Enhanced Dispersion of Repolarization Explains Increased Arrhythmogenesis in Severe vs. Therapeutic Hypothermia

Running Title: Piktel et al: Arrhythmia Substrates in Hypothermia


The Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio


Correspondence to:
Joseph S. Piktel, M.D.
MetroHealth Campus,
Case Western Reserve University
2500 MetroHealth Drive
Cleveland, Ohio 44109-1998
Phone (216)778-5293
Fax (216)778-5349
Email: jpiktel@metrohealth.org

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Abstract

Background—Hypothermia is proarrhythmic and as the use of therapeutic hypothermia (TH) increases, it is critically important to understand the electrophysiologic effects of hypothermia on cardiac myocytes and arrhythmia substrates. We tested the hypothesis that hypothermia-enhanced transmural dispersion of repolarization (DOR) is a mechanism of arrhythmogenesis in hypothermia. In addition, we investigated whether the degree of hypothermia, the rate of temperature change, and cooling vs. rewarming would alter hypothermia-induced arrhythmia substrates.

Methods and Results—Optical action potentials were recorded from cells spanning the transmural wall of canine left ventricular wedge preparations at baseline (36 °C), during cooling, and during rewarming. Electrophysiologic parameters were examined while varying the depth of hypothermia. Upon cooling to 26°C DOR increased from 26±4 ms to 93±18 ms (p=.021), conduction velocity (CV) decreased from 35±5 cm/s to 22±5 cm/s (p=.010). Upon rewarming to 36°C, DOR remained prolonged while CV returned to baseline. Conduction block and reentry was observed in all SH preparations. VF/VT was seen more during rewarming (4/5) vs. cooling (2/6). In TH (n=7), cooling to 32 °C mildly increased DOR (31±6 to 50±9, p=.012) with return to baseline upon rewarming and was associated with decreased arrhythmia susceptibility. Increased rate of cooling did not further enhance DOR or arrhythmogenesis.

Conclusions—Hypothermia amplifies DOR and is mechanism for arrhythmogenesis. DOR is directly dependent on the depth of cooling and rewarming. This provides insight into the clinical observation of a low incidence of arrhythmias in TH, and has implications for protocols for the clinical application of TH.

Key Words: hypothermia, dispersion of repolarization, arrhythmias, ventricular fibrillation, optical mapping
Glossary of Abbreviations:

APD - action potential duration
CV –conduction velocity
DOR - dispersion of repolarization
ENDO – endocardial
EPI - epicardial
LV - left ventricle
M– mid-myocardial
ROSC – return of spontaneous circulation
SCD - sudden cardiac death
TH – therapeutic hypothermia
VF - ventricular fibrillation
Therapeutic hypothermia (TH) is a recommended therapy for patients who suffer cardiac arrest due to ventricular fibrillation (VF) and have subsequent return of spontaneous circulation (ROSC) as it improves neurologic function and mortality. However, hypothermia is also proarrhythmic. Accidental hypothermia accounts for approximately 700 deaths per year. Arrhythmias are encountered in the majority of patients with severe hypothermia (less than 30 °C), including VF that can be refractory to standard therapy. Although arrhythmias are common in severe hypothermia, an increased susceptibility to arrhythmias was not observed in post-resuscitation patients treated with TH. The reason for the relatively low incidence of arrhythmias in patients undergoing TH is unknown.

The mechanisms underlying arrhythmogenesis in hypothermia remain unclear. Hypothermia has well known effects on ventricular repolarization, prolonging action potential duration (APD) and resulting in prolongation of the QT interval. Multiple sarcolemmal ionic currents which govern repolarization are particularly susceptible to hypothermia (exp. Ito, Ica,L, NCX, IKr). Importantly, hypothermia enhances heterogeneities of repolarization. Enhanced heterogeneities of repolarization are associated with increased susceptibility to reentrant excitation and arrhythmogenesis. In particular, disease-induced enhancement of the electrophysiological heterogeneities between the transmural cell types of ventricle are mechanistically related to genesis of arrhythmias. As there is heterogeneous transmural expression of temperature-dependent sarcolemmal membrane currents, it is likely that hypothermia-induced transmural dispersion of repolarization (DOR) may be important in the mechanism of hypothermia-induced arrhythmogenesis. Given the increasing use of TH and development of technologies for rapid cooling and rewarming, particularly with the known
proarrhythmic effects of severe hypothermia, it is important to understand the electrophysiologic effects of hypothermia on cardiac myocytes and arrhythmia substrates.

