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# Hypothermia and cardiac electrophysiology – a systematic review of clinical and experimental data

Erik Sveberg Dietrichs [a, b], Torkjel Tveita [c, d], Godfrey Smith [e]

[a] *Experimental and Clinical Pharmacology Research Group, Department of Medical Biology, UiT, The Arctic University of Norway, 9037 Tromsø, Norway*

[b] *Department of Clinical Pharmacology, Division of Diagnostic Services, University Hospital of North Norway, 9038 Tromsø, Norway*

[c] *Anesthesia and Critical Care Research Group, Department of Clinical Medicine, UiT, The Arctic University of Norway, 9037 Tromsø, Norway*

[d] *Division of Surgical Medicine and Intensive Care, University Hospital of North Norway, 9038 Tromsø, Norway*

[e] *Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK.*

E-mail: Erik Sveberg Dietrichs: erik.sveberg.dietrichs@uit.no, Torkjel Tveita: torkjel.tveita@uit.no,

Godfrey Smith: godfrey.smith@glasgow.ac.uk

Address proof correspondence to:

Erik Sveberg Dietrichs:

- E-mail: erik.sveberg.dietrichs@uit.no
- Address: Experimental and Clinical Pharmacology Research Group, The Arctic University of Norway, 9037 Tromsø, Norway
- Telephone: +47 77698236
- Fax-number: +47 77645300

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## Abstract

Moderate therapeutic hypothermia procedures are used in post-cardiac arrest care, while in surgical procedures, lower core temperatures are often utilized to provide cerebral protection. Involuntary reduction of core body temperature takes place in accidental hypothermia and ventricular arrhythmias are recognised as a principal cause for a high mortality rate in these patients. We assessed both clinical and experimental literature through a systematic literature search in the PubMed database, to review the effect of hypothermia on cardiac electrophysiology. From included studies, there is common experimental and clinical evidence that progressive cooling will induce changes in cardiac electrophysiology. The QT-interval is prolonged and appears more sensitive to decreases in temperature than the QRS-interval. Severe hypothermia is associated with more pronounced changes, some of which are pro-arrhythmic. This is supported clinically where severe accidental hypothermia is commonly associated with ventricular fibrillation or asystole. J-waves in human ECG-recordings are regularly but not always observed in hypothermia. Its relation to ventricular repolarisation and arrhythmias is not obvious. Little clinical data exist on efficacy of anti-arrhythmic drugs in hypothermia, while experimental data show the potential of some agents, such as the class III antiarrhythmic bretylium. It is apparent that QT-prolonging drugs should be avoided.

## 1. Introduction

Hypothermia can be accidental or a therapeutic measure to lower metabolic demands and protect against hypoxic damage. The impact of hypothermia could be more severe when comorbidities exist (1). Therapeutic temperature management is used after severe injury or disease like cardiac arrest. Comatose survivors are cooled to below 36°C, although doubt have been raised whether more profound cooling is beneficial. Avoiding hyperthermia could be the principal mechanism for providing neuroprotection in these patients (2). In trauma patients, hypothermia has a negative impact, giving 3-fold increase in mortality (3).

The degree of cooling varies greatly between types of accidental or therapeutic exposure. Based on clinical studies, hypothermia has been classified into 3 broad categories: Mild 35°C -34°C, moderate 30°C-34°C or severe <30°C (1). The overall mortality of accidental hypothermia is estimated between 25-40% in most studies (4,5) and arrhythmias are a major concern both during cooling and rewarming. Submersion and immersion hypothermia deaths could incorrectly be ascribed to drowning, with patients succumbing to hypothermia induced arrhythmias or an autonomic conflict. It is hypothesised that ventricular arrhythmia can arise from a simultaneous activation of the diving response and cold shock; triggering a parasympathetically driven bradycardia, and sympathetically driven tachycardia (6).

Detailed measurements of cardiac electrophysiology during hypothermia are challenging to obtain. Invasive electrical measurements provide higher resolution and more detailed regional information. Due to these benefits, experimental studies give important information. However, a large proportion of such studies are carried out at room temperature, thus only observing electrophysiology at temperatures corresponding to severe hypothermia, without

comparing findings to normothermic conditions (7-9). It is therefore important to assess literature that compares electrophysiology at both low and normal core temperatures. Cardiac electrophysiology is largely species-dependent, with hibernators being resistant to lethal ventricular fibrillation (10). Comparison and critical review of experimental and clinical findings is therefore essential for a better understanding of the pro-arrhythmic impact of hypothermia.

## 2. Materials and methods

A systematic literature search was conducted on 27 March 2017 in the electronic PubMed database. All articles retrieved for: #1 Hypothermia AND electrophysiology, and #2 hypothermia AND ECG, were assessed.

