Hypophosphatemia after Cardiopulmonary Bypass - Incidence and Clinical Significance,

from a single centre in South Africa

Laurence Edward Grobbelaar

M.Med(Anes): Research Report

University of the Free State

Department Anaesthesiology

Student Number: 2005012956

Submission: July 2018

Study leaders: Prof G Joubert[1] and Prof BJS Diedericks[2]

1. Department of Biostatistics, Faculty of Health Sciences, University of Free State, Bloemfontein, South Africa
2. Department of Anaesthesiology, Faculty of Health Sciences, University of Free State, Bloemfontein, South Africa.

Table of Contents

Declaration of Own Work

I, Laurence Edward Grobbelaar, hereby declare that the information presented here is factual. This research is of my own effort with collaboration of my study leaders, Professor BJS Diedericks and Professor G Joubert. All additional information has been sited accordingly in the references section. This research will form part of my Master of Medicine degree in Anaesthesiology at the University of the Free State. Student number: 2005012956.

Signed: _____

L.E. Grobbelaar

Acknowledgements and Dedication

I would like to dedicate my research to my family whom supported me through the many years of studies that enabled me to deliver this research document.

I want to acknowledge the following people who provided assistance or guidance with this research project.

Moderators:

- Prof BJS Diedericks (Former Head of the Department of Anaesthesiology at the University of the Free State)
- Prof G Joubert (Head of the Department of Biostatistics at the University of the Free State)

Assistance with the study:

- Department Cardiothoracic Surgery for the opportunity to conduct research on their patient population
- The Anaesthesiologists and Perfusion Technologists at the Universitas Hospital whom assisted with data collection
- The Ward and Intensive Care Unit staff that assisted with the sample collection
- University of the Free State Ethics Committee and the Free State Department of Health which permitted for this research to be conducted

Abbreviations

CI	-	Confidence Interval
FFP	-	Fresh Frozen Plasma
g/l	-	Gram per Litre
ICU	-	Intensive Care Unit
IQR	-	Interquartile range
mg/L	-	Milligram per litre
ml	-	Millilitre
$mmol.l^{-1}$	-	Millimole per litre
Post-op	-	Post-operatively
SD	-	Standard deviation

Tables

Protocol (Chapter 1):

Article (Chapter 2):

Figures

Article (Chapter 2)

Chapter 1 - Protocol

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective

"Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective"

Pneumonic**:** **PO**$_4$ after **C**ardiopulmonary Bypass, **I**ncidence and Clinical **S**ignificance

POCIS

Researchers:

L.E. Grobbelaar, Department of Anaesthesiology at the University of Free State,

B.J.S. Diedericks, Department of Anaesthesiology at University of the Free State,

G. Joubert, Department of Biostatistics at University of the Free State.

Introduction

Information Available on the Subject

A Brief Overview of Phosphate Physiological Role

Phosphate is an important electrolyte involved in numerous critical physiological functions.

Energy Metabolism:

> Phosphate is central in energy metabolism. It is found in adenosine triphosphate and creatinine phosphate and therefore severe hypophosphatemia will result in energy depletion.[1]
>
> Phosphate also plays a central role in oxygen delivery as it is present in 2, 3 di-phosphoglycerate which is one of the factors that regulates haemoglobins affinity for oxygen.[1, 2]

Second Messenger:

> In the secondary messenger system, phosphate plays a critical role as cyclic adenosine monophosphate (cAMP) and phosphoinositide's.[1] It is also involved in the regulation of enzyme function where de-phosphorylation or phosphorylation can activate or deactivate different enzymes.

Structural:

> Phosphate is also structurally incorporated into the skeletal system (Hydroxyapatite)[2], cell membranes (phospholipids)[2] and nucleic acids.[1]

Renal:

Phosphate also acts as a urinary buffer where it binds with free hydrogen ions. Hydrogen ions is a product of cellular metabolism or it can be generated when new bicarbonate ions are formed

($H_2O + CO_2 \leftrightarrow H_2CO_2 \leftrightarrow H^+ + HCO_3^-$).[2]

The physiological control of phosphate consists of the interaction between absorption in the small bowl, mobilization from skeletal system, urinary excretion and the various factors that control these functions.

Absorption of phosphate takes place in the duodenum and jejunum, influenced by plasma concentration of activated Vitamin D (1,25 dihydroxycholecalciferol).

Regarding excretion: The unbound phosphate fraction, in the plasma, is freely filtered at the glomeruli and reabsorbed, via secondary active transport, in the proximal tubule.

The parathyroid hormone regulates the phosphate reabsorption. In cases of volume overload, with high glomerular filtration rate, the phosphate reabsorption fraction decreases[1].

Intracellular shifts of phosphate take place with a glucose or insulin load that result in the intracellular phosphorylation of glucose[1].

Normal Physiological Values

From the above it is clear why phosphate is considered an essential micronutrient. Phosphate levels are tightly controlled to maintain a total body phosphate of 500 – 800 g (or 16.1 - 25.8 mol). Most of the phosphate (85% - 90%)[1] is usually in the form of calcium phosphate (hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$) in the skeletal system. 10% -15% of the total body phosphate is found intra-cellular and < 1%[1, 3] is present in the plasma with a concentration of 12 mg/dl (3.876 mmol/l). 45% of the phosphate in the plasma is in the organic form, bound to proteins and lipids (12%) or as a complex ion (33%). The remaining (55%) is in the inorganic form (H_2PO4^-, HPO_4^{-2} and PO_4^{-3}). Normal serum phosphate range varies according to the reference used. For example: Barash states the normal range is 0.87 to 1.45 mmol/l (2.7 – 4.5mg/dl)[1], whereas Ganong states it as 0.78 - 1.45 mmol/l (2.5 - 4.5 mg/dl)[2] or 0.78 – 1.32 mmol/l (2.4 to 4.1 mg/dl) according to Millers Anesthesia 7th Edition [4].

Hypophosphatemia – Clinical Implications

The clinical implication of hypophosphatemia has been known to the intensive care environment for numerous years, especially in refeeding syndrome. The definitions of hypophosphatemia that will be used in this study are as follow:

Hypophosphatemia, as determined by the serum inorganic phosphate level, is classified as mild (0.8 - 0.66 mmol/l)[5], moderate (0.48 - 0.66 mmol/l)[1, 6] and severe(< 0.48 mmol/l).[1, 6]

The effects of severe hypophosphatemia include:[6]

Cardiovascular System:

- Decreased myocardial contractility
- Acute cardiac failure*

Neurological:[1]

- Paraesthesia
- Encephalopathy
- Delirium
- Seizures
- Coma

Haematological:[1, 6]

- Right shift of oxygen-haemoglobin dissociation curve (depletion of 2,3 di-phosphoglycerate)
- Haemolysis
- Impaired leucocyte function – impaired immune function
- Platelet dysfunction

Musculoskeletal

- Myopathy
- Muscle weakness
- Rhabdomyolysis
- Respiratory muscle failure*
- Skeletal demineralisation

Metabolic

- Metabolic acidosis
- Hepatic dysfunction
- Glucose intolerance

* Most important post-operative complications

Causes for hypophosphatemia post-operatively:

1. Intracellular shift of inorganic phosphate
    a. The use of extra corporal circuits is associated with an inflammatory response, with subsequent release of acute-phase proteins, namely interleukin 1B, 6, 8 and Tumour necrosis factor α amongst other pro-inflammatory cytokines. These cytokines are associated with hypophosphatemia.[7, 8, 9]
    b. A carbohydrate load intra-operatively can cause an inward shift of phosphate.[10] This is the mechanism seen in refeeding syndrome where there is an intracellular shift of phosphate mediated by insulin. Adrenaline and lactate can also cause an intracellular shift of phosphate by the same mechanism.
    c. When there is a change from a catabolic state to an anabolic state, there will be an inward shift of phosphate. This may explain the delayed presentation of hypophosphatemia seen in some studies.[10]
    d. Acute alkalemia - respiratory alkalosis, increases the rate of glycolysis and therefore the rate of intracellular phosphate consumption.
    e. Hyperventilation also causes an inward shift with a prolonged effect, even after hyperventilation has been ceased.

2. Increased losses of phosphate
    a. Renal
        i. Hypothermia – cooling on cardiopulmonary bypass
        ii. Hypomagnesemia
        iii. Diuretics – If mannitol is added to pump priming fluid
        iv. Renal tubular defects – Renal phosphate wasting (transient isolated hyperphosphaturia).[11]
        v. Pre-existing Hyperparathyroidism (
    b. Extra-renal
        i. Gastro intestinal losses – vomiting, nasogastric tube suctioning, chronic use of phosphate binding anti-acids
        ii. Fluid replacement with minimal phosphate[10]

3. Delayed in initiation of post-operative enteral feeding and the use of total parenteral nutrition post-operatively.[7]

Current understanding of the Incidence of Hypophosphatemia

A summary of previous research which has been completed on the incidence of hypophosphatemia is provided in Table 1.

Table 1. Summary of Various Data on the Incidence of Hypophosphatemia

Author	Year	Population/ Disease	Number of patients	Definition of hypophosphatemia	Incidence
Surgical Intensive Care Unit Patients					
Goldstein *et al*. [10]	1985	Thoracic Surgery -	34	< 0.80 mmol/L	56%
		Cardiac Surgery	40	< 0.80 mmol/L	50%
Zazzo *et al*. [12]	1995	Surgical Intensive Care Unit	208	< 0.80 mmol/L	28.8%
				< 0.50 mmol/L	17.3%
				≤ 0.20 mmol/L	2.4%
Buell *et al*. [13]	1998	Hepatic Surgery	35	< 0.80 mmol/L	67%
Cohen *et al*. [7]	2004	Cardiac Surgery	566	< 0.48 mmol/L	34.3%
Salem et al. [11]	2005	Hepatic Surgery	20	< 0.70 mmol/L	100%
Medical Intensive Care Unit Patients					
Daily *et al*. [14]	1990	Trauma Patients	12	< 0.80 mmol/L	75%
				< 0.50 mmol/L	56%
Kruse *et al.* [15]	1992	General Intensive Care Unit Patients	418	< 0.80 mmol/L	28%

Adapted from "*Treatment of Hypophosphatemia in the Intensive Care Unit*", a review by DA Geerse *et al*. published in *Critical Care* 2010.[16]

One of the first observational studies describing hypophosphatemia after cardiothoracic surgery, by Goldstein *et al*. (1985), reported an incidence of 56% (19 of 34 patients) after thoracic surgery and 50% (20 of 40 patients) after cardiac surgery.[10]

This study also demonstrated that patients that were transfused intra-operatively had decreased or delayed presentation of hypophosphatemia due to the citrate-phosphate-dextrose solution in the red cell concentrate.

The largest observational study done regarding hypophosphatemia in cardiac surgery patients was performed by Cohen *et al*. (2004) [7]. It demonstrated that 34.3% (194 of 566) of their patients had hypophosphatemia following open cardiac surgery. The value used as significant hypophosphatemia was a value of < 0.48 mmol/L. They also demonstrated an association between the volume of blood products given and the serum phosphate level post-operatively. Patients with a high transfusion requirement had a higher incidence of post-operative hypophosphatemia. The type of anticoagulant

(for example: citrate-phosphate-dextrose) used in the storage of these blood products were however not described.

In the same study there was a clear association between hypophosphatemia and duration of post-operative mechanical ventilation (2.1 ± 1.7 versus 1.1 ± 0.9 days, P = 0,05); duration of post-operative (12 - 24 hours) cardio active drugs requirements versus (16% versus 10.9%, P = 0,05); and > 24 hours post-operative (23.5% versus 13.8%, P = 0,05); and a prolonged hospital stay (7.8 ± 3.4 days versus 5.6 ± 2.5 days, P = 0,05).

