

Changes in Left Ventricular Electromechanical Relations During Targeted Hypothermia

Kristin Wisløff-Aase (✉ uxwisk@ous-hf.no)

Oslo University Hospital, Rikshospitalet, Norway <https://orcid.org/0000-0003-2507-1764>

Viesturs Kerans

Oslo University Hospital, Rikshospitalet

Kristina Haugaa

Oslo University Hospital, Rikshospitalet

Per Steinar Halvorsen

Oslo University Hospital, Rikshospitalet

Helge Skulstad

Oslo University Hospital, Rikshospitalet

Andreas Espinoza

Oslo University Hospital, Rikshospitalet

Research

Keywords: Targeted hypothermia, Ventricular arrhythmia, Echocardiography, Myocardial function, Electromechanical relations, Electromechanical window

Posted Date: August 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-52353/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on December 14th, 2020. See the published version at <https://doi.org/10.1186/s40635-020-00363-7>.

Abstract

Background:

Targeted hypothermia, as used after cardiac arrest, increases electrical and mechanical systolic duration. Differences in duration of mechanical and electrical systole are correlated to ventricular arrhythmias. The electromechanical window (EMW) becomes negative when electrical systole outlasts the mechanical systole. Prolonged electrical systole is also associated with electrical and mechanical dispersion, both predisposing for arrhythmias. The electromechanical relations during targeted hypothermia are unknown, but treatment after cardiac arrest has not demonstrated increased incidence of ventricular arrhythmic events.

We wanted to explore the electromechanical relations during hypothermia at 33 °C. We hypothesized that targeted hypothermia would increase electrical and mechanical systolic duration without an increase in electromechanical negativity, nor an increase in electrical and mechanical dispersion.

Methods:

In a porcine model (n = 14) we registered electrocardiogram (ECG) and echocardiographic recordings during 38 °C and 33 °C, at spontaneous and atrial paced heart rate 100 beats/min. EMW was calculated by subtracting electrical systole, QT interval, from the corresponding mechanical systole, recorded from onset QRS to aortic valve closure. Electrical dispersion was measured as time from peak to end of the ECG T wave. Mechanical dispersion was calculated by strain echocardiography as standard deviation of time to peak strain.

Results:

Electrical systole increased during hypothermia at spontaneous heart rate ($p < 0.001$) and heart rate 100 beats/min ($p = 0.005$). Mechanical systolic duration was prolonged and outlasted electrical systole independently of heart rate ($p < 0.001$). EMW changed from negative to positive value (-20 ± 19 to 27 ± 34 ms, $p = 0.001$). The positivity was even more pronounced at heart rate 100 beats/min (-25 ± 26 to 41 ± 18 ms, $p < 0.001$). Electrical dispersion decreased ($p = 0.027$ and $p = 0.003$), while mechanical dispersion did not differ ($p = 0.078$ and $p = 0.297$).

Conclusion:

Targeted hypothermia increased electrical and mechanical systolic duration, the electromechanical window became positive, electrical dispersion was reduced and mechanical dispersion was unchanged. These alterations may have clinical importance. Further clinical studies are required to clarify whether corresponding electromechanical alterations are accommodating in humans.

Background

Targeted hypothermia (32-36 °C) is recommended in comatose cardiac arrest survivors to improve outcome [1]. However, hypothermia alters cardiac electrical and mechanical function with reduced heart rate, increased QT interval on the electrocardiogram (ECG) [2, 3] and prolonged mechanical systolic duration [4-6]. Increased QT interval has been shown to be pro-arrhythmic during normothermia and deep hypothermia (below 30 °C) [7-11].

When the QT interval outlasts the mechanical systole, electromechanical window (EMW) becomes negative. This electromechanical negativity is correlated to arrhythmic events [12-14]. In addition, prolonged QT interval predisposes for increased electrical dispersion which is also associated with arrhythmias [15, 16]. Whether the prolonged mechanical systole during hypothermia is a result of synchronous slowed activation of the left ventricle, or is due to increased mechanical dispersion with an asynchronous activation and relaxation is unexplored. Mechanical dispersion predisposes to arrhythmias [17-19].

There has not been observed increased incidence of adverse ventricular arrhythmic events during treatment with targeted hypothermia in cardiac arrest survivors [20, 21]. The beneficial and harmful effects of targeted hypothermia when compared to normothermia and the optimal temperature, is still not clarified [22, 23]. EMW, electrical dispersion and mechanical dispersion are all novel parameters with clinical relevance to understand the effect of hypothermia and are not previously analysed and described. The present experimental animal study aimed to explore the electromechanical relations during targeted hypothermia at 33 °C.

We hypothesized that hypothermia increases electrical and mechanical systolic duration without an increase in electromechanical negativity independently of heart rate. Furthermore, we hypothesized that electrical and mechanical dispersion, remain unchanged during hypothermia.

Methods

Animal model

The experiment was performed in an open chest porcine model. Data for the present study were collected from experiment series published in two previous articles [6, 24]. The open model facilitated recording of high quality echocardiographic images needed for the study, otherwise difficult to obtain in the pigs.

The study was approved by National Animal Research Authority of Norway (trial registration number: FOTS 3866) and carried out in accordance to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, the European Union Directive 2010/63/EU [25].

