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Complete List of Authors:	Papazisi, Olga; Leiden University Medical Center, Department of Cardiothoracic Surgery Bruggemans, Eline F.; Leiden University Medical Center, Department of Cardiothoracic Surgery Berendsen, Remco; Leids Universitair Medisch Centrum, Department of Anaesthesiology Hugo, Juan D.V.; Leiden University Medical Center, Department of Cardiothoracic Surgery Lindeman, Jan; Leiden University Medical Center, Department of Vascular Surgery Beeres, Saskia; Leiden University Medical Center, Department of Cardiology Arbous, Mendi; LUMC, Intensive Care; LUMC, Epidemiology van den Hout, Wilbert; Leiden University Medical Center, Medical Decisionmaking Mertens, Bart J.A.; Leiden University Medical Center, Department of Biomedical Data Sciences Ince, Can; Erasmus University Rotterdam, Department of Translational Physiology Klautz, Robert; Leiden University Medical Center, Department of Cardiothoracic Surgery Palmen, Meindert; Leiden University Medical Center, Department of Cardiothoracic Surgery
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Prevention of vasoplegia with CytoSorb in heart failure patients undergoing cardiac surgery (CytoSorb-HF Trial): a randomized controlled trial

Olga Papazisi[1], Eline F. Bruggemans[1], Remco R. Berendsen[2], Juan D.V. Hugo[1], Jan H.N. Lindeman[3], Saskia L.M.A. Beeres[4], M. Sesmu Arbous[5], Wilbert B. van den Hout[6], Bart J.A. Mertens[6], Can Ince[7], Robert J.M. Klautz[1], Meindert Palmen[1]

[1]Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands.
[2]Department of Anaesthesiology, Leiden University Medical Center, Leiden, The Netherlands.
[3]Department of Vascular Surgery, Leiden University Medical Center, Leiden, The Netherlands.
[4]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.
[5]Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands.
[6]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.
[7]Department of Intensive Care, Laboratory of Translational Intensive Care, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Correspondence to:
Meindert Palmen;
m.palmen@lumc.nl

Abstract

Introduction. Vasoplegia is a common complication after cardiac surgery and is associated with poor prognosis. It is characterized by refractory hypotension despite normal or even increased cardiac output. The pathophysiology is complex and includes the systemic inflammatory response caused by cardiopulmonary bypass (CPB) and surgical trauma. Patients with end-stage heart failure (HF) are at increased risk for developing vasoplegia. The CytoSorb adsorber is a relatively new haemoadsorption device which can remove circulating inflammatory mediators in a concentration based manner. The CytoSorb-HF Trial aims to evaluate the efficacy of CytoSorb haemoadsorption in limiting the systemic inflammatory response and preventing postoperative vasoplegia in HF patients undergoing cardiac surgery with CPB.

Methods and analysis. This is an investigator-initiated, single-center, randomized, controlled clinical trial. In total 36 HF patients undergoing elective cardiac surgery with an expected CPB duration of more than 120 minutes will be randomized to receive CytoSorb haemoadsorption along with standard surgical treatment or standard surgical treatment alone. The primary endpoint is the change in the systemic vascular resistance index (delta SVRi) with phenylephrine challenge after CPB. Secondary endpoints include inflammatory markers, sublingual microcirculation parameters, and 30-day clinical indices. In addition, we will assess the cost-effectiveness of using the CytoSorb adsorber. Vascular reactivity in response to phenylephrine challenge will be assessed after induction, after CPB, and on postoperative day 1. At the same time points, and before induction and on postoperative day 4 (5 time points in total), blood samples will be collected and the sublingual microcirculation will be recorded. Study participants will be followed up until day 30.

Ethics and dissemination. The trial protocol was approved by the Medical Ethical Committee of Leiden The Hague Delft (METC LDD, registration number P20.039). The

results of the trial will be published in peer-reviewed medical journals and through scientific conferences.

Trial registration number. ClinicalTrials.gov identifier: NCT04812717.

Protocol version. Version 2.0, 28 July 2021.

Keywords: vasoplegia, heart failure, cardiopulmonary bypass, CytoSorb, cytokines, systemic inflammatory response

Strengths and limitations

- This is the first randomized controlled trial evaluating the efficacy of CytoSorb in preventing vasoplegia in HF patients undergoing cardiac surgery with CPB.
- Postoperative vasoplegia is associated with poor outcomes highlighting the importance of new therapeutic or preventive options for this complication.
- Except for the perfusionists, patients, clinicians, and non-clinician investigators involved in the trial will be blinded for treatment allocation to minimize potential bias.
- The effect of CytoSorb will be investigated also at the microcirculatory level.
- The trial involves only one center which might limit the generalizability of the results.

Introduction

Vasoplegia is a common complication after cardiac surgery with cardiopulmonary bypass (CPB) with an incidence that ranges between 5-47%, depending on the population being investigated and the definition used[1-4]. It is characterized by low systemic vascular resistance (SVR) which results in severe hypotension in the presence of normal or even increased cardiac output (CO) and blunted or no response to administration of vasopressors[5]. The complication is associated with increased morbidity and mortality rates and, consequently, has important negative consequences for patients and healthcare costs[2, 6].

The precise aetiology of postoperative vasoplegia is still unclear. However, different mechanisms are thought to be involved[5]. The combination of exposure of blood to the foreign surfaces of CPB and surgical trauma triggers a systemic inflammatory response, which is considered a causative factor in the development of vasoplegia. The sequential release of numerous inflammatory mediators leads to the inactivation of vasoconstrictor mechanisms and the concurrent activation of vasodilatory pathways that may lead to systemic hypotension and subsequent potential organ injury[7].

Patients with end-stage heart failure (HF) undergoing cardiac surgery with CPB are known to be more susceptible to vasoplegia than patients without HF[8]. More specifically, left ventricular ejection fraction <35-40% has been reported to be an independent predictor of vasoplegia after cardiac surgery with CPB[1, 9]. A preexisting, increased inflammatory profile along with the compensatory chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system may be responsible for the development of postoperative vasoplegia in HF patients[10-12].

Recently, we demonstrated in the VASOR study performed at our institution[13] that HF patients exhibit a diminished vascular responsiveness to the administration of phenylephrine (α_1-agonist) already before surgery compared to patients without HF. Further, we showed that the vascular responsiveness is almost completely abolished in HF patients after the use of CPB. We speculate that the results of this study reflect a possible downregulation and/or desensitization of vascular α_1-adrenoreceptors due to chronic endogenous adrenergic stimulation in HF patients, as it has already been documented for β_1- and β_2-adrenoreceptors[14]. We hypothesize that this reduced vascular responsiveness may render HF patients more sensitive to the systemic inflammatory response during cardiac surgery. Thus, minimalizing the systemic inflammatory response could be a treatment strategy to mitigate vasoplegia in this patient population.

The CytoSorb adsorber (CytoSorbents Corporation, New Jersey, USA) is a haemoadsorption device that was approved for use in Europe in 2011. It is a single-use device that contains polymer beads that adsorb cytokines as blood passes through the device. The use of the device has already been tested in multiple studies which report its safety and efficacy in cytokine reduction and, consequently, inflammation reduction[15-17]. However, until the time this protocol was written, no studies had been conducted to assess the efficacy of the use of CytoSorb in HF patients undergoing cardiac surgery.

Trial objectives

Primary objective: to evaluate the efficacy of CytoSorb use in HF patients undergoing cardiac surgery in improving vascular responsiveness after CPB and, consequently, in reducing the incidence of postoperative vasoplegia.

Secondary objectives:

- to investigate the performance of the device in reducing inflammatory mediators.
- to investigate the performance of the device in improving clinical outcomes,

- to investigate the performance of the device in improving microcirculation,
- to investigate the cost-effectiveness of using the device.

Methods and analysis

The trial protocol is written in accordance with the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) checklist[18] (supplement 1). The trial is registered in ClinicalTrials.gov registry (NCT04812717).

Trial design and study setting

This is an investigator-initiated, single-center, randomized controlled clinical trial in patients with HF who undergo cardiac surgery with CPB. The trial will be conducted at Leiden University Medical Center (LUMC).

Trial population

Patients with HF planned for cardiac surgery with CPB with an anticipated duration of at least 120 minutes will be considered for participation in the trial. Detailed inclusion and exclusion criteria are:

Inclusion criteria

- Diagnosed with HF in line with the European Society of Cardiology (ESC) guidelines[19].
- Left ventricular ejection fraction ≤35%.
- Undergoing cardiac surgery with CPB with an anticipated duration of >120 minutes.
- Age ≥18 years.

