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Review

The impact of hypothermia on serum potassium concentration: A systematic review

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ABSTRACT

Background: Blood potassium is the main prognostic biomarker used for triage in hypothermic cardiac arrest. The aim of this review was to assess the impact of hypothermia on blood potassium levels and compare the underlying pathophysiological theories.
Methods: The Medline electronic database was searched via PubMed for articles published from January 1970 to December 2016. The search strategy included studies related to hypothermia and potassium levels. The relevant literature on clinical studies and experimental studies was reviewed by the authors.
Results: Among the 50 studies included in the review, 39 (78%) reported a decrease in blood potassium levels upon hypothermia onset. Hypothermic hypokalaemia is linked to an intracellular shift rather than an actual net loss. The intracellular shift is caused by a variety of factors such as enhanced functioning of Na + K + ATPase, beta-adrenergic stimulation, pH and membrane stabilisation in deep hypothermia. In contrast, hypothermia can act as an aggravating factor in severe trauma with hyperkalaemia being an indicator of an irreversible state of cell death. An increase in the blood potassium level during hypothermia may result from a lack of enzyme functioning at cold temperatures and blocked active transport.
Conclusion: Hypothermia causes an initial decrease of potassium levels; however, the final stage of hypothermic cardiac arrest can induce hyperkalaemia due to cell lysis and final depolarisation. Better understanding the physiopathology of potassium levels during accidental hypothermia could be critically important to better select patients who could benefit from aggressive resuscitation therapy such as extracorporeal cardiopulmonary resuscitation.

Introduction

Primary accidental hypothermia accounts for almost 1500 deaths per year in the United States [1]. Cardiac arrest (CA) can occur at body temperatures under 30 °C [2]. It is generally associated with better outcome as compared with asphyxia or trauma-related CA [3].

Distinguishing hypothermia-related CA from non-hypothermic CA is challenging. A potassium cut-off at 8 mmol/L for patients in accidental hypothermia is used in the decision-making process on whether or not to start extracorporeal life support (ECLS) rewarming [2,4]. Hyperkalaemia is an indicator of hypoxic cell death [5] and an increase of 2 mmol/h following exitus has been reported [6]. Other reasons to withhold ECLS in these patients are death by hypoxia with an non-patent airway, a burial time less than 60 min, a body temperature over 30 °C or lethal injuries [7,8]. Elevated arterial lactate concentration, low pH level and coagulation disorder have also been described as prognostic factors in accidental hypothermia but no specific threshold were validated for ECLS rewarming indication [9,10]. The current guidelines are referring the serum potassium concentration as the only valid prognostic biomarker for decision-making in ECLS-rewarming [2].

While the potassium level in accidental hypothermia is generally expected to increase, hypokalaemia is a frequent complication of therapeutic hypothermia [11–13] and clinical studies have shown a decrease in the potassium rate as the patient becomes hypothermic [14,15]. Experimental studies have also proven

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hypokalaemia upon the induction of hypothermia, concluding that the absence of trauma and ischaemia in pure hypothermia instead produces a decrease in measured serum potassium [16,17].

In contrast to this observation, there are some findings of cold exposure presenting hyperkalaemia despite the absence of causes other than hypothermia [18].

In a recent study by Cohen et al, a lower threshold of 4.35 mmol/L serum potassium was associated with 100% specificity to predict brain anoxia on brain CT scan in hypothermic cardiac arrest [19]. These results suggest a relationship between any elevation of potassium level and cellular lesion in the specific context of deep accidental hypothermia.

We aimed to systematically review the pathophysiological implications of hypothermia and its impact on blood potassium levels and thereby facilitate clinical interpretation for triage toward ECLS rewarming in hypothermia-related CA.

Methods

Identification and protocol

A systematic review of the literature was conducted following the PRISMA Guidelines for systematic reviews [20].

Eligibility criteria

The Medline electronic database was searched on 28.12.2016 via PubMed for articles published from January 1970 to December 2016. No restrictions for the study type were imposed and all types of studies were considered. Only articles in English, French or German were selected.

Information sources and search strategy

The MEDLINE search strategy was developed by a member of the project team (SB). The search concepts included hypothermia and potassium; the detailed search strategy is available in Appendix A. No type of document restriction was applied and no methodology filters were used. Additional hand searching for relevant studies was performed.

Study records (selection process, data collection process) and data items

During the selection process, two review authors (SB and GD) independently screened citation titles and abstracts, where available, yielded by the literature search against pre-specified eligibility criteria. The screening process assessed whether the citation: (1) reported data from an original research study (i.e. cohort study or randomised controlled trial) and (2) focused on hypothermia and potassium disorders using any of the following three main criteria: (i) influence of hypothermia on the potassium rate, (ii) alteration of blood potassium and (iii) no interfering factors, e.g. medication. If all three main criteria were met, the study was considered valid.

The two review authors rated each citation using a “relevant”, “irrelevant” or “unsure” designation. Only full-text articles that received a “relevant” or “unsure” classification from at least one of the two review authors were retrieved for citations.

The two review authors independently assessed full-text articles and decided if they met pre-specified eligibility criteria. Disagreements were resolved by discussion between the two review authors. The reasons for excluding study records were recorded (see Fig. 1).

Table 1
ILCOR[a] C2010 Levels of Evidence for Prognostic Studies.

LOE P1	Inception (prospective) cohort studies (or meta-analyses of inception cohort studies), or validation of Clinical Decision Rules (CDRs)
LOE P2	Follow-up of untreated control groups in RCTs (or meta-analyses of follow-up studies), or derivation of CDRs, or rules validated on a split-sample only
LOE P3	Retrospective cohort studies
LOE P4	Case series
LOE P5	Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models, etc.)

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Risk of bias (quality) assessment

Eligible studies were reviewed in detail by a review author (SB) and classified by level of evidence (LOE) and methodological quality as defined by the ILCOR [21,22] Guidelines (Table 1). The results are summarised in Table 2.

Data synthesis

Our primary outcome was the consequences of hypothermia on the potassium rate. All cases of hypothermic patients were compared according to appearance of a decrease or increase in serum potassium. No difference was made between accidental hypothermia or therapeutic hypothermia. In the second step, the different pathophysiological theories were extracted from the discussions and visualised in a diagram as well as a text format.

Results

Study selection

The search strategy allowed 115 studies to be assessed for eligibility (Fig. 1). An additional eight studies were identified by checking the references of located, relevant papers and searching for studies that had cited these papers. Finally, 50 studies met the inclusion criteria and were included in the systematic review (see Fig. 1. PRISMA flow diagram).

Study characteristics

The different types of studies selected for the review are presented in Table 3. The results are summarised in Table 4 providing an overview of the relations between the different factors and linking them to an increase or decrease of potassium level.

Synthesis of results in favour of hypokalaemia

Overall, 39 (78%) articles found a decrease in potassium levels upon the onset of hypothermia. Five different pathophysiological theories were extracted from the discussions, and are summarised below.

Temperature-induced reduction of physiological processes, i.e. metabolism and brain function

Low-temperature-induced reduction of brain function [23] and metabolism have a protective effect on ischemic processes enabling the human body to resist ischaemia [24,25]. Filseth et al showed an almost linear decrease of oxygen consumption with decreasing core body temperatures [26].

There is also evidence of an uncoupling of oxygen supply and oxygen demand in hypothermic ischaemic rats [27]. During