Critical repolarization gradients determine the induction of reentry-based torsades de pointes arrhythmia in models of long QT syndrome

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BACKGROUND Torsades de pointes arrhythmia is a potentially lethal polymorphic ventricular tachyarrhythmia (pVT) in the setting of long QT syndrome. Arrhythmia susceptibility is influenced by risk factors modifying repolarization.

OBJECTIVE The purpose of this article was to characterize repolarization duration and heterogeneity in relation to pVT inducibility and maintenance.

METHODS Sotalol was infused regionally or globally in isolated Langendorff blood-perfused pig hearts (N = 7) to create repolarization time (RT) heterogeneities. Programmed stimulation and epicardial activation and repolarization mapping were performed. The role of RT (heterogeneities) was studied in more detail using a computer model of the human heart.

RESULTS pVTS (n = 11) were inducible at a critical combination of RT and RT heterogeneities. The pVT cycle lengths were similar in the short and long RT regions. Short-lasting pVTS were maintained by focal activity while longer-lasting pVTS by reentry wandering along the interface between the 2 regions. Local restitution curves from the long and short RT regions crossed. This was associated with T-wave inversion at coupling intervals at either side of the crossing point. These experimental observations were confirmed by the computer simulations.

CONCLUSION pVTS are inducible within a critical range of RT and RT heterogeneities and are maintained by reentry wandering along the repolarization gradient. Double potentials localize at the core of the reentrant circuit and reflect phase singularities. RT gradient and T waves invert with short-coupled premature beats in the long RT region as a result of the crossing of the restitution curves allowing reentry initiation.

KEYWORDS Long QT syndrome; Torsades de pointes arrhythmia; Repolarization; Reentry; Restitution (Heart Rhythm 2021;18:278–287) © 2020 Heart Rhythm Society. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Torsades de pointes (TdP) arrhythmia is a common and potentially lethal polymorphic ventricular tachyarrhythmia (pVT) in the setting of long QT syndrome (LQTS).1 LQTS can be brought about by adverse drug actions and/or loss-of-function mutations in the ion channels that carry repolarizing currents. TdP susceptibility is increased by factors that increase repolarization time (RT): hypokalemia,2 bradycardia,3 and short-long-short cycles.4,5 Heterogeneity in RT rather than prolonged RT plays a determinant role in arrhythmia risk.6,7 Indeed, steep RT gradients (∆RT) have been observed in patients with LQTS.8 Genetic and pharmacological factors may amplify ∆RT.9

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The initiating activations of TdP arrhythmia in LQTS are thought to emanate from focal activity caused by triggered activity on the basis of early afterdepolarizations (EADs). Evidence suggests that EADs preceding a TdP in LQTS mostly originate from the outflow tract regions and the consecutive activations of TdP are of reentrant origin. $\Delta$RT likely underlie the inducibility of reentry by creation of unidirectional block. Although T-wave changes on the electrocardiogram supportive of alterations in regional differences in repolarization have been observed, the exact interaction between repolarization changes (and the heterogeneity thereof) and arrhythmogenesis is unknown.

We hypothesized that the presence of critical $\Delta$RT facilitates reentrant activation and pVT and that the resulting differences in restitution characteristics between the areas with long and short repolarization are related to the maintenance of the arrhythmia.

We therefore studied the role of RT (heterogeneity) and restitution in relation to the initiation and maintenance of pVT in a pig model of LQTS on the basis of regional or global perfusion of a repolarization-prolonging drug. In addition, we studied these at a higher spatial resolution using a human heart computer model. This work sheds light on the causal relation between RT duration and heterogeneity and the occurrence of pVT. We further demonstrate that pVT is associated with reentrant circuits wandering along the border separating areas with short and long RTs. Double potentials (DPs) in local electrograms occur at the core of the reentrant circuits reflecting phase singularities (PSs). These DPs in local electrograms may aid in localizing stable singularity points as ablation targets in patients with arrhythmia syndrome. Finally, the local RT restitution curves from the short and long RT regions cross, explaining how not 1 but several premature beats in the initially long RT region can initiate reentry in patients with LQTS.

