Point-of-care laboratory analyses of intraosseous, arterial and central venous samples during experimental cardiopulmonary resuscitation

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Abstract

Introduction
Screening and correcting reversible causes of cardiac arrest (CA) are an essential part of cardiopulmonary resuscitation (CPR). Point-of-care (POC) laboratory analyses are used for screening pre-arrest pathologies, such as electrolyte disorders and acid-base balance disturbances. The aims of this study were to compare the intraosseous (IO), arterial and central venous POC values during CA and CPR and to see how the CPR values reflect the pre-arrest state.

Methods
We performed an experimental study on 23 anaesthetised pigs. After induction of ventricular fibrillation (VF), we obtained POC samples from the IO space, artery and central vein simultaneously at three consecutive time points. We observed the development of the values during CA and CPR and compared the CPR values to the pre-arrest values.

Results
The IO, arterial and venous values changed differently from one another during the course of CA and CPR. Base excess and pH decreased in the venous and IO samples during untreated VF, but in the arterial samples, this only occurred after the onset of CPR. The IO, arterial and venous potassium values were higher during CPR compared to the pre-arrest arterial values (mean elevations 4.4 mmol/l (SD 0.72), 3.3 mmol/l (0.78) and 2.8 mmol/l (0.94), respectively).

Conclusions
A dynamic change occurs in the common laboratory values during CA and CPR. POC analyses of lactate, pH, sodium and calcium within IO samples are not different from analyses of arterial or venous blood. Potassium values in IO, arterial and venous samples during CPR are higher than the pre-arrest arterial values.

Institutional protocol numbers
The Finnish National Animal Experiment Board (ESAVI/1077/04.10.07/2016).

Keywords
Introduction

During cardiopulmonary resuscitation (CPR), screening and correcting reversible causes of cardiac arrest (CA) are an essential part of the advanced life support algorithm [1]. Information about a patient’s history and events prior to CA is crucial, but supplementary information about the pre-arrest pathologies, such as electrolyte disorders, acid-base balance disturbances or bleeding, could be easily and rapidly gathered with point-of-care (POC) laboratory analyses. The European Resuscitation Council (ERC) Guidelines for Resuscitation 2015 state that electrolyte and metabolic disorders should be screened with biochemical tests during CPR, even though the results might be difficult to interpret [1].

The circulatory conditions change drastically during CA and CPR compared to the pre-arrest state, and it is currently unclear how the blood samples taken during CPR reflect the pre-arrest situation. Additionally, blood samples taken from different sources (artery, vein) have different acid-base balance and blood gas values during different phases of CA and CPR [2–4]. Thus, it has been suggested that central venous blood could provide a better estimation than arterial blood of the tissue acid-base state during CA [5]. Indeed, tissue acidosis is not detectable in the peripheral blood until at least some perfusion is re-established through CPR [3].

Intraosseous (IO) access is used as an optional vascular route for critically ill patients, especially in the pre-hospital setting, but based on current knowledge, only for administering medication and fluids [6–8]. The use of an IO blood sample for intra-arrest POC testing has appeal, given the problems with obtaining arterial or venous samples from unstable patients in difficult environments. POC analyses of IO samples have proven to be feasible in several studies, but it is still unclear whether the IO values agree with arterial and venous values, especially during resuscitation and in low-flow states [9–16]. Until now, only one study evaluating the analysis of IO samples during human CPR has been published [9]. The observational prospective study compared venous and IO POC samples from 17 patients during CPR in emergency department (ED). Acceptable agreement was described between IO...
and venous results for pH, bicarbonate, sodium and base excess, but the small amount of observations limits the confidence. High mortality (7 in ED and 13 during hospital stay) and missing information about the initial rhythms or the delay from the onset of CA to the POC sampling impair the applicability of the results.

Accordingly, we designed an experimental study to observe and compare the changes in IO, arterial and central venous POC values of blood gases, acid-base balance, lactate, glucose, electrolytes and haemoglobin during experimental CPR. We hypothesised that blood samples from the IO route would not differ from arterial and venous samples in estimating electrolyte and acid-base values during CPR. Additionally, we compared IO, arterial and venous samples taken during CPR to the pre-arrest arterial values to see which one of them best reflects the pre-arrest state.