Animal preparations

The animals (n = 14, Norwegian land race swine, mean weight 52 ± 4.3 kg) were fasting overnight aside from free water access. Before transportation to the laboratory they were pre-medicated by an

intramuscular injection with ketamine (20 mg/kg), azaperone (3 mg/kg) and atropine (20 µg/kg). Anaesthesia was induced with intravenous pentobarbital (3 mg/kg) and morphine (2 mg/kg), and maintained with morphine-infusion (1-2 mg/kg/h) and isoflurane-inhalation (1 to 1.5 %). Neuromuscular blocking agents were not used. Level of anaesthesia was monitored by continually hemodynamic measurements and observation of clinical signs. When the protocol was finished, the animals were euthanatized by bolus infusion of 80 mmol potassium chloride and 1000 mg pentobarbital. The animals were mechanically ventilated via a tracheostomy tube by a fraction of air/oxygen (FiO₂ 0.4), with tidal volumes of 10 to 15 ml/kg and surgically prepared with sternotomy as previously reported [6, 24]. Three-lead ECG was obtained by surface leads. Pacemaker leads were sutured to the right atrium. For temperature control, a water circulated catheter (Cool Line; Zoll, Chelmsford, MA, USA), was inserted into the inferior vena cava by cannulation of the left femoral vein and connected to the thermal regulation system (Coolgard 3000; Zoll). A pulmonary artery catheter (Swan-Ganz CCO; Edwards Lifesciences, Irvin, CA, USA) was inserted through the right jugular vein to measure central temperature and hemodynamic variables. Left ventricular pressure was measured by a micro-manometer pressure transducer (MPR-500; Millar Instruments, Houston, TX) placed via the right carotid artery. A Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway) with 2.5 / 2.75 MHz probe directly on the heart, was used for echocardiographic and Doppler recordings.

Hemodynamic data regarding systolic and diastolic function obtained from the experiment has been published [6, 24], but is included as background data in the current manuscript. All data presented concerning the electromechanical relations, has been analysed for this study.

Measurements and analysis

Measurements were obtained at body temperature 38 °C and 33 °C. 33 °C was chosen representing the median temperature according to the current recommended guidelines at that time, with a targeted temperature of 32-34 °C [26]. In addition, the pigs' baseline temperature was 38 °C, and a drop to 33 °C corresponded to a drop from 37 °C to 32 °C in humans. Measurements were made at both spontaneous heart rate (HR) and during atrial pacing, 100 beats/min (bpm). All measurements and recordings were made in three echocardiographic views over three consecutive heart cycles and the mean values were calculated. The pacing enabled measurements at heart rate 100 bpm, thereby compensating for individual variability and hypothermia induced heart rate reduction. ECG, two-dimensional (2D) and Doppler echocardiography were recorded and analysed offline (EchoPac version 202, GE Healthcare, Horten, Norway).

Calculations of the electrical events

The ECG lead II was used for electrical measurements. The electrical systole (QT interval) was measured from onset of QRS to end of T wave (T end) in ECG. The QT interval was heart rate corrected according to the Bazett's formula (QTc) [27]. T end was determined by using the manual tangent method and defined as the intersection of the isoelectric line with the tangent to the steepest downslope of the T wave. T peak

was defined as the maximum positive or negative deflection of the T wave from the isoelectric line [28, 29]. Electrical dispersion was measured as variation in T peak to T end duration (TpTe).

Calculation of the mechanical events

From the echocardiographic apical 4-chamber long axis view, mitral and aortic valve (AV) opening (O) and closing (C) were recorded. Isovolumic contraction and isovolumic relaxation time were measured in long axis view from mitral valve closing to aortic valve opening and aortic valve closing to mitral valve opening respectively.

Ejection time was measured as the duration of the pulsed wave Doppler signal in left ventricular outflow tract (ET_{PW}). The interval from onset of QRS to the Doppler registered AVC represented the duration of the mechanical systole (QAVC). EMW was calculated by subtracting the electrical systole from the duration of the mechanical systole in the same heartbeat, QAVC-QT interval, (Fig 1).

Global cardiac function

Left ventricular volumes were measured from 2D echocardiographic images (apical 4- and 2-chamber views), and ejection fraction was calculated by the modified Simpson biplane method. Systolic velocity was recorded from mitral ring tissue Doppler velocity images in apical 4-chamber views. Cardiac output was measured by pulmonary artery catheter thermodilution and stroke volume calculated. Peak systolic left ventricular pressure was recorded by the micromanometer catheter placed in the left ventricle.

Regional strain and mechanical dispersion

Longitudinal strain was obtained by speckle tracking echocardiography from the basal and mid segments in three apical left ventricular projections (4-chamber, 2-chamber and long axis, framerate 63 ± 15 ms). The endocardial border was traced manually, and region of interest was adjusted to fit the myocardial thickness. Segments that failed to track were manually adjusted, and if subsequent failing the segments were excluded. The echocardiographic probe was directly placed on the heart with a subsequent loss of the apical segments, whereof peak strain was derived from 12 segments. Time to peak strain in each segment was defined as the time from Q onset on ECG to peak longitudinal strain in three cycles and averaged. Mechanical dispersion was defined as the standard deviation of time to peak negative strain [18] in the 12 left ventricular segments. Septal and lateral strains were measured from basal segments in 4-chamber view.

Observer variability

Doppler registered QT and QAVC were re-measured by the same observer to assess intraobserver repeatability. A second observer measured the same variables in seven random selected animals to assess interobserver reproducibility.

Statistical analyses

Statistical analyses were performed in SPSSv.25 software (SPSS, Inc., Chicago, IL, USA). Parametric data are presented as mean \pm standard deviation. Data from normothermia and hypothermia at spontaneous and heart rate 100 bpm were compared by Student's t-test. P-value, $p < 0.05$ was considered statistically significant. Intra- and interobserver variations were analysed by using intraclass correlation coefficient concerning single measures [30].

Results

All recordings were of good quality. Three animals had a spontaneous heart rate above 100 bpm at 38 °C, and were not paced during normothermia. One animal did not receive pacing due to malfunction of the pacemaker electrode.

Hemodynamic parameters and myocardial function during hypothermia

During hypothermia mean arterial pressure and left ventricular pressure were reduced at both spontaneous rhythm and heart rate 100 bpm (Table 1). Strain, systolic velocity and cardiac output decreased. Stroke volume and ejection fraction remained unchanged at spontaneous heart rate, but decreased at 100 bpm, indicating that the left ventricle is less tolerant to increased frequency during hypothermia [6, 24].