We used a previously developed model for studying transmural heterogeneities of repolarization, the canine ventricular wedge preparation, to test the hypothesis that hypothermia-enhanced transmural DOR is a mechanism of arrhythmogenesis in hypothermia. In addition, we investigated whether the degree of hypothermia, the rate of temperature change, and the effects of cooling vs. rewarming might alter hypothermia-induced arrhythmia substrates.

Methods

Optical Mapping in the Canine Wedge Preparation

Experiments were carried out in accordance with Public Health Service guidelines for the care and use of laboratory animals. The details of our system for high resolution transmural optical mapping of the arterial perfused canine wedge preparation were described previously. Briefly, wedges of myocardium harvested from the LV were isolated, and perfused. Wedges were then placed in an imaging chamber, a water bath with a clear vertical surface for imaging. The wedge was then placed in the chamber with the transmural surface against the glass imaging plate, to allow for excitation and signal transduction. The wedges were optically mapped to assess electrophysiologic properties of all cell types spanning the transmural wall. The wedge was perfused with a voltage sensitive dye (di-4-ANNEPS, 15 μM). Action potentials were recorded from 256 sites simultaneously with high spatial (.89 mm), temporal (.5 ms) and voltage (.5mv) resolution. Optical magnification of 1 to 1.2x was used. Cytochalasin D (6μM) was used to eliminate motion artifact from the optical signals. Perfusion pressure was maintained between 50-60 mmHg. Preparations remained stable for at least 4 hours, with
no changes in CV or DOR based on time control studies. A validation study was also performed to insure that the cytochalasin D did not affect DOR and arrhythmogenesis during hypothermia. There were no significant differences in CV, DOR, APD or arrhythmia inducibility between preparations in which cytochalasin D was used when compared to the validation set without cytochalasin-D.

**Temperature Manipulation and Hypothermia Protocols**

The imaging chamber was encased in a water insulated circuit, which allowed for precise temperature manipulation. Temperature was measured using a digital temperature probe (Omega) in the water bath, allowing for temperature precision of 0.1°C. Care was taken to measure temperature at multiple sites along the transmural surface to ensure homogeneous transmural temperature in the preparations throughout the experiments. A subset of experiments were performed in order to detect time and sight-dependent differences in temperature throughout cooling and rewarming. Temperature was measured in the 1) water bath, 2) epicardial surface of the imaging window, 3) endocardial surface of the imaging window, and 4) middle of the wedge on the imaging window, and these data were compared. There was minimal difference across the transmural surface of the imaging window throughout cooling and rewarming (0.1±0.02°C). There was also minimal difference between the water bath and the imaging surface (0.2±0.02°C).

To simulate severe hypothermia, left ventricular canine wedge preparations from 6 dogs were cooled from baseline temperature of 36 °C to 26 °C at a rate of 11 deg/hr with measurements every 2 °C (SH group). This rate was used in order to achieve temperatures typically associated with hypothermia-induced VF and to insure stability of the preparation during the duration of the experiments. The wedges were then rewarmed to baseline
temperature of 36 °C at the same rate. To simulate TH, wedges from a separate set of animals were cooled from 36 °C to 32 °C at a rate of 3 deg/hr (n=7) and subsequently rewarmed (TH group). This rate was chosen to simulate current therapeutic hypothermia protocols.1,2 A second therapeutic hypothermia group was cooled and rewarmed at faster rate (9 deg/hr, n=8, fast TH group), similar to that of the SH group, in order to examine the effects of the rate of cooling and rewarming on arrhythmia substrates.

Data Analysis

Action potential duration (APD) was measured by using an average of 5 epicardial (EPI), mid-myocardial (M), and endocardial (ENDO) cells, respectively at each temperature. Transmural cell types were defined by previously validated anatomic and functional criterion.25,28 Epicardial cells were defined as cells 1-2 mm from the epicardial surface. ENDO cells were defined as cells 1-2 mm from the endocardial surface.25 M cells were defined as the cells with the longest APD that were not EPI or ENDO cells.25 Dispersion of repolarization (DOR) was defined as the difference between the APD of the longest and shortest cell type. T-peak to T-end (Tp-Te) was also measured in all groups as a more global and clinically applicable measurement of DOR. Tp-Te was measured by the distance of the peak of the T-wave to the end of the T-wave. Conduction velocity (CV) and repolarization time gradients were determined by a previously validated vector analysis technique.28 To assess arrhythmia susceptibility, an identical programmed electrical stimulation (PES) protocol was performed at each temperature and in each group.29 During endocardial pacing (S1), up to two premature beats were delivered from the epicardial surface (S2 and S3), until failure to capture the preparation or an arrhythmia
was induced. Typically, induced arrhythmias self-terminate in the wedge preparation allowing for serial comparison of arrhythmia susceptibility in any one preparation.

