RENAL PERFUSION, FUNCTION AND OXYGENATION AFTER MAJOR SURGERY AND IN SEPTIC SHOCK

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TO MY BELOVED DAUGHTERS

ABSTRACT

Acute kidney injury (AKI) is a common and dreaded complication to severe illness and major surgery, with major impact on morbidity and mortality. The aim of this doctoral thesis was to increase the knowledge on renal pathophysiology and to explore potential interventions for treatment and prevention of AKI after cardiac surgery, liver transplantation and in early clinical septic shock.

Patients and methods: Patients were studied in the intensive care unit (ICU) immediately after surgery, and in septic shock patients within 24 hours from admission to ICU. We studied the renal effects of a crystalloid (Ringers-acetate®) and a colloid (Venofundin®) fluid as plasma volume expanders after uncomplicated cardiac surgery (paper I, n=30), renal pathophysiology and the renal effects of target mean arterial pressure (tMAP) after liver transplantation (paper II n=12, and II, respectively, n=10), and renal pathophysiology in early clinical septic shock (paper IV, n=8). Renal blood flow (RBF) and glomerular filtration rate (GFR) were measured by renal vein thermodilution and renal extraction of ^{51}Cr-EDTA, respectively. In paper IV, RBF was measured by infusion clearance for para-aminohippurate (PAH).

Results: RBF is increased by both crystalloid and colloid fluid when used as plasma volume expander after cardiac surgery, but due to hemodilution, neither of the fluids increases renal oxygen delivery (RDO_2). The crystalloid-induced increase in GFR is associated with impaired renal oxygenation, which is not seen with the colloid. After liver transplantation, vasodilation of the efferent arterioles causes a renal vasodilation and a fall in GFR. Renal oxygen consumption (RVO_2) is considerably increased early after liver transplantation, despite the lower GFR. The increased RBF seen after liver transplantation is not sufficient to meet the increased RVO_2, resulting in an impaired renal oxygenation. Early after liver transplantation, a tMAP of 75 mmHg, compared to 60 mmHg, improves RBF and GFR without impairing renal oxygenation. In early clinical septic shock, there is a fall in GFR and RDO_2 caused by a constriction of renal afferent arterioles, accompanied by a sodium reabsorption at a high oxygen cost, which together with the reduced RDO_2 impairs renal oxygenation, causing renal tubular injury.

Conclusions: Treatment of hypovolemia with a bolus dose of crystalloid fluid impairs renal oxygenation after uncomplicated cardiac surgery. In liver transplant recipients, renal function is severely reduced and renal oxygenation is impaired due to a high RVO_2 not matched by a proportional increase in RDO_2. In liver recipients, RBF and GFR are pressure-dependent due to the loss of renal autoregulation at a MAP < 75 mmHg. In early clinical septic shock, GFR and RDO_2 are reduced because of renal vasoconstriction, causing impaired renal oxygenation and a tubular injury.

Keywords: Acute kidney injury, glomerular filtration rate, renal oxygenation, liver transplantation, septic shock.
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SAMMANFATTNING PÅ SVENSKA

Akut njursvikt drabbar upp till ca 65% av intensivvårdskrävande patienter, med ökad sjuklighet och dödlighet som följd. Dödligheten för IVA-patienter utan njursvikt är 8%, att jämföra med en dödlighet på upp mot hela 60% för patienter som utvecklar njursvikt i samband med svår sjuka eller efter stora operationer.

Den vanligaste orsaken till njursvikt inom intensivvården är blodförgiftning, men njursvikt är också en vanlig komplikation efter stor kirurgi som tex hjärtkirurgi och levertransplantation.

Lågt blodflöde till njuren, pga tex blodförlust under operationer, anses vara en av orsakerna till njursvikt. Det råder delade meningar om hur blodförlusten ska ersättas. Det finns risker med blodtransfusioner, varför man helst ersätter blodförlust med vanliga dropp. Vilket dropp som är minst skadligt för njuren har orsakat en stor internationell diskussion utan att forskarna har kunnat enas om hur blodförlusten bäst ersätts för att undvika njurskada. En annan orsak till njursvikt har antagits vara syrebrist, och flera olika teorier till syrebristen har diskuterats utan att man har kunnat enas.

Studier av njurarna är mycket svåra att göra på människa, varför de i huvudsak sker på djur. Djuren kan dock inte fås att efterlikna den speciella situation människan utsätts för vid blodförgiftning och leversvikt, eller efter stora operationer. Vår forskningsgrupp har en unik metod med vilken vi kan undersöka njuren på människa, vilket kan bidra till att förstå njurarnas situation i den sjuka kroppen.

Den här avhandlingen har undersökt dels hur njurarna fungerar vid blodförgiftning och efter levertransplantation, dels vad man kan göra för att förbättra njurarnas förutsättningar vid blodförgiftning, levertransplantation och efter hjärtkirurgi. Vi har kommit fram till att det finns fördelar med att använda en viss typ av dropp framför en annan för att ersätta måttlig blodförlust vid hjärtkirurgi, att det finns en undre gräns för blodtrycket för att njurarna ska må bra efter levertransplantation, att vid blodförgiftning och levertransplantation så leder kroppen blodet, dvs syrgasen, iväg från njurarna, och att det vid så stora påfrestningar också kostar mer syrgas för njurarna bara att fungera.

Kombinationen av mindre syrgas till njurarna och ökad syrgaskostnad för samma arbete bidrar till njursvikten vid blodförgiftning och i samband med levertransplantation. Den nyvunna kunskapen att val av vätska efter stor kirurgi, och val av blodtrycksnivå efter levertransplantation, kan minska belastningen på njurarna, bidrar till att bättre kunna förebygga njursvikt vid blodförgiftning, i samband med blodförlust vid hjärtkirurgi samt vid levertransplantation.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. J. Skytte Larsson, G. Bragadottir, V. Krumbholz, B. Redfors, J. Sellgren and S.-E. Ricksten.

Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid vs colloid.

British Journal of Anaesthesia, 115 (5): 736–42 (2015)

II. Jenny Skytte Larsson, Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten

Renal function and oxygenation are impaired early after liver transplantation despite hyperdynamic systemic circulation.

Critical Care (2017) 21:87

III. Jenny Skytte Larsson, Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten.

Renal effects of norepinephrine-induced variations in mean arterial pressure after liver transplantation: a randomised cross-over trial.

Submitted

IV. J. Skytte Larsson, G. Bragadottir, V. Krumbholz, B. Redfors, J. Sellgren and S.-E. Ricksten.

Renal blood flow, glomerular filtration rate and renal oxygenation in early clinical septic shock.

Submitted

CONTENT

ABBREVIATIONS

AKI	Acute kidney injury
ANOVA	Analysis of variance
CI	Cardiac index
CVP	Central venous pressure
^{51}Cr-EDTA	Chromium ethylene diamine tetraacetic acid
eGFR	estimated glomerular filtration rate according to the MDRD formula
FF	Filtration fraction
GFR	Glomerular filtration rate
ICU	Intensive care unit
MAP	Mean arterial pressure
MDRD	Modification of diet in renal disease, calculation of GFR
mGFR	Measured GFR
NO	Nitric oxide
P_{Bow}	Hydrostatic pressure in the capsule of Bowman
P_{glom}	Hydrostatic pressure in the glomeruli
PAH	Paraaminohippuric acid
PCWP	Pulmonary capillary wedge pressure
π_{Bow}	Osmotic pressure in the capsule of Bowman
π_{glom}	Osmotic pressure in the glomeruli
RASS	Richmond agitation-sedation scale
$RAVO_2$-diff	Arterial–renal vein oxygen content difference
RBF	Renal blood flow
RBF_{IC}	Renal blood flow, infusion clearance technique
RBF_{TD}	Renal blood flow, thermodilution technique
RDO_2	Renal oxygen delivery
RO_2Ex	Renal oxygen extraction
RPF	Renal plasma flow
RVO_2	Renal oxygen consumption

RVR	Renal vascular resistance
SAS	Statistical Analysis Software
SD	Standard deviation
SPSS	Statistical packages for the social sciences
SVI	Stroke volume index
SVRI	Systemic vascular resistance index

DEFINITIONS IN SHORT

Acute Kidney Injury, AKI	According to KDIGO *(Kidney Disease: Improving Global Outcomes)*; Increase in SCr by 0.3 mg/dl (26.5 mmol/l) within 48 hours or Increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or Urine volume of 0.5 ml/kg/h for 6 hours.
Child-Pugh score	1- and 2-year survival in liver disease It contains five variables including serum levels of bilirubin and albumin, prothrombin time, ascites, and encephalopathy. CPS divides patients class A, intermediate (class B), and poor (class C)
MELD score	3-months mortality for liver disease The difficulties and interobserver variability for the subjective parameters in the CPS classification led to the development of the "model for end stage liver disease" (MELD) score based on laboratory values only, which should be more objective and accurate than CPS. MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

"Educating the mind without educating the heart is no education at all"

Aristotle

INTRODUCTION

1.1 Definition of AKI

Acute kidney injury (AKI) is defined as an abrupt decrease in renal function. It is a common and deleterious complication after major surgery and in critical illness. The epidemiology of AKI has up until recently been hard to assess since a uniform definition has been lacking. This rendered a collaborating group, the Acute Dialysis Quality Initiative (ADQI), to present the RIFLE criteria for the definition of AKI [1]. Based on the increase in serum creatinine level and/or the duration of oliguria, this definition presented three stages of AKI, namely Risk, Injury, and Failure. Moreover, the RIFLE definition identified Loss of kidney function and End-stage kidney disease as outcome criteria. In 2004, Lassnig et al found that even a small increase in SCr had a negative impact on survival after cardiac surgery [2], hence it became obvious that it was the change, and not only the absolute number, of SCr that mattered. The RIFLE criteria was therefore modified by the AKI Network (AKIN) group, presenting the AKIN criteria in 2007, adding an absolute value for the raise in SCr [3]. The advantage of the AKIN criteria over the RIFLE criteria is that it enables an AKI diagnosis based on small absolute changes in SCr. In 2012, the Kidney disease: Improving Global Outcomes (KDIGO) unified the definition of AKI by combining the RIFLE and AKIN criteria, resulting in the KDIGO classification, defining the time frame of SCr changes, and adding the need for renal replacements therapy as a staging parameter [4]. The KDIGO criteria is evaluated as the most accurate diagnostic tool to use in patients with liver cirrhosis, in whom SCr is a very poor tool for evaluation of renal function, and where the urinary output measure is not applicable [5, 6]. Pereira et al recently found that, among septic patients, using the RIFLE and KDIGO criteria diagnosed AKI more often than the use of AKIN, but the in-hospital mortality did not differ between the different diagnostic criteria [7].

Table 1: Definitions of AKI. Urine output <0.5 ml/kg/h >6 h.

	RIFLE (2004)	AKIN (2007)	KDIGO (2012)
S-Creatinine increase	≥1.5 times baseline within 7 days	≥1.5 times baseline **or** 0.3 mg/dl (26 µmol/L) within 48 hrs	1.5-1.9 times baseline known or presumed to have occurred within the prior 7 days **or** 0.3 mg/dl (26 µmol/L) within 48 hrs

1.2 Epidemiology and consequences of AKI

AKI have an extraordinary negative impact on morbidity, i.e. chronic kidney disease (CKD) with the need for renal replacement therapy (RRT), and furthermore on both mortality and society costs [8-10]. As recently reported in an epidemiological multicenter international study, over 60% of the patients admitted to the intensive care unit (ICU) develop AKI according to the KDIGO criteria, the most common causes being sepsis and hypovolemia [9]. AKI has been found to occur in 37-84 % of septic ICU patients. The higher the stage of AKI, the higher the mortality risk. For AKI stage 2 and 3, mortality is reported to be 3.9 and 7.2 times higher, respectively, than in septic shock without AKI [7, 9, 11, 12]. Cardiac surgery is associated with an AKI incidence of up to 40%, and mortality is independently increased for up to ten years after surgery [13-15]. AKI needing renal replacement therapy (RRT) after cardiac surgery is uncommon, but associated with an almost eight-fold increase in mortality [13]. Liver transplantation without postoperative AKI carries a mortality of 2-6%, to be compared to a mortality of 47-55% in the case of postoperative AKI [16, 17]. Even a minimal increase in SCr is associated not only with a higher mortality, but also with a shorter graft survival, resulting in severe consequences for both the individual patient, patients on the waiting list for liver transplantation and society [18-20]. Moreover, hospital costs have been found to be almost 60% higher for patients with AKI compared to those without [10].

1.3 Risk factors for AKI after cardiac surgery, liver transplantation and in septic shock

The female sex is a risk factor for developing AKI after cardiac surgery, liver transplantation and in septic shock [21-24].

In cardiac surgery with cardiopulmonary bypass, the major risk factors include left ventricular ejection fraction <40%, diabetes mellitus, preoperative use of an intraaortic balloon pump, emergency surgery and an elevated preoperative serum creatinine [21, 22].

Preoperative risk factors for AKI after liver transplantation includes obesity,

severe liver failure defined as a high Child-Pugh score, diabetes mellitus, renal failure, liver graft dysfunction and cold and warm ischemic time for the liver graft. Perioperative risk factors associated with postoperative AKI are the amount of required transfusions, intraoperative blood loss and occurrence of postreperfusion syndrome (PRS), defined as a 30% reduction in MAP lasting for > 1 minute within 5 minutes after peroperative reperfusion of the liver graft [18, 20, 23-27].

