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*Masterthesis*

# Predisposing Factors and Impact of Phosphate Substitution in Hypophosphatemia After Cardiac Surgery: A Retrospective Single-center Trial

Janssens U.[1], Calliauw L.[1], Van de Velde S.[2], Cools W.[3], MSc, Vanhonacker D.[3], Heerman J.[2], Lapage K.[2]

*[1]Department of Anesthesiology, University Hospital Brussels, Laerbeeklaan 101, 1090 Jette, Belgium; 2Department of Anesthesiology, Intensive Care and Pain Medicine, General Hospital Maria Middelares, Buitenring-Sint-Denijs 30, 9000 Gent, Belgium; [3]Free University of Brussels, Faculty of Medicine and Pharmacy, Laerbeeklaan 103, 1090 Jette, Belgium.*

Corresponding author: Ulrich Janssens, Laerbeeklaan 101, 1090 Jette. E-mail: Janssens.Ulrich@gmail.com

## *Abstract*

***Background:*** **Hypophosphatemia is a common occurrence following cardiac surgery. Hypophosphatemia is often clinically insignificant due to its mild severity and brief duration during intensive care unit (ICU) admission. Evidence to support hypophosphatemia treatment for mild and moderate hypophosphatemia remains scarce.**
***Objectives:*** **This retrospective cohort study aimed to determine the prevalence of hypophosphatemia, assess the impact of phosphate supplementation on postoperative serum phosphate changes over time and identify patient characteristics that may predispose patients to hypophosphatemia in an elective on-pump cardiac surgical population.**
***Design:*** **This retrospective analysis involved 1003 patients who underwent elective on-pump cardiac surgery as part of a single-center cohort, spanning surgeries performed between January 1st, 2019 and January 2nd, 2022.**
***Setting:*** **At the General Hospital Maria Middelares, Gent, Belgium.**
***Patients:*** **Adults undergoing elective on-pump cardiac surgery between January 1, 2019, and January 2, 2022.**
***Interventions:*** **Patients were categorized into three groups based on their serum phosphate concentrations: no hypophosphatemia (> 0.8 mmol l-1), hypophosphatasemia with and without phosphate supplementation.**
**Main outcome measure: The primary outcome was the postoperative change in serum phosphate concentration within the first 48 hours after ICU admission.**
***Results:*** **Phosphate supplementation resulted in a greater increase in serum phosphate concentration on day 1 (estimate: +0.237 ± 0.026; P < 0.001) and a less pronounced decrease on day 2 (+0.082 ± 0.030; P = 0.006). Postoperative hypophosphatemia occurred in 63.3% of this patient cohort. Higher baseline serum phosphate concentrations, female sex and longer surgical duration were associated with significant changes in postoperative serum phosphate concentrations.**
***Conclusion:*** **This retrospective cohort study acknowledges hypophosphatemia as a common occurrence in adults undergoing on-pump cardiac surgery. A clear benefit of phosphate supplementation could however not be demonstrated, as serum phosphate concentrations seem to normalize, regardless of the severity of hypophosphatemia. Certain patient characteristics predispose patients to more pronounced changes in postoperative serum phosphate concentrations. Future research is needed to explore the role of these patient characteristics and to determine whether phosphate supplementation should be limited to patients with severe hypophosphatemia.**

***Keypoints:***
- **Postoperative hypophosphatemia is a common occurrence in adults undergoing on-pump cardiac surgery.**
- **Regardless of the severity of hypophosphatemia, phosphate supplementation appears ineffective as serum phosphate concentrations seem to normalize.**

*This study was approved by the Institutional Review Board at the General Hospital Maria Middelares with study ID MMS.2022.034 on July 1st, 2022. Chairman of the EC: Prof. dr. Paul Germonpré.*

- **Preoperative serum phosphate concentration, female sex, and duration of surgery were identified as significant predictors of postoperative changes in serum phosphate concentration.**

## Introduction

Hypophosphatemia is a common occurrence after cardiac surgery with reported incidence 26 to 52%[1-3]. Despite its high incidence, research investigating the clinical implications, treatment effectiveness, and predictors of hypophosphatemia in adult cardiac surgical patients remains sparse to date. Phosphate plays a pivotal role in key biochemical pathways such as adenosine triphosphate (ATP) production and is involved in the regulation of subcellular processes through enzyme phosphorylation[4].