Electromechanical changes at spontaneous heart rate during hypothermia

Hypothermia reduced spontaneous heart rate, prolonged QRS duration and increased QT interval (Table 2). Isovolumic contraction and relaxation times did not change. Both the ET_{PW} and the echocardiographic recorded interval from aortic valve opening to aortic valve closing increased. QAVC increased accordingly, and more than the QT interval (42 % vs 20 % respectively). The mechanical systolic duration outlasted the electrical systole, and EMW changed from -20 ± 19 to 27 ± 34 ms ($p = 0.001$), (Fig. 2). Electrical dispersion was reduced also when corrected for QT interval (Table 2). Mechanical dispersion remained unchanged compared to normothermia (Table 3).

Electromechanical changes at heart rate 100bpm during hypothermia

At heart rate 100 bpm, electromechanical alterations during hypothermia were similar as during spontaneous heart rate, but even more pronounced. The QRS complex and the QT interval was widened (Table 2). The mechanical systole was prolonged but shorter compared to the duration at spontaneous heart rate (Table 3). The QAVC increased with 34 % and the QT interval with 6 % though the electromechanical positivity was more pronounced during heart rate 100 bpm, -25 ± 26 to 41 ± 18 ms, ($p = 0.001$), (Fig.2). Electrical dispersion was reduced (Table 1) and mechanical dispersion unchanged at 100 bpm (Table 3).

Observer variability

Intraobserver correlation coefficient for QT and QAVC were 0.99 (95 % confidence interval (CI): 0.98 to 1.0) and 0.99 (95 % CI: 0.99 to 1.0). Interobserver correlation coefficient for the same parameters were 0.99 (95 % CI: 0.98 to 1.0) and 0.99 (95 % CI: 0.77 to 1.0).

Discussion

In this experimental study, targeted hypothermia increased both electrical and mechanical systolic duration. Indeed, the mechanical systole outlasted the electrical systole independently of heart rate and therefore the EMW became positive at hypothermia. Electrical dispersion was reduced, and mechanical dispersion was unchanged during hypothermia, at both spontaneous and at heart rate 100bpm. These findings could indicate an electromechanical adjustment during targeted hypothermia.

The shift in electromechanical window

Prolonged duration of the QT interval is associated with increased risk of arrhythmias. When the QT interval exceeds the mechanical systole, the corresponding electromechanical negativity is an independent predictor for arrhythmias, as shown both experimentally [12] and in patients [13]. In our study we found that despite the increased QT interval there was significant change to electromechanical positivity during hypothermia, due to the even more prolonged mechanical systolic duration. The QRS interval and isovolumic contraction time were slightly prolonged but gave only a small contribution to the extended QAVC at spontaneous heart rate. The increase in ejection time was the main reason for the prolonged mechanical systole.

The normal value for EMW in land race pigs during normothermia is unknown. In an ex-vivo model, isolated Langendorff-perfused Göttingen minipig hearts baseline EMW was 134 ms [31]. However, moving the heart outside the thoracic cavity may have exerted substantial electromechanical influence. In our in vivo model with farm pigs, baseline EMW was -20 ± 19 ms during spontaneous heart rate and -25 ± 26 ms at heart rate 100 bpm. As known from the literature, an open chest model leads to a prolonged QT interval which may contribute to the negativity [32]. Our findings at baseline may reflect the empirical knowledge that farm pigs are susceptible to arrhythmias during anaesthesia and cardiac manipulation [33]. During hypothermia there was a difference between electrical repolarization and mechanical systole as the end of the T wave preceded the AVC independently of heart rate, thus EMW changed from negative to positive. A corresponding tendency with preserved or increased EMW during cooling is reported [12, 34]. In normothermic patients with short QT syndrome the electromechanical positivity exceeds 100 ms [35]. Normal value in healthy individuals is 22 ± 19 ms [13]. Such extended positive EMW, is associated with increased risk for arrhythmias. It is reasonable to assume that less negativity or slight electromechanical positivity as seen in this study may reduce arrhythmia susceptibility. A larger negativity or positivity may have a pro-arrhythmic impact [36].

Electrical dispersion

Increased electrical dispersion of repolarization is associated with ventricular arrhythmias in patients [15, 16]. In our study electrical dispersion was reduced during hypothermia seen as reduced T peak to T end duration. It is notable that at heart rate 100 bpm during hypothermia, electrical dispersion was further decreased from what was seen at spontaneous heart rate. Shortening of the T peak to T end interval, indicating reduced electrical dispersion has been described as a u-shaped association to the risk for ventricular arrhythmias in patients with electrical and structural disease [37]. Patients with symptomatic long QT syndrome have more pronounced electrical dispersion, and arrhythmic storm in these patients may be terminated by atrial pacing in the range 80–100 bpm by the assumed mechanism of reduced electrical dispersion [38].

It has previously been shown that targeted hypothermia induces slowing of conduction velocity and increased action potential duration but no increase in transmural electrical dispersion of repolarization [39]. Inducing repolarization abnormalities by ventricular pacing did neither increase risk of arrhythmia at 33 °C compared to normothermia [39, 40]. Pro-arrhythmic parameters such as slowing of conduction velocity and prolonged action potential duration were attenuated at 33 °C [40]. Thus, our findings are in accordance with other studies on this topic. Experimental studies actually suggest an additional direct anti-arrhythmic effect on the myocardial cells by an increase in membrane stability during targeted hypothermia [41].

Mechanical dispersion

The prolongation and slowing of systolic contraction during hypothermia, is previously described [6, 24]. However, it is not known whether this is due to asynchronous activation of left ventricular segments with a prolonged systole, or as synchronous prolongation of all segments simultaneously. Pathological mechanical dispersion occurs as a mechanical consequence of electrical alterations or myocardial dysfunction [42]. Mechanical dispersion has been shown to be a marker of arrhythmias in cardiac diseases, and correlation with increased QT interval, contraction duration and electromechanical negativity has been reported [14, 43].