A total of 1412 publications were identified. The main criterion for inclusion was that they had a hypothermia protocol and a measure of cardiac electrophysiology. Case reports, studies in children and neonates, studies on non-mammals, studies in which hypothermia was induced with drugs or local injection of cold fluids, regional cooling of hearts and studies where cardioplegic solutions were used prior to cooling, were excluded.

Studies were considered for inclusion based on the abstract. If this was inadequate or absent, the full text was assessed to examine whether they met inclusion criteria. A total of 86 studies were included, of which 38 were clinical and the remainder were experimental in different species. Articles that were not detected through the literature search were found in reference-lists of included papers or other literature reviews.

## 3. Ventricular action potential and ion-channels (Fig1, table1)

To initiate an action potential (AP) and subsequent contraction of resting ventricular cardiomyocytes (phase 4 of the AP), depolarisation must be initiated by increased sodium conductance via voltage-gated $Na^+$-channels (phase 0). In severe hypothermia (27°C) sodium current appears impaired (11), thus prolonging phase 0. Phase 1 is initiated by rapid inactivation of the $Na^+$-channels and activation of a transient outward current ($I_{to}$),. This leads to a transient increase in potassium conductance, causing the rapid and transient repolarisation seen as the AP notch. Some studies suggest a heterogenic effect of hypothermia on $I_{to}$ (12) with a larger epicardial outward potassium current, causing a more prominent epicardial AP notch (13). Phase 1 is followed by the plateau phase (phase 2), where the membrane potential is more stable and repolarisation is slowly initiated by opening of delayed rectifier $K^+$-channels, increasing membrane potassium conductance. Simultaneously, calcium influx is initiated due to opening of L-type $Ca^{2+}$ channels. In severely hypothermic cardiomyocytes, the transient calcium influx during phase 2 is prolonged and the cytosolic calcium concentration is increased (14). During phase 3, the L-type $Ca^{2+}$ channels close, while the delayed rectifier $K^+$-channels remains open. Thus, a change in membrane potential to more negative potentials occurs and which engages the background inwardly rectifying $K^+$ conductance, contributing to repolarisation of the cardiomyocyte. Both delayed and inward rectifying $K^+$-channel function appears temperature-sensitive. A reduction in core temperature will therefore impair potassium channel function and prolong phase 2 and 3 (11,15,16). In general, ion-channel function is severely affected by hypothermia and studies aiming at describing normothermic electrophysiology, should not be carried out at room-temperature.

## 4. Atrial depolarisation and atrio-ventricular conduction (Fig1, table1)

4.1 *Experimental studies*

In ECG-recordings, atrial depolarisation underlies the P-wave, while ventricular depolarisation underlies the QRS-complex and the PR interval reflects conduction through the atrio-ventricular (AV) node. PR-interval prolongation can occur in different pathological situations; typically AV-block (17). In hypothermic dogs the PR-interval became prolonged after cooling to 29°C (18) and was doubled at 24°C (19). PR-prolongation is smaller in monkeys, with a 11% - 38% change during cooling to 25°C (20). In hibernating squirrels, where core temperature fell below 11°C, PR-interval was prolonged by a factor of 7. The T-P segment (representing diastole) was increased 40-70 times, underlying pronounced bradycardia (21). While heart rate is decreased, inter-beat interval variability is increased in hypothermic rat hearts during cooling to 27°C. The authors concluded that this change was attributed to the sino-atrial (SA) node. Regularity of discharge of pacemaker cells was impaired by low temperature, while AV conduction appeared unaffected (22). However, in vivo cooling does produce conduction disturbances spanning from first degree AV block to total heart block (23-25). In rats, these disturbances present through a sudden increase in PR-interval at 22°C. If rats received respiratory support, such block was delayed to below 18°C. Subsequently, atrial arrest would occur prior to ventricular arrest (26). In isolated rabbit atria, arrest occurs after cooling to 21°C (27).

4.2 *Clinical studies*

Bradycardia is a well-known effect of cooling, but is not always observed during moderate hypothermia. 15 accidental hypothermia patients in sinus rhythm, with an average core temperature of 30.5°C, had heart rates ranging from 13-100 beats/minute (28). A sympathetically mediated increase second to initial cooling, could contribute to large variations in heart rate. In sedated patients, subjected to therapeutic hypothermia, bradycardia

seems more consistent. Patients cooled to a target of 33°C had an average heart rate reduction of 19 beats/minute (29).