Patients at risk for AKI in association with septic shock are older, have more co-morbidities, have a higher severity of illness score and are more often admitted to the ICU for non-surgical medical disease, than patients with septic shock that do not develop AKI. Moreover, the more unstable the respiratory and hemodynamic situation is for the septic patient, the greater the risk for development of AKI [28].

1.4 Renal physiology at a glance

Filtration of fluid and waste products from the blood into the renal tubular system occurs in the glomerular capillaries. The ultrafiltrate enters the Bowman's capsule and the glomerular filtration rate (GFR) is determined by the permeability of the filtration barrier (ultrafiltration coefficient K_{uf}), and by the Starling forces, such as the hydrostatic (P_{glom}) and mean colloid osmotic (π_{glom}) pressure in the glomerular capillaries, and in Bowman's capsule (P_{Bow} and π_{Bow}, respectively), according to the formula:

$$GFR = K_{uf} \times ((P_{glom} + \pi_{Bow}) - (P_{Bow} + \pi_{glom}))$$

From this formula, one can understand that there are two forces; P_{glom} and π_{Bow} promoting, and P_{Bow} + π_{glom} opposing, filtration.

The glomeruli are supplied by a single afferent arteriole, which divides into glomerular capillaries, and converge in an efferent arteriole. The hydrostatic pressure in the glomerular capillaries is dependent on the tone of the afferent and the efferent arterioles. Vasoconstriction of the afferent arteriole lowers the flow through and pressure in the capillaries and hence GFR is reduced. On the contrary, if the efferent arteriole is constricted, blood flow is decreased, while the pressure in the capillaries is increased, leading to an augmentation of GFR.

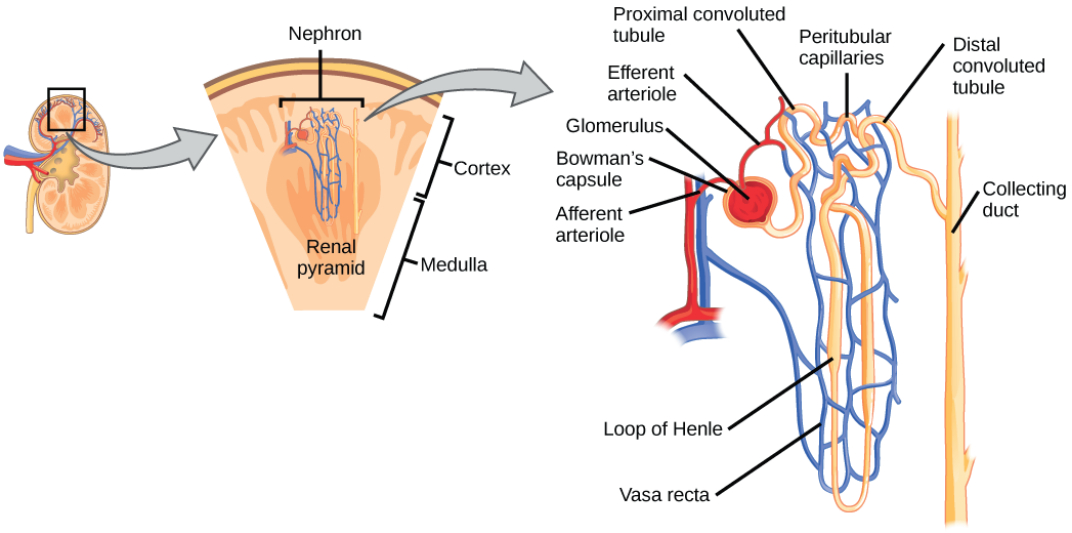

Fig 1: The nephron is the functional unit of the kidney. The glomerulus and convoluted tubules of the nephron are located in the cortex of the kidney, while the collecting ducts are located in the pyramids of the kidney's medulla.

Reproduced from Boundless learning, CC permission.

GFR is also, to some extent, dependent on glomerular plasma flow, because of flow-dependent changes in capillary protein concentration. Lowering RBF, the glomerular transit time for plasma increases, leaving more time for filtration. The more plasma that is filtrated per time unit, the higher the colloid osmotic pressure in the glomerulus (π_{glom}), and hence the lower the GFR. Increasing RBF causes the opposite situation [29].

It is important that the elimination of water and waste products, and the regulation of the salt and water content of the body, is kept constant independently of the strains the body is subjected to. Systemic extrinsic ways to maintain homeostasis includes activation of hormones (renin-angiotensin system and natriuretic peptides) and of the sympathetic nervous system in cases of e.g. extreme fluid loss. Furthermore, RBF and GFR is kept constant by intrinsic autoregulatory mechanisms affecting the afferent arteriole:

1. Myogenic mechanism

   At a higher blood pressure, sensed by the afferent arteriole as an increase in transmural pressure, the afferent arteriole constricts, maintaining RBF and GFR constant, despite the higher blood pressure. This is the faster of the two mechanisms.

2. Tubuloglomerular feedback mechanism (TGF)

   At higher blood pressure, GFR and sodium filtration increases due to increased tubular flow, resulting in a higher concentration of NaCl in the early distal tubule. The concentration of NaCl is sensed

by chemoreceptors in the macula densa, which is a collection of epithelial cells in the distal tubule, situated adjacent to the afferent and efferent arterioles. At an increased concentration of NaCl in the filtrate reaching the macula densa, the afferent arteriole vasoconstricts, adjusting flow and keeping GFR unaffected by the variations in blood pressure.

The range within which renal autoregulation operates in humans is not well understood, but in the literature it has been assumed to be in the range of 80-130 mmHg. The lower limit for renal autoregulation has been shown to be a mean arterial pressure (MAP) of >75 mmHg in patients with septic shock [30, 31].

After the filtration of the primary urine into Bowman's capsule, the renal tubules have the task to reabsorb and concentrate the primary urine from approximately 180 L/day to 1-2 L/day. This is done in the tubular system, extending from the Bowman's capsule, situated in the renal cortex, via the proximal tubule, further on to the loop of Henle, the distal tubule, and ending in the collecting duct. Water and sodium is filtered into the Bowman's capsule, and then reabsorbed to 99% in the tubular system according to the current needs of the body. Sodium molecules enter the tubuli cells by passive diffusion, but are then actively pumped through the basolateral membrane into the interstitium by a Na+/K+-ATPas. From the interstitium, sodium is passively diffusing into the peritubular capillaries. Intercellular apical tight junctions in the tubular cells hinder sodium from reentering the tubular lumen from the interstitium. While the filtration process is a passive process, the reabsorption of sodium is an active and energy and oxygen consuming process. A great part of the renal oxygen consumption is used for tubular sodium reabsorption.

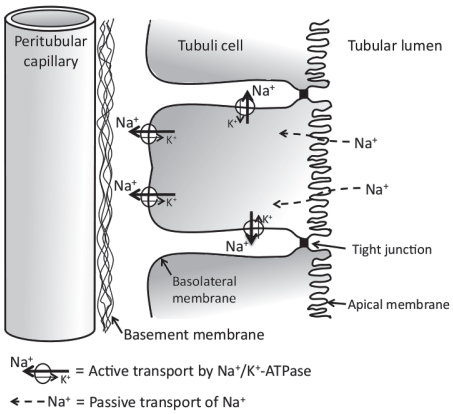

Fig 2: Sodium passively diffuses through the apical membrane into the tubuli cells due to a concentration gradient. It is then actively pumped into the interstitium, from where it is absorbed into the peritubular capillaries, drawn by the intravasal colloid osmotic pressure. Tight junctions between the tubuli cells hinder the sodium from leaking back into the tubular lumen.

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The kidney receives 20-25% of the total cardiac output (CO). This redundant blood supply is necessary to maintain a high GFR. RBF is however not evenly distributed in the kidney; the renal cortex receives ≈80%, the outer medulla ≈20% and the inner medulla receives ≈1-2% of the RBF. This distribution of RBF is necessary to optimize GFR in the cortex, and to maintain the osmotic gradient for concentration of urine in the medulla. Oxygen tension is 6-7 kPa in the cortex compared to only 1.5-2.5 kPa in the medulla [32]. The low tissue pO_2 in the medulla is caused by the relatively low medullary blood flow [33] and by the high levels of renal oxygen consumption of the medullary thick ascending limbs of Henle's loop, which reabsorb a large proportion of the filtered sodium by active, O_2 - demanding transport. As almost 99% of the glomerular filtrate is reabsorbed, the renal oxygen consumption (RVO_2) is high, second only to the heart [34].

The uneven distribution of RBF and oxygen consumption between the various parts of the kidney affects the local balance between renal oxygen delivery (RDO_2) and consumption (RVO_2). This balance is crucial for local renal oxygenation. The renal medulla, particularly the outer portion, is susceptible to hypoxia. The global renal oxygen supply/demand relationship can be expressed as renal oxygen extraction (RO_2Ex). An increase in RVO_2 that is not met by a proportional increase in RDO_2, results in an increased RO_2Ex, i.e. renal oxygenation is impaired and vice versa.

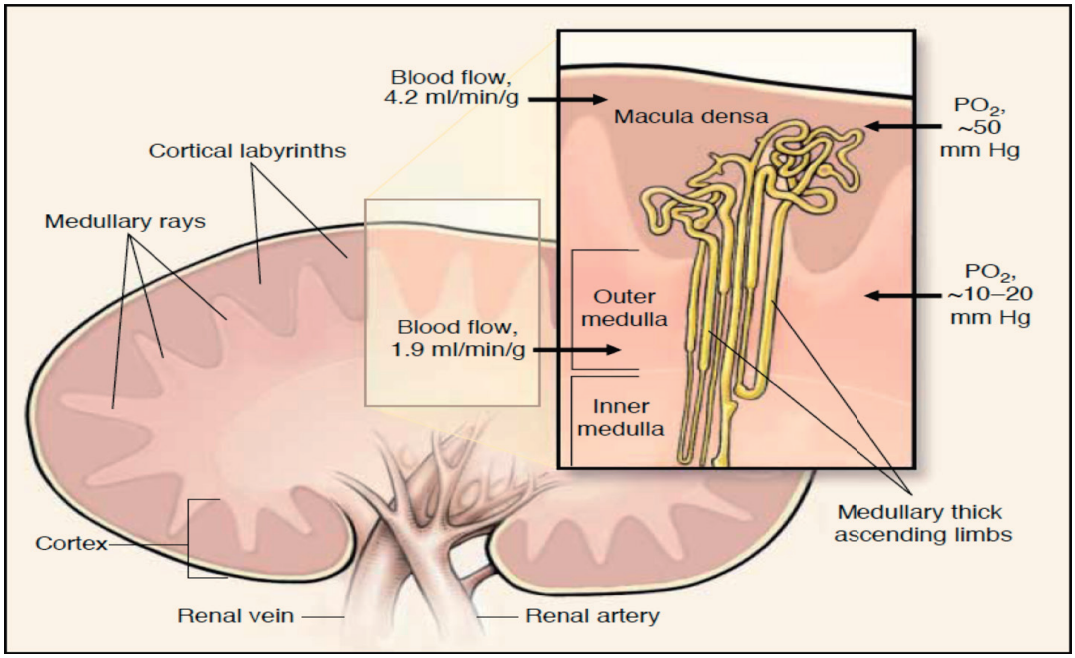

Fig 3: Blood supply and partial pressure of oxygen (pO2) of the renal cortex and medulla.

It has been shown that there is a close correlation between tubular sodium reabsorption and RVO_2 [35]. Furthermore, there are several studies showing a linear relationship between GFR, RVO_2 and renal sodium reabsorption in different clinical conditions [36-38]. Thus, in general, the major determinant of RVO_2 is GFR. Since an increase in RBF results in an increase in GFR and the filtered amount of sodium, renal oxygen consumption increases as a result of the augmented renal blood flow and filtered sodium. Thus, in contrast to other organs, RVO_2 is flow-dependent as long as RBF and GFR changes in parallel.

Besides the renal oxygen used for sodium reabsorption, there is an oxygen demand for renal basal metabolism. In a study by Redfors et al, comparing patients after cardiac surgery with and without AKI, it was found that basal metabolism constituted around 25% of the total renal oxygen consumption in both groups [36].

In conclusion, GFR is determined by RBF and the relationship between afferent and efferent arteriolar resistances with direct effects on glomerular filtration pressure. The kidneys receive a great proportion of the cardiac output for the filtration process. Due to intrarenal distribution of blood flow in combination with the uneven distributed oxygen demand, the renal oxygenation, i.e. the balance between oxygen supply and demand, is susceptible to increased oxygen consumption or impaired renal oxygen delivery. Particularly the outer part of the renal medulla is vulnerable and already under normal conditions on the verge of hypoxia.

1.5 AKI – pathophysiologic theories

It is beyond all doubt that the ethiology of AKI is multifactorial and complex. It has been stressed that due to the limited understanding of renal pathophysiology, our possibilities to prevent and treat AKI is limited, and that further understanding of the mechanisms behind the renal dysfunction in AKI is needed [39, 40]. Our knowledge on renal pathophysiology in AKI is based on experimental ischemia-reperfusion models, usually in the rat, induced by renal artery occlusion. Depending on the time of occlusion, an extensive tubular necrosis is seen, in striking contrast to the very limited necrosis seen in biopsies of patients with AKI [41, 42]. Thus, this experimental model used to better understand the pathophysiology of AKI has been questioned [42]. New radiological non-invasive imaging techniques have been suggested for the study of the renal pathophysiology of clinical AKI [43, 44]. These techniques are, however, less suited for the critically ill patient requiring extensive treatment for multiple organ support, as the patients need to be transported to a scanner for e.g. magnetic resonance imaging (MRI) and the need for removal of any invasive device not compatible with MRI.

