the upslope or downslope for negative and positive T-waves, respectively. As previously demonstrated (Anter et al), traditional bipolar electrogram (EGM) abnormalities including duration, fractionation, split and late potentials lacked specificity as they were equally found in non-isthmus sites. However, ARI was significantly shorter in isthmus sites compared to adjacent non-isthmus sites (420.2ms vs 462.5ms). Impressively, ARI was found to be shortest at 3 of 4 patients with first-ablation lesion VT termination. Possible mechanistic
explanations of these findings may relate to earlier porcine work showing remodelling-associated upregulation of $I_{Ks}$ channels shortened APD was specific to the isthmus (Kelemen et al). Furthermore, genetic transfer of a negative potassium channel gene prevented VT, providing validation that normalizing repolarization gradients and the role of genetic therapy may be a therapeutic target.

It is important to note that these mapping efforts detailed in these above studies are retrospectively, manually annotated unipolar EGMs, and are not live active mapping schema. Developing wavetail mapping and assessing repolarization in live mapping schema similar to our current activation paradigm will be mandatory in prospectively testing the thesis of the this review.

**Merging wavefront and wave tail mapping in ablation targeting**

Merging depolarisation and repolarization mapping together could provide best value in assessing cardiac tissue vulnerabilities to abnormal reentrant arrhythmia. It is plausible that regions of depolarization abnormalities also harbor repolarization changes. In fact, repolarization vulnerability index (RVI) is one such measure where timing of repolarization (APD90) of ‘proximal’ tissue with S2 is subtracted from the start of S2 depolarization in ‘distal’ tissue. RVI is a conceptual model integrating both activation and repolarization alterations. Theoretically, for the fundamental prerequisite of unidirectional block to occur and permit re-entry around fixed or functional block, the repolarization time (RT) of the antidromic wavefront must be shorter than the activation time (AT) of the returning or orthodromic distal wavefront (i.e $RVI = RT – AT < 0$). If the RT is longer than the AT, then bi-directional block ensues. Orini and colleagues (Orini et al) have outlined a novel use of RVI to identify critical VT sites in 18 patients with ischemic and non-ischemic cardiomyopathy. VT exit sites were determined in the majority of cases with pacemap
mapping (67%) and remainder using activation/entrainment (33%). High-density substrate maps were created using multipolar catheter during ventricular extrastimulus mapping (either single or using a drive train) to further expose channels of slow conduction. Retrospective analysis of each point on the map was performed examining the surrounding points within a predefined radius of 8mm. As the shorter the RVI is more likely to allow reentry, the shortest RVI from the surrounding points was annotated and a color-displayed RVI map created. Importantly, AT, RT and ARI was calculated for each point. As activation time window of interest ended after QRS duration, electrograms with complex morphologies and late components typically seen within the perimeter of scar would have been automatically excluded. Even within this limitation, VT ‘exit sites’ which are commonly located just outside the scar regions were localized with reasonable accuracy. Interestingly, RVI was the most accurate index when all other activation-repolarization markers were assessed where AT and ARI were closest proximity to RVI. The overall accuracy of RVI to localize the critical VT site (within 10mm) was 72.2%, whereas in 5.6% of cases, the shortest RVI was incorrect and remote. Again, RVI was the least inaccurate index compared to AT, RT and RVI. Prospective empirical targeting of low RVI sites was not performed in this study presumably due to the lack of ability perform real-time wavetail mapping.

A unique feature is that RVI will not only identify the critical VT site involved in the clinical VT, but all possible sites susceptible to re-entry. Due to selective mapping, studies have not evaluated the possibility of global repolarization mapping strategy in detail. Using non-contact RV mapping, the same group has previously also demonstrated RVI closely co-localizes the endocardial VT exit sites in patients with arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome (Martin et al). Additionally, they explored the role of the RVI being a ‘global’ indicator (RVIG) of vulnerability to re-entrant arrhythmias. Indeed, a lower RVIG was associated
with inducible VT and clinical VT events during follow-up. Further support for its mechanistic underpinning relating to detecting susceptible regions of unidirectional conduction block and local re-entry is evidenced by its inaccuracy to detect focal ventricular sources caused by automatic or triggered activity.

**Wave tail Mapping**

Repolarization can be analyzed using a multitude of techniques. Refractory period determination focuses on calculating the reexcitation phase after extrastimuli delivery, but is limited by the onerous need to test at each individual site. Unipolar measurement of potential APD gradients omits the 3-dimensional contribution of repolarization. ARI is a clinically useful method as it correlates to APDs as determined by both refractory period determination and mapping using intracellular electrodes, but potential errors in anisotropic membrane potentials and inconsistent coupling resistances reduce its accuracy. Measurement of monophasic APs with contact or intracellular electrodes is limited by the potential damage to the underlying tissue as well as difficulty to use in the beating heart. Optical mapping has been shown to correlate to intracellular electrode-measured APs (Salama et al 1988). Compared to unipolar and bipolar EGMs, the major advantage of optical mapping is their uniform high-density signals that have no far-field contamination and is independent of wavefront directionality. The major downside of optimal mapping is the inability to apply it in a clinical setting. However, determination of the voltage-dependent response is well described. Firstly, depolarization is typically defined as the maximum first derivative of the AP upstroke \((dV/dt)_{max}\). Although no clear definition is used for determining repolarization, most use values of the AP downstroke to baseline (either 50%, 75% or 90%). Alternatively, the peak of the second derivative \((d^2F/dt^2)_{max}\) has been shown to be a practical and
reliable time point in repolarization. In an optimal mapping animal study supplemented by detailed evaluation of fiber orientation to record activation and repolarization wavefronts from the endocardium and epicardium, Kanai (Kanai Salama 1995) showed that epicardial repolarization indeed spreads anisotropically and is connivingly determined by epicardial fiber arrangement. Here, repolarization patterns were not influenced by pacing rate, site or engagement of the Purkinje system and was reproducibly initiated from the apex, indicating that apical cells have the shortest APD, independent of the myocardial contractible state. Epicardial repolarization patterns were not a result of a phase wave due to intrinsic repolarization of individual cells, but were spread from cell-to-cell, linked by intracellular electrical coupling, analogous to ventricular activation. Endocardially, the first sites to depolarize were the first sites to repolarize. However, due to heterogeneity in APD, random repolarization patterns were seen.