Statistical analysis was performed using SPSS Statistics 17.0 (WinWarp, 2008). Pairwise comparisons were used for repeated measure analysis of variance (ANOVA) for different temperatures in each separate groups. Repeated measures ANOVA was also used to compare differences between all three hypothermia groups, and between the two TH groups. When temperature dependent differences or group differences were found by ANOVA, comparisons were made between specific means using least square difference post-hoc test. Statistical differences referred to in the text and figures are derived from the least square difference post-hoc test. Group effects and differences between specific means were considered significant with a p<0.05. All mean data is represented with the value and standard error of the mean. Statistical significance for the figures is represented by an asterix (*) or as otherwise stated in the figure legends.

Results

Severe Cooling and Rewarming Promote DOR and Arrhythmogenesis

The effect of hypothermia on APD, DOR, and conduction time during cooling and rewarming in a representative SH experiment are shown in Figure 1. At baseline, DOR is 28 ms. The repolarization gradient is minimal, as the intrinsic difference in APD of the EPI and M cells is similar to the difference in activation time between the cell types during normal conditions. (Figure 1, left) Upon cooling, there is an increase in APD in all cell types, as well as a significant increase in DOR, because of the relatively greater prolongation of M and ENDO cell
APD. As expected, conduction time significantly increased during cooling (Figure 1, middle panel). Transmural activation and repolarization are further characterized in Figure 2.

Upon rewarming, APD of the EPI cells return to near baseline. However, ENDO and M cells remain prolonged and therefore DOR remained elevated. Whereas during cooling, conduction slowing somewhat attenuated repolarization gradients introduced by elevated DOR, during rewarming conduction time returned to baseline, which further contributed to the significant repolarization gradients introduced during rewarming (Figure 1 right panel and Figure 2, right panel).

Summary data of DOR and CV for the SH group is shown in Figure 3. Cooling resulted in an increase in both mean APD and DOR. Hypothermia caused a significant increase in mean APD from 224±7 ms to 600± 83 ms (p=.001) and an increase in DOR form 26±4 ms to 93±18 ms (p=.021) . CV decreased during cooling 35±5 cm/s to 22±5 cm/s (p=.010). The average DOR increased with each increment of cooling. Upon rewarming, mean APD decreased to 252±18 ms. Importantly, CV returned to baseline (35±2 cm/s) while DOR remained significantly prolonged compared to baseline (78±29, p=.021). Tp-Te measurements closely correlated with DOR. Tp-Te increased from 44±2 ms at baseline to 120±7 ms at 26°C and, upon rewarming to 36°C, remained elevated when compared to baseline (86±4 ms, p=.035,).

Figure 4 demonstrates a representative arrhythmia induced by PES in the severe hypothermia group. ECG and action potentials from ENDO, M, and EPI cells are during baseline endocardial pacing (S1) are followed by two epicardial stimulated beats (S2 and S3) are shown in the top panel (3A), while transmural conduction and repolarization time maps for each beat are shown below (panel 3B). On the second epicardial premature beat (S3), block occurs (thick red line, S3 activation map, panel 3B) in the sub-endocardial region precisely at the
location of the steepest gradients of repolarization (crowding of isochrones on S2 beat, repolarization map, lower panel, 3B). Block is followed by initiation of polymorphic ventricular tachycardia (VT). These data demonstrate that during severe hypothermia, enhanced DOR, due to heterogeneous prolongation of myocardial cells, produces a substrate for conduction block and reentrant arrhythmias.