Exclusion criteria

- Mentally incapacitated.
- Emergency operation.
- Need for pre-operative vasopressor support and/or moderate or high dosages of intravenous inotropic support (>4 gamma dobutamine or dopamine).
- Severe tricuspid regurgitation.
- Daily use of nitroglycerine or isosorbide dinitrate.
- Use of alpha blockers.
- Being heparin-induced thrombocytopenia positive and citrate regional anticoagulation is unavailable as an alternative anticoagulation method.
- Platelet count <20,000/μL.

Randomization and blinding

Patients will be randomized to receive either CytoSorb haemoadsorption along with standard surgical treatment (intervention) or standard surgical treatment without CytoSorb (control) in a 1:1 ratio, using block randomization with random block sizes of 4 and 6. Randomization will be performed in Castor EDC (Amsterdam, The Netherlands) by the responsible perfusionist (JDVH). Castor uses a validated random block randomization model which ensures true randomness during the allocation procedure. Patients, clinicians (surgeons, anaesthesiologists, other practitioners), and non-clinician investigators will be blinded to treatment allocation until after statistical analysis. Perfusionists will hide the CytoSorb device

(or the absence of it) from the sight of the surgeons and anaesthesiologists. Therefore, blinding of perfusionists during CytoSorb use is not feasible. No sham device will be used.

Anaesthetics and haemodynamic monitoring

A standardized anaesthetic protocol will be used. Patients will be given propofol, remifentanil, and sufentanyl using target-controlled infusion. Administration of ketamine and sevoflurane is not allowed. For measurement of change in systemic vascular resistance index (delta SVRi), the main study parameter, all patients will receive a pulmonary artery catheter. The catheter will be placed after induction and will be connected to a HemoSphere advanced monitoring system (Edwards LifeSciences, Irvine, CA, USA).

Intervention

The CytoSorb device will be incorporated as a parallel shunt off of the main CPB system by perfusionists trained in the use of the device (Figure 1).

Study time points and procedures

Vascular reactivity in response to phenylephrine challenge will be assessed in all trial participants after induction, after termination of CPB, and on postoperative day 1. Taking of blood samples and assessment of sublingual microcirculation will be at the same time points and, additionally, before induction and on postoperative day 4 (5 time points in total). Clinical outcomes will be collected until postoperative day 30. The flowchart of the trial can be found in Figure 2.

Phenylephrine challenge

A bolus of 2 µg/kg phenylephrine will be given intravenously (same protocol as in the VASOR study) to measure its effect on SVRi, mean arterial pressure (MAP), and other haemodynamic parameters. When the treating physician decides that it is unsafe for the patient to administer a vasoconstrictor, the challenge will not be performed.

Blood samples

At each time point, blood samples will be collected into 2 tubes of 10 ml to analyze the inflammatory markers interleukin [IL]-6, IL-8, and IL-10. The samples will be centrifuged (1550g, 10 min, 4°C) and the plasma and serum will be stored at minus 80 °C until analysis. Additional blood analysis other than prespecified may be planned based on the findings of this study.

Sublingual microcirculation

Sublingual microcirculation measurements will be performed using incident dark field imaging (Cytocam™, Braedius Medical, Huizen, The Netherlands). On each time point, three image sequences at three different sublingual spots will be recorded per patient by two trained professionals. Each video clip of the microcirculatory flow will be assessed for adequate quality using the microcirculation image quality score proposed by Massey et al.[20]. The completely automated MicroTools Software and the semi-automated Automated Vascular Analysis (AVA) software v3.2 (MicroVision Medical, Amsterdam, The Netherlands) will be used to obtain the microcirculatory parameters[21, 22]. The mean of the three measurements per spot will be noted.

Study parameters

Primary endpoints

- Delta SVRi with phenylephrine challenge (defined as the SVRi after phenylephrine administration minus the SVRi before the challenge) after CPB.
- The occurrence of vasoplegia, defined as the continuous need of vasopressors (norepinephrine ≥0.2 µg/kg/min and/or terlipressin [any dose]) combined with a cardiac index (CI) ≥2.2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days postoperatively.

Secondary endpoints

- Delta SVRi with phenylephrine challenge on postoperative day 1.
- Total administered dosage of vasopressors.
- Change in interleukin IL-6, IL-8, IL-10 levels.
- Change in sublingual microcirculation parameters (microvascular flow index [MFI], capillary density, functional capillary density, total vessel density, proportion of perfused vessels, perfused vessel density, rolling leucocytes, mean cell velocity, capillary hematocrit, red blood cell velocity, heterogeneity index [calculated as the difference between the highest MFI minus the lowest MFI and divided by the mean MFI]).
- Change in MAP with phenylephrine challenge after CPB and on postoperative day 1.
- Hours on mechanical ventilation.
- Hours on mechanical circulatory support.
- Hours on postoperative renal replacement therapy.
- End organ damage (kidney dysfunction).
- Change in total Sequential Organ Failure Assessment (SOFA) Score.
- Amount of used blood transfusion products.
- Amount of used resuscitation fluids.
- Length of ICU stay.
- Length of hospital stay.
- 30-Day hospital readmissions.
- All-cause mortality.

Main cost-effectiveness parameters

- Total administered dosage of vasopressors.
- Amount of used blood transfusion products.
- Amount of used resuscitation fluids.
- Duration of surgery.
- Length of ICU stay.
- Length of hospital stay.

Other study parameters

Other parameters include baseline characteristics (e.g., age, gender, EuroSCORE, comorbidity, medication), routine perioperative blood values, other haemodynamic and oxygenation parameters (i.e., central venous pressure, MAP, CI, heart rate, stroke volume, right ventricular ejection fraction, mixed venous oxygen saturation, tissue oxygen saturation), CPB and cross-clamp time.

Sample size calculation

The primary endpoint is delta SVRi with phenylephrine challenge after CPB. A sample size of 17 patients in each treatment group will have 90% power to detect a difference in means of 400 dyn·s/cm^5 assuming that the common standard deviation is 350 dyn·s/cm^5[23] and when using a 0.05 two-sided significance level. To compensate for possible loss of data due to failing of the vasoconstriction test, 1 extra patient will be included in each group, resulting in a total sample size of 36 patients.

Statistical analysis

The intention-to-treat principle will be applied in all analyses. No missing outcome data will be imputed. All analyses will be performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A P-value <0.05 will be considered statistically significant (two-sided).

Primary and secondary efficacy analysis

For comparison of primary and secondary continuous endpoints, the Student's t-test for independent samples or the Mann-Whitney U test will be used, where appropriate. For discontinuous endpoints, the Pearson chi-square test or the Fisher's exact test will be used, where appropriate. Longitudinal data will be analyzed using the linear mixed-effects model approach.

Cost-effectiveness analysis

A cost analysis will be performed, estimating costs during the index hospitalization in the LUMC. Costs will include the CytoSorb use, vasopressor medication, blood transfusion products, amount of used resuscitation fluids, duration of surgery, ICU stay, and non-ICU hospital stay. The CytoSorb device and medication will be valued using market prices. For other healthcare, reference prices will be used from the Dutch guidelines for economic evaluations in healthcare. Also, a cost-effectiveness analysis will be performed relating CytoSorb use costs to the occurrence of postoperative vasoplegia ("costs per prevented patient with vasoplegia").

Patient and public involvement

Patients and the public are not involved in the trial, including the trial design, conduct, evaluation, and dissemination.

Ethics and dissemination

The current trial protocol was approved by the Medical Ethical Committee Leiden The Hague Delft (in Dutch: Medisch Ethische Toetsingscommissie Leiden Den Haag Delft [METC LDD], registration number P20.039). The initial trial protocol was approved on 27 November 2020. Prior to patient enrollment, the protocol was amended to include the sublingual microcirculation measurements and version 2.0 was approved by the METC LDD on 13 August 2021. The trial will be conducted in agreement with the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen [WMO]) and Good Clinical Practice. Subsequent protocol amendments will be submitted to the METC LDD and registered on ClinicalTrial.gov. The LUMC has a liability insurance and, in addition, a medical research subject insurance which are both in accordance with the WMO.