1.5.1 Septic AKI

Based on large animal experimental models of early sepsis, it has been suggested that renal dysfunction, i.e. a fall

in GFR, may occur in spite of hyperdynamic circulation with an increase in RBF [45, 46]. The reason for this is, up to the present, unknown. One theory is that the increase in RBF in early sepsis is mainly due to a vasodilation of the efferent arterioles, resulting in a decreased pressure over glomeruli and hence a lower GFR. Another theory is that there is an shunting mechanism, redistributing the intrarenal blood flow from the medulla to the cortex, causing a mismatch in local renal oxygen supply/demand balance, and hence a hypoxic state in the medulla [47].

An increased production of nitric oxide (NO) has been demonstrated to result in a systemic vasodilation and hypotension in both clinical and experimental sepsis [48-51]. Hypotension in sepsis elicits a baroreflex-mediated activation of the sympathetic nervous system, including the renal sympathetic nerves, as demonstrated in animal models of sepsis [52, 53] and in clinical sepsis as an elevated plasma norepinephrine level [54]. Thus, a NO-mediated renal vasodilation may be antagonised by the increase in renal sympathetic activity in sepsis. Ramchandra et al demonstrated, in conscious septic sheep, that the previously described renal vasodilatation [45] was accompanied by an increase in renal sympathetic nerve activity, which would promote renal vasoconstriction [53]. They suggested that the profound increase in NO in septic shock will override this sympathetically mediated renal vasoconstriction, causing a net renal vasodilation and an increased RBF because of vasodilated efferent arterioles. However, there is no report on RBF, GFR and renal oxygenation in early clinical septic shock.

1.5.2 Ischemic AKI

Ischemic/reperfusion injury (IRI) as a cause of AKI is common, and is caused by a reduced RBF and a decreased RDO_2. The reduction in RBF and RDO_2 is caused either by hypovolemia, by an increased renal vascular resistance (RVR) or by alterations in the intrarenal microcirculation. Hypovolemia can be the consequence of a reduced circulating blood volume due to perioperative bleeding, or by a decreased effective intravascular blood volume caused by for example liver failure and cirrhosis [55, 56].

Increased RVR is partly a consequence of a decreased production of the vasodilator NO, caused by damaged endothelial cells. This results in a decreased vasodilation [57]. Moreover, the inflammatory response gives rise to an activation of the endothelium, enhancing adhesion of activated leukocytes to the endothelial cells. Furthermore, cytokines like TNF-α and IL-1 disrupts cell matrix and causes cell debris to shed into the lumen. These consequences of IRI results in an increased resistance in the renal microcirculation, and an elevated RVR [58].

In the maintenance and repair phases of ischemic AKI, the tubular cells start to proliferate, function and RBF is being restored. Renal blood flow, though, is not fully restored after an ischemic event, this is known as the "no-reflow"

phenomenon. The resulting changes in the vascular morphology causes an increased permeability of the vascular walls and an endothelial cell dysfunction, resulting in interstitial and cellular edema. This in turn causes further obstruction of renal microcirculation, lower oxygen delivery and promotes renal injury [59-62].

1.6 Plasma volume expansion in hypovolemia –colloid vs. crystalloid

To ameliorate ischemic AKI after major surgery, crystalloid or colloid fluid is used for plasma volume expansion if serum hemoglobin and coagulation are within the normal range [42]. This restores normovolemia and renal perfusion, but induces a hemodilution, potentially resulting in little or no net effect on oxygen delivery. It has been shown in animal studies that neither colloids nor crystalloids increase RDO_2 despite increases in cardiac output, and that crystalloids even can negatively affect renal microvascular oxygenation [43, 44]. In patients with severe sepsis, fluid resuscitation with the colloid hydroxyethyl starch, had an increased mortality and a higher incidence of AKI [63]. Effects of postoperative plasma volume expansion with i.v. fluids on RDO_2 and renal oxygenation have not previously been studied in man. Furthermore, perioperative data on the effects of crystalloids and colloids on RBF, GFR, and renal oxygenation, defined as the renal oxygen supply–demand relationship, are lacking.

1.7 Treatment of hypotension, preserving autoregulation of RBF.

In a volume resuscitated vasodilatory state, as for example in septic shock and liver failure, the systemic vasodilation results in a hypotension threatening to induce hypoperfusion of vital organs, particularly when organ autoregulation of blood flow is exhausted. Vasodilation is most commonly treated with the vasopressor norepinephrine. Norepinephrine has been shown to induce renal vasoconstriction and to reduce RBF in healthy volunteers [64, 65]. On the other hand, there is a risk of pressure dependent RBF if the blood pressure is allowed to decrease below the limit of the renal autoregulatory capacity. Indeed, it was recently found that restoring mean arterial pressure from 60 to 75 mmHg in vasodilatory shock, by the use of norepinephrine, increased both RDO_2 and GFR with preserved renal oxygenation [30]. However, the effects of norepinephrine-controlled target MAP on renal filtration, perfusion and oxygenation early after liver transplantation have not previously been studied in humans.

AIM

1. To evaluate the differential renal effects of a crystalloid vs a colloid for plasma volume expansion on renal perfusion, filtration and oxygenation after uncomplicated cardiac surgery (paper I).

2. To study renal hemodynamics, function and oxygenation after liver transplantation (paper II).

3. To evaluate the effects of three various target levels of MAP on renal perfusion, function and oxygenation early after liver transplantation (paper III).

4. To study renal hemodynamics, function and oxygenation in volume-resuscitated norepinephrine-dependent early clinical septic shock (paper IV).

PATIENTS AND METHODS

The Gothenburg Regional Ethical Review Board approved the study protocols of all four papers included in this thesis. For conscious patients scheduled for cardiac surgery and liver transplantation, respectively, written informed consent was obtained at the preoperative evaluation. For the sedated patients with septic shock in paper number IV, the next of kin was informed prior to inclusion.

3.1 Patients

In this thesis, three groups of patients were studied, namely patients undergoing uncomplicated cardiac surgery with cardiopulmonary bypass (CPB) (n=30), patients immediately after liver transplantation (n=12) and patients in early septic shock (n=8). The patients included in each study group all had a normal preoperative (I, II, III) or premorbid (IV) serum creatinine. In addition, in papers II and III, the patients had normal pretransplant renal function, as assessed by measurements of GFR while on the waiting list for transplantation. Notably, both the liver recipients in papers II and III, and the septic patients in paper IV, had MELD- and SOFA-scores in the lower range (14.0 and 7.9 respectively), i.e. the patients included in the study-groups in papers II-IV had an expected mortality rate of less than 20% and were, thus, not exceptionally ill. The control groups in paper II (n=73) and IV (n=58) had earlier been included in pharmacological studies performed by our study group [37, 66-69]. These patients where all subjected to uncomplicated cardiac surgery, with no postoperative impairment of renal function. The baseline renal and systemic data of these patients, i.e. before pharmacological intervention, were used for comparison with the studied patients in papers II and IV).

3.2 Measurements of systemic hemodynamics

Cardiac output (CO) was measured in triplicates using, in paper I, control groups and parts of the patients in paper IV, a pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA). In the remaining patients, a PiCCO® catheter (PULSION Ltd, Munich, Germany) for transthoracic thermodilution pulse contour technique, was inserted in the femoral artery and used for CO measurement. The mean arterial pressure (MAP) was measured via a radial or femoral artery line. The central venous pressure (CVP) was measured via a catheter placed in vena cava superior. MAP, CVP and in paper I, pulmonary arterial pressure, was measured continuously, while pulmonary

artery wedge pressure (PCWP, paper I) was measured intermittently. Stroke volume (SV), systemic and pulmonary vascular resistance (SVR and PVR, respectively) were calculated according to standard formulae.

3.3 Measurements of renal variables

All renal data were normalised to a body surface area of 1.73 m^2.

3.3.1 The renal vein catheter

A ball-ended 8-fr catheter for retrograde venous thermodilution (Webster Laboratories, Baldwin Park, CA) was inserted into either of the renal veins via the right femoral vein. The femoral vein was identified blindly in paper I, and by the use of ultrasound in papers II-IV. After punction of the femoral vein, the catheter was introduced into the left or right renal vein under fluoroscopic guidance. The tip of the catheter was placed in the central part of the renal vein, it's position being confirmed by venography using ultralow doses of iohexol (Omnipaque® 300 mg I/ml, GE Healthcare, Stockholm, Sweden) [70]. There are two thermistors located at the distal part of the renal vein catheter, one indicator and one external thermistor, the latter being located 2.5 cm proximal to the catheter tip.

3.3.2 Renal blood flow by continuous thermodilution (papers I, II, III)

A two-channelled Wheatstone bridge, for measurement of changes in resistance, was connected to the renal vein catheter. The changes in resistance were achieved by creating a temperature difference between the indicator (internal thermistor) and the renal vein blood (external thermistor). To do so, room tempered isotonic crystalloid solution was infused for 15-30 seconds into the catheter at a constant rate of 53.7 ml/min. The infusion was repeated three times for each measurement. The correct position of the renal vein catheter was defined as one that did not yield a variation in renal blood flow of more than 10% in the three consecutive measurements. Analogue signals from the Wheatstone bridge were stored and analysed in a computer, using data acquisition software (fig 4). The proportion of cooling between the two thermistors was then used to calculate the renal blood flow of one kidney. To get the total renal blood flow, the value from the measurement of RBF from one kidney was doubled, and urine flow was added, according to the formula 1.

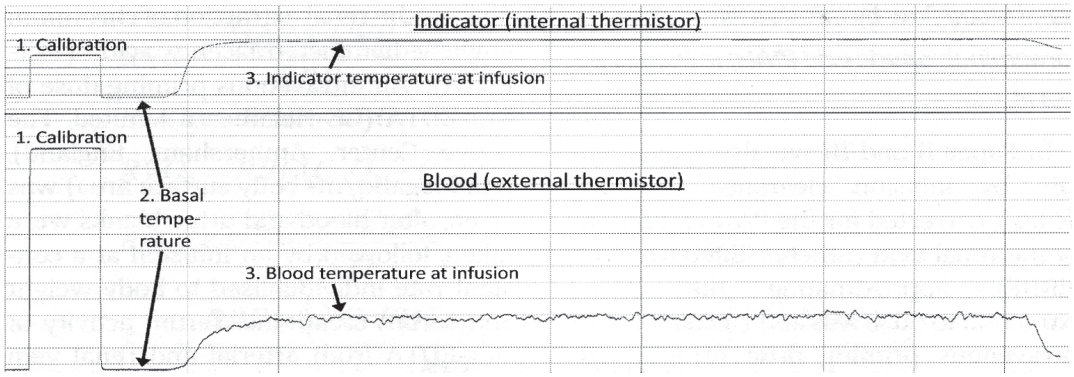

Fig 4: A recording of a continuous renal vein thermodilution blood flow measurement in the software. The upper graph reflects the temperature of the indicator (internal thermistor), and the lower reflects the temperature of the renal blood flow (external thermistor). A decrease in temperature causes an elevation of the graph. To calculate RBF, calibration signal strength (1), basal blood temperature (2) and temperatures at infusion (3) were used. Three measurements at the time were made, defined manually and then the program calculated the mean signal strength for each period and each channel separately.
With permission from B. Redfors

3.3.3 Renal blood flow by infusion clearance of paraaminohippuric acid (paper IV)

Paraaminohippuric acid (PAH) is a crystalline acid administered intravenously in the form of its sodium salt. Since PAH is completely removed from the blood by the kidneys by both glomerular filtration and tubular secretion, the rate of clearance of PAH from the blood reflects RBF_{IC}. An intravenous priming dose of PAH was given, followed by a constant rate infusion individualized to body weight and serum creatinine. Serum concentration of PAH in arterial and renal vein blood were measured using a spectrophotometer. RPF was calculated as the amount of infused PAH divided by the difference in PAH concentration between arterial and renal vein blood. RBF was then calculated by RPF / (1-hematocrit).

3.3.4 Glomerular filtration rate (GFR)

Renal filtration fraction is the proportion of fluid reaching the tubules, i.e. the relationship between glomerular filtration rate (GFR) and renal plasma flow (RPF), and is, in this thesis, measured as the renal extraction of the filtration marker chromium ethylenediamine-tetraacetic acid (^{51}Cr-EDTA). After blood and urine blanks were collected, an intravenous priming dose of ^{51}Cr-EDTA was given to all patients. The priming dose was followed by an infusion at a constant rate, individualized to body weight and serum creatinine. Serum ^{51}Cr-EDTA activities from arterial and renal vein blood were measured using a well counter. In order to eliminate errors due to high diuresis, the formula for calculation of FF was corrected taking the urine flow into account. GFR was then calculated as FF x RPF.

3.3.5 Urine flow

All patients included in this thesis had a Foley catheter draining the bladder of urine. Measurements were made of urine flow, concentration of sodium, of creatinine and of the tubular injury marker N-acetyl-β-d-glucosaminidase (NAG).

Analysis of oxygen, sodium and hemoglobin

Arterial blood was analyzed for the content of oxygen, sodium and hemoglobin using an automated blood gas analyser (Siemens RAPIDPoint 500®). Blood samples from central vein and pulmonary catheters, and from the renal vein catheter were analyzed for oxygen content, using the same analyzer.