An interesting result in our study was that mechanical dispersion did not increase during hypothermia and suggests that this is not of increased importance during targeted hypothermia. The prolonged mechanical systole is therefore not a result of regional variation on contraction onset and duration, but rather a result of a synchronous prolonged duration of contraction in the left ventricle.

Clinical implications

The beneficial and harmful effects of the targeted hypothermia treatment, is not completely clarified. After cardiac arrest it might be difficult to distinguish whether myocardial dysfunction, arrhythmias or other adverse events are due to myocardial injury or to hypothermia itself. This may contribute to a possible restraint regarding clinical implementation [44]. Our experimental model describes changes in the electromechanical relations during hypothermia in healthy animal hearts. Neither electromechanical negativity, electrical nor mechanical dispersion were enhanced during targeted hypothermia, rather

decreased. Our findings in this experimental model indicate a beneficial electromechanical change that could infer decreased arrhythmia susceptibility during hypothermia at 33 °C. This study gives important contribution to explore and understand the effect of hypothermia on the electromechanical relations in clinical studies. Further studies are required to clarify whether these electromechanical alterations during hypothermia are accommodating in humans.

Limitations

Three-lead ECG were connected to the echocardiographic scanner, giving ECG's with variable quality from lead II. Manual ECG measurements were the method available, and the precision level was subjective with a risk of misinterpretation. Digital ECG and automatic analyses with multi-lead representations would have made the results more valid but were not possible due to the already accomplished animal study, though reproducibility of the measurements were excellent.

The open chest model may have altered the preload and afterload conditions [32]. However, we analysed the absolute change in the parameters during the intervention in a controlled manner with no surgical or physiological modification. Furthermore, this work was carried out with pigs anaesthetized with isoflurane and morphine after induction with pentobarbital. The anaesthetic regime used is routinely applied and empirically recommended in experimental settings when cardiothoracic surgery is needed [33], despite the well-known pharmacological impact on the cardiovascular system and the autonomic balance [45-47]. Importantly, the anaesthetics were maintained at the same rate with no modifications throughout the experiment.

In addition, the possible pharmacological heart rate effect was superseded by the temperature effect, and compensated by atrial paced heart rate 100 bpm during normo- and hypothermia.

Each animal represented its own control from baseline to hypothermia with no other adjustments than temperature and HR during the experiment. These aspects belay the measurements reliability and make them comparable.

Conclusions

Targeted hypothermia increased the duration of both the electrical and mechanical systole. The prolonged duration of the mechanical systole was relatively greater and outlasted the electrical systole at hypothermia. This led to a positive EMW. Hypothermia reduced electrical dispersion, while mechanical dispersion remained unchanged. Further clinical studies are required to elucidate whether these electromechanical alterations during hypothermia are presented in humans.

Abbreviations

ECG: electrocardiogram, QT-interval: electrical systole, QTc = Corrected QT interval, bpm: beats per minute, 2D: two dimensional, TpTe: T wave peak to T wave end; electrical dispersion of repolarization, O: opening,

C: closing, AV: aortic valve, AVC: aortic valve closing, ET_{pw} : ejection time pulsed wave doppler signal in left ventricular outflow tract, EMW: electromechanical window, QAVC: Q onset to aortic valve closing ; mechanical systole, MAP: mean arterial pressure , SVR: systemic vascular resistance, LVP: left ventricular pressure, CO: cardiac output, SV: stroke volume, EF: ejection fraction, SS: strain septal, SL: strain longitudinal, s' : systolic velocity, HR: heart rate, QRS: QRS complex on ECG, RR: interval from R to R between two QRS complexes, IVCT: isovolumic contraction time, IVRT: isovolumic relaxation time, MD: mechanical dispersion

Declarations

Ethics approval

The study was approved by National Animal Research Authority of Norway (trial registration number: FOTS 3866) and carried out in accordance to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, the European Union Directive 2010/63/EU [25] and the ARRIVE guidelines [48].

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

There was no external funding of the project. The study was administratively supported by the Intervention Centre, Oslo University Hospital.

Authors' contributions

KWA analysed and interpreted data. KWA drafted the manuscript with significant contributions from AE and HS. All authors have been involved in planning the study design, and have read and approved the final manuscript.

Acknowledgements

This work was performed at The Intervention Centre, Oslo University Hospital. The authors thank the staff at the animal research veterinary, the Department of Comparative Medicine for care of the animals and The Intervention Centre for assistance during the experiments. We are grateful to Marte Sævik (MD) who performed measurements for assessment of interobserver reproducibility.

References

1. Nolan JP, Soar J, Cariou A, Cronberg T, Moulart VR, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C, (2015) European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for resuscitation 2015. *Resuscitation* 95: 202-222
2. Bigelow WG, Lindsay WK, Greenwood WF, (1950) Hypothermia; its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. *Ann Surg* 132: 849-866
3. Emslie-Smith D, Sladden GE, Stirling GR, (1959) The significance of changes in the electrocardiogram in hypothermia. *Br Heart J* 21: 343-351
4. Berne RM, (1954) Myocardial function in severe hypothermia. *Circ Res* 2: 90-95
5. Post H, Schmitto JD, Steendijk P, Christoph J, Holland R, Wachter R, Schondube FW, Pieske B, (2010) Cardiac function during mild hypothermia in pigs: increased inotropy at the expense of diastolic dysfunction. *Acta Physiol (Oxf)* 199: 43-52
6. Espinoza A, Kerans V, Opdahl A, Skulstad H, Halvorsen PS, Bugge JF, Fosse E, Edvardsen T, (2013) Effects of therapeutic hypothermia on left ventricular function assessed by ultrasound imaging. *J Am Soc Echocardiogr* 26: 1353-1363
7. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D, (2003) Risk stratification in the long-QT syndrome. *N Engl J Med* 348: 1866-1874
8. Kannankeril PJ, Roden DM, (2007) Drug-induced long QT and torsade de pointes: recent advances. *Curr Opin Cardiol* 22: 39-43
9. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J, (1991) QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 83: 1888-1894
10. Polderman KH, (2009) Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 37: S186-202
11. Polderman KH, Herold I, (2009) Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 37: 1101-1120
12. van der Linde HJ, Van Deuren B, Somers Y, Loenders B, Towart R, Gallacher DJ, (2010) The Electro-Mechanical window: a risk marker for Torsade de Pointes in a canine model of drug induced arrhythmias. *Br J Pharmacol* 161: 1444-1454