In a study done by Geerse *et al.* (2012)[17], in the Netherlands various Intensivists, from 67 ICUs, were asked what the causes for hypophosphatemia in the ICU patient were. The major risk factors were indicated as major surgery and cardio pulmonary bypass. [17]

Hypophosphatemia has been demonstrated in surgey other than cardiac surgery. It has been described in patients following major hepatic surgery, with an incidence of 67% (21 of 35 patients.[13] Buell *et al*. (1998) identified the use of anti-acids as one of the major risk factors for post-operative hypophosphatemia. They did not find any correlation between transfusion requirement and post-operative serum phosphate values.[13]

Hypophosphatemia after hepatic resection has been identified as a common phenomenon. Salem *et al*. (2005) described an average decrease in serum phosphate level of 47% in the 20 patients they studied. All patients developed hypophosphatemia post-operatively. The hypophosphatemia was attributed to a post-operative transient hyper-phosphaturia.[11]

A observational study done by Švagždienė *et al*. (2006) in Lithuania on 82 patients that underwent elective coronary artery bypass grafting, demonstrated a decrease in serum phosphate levels[18], but to a much smaller degree than the study done by Cohen *et al*. (2004).[7] Švagždienė *et al*. (2006) demonstrated that their patients' serum phosphate levels decreased post-operatively but was still within normal limits. In the 2 groups which they studied; (Group 1: patients whom developed atrial fibrillation post-operatively and Group 2: patients who did not develop atrial fibrillation post-operatively), the post-operative serum phosphate decreased to 0.98 mmol/L ± 0.15 mmol/L and 1.09 mmol/L ± 0.19 mmol/L, respectively.

Zazzo *et al*. (1995) studied 208 patients whom were admitted to the surgical ICU post-operatively and described an incidence of 60/208 (28.8%) of hypophosphatemia.[12] Of the 60 patients who had hypophosphatemia, 36 (60.0%) had mild hypophosphatemia (0.51 - 0.79 mmol/l), 19 (31.7%) had moderate hypophosphatemia (0.21 - 0.5 mmol/l) and 5 (8.3%) had severe hypophosphatemia. Three major risk factors for hypophosphatemia namely; sepsis, diuretic use and parenteral nutrition were identified.

What our study hopes to achieve

The incidence in the South African population is unknown. As far as we are aware there are no studies available in our local population. The effect of hypophosphatemia on Post-Operative care indicators has therefore also not been documented.

We also want to attempt to find associations between the perioperative care and the degree of hypophosphatemia.

This study could lead to future research aimed at proving causality of possible associations found.

Aims

Primary Aim

- The incidence of significant hypophosphatemia after cardiopulmonary bypass with the Bloemfontein, South Africa, Cardiac surgery protocols.

Secondary Aims

- The effect of significant hypophosphatemia on post-operative ICU stay, length of post-operative mechanical ventilation and duration of inotropic/vasopressor support.
- The effect of different cardioplegic solutions on the incidence of post-operative hypophosphatemia.

Methodology

Study design

This study design will be an observational study in the form of a Prospective Cohort Analytical Study.

Study participants

All Adult patients scheduled for open cardiac surgery at Universitas Academic Hospital, from January 2017 will be screened for inclusion according to the study criteria.

The study will commence in February 2017 and the first 100 patients, that meet the inclusion criteria, will be included. This is the number of patients needed to show a statistical significance in the primary outcome, as determined by the Department of Biostatistics at the University of the Free State (UFS). There are 2 cardiac theatres: Theatre 6 conducts adult cardiac cases twice a week and theatre 7 conducts adult cases 2-3 times a week. The aim would be to include 4-5 patients each week.

The sample size selected was based on the primary outcome. Given an estimate incidence of post-operative Hypophosphatemia of 40%, a sample of 100 will give a confidence interval of 30% - 50%. The two techniques used for cardioplegia, as stated below, will also be compared to each other. It is estimated that 40% of patients will receive commercial cardioplegia (Group1) and 60% of patients will receive locally mixed cardioplegic solution (Group 2).

The principle investigator will evaluate the patients scheduled for cardiac surgery pre operatively and, if the patient meets the inclusion criteria, informed consent will be obtained by the principle investigator.

Inclusion criteria:

1. Adult patients (older than 18 years)
2. Scheduled for elective and urgent open-heart surgery
3. The surgery needs to be performed on bypass
4. EuroScore 2 risk evaluation will be done on all patients. The estimated mortality based on the values entered on the data sheet will be calculated. If the estimated mortality rate is less than 5%, the patient will be included in the study (Low risk 0 – 2% estimated mortality, Medium risk 3 – 5% estimated mortality, High risk > 5% estimated mortality).
5. The Patient needs to be ventilated post-operatively in the ICU
6. The Patient must be able to speak English, Afrikaans or Sesotho.

If the patient meets the inclusion criteria and provides consent to be included in the study, then the patient will be included.

Cardioplegic solution used:

Both solutions are routinely used in our institution and the choice will be based on the surgeon's preference, and be given antegrade or retrograde.

- Group 1:
    - Commercially available "Fresenius Kabi – Medsol Cardioplegic solution". The initial 500 ml cardioplegic solution used is known as the Cardiologic Induction solution, this is then followed by the Cardioplegic Maintenance solution, when cardioplegia needs to be repeated.
    - This Cardioplegic Induction solution contains:
        - Potassium Chloride 3757 g/500 ml
        - Sodium chloride 0.777 g/500 ml
        - Sodium Citrate 0.832 g/500 ml
        - Citric Acid – H2O 0.104 g/500 ml
        - Sodium phosphate 0.079 g/500 ml
        - Tromethamine 4.548 g/500 ml
        - 35 ml of 50% dextrose solution is added to each bag
    - The Cardioplegic Maintenance solution contains
        - Potassium Chloride 1375 g/500 ml
        - Sodium chloride 0.735 g/500 ml
        - Sodium Citrate 0.785 g/500 ml
        - Citric Acid – H_2O 0.098 g/500 ml
        - Sodium biphosphate 0.075 g/500 ml
        - Tromethamine 4.28 g/500 ml
        - 35 ml of 50% dextrose solution is added to each bag
- Group 2: Locally mixed Cardioplegic solution containing for induction and maintenance of cardioplegia. The below mentioned substances are added to one litre of Ringer's lactate:
    - Potassium chloride 15 mmol/l (1118.27 g/l)
    - Lignocaine 200 mg/l
    - Magnesium sulphate 4 g/l
    - Sodium bicarbonate 30 mmol/l
    - Hydroxyethyl starch (Voluven®) 50 ml

Criteria for withdrawal from study

1) If the patient develops a complication post-operatively, that necessitates emergency surgery post-operatively, the patient information on post-operative course will not be included when associations are made.
2) If the patient develops any condition post-operatively that will influence the accuracy of the post-operative course variables that will be measured, then this patient's information will not be included when associations are made.
3) Patients with incomplete biochemical results.
4) If the patient refuses to take any further part in the observational study.

Sample size:

The sample size will be determined based on the primary outcome, namely the incidence of hypophosphatemia after cardiac bypass surgery when using the Universitas Hospital, Bloemfontein's Cardiac surgery protocols.

The expected incidence of hypophosphatemia, based on the studies mentioned in the introduction, varies from 34 to 46%. A serum phosphate level of 0.79 mmol/l or less will be used te define hypophosphatemia.

Based on the Chemical Pathological variations, described below, a change in serum phosphate level greater than 23.95%, from the pre-operative value, would be seen as a true change that cannot be attributed to either biological variation or analytical variation.

Both criteria need to be met before the result will be seen as true hypophosphatemia.

Chemical Pathology

Uncertainty of Measurement (UM) is defined [ISO15189 (3.17) [19]] as "a parameter associated with the result of a measured that characterises the dispersion of values.[6]

The 4 major components involved in the variability of test results are: pre-analytical factors, biological intra-individual variation, analytical variation and operator differences.

1. Pre-analytical Factors

   Fasting, other drug administrations, difficulty in collecting samples, care of sample after collection: uncertainty of measurement usually excludes pre-analytical errors.

   The current study will manage these factors as follows: all patients will be fasted pre-operatively, as routine practice in the same way. Standardisation of the sample collection and care (blood to be drawn from the central venous line by the nursing staff and taken to the laboratory within 30 minutes after collection). Lastly factors that could influence the serum

phosphate levels will be documented, including: the administration of glucose, insulin, corticosteroids and diuretics.[5]

2. Biological Variation:

   Can be defined as the cyclic or random variations in an analyte, for example serum Phosphate level, which consists of random fluctuation around a certain set point of an individual and is known as the intra-individual biological variation. The set point is unique to a specific individual. This is known as inter-individual biologic variation.

   To state that a change in an analyte level is pathological and not just part of the individual's biological variation, it must be proven that the change in the analyte level is greater than the change that can be attributed to biological variation.

   According to tabular data presented in Recos *et al*. (2014)[20] biological variation for serum phosphate was found to be 8.15%. Therefore, a change of more than 8.15% in serum phosphate levels cannot be contributed to the biological variation.

3. Analytical Variation

   The standard deviation of serum phosphate on the current study's laboratory's machine is 0.036 mmol/L (2.87%).

   Our aim will be to have a 95% confidence interval that the change in serum phosphate level is not due to a standard deviation of the machine.

   The reference change value:

   If the difference between 2 results is greater than the Reference Change Value (RCV) then the difference is not due to assay impression alone.

   If a confidence interval of 95% is used then Z = 1.96

   RCV = ($\sqrt{2}$ x Z) x Standard Deviation (SD)

   = 2.77 x 0.036

   = 0.099786

   = ± 0.1 mmol change

4. Operator differences

   In order to limit operator differences in different machines or laboratories, all tests will be performed on the same machine by the National Health Laboratory Services at Universitas Hospital, Bloemfontein.

Combined Variation Value

The combination of the analytical and biological variation into a single formula, is described as the Combined Variation Value.

RCV, defined as the critical difference that must be exceeded between 2 sequential results for a significant (or true) change to occur, incorporates the total variation associated with both results and is demonstrated by an equation [$RCV = 2^{½} x\ Z\ x\ (CVa^2 + CVw^2)^{½}$]. This equation is based on the random variations associated with a result and follows a Gaussian distribution.[6] Important factors of the equation to consider are the Z-score (i.e., the desired level of statistical significance; Z = 1.96 for 95% significance when evaluating a bidirectional change), the analytical variation (CVa) (2.87%) and the intra-individual BV (CVw) which is often the largest contributor to the variation (8.15%)

$$RCV = 2^{½} x\ Z\ x\ (CVa^2 + CVw^2)^{½}$$
$$= 2^{½} \text{ x } 1.96 \text{ x } (8.15^2 + 2.87^2)^{½}$$
$$= 23.95 \text{ \% change}$$

Therefore, a change greater than 23.95% cannot be attributed to either biological variation or analytical variation.

Measurement

Pre-operatively

- Consent will be obtained by the primary researcher, Dr L.E. Grobbelaar, the evening prior to the scheduled surgery. Please see the attached informed consent form.
- Blood will be drawn pre-operatively from each patient, as per our institution's protocol. This will be performed for all the patients scheduled for open cardiac surgery and this includes the measurement of the serum phosphate level. This level will be used to establish a baseline.
- EuroScore 2 will be calculated on each patient.
- Basic patient details will be collected
- See Data Sheet 1

Intra-operatively**:**

- The patient will receive a routine anaesthetic, as per the primary anaesthetist's sole judgment for each patient.
- Information obtained from the intra-operative cause will be collected with a data sheet by the applicable anaesthesiologist and perfusion technologist, containing the following information (See Data Sheet 2.1 and 2.2)
    - Fluids given intra-operatively
    - Blood products given intra-operatively
    - Prime solution used for the cardiopulmonary bypass machine – type and volume
    - Type and volume of cardioplegic solution used
    - Time on cardio pulmonary bypass

- Degree and duration of hypothermia during cardiopulmonary bypass
- Cell saved blood transfused back to the patient
- Drugs given that can possibly effect the serum phosphate level: glucose, insulin, corticosteroids and diuretics.[5]

The intra-operative datasheets will be placed in a data collection box in the 2 theatres.