Recruitment and consent

Eligible patients will receive oral and written information about the trial and will be given at least 24 hours for consideration. Participation will be voluntary and written informed consent will be obtained the day before surgery by the Principal Investigator (MP) or the operating surgeon. Study participants can withdraw their consent at any time and without any consequences. Individuals that withdraw before data collection has started, will be replaced.

Data management

Handling of data complies with the General Data Protection Regulation (in Dutch: Algemene verordening gegevensbescherming [AVG]). Data collection will be pseudonymized and the code key will be stored on a secured server from the LUMC that is backed up daily. Trial data will be stored and maintained in a database created in Castor EDC. Castor EDC complies with ICH E6 (R2) on Good Clinical Practice. Everyone involved in the trial will have authorized access to the data with own accounts and user rights. Reading rights will be allowed to persons carrying out data quality inspections. Data monitoring is provided throughout the study period by independent monitors of the department of Good Research Practice of the LUMC.

Safety monitoring and adverse events

A Data Safety Monitoring Board was not deemed necessary since this is a clinical trial evaluating a CE-marked medical device in the intended patient population and without known device-related complications. Serious adverse events (SAEs) will be reported through the web portal ToetsingOnline to the METC LDD within 7 days after the responsible investigator has first knowledge of the SAE. Adverse events and protocol deviations will be recorded. The Principal Investigator will submit a summary of the trial status, including SAE reports, to the METC LDD once a year.

Dissemination

The results of this trial will be published in peer-reviewed medical journals and presented at scientific conferences. De-identified (including patient codes) trial datasets will be made available from the Principal Investigator upon reasonable request. A data transfer agreement between the LUMC and the receiving institution will cover the transfer of the data.

Trial status

The first patient was enrolled into the trial on 27 October 2021. Study enrollment is currently limited due to the COVID-19 pandemic.

Discussion

Vasoplegia is a serious complication after cardiac surgery in patients with end-stage HF. In recent retrospective studies at our institution, vasoplegia occurred in 19-23% of HF patients undergoing cardiac surgery with CPB, depending on the (sub)population studied, and was a significant contributor to mortality[6]. The increasing prevalence of end-stage HF and the advent of more surgical options for this patient population highlight the importance of developing new strategies for the prevention or treatment of this postoperative complication. The CytoSorb adsorber, a haemoadsorption device capable of removing circulating inflammatory mediators, has shown promising results in a variety of patient populations. However, up until this study protocol was written, no study existed that had tested the efficacy of CytoSorb use in end-stage HF patients undergoing cardiac surgery with CPB. Therefore, with this randomized controlled clinical trial we aim to investigate the efficacy

and cost-effectiveness of CytoSorb use in preventing vasoplegia and improving clinical outcomes in this fragile patient population.

Footnotes

Contributors

MP and OP conceptualised the study. OP, EFB, RRB, JHNL, and MP drafted the protocol. MP obtained funding. JDVH conceived the blinding procedure for non-perfusionists. OP, EFB, and BJAM wrote the statistical analysis plan for the primary and secondary efficacy analysis. WBH wrote the analysis plan for the cost-effectiveness analysis. All authors contributed to refinement of the protocol and approved the final manuscript.

Funding

This trial is financially supported by the Zabawas Foundation and by CytoSorbents Europe GmbH. Neither of the two funders had any role in the trial design. Data collection, analysis, interpretation of the results, and dissemination will be done by the trial's investigators independently from any potential conflicting interest of CytoSorbents Europe GmbH.

Competing interests

All authors have no conflicts to declare.

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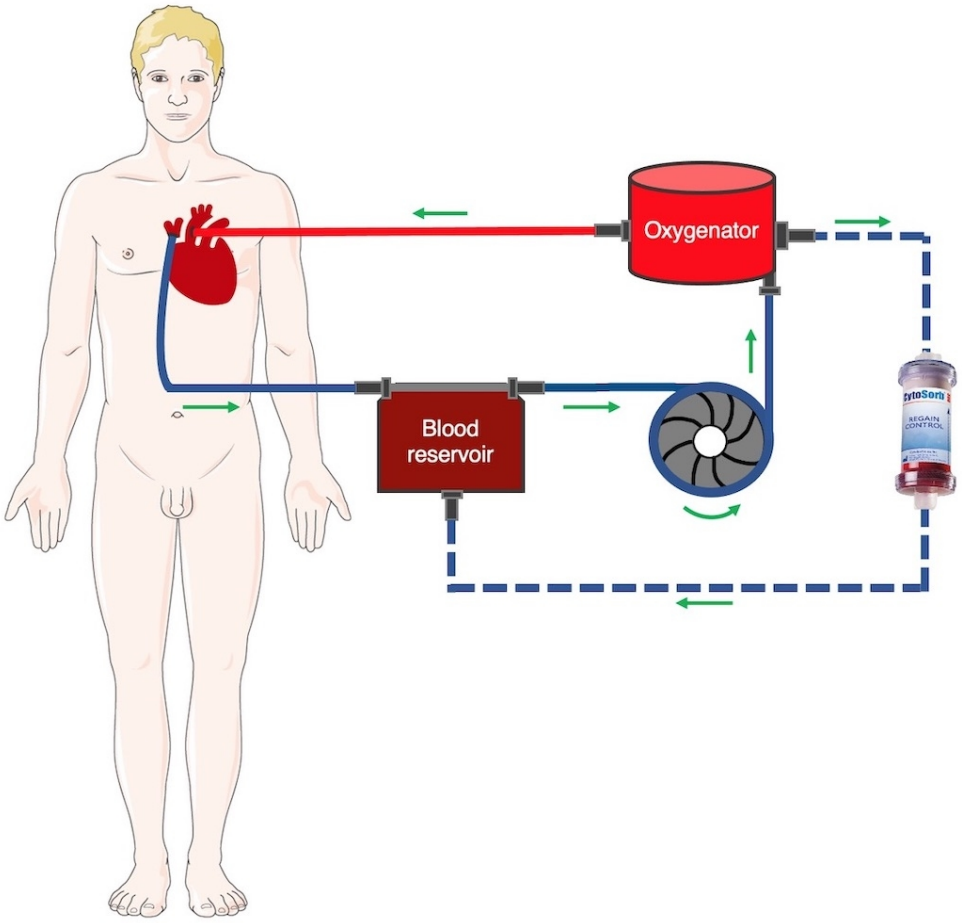
Figures

Figure 1. CytoSorb integration in the cardiopulmonary bypass (CPB) system.

Figure 2. Study flowchart



CytoSorb integration in the cardiopulmonary bypass (CPB) system.

90x85mm (300 x 300 DPI)

			STUDY PERIOD						
	Enrolment		Post-allocation						
	Pre visit	Day before surgery	Day 0				POD 1	POD 4	POD 30
TIMEPOINT**			Pre induction	Post induction	CPB	Post CPB			
ENROLMENT:									
Eligibility screen	X	X							
Informed consent		X							
Randomization		X							
INTERVENTION: *CytoSorb*					X				
ASSESSMENTS:									
SVRi (Phenylephrine challenge)				X		X	X		
Inflammatory markers (Blood sampling)			X	X		X	X	X	
Microcirculatory parameters (Sublingual microcirculation)			X	X		X	X	X	
Baseline variables		X							
Routine blood values			←	—	—	—	—	→	
Haemodynamic parameters			←	—	—	—	—	→	
Clinical data		←	—	—	—	—	—	—	→

CPB, cardiopulmonary bypass; day 0, day of surgery; POD 1, postoperative day 1; POD 4, postoperative day 4; POD 30, postoperative day 30; SVRi, systemic vascular resistance index.
Haemodynamic parameters will be registered until discharge from the Intensive Care.

Study flowchart.

