Cardiopulmonary bypass

Clinical studies in cardiac surgery patients

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Cover illustration: Emma Johansson

Heart and lungs with roller pump, aquarelle

Opposite: Diagram of early heart-lung machine used by CW Lillehei 1955

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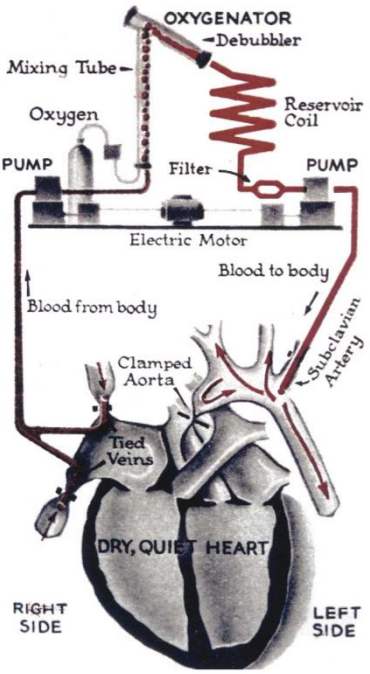
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Clamped Aorta
Tied Veins
DRY, QUIET HEART
RIGHT SIDE
LEFT SIDE

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ABSTRACT

BACKGROUND: Cardiopulmonary bypass (CPB) is necessary to facilitate most cardiac operations. Although the vast majority of patients tolerate CPB physiology in conjunction with cardiac surgery well, there is risks of adverse outcomes. Optimal CPB perfusion is not defined, and may vary according to operation and patient specific factors.

AIMS: The project aims to study different aspects of CPB management and risk in adult cardiac surgery. The first part of the project investigates the efficacy and safety of dextran 40 based colloid prime compared to crystalloid prime. The second part aimed to describe the dynamics of brain injury markers in peripheral blood after routine cardiac surgery. Lastly, we aimed to identify manageable CPB variables associated to risk of acute kidney injury (AKI).

METHODS: We conducted a prospective, randomized, double-blinded, single-center study to compare dextran 40 based colloid prime with ringer acetate with added mannitol prime in elective adult cardiac surgery patients. Serum colloid osmotic pressure was measured before, during, and after CPB. Biochemical markers for organ injury, inflammation, hemolysis, hemostasis, pulmonary function, and brain injury markers were measured before and after CPB. Fluid balance, bleeding and transfusion requirements were recorded during and after operation. To analyze risk of AKI in relation to CPB management, we conducted a registry based study combining prospectively collected outcome data from the SWEDEHEART registry with our institutions automated CPB registry.

RESULTS: Dextran 40 based prime was better at maintaining serum colloid osmotic pressure during and shortly after CPB, and also improved total fluid balance compared to crystalloid prime. Although dextran treated patients had a measurable effect on laboratory and functional coagulation values, it did not increase the risk of bleeding or transfusion. Acute renal tubular injury and hemolysis was less pronounced in dextran prime patients, however, there were no difference in AKI rates. In adjusted observational data, we identified an association between risk of AKI and time on CPB, aortic clamp time, compromised flow, and nadir hematocrit during CPB, along with several patient specific risk factors. Markers of brain injury in serum and plasma were all significantly elevated in the first 24 hours after CPB compared to preoperative baseline values. The individual markers had different temporal distribution and large variability in magnitude and inter-individual differences. The increase was independent of blood-brain barrier damage, and levels were correlated with patient age, CPB duration, and/or hemolysis.

CONCLUSION: CPB prime with dextran 40 is safe and effective in adult cardiac surgery, and seems to attenuate CPB induced renal tubular injury and hemolysis. To reduce the risk of cardiac surgery associated AKI, it is important to keep the time on CPB and aortic cross clamp short, and to maintain hematocrit and pump flow during CPB. There is a release of brain injury biomarkers in peripheral blood after cardiac surgery that is not attributed to evident neurologic damage or blood-brain barrier dysfunction.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their roman numerals:

I. Barbu M, Kolsrud O, Ricksten SE, Dellgren G, Zetterberg H, Blennow K, Björk K, Thorén A, Hansson C, Jeppsson A.

Dextran- versus crystalloid-based prime in cardiac surgery: A prospective randomized pilot study
Ann Thorac Surg 2020;110:1541-48

II. Kolsrud O, Barbu M, Dellgren G, Björk K, Corderfeldt A, Thóren A, Jeppsson A, Ricksten SE.

Dextran-based priming solution during cardiopulmonary bypass attenuates renal tubular injury – A secondary analysis of randomized controlled trial in adult cardiac surgery patients
Acta Anaesthesiol Scand 2022;66:40-47

III. Barbu M, Kolsrud O, Radulovic V, Dellgren G, Björk K, Thóren A, Pivodic A, Ricksten SE, Jeppsson A.

Hemostatic effects of a dextran-based priming solution for cardiopulmonary bypass: A secondary analysis of a randomized clinical trial
Submitted

IV. Barbu M, Jónsson K, Zetterberg H, Blennow K, Kolsrud O, Ricksten SE, Dellgren G, Björk K, Jeppsson A.

Serum biomarkers of brain injury after uncomplicated cardiac surgery: Secondary analysis from a randomized trial
Acta Anaesthesiol Scand 2022;66:447-53

V. Barbu M, Hjärpe A, Martinsson A, Dellgren G, Ricksten SE, Lannemyr L, Pivodic A, Taha A, Jeppsson A.

Associations between cardiopulmonary bypass variables and acute kidney injury in cardiac surgery patients
(Submitted)

SAMMANFATTNING PÅ SVENSKA

En hjärtlungmaskin (HL-maskin) används för att möjliggöra kirurgi på stillastående hjärta samtidigt som helkroppscirkulation med syresatt blod kan bibehållas. Att cirkulera blodet med en HL-maskin leder till stora omställningar i kroppen som kan ge upphov till biverkningar. Akut njursvikt, hjärnpåverkan, inflammation, ödem, och blödningsrubbningar är alla förekommande komplikationer. Detta forskningsprojekt syftar till att studera hur tillämpning av HL-maskinen påverkar risken för biverkningar.

Innan andvänding av HL-maskin kan påbörjas behöver maskinen fyllas med vätska, kallad prime. Denna prime är till för att motverka luft i systemet och kompensera för den volymsförlust som tillkommer då en del av blodet cirkuleras utanför kroppen under ingreppet. Tillskottet av primevätska till blodbanan (standard ca 1.2-1.6 L) medför en påverkan på blodet, bland annat en spädning av blodets makromolekyler. Makromolekyler bidrar till det kolloidosmotiska trycket i blodet, vilket är viktigt för att hålla vätska kvar inne i blodbanan och hindra vävnadsödem. I syfte att försöka förhindra utspädningen av blodets makromolekyler genomförde vi en klinisk studie där patienter fördelades slumpvis till att genomgå hjärtkirurgi med antingen prime med tillsatts av makromolekyler (dextran 40 kolloid) eller prime utan makromolekyler (kristalloid). Då HL-maskinen påverkar hela kroppen undersöktes även påverkan på andra organsystem liksom blödning och vätskebalans. I en andra del av projektet undersöktes hur hjärtkirurgi påverkade nivåerna av hjärnskademarkörer i blodet. Detta är en ny möjlighet, då tidigare mätmetoder inte har varit lika känsliga och har behövt prov från ryggmärgsvätska för analys, där eftersökta markörer förekommer i högre koncentration. Den nya metoden skulle i framtiden kunna innebära en förenklad diagnostik av hjärnskada i samband med hjärtkirurgi. Sista delen av projektet studerade med hjälp av registerdata hur olika justerbara variabler för HL-maskinen påverkar risken för postoperativ akut njursvikt.

Vi fann att prime med dextran 40 var bättre på att bibehålla det kolloidosmotiska trycket i blodet under tiden för HL-maskinanvändning, vilket även förbättrade patienternas vätskebalans. Dessutom kunde vi notera mindre tubulär njurskada och mindre hemolys hos personer med dextran 40 prime. Däremot hade patienter med dextran prime ett lägre blodvärde under maskinanvändning, vilket inte berodde på ökad blödning. Sannolikt var det lägre blodvärdet en utspädningseffekt till följd av att mer vätska stannade kvar i blodbanan. Vi fann att samtliga fem analyserade hjärnskademarkörer ökade i blodet efter hjärtkirurgi oavsett primebehandling. Mängden hjärnskademarkör var dessutom kopplat till individens ålder, tid i HL-maskin, och hemolys. Resultaten från hjärtskademarkörerna var inte kontrollerade mot någon form av bilddiagnostik eller kognitionstest varför det inte säkert går att säga vad ökningen beror på. Från registerdata kunde vi finna att 14.5% av alla hjärtopererade drabbades av akut njursvikt. Risken att drabbas av njursvikt ökade i förhållande till hur länge HL-maskinen användes, hur länge kroppspulsådern var avstängd, hur lågt blodvärdet var under tiden för HL-maskin, samt om det förekom någon påverkan på HL-maskinens pumpflöde. Slutsatser från projektet innefattar att prime med dextran 40 har en positiv inverkan på det kolloidosmotiska trycket, att det är viktigt att bibehålla blodvärde och pumpflöde under operation, samt hålla HL-maskintiden så kort som möjligt.

TABLE OF CONTENTS

ABBREVIATIONS

AKI	Acute kidney injury
ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ASAT	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
BBB	Blood-brain barrier
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass
COP	Colloid osmotic pressure
CPB	Cardiopulmonary bypass
CSF	Cerebrospinal fluid
DO_2	Oxygen delivery
GFAP	Glial fibrillary acid protein
GFR	Glomerular filtration rate
IL	Interleukin
KIDIGO	Kidney Disease Improving Global Outcomes
LVEF	Left ventricular ejection fraction
INR	International normalized ratio
IQR	Interquartile range
MAP	Mean artery pressure
NAG	N-acetyl beta-D-glucosaminidase
NfL	Neurofilament light chain
NSE	Neuron-specific enolase
NYHA	New York Heart Association
PaO_2/FiO_2	Partial pressure oxygen in arterial blood/percent inspired oxygen
POCD	Postoperative cognitive dysfunction
PT	Prothrombin time
SD	Standard deviation
T-tau	Total tau protein
VO_2	Oxygen consumtion

1 INTRODUCTION

1.1 The advent of CPB

Cardiopulmonary bypass (CPB) provides perfusion with oxygen rich blood to the body's vital organs during advanced surgical treatments of the heart and the great vessels. The first clinical series of open heart operations with cardiopulmonary bypass were conducted in 1955 by two separate groups (1, 2). This revolutionary breakthrough was preceded by the work of John H. Gibbon, who spent 22 years of research to develop the IBM Gibbon Model II heart-lung machine. With it he performed the first ever successful operation with CPB in May 1953 when he surgically repaired a large atrial septum defect in an 18 year old female (3).

Cardiopulmonary bypass is achieved by draining venous blood intended for the right atrium and the lungs, diverting it to an extracorporeal oxygenator, and subsequently pumping it back into the patient's arterial system, Figure 1. This enables the surgical team to exclude the heart from the circulatory system and perform direct vision surgery on an arrested heart under fairly blood-less conditions.

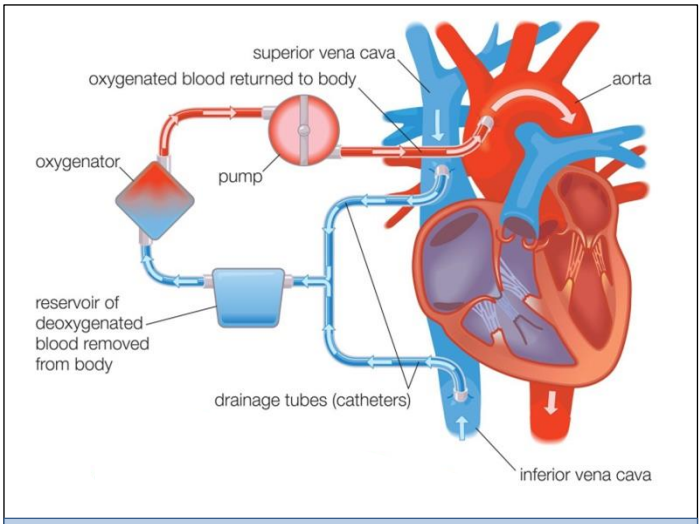


Figure 1. The general principle of cardiopulmonary bypass Image adapted from public domain. https://www.britannica.com/science/heart-lung-machine/images-videos#/media /1/258457/120768videos#/media/1/258457/120768

The CPB unit may have many components, but standard CPB generally require a blood reservoir, an oxygenator, a pump system, a heater/cooler unit, and tubing. The CPB circuit needs to be filled with fluid, a prime, before it's connected to the patient's circulatory system to avoid air embolism and to compensate for the loss of drained blood volume at the start of CPB.