3.4 Experimental procedures

Written informed consent was obtained from all patients in papers I, II and III. Informed consent from next of kin was obtained in paper IV. All patients, both in the study groups and in the control groups, were studied in the ICU, during sedation with propofol and an opioid to RASS -5, and during mechanical ventilation to normocarbia. Infusion rates of fluids and drugs, other than study related, were not changed during the experimental procedures. The renal vein catheter was inserted in the ICU in all patients, and an equibrilation period of at least 60 minutes was applied before start of the experimental procedures. A total of 5 patients in the study groups were excluded due to unsuccessful placement or function of the renal vein catheter.

Statistics: All statistical analyses have been performed using Statistical Package Social Sciences (SPSS) version 24, except for analyses of repeated measures of creatinine in paper II, where Statistical Analysis System (SAS) was used. Continuous data was checked for normal distribution using the Shapiro-Wilk test, in combination with visual assessment of Q-Q plots [71]. Categorical data was compared using Fischer's exact test. Values are presented as mean and standard deviation (± SD) of the mean. A probability level (p-value) of less than 0.05 has been considered to indicate statistical significance.

3.4.1 Renal effects of plasma volume expansion: a randomised study on crystalloid vs. colloid (paper I)

30 patients were studied after uncomplicated cardiac surgery. Postoperative hemodynamic goals were CVP 5-10 mmHg, MAP >70 mmHg and a mixed venous oxygen saturation (SVO_2) > 60%. Plasma volume expansion was achieved using Ringers-Acetate® 20 ml/kg as crystalloid, and hydroxyethylstarch 60 mg/ml, 130/0.62 (Venofundin®) 10 ml/kg as colloid. Randomization between crystalloid and colloid fluid was performed using sealed envelopes. The fluid was administered during 20-30 minutes. Thermodilution measurements of RBF and CI were conducted, and blood and urine samples were obtained, at 20, 40 and 60 minutes after the end of the fluid administration.

Statistics: Intragroup effects were analyzed using one-way ANOVA for repeated measurements. Mauchley's

test of sphericity was used to test the difference in variance between the points of measurements. When sphericity was not confirmed, Greenhouse-Geisser was used to report the p-values, instead of the otherwise used Sphericity assumed. Intergroup effects were compared by ANCOVA for repeated measurements, with the mean of baseline measurements as a covariate, and after linearity between the variables were checked.

3.4.2 Renal hemodynamics, function and oxygenation early after liver transplantation (paper II)

Twelve liver recipients with pretransplant normal renal function were included in this study. Postoperative hemodynamic goals were pulse pressure variation of < 12% and a MAP of 70-80 mmHg. Hypovolemia was treated according to routine clinical practice, and if there was a persistent hypotensive state despite resuscitation with fluids, norepinephrine was used as a vasopressor, titrated according to the attending intensivist. Two 30 minutes urine collection periods were then started, and thermodilution measurements of RBF and CO were conducted at the end of each urine collection period, followed by blood and urine sampling. The results from the liver recipients were compared to a control group consisting of 73 patients after uncomplicated cardiac surgery with cardiopulmonary bypass, data derived from previous studies conducted by our research team. The control group had normal cardiac and renal function.

Statistics: Intergroup differences were compared using independent-samples t-test for normally distributed data, consideration taken to Levene's test of equality. Mann-Whitney U test was used for non-parametric data. Linear regression analyses were used to correlate renal oxygen consumption to renal sodium reabsorption and GFR, respectively. A mixed model using SAS was performed to analyse within- and intergroup repeated measurements of serum creatinine.

3.4.3 Renal effects of norepinephrine-induced changes in mean arterial pressure after liver transplantation (paper III)

In this study, the same patients were studied as in paper II, although two patients were excluded after randomization, due to occlusion of the renal vein catheter, leaving 10 liver recipients with a preoperative normal renal function to be included in this paper.

After an equilibration period of at least 60 minutes, two 30-min control periods ensued at a target MAP of 75 mmHg. The infusion rate of norepinephrine was then randomly increased or decreased, in a cross-over design to obtain a 30-min period at a MAP of either 60 or 90 mmHg. A titration period of 15 min was needed for each new MAP level to obtain the target pressure. Randomisation was accomplished using sealed envelopes in two blocks. At each target MAP, urine was collected for 30 minutes. At the end of each period, cardiac output and renal thermodilution measurements were performed and blood samples were taken from radial artery and re-

nal vein for measurements of serum concentrations of sodium, ^{51}Cr-EDTA, hemoglobin as well as oxygen content.

Statistics: Intragroup data from the two control measurements at MAP 70-80 mmHg were pooled, and then compared to the two other levels of target MAP using repeated measure ANOVA in combination with LSD post-hoc test.

3.4.4 Renal hemodynamics, function and oxygenation in early clinical septic shock (paper IV)

Eight patients with a premorbid normal serum creatinine and norepinephrine-dependent septic shock were studied within 24 hours from ICU admission. Hemodynamic targets in the ICU were a pulse pressure variation of <12% and a MAP 70-80 mmHg. The data from the study group was compared to 58 post cardiac surgery patients without AKI, data derived from previous studies performed by our research group. In this study, RBF was measured using the technique of infusion clearance of PAH, instead of thermodilution. In addition to renal and systemic hemodynamics and oxygenation states, urine was analysed for NAG and creatinine to get the U-NAG/U-creatinine ratio in the septic group. After the equilibration period, two 30 minutes urine collection periods were conducted. CO was measured, followed by arterial, renal vein and mixed venous blood sampling, at the end of each urine collection period.

Statistics: IIntragroup data from the two 30 minutes measurements was pooled. Intergroup differences were compared using the independent t-test for parametric data, consideration taken to Levene's test of equality. The Mann-Whitney U test was used for analysis of non-parametric data.

RESULTS

4.1 Renal effects of plasma volume expansion: a randomised study on crystalloid vs. colloid (paper I)

To evaluate the renal effects of crystalloid and colloid for plasma volume expansion after uncomplicated cardiac surgery, a total of 30 patients with preoperative normal cardiac and renal function were randomized to receive either crystalloid (n=15, Ringers-acetate® 20 mg/kg) or colloid (n=15, Venofundin® 10 mg/kg) solution. Data obtained during the two control periods before intervention did not differ significantly between the groups. The induced plasma volume expansion effect, measured as effects on CI, did not differ, significantly between the groups

4.1.1 Effects of i.v. fluids on systemic variables

In the crystalloid group, there was a peak increase in MAP, SVI and CI at 20 minutes after the end of fluid infusion, declining back to baseline at 60 minutes after end of infusion. Using colloid fluid, there was a more persistent rise in MAP, SVI and CI during the whole experimental procedure, the increase in CI being significantly greater than in the crystalloid group. In both groups, filling pressures increased and SVRI decreased. HR was left unaffected by both fluids. Both fluids induced hemodilution with a consequent decrease in arterial oxygen content, the effect being more pronounced in the colloid than in the crystalloid group. Despite this, there was no significant difference in DO_2I between the groups.

4.1.2 Effects of i.v. fluids on renal variables (Table II)

RBF increased significantly in both groups without any intergroup statistically significant difference. RBF increased only transiently in the crystalloid group, whereas the increase was more consistent in the colloid group. Despite the increase in RBF, RDO_2 was not statistically affected in any group, because of hemodilution. GFR, sodium filtration, sodium reabsorption, FF, RVO_2, RO_2Ex and $RAVO_2$-diff increased only in the crystalloid group, with intergroup significance only for FF, RO_2Ex and $RAVO_2$. Renal oxygen extraction was increased only in the crystalloid group, leading to a statistical difference between the groups (fig. 5).

Table 2: Renal variables crystalloid vs colloid after uncomplicated cardiac surgery

	CRYSTALLOID				One-way ANOVA p-value	COLLOID				One-way ANOVA p-value	ANCOVA inter-group p-value
	Baseline	20 min	40 min	60 min		Baseline	20 min	40 min	60 min		
RBF (ml min^{-1})	674 (170)	738 (178)	688 (226)	673 (201)	0.025	706 (199)	827 (164)	787 (207)	792 (184)	0.020	0.089
RVR (mmHg ml^{-1} min^{-1})	0.108 (0.03)	0.107 (0.03)	0.112 (0.04)	0.112 (0.03)	0.625	0.104 (0.04)	0.093 (0.02)	0.098 (0.03)	0.098 (0.03)	0.394	0.165
RDO_2 (ml min^{-1})	99.2 (25.0)	99.7 (23.0)	95.9 (26.7)	93.1 (25.0)	0.176	102.5 (24.9)	105.4 (27.4)	99.7 (30.6)	101.6 (27.7)	0.750	0.582
GFR (mlmin^{-1})	68.6 (14.3)	79.5 (21.1)	87.5 (22.7)	76.4 (16.0)	<0.001	70.9 (15.3)	85.7 (23.5)	78.3 (29.0)	83.9 (38.8)	0.291	0.989
Sodium filtration (mmolmin^{-1})	9.42 (2.02)	10.88 (2.97)	12.00 (3.28)	10.44 (2.25)	<0.001	9.69 (2.03)	11.72 (3.27)	10.73 (4.05)	11.52 (5.41)	0.288	1.000
Sodium reabsorption (mmolmin^{-1})	9.10 (2.01)	9.63 (3.00)	11.18 (3.21)	9.89 (2.14)	0.002	9.30 (2.05)	11.33 (3.22)	10.19 (4.01)	11.26 (5.20)	0.235	0.573
Fitration fraction	0.157 (0.03)	0.161 (0.05)	0.194 (0.05)	0.174 (0.05)	<0.001	0.154 (0.05)	0.148 (0.04)	0.142 (0.05)	0.146 (0.05)	0.773	0.030
Urine flow (ml min^{-1})	2.7 (1.2)	8.7 (4.9)	6.5 (4.3)	4.1 (1.9)	<0.001	2.5 (1.2)	2.4 (1.3)	3.5 (2.0)	3.9 (2.3)	0.003	0.002
RVO_2 (ml min^{-1})	9.5 (2.4)	11.1 (2.3)	11.5 (2.9)	11.0 (3.4)	<0.001	10.1 (3.3)	10.6 (4.7)	10.1 (3.0)	10.3 (3.0)	0.964	0.085
$S_{rv}O_2$ (%)	88.9 (3.2)	87.2 (3.3)	86.2 (3.6)	86.5 (3.9)	<0.001	88.4 (4.0)	88.0 (4.2)	87.5 (4.1)	87.8 (3.8)	0.452	0.019
RO_2Ex	0.099 (0.03)	0.113 (0.03)	0.121 (0.03)	0.120 (0.04)	<0.001	0.104 (0.04)	0.106 (0.04)	0.111 (0.04)	0.109 (0.04)	0.653	0.032
$RAVO_2$-diff (ml)	14.3 (3.2)	15.4 (3.3)	17.3 (4.3)	16.8 (5.3)	0.004	15.3 (5.4)	13.4 (5.1)	13.8 (4.6)	13.8 (4.1)	0.169	0.002
RBF/CI	0.274 (0.05)	0.261 (0.06)	0.243 (0.01)	0.257 (0.01)	0.015	0.278 (0.09)	0.258 (0.05)	0.250 (0.07)	0.254 (0.07)	0.202	0.904

Values are mean (SD). RBF; renal blood flow, RVR renal vascular resistance, RDO_2; renal oxygen delivery, GFR; glomerular filtration rate, RVO_2; renal oxygen consumption, $SrvO_2$; Renal vein oxygen saturation, RO_2Ex; renal oxygen extraction, RAVO2-diff; Arterial-renal vein oxygen content difference, RBF/CI; relationship between RBF and cardiac index. ANOVA; within-group analysis of variance, ANCOVA; between-groups analysis of variance with baseline as a co-variate.

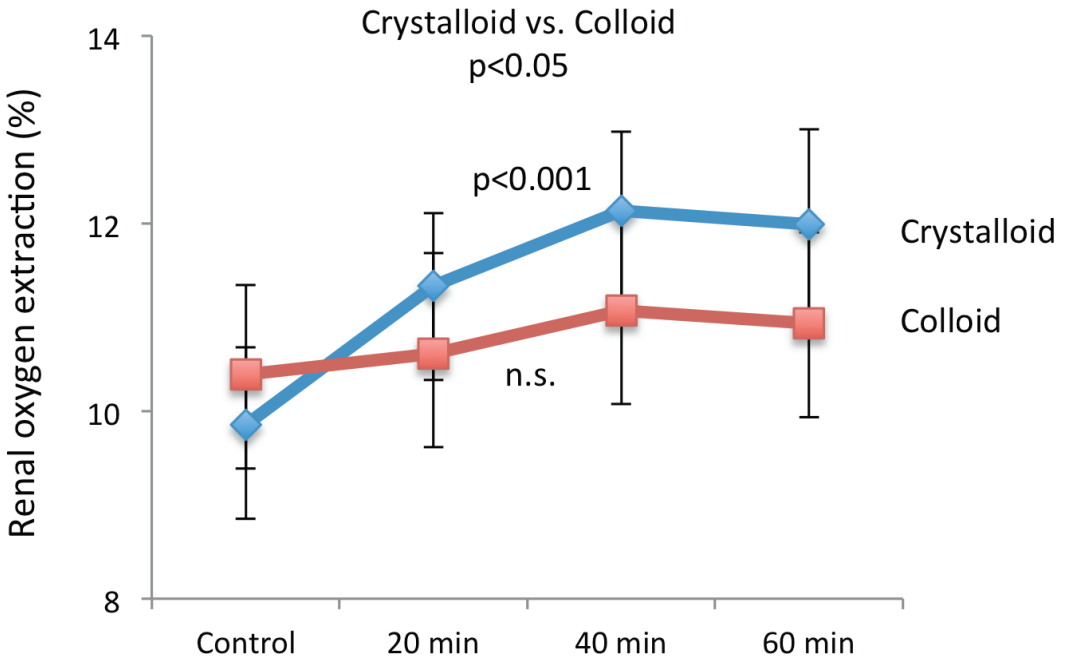

Fig 5: Effects of a crystalloid (10 ml kg–1) and a colloid (20 ml kg–1) bolus on renal oxygen extraction after cardiac surgery. The crystalloid increased renal oxygen extraction (P<0.001) 20, 40 and 60 min after the bolus, in contrast to the colloid (NS), suggesting impairment of renal oxygenation. The change in renal oxygen extraction was significantly (P<0.05) more pronounced in the crystalloid group compared with the colloid group.

