No change in plasma potassium concentration during 10 minutes of apnoea: An observational study on potential organ donors

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Background: Acute acidosis can increase the plasma potassium concentration. However, data on the effects of acute respiratory acidosis on plasma potassium concentration are conflicting. This study aimed to determine whether acute respiratory acidosis induces an immediate increase in plasma potassium concentration.

Methods: This observational study was conducted on participants undergoing apnoea testing prior to final radiological examination, registered in an internal quality registry at Oslo University Hospital between 25 April 2013 and 1 May 2020. A total of 124 donors were assessed for inclusion. Sixteen donors with blood glucose concentrations exceeding 10 mmol L\(^{-1}\) were excluded; finally, data from 108 donors were included in the study. The apnoea test, which is a standard neurological test performed in potential organ donors prior to radiological confirmation of ceased brain circulation, induces respiratory acidosis. The arterial plasma potassium concentration, pH and PaCO\(_2\) before and after the apnoea test were compared. Statistical analysis was conducted using the paired t test.

Results: The pre-apnoea and post-apnoea mean plasma potassium concentrations were 3.79 (95% confidence intervals [CI] 3.70–3.87) and 3.79 mmol L\(^{-1}\) (95% CI 3.70–3.88), respectively. The mean difference was −0.002 mmol L\(^{-1}\) (95% CI −0.04 to 0.04); the difference was not significant. The pre-apnoea and post-apnoea mean pH were 7.39 and 7.21, respectively, and the mean difference was 0.175 (\(P\) < .01). The pre-apnoea and post-apnoea mean PaCO\(_2\) were 5.66 and 9.48 kPa, respectively, and the mean difference was −3.83 (\(P\) < .01).

Conclusions: Acute respiratory acidosis does not lead to rapid changes in plasma potassium concentration during apnoea testing in potential organ donors.
1 | INTRODUCTION

Potassium (K) is crucial for normal cellular function, and changes in K concentration [K] may cause organ failure and even death. Critically ill patients often require drugs and interventions that affect the electrolyte and acid-base homeostasis. Any intervention with a potential effect on [K] must be evaluated and monitored carefully. However, the relationship between [K] and changes in partial pressure of carbon dioxide (PaCO₂) is not fully understood. Transcellular concentration gradients of the primary extracellular cation sodium [Na] and the primary intracellular cation K play a decisive role in the cell membrane potential. The homeostatic mechanisms regulating their respective concentrations are complex (Figures 1 and 2). Acute respiratory acidosis is common and is often interpreted as a direct cause of increased plasma [K]. However, the representation of this phenomenon in the literature is limited and contradictory. Several studies have shown an increase in plasma [K] during acute respiratory acidosis,¹² as opposed to others who have revealed no immediate changes.³⁴

These contradictory findings on the influence of acute acidosis on plasma [K] prompted executing this observational cohort study. The aim of this study was to determine whether acute respiratory acidosis induces changes in plasma [K] during a standard apnoea test in potential organ donors.

2 | METHODS

This was an observational cohort study on all potential organ donors undergoing apnoea testing prior to final radiological examination. All cases were registered in an internal quality registry at Oslo University Hospital between 25 April 2013 and 1 May 2020 (n = 316). Study data were retrieved 5 June 2020. The study protocol was approved by the Committee for Medical Research Ethics, South-East region, Oslo, Norway (REC Number 2017/1557) on 8 March 2018, and the committee granted an exemption from the general rule of informed consent. The apnoea tests were performed as the final part of clinical testing prior to radiologic examination.

Of the 316 brain-dead donors, complete data were available for only 124 donors, whilst for the remaining 192 donors, data necessary for the analyses were missing, and in some cases, the apnoea test had not been performed according to the recommended procedure. In addition, donors with a blood glucose concentration exceeding 10 mmol L⁻¹ were excluded (n = 16) since large variations of insulin and blood glucose concentrations could affect the [K]. Of the 108 donors, 34 were administered insulin for blood glucose regulation and 70 were administered vasopressors.

Data were collected from either paper or electronic patient journal, and all routine blood-gas analyses were performed before and immediately following the apnoea test.

In accordance with the Norwegian law, cerebral arteriography or computed tomography angiography must confirm the cessation of brain circulation before permitting any organ donation. As per the organ donor criteria, all brain function tests must reveal an irreversible loss of brain function. Consequently, in all potential organ donors, a standard neurologic examination was performed, and the absence of any response to either of these tests was confirmed. Any potential depressing effect of drugs, alcohol, neuromuscular blocking agents, endocrine substances or hypothermia on the central nervous system must be excluded whilst evaluating a potential donor. In this particular study, no neurologic response was observed in any potential donor during the clinical testing, and ceased brain circulation was confirmed by the radiological examination.