90x69mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Not applicable
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not applicable
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prevention of vasoplegia with CytoSorb in heart failure patients undergoing cardiac surgery (CytoSorb-HF Trial): protocol for a randomized controlled trial

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Prevention of vasoplegia with CytoSorb in heart failure patients undergoing cardiac surgery (CytoSorb-HF Trial): protocol for a randomized controlled trial

Olga Papazisi[1], Eline F. Bruggemans[1], Remco R. Berendsen[2], Juan D.V. Hugo[1], Jan H.N. Lindeman[3], Saskia L.M.A. Beeres[4], M. Sesmu Arbous[5], Wilbert B. van den Hout[6], Bart J.A. Mertens[6], Can Ince[7], Robert J.M. Klautz[1], Meindert Palmen[1]

[1]Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands.
[2]Department of Anaesthesiology, Leiden University Medical Center, Leiden, The Netherlands.
[3]Department of Vascular Surgery, Leiden University Medical Center, Leiden, The Netherlands.
[4]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.
[5]Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands.
[6]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.
[7]Department of Intensive Care, Laboratory of Translational Intensive Care, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Correspondence to:
Meindert Palmen;
m.palmen@lumc.nl

Abstract

Introduction. Vasoplegia is a common complication after cardiac surgery and is associated with poor prognosis. It is characterized by refractory hypotension despite normal or even increased cardiac output. The pathophysiology is complex and includes the systemic inflammatory response caused by cardiopulmonary bypass (CPB) and surgical trauma. Patients with end-stage heart failure (HF) are at increased risk for developing vasoplegia. The CytoSorb adsorber is a relatively new haemoadsorption device which can remove circulating inflammatory mediators in a concentration based manner. The CytoSorb-HF Trial aims to evaluate the efficacy of CytoSorb haemoadsorption in limiting the systemic inflammatory response and preventing postoperative vasoplegia in HF patients undergoing cardiac surgery with CPB.

Methods and analysis. This is an investigator-initiated, single-center, randomized, controlled clinical trial. In total 36 HF patients undergoing elective cardiac surgery with an expected CPB duration of more than 120 minutes will be randomized to receive CytoSorb haemoadsorption along with standard surgical treatment or standard surgical treatment alone. The primary endpoint is the change in the systemic vascular resistance index (delta SVRi) with phenylephrine challenge after CPB. Secondary endpoints include inflammatory markers, sublingual microcirculation parameters, and 30-day clinical indices. In addition, we will assess the cost-effectiveness of using the CytoSorb adsorber. Vascular reactivity in response to phenylephrine challenge will be assessed after induction, after CPB, and on postoperative day 1. At the same time points, and before induction and on postoperative day 4 (5 time points in total), blood samples will be collected and the sublingual microcirculation will be recorded. Study participants will be followed up until day 30.

Ethics and dissemination. The trial protocol was approved by the Medical Ethical Committee of Leiden The Hague Delft (METC LDD, registration number P20.039). The

results of the trial will be published in peer-reviewed medical journals and through scientific conferences.

Trial registration number. ClinicalTrials.gov identifier: NCT04812717.

Protocol version. Version 2.0, 28 July 2021.

Keywords: vasoplegia, heart failure, cardiopulmonary bypass, CytoSorb, cytokines, systemic inflammatory response

Strengths and limitations

- This is the first randomized controlled trial evaluating the efficacy of CytoSorb in preventing vasoplegia in HF patients undergoing cardiac surgery with CPB.
- Postoperative vasoplegia is associated with poor outcomes highlighting the importance of new therapeutic or preventive options for this complication.
- Except for the perfusionists, patients, clinicians, and non-clinician investigators involved in the trial will be blinded for treatment allocation to minimize potential bias.
- The effect of CytoSorb will be investigated also at the microcirculatory level.
- The trial involves only one center which might limit the generalizability of the results.

Introduction

Vasoplegia is a common complication after cardiac surgery with cardiopulmonary bypass (CPB) with an incidence that ranges between 5-47%, depending on the population being investigated and the definition used[1-4]. It is characterized by low systemic vascular resistance (SVR) which results in severe hypotension in the presence of normal or even increased cardiac output (CO) and blunted or no response to administration of vasopressors[5]. The complication is associated with increased morbidity and mortality rates and, consequently, has important negative consequences for patients and healthcare costs[2, 6].

The precise aetiology of postoperative vasoplegia is still unclear. However, different mechanisms are thought to be involved[5]. The combination of exposure of blood to the foreign surfaces of CPB and surgical trauma triggers a systemic inflammatory response, which is considered a causative factor in the development of vasoplegia. The sequential release of numerous inflammatory mediators leads to the inactivation of vasoconstrictor mechanisms and the concurrent activation of vasodilatory pathways that may lead to systemic hypotension and subsequent potential organ injury[7].

Patients with end-stage heart failure (HF) undergoing cardiac surgery with CPB are known to be more susceptible to vasoplegia than patients without HF[8]. More specifically, left ventricular ejection fraction <35-40% has been reported to be an independent predictor of vasoplegia after cardiac surgery with CPB[1, 9]. A preexisting, increased inflammatory profile along with the compensatory chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system may be responsible for the development of postoperative vasoplegia in HF patients[10-12].

Recently, we demonstrated in the VASOR study performed at our institution[13] that HF patients exhibit a diminished vascular responsiveness to the administration of phenylephrine (α_1-agonist) already before surgery compared to patients without HF. Further, we showed that the vascular responsiveness is almost completely abolished in HF patients after the use of CPB. We speculate that the results of this study reflect a possible downregulation and/or desensitization of vascular α_1-adrenoreceptors due to chronic endogenous adrenergic stimulation in HF patients, as it has already been documented for β_1- and β_2-adrenoreceptors[14]. We hypothesize that this reduced vascular responsiveness may render HF patients more sensitive to the systemic inflammatory response during cardiac surgery. Thus, minimalizing the systemic inflammatory response could be a treatment strategy to mitigate vasoplegia in this patient population.

The CytoSorb adsorber (CytoSorbents Corporation, New Jersey, USA) is a haemoadsorption device that was approved for use in Europe in 2011. It is a single-use device that contains polymer beads that adsorb cytokines as blood passes through the device. The use of the device has already been tested in multiple studies which report its safety and efficacy in cytokine reduction and, consequently, inflammation reduction[15-17]. However, until the time this protocol was written, no studies had been conducted to assess the efficacy of the use of CytoSorb in HF patients undergoing cardiac surgery.

Trial objectives

Primary objective: to evaluate the efficacy of CytoSorb use in HF patients undergoing cardiac surgery in improving vascular responsiveness after CPB and, consequently, in preventing postoperative vasoplegia.

Secondary objectives:

- to investigate the performance of the device in reducing inflammatory mediators.
- to investigate the performance of the device in improving clinical outcomes,

- to investigate the performance of the device in improving microcirculation,
- to investigate the cost-effectiveness of using the device.

Methods and analysis

The trial protocol is written in accordance with the "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) checklist[18] (supplement 1). The trial is registered in ClinicalTrials.gov registry (NCT04812717).

Trial design and study setting

This is an investigator-initiated, single-center, randomized controlled clinical trial in patients with HF who undergo cardiac surgery with CPB. The trial will be conducted at Leiden University Medical Center (LUMC).

Trial population

Patients with HF planned for cardiac surgery with CPB with an anticipated duration of at least 120 minutes will be considered for participation in the trial. Detailed inclusion and exclusion criteria are:

Inclusion criteria

- Diagnosed with HF in line with the European Society of Cardiology (ESC) guidelines[19].
- Left ventricular ejection fraction ≤35%.
- Undergoing cardiac surgery with CPB with an anticipated duration of >120 minutes.
- Age ≥18 years.

Exclusion criteria

- Mentally incapacitated.
- Emergency operation.
- Need for pre-operative vasopressor support and/or moderate or high dosages of intravenous inotropic support (>4 gamma dobutamine or dopamine).
- Severe tricuspid regurgitation.
- Daily use of nitroglycerine or isosorbide dinitrate.
- Use of alpha blockers.
- Being heparin-induced thrombocytopenia positive and citrate regional anticoagulation is unavailable as an alternative anticoagulation method.
- Platelet count <20,000/μL.

Randomization and blinding

Patients will be randomized to receive either CytoSorb haemoadsorption along with standard surgical treatment (intervention) or standard surgical treatment without CytoSorb (control) in a 1:1 ratio, using block randomization with random block sizes of 4 and 6. Randomization will be performed in Castor EDC (Amsterdam, The Netherlands) by the responsible perfusionist (JDVH). Castor uses a validated random block randomization model which ensures true randomness during the allocation procedure. Patients, clinicians (surgeons, anaesthesiologists, other practitioners), and non-clinician investigators will be blinded to treatment allocation until after statistical analysis. Perfusionists will hide the CytoSorb device

(or the absence of it) from the sight of the surgeons and anaesthesiologists. Therefore, blinding of perfusionists during CytoSorb use is not feasible. No sham device will be used.