### Results

#### Critical repolarization heterogeneity and arrhythmia induction

Figure 1A shows maps of activation times, RTs, and activation recovery intervals (ARIs) before and after creation of RT heterogeneities by infusion of sotalol in 1 heart. Pacing was performed on the left ventricular free wall (pulse symbol). The paced activation sequence is not altered by the drug (top panels in Figure 1A). RT was earliest near the left ventricular stimulation site and was latest in the apex of the right ventricle. Infusion of sotalol changed the maximum $\Delta$RT ($\Delta$RT = 95th percentile − 5th percentile) from 60 to 80 ms, with a sharp $\Delta$RT in the left ventricular wall. In the example of Figure 1A, the average local increase in ARIs in the perfused area was 59 ± 9 ms (bottom panels).

Figure 1B shows a difference map of ARIs where the region of increased RT now stands out more clearly. Overall (N = 7 hearts), infusion of sotalol resulted in a mean increase in RT by 57 ± 14 ms and in ARIs by 55 ± 16 ms either in the entire heart (global infusion) or in the area of the left anterior descending coronary artery (regional infusion) (Figure 1C).

Examples of RT maps after sotalol infusion are displayed in Figure 2A for 2 different hearts. The 2 hearts display the same RT heterogeneity ($\Delta$RT = 80 ms), but RTs are longer in heart 1 than in heart 2 (earliest 319 ms vs 261 ms, respectively). Arrhythmia induction protocols led to a self-terminating pVT in heart 2, but not in heart 1 (Figure 2B). Note that T waves in the long RT region are negative and those in the short RT region are positive as a reflection of the repolarization differences.

VTs were inducible after infusion of sotalol in 4 of 7 hearts (57%). In total, 11 (92%) pVTs and 1 (8%) monomorphic ventricular tachyarrhythmia (monoVT) were induced. Arrhythmia induction was also performed at baseline and led to ventricular fibrillation (VF) in 1 heart only. In this heart, we used a less aggressive pacing protocol for subsequent pVT induction. Figure 2C shows the relation between minimum RT (RTShort) and $\Delta$RT preceding the induced pVT. pVTs and monoVT are indicated in black and gray dots, respectively, and no ventricular tachyarrhythmia and VF are indicated in white. pVTs were inducible only within a critical range of RTShort (RTShort < 315 ms; y-axis) and $\Delta$RT (70 ms < $\Delta$RT < 92 ms; x-axis) (Figure 2C).

The RT and RT heterogeneity within a heart could not be fully controlled experimentally because they depend on infusion rates, recirculation times, relative sizes of the perfusion beds and perfusion volumes. Thus, we performed a computational study in order to systematically test arrhythmia inducibility along a range of baseline RTs and $\Delta$RT and to provide insight into arrhythmia mechanisms at a higher spatial resolution than in the experimental study (Figure 2D). Figure 2E shows that VTs were inducible when $\Delta$RT was larger than 69 ms and RTShort was not higher than 331 ms. Note that more monoVTs were induced in silico than experimentally.

### Methods

#### Study approval

All experiments were performed in accordance with governmental and institutional guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes. Experimental protocols were approved by the local animal research ethics committee (CEEA50) on animal experimentation at the University of Bordeaux.

In brief, RT heterogeneities were created in Langendorff-perfused pig hearts by infusion of sotalol either globally in the entire perfusion system or regionally into the left anterior descending coronary artery (Online Supplemental Figure 1). Restitution and arrhythmia inducibility protocols were performed before and after infusion of sotalol. Details about analysis and the human computer model can be found in the Online Supplement.
Overall, these results show that a critical range not only of ΔRT but also of RT in the short repolarized myocardium is necessary for the induction of pVTs (Figure 2F). Outside this critical range, a shorter RTShort will induce VF whereas a longer RTShort is antiarrhythmic (Figure 2).