Post-operatively

- Immediately on arrival and after stabilisation of the patient, routine blood collections will be repeated as per hospital protocol (See Data Sheet 3)
- The serum phosphate level will then be repeated daily from post-operative, until discharge from the unit or death, as per hospital protocol.
- The post-operative care measurements which will be recorded are: the duration of mechanical ventilation, duration of ICU stay and the duration that inotropes which were needed post-operatively.

The information collected will then be analysed in order to identify the following:

- Incidence of hypophosphatemia after open cardiac surgery in our Facility
- Associations between intra-operative information collected and post-operative hypophosphatemia
- Association between the post-operative serum phosphate levels and the post-operative care measures, as described above.
- Association between the post-operative serum phosphate level and the Particular Cardioplegic solution used.

Measurement Errors and Measures Taken to Reduce this Random Variation

The values recorded will be numerical and this will minimize any observer variation. Regarding biological variation and analytical variation of the blood results – this was discussed above. A statistical significant difference will be considered if the values from pre-operative and post-operative serum phosphate levels differ with more than 23.95%. Regarding clinical significance, moderate and severe hypophosphatemia will be documented and this will be compared to the post-operative care indicators.

Systematic Errors

The National Health Laboratory Service makes use of the Roche® Cobas 6000 for evaluation of serum calcium, magnesium and phosphate levels. The machine undergoes a quality control check twice a day. Calibration on the machine is done every 28 days, if a new reagent is inserted or if any problems are detected in the quality control check. The machine also undergoes an external THISTLE external Quality control check every month.

The Laboratory is ISO: SANAS 15189 compliant.

Blinding

Neither the surgeon, perfusionist, nor anaesthesiologists (including the primary anaesthesiologist) will be able to predict which patients will develop post-operative hypophosphatemia. It will not be possible to adjust their technique based on the predicted outcome. The only intravenous phosphate available in the Universitas Hospital Complex is potassium phosphate. This is mainly used intra-operatively in order to correct hypokalaemia or post-operatively in order to correct hypophosphatemia. The blood gas analyser which is available in the theatre complex does not evaluate the serum phosphate level and therefore potassium phosphate is not used intra-operatively to treat hypophosphatemia, as we are unable to diagnose it at that time. The acting anaesthesiologist will therefore be requested to use potassium chloride if potassium replacement is deemed necessary. Post-operative serum phosphate replacement will only be implemented based on the serum phosphate levels done at the laboratory. If any phosphate-containing product is given post-operatively it will be documented.

Confounding Variables

Possible confounding variables will include:

- Pre-operative condition of the patient
- Type of surgery of the patient
- Duration of the surgery
- Surgeon preference regarding procedures performed. It is known that the two primary surgeons in the Department of Cardiothoracic Surgery make use of different cardioplegic solutions. This might be a possible confounder if we compare the two surgeons' patients' post-operative incidence of hypophosphatemia.
- Variation in the fluid and drug administration intra-operatively might influence the serum phosphate level measured post-operatively.
- The incidence of post-operative hypophosphatemia in various races has not been studied, therefore the effect of race is unpredictable.

Attempts to minimize these confounding variables:

- To have a comparable patient population, only patients with a EuroScore 2 of less than 5% will be included in the study. The EuroScore 2, includes the patients pre-operative state and planned surgery.
- The duration of surgery, drug and fluid administration will be documented and a comparison will be done with the incidence of hypophosphatemia in an attempt to demonstrate any possible associations.
- The type of surgery performed under the guidance of each surgeon will be collected and taken into account when a comparison is done between the different techniques.

- Basic information on the patient will be collected and taken into account.

Pilot Study

A pilot study will be done on 3 patients in order to screen for any problems with the datasheets and to familiarise the personnel whom nurses these patients. It is planned that the pilot study will be conducted in January 2017.

The pilot study will follow the same process of the planned study but if any problems arise this will be re-addressed and resubmitted for ethics approval before the study commences.

If there were no problems identified during the pilot study and the data collection is complete, these patients will be included in the study.

Data Analysis

The collected data will be typed into an Excel spreadsheet by the researcher.

The data analysis will be handled by the Department of Biostatistics at the UFS. The incidence of hypophosphatemia, with differentiation between groups will be indicated. The implications of the degree of hypophosphatemia on the post-operative clinical determinants will be indicated.

Results will be summarised by frequencies and percentages (categorical variables), means and standard deviations or percentiles (numerical variables). Subgroup comparisons will be done using a 95% confidence interval for differences in means, medians or percentiles, with appropriate hypothesis testing.

Implementation of the Findings

The findings collected will be written in an article format as part of Dr. L.E. Grobbelaar's Masters in Medicine degree at the UFS.

If the results proof to be of value, the article will also be presented to an appropriate journal for publishing.

This practical implementation of the proposed research will be:

- Intentional evaluation for hypophosphatemia intra-operatively and post-operatively with prompt treatment. The serum phosphate level can be added to the test done on a routine blood gas analysis.
- Hypophosphatemia, once identified intra-operatively, can be treated post-operatively with intravenous or oral phosphate supplementation.
- Hypophosphatemia can possibly be prevented by using Potassium Phosphate routinely intra-operatively and post-operatively.

- Any improvement in post-operative measurements could have a noticeable effect in reducing the cost of post-operative care.

Time Schedule

The study will be presented to the Health Sciences Research Ethics Committee of the University of the Free State for evaluation in November 2016. If the study is approved then the study will be presented to the Free State Department of Health for evaluation and approval.

This study aims to include 100 patients, based on an estimated incidence of 40%. It is planned that the study will commence on 15 February 2017. If 4-5 patients are included every week, then the estimated time to complete the study will be 6 months. Therefore, it is planned that the data collection will be completed in August 2017.

Data analysis will be performed by the Department of Biostatistics; the planned time for this analysis will be two months.

It is aimed that the writing of the report and the completion of the study will be done before June 2018. Thereafter the study will be presented for publication.

Budget

Cost of the research:

- Paper and printing – will be done at the Department Anaesthesiology at a cost of R0.50 per page. Estimated copies needed: Informed consent document and duplicate, that the patient can keep with them, – four pages per patient. Data sheet: four pages per patient. Therefore, a total of 8 pages for every patient. Estimated cost for 100 patients: 800 copies at R0.50 per page – R400
- Translation Cost: Translating the consent form to Sesotho: This was done by doctor AS Motsei, Lecturer at the Department of African Languages at the University of the Free State. The cost for translation was R564.80. This was paid for by the primary researcher, Dr L.E. Grobbelaar.
- Laboratory testing – no additional cost as this forms part of routine blood tests done for all patients admitted, after cardio pulmonary bypass, into the intensive care unit.
- No additional cost for traveling or data collection.

Ethical Aspects

The study will be presented to the Health Sciences Research Ethics Committee of the UFS for evaluation. If approved, then the study will also be presented to the Free State Department of Health for evaluation.

This study does not pose harm to any patient included in the study, as the data collected will not affect the primary treating surgeon and anaesthesiologist's management.

If clinical significant electrolyte abnormalities are noted it will, however, be brought under the attention of the treating doctor. The bloods collected are part of the routine peri-operative care and therefor the treating doctor will have access to all the results.

All information collected will be handled confidentially; personal particulars will not be shared with third parties. Patients' name and hospital number will solely be collected for practical purposes. There will be 4 data sheets and an informed consent document for each patient that needs to be captured, although these will be collected separately. The data collected will be expressed as part of the group data.

Consent forms will be available in the three most common languages used in the Free State: English, Afrikaans and Sesotho. The researcher will explain the study to the patient and a translator will be used if the patient prefers Sesotho as the primary communication language.

There is no conflict of interests from any of the researchers in this study.

The report of the study findings will be available to any of the participants on request.

References

1. Prough DS, Funston JS, Svensén CH and Wolf SW. Fluids, Electrolytes and Acid-Base Physiology. In: Barash PG, editor. Clinical Anesthesia 7th Edition, Lippincott Williams & Wilkins, a Wolters Kluwer Business, Philadelphia. 2013. Chapter 14.
2. Barrett KM, Barman SM, Boitano S, Brooks HL. Phosphorus. Control of Calcium & Phosphate Metabolism & the Physiology of Bone. In: Ganong Review of Medical Physiology 24th Edition. The McGraw-Hill, Singapore. 2012. Chapter 21.
3. Guyton AC and Hall JE. Parathyroid Hormone, Calcitonin, Calcium and Phosphate Metabolism. In: Textbook of Medical Physiology 10th Edition. The Curtis Center, Philadelphia. 2000. Chapter 79.
4. Kaye AD and Riopelle JM. Intravascular Fluid and Electrolyte Physiology. In: Miller RD, editor. Millers Anesthesia 7th Edition. Churchill Livingston Elsevier. 2009. Chapter 54.
5. Basri MN, Janattul AJ, Azrina MR and Abdul HM. Hypophosphatemia in the Intensive Care Unit: Incidence, Predictors and Management. The International Medical Journal of Malaysia 2012, 11: 31 36.
6. Morgan GE, Mikhail MS and Murry MJ. Management of Patients with Fluid and Electrolyte Disturbances. In: Clinical Anesthesiology 4th Edition. McGraw-Hill Companies, United States of America. 2006. Chapter 28.
7. Cohen J, Kogan A, Sahar G, Leva S, Vidneb B, Singera, P. Hypophosphatemia following open heart surgery: incidence and consequences. *European Journal of Cardio-thoracic Surgery* 2004:26: 306–310
8. Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. *Am J Med* 1998;104:40–7.
9. Paparella D, Yau TM and Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur J Cardiothorac Surg* 2002;21:232–44.
10. Goldstein J, Vincent J-L, Leclerc J-L, Vanderhoeft P and Kahn RJ. Hypophosphatemia after cardiothoracic surgery. *Intensive Care Med* (1985) 11:144–148.
11. Salem RR and Tray K. Hepatic Resection-Related Hypophosphatemia Is of Renal Origin as Manifested by Isolated Hyperphosphaturia. Annals of Surgery 2005:241(2): 343–348.
12. Zazzo JF, Troche G, Ruel P and Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. *Intensive Care Med* 1995;10:826–31.
13. Buell JF, Berger AC, Plotkin JS, Kuo PC and Johnson LB. The Clinical Implications of Hypophosphatemia Following Major Hepatic Resection or Cryosurgery. *Arch Surg*. 1998;133(7):757-761. doi:10.1001/archsurg.133.7.757.

14. Daily WH, Tonnesen AS and Allen SJ: Hypophosphatemia: incidence, etiology, and prevention in the trauma patient. *Crit Care Med* 1990, 18:1210-1214
15. Kruse JA, Al-Douahji M and Carlson RW: Hypophosphatemia in critically ill patients: incidence and associations. *Crit Care Med* 1992, 20:S104.
16. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE and Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. *Critical Care* 2010, 14:R147.
17. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE and Schultz MJ. Approach to hypophosphataemia in intensive care units – a nationwide survey. The Netherlands *Journal of Medicine*, 2012 (11):70(9)425-430.
18. Švagždienė M and Širvinskas E. Changes in serum electrolyte levels and their influence on the incidence of atrial fibrillation after coronary artery bypass grafting surgery. Institute for Biomedical Research, Clinic of Cardiac Surgery, Kaunas University of Medicine, Lithuan. *Medicina (Kaunas)* 2006; 42(3): 208-14
19. International Standard ISO 15189. First edition 2003- 02-15. Medical laboratories – particular requirements for quality and competence. Reference number ISO 15189; 2003(E)
20. Ricos C, Alvarez V, Cava F, et al. Current databases on biologic variation: pros, cons and progress. Westgard QC, Desirable Biological Variation Database Specifications [Internet]. 2014. [cited 2016 October 30]. Available from https://www.westgard.com/biodatabase1.htm

Chapter 2 - Manuscript

Article for publication in
Journal of Cardiothoracic and Vascular Anesthesia

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, from a single centre in South Africa

Cover Letter

To the Editor in Chief of the Journal of Cardiothoracic and Vascular Anesthesia

As the authors of the Research Article titled "Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective ", we hereby agree and are responsible for the data presented in the manuscript. We hereby confirm that according to our knowledge no potential conflicts of interest, including commercial relationships such as consultation and equity interests, exist.

