Experimental and clinical studies on the use of colloids and hyperosmolar additives during CPB: effects on perioperative total fluid load, edema generation and organ function

Venny Lise Kvalheim

Dissertation for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Content

1. Acknowledgement

This work has been carried out under supervision of Professor Paul Husby. I want to express my deepest gratitude for the privilege of working in his scientific group. His always enthusiastic and optimistic behaviour is a great inspiration, and the energy, unfailing interest and impatience are greatly valued.

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Finally I wish to express my gratitude to Martin and Ann Linnea for their love, their laughter and support, reminding me what life is about.

2. Scientific environment

The Circulatory Research Group at the Institute for Surgical Sciences, University of Bergen is directed by Professor Paul Husby. This is an interdisciplinary group of surgeons, anesthesiologists and perfusionists that have worked with large animal models (pigs) for several years. The focus of the Circulatory Research Group is different aspects of fluid homeostasis and flow-and pressure-strategies during normothermic as well as hypothermic cardiopulmonary bypass (CPB).

The experimental studies of this thesis were performed between 2004-2008 at the Vivarium at Haukeland University Hospital under the direction of the Faculty of Medicine.

The clinical study was performed between 2007-2008 on patients admitted to the Department of Heart Diseases, at Haukeland University Hospital, who were undergoing cardiac surgery. The study was carried out in collaboration with the staff from the Department of Anesthesia and Intensive Care.

3. Abbreviations

Alb	Albumin
BMI	Body mass index
BV	Blood volume
CABG	Coronary artery bypass grafting
CI	Indexed values of cardiac output
CO	Carbon monoxide
C.O.	Cardiac output
COP	Colloid osmotic pressure
COPp	Colloid osmotic pressure in plasma
COPi	Colloid osmotic pressure in interstitial fluid
CPB	Cardiopulmonary bypass
CVP	Central venous pressure
EVLW	Extravascular lung water
FER	Fluid extravasation rate
F_iO_2	Inspiratory fraction of oxygen
GEDV	Global end-diastolic volume
Hb	Hemoglobin
HbCO	Carboxyhemoglobin
HES	Hydroxyethyl starch
HSD	Hypertonic saline / dextran
HSH	Hypertonic saline / Hydroxyethyl starch
I	Index (CI = cardiac index; SVRI = indexed value of SVR, etc)
ICP	Intracranial pressure
ICU	Intensive care unit
ITBV	Intrathoracic blood volume
Jv	Net capillary filtration
J_L	Lymph flow
K_{fc}	Capillary filtration coefficient
kD	kilo Dalton
LVEF	Left ventricle ejection fraction
MAP	Mean arterial pressure
Mw	Molecular weight
NFB	Net fluid balance
PCWP	Pulmonary capillary wedge pressure
Pc	Capillary hydrostatic pressure
PEEP	Positive end-expiratory pressure
Pi	Interstitial fluid hydrostatic pressure
PV	Plasma volume
SVR	Systemic vascular resistance
σ	Sigma = Capillary reflection coefficient
TTW	Total tissue water content
TEG	Thromboelastography
V_{RBC}	Red cell volume

4. List of original papers

I Farstad M, **Kvalheim VL**, Husby P. Cold-induced fluid extravasation during cardiopulmonary bypass in piglets can be counteracted by use of iso-oncotic prime.
J Thorac Cardiovasc Surg 2005; 130: 287-94

II Farstad M, Haugen O, **Kvalheim V**, Hammersborg S, Rynning SE, Mongstad A, Nygreen E, Husby P. Reduced fluid gain during cardiopulmonary bypass in piglets using a continuous infusion of a hyperosmolar/hyperoncotic solution.
Acta Anaesthesiol Scand 2006; 50: 855-862

III **Kvalheim VL**, Rynning SE, Farstad M, Haugen O, Nygreen E, Mongstad A, Husby P. Fluid overload during cardiopulmonary bypass is effectively reduced by a continuous infusion of hypertonic saline/dextran (HSD).
Scand Cardiovasc J 2008; 42: 63-70

IV **Kvalheim VL**, Farstad M, Haugen O, Brekke HK, Mongstad A, Nygreen E, Husby P. A hyperosmolar-colloidal additive to the CPB-priming solution reduces fluid load and fluid extravasation during tepid CPB.
Perfusion 2008; 23: 57-63

V **Kvalheim VL**, Farstad M, Steien E, Mongstad A, Borge BA, Kvitting PM, Husby P. Infusion of hypertonic saline/starch during cardiopulmonary bypass reduces fluid overload and may impact cardiac function.
Acta Anaesthesiol Scand; 2010; 54(4): 485-93

5. Introduction

5.1. Background

5.1.1. Start of cardiac surgery

Cardiac surgery has been regarded as one of the most important medical advances in the twentieth century. Different extracorporeal circulation techniques were developed more than 50 years ago to facilate treatment of congenital cardiac anomalies.

The first surgical procedures on these patients were performed using hypothermia and inflow occlusion (Moller *et al.* 2009). Hypothermia decreased tissue oxygen requirements (Bigelow *et al.* 1954) providing organs protection against ischemic injury, and allowed the surgeon to interrupt circulation for a short time. The procedures performed with this technique were mainly repair of atrial septum defects that could be closed within a few minutes.

For longer procedures new techniques were needed. John Gibbon successfully used a screen oxygenator he had developed in 1953 for closure of an atrial septal defect in a 19-year-old woman. The use of this equipment in the next 5 patients was, however, unsuccessful and further attempts were discontinued.

In 1954 Lillehei and co-workers developed a new technique for “cardio-pulmonary-bypass” where a human donor was used for “cross circulation” (Figure 1).

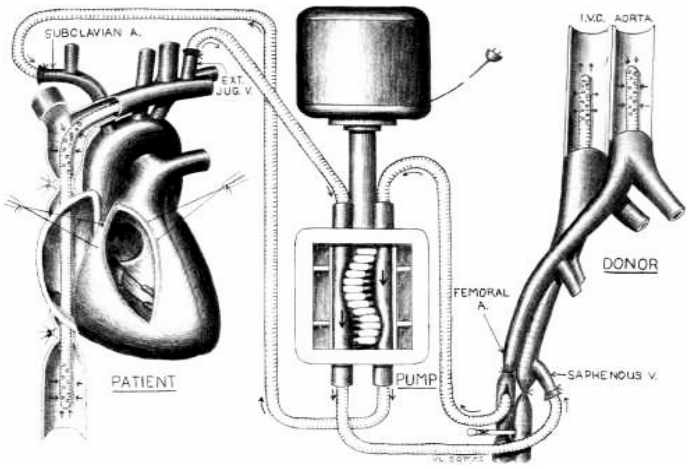


Figure 1: *Cross circulation technique; (Adapted from Moller et al. 2009 Ann Thorac Surg 88: 1044-46, reprint with permission from author)*

The donor, often a relative, served as the oxygenator, and a pump provided blood flow between the patient and donor. During a 14-month period 45 children were operated by use of this technique and 28 patients were successfully repaired and discharged from the hospital. A surgical mortality of 38 % would hardly have been accepted today, but it is important to remember that most patients with congenital heart disease had a poor prognosis, often leading to early fatality, before the development of the heart-lung machine.

In a 53-year follow-up study, 20 of the patients operated by use of the "cross circulation technique" were still alive and had no limitations related to the previous cardiac operation they had gone through (Moller *et al*. 2009).

The "cross-circulation technique" had limitations and was a risky procedure both for the patient and the donor, and the search for more suitable strategies continued.

In 1955 the DeWall bubble oxygenator, that was developed in co-operation with Lillehei and his group, was used for the first time (DeWall 2003). A 13-year-old boy with a ventricular septal defect was the first patient. The system worked well, was widely accepted and was used with an increasing frequency for open-heart surgery. The technology was, however, complex and therefore slow to develop.

Throughout the years the equipment used in a typical extracorporeal circuit has advanced considerably. Although the different circuits used today vary considerably between hospitals, the basic concepts of extracorporeal circulation are essentially common to all CPB circuits in use.

5.1.2. The heart-lung machine and priming solutions

The standard equipment used in a heart-lung machine at present includes the main elements of pump, oxygenator, venous reservoir, tubings, gas supply systems, different filters, bubble traps as well as suckers and venting systems. In addition cardioplegia delivery systems and in-line monitoring equipment are available together with a number of alarm systems.

Before use the machine has to be primed with a fluid solution, so that adequate flow rates can rapidly be achieved upon initiation of cardiopulmonary bypass without any risk of air embolism. Lactated or acetated Ringer's solution is at present used as the main prime component. This solution is capable, when mixed with the patient's blood, to maintain oxygen delivery and carbon dioxide removal and physiological homeostasis during extracorporeal circulation. Although agreements on the use of non-blood prime, the final composition of the priming solution is continuously under discussion.

5.1.3. Cardiac surgery – at present

A great challenge in cardiac surgery is the change in patient population during the last decades. Older age, more comorbidity, emergency surgery and female gender are all contributing to increased risk during cardiac surgery (Kurki *et al.* 2003; Higgins 1998). Still, an increasing number of high-risk patients are admitted to advanced surgery (Scrutinio & Giannuzzi 2008).

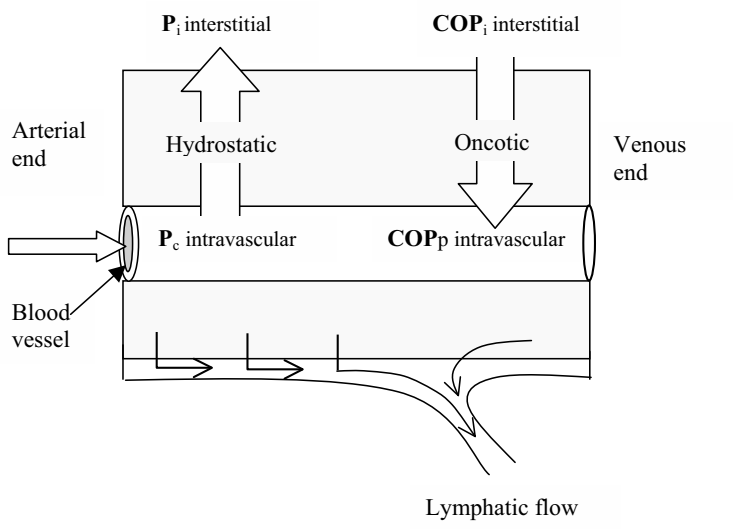
To maintain low morbidity and mortality in this population it is important to optimize all parts of their treatment. Small improvements may be the decisive factor when handling high-risk patients.

Fluid therapy in cardiac surgery offers challenges beyond other surgical specialities. The patients` underlying cardiac disease, the complexity of the surgical intervention (including cardiac arrest and hypothermia) and the pathophysiological impact of extracorporal circulation, all contribute to the need for critical reflection when instituting fluid treatment protocols.

5.2. Fluid shifts

Starling`s observations (Starling 1896), which led to Starling equation, illustrates how the fluid filtration through capillary membranes is dependent on the balance between the hydrostatic pressure and the osmotic pressure of the membranes.

Figure 2:



$$J_v \text{ (Net capillary filtration)} = K_{fc}\,[(P_c - P_i) - \sigma(COP_p - COP_i)]$$

K_{fc} capillary filtration coefficient (a product of surface area and hydraulic conductance)

P_c capillary hydrostatic pressure

P_i interstitial fluid hydrostatic pressure

COP_p intravascular oncotic pressure (COP in plasma)

COP_i interstitial oncotic pressure (COP in interstitium)

σ reflection coefficient (related to imperfect semipermeability, for plasma proteins usually 0.80-0.95)

Edema is an excess of interstital fluid, and is a result of:

Net Capillary Filtration > Lymphatic drainage rate

and may be caused by

- elevated capillary pressure (e.g. heart failure, over-transfusion, deep venous thrombosis)
- reduced plasma COP (e.g. malnutrition, malabsorption (lack of proteins) or hemodilution)
- reduced reflection coefficient (inflammation)

5.3. Additives

5.3.1. Colloides

Starlings discovery led to the use of solutions of artificial colloids to replace lost plasma in wounded soldiers already during World War I. Development of a safe and inexpensive colloid solution has been an ongoing process since. A selection of available products today is:

5.3.1.1. Albumin

Albumin is derived from human plasma. Due to ethanol and heat treatment viral transmissions are unlikely. 60 % of total protein present in plasma is albumin. There is a constant movement of albumin between intra- and extravascular compartments.