pVTs are maintained by reentry

We performed epicardial activation mapping of each beat of self-terminating arrhythmias and the first 15 activations of sustained arrhythmias. Figure 3A shows a pseudo-electrocardiogram of a self-terminating pVT. The reference time is placed at the last given premature stimulus artifact (dashed line), and the red star indicates the last stimulated activation. For the first spontaneous activations, no continuous diastolic activity could be detected and the beats were classified as of focal origin (Figure 3B). After these focal activations, reentry occurs. Figure 3C shows 2 continuous reentrant activations (marked red and green in panel A; reference time arbitrarily placed in the isthmus). The maps show activation block (black lines). The activation waves follow a figure-of-8 reentry pattern (clockwise and anticlockwise loops) for 2 consecutive activations. The reentrant circuits encompass both the short and long RT regions. Selected unipolar electrograms (clockwise loop: a-b-c-d-e-f-g-h-a and anticlockwise loop: m-n-o-p-q-r-s-t-m) organized along the 2 reentrant circles and displayed on the right show that the diastolic interval is bridged by local activations. Overall, activation mapping of pVTs revealed that short pVTs (n = 6; <8
activations) or the start of longer pVTs were generated by focal activity whereas longer pVTs \((n = 5)\) were maintained by reentry.

We observed that the arrhythmia cycle length was the same in electrograms recorded from the short or long RT regions supporting a common reentrant mechanism underlying activation in both myocardial areas. Therefore, the averaged cycle length was measured in 1 representative electrogram in each of the 2 regions during the entire arrhythmia for all arrhythmias. Figure 4A shows a linear relation between the arrhythmia cycle length in the short and long RT regions \((R^2 = 0.92)\). A similar linear relation was also observed in the human computer model \((R^2 = 0.89)\) (Figure 4B).

**DPs wander along the repolarization gradient**

In the pVTs of longer duration, we observed episodes during which the cycle length was halved in specific electrograms and the amplitude was reduced (examples in Figure 5C, red lines). Similar electrograms have been recorded from the line of block of a reentrant circuit.\(^{15}\) We have used this characteristic, termed double potentials (DPs), to track the path of the core of a reentrant pathway. Figure 5A shows that during a pVT, DPs (white stars) were recorded near the repolarization gradient (dashed line in the \(\Delta\text{ARI}\) map). We measured the distance (as number of intermediate epicardial electrodes) between the sites with DPs and the closest border between the short and long RT regions. Figure 5B shows that the majority of the sites with DPs cluster along the demarcation line of the repolarization gradient for 3 pVTs during which the entire epicardial surface was covered. Figure 5C shows that the sites of DPs wander along the repolarization gradient. Note that DPs in electrograms \(b, c,\) and \(d\) correlate with sites of the line of block of the reentrant activations in Figure 3C. In electrogram \(e,\) far from the repolarization gradient, no DPs occurred. DPs also occurred at the subendocardial myocardium and only at the same time of the occurrence of epicardial DPs (transmural needle 4 in Figure 5C). Thus, the areas of DPs are transmurally homogeneous and move along the repolarization gradient.
Inversion of repolarization gradients at short coupling intervals

pVTs were induced with short-coupled premature beats. This suggests that the changes in RT and ΔRT following premature beats may contribute to arrhythmia initiation. We reconstructed local restitution curves from the short and long RT regions under steady-state conditions at the same basic cycle length in 4 hearts. A local restitution curve was constructed from measured RT on the local epicardial electrograms located closest to the stimulation site at which an S1-S2 pacing protocol was delivered. At baseline, the repolarization restitution curves (RT as a function of diastolic interval) were almost identical in both regions, as expected (Online Supplemental Figure 2). Figure 6A shows 2 restitution curves from the short and long RT regions after sotalol infusion. Figure 6B shows the same RTs plotted against coupling intervals relative to S2 in order to correct for the influence of activation changes initiated by the

Figure 3 Nonsustained polymorphic ventricular tachycardias (pVTs) are maintained by reentry. A: Pseudo-ECG showing a nonsustained pVT (dashed black line: time reference; red star: last paced activation; 1 and 2: spontaneous activations; red and green activations mapped below). B and C: Activation maps of the corresponding activations. The reference time on panel C is the activation time of the red activation electrode. Dotted lines: Borders of the region with increased activation recovery intervals (ARIs). Solid black lines: Activation block. White arrows: Activation sequence (figure-of-8 reentry). Activation times in electrodes f, q, and r are derived from intramural electrodes. Right panels: Local electrograms along 2 circles at locations a–i and a–t. Note diastolic bridging.
premature beat. The figure shows that at coupling intervals greater than 365 ms, the RT in the long RT region is longer than in the short RT region. However, at coupling intervals less than 365 ms, RT in the long RT region became shorter than in the short RT region. The crossing of restitution curves is further illustrated by the reversal of the repolarization gradient following a short-coupled S2 beat compared with an S1 steady-state beat (Figure 6C). The reversal of the repolarization gradient at short coupling intervals was observed in all 4 hearts (100%).