During cooling to 28°C - 30°C, 7 of 13 patients had prolonged PR-interval (30). Although some reports find unchanged PR-interval after cooling (31), it is generally increased in therapeutic hypothermia (29,32-35). Hypothermia-induced PR-prolongation is found in some (36,37), but not all (38,39) ECG-studies during rewarming from accidental hypothermia. In severely hypothermic patients, Darocha et al. found low P-wave amplitude (0.1mV) (37), while Kim et al. found unchanged (0.16 mV) amplitude at 33.5°C (31).

Serious AV-nodal pathology is not observed in all studies. Only 3 of 25 Scottish accidental hypothermia patients (mean core temperature: 30.3°C) presented with varying degrees of AV block (28). In a Brazilian study, AV block was seen in 3 of 59 patients but only 10 patients had core temperatures below 28°C (36). Severe accidental hypothermia does however promote AV block (40,41). This relationship is also observed in patients subjected to direct cardiac cooling (42).

### 4.3 *Summary*

Hypothermia induces bradycardia and prolongs AV nodal conduction, as observed by elongated PR-interval. Severity can span from first degree AV-block to total heart block and is dependent on temperature reduction. These effects are demonstrated more clearly below 20°C in experimental animal models, compared to human studies of moderate hypothermia.

## 5. Ventricular depolarisation (Fig1, table1)

### 5.1 *Experimental studies*

During hypothermia, reduced conductance of $Na^+$-channels is reflected by reduced maximum rate of depolarisation in guinea-pig papillary muscle at 27°C (11) and ventricular depolarisation is slowed in sheep (43). Hypothermia-induced prolongation of depolarisation is reflected in ECG recordings. In rats, ventricular activation time (QR-time) increased during progressive cooling to cardiac arrest (44).

### 5.2 *Clinical studies*

QRS duration appears increased in severe accidental and therapeutic hypothermia (33,37). In moderate hypothermia, there are reports of prolonged QRS duration (31,34) but it is more often unaffected or decreased (29,38,39,45-47). Lam et al. found an 8 ms (7%) decrease in QRS interval of 101 cardiac arrest survivors at 33°C, indicating increased endocardial to epicardial conduction. Interestingly, there was a trend towards non-survivors having shorter QRS-interval compared to survivors ($P<0.1$) (29). After cooling to 28°C - 30°C, 7 of 13 patients had prolonged QRS-interval (30).

### 5.3 *Summary*

Progressive cooling slows ventricular depolarisation. This effect appears to be non-linear and is only consistently observed after cooling below 30°C, which appears to be a threshold temperature for this effect. Some studies even suggest faster depolarisation during moderate hypothermia in humans (29).

## 6. Ventricular repolarisation (Fig1, table1)

### 6.1 *Experimental studies*

Lengthening of cardiac repolarisation is a prominent feature of cooling (11). Studies in isolated cardiomyocytes indicate that both $I_K$ and $I_{K1}$-channels are temperature-sensitive (11,15,16). Impaired potassium conductance mediates prolonged repolarisation, reflected in QT-interval of the ECG-signal. In dogs cooled to 34.2°C (48) and rats cooled to cardiac arrest, QTc-interval was prolonged in a linear relationship with decreasing core temperature. Cooling-induced QT-prolongation is also observed in rats (44), cats (49) and rabbit hearts (50). Siems et al. reported that after the initial prolongation of QTc, a threshold was reached, thereafter no change occurred during further cooling of dogs (51). Further, epicardial mapping of intact rabbit hearts at 32°C, showed nonuniform repolarisation-changes, which was particularly pronounced at the left ventricular (LV) apex (52). When studying action potential duration (APD) in endocardial and epicardial canine LV cells at 26°C, Piktel et al. found increased (358%) dispersion of repolarisation. At the same temperature, conduction time was increased by 37%. During rewarming conduction time normalised, while dispersion of repolarisation remained increased (53). It is also enhanced in hypothermic guinea-pig hearts (54).

Repolarisation is more slowed by hypothermia (32°C) in Purkinje fibres than in ventricular cardiomyocytes. This is thought to found basis for the U-wave, occurring after the T-wave in ECG-recordings (55). Further, mathematical simulation indicate that prolonged epicardial APD and unchanged endocardial APD, could explain increased transmural repolarisation gradient during hypothermia (56). However, in canine right ventricular preparations, phase 1

epicardial repolarisation is enhanced at 32°C (12). Hibernating hedgehogs that lack a physiological AP plateau phase seem less vulnerable to hypothermia than guinea-pigs, where slow conduction and dispersion of repolarisation is more apparent after cooling to 15°C (57). This could explain why hedgehogs rarely develop VF during hypothermia (58).