Table (left column) summarizes the arrhythmia susceptibility for the severe hypothermia group. No spontaneous or induced arrhythmias occurred upon cooling to 34 °C. Upon further cooling, conduction block with reentry was induced in 6/6 preparations. In one preparation VT was induced and another preparation developed persistent spontaneous ventricular fibrillation (VF). Interestingly, the incidence of VT/VF was greater during rewarming. In 2 preparations, spontaneous VF was observed and in 2 preparations reentrant polymorphic ventricular tachycardia was induced. These data suggest that enhanced transmural DOR induced during cooling and maintained during rewarming is a mechanism of hypothermia-induced arrhythmogenesis, with rewarming being particularly arrhythmogenic.

**In Therapeutic Cooling and Rewarming, Hypothermia-induced DOR and Arrhythmogenesis is Attenuated**

A second group of preparations (n=7) was cooled to 32 °C and rewarmed at a slower rate to model clinical TH. In the TH group, cooling mildly increased mean APD and DOR. Mean APD increased from 211±8 ms to 310±12 ms (p<.001) and returned toward baseline upon rewarming (249±9 ms, p=.007 compared to baseline). CV decreased from 30±3 cm/s to 25±5 cm/s (p=.026) upon cooling to 32 °C and returned to baseline upon rewarming (27±6 cm/s, p=NS compared to baseline). DOR increased from 31±6 ms to 50±9 ms (p=.012) similar to what was seen in the SH group at the same degree of hypothermia. However, a persistent prolongation of
DOR was not observed during rewarming in the TH group (Figure 5, open bars), as DOR returned to baseline (39±7 ms, p=NS compared to baseline during rewarming. Tp-Te measurements again closely correlated with DOR, increasing from 50±5 ms at baseline to 65±10 ms at 32°C (p=0.49) and subsequently returned to baseline (43±2 ms).

Table (right column) summarizes the arrhythmias seen in the TH group. Compared to the SH group, there was a decrease in conduction block, reentry, or VT upon cooling (2/7 vs 6/6) and VT during rewarming (1/7 vs 4/5).

**Increasing rate of cooling and rewarming does not increase DOR in Therapeutic Hypothermia**

To independently assess the effects of rate of temperature change, a second group of TH experiments were performed using increased rates of cooling and rewarming, (9 deg/hr, n=8). During cooling, similarly to the slow TH group, APD increased from 244±10 ms to 356±19 ms (p=.001), and CV decreased from 32±2 cm/s to 25±2 cm/s (p=.016). Upon rewarming to 36°C mean APD shortened mildly from baseline (226±12 ms, p=NS). CV also returned to baseline (32±2 cm/s, p=NS compared to baseline). DOR did not vary significantly upon cooling and rewarming. Tp-Te significantly increased from 41±2 ms at baseline to 60±7 (p=.018) at 32°C and subsequently returned to baseline.

Figure 5 shows summary data for both TH groups (labeled slow and fast) compared to the SH group at similar temperatures. Increasing the rate of cooling did not significantly alter mean APD, DOR or CV when compared to the slow TH group. When compared to the two TH groups, DOR remained increased in the SH group upon rewarming at 34°C and 36°C (SH vs TH slow at 34 and 36 p=.000, .036, respectively, SH vs TH fast at 34 and 36 p=.002, .027,
respectively). Importantly, arrhythmia susceptibility was not further enhanced in the fast TH group. This data suggests it is the depth of cooling, rather than the rate of cooling, that is most important in determining arrhythmogenesis in hypothermia.

**Discussion**

Our data in a model of severe hypothermia demonstrated that enhanced transmural DOR is a mechanism for arrhythmogenesis in hypothermia. Optical mapping revealed that hypothermia heterogeneously prolonged APD and that conduction block and reentry (initiating VT) occurred precisely where hypothermia-induced APD gradients were greatest. Arrhythmia susceptibility increased as the preparations were cooled and correlated with increased DOR. As the preparations were rewarmed, CV returned to baseline while DOR remained increased (due to more rapid normalization of APD in EPI myocytes than M or ENDO), further enhancing both repolarization gradients and arrhythmia susceptibility. Cooling and rewarming to temperatures typically used clinically in TH was not arrhythmogenic. Although CV slowed and APD was increased during TH, there was no significant increased in DOR observed, suggesting that it is only when hypothermia enhances DOR is arrhythmia susceptibility increased. Only one sustained arrhythmia was observed during rewarming during TH and, interestingly, occurred in the preparation with the largest hypothermia-induced enhancement of DOR.