Multiple factors contribute to frequent observed postoperative decline in serum phosphate concentrations in cardiac surgical patients. Cardiopulmonary bypass-assisted cardiac surgery is known to induce an acute-phase reaction, characterized by elevated serum concentrations of interleukin-6 and other pro-inflammatory cytokines, decreasing phosphate concentrations[5,6]. Additionally, various pharmacological agents – including mannitol, cardioplegic solutions, sympathomimetic agents, corticosteroids and insulin - can facilitate hypophosphatemia, a phenomenon referred to as drug-induced hypophosphatemia[4,7-12]. In the early postoperative period, complications such as pain-mediated or ventilator-associated hyperventilation may cause respiratory alkalosis, which promotes the intracellular shift of phosphate[13].

Hypophosphatemia is associated with clinical features driven by two key mechanisms: reduced intracellular ATP levels and 2,3-diphosphoglycerate (2,3-DPG) concentrations[13], symptoms of clinically relevant hypophosphatemia, including myocardial depression and respiratory failure, usually occur only in the case of severe hypophosphatemia[13-19]. Moreover, in on-pump cardiac surgical patients, particularly those requiring high-dose insulin therapy, hypophosphatemia may contribute to severe lactic acidosis[19]. Hypophosphatemia has also been correlated with an increased incidence muscle weakness, respiratory failure, ileus, immune dysfunction, and encephalopathy[1]. Sin et al. reported that hypophosphatemia is associated with a prolonged ICU stay[20], yet other studies highlighted the lack of evidence to support treatment for mild and moderate hypophosphatemia[1,21]. Grobbelaar et al. suggested hypophosphatemia is often of limited clinical consequence due to its mild severity and transient nature during ICU stay[22].

Although the severity of hypophosphatemia is well defined, its postoperative incidence in cardiac surgical patients remains highly variable. The role of phosphate supplementation as a treatment and the contribution of patient-specific factors to hypophosphatemia development remain subject to debate.

The aim of this study is firstly to determine the prevalence of hypophosphatemia and secondly to evaluate the effect of phosphate substitution treatment on serum phosphate concentrations during the first 48 hours after on-pump cardiac surgery. Our hypotheses are the following: An overall incidence of hypophosphatemia, in accordance with existing literature, around 20-50% and mostly mild. Secondly, we hypothesize phosphate substitution to have a positive influence, leading to a significant increase in serum levels. Thirdly, we expect to identify patient characteristics – such as baseline serum phosphate concentration, age, sex, kidney function, type of surgery and operation time – that may predispose patients to develop hypophosphatemia in the early postoperative period.

## Methods

### *Study design and population*

The authors conducted a retrospective single-center cohort study of patients who underwent cardiac surgery with cardiopulmonary bypass at the General Hospital Maria Middelares (Gent, Belgium) between January 1, 2019, and January 2, 2022. They obtained approval from the Institutional Review Board (IRB) at the General Hospital Maria Middelares (study ID MMS.2022.034; approval date: July 1, 2022). IRB waived the informed consent due to the retrospective nature of the analysis. All data was anonymized after collection and handled according to GDPR guidelines. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[23]. Inclusion criteria were age ≥ 18 years, American Society of Anesthesiologists class II to IV, serum phosphate concentration available at predefined timepoints (baseline, at admission on ICU and on the first postoperative day) and scheduled for on-pump cardiac surgery. Exclusion criteria were age < 18 years, absence of preoperative or postoperative serum phosphate concentration, chronic kidney disease, eGFR < 45 ml/min, pre-existing serum phosphate concentration hypo- or hyperphosphatemia, underwent deep cooling during surgery or emergency surgery.