An important part of the pioneering history of CPB took place in Sweden. The second ever successful use of a heart-lung machine in clinical context was performed in Stockholm by Dr. Clarence Crafoord in 1954 with a patient operated for a myxoma of the left atrium. Crafoord and colleagues further developed the heart-lung machine and reported their first 25 patients in 1957 (4), Table 1. Although the ~50% survival rate, the results should be viewed as a success considering that almost all patients were severely ill and could not have received treatment without the new CPB technique.

Table 1. Operations with heart-lung machine at the Sabbatsberg Hospital 1953-1957

Case	Date	Gender, Age	Diagnosis	Operation	CPB (min)	Operation Survivor
1	July 1954	F 42	Myxoma	Exstirpation	33	Y
2	Nov 1954	F 1	VSD	Suture	?	N
3	Dec 1955	M 17	Aneur.sinus Valsalva	Suture	?	N
4	May 1956	M 5	VSD	Suture	?	N
5	June 1956	M 52	LV-aneurysm	Resection	20	Y
6	July 1956	M 16	Fallot	Correction	36	N
7	July 1956	F 31	ASD primum	Ivalon patch	21	Y
8	July 1956	M 6	VSD	Ivalon patch	41	Y
9	July 1956	F 2	ASD + VSD	Suture + Ivalon patch	40	N
10	Aug 1956	M 21	ASD primum	Ivalon patch	30	Y
11	Sept 1956	M 14	AS	Commissurotomy	7	Y
12	Sept 1956	M 4	Transp. + VSD	Switch + Ivalon patch	100	N
13	Oct 1956	F 41	AS	Commissurotomy	9	N
14	Oct 1956	M 17	Infundib. Stenosis	Resection	11	Y
15	Oct 1956	F 21	ASD	Ivalon patch	26	Y
16	Oct 1956	F 48	MS + AS + TI	Comm.tomies M + A	7	N
17	Nov 1956	M 34	VSD + valv. PS	VSD patchc + outflow patch	60	Y
18	Nov 1956	M 52	AS	Commissurotomy	?	N
19	Nov 1956	M 11	ASD	Ivalon patch	?	Y
20	Nov 1956	M 38	AS	Commissurotomy	?	N
21	Jan 1957	M 1	VSD	Suture	?	N
22	Feb 1957	M 15	ASD primum	Ivalon patch	?	Y
23	Mar 1957	F 10	Transp. + VSD	Switch + suture	?	N
24	Apr 1957	F 18	ASD	Ivalon patch	?	N
25	May 1957	F 30	ASD	Ivalon patch	?	Y

AS=aortic stenosis; ASD=atrial septal defect; LV=left ventricle; PS=pulmonarystenosis; MS=mitral stenosis; TI=tricuspid insufficiency; Transp=transposition; VSD=ventricular septum defect. Reprinted from Rådegran K. J Card Surg. 2003;18 (6):564-72. With permission from John Wiley and Sons.

1.2 Initial methodological concerns

The development of CPB could not have been possible without the introduction of heparin for anticoagulation, and the possibility to reverse its effect with protamine (5). Effective blood oxygenation to support human blood flow was an initial challenge. Bubble oxygenators arterialized blood by introducing gas bubbles into direct contact with the blood, but provided difficulties with air embolism and foam buildup. The use of silicone coated surfaces for antifoam purpose and the addition of a bubble reservoir made these oxygenators reliable and widely used (6), Figure 1. The mechanical trauma on the blood elements by the gas bubbles and the artificial surfaces of the CPB machine resulted in red blood cell damage, platelet depletion and protein denaturation. A profound inflammatory activation was evident, and prolonged (>4h) periods of use risked serious complications with bleeding, diffuse capillary leakage and organ failure (7, 8). Rotating disk oxygenators were less traumatic by creating a thin blood film in an oxygen rich atmosphere where gas exchange could take place. These early oxygenators needed a large surface area and required large volumes (3L) of allogenic blood for priming.

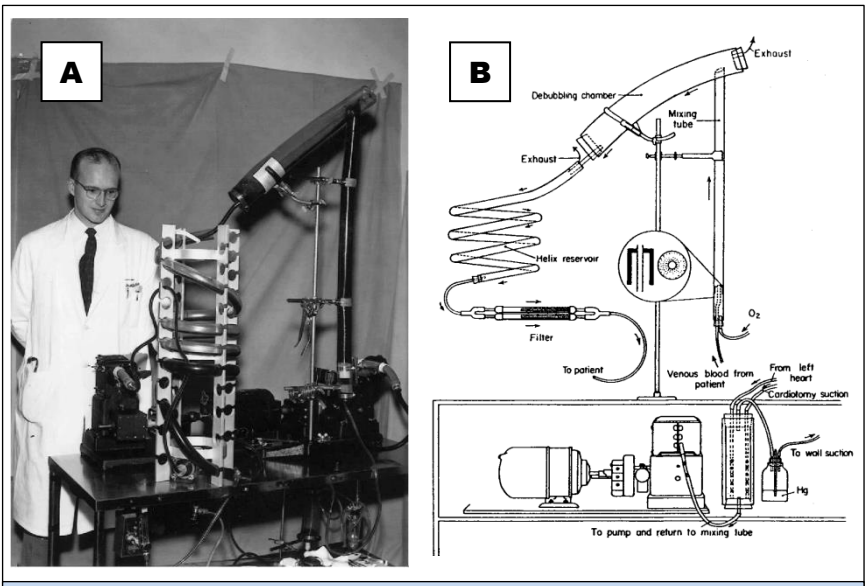


Figure 1. A. Photograph of the helix reservoir bubble oxygenator together with Dr. Richard A. DeWall. The apparatus was successfully used by Dr. DeWall and Dr. Lillehei for pioneering open heart surgery in 1955. **B.** Drawing of the helix reservoir bubble oxygenator. Blood and oxygen was mixed in the vertical tube and reached the large debubbling chamber (top). The blood was further settled in the helix reservoir before filtered and re-infused into the patient. Reprinted from DeWall RA. Perfusion 2003;18:163-169. With permission from SAGE Publications

1.2 Modern day practice

CPB is performed routinely in all cardiac surgery centers today. According to the Swedish Cardiac Surgery Registry there were 5 446 operations with CPB nationally in 2021, with a combined 30-day mortality rate of 2.4% (9).

A dedicated and trained clinician, titled perfusionist, is responsible for CPB management in collaboration with the attending surgeons and anesthesiologists. Integrated physiologic monitoring and safety systems alert the perfusionist on CPB performance and metabolic demands of the patients. During standard bypass, mean artery pressure (MAP) is usually kept between 50-80 mmHg and pump flow between 2.2-2.5 L/min/m^2. This corresponds to the general needs of a normothermic anesthetized patient with normal hematocrit. However, there is no accepted definition of optimal perfusion, and the oxygen delivery (DO_2) and oxygen consumption (VO_2) of end tissue are dependent on MAP, pump flow, body temperature, hematocrit, acid balance, depth of anesthesia, peripheral vascular resistance and specific organ autoregulation (10). A goal directed hemodynamic therapy emphasizes on maintaining a minimum DO_2 during CPB in any given clinical scenario rather than having a fixed target MAP or pump flow (11).

Currently, hollow fiber membrane oxygenators are exclusively used. They separate the blood elements from the gas flow by using diffusion for gas exchange. This reduces the level of trauma and contact activation to the blood components and extends the possible time of CPB use (12). Cold blood cardioplegia is the most prevalent cardioprotection used. Several variations on CPB components exist to reduce the contact activation of the blood and attenuate the systemic inflammatory response and coagulation activation induced by CPB. This is seemingly important, as the degree of systemic inflammation and the amount of bleeding are both strongly associated with adverse events, including neurologic and renal injury, and increased mortality (13-17). Biocompatible heparin coated CPB surfaces, and miniaturized closed circuit CPB that eliminate the blood/air interface in the venous reservoir contribute to less blood activation and may improve outcome (18-22). However, a closed system adds complexity and is considered more difficult to manage (10). Centrifugal pumps are less traumatic than standard roller pumps, but their ability to improve outcome is not well established (23). Bleeding from the surgical field has traditionally been collected into the venous reservoir and reinfused to the systemic circulation to reduce blood loss. However, it has been shown that shed mediastinal blood contains activated leukocytes, hemolyzed

cells, and fat particles that together stimulate inflammation and promotes thrombin generation, leading to increased bleeding and organ damage (24-26). A separate reservoir with processing of shed mediastinal blood by using centrifugal cell washing and secondary filtration before re-transfusion is therefore recommended (27, 28).

There are widespread differences in CPB practices among cardiac centers, and institutional practice often vary due to personal beliefs, experiences of individual surgical groups, clinical impressions, and industry promotion (29, 30). The reason why a evidence based practice is less prevalent might be attributed to a shortage in high-quality comparative studies with enough power to provide evidence in clinically important outcome measurements (31). The European associations for cardiac surgeons, anesthetists and perfusionists published in 2019 the first ever European guidelines with comprehensive recommendations on CPB management. They conclude that there were "*several gaps in knowledge and areas in which evidence is conflicting or lacking, resulting in expert consensus statements, based on expert opinion*" and that *"high-quality clinical research is necessary in the near future to fill the knowledge gaps and improve the current recommendations"*(32).

1.3 Pump priming

Pump priming volume has gradually decreased because of smaller circuit surface areas. Approximate 1.2-1.6 L is needed for conventional priming, but as little as 0.6 L can be required for a minimized perfusion circuit (33). Most centers use a balanced crystalloid fluid, although considerable variation in priming practices exists in regard of fluid type and prime additives (34, 35). Only a minority of centers use a pure colloid solution, Figure 2. The use of a bloodless prime means hemodilution will occur, and the degree of hemodilution is dependent on the priming volume, the patient's blood volume, and the patient's hematocrit. A certain degree of hemodilution is part of routine CPB management, as it reduces blood viscosity and improves microcirculatory flow, especially during procedures with hypothermia. However, excessive hemodilution (<25-21%) decreases DO_2 and impairs coagulation by a dilutional coagulopathy. The association between nadir hematocrit during bypass and the risk of adverse outcome, including mortality, is well established, (36-40). Paradoxically, transfusion of red blood cells to reverse tissue hypoxemia during low hematocrit might add to the risk of adverse events (41, 42). The general consensus is to reduce hemodilution by limiting prime volumes to avoid subsequent allogenic blood transfusion. Autologous priming of the CPB circuit is an effective way to reduce hemodilution and avoid allogenic blood transfusion, especially in individuals with low body surface area (43). This is done by displacing and removing pump prime from the circuit with autologous heparinized blood, usually in a retrograde manner, right before CPB start.

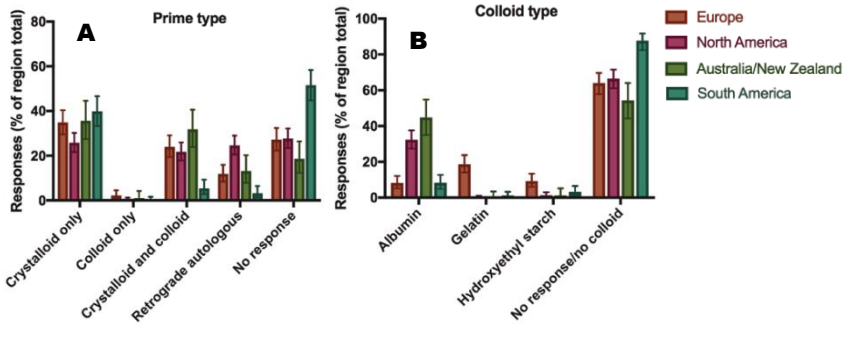


Figure 2. A. Distribution of pump prime types divided among world regions. Crystalloid solution alone or in combination with a colloid is the most prevailing pump prime. North American centers have the highest prevalence of retrograde autologous prime. Only a limited number of centers use a pure colloid solution. **B.** For centers that use colloid prime, albumin is the most prevailing colloid used in North America and Australia. European centers have a higher use of the artificial colloids gelatin and hydroxyethyl starch. The use of dextran solution is not reported. Results from the Global Cardiopulmonary Bypass Survey. Reprinted from Miles et al. Anesth Analg 2017;125:1871–1877 with permission from Wolters Kluwer Health, Inc.

