# Optimization of prime fluid strategy to preserve microcirculatory perfusion during cardiac surgery with cardiopulmonary bypass

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- Part I: determine the difference in microcirculatory perfusion between three different prime fluid strategies in patients undergoing elective cardiac surgery with cardiopulmonary bypass.- Part II: To determine the effect of limiting hemodilution…

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Cardiac therapeutic procedures |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53959

**Source**
ToetsingOnline

**Brief title**
PRIME study

### Condition

- Cardiac therapeutic procedures

**Synonym**
Capillary dysfunction, microcirculatory dysfunction

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum

**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** cardiopulmonary bypass, colloid oncotic pressure, hemodilution, microcirculation

## Outcome measures

### Primary outcome

- Part I. Is there a difference in the change in perfused vessel density between three types of prime fluid strategies following cardiac surgery with CPB?

- Part II. Is there a difference in the change in perfused vessel density between additional albumin administration and ringers during CPB?

### Secondary outcome

Part I

- Is the CPB induced change in COP correlated with perfused vessel density?

- Does the type of prime fluid reduce fluid balance and requirements by preservation of COP?

- Is the CPB induced change in fluid balance correlated with perfused vessel density?

- Is there a difference in markers of endothelial damage, glycocalyx shedding, inflammation, or renal damage among three types of primary fluid strategies after cardiac surgery with CPB?

Part II.

- Does additional albumin administration during CPB reduces the hemolysis index?

- Does additional albumin administration during CPB reduces NO consumption?

- Is CPB induced hemolysis correlated with perfused vessel density?.

- Is NO consumption correlated with perfused vessel density?

Niet-substantieel amendement 18-10-2023

- Do the three types of priming fluid strategies affect acid-base homeostasis?

- Does microcirculatory dysfynction affect resolution of acid-base

abnormalities?

Amendment 26-02-2024

- Do the three types of priming fluid strategies affect the change in oxygen

delivery?

- Is the change in microcirculatory perfusion related to oxygen delivery?

Non-substantial amendment 24-07-24

Do the three types of priming fluids influence the occurrence and maintenance

of acid-base abnormalities before, during, and after CPB?

Is there a relationship between the onset and resolution of acid-base

abnormalities and renal dysfunction?

Is there an independent effect of acid-base abnormalities on microcirculatory

dysfunction before, during, and after CPB?

# Study description

**Background summary**

Acute microcirculatory perfusion disturbances is common in critical illness and associated with increased morbidity and mortality. Recent findings by our group

showed that microcirculatory perfusion is disturbed during cardiac surgery with cardiopulmonary bypass (CPB) and remain disturbed up to 72 hours after surgery. This disturbed microcirculation is associated with organ dysfunction induced by cardiac surgery using CPB, which is frequently seen (up to 42%) and results in a 6-fold increase in mortality rate. The underlying cause of disturbed microcirculation is an increase of endothelial permeability and vascular leakage and are a consequence of systemic inflammation, hemodilution, hypothermia and hemolysis. To increase the knowledge regarding disturbed microcirculation we previously showed that hemodilution attributes to this disturbed perfusion. Hemodilution lowers colloid oncotic pressure (COP). Also, COP is affected by free hemoglobin, which increases with hemolysis and attributes to a disturbed microcirculation following CPB. This is interesting, as to the best of our knowledge, the effect of minimizing hemodilution and hemolysis during cardiac surgery on the microcirculatory perfusion has never been investigated, but could be the key factor in reducing organ dysfunction.

Non-substantial amendment (Oct 18, 2023)
Metabolic acid-base derangement is a known complication of cardiac surgery with cardiopulmonary bypass. Previous investigations have assessed the effects of different priming crystalloids on post-surgery metabolic acid-base status. Crystalloid priming fluid unequivocally cause a dilution of plasma albumin and a corresponding hyperchloraemic acidosis. This is problematic as it may lead to persistent acid-base abnormalities, especially in the context of renal (microcirculatory) dysfunction. The effects of priming strategies with colloids on post-surgical acid-base status and resolution has not been assessed. In this study, these effects may be readily and adequately characterized using Stewart*s physicochemical analysis method on previously collected plasma electrolytes.