Cardiac surgery with cardiopulmonary bypass included isolated coronary bypass graft, isolated single heart valve surgery, multiple heart valve surgery and combined coronary bypass graft with heart valve surgery. Surgical approach to the heart included both conventional median sternotomy and minimal access thoracotomy. Anesthesia and surgery were performed according to the standardized operating procedures. The anesthetic technique consists of a total intravenous anesthesia in combination with rocuronium (1 mg/kg) as muscle relaxant. Propofol was titrated to achieve a BiSpectral Index between 40 and 60 with the use of the Schnider target controlled infusion (TCI) model. Remifentanil was dosed at the discretion of the attending anesthesiologist using the Minto TCI model. As per standard operating procedure, cardiopulmonary bypass was primed with Geloplasma®. Our teams used Custodiol® as cardioplegic solution. Myocardial protection, goal-directed perfusion and cell saving techniques were executed as per institutional protocol. The use of inotropes and antifibrinolytic therapy was left to the discretion of the attending team. After skin closure and termination of the surgical procedure, the patients were kept sedated for transfer to the Intensive Care Unit (ICU). Cooperative, hemodynamical stable patients were weaned from mechanical ventilation under the condition of acceptable blood loss and normothermia. As per standard operating procedure, perioperative insulin administration was adapted according to the institutional protocol. Glycophos® 20 mEq (natriumglycerophopsphate) was administered over 8 hours to achieve intravenous phosphate substitution. At the discretion of the attending Intensive Care physician, postoperative serum phosphate concentrations (< 0.8 mmol/L) triggered phosphate substitution.

### *Data-collection*

Patient demographic and perioperative variables were extracted from the electronic health record (EHR) at the author's hospital. The available demographic and perioperative independent variables included age, sex, serum creatinine concentration, eGFR, surgical procedural time and classification of surgical urgency (elective or emergency). The dependent variable is the serum phosphate concentration measured on predefined timepoints: before the surgical intervention (baseline [$t_b$]), at admission on ICU ($t_0$), on the first ($t_1$) and second ($t_2$) postoperative day. Based on previous consensus, hypophosphatemia was defined as a serum phosphate concentration less than 0.8 mmol/L[4]. The phosphate depletion severity was categorized into mild (0.64-0.8mmol/L), moderate (0.32-0.63mol/L) or severe (<0.32mmol/L)[4,24]. In the hypophosphatemia group, patients were grouped in either received substitution treatment (HP+) or received no substitution treatment (HP-), a third group consisted of patients with a serum phosphate ≥0.8mmol/L on t0 (No-HP)

Our first outcome is defined as the incidence of hypophosphatemia (serum phosphate <0.8mmol/L) in the complete study population. The secondary outcome is a significant difference in change in serum phosphate levels from $t_0$ to $t_1$ and from $t_0$ to $t_2$ between the treatment and non-treatment group. Our third outcome is defined as a significant difference in serum changes at t0 regarding the other available variables (age, sex, serum creatinine concentration, eGFR, surgical procedural time and classification of surgical urgency (elective or emergency)).

### *Statistics*

Continuous variables were assessed for normality using Q-Q plots and are reported as mean (± standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. Categorical data is presented as frequency (percentage). Missing data was assessed by missingness mechanism and variables with > 50% missing data are excluded from the analyses. We assumed the missingness pattern to be missing at random.

Mixed-effects linear regression modelling is conducted for the secondary question to infer whether the evolution of serum phosphate concentrations is different for the two different treatment conditions (phosphate substitution versus none) in hypophosphatemic patients (< 0.8 mmol/L) at $t_0$. The absolute differences in serum phosphate levels at baseline (tb), arrival on ICU ($t_0$), postoperative day 1 ($t_1$) and day 2 ($t_2$), between the above-described groups (HP-, HP+, No-HP) are examined. Treatment condition, timepoint and baseline serum phosphate concentration are included as fixed effects, individual subject as a random effect and the interaction between the treatment condition and timepoint is included in the model. Based on the Akaike information criterion (AIC), a stepwise variable selection is performed to evaluate the rest of the perioperative independent variables in the model. Possible subset specific variance will be addressed by weighting. Model quality will be tested via cross validation. The goodness-of-fit of the model is checked by residual analysis. The type I error rate was set to 0.05. Where applicable, the Bonferroni adjustment of the significance threshold is used to control the family-wise error rate[25]. All analyses were conducted in R version 4.2.2[26].