It was interesting that, although the depth of hypothermia was associated with arrhythmias, more arrhythmias were seen during rewarming in the SH group. Steep gradients of repolarization are a substrate for conduction block and reentrant excitation. The profound conduction slowing during induction of hypothermia we observed may attenuate arrhythmia susceptibility because it attenuates hypothermia-induced repolarization gradients (Figure 1).
During rewarming, conduction velocity normalized faster than DOR, which contributed to enhanced repolarization gradients and therefore created a persistent substrate for arrhythmogenesis. This phenomenon was not observed in the TH group. Importantly, these data, and specifically the attenuated DOR and repolarization gradients observed at temperatures targeted during TH, may provide a mechanistic explanation of the low clinical incidence of arrhythmias in patients treated with TH.

It is likely that several temperature-dependent sarcolemmal ion channels play a role in the heterogeneous APD prolongation and arrhythmogenesis observed during severe hypothermia compared to TH, potentially including \( I_{K_{r}} \) and \( I_{K_{s}} \), as well as \( I_{Na} \), \( I_{on} \), and \( I_{Ca,L} \). Additional mechanisms by which hypothermia might also enhance DOR include hypothermia-induced intracellular uncoupling, which might enhance intrinsic transmural repolarization heterogeneities, as well as contribute to the conduction slowing observed secondary to hypothermia. Further studies will be required to investigate the cellular and subcellular mechanisms responsible for hypothermia-induced enhancement of DOR.

**Limitations**

These experiments have several limitations. First, electrophysiologic effects of hypothermia were evaluated only in the canine wedge preparation, and therefore in a two dimensional area of a small portion of the left ventricle. Although these data suggest that transmural heterogeneities may be responsible for hypothermia-induced ventricular arrhythmias, as we did not examine heterogeneities in the intact heart in our experiments, we can not exclude that other hypothermia induced repolarization heterogeneities may be important in hypothermia-related arrhythmogenesis. We can not account for changes in interventricular conduction or repolarization, or other heterogeneities (such as apex to base heterogeneities) which could
potentially play a role in arrhythmia susceptibility. We did, however, examine the effects of hypothermia in canine wedges taken from the right ventricle which demonstrated similar temperature-dependent effects on APD as was observed in left ventricle (data not shown), suggesting that interventricular heterogeneities in response to hypothermia may not be as important.

Based on the stability of the preparation determined from time control experiments, our study protocol was limited to approximately 4 hours, thus limiting the rates of cooling and rewarming that could be studied. In the accidental hypothermia protocol, the average cooling and rewarming was approximately 11°C/hr. This is likely a faster cooling rate than typically occurs in most cases of accidental hypothermia (although may be observed in cold water submersion). Unfortunately, we were unable to study slower rates, and these rates were chosen in order to insure complete stability of preparation and arrhythmia substrates throughout the protocol. The TH model was closer to likely clinical conditions (typically 1-2 °C/hr)\(^1,2\) with cooling and rewarming at 3 °C/hr. Our study was limited to cooling to a low temperature of 26 °C. We found that further cooling to lower temperatures prevented maintaining viable preparations for rewarming, as in preliminary studies cooling further caused refractory VF in these preparations.

Conclusion

Hypothermia heterogeneously effects repolarization of ventricular cells, which amplifies DOR and represents a mechanism for arrhythmogenesis. Hypothermia-induced changes in DOR and resultant arrhythmia susceptibility is dependent on the severity of hypothermia during both cooling and rewarming. Importantly, there is an increased risk of arrhythmogenesis during rewarming during severe hypothermia, secondary to a persistent elevation in DOR. In our
studies, cooling and rewarming as in TH resulted in a mild increase in DOR and an attenuation of arrhythmogenesis. This observation may explain why therapeutic hypothermia is not associated with significant arrhythmogenic risk, as current protocols induce only mild hypothermia slowly and rewarm gradually over 24 hrs. The increased DOR and incidence of arrhythmias observed during rewarming from severe hypothermia suggests that patients are at highest risk for arrhythmogenesis during rewarming from severe hypothermia. As Tp-Te correlated closely with arrhythmogenic DOR during hypothermia and rewarming, these data suggest that it may provide a clinically useful metric for evaluation of arrhythmogenic substrates in hypothermia.
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Disclosures

None.
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Inducible = induced with PES. Spontaneous = occurred during observation without PES. Temperature noted is where arrhythmia was first induced or observed during cooling or rewarming protocol. Block and reentry = conduction block and single reentrant beat mapped during PES. All VT was nonsustained polymorphic unless otherwise noted. All arrhythmias resolved spontaneously. VF = sustained ventricular fibrillation.