4.2 Renal hemodynamics, function and oxygenation early after liver transplantation (paper II)

To study the effects of liver transplantation on renal variables early after liver transplantation, we studied 12 liver recipients with pre-transplant GFR >60 ml/min, and compared the results to a control group consisting of 73 post cardiac surgery patients without AKI, previously studied by our research group [66-69, 72].

Preoperative data on the liver recipients are presented in table 5. Notably, the MELD- and Child-Pugh-scores are in a medium range, i.e. the symptoms of liver failure were moderate. Primary sclerotic cholangitis was the most common diagnosis, followed by cirrhosis due to viral infection.

There was a significant difference between the study and the control group regarding preoperative serum creatinine, being 14% lower in the study group (p=0.001), than in the control group. This was anticipated since liver failure per se lowers serum creatinine by a lower conversion of creatine to creatinine, and by the reduced muscle mass in patients with liver failure. However, eGFR, calculated according to the MDRD formula, did not differ between the groups. Serum creatinine increased in the liver transplanted group by over 40% per day during the first two postoperative days and 67% of the patients developed AKI.

Table 3. Preoperative individual data, liver transplant recipients

Patient number	Diagnosis	MELD score	Child-Pugh score	Serum bilirubin (mmol/l)	mGFR (ml/min/1.73m²)	Serum creatinine (µmol/l)	ASA
1	Primära biliary cirrhosis	15	10	36	75	67	3
2	Hepatitis C virus, cirrhosis	17	10	32	95	109	2
3	Primary sclerosing cholanigitis	6	9	8	72	60	2
4	Primary sclerosing cholanigitis	22	11	110	62	59	3
5	Hepatitis C virus, Hepatocellular carcinoma,	8	7	10	105	74	2
6	Alpha-1 antitrypsin deficiency	16	11	43	94	75	3
7	Alcoholic liver cirrhosis	24	12	150	72	62	3
8	Primary sclerosing cholanigitis	13	9	60	102	73	2
9	Primary sclerosing cholanigitis	9	6	32	89	76	2
10	Hepatitis C virus, Hepatocellular carcinoma,	9	9	14	122	60	3
11	Primary sclerosing cholanigitis, Hepatitis B virus	18	10	340	77	60	2
12	Hepatitis C virus, Hepatocellular carcinoma	11	8	24	61	75	3
Mean		**14.0**	**9.3**	**71.6**	**85.5**	**70.8**	**2.50**
SD		**5.7**	**1.7**	**94.6**	**18.7**	**13.9**	**0.52**

Data presented as mean ± SD. MELD; Model For End-Stage Liver Disease, mGFR; measured glomerular filtration rate, ASA; American Society of Anesthesiologists

4.2.1 Effects on systemic variables

The circulation after liver transplantation was more hyperdynamic than after cardiac surgery, with a significant higher CI and DO_2I, but a lower SVRI, compared to the control group. All liver recipients required norepineph-

rine at a mean dose of 0.28 ± 0.17µg/kg/min to maintain a MAP of 70-80 mmHg.

4.2.2 Effects on renal variables (table 4)

There was a 40% decline in mGFR, and a 24% increase in serum creatinine immediately after liver transplantation compared to the pretransplant value (fig 6).

Compared to the control group, RVR was lower and RBF was higher in the liver transplanted group. Despite the renal vasodilation, the ratio between RBF and CI was significantly lower after liver transplantation than after cardiac surgery. GFR, FF and renal sodium reabsorption were all lower amongst liver recipients. Despite the lower sodium reabsorption, RVO_2 was considerably higher in the study group than in the control group. Thus, the ratio RVO_2 per mmol/min of reabsorbed sodium was 2.7 times higher after liver transplantation than after uncomplicated surgery (fig 7). The higher oxygen consumption in liver recipients was not met by a proportional increase in RDO_2, resulting in a higher renal oxygen extraction in the study group than in the control group, i.e. impaired renal oxygenation.

Table 4: Renal data in the immediate postoperative period after liver transplantation

Variable	Control group (n=73)	Liver transplant recipients (n=12)	p-value
Renal oxygen extraction	0.100 ± 0.03	0.124 ± 0.04	0.042
Urine flow (ml/min)	3.13 ± 1.7	2.54 ± 2.2	0.065
Renal blood flow (ml/min)	716 ± 209	843 ± 197	0.024
Renal blood flow /cardiac index	0.277 ± 0.08	0.202 ± 0.05	<0.001
Renal vascular resistance (mmHg/ml/min)	0.100 ± 0.03	0.085 ± 0.02	0.051
Glomerular filtration rate (ml/min)	70.9 ± 23.3	51.5 ± 30.4	0.043
Filtration fraction	0.15 ± 0.04	0.09 ± 0.06	0.006
Renal sodium filtration (mmol/min)	9.67 ± 3.2	7.63 ± 5.6	0.052
Renal sodium reabsorption (mmol/min)	9.28 ± 3.2	7. 50 ± 5.5	0.065
Fractional sodium excretion (%)	5.0 ± 4.0	2.5 ± 3.5	0.002
Renal oxygen delivery (ml/min)	103.5 ± 32.1	119.7 ± 29.7	0.048
Renal oxygen consumption (ml/min)	10.0 ± 3.2	14.4 ± 4.8	0.001
Renal oxygen consumption / renal sodium reabsorption (ml/mmol)	1.15 ± 0.3	3.13 ± 2.4	<0.001
Serum creatinine day 1 (µmol/l)	75.1 ± 13.9	99.8 ± 32.7	0.025

Data are presented as mean ± SD

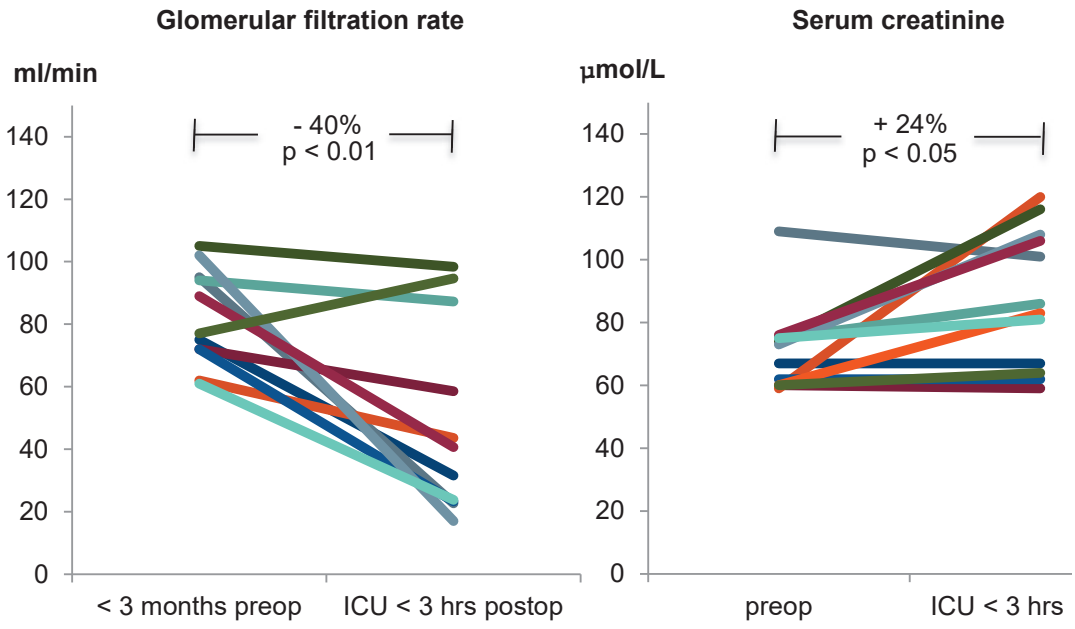

Fig 6 Individual data on measured glomerular filtration rate (GFR) and serum creatinine before (preoperative) and early after liver transplantation (intensive care unit [26] ≤ 3 hours) (n = 12)

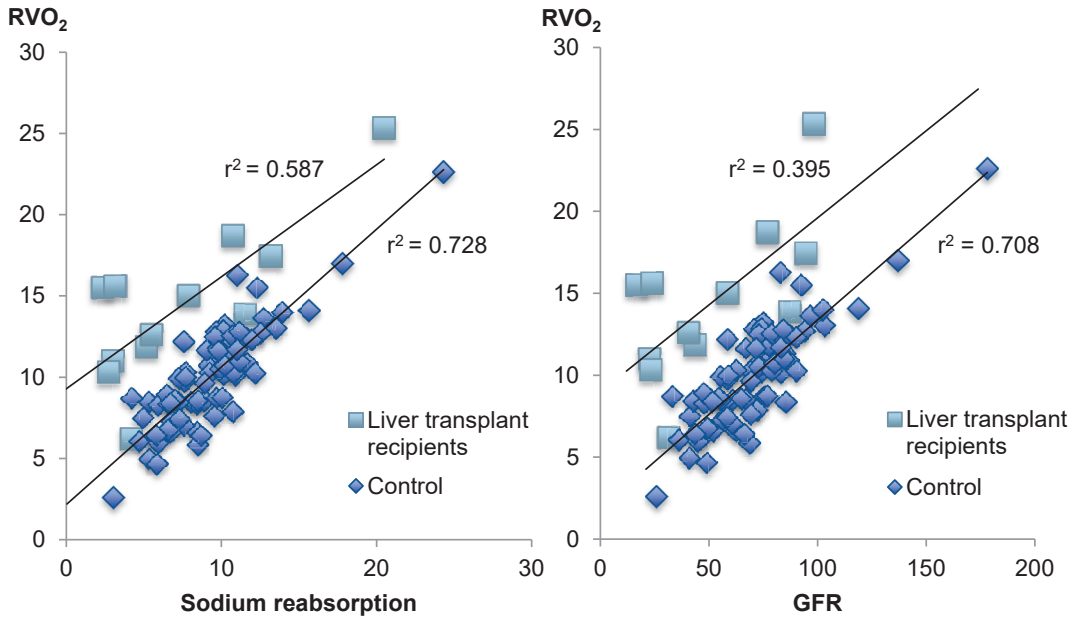

Fig 7: Relationship between renal oxygen consumption (RVO_2) and renal sodium reabsorption, and between renal oxygen consumption and glomerular filtration rate (GFR), in the early postoperative period in liver recipients and after uncomplicated cardiac surgery (controls)

4.3 Renal effects of norepinephrine-induced changes in mean arterial pressure after liver transplantation (paper III)

To study the renal effects of norepinephrine-induced changes in target MAP, 10 liver recipients with pretransplant normal renal function were included in this paper. Target MAP was randomized to 60, 75 and 90 mmHg, and the infusion rates of norepinephrine to achieve these targets were 0.13 ± 0.11, 0.25 ± 0.16 and 0.38 ± 0.28 µg/kg/min, respectively. Sixty percent of the patients included in this study developed AKI during the two first postoperative days.

4.3.1 Effects on systemic variables (table 5)

SVRI and serum haemoglobin increased significantly as the infusion rate of norepinephrine was adjusted to reach the higher target MAPs. Increasing MAP from 60 to 75 mmHg caused a significant augmentation in CI, SVI, and DO_2I, while VO_2I was left unaffected. Increasing target MAP further to 90 mmHg increased SVI in addition to SVRI and serum haemoglobin with no changes in CI.

Table 5: Effects of varying doses of norepinephrine on systemic variables after liver transplantation (n=10)

	60 mmHg	75 mmHg	90 mmHg
Norepinephrine (µg/kg/min)	0.13 ± 0.11	0.25 ± 0.16***	0.38 ± 0.28##
Cardiac index (l/min/m²)	3.8 ± 1.0	4.3 ± 1.1***	4.1 ± 1.1
Heart rate (beats/min)	72 ± 15	72 ± 16	65 ± 19##
Stroke volume index (ml/m²)	53.2 ±11.7	59.9 ± 11.6**	63.9 ± 10.9##
Central venous pressure (mmHg)	7.1 ± 3.0	7.9 ± 2.8	8.4 ± 3.1
SVRI (dynes x sec/cm³/m²)	1183 ± 374	1352 ± 431**	1707 ± 474###
$ScvO_2$ (%)	78.0 ± 6.4	81.5 ± 7.4***	81.3 ± 7.2
Serum haemoglobin (g/l)	102.4 ± 14.2	106.6 ± 16.2***	109.5 ± 14.5##
DO_2I (ml/min/min2)	521 ± 122	614 ± 156***	604 ± 150
VO_2I (ml/min/min2)	97 ± 14	92 ± 19	93 ± 19
Body temperature	36.7 ± 0.4	36.9 ± 0.4*	36.8 ± 0.3

*Data are presented as mean ± SD. 75 mmHg versus 60 mmHg *p <0.05, ** p < 0.01, *** p < 0.001; 90 mmHg versus 75 mmHg # p <0.05, ## p < 0.01, ### p < 0.001*
SVRI, systemic vascular resistance index; ScvO2, central venous oxygen saturation
DO2I, systemic oxygen delivery index; VO2I, systemic oxygen consumption index.
The following data are non-parametric: heart rate.