1.3.1 Colloid osmotic pressure and the Starling equation

The prime composition has a profound effect on blood homeostasis during CPB. A crystalloid solution, in contrast to a colloid solution, does not have any macromolecules and will therefore reduce the colloid osmotic pressure (COP) of the plasma when infused. According to the Starling equation this will lead to a transcapillary net fluid shift towards the interstitial space, Figure 3. If the fluid shift is large, interstitial edema will form. Interstitial edema have the potential to cause adverse effects as it obstructs capillary to cell DO_2, inflicting hypoxic tissue injury (44). The increased capillary permeability due to the pro-inflammatory environment of CPB also affects the Starling equilibrium towards interstitial edema. Tissue hypoxia induced by interstitial edema might further promote inflammatory pathways and aggravate endothelial leakage (45).

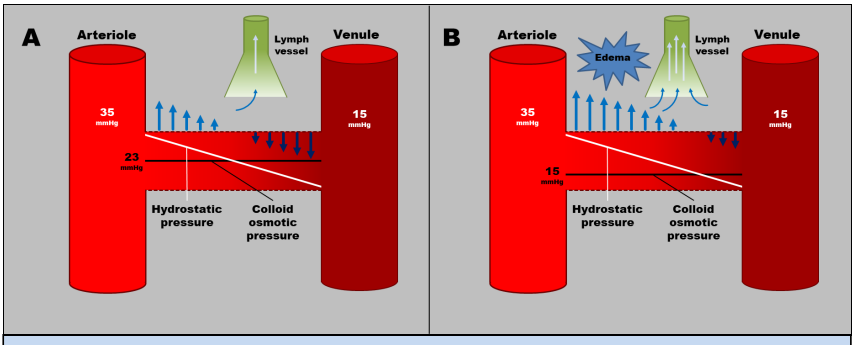


Figure 3. The effect of colloid osmotic pressure on transcapillary fluid shift. There are two predominant forces determining fluid shift over a normal capillary bed; the hydrostatic pressure and the colloid osmotic pressure. Both forces exist on either side of the semi-permeable capillary bed, creating a gradient, and are measured in mmHg. **A.** The intracapillary colloid osmotic pressure is maintained stable during normal physiologic conditions. The hydrostatic gradient is greater on the arteriolar end than on the venular end of the capillary. This promotes a transcapillary outward fluid shift at the arteriolar end of the capillary and an opposite inward fluid shift at the venular end. Excess fluid in the interstitial space is reabsorbed by lymphatic flow. **B.** If the intracapillary colloid osmotic pressure drops suddenly, there will be an increased net outward fluid shift. The lymphatic flow can compensate some of the increased interstitial fluid load, but if the transcapillary fluid shift is large, it will lead to edema formation. M.Barbu©

1.4 Dextran 40

Dextran is a polysaccharide macromolecule of repeated glucose subunits, synthesized from sucrose by the Leuconostoc mesenteroides bacteria, Figure 4. It has suitable colloidal properties and was commercially introduced as a plasma expander by Swedish scientists in the 1950's (46). Dextran 40 preparations have a mean molecular size of 40 000 Dalton, and dextran 70, the other available medical preparation, have a mean molecular size of 70 000 Dalton. Dextran is eliminated by renal clearance in an inverse relationship to its molecular size. According to early pharmacokinetic studies in healthy subjects, 50% of infused dextran 40 is eliminated after 3 h, and 70% after 24 h (47). For dextran 40 preparations, individual polysaccharide size can vary in-between 10 000 – 75 000 Dalton. Molecules >50 000 Dalton are not readily permeable to glomerular filtration and needs to be hydrolyzed into smaller units by endogenous dextranas before renal clearance, hence the prolonged late phase clearance. To prevent the rare event of dextran induced anaphylactic reaction, administration of dextran 1 (promiten) is recommended in proximity to start of dextran infusion.

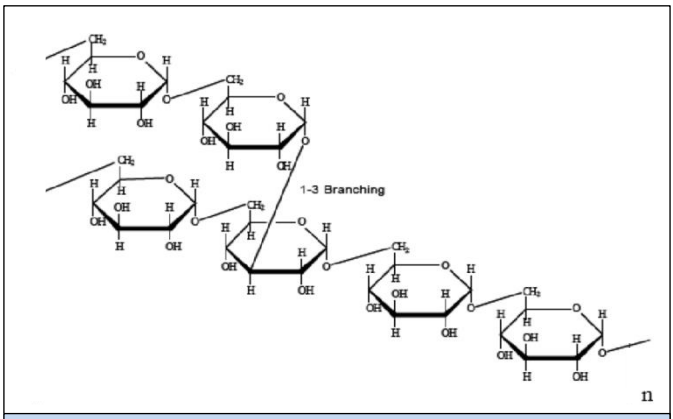


Figure 4. Typical structure of dextran. Reprinted from Abir et al. Vascular and Endovascular Surgery, 2004. 38(6): p. 483-491 with permission from SAGE journals

Besides from its volume expanding effect, dextran also have antithrombotic properties. Dextran preparations have been used for postoperative thrombo-embolic prophylaxis, anti-embolic treatment after carotid endarterectomy, and to improve graft patency in subinguinal vascular surgery (48). The mechanism

of dextran antithrombotic properties is incompletely understood, but it is recognized to reduce circulating levels of factor VIII and von Willebrand factor (vWf) complex (49), affect fibrin polymerization, enhance fibrinolysis (50), and inhibit platelet activation (51). Furthermore, dextran 40 also presents coating-like properties on endothelial and red blood cells surfaces, reducing red blood cell adhesion with improved capillary flow (52), increases red blood cell resilience against sheer stress (53, 54), and attenuates leukocyte/endothelial cell interaction limiting leukocyte tissue infiltration (55, 56).

The colloidal property of dextran 40 together with its limited exposure time in plasma and possible rheological effects makes it an interesting candidate for pump prime to prevent interstitial edema and improve tissue oxygen delivery during CPB. It also has a favorable cost benefit compared to albumin. Even if dextran has been available for seven decades as a plasma expander, its use has mainly been limited to the Nordic countries. As indicated by the Global Cardiopulmonary Bypass Survey (34), there seem to be limited-to-none clinical experience for dextran as pump prime, Figure 2. Only one small randomized clinical trial have studied dextran 40 for pump prime, indicating less fluid loading in patients with dextran 40 prime compared to patients with Ringer's lactate prime (57). ***The scope of paper I-III for this thesis was to investigate the use of a dextran 40 based prime solution.***

1.6 Acute kidney injury in cardiac surgery

Acute kidney injury (AKI) is a rapid deterioration of kidney function, defined as a loss of glomerular filtration rate (GFR). GFR is difficult to measure and is commonly estimated from circulating levels of endogenous creatinine in serum (e-GFR). There have been many clinical definitions of AKI, which has created considerable difficulties to compare incidence and results between trials. Since 2012 a consensus definition of AKI have been published by Kidney Disease Improving Global Outcomes (KDIGO) (58). The staging of AKI is based on both serum-creatinine and urine output, Table 2.

Table 2. AKI definition and staging according to KIDIGO

Stage	Serum creatinine	Urine output
1	1.5 – 1.9 times baseline [a] OR ≥26.5 µmol/L increase in S-Cr [b]	<0.5 ml/kg/h for 6-12h
2	2.0 – 2.9 times baseline [a]	<0.5 ml/kg/h for ≥12h
3	≥3.0 times baseline OR ≥353.6 µmol/L increase in S-Cr OR Initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24h OR Anuria for ≥12h

[a] =within 7 days, [b] =within 48h, S-Cr=serum creatinine. Adapted from Khwaja et al. Nephron clinical practice. 2012.

AKI is common following cardiac surgery, affecting 20-30% of patients (59). For up to 90% of those affected, stage 1 AKI is diagnosed. However, even a small increase in S-creatinine is associated with increased mortality and hospital costs (60, 61). For the 1-2% of patients who develop severe AKI requiring renal replacement therapy, 30-day mortality amounts to approximately 50% (59).

The pathophysiology of cardiac surgery-associated AKI is complex and not fully understood. Several variables have been identified as independent risk factors, involving preoperative patient dependent characteristics, intraoperative management, and postoperative care (62-64), Table 3. To date, there are no specific pharmacological therapies to prevent or mitigate AKI (65). The contribution of CPB to the development of AKI is well documented, and time on CPB is a consistent independent risk factor (66). CABG with off-pump technique as opposed to on-pump is associated with lower incidence of mild to

moderate AKI (67, 68). Renal hypoxia has been identified as a key element in the development of cardiac surgery associated AKI (69). A critical DO_2 index of 225-272 ml/min/m^2 during CPB has been identified as a cut off point for increased risk of AKI (70-72). Several pathways may contribute to a disruption in renal DO_2/VO_2 ratio, including hemodilution, systemic inflammation, neurohormonal changes, endothelial dysfunction, increased intra-abdominal pressure, and microembolic injury (65). In addition, hemolysis from CPB, allogenic transfusions, and re-transfused shed mediastinal blood may cause direct nephrotoxic injury by oxidative stress (73), and impair microcirculation due to diminished nitric oxide with vasoconstriction (59).

Many retrospective studies that evaluate risk factors for cardiac surgery associated AKI have focused on non-modifiable patient and procedure related risk factors. Only a few studies have reported on modifiable intraoperative variables (64, 74-77). ***The aim of paper V in this thesis was to study the association between modifiable CPB variables and the risk of postoperative AKI.***

Table 3. Risk factors for cardiac surgery associated acute kidney injury

Preoperative	Intraoperative	Postoperative
Age	CPB time	Low cardiac output
Female gender	Aortic cross clamp time	Vasopressor support
Anemia	Complex surgery	Re-exploration
Heart failure	Nadir hematocrit	Nadir hematocrit
Diabetes mellitus	RBC transfusion	RBC transfusion
Hypertension		
Atrial fibrillation		
COPD		
Elevated S-creatinine		
Previous cardiac surgery		
Emergency surgery		

COPD=Chronic obstructive pulmonary disease, RBC=red blood cell. Adaped from Thakar et al. J Am Soc Nephrol, 2005 (62); Salis et al. J Cardiothorac Vasc Anesth, 2008 (63); and Karkouti et al. Circulation 2009 (64).

1.7 Postoperative cognitive dysfunction

The incidence of postoperative cognitive dysfunction (POCD) in cardiac surgery is reported to be >50%, twice as many as observed after non-cardiac surgery (78, 79). POCD is a cognitive decline following anesthesia and surgery that can be measured with neurocognitive tests. POCD affects the individual's abilities for learning, memory, comprehension, attention, decision making, and reasoning, with a negative impact on quality of life and for those affected and their relatives (80). Unlike delirium, there is no consensus on the clinical definition of POCD, and the heterogeneity of tests batteries, cut off limits, and different measurement intervals makes comparisons between studies difficult. Although considered a transient state with cognitive recovery within months to years, there are concerns for the risk of long time cognitive decline (78).

The pathophysiology behind POCD is unclear. Risk factors that have been identified are advanced age, low educational level, diabetes mellitus, established cerebrovascular disease, and postoperative complications (infections, respiratory complications, delirium) (81). The higher incidence rate in cardiac surgery has previously been thought to be attributed to the use of CPB. Several aspects of CPB can provide a plausible mechanistic pathway to brain injury, such as solid or gaseous cerebral microembolization, brain hypoxia by altered perfusion flow and hemodilution, and injury from inflammatory activation (82). However, studies on off-pump vs. on-pump coronary artery bypass surgery (CABG) have not presented convincing evidence for the benefit with off-pump surgery on cognitive function (83-86). Investigations on procedural aspects of CPB and therapeutic strategies have contributed with insight on the multifactorial and complex pathophysiology of POCD. Today, an increasing scientific interest is focused on the neuroinflammatory pathway for POCD triggered by peripheral surgical trauma (87).

1.7.1 Biochemical markers of brain injury

Specific markers for brain injury are an emerging field with the potential to aid in diagnostics, prognostics and monitoring of patients with neurological insults. Some markers, like S-100B and neuron-specific enolase (NSE), are established injury markers and an integrated part in clinical practice today (88, 89). The blood-brain barrier (BBB) protects the brain and upholds a gradient between proteins and molecules in the cerebrospinal fluid (CSF) and blood. BBB dysfunction is a recognized component in many neurological disorders, and could be a cause of increased serum levels of injury markers (90). New, sensitive assays with the ability to measure normal serum levels of brain injury markers have been developed, substantially facilitating applicability compared to CSF-sampling. Studies are warranted to establish their clinical significance and limitations before they can reach clinical usability**.** Blood-based biomarkers have not been widely studied in cardiac surgery, and possible applications could be early recognition of postoperative stroke or POCD. ***The aim of paper IV in this thesis was to study the release patterns of neuronal and glial cell injury markers after uncomplicated cardiac surgery.***

S-100B

S-100B is a calcium-binding protein in perivascular astrocytes. Increased serum-levels are observed in response to various CNS injuries, including traumatic brain injury, ischemic stroke, following resuscitation in cardiac arrest patients, and in BBB damage (91-93). S-100B screening is wieldy practiced for the early evaluation of mild to moderate head trauma (88). S-100B is also expressed in non-glial cells, including adipocytes, chondrocytes, and melanocytes, and circulating serum levels of S-100B can thus have substantial extra-cerebral sources in multi-trauma victims and after cardiac surgery (92). S-100B has a short serum half-life of 25 minutes (92).