Anaesthetics and haemodynamic monitoring

A standardized anaesthetic protocol will be used. Patients will be given propofol, remifentanil, and sufentanyl using target-controlled infusion. Administration of ketamine and sevoflurane is not allowed. For measurement of change in systemic vascular resistance index (delta SVRi), the main study parameter, all patients will receive a pulmonary artery catheter. The catheter will be placed after induction and will be connected to a HemoSphere advanced monitoring system (Edwards LifeSciences, Irvine, CA, USA).

Intervention

The CytoSorb device will be incorporated as a parallel shunt off of the main CPB system by perfusionists trained in the use of the device (Figure 1).

Study time points and procedures

Vascular reactivity in response to phenylephrine challenge will be assessed in all trial participants after induction, after termination of CPB, and on postoperative day 1. Taking of blood samples and assessment of sublingual microcirculation will be at the same time points and, additionally, before induction and on postoperative day 4 (5 time points in total). Clinical outcomes will be collected until postoperative day 30. The trial schedule can be found in Figure 2.

Phenylephrine challenge

A bolus of 2 µg/kg phenylephrine will be given intravenously (same protocol as in the VASOR study) to measure its effect on SVRi, mean arterial pressure (MAP), and other haemodynamic parameters. When the treating physician decides that it is unsafe for the patient to administer a vasoconstrictor, the challenge will not be performed.

Blood samples

At each time point, blood samples will be collected into 2 tubes of 10 ml to analyze the inflammatory markers interleukin [IL]-6, IL-8, and IL-10. The samples will be centrifuged (1550g, 10 min, 4°C) and the plasma and serum will be stored at minus 80 °C until analysis. Additional blood analysis other than prespecified may be planned based on the findings of this study.

Sublingual microcirculation

Sublingual microcirculation measurements will be performed using incident dark field imaging (Cytocam™, Braedius Medical, Huizen, The Netherlands). On each time point, three image sequences at three different sublingual spots will be recorded per patient by two trained professionals. Each video clip of the microcirculatory flow will be assessed for adequate quality using the microcirculation image quality score proposed by Massey et al.[20]. The completely automated MicroTools Software and the semi-automated Automated Vascular Analysis (AVA) software v3.2 (MicroVision Medical, Amsterdam, The Netherlands) will be used to obtain the microcirculatory parameters[21, 22]. The mean of the three measurements per spot will be noted.

Study parameters

Primary endpoints

- Delta SVRi with phenylephrine challenge (defined as the SVRi after phenylephrine administration minus the SVRi before the challenge) after CPB.
- The occurrence of vasoplegia, defined as the continuous need of vasopressors (norepinephrine ≥0.2 µg/kg/min and/or terlipressin [any dose]) combined with a cardiac index (CI) ≥2.2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days postoperatively.

Secondary endpoints

- Delta SVRi with phenylephrine challenge on postoperative day 1.
- Total administered dosage of vasopressors.
- Change in interleukin IL-6, IL-8, IL-10 levels.
- Change in sublingual microcirculation parameters (microvascular flow index [MFI], capillary density, functional capillary density, total vessel density, proportion of perfused vessels, perfused vessel density, rolling leucocytes, mean cell velocity, capillary hematocrit, red blood cell velocity, heterogeneity index [calculated as the difference between the highest MFI minus the lowest MFI and divided by the mean MFI]).
- Change in MAP with phenylephrine challenge after CPB and on postoperative day 1.
- Hours on mechanical ventilation.
- Hours on mechanical circulatory support.
- Hours on postoperative renal replacement therapy.
- End organ damage (kidney dysfunction).
- Change in total Sequential Organ Failure Assessment (SOFA) Score.
- Amount of used blood transfusion products.
- Amount of used resuscitation fluids.
- Length of ICU stay.
- Length of hospital stay.
- 30-Day hospital readmissions.
- All-cause mortality.

Main cost-effectiveness parameters

- Total administered dosage of vasopressors.
- Amount of used blood transfusion products.
- Amount of used resuscitation fluids.
- Duration of surgery.
- Length of ICU stay.
- Length of hospital stay.

Other study parameters

Other parameters include baseline characteristics (e.g., age, gender, EuroSCORE, comorbidity, medication), routine perioperative blood values, other haemodynamic and oxygenation parameters (i.e., central venous pressure, MAP, CI, heart rate, stroke volume, right ventricular ejection fraction, mixed venous oxygen saturation, tissue oxygen saturation), CPB and cross-clamp time.

Sample size calculation

The primary endpoint is delta SVRi with phenylephrine challenge after CPB. A sample size of 17 patients in each treatment group will have 90% power to detect a difference in means of 400 dyn·s/cm^5 assuming that the common standard deviation is 350 dyn·s/cm^5[23] and when using a 0.05 two-sided significance level. To compensate for possible loss of data due to failing of the vasoconstriction test, 1 extra patient will be included in each group, resulting in a total sample size of 36 patients.

Statistical analysis

The intention-to-treat principle will be applied in all analyses. No missing outcome data will be imputed. All analyses will be performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A P-value <0.05 will be considered statistically significant (two-sided).

Primary and secondary efficacy analysis

For comparison of primary and secondary continuous endpoints, the Student's t-test for independent samples or the Mann-Whitney U test will be used, where appropriate. For discontinuous endpoints, the Pearson chi-square test or the Fisher's exact test will be used, where appropriate. Longitudinal data will be analyzed using the linear mixed-effects model approach.

Cost-effectiveness analysis

A cost analysis will be performed, estimating costs during the index hospitalization in the LUMC. Costs will include the CytoSorb use, vasopressor medication, blood transfusion products, amount of used resuscitation fluids, duration of surgery, ICU stay, and non-ICU hospital stay. The CytoSorb device and medication will be valued using market prices. For other healthcare, reference prices will be used from the Dutch guidelines for economic evaluations in healthcare. Also, a cost-effectiveness analysis will be performed relating CytoSorb use costs to the occurrence of postoperative vasoplegia ("costs per prevented patient with vasoplegia").

Patient and public involvement

Patients and the public are not involved in the trial, including the trial design, conduct, evaluation, and dissemination.

Ethics and dissemination

The current trial protocol was approved by the Medical Ethical Committee Leiden The Hague Delft (in Dutch: Medisch Ethische Toetsingscommissie Leiden Den Haag Delft [METC LDD], registration number P20.039). The initial trial protocol was approved on 27 November 2020. Prior to patient enrollment, the protocol was amended to include the sublingual microcirculation measurements and version 2.0 was approved by the METC LDD on 13 August 2021. The trial will be conducted in agreement with the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen [WMO]) and Good Clinical Practice. Subsequent protocol amendments will be submitted to the METC LDD and registered on ClinicalTrial.gov. The LUMC has a liability insurance and, in addition, a medical research subject insurance which are both in accordance with the WMO.

Recruitment and consent

Eligible patients will receive oral and written information about the trial and will be given at least 24 hours for consideration (supplement 2). Participation will be voluntary and written informed consent will be obtained the day before surgery by the Principal Investigator (MP) or the operating surgeon. Study participants can withdraw their consent at any time and without any consequences. Individuals that withdraw before data collection has started, will be replaced.

Data management

Handling of data complies with the General Data Protection Regulation (in Dutch: Algemene verordening gegevensbescherming [AVG]). Data collection will be pseudonymized and the code key will be stored on a secured server from the LUMC that is backed up daily. Trial data will be stored and maintained in a database created in Castor EDC. Castor EDC complies with ICH E6 (R2) on Good Clinical Practice. Everyone involved in the trial will have authorized access to the data with own accounts and user rights. Reading rights will be allowed to persons carrying out data quality inspections. Data monitoring is provided throughout the study period by independent monitors of the department of Good Research Practice of the LUMC.

Safety monitoring and adverse events

A Data Safety Monitoring Board was not deemed necessary since this is a clinical trial evaluating a CE-marked medical device in the intended patient population and without known device-related complications. Serious adverse events (SAEs) will be reported through the web portal ToetsingOnline to the METC LDD within 7 days after the responsible investigator has first knowledge of the SAE. Adverse events and protocol deviations will be recorded. The Principal Investigator will submit a summary of the trial status, including SAE reports, to the METC LDD once a year.

Dissemination

The results of this trial will be published in peer-reviewed medical journals and presented at scientific conferences. De-identified (including patient codes) trial datasets will be made available from the Principal Investigator upon reasonable request. A data transfer agreement between the LUMC and the receiving institution will cover the transfer of the data.