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<th>Severe Hypothermia</th>
<th>Therapeutic Hypothermia</th>
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<tr>
<td></td>
<td>Cooling</td>
<td>Warming</td>
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<tr>
<td>1</td>
<td>32 to 26 Inducible Block and reentry</td>
<td>34 Inducible Block and reentry</td>
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<td>2</td>
<td>30°C Inducible Block and reentry</td>
<td>32°C Inducible VT</td>
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<td>32°C Inducible Block and reentry</td>
<td>Not rewarmed 26°C Spontaneous VF</td>
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<td>30°C Spontaneous VT</td>
<td>30°C Spontaneous VF</td>
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<td>28°C Inducible Block and reentry 32°C Inducible VT</td>
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<td>7</td>
<td>32°C Spontaneous VT</td>
<td>34°C Block and reentry</td>
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Figure Legends

Figure 1. Hypothermia profoundly enhances transmural DOR and slows conduction.
Representative action potentials from EPI, M, and ENDO cells during cooling and rewarming are shown. ECG is also shown. Striped shading denotes conduction time, dotted shading denotes repolarization gradient. Tp-Te is shown in red on the ECG. **Left Panel.** Action potentials at 36 °C demonstrate a baseline DOR of 28 ms and CV of 26 cm/s, with a Tp-Te of 44 ms. **Middle Panel.** When the preparation is cooled to 26 °C, marked prolongation of APD, enhancement of DOR and conduction slowing is observed, with increased Tp-Te. **Right Panel.** After rewarming to 36 °C, conduction time normalizes, but DOR and Tp-Te remains increased, resulting in marked gradients of repolarization.

Figure 2. Rewarming from severe hypothermia promotes persistent enhancement of transmural dispersion of APD and repolarization gradients, while conduction time returns to baseline. Activation maps of the transmural surface of the canine wedge preparation for conduction time, repolarization time, and APD at baseline (36°C), cooling to 26°C, and returning to baseline (36°C). **Top.** Cooling resulted in an increase in conduction time with return to baseline upon rewarming. **Middle** Repolarization time gradients are enhanced during cooling and upon rewarming. **Bottom.** APD markedly and heterogeneously prolonged during cooling and returned near baseline upon rewarming but, importantly, significant heterogeneities of APD remain upon rewarming.
Figure 3. Hypothermia enhances DOR and slows conduction, but DOR remains increased after rewarming. Panel A. Summary data of DOR and CV is shown for LV (n=6) during cooling and subsequent rewarming (r). Importantly, although CV returns to baseline during rewarming, DOR remains increased. Compared to baseline, all DOR statistically significant (denoted by *). For CV, statistical significance from baseline denoted by (*).

Figure 4. Arrhythmia induced during hypothermia (32 °C) using PES. Panel A. ECG and action potentials shown during baseline endocardial pacing (S1) are followed by two epicardial stimulated beats (S2 and S3) which initiate conduction block followed by VT. Panel B. Activation and repolarization maps for each beat in panel A are shown. Pacing site is noted by *. On the second epicardial premature beat (S3), block occurs (thick red line) in the M cell region, precisely at the location of the steepest gradients of repolarization (crowding of isochrones on S2 beat, lower panel). Block is followed by initiation of VT. Enhanced DOR, predominantly due to marked hypothermia-induced prolongation of M and ENDO cells, produces a substrate for conduction block and reentrant arrhythmias.

Figure 5. Increasing the temperature rate of change does not enhance DOR. Summary data of DOR is shown for LV during cooling in the slow TH group (3 °C/hour, n=7) the fast TH group (9 °C/hour, n=8) and the SH group for comparison with subsequent rewarming (r). Statistical differences between the severe compared to the two TH groups are noted (*=p<.05), No significant difference is seen between the two TH groups.
Conduction Time (ms)

- Color scale: 0 to 90

Repolarization Time (ms)

- Color scale: 0 to 145

APD (ms)

- Color scale: 200 to 650
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Joseph S. Piktel, Darwin Jeyaraj, Tamer H. Said, David S. Rosenbaum and Lance D. Wilson

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