Neuron specific enolase

NSE is a glycolytic enzyme expressed in the cytoplasm of neurons, platelets, red blood cells, and neuroendocrine derived tumors (92). Elevated levels in serum have been found to covariate with hemolysis, limiting its usability in cardiac surgery where hemolysis is common (94). NSE is an integrated part in the evaluation of unconscious cardiac arrest patients (95), but might also be useful to assess neuronal damage in traumatic brain injury (93, 96), and ischemic stroke (97). Half-life of NSE in serum is 24 h (92).

Neurofilament light chain

NfL is a protein for the neuronal cytoskeleton where it together with its medium and heavy chain counterpart gives structural support and assists in axonal transport in long myelinated axons (98). Elevated levels in CSF and blood is highly specific for neuronal axonal damage, and have been associated with CNS engagements by neurodegenerative disease, stroke and traumatic brain injury (99-101). NfL half-life in serum is very long, several weeks (102).

Tau

Tau protein is part of the neuronal microtubule and is primarily located in axonal cytoskeletons in unmyelinated neurons of the brain cortex (103). Tau levels in peripheral blood are highly specific for CNS damage, and hyperphosphorylated tau isoforms (p-tau) are a hallmark for neurodegenerative disorders including Alzheimer's disease (104). Total-tau (t-tau) in peripheral samples have been reported to correlate with brain injury in trauma, stroke, and after cardiac arrest, although not implemented in current clinical praxis. Half-life of t-tau in plasma is 10 h (102).

GFAP

Glial fibrillary acidic protein is the main filament protein found in the astrocyte cytoskeleton (105). Astrocyte damage leads to the release of GFAP into peripheral blood, and elevated serum levels have been described to correlate with the size and severity of the brain injury (106). No extra-cerebral sources of GFAP have been identified, and unlike the astrocyte protein S-100B, no increased levels are noted in multi-trauma patients without traumatic brain injury (107). Serum half-life of GFAP is 24-48h (93).

ß-trace

ß-trace protein is a brain specific protein secreted into the CSF by the pia-arachnoid meninges and choroid plexus (108). Very low levels are normally detectible in serum, and elevated concentrations are used to identify BBB-disruption (108).

1.8 CPB and coagulopathy

Coagulopathy after CPB is associated with excessive bleeding and adverse patient outcomes. According to the Universal Definition of Perioperative Bleeding (UDPB), approximately 10% of cardiac surgery patients bleed excessively, with an eight-fold increase in 30-day mortality after adjustment for other factors (16), Figure 5. Patients who need to be re-explored for bleeding are overrepresented in postoperative complications such as sternal wound infection, AKI, stroke, and prolonged mechanical ventilation (109). There are also indications that the increased risk of mortality associated with re-exploration due to bleeding extends beyond the operative period, possibly diminishing the preventive measures of the performed intervention itself (17).

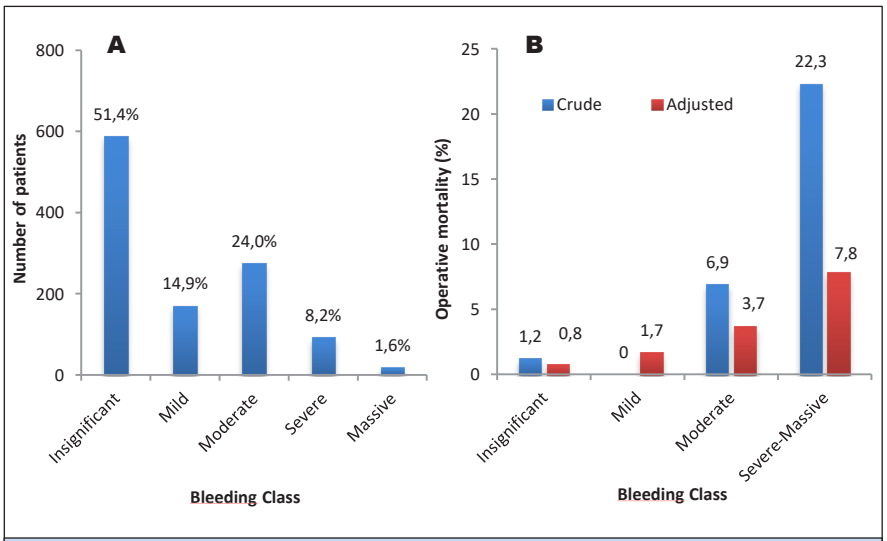


Figure 5. Bleeding and mortality after cardiac surgery. A. Bleeding classification according to UDPB. **B.** Mortality according to UDPB class. The risk of mortality is doubled for each increasing bleeding class OR:2.18 CI95% [1.55-3.07]. N=1 144 for both. UDPB= Universal Definition of Perioperative Bleeding. Adapted from Dyke C. et al. J Thorac Cardiovasc Surg 2014;147:1458-1463.e1, with permission from Elsevier.

Patient and procedure dependent risk factors can be used to precede the risk of postoperative bleeding (110-112), Table 4. Several CPB related aspects contribute to a state of coagulopathy, and CPB duration is a strong independent risk factor for bleeding (17, 110). During CPB, there is a consumption of coagulation factors and platelets by activation from the non-endothelial CPB surfaces and the surgical wound. Together with losses from any active bleeding

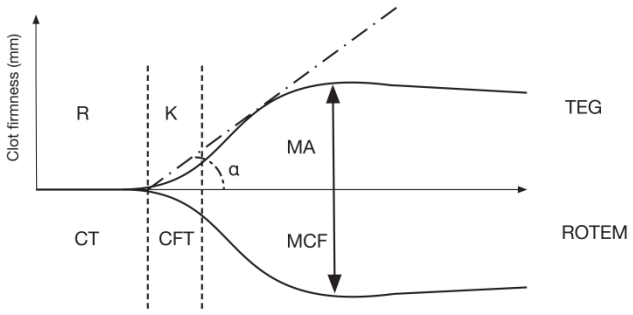
Table 4. Risk factors for postoperative transfusion in cardiac surgery	
Patient dependent	**Risk increase (suggested cut off)**
Preoperative anemia	Low (100-130 g/L) Moderate (<100 g/L)
Low platelet count	Low (150-100 x10^9) High (<100 x 10^9/L)
Low fibrinogen	Low (<1.5 g/L)
Low BSA	Low (1.5-1.9 m^2) Moderate (≤1,5m^2)
Age	Low (70-80 years) Moderate (>80 years)
Preoperative renal impairment	Low eGFR (<45ml/min/1.75m^2)
Procedure complexity	Low (CABG as baseline)
Previous cardiac surgery	Moderate
Non elective surgery	Low
Critical preoperative state	Very high
Procedure dependent	
CPB duration	Moderate (120-180 min) Very high (>180 min)
Circulatory arrest	Low (0-30 min) High (> 30 min)
Nadir CPB hematocrit	Low (18-22%) High (≤18%)

Adapted from Karkouti et al. Can J Anesth 2006; Biancari et al. Thromb Haemost 2017; and Karlsson et al. Transfusion 2008. BSA=Body surface area, CPB=cardiopulmonary bypass, eGFR=estimated glomerular filtration rate

and blood dilution, there is a ~25-50% reduction in circulating levels of coagulation factors and functional platelets that might lead to impaired thrombin generation and reduced clot strength (113). Hyperfibrinolysis is frequently experienced in the postoperative setting of cardiac surgery due to the endothelial release of tissue plasminogen activator (tPA) (36). Additional acidosis, hypothermia, remnant heparin effect, or ongoing platelet therapy, may further contribute to a multifactorial coagulopathy (36).

1.8.1 Viscoelastic testing

Whole blood viscoelastic tests are recommended in contemporary guidelines for postoperative cardiac surgery bleeding as part of a standardized patient blood management (114), together with standard coagulation tests and clinical evaluation. Thromboelastography or thromboelastometry, commercially available as TEG® or ROTEM®, respectively, graphically illustrates all parts of clot formation, stabilization, and degradation, and provide a collective assessment of several laboratory values figure (115), Figure 6.



Measurement	TEG® nomenclature	ROTEM® nomenclature	Signification
Time to an amplitude of 2 mm	Reaction time or R time	Clotting time (CT)	Informs about thrombin generation. Prolongation is associated with clotting factor deficiency, inhibitors or anticoagulant.
Time from 2 mm to 20 mm	K time	Clot Formation Time (CFT)	Depicts how fast a visible clot is formed. Depends on thrombin, thrombin generation, fibrinogen and platelets.
Angle formed by a tangential line to the curve starting from the split point.	α-Angle	α-Angle	Closely related to the K time but more precise because it can be determined even when the split does not reach 20 mm of amplitude
Greater width of the tracing	Maximal Amplitude (MA)	Maximal Clot Firmness (MCF)	Mainly affected by platelets and the fibrinogen level.
Per cent reduction of area under the curve (TEG®) or per cent of MCF (ROTEM®) 30 and 60 min after CT.	CLI30 and CL60	LY30 and LY60	Useful in the diagnosis of hyperfibrinolytic states.

Figure 6. **Viscoelastic analysis.** Top panel illustrates typical tracing results with nomenclature used by TEG and ROTEM. Bottom table describes the most commonly used parameters. Reprinted from Hans GA and Besser MW. Place of viscoelastic testing in clinical practice. Br J Haematol, 173: 37-48 with permission from John Wiley and Sons.

1.8.2 Platelet function testing

Significant platelet dysfunction from CPB surface contact activation or ongoing anti-platelet therapy in acute coronary syndrome patients is common in cardiac surgery patients (36). Standard viscoelastic tests are unable to detect pharmacologically induced platelet inhibition, for which specific testing is required (116). Whole blood platelet aggregometry allows easy and rapid evaluation of platelet function in the perioperative setting. Receptor specific agonists are added to the sample and platelet reactivity is recorded in an assay specific manner. In paper III, impedance aggregometry was used to measure platelet function, an assay where platelet aggregation is displayed graphically and reported as an area under the aggregation curve (AUC).

2 GENERAL AIM

CPB management is largely a methodological development from clinical experimental protocols where comparative studies on different procedural techniques are often limited in size or completely lacking. The aim of this thesis is to increase the understanding for CPB management and ultimately, to reduce the risk of adverse events following cardiac surgery with CPB.

2.1 Knowledge gaps and objectives

Paper	Knowledge gaps	Objective
I	Balanced colloid prime with dextran 40 has only been previously reported in one small RCT. The effect size in colloid osmotic pressure and the relative safety compared to a balanced crystalloid solution is unknown.	To describe the effect on serum colloid osmotic pressure in cardiac surgery patients undergoing CPB with dextran 40 based colloid prime and its potential effects on organ function compared to crystalloid prime.
II	It is not known if the use of dextran 40 based colloid prime influences the risk for renal injury following cardiac surgery.	To investigate if colloid prime with dextran 40 affects the extent of acute tubular injury for patients undergoing cardiac surgery with CPB compared to crystalloid prime.
III	Dextran has a known impact on blood coagulation. However, the hemostatic effect of dextran 40 based prime for CPB in cardiac surgery patients has not been investigated.	To compare the effect of dextran 40 and crystalloid based prime on blood coagulation, platelet activation, and bleeding volume in patients undergoing cardiac surgery with CPB.
IV	Neurologic complications after cardiac surgery are a common concern. Serum biomarkers are a novel method to estimate brain injury, but evidence for its practical usability in cardiac surgery is lacking.	To describe the magnitude and time course of five brain injury markers in peripheral blood following uncomplicated cardiac surgery with CPB.
V	Patients with acute kidney injury following cardiac surgery have an increased mortality and morbidity. How management of individual CPB variables during surgery modifies the risk of acute kidney injury is incompletely understood	To investigate how individual CPB variables associates with postoperative acute kidney injury

3 PATIENTS AND METHODS

3.1 Patients

The study population for paper I-IV consists of patients from a randomized clinical trial that prospectively included elective cardiac surgery patients at Sahlgrenska University Hospital. The trial is onwards called the Prime-study. Paper V has a registry based study population with patients operated with CPB at Sahlgrenska University Hospital. Both studies were conducted in accordance with the Declaration of Helsinki. Study I-IV was approved by the Regional Research Ethics Committee in Gothenburg (registration number 1003-15), and study V was approved by the Swedish Ethical Review Authority (registration number 012-12). The Prime-study was registered at ClinicalTrials.gov prior to enrolment (identifier: NCT02767154) and written informed consent was obtained from all patients. The need for individual patient consent for paper V was waived by the ethical authority. Patient characteristics are summarized in Table 5.