13. ter Bekke RM, Haugaa KH, van den Wijngaard A, Bos JM, Ackerman MJ, Edvardsen T, Volders PG, (2015) Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk. *Eur Heart J* 36: 179-186
14. Leren IS, Hasselberg NE, Saberniak J, Haland TF, Kongsgard E, Smiseth OA, Edvardsen T, Haugaa KH, (2015) Cardiac mechanical alterations and genotype specific differences in subjects with long QT syndrome. *JACC Cardiovasc Imaging* 8: 501-510
15. Hetland M, Haugaa KH, Sarvari SI, Erikssen G, Kongsgaard E, Edvardsen T, (2014) A novel ECG-index for prediction of ventricular arrhythmias in patients after myocardial infarction. *Ann Noninvasive Electrocardiol* 19: 330-337
16. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, Mikami Y, Adachi T, Ryu S, Miyata A, Katagiri T, (2004) Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol* 37: 191-200
17. Haugaa KH, Smedsrud MK, Steen T, Kongsgaard E, Loennechen JP, Skjaerpe T, Voigt JU, Willems R, Smith G, Smiseth OA, Amlie JP, Edvardsen T, (2010) Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. *JACC Cardiovasc Imaging* 3: 247-256
18. Haugaa KH, Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP, (2009) Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. *Eur Heart J* 30: 330-337
19. Haland TF, Almaas VM, Hasselberg NE, Saberniak J, Leren IS, Hopp E, Edvardsen T, Haugaa KH, (2016) Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 17: 613-621
20. Nielsen N, Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, Nilsson F, Friberg H, (2011) Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. *Crit Care Med* 39: 57-64
21. Storm C, Hasper D, Nee J, Joerres A, Schefold JC, Kaufmann J, Roser M, (2011) Severe QTc prolongation under mild hypothermia treatment and incidence of arrhythmias after cardiac arrest—a prospective study in 34 survivors with continuous Holter ECG. *Resuscitation* 82: 859-862
22. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Belohlavek J, Callaway C, Cariou A, Eastwood G, Erlinge D, Hovdenes J, Joannidis M, Kirkegaard H, Kuiper M, Levin H, Morgan MPG, Nichol AD, Nordberg P, Oddo M, Pelosi P, Rylander C, Saxena M, Storm C, Taccone F, Ullen S, Wise MP, Young P, Friberg H, Nielsen N, (2019) Targeted hypothermia versus targeted Normothermia after out-of-hospital cardiac arrest (TTM2): A randomized clinical trial-Rationale and design. *Am Heart J* 217: 23-31
23. Polderman KH, Varon J, (2015) How low should we go? Hypothermia or strict normothermia after cardiac arrest? *Circulation* 131: 669-675
24. Kerans V, Espinoza A, Skulstad H, Halvorsen PS, Edvardsen T, Bugge JF, (2015) Systolic left ventricular function is preserved during therapeutic hypothermia, also during increases in heart rate

- with impaired diastolic filling. *Intensive care medicine experimental* 3: 41
25. Olsson IAS, Silva SPD, Townend D, Sandoe P, (2016) Protecting Animals and Enabling Research in the European Union: An overview of development and implementation of directive 2010/63/EU. *ILAR journal* 57: 347-357
 26. Nolan JP, Morley PT, Hoek TL, Hickey RW, (2003) Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation. *Resuscitation* 57: 231-235
 27. Bazett HC, (1920) An analysis of the time relations of electrocardiograms. *Heart* 7: 353-370
 28. Charbit B, Samain E, Merckx P, Funck-Brentano C, (2006) QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. *Anesthesiology* 104: 255-260
 29. Erikssen G, Liestol K, Gullestad L, Haugaa KH, Bendz B, Amlie JP, (2012) The terminal part of the QT interval (T peak to T end): a predictor of mortality after acute myocardial infarction. *Ann Noninvasive Electrocardiol* 17: 85-94
 30. Popovic ZB, Thomas JD, (2017) Assessing observer variability: a user's guide. *Cardiovascular diagnosis and therapy* 7: 317-324
 31. Laursen M, Grunnet M, Olesen SP, Jespersen T, Mow T, (2011) Keeping the rhythm – pro-arrhythmic investigations in isolated Göttingen minipig hearts. *J Pharmacol Toxicol Methods* 64: 134-144
 32. Lubberding AF, Sattler SM, Flethøj M, Tfelt-Hansen J, Jespersen T, (2020) Comparison of hemodynamics, cardiac electrophysiology, and ventricular arrhythmia in an open- and a closed-chest porcine model of acute myocardial infarction. *Am J Physiol Heart Circ Physiol* 318: H391-h400
 33. Swindle MM, Smith AC (2015) *Swine in the laboratory: surgery, anesthesia, imaging, and experimental techniques*. CRC press,
 34. Guns PJ, Johnson DM, Van Op den Bosch J, Weltens E, Lissens J, (2012) The electro-mechanical window in anaesthetized guinea pigs: a new marker in screening for Torsade de Pointes risk. *Br J Pharmacol* 166: 689-701
 35. Schimpf R, Wolpert C, Gaita F, Giustetto C, Borggreffe M, (2005) Short QT syndrome. *Cardiovasc Res* 67: 357-366
 36. Limprasutr V, Pirintr P, Kijawornrat A, Hamlin RL, (2018) An increasing electromechanical window is a predictive marker of ventricular fibrillation in anesthetized rabbit with ischemic heart. *Exp Anim* 67: 175-183
 37. Bachmann TN, Skov MW, Rasmussen PV, Graff C, Pietersen A, Lind B, Struijk JJ, Olesen MS, Haunso S, Kober L, Svendsen JH, Holst AG, Nielsen JB, (2016) Electrocardiographic Tpeak-Tend interval and risk of cardiovascular morbidity and mortality: Results from the Copenhagen ECG study. *Heart Rhythm* 13: 915-924
 38. Moss AJ, Liu JE, Gottlieb S, Locati EH, Schwartz PJ, Robinson JL, (1991) Efficacy of permanent pacing in the management of high-risk patients with long QT syndrome. *Circulation* 84: 1524-1529