_____

Dr Laurence Grobbelaar

MBChB, DA(SA), FCA (SA), Department of Anaesthesiology at the University of Free State, Bloemfontein, South Africa

_____

Prof Gina Joubert

BA, MSc, Department of Biostatistics at University of the Free State, Bloemfontein, South Africa

_____

Prof Johan Diedericks

M.Med (Anes), FCA (SA), MBChB, BA, Department of Anaesthesiology at the University of Free State, Bloemfontein, South Africa

Abstract

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective

Laurence Grobbelaar, MBChB, DA(SA), FCA (SA)[a*], Gina Joubert, BA, MSc[b], Johan Diedericks, MBChB, MMed (Anes), FCA (SA), BA[a]

Objective:

Defining the incidence of hypophosphatemia after cardiopulmonary bypass in a South African population. Secondary aims include the clinical implication of hypophosphatemia in terms of duration of mechanical ventilation, intensive care unit (ICU) stay and cardio active drug support.

Design:

A single centre, non-blinded, prospective cohort analytical study was done.

Setting:

The study was conducted at Universitas Academic Hospital, Bloemfontein, South Africa.

Participants:

Patients presenting for open cardiac surgery during the period of April 2017 to March 2018 were screened for inclusion into the study, and 101 patients were included.

Measurements:

The pre-operative variables included all the factors of the Euro2 score risk evaluation score. Intra-operative variables included drug and blood product administration, cardioplegic solution used and cardiopulmonary bypass-related variables. Post-operatively the serum phosphate levels were taken daily and post-operative care measures, such as duration of cardio active drug support, mechanical ventilation and ICU stay, were recorded.

Results:

The incidence of hypophosphatemia, immediately post-operatively, was 12.6% (95% Confidence Interval [CI] 6.7% -21.0%) and peaked on Day 3 at 29.0% (95% CI 20.1% - 39.4%). New onset hypophosphatemia at any stage stay was 52.6% (95% CI 42.1% - 63.0%). Regarding the secondary aims: no associations were identified.

Conclusions:

Hypophosphatemia was common with an incidence higher than expected. This, however, did not translate into a clinical implication, as the degree was usually mild (0.66 - 0.79 mmol.l-1).

Keywords:

Hypophosphatemia, Cardiopulmonary bypass, ICU stay, Cardioplegic Solutions

Manuscript

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective

Laurence Grobbelaar, MBChB, DA(SA), FCA (SA)[a*], Gina Joubert, BA, MSc[b], Johan Diedericks, MBChB, MMed (Anes), FCA (SA), BA[a]

[a]Department of Anaesthesiology, University of Free State, Bloemfontein, South Africa.

[b]Department of Biostatistics, University of the Free State, Bloemfontein, South Africa

[*]Corresponding author, email: laurence.grobbelaar@gmail.com, Postal Address: PO BOX 30022, Pellissier, Bloemfontein, 9322, South Africa, Mobile: +27722651624

Introduction

Phosphate is an essential micronutrient involved in numerous critical structural and physiological functions. It is structurally incorporated into the skeletal system (hydroxyapatite), cell membranes (phospholipids) and the cell nucleus (nucleic acids).[1,2] Phosphate is central in metabolism, functioning as a key component of adenosine triphosphate and creatinine phosphate. Severe decrease in phosphate levels may, therefore, result in energy depletion.[1] Phosphate is also present in 2,3di-phosphoglycerate which is a crucial factor that regulates haemoglobin's affinity for oxygen.[1,2] In the secondary messenger system, phosphate plays a critical role as cyclic adenosine monophosphate and phosphoinositide.[1] It is also involved in the regulation of protein function where de-phosphorylation or phosphorylation can activate or deactivate different enzymes. Renally it acts as a urinary buffer where it binds with free hydrogen ions.[2] Less than one percent of phosphate is present in plasma and two thirds of this phosphate is in the organic form, as a complex ion, or bound to proteins and lipids. The rest of the plasma phosphate is in the inorganic form ($H_2PO_4^-$, HPO_4^{-2} and PO_4^{-3}).[1,2] Intra-cellular shifts of phosphate take place with a glucose or insulin load that result in the intra-cellular phosphorylation of glucose.[1]

Hypophosphatemia, as determined by the serum inorganic phosphate level, is defined as a serum phosphate level below 0.80 mmol/l and is classified as mild (0.79 - 0.66 mmol/l), moderate (0.32- 0.65 mmol/l) and severe (< 0.32mmol/l).[3] The clinical implications of severe hypophosphatemia vary and include: Cardiac effects (decreased contractility, acute cardiac failure), effects on the central nervous system (encephalopathy, delirium, seizures, coma), effects on the musculoskeletal system (skeletal myopathy, respiratory muscle failure, skeletal demineralisation), and metabolic disturbances (metabolic acidosis, hepatic dysfunction, glucose intolerance).[1,4,5] The acute

cardiac and respiratory muscle failure are considered the most important post-operative complications.

Current available research demonstrates an incidence of hypophosphatemia after cardiac surgery ranging from 34.3% to 50%. The definition of hypophosphatemia unfortunately varies with values < 0.08 mmol/l, < 0.48 mmol/l and < 0.6 mmol/l.[6,7,8]

A number of small studies have been done in the patients undergoing hepatic surgery. Hypophosphatemia was common, with an incidence of 67% to 100%.[9,10] These were however small studies and should be interpreted in light thereof. There is also a transient hyper-phosphaturia present after hepatic surgery, that could exacerbate the hypophosphatemia.[11] Larger Studies done in surgical and general intensive care units (ICUs) presented an incidence of 28% to 28.8%.[11,12]

The incidence of post-operative hypophosphatemia, and the clinical implication thereof, has not been investigated in a South African Population.

Objective

The primary objective was to assess the incidence of hypophosphatemia after cardiopulmonary bypass. Secondary objectives were the effect of hypophosphatemia on post-operative ICU stay, length of post-operative mechanical ventilation and duration of cardio active drug (inotrope or vasopressor) support in the investigated patient population. A further secondary aim was to determine if the use of different cardioplegic solutions had an effect on the incidence of post-operative hypophosphatemia. Other possible associations were sought between intra-operative variables and the immediate post-operative serum phosphate levels.

Methods

Design

After obtaining approval from the Health Sciences Research Ethics Committee of the University of the Free State, South Africa (HSREC 187/2016, UFS-HSD2016/1509), provincial health authorities and patients' written informed consent, a non-blinded, prospective cohort analytical study was carried out.

A pilot study was performed in January 2017 with 3 patients in order to screen for any problems with the design, datasheets and to familiarise the personnel with the needed procedures. The pilot study followed the same process as the planned study and since no problems were identified, these patients were included in the study population.

Population and setting

Adults patients (aged > 18 years), of either sex and various races were screened for inclusion. This study was carried out between April 2017 and March 2018 at our institution (Universitas Hospital

Complex). Patients included, were scheduled to receive elective or urgent open-heart surgery and for whom post-operative mechanical ventilation had been planned in the ICU. Patients with an estimated mortality above 5%, based on the EuroSCORE II Risk Evaluation, were excluded from the study.[13] The EuroSCORE II Risk Evaluation predicts perioperative mortality based on numerous pre-operative indicators as well as the procedure performed.

Patients were also excluded from the study if they underwent off-pump surgery, had incomplete biochemical results or developed a complication post-operatively, which would necessitate emergency surgery or would have influenced the accuracy of the post-operative course variables. Patients were free to withdraw from the study at any time.

Assessments

Patients had a routine pre-operative biochemistry blood profile,, which included a baseline serum phosphate level. As per the primary anaesthetist's sole judgment for each patient, a routine anaesthetic was given. Data on the intra-operative course, interventions and treatment were recorded by the anaesthesiologist and perfusion technologists. Post-operatively, on arrival in the ICU and then daily thereafter, a biochemical profile was performed. The serum phosphate level, along with the post-operative care measurements such as the duration of mechanical ventilation, duration of ICU stay and the duration of cardioactive drug support, were recorded. A Roche® Cobas 6000 was used to analyse the biochemical profile. The machine was maintained and calibrated according to the standard operating procedures of the National Health Laboratory Service, Universitas Hospital Complex, which is ISO: SANAS 15189 compliant.

Cardioplegic solutions

The type of cardioplegic solution used for each patient was dependent on the surgeon's preference. The two types of cardioplegic solutions used in the unit are the Bucksberg Solution and the Modified St Thomas solution. The Bucksberg solution is commercially available ("Fresenius Kabi–Medsol" cardioplegic solution). The initial 500 ml solution used, is known as the cardiologic induction solution. When the cardioplegia had to be repeated, this was then followed by the cardioplegic maintenance solution. The Modified St Thomas solution was prepared pre-operatively and used for induction and maintenance of cardioplegia. The solution consisted of potassium chloride (15 $mmol.l^{-1}$), lignocaine (200 $mg.l^{-1}$), magnesium sulphate (4 $g.l^{-1}$), sodium bicarbonate (30 $mmol.l^{-1}$) and hydroxyethyl starch 6% 130/0.4 (50 $ml.l^{-1}$) that is added to one litre of Ringer's Lactate Solution.

Statistical analysis

A sample size of 100 patients was selected based on a power analysis done by our institutes biostatistical department. This was calculated based on an estimated incidence of hypophosphatemia

after cardiopulmonary bypass of 40%, as estimated from previous research. A sample of 100 patients gave a confidence interval of 30% to 50%.

Factors that could have affected the absolute value of electrolytes at any given time, included biological intra-individual variation (cyclic or random variations in an analyte, fluctuation around a certain set point) and analytical variation (standard deviation [SD] of the laboratory's machine around a given setpoint).

The biological variation for serum phosphate is 8.15%.[14] When considering the analytical variation, the SD of serum phosphate on the current study's laboratory's machine was 0.036 mmol.l^{-1}. To achieve a 95% confidence interval, in order to confirm that the change in serum phosphate level is not due to a SD of the machine, the Reference Change Value was calculated as 0.1 mmol.l^{-1}.[15] These two factors were combined to calculate the Combined Variation Value of 23.95%.[15] Therefore, a change in serum phosphate level > 23.95% cannot be attributed to either biological variation or analytical variation. This is presented in the data as a significant change in serum phosphate value.

The collected data was captured in Excel spreadsheet and analysed by our institutes biostatistical department using SAS Version 9.4.

Results are summarised by frequencies and percentages (categorical variables), median and interquartile range [IQR] (numerical variables, due to skew distributions). Subgroup comparisons were done using appropriate hypothesis testing.

Results

Patient characteristics

A total of 140 patients were screened and 101 patients were included according to inclusion criteria. Most patients were male with a median age of 50 years (Tables 1 and 2). Six patients had a low starting serum phosphate and were not used in evaluating post-operative clinical variables, therefor 95 patients were evaluated for associations between intraoperative care measures and post-operative serum phosphate and clinical care indicators(Duration of mechanical ventilation, duration of cardioactive drug support and duration of ICU stay).

Table 1: Pre-operative and Intra-operative Characteristics of the Sample Population – Numerical Data (n = 101).