Table 5. Patient characteristics

	Paper I-III	Paper IV	Paper V
N	80	61	2661
Male gender	57 (71%)	45 (74%)	2060 (77%)
Age, years	67±7	66±7	68±9
Body mass index, kg/m^2	27±4	27±4	27±4
Diabetes mellitus, n	10 (13%)	8 (13%)	634 (24%)
Preop stroke, n	2 (3%)	2 (3%)	233 (9%)
Preop S-creatinine, µmol/L	85±22	84±19	89±30
Hemoglobin, g/L	140±14	141±14	138±14
Euroscore II, %	2.0±2.1	2.1±2.3	2.3±2.2
Total operation time, min	191±51	188±52	170±47
CPB time, min	99±34	98±36	85±34
Aortic clamp time, min	73±29	73±31	61±29

Mean ± SD or number (percentage)

The Prime-study was designed to study the effects of a colloid prime on serum colloid osmotic pressure compared to a crystalloid prime. We expected there to be a more noticeable effect in patients with longer CPB time, as time on pump regularly requires fluid supplementation to maintain adequate venous return and sustained pump flow. The initial inclusion criteria were specified to an expected CPB time >90 min and subject age 50-75 years. Due to a limited inclusion rate, the inclusion criteria were broadened to include an expected CPB time >75 min and subject age 50-80 years, after an amendment approved by the Regional Research Ethics Committee. Exclusion criteria were used to limit the variability of procedures and to avoid confounding factors (117). For paper I-III, 84 patients were included during May 2016 to July 2017, Figure 7 presents the patient flow chart. Four patients were excluded before analysis; one patient did not receive the allocated treatment due to unexpected finding of chronic aortic dissection with the decision to cancel the planned operation. One patient was excluded due to a change of the procedure with the need of circulatory arrest, one patient was excluded due to sudden cardiac arrest at induction of anesthesia, and one patient was excluded because of extensive intraoperative ultrafiltration. The excluded patients are not expected to introduce any bias as the missing data was not due to allocation or any specific patient characteristic.

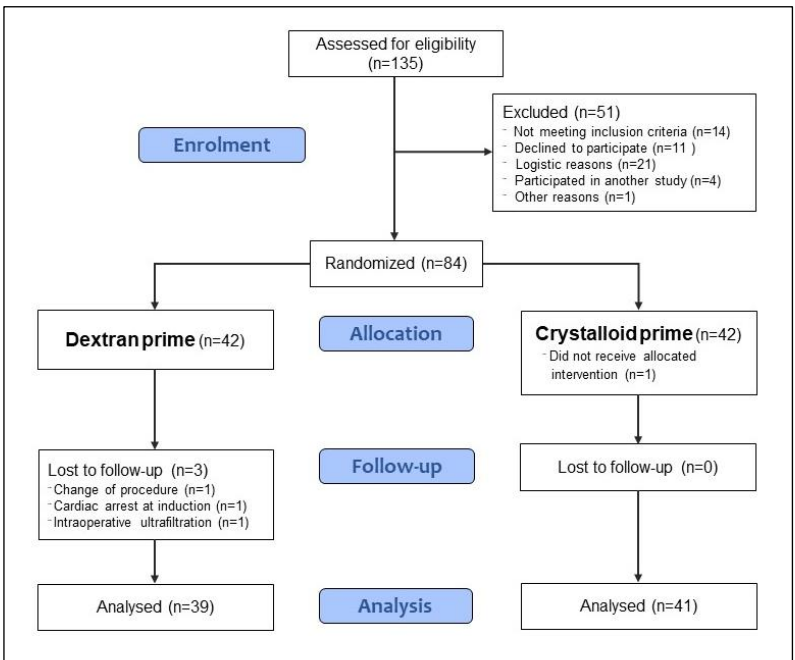


Figure 7. Patient flow chart for Prime-study (paper I-III)

Paper IV included 61 out of 80 patients from the Prime-study. For 18 patients, blood samples could not be prepared for the analysis of brain injury markers as research staff was unavailable after office hours. One patient was excluded from analysis due to debilitating postoperative stroke.

Paper V is a registry based study where the study population was identified in the Swedish Cardiac Surgery Registry. All patients that underwent first time cardiac surgery for CABG, valve surgery, or the combination of CABG and valve surgery at our institution from October 2016 – September 2020 were eligible. Patients with preoperative renal replacement therapy, a critical preoperative state, active endocarditis, congenital heart disease, or patients who underwent aortic surgery were excluded. Patient flow chart is presented in Figure 8.

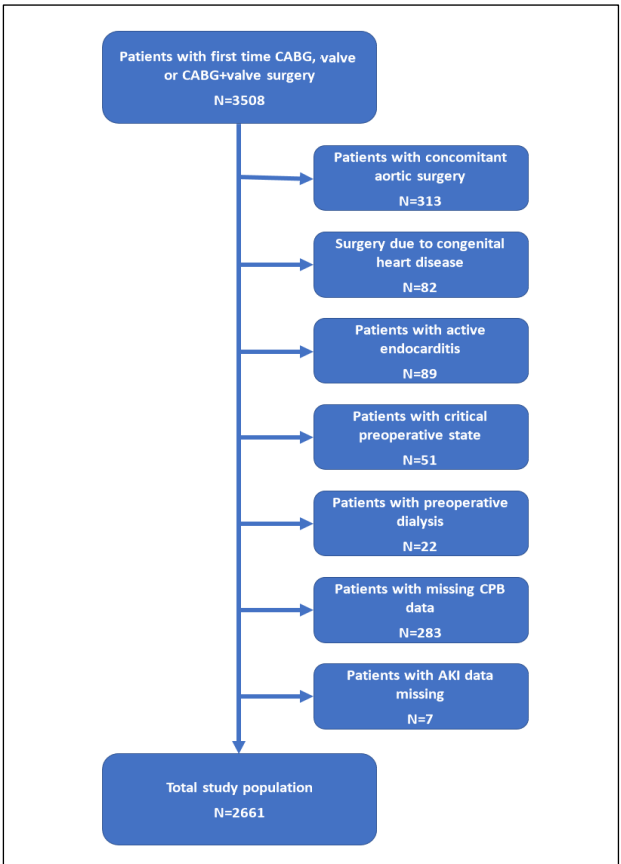


Figure 8. **Patient flow chart for the register based study (paper V)**

3.2 Methods

Paper I-IV

The Prime-study is a prospective, 1:1 randomized, single-center, double-blind, controlled trial. Primary outcome was serum COP during CPB. Power analysis indicated that a sample size of 80 patients would show a 30% difference between the groups with 90% power and a significance level of 0.05. The CPB circuit was primed according to allocation by a perfusionist not otherwise assigned to the case. Either 1300 ml of dextran 40 based colloid prime or institution standard prime of 1100 ml Ringer-Acetate with 200 ml added mannitol was used. Blood and urine samples for analysis of COP and secondary safety markers were collected according to table 6.

	After induction of anesthesia	At release of aortic clamp	10 min post CPB	1 h post CPB	2 h post CPB	24 h post CPB	48 h post CPB
Colloid osmotic pressure	✓	✓	✓		✓	✓	
Hemoglobin	✓				✓	✓	
Hematocrit	✓				✓	✓	
Platelet count	✓				✓	✓	
S-Creatinine	✓					✓	✓
PT-INR	✓				✓	✓	
aPTT	✓				✓	✓	
Fibrinogen	✓				✓	✓	
ASAT	✓				✓	✓	
ALAT	✓				✓	✓	
Troponin-T	✓				✓	✓	
S-100B*	✓				✓	✓	
IL-6	✓				✓	✓	
Free hemoglobin	✓				✓	✓	
PaO_2/FiO_2	✓				✓		
Thromboelastometry	✓				✓	✓	
Impedance aggregometry	✓				✓	✓	
U-NAG	✓	✓		✓		✓	
U-Creatinine	✓	✓		✓		✓	

Table 6. Time points of data acquisition in paper I-III. ALAT=alanine aminotransferase; ASAT= aspartate aminotransferase; aPTT=activated partial thromboplastin time; CPB=cardiopulmonary bypass; IL=Interleukin; INR=international normalized ratio; PaO2/FiO2= Partial pressure of oxygen in arterial blood/percent inspired oxygen ratio; PT=prothrombin time; *=for study IV also neuron specific enolase, neurofilament light chain, total-tau, glial fibrillary acid protein, and ß-trace

Standardized CPB management was used for all patients. Before cannulation, anticoagulation with heparin was used to achieve ACT >480 s. CPB was maintained with a non-pulsatile flow rate targeted at 2.4 L/min/m^2 and mean arterial pressure regulated to 50-70 mmHg. Cold blood cardioplegia was used for cardioprotection. Bladder temperature was kept at normothermia or mild hypothermia. Retrograde autologous priming was not applied. After CPB weaning, residual blood in the CPB circuit was pushed anterograde trough the arterial cannula with Ringer-Acetate. Red blood cell transfusion during CPB was considered if hemoglobin <70 g/L or hematocrit <24%.

Paper I

COP in serum was analyzed at the five time points specified in Table 6. Fluid balance was recorded during, and up to 12 hours after surgery. Bleeding volume and transfusion requirements were recorded during, and up to 24 hours after surgery. Secondary safety markers were studied to assess any possible organ injury. Measurements included markers for cardiac (troponin-T), hepatic (ASAT and ALAT), renal (creatinine), neurologic (S-100B), and pulmonary injury (PaO_2/FiO_2). Hematology was evaluated by hemoglobin, hematocrit, and free hemoglobin, and inflammatory activation by interleukin 6.

Paper II

N-acetyl beta-D-glucosaminidase (NAG) is an enzyme present in the lysosomes of proximal tubule epithelial cells. Urinary excretion of NAG is a sensitive and reliable indicator of acute tubular injury (118). In paper II, U-NAG/U-creatinine ratio from patients in the Prime-study was analyzed.

Paper III

Blood samples from patients in the Prime-study were analyzed with standard coagulation tests and point of care thromboelastometry and impedance aggregometry. Thromboelastometry with ROTEM® (TEM International GmbH, Munich, Germany) was performed using the EXTEM and FIBTEM assays. Platelet function was estimated with impedance aggregometry by the Multiplate® platform (Roche Diagnostics, Risch-Rotkreuz, Switzerland) using adenosine diphosphate (ADP), arachidonic acid (AA), and thrombin receptor-activating peptide (TRAP) as initiators. Intraoperative bleeding and postoperative chest drain output was measured up to 12h after the operation. Allogenic transfusion requirements were recorded during the index hospital stay.

Paper IV

Patients included in Prime-study were used to examine the potential neurologic damage inflicted during routine cardiac surgery with CPB by analyzing the levels of five brain injury markers in peripheral blood. S-100B, GFAP, t-tau, NSE, and NfL were measured to assess glial and neuronal cell damage. β-trace protein was analyzed to assess damage to the blood-brain barrier. The markers were selected for their recognized use in trauma, stroke, and evaluation after successful resuscitation of cardiac arrest. As NSE analysis is known to interact with red blood cell damage, free hemoglobin was measured in the same samples and NSE results were excluded if free hemoglobin was >0.5 g/L.

Paper V

All patients who undergo any cardiac operation are registered in the Swedish Cardiac Surgery Registry, part of the Swedish Heart Registry (SWEDEHEART), Figure 9. Data is prospectively collected since 1992 and have coverage of 98-99%. We designed an observational study where SWEDEHART data was matched with CPB-data from our institution. CPB software LivaNova Connect data management system® (LivaNova, London, United Kingdom) automatically collects and stores CPB variables every 20 seconds on the CPB hardware. CPB data was downloaded from all institutional heart-lung machines and compiled into a single CPB dataset used for this study. Mortality data was added from The National Cause of Death Registry. Individual data was linked between the registers with the Swedish personal identification number.

Preoperative S-creatinine was compared to the highest postoperative S-creatinine from the index hospitalization according to the Swedish Cardiac Surgery Registry. Postop values 1.5x preop values were recognised as AKI.