### 6.2 *Clinical studies*

Clinical ECG-studies in therapeutic and accidental hypothermia show consistent increased QTc-interval and thus prolonged repolarisation, mainly without QRS-interval change (29,31-39,45-47,59-63). Prolongation of QTc (64,65) in presence of unchanged QRS-interval is also found in patients with acquired poikilothermia (average core temperature 33.9°C) (64). Fast induction of therapeutic hypothermia gives a larger increase in QTc duration than slow cooling (47) . No relation to increased incidence of arrhythmias or mortality was however found in a study on therapeutic hypothermia patients (29). Despite this, cooling of patients with long QT syndrome should be done with great caution (34) as rate of repolarisation appears more temperature-sensitive than rate of depolarisation.

T-wave flattening or inversion can also occur during cooling, sometimes in concert with increased J-wave amplitude (32). Flattening or inversion of T-waves occurred in 8 of 13 patients cooled prior to neurosurgery (30), and was the most common ECG-finding during duodenal ulcer-treatment with gastric hypothermia (66).

Increased dispersion of repolarisation is found in animal models after cooling below 32°C (54,57,67) and is associated with ventricular arrhythmias. In ECG-recordings, the interval

from peak to end of the T-wave (TpTe), can be used as a marker of transmural dispersion of repolarisation. Kim et al. did not find any significant change in TpTe after therapeutic cooling of patients to 33.5°C (31). In accidental hypothermia patients however, increased QTc dispersion was found (38).

### 6.3 *Summary*

Cardiac repolarisation is prolonged with an approximately linear relationship with decreasing core temperature, and is evident during early cooling. This is basis for the consistent QTc-prolongation observed in both therapeutic and accidental hypothermia in humans.

## 7. J-wave (Fig1, table1)

The J-wave is a hypothermia-associated deflection between the end of the QRS complex and the beginning of the ST segment. Although first described by Tomaszewski in 1938 (68,69), it is often named the Osborn-wave, after an experimental dog study from 1953. The appearance of a J-wave at 25°C was described as “a current of injury” and correlated to the later onset of VF (70), a finding that was supported by Boba (71).

### 7.1 *Experimental studies*

Temperature of onset and proportion of animals that develop J-waves varies between studies. Siems et al. described the J-wave as Ta and reported occurrence in 9 of 28 cooled dogs at a mean core temperature of 31.6°C (51). Epicardial cooling of dogs resulted in J-waves at 29.7°C (72) and at 27°C in dogs immersed in an ice-bath. Authors related this with a net loss

of myocardial potassium (73). In transmural, canine wedge-preparations, hypothermia-induced J-waves is associated with a prominent AP notch only in the epicardium. This suggests a heterogeneous distribution of transient outward current ($I_{to}$) that underlies the occurrence of J-waves (13). Findings from Morita et al. concur with this theory, as blocking of $I_{to}$ with 4-aminopyridine, reduced J-wave elevation at 32°C (12). In a canine wedge preparation model, J-waves were increased during cooling to 32°C. Simulating early repolarisation syndrome during hypothermia, accentuated the epicardial AP notch (74).

### 7.2 *Clinical studies*

The proportion of hypothermic patients presenting with J-waves varies greatly between studies and is temperature dependent. J-waves occured in 100% of patients with core temperatures below 32°C (76) or 30°C (75). This is in accordance with a study on induced hypothermia prior to surgery. 9 of 60 patients developed J-waves, which with one exception, was first observed after cooling below 30°C (71). A temperature-dependent relationship is not clear in all accidental hypothermia studies. Darocha et al. found J-waves in only 3 of 19 patients with core temperatures below 26.2°C (37) and Duraković showed that >70% of elderly patients presented with J-waves both at temperatures between 32°C - 35°C and below 32°C (38,63).

Vectorcardiographic recordings show the three-dimensional direction of electrical conduction in the heart. After cooling, a J-loop deflection related to J-wave occurrence appeared in 5 therapeutic (30,5°C-31,5°C) (77) and 23 accidental hypothermia patients (22.8°C–34.4°C) (78). Further, J-wave amplitude seems inversely correlated with core temperature-reduction (36,76,79), but an association with ventricular arrhythmias is not supported by all clinical

studies. In 30 accidental hypothermia patients (29.4°C–33.5°C) with J-waves, only one developed ventricular tachycardia (VT) (75) and J-waves does not predict survival chance (39). A multi-centre study from South Korea observed J-waves in 41% of therapeutic hypothermia patients, while VF only occurred in 1.7% (80), which concurs with other studies (81). J-waves are more common in hypothermic STEMI (38.6%) than non-STEMI (15.2%) patients (45). Further, Williams et al. reported that early repolarisation and J-waves are more common in survivors of idiopathic (100%) than coronary artery disease-associated ventricular fibrillation (66.7%) (82). This reflects on underlying differences in cardiac pathophysiology and necessitates careful cooling of patients vulnerable to early repolarisation.