Human albumin has few adverse effects and is considered to be the colloid with least influence on the coagulation. Still albumin may inhibit platelet aggregation and influence bleeding (Vincent 2009). Interference with blood typing and allergic reactions is possible (0.003 %), though less frequent compared to other colloides (Ring & Messmer 1977). Albumin is a transport molecule, which should be kept in mind when treating patients exposed to multi-pharmacia. Compared to other colloides it is expensive.

Available solutions are:

4 % (40 mg/ml) Albumin used in study I

20 % (200 mg/ml) Albumin

5.3.1.2. Hydroxyethylstarch (HES)

HES is frequently used as a plasma substitute, and is a modified natural polymer of amylopectin (polysaccharide) found in plants such as potato and corn. A variety of different HES solutions exist, and it is important to distinguish between the different preparations because of the effect of plasma volume expansion as well as their effects on coagulation and other clinical variables. Consentration, its molecular weight, its molar substitution, and the C2/C6 ratio define HES solutions` physical and chemical characteristics. The molecules show great polydispersity, and molecule size in the solutions follows a bell-shaped distribution, ranging from a few thousand to a few millon daltons. The number and weight of molecules (70kD - 480kD) determines colloidal activity.

The molar substitution expresses the average number of hydroxyethyl groups per unit of glucose, and varies from 0.4-0.7, (how many hydroxyethyl groups exist/10 u of glucose). The C2/C6 ratio describes more precisely the substitution pattern (the hydroxyethyl units are most frequently at position C2 and C6) (Treib *et al.* 1999). High molar substitution and high ratio indicates delay in breakdown and elimination of hydroxyethyl starch, resulting in a relatively long-lasting effect, but also risk of accumulation of molecules, and subsequently a higher risk of adverse effects. The first generations had a molecular weight of 400-600 kD, and molar substitution of 0.7. There has been a continuous improvement of these solutions, with the newest ones weighing only 130 kD, and with a molar substitution of 0.4.

HES might interfere with normal hemostasis at different levels. Large molecules can interfere with fibrinogen, coagulation factor VIII, and the von Willebrand factor (Kozek-Langenecker 2005). Anaphylactic reactions are, estimated to a frequency of 0.006%, lower than for both dextran and gelantine (Ring & Messmer 1977). The frequency is slightly higher than for albumin, even though some studies report similar values for albumin and HES (Laxenaire *et al.* 1994).

There has been increasing interest concerning the effects of HES on renal function. Impaired renal function has been described (Cittanova *et al.* 1996), as well as swelling of renal tubular cells after administration of certain HES preparations (Boldt 2009a). A suggested mechanism of renal dysfunction is the induction of hyperviscosity of the urine by infusion of hyperoncotic colloids in dehydrated patients, and can be avoided by adequate hydration (Boldt 2009a).

Available solutions are:

HAES®; (6% HES 200/05), used in study I

Voluven®; (6% HES 130/04)

5.3.1.3. Dextran

Dextran is polysaccaride molecules of high molecular weight, synthesised from sucrose from lactic-acid bacteria and with a molecular weight ranging from 40-70 kD. Dextrans may induce abnormal bleeding due to their effects on primary hemostasis and on the fibrinolytic system. Infusions may induce a "von Willebrand syndrome" with decreased levels of von Willebrand factor and associated factor VIII (Van der Linden & Ickx 2006). Dextrans also enhance fibrinolysis. They are more often than other colloides associated with anaphylactoid reactions (Ring & Messmer 1977), and the use of dextran 1 (hapten inhibition) are usually recomended to reduce the risk for DIAR (dextrane induced anafylactoid reactions).

Available solutions are:

Macrodex®; (6 % dextran 70)

Plasmodex®; (6% dextran 30)

5.3.2. Hypertonic saline/colloidal solutions

Hyperosmolar solutions intend to make use of the large interstitial and intracellular reservoirs. The first study from Velasco (Velasco *et al.* 1980) and co-workers reported that a small infusion of hypertonic saline (7.5 % NaCl) of only 10 % of shed blood volume rapidly restored arterial pressure and cardiac output to baseline values.

The use of hypertonic saline started as development of solutions for small-volume resuscitation. Several beneficial effects were observed; increased cardiac output, fall in total peripheral resistance and improved renal perfusion (Nakayama *et al.* 1984). Different hyperosmolar solutions have been tested, like mannitol and glucose, and the increased osmolality of all solutions produced rapid initial improvements. The response did not require sodium or chloride. However, the decline in improvements was slowest with hypertonic saline (Kramer 2003).

As these improvements were short-lived, combination fluids were developed. Several studies observed improved results of hypertonic saline in combination with colloides, compared with one of the solutions used alone (Kramer 2003; Holcroft *et al.* 1987; Smith *et al.* 1985).

By maintaining the COP with colloides, fluid mobilized from the extravascular space by the osmotic effect of hypertonic saline, remained for a longer period in the intravascular compartment.

Available solutions are:

HyperHaes®; (6% HES (200/05), 7,2 % NaCl) used in study II, IV and V

Rescueflow®; (6 % dextran (70), 7,5 % NaCl) used in study III.

5.3.3. Crystalloides

Crystalloides are aqueous solutions of mineral salts or other water-soluble molecules and are disseminated homogenously throughout the plasma volume and interstitium. Due to this fact, a four-fold amount of fluids is needed in order to achieve the same intravasal volume effect as whole blood or colloid plasma substitution (Schumacher and Klotz 2009). Most solutions are balanced electrolyts solutions largely corresponding to plasma composition. Lactated or acetated Ringer's solutions are most commonly used. Lactated Ringer's solution might exacerbate pre-existing acidosis and interfer with lactate as a marker of hypoxia (Zander Rolf 2006). In Norway actated Ringer's solutions is most common.

6.0 Aims of the study

Negative impact of fluid overload has gained increasing interest during the last years. Fluid overloading with edema formation is a regular finding following on-pump cardiac surgery. Hemodilution is one of the important contributors to this fluid loading.

The aim of the present study was to evaluate the effect of different colloidal additives on fluid loading and edema generation during CPB in an experimental model, and to translate the results into a clinical setting focusing on eventual consequences for organ function.

The specific aims of the different sub-projects were to investigate:

- Whether maintainance of COP by use of iso-oncotic prime could reduce fluid leakage during CPB (Paper I)

- How a slow infusion of hypertonic saline/hydroxyethyl starch during CPB influenced fluid shifts and edema generation in the different organs, brain included (Paper II)

- The effects of hypertonic saline/dextran infusion during CPB on fluid homeostasis (Paper III)

- To what extent a given amount of hypertonic saline/hydroxyethyl administered as prime additive during CPB could influence fluid balance/distribution (Paper IV)

- Wheather a hypertonic saline/hydroxyethyl additive influenced fluid balance also during tepid CPB (Paper IV)

- **A:** If the results of the experimental studies could be translated into clinical practice, and **B:** How can a conceivable reduction in NFB by infusion of hypertonic saline/hydroxyethyl starch to CABG patients during CPB impact cardiopulmonary function in the early postoperative hours (Study V)

7. Materials and methods

7.1 Experimental studies (paper I-IV)

7.1.1. Animals and animal handling

Pigs are commonly used in cardiovascular research because they share important anatomic and physiologic characteristics with humans. Their hearts are approximately of the same size, and coronary blood flow, hemodynamics and myocardial contractility are analogous (Becker *et al.* 1972; Swindle 1984; Hughes 1986). Compared to former use of dogs, they are more suitable both from an anatomic and physiologic viewpoint. The availability and price is also considerably lower (Swindle 1984). A piglet model (Norwegian landrace-Yorkshire hybrid) is well established in our research lab, and has been used for studies on fluid shifts during CPB for several years (Heltne 2002, Farstad 2006, Haugen 2008).
All experimental studies were carried out in pigs weighing 28-35 kg. Handling of the animals and procedures described were approved and in accordance with recommendations given by Norwegian Animal Research Authority. The animals were acclimatised in the laboratory animal housing area for at least 3 days prior to the experiments. Water was available until pre-medication was given, while food was withdrawn 8-12 hours before.

Anesthesia and surgery

The piglets were anesthetized according to a standard protocol (Husby *et al.* 1998). 20 min prior to induction of anesthesia, ketamine 15 mg/kg, diazepam 0.3 mg/kg and atropine 1 mg was given i.m. Inhalation of isoflurane 1-3 % in oxygen was used for induction of general anesthesia. Additionally thiopenthone 5 mg/kg was given i.v. prior to tracheal intubation and start of mechanical ventilation. Isoflurane inhalation 0.5-1.5 % delivered in 50% oxygen in air via a ventilator was used together with an infusion of midazolam 0.5 mg/kg/h and fentanyl 7.5 µg/kg/h to maintain anesthesia. In addition pancuronium 45 µg/kg/h was given as an infusion in paper II-IV to avoid shiverings during temperature reduction.
In paper II and III an ICP transducer and a microdialysis catheter was placed into brain parenchyma through a burr hole as described in the respective papers.

Mid-line sternotomy was performed along with cannulation of the aorta (18 Fr) and the right atrium (35 Fr). The left ventricle was vented (17 Fr) via the apex. A 5 Fr pulmonary artery catheter was introduced until wedging position was achived in the pulmonary artery (Edwards Lifesciences, Irvine, Ca, USA).

Intravascular catheters were placed in the femoral artery for recording of MAP and blood sampling, and in femoral vein for fluid substitution and CVP-measurements. Surgery was normally completed within 30 min.

In the end of the experiment, when fully anesthetized, the animals were euthanized with an injection of potassium chloride.

Cardiopulmonary bypass

Standard equipment for open-heart surgery (Quadrox, hollow fibre membrane oxygenator with venous hardshell cardiotomy reservoir, VHK 4200, Jostra, AG, Hirrlingen, Germany) was used. The machine reservoir was filled to a level of 300 ml (400 ml in paper I) and maintained at that level during the bypass period. Initial prime volume was 1115 ml (1000ml in paper I). Pump flow was set to 2.7 l/min/m^2. Flow pattern was non-pulsatile. The CPB head pressures were in the range of 200-250 mmHg. During CPB the height difference between the machine reservoir and the right atrium was fixed (73 ± 3 cm). Left ventricle was vented by use of a 17 Fr. vent catheter. Free venous drainage was ensured continuously by visual inspection and by monitoring of the central venous pressure (CVP) in the right atrium.

7.1.2. Experimental protocol

Paper I

Three groups were studied: CT-group (control group) where the CPB circuit was primed with acetated Ringer`s solution, and when needed, acetated Ringer`s solution was added to the reservoir. In the Alb-group the CPB circuit was primed with 4% albumin, and when needed, albumin 4% was added to the reservoir. In the last group, HES-group, HES (200/05), was mixed with acetated Ringer`s solution to obtain a COP equivalent to the in vivo plasma COP in each animal, this mixture was also added to the reservoir when needed. In all groups the primimg volum was 1000 ml, including 400 ml in the reservoir. After stabilization for 60 min, normothermic CPB (38ºC-39ºC) was initiated and continued for 60 minutes followed by 90 minutes of hypothermic CPB (28ºC).

Paper II

In this study two groups of animals received a continuos infusion. In the CT-group (control group) an infusion of acetated Ringer´s solution 5 ml/kg/hour was started immediately after anesthesia, and continued until termination of CPB. In the HSH-group the infusion was 1 ml/kg/h of hypertonic saline/hetastarch (HyperHaes®) combined with 4 ml/kg/h of acetated Ringer´s solution and was given in the same period. After stabilization for 60 min, normothermic

CPB (38 ºC-39 ºC) was initiated and continued for 60 minutes followed by 90 minutes of hypothermic CPB (28 ºC). In both groups the primimg volum was 1115 ml, including 300 ml in the reservoir. Acetated Ringer´s solution was used when needed in the resvoir.

Paper III

In this study exactly the same protocoll as in study II was used, with the exeception of the study fluid. HSH was replaced with hypertonic saline/dextran (Rescueflow®).

Paper IV

An addition in the prime was used in this study. In the interventional group (H-group), 4 ml/kg hypertonic saline/hetastarch (HyperHaes®) replaced acetated Ringer´s solution in the prime, whearas only acetated Ringer´s solution was used in the control group (C-group). After stabilization for 60 min, CPB was initiated and continued for 120 min. During CPB the temperature drifted to a ”tepid” level (33 ºC -35 ºC). In both groups the priming volume was 1115 ml, including 300 ml in the reservoir. Acetated Ringer´s solution was used when needed in the reservoir.