Variable	Median	Range
Age (years)	50	18 – 74
Final Euro II score	1.9	0.6 – 5
Duration of cardiopulmonary bypass (min)	134	39 – 501
Degree of hypothermia (˚C)	30	15.8 – 36.6
Cell saved blood transfused (ml)	638	150 – 2403

Table 2: Pre-operative and Intra-operative Characteristics of the Sample Population – Categorical Data. (n = 101)

Variable	Frequency (n = 101)	Percentage of Study Population (%)
Gender		
Male	61	60.4
Female	40	39.6
Race		
Black	53	52.5
White	30	29.7
Mixed race	11	10.9
Indian	7	6.9
Surgery Urgency		
Elective	49	48.5
Urgent	52	51.5
Weight of Intervention		
Isolated CABG	34	33.7
Single Non-CABG	43	42.6
2 Procedures	23	22.8
≥ 3 Procedures	1	1
Cardioplegic Solution		
Bucksberg Solution	55	54.5
Modified St Thomas	46	45.5

Abbreviation: CABG, Coronary artery bypass grafting; Single Non-CABG – Any single cardiac surgical procedure excluding CABG.

The drug and blood products administered intraoperatively are compared to the immediate post-operative serum phosphate level in Table 3. There were 12 patients with a serum phosphate level <0.8 $mmol.l^{-1}$ and 83 patients that had a serum phosphate level ≥ 0.8$mmol.l^{-1}$.

Table 3. Correlation between intraoperative drug and blood product administration to post-operative serum phosphate level

Variable	Immediate Post-operative serum Phosphate level	Frequency	Study Population	Percentage of Study Population (%)
Blood Products Transfused Intra-op				
Packed Red Cells	Immediate post-op Phosphate ≥ 0.8	46	83	55.4
	Immediate post-op phosphate < 0.8	7	12	58.3
Fresh Frozen Plasma	Immediate post-op Phosphate ≥ 0.8	29	83	34.9
	Immediate post-op phosphate < 0.8	2	12	16.7
Pooled Platelets	Immediate post-op Phosphate ≥ 0.8	35	83	42.2
	Immediate post-op phosphate < 0.8	3	12	25.0
Cryoprecipitate	Immediate post-op Phosphate ≥ 0.8	33	83	39.8
	Immediate post-op phosphate < 0.8	3	12	25
Intra-operative Drug Administration				
Corticosteroids	Immediate post-op Phosphate ≥ 0.8	72	83	86.7
	Immediate post-op phosphate < 0.8	11	12	91.7
Insulin	Immediate post-op Phosphate ≥ 0.8	52	83	62.7
	Immediate post-op phosphate < 0.8	11	12	91.7
Dextrose	Immediate post-op Phosphate ≥ 0.8	8	83	9.6
	Immediate post-op phosphate < 0.8	4	12	33.3

Incidence of Hypophosphatemia

Serum phosphate levels were evaluated daily and are graphically represented in Figure 1. As seen in Figure 1, the incidence of hypophosphatemia was 12.6% immediately post-operatively (95% CI 6.7% to 21.0%); 9.5% on day 1 (95% CI 4.4% to 17.2%), 25.3% on day 2 (95% CI 16.9% to 35.2%) and 29.0% on day 3 (95% CI 20.1% to 39.4%). The incidence of hypophosphatemia at any stage during post-operative ICU stay was 52.6% (95% CI 42.1% to 63.0%). The sample size decreased as patients were discharged from the ICU.

A significant decrease in serum phosphate level (> 23.95%) was present in 26.3% (95% CI 17.8% to 36.4%) of patients immediately post-operatively and 66.3% (95% CI 55.9% to 75.7%) had a significant decrease in serum phosphate level in their post-operative stay.

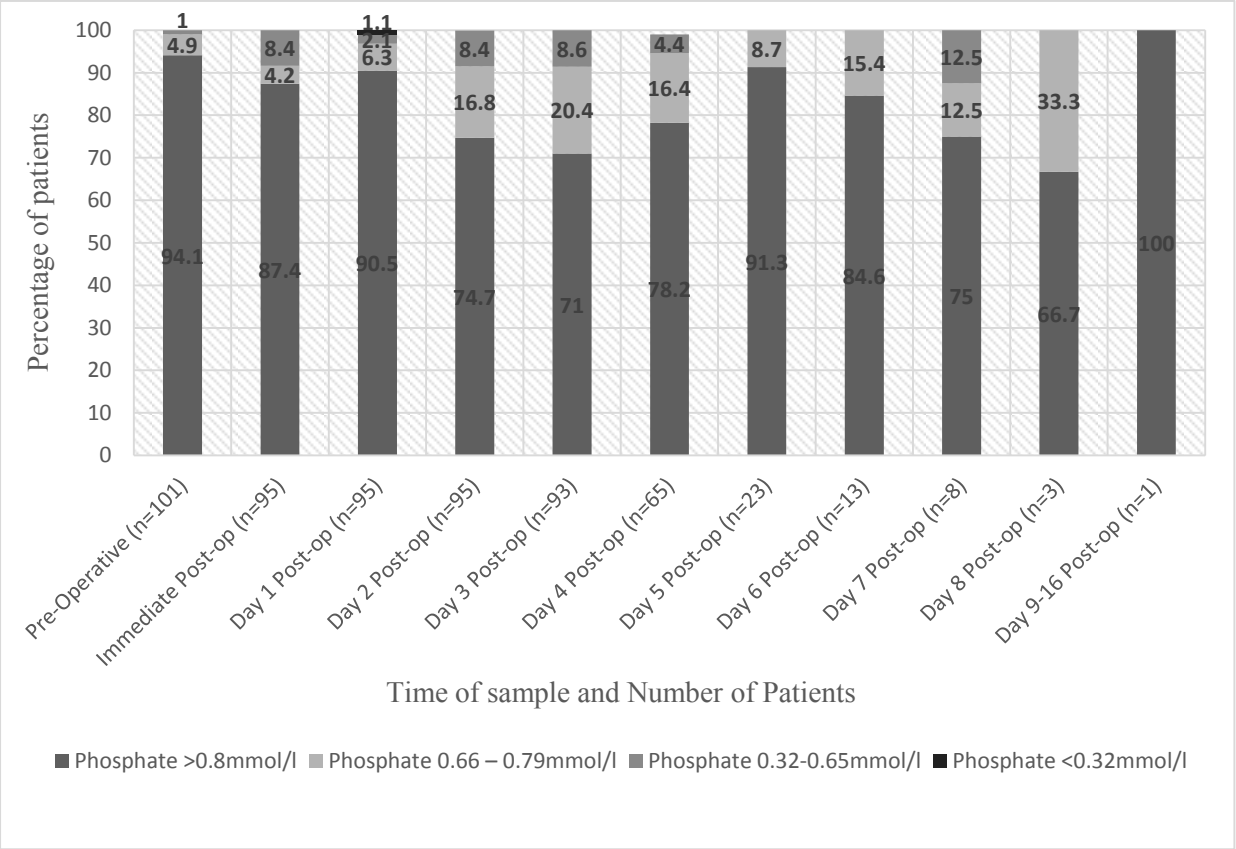

Figure 1: Serum phosphate levels of the study population taken pre-operatively, immediately post-operatively and daily in the post-operative period, until discharge from ICU.

The association between the patients' race and the incidence of hypophosphatemia is demonstrated in Table 3, using various definitions of hypophosphatemia. No specific race was associated with an increased incidence of post-operative hypophosphatemia.

Table 4: Association of Hypophosphatemia with Race

Hypophosphatemia (%)	Race				Significance
	Black	Coloured	Indian	White	
Immediate post-op hypophosphatemia	14.0	18.2	16.7	7.1	p = 0.64
Incidence of hypophosphatemia during total post-op stay	42.0	54.6	66.7	67.9	p = 0.14
Immediate significant decrease	24.0	45.5	33.3	21.4	p = 0.41
Incidence of significant decrease during total post-op stay	58.0	81.8	83.3	71.4	p = 0.34

Abbreviation: post-op - post-operative

The two different cardioplegic solutions used were compared in terms of incidence of hypophosphatemia, by using various definitions (Table 4). No statistically significant difference was identified.

Table 5: Incidence of Hypophosphatemia in the Patient Population Groups that Received Different Cardioplegic Solutions

Hypophosphatemia	Bucksberg Solution	Modified St Thomas	Statistical Significance*
Immediate post-op	13.7%	11.4%	p = 0.73
Anytime in post-op period	56.9%	47.7%	p = 0.37
Significant decrease immediate post-op	23.5%	29.6%	p = 0.51
Anytime significant decrease in phosphate	66.7%	65.9%	p = 0.94

Abbreviation: post-op - post-operative

NOTE. *No statistically significant difference between the Bucksberg and Modified St Thomas solutions.

The volumes of the provided cardioplegic solutions were also comparable. In the Bucksburg group, the volume of cardioplegic solution given in the hypophosphatemia and non-hypophosphatemia groups had medians of 2533 ml (IQR 1313 ml) and 2470 ml (IQR 1268.5 ml), respectively. In the modified St Thomas group the volume of cardioplegic solution given in the hypophosphatemia and non-hypophosphatemia groups had medians of 1887 ml (IQR 1107 ml) and 1906 ml (IQR 1068 ml), respectively.

The clinical implication of the hypophosphatemia in terms of duration of mechanical ventilation and ICU stay are demonstrated in Figures 2 and 3. No statistically significant association was found

between the immediate post-operative serum phosphate level and the duration of mechanical ventilation (Figure 2, $p = 0.81$). Figure 3 demonstrates no association between any of the serum phosphate measurements and duration of ICU stay. This was demonstrated by comparing any episodes of low serum phosphate to duration of ICU stay: $p = 0.52$, and any significant decrease in serum phosphate to duration of ICU stay: $p = 0.96$.

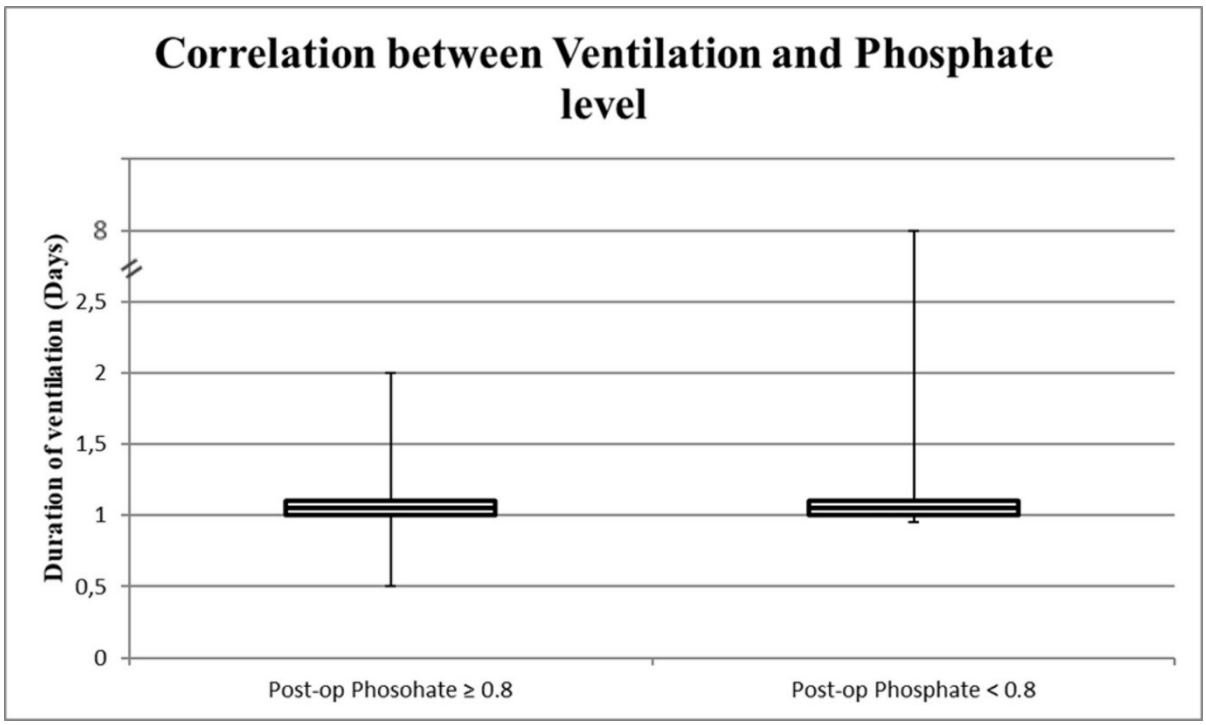

Figure 2: Box plots of association between duration of post-operative mechanical ventilation and the measured serum phosphate levels.