39. Piktel JS, Jeyaraj D, Said TH, Rosenbaum DS, Wilson LD, (2011) Enhanced dispersion of repolarization explains increased arrhythmogenesis in severe versus therapeutic hypothermia. *Circulation Arrhythmia and electrophysiology* 4: 79-86
40. Hsieh YC, Lin SF, Huang JL, Hung CY, Lin JC, Liao YC, Lo CP, Wang KY, Wu TJ, (2014) Moderate hypothermia (33 degrees C) decreases the susceptibility to pacing-induced ventricular fibrillation compared with severe hypothermia (30 degrees C) by attenuating spatially discordant alternans in isolated rabbit hearts. *Acta Cardiologica Sinica* 30: 455-465
41. Boddicker KA, Zhang Y, Zimmerman MB, Davies LR, Kerber RE, (2005) Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. *Circulation* 111: 3195-3201
42. Haugaa KH, Grenne BL, Eek CH, Ersboll M, Valeur N, Svendsen JH, Florian A, Sjoli B, Brunvand H, Kober L, Voigt JU, Desmet W, Smiseth OA, Edvardsen T, (2013) Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging* 6: 841-850
43. Stankovic I, Putnikovic B, Janicijevic A, Jankovic M, Cvjetan R, Pavlovic S, Kalezic-Radmili T, Panic M, Milicevic P, Ilic I, Cvorovic V, Neskovic AN, (2015) Myocardial mechanical and QTc dispersion for the detection of significant coronary artery disease. *Eur Heart J Cardiovasc Imaging* 16: 1015-1022
44. Mikkelsen ME, Christie JD, Abella BS, Kerlin MP, Fuchs BD, Schweickert WD, Berg RA, Mosesso VN, Shofer FS, Gaieski DF, (2013) Use of therapeutic hypothermia after in-hospital cardiac arrest. *Crit Care Med* 41: 1385-1395
45. Van Deuren B, Van Ammel K, Somers Y, Cools F, Straetemans R, van der Linde HJ, Gallacher DJ, (2009) The fentanyl/etomidate-anaesthetised beagle (FEAB) dog: a versatile in vivo model in cardiovascular safety research. *J Pharmacol Toxicol Methods* 60: 11-23
46. Hotvedt R, Platou ES, Koppang ER, Refsum H, (1982) Pentobarbital plasma concentrations and cardiac electrophysiology during prolonged pentobarbital infusion anaesthesia in the dog. *Acta Anaesthesiol Scand* 26: 638-642
47. Nagasaki G, Tanaka M, Nishikawa T, (2001) The recovery profile of baroreflex control of heart rate after isoflurane or sevoflurane anesthesia in humans. *Anesth Analg* 93: 1127-1131
48. Kilkenney C, Browne WJ, Cuthill IC, Emerson M, Altman DG, (2010) Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol* 8: e1000412

Tables

Table 1: Hemodynamic variables

| Spontaneous HR | HR 100 bpm | | <i>p</i> | 38 °C | 33 °C | <i>p</i> | |
|-------------------------------|-------------|-------------|----------|-------------|-------------|----------|--|
| | 38 °C | 33 °C | | | | | |
| MAP(mmHg) | 62 ± 8 | 53 ± 9 | 0.009 | 65 ± 9 | 54 ± 7 | 0.007 | |
| SVR(dynes/s/cm ⁵) | 930 ± 181 | 966 ± 166 | 0.591 | 864 ± 141 | 915 ± 107 | 0.325 | |
| LVP(mmHg) | 84 ± 6 | 69 ± 11 | <0.001 | 86 ± 6 | 67 ± 11 | <0.001 | |
| CO(l/min) | 4.7 ± 0.9 | 3.7 ± 0.7 | 0.001 | 5.3 ± 0,6 | 4.0 ± 0,8 | <0.001 | |
| SV(ml/beat) | 54 ± 7 | 50 ± 11 | 0.241 | 53 ± 7 | 40 ± 8 | <0.001 | |
| EF(%) | 57 ± 6 | 55 ± 8 | 0.309 | 60 ± 6 | 50 ± 5 | <0.001 | |
| SS(%) | 32 ± 7 | 23 ± 6 | <0.001 | 27 ± 7 | 17 ± 5 | <0.001 | |
| SL(%) | 30 ± 7 | 23 ± 7 | <0.001 | 26 ± 7 | 17 ± 3 | <0.001 | |
| s'(m/s) | 0.06 ± 0.01 | 0.05 ± 0.01 | 0.023 | 0.06 ± 0.01 | 0.05 ± 0.01 | 0.012 | |

Data are expressed as Mean ± SD.