4.3.2 Effects on renal variables (table 6)

Increasing MAP from 60 to 75 mmHg increased GFR, sodium filtration and reabsorption, RBF, RDO_2, and RVO_2, but left RVR and RO_2Ex unaffected. Increasing MAP further, to 90 mmHg, increased RVR as the only affected renal variable.

Table 6: Effects of varying doses of norepinephrine on renal variables after liver transplantation (n=10)

	60 mmHg	75 mmHg	90 mmHg
Renal oxygen extraction	0.121 ± 0.05	0.120 ± 0.04	0.125 ± 0.05
Urine flow (ml/min)	1.27 ± 0.7	2.74 ± 2.5	2.52 ± 2.9
Renal blood flow (ml/min)	694 ± 243	820 ± 208*	767 ± 272
Renal blood flow /cardiac index	0.185 ± 0.06	0.200 ± 0.06	0.190 ± 0.06
Renal vascular resistance (mmHg/ml/min)	0.083 ± 0.03	0.087 ± 0.02	0.120 ± 0.04##
Glomerular filtration rate (ml/min)	42.6 ± 44.4	55.9 ± 38.3**	58.8 ± 58.8
Filtration fraction	0.08 ± 0.07	0.10 ± 0.05	0.11 ± 0.09
Renal sodium filtration (mmol/min)	5.84 ± 6.2	7.64 ± 5.4**	8.02 ± 8.2
Renal sodium reabsorption (mmol/min)	5.80 ± 6.2	7. 51 ± 5.4**	7.93 ± 8.2
Fractional sodium excretion (%)	2.4 ± 3.2	2.7 ± 3.8	1.6 ± 2.5#
Renal oxygen delivery (ml/min)	95.1 ± 33.8	119.0 ± 34.1**	114.3 ± 41.7
Renal oxygen consumption (ml/min)	11.4 ± 5.8	13.7 ± 4.5*	14.1 ± 7.4

*Data are presented as mean ± SD. 75 mmHg versus 60 mmHg *p <0.05, ** p < 0.01, *** p < 0.001; 90 mmHg versus 75 mmHg # p <0.05, ## p < 0.01, ### p < 0.001.*
The following data are non-parametric: urine flow, fractional sodium excretion.

4.4 Renal hemodynamics, function and oxygenation in early clinical septic shock (paper IV)

To evaluate renal perfusion, function and oxygenation in early clinical septic shock, we studied 8 patients within 24 hrs from ICU admission due to septic shock, and compared those data with data from 58 post cardiac surgery patients, previously included in studies conducted by our research group. In the study group, there were 5 cases of abdominal sepsis and 3 cases of septic pneumonia. Premorbid serum creatinine was significantly lower, and hence eGFR higher, in the study group than in the control group (table 7). The mean SOFA score was 7.9 ± 2.6 at the time of the study. The mean serum creatinine had increased from 71 ± 15 (premorbid) to 91 ± 22 µumol/l at the time of the experimental procedure.

Table 7: Patient characteristics; septic shock vs control group

Variable	Control group (n=58)	Septic shock (n=8)	p-value
Gender, n (% female)	4 (7)	6 (75)	<0.001
Age, mean (SD)	66 ± 10	64 ± 19	0.667
Body surface area (m^2)	2.0 ± 0.2	1.8 ±0.1	0.019
Hypertension, n (%)	33 (57)	1 (8.3)	0.022
Diabetes, n (%)	6 (10)	0 (0)	0.445
Beta-adrenergic blocker, n (%)	46 (79)	1 (12.5)	<0.001
ACE-inhibitor, n (%)	31 (53)	0 (0)	0.004
Calcium antagonist, n (%)	9 (16)	2 (25)	0.399
Serum creatinine (µmol/l)	83 ± 12	64 ± 13	<0.001
eGFR (MDRD)	81 ± 13	92 ± 17	0.049

Values are means ± SD, n = number of patients (%)
ACE-inhibitor; angiotensin converting enzyme-inhibitor

4.4.1 Systemic variables in septic shock

Despite a mean dose of norepinephrine of 0.23 ± 0.17 µg/kg/min in the study group, MAP was slightly lower, but CVP was higher, than in the control group. Other systemic hemodynamic variables did not differ between the groups.

4.4.2 Renal variables in septic shock (table 8)

GFR, sodium filtration and sodium reabsorption was significantly lower in the septic group than in the control group. Despite the lower sodium reabsorption, RVO_2 did not differ between the groups. Thus, the ratio RVO_2 per mmol of reabsorbed sodium was 45% higher in the septic group (p=0.057). There was a trend for a lower RBF (-19%, p = 0.068) and a higher RVR (20%, p = 0.069), and the RBF/CI ratio was significantly lower, in the septic group than in the control group. However, RDO_2 was significantly lower (-24%, p = 0.037) in the septic group than in the control group. Hence, RO_2Ex was significantly higher in septic shock than after uncomplicated cardiac surgery.

Urinary NAG/creatinine ratio was 5.4 ± 3.4 units/µmol creatinine in the study group. This variable was not measured in the control group.

Table 8: Renal data; septic shock vs control group

Variable	Control group (n=58)	Septic shock (n=8)	p-value
Renal oxygen extraction	0.097 ± 0.027	0.124 ± 0.039	0.022
Urine flow (ml/min)	3.8 ± 2.3	1.8 ± 1.0	0.007
Renal blood flow (ml/min)	858 ± 261	696 ± 166	0.068
Renal blood flow/cardiac index	0.31 ± 0.79	0.22 ± 0.67	0.003
Renal blood flow/cardiac output	0.16 ± 0.42	0.12 ± 0.43	0.028
Renal vascular resistance (mmHg/ml/min)	0.082 ± 0.023	0.098 ± 0.023	0.069
Glomerular filtration rate (ml/min)	79.8 ± 24.3	54.4 ± 17.6	0.006
Filtration fraction	0.140 ± 0.033	0.120 ± 0.052	0.306
Renal sodium filtration (mmol/min)	11.0 ± 3.4	7.6 ± 2.5	0.008
Renal sodium reabsorption (mmol/min)	10.5 ± 3.3	7.5 ± 2.5	0.014
Renal oxygen delivery (ml/min)	122.3 ± 42.4	92.7 ± 23.5	0.037
Renal oxygen consumption (ml/min)	11.4 ± 3.1	11.4 ± 4.0	0.956
Renal oxygen consumption / renal sodium reabsorption (ml/mmol)	1.12 ± 0.25	1.62 ± 0.71	0.057
Renal extraction of para-aminohippurate	0.84 ± 0.07	0.66 ± 0.21	0.005

Syrgasextraktionen är högre trots att GFR och natriumreabsorptionen är lägre, vilket skulle ha renderat en LÄGRE syrgasextraktion.
Mismatchen beror på en försämrad syrgastillförsel till njuren, för syrgaskonsumtionen är ju densamma
Trender är att RDO_2 är lägre pga en afferent vasokonstriktion vilken ses här som en trend att RVR ökar, och RBF minskar, dvs en redistribution av blod från njuren. Varför? Ingen aning... Uppenbarligen är inte njurens blodförsörjning så extensivt tilltagen att den klarar av denna nedgång utan att få en negativ påverkan på GFR.

DISCUSSION

5.1 Methodological and experimental considerations

In this thesis, the differential renal effects of crystalloid and colloid fluids for plasma volume expansion were studied after cardiac surgery with cardiopulmonary bypass. Furthermore, we have studied the renal pathophysiology and the renal effects of three levels of target MAP early after liver transplantation, as well as, renal perfusion, function and oxygenation in early clinical septic shock. All studies were performed within 24 hours from ICU admission and all patients were sedated and mechanically ventilated. Three out of four experimental procedures were performed out of office hours, due to the character of the studied procedures and circumstances.

5.2 Ethical issues

Some ethical considerations have been made during the planning of the studies. First of all, in paper I, plasma volume expansion was performed in patients considered haemodynamically stable, according to our local postoperative treatment protocol. The reason for this approach was that we considered it unethical to include patients with obvious haemodynamic signs of hypovolemia, without treating this condition during the preparation for the experimental procedure, including time to reach a body temperature > 36°C, time needed for serum ^{51}Cr-EDTA to reach steady state (at least 60 minutes) and baseline measurements (60 minutes) before start of the plasma volume expansion. However, over 80% of the patients studied in paper I did respond to the given volume with an increase in CI. This is fundamental to our belief that the renal results of plasma volume expansion with colloid and crystalloid fluid reported in our study are valid also for hypovolemic patients after major surgery. Second, the septic patients in paper IV were not included after informed consent, but rather approval from the next of kin since the septic patients all were already sedated and mechanically ventilated at inclusion. This approach was approved by the ethical committee before inclusion of the first patient.

5.3 Study population

In two of the papers included in this thesis (Papers II and IV), we have included uncomplicated postoperative patients with no renal impairment (no AKI) from earlier studies by our group, as controls. The baseline systemic and renal data of these patients were used for comparison with the liver recip-

ients and the septic patients, respectively. Factors shared by the patients in the control and the study groups are that they are all sedated and mechanically ventilated, and all are in an inflammatory state of different severity, the patients included in the control groups being studied after cardiac surgery with CPB. One major difference between the control groups and the study groups, is the distribution with regard to gender. In the control groups, the proportion of women is below 15% in all studies, compared to over 50% among liver recipients and patients with septic shock. This is simply caused by the distribution of gender in the Swedish population undergoing cardiac surgery, where women constitutes only 19% [73].

One common limitation in the studies included in this thesis, is the relatively low sample size of liver recipients and patients with septic shock (Paper II and IV). Even though sepsis is a common diagnosis among ICU patients, the severity of the septic disease at ICU admission has increased over the years, resulting in early initiation of RRT in many of these patients in the ICU, which together with strict inclusion and exclusion criteria, limited the number of patients eligible for inclusion. Moreover, it proved to be challenging to include, get informed consent from the next of kin, perform catheterisation of the pulmonary artery and the renal vein and achieve a steady state of PAH and ^{51}Cr-EDTA within 24 hrs after arrival to the ICU. The strength of the study on septic patients, was the large control group made up by post-cardiac surgery patients with CPB, and hence also in a state of systemic inflammatory response syndrome (SIRS) [74, 75]. Another reason is that many patients were eligible only off-hours.

In paper II, we did not assess whether or not there was a structural tubular cell injury in the early postoperative period in this group, as we did not measure tubular injury markers. However, the incidence of AKI in the

present study was high (67%), when compared to previous studies on tubular injury markers after liver transplantation (38–46%) [28, 29], and it is likely that release of tubular injury markers occurred also in the present study.

In paper III, it could be argued that changes in systemic and renal variables induced by varying infusion rates of norepinephrine, to obtain pre-determined levels of MAP, was caused by time-dependent spontaneous fluctuations and not to norepinephrine itself. Thus, a time-control group is lacking in paper III. One way to circumvent this problem was to change the infusion rates of norepinephrine to achieve the target MAP:s in a random fashion. Furthermore, the measured variables did not differ significantly between the two control values separated by 30 minutes, indicating stability over time.

5.4 Measurement of renal blood flow (RBF), filtration fraction (FF) and GFR

5.4.1 RBF by thermodilution

Using a renal vein catheter for thermodilution measurement of RBF, either by a bolus or by a continuous infusion, has previously been described and validated [76-78]. The most crucial factor for successful measurements of RBF using the renal vein catheter, is to find the correct position and then to retain that position throughout the experimental procedure. The possibility to estimate RBF repeatedly and without the need of a steady state or urine collection, makes it possible to bedside detect rapid fluctuations in RBF using the renal vein catheter and the retrograde thermodilution technique.

Assumptions made for accurate thermodilution measurements of RBF are that there is only one renal vein at the site for measurement, that the renal blood flow is equal in both kidneys, that admixture of blood from other adjacent vessels like spermatic, ovarian or adrenal veins are negligible, and that the injectate mixes completely with the renal vein blood. The technique of thermodilution measurement of renal blood flow is validated against the standard technique for RBF measurement using urinary clearance of PAH, and was initially found to produce a repeatability comparable to the PAH technique [76]. The repeatability was found to have improved when it was reevaluated ten years later, and the coefficient of variation of repeated estimations was 5.2% in a material presented by Bragadottir et al [68, 69].