Trial status

The first patient was enrolled into the trial on 27 October 2021. Study enrollment is currently limited due to the COVID-19 pandemic. Under normal circumstances, the recruitment rate is expected to be approximately 2 patients per month.

Discussion

Vasoplegia is a serious complication after cardiac surgery in patients with end-stage HF. In recent retrospective studies at our institution, vasoplegia occurred in 19-23% of HF patients undergoing cardiac surgery with CPB, depending on the (sub)population studied, and was a significant contributor to mortality[6]. The increasing prevalence of end-stage HF and the advent of more surgical options for this patient population highlight the importance of developing new strategies for the prevention or treatment of this postoperative complication. The CytoSorb adsorber, a haemoadsorption device capable of removing circulating inflammatory mediators, has shown promising results in a variety of patient populations. However, up until this study protocol was written, no study existed that had tested the efficacy of CytoSorb use in end-stage HF patients undergoing cardiac surgery with CPB.

Therefore, with this randomized controlled clinical trial we aim to investigate the efficacy and cost-effectiveness of CytoSorb use in preventing vasoplegia and improving clinical outcomes in this fragile patient population.

Footnotes

Contributors

MP and OP conceptualised the study. OP, EFB, RRB, JHNL, and MP drafted the protocol. MP obtained funding. JDVH conceived the blinding procedure for non-perfusionists. OP, EFB, and BJAM wrote the statistical analysis plan for the primary and secondary efficacy analysis. WBH wrote the analysis plan for the cost-effectiveness analysis.
OP, EFB, RRB, JDVH, JHNL, SLMAB, MSA, WBvdH, BJAM, CI, RJMK and MP contributed to refinement of the protocol and approved the final manuscript.

Funding

This trial is financially supported by the Zabawas Foundation and by CytoSorbents Europe GmbH. Neither of the two funders had any role in the trial design. Data collection, analysis, interpretation of the results, and dissemination will be done by the trial's investigators independently from any potential conflicting interest of CytoSorbents Europe GmbH.

Competing interests

All authors have no conflicts to declare.

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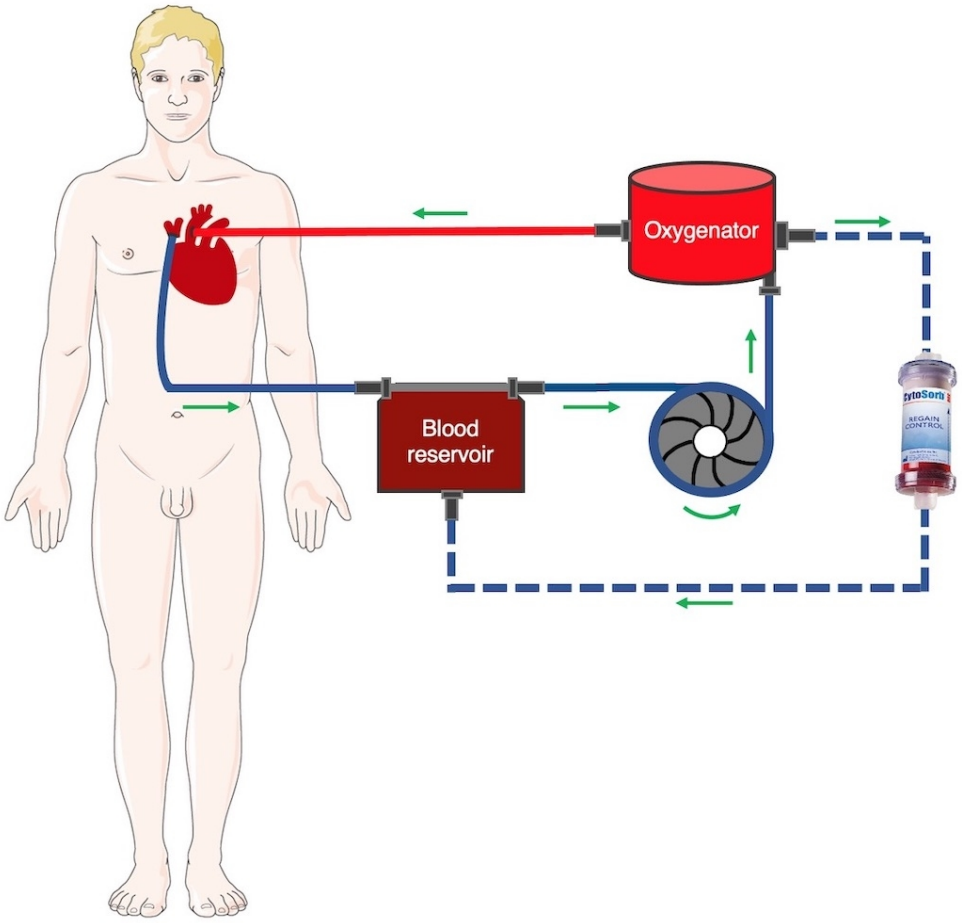
Figures

Figure 1. CytoSorb integration in the cardiopulmonary bypass (CPB) system.

Figure 2. Trial schedule.



CytoSorb integration in the cardiopulmonary bypass (CPB) system.

90x85mm (300 x 300 DPI)

			STUDY PERIOD						
	Enrolment		Post-allocation						
	Pre visit	Day before surgery	Day 0				POD 1	POD 4	POD 30
TIMEPOINT**			Pre induction	Post induction	CPB	Post CPB			
ENROLMENT:									
Eligibility screen	X	X							
Informed consent		X							
Randomization		X							
INTERVENTION: *CytoSorb*					X				
ASSESSMENTS:									
SVRi (Phenylephrine challenge)				X		X	X		
Inflammatory markers (Blood sampling)			X	X		X	X	X	
Microcirculatory parameters (Sublingual microcirculation)			X	X		X	X	X	
Baseline variables		X							
Routine blood values			←	—	—	—	—	→	
Haemodynamic parameters			←	—	—	—	—	→	
Clinical data		←	—	—	—	—	—	—	→

CPB, cardiopulmonary bypass; day 0, day of surgery; POD 1, postoperative day 1; POD 4, postoperative day 4; POD 30, postoperative day 30; SVRi, systemic vascular resistance index.
Haemodynamic parameters will be registered until discharge from the Intensive Care.

Study flowchart.

90x69mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Not applicable
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not applicable
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

CYTOSORB-HF TRIAL

Titel: Preventie van vasoplegie (de bloedvaten kunnen niet meer goed samenknijpen waardoor er lage bloeddruk ontstaat) na een hartoperatie met het gebruik van het CytoSorb filter

Hoofdonderzoeker LUMC: Dr. M. Palmen

Geachte heer/mevrouw,

Wij vragen u om mee te doen aan een medisch-wetenschappelijk onderzoek dat momenteel op de afdeling Thoraxchirurgie plaatsvindt. U ontvangt deze brief omdat bij u hartfalen is vastgesteld waarvoor u binnenkort een hartoperatie ondergaat. Het onderzoek heeft op deze doelgroep betrekking.

Meedoen aan het onderzoek is vrijwillig. Om mee te doen is wel uw schriftelijke toestemming nodig. Voordat u beslist of u wilt meedoen aan dit onderzoek, krijgt u informatie over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag uw chirurg of het onderzoeksteam om uitleg als u vragen heeft. U kunt ook de onafhankelijk deskundige voor dit onderzoek om aanvullende informatie vragen. Alle contactgegevens vindt u in bijlage A bij deze brief. U kunt ook met uw partner, vrienden of familie over meedoen aan dit onderzoek praten.
Algemene informatie over meedoen aan medisch-wetenschappelijk onderzoek vindt u op de website van de Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

Wanneer u voldoende bedenktijd (tenminste 24 uur) heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek. Zowel uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.

1. Algemene informatie

Dit onderzoek wordt uitgevoerd in het Leids Universitair Medisch Centrum (LUMC). In totaal zullen 36 patiënten met hartfalen meedoen.

De medisch-ethische toetsingscommissie Leiden Den Haag Delft (METC LDD) heeft dit onderzoek goedgekeurd.
Algemene informatie over de toetsing van onderzoek vindt u op de website van de Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

2. Doel van het onderzoek

Het doel van dit onderzoek is uitzoeken of het gebruik van een speciaal filter tijdens een hartoperatie voor hartfalen het optreden van een ernstige complicatie, vasoplegie genaamd, kan voorkomen.