The crossing of the restitution curves implies that T-wave morphology and polarity are dependent on the coupling interval. We tested this by comparing T-wave morphology at coupling intervals at either side of the point of crossing. Figure 6D shows electrograms from the short and long RT regions at a coupling interval larger than the crossing point.
The red dots indicate moments of repolarization and show that RT was later in the long than in the short RT region. When the coupling interval was reduced and was below the value of the crossing point (290 ms), the T wave became positive in the long RT region and RT was later in the short than in the long RT region. The same phenomenon was observed in all 4 hearts (100%).

Simulation study: Arrhythmia mechanisms

In the simulation study, monoVTs were explained by 2 reentrant circuits remaining at fixed locations throughout the duration of the simulation (Figure 7A and Online Supplemental Figure 3). pVTs were explained by a more complex behavior: their vortex-like reentry changed in position over time but remained near the boundary between the short and long RT modeled regions (Figure 7B). Specifically, the movies in Online Supplemental Figure 4 (corresponding to the pVT displayed in Figure 7B) showed that a relatively fixed reentrant circuit was present in the ventricular apex, along with 1 or more secondary reentrant circuits at the interface of the short and long RT regions. These asymmetric secondary reentrant circuits were temporary and drifted along this border with varying rotational direction. When the system reached a critical limit of secondary reentrant circuits, it became unstable and terminated the apical reentrant circuit and eventually the pVT.

Coinciding with these reentrant mechanisms, the PSs and sites of DP during pVTs were distributed along the interface between the short and long RT regions (Figure 7B). DP in the local electrograms occurred at the same locations and time as the PS during the arrhythmias. In pVT, the movement of the PS and DP was associated with the typical TdP morphology of the simulated electrocardiogram (Figure 7B, upper left panel). This was explained by scroll waves terminating, changing their direction of rotation, or reappearing from functional block during their movement and fractionation around the border of the short and long RT regions. For monoVTs, the number of PS remained constant at 2.

Discussion

In this study, we demonstrated that pVTs can be induced only in a critical range of RT values. Second, we showed that the
mechanism for the maintenance of the arrhythmia is figure-of-8 reentry circulating along the border between short and long repolarization regions. DPs and PSs occur predominantly at the border between the regions and wander along this line. Appearance and disappearance of one of the reentrant activations are associated with the typical electrocardiographic TdP morphology. Restitution curves constructed from the short and long RT regions cross. Therefore, DRT invert at coupling intervals shorter than the intersection point. This is associated with the inversion of T-wave polarity in local electrograms at short cycle lengths. During the arrhythmia, the cycle lengths are the same in the 2 regions. This is the result of the presence of a single reentrant mechanism occurring at the border between the long and short RT regions at the cycle length that is common to the restitution characteristics of the 2 regions.

The mechanism of TdP arrhythmias has been studied previously. It has been commonly accepted that the first activations of the arrhythmia are caused by a focal mechanism whereas the maintenance is more likely associated with reentrant activity. Our study focused on the mechanism of maintenance, although the data in

Figure 7 Arrhythmia mechanisms in the human computer model. Reentry in transmembrane potential (Vm) underlies sustained monoVT (A: baseline RT = 303 ms; ΔRT = 93 ms; average sotalol cycle length (CL) = 249 ms; average normal CL = 248 ms) and nonsustained pVT with TdP-like electrograms (B: baseline RT = 255 ms; ΔRT = 91 ms; average sotalol CL = 231 ms; average normal CL = 183 ms) initiated in the presence of regional repolarization gradients. Electrograms are shown for the border of the sotalol and normal regions. Phase singularity (PS) and double potential (DP) maps show similar distributions over the duration of the simulation.
Figure 6 shed light on induction. Our mapping data are in agreement with a reentrant mechanism based on figure-of-8 reentry. This idea is further supported by a critical dependence on RT heterogeneities. Remarkably, inducibility of the arrhythmia is limited by RTShort; if it is longer than about 315 ms, no arrhythmias could be induced irrespective of the degree of heterogeneities. This is likely related to the mass of the tissue in relation to the theoretical wavelength.