Methods

This experimental animal study was conducted in the Research and Development Unit of Helsinki University Hospital, Helsinki, Finland between March and June 2016.

The Finnish National Animal Experiment Board (ESAVI/1077/04.10.07/2016) and the hospital board (HUS/215/2016, §7 30.3.2016) approved the study plan. The study adhered to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

Preparation and monitoring

We included 23 healthy landrace pigs of both genders weighing 26 – 38 kg. Prior to the procedural day, the animals had free access to food and water. The animals were pre-medicated with a mixture of ketamine (600 mg), atropine (1 mg), and medetomidine (2 mg), which was injected intramuscularly 30 minutes before the procedure. We cannulated a peripheral vein in the ear and started an infusion of Ringer’s acetate (Ringer-Acetate Baxter Medical, Kista, Sweden). We induced anaesthesia with intravenous propofol (20–100 mg) and fentanyl (100–200μg) and intubated (endotracheal tube size 6.0) and mechanically ventilated (Servo Ventilator 900C, Siemens-Elema, Solna, Sweden) the pigs with 21% oxygen (O₂) before inducing cardiac arrest. Ventilation was regulated, with a target end-tidal carbon dioxide
(etCO₂) level of 5% (5.1 kPa). The arterial oxygen saturation (SpO₂) was monitored with a pulse oximeter attached to the pig’s tail. Anaesthesia was maintained with propofol infusion (20 mg/ml, 5 – 25 ml/h). An oesophageal temperature probe was inserted, and an external radiant heater and a warming mattress were used to maintain a normal body temperature (38–39 °C). The haemodynamic and respiratory variables were monitored with a Datex-Ohmeda AS/3 monitor (GE Healthcare, Helsinki, Finland).

We surgically prepared the femoral artery and cannulated it with a vascular sheath (Arrow, size 7 Fr, length 15 cm) to take arterial blood samples and measure invasive blood pressure. We cannulated the internal jugular vein using Seldinger’s technique and inserted an introducer catheter (Arrow, size 7 Fr) for venous blood sampling, medication and pacemaker catheter insertion. A temporary balloon-tipped pacing wire was inserted into the right ventricular wall, and the correct placement was confirmed by initiating pacing with a Medtronic 5348 Single Chamber Temporary Pacemaker (Medtronic Inc., Minneapolis, MN, USA).

**Experimental procedures**

We induced ventricular fibrillation (VF) by delivering a 4 V electrical current to the pacing wire. The sedation was ceased a few minutes before inducing CA. After seven minutes of untreated VF, we started CPR with mechanical chest compressions (LUCAS™ Chest Compression System, Lund, Sweden) with a frequency of 100 compressions / min and manual bag valve ventilation (Laerdal Silicone Resuscitator, Norway) with a frequency of 10 ventilations / min. The pigs were randomised using sealed envelopes to be ventilated either with approximately 50% or 100% inspired oxygen for another study protocol, which compared the effect of a 50% or 100% inspired oxygen fraction (FiO₂) during CPR on brain oxygenation and post-CA mitochondrial function [17]. The FiO₂ was titrated with continuous monitoring of inspiratory oxygen using a D-lite gas sampler and flow sensor (GE Healthcare, IL, USA) attached between the endotracheal tube and the ventilation bag, and the oxygen flow (2 –15 l/min) was adjusted accordingly to reach the desired FiO₂ level. After six minutes of CPR, we performed defibrillation with a Zoll M-series defibrillator (ZOLL Medical Corporation, Chelmsford, MA, USA). If sinus rhythm was not achieved, we administered a 1-mg bolus of adrenaline
intravenously and continued CPR. We continued resuscitation with defibrillations (if still in a shockable rhythm) and boluses of adrenaline every two minutes until the return of spontaneous circulation (ROSC) or for at least 20 minutes (i.e. 27 minutes from cardiac arrest). ROSC was defined as the sustained restoration of an organised cardiac rhythm with a mean arterial pressure (MAP) of more than 50 mmHg. If the animal had a clear transient pulsating rhythm but recurring VF, we performed stacked immediate defibrillations. The MAP target after ROSC was above 70 mmHg with an infusion of noradrenaline (0.04 mg/ml). In the end of the experiment, we euthanised the pigs with a lethal dose of potassium chloride (40 mmol).