### 7.3 *Summary*

The likely cause of the J-wave is late and slow depolarisation of a significant region of the ventricle immediately after the QRS complex, or conversely an early repolarisation of an area of the ventricle. Both cases create an area of the ventricle that is polarised relative to the remainder. In both human and experimental studies, the occurrence of J-waves, and the temperatures at which it arises, varies greatly. Although postulated by Osborne (70), there is apparently no consistent relationship between presence of J-waves and risk for ventricular arrhythmias during hypothermia.

## 8. Incidence of Arrhythmias during cooling (table1)

### 8.1 *Experimental studies*

During progressive cooling of 15 dogs, cardiac arrest occurred after ventricular fibrillation (VF) in 60% of animals (51). During VF, cooling does not affect intramyocardial voltage (83) but VF morphology is changed (84). Further, compared to at 37°C and 30°C, spiral wave

311 excitations are more disorganised at 33°C. Optical mapping showed that such disorganisation
312 favoured spiral wave collision and self-termination of VT/VF (85). These findings concur
313 with pig experiments showing that successful defibrillation from VF was achieved more often
314 at 33°C, than at 30°C or 37°C (86). Cooling to 30°C however, enhanced epicardial APD
315 dispersion, wavebreaks and re-entry, thus increasing the vulnerability to pacing-induced VF
316 (87), similar to studies in other dog (88) and pig models (89). Reduced VF-threshold is found
317 in concert with electrical alternans, detected in both QRS-complex and T-waves (90,91).

318

319 VF-risk appears dependent on cooling method. Smith et al. investigated whether hemodilution
320 during therapeutic hypothermia could be beneficial. They showed that rapid cooling to 20°C
321 in non-hemodiluted dogs resulted in cardiac arrest in 50% of animals (92), similar to findings
322 of Wynne et al (93). In dogs hemodiluted with 50% of their calculated blood volume replaced
323 by Ringer's lactate solution, cardiac arrest (VF) occurred in only 5% (92). Rapid and
324 profound cooling could however also terminate VF in vitro, as found by Chorro et al. in rabbit
325 hearts that were perfused with cold (4°C), oxygenated Tyrode's solution (94). Cardiac
326 vulnerability is promoted further by rewarming. In canine wedge preparations cooled to 26°C,
327 VF and VT was more frequent during rewarming than cooling (53). In a similar model,
328 simulating early repolarisation syndrome, hypothermia (32°C) caused local re-excitation and
329 polymorphic VT/VF (74).

330

331 Development of VF during hypothermia and rewarming could be triggered by adrenergic
332 stimuli. In a feline model of hypothermia, ventricular arrhythmias were triggered in 100% of
333 hearts when adrenaline, noradrenaline or isoprenaline were provided at 21°C, in doses that
334 were safe at 37°C (95).

335

336 8.2 *Clinical studies*

337 Risk for ventricular arrhythmias is dependent of severity of hypothermia and pose a
338 significant challenge during rewarming. Of 19 accidental hypothermia patients, admitted with
339 core temperatures between 16.9°C–29°C, 7 were in ventricular fibrillation, while 2 presented
340 with asystole (37). In a Japanese study of 60 patients however, no patients with a core
341 temperature above 26°C had VF (96). In urban accidental hypothermia, underlying conditions
342 and substance abuse can be as important predisposing factors for cardiac arrest as core
343 temperature (61). In therapeutic hypothermia, ventricular ectopic activity is increased (97) and
344 non-sustained VT can occur frequently (34), but sustained ventricular arrhythmias are
345 uncommon in most (34,35,45,62,80) but not all studies. Mirzoyev found polymorphic VT in
346 11.7% of therapeutic hypothermia patients. VT onset occurred at an average of 34.7°C during
347 cooling in patients that were hypokalaemic and had QTc interval-prolongation (46). When VF
348 is induced during cooling prior to coronary surgery, fibrillation frequency is significantly
349 higher if induced at 34°C, compared to at 30°C. Further, Strohmenger et al. found that
350 defibrillation success increased if fibrillation frequency was allowed to increase above 5 Hz,
351 prior to counter-shock attempts during rewarming (98).