We further demonstrate that a relatively large figure-of-8 reentrant activation lies at the basis of the arrhythmia. This makes the arrhythmia susceptible to termination by focal mechanisms or by prolongation of its wavelength. Indeed, TdP is characterized by spontaneous termination, although it may progress to VF.1 The latter transition is likely explained by a conversion of a figure-of-8 to a multiple wavelet reentry. The relatively large dimension of the reentrant circuit during a pVT is also supported by the observation that episodes of epicardial DPs occur simultaneously transmurally and that no transmural gradients exist.

**Model of TdP**

We used a model of TdP by pharmacologically generating regionally prolonged repolarization. Other large animal models of TdP involve chronic atrioventricular block in dogs in combination with the global infusion of a delayed rectifier potassium current blocking agent.7 In this model, Dunnink et al7 have shown that transmural repolarization gradients are important. In a LQTS rabbit model, optical mapping has demonstrated that PS during a pVT clustered along the border between the short and long repolarization regions.16 This is compatible with our present data, where we show that rotors and lines of block during pVTs cluster along the border between the short and long repolarization regions.

**Genesis of focal activity and reentry**

EADs are generated in tissue with the longer action potential duration, whereas reentry is usually induced by premature stimulation from the area with the shorter action potential duration. Thus, it is still unclear how premature activation in patients with LQTS can induce reentry. On the basis of our observations of the intersection of restitution curves, we speculate that with short-coupled premature activations in the long RT region, the repolarization gradients reverse and a second closely coupled activation can encounter unidirectional block leading to reentry. The inversion of a T wave in the electrocardiogram with premature stimulation has been demonstrated.13 The basis for the required multiple premature beats is likely formed by triggered activity by EADs. This mechanism also explains that TdPs start with more than 1 premature beat before developing into reentry.5

**Clinical implications in patients with LQTS**

We describe that pVT occurred only within a certain range of RT heterogeneity. In addition to QT interval, heterogeneity of repolarization through invasive or noninvasive mapping (width of the T wave) may prove a better differentiator for patients at risk, as indicated previously.8 We showed that PSs localize with DPs (low-amplitude double-frequency activations) in unipolar electrograms, especially at the interface between the long and short RT regions. This allows the localization of RT gradients by unipolar electrograms, and if stable, may aid catheter ablation for arrhythmia prevention in LQTS or other arrhythmogenic syndromes.

**Limitations**

We cannot directly translate our results to genetic LQTS. However, intrinsic heterogeneous expression of ion channels in the heart could lead to a similarly large heterogeneity in repolarization, especially if the channel is mutated. Indeed, patients with the hereditary form of LQTS also have large heterogeneity in repolarization.8 Also, homogeneous infusion of an delayed rectifier potassium current blocker, as done partially for this study and previously in dog hearts, leads to increased dispersion in repolarization.17

The computer model does not include a septum or endocardium. Thus, local electrograms and activation times in the model are only an approximation of the experimental values. The frequent occurrence of monoVTs (unlike the porcine experiments) is likely explained by the lack of a third dimension that introduces additional heterogeneity. Nevertheless, a good resemblance between the experimental and in silico data was obtained.

**Conclusion**

pVTs are inducible only in a critical combination of ΔRT duration and ΔRT in models of LQTS. The arrhythmias are maintained by reentry with DPs found at the core of the reentrant circuits and wander along the repolarization gradient. DPs reflect sites of PSs that can be mapped by unipolar catheters in patients and guide ablation. T-wave inversion occurs during pacing at coupling intervals shorter than the repolarization restitution crossing point. The latter suggests that in patients with LQTS, several premature beats from a long repolarization region can initiate reentry.

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**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.09.020.

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