**Blood samples**

We took POC samples from the femoral artery, central vein and IO space simultaneously at four consecutive time points: before inducing VF (T0), after five minutes of untreated VF (T1), 5 minutes after initiation of CPR (T2) and 10 minutes after ROSC (T3) (Fig 1.). To take a blood sample from the IO space, we inserted a 15G 25-mm needle into the proximal tibia using an EZ-IO® device (Teleflex® Inc., PA, USA). We inserted a new needle for each sample because, due to clotting, it was impossible to draw repeated blood samples using the same needle, and we did not want to flush the needle and risk contaminating the samples with saline. We drew the initial 0.5–2 ml of blood from the IO space by using a 3-ml dry heparin (70 IU) blood gas syringe (RAPIDLyte®, Siemens Healthcare Diagnostics GmbH®, Erlangen, Germany) without discarding any waste blood. We analysed all samples immediately using an i-STAT® handheld point-of-care device (Abbott Point of Care Inc., Princeton, NJ, USA) with CG4+ and CG8+ cartridges. We analysed the following parameters, which we consider to be the values of interest in critically ill patients and during CA: partial pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂), base excess (BE), standard bicarbonate (HCO₃⁻), pH, lactate, sodium (Na), potassium (K), ionised calcium (iCa), glucose and haemoglobin (Hb).

**Statistical analysis**

We plotted the laboratory parameters at different time points to demonstrate the development of the values during the course of CA and CPR. The data are presented as the means with 95% confidence intervals (Fig. 2 and 3).
To assess how the blood samples taken during resuscitation reflect the pre-arrest state, we calculated the individual differences in the laboratory parameters between the resuscitation samples (IO, artery and vein) and arterial baseline samples (golden standard representing the pre-arrest state) (Fig. 4 and 5).

We drew the figures with GraphPad Prism version 7.0c (GraphPad Software, Inc., California, USA).

Results

VF induction was successful in 23 pigs, and 16 of them reached ROSC. During the data analysis, we decided to exclude baseline (T0) IO results from 8 pigs and the VF (T1), resuscitation (T2) and ROSC (T3) IO results from 11 pigs because of missing information regarding the IO sampling side (left vs. right leg). We determined that it was possible that if the IO samples were taken from the same leg where we had inserted the femoral artery catheter, the partial obstruction of arterial blood flow in the main artery of the limb could have distorted the IO results. To evaluate the possible bias, we performed a sensitivity analysis with the complete set of samples (i.e. including the previously excluded IO-results). This new analysis showed no major difference compared to the original analysis. (Suppl. 1).

Change in IO, arterial and venous values during the course of CA and CPR

The blood gas, acid-base balance, lactate, glucose, electrolytes and haemoglobin values during CA and CPR are shown in Figures 2 and 3. Lactate levels increased in the IO samples during VF. Such a change was not evident in the arterial and venous samples, in which the increase occurred only during CPR. Decreases in pH and BE were evident in the IO and venous samples during VF, but they only occurred within the arterial samples after the initiation of CPR. Potassium levels were higher and sodium levels were lower in the IO samples compared to those in venous and arterial samples at all studied time points. Elevated glucose levels during CPR were seen in the arterial and venous samples but not in the IO samples. The IO values of pO₂ and pCO₂ closely followed the venous values.
Comparison of IO, arterial and venous values during CPR with the pre-arrest arterial values

The changes in the studied parameters are shown in Figures 4 and 5. The electrolyte and acid-base values from all sampling sites during CPR differed markedly from the pre-arrest values. Most changes followed the expected physiological pattern. Potassium values from all sampling sites during CPR were clearly higher than those before VF. Glucose values were elevated in the venous and arterial samples, whereas in the IO samples they resembled the pre-arrest state. In contrast to the arterial and venous values, the IO values of BE and HCO$_3$ represented the pre-arrest state. POC analyses of haemoglobin revealed a large variance in the results, but there was no significant difference between the sampling sites.