There are diverse protocols around the world on the determination of brain death.⁵ In Norway, the standard clinical examination includes coma, noxious stimulation to the face and limbs, the pupillary reflex, the corneal reflex, the oculocephalic reflex, the gag reflex, the cough reflex and finally the apnoea test, as defined in the Norwegian national standard operating procedure.⁶ Reduced or abolished brainstem function is associated with vasodilation, and treatment with vasopressors is frequently required. Based on the departmental procedures, the apnoea test is not performed until the potential organ donor reaches a stable circulatory phase, if necessary, by administration of vasopressors.

In our hospital, all potential donors were treated with 100% oxygen for 15 minutes whilst being normoventilated. Blood sample for blood-gas analyses was collected in a plastic syringe containing 80 units of electrolyte-balanced heparin (Radiometer, Åkandevej 21) from a catheter placed in the radial artery. The ventilator was then disconnected, and a catheter with a continuous flow of 6 L min⁻¹ of oxygen was inserted in the endotracheal tube. Ten minutes later, another blood sample was collected, and the donor was reconnected to the ventilator.

The intensive care units had two different blood-gas analysers: ABL 800 (Radiometer, Åkandevej 21) and COBAS b22 (Roche Diagnostics, Industriestrasse 7). The pre-apnoea and post-apnoea blood samples from individual potential donors were analysed using the same instrument, and the arterial pH, PaCO₂ and partial pressure of oxygen (PaO₂) and HCO₃⁻, base excess, Na, K and glucose concentrations were recorded.

2.1 | Statistical analyses

The arterial pH, PaCO₂ and plasma [K] before and immediately following the apnoea test are presented as mean, standard deviation (SD)
and 95% confidence intervals (CI) of the mean (mean ± 2 standard error of mean [SEM]). The pre-apnoea and post-apnoea test measurement values were evaluated for statistical differences using a paired sample t test if normally distributed and Wilcoxon signed-rank test if not. Normality was tested using the Kolmogorov–Smirnov test. All tests were performed using the SPSS version 26 (IBM Corp.). A significance level of 5% was considered statistically significant. The t-value and degrees for freedom (df) are presented. A previously published study reported a plasma [K] of 3.8 (SD = 0.3) mmol L⁻¹ before and 3.5 (SD = 0.3) mmol L⁻¹ after a comparable intervention. Detection of a 0.2 mmol L⁻¹ change requires a sample size of 30 if statistical power of 95% is chosen (α = 0.05, paired sample, two-tailed t test). The strength of the relationship between pH and arterial PaCO₂ was evaluated by the linear regression analysis using SigmaPlot (version 14.0; Systat Software, Inc.).

3 | RESULTS

Finally, data from 108 potential donors were included in the statistical analysis. The mean age of the potential donors was 50 years (range: 2–89).

The pre-apnoea and post-apnoea mean plasma [K] were 3.79 mmol L⁻¹ (95% CI 3.70–3.87) and 3.79 (95% CI 3.70–3.88), respectively (Figure 3). The pre-apnoea and post-apnoea differences were normally distributed; the mean difference was −0.002 mmol L⁻¹ (SD = 0.3), 95% CI −0.04 to 0.04, and the difference was not significant (paired t test, t = −0.098, df = 108).

The pre-apnoea and post-apnoea mean pH were 7.39 (95% CI 7.38–7.40) and 7.21 (95% CI 7.20–7.22), respectively (Figure 3), and the mean difference was 0.175 (SD = 0.05, 95% CI 0.166–0.184) (paired t test, t = 38.38, df = 108, P < .01).

The pre-apnoea and post-apnoea mean PaCO₂ were 5.66 kPa (95% CI 5.50–5.81) and 9.48 kPa (95% CI 9.22–9.74), respectively (Figure 3), and the mean difference was −3.83 (SD = 1.16, 95% CI −4.05 to −3.61) (paired t test, t = 34.36, df = 107, P < .01).

A relationship was evident between a decrease in pH and an increase in PaCO₂, with an R² of 0.755 (adjusted R², 0.754; P < .01).

4 | DISCUSSION

This study demonstrated that plasma [K] does not change with significant variation in PaCO₂ and that respiratory acidosis does not affect K homeostasis. This is in accordance with Natalini² and Weinberg³ who concluded that there was no significant association between acute hypercarbia and plasma [K] in anaesthesia and surgery settings.

However, most previous studies have concluded that respiratory acidosis increases the plasma [K]. According to a review by Adrogué et al., acute respiratory acidosis increases the plasma [K].² Finsterer et al. also concluded that respiratory acidosis increases the plasma [K]¹; however, the study was weighed down by critical limitations. First, the anaesthetic protocols were not standardised for the infused load of 5% glucose, disregarding that variable insulin production would affect the plasma [K]. Second, the use of opioids was not standardised; moreover, stress-related release of catecholamines during surgery is reportedly reduced by opioids.⁷,⁸

K is an intracellular ion that accounts for nearly 98% of the total body K. The transmembrane [K] gradient is critical for the life-giving membrane potential. An extensive number of endocrine and renal mechanisms are involved in K homeostasis, and insulin has a significant effect on the transcellular movement of K.⁹ Insulin stimulates the exchange of Na⁺ and H⁺, causing cellular Na influx (Figure 1A). Na is then extruded by Na/K-ATPase in exchange for K. In addition, catecholamine-mediated β-receptor stimulation induces K influx by increasing the Na/K-ATPase activity (Figure 1B).