Contention exists as to whether wavetail is truly a ‘wave’, electrically coupled at a cellular level or only appears as a phase wave due to independent repolarization of individual cells. In experimental studies, multiple lines of evidence suggest a wavetail is true wave. Repolarization anisotropic spread along the direction of myofiber orientation, strongly reproducible beat-to-beat repolarization patterns and slow velocities driven by the AP downstroke, repolarization that is pacing and Purkinje activation site independent and alternation of repolarization to random patterns during hypoxia all strongly suggest that repolarization is not a phase wave (Kanai Salama 1995). In mathematically modelling data, APDs have been shown to be modulated by low resistance cell-to-cell electrical coupling where APD variation equalizes under normal conditions but increases along with resistance in the setting of ischemia and cellular uncoupling (Joyner 1986; Lesh et al., 1989).
Clinical Wavetail Mapping for Catheter Ablation

The current state of clinical wavetail mapping is rudimentary as it has mostly been used in experimental situations as optically mapping is not possible in the clinical setting. Its limited use in the human studies requires post hoc analysis. Only monophasic action potential (MAP) mapping provides real-time assessment but point-by-point ARI is post hoc thus not allowing for true wave tail mapping. Non-invasive epicardial mapping using electrocardiographic imaging is currently limited in its accuracy to be reliably used for this purpose. A recent direct comparison of non-contact ECGI to epicardial contact mapping points demonstrated only moderate correlation of unipolar morphology, AT and RT maps with a displacement error of approximately 13mm (Graham et al., 2019). Aside from the challenges in optimizing and simplifying clinical wave tail mapping, other obstacles need to be highlighted. As wave tail mapping examines local repolarization that occurs at a lower frequency and over a longer time scale, annotation is prone to errors due to contamination of other low frequency waveforms (for example, far-field activation, respiration, cardiac motion, ambient electrical noise of recording systems). The ‘smudging effect’ is certainly relevant in a heterogeneous tissue where timing of local repolarization cannot be easily defined and perhaps even harder to determine than time of local depolarization in a multi-component bipolar electrogram.

Signature surface 12-lead ECG atrial or ventricular T-wave morphology of different exit sites (relevant for pace-mapping) are also unknown. In fact, it is quite possible that patterns of summed repolarization vectors of different exits cannot be resolved purely on the body surface using our standard 12-lead ECG bandwidth. Additional tools such as ECGI are almost necessary. Controversy exists in determining time of local repolarization. Using action potential recording with potassium-loaded microelectrodes and Laplacian electrogram analysis, time of local
repolarization on unipolar electrograms has been shown to coincide with the upslope of the local T wave. Biophysical recording variables (electrode size, interelectrode spacing, orientation, far-field contamination) that are known to influence unipolar and bipolar electrogram waveforms will be relevant for repolarization mapping. Furthermore, assessment of the effect of bipolar directionality on repolarization markers is needed, especially given scar anisotropy (Lambiase, 2022 editorial). Fixed-grid electrode platforms (Advisor HD Grid, Abbott Laboratories) are a paradigm shift in cardiac mapping permitting direction-aware solutions to reduce the effect of directional dependency. Omnipolar activation directional mapping bypasses many of the limitations of LAT-based mapping, including bipolar orientation, unstable cycle length and reference timings and annotation of complex fractionated electrograms (Deno et al., 2020). Furthermore, beat-to-beat spatial repolarization omnipolar mapping is possible and the next logical step in advancing repolarization mapping.

**Summary**

The reemerging interest of repolarization in ventricular electrophysiology has been reinvigorated with an accumulating role of wave tail mapping to determine critical sites above what is currently understood with depolarization or wavefront mapping alone. Despite the ability to study diseased substrate in detail with a myriad of techniques, clinical outcomes remain unchanged. There is a need to explore alternative VT-mapping techniques beyond bipolar EGM-based depolarization abnormalities, especially in primary electrical conditions where conventional scar ablation endpoints are limited or non-existent. Wave tail mapping has potential to fill this void. There are currently multiple barriers precluding its clinical utility, however, ventricular repolarization mapping has a major potential adjunct role in determining critical and vulnerable
VT sites and provides the impetus to develop wave tail mapping and may help improving determining targets in ischemic and non-ischemic substrate. Improvements in clinical repolarization phase mapping is needed, especially defining mapping surrogate and improving the accuracy of automatic live annotation using electroanatomical mapping systems.
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