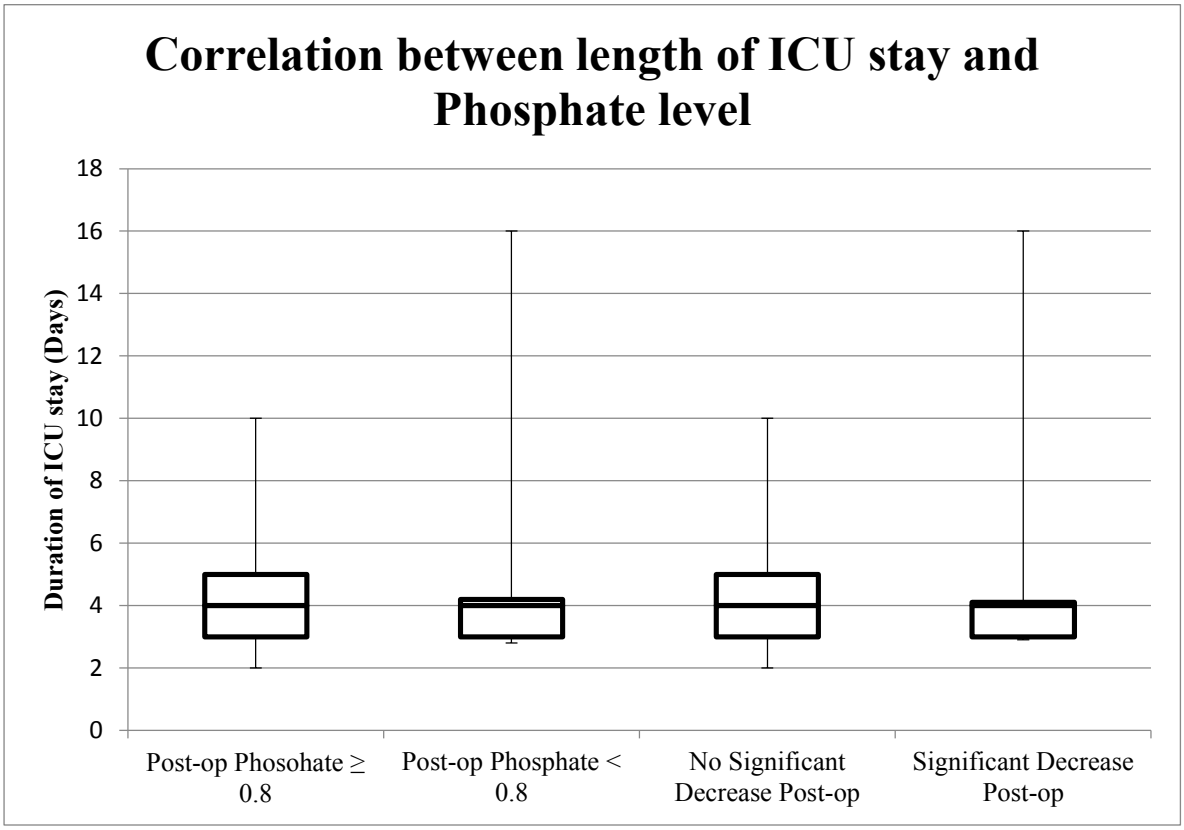

Figure 3: Box plot of association between the length of ICU stay and the measured serum phosphate levels.

No statistically significant differences were found between the two groups, in terms of duration of cardioactive drug support, with any of the commonly use inotropic and vasopressor agents (Table 5).

Table 6: Duration of Post-operative Cardioactive Drug Administration Associated with Serum Phosphate Level in the First 24-hours Post-operatively.

Drug	Median (days)	IQR (days)	Significance
Adrenaline			
Phosphate > 0.8 mmol.l^{-1}	0	1	p = 0.51
Phosphate ≤ 0.8 mmol.l^{-1}	0.5	1	
Noradrenaline			
Phosphate > 0.8 mmol.l^{-1}	0	1	p = 0.11
Phosphate ≤ 0.8 mmol.l^{-1}	0.5	1.5	
Phenylephrine			
Phosphate > 0.8 mmol.l^{-1}	0	0	p = 0.13
Phosphate ≤ 0.8 mmol.l^{-1}	0	0	

Abbreviation: IQR: interquartile range

Factors, evaluated for possible association with immediate post-operative hypophosphatemia and which did not demonstrate a statistically significant association, included: gender (p = 0.52 intra-operative steroid use (p = 1.00), intra-operative dextrose administration (p = 0.25), total intra-operative crystalloids used (p = 0.59), intra-operative cell saved blood transfused (p = 0.45), duration of cardiopulmonary bypass (p = 0.85) and duration of hypothermia (p = 0.95).

Intra-operative variables that was associated with a lower incidence of hypophosphatemia in the total post-operative period included fresh frozen plasma transfused (p = 0.0056) and pooled platelet transfusion (p = 0.036).

Insulin administration intra-operatively lead to higher incidence of immediate post-operative significant decrease in serum phosphate (p = 0.034).

Discussion

The median age of the study population was younger than in previously performed studies.[6,7,8,16] This can be expected due to the lower life expectancy in the South African population, which is 59 years.[17] The study population included a larger percentage of females than previous studies, although this is not yet equal to the sex ratio in the South African population (female 51.3%, male 48.7%).[18] This can be expected as the incidence of cardiovascular disease is higher in males than females at an age less than 75 years.[19] Due to the diverse South African population, different races formed part of the study population. The population distribution according to the 2011 national census done in South Africa, described the population composition as follows: Black 79.2%, Coloured 8.9%, White 8.9% and Indian/Asian 2.5%. Although the largest race group in this study was Black, the White population composed a relatively large percentage of the study population – presumably due to the historically higher incidence of cardiovascular disease associated with diseases of lifestyle in this population.[19]

Hypophosphatemia occurred in 52.6% of the study population during the post-operative stay. This correlated with results found by Goldstein et al. (1985).[7] Immediate post-operative hypophosphatemia was only demonstrated in 12.6% of the study population which was lower than expected. There was a delayed presentation of hypophosphatemia with the highest incidence of hypophosphatemia on days 2 and 3 post-operatively.

The postulated causes for the decrease in serum phosphate post-operatively can be divided into intra-cellular shifting, increased losses and delayed replacement. Intra-cellular shifting of phosphate is seen together with a severe inflammatory response, due to the release of proinflammatory cytokines. This is expected due to the exposure to the extra-corporeal circuit.[6,20,21] Intra-cellular shifting also occurs with a glucose load and with increased glycolysis, as is seen in acute alkalosis (perioperative hyperventilation). It is well described in refeeding syndrome and is commonly seen on the second to third day post-operatively when the patient changes from a catabolic to an anabolic state.[1,5,7] The delayed response noted in this patient group can be attributed to the current post-operative care protocol of enteral feeding being initiated on Day 1 post-operatively.

The increased loss of phosphate can also be ascribed to the cold diuresis that is typically seen with hypothermic conditions during cardiopulmonary bypass. In this study only three patients were kept at an intra-operative temperature of > 32˚C. This, coupled with the use of osmotic diuretics, as part of the pump priming solution, can increase phosphate excretion.

Associated factors such as hypomagnesemia or other co-morbidities, hypothyroidism and renal phosphate wasting, compounds the situation. Extra renal losses from vomiting, nasogastric tube suctioning or the chronic use of phosphate binding anti-acids can also cause hypophosphatemia.[1,7,9] These additional factors were however not present in the study population.

The use of intravenous fluid, without phosphate, led to inadequate replacement of the phosphate that was lost and with the end result being hypophosphatemia.[6] At the study site, a balanced crystalloid, without phosphate, was used for intra-operative maintenance and cell saving. No association was demonstrated between the volume of crystalloid and the incidence of hypophosphatemia in the study ($p = 0.59$).

The two cardioplegic solutions were compared in terms of incidence of hypophosphatemia (Table 3). No significant difference in post-operative serum phosphate levels could be demonstrated. The volumes of cardioplegic solutions given also did not differ significantly between the two types of cardioplegic solutions.

Both the hypophosphatemia and non-hypophosphatemia groups were ventilated for a median duration of 1 day (IQR 0). A conservative extubation protocol was followed where patients were only assessed on the first post-operative day for tracheal extubation. Only one patient developed a serum phosphate level below 0.32 mmol/l and this improved the following day. Respiratory muscle weakness and other major effects of hypophosphatemia predominantly occur with serum phosphate levels < 0.32 mmol/l. This could possibly explain why no difference could be demonstrated in this study group – a fast track protocol might show a difference in duration of mechanical ventilation.

When comparing this data to previous research, Cohen et al. demonstrated prolonged post-operative mechanical ventilation in the hypophosphatemia group (defined as < 0.48 mmol/l).[6] The duration mechanical ventilation (days) was a mean of 2.1 (SD 1.7) in the hypophosphatemia group and 1.1 (SD 0.9) in the non-hypophosphatemia group, with $p = 0.05$. The difference in results could be attributed to the fact that the post-operative serum phosphate levels in their study were significantly lower than in the current study.

A recent publication by Naeem et al. found an increase in the duration of mechanical ventilation (11.9 ± 11.6 hours versus 6.15 ± 5.5 hours, $p = 0.002$), in the hypophosphatemia (defined as < 0.8 mmol/l) group.[16] A more liberal extubation protocol was followed and the level of hypophosphatemia was not specified in this study.

No significant difference could be demonstrated ($p = 0.54$) when comparing the onset of any new post-operative hypophosphatemia versus normophosphatemia to the ICU stay. The duration of ICU stay (days) in the hypophosphatemia and non-hypophosphatemia groups were 4 (IQR 1) and 4 (IQR 2), respectively. This is in line with the results by Cohen et al. that demonstrated a mean duration of ICU stay (days) of 2.6 (SD 2.9) and 2.1 (SD 2.7), which was not found to be statistically significant.[6] Naeem et al., however, found an increase in duration of ICU stay (3.5 ± 1.5 versus 2.4 ± 0.7 days, $p = 0.01$). A difference in ICU discharge criteria could possibly confound these results.[16]

No association could be demonstrated between duration of inotropic or vasopressor use with the serum phosphate level. There was a trend towards longer duration of adrenaline and noradrenaline

use in the hypophosphatemia group, although statistical significance was not reached. In contrast to the results of the current study, previous studies suggested a prolonged duration of cardioactive drug support in hypophosphatemia patients, with a longer duration of cardioactive support.[6,16]

In the current study the intra-operative administration of fresh frozen plasma (FFP) and pooled platelets led to a lower incidence of hypophosphatemia immediately post-operatively. This may be attributed to the citrate phosphate dextrose anticoagulant that is added to donor blood before plasmapheresis. This was not seen with packed red cell transfusion, as these products were also given while the patient was on cardiopulmonary bypass and red cells were washed before administration which would eliminate most of the red cell preservatives. Fresh Frozen plasma and pooled platelets were given only after liberation from the cardiopulmonary bypass circuit, therefore having a smaller volume of distribution and a greater clinical effect.

Limitations of this study include that the study was a single-centre study and did not necessarily represent the total South African population. The patient's pre-operative disease profile is a major determining factor of the post-operative ICU clinical care indicators. In an attempt to minimize the variation in the pre-operative factors of the study population, patients with an estimated perioperative mortality greater than 5% were excluded from the study. Since the sample size calculation was based on the primary outcome, the study may have lacked power to detect all potentially significant associations or differences.

Patients were assessed for extubation post-operatively only on the morning of the first post-operative day, as per unit protocol. This was done to ensure the availability of senior staff, during normal working hours, if reintubation was deemed necessary. In clinical units that follow a more liberal extubation approach, (i.e. "fast-tracking") a difference in duration of post-operative mechanical ventilation may be demonstrated.