## Results

A total of 1005 adult patients who underwent on-pump cardiac surgery had at least serum phosphate concentrations at baseline, within 30 minutes after admission on ICU and on the first postoperative day. Two patients had serum phosphate concentrations > 1.45 mmol/L and were excluded from the analysis. At admission on ICU, the hypophosphatemia group consisted of 635 patients and 368 patients had a normal serum phosphate concentration. On the 2nd postoperative day, we noted 246 patients with missing values as these were already discharged to the ward. Figure 1 shows a STROBE flow diagram of the patients included. Patient demographics and perioperative data are presented in Table I and were compared among the three individual groups (No hypophosphatemia on t0 (No HP) vs HP+ vs HP-) using a Kruskal Wallis test non-parametric test in case of continuous variables and chi square tests in case of categorical variables.

At baseline, all patients presented with normal serum phosphate concentrations. Measurements at ICU admission learned that hypophosphatemia occurred in 635 out of 1003 (63.3%) patients. We noted mild hypophosphatemia in 288 (28.7%) patients, moderate hypophosphatemia in 336 (33.5%) patients and 11 (1.1%) patients with severe hypophosphatemia. In 120 (18.9%) patients, phosphate substitution was administered based on the serum phosphate concentration on $t_0$. On respectively the first and the second day after surgery, 968 (96.5%) and 413 (54.7%) patients presented with normal serum phosphate concentrations. On the second postoperative day, respectively 247 (32.7%) and 97 (12.8%) patients had mild and moderate hypophosphatemia. Figure 2 depicts the temporal pattern of serum phosphate levels of the three groups.

Hypophosphatemic patients, treated with intravenous phosphate substitution, had a significant lower serum phosphate concentration