5.4.2 RBF by infusion clearance of paraaminohippurate (PAH)

PAH is eliminated to approximately 90% by the kidneys [79] and have an extra-renal elimination of 15% in patients after major surgery [30, 76]. There are some limitations to the golden standard of RBF measurement using the urinary clearance technique corrected for by extraction of PAH. Swärd et al have compared the within-method error of infusion clearance for PAH to that of the urinary clearance of PAH and found that the within-method error was 16% and 33%, respectively [76]. The collection of urine is probably the main source of error using the urinary clearance technique, despite the use of urine catheters. By the use of the infusion clearance technique for PAH, urine collection can be avoided, but it requires that PAH is not metabolized and that there is an equilibrium between the rate of infusion and excretion of PAH, and that the volume of distribution of PAH is constant during the measurement. PAH extraction has repeatedly been found to be 0.67- 0.95 in patients after uncomplicated cardiac surgery [30, 76]. However, Brenner et al found that PAH extraction was decreased in patients with septic shock and acute renal impairment, something that was also demonstrated in patients with AKI after cardiac surgery by Redfors et al several years later [30, 77]. This would severely underestimate RBF in critically ill patients, if not renal vein concentration of PAH was measured and taken into account in calculating RBF in patients with sep-

tic shock. Redfors et al described that the half time of PAH in critically ill patients is four times longer than in uncomplicated postoperative patients, and hence it was concluded that the infusion clearance of PAH-technique was inappropriate for estimations of dynamic changes in RBF in critically sick patients (unpublished data presented in the thesis "Prevention and treatment of acute kidney injury after cardiac surgery").

In paper IV, the arterial concentration of PAH did not differ between the two measurement periods, neither in the septic nor in the control group, indicating that steady state, required for measurement of RBF by infusion clearance of PAH, was achieved. Since the study on septic patients did not contain any intervention after start of infusion and baseline measurements, there were no dynamic changes to be expected.

5.4.3 Estimation of GFR by filtration fraction (FF) and by renal plasma flow (RPF)

In 1951, Homer W. Smith published the textbook 'The Kidney: Structure and Function in Health and Disease', in which it was stated that glomerular filtration rate (GFR) was the best evaluation of renal function. Assessment of GFR by infusion or urinary clearance of a filtration marker, such as ^{51}CrEDTA, is by many considered to be the method of choice for clinical assessment of renal function [80, 81]. ^{51}CrEDTA is an isotope undergoing glomerular filtration, is not reabsorbed or secreted by the tubules and the extra-renal elimination is under 5%. It has recently been found that the repeatability of infusion clearance of ^{51}CrEDTA is high with a low with-in method error and a low coefficient of variation in critically ill patients, confirming it to be the method of choice also in the ICU setting [82]. However, the ^{51}CrEDTA infusion and urinary clearance techniques for estimation of GFR require equilibrium between rate of infusion and rate of excretion, i.e. steady state. However, repeated estimations of GFR at short intervals, can be performed by the renal vein thermodilution technique for measurement of the renal extraction fraction of ^{51}CrEDTA and RPF, [(RPF=RBF x (1-hematocrit)], without the requirement of a steady state. Thus, this technique allows instant and correct measurements of renal function. One issue with measurement of FF, using the renal extraction technique, is that the production of urine induces a hemoconcentration affecting also the concentration of ^{51}CrEDTA in the renal vein. This becomes incorrectly high, and the FF and GFR are therefore underestimated. To evade this error, the renal extraction of ^{51}CrEDTA has been corrected for the differences in renal vein hemoconcentration caused by diuresis.

5.4.4 Estimated GFR (eGFR)

To compare basal preoperative renal function between patients with liver failure waiting for liver transplantation, and the patients prior to cardiac surgery constituting the control group, we used the MDRD formula (Modification of Diet in Renal disease) to calculate eGFR [83]. This formula was found to best correspond to measured GFR in cirrhotic patients [84],

and is based on age, gender, ethnic origin and serum creatinine. Creatinine is a molecule derived from creatine. Creatine is produced in the liver and stored in muscle mass. Hence, the limitations of serum creatinine as a filtration marker in liver failure is mainly based on the reduced production of creatine and the decreased muscle mass in patients with liver failure [85, 86]. Hence, creatinine based formulae tends to overestimate eGFR in patients with cirrhosis, especially in patients with GFR < 60 ml/min [85]. The preoperative measured GFR was > 80 ml/min and there was no significant difference between the measured and the estimated GFR among the liver transplant recipients presented in this thesis (papers II and III).

5.5 Renal physiology in vasodilatory shock

We have studied renal hemodynamics, function and oxygenation in two different vasodilatory states, namely early after liver transplantation and in patients with early septic shock (papers II and IV). In both studies, the vasopressor norepinephrine was needed also after fluid resuscitation to evade the vasodilation and to be able to maintain a target MAP of 75 mmHg.

A common strength between the two studies discussed in this part, is the large control groups that were used in both studies. The control groups consists of patients after uncomplicated cardiac surgery and with uncompromised renal function. Several parameters are in common between the control and the studied groups, namely the presence of an inflammatory state, and moreover that all patients are sedation and mechanical ventilated in the ICU [74, 75].

5.5.1 Renal hemodynamics in vasodilatory shock

Even though liver transplantation and septic shock share the common path of a hyperdynamic circulation with a pronounced vasodilatation, our results bear witness that the renal hemodynamics contributing to the fall in GFR differs between these two conditions. GFR is partly controlled by the pressure across the glomeruli created by the balance in vascular tone of the afferent and the efferent arterioles. If the reduction in GFR is accompanied by a reduction in RBF, the most tentative cause would be a vasoconstriction of the afferent arteriole. On the contrary, if the reduction in GFR is accompanied by an increase in RBF, the cause would be assumed to be a vasodilation of the efferent arteriole.

RBF is increased, and GFR is decreased, after liver transplantation. This is presumably a result of a vasodilation of the efferent arteriole. In septic shock, on the other hand, the lower GFR is combined with, if anything, a reduced RBF and hence most likely due to a vasoconstriction of the afferent arteriole. These findings are both in contrast with previously assumed theories that the reduction in GFR in patients with liver failure is due to a vasoconstrictive reduction in RBF and an increase in RVR as presumed in HRS [87], and that AKI in septic shock is due to increased renal vasodilation and an increased RBF [45]. On

the contrary, the findings regarding septic AKI in this thesis are in line with other previously described tentative mechanisms of septic AKI, where RBF is hypothesized to be low due to renal vasoconstriction [88, 89].

Activation of the renal sympathetic nerve activity has been shown to cause a reduction in both RBF and GFR, suggesting an effect on preferentially the afferent arterioles [90], which could explain the increased renal vascular resistance in septic shock as shown in paper IV. Another explanation could be an activation of the tubulo-glomerular feedback (TGF) mechanism, caused by tubular dysfunction. This would reduce sodium reabsorption of individual tubules, increasing the sodium delivery to the macula densa, activating the TGF response, inducing afferent arteriolar vasoconstriction with a decrease in both RBF and GFR [88, 91]. This hypothesis is supported by the finding that renal extraction of PAH, an indicator of tubular function, was significantly lower in septic shock patients than in the control group in paper IV. We find the early fall in GFR, in this study unlikely to be caused by shedding of tubular cells causing tubular obstruction[88], as postmortal histopathological findings in septic AKI shows limited tubular injury [41], suggesting that the early fall in GFR in clinical sepsis is functional rather than structural in nature. It is not likely, however, that TGF plays any major role in the mechanism causing the fall in GFR after liver transplantation, since RVR was lower and RBF higher when compared to the control group.

An interesting renal hemodynamic variable in the two hyperdynamic states of post liver transplantation and septic shock, is the ratio between RBF and cardiac index, i.e. the relationship between systemic and renal blood flow. This ratio, RBF/CI, is reduced in the states of vasodilatory shock studied here, indicating that blood flow is directed away from the kidneys in vasodilatory shock. In septic shock, CI did not differ between the study and the control group, and the reduced RBF/CI could be caused by the afferent arteriolar vasoconstriction mediated by an increase in renal sympathetic nerve activity and/or TGF, resulting in the reduced RBF. In liver recipients, on the other hand, both CI and RBF were increased compared to the control group, hence the reduced RBF/CI is more likely caused by the greater increase in CI than in RBF. This could be the result of altered renal haemodynamics seen in liver failure, i.e. an increased renal vasoconstriction as a result of splanchnic vasodilation, and a neurohormonal response resulting in renal vasoconstriction, without which RBF might have increased enough not to cause a reduction in RBF/CI (fig 8). Since the patients in both studied groups were treated with norepinephrine to treat the vasodilatory shock state, and since norepinephrine has been shown to decrease RBF in healthy volunteers [64, 65], one could argue that the norepinephrine could be at least partly responsible for the redistribution of blood away from the kidneys. However, it has been proven that GFR, renal oxygen delivery and renal oxygenation are improved by restoring MAP to 75 mmHg by the use of norepinephrine in vasodilatory shock [30].

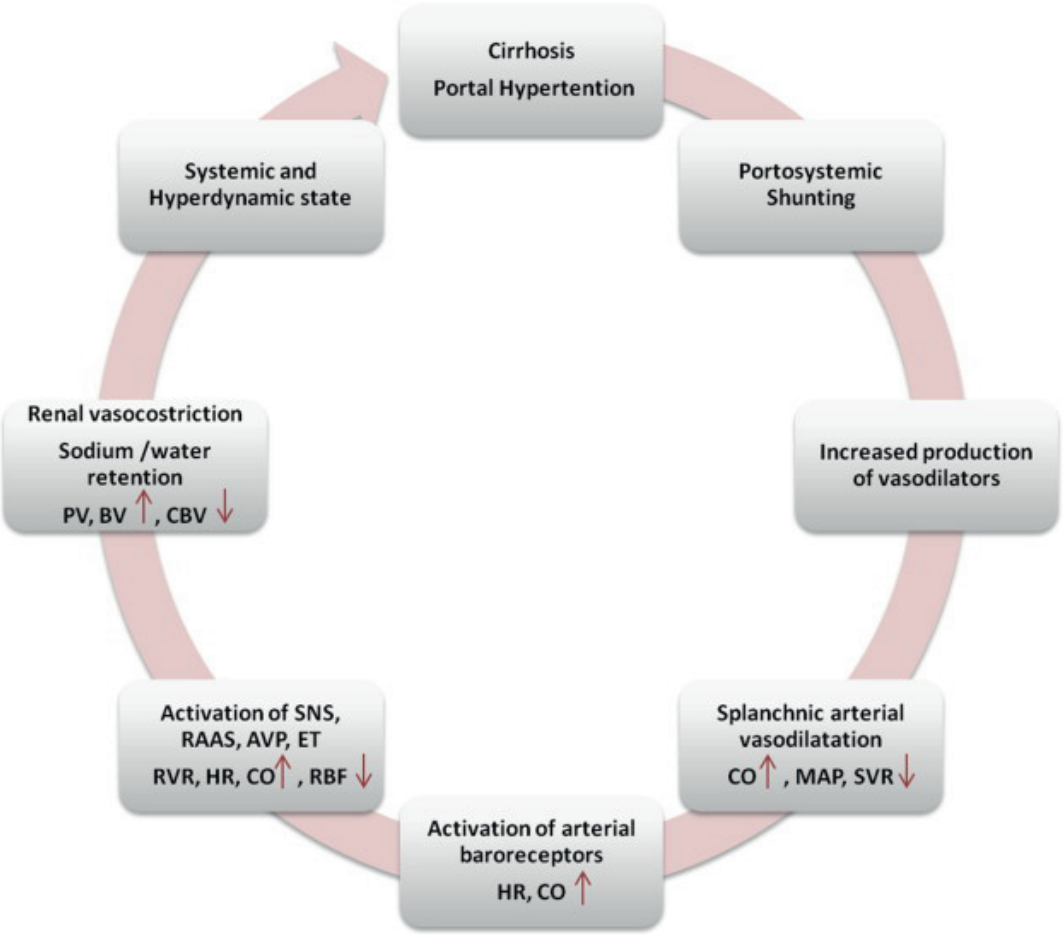

Fig 8. Mechanisms leading to hyperdynamic circulation in hepatic failure. Two hypotheses are advanced to explain the mechanism leading to hyperdynamic circulation: The humoral includes an overproduction of circulating vasodilators (intestinal or systemic); vasodilators escaping the degradation in the diseased liver or bypassing the liver through the porto-systemic shunts; a reduction in vasoconstrictors, and an increase in vasodilators. Porto-systemic vessels allow gut-derived humoral substances, such as glucagon, bile acid and calcitonin gene-related peptide to enter into the systemic circulation. The neural dysregulation hypothesis suggests that chemoreceptors and baroreceptors of the mesenteric area are activated by PH, and signals are related to central cardiovascular-regulatory nuclei via afferent nerves. (CBV: central blood volume; HVPG: hepatic vein portal gradient; CO: cardiac output ; HR: heart rate; PV: plasma volume; BV: blood volumes; RVR: renal vascular resistance; RBF: renal blood flow; SVR: systemic vascular resistance; MAP: mean arterial blood pressure; SNS: sympathetic nervous system; RAAS: renin–angiotensin–aldosterone system; AVP: arginine vasopressin; ET: endothelin).

5.5.2 Renal oxygenation in vasodilatory shock

The kidneys have a high energy demand and oxygen requirements, particularly the outer portion of the medulla, due to the reabsorptive processes. In addition, this region has, relative to the cortex, a low blood supply. Thus, the medulla is on the verge of being ischaemic already under normal conditions. This makes the kidneys sensitive to hypoxaemic injury. Renal oxygenation is the balance between renal oxygen supply

and demand. Renal oxygen supply is dependent on RBF and arterial oxygen content, while RVO_2, to a large extent (60-80%), is dependent on tubular reabsorption of sodium. There is a verified close relationship between GFR, tubular sodium reabsorption and RVO_2, both in postoperative patients and, as shown previously by our study group and now in paper II in this thesis, after liver transplantation [36, 37, 69, 92]. The higher the glomerular filtration of sodium, the higher the tubular sodium reabsorption and RVO_2. Thus, GFR is in general the major determinant of RVO_2.