Discussion

Our data show that during experimental CPR, POC analyses from IO access may act as a reasonable substitute for arterial and venous samples for quantifying lactate, pH, sodium and calcium levels. Interestingly, the IO levels of oxygen and carbon dioxide closely resembled the venous levels but were, as expected, very different from those in the arterial samples. However, the IO values of potassium and glucose appeared to differ from the arterial and venous levels. If our results are replicated in patients, they may suggest a limited but important role for the use of POC analysis for IO samples during clinical CPR.

The reliability of POC analysis of IO blood samples has become a relevant issue because of the wider implementation of IO devices and POC diagnostics in pre-hospital and emergency care. Our study is the first to compare IO samples with simultaneous arterial and venous samples during different stages of resuscitation. Previous studies have compared IO samples to venous samples in experimental resuscitation models [13–15, 18]. In our own previous study, the agreement of IO, arterial and venous blood samples was studied in 31 healthy volunteers [16]. Recently, Tallman et al. reported a prospective human study in which POC IO blood samples were compared with venous samples of 17 patients arriving to the hospital in CA and being resuscitated [9].
According to the ERC Resuscitation Guidelines 2015, the potential causes or aggravating factors that a specific treatment addresses must be considered during CA [1]. These include electrolyte disorders, acidosis and other metabolic disorders, which can be detected by biochemical tests or suggested by the patient’s medical history. The guidelines state that during CA, arterial blood gas values may be misleading and are unrelated to the tissue acid-base state; hence, analysis of central venous blood might provide a better estimation of tissue pH [1]. Accordingly, the degree of detected acidaemia is dependent on the timing of the blood sample, the degree of tissue acidosis and the effectiveness of wash-out with CPR [19]. Interestingly, our study shows the previously identified phenomenon of the paradoxical elevation of BE and pH in arterial samples during VF [2–4]. Because acidosis shifts potassium from the intracellular space, the effects of changes in serum pH must be considered in the evaluation of potassium levels [20]. According to the guidelines, there is little or no evidence supporting the treatment of electrolyte abnormalities during CA [20]. Our study shows that potassium values during CPR from different sampling sites are, on average, 2.8 – 4.4 mmol/l higher than those before cardiac arrest. This indicates that hyperkalaemia during CPR does not necessarily refer to elevated potassium levels before CA, which renders the diagnosis of pre-arrest hyperkalaemia as a cause of the CA particularly difficult. Since the current resuscitation guidelines recommend considering buffer therapy during CPR only in cases of hyperkalaemia and tricyclic overdose, the implications for POC blood analyses during resuscitation should be re-evaluated.

An interesting issue is the prognostic value of certain laboratory parameters and whether they can provide some supporting information for decision-making during CPR. Spindelboeck et al. prospectively studied the arterio-alveolar CO₂ difference (AaDCO₂) in 115 patients being resuscitated from out-of-hospital CA (OHCA) and found that lower AaDCO₂ values predicted survival until hospital admission [21]. In this study, we did not compare the POC values between the animals not reaching ROSC and those that did due to the small sample size.

This study shows that IO, arterial and venous values change differently during CA and CPR. The reasons for the differences are not evident. IO blood can be considered to be like capillary blood and thus, during circulatory arrest represent better the tissue metabolism compared to the stationary blood in arteries and veins. Therefore, the lactate levels increase in arterial and
venous blood only when wash-out of the metabolites with CPR is initiated. Elevated potassium levels in the IO samples can be caused by haemolysis from the aspiration. The variation in haemoglobin levels in IO samples might be explained by the haematopoiesis in the bone marrow.

There is still very little evidence about the use of the IO blood samples during human CA. In clinical practice, if venous or arterial blood samples are unavailable, IO samples can be considered as a substitute, keeping the physiologic differences and limitations in mind. Excluding hyperkalaemia from an IO sample sounds reliable but diagnosing hyperkalaemia as a cause of CA from IO samples has a major risk of false positive diagnosis. Though, based on this study, the same risk exists with arterial and venous samples. However, when estimating the ischemia burden during CA and CPR, IO blood samples might provide better results than arterial or venous blood samples.