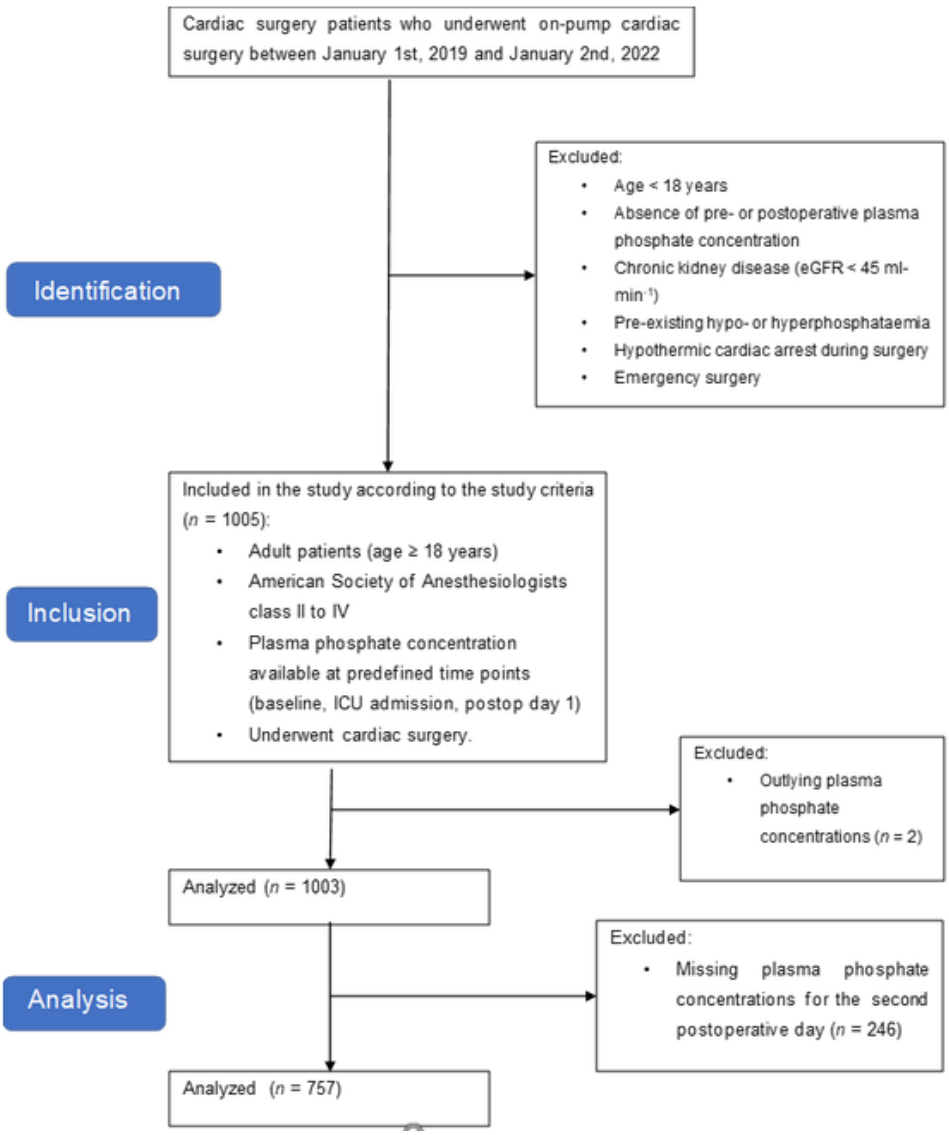


*Fig. 1* — STROBE diagram of included patients.

**Table I.** — Patient baseline characteristics and procedural data.

| | | No HP | HP+ | HP- | P-value |
|---|---|---|---|---|---|
| Total | | 368 (36.7%) | 120 (12.0%) | 515 (51.3%) | |
| Age (y) | | 72 [64 - 78] | 72 [64 - 77] | 73 [65 - 78] | 0.607 |
| Sex | | | | | 0.089 |
| | Male | 287 (37.1%) | 98 (12.8%) | 378 (49.5%) | |
| | Female | 81 (33.8%) | 22 (9.2%) | 137 (57.1%) | |
| Operation Time (h) | | 4.33 [3.58 - 5.19] | 3.59 [3.38 - 4.36] | 4.15 [3.4 - 4.54] | < 0.001 |
| Operation type | | | | | 0.085 |
| | Valve only | 44 (36.7%) | 125 (10%) | 64 (53.3%) | |
| | Combined | 53 (50%) | 8 (7.5%) | 45 (42.5%) | |
| | Minimal invasive | 46 (31.2%) | 18 (12.5%) | 80 (55.6%) | |
| | CABG only | 225 (35.5%) | 82 (13%) | 326 (51.5%) | |

Patient baseline characteristics and procedural data. Data are reported as n(%), median[IQR] or mean ± SD. HP: hypophosphatemia, HP+: hypophosphatemia with phosphate supplementation, HP-: hypophosphatemia without phosphate supplementation, y: years of age, h: hours, IQR: interquartile range, SD: standard deviation.