MAP = Mean Arterial Pressure,

SVR = Systemic Vascular Resistance,

LVP = Left Ventricular Pressure,

CO = Cardiac Output,

SV = Stroke Volume,

EF = Ejection Fraction,

SS = Longitudinal septal LV strain,

SL = Longitudinal lateral LV strain,

s' = Systolic Velocity

Table 2: Electrocardiographic variables

| Spontaneous HR | HR 100 bpm | | | | | |
|----------------|-------------|-------------|--------|-------------|-------------|--------|
| 38 °C | 33 °C | P value | 38 °C | 33 °C | P value | |
| HR(bpm) | 88 ± 10 | 80 ± 7 | <0.001 | 100 ± 1 | 100 ± 1 | 0.326 |
| QRS(ms) | 67 ± 10 | 75 ± 12 | <0.001 | 64 ± 10 | 74 ± 11 | <0.001 |
| RR(ms) | 694 ± 80 | 748 ± 69 | <0.001 | 601 ± 4 | 602 ± 3 | 0.177 |
| QT(ms) | 395 ± 45 | 473 ± 51 | <0.001 | 382 ± 32 | 406 ± 32 | 0.005 |
| QTc (ms) | 475 ± 50 | 551 ± 54 | <0.001 | 494 ± 47 | 524 ± 43 | 0.079 |
| TpTe(ms) | 45 ± 11 | 40 ± 10 | 0.027 | 41 ± 14 | 32 ± 7 | 0.003 |
| TpTe/QT | 0.12 ± 0.03 | 0.08 ± 0.02 | <0.001 | 0.11 ± 0.03 | 0.08 ± 0.02 | 0.003 |

Data are expressed as Mean ± SD

HR = Heart rate,

QRS = QRS complex on ECG,

RR = Interval from R to R between two QRS complexes,

QT = QT interval,

QTc = QT interval corrected for heart rate,

TpTe = T wave peak to T wave end duration, electrical dispersion of repolarization,

TpTe/QT = Electrical dispersion of repolarization corrected for QT interval

Table 3: Mechanical and electromechanical variables

| Spontaneous HR | | HR 100 bpm | | | | |
|-----------------------|----------|------------|--------|----------|----------|--------|
| 38 °C | 33 °C | <i>p</i> | 38 °C | 33 °C | <i>p</i> | |
| QAVO(ms) | 91 ± 11 | 97 ± 10 | 0.071 | 89 ± 8 | 99 ± 7 | 0.076 |
| QAVC(ms) | 353 ± 17 | 501 ± 24 | <0.001 | 341 ± 20 | 456 ± 11 | <0.001 |
| AVO-AVC(ms) | 275 ± 47 | 379 ± 27 | <0.001 | 257 ± 20 | 336 ± 17 | <0.001 |
| ET _{pw} (ms) | 302 ± 36 | 382 ± 43 | 0.001 | 282 ± 22 | 344 ± 49 | 0.014 |
| IVCT(ms) | 39 ± 11 | 43 ± 12 | 0.409 | 45 ± 2 | 51 ± 10 | 0.301 |
| IVRT(ms) | 62 ± 13 | 71 ± 20 | 0.081 | 64 ± 19 | 67 ± 21 | 0.685 |
| EMW(ms) | -20 ± 19 | 27 ± 34 | 0.001 | -25 ± 26 | 41 ± 18 | <0.001 |
| MD(ms) | 29 ± 11 | 36 ± 17 | 0.078 | 47 ± 16 | 40 ± 23 | 0.297 |