Both activation and inhibition of the glucose and insulin release may influence the transcellular K shift. Vasoactive drug administration, pain, stress-related catecholamine response and drugs inhibiting catecholamine response are crucial. The observed increase in the plasma [K] in respiratory acidosis, as claimed by several authors, could be due to these mechanisms and not the respiratory acidosis as such.

Apart from the aldosterone-mediated regulation in the juxtaglomerular cells of the kidneys and the parietal cells of the gastric glands in the fundus of the stomach, there are no K/H⁺ exchangers in the cell membranes of the body.¹⁰ However, apparent K/H⁺ changes may be regulated by additional transport pathways such as Na/H⁺ exchanger, Na/K-ATPase, Cl/HCO₃ exchanger and KCl cotransporter (Figure 2).²,⁴,¹¹–¹⁴ Overall, none of these mechanisms support the possible increase in [K] in respiratory acidosis.

In contrast, two recent trials found no increase in the plasma [K] in respiratory acidosis, and our findings are consistent with these results. In one of the studies, the intervention time was 20 minutes, and the patients were randomised into the intermittent negative-pressure ventilation and spontaneous-assisted ventilation groups.³
The spontaneous-assisted ventilation group showed an increase in PaCO$_2$ to an average of 9.0 kPa, whilst the intermittent negative-pressure ventilation group showed an average PaCO$_2$ of 5.4 kPa. In addition, the anaesthetic protocol was the same for all patients. Pre-operative [K], pH and PaCO$_2$ were compared with those obtained after the induction of general anaesthesia. In the other study, patients under general anaesthesia were observed for 15 minutes with increasing levels of hypercapnia during surgery. Neither of these studies observed any relevant changes in the plasma [K].

Our study showed unchanged plasma [K] during acute respiratory acidosis, but the methodology differs from that of the two studies in some important aspects. The observation time in our study was only 10 minutes as opposed to 15 and 20 minutes of the other studies. The short observation period was decided based on the protocol for organ preservation. The fact that the potential donors included in our study acted as their own controls represents strength, reducing the variance and increasing the statistical power. This is the first observational study on K homeostasis in brain-dead potential organ donors. An obvious strength of our model is the elimination of the central nervous system activity. Normal, or at least some, central nervous system reflexes may influence the transeellular P-K shift. In particular, the lack of brain stem regulation of the ventilatory response is a major advantage. In fact, the only variable in our model with a potential impact on the P-K change was the induction of acute respiratory acidosis during apnoea.

A retrospective study using laparoscopic surgery under general anaesthesia indicated a slight increase in [K] associated with increased PaCO$_2$. Laparoscopic surgery is a well-described model of carbon dioxide absorption and subsequent hypercapnia during anaesthesia. Carbon dioxide diffuses freely across cell membranes. Whether it originates inside the cells or is introduced during laparoscopy, the cells become acidic due to the increased CO$_2$. The median duration of surgery was 184 minutes, and blood samples were collected before induction of anaesthesia and within 15 minutes of surgery completion. The PaCO$_2$ and [K] were compared, and it was concluded that for a 1.33-kPa increment of PaCO$_2$, the [K] increased by 0.18 mmol L$^{-1}$. The observation period was longer than in our study, and there were several factors which could possibly explain the increasing [K]; the respiratory acidosis could influence the hormonal mechanisms or K feedback mechanisms. Acute acidosis could increase the K reabsorption from the renal distal tubuli.

We found a strong correlation between the decrease in pH and increase in CO$_2$ ($R^2$, 0.755). This suggests the acute acidosis to be
of respiratory nature and that metabolic factors are unlikely. Blood glucose concentration variations necessitating insulin infusion in the period before or during the apnoea test could interfere with the plasma [K]. To minimise the potential influence of glucose/insulin on the analyses, we excluded donors with blood glucose concentration >10 mmol L⁻¹. However, most potential donors in the registry received steady infusions of insulin and potassium. Furthermore, in our model with nonexistent brainstem regulation, the transmembrane K shifts were not influenced by the endogenous catecholamine response. Our study indicates that permissive hypercapnia can be tolerated without inducing high plasma [K] and that acute respiratory acidosis does not influence plasma [K].

The short observation period determined by the protocol for organ preservation is a limitation of this study, and a longer observation period would be an interesting goal in further studies. These findings are applicable in the managements of patients with respiratory failure and high [K]. Acute hypercapnia of short duration is probably safe with a minimal effect on plasma [K]. Thus, our observations may have implications in clinical practice and the choice for ventilatory strategies.

5 | CONCLUSIONS

Acute respiratory acidosis does not lead to rapid changes in plasma [K] during apnoea testing in potential organ donors.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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