Figure 9. The SWEDEHEART logo. *With permission*

3.1 Statistical analysis

For all studies, descriptive statistics are presented as mean with standard deviation (SD) or 95%CI, or median with range or interquartile range (IQR) for contiuous variables and frequencies and percentage for categorical varibles. Normality of distribution was tested with the ShapiroWilk test or Kolmogorov Smirnoff's test. Statistical significance was defined as a p-value <0.05.

Paper I

Group comparison for continuous variables were performed with Student's *t*-test for normally distributed variables or the Mann-Whitney U-test for not normally distributed variables. Categorical variables were compared with Chi-square test. Variables measured at more than 2 time points were analyzed with analysis of variance for repeated measurements (ANOVA). Whenever significant group*time difference was detected, Student's *t*-test was used to compare means at the individual time points. The influence of CPB time on variables statistically different between groups was tested with analysis of covariance with group and CPB time as covariates. Correlations between CPB time and secondary outcome variables were assessed with Pearson's product-moment test. Statistica software (StatSoft, Tulsa, OK) was used for statistical analyses.

Paper II

Continuous variables were compared with Student's *t*-test or the Mann-Whitney U-test and categorical variables were compared using Chi-square test. A two-way repeated-measures ANOVA was performed to evaluate differences between groups for variables measured at more than 2 time points. Student's t-test with Welch correction was used to analyze any differences between the two groups at the individual time points. The GraphPad Prism 7.0c statistical software (GraphPad software) was used for all statistical analysis.

Paper III

The two groups were compared with Student's t-test or the Mann–Whitney U-test for continuous variables, and by Fisher's exact test for categorical variables. Two-way repeated-measures ANOVA was used to evaluate group vs. time differences for coagulation values, and whenever significant, further comparison with Student's *t*-test was performed. Mean differences between preoperative coagulation values and at 2h and 24 h was analyzed with analysis of covariance (ANCOVA) using preoperative values as covariates. Version 28 of SPSS (IBM, Chicago, IL, USA) and version 9.4 of SAS (SAS institute, Cary, NC, USA) were used for statistical calculations.

Paper IV

Changes from baseline were analyzed with paired t-test or Wilcoxon's test. Group comparison was performed with Student's *t*-test or the Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables. ANOVA for repeated measurements was used to analyze between group differences over time. If the ANOVA indicated significant variation, Students t-test was used to test the difference at the individual time points. Correlations between brain injury markers and patient age, CPB time and hemolysis were analyzed with Spearman's rank sum test. Statistica software (StatSoft, Tulsa, OK, USA) or SPSS version 25 (IBM, Armonk, NY, USA) was used for statistical analyses.

Paper V

Continuous variables were compared with Student's *t*-test or the Mann-Whitney U-test. Categorical variables were compared with Fisher's exact test. Non-ordered categorical variables were analyzed with Chi-square test, and ordered categorical variables with Mantel-Haenszel Chi-square trend test. Logistic regression was used to identify patient characteristics associated to AKI. Multivariate logistic regression for machine variables with adjustment for patient age and sex was performed for model 1, and additional adjustment for patient characteristics with $p<0.10$ in univariate analysis for model 2 (body mass index, diabetes mellitus, hypertension, chronic lung disease, atrial fibrillation, creatinine clearance, preoperative hemoglobin, left ventricular ejection fraction, NYHA class, operative priority and surgical procedure). Version 28 of SPSS (IBM, Chicago, IL, USA) and version 9.4 of SAS (SAS institute, Cary, NC, USA) were used for statistical calculations.

4 RESULTS

4.1 Colloid osmotic pressure and fluid balance with dextran 40 based prime

Patients who received dextran 40 based colloid prime had a significant higher COP during and 10 minutes after CPB weaning, $p<0.001$ for both, Figure 10. The difference was a result of a larger decrease in COP in the crystalloid than in the dextran group. Patients in the crystalloid group recorded higher diuresis during CPB, and required more intravenous fluids during surgery than the dextran group. Postoperative diuresis, intravenous fluids, and oral fluid intake were comparable between the groups. Total fluid balance from up to 12 h after surgery was less positive for patients who received dextran prime, Figure 11.

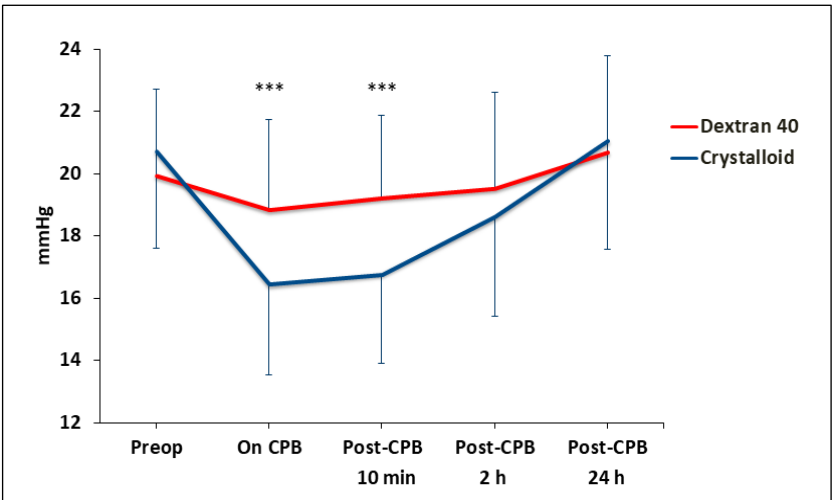


Figure 10. Colloid osmotic pressure for the two prime groups. Patients with dextran prime better maintained their colloid osmotic pressure during and immediately after CPB. ANOVA interaction $p<0.001$. *** = $p<0.001$; CPB=cardiopulmonary bypass

4.2 Organ safety with dextran 40 colloid prime

Biochemical markers of organ injury are presented in Table 7. More extensive analysis of renal injury, hemostatic variables and bleeding, and neurologic injury were performed and reported separately in paper II-IV. In paper I, hematology variables were affected with lower levels of hemoglobin and hematocrit, and lower levels of free hemoglobin in the dextran group 2 hours after CPB.

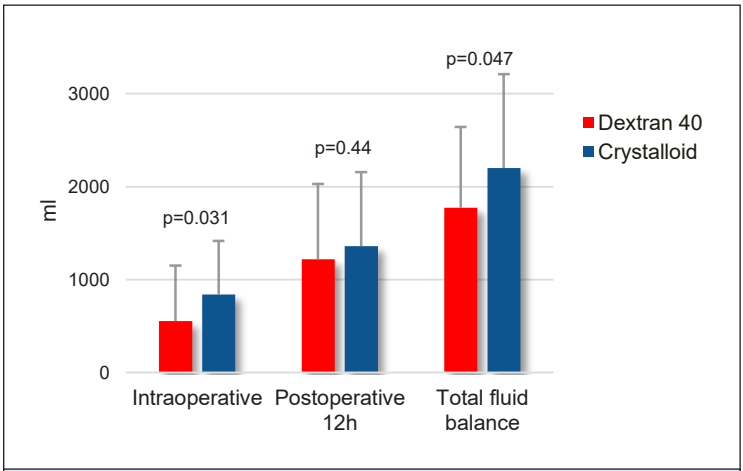


Figure 11. **Mean fluid balance between the two prime groups**

Table 7. Markers for organ damage

	Dextran 40	Crystalloid	p-value (ANOVA)
Troponin-T, ng/L			
Preop	26±53	13±10	0.40
Post CPB 2h	756±1088	1384±2787	
Post CPB 24h	581± 581	899±1460	
S-100B, µg/L			
Preop	0.05±0.04	0.05±0.02	0.078
Post CPB 2h	0.67±0.46	0.94±0.80	
Post CPB 24h	0.18±0.27	0.15±0.07	
ASAT, IU/L			
Preop	22.9±7.1	24.7±16.5	0.092
Post CPB 2h	49.4±30.0	75.9±90.0	
Post CPB 24h	77.1±42.9	78.2±64.7	
ALAT, IU/L			
Preop	27.7±13.5	31.8±33.5	0.27
Post CPB 2h	27.0±10.6	40.0±48.2	
Post CPB 24h	34.7±24.1	41.2±48.2	
S-Creatinine, µmol/L			
Preop	84±20	83±18	0.35
Post CPB 24h	100±27	102±38	
Post CPB 48h	98±29	106±43	
PaO_2/FiO_2			
Preop	0.43±0.19	0.37±0.18	0.084
Post CPB 2h	0.33±0.10	0.38±0.13	
Hemoglobin, g/L			
Preop	125±14	126±14	0.008
Post CPB 2h	107±10 **	115±12	
Post CPB 24h	109±11	109±13	
Hematocrit			
Preop	0.36±0.05	0.37±0.04	0.030
Post CPB 2h	0.31±0.03**	0.34±0.04	
Post CPB 24h	0.32±0.03	0.32±0.04	
Free hemoglobin, g/L			
Preop	0.08±0.03	0.07±0.02	0.001
Post CPB 2h	0.20±0.10**	0.42±0.32	
Post CPB 24h	0.05±0.04	0.05±0.02	
IL-6, ng/L			
Preop	3.4±3.1	4.7±5.5	0.91
Post CPB 2h	121±97	134±124	
Post CPB 24h	198±140	212±173	

Mean and SD. ** = p<0.01 ALAT=Alanine aminotransferase; ASAT= Aspartate aminotransferase; IL=Interleukin; PaO2/FiO2= Partial pressure of oxygen in arterial blood/percent inspired oxygen ratio

4.3 Renal tubular injury with dextran 40 colloid prime

U-NAG/U-creatinine ratio increased in both dextran and crystalloid treated patients during and after CPB in comparison to preoperative levels. Patients who underwent CPB with dextran prime had a less pronounced increase than patients with crystalloid prime (p=0.038). Peak ratio was observed 1 hour after CPB, with 88% higher values in the crystalloid group, p=0.045, Figure 12. The ratio had returned to baseline level 24 hours after CPB, with no group difference remaining. There was no statistical difference in postoperative AKI prevalence between the group, n=7 in the dextran group and n=9 in the crystalloid group.

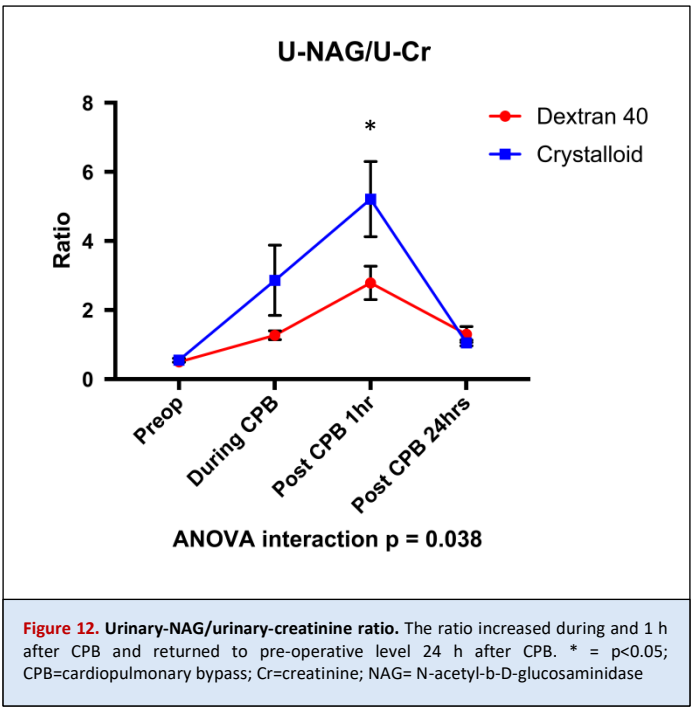


Figure 12. Urinary-NAG/urinary-creatinine ratio. The ratio increased during and 1 h after CPB and returned to pre-operative level 24 h after CPB. * = p<0.05; CPB=cardiopulmonary bypass; Cr=creatinine; NAG= N-acetyl-b-D-glucosaminidase

4.4 Dextran 40 prime impact on coagulation

General

One patient in the crystalloid group and two in the dextran group were re-explored due to bleeding. There was no significant difference between the groups in administration of fibrinogen concentrate, coagulation factor concentrate, desmopressin, protamine, or antifibrinolytic agent. MAP, mean pump flow, vasopressor support, and bladder temperature did not differ between the groups. There was no difference between the groups for baseline hemostatic values.

Standard tests

Patients who underwent CPB with dextran rather than crystalloid prime had significant lower hemoglobin and hematocrit levels 2 h after termination of CPB, Table 7. This was not due to increased surgical bleeding, as both groups had comparable bleeding volumes and transfusion requirements, Table 8. Among the standard tests for coagulation, activated partial thromboplastin time (aPTT) was significantly longer in the dextran group, p=0.002. aPTT assesses the intrinsic pathway, where dextran might contribute by lowering circulating levels of factor VIII. There was no difference in PT-INR, platelet count, or fibrinogen levels between the groups.