3. Achtergrond van het onderzoek

Vasoplegie is een veel voorkomende complicatie na een hartoperatie voor hartfalen. Bij vasoplegie kunnen de bloedvaten niet meer goed samenknijpen waardoor er lage bloeddruk ontstaat die zich soms moeilijk laat behandelen met medicijnen. Een van de oorzaken van deze complicatie is waarschijnlijk het gebruik van de hart-long machine, een apparaat dat tijdens de operatie de functie van het hart en de longen overneemt. Het bloed komt dan in aanraking met een lichaamsvreemde omgeving en dit kan een reactie van het immuunsysteem veroorzaken. Voor deze reactie zijn patiënten met hartfalen extra gevoelig.

Het CytoSorb filter is een filter dat in de hart-long machine kan worden ingebouwd en dat de reactie van het immuunsysteem kan verminderen. Het filter is reeds enige tijd op de markt beschikbaar en is ook al tijdens vele hartoperaties gebruikt. Er zijn echter nog geen studies uitgevoerd om bij patiënten met hartfalen te onderzoeken of het gebruik van dit filter leidt tot het minder vaak voorkomen van vasoplegie na de hartoperatie.

4. Wat meedoen inhoudt

Hoe wordt het onderzoek uitgevoerd?
Indien u besluit aan het onderzoek deel te nemen, zal door loting worden bepaald of tijdens uw hartoperatie het CytoSorb filter wel of niet wordt gebruikt. De kans dat het filter bij u wordt gebruikt is even groot als de kans dat het niet wordt gebruikt. De deelnemers aan het onderzoek worden zo in twee gelijke groepen verdeeld. Door vergelijking van de groepen kan worden onderzocht of het gebruik van het filter minder vaak vasoplegie tot gevolg heeft.
U weet niet in welke groep u zit. Als u het belangrijk vindt, kan dit wel worden verteld nadat het onderzoek is afgelopen.

Procedures voor het onderzoek anders dan bij gebruikelijke zorg
Het onderzoek start op de dag van de hartoperatie (dag 0). U gaat naar de operatiekamer. Als

u hier bent aangekomen, wordt er standaard een dun slangetje in een slagader (arterielijn) geplaatst voor het controleren van uw bloed tijdens de operatie. Via deze arterielijn wordt een extra buisje bloed (20 ml) afgenomen voor het onderzoek. Vervolgens wordt er een filmpje gemaakt van uw bloedcirculatie. Dit zal met een speciale camera worden uitgevoerd die de kleine bloedvaatjes onder uw tong zal registreren. Na het toedienen van alle medicijnen die u standaard voor de operatie krijgt, wordt er nogmaals een extra buisje bloed afgenomen. Vervolgens wordt er voor dit onderzoek een extra test uitgevoerd om te zien hoe uw bloedvaten reageren op een medicijn (fenylefrine) dat ervoor zorgt dat de bloeddruk tijdelijk stijgt en dat het hart sneller gaat kloppen. Dit medicijn wordt toegediend via een infuus dat u standaard krijgt. Tijdens deze test zal er nogmaals een filmpje onder uw tong worden gemaakt. De anesthesist zal u hierna in slaap maken voor de hartoperatie. De hartoperatie zal vervolgens, behalve dat het CytoSorb filter wel of niet zal worden gebruikt, volgens de standaard procedure worden uitgevoerd. Tenslotte zal aan het einde van de hartoperatie er nogmaals een extra buisje bloed worden afgenomen en zullen de test met fenylefrine en het filmpje van uw bloedcirculatie nogmaals plaatsvinden.
Dag 1 is de dag na de hartoperatie. 's Ochtends wordt via de arterielijn (die u dan nog steeds heeft) weer een extra buisje bloed afgenomen voor het onderzoek. Daarnaast wordt nogmaals de test met fenylefrine via het standaard infuus uitgevoerd en het filmpje van uw bloedcirculatie gemaakt.
Op dag 4 wordt er voor een laatste maal een extra buisje bloed afgenomen. De test met fenylefrine wordt nu niet meer herhaald. Op dezelfde dag zal er wel nogmaals een filmpje van uw bloedcirculatie worden gemaakt.
Een overzicht met alle onderzoeksmetingen/ -handelingen vindt u in bijlage B.

Verzamelen van medische gegevens
Voor dit onderzoek worden gegevens over uw hartoperatie en uw herstel (bijv. het optreden van eventuele complicaties) verzameld tot 30 dagen na uw operatie. Dit betekent dat wanneer u na uw hartoperatie in het LUMC mogelijk naar uw eigen ziekenhuis wordt overgeplaatst, deze klinische gegevens bij uw cardioloog/in uw eigen ziekenhuis zullen worden opgevraagd. Na 30 dagen zult u ook thuis worden opgebeld om te vragen hoe het met u gaat. Bij eventuele nieuwe ziekenhuis-opnamen of complicaties zullen de voor dit onderzoek belangrijke klinische gegevens worden opgevraagd bij uw behandelend arts.

5. Mogelijke bijwerkingen en nadelige effecten

Het CytoSorb filter is een geregistreerd medisch hulpmiddel (dat wil zeggen dat het is voorzien van een CE-markering) dat al geruime tijd op de markt beschikbaar is. Het gebruik van dit filter wordt als veilig beschouwd en er zijn geen grote risico's of bijwerkingen bekend. In zeldzame gevallen zou een overgevoeligheidsreactie kunnen optreden, maar dit is nog niet eerder gemeld.

De mogelijke bijwerkingen van het medicijn fenylefrine dat tijdens de extra testen wordt gebruikt zijn: tijdelijk hoge bloeddruk, hoofdpijn, misselijkheid, hartkloppingen, trage hartslag, lage bloeddruk, zweten. Deze eventuele bijwerkingen verdwijnen binnen enkele minuten.

Er zijn geen mogelijke nadelige effecten van het gebruik van de camera om uw bloedcirculatie te registreren.

6. Mogelijke voordelen

Wanneer het CytoSorb filter wordt gebruikt kan dit leiden tot het voorkomen van vasoplegie, een ernstige complicatie na het ondergaan van een hartoperatie, maar dit is niet zeker. Bovendien kan uw deelname aan het onderzoek bijdragen aan het ontdekken van mogelijkheden om vasoplegie te voorkomen, wat leidt tot meer veilige operaties en een verbeterd klinisch resultaat.

7. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u niet wilt meedoen, wordt uw hartoperatie op de gebruikelijke manier uitgevoerd. Er zal dan tijdens de operatie geen gebruik worden gemaakt van het CytoSorb filter. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen, ook tijdens het onderzoek. U wordt dan verder op de gebruikelijke manier behandeld. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan het onderzoeksteam.

Als er nieuwe informatie over het CytoSorb filter of het onderzoek beschikbaar komt die belangrijk voor u is, laat het onderzoeksteam dit aan u weten. U wordt dan, indien dit van toepassing is, gevraagd of u blijft meedoen.

8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als:
- alle metingen voor het onderzoek voorbij zijn (dit is 30 dagen na uw hartoperatie),
- u zelf kiest om te stoppen,
- uw chirurg of het onderzoeksteam het beter voor u vindt om te stoppen,
- het LUMC, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle 36 deelnemers klaar zijn.

9. Gebruik en bewaren van uw gegevens en lichaamsmateriaal

Voor dit onderzoek worden door het onderzoeksteam in het LUMC uw persoonsgegevens verzameld, verwerkt en bewaard. Het gaat hierbij om gegevens zoals uw naam, geboortedatum, en om gegevens over uw hartoperatie en gezondheid. Daarnaast is voor dit onderzoek ook bloed (lichaamsmateriaal) nodig dat in het LUMC zal worden geanalyseerd. Het verzamelen, verwerken en bewaren van uw persoonsgegevens en bloed is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren. Wij vragen voor dit gebruik en bewaren van uw gegevens en bloed uw toestemming.

Vertrouwelijkheid van uw gegevens en lichaamsmateriaal
Om uw privacy te beschermen krijgen uw gegevens en het extra bloed dat bij u wordt afgenomen een code. Uw naam en andere gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel van de code zijn de gegevens voor het onderzoek tot u te herleiden. De sleutel van de code blijft veilig en op een andere plaats dan de onderzoeksgegevens opgeborgen in het

LUMC. Uw gecodeerde onderzoeksgegevens blijven in het LUMC en zullen door het onderzoeksteam worden verwerkt tot rapporten en publicaties. In deze rapporten en publicaties over het onderzoek zijn de gegevens niet tot u te herleiden.