352

353 Atrial fibrillation (AF) is reported to have high incidence in several accidental (61,63,76,99)
354 and therapeutic hypothermia studies (34,45). Some reports suggest otherwise, most notably in
355 a recent study where only 2 of 59 accidental hypothermia patients presented with AF (36).
356 Like ventricular arrhythmias, onset appears temperature-dependent. In a study from Tokyo, 1
357 of 18 accidental hypothermia patients with core temperature above 32°C and 23 of 42 patients
358 with temperatures below 32°C presented with AF (96). During therapeutic cooling in

preparation for neurosurgery, AF occurred at a mean temperature of 28.9°C (32). Graham et al. associated onset of AF during accidental hypothermia with a poor prognosis, as 60% of patients presenting with this rhythm died (39). Earlier findings are conflicting. In 25 patients cooled for cardiac surgery, mortality rate was 29% when AF was observed, compared to 75% in patients in sinus rhythm (100).

### 8.3 *Summary*

Vulnerability for ventricular arrhythmias in animal models seem dependant on cooling method and is promoted by adrenergic stimuli. In humans, VF or asystole is more common in accidental hypothermia patients admitted with low core temperatures. Serious ventricular arrhythmias are uncommon in therapeutic hypothermia.

## 9. Pharmacological treatment

Few clinical studies have examined the properties of antiarrhythmic agents during hypothermia and rewarming. Although limited, most evidence is provided by preclinical studies using various species.

### 9.1 *Class I antiarrhythmic agents*

Quinidine is a class I antiarrhythmic agent and blocks voltage-gated $Na^+$-channels. It also blocks $I_{to}$, which prevents loss of AP dome during cooling to 32°C in canine wedge preparations. Thus, in presence of this pathophysiological substrate for re-excitation and phase 2 re-entry during hypothermia, quinidine prevented development of VT/VF (74).

Another $Na^+$-channel blocker; procainamide prolonged PR- and QT-intervals during cooling in dogs and evaluation of its antiarrhythmic effect was inconclusive (101).

9.2 *Class III antiarrhythmic agents*

Bretylium possess antiadrenergic activity through sympathetic ganglion blockade. It is also a $K^+$-channel blocker. On the hypothesis that cooling would promote ventricular arrhythmias through increased adrenergic activity, effects of bretylium were studied during rewarming from 25°C in dogs. Although plasma catecholamine levels remained unchanged, bretylium increased VF-threshold (102). The same antiarrhythmic effects are found after cooling to 27°C (103) and during rewarming from 24°C (104). However, these positive effects of bretylium might be limited to preventive treatment. Antiarrhythmic effects were not found during rewarming of dogs in VF. In the latter study, defibrillation was attempted following 10 min of CPR following drug administration at 22°C, the animals were not actively rewarmed before defibrillation (105). At such temperatures, defibrillation is challenging independent of treatment (106).

Amiodarone has diverse effects, among them is $K^+$-channel blockade and it therefore prolongs repolarisation. In amiodarone-treated dogs with VF at 22°C, 1/10 were successfully resuscitated. Resuscitation rate was 4/10 in bretylium treated, and 3/10 in placebo-treated animals (105). This indicates that pharmacological APD prolongation during hypothermia is unfavourable. A study on $K^+$-channel blocker sotalol gave the same outcome; sotalol-treatment was more effective in prolonging APD during hypothermic than normothermic conditions and authors thought this effect to be pro-arrhythmic (11,107)

### 9.3 *Class IV antiarrhythmic agents*

The class IV antiarrhythmic agent diltiazem is a $Ca^{2+}$-channel blocker which shortens APD. Bjørnstad et al. found a progressive AP prolongation during cooling to 25°C, in concert with reduced VF-threshold. Addition of diltiazem failed to increase VF-threshold in hypothermic dogs. At 27°C, the $Ca^{2+}$-channel blocker nisoldipine also shortened APD to within normothermic values in isolated guinea-pig papillary muscle (108).

### 9.4 *Other pharmacological agents*

In an early repolarisation syndrome model, phosphodiesterase III inhibitors milrinone and cilostazol were used to increase cAMP and thus augment the inward $Ca^{2+}$ current ($I_{ca}$), which prevented phase 2 re-entry and VT/VF during cooling to 32°C (74). In intact cardiomyocytes, dopamine will also increase cAMP through β-receptor stimulation. In excised muscle strips from pig ventricular septum, dopamine prolonged APD at 32°C (109). Regulation of $Ca^{2+}$-homeostasis could therefore be promising in treatment of hypothermia-induced arrhythmias. In a canine model of hypothermia, dipyridamole is thought to mediate such effect (110) and reduced the core temperature of which dogs would go into VF (111).