Amendment (Feb 26, 2024)
1. Randomisation of trial subjects into 3 groups (groups A/B/C) will be conducted via Castor in a 1:1:1 ratio with block sizes of 3/6/9. Due to exclusion of patients prior to the surgery date, but after inclusion and randomisation, a skewed distribution has occurred in the groups. The reason patients were excluded in this manner is that the surgery date was rescheduled or patients opted for a different procedure (e.g., PCI instead of CABG). The cause of the skewed distribution among the groups is that Castor does not account for exclusions, despite participants being indicated as excluded in Castor. Therefore, we will continue to include participants until the sample size per arm reaches 10 participants.
2A. Addition of oxygen delivery as a secondary endpoint. Recent literature indicates that low oxygen delivery during cardiopulmonary bypass is associated with the development of acute kidney injury postoperatively. However, there is no literature comparing the level of oxygen supply, measured in oxygen delivery, between patients undergoing cardiopulmonary bypass with different priming fluids. Oxygen delivery, calculated through previously determined blood gas analysis and the flow rate during bypass, will be determined during CPB.

The results are exploratory, considering the power analysis was conducted on the primary endpoint.
2B. Adding biomarkers (endothelial, inflammation, and renal function). It has been shown in the literature that the destruction of the glycocalyx, an important component of the microvasculature, is less when albumin is used as a fluid (Cardiovasc Res 2010;87:300-310, Transplantation 2009;87:956-965, J Extra Corpor Technol 2017; 49:174-171). Additional biomarkers are being measured to assess the potential effect of the priming fluid on endothelial, inflammation, and renal function through biomarkers.

Non-substantial amendment (24-07-24)
Adding secondary endpoints related to acid-base status before, during, and after CPB when using three different colloid priming strategies: A. The infusion of crystalloids, priming fluids, and cardioplegia during cardiothoracic procedures can lead to acid-base disturbances. Colloids, particularly albumin, serve as a buffer function in plasma. However, there is no literature describing the effects of various colloid priming fluids on the occurrence and course of acid-base disturbances. The existence or induction of acid-base disturbances may also be an independent risk factor for the development and maintenance of microcirculatory abnormalities, due to changes in electrical and osmotic transmembrane gradients (such as the Gibbs-Donnan equilibrium). Calculating acid-base endpoints only requires determining sodium, potassium, magnesium, calcium, albumin, bicarbonate, chloride, lactate, and phosphate at predefined measurement points. Additionally, markers of renal damage, such as creatinine, will be included in the statistical model, as they may interact with the occurrence of acid-base disturbances. Multivariate testing will also assess whether the degree of acid-base disturbances is independently associated with microcirculatory abnormalities.

## Study objective

- Part I: determine the difference in microcirculatory perfusion between three different prime fluid strategies in patients undergoing elective cardiac surgery with cardiopulmonary bypass.
- Part II: To determine the effect of limiting hemodilution and hemolysis on reduction of CPB induced microcirculatory perfusion disturbances in cardiac surgery.

## Study design

Two randomized controlled trials, double blind

## Intervention

- Part I: Prime fluid strategies containing gelofusine and ringers (A), albumin and ringers (B) or ringers with retrograde autologous priming (C).

- Part II: The best prime fluid to preserve microcirculatory perfusion from Part I combined with either administration of additional human albumin (T) or ringers (C) during CPB.

**Study burden and risks**

The investigation of the effect of different prime fluid strategies on microcirculatory perfusion is justified because it serves a greater social interest in relation to the load and the risks. The different priming strategies are used by various centers in the Netherlands as standard care, whereby the standards of safe cardiac surgery are met in the Netherlands. It is of greater importance to investigate whether the priming strategy can contribute to the prevention of microcirculatory dysfunction during cardiac surgery. In addition, whether the effect of hemolysis can be reduced to prevent microcirculatory dysfunction. With both pieces, we hope to gain insight into reducing microcirculatory dysfunction to improve organ perfusion during cardiac surgical procedures and preserve organ function. It can also contribute to an evidence-based protocol for priming strategies in cardiac surgical care.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Informed consent
Elective surgery
CABG with CPB
Adult subjects

## Exclusion criteria

Emergency operations
Re-operation
Elective thoracic aortic surgery
Combined procedure CABG and Valve surgery
Known allergy for human albumin or gelofusine

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Active |
| Primary purpose: | Prevention |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 10-07-2023 |

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| Enrollment: | 94 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 17-04-2023 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 30-05-2024 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| ClinicalTrials.gov | NCT05647200 |
| CCMO | NL82500.029.22 |