7.1.3. Monitoring, measurements and calculations

Plasma and blood volume determination

To calculate changes in plasma volum and fluid-shifts the exact volume of the blood need to be determinated. Several tracers have been used. Carbonmonoxide has been used as tracer in different studies during the last years, initially developed by Fogh-Andersen and co-workers (Fogh-Andersen *et al.* 1987). The technique was further sophisticated by Burge and Skinner who presented a detailed description of all calculations leading to hemoglobin (Hb) mass and blood volume determination (Burge & Skinner 1995). Heltne and co-workers further developed the technique for use in pigs (Heltne *et al.* 2002). 30ml of CO was administered into a closed circle re-breathing system. The amount of Hb in the blood was calculated from the increase in HbCO fraction after 10 min. The method was used in paper I-IV.

Baseline plasma volume was calculated from the following equations:

nCO = 1000 x [(P_B/1013,33) x V_{CO}/0,08206 x (273+T)]

nHb = **(**nCO x 25)/ΔCOHb

V_{RBC} = (644 x Hct x nHb) / Hb

BV = (V_{RBC} x 100) / Hct x F_{cell} ratio

PV = BV - V_{RBC}

nCO = number of mmol CO added to the breathing system

P_B = barometric pressure (kPa)

V_{CO} = volume of CO added to the breathing system (litre)

T = room temperature (°C)

nHb = number of mmol hemoglobin in the animal

ΔCOHb = difference in HbCO before and after CO administration

V_{RBC} = erythrocyte volume in the animal (millilitre)

Hct = hematocrit (%)

Hb = hemoglobin (gram per litre)

BV = blood volume in the animal (millilitre)

F_{cell} ratio = correction factor for trapped plasma (0.96 – 0.98)

PV = plasma volume in the animal (millilitre)

Δ PV = change in PV from one time intervall to the next

Blood losses were measured, and blood samples taken every 30 min. From the Hb and the hematocrit values obtained, together with the blood loss, changes in plasma volume were calculated;

New V_{RBC} = Previous V_{RBC} - blood loss x [(Hct start of period + Hct end of period): 2]

New PV = (New V_{RBC} / Hct end of period) – New V_{RBC}

During CPB the calculated total PV was corrected according to the volume in the heart-lung-maschine.

NFB (Net Fluid Balance) is the total amount fluids added minus diuresis and bleeding

.

FER (Fluid Extravasation Rate) is NFB minus Δ PV

Both values measured as ml/kg/h unit and were calculated every 30 min.

Total tissue water content

Immediately after the animals had been killed, samples were collected from the brain, heart, lungs, intestinal organs, muscle and skin. The samples were placed in preweighed vials to determine weight. Thereafter they were dried at 70 °C, and weighed repeatedly until stable weight. The difference between first and last measurement is presented as total tissue water.

Colloid osmotic pressure (COP)

Measurements of COP in interstitial fluid (COP_i) and plasma (COP_p) are well established methods in our research group. The technique is based on the wick-method (Aukland *et al.* 1975) and has been evaluated in pigs (Heltne *et al.* 1998). By keeping the nylon wicks,

soaked in saline, *in situ* for 90-120 min before removal, the best correlation between obtained values and true COP_i (interstitial) was found. The wicks were centrifuged under mineral oil to obtain undiluted wick fluid. Blood samples for measuring COP_p were taken every 30-min and centrifuged before analyzing. Fluids from both the interstitia and plasma were then measured with a colloid osmometer using a semi-permeable membrane with a cut-off level at 30.000 (PM-30 Amicon, Lexington, USA) with acetated Ringer`s solution in the reference chamber. Pressure was measured by a pressure transducer (Gold-Statham, Spectramed, USA) connected to a recorder (Easy-Graph 240.Gould Inc., USA).
This method was used in paper I-IV.

Cerebral monitoring

Intracranial pressure (ICP) monitoring was included in study II-IV. In addition microdialysis was included in study II to obtain markers of cerebral metabolism. The basic principle of this technique is to mimic the function of a capillary blood vessel by perfusing a thin dialysis catheter implanted into the tissue with a physiological solution (Ungerstedt 1991). The analyzed perfusate reflects the composition of the extracellular fluid. The catheter was perfused with CNS perfusion fluid (CMA) 0.3 µl/min by a microinfusion pump (CMA 107). Samples were collected every 30-min and analyzed with respect to glucose, glycerol, lactate and pyruvate in a CMA 600 Microdialysis Analyzer (CMA Microdialysis AB, Stocholm, Sweden).

7.2. Clinical study (paper V)

49 patients scheduled for elective CABG were included in this double-blinded, randomized clinical control trial. The study was approved by the Regional Committee for Medical Research Ethics in Western Norway, the Norwegian Social Science Data Services, and the Directorate for Health and Social Affairs and by the Norwegian Medicines Agency.

Anesthesia and surgery

The patients were anesthetized according to standard procedyre in our department, using midazolam, fentanyl, thiopentone, pancuronium, and isoflurane in oxygen/air for maintainance of general anesthesia. After induction of anesthesia a thermistor catheter (PVPK2015L20; Pulsion Medical Systems AG, Munich, Germany) was placed in the right femoral artery, and the transpulmonary thermodilution technique PiCCO®plus system was used for monitoring cardiac output (C.O.), intrathoracic blood volume (ITBV), extravascular lung water (EVLW) and global

end-diastolic volume (GEDV) at different time intervals. Only two surgeons performed the surgery of the patients, using the same technique.

Cardiopulmonary bypass

The CPB circuit consisted of roller pump, venous cardiotomy reservoir, arterial line filter (Medtronic Affinity 38μ, Trillium Biopassive Surface), tubings and a hollowfiber oxygenator (Affinity Trillium coating NT, Medtronic INC, Minneapolis, MN, USA). Flow pattern was non-pulsatile and mean arterial pressure was maintained between 50 and 70 mmHg. Standard cannulation in the ascending aorta (Medtronic 22 FR, DLP 89022) and the right atrium (Medtronic Threestage, MC2X-91429-29 FR) were used. Acid-base parameters were regulated according to the α-stat strategy. Tepid temperature (≈ 34 °C) was used in all patients. Myocardial protection was performed with cold blood cardioplegia (modified St.Thomas solution with blood, 10 °C), at 20-minute intervals.

Postoperative care

Assisted ventilation was maintained until following standard criteria were fulfilled: the patient was hemodynamic stable, thoracic drainage <50 ml/h, bladder temperature, >36.5°C. Extubation was performed when the patient was awake, arterial $pO_2 > 9.5$ kPa, $pCO_2 < 6.5$ kPa and tidal volume > 7 ml/kg during CPAP (Continuous Positive Airway Pressure)-ventilation. Fluid supplementation and diuretics were used according to the physician on duty.

Study Protocol

Patients were randomized to receive either a continuous infusion of HyperHAES® (HSH-group), which consists of 60 mg/ml of poly (O-2-hydroxyethyl) starch (Hetastarch 200/05, 1232 mmol/l sodium, 1232 mmol/ml chloride, osmolality 2464 mosmol/l (Fresenius Kabi, Uppsala, Sweden) or acetated Ringer's solution (CT-group). Infusion started upon arrival in the operating theatre just after preoperative hemodynamic baseline values were obtained (PiCCO®plus system). Both groups received acetated Ringer's solution 4 ml/kg/h and 1 ml/kg/h of the blinded test solution throughout 4 hours. Accurate accounts of fluid additions, blood loss and diuresis were kept.

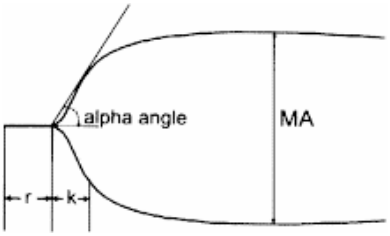
Laboratory data

Acid-base samples were measured regulary. Blood samples of Hb, Evf, Tpk, serum-sodium, serum-chloride, serum-glucose and serum-creatinine were measured pre-and postoperatively and additionally at day 1, 2 and 3 after operation.

Thrombelastography (TEG®)

Thrombelastography (TEG®, Haemoscope Corpotation, Niles, IL, USA) was used for evaluating blood coagulation, and shows the viscoelastic changes that occur during coagulation, and enable an evaluation of the process of clot initiation, formation and stability. The TEG gives a graphic representation of clot formation and subsequent lysis (Luddington 2005).

Figure 3.



I← Thrombosis →← Fibrinolysis →

TEG variables include:

r	(reaction time), time to initial fibrin formation (Prolongation of r time may be a result of coagulation factor defiencies, anticoagulation (heparin) or severe hypofibrinogenaemia. A small *r* value may be present in hyper-coagulability syndroms.
k	(clot formation time)
rk	(r +k, or coagulation time)
α-angle	(clot formation rate)
MA	(maximum amplitude, cloth strength). Platelet abnormalities, both qualitative and quantitative, disturb MA
CI	(TEG coagulation index, which is derived from a linear equation that combines all the TEG variables, and the normal range is + 2 to – 2.)

Blood was sampled after induction of anesthesia and 1 hour postoperatively, and analyzed.

Cytokines / Cytokine analysis

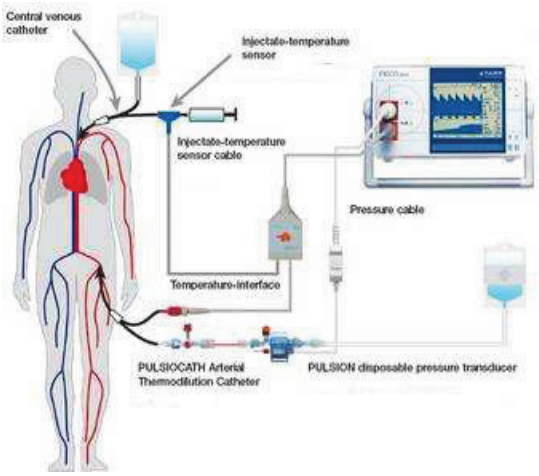
A panel of cytokines was quantified in plasma from samples collected at different time points. A multiplex fluorescent bead immunoassay kit (Linco Research Inc, St. Charles, MI,

USA) was used for the simultaneous quantification of the following cytokines: IL-6, IL-8, IL-10 and TNF-α. The samples were prepared for analysis by dilution with serum matrix diluent and the analysis performed as specified by the manufacturer. Total surface fluorescence was measured with a flow-based dual laser system (Luminex^{100}, Luminex Corporation, Austin, TX, USA). The concentration of cytokines was calculated with reference to a standard curve based on a broad range of standards (4.8-20 000 pg/ml), providing the lower and upper detection level for all the assayed cytokines.

Transpulmonary thermodilution tecnique ***PICCO®***

Determination of cardiac output (C.O.), intrathoracic blood volume (ITBV), extravascular lung water (EVLW) and global end diastolic volume (GEDV) was monitored by use of the transpulmonary thermodilution technique PiCCO®plus system (Pulsion Medical Systems AG, Munich, Germany). The thermodilution technique is less invasive then pulmonary-artery (PA)-catheters. It is a well tested, simple and accurate technique (Ganz *et al.* 1971). The PICCO catheter consists of two parts; an arterial catheter and a temperature sensor (se fig.4). In addition a CVK (central venous catheter) is needed to perform measurements and calculations. A bolus of sodium chloride administered by a central venous injection passes through the cardiopulmonary system. The temperature sensor at the tip of the PICCO-catheter, which measures continuous invasive body temperature, captures then the thermodilution curve. From this thermodilution curve, patients C.O., ITVB, EVLW, and GEDV are calculated. Indexed values are estimated according to patient's body surface.

Figure 4.



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8. Synopsis of results

Paper I

(The Journal of Thoracic and Cardiovascular Surgery 2005 Aug; 130(2): 287-94)

This study aimed to compare iso-oncotic priming solutions to crystalloid priming (acetated Ringer`s solution), with regard to fluid extravasation during cardiopulmonary bypass in piglets. Three groups were compared. One group received only acetated Ringers`s solution as prime, one group received 4 % albumin as prime and the last group received HES 200/0.5 mixed with acetated Ringers`s solution as prime. The mixture was composed to obtain a COP equivalent to the *in vivo* plasma COP present in each individual animal.
Upon initiation of hypothermia FER increased in the Ringer-group, whereas FER remained stable in the two other groups. Preservation of COP reduced fluid extravasation during CPB. Total tissue water increased in most organs when acetated Ringer`s solution was used. The use of colloidal priming reduced the amount of tissue water in a number of organs. In this study albumin turned out to be more effective than HES in reducing the cold-related fluid shifts.