Fluid treatment with low or high molecular weight dextran did not have any effect on the ECG of dogs cooled to 20°C-22°C (112). Further, benzodiazepines such as diazepam produce $Ca^{2+}$-channel blockade and has been tested in a guinea-pig model of hypothermia, to explore potential anti-arrhythmic effect. However, significant shortening of APD was only obtained by a 100μM dose and the effect was subtle compared to the $Ca^{2+}$ channel blocker nisoldipine. It was therefore concluded that diazepam has little clinical potential in prevention of arrhythmias in hypothermic patients (108).

### 9.5 *Summary*

Little information on the effect of antiarrhythmic treatment exists from clinical hypothermia studies, but preclinical reports suggest favourable properties of some drugs. Quinidine and other $Na^+$-channel blockers could prevent VF by inhibiting hypothermia-induced phase 2 re-entry. Further, bretylium prevents VF in dogs suffering severe hypothermia, probably attributed to its antiadrenergic effects.

## 10. Conclusion and clinical recommendations

The impact of hypothermia on cardiac electrophysiology largely depends on the extent of cooling and resultant core temperature. Severe cooling generates more profound changes as reported in both clinical and experimental studies. Interestingly, the observed changes are not uniform. In clinical studies, prolongation of QT-interval is observed during cooling to moderate therapeutic hypothermia, while the temperature-dependent effects on QRS- and PR-interval are inconsistent. Accordingly, repolarisation seems more vulnerable to smaller changes in temperature. Experimental studies reflect these findings and show a heterogenic prolongation of repolarisation both on the epicardial surface and transmurally during hypothermia, while depolarisation seems largely unaffected during initial cooling.

Efforts to provide evidence-based information for anti-arrhythmic treatment during hypothermia and rewarming is largely derived from experimental models. The underlying, heterogenic effect of moderate hypothermia; i.e. cardiac depolarisation largely unaffected by cooling, while repolarisation is prolonged, could be a pro-arrhythmic substrate that is worsened by QT-prolonging drugs. Consequently, treatment of accidental hypothermia

patients and use of therapeutic hypothermia is complicated by drugs of non-cardiac indication that prolong the QT-interval, e.g. a wide range of antidepressants, antipsychotics, antibiotics and methadone (113).

On this background, it is vital to monitor cardiac electrophysiology closely in hypothermic patients. Administering cardioactive drugs should be carried out with great caution during rewarming. Medication that prolongs repolarisation (increases QT-interval) or promotes cardiac excitation should largely be avoided in accidental hypothermia-patients in sinus rhythm. Before and during therapeutic hypothermia, clinicians should consider dose-reduction of such drugs. Monitoring their serum concentrations during prolonged therapeutic hypothermia is indicated, as drug metabolism is altered by cooling, increasing the risk for cardiotoxic effects. Further, the profound absence of experimental and clinical evidence for anti-arrhythmic treatment in hypothermic patients, yields a demand for translational and clinical studies to lay foundation for clinical guidelines.

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753 **Figure and table legends**

754

755 Figure 1: A schematic drawing of a human action potential (AP) and ECG-signal during
756 normothermia and hypothermia. Reduction of core temperature appears to have a heterogenic
757 effect of depolarisation (phase 0 of the AP and QRS-interval of the ECG) and repolarisation
758 (phase 2-3 of the AP and QT-interval of the ECG). During moderate hypothermia
759 depolarisation is largely unaffected or shortened, while repolarisation is prolonged. In severe
760 hypothermia, both depolarisation and repolarisation is prolonged. Several ECG-findings could
761 be found in hypothermic patients and are reflected in the AP. Dispersion of beat-to-beat QT-
762 interval indicated dispersed repolarisation, while appearance of J-waves during hypothermia
763 could be caused by a transmural heterogenity in phase 1 repolarisation, with a large epicardial
764 notch.

765

766 Table 1: General electrophysiological findings during mild and moderate (>30°C) and severe
767 hypothermia (<30°C)

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| Hypothermia | | Sinus rhythm | Atrio-ventricular conduction | Ventricular depolarisation | Ventricular repolarisation | Arrhythmias |
|---|---|---|---|---|---|---|
| Mild and moderate (>30°C) | *Descriptive changes* | Unaltered or slowed | Unaltered or slowed | Faster, unaltered or slowed | Slowed | Atrial fibrillation, ventricular ectopic activity, ventricular tachycardia |
| | *ECG-findings* | Unchanged or increased RR-interval | Unchanged or increased PR-interval | Decreased, unchanged or increased QRS-interval | Increased QT-interval, J-wave | |
| Severe (<30°C) | *Descriptive changes* | Slowed until arrest | Slowed or halted | Slowed or unchanged | Slowed. Dispersed repolarisation | Atrial fibrillation, ventricular fibrillation, asystole |
| | *ECG-findings* | Increased RR-interval, low P-wave amplitude | Increased PR-interval, 1st-3rd degree AV-block | Increased or unchanged QRS-interval | Increased QT-interval, QT-interval dispersion, Flattened or inversed T-wave, J-wave. | |