Data are expressed as Mean ± SD

QAVO = Q onset to aortic valve opening,

QAVC = Q onset to aortic valve closing,

AVO-AVC = Aortic valve opening to aortic valve closing, 2D registered,

ET_{pw} = Left ventricular outflow tract ejection time, Doppler registered,

IVCT = Isovolumic contraction time,

IVRT = Isovolumic relaxation time,

EMW = Electromechanical window: QAVC – QT,

MD = Mechanical Dispersion

Figures

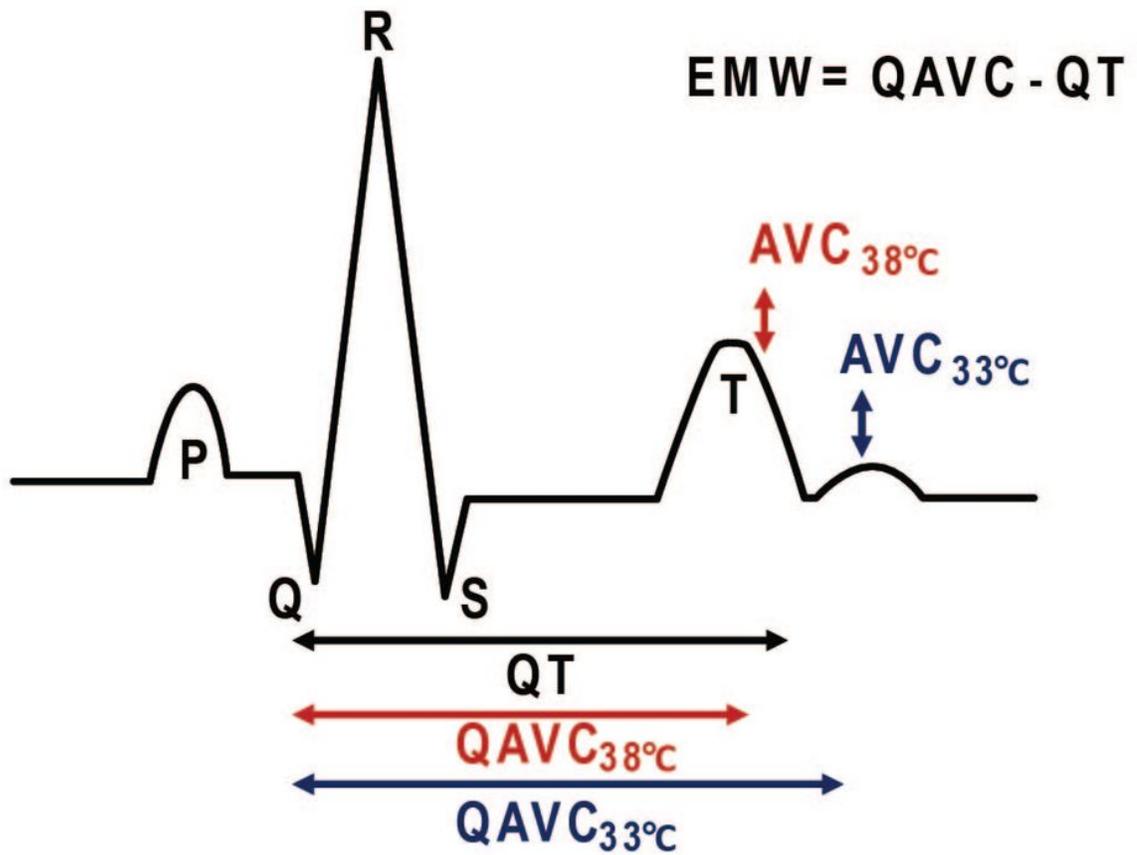


Figure 1

ECG with remarked echocardiographic timing A schematic drawing of an ECG signal combined with remarked echocardiographic timing of the aortic valve closure (AVC). QT interval is prolonged at 33 °C, but QAVC even more extended. Electromechanical window (EMW) is calculated as $EMW = QAVC - QT$.

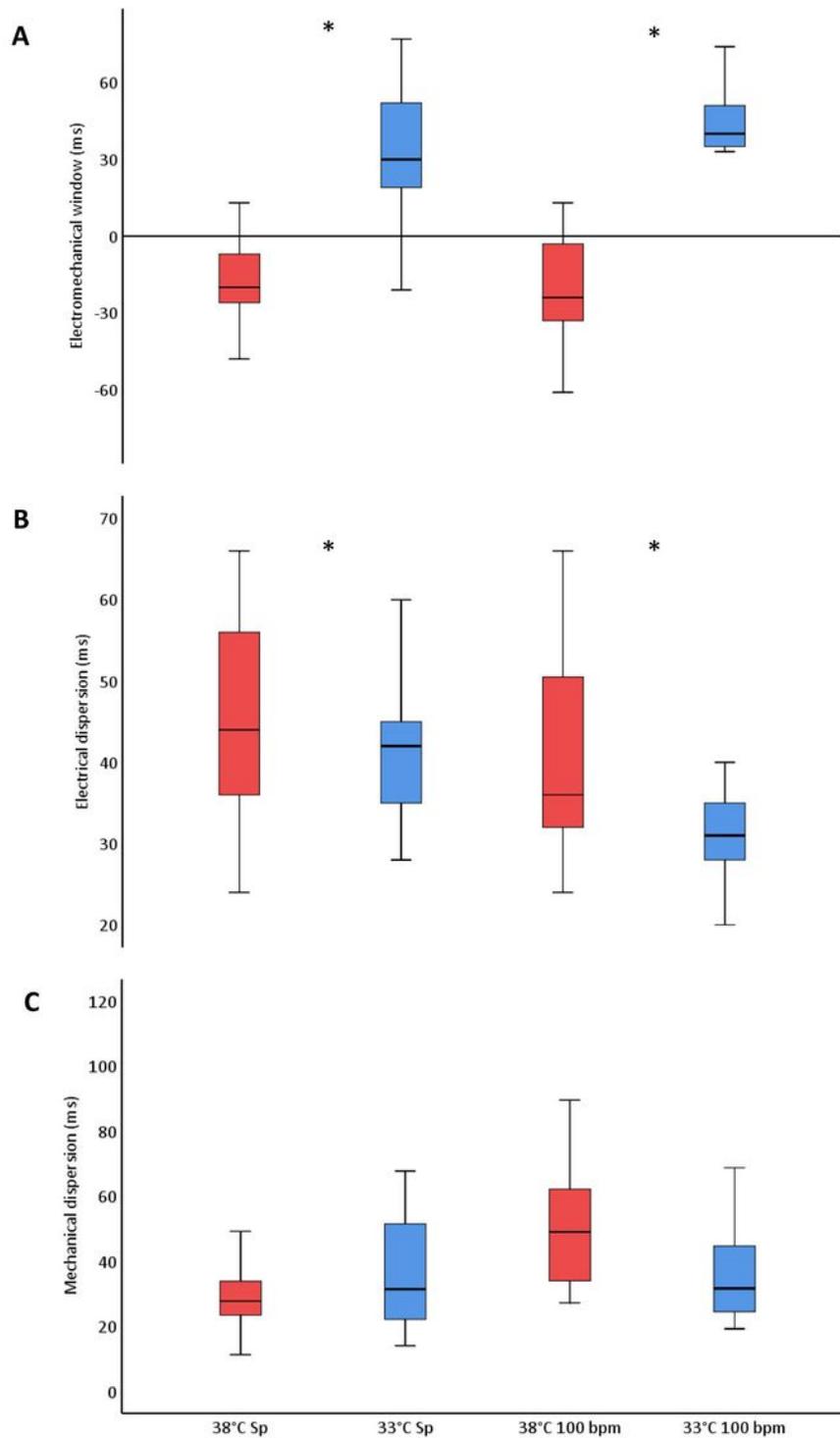


Figure 2

Electromechanical window, electrical dispersion and mechanical dispersion Electromechanical Window (A), electrical dispersion (B) and mechanical dispersion (C) during normothermia (38 °C) and hypothermia (33 °C) at spontaneous (Sp) and heart rate 100 bpm. The plots are computed from 13 (A) and 14 (B, C) animals at spontaneous heart rate, and 12 (A) / 13 (B, C) animals for paced heart rate. Asterisk indicates statistical significance, $p < 0.05$.