Paper II

(Acta Anaesthesiologica Scandinavica 2006 Aug; 50(7): 855-62)

During 60 min normo- and 90 min hypo-thermic CPB, an infusion of 5 ml/kg/h of acetated Ringer`s solution was given to the control animals (CT-group). In the interventional group (HSH-group) 1ml/kg/h was replaced with hypertonic saline/ hydroxyethyl starch 200/0.5 (HSH). This dose of HSH effectively reduced total fluid gain about 50 % during the CPB period. During hypothermic CPB there was an increase in FER in both groups. FER increased in the HSH-group, from 0.15 (0.08) to 0.33 (0.08) ml/kg/min and in CT-group from 0.19 (0.14) to 0.51 (0.10) ml/kg/min. FER of the HSH-group was significantly lower than FER of the CT-group. Total tissue water content of the heart and the lungs was significantly lower in the HSH-group compared to the CT-group. Administration of HSH infusion was associated with stable ICP values wheras ICP of the CT-group increased significantly during bypass.

Paper III

(Scandinavian Cardiovascular journal 2008 Feb; 42(1): 63-70)

In this study we used the same protocol as in study II. HSH was replaced by HSD (hypertonic saline /dextran). HSD was given at a rate at 1ml/kg/h which resulted in a reduction of total fluid gain by 60 % when compared to the CT-group which was given the same amount of acetated Ringer's solution. The study was performed in14 piglets, 7 in each group, during normothermic followed by hypothermic CPB. During hypothermic CPB there was an increase in FER in both groups. FER increased in the HSD-group, from 0.01 (0.04) to 0.17 (0.07) ml/kg/min and in CT-group from 0.25 (0.23) to 0.57 (0.14) ml/kg/min. TTW was significantly lower in the heart and some of the visceral organs in the HSD-group. ICP remained stable in HSD-group, whereas a significant increase was observed in the CT-group. No adverse effects were observed.

Paper IV

(Perfusion 2008 Jan; 23(1): 57-63)

A protocol with "tepid" temperature during cardiopulmonary bypass was used in this study. A solution of HSH, 4ml/kg, replaced the same amount of acetated Ringer's solution in the prime (H-group). In the control-group (C-group) the prime was only acetated Ringers`s solution. The animals were allowed to drift to tepid temperature (35 ℃). Total fluid needs during 120 min CPB was reduced by 60% in H-group related to lowered values of fluid extravasation. The effect was most pronounced during the first 30 min on CPB. FER increased from 0.13 (0.04) to 1.6 (0.4) ml/kg/min in C-group, compared with 0.17 (0.11) and 0.68 (0.42) ml/kg/min in H-group, respectively. Hemodynamics and laboratory parameters were similar in both groups.

Paper V

(Acta Anaesthesiologica Scandinavica :2010 april; 54(4): 485-93)

In this clinical double-blinded study we randomized 50 patients scheduled for elective CABG surgery into two groups. In the interventional group an infusion of 1 ml/kg /h of HSH was given during 4 hours. In the control group the same amount of acetate Ringers`s solution was given. Hemodynamic parameters were obtained using the PICCO-system. All fluid additives and

losses until next morning were registered. Net fluid balance (NFB) was 4 times higher in the CT-group compared to the HSH-group during the first 6 hours postoperatively. Total fluid gain until next morning was significantly lower in the HSH-group (2993.9 (938.6) ml) compared to the CT-group (4298.7 (1059.3) ml) ($P< 0.001$). Normalized values (i.e. %-changes from baseline) of cardiac index and global end diastolic volume index increased postoperatively in both groups. Both parameters were significantly higher at 6 h in the HSH-group compared to CT-group. Normalized values of intrathoracic blood volume index were lower in the HSH-group at 6 h postoperatively when compared to CT-group. P_aO_2/F_iO_2 ratio decreased similarly in both groups early postoperatively, but recovery tended to be more rapid and pronounced in the HSH-group. Although serum-sodium and serum-chloride levels were significantly higher in the HSH-group the acid-base parameters remained similar and within normal range. No adverse effects of the HSH infusion were observed.

9.1. Discussion

9.1. Fluid Load

Cardiac surgery impacts fluid homeostasis more than other surgical interventions. Factors responsible for increased fluid accumulation during cardiac surgery are the use of hemodilution, hypothermia as well as a general inflammatory response caused by contact of blood with foreign surfaces of the extracorporeal circuit and the surgical trauma. The adverse consequences of extensive fluid loading and edema formation have during recent years gained increasing attention. Even though the fluid load today is less than some decades ago, the amount of fluid accumulated still has a clinical impact.

9.1.1. Hemodilution

Because of a number of unwanted adverse effects, heavy strain on blood banks, limited resources and high cost, hemodilution was introduced by Panico and co-workers in 1960 (Panico & Neptune 1960). Some amounts of blood, however, continued to be used as prime additive. Lilleaasen studied extreme hemodilution where all blood prime was replaced with non-sanguineous fluid. This resulted in a 70% reduction in the use of donor blood perioperatively (Lilleaasen 1977). Today lactated or acetated Ringer's solution is the main prime component in most cardiac surgery centers.

The volume of prime utilized is determined by the patient's body surface area, initial hematocrit and the "minimum safe volume", which is the amount needed to fill the circuit and maintain an adequate volume in the venous reservoir. Commonly the prime volume is in the range of 1400-2200 ml, resulting in a hematocrit level of 25-30 % after initiation of CPB. The lowest safe hematocrit value has been a matter of debate. Hematocrit as low as *14 % or lower* has been associated with an increased risk for mortality (Fang *et al.* 1997). Other investigators report adverse effects at much higher hematocrit levels. DeFoe and co-workers studied 7000 patients. Hematocrit values of 23 % or below tended to increase the risk of mortality (DeFoe *et al.* 2001). This is in line with an analysis of 5000 cardiac operations where hematocrit levels below 22 % were associated with peri-operative higher incidence of vital organ dysfunction, prolonged hospital stay, as well as increased short-and intermediate mortality (Habib *et al.* 2003). Reviews of almost 11.000 patients strengthened these findings, showing that from hematocrit values of 29 %, the odds of stroke increased by 10 % for each 1 %-decrease of hematocrit during CPB (Karkouti *et al.* 2005).

Mathew and co-workers found an associated risk of cerebral injury at low hematocrit levels (hematocrit on CPB of 15-18 %) during CPB in their study of neurological outcome. This study was interrupted due to higher incidence of adverse event in the low-hematocrit group, including greater cognitive decline 6 weeks after surgery (Mathew *et al.* 2007).

In our animal studies the degree of hemodilution was similar in all groups, with a drop in the Hct-values in the range of 26-28 %, except for the HES-group of study I, where Hct decreased close to 40 % (table 1).

In our clinical study the reduction of hematocrit was in the range of 25 %, similar in both groups, and well above any hematocrit level of concern.

Table 1.

	CT-I	**Alb-I**	**HES-I**	**CT-II**	**HSH-II**	**CT-III**	**HSD-III**	**CT-IV**	**HSH-IV**
Hct before CPB	30.0(0.8)	30.0(0.8)	29.0(1.3)	30.0(2.5)	28.8(2.5)	29.5(2.8)	28.3(2.3)	30.1(1.2)	31.0(2.4)
Hct after 60 minCPB	24.0(0.6)	23.0(0.9)	19.0(1.2)	24.4(2.1)	23.2(2.5)	23.1(2.4)	23.3(1.4)	23.0(2.3)	23.9(0.7)
Hct after120 CPB	22.0(0.5)	22.0(1.0)	18.0(1.3)	21.8(1.8)	22.0(2.5)	20.7(0.9)	22.4(1.3)	23.7(3.0)*	23.7(0.9)*

*tepid CPB

9.1.2. Hypothermia

Concomittant with hemodilution, - hypothermia was reintroduced to cardiac surgery in 1958 (Sealy *et al.* 1958). Moderate hypothermia (28-32 °C) decreases tissue oxygen requirements by approximately 50% and provides organ protection against ischemic injury (Bigelow *et al.*1954). A reduced tissue oxygen requirement implies the possibilities for lower flow rates, which again might decrease shear stress of red cells and reduce hemolysis.

The blood viscosity changes inversely related to the changes of body temperature. The higher blood viscosity under hypothermic conditions is counteracted by the effect of concomitant hemodilution.

During the last decade there has been a change in temperature strategy during CPB from hypothermia (28°C) to a level of tepid temperature (34 °C) (Cook 1999). The change in temperature level during CPB arose from studies of alternate cardioplegia techniques. Clinical literature indicated advantages of warm continuous cardioplegia, and the investigation of systemic normothermia followed (Lichtenstein *et al.* 1991). Normothermia allowed prompt separation from CPB and cardiac output was found to improve. CK-MB release and the incidence of myocardial infarction were less. 99 % of patients converted spontaneously to sinus

rhythm, additionally these patients had much lower incidence of conduction abnormalities postoperatively, and at long-term follow-up (Cook 1999).

However, normothermic CPB patients were reported to require larger doses of vasoconstrictors, greater fluid supplementation or higher CPB pump flows to maintain mean arterial pressure (MAP) during CPB (Christakis *et al.* 1992; Cook 1999). Tepid/drifted temperature (34 °C) seemed to have less disadvantages than both hypothermia and normothermia, and was recommended for CPB (Arom *et al.* 1995; Cook 1999).

Studies confirmed similar neurological outcome following tepid, "drifted" CPB (32-34°C) compared with hypothermic CPB (about 28 °C) (Grigore *et al.* 2001). Most surgical centres now use "tepid" strategy for uncomplicated CABG surgery.

Previous studies in our group have demonstrated increased fluid shifts from the circulation to the interstitial space during hypothermia (Farstad *et al.* 2003; Farstad *et al.* 2004; Heltne *et al.* 2000). In study I-III there is an increase in fluid extravasation in the control groups after induction of hypothermia, confirming earlier findings from our group. This increase in fluid extravasation could be partly counteracted by the specific interventions in the respective groups (see table 2).

Table 2.

	CT-I	**Alb-I**	**HES-I**	**CT-II**	**HSH-II**	**CT-III**	**HSD-III**
FER normothermia 30-60 (ml/kg/min)	0.15(0.1)	0.14(0.05)	0.33(0.10)	0.19(0.05)	0.15(0.03)	0.25(0.23)	0.01(0.04)
FER hypothermia 60-150 (ml/kg/min)	0.55(0.21)	0.12(0.09)	0.32(0.07)	0.51(0.10)	0.33(0.08)	0.57(0.14)	0.17(0.07)

By changing the temperature level from hypothermia in the direction of tepid temperature in study IV we observed a reduction in fluid extravasation in both groups. Compared with previous studies obtained from our group (Heltne *et al.* 2001) the fluid extravasation rate in CT-group during tepid CPB was 25 % above the values observed during normothermic CPB. Using HSH as prime additive the fluid leakage was significantly reduced compared to the CT-group (Table 3).

Table 3.

	0-60 min CPB FER(ml/kg/min) /Hct	**60-120 min CPB FER(ml/kg/min) / Hct**
HSH-group-tepid	0.47 (0.20) / 23.9 (0.7)	0.17 (0.08) / 23.7 (0.9)
CT-group-tepid	1.00 (0.29) / 23.0 (2.3)	0.30 (0.08) / 23.7 (3.0)
Normotermia*	0.80 (0.2) / 24.6 (0.8)	0.10 (0.1) / 23.9 (0.9)
Hypothermia*	1.80 (0.2) / 19.1 (1.1)	1.1 (0.2) / 19.0 (1.0)

*(Heltne, *et al.* 2001)

9.1.3. Inflammation

Cardiac surgery is associated with a systemic inflammatory reaction. The contact of blood with surfaces of the CPB circuit, ischemia-reperfusion injury and release of endotoxins all contributes to trigger the inflammatory response (Paparella *et al.* 2002). Also cardiac surgery without the use of CPB contributes to activate inflammation (Gu *et al.* 1999). Tissue injury itself caused by the surgical trauma is enough to trigger the response. The consequense of the inflammatory response is leukocyte activation and a generalized impairment of the endothelial barrier, resulting in increased microvascular permeability and diffuse capillary leakage. This leads to leak of proteins, electrolytes and water from the intravascular compartment to the interstitial space (Seghaye *et al.* 1996). The activation of inflammation involves several complex pathways, too extensive to handle in this thesis. Only one will be mentioned briefly.

Surgery and CPB triggers a cascade of events, mediated by cytokines, including TNF-α, IL-6 and IL-8. Levels of these pro-inflammatory cytokines have all been shown to increase after CPB, and they are recognised as early mediators of organ injury (Teoh *et al.* 1995). The pro-inflammatory cytokines might depress human myocardial contractile function, increase systemic vascular permeability, and induce pulmonary vascular barrier dysfunction with increased lung water content (Paparella *et al.* 2002).