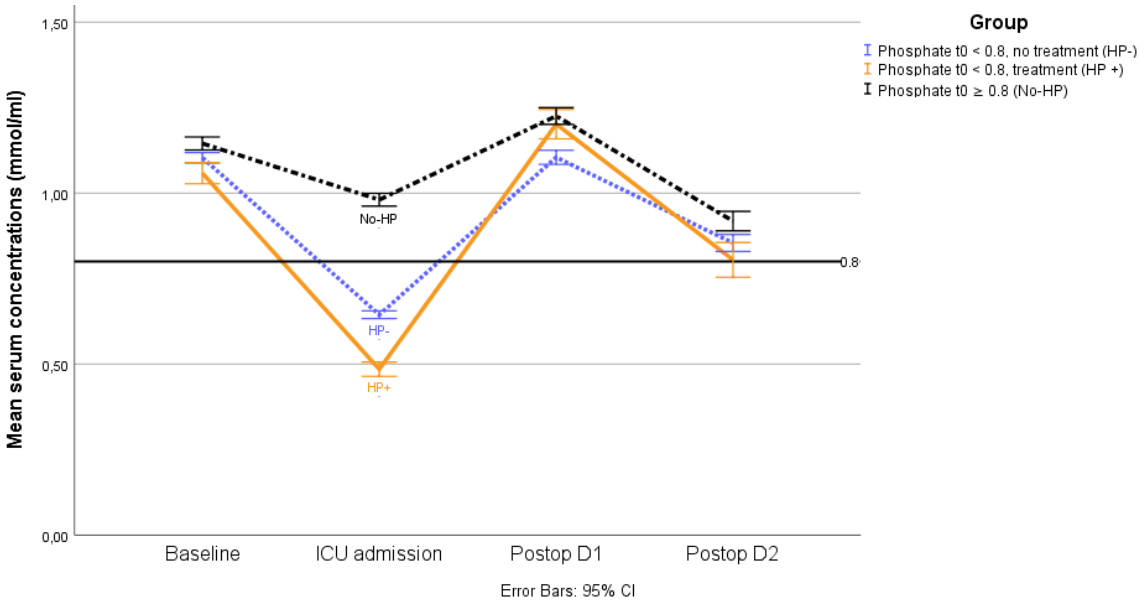


*Fig. 2* — Mean Serum phosphate concentrations.

at ICU admission (estimate: -0.147 [95%CI -0.185 to -0.108], p <0.0001). Subsequently, substituted patients exhibit significant higher serum phosphate concentrations on the first (regression coefficient (RC): 0.231 [95%CI 0.182 to 0.28], p < 0.0001) and second (RC: 0.082 [95%CI 0.027 to 0.137], p < 0.005) postoperative day. The substitution of phosphate causes serum phosphate concentrations to change significantly in the first 48 hours after on-pump cardiac surgery.

To help explain this temporal pattern, the available potential predictors were considered and selected using AIC to guide selection. Sex, age, duration of surgery, preoperative eGFR and serum creatinine concentration as well as the preoperative serum phosphate concentration. None of these predictors helped explain the substitution-induced serum phosphate concentration changes over time. In this patient cohort however, the prevalence of hypophosphatemia on the first postoperative day did not differ significantly between the treatment conditions (1.7% (treated) versus 5% (not treated), p = 0.246). Even though the prevalence of hypophosphatemia increased for the two treatment conditions on $t_2$, the difference remained not significant (52.6% (treated) versus 49.3% (not treated), p = 0.604).

In our patient cohort, we found that higher preoperative serum phosphate concentrations lead to a more pronounced decrease in serum phosphate concentrations (RC: -0.757 [95%CI -0.857 to -0.657], p < 0.0001) after on-pump cardiac surgery at the ICU admission. A negative interaction was found for women indicating that the aforementioned decrease is even more pronounced in women (RC: -0.06 [95% CI -0.1 to -0.02], p = 0.008). Women also start with higher baseline serum phosphate concentrations in our patient cohort (RC: 0.066

[95%CI 0.037 to 0.095], $p < 0.0001$). A positive interaction with surgical duration was noted, indicating an attenuated decrease as the time of surgery increases (RC: 0.0014 [95%CI 0.001 to 0.0018], $p < 0.0001$). Age, preoperative serum creatinine concentration and eGFR could not be withhold as predisposing factors.

## Discussion

In this single-center, retrospective cohort study of patients who underwent on-pump cardiac surgery, hypophosphatemia occurred in 63.3% of eligible patients. Hypophosphatemic patients treated with intravenous phosphate had higher serum phosphate concentrations on the first and second postoperative day despite the lower serum phosphate concentration at ICU admission. In our cohort, a higher baseline serum phosphate concentration and female sex predispose to more pronounced serum phosphate decrements. Surgical duration seems to hamper the decrease in serum phosphate concentration as procedural time prolongs.

Despite the limited number of studies on its incidence, hypophosphatemia is frequently encountered in patients on the intensive care unit. In cardiac surgical patients on ICU, reported incidences of hypophosphatemia range from 21% to 52%[19,22,27]. In our patient cohort, hypophosphatemia occurred more frequently (63.1%) after on-pump cardiac surgery with the majority exhibiting mild to moderate hypophosphatemia. However, the clinical significance of hypophosphatemia remains to be questioned[1,19].

Subsequently, the substitution of phosphate can be questioned. Our retrospective study learned that substituted patients had a lower serum phosphate concentration before treatment and higher serum phosphate concentrations in the first 48 postoperative hours after treatment. However, the difference in hypophosphatemia occurrence was not significant on the first or the second postoperative day. This finding suggests patients with mild to moderate hypophosphatemia at ICU admission redistribute inorganic phosphate in order to correct their serum phosphate concentration. The authors need to stress that all patients had normal serum phosphate concentrations at baseline and were not phosphate depleted. The re-occurrence of hypophosphatemia on the second postoperative day may be a consequence of phosphate redistribution on the first postoperative day. Possible causes for this phenomenon are beyond the scope of this retrospective study.