When comparing the two cardioplegic solutions, blinding was not done as this study was of a prospective cohort analytical study design. The patients were not randomised and the type of cardioplegic solution was determined by the surgeon's preference. This study therefore serves as an indicator but future randomised, controlled trials may provide additional information.

Declarations of Interest: None

Role of the funding source: Department of Anaesthesiology at the University of Free State, which provided financial support for the conduct of the research, had no direct involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The researcher and study leader are members of the department and other personnel of the department assisted with data collection.

Conclusion

Hypophosphatemia was common after cardiopulmonary bypass in this population. The incidence was higher than expected, with 52.6% (95% CI 42.1% to 63.0%) of patients developing hypophosphatemia postoperatively. This did however not translate into a clinically significant implication, as the degree was usually mild (0.66 - 0.79 mmol/l).

References

1. Prough DS, Funston JS, Svensén CH, Wolf SW. Fluids, electrolytes and acid-base physiology. in: Barash PG (ed): *Clinical Anesthesia 7th Edition*, a Wolters Kluwer Business, Philadelphia: Williams & Wilkins, 2013, pp 327-361, Chapter 14.
2. Barrett KM, Barman SM, Boitano S, Brooks HL. Hormonal Control of Calcium & Phosphate Metabolism & The Physiology of Bone in: *Ganong's Review of Medical Physiology 25th Edition*, The McGraw-Hill Education, China: 2016. pp 375-388 Chapter 21.
3. Basri MN, Janattul AJ, Azrina MR, et al. Hypophosphatemia in the intensive care unit: incidence, predictors and management. IMJM 2012;11:31-36.
4. Butterworth JF, Mackey DC, Wasnick JD. Management of patients with fluid and electrolyte disturbances in Morgan and Mikhail's *Clinical Anesthesiology 5th Edition*. McGraw-Hill Companies, USA, 2013. pp 1107-1139, Chapter 49.
5. Wadsworth RL, Siddiqui S. Phosphate homeostasis in critical care. BJA Education, 2016, 9:305–309.
6. Cohen J, Kogan A, Sahar G, et al. Hypophosphatemia following open heart surgery: incidence and consequences. Eur J Cardiothor Surg 2004;26:306-310.
7. Goldstein J, Vincent J-L, Leclerc J-L, et al. Hypophosphatemia after cardiothoracic surgery. Department of Surgery and Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Belgium. Intensive Care Med 1985;11:144–148.
8. Polderman KH, Girbes ARJ. Severe electrolyte disorders following cardiac surgery: a prospective controlled observational study. Critical Care 2004,8:R459-R466 (http://doi:10.1186/cc2973).
9. Salem RR, Tray K. Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. Annals of Surgery 2005;241:343–348.
10. Buell JF, Berger AC, Plotkin JS, et al. The clinical implications of hypophosphatemia following major hepatic resection or cryosurgery. Arch Surg. 1998;133(7):757-761. http://doi:10.1001/archsurg.133.7.757.
11. Zazzo JF, Troche G, Ruel P, Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. Intensive Care Med 1995;10:826–831.
12. Kruse JA, Al-Douahji M, Carlson RW. Hypophosphatemia in critically ill patients: incidence and associations. Crit Care Med 1992,20:S104.
13. Nashefa SAM, Roquesb F, Sharplesc LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012. 41: 734–745. http://doi:10.1093/ejcts/ezs043
14. Ricos C, Alvarez V, Cava F, et al. Current databases on biologic variation: pros, cons and progress. Westgard QC, Desirable Biological Variation Database Specifications [Internet]. 2014. [cited 2018 June 13]. Available from https://www.westgard.com/biodatabase1.htm

15. Badrick T, Hawkins RC, Wilson SR, Hickman PE. Uncertainty of Measurement: What it is and What it Should Be. Clin Biochem Rev Nov 2005,26:155-158
16. Naeem M, Khahro AA, Anees F, Dar MI. Effect of hypophosphatemia on post operative outcomes in cardiac surgery. Pak Heart J, 2017, 50 (02): 116 – 121
17. South Africa: WHO statistical profile. Country statistics and global health estimates by WHO and UN partner [Internet]. 2015. [cited 2018 June 14]. Available from http://www.who.int/gho/countries/zaf.pdf?ua=1
18. Census 2011 – Census in Brief. Statistics South Africa, 102 pp [Internet]. 2012 [cited 02 July 2018]. Available from http://www.statssa.gov.za/census/census_2011/census_products/ Census_2011_Census_in_brief.pdf
19. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2015 Update. Circulation, 2015;131:e29-e322. http://doi10.1161/CIR.0000000000000152
20. Barak V, Schwartz A, Kalickman I, et al. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. Am J Med 1998;104:40–47.
21. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232-244.
22. Švagždienė M, Širvinskas E. Changes in serum electrolyte levels and their influence on the incidence of atrial fibrillation after coronary artery bypass grafting surgery. Institute for Biomedical Research, Clinic of Cardiac Surgery, Kaunas University of Medicine, Lithuan. Medicina (Kaunas) 2006;42(3).

Chapter 3 - Suggestions for Further Research and Application Stemming from Findings

Intra-operative phosphate level monitoring, with the addition of a phosphate analysis, cartilage, to the standard blood gas analysis machine would assist in identifying the 12% of patients that would have developed a low serum phosphate level post-operatively. This can be addressed intra-operatively by, for example, altering the modified St Thomas cardioplegic solution, replacing the potassium chloride in this solution with potassium phosphate.

Findings in this study demonstrated the highest incidence of hypophosphatemia on the second and third post-operative day. Serum phosphate levels should be monitored closely during this period and replaced as clinically appropriate. Consideration should be given to increase the phosphate intake, for the first two days, once enteral feeding is re-initiated.

This study was a done in a single centre and had a relatively small sample population. A multicentre, larger trail may provide a smaller confidence interval and will be able to identify associations that could not reach statistical significance in this study.

The study can be repeated and a liberal fast-tract extubation protocol employed, with frequent assessment of strict extubation criteria, to re-evaluate the association between duration of mechanical ventilation and hypophosphatemia.

This study evaluated the effect of serum phosphate levels of the peri-operative care measures, but further research can be done on the effects of other electrolytes on these variables.

Appendices

A. Ethics Permission

B. Permission of Department of Health

C. Permission form Head of Department

D. Participant Information and Consent Forms

E. Forms for Collecting Data

F. Raw Data Collected

G. Instructions to Authors – Journal of Cardiothoracic and Vascular Anesthesia

Appendix A - Ethics Permission

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

01 March 2017

MR LE GROBBELAAR
DEPT OF ANAESTHESIOLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Mr LE Grobbelaar

HSREC 187/2016 (UFS-HSD2016/1509)
PROJECT TITLE: HYPOPHOSPHATEMIA AFTER CARDIOPULMONARY BYPASS INCIDENCE AND CLINICAL SIGNIFICANCE A SOUTH AFRICAN PERSPECTIVE

1. You are hereby kindly informed that, at the meeting held on 28 February 2017, the Health Sciences Research Ethics Committee (HSREC) approved this protocol after all conditions were met.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval and annually for long term studies.

5. A final report should be submitted at the completion of the study.

6. Kindly use the **HSREC NR** as reference in correspondence to the HSREC Secretariat.

7. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

.....
DR SM LE GRANGE
CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE
Cc Prof BJS Diedericks

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | F: +27 (0)51 444 4359 | E: ethicsfhs@ufs.ac.za
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za

Appendix B - Permission of Department Health

health
Department of
Health
FREE STATE PROVINCE

30 January 2017

Mr. LE Grobbelaar
Dept. of Anaesthesiology
Faculty of Health Science
UFS

Dear Mr. LE Grobbelaar

Subject: Hypophosphatemia After Cardiopulmonary Bypass – Incidence and Clinical Significance a South African Perspective

- Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participants must be obtained
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 31/01/2017

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za/chikobvup@fshealth.gov.za
www.fs.gov.za

Appendix C - Permission form Head of Department

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

07 November 2016

Faculty of Health Sciences
Research Ethics Committee
University of the Free State

RE: DR LE GROBBELAAR: STUDENT NUMBER 2005012956

I hereby confirm that I am aware of the planed research by Doctor L.E. Grobbelaar under the department of Anaesthesiology at the University of the Free State

I have evaluated the study, "Hypophosphatemia After Cardiopulmonary Bypass – Incidence and Clinical Significance a South African Perspective", and agrees to the research.

Consent will be obtained from the Department of Health after ethics approval has been obtained.

Yours sincerely

PROF BJS DIEDERICKS
HEAD OF DEPARTMENT: ANAESTHESIOLOGY

CONSULTANTS/KONSULTANTE: Proff J Diedericks | G Lamacraft | AM Kachelhoffer | CL Odendaal | Drr WP König | M Reyneke | EW Turton | MA Pearson | A Kuhn | LJ van der Nest | MG Senekal | JH Potgieter | M Scheepers | AM Ackermann | PA de Wet | TD Boleke | J Lemmer | L le Roux.

Department of Anaesthesiology / Departement Anestesiologie / Lefapha la Barobatsi
T: +27 (0)51 405 3071/405 3307 | F: +27 (0)51 444 3414 | E: nellucia@ufs.ac.za/maribemn@ufs.ac.za and/en (Prof. BJS. Diedericks) diedericksbjs@ufs.ac.za
205 Nelson Mandela Drive/Rylaan | Universitas | Bloemfontein 9301 | South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G67) | Bloemfontein 9300 | South Africa/Suid-Afrika | www.ufs.ac.za

Appendix D - Participant Information and Consent Forms

INFORMATION DOCUMENT

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective

Dear Study participant

You are scheduled for an open-heart operation tomorrow. Thank you for taking the time to read this information document.

We have noticed that patients have some electrolyte (salts) abnormalities in their blood after this surgery. We are particularly interested in the serum phosphate level (one of these salts).

We want to request your participation in a study we are conducting on this. What this will entail is the following:

- We will review your blood results before and after the operation and look at the electrolytes
- We will review your charts that was recorded in the operation and record the treatment that was given to you – for example medicine or blood products.
- After the operation, we will document the treatment you received. This includes documenting how long you stayed in the ICU and what medicine you received in the ICU.

We will then compare your blood results with your treatment to evaluate if a change in electrolyte levels influenced your treatment.

Participating in this study is voluntary and will not affect your treatment or operation at all. We will not be involved in any of the decisions made regarding your treatment. No additional bloods will be taken – we will just review your results and observing your hospital stay. There is no additional risk to you in participating in this study.

All your information will be handled as strictly confidential and none of your personal details will be shared with third parties. The results of this study may be published but you will remain anonymous.

If we can demonstrate that the serum phosphate level has an influence on patient's treatment after surgery, then we can improve our future decisions regarding prevention and treatment.

If you have any questions, please feel free to ask Dr L.E. Grobbelaar by dialling 7992 from any of the hospitals phones. Please ask any of the hospital staff to assist you with this.

Regards

Dr L.E. Grobbelaar and research associates.

CONSENT TO PARTICIPATE IN RESEARCH

Dear Study participant

You have been asked to participate in a research study.

You have been informed about the study by Dr L.E. Grobbelaar.

You may contact Dr Grobbelaar at 7992 any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

_____ _____

Signature of Translator Date

(Where applicable)

INLIGTINGSDOKUMENT

Hypophosphatemia after Cardiopulmonary Bypass – Incidence and Clinical Significance, a South African Perspective

Geagte studie deelnemer

U is geskeduleer om ope hart operasie more te ondergaan. Baie dankie dat u die tyd neem om die inligtingstuk te lees.

Dit het onlangs onder ons aandag gekom dat Pasiente wat ope hart operasie ondergaan abnormale elektroliet (sout) vlakke in hul bloed het na die operasie. Ons stel veral belang in een van die elektroliete, naamlik fosfaat.