The anti-inflammatory cytokine IL-10 is an inhibitor of pro-inflammatory cytokines, and might have a role in limiting the duration and extent of the acute inflammatory response. IL-10 either directly inhibits the release of pro-inflammatory cytokines or indirectly exerts an anti-inflammatory effect (Wan *et al.* 1997). Increased values might suggest a lower systemic inflammatory reaction and a better hemodynamic performance (Giomarelli *et al.* 2003). Studies

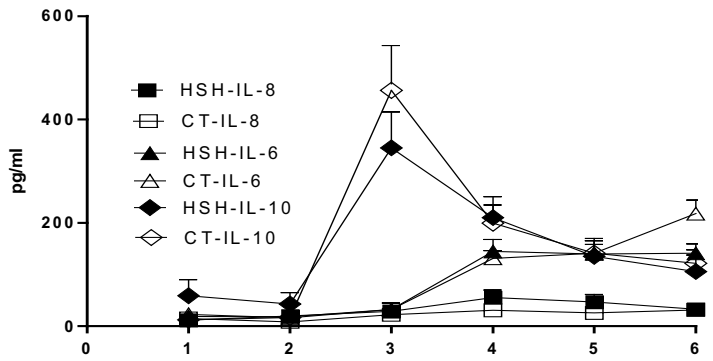
indicate that inflammatory cytokines and their suppressive cytokines increase but maintain their balance during cardiac surgery (Kawamura *et al.* 1997). The balance among these cytokines may be important in determining the level of the inflammatory response. If the balance tips over to an overtly pro-inflammatory state the consequences may lead to myocardial damage.

Levels of TNF-α, IL-6, IL-8, and also IL-10 have peak values after surgery, 2-6 hours (Teoh *et al.*1995; Kawamura *et al.*1997). Some studies indicate a peak of IL –10 before the pro-inflammatory cytokines (Risnes *et al.* 2003; Kawamura *et al*. 1997). This might represent a physiolgical mechanism to limit tissue damage and inflammation, and can indicate a delayed capillary leakage. The process starts probably peroperativly, but the leakage continues for hours after surgery. Local release of cytokines in the heart might be a contributing factor causing the transient post-operative myocardial dysfunction ("stunning") the first hours after CPB (Wan *et al*.1997).

Hydroxyethyl starch seems to exert beneficial anti-inflammatory effects (Handrigan *et al.* 2005; Boldt 2006; Gurfinkel *et al.* 2003), and to inhibit cytokines in experimental sepis (Tian *et al.* 2005). The use of hypertonic saline has also been shown to reduce systemic and pulmonary inflammatory responses (reduced levels of TNF-α and IL-6) (Gurfinkel *et al.* 2003).

In our clinical study we evaluated TNF-α, IL-6, IL-8 and IL-10 at baseline (1), after onset of CPB (2), before weaning from CPB (3), after 2 hours (4), after 6 hours (5) and next morning (6). TNF-α remained essentially unchanged compared with the initial values. IL-6, IL-8, IL-10 changed in similar patterns as described in other studies (Kawamura *et al*.1997; Risnes *et al.* 2003) with significant increases in both groups at 6 hours, but with no between-group differences. In this study we did not observe any anti-inflammatory effect of HSH.

Figure 5.



9.2. Negative impact of fluid overload

Fluid overloading with edema formation is a regular finding following on-pump cardiac surgery. Tølløfsrud and co-workers found a fluid load of 5200 ml at the end of surgery when acetated Ringer`s solution was used as prime (Tølløfsrud *et al.* 1995). This is in line with a previous report by Utley on extensive fluid overloading following cardiac surgery with the use of CPB (Utley JR & Stephens DB 1982). A mean accumulation of 800 ml/m^2/hour during CPB was determined. Hallowell and co-workers, found that almost 50 % of CABG patients had a fluid balance greater than 5000 ml (Hallowell *et al.* 1978). Today most centres experience lower fluid accumulation. 2000-2500 ml is often reported (Sirvinskas *et al.* 2007; Eising *et al.* 2001; Kvalheim *et al.* 2009). Explanations for reduced fluid load today, is related to a change in temperature strategy with reduced CPB time as well as smaller CPB-circuits.

In a study of patients admitted to surgical ICU significantly greater morbidity and length of ICU stay was observed for patients who gained more than 10 % weight, indicating fluid overload. Also mortality tended to increase as fluid overload increased (Lowell *et al.* 1990).

An association between highly positive intraoperative fluid loading and postoperative adverse outcome has been demonstrated in cardiac patients in recent years (Toraman *et al.* 2004). In a study of 1200 patients undergoing on-pump CABG, a fluid load of more than 500 ml at the end of surgery was one of the predictors for increased transfusion needs and increased length of hospital stay.

Also following pulmonary surgery adverse outcome has been associated with heavy fluid loading (Møller *et al.* 2002). In a regression analysis of elective patients undergoing pneumonectomy, fluid balance exceeding 4000 ml was found to be the strongest risk factor for post-operative pulmonary complications and in-hospital mortality (Møller *et al.* 2002).

Several authors have found fewer complications and earlier discharge by restrictive fluid therapy in gastric patients (Lobo *et al.* 2006; Tambyraja *et al.* 2004).

In a randomized multicenter trial (Brandstrup *et al.* 2003) patients were allocated to a restricted or a standard fluid regimen during and after gastrointestinal surgery. Complications, including anastomotic leakage, infections and transfusion needs were reduced in the restricted fluid regimen group. Impeded tissue healing due to general edema may be one of the possible explanations.

9.2.1. Heart

Myocardial edema has been reported to impair both systolic and diastolic function (Mehlhorn *et al.* 2001). One study demonstrated a decrease in cardiac output by 40% for a given preload when myocardial water content was increased by 3.5% (Laine & Allen 1991). Several mechanisms may account for the reduction in cardiac performance. Tissue edema accumulates in the interstitial spaces, thus increasing chamber stiffness and compromises the hearts ability to contract efficiently. An increase in interstitial volume and pressure may also displace collagen fibers, which might impact negatively on heart function (Laine & Allen 1991). Additionally, myocardial edema will increase the diffusion distance for oxygen to the myocytes, resulting in ischemia (Ziegler & Goresky 1971).

In our studies I-III, we observed significantly reduced water content in the heart tissue of the study groups receiving colloides compared to the control groups. In study IV we used tepid temperature, and the fluid leakage was less than that obtained in hypothermic studies (I-III).

In the clinical study (V), a more favourable fluid balance was observed in the HSH-group that was aproximatly 30 % below the values of the CT-group. The reduction, about 75%, was most pronounced during the first 6-postoperative hours. Concomittant with this observation CI (normalized values) was significantly higher in the HSH-group compared with CT-group. Similar observations from previous studies confirms an association of reduced fluid load and improved cardiac function (Oliveira *et al.* 1995; Tølløfsrud & Noddeland 1998; Schroth *et al.* 2006; Sirvinskas *et al.* 2007).

9.2.2. Lungs

In a review of more than 8000 patients undergoing major surgery, Arieff found that the overall incidence of postoperative pulmonary edema was 7.6 %, being fatal in 11.9 % of the cases (Arieff 1999).

Edema might compromise both pulmonary gas exchange and tissue oxygenation leading to decreased pulmonary function. In a study of healthy volunteers receiving 40 ml/kg of Ringer`s solution, Holte and co-workers found a decreased pulmonary function for 8 hours and a significant weight gain after 24 hours (Holte *et al.* 2003). Boldt and co-workers found that an increase in extravascular lung water was accompanied by deterioration of pulmonary gas exchange (Boldt *et al.* 1986). In study I, we found a significant increase in water content in the lungs in the CT-group compared to a group of non-CPB animals. This fluid accumulation was not found in the albumin and HES group. Preservation of COP seemed to prohibit the increase in water accumulation in the lungs. In study II, we observed a significant reduction in total tissue water in the lungs of the animals in the HSH-group compared to the animals of the CT-group.

These findings were not reproduced in study III and IV, where no significant differences were found. In study IV shorter CPB time and changed temperature strategy might explain these results.

In study V, the clinical study, we were unable to find a significant difference in EVLWI in the two groups, but normalized values of ITBVI was significantly higher in CT-group, and GEDVI was significantly larger in HSH-group. These results are in line with the presence of an increased intravascular pulmonary blood volume. The implications of that can so far only be speculated on.

PaO_2/FiO_2 ratio behaved similarily in the two study groups initially. After 6 h the PaO_2/FiO_2 ratio tended to rise more rapidly in the HSH-group compared to the CT-group. The lack of significance between these two groups might be related to the variability of the patients within the respective groups. Preoperative lung-examination was not done in these patients, and even though the patients were described as healthy when considering lung disease, a greater variation might be expected with increasing age (Gunnarsson *et al.* 1996).

9.2.3. Brain

Cerebral injury is a frequent and feared complication after cardiac surgery. Manifestations might vary from severe stroke resulting in death, paralysis /paresis to temporary cognitive dysfunction. Mechanisms of cerebral injury from cardiac surgery might be caused by air, by emboli, by peri-operative anemia or by hypoperfusion related to loss of cerebral autoregulation (Hogue *et al.* 2008). Increased ICP and cerebral edema may worsen this ischemia. By reducing ICP and brain water, improved cerebral perfusion pressure may be obtained.

The use of HES in the prime-solution during coronary artery bypass was associated with significant positive effects on informative-cognitive tests when compared to Ringer's solution (Iriz *et al.* 2005). The infusion of hypertonic saline/dextran in pigs before and after hypothermic circulatory arrest was found to lower ICP and to significantly improve neurologic recovery in the HSD –group (Kaakinen *et al.* 2006). McDaniel and co-workers added hypertonic saline/dextran in the prime in an animal study, and observed stable ICP values and reduced cerebellar water content in the animals (McDaniel *et al.* 1994). This is in line with our findings. In study II and III we observed an increased ICP in the CT-group, whereas the ICP in the HSD- and HSH-groups remained stable.

9.3. Effects of colloid additives during CPB

Hemodilution with crystalloid additives causes a reduction in COP. Approaches to reduce this fall in COP could have a positive effect on outcomes after cardiac surgery. In animal studies colloid hemodilution has been found to prevent the development of myocardial edema which occurred with crystalloid hemodilution (Laks *et al.* 1977). Also pulmonary edema is found to be reduced by colloid hemodilution (Eising *et al*. 2001). This is in line with our observations. In study I we maintained COP by using colloides in the prime, and the fluid overload was significantly reduced. We observed reduced tissue water in the hearts of the animals receiving colloid compared to the animals receiving crystalloid prime. In study II and III the colloides were administrated as a peroperative infusion. In both studies we observed more stable COP values and reduction in fluid extravasation. As a result we observed a reduction of total tissue water content in the heart, lungs and intestinal organs compared to the control animals.
Table 4 presents the average extravasation rate from initiation of CPB till the end of the experiments, which was 150 min in study I-III, and 120 min in study IV.

Table 4.

Total FER during CPB

Study group	**FER ml/kg/min**	Study group	**FER ml/kg/min**
CT-I	0.58 (0.14)	**Alb-I**	0.13 (0.10)
		HES-I	0.20 (0.08)
CT-II	0.66 (0.17)	**HSH-I**	0.39 (0.03)
CT-III	0.78 (0.17)	**HSD-II**	0.41 (0.06)
***CT-IV**	0.66 (0.18)	***HSH-IV**	0.31 (0.08)

*tepid CPB

In study I fluid addition to the reservoir as well as blood replacements were isooncotic. Consequently COP was maintained throughout the study, and might explain the low FER values in study I.

9.3.1. Albumin

In study I the CPB circuit was primed with Albumin 4 %, and when needed, albumin was added to the reservoir. The cold-induced fluid leakage, as previously reported (Farstad *et al.* 2004; Heltne *et al.* 2000), was significantly reduced in the presence of albumin. Similar findings were reported from a meta-analysis involving more than 1300 patients (Russell *et al.* 2004)

where albumin favourably influenced COP and fluid balance. Marelli and co-workers concluded on the other hand that there was no advantage adding albumin in the prime (Marelli *et al.* 1989). Himpe reports in a meta-analysis including almost 1000 patients of a more favourably fluid balance when colloids were added to the priming solution. Albumin was, however, not associated with better outcome than other colloides in this review (Himpe 2003).

In a retrospective study (Sedrakyan *et al.* 2003) of 20.000 patients undergoing cardiac surgery through 1997 and 1998 albumin appeared to be associated with lower incidence of mortality. Albumin was however, compared with all non-protein colloides, including dextrans, gelantines and first generations of starch, and no separation of under-groups was done.