This study has a number of strengths. Because it used a standardised experimental resuscitation model, we were able to obtain simultaneous IO, arterial and venous POC samples at precisely defined time points, which makes the comparison of the values reliable. The curves (Fig. 2–3) clearly illustrate the different changes in the analysed values during the course of the CA and CPR, and they show that POC analyses yield different results from the IO, arterial and venous samples. The timeline of the experiment simulates real-life resuscitations, as the timing of the resuscitation blood samples parallels the time when paramedics or emergency doctors in real life would likely open the vascular access and draw blood samples for POC analysis. Nonetheless, some limitations are worth mentioning. First, the pigs were healthy before the electrically induced VF. Severely abnormal pre-arrest laboratory values were not present, which does not represent real-life situations. A second limitation is the small sample size. We excluded several IO-samples because of a potential bias in the results caused by obstruction of the blood flow in the femoral artery. However, sensitivity analysis with a complete set of samples (i.e. including previously excluded samples) showed no significant differences within the results. Statistical proving of the null hypothesis is theoretically impossible with this set of samples; thus, the conclusions are based on comparison of the values and their variance.
Conclusions

We conclude that, as expected, there is a dynamic change in the POC laboratory values during CA and CPR, and arterial, central venous and IO values change differently. The results of POC analyses of IO samples during CPR were similar to those of arterial or venous blood and may thus represent an alternative for the evaluation of lactate, pH, sodium and calcium. The potassium values in the venous, arterial and IO POC samples during CPR were higher than the pre-arrest values, leading to a risk of false interpretation of hyperkalaemia as a cause of the CA.

Conflicts of Interest

Markus Skrifvars reports having received research grants from GE Healthcare, travel reimbursements and lecture fees from Orion Pharma, COVIDIEN, Astellas Pharma and Axis-Shield. All other authors report that they have no conflicts of interest. The study was initiated by the investigators. There has been no financial support for this work that has influenced the study design, its outcome or decision to submit the manuscript for publication.

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References


Legends to figures

Figure 1

Timeline of the experiment

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Blood sample at baseline before induction of VF</td>
</tr>
<tr>
<td>T1</td>
<td>Blood sample 5 minutes after induction of VF</td>
</tr>
<tr>
<td>T2</td>
<td>Blood sample 5 minutes after initiation of CPR</td>
</tr>
<tr>
<td>T3</td>
<td>Blood sample 10 minutes after ROSC</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
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<tr>
<td>CPR</td>
<td>Ventilation (FiO₂ 50% or 100%) and chest compressions (100/min) with LUCAS™</td>
</tr>
<tr>
<td>Advanced CPR</td>
<td>Defibrillation every 2 min, adrenalin 1 mg every 2 min until ROSC or at least 20 min</td>
</tr>
<tr>
<td>ROSC</td>
<td>Return of spontaneous circulation</td>
</tr>
</tbody>
</table>
Figures 2

Parameters analysed from arterial, venous and IO samples at four consecutive time points. Data are presented as the means with 95% CI.

BL: Baseline, before induction of VF
VF: Five minutes after induction of VF
RESUSC: Five minutes after initiation of CPR
ROSC: Ten minutes after ROSC
Parameters analysed from arterial, venous and IO samples at four consecutive time points. Data are presented as the means with 95% CI.

- **BL**: Baseline, before induction of VF
- **VF**: Five minutes after induction of VF
- **RESUSC**: Five minutes after initiation of CPR
- **ROSC**: Ten minutes after ROSC
The figures demonstrate how the laboratory values from artery, IO and vein during resuscitation differ from the pre-arrest arterial values. Medians, IQRs and ranges are displayed.

**Legend for Figure 5**

The figures demonstrate how the laboratory values from artery, IO and vein during resuscitation differ from the pre-arrest arterial values. Medians, IQRs and ranges are displayed.
ART  Difference RESUSC ARTERY minus BASELINE ARTERY
VEIN  Difference RESUSC VEIN minus BASELINE ARTERY
IO   Difference RESUSC IO minus BASELINE ARTERY