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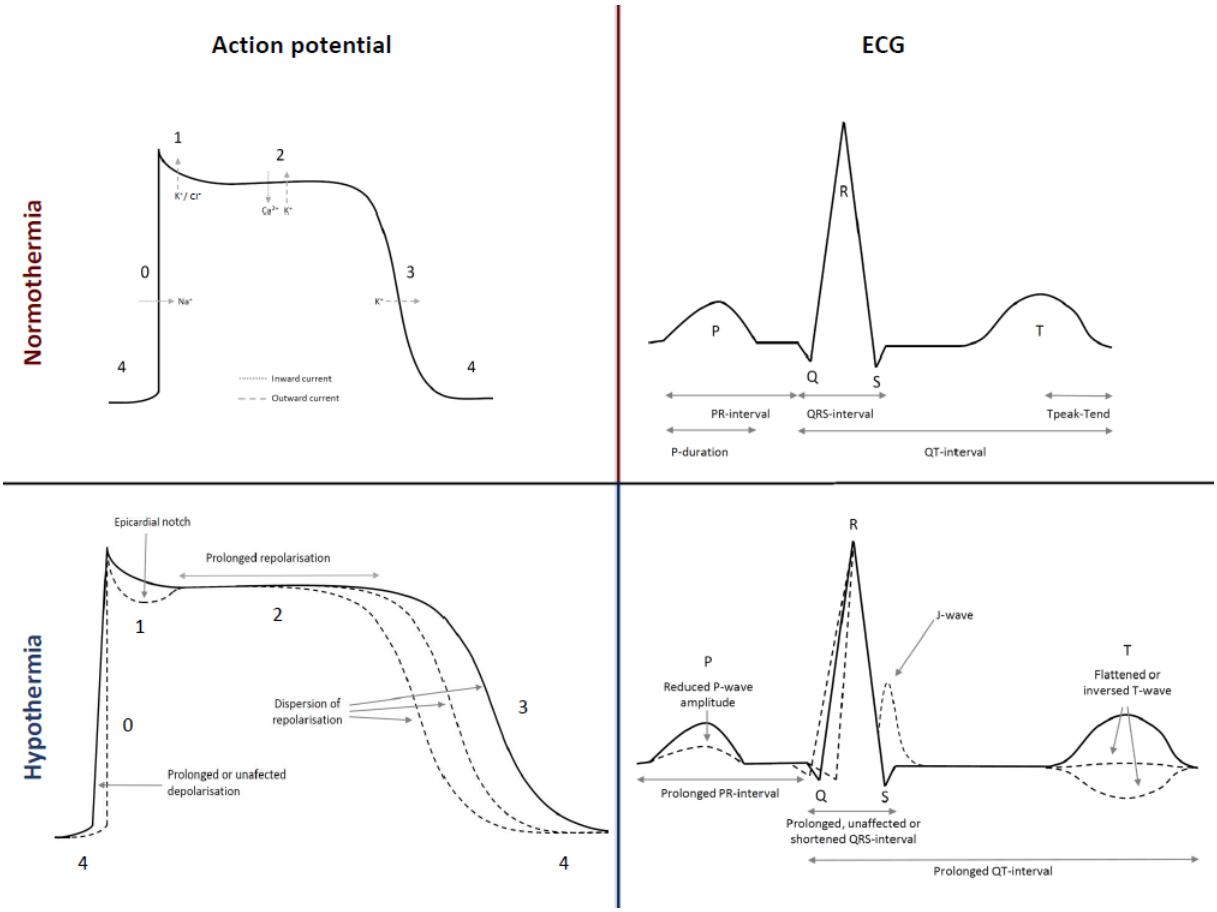
Action potential
ECG
Normothermia
1
2
0
3
4
4
K+ / Cl-
Ca2+ K+
Na+
K+
Inward current
Outward current
R
P
T
Q
S
PR-interval
QRS-interval
Tpeak-Tend
P-duration
QT-interval
Hypothermia
Epicardial notch
Prolonged repolarisation
1
2
0
3
Dispersion of repolarisation
Prolonged or unafected depolarisation
4
4
R
J-wave
P
Reduced P-wave amplitude
T
Flattened or inversed T-wave
Prolonged PR-interval
Q
S
Prolonged, unaffected or shortened QRS-interval
Prolonged QT-interval

777