A Cochran meta-analysis in 1998 suggested a worse outcome for patients given albumin in ICU (Cochran 1998). In the SAFE study (Finfer *et al.* 2004), which was a prospective study including 7000 intensive care patients, no advantages of albumin as a plasma substitute was observed and the worsended outcome as proposed the Cochran meta-analysis could not be confirmed. Whether it is worth the price or not, is a still matter of debate.

9.3.2. Hydroxyethyl starch (HES)

HES is the most often used colloid in Europe (Schortgen *et al.* 2004). A variety of different solutions exist, which differ greatly in their pharmacological properties.

Postoperative bleeding is a common complication of cardiac surgery, and it is estimated that 50 % of cases undergoing re-operation because of bleeding results from multifactorial coagulopathy (Paparella *et al.* 2004). It is of great importance that fluids added during and after CPB do not worsen bleeding.

Hydroxyethyl starches can interfere with normal hemostasis at different levels and an impact on coagulation might occur (Kozek-Langenecker 2005).These findings are mostly based on the use of first-generation starch-preparations with a molecular weight of 450 kD or higher, and a high degree of molar substitution. The negative effect of HES on coagulation and bleeding can probably be avoided by use of low- molar-weight, low-degree substitution HES in recommended amounts (Boldt 2009a; Thyes *et al.* 2006; Kozek-Langenecker 2005).

Starch with lower Mw (130-200) and lower molar substitution (0.5 or less) have significantly less impact on coagulation (Entholzner *et al.* 2000; Treib *et al.* 1996). Not only weight and molar substitution but also the administered volume, have an influence on coagulation (Thyes *et al.* 2006). Nevertheless, some studies demonstrate no adverse effects after administration of larger volumes to multitrauma or orthopedic patients (Shatney *et al.* 1983; Vogt *et al.* 1996). Also in cardiac surgery, low weight, low molar HES (130/0.40) at larger doses has been found to be safe with regard to hemostasis (Boldt *et al.* 2009; Kasper *et al.* 2003).

A large meta-analysis reports increased blood loss in CPB patients exposed to HES (Wilkes *et al.* 2001). This meta-analysis compared studies from the previous 20 years, - where both HES 200 kD and HES 450 kD were used. There was no subgroup analysis, neither according to molar substitution nor volume of transfusion.

In study I-IV the effect on coagulation was not measured, as the animals were killed after CPB and on-pump values are of limited interest. In study V, the effect on coagulation was evaluated by the amount of bleeding from the chest drains, transfusions needs, as well as the direct impact on the TEG-values. The TEG values were within normal range in both groups, although a significant difference between the groups could indicate that HSH impaired coagulation slightly. Coagulation index postoperatively was in HSH-group –1.3 (1.9) and in CT-group -0.10 (1.7) (P = 0.024). Despite differences in TEG values, blood loss and transfusion needs were similiar in the two groups.

Others have experienced similiar observation; HES (200/0.5 or 130/0.4) solutions can induce an impairment in fibrin formation and clot seen in TEG values, although no clinical impacts concerning chest tube drainage and transfusion needs were observed (Schramko *et al.* 2009; Kuitunen *et al.* 2004).

Renal dysfunction after cardiac surgery is in the range of 5 % (Antunes *et al.* 2004; Boldt *et al.* 2003) and the causes are multifactorial, though usually attributed to the use of CPB. A possible detrimental impact of HES on kidney function has become an objection to use HES.

In a multicenter study of patients with severe sepsis higher frequency of acute renal failure in the HES group than in the gelantin group was observed (Schortgen *et al.* 2001). However, in this study HES 200/*0.62 at doses of 31ml/kg* were used. Additionally the study was followed by criticism since serum creatinine was higher in the HES-group at baseline. In a study of patients undergoing CABG, the use of HES was associated with a modest impairment in renal function (Winkelmayer *et al.* 2003).In this study HES 670/0.75 was used.

Several studies show no negative effects on kidney function by use of HES; a large observational study of 3147 critically ill intensive-care patients did not show higher incidence of acute renal dysfunction in HES-treated patients compared to other plasma substitutes (Sakr *et al.* 2007). The use of HES 200/05 at doses of 15 ml/kg/day over five days to patients at ICU including septic and trauma patients was also without negative effects on renal function (Boldt 2009b). By using the latest generations low weight (Mw< 200 kD), low molar substitution (MS < 0.5), kidney function is not affected, suggesting no negative effects even in patients with significantly altered kidney function (Boldt *et al.* 2007).

Adverse renal effects were not evaluted in the experimental studies (I-IV). In study V, however, we followed serum-creatinine levels during day 1, 2 and 3. No increases in the

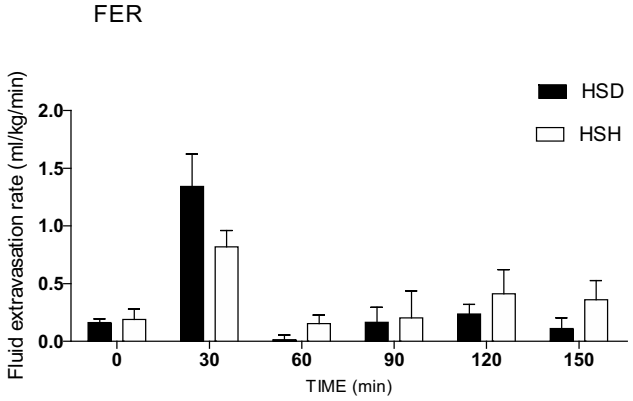
creatinine levels were found. We observed significantly higher diuresis the first 24-h in the HSH-group compared to the CT-group.

9.3.3. Dextran

Dextrans have well documented plasma expanding effects, and was the first colloid combined in solution with hypertonic saline (Kramer 2003). Because of dextrans anticoagulant effects they have shown to be effective in preventing postoperative venous thrombosis and pulmonary embolism (Coats & Heron 2004). This effect might however be difficult to control in the cardiac surgery patient, and combined with potential allergic reactions, a decrease in use is seen. Dextrans do not longer play a role in cardiac surgery (Van der Linden & Ickx 2006; Kreimeier & Peter 1998; Schumacher 2009).

In study III we used the same protocol as in study II, which gave us an opportunity to compare HSD and HSH with regard to their effect on fluid extravasation. No significant between-groups values were observed. Total FER was more or less identical in the two groups, 0.39 (0.03) ml/kg/min in HSH group, and 0.41(0.06) ml/kg/min in HSD-group (table 4).

Fig.6.



9.3.4. Combination fluids

The main use of combination fluids has been as small volume resuscitation in emergency situations. There is no study demonstrating obvious adverse effects of hypertonic saline when used in recommended amounts.

An increased plasma chloride concentration could produce metabolic acidose that might compromise cardiac function or cause arrhythmia. In a study from Vassar concerning potential

risk associated with infusion of hypertonic saline in resuscitation situations a non-significant correlation between pH and chloride concentration was found (Vassar *et al.* 1990). This is in line with our findings. Although serum-chloride increased significantly, acid-base parameters remained within normal ranges with no between-group differences.

Austria was one of the first countries to approve hypertonic saline/ colloidal solutions, and the patient material for registration of adverse drug reactions (ADR) is large. A review of a 10-year period concluded that ADR after use of HSH/HSD was low, and these solutions couldt be considered relatively safe (Schimetta *et al.* 2002).

Considerably elevated serum sodium levels have been reported after use of HSD/HSH in cardiac surgery. Levels of 166 mmol/l has been seen by use of bolus administration of 3-4 ml/kg of HSD (Oliveira *et al*.1995), however, with no neurological symptoms observed. In study II-V serum sodium increased significantly, but remained at or below 150 mmol/l and no adverse effects were seen.

Experience with use of HSH/HSD is mostly obtained from treatment of severe hypovolemia and shock, and recommended doses have been 4 ml/kg. Also studies dealing with administration of HSD/HSH in cardiac surgery reports of doses reaching 4.5 ml/kg at most (Tølløfsrud *et al.* 1998).

9.4. Administration forms

Administration of hyperosmolar and/or colloidal additives has been given before and after CPB, as well as an additive to the priming solution.

Bueno and co-workers infused HSD as a bolus before valve surgery (Bueno *et al.* 2004). Hemodynamic and respiratory function improved, peak values were obtainded shortly after administration. Altough the effect declined postoperatively, the cardiorespiratory function were better in the HSD-group compared to the control-group. Similiar findings were observed in a group of Jehovaha`s witness (Oliveira *et al.*1995). Hemodynamic parameters improved shortly after administration. In this study the effects on on hemodynamic were short-lived. In both studies the fluid balance was favourable with the use of HSD.

Eising and co-workers used HES in the prime, and observed improved CI and reduced EVLW in the HES-group compared to a group with only crystalloid solution in the prime (Eising *et al*. 2001). The improved hemodynamic and respiratory effects did not have peak values, but seemed to gradually improve postoperatively. A significantly reduced fluid load was observed in the HES-group.

Tølløfsrud and co-workers administered a bolus of HSD immediately after cardiac surgery (Tølløfsrud & Noddeland 1998). They observed improved cardiac output, with peak values shortly after administration. Fluid balance was lower in the HSD-group compared to the control-group. Similiar findings were observed when HSH was administered as a bolus infusion after arrival at the ICU (Sirvinskas *et al.* 2007). Positive impacts on hemodynamic parameters were observed, also here peak values obtained shortly after infusion. Improved fluid balance in the HSH-group compared to the control-group was found.

Bolus administration of HSH has also been used after pediatric cardiac surgery (Schroth *et al.* 2006). They observed improved CI, reduced SVRI, as well as reduced ELWI. Also in this study group peak values were obtained shortly after administration of HSH.

In our clinical practice we have used HSD or HSH as an infusion of 1ml/kg/h during 4 hours during resuscitation of victims with accidental hyopthermia. We observed lower fluid needs and more stable hemodynamic variables during rewarming compared with treatment protocols using crystalloid solution alone. In study V we used this administration form, 1ml/kg/h HSH during 4 hours, starting preoperatively. We observed still increasing CI values 6 hours postoperatively, and belive this administration form might be of benefit during the first vulnerable hours postoperatively.

Both the experimental studies and the clinical study confirm the effect of reduced fluid load. Weather a slow peroperative infusion is favourable compared to a bolus infusion conserning amount of fluid overload is uncertain.

Administration of HSH as a bolus, given within minutes, might under *given circumstances* induce post-infusion hypervolemic left heart failure and/or pulmonary edema, as Prien and co-workers observed as transient findings after bolus infusion of HSH in CABG patients (Prien *et al.* 1993). A review of hypertonic solutions in the operating room concludes with benificial hemodynamic effects, and suggests that the rate of infusion should be slow (Azoubel *et al.* 2008).To our knowledge there is no former study where HSH/HSD have been administrated as a slow peroperative infusion during cardiac surgery. We observed that this administration form caused a reduction in the total fluid load and an improvement of cardiac performance in the early post-operative period.

9.5. Future aspects

The focus in fluid treatment for cardiac surgery should be to prohibit fluid loading, not to replace losses. Numerous studies conserning negative impact of fluid overload exisist. Also the adverse effects of high degree hemodilution are described. High-risk patients are an increasing population in cardiac surgery, and these patients are vulnerable to the negative impacts of hemodilution as well as fluid overload. The most obvious strategies to counteract these effects of CPB are changes in the fluid additives and/or a reduction in the prime volume.

The ideal fluid additive during and after cardiac surgery does still not exist. Controversy consering crystalloid-colloid as well as colloid-colloid is still exisisting. The latest generation of HES gives promising results, though further investigations are needed.

By using a small volume of HSH as a slow infusion, we obtained favourable results observing CABG patients with no co-morbidity, although these patients usually recover fast anyway. We belive high-risk patients will have even more benefit of reduced fluid loading. Their tolerance for hypervolemia is lower and the incidence for hemodynamic instability first hours postoperatively is greater. A clinical study including high-risk patients is planned and has to be performed.

Mini-bypass circuits are gaining increasing popularity. The reduced prime volume and the antegrad priming of these circuits results in redused hemodilution, and lowered transcapillary fluid leakage. Different priming alternatives in these mini-systems could contribute to even more sophisticated fluid treatments protocols in the future.