Table 8. Bleeding and transfusion data for the Prime-study

	Dextran 40	Crystalloid	P-value (ANOVA)
Bleeding volume (ml)			
Intraop	446±348	562±504	0.32
Postop first 12h	500±198	511±216	
Total (preop+postop)	946±434	1056±557	
Red blood cell transfusion (unit)			
Proportion	11 (28.2)	14 (34.1)	0.62
Mean	1.00±2.11	1.10±1.79	
Median	0 (0-2)	0 (0-2)	
Plasma transfusion (unit)			
Proportion	3 (7.7)	6 (14.6)	0.62
Mean	0.26±1.04	0.27±0.71	
Median	0 (0-0)	0 (0-0)	
Platelet transfusion (unit)			
Proportion	7 (17.9)	3 (7.3)	0.44
Mean	0.28±0.76	0.12±0.78	
Median	0 (0-0)	0 (0-0)	

Mean and SD, number and (%), median and (IQR)

Thromboelastometry

Two hours after CPB, mean EXTEM CFT was significantly longer (103 ± 22 vs. 80 ± 16 s, $p < 0.001$) and mean FIBTEM MCF significantly lower (11 ± 3 vs. 15 ± 5 mm, $p < 0.001$) in the dextran group compared to the crystalloid group. No significant difference remained 24 hours after CPB. When comparing mean difference from preoperative baseline values to 2 h after CPB, the dextran group displayed additionally a larger decrease in EXTEM MCF (-4 [-5; -3] mm, $p <0.001$).

Impedance aggregometry

There was no significant mean difference in AUC for ADP, AA or TRAP mediated platelet aggregation. The dextran group had a larger reduction of mean difference in platelet aggregation with ADP mediated activation at 2 h after CPB, -10 [-19; -0.4] aggregation units, $p=0.041$.

4.5 Brain injury markers in routine cardiac surgery

All biomarkers recorded a significant increase in postoperative levels compared to baseline values, with no significant difference between the colloid and crystalloid groups, Figure 13. Large variability in marker levels was observed, both between the different markers and between patients for the same marker, Table 9. S-100B, plasma t-tau, and NSE recorded their highest levels 2 h after CPB, while GFAP and NfL recorded their highest value 24 h after CPB.

Levels of β-trace protein decreased in comparison to baseline levels, with no intergroup difference.

Postoperative values for S-100B, NfL, and GFAP significantly correlated with patient age. S-100B, GFAP, t-tau, and NSE correlated with CPB time, and NSE and S-100B correlated with hemolysis.

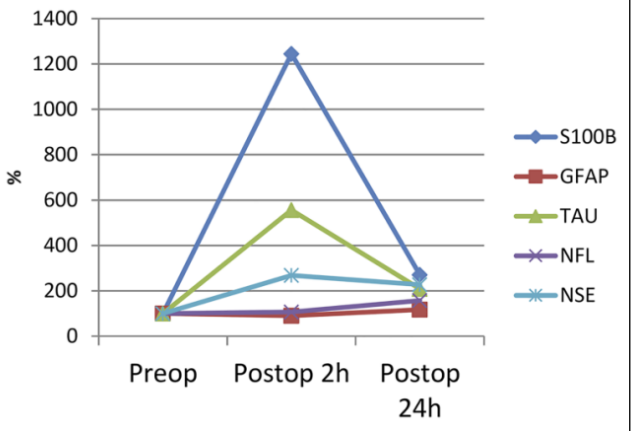


Figure 13. Percentage median change of brain injury markers. Change compared to preoperative value. The variability at each time point is presented in Table 9. GFAP=glial fibrillary acidic protein; NFL =neurofilament light; NSE =neuron-specific enolase

Table 9. Levels of brain injury markers and β-trace protein

	All patients N = 61	p-value
S-100B, µg/L		
Preop	0.04 (0.03-0.07)	
Post CPB 2h	0.59 (0.35-0.98)	<0.001
Post CPB 24h	0.13 (0.09-0.18)	<0.001
GFAP, pg/mL		
Preop	148 (100-235)	
Post CPB 2h	144 (100-192)	0.022
Post CPB 24h	173 (122-262)	0.003
Tau, pg/ml		
Preop	3.1 (2.6-3.7)	
Post CPB 2h	16.9 (12.8-25.2)	<0.001
Post CPB 24h	6.3 (4.9-8.6)	<0.001
NfL, pg/ml		
Preop	13.1 (10.5-20.5)	
Post CPB 2h	14.3 (10.6-21.3)	0.17
Post CPB 24h	19.3 (14.6-30.0)	<0.001
NSE, ng/mL	(n=51)	
Preop	11.7 (9.9-13.2)	
Post CPB 2h	31.7 (24.4-35.5)	<0.001
Post CPB 24h	25.6 (21.4-32.1)	<0.001
β-trace protein, mg/L		
Preop	0.67 (0.59-0.76)	
Post CPB 2h	0.60 (0.52-0.72)	<0.001
Post CPB 24h	0.60 (0.52-0.73)	0.014

P-value with Wilcoxon's test, compared to baseline. Median and (IQR). GFAP=glial fibrillary acidic protein; NfL=neurofilament light; NSE=neuron-specific enolase

4.6 CPB management and association to AKI

General

Of the 2661 patients included in the study, 14.5% developed postoperative AKI. A higher rate of AKI was observed among patients who underwent valve surgery (15.2%) or combined CABG and valve surgery (24.0%). Patients who developed AKI had an increased length of postoperative hospital stay at the surgical unit, median 7 vs. 4 days ($p<0.001$), and had almost a 20-fold higher risk of 30-day mortality, 5.7% vs 0.3% ($p<0.001$).

Association with AKI

Patients who developed AKI were generally older, and the condition affected more often females. When adjusted for age and sex, comorbidities associated with AKI were higher BMI, diagnosis of diabetes mellitus, hypertension, atrial fibrillation, or reduced left ventricular ejection fraction. Estimated GFR based on s-creatinine, and preoperative hemoglobin both displayed a U-shaped risk association, with higher risk at reduced or elevated levels. Lowest risk was observed at e-GFR 70-80 ml/min/m2 and hemoglobin 140-160 g/L.

With multiple regression, after adjustments, time on CPB, time on aortic cross clamp, periods of compromised flow during aortic cross clamp, and nadir hematocrit during CPB were significantly associated with postoperative AKI (results unpublished)

5 DISCUSSION

This thesis aims to investigate different aspects of cardiopulmonary bypass management and the risk of adverse outcomes. The Prime-study investigated several factors on dextran 40 colloid prime, a relative uncommon additive. The effects on serum colloid osmotic pressure, fluid balance, and general safety is presented in paper I, while paper II and III report specific renal and coagulation results, which is of particular concern when it comes to the use of colloids. Paper IV uses the study population from the Prime-study to describe how five different serum and plasma brain injury markers is affected in routine cardiac surgery with CPB. Paper V studied the association between manageable CPB variables and renal outcome.

5.1 Which priming solution should be used in adult cardiac surgery?

An optimal prime should ensure that the CPB circuit can be de-aired and safely connected to the patients circulatory system, and contribute to maintain euvolemia during CPB. The composition of the prime fluid should be homologous to that of the patient's blood, with minimal impact on homeostasis and organ function.

According to the Global Cardiopulmonary Bypass Survey (34), crystalloid solutions remain the most frequently used prime in current practice. An electrolyte balanced solution is likely to be preferred over regular saline to avoid hyperchloremic metabolic acidosis. Although colloids are superior plasma expanders, crystalloid solutions are inexpensive and don't have the risk of allergic reactions or the same impact on coagulation (119). In the Prime-study, we could demonstrate that 1100 ml of crystalloid pump prime with 200 ml of added mannitol decreased mean serum COP with 20% during bypass. This resulted in less intraoperative fluid loading and a less positive net fluid balance (-426 ml) 12 hours after CPB for patients with dextran prime compared to patients with crystalloid prime. The difference would likely have been more pronounced if a pure crystalloid solution without mannitol additive had been used. However, even if there was less fluid loading in the colloid group, the greater plasma expanding effect of dextran contributed to lower hematocrit values in dextran treated patients. 10% dextran 40 solutions has an estimated

plasma expanding effect of 100-200% in relation to infused volume, whereas crystalloids only have 20-25% (119). For reference, the colloid solution in the Prime-study had 3.5% dextran 40. Hematocrit levels during bypass were not recorded for paper I, but do not seem to have been critically low as both CPB flow and the number of transfused red blood cell units did not differ significantly between the groups. The increased intraluminal volume with colloid prime should arguably facilitate venous return and have a positive contribution to bypass ease of use. The possible effects from the change in different fluid compartments, including endothelial cell activation and glycocalyx integrity, by either a crystalloid or colloid prime are difficult to estimate. Increased tissue edema or lower hematocrit can both contribute to decrease of tissue DO_2. Unique organ autoregulation and physiological conditions contribute to the complex and difficult context of CPB physiology (10). There is limited evidence available on this subject, which gives rise to an ongoing crystalloid vs. colloid debate. A meta-analysis from 2003 comparing crystalloid with colloid prime concluded that there were too few, and too small, prospective trials for any definitive conclusions (120). Newly, Pesonen and colleagues report the first large interventional trial on pump prime with outcome data. In the Albumin in Cardiac Surgery trial (ALBICS), 1386 cardiac surgery patients were included comparing either 4% albumin solution or Ringer acetate as CPB prime and perioperative intravenous fluid regimen. Like in our study, better total fluid balance with colloid was observed in the ALBICS trial, but there was no difference in the combined 90-day incidence of major adverse events (121). Patients treated with albumin had lower incidence of myocardial injury as measured by creatine kinase-MB, but increased risk of major bleeding, resternotomy, and infection. The ALBICS trial is first of its kind and does not provide any final evidence for the colloid/crystalloid debate. But without any clear clinical benefits over balanced crystalloid prime, it seems difficult to justify the increased risk of bleeding and allergic reactions with colloids, as well as the greater cost.

In addition to the fluid composition of the prime solution or any intravenous fluid used, autologous retrograde priming (RAP) or modified ultrafiltration may be considered to regulate hemodilution and tissue edema during CPB. Compared to conventional priming, RAP may reduce the need for allogenic transfusions (122), but studies have so far not provided reliable evidence for any improvements in clinical outcome (43).

5.2 Dextran 40 in CPB prime

Of all the colloids, dextran is relatively unexplored as pump priming in cardiac surgery, and often overlooked in general volume resuscitation practice (123). This is likely derived from the early reports of anaphylactic reactions and impact on hemostasis, which led dextran to fall out of practice as a plasma expander. In this regard, although limited in size, the Prime-study provides valuable clinical information for dextran 40 as a priming solution. In light of the mounting evidence and regulatory warnings for the increased risk of AKI and mortality with the use of hydroxyethyl starch in critically ill patients (124, 125), and now following the results of the recently published ALBICS trial, it is uncertain if dextran will stand to gain or lose in clinical and scientific interest in colloid prime.

Since the introduction of hapten pretreatment, allergic reactions with dextran are rare. Hapten reduces allergic reaction 35-fold, with an average incidence rate of 1/4600 injections (126). Besides the ability of dextran 40 prime to maintain serum COP during bypass, this thesis provides additional interesting findings. First; Dextran prime reduced free hemoglobin after bypass with >50%. CPB induced red blood cell damage increases levels of cell free hemoglobin, and consequently leads to the formation of reactive oxygen species and diminished nitric oxide bioavailability (127). Reactive oxygen species have a direct tissue damaging effect, and low nitric oxide alters microcirculation towards decreased organ perfusion, which may significantly contribute to organ damage in cardiac surgery (127, 128). Secondly; Dextran attenuated renal tubular injury during CPB. Possible pathways could be by microcirculatory improvements with better DO_2 / VO_2 ratio, or less toxic injury from reactive oxygen species as described above. Thirdly; Dextran 40 did not increase bleeding or transfusion requirements. This is of particular importance given the antithrombotic properties of dextran and the strong association between bleeding and poor outcome in cardiac surgery (16). Blood samples from patients with dextran prime did display impaired clot formation, reduced clot strength, and reduced ADP-dependent platelet aggregation as measured by thromboelastometry and impedance aggregometry. However, the amplification of the coagulation cascade is many times stronger than needed for thrombin generation (113), why a measurable decrease in the described tests may not be enough to induce clinical bleeding.