Toegang tot uw gegevens voor controle
Sommige personen kunnen in het LUMC toegang krijgen tot al uw gegevens. Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek goed en betrouwbaar is uitgevoerd. Personen die ter controle inzage krijgen in uw gegevens zijn: een monitor die voor LUMC werkt, nationale en internationale toezichthoudende autoriteiten, bijvoorbeeld, de Inspectie Gezondheidszorg en Jeugd. Zij houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Bewaartermijn gegevens en lichaamsmateriaal
Uw gegevens moeten 15 jaar worden bewaard op de onderzoekslocatie (het LUMC). Ook het bloed dat bij u wordt afgenomen zal niet onmiddellijk na de bloedbepalingen worden vernietigd. Het wordt bewaard om daarop in de loop van dit onderzoek en daarna (tot 15 jaar na uw hartoperatie) nog nieuwe bepalingen te kunnen doen die te maken hebben met dit onderzoek.

Gebruik van gegevens en lichaamsmateriaal voor ander onderzoek
Uw gegevens en bloed kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander medisch-wetenschappelijk onderzoek op het gebied van hartoperaties en/of hartfalen. U kunt op het toestemmingsformulier aangeven of u wel of niet instemt met het gebruik van uw gegevens voor toekomstig onderzoek. Indien u hier niet mee instemt, kunt u gewoon deelnemen aan het huidige onderzoek.

Intrekken toestemming
U kunt uw toestemming voor gebruik van uw gegevens en bloed altijd weer intrekken. Dit geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor toekomstig onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat u uw toestemming intrekt worden nog wel gebruikt in dit onderzoek. Uw bloed wordt na intrekking van uw toestemming vernietigd. Als er al bloedbepalingen zijn gedaan, dan worden die gegevens nog wel gebruikt.

Meer informatie over uw rechten bij verwerking van gegevens
Bij vragen over de verwerking van uw persoonsgegevens kunt u contact opnemen met het onderzoeksteam. Voor algemene vragen of klachten over de verwerking van uw gegevens kunt u ook contact opnemen met de functionaris gegevensbescherming van het LUMC. Bekijk voor meer informatie over privacy het privacy statement van het LUMC op de LUMC-website. Tenslotte kunt u voor algemene informatie over uw rechten bij verwerking van uw gegevens de website van de Autoriteit Persoonsgegevens raadplegen. U vindt alle contactgegevens in bijlage A.

Registratie van het onderzoek
Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken, te vinden via de website van de Centrale Commissie Mensgebonden Onderzoek. Daarin zijn geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website

een samenvatting van de resultaten van dit onderzoek tonen. U vindt dit onderzoek onder CytoSorb-HF Trial.

10. Verzekering voor proefpersonen

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. Niet alle schade is gedekt. In bijlage C vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

11. Informeren huisarts en/of behandelend specialist

Wij informeren bij ontslag uit het LUMC uw huisarts en uw cardioloog dat u aan het onderzoek heeft deelgenomen. Indien nodig, zullen wij contact met uw huisarts of cardioloog opnemen, bijvoorbeeld als er gegevens over uw gezondheid of medicijngebruik voorafgaand aan uw hartoperatie ontbreken of als er vragen zijn over uw herstel na uw hartoperatie (tot 30 dagen na uw operatie).

12. Geen vergoeding voor meedoen

Het eventueel gebruik maken van het CytoSorb filter en de extra procedures (bloedafnamen, extra testen met fenylefrine) voor het onderzoek kosten u niets. U wordt niet betaald voor het meedoen aan dit onderzoek.

13. Heeft u vragen?

Bij vragen kunt u contact opnemen met het onderzoeksteam. Voor onafhankelijk advies over meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke deskundige. Hij weet veel over het onderzoek, maar heeft niets met dit onderzoek te maken.

Indien u een klacht heeft over het onderzoek en dit liever niet wilt bespreken met het onderzoeks-team, dan kunt u contact opnemen met de klachtenfunctionaris van het LUMC. De contactgegevens vindt u in bijlage A.

Bijlage A: Contactgegevens LUMC

Hoofdonderzoeker:
Dr. M. Palmen, cardiothoracaal chirurg
Afdeling Thoraxchirurgie, LUMC
Telefoon: 071 526 4022 (secretaresse)
E-mail: m.palmen@lumc.nl

Coördinator onderzoek:
Mevr. drs. E.F. Bruggemans
Afdeling Thoraxchirurgie, LUMC
Telefoon: 071 526 4581 of 526 4022 (secretaresse)
E-mail: e.f.bruggemans@lum.nl

Onafhankelijk deskundige:
Dr. J.Hjortnaes, cardiothoracaal chirurg
Afdeling Thoraxchirurgie, LUMC
Telefoon: 071 526 4022 (secretaresse)
E-mail: j.hjortnaes@lumc.nl

Klachten:
In geval van klachten over het onderzoek kunt u zich wenden tot de klachtenfunctionaris van het LUMC via e-mail: klachtenfunctionaris@lumc.nl. U kunt ook telefonisch contact opnemen met het secretariaat van het Directoraat Kwaliteit en Patiëntveiligheid (071-5264646; tijdens kantooruren). Zij zullen u doorverbinden naar de dienstdoende klachtenfunctionaris.

Functionaris voor de Gegevensbescherming van de instelling:
Wanneer u vragen heeft over de bescherming van uw privacy kunt u per email contact opnemen met de functionarissen gegevensbescherming van het LUMC via infoavg@lumc.nl

Voor meer informatie over uw rechten zie de LUMC-website:
www.lumc.nl/over-het-lumc/privacy/

Contactgegevens LUMC
Albinusdreef 2
2333 ZA Leiden
Centraal telefoonnummer: (071) 526 91 11
Voor meer informatie over uw rechten zie de website van het LUMC
https://www.lumc.nl/12367/Deelnemers-wetenschappelijk-onderzoek/

Bijlage B: Overzicht van de onderzoeksmetingen en -handelingen

Moment / Behandelingen	Dag van de operatie (Dag 0)				Dag 1	Dag 4
	Vóór anesthesie	Na anesthesie	Hart-longmachine Wel of geen CytoSorb	Einde operatie	Intensive Care	
Fenylefrine test		X		X	X	
Bloedmonster	X	X		X	X	X
Filmpje bloedcirculatie	X	X		X	X	X

Bijlage C: Informatie over de verzekering

LUMC heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Heeft u schade door het onderzoek? Meld dit dan bij deze verzekeraar:

Naam:	Centramed
Adres:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telefoonnummer:	070 301 70 70
E-mail:	info@centramed.nl
Polisnummer:	624.530.305

De verzekering betaalt maximaal € 650.000 zijn per persoon en € 5.000.000 voor het hele onderzoek (en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever).

Let op: de verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

TOESTEMMINGSFORMULIER

CytoSorb-HF Trial

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.

- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.

- Ik geef toestemming voor het informeren van mijn huisarts/specialist(en) die mij behandelt dat ik meedoe aan dit onderzoek.

- Ik geef toestemming voor het opvragen van informatie bij mijn huisarts/specialist(en) die mij behandelt gedurende de eerste 30 dagen na mijn hartoperatie.

- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens en bloedmonsters voor de beantwoording van de onderzoeksvraag in dit onderzoek.

- Ik geef toestemming om mijn gegevens op de onderzoekslocatie (het LUMC) nog 15 jaar na dit onderzoek te bewaren.

- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.

- Ik geef toestemming voor het informeren van mijn huisarts en/of behandelend specialist van onverwachte bevindingen die van belang (kunnen) zijn voor mijn gezondheid.

- Ik geef □ **wel**
  □ **geen**
  toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van hartoperaties en/of hartfalen.

- Ik geef □ **wel**
  □ **geen**
  toestemming om mijn bloed na dit onderzoek te bewaren en om dit later nog voor ander onderzoek te gebruiken, zoals in de informatiebrief staat.

- Ik geef □ **wel**
  □ **geen**
  toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolg-onderzoek.

- Ik wil □ **wel**
  □ **niet**
  geïnformeerd worden over welke behandeling ik heb gehad/in welke groep ik zat.

- Ik wil meedoen aan dit onderzoek.

Naam proefpersoon:

Handtekening: Datum: __ / __ / __

- Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

- Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker (of diens vertegenwoordiger):

Handtekening: Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.