10. Conclusion

Based on the results from these studies we conclude;

- Maintainance of COP with an iso-oncotic prime during CPB reduces the cold-induced fluid leakage
- A small infusion, 1ml/kg/h, of hyperosmolar/colloidal solution during CPB reduces FER and NFB in pigs
- The infusions of HSH/HSD contributed to maintenance of ICP during hypothermic CPB, while an increase of ICP was observed in the control group
- An additon of 4 ml/kg hyperosmolar/colloid solution in the prime reduced transcapillary fluid leakage and NFB during tepid CPB
- Initiation of CPB caused highest FER values, this was significantly reduced by using hyperosmolar/colloid in prime
- A small infusion, 1ml/kg/h during 4 h of hyperosmolar/colloid solution to elective CABG patients reduced NFB and improved cardiac function
- By using small volumes of HSD/HSH as a slow infusion during CPB we obtained significantly less fluid load and organ edema. No adverse effects neither in the animals studies, nor in the clinical study were observed.

Reference List

1. **(1998) Cochrane, Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers.*BMJ* 317, 235-240.**

2. **Antunes PE, Prieto D, Ferrao dO, & Antunes MJ (2004) Renal dysfunction after myocardial revascularization.*Eur.J.Cardiothorac.Surg.* 25, 597-604.**

3. **Arieff AI (1999) Fatal postoperative pulmonary edema: pathogenesis and literature review.*Chest* 115, 1371-1377.**

4. **Arom KV, Emery RW, & Northrup WF, III (1995) Warm heart surgery: a prospective comparison between normothermic and tepid temperature.*J.Card Surg.* 10, 221-226.**

5. **Aukland K, Fadnes HO, & Johnsen HM (1975) Protein concentration and oncotic pressure of interstitial fluid collected by wick technique.*Bibl.Anat* 13, 43-46.**

6. **Azoubel G, Nascimento B, Ferri M, & Rizoli S (2008) Operating room use of hypertonic solutions: a clinical review.*Clinics.(Sao Paulo)* 63, 833-840.**

7. **Becker DM, Lord L, & Dobell AR (1972) Techniques and pitfalls of anesthesia and thoracic surgery in the pig.*J.Surg.Res.* 13, 215-219.**

8. **Bigelow WG, Mustard WT, & Evans JG (1954) Some physiologic concepts of hypothermia and their applications to cardiac surgery.*J.Thorac.Surg.* 28, 463-480.**

9. **Boldt J (2006) Do plasma substitutes have additional properties beyond correcting volume deficits?*Shock* 25, 103-116.**

10. **Boldt J (2009a) Modern rapidly degradable hydroxyethyl starches: current concepts. *Anesth.Analg.* 108, 1574-1582.**

11. **Boldt J (2009b) PRO: hydroxyethylstarch can be safely used in the intensive care patient-the renal debate.*Intensive Care Med.* 35, 1331-1336.**

12. **Boldt J, Brenner T, Lang J, Kumle B, & Isgro F (2003) Kidney-specific proteins in elderly patients undergoing cardiac surgery with cardiopulmonary bypass.*Anesth.Analg.* 97, 1582-1589.**

13. **Boldt J, Brosch C, Ducke M, Papsdorf M, & Lehmann A (2007) Influence of volume therapy with a modern hydroxyethylstarch preparation on kidney function in cardiac surgery patients with compromised renal function: a comparison with human albumin.*Crit Care Med.* 35, 2740-2746.**

14. **Boldt J, Suttner S, Brosch C, Lehmann A, & Mengistu A (2009) Influence on coagulation of a potato-derived hydroxethylstarch (HES 130/0.42) and a maize-derived hydroxethylstarch (HES 130/0.4) in patients undergoing cardiac surgery.*Br.J.Anaesth.* 102, 191-197.**

15. **Boldt J, von Bormann B, Kling D, Scheld HH, & Hempelmann G (1986) The influence of extracorporeal circulation on extravascular lung water in coronary surgery patients.*Thorac.Cardiovasc.Surg* 34, 110-115.**

16. **Brandstrup B, Tonnesen H, Beier-Holgersen R *et al.* (2003) Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial.*Ann.Surg.* 238, 641-648.**

17. **Bueno R, Resende AC, Melo R, Neto VA, & Stolf NA (2004) Effects of hypertonic saline-dextran solution in cardiac valve surgery with cardiopulmonary bypass.*Ann.Thorac.Surg.* 77, 604-611.**

18. **Burge CM & Skinner SL (1995) Determination of hemoglobin mass and blood volume with CO: evaluation and application of a method.*J.Appl.Physiol* 79, 623-631.**

19. **Christakis GT, Koch JP, Deemar KA *et al.* (1992) A randomized study of the systemic effects of warm heart surgery.*Ann.Thorac.Surg.* 54, 449-457.**

20. **Cittanova ML, Leblanc I, Legendre C *et al.* (1996) Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients.*Lancet* 348, 1620-1622.**

21. **Coats TJ & Heron M (2004) The effect of hypertonic saline dextran on whole blood coagulation.*Resuscitation* 60, 101-104.**

22. **Cook DJ (1999) Changing temperature management for cardiopulmonary bypass. *Anesth.Analg.* 88, 1254-1271.**

23. **DeFoe GR, Ross CS, Olmstead EM *et al.* (2001) Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group.*Ann.Thorac.Surg.* 71, 769-776.**

24. **DeWall RA (2003) Origin of the helical reservoir bubble oxygenator heart-lung machine. *Perfusion* 18, 163-169.**

25. **Eising GP, Niemeyer M, Gunther T *et al.* (2001) Does a hyperoncotic cardiopulmonary bypass prime affect extravascular lung water and cardiopulmonary function in patients undergoing coronary artery bypass surgery?*Eur.J.Cardiothorac.Surg.* 20, 282-289.**

26. **Entholzner EK, Mielke LL, Calatzis AN *et al.* (2000) Coagulation effects of a recently developed hydroxyethyl starch (HES 130/0.4) compared to hydroxyethyl starches with higher molecular weight.*Acta Anaesthesiol.Scand.* 44, 1116-1121.**

27. **Fang WC, Helm RE, Krieger KH *et al.* (1997) Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery.*Circulation* 96, II-9.**

28. **Farstad M, Fluid extravastion and edema preventing interventions during normothermic and hypothermic cardiopulmonary bypass (CPB). *Doctoral thesis 2006. University of Bergen, Bergen, Norway***

29. **Farstad M, Heltne JK, Rynning SE *et al.* (2003) Fluid extravasation during cardiopulmonary bypass in piglets--effects of hypothermia and different cooling protocols.*Acta Anaesthesiol.Scand.* 47, 397-406.**

30. **Farstad M, Heltne JK, Rynning SE *et al.* (2004) Can the use of methylprednisolone, vitamin C, or alpha-trinositol prevent cold-induced fluid extravasation during cardiopulmonary bypass in piglets?*J.Thorac.Cardiovasc.Surg.* 127, 525-534.**

31. **Finfer S, Bellomo R, Boyce N *et al.* (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit.*N.Engl.J.Med.* 350, 2247-2256.**

32. Fogh-Andersen N, Siggaard-Andersen O, Lundsgaard FC, & Wimberley PD (1987) Diode-array spectrophotometry for simultaneous measurement of hemoglobin pigments.*Clin.Chim.Acta* 166, 283-289.

33. Ganz W, Donoso R, Marcus HS, Forrester JS, & Swan HJ (1971) A new technique for measurement of cardiac output by thermodilution in man.*Am.J.Cardiol.* 27, 392-396.

34. Giomarelli P, Scolletta S, Borrelli E, & Biagioli B (2003) Myocardial and lung injury after cardiopulmonary bypass: role of interleukin (IL)-10.*Ann.Thorac.Surg.* 76, 117-123.

35. Grigore AM, Mathew J, Grocott HP *et al.* (2001) Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery.*Anesthesiology* 95, 1110-1119.

36. Gu YJ, Mariani MA, Boonstra PW, Grandjean JG, & van Oeveren W (1999) Complement activation in coronary artery bypass grafting patients without cardiopulmonary bypass: the role of tissue injury by surgical incision.*Chest* 116, 892-898.

37. Gunnarsson L, Tokics L, Brismar B, & Hedenstierna G (1996) Influence of age on circulation and arterial blood gases in man.*Acta Anaesthesiol.Scand.* 40, 237-243.

38. Gurfinkel V, Poggetti RS, Fontes B, Costa Ferreira NF, & Birolini D (2003) Hypertonic saline improves tissue oxygenation and reduces systemic and pulmonary inflammatory response caused by hemorrhagic shock.*J.Trauma* 54, 1137-1145.

39. Habib RH, Zacharias A, Schwann TA *et al.* (2003) Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed?*J.Thorac.Cardiovasc.Surg.* 125, 1438-1450.

40. Hallowell P, Bland JH, Dalton BC *et al.* (1978) The effect of hemodilution with albumin or Ringer's lactate on water balance and blood use in open-heart surgery.*Ann.Thorac.Surg.* 25, 22-29.

41. Handrigan MT, Burns AR, Donnachie EM, & Bowden RA (2005) Hydroxyethyl starch inhibits neutrophil adhesion and transendothelial migration.*Shock* 24, 434-439.

42. Haugen O, Intervention on arterial pressure and perfusion flow rate during cardiopulmonary bypass: Effects on global fluid shifts, cerebral metabolic and structural markers in a porcine model. *Doctoral thesis 2008. University of Bergen, Bergen, Norway*

43. Heltne JK, Microvascular fluid exchange during cardiopulmonary bypass (CPB) Establishment and evaluation of a piglet model and its use during hypothermic and normothermic CPB. *Doctoral thesis 2002. University of Bergen, Bergen, Norway*

44. Heltne JK, Farstad M, Lund T *et al.* (2002) Determination of plasma volume in anaesthetized piglets using the carbon monoxide (CO) method.*Lab Anim* 36, 344-350.

45. Heltne JK, Husby P, Koller ME, & Lund T (1998) Sampling of interstitial fluid and measurement of colloid osmotic pressure (COPi) in pigs: evaluation of the wick method.*Lab Anim* 32, 439-445.

46. Heltne JK, Koller ME, Lund T *et al.* (2000) Dynamic evaluation of fluid shifts during normothermic and hypothermic cardiopulmonary bypass in piglets.*Acta Anaesthesiol.Scand* 44, 1220-1225.

47. Heltne JK, Koller ME, Lund T *et al.* (2001) Studies on fluid extravasation related to induced hypothermia during cardiopulmonary bypass in piglets.*Acta Anaesthesiol.Scand.* 45, 720-728.

48. Higgins TL (1998) Quantifying risk and assessing outcome in cardiac surgery. *J.Cardiothorac.Vasc.Anesth.* 12, 330-340.

49. Himpe D (2003) Colloids versus crystalloids as priming solutions for cardiopulmonary bypass: a meta-analysis of prospective, randomised clinical trials.*Acta Anaesthesiol.Belg.* 54, 207-215.

50. Hogue CW, Gottesman RF, & Stearns J (2008) Mechanisms of cerebral injury from cardiac surgery.*Crit Care Clin.* 24, 83-ix.

51. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, & Kramer GC (1987) 3% NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients.*Ann.Surg.* 206, 279-288.

52. Holte K, Jensen P, & Kehlet H (2003) Physiologic effects of intravenous fluid administration in healthy volunteers.*Anesth.Analg.* 96, 1504-9, table.

53. Hughes HC (1986) Swine in cardiovascular research.*Lab Anim Sci.* 36, 348-350.

54. Husby P, Heltne JK, Koller ME *et al.* (1998) Midazolam-fentanyl-isoflurane anaesthesia is suitable for haemodynamic and fluid balance studies in pigs.*Lab Anim* 32, 316-323.

55. Iriz E, Kolbakir F, Akar H, Adam B, & Keceligil HT (2005) Comparison of hydroxyethyl starch and ringer lactate as a prime solution regarding S-100beta protein levels and informative cognitive tests in cerebral injury.*Ann.Thorac.Surg.* 79, 666-671.

56. Kaakinen T, Alaoja H, Heikkinen J *et al.* (2006) Hypertonic saline dextran improves outcome after hypothermic circulatory arrest: a study in a surviving porcine model.*Ann.Thorac.Surg.* 81, 183-190.

57. Karkouti K, Djaiani G, Borger MA *et al.* (2005) Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery.*Ann.Thorac.Surg.* 80, 1381-1387.

58. Kasper SM, Meinert P, Kampe S *et al.* (2003) Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses.*Anesthesiology* 99, 42-47.

59. Kawamura T, Wakusawa R, & Inada K (1997) Interleukin-10 and interleukin-1 receptor antagonists increase during cardiac surgery.*Can.J.Anaesth.* 44, 38-42.

60. Kozek-Langenecker SA (2005) Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 103, 654-660.

61. Kramer GC (2003) Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care.*J.Trauma* 54, S89-S99.

62. Kreimeier U & Peter K (1998) Strategies of volume therapy in sepsis and systemic inflammatory response syndrome.*Kidney Int.Suppl* 64, S75-S79.