Additionally, previous studies have indicated the potential of dextran to mitigate endothelial activation, leucocyte rolling, and subsequent tissue inflammatory infiltration (55, 56, 129). Severe systemic inflammatory response in cardiac surgery can mediate organ damage (15), and neuroinflammation have been identified as a key feature in the process of POCD (130, 131). This stimulates further studies designed to investigate dextran 40's impact on the inflammatory response in cardiac surgery, evaluating any relevant clinical outcome.

5.3 Brain injury markers in cardiac surgery

Neurologic injury is a common concern in cardiac surgery, where stroke remains a devastating complication. According to a Swedish study, 1.2% of CABG patients are affected of stroke (132), and between 4.4-7.2% in more complex combined cardiac operations (133, 134). POCD is far more prevalent, but is often overlooked in the clinical context as it is often mild and transient. Furthermore, to ensure a correct POCD diagnosis, pre- and postoperative neurocognitive testing is required. Subclinical strokes affects 15-60% of cardiac surgery patients according to imaging studies, and may be part of POCD (135). Other mechanism for POCD may include episodes of cerebral oxygen desaturation and neuroinflammation (87, 136). With the introduction of sensitive assays to measure brain injury markers, there might be a potential to quantify neurologic injury in cardiac surgery by a simple blood test (137). In paper IV we reported an increase in all measured glia (S-100B, GFAP) and neuron (NSE, total-tau, NfL) injury markers following uncomplicated cardiac surgery. Samples were not related to any neuroimaging, neurocognitive tests, or transcranial doppler, why the results are only descriptive. The increase was not dependent on a BBB disruption. This is in part conflicting with previous studies, were BBB damage and increased BBB permeability was observed in up to 50% of patients after cardiac surgery (138, 139). BBB disruption is central in the neuroinflammatory theory of POCD, currently gaining scientific evidence (87), where patients with BBB disruption were also more likely to be subject to POCD (139). Previous studies in cardiac surgery have used CSF/serum albumin ratio or MRI evaluation to detect BBB disruption. β-trace protein, that was used in paper IV, has a smaller molecular weight than albumin and is not dependent on any active transportation (108). Hence, there should not be any issues of sensitivity. Further studies are warranted to investigate the association between β-trace protein and BBB-disruption in cardiac surgery.

The rise in brain injury markers correlated moderately with age and/or CPB time. The study does not reveal if the correlation in fact depicts larger subclinical brain injury in older patients with longer CPB-runs, or if the correlation represents any other mechanism unrelated to brain injury size.

The risk of substantial extracerebral release of S-100B and NSE in peripheral samples needs to be considered in the postoperative setting of cardiac surgery (92, 94). In paper V, both injury markers correlated significantly with the level of hemolysis. As a result of their relative short half-life, brain damage specificity is likely normalized within hours (S-100B) or days (NSE) after surgical trauma or extracorporeal circulation.

To establish the usefulness of peripherally sampled brain injury markers, further studies needs to investigate their relationship to imaging and functional measurements of neural damage, and also describe the dynamics after injury. Our results contribute with information on early postoperative dynamics of brain injury markers after uneventful cardiac surgery.

5.4 Modifiable CPB variables and AKI risk

In view of the absence of effective therapeutic strategies for AKI, the identification of potentially modifiable risk factors is important for the development of treatment strategies to improve patient outcome. The finding that the choice of dextran 40 based prime attenuates acute tubular injury is interesting, and motivates further investigation. In paper V, after adjustments, we identified time on CPB, aortic cross-clamp time, periods of compromised pump flow during aortic cross-clamp, and nadir hematocrit during CPB to be associated with increased odds ratios for AKI, generally in line with previous research (64, 74-77). Time on CPB and aortic cross clamp time are mainly dependent on procedure complexity and intraoperative complications, and may be considered as mostly non-modifiable. Instead, it highlights the importance of the preoperative heart team discussion to carefully consider patient-related factors and decide on the optimal operative strategy and the extent of the surgical intervention. Among the patient specific variables, we identified preoperative hemoglobin and preoperative e-GFR to have a U-shaped risk association for AKI. The non-linear relationship between preoperative hemoglobin and AKI may support the hypothesis of improved renal microcirculatory perfusion during bypass with a certain degree of hemodilution, but only down to a critical DO_2 level (41, 76). It also re-confirms the

importance of optimization of preoperative anemia in elective patients (114). Why preoperative e-GFR have a similar non-linear risk association to AKI, with increasing risk in high e-GFR individuals, is not apparent, but unregistered confounders or creatinine to e-GFR conversion bias is possible.

Most of our knowledge on CPB related AKI risk is based on observational data. Only during recent years have randomized trials begun to investigate how modifiable physiologic CPB variables relate to renal physiology and outcome. In a study by Lannemyr et al., increased CPB flow rate of 3.0 L/min/m^2 improved renal oxygen supply/demand ratio with 30% compared to a flow rate of 2.4 L/min/m^2 (140). The importance of flow is also supported by Ranucci et al., who reported that a goal-directed perfusion strategy, aiming at maintaining a minimum DO_2 by adjusting the arterial pump flow, reduced postoperative AKI rates compared to a standard fixed target pump flow of 2.4 L/min/m^2 (141). However, a higher pump flow rate likely causes more blood trauma, and might increase cerebral embolic load and tissue bleeding, while possibly reducing cardioprotection by increased non-coronary collateral flow, counteracting the benefit of reduced hypoxic risk (10).

Studies on variable MAP levels have so far not provided evidence on the superiority of higher MAP in relation to renal outcome (142-144). The study by Vendel et al. aimed to investigate high (70-80 mmHg) vs. low (40-50 mmHg) target MAP during CPB to prevent cerebral injury, did in fact observe a significant larger number of patients where creatinine had doubled in the high intervention group (145). The higher MAP target accounted for an increase in vasopressor use, possibly affecting glomerular filtration. In our results from paper V, compromised MAP during CPB was not associated with postoperative AKI. Apart from a lack in causality, this could be due to confounding factors, such as vasopressor use, not adjusted for in the statistical models. Whatever the cause, it pin-points the multi-factorial aspects of CPB associated AKI. Current evidence seem to point towards the importance of renal DO_2, consisting of pump flow and hematocrit, rather than driving pressure during CPB for renal outcome.

Body temperature and arterial oxygen content are also CPB variables determining renal DO_2/VO_2 ratio, where arterial oxygen saturation seldom diverge. Normothermic vs. hypothermic CPB is not considered a risk factor for AKI (146), but if hypothermic perfusion is performed, oxygenator rewarming temperature >37°C has been reported to be an independent risk factor of AKI (147).

5.5 A note on evidence based CPB management

Cardiopulmonary bypass management varies considerably among cardiac surgery centers (148). One striking example is made by a regional study surveying priming practices in United Kingdom and Ireland where none of the 31 responding centers used the same prime (35). A quarter of responders stated that their main reason for their current prime practice was due to "historic use", suggesting that there was little reflection to current evidence. Some variability may however been due to clinical uncertainty. Current European guidelines offer guidance on the "optimal" CPB management based on systematic review of the current evidence (32). However, out of the 113 recommendations made, only 6% were supported by multiple randomized clinical trials, the highest level of evidence (Level A). For 44% of recommendations, including several of the strongest class I and class III recommendations, there are no randomized clinical evidence or large observational studies, i.e. the recommendations are based on expert opinions alone (Level C) (31). The limited high class evidence likely contributes to clinical variability, which may hinder attempts to improve outcome after CPB.

It is central that our best practice is firmly based on evidence with clinically important outcomes. Individual studies on organ specific outcomes contribute to our knowledge, but with complex CPB physiology, subsequent trials need to take the full clinical context of any intervention into account, in order not to overlook important side effects. The off pump technique for CABG was developed in the late 90's to evade the harmful effects of CPB, with encouraging initial data indicating reduced risk of bleeding and organ specific injury (149). The technique gained in popularity until well designed randomized trials did in fact establish that off-pump surgery did not provide any benefit over standard on-pump CABG (150-152). One study also reported higher 5-year mortality with the off pump technique due to more frequent incomplete revascularization and lower rate of graft patency (151). The absence of high-level clinical evidence for many of the possible variations in CPB equipment and management is, although the best of intentions, a potential risk for suboptimal outcome. Off-pump CABG is still an option that may be advantageous in selected patients, and emphasizes how skilled clinicians need to make case by case decisions based on current evidence and patient specific factors.

5.6 Limitations

The sample size in the Prime-study was designed to detect differences in COP, and does not provide sufficient power to detect differences in clinical outcome variables. The results from study II-IV is hence limited from being secondary analyses, although pre-specified. Only elective cases were included in the Prime-study, limiting the generalizability to acute cases. Because of the nature of retrospective observational studies, interpretation of the results in paper V is limited by selection bias, missing variables and unregistered confounders. In paper V, confounders were adjusted with multivariable regression, and missing data for adjusted variables were categorized as unknown to avoid any loss of power. Imputation would have been an alternative option to handle missing data, but because missing values were limited for each variable (max 7%), the addition of imputation would have been small. Both studies are single center based, and results would have been more generalizable if a multicenter approach had been applied.

More specific limitations, and strengths, are discussed separately in each paper.

6 SUMMARY

1. Colloid prime with dextran 40 better maintained serum colloid osmotic pressure during CPB compared to a crystalloid prime. Patients treated with dextran-based prime had a more effective intravascular volume expansion, with a reduction in total fluid balance **(paper I)**.

2. Circulating levels of free hemoglobin 2 h after CPB was markedly reduced when dextran-based prime was used compared to a crystalloid prime **(paper I)**.

3. Dextran 40 colloid prime induced less renal tubular injury during bypass compared to crystalloid-based prime **(paper II)**.

4. Colloid prime with dextran 40 did not increase per- or postoperative bleeding or transfusion requirements compared to a crystalloid prime **(paper I and III)**.

5. Compared to a crystalloid solution, dextran 40 based colloid prime induced an impaired clot formation, clot strength, and ADP-dependent platelet aggregation measured with thromboelastometry and impedance aggregometry **(paper III)**.

6. Levels of glial cell injury marker S-100B and GFAP, and neuronal cell injury marker NSE, total-tau, and NfL all increased in peripheral blood within 24 h after uncomplicated cardiac surgery compared to preoperative values **(paper IV)**.

7. Time on CPB, aortic cross-clamp time, compromised pump flow during aortic cross-clamp, and nadir hematocrit during CPB increased adjusted odds ratio for postoperative AKI **(paper V)**.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

Cardiopulmonary bypass is a necessary part to safely perform many of our cardiac surgery operations, but it comes with several common side effects and sometimes clinical complications. Hemodilution and a systemic inflammatory response are to be expected, as well as a certain amount of bleeding. The anticipated fall in colloid osmotic pressure from the use of bloodless prime can be mitigated by the use of dextran 40 based prime compared to a crystalloid prime. Dextran 40 is rather unexplored as cardiac surgery prime, but like other colloids it reduces fluid loading and improves total fluid balance after surgery. We identified various new features that stimulate further investigation. Dextran 40 prime attenuates the extent of renal tubular injury and hemolysis during CPB. Efforts should be focused to establish if dextran 40 lowers the risk of acute kidney injury and other organ damage due to improved perfusion and/or reduced oxidative stress from less destruction of red blood cells. Although dextran 40 prime has a measurable impact on laboratory coagulation values, it did not increase bleeding or the need of allogenic blood products. This is important, as bleeding complications are a determining factor in cardiac surgery and there are known safety concerns for colloid induced bleeding (121, 123). To establish dextran 40 prime as safe and cost effective, the results needs to be reproducible in multicenter randomized trials with sufficient statistical power for clinically relevant endpoints.

Organ specific pathophysiology during cardiac surgery with CPB is incompletely understood, and warrants further investigation. Postoperative cognitive dysfunction is a widespread complication after cardiac surgery, with impact on the quality of life for those affected and their relatives. We found that levels of glia and neuron injury markers in peripheral blood increased after cardiac surgery without any evident neurological or neurocognitive symptoms. Before blood analysis of brain injury markers may be clinically useful in cardiac surgery, further research is needed to study the associations between perioperative release of biomarkers and neurological clinical outcome.

Cardiac surgery associated acute kidney injury is common, and entails a substantial increase in hospital costs and mortality. To minimize the risk of acute kidney injury, CPB time and aortic cross clamp time should be as short as possible, and hematocrit and pump flow maintained at adequate levels at all times. Preoperative anemia and low glomerular filtration should be recognized and optimized before surgery whenever possible.

With ongoing demographic changes, a larger proportion of older individuals with more comorbidity will be accepted for cardiac surgery. It is important that the cardiac surgery team continuously evaluate their CPB practice based on current evidence, and may allow for individualized CPB technique based on the patients risk profile.

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