Grobbelaar et al noted a significant postoperative decrease in serum phosphate concentration after on-pump cardiac surgery[22]. In this retrospective cohort analysis, the authors note a comparable decrease in serum phosphate concentration between baseline and at ICU admission. Moreover, the higher the baseline value, the more pronounced the decrease postoperatively. The authors note that women were significantly predisposed to the same pronounced decrease in serum phosphate concentration at ICU admission despite having the same values at baseline. A possible explanation is estrogenic related downregulation of sodium dependent phosphor reabsorption in the kidney[28]. Surgical time seems to hamper the decrease of serum phosphate concentration, meaning the longer the procedure takes, the less pronounced serum phosphate concentration decreases. Time to redistribute inorganic phosphate may stabilize serum phosphate concentrations, however this is subject to debate. Preoperative serum creatinine concentration and age were not withheld as predictors of immediate postoperative hypophosphatemia.

### *Limitations*

As a result of its retrospective design, the authors' study suffers from limitations. Firstly, treatment of hypophosphatemia was at the discretion of the attending intensive care physician and thus not standardized. This could introduce an indication bias. Indeed, we notice a small decreased serum phosphate on $t_0$ in those who received substitution compared to those who didn't. Although the mixed model is largely able to account for this; a possible bias could however remain. Secondly, our dataset lacks information on the administration of insulin and sympathomimetic agents. As these agents interfere with phosphate homeostasis, possible interactions or associations may have been overlooked. The authors' institution applies a tight glycemic control regimen which leads to more frequent insulin administration. Thirdly, cardiopulmonary bypass (CPB) data were not available for dataset inclusion. However, duration of CPB in general is linked to the duration of surgery. Moreover, the CPB priming as well as the use of cardioplegia is standardized within the author's institution. Therefore, the possible bias, induced by the variation in these CPB specific parameters, is kept low. Fourthly, the present study does not account for preoperative nutritional state, iron supplementation, or transfusion into account. At the authors' institution, the preoperative assessment of elective cardiac surgical patients has been standardized, and these parameters are now routinely recorded. However, for the patient

cohort analysed in this study, these data were not available. Of note concerning these last points is that results may not be generalized to other centres and patient populations. Fifthly, as this is a retrospective study, not all data where available. We have no clinical postoperative data, eg. ventilation, ICU length of stay, complications, etc… on our patients. This study is thus not able to infer a clinical effect. Finally, on the second postoperative day, in respectively 35% of substituted patients and 26% of the non-substituted patients, missing data were detected. The use of a linear mixed model dealt with this issue as missing data was missing completely at random.

## Conclusion

This single-center retrospective study acknowledges hypophosphatemia as frequent in adults undergoing on-pump cardiac surgery. We could not demonstrate a clear effect of phosphate substitution on serum levels, and postoperative serum phosphate levels seem to normalize, irrespective of its severity. Preoperative serum phosphate concentration, female sex and duration of surgery seem to predispose significant changes in postoperative serum phosphate concentrations. Future research is needed to investigate the clinical impact of intravenous phosphate substitution in postoperative hypophosphatemic adult patients after on-pump cardiac surgery. Prediction of hypophosphatemia, based on preoperative patient characteristics, may lead to prevention of severe postoperative hypophosphatemia thereby increasing patient safety.

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*Data sharing:* The data and/or analyses generated during/after the presented study are not publicly available but may be from the corresponding author upon reasonable request.

*Authorship:* Ulrich Janssen, Lucas Calliauw: these authors contributed equally to and share first authorship of this study.
Ulrich Janssen, Lucas Calliauw: Conceptualization, Investigation, Visualization, Writing – original draft.
Stijn Van de Velde, Domien Vanhonacker, Jan Heerman: Conceptualization, Resources, Writing – review & editing.
Willy Cools: Methodology, Formal analysis.
Koen Lapage: Validation, Visualization, Writing – original draft, Writing – review & editing. ESAIC Tracking ID: ESAIC_MSP_KL_2023

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