Ons versoek u deelname an ‘n studie waarmee ons tans besig is, dit behels die volgende:

- Ons Sal u bloedresultate voor en na die operasie nagaan.
- Ons sal u kaarte wat tydens die operasie gedokumenteer is nagaan en die behandeling wat u ontvang het dokumenteer – dit sluit byvoorbeel in die mediekasie wat u ontvang het, of bloedprodukte.
- Na afloop van die operasie sal on dokumenteer hoe lank u in die Intensiewe sorg eenheid (ICU) was asook die behandeling wat u ontvang het.

Ons sal dan u bloedresultate vergelyk met die behandeling wat u ontvang het, om daardeur te bepaal of n verandering in elektroliete u behandeling beïnvloed het.

U deelname aan die studie is vrywillig en sal geen invloed hê op die behandeling wat u ontvang of op u operasie nie. Die navorsers is nie betrokke by enige besluitneming oor u behandeing nie. Geen addisionele bloed toetse sal gedoen word nie. Ons gaan slegs u bloedresultate na en dokumenteer die verloop van u post-operatiewe hospital verblyf. Daar is dus geen addisionele risiko betrokke om aan die studie deel te neem nie.

Al u besonderhede sal streng konfidensieel hanteer word en geen van u persoonlike inligting sal met derde partye gedeel word nie. Die resultate van die studie kan moontlik gepubliseer word maar u sal anoniem bly.

Indien daar wel bewys kan word dat die elektroliet vlakke die post-operatiewe veloop en behandeling beïnvloed kan ons, in die toekoms, beter besluite oor behandeling of voorkoming neem.

Indien u enige veredere navrae het is u welkom om Dr L.E. Grobbelaar te skakel by die telefoon nommer 7992 vanaf enige van die telefone in die hospitaal. Die Hospitaal staf kan u Bystaan om te skakel indien u veredere inligting verlang.

Groete

Dr L.E. Grobbelaar en Navorsings vennote

TOESTEMMING TOT DEELNAME AAN NAVORSING

Geagte studie deelnemer

U is versoek om aan ‘n navorsingstudie deel te neem.

U is oor die studie ingelig deur Dr L.E. Grobbelaar.

U kan Dr Grobbelaar enige tyd kontak by 7992 indien u vrae oor die navorsing.

U kan die Sekretariaat van die Etiekkomitee van die Fakulteit Gesondheidsweteskappe, UV by telefoonnommer (051) 4052812 kontak indien u enige vrae het oor u regte as ‘n proefpersoon.

U deelname aan hierdie navorsing is vrywillig, en u sal nie gepenaliseer word of voordele verbeur as u weier om deel te neem of besluit om deelname te staak nie.

As u instem om deel te neem, sal ‘n ondertekende kopie van hierdie dokument sowel as die deelnemerinligtingsblad, wat ‘n geskrewe opsomming van die navorsing is, aan u gegee word.

Die navorsingstudie, insluitend die bogenoemde inligting is verbaal aan my beskryf. Ek begryp wat my betrokkenheid by die studie beteken en ek stem vrywillig in om deel te neem.

_____ _____

Handtekening van deelnemer Datum

_____ _____

Handtekening van getuie Datum

_____ _____

Handtekening van Vertaler Datum

(Waar van toepassing)

TOKOMANE YA TLHAHISOLESEDING

Boemo ba letswai la fosfeite bo tlase ho 2.5 mg/dL (0.81 mmol/L) (Hypophosphatemia) ka morao ho tsela e sebediswang nakwana bakeng sa ho pompa tsamaiso ya madi le oksejene mmeleng nakong ya opereishene hore madi le oksejene a bolokehe a ntse a potoloha hantle – Diketsahalo le Bohlokwa ba Phekolo Lehlakoreng la Afrika Borwa

Monkakarolo ya kgabane diphuputsong

O lenaneng la opereishene ya pelo e tla bulwa hosane. Ke a leboha ha o nkile nako ya ho bala tokomane ena ya tlhahisoleseding.

Re hlokometse hore bakudi ba na le letswai (elektrolaete) le sa tlwaelehang mading a bona ka mora opereishene ena. Re na le kgahleho ka le leng la matswai ana e leng le boemong ba fosfeite

Re batla ho o kopa ho ba le seabo ha hao boithutong bona boo re bo etsang ka tse latelang: Boithuto bona bo kenyelleditse tse latelang:

- Re tla lekola diphetho pele le ka morao ho opereishene, mme re sheba letswai lena e leng elektrolaete.
- Re tla lekola tjhate ya hao eo e ileng ya rekotwa nakong ya opereishene ebile re rekote le meriana eo o ileng wa e fuwa - mohlala moriana kapa dihlahiswa tsa madi.
- Ka morao ho opereishene, re tla ngola meriana eo o e fumantshitsweng. Sena se kenyelleditse hore e tla ba nako e kae eo o e dutseng ka ICU le moriana oo o tla be o o fumantshwe ha o le ka ICU.

Re tla be re bapisa diphetho tsa madi a hao le meriana ho lekola hore na ho na le phetoho maemong a letswai (elektrolaete) a susumetswang ke meriana eo o e fumaneng.

Ho ba le seabo diphuputsong tsena ke boithaopo, mme ho ke ke ha ba le kgahlamemo merianeng kapa opereisheneng ya hao ho hang. Re ke ke ra ba teng diqetong dife kapa dife tse entsweng mabapi le meriana ya hao. Ha ho na madi a tlatsetso a tla nkuwa – re tla lekola feela diphetho, mme re shebe feela ho dula ha hao sepetlele. Ha ho na ditlamorao kapa ho ipheha tsietsing ho ka bang teng ha o ba le seabo diphuputsong tsena tsa boithuto.

Tlhahisoleseding ka wena e tla bolokwa e le lekunutu, mme ha ho na tlhahisoleseding ka wena e tla bolellwa mekgatlo e meng. Diphetho tsa boithuto bona di tla phatlalatswa, empa lebitso la hao le tla dula le sa tsejwe.

Ha eba re ka bontsha hore boemo ba letswai la fosfeite le bile le tshusumetso merianeng ya mokudi ka morao ho opereishene, re ka ntlafatsa diqeto tsa rona mabapi le ho thibela ekasitana le meriana.

Ha eba o na le dipotso dife kapa dife, ka kopo hle botsa Ngaka L.E. Grobbelaar ka ho letsetsa nomorong ena ya mohala 7992 ho tswa mehaleng efe kapa efe ya sepetlele. Ka kopo hle botsa mosebeletsi ofe kapa ofe wa sepetlele ho o thusa mabapi le sena.

Ke a leboha

Ngaka L.E. Grobbelaar le basebetsimmoho diphuputsong.

TUMELLO YA HO BA LE SEABO BOITHUTONG BONA

Monkakarolo ya kgabane

O kopilwe ho ba le seabo diphuputsong tsena tsa boithuto.

O tsebisitswe ka boithuto ke Ngaka L.E. Grobbelaar.

O ka iteanya le Ngaka Grobbelaar nomorong tsena 7992 nako e nngwe le e nngwe ha eba o na le dipotso ka diphuputso tsena.

O ka iteanya le Mongodi wa Komiti ya tsa Boitshwaro wa Fakhalthi ya Saense ya tsa Bophelo nomorong ya mohala (051) 405 2812, ha eba o na le dipotso ka ditokelo tsa hao jwalo ka motho ya nang le seabo diphuputsong tsena.

Ho ba le seabo ha hao ke boithaopo, mme ha ho kotlo ya letho eo o tla e fumantshwa kapa ho lahlehelwa ke menyetla eo o ntseng o e fumana ha eba o hana ho ba le seabo kapa o ikgula diphuputsong tsena.

Ha o dumela ho ba le seabo, o tla fuwa tokomane e saennweng ya khopi ena hammoho le leqephe la tlhahisoleseding leo ho ngotsweng kgutsufatso ya diphuputso tsena.

Diphuputso tsa boithuto bona, ho kenyelleditswe le tlhahisoleseding e ka hodimo ke di hlaloseditswe ka molomo. Ke utlwisisa ho ba le seabo ha ka boithutong bona ho bolelang hore ke dumela ho ithaopa ho ba le kabelo.

_____	_____
Motekeno wa ya nang le seabo	Letsatsi
_____	_____
Motekeno wa paki	Letsatsi
_____	_____
Motekeno wa mofetoledi	Letsatsi

(Moo ho hlokehang)

Appendix E - Forms for Collecting Data

Pre-operative Data Sheet – POCIS Trial Data sheet 1

Patient Hospital Number _____

Study number _____

Consent signed: | YES | NO |

Date: ____/_____/_____

Patient's race: _____

Additional information: Euro 2 Score

Patient related factors		**Cardiac related factors**	
Age (years)	_____	NYHA	_____
Gender	_____	CCS class 4 angina	_____
Renal impairment (Cr clearance)	_____	LV function	_____
Extra cardiac arteriopathy	_____	Recent MI	_____
Poor mobility	_____	Pulmonary hypertension	_____
Previous cardiac surgery	_____		
Chronic lung disease	_____	**Operation related factors**	
Active endocarditis	_____	Urgency	_____
Critical pre-operative state	_____	Weight of the intervention	_____
Diabetes on insulin	_____	Surgery on thoracic aorta	_____

Final EuroSCORE II: _____

Pre-operative:

Calcium: _____

Magnesium: _____

Phosphate: _____

Albumin: _____

Intra-operative Data Sheet – POCIS Trial

Data Sheet 2.1

Anaesthesiologist: Administered by anaesthesiologist

Patient Hospital number: _____

Date: ____/____/_____

Intra-operative fluid administration

Crystalloids: Type _____ Total Volume_____

Colloids: Type _____ Total Volume: _____

Blood Products:

Red cell concentrate: Units (311ml): _____

Cell Saved Blood Transfused (ml): _____

Fresh frozen plasma: Units (250ml): _____

Pooled Platelets: Units (250ml): _____

Cryoprecipitate: Units (30ml): _____

Drugs administered and dose (of importance: dextrose, insulin, corticosteroids)

Drug: _____ Dose: _____

Drug _____ Dose: _____

Drug: _____ Dose: _____

Drug: _____ Dose: _____

Intra-operative Data Sheet – POCIS Trial_____

Data Sheet 2.2

Perfusionist:

Patient Hospital Number: _____

Date: ____/_____/_____

Pump Prime: _____

Duration of Cardiac Bypass: _____

Degree of hypothermia: _____

Duration of hypothermia: _____

Cardiolplegic solution given: _____

Volume of cardioplegia given: _____

Additional fluid administration during bypass

Crystalloids: Type: _____ Volume: _____

Colloids: Type: _____ Volume: _____

Red cell concentrate: _____

Fresh frozen Plasma: _____

Total Volume of Cell saved Blood: _____

Other: _____

Drugs administered on Pump and dose (of importance: dextrose, insulin, corticosteroids)

Drug: _____ Dose: _____

Drug: _____ Dose: _____

Drug: _____ Dose: _____

Drug: _____ Dose: _____

Post-operative Data Sheet – POCIS Trial Data Sheet 3

Patient Hospital Number: _____

Date: ____/_____/_____

Post-operative blood results

	Post-operative					
Variable	Immediate	Day 1	Day 2	Day 3	Day 4	Day 5
Calcium						
Magnesium						
Phosphate						
Albumin						

Cell saved blood Transfused: _____

Duration of ICU Stay: _____

Duration of Post-operative mechanical ventilation: _____

Duration of post-operative inotropic or vasopressor support

Drug: _____ Duration: _____

Drug: _____ Duration: _____

Appendix F - Raw Data Collected

The raw data which were collected during the conduct of this study has been captured in Excel format and is available upon request.

Appendix G - Instructions to Authors – Journal of Cardiothoracic and Vascular Anesthesia

Please find attached the Instructions to Authors as requested by the Journal of Cardiothoracic and Vascular Anesthesia.