63. Kuitunen AH, Hynynen MJ, Vahtera E, & Salmenpera MT (2004) Hydroxyethyl starch as a priming solution for cardiopulmonary bypass impairs hemostasis after cardiac surgery.*Anesth.Analg.* 98, 291-7, table.

64. Kurki TS, Kataja M, & Reich DL (2003) Emergency and elective coronary artery bypass grafting: comparisons of risk profiles, postoperative outcomes, and resource requirements.*J.Cardiothorac.Vasc.Anesth.* 17, 594-597.

65. Kvalheim VL, Farstad M, Steien E *et al.* (2009) Infusion of hypertonic saline/starch during cardiopulmonary bypass reduces fluid overload and may impact cardiac function.*Acta Anaesthesiol.Scand.*

66. Laine GA & Allen SJ (1991) Left ventricular myocardial edema. Lymph flow, interstitial fibrosis, and cardiac function.*Circ Res* 68, 1713-1721.

67. Laks H, Standeven J, Blair O *et al.* (1977) The effects of cardiopulmonary bypass with crystalloid and colloid hemodilution on myocardial extravascular water.*J.Thorac.Cardiovasc.Surg.* 73, 129-138.

68. Laxenaire MC, Charpentier C, & Feldman L (1994) [Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study].*Ann.Fr.Anesth.Reanim.* 13, 301-310.

69. Lichtenstein SV, Ashe KA, el Dalati H *et al.* (1991) Warm heart surgery. *J.Thorac.Cardiovasc.Surg.* 101, 269-274.

70. Lilleaasen P (1977) Moderate and extreme haemodilution in open-heart surgery. Blood requirements, bleeding and platelet counts.*Scand.J.Thorac.Cardiovasc.Surg.* 11, 97-103.

71. Lobo DN, Macafee DA, & Allison SP (2006) How perioperative fluid balance influences postoperative outcomes.*Best.Pract.Res.Clin.Anaesthesiol.* 20, 439-455.

72. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, & Bistrian BR (1990) Postoperative fluid overload: not a benign problem.*Crit Care Med.* 18, 728-733.

73. Luddington RJ (2005) Thrombelastography/thromboelastometry.*Clin.Lab Haematol.* 27, 81-90.

74. Marelli D, Paul A, Samson R *et al.* (1989) Does the addition of albumin to the prime solution in cardiopulmonary bypass affect clinical outcome? A prospective randomized study.*J.Thorac.Cardiovasc.Surg.* 98, 751-756.

75. Mathew JP, Mackensen GB, Phillips-Bute B *et al.* (2007) Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly.*Anesthesiology* 107, 577-584.

76. McDaniel LB, Nguyen T, Zwischenberger JB *et al.* (1994) Hypertonic saline dextran prime reduces increased intracranial pressure during cardiopulmonary bypass in pigs.*Anesth.Analg.* 78, 435-441.

77. Mehlhorn U, Geissler HJ, Laine GA, & Allen SJ (2001) Myocardial fluid balance. *Eur.J.Cardiothorac.Surg.* 20, 1220-1230.

78. Møller AM, Pedersen T, Svendsen PE, & Engquist A (2002) Perioperative risk factors in elective pneumonectomy: the impact of excess fluid balance.*Eur.J.Anaesthesiol.* 19, 57-62.

79. Moller JH, Shumway SJ, & Gott VL (2009) The first open-heart repairs using extracorporeal circulation by cross-circulation: a 53-year follow-up.*Ann.Thorac.Surg.* 88, 1044-1046.

80. Nakayama S, Sibley L, Gunther RA, Holcroft JW, & Kramer GC (1984) Small-volume resuscitation with hypertonic saline (2,400 mOsm/liter) during hemorrhagic shock.*Circ.Shock* 13, 149-159.

81. Oliveira SA, Bueno RM, Souza JM, Senra DF, & Rocha-e-Silva (1995) Effects of hypertonic saline dextran on the postoperative evolution of Jehovah's Witness patients submitted to cardiac surgery with cardiopulmonary bypass.*Shock* 3, 391-394.

82. Panico FG & Neptune WB (1960) A mechanism to eliminate the donor blood prime from the pump-oxygenator.*Surg.Forum* 10, 605-609.

83. Paparella D, Brister SJ, & Buchanan MR (2004) Coagulation disorders of cardiopulmonary bypass: a review.*Intensive Care Med.* 30, 1873-1881.

84. Paparella D, Yau TM, & Young E (2002) Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update.*Eur.J.Cardiothorac.Surg.* 21, 232-244.

85. Prien T, Thulig B, Wusten R *et al.* (1993) [Hypertonic-hyperoncotic volume replacement (7.5% NaCl/10% hydroxyethyl starch 200.000/0.5) in patients with coronary artery stenoses].*Zentralbl.Chir* 118, 257-263.

86. Ring J & Messmer K (1977) Incidence and severity of anaphylactoid reactions to colloid volume substitutes.*Lancet* 1, 466-469.

87. Risnes I, Ueland T, Lundblad R *et al.* (2003) Changes in the cytokine network and complement parameters during open heart surgery.*Interact.Cardiovasc.Thorac.Surg.* 2, 19-24.

88. Russell JA, Navickis RJ, & Wilkes MM (2004) Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials.*J.Cardiothorac.Vasc.Anesth.* 18, 429-437.

89. Sakr Y, Payen D, Reinhart K *et al.* (2007) Effects of hydroxyethyl starch administration on renal function in critically ill patients.*Br.J.Anaesth.* 98, 216-224.

90. Schimetta W, Schochl H, Kroll W *et al.* (2002) Safety of hypertonic hyperoncotic solutions--a survey from Austria.*Wien.Klin.Wochenschr.* 114, 89-95.

91. Schortgen F, Deye N, & Brochard L (2004) Preferred plasma volume expanders for critically ill patients: results of an international survey.*Intensive Care Med.* 30, 2222-2229.

92. Schortgen F, Lacherade JC, Bruneel F *et al.* (2001) Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study.*Lancet* 357, 911-916.

93. Schramko AA, Suojaranta-Ylinen RT, Kuitunen AH, Kukkonen SI, & Niemi TT (2009) Rapidly degradable hydroxyethyl starch solutions impair blood coagulation after cardiac surgery: a prospective randomized trial.*Anesth.Analg.* 108, 30-36.

94. Schroth M, Plank C, Meissner U *et al.* (2006) Hypertonic-hyperoncotic solutions improve cardiac function in children after open-heart surgery.*Pediatrics* 118, e76-e84.

**95. Schumacher, K.-F. Klotz. Fluid therapy in cardiac surgery patients. Cardiopulmonary Pathophysiology 13, 138-142. 2009.
Ref Type: Generic**

96. Scrutinio D & Giannuzzi P (2008) Comorbidity in patients undergoing coronary artery bypass graft surgery: impact on outcome and implications for cardiac rehabilitation.*Eur.J.Cardiovasc.Prev.Rehabil.* 15, 379-385.

97. Sealy WC, Brown IW, Jr., & Young WG, Jr. (1958) A report on the use of both extracorporeal circulation and hypothermia for open heart surgery.*Ann.Surg.* 147, 603-613.

98. Sedrakyan A, Gondek K, Paltiel D, & Elefteriades JA (2003) Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery.*Chest* 123, 1853-1857.

99. Seghaye MC, Grabitz RG, Duchateau J *et al.* (1996) Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations.*J.Thorac.Cardiovasc.Surg.* 112, 687-697.

100. Shatney CH, Deepika K, Militello PR, Majerus TC, & Dawson RB (1983) Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock.*Arch.Surg.* 118, 804-809.

101. Sirvinskas E, Sneider E, Svagzdiene M *et al.* (2007) Hypertonic hydroxyethyl starch solution for hypovolaemia correction following heart surgery.*Perfusion* 22, 121-127.

102. Smith GJ, Kramer GC, Perron P *et al.* (1985) A comparison of several hypertonic solutions for resuscitation of bled sheep.*J.Surg.Res.* 39, 517-528.

103. Starling EH (1896) On the Absorption of Fluids from the Connective Tissue Spaces. *J.Physiol* 19, 312-326.

104. Swindle MM (1984) Swine as replacements for dogs in the surgical teaching and research laboratory.*Lab Anim Sci.* 34, 383-385.

105. Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, & Fearon KC (2004) Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection.*World J.Surg.* 28, 1046-1051.

106. Teoh KH, Bradley CA, Gauldie J, & Burrows H (1995) Steroid inhibition of cytokine-mediated vasodilation after warm heart surgery.*Circulation* 92, II347-II353.

107. Thyes C, Madjdpour C, Frascarolo P *et al.* (2006) Effect of high- and low-molecular-weight low-substituted hydroxyethyl starch on blood coagulation during acute normovolemic hemodilution in pigs.*Anesthesiology* 105, 1228-1237.

108. Tian J, Lin X, Li YH, & Xu JG (2005) Influence of hydroxyethyl starch on lipopolysaccharide-induced tissue nuclear factor kappa B activation and systemic TNF-alpha expression.*Acta Anaesthesiol.Scand.* 49, 1311-1317.

109. Tølløfsrud S, Mathru M, & Kramer GC (1998) Hypertonic-hyperoncotic solutions in open-heart surgery.*Perfusion* 13, 289-296.

110. Tølløfsrud S & Noddeland H (1998) Hypertonic saline and dextran after coronary artery surgery mobilises fluid excess and improves cardiorespiratory functions.*Acta Anaesthesiol.Scand.* 42, 154-161.

111. Tølløfsrud S, Svennevig JL, Breivik H *et al.* (1995) Fluid balance and pulmonary functions during and after coronary artery bypass surgery: Ringer's acetate compared with dextran, polygeline, or albumin.*Acta Anaesthesiol.Scand.* 39, 671-677.

112. Toraman F, Evrenkaya S, Yuce M *et al.* (2004) Highly positive intraoperative fluid balance during cardiac surgery is associated with adverse outcome.*Perfusion* 19, 85-91.

113. Treib J, Baron JF, Grauer MT, & Strauss RG (1999) An international view of hydroxyethyl starches.*Intensive Care Med.* 25, 258-268.

114. Treib J, Haass A, Pindur G *et al.* (1996) All medium starches are not the same: influence of the degree of hydroxyethyl substitution of hydroxyethyl starch on plasma volume, hemorrheologic conditions, and coagulation.*Transfusion* 36, 450-455.

115. Ungerstedt U (1991) Microdialysis--principles and applications for studies in animals and man.*J.Intern.Med.* 230, 365-373.

116. Utley JR and Stephens DB. Fluid balance during cardiopulmonary bypass.In: Pathophysiology and techniques of cardiopulmonary bypass. Williams & Williams. 23-35. 1982. Baltimore. Ref Type: Serial (Book,Monograph)

117. Van der Linden P & Ickx BE (2006) The effects of colloid solutions on hemostasis. *Can.J.Anaesth.* 53, S30-S39.

118. Vassar MJ, Perry CA, & Holcroft JW (1990) Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock.*Arch.Surg.* 125, 1309-1315.

119. Velasco IT, Pontieri V, Rocha e Silva, & Lopes OU (1980) Hyperosmotic NaCl and severe hemorrhagic shock.*Am.J.Physiol* 239, H664-H673.

120. Vincent JL (2009) Relevance of albumin in modern critical care medicine. *Best.Pract.Res.Clin.Anaesthesiol.* 23, 183-191.

121. Vogt NH, Bothner U, Lerch G, Lindner KH, & Georgieff M (1996) Large-dose administration of 6% hydroxyethyl starch 200/0.5 total hip arthroplasty: plasma homeostasis, hemostasis, and renal function compared to use of 5% human albumin.*Anesth.Analg.* 83, 262-268.

122. Wan S, LeClerc JL, & Vincent JL (1997) Cytokine responses to cardiopulmonary bypass: lessons learned from cardiac transplantation.*Ann.Thorac.Surg.* 63, 269-276.

123. Wilkes MM, Navickis RJ, & Sibbald WJ (2001) Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding.*Ann.Thorac.Surg.* 72, 527-533.

124. Winkelmayer WC, Glynn RJ, Levin R, & Avorn J (2003) Hydroxyethyl starch and change in renal function in patients undergoing coronary artery bypass graft surgery.*Kidney Int.* 64, 1046-1049.

125. Zander Rolf (2006) Infusion fluids: Why should they be balanced solutions? *EJHP Practice* 12.

126. Ziegler WH & Goresky CA (1971) Transcapillary exchange in the working left ventricle of the dog.*Circ.Res.* 29, 181-207.