In this thesis, there was a disconnection between renal function (GFR) and oxygen consumption, with an increased RVO_2 despite a decreased GFR and sodium reabsorption, with a resulting mismatch in renal oxygen supply/demand relationship, both after liver transplantation and in septic shock. This results in an increased renal oxygen extraction, a direct measure of renal oxygen supply/demand relationship and hence an impaired renal oxygenation in these two vasodilatory states. However, after liver transplantation, the pathophysiology of the impaired oxygenation seems to be of a different nature than in septic shock, since renal oxygen consumption was increased which was not seen in septic shock. Moreover, there was a significant increase of 2.7 times in renal oxygen consumption per reabsorbed molecule of sodium in liver recipients. This could either be caused by a tubular injury and a subsequent inefficient tubular sodium transport, as demonstrated by our group in a previous study on renal effects in early ischemic AKI [36], or by an increased oxygen requirement for basal renal metabolism. This latter explanation is plausible since extrapolation of the regression lines in fig 7 shows that the presumed oxygen consumption at GFR of 0 ml/min is increased after liver transplantation compared to after cardiac surgery. The explanation to this is unclear, however it is not likely to be a generalized systemic increase in oxygen requirements since systemic oxygen consumption was equal between the groups. The ensuing impairment in renal oxygenation, in turn, most likely gives rise to an ischemic tubular injury, presumably originating from the renal medulla where oxygen tension is low even under normal conditions, since it has previously been shown that tubular injury markers are elevated early after liver transplantation [93-95]

The impaired renal oxygenation in patients with septic vasodilated shock seems to have another explanation than after liver transplantation. Since there was no difference between the septic and the control group regarding renal oxygen consumption, but instead a significant and pronounced reduction in RBF/CI and hence in renal oxygen delivery in the septic group, the main cause of the impaired renal oxygenation in septic shock seems to be due to renal vasoconstriction and a redistribution of blood flow away from the kidneys. In septic shock, hypotension is caused by an increased production of nitric oxide (NO) [48-51]. Based on animal studies, it has been suggested that the hypotension

elicits an elevation of plasma norepinephrine levels and an increase in renal sympathetic nerve activity, which however has been suggested to be overridden by the profound increase in NO, resulting in a net renal vasodilation [52-54]. The redistribution of renal blood flow presented in this thesis in patients with clinical sepsis, is most likely due to an increased tone of the afferent arteriole, since there is a reduction in both RBF and GFR. This is most likely caused by an increase in renal sympathetic nerve activity overriding the NO-induced vasodilation, resulting in a renal vasoconstriction. These findings and the interpretation presented in Paper IV is hence in contrast to the previously described pathophysiology in experimental septic AKI. Another tentative explanation to the renal afferent vasoconstriction could be a tubular dysfunction, resulting in a reduced sodium reabsorption and a subsequent activation of TGF causing a vasoconstriction of the renal afferent arteriole [88, 96]. This hypothesis is supported by the finding that renal extraction of PAH, an indicator of tubular function, was lower among patients with septic shock than in the control group. Moreover, we found that urinary N-acetyl-β-D-glucosaminidase (NAG)/creatinine, a marker for tubular injury, was elevated in early clinical septic shock compared to the urinary NAG/creatinine in anesthetized mechanically ventilated patients with normal renal function [97], suggesting tubular injury in early clinical septic shock.

There is an impairment of tubular oxygen utilization, manifested as an increased oxygen consumption per mmol reabsorbed sodium, both in septic shock and after liver transplantation. There could be several explanations to the impaired renal oxygen utilization in vasodilatory shock. One explanation could be a hypoxia-induced loss of epithelial cell polarization and tight junction integrity, leading to a possible leakage of sodium back to the tubuli. Another explanation could be a reduced renal production of NO that would cause an increase in RVO_2, although this theory is less likely in septic shock since there was no difference in RVO_2 between the groups. Yet another explanation to the impaired oxygen utilization in septic shock and after liver transplantation could be a reaction to oxidative stress, giving rise to an increased mitochondrial oxygen consumption. The increased oxygen consumption for basal renal metabolism seen after liver transplantation could be a reaction to reactive oxygen species (ROS) that are released at reperfusion of the liver graft, causing an oxidative stress known to increase mitochondrial oxygen consumption [98]

5.6 Measures to minimize the risk of renal harm in vasodilatory states

Impaired oxygenation is thus a major cause of renal failure after major surgery and in septic shock. Since oxygenation is dependent on oxygen delivery and consumption, one could try either to increase oxygen delivery, or to decrease oxygen consumption to

improve renal oxygenation. Postoperative hypovolemia is commonly treated with i.v. fluids, such as colloids and crystalloids, as a measure to preserve organ perfusion, and hence oxygen delivery, despite perioperative blood loss.

5.6.1 Renal oxygen delivery by plasma volume expansion

Plasma volume expansion with fluids increases cardiac output and RBF, but at the same time i.v. fluids can cause a haemodilution and a decreased arterial oxygen content that could counteract the positive effect on renal oxygen delivery. This has been demonstrated in several animal studies [99, 100], and this was also the case in paper I, where plasma volume expansion with both crystalloid and colloid fluid after uncomplicated surgery resulted in an increased CI and RBF, but with no net effect on renal oxygen delivery using any of the fluids. GFR, the major determinant of sodium reabsorption, and hence of RVO_2, was increased using crystalloid for plasma volume expansion. It is evident that this increase in GFR was not met by a sufficient increase in RBF, since FF was increased, supporting the finding of an increased renal oxygen extraction and a mismatch in renal oxygen supply/demand using a bolus of crystalloid for plasma volume expansion. This finding is in line with an experimental study showing decreased renal microvascular oxygenation using crystalloid fluid for normovolemic haemodilution, compared to colloid that maintained renal oxygenation [101]. The explanation to the mismatch in renal oxygen balance with crystalloid, in addition to hemodilution, is that renal blood flow is redistributed away from the kidneys, as demonstrated by the reduction in the ratio RBF/CI, which points at an insufficient increase in RBF compared to the increase in CI, GFR and RVO_2, which was not seen with the colloid.

A bolus dose of colloid fluid had a more persistent effect on renal hemodynamics than crystalloid, but did not improve renal function, as demonstrated by the unchanged GFR over time. Hence, the sodium reabsorption and the oxygen consumption were unaffected by the bolus of colloid, and renal oxygenation was preserved.

The effect of the colloid solution on plasma volume expansion endured for at least 60 minutes, as demonstrated by the persistent rise in filling pressures and CI. However, since the distribution half-time is short for crystalloid solutions (8-10 min) [102, 103], the effect of a bolus dose of Ringer's solution is more transient, and the effect on plasma volume expansion declined already after 60 minutes. To maintain the effect on plasma volume expansion after a crystalloid bolus, it has to be repeated, with a repeated impairment of renal oxygenation in already hypovolemic patients. Another way could be to use a larger dose of the crystalloid to induce a more pronounced increase in CI, RBF and renal oxygen delivery. However, this would induce an increased haemodilution with potentially no effect on RDO_2, and potentially an even higher RVO_2 since the haemodilution decreases oncotic pressure in the glomeruli resulting

in a higher GFR and hence a higher RVO_2. This would induce a lower renal oxygen supply/demand ratio and a worsened renal oxygenation.

5.6.2 Renal oxygen delivery by blood pressure targeting

RBF and GFR are maintained constant despite fluctuations in MAP, within certain limits of MAP by renal autoregulatory changes in the tone of the afferent arterioles [104, 105]. At MAP levels below the lower limit of autoregulation, RBF and GFR becomes pressure-dependent and both therefore decrease. RDO_2 is hence reduced and ischemic AKI may develop. Hypotension has been found to be more common in patients who develop in-hospital AKI than in patients that do not [106], and MAP has been recommended to be kept >65 mmHg in states of vasodilatory shock [107]. However, it has been found that a higher MAP than the recommended level of 65 mmHg could be necessary to avoid reduction in renal function in patients in shock, especially of septic origin [108].

Perioperative MAP has in several studies been found to have an impact on postoperative AKI [109, 110]. It has not previously been evaluated whether the level of MAP matters in the vasodilatory shock seen in liver transplantation. In 2016, Mizota et al found that the lowest intraoperative blood pressure during liver transplantation was an independent risk factor for postoperative AKI, even if the duration of hypotension, i.e. MAP <50 mmHg, was very short and regardless of the high CI seen in liver recipients [111]. Splanchnic vasodilation and increased NO levels in combination with intraoperative inflammatory substances released at reperfusion of the liver graft, results in the hyperdynamic vasodilated state of shock seen in liver recipients. The splanchnic vasodilation and relative central hypovolemia induces a release of vasoconstrictive substances and an altered renal circulation [112-115]. These findings are reproduced in this thesis, where liver graft recipients had a redistribution of RBF away from the kidneys, as demonstrated by the lower RBF/CI in liver recipients compared to the control group. One could argue that the redistribution of blood away from the kidneys could be caused by the vasopressor norepinephrine itself. This is however highly unlikely since RVR was unaffected by the increase in infusion rate of norepinephrine at increasing target MAP from 60 to 75 mmHg. This has previously been shown in postoperative patients with norepinephrine-treated vasodilatory shock [30].

In paper III, target MAP was randomly set to 60, 75 and 90 mmHg, respectively, in normovolemic patients after liver transplantation, by changing the infusion rate of the vasopressor norepinephrine. Since RBF and GFR both increased on increasing MAP from 60 to 75 mmHg, but without any effect on RVR, renal autoregulation seems to be lost at MAP lower than 75 mmHg after liver transplantation. Increasing MAP from 75 to 90 mmHg did only induce an increase in RVR and no further effect on either GFR, RBF or FF. Hence, RVR is most likely controlled mainly by the autoregulatory afferent vaso-

constriction in liver recipients and to a lesser exten by norepinephrine itself [116]. At restoring target MAP from 60 to 75 mmHg, there was an increase in RDO_2 due to the increase in RBF. At the same time, there was an increase in GFR, leading to an elevated RVO_2. However, the increase in RVO_2 was well matched by the increase in RDO_2, leaving renal oxygenation intact despite the better renal function at MAP 75 compared to MAP 60 mmHg.

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CONCLUSION

- Postoperative plasma volume expansion with both crystalloid and colloid increase renal blood flow with no effect on renal oxygen delivery, this because of haemodilution.

- The crystalloid-induced increase in GFR was associated with impaired renal oxygenation, which was not seen with a colloid fluid as plasma volume expander.

- After liver transplantation, vasodilation of the efferent arterioles causes a renal vasodilation and a fall in GFR.

- Renal oxygen consumption is considerably increased early after liver transplantation, despite the lower GFR.

- The increased renal blood flow seen after liver transplantation is not sufficient to meet the increased renal metabolic demand, resulting in impaired renal oxygenation.

- Early after liver transplantation, a target mean arterial pressure of 75 mmHg, compared to 60 mmHg, improves renal perfusion and function without impairing renal oxygenation.

- In early clinical septic shock, there is a fall in GFR and renal oxygen delivery caused by a constriction of afferent arterioles.

- In early clinical septic shock, sodium is reabsorbed at a high oxygen cost, which together with reduced oxygen delivery impairs renal oxygenation, causing renal tubular injury.

FUTURE PERSPECTIVES

In paper I it was shown that a bolus infusion of a crystalloid impairs renal oxygenation. It would be interesting to perform a randomised trial comparing volume resuscitation with crystalloid and a colloid, other than hydroxiethylstarch, on renal outcome in major surgery and critical illness

The use of the vasopressin-analogue terlipressin could be an alternative approach to treat systemic vasodilation during and after liver transplantation. Mukhtar et al found that terlipressin improved renal function, as serum levels of creatinine and cystatin C significantly decreased during the two first postoperative days after liver transplantation [117]. However, in a pharmacodynamic study on uncomplicated post-cardiac surgery patients, Bragadottir et al analyzed the renal effects of vasopressin and found that vasopressin induces a vasoconstriction of the efferent arterioles causing an increase in GFR and RVO_2 but a decrease in renal blood flow [69]. Thus, vasopressin caused an impairment of renal oxygenation, as demonstrated by an increase in renal oxygen extraction, suggesting that the use of vasopressin in liver transplantation might be a two-edged sword. The effects of vasopressin/terlipressin on renal perfusion, filtration and oxygenation in patients undergoing liver transplantation needs to be investigated.

Since the reduction in GFR after liver transplantation is evident and profound immediately after the operation, it would be highly interesting to assess renal perfusion, filtration and oxygenation perioperatively, measuring RBF, GFR and oxygenation prior to and after the anhepatic phase.

It would also be interesting to study the renal effects of atrial natriuretic peptide (ANP), both in early clinical sepsis and after liver transplantation. ANP has been shown to increase GFR, by afferent areriolor vasodilation, in acute kidney injury after cardiovascular surgery. Can ANP improve renal outcome in sepsis and after liver transplantation?

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FORMULAE

1. The formula to calculate RBF_{TD}, corrected to body surface area (BSA). Subscript denotes internal thermistor (ind=indicator measurements) or external thermistor (blood = blood measurements). Superscript denotes calibration (cal) or registration signal.

$$RBF_{TD} = \frac{1.73}{BSA}\left(2 \times 53.7\left(\frac{\left(\frac{1000 \times \Delta T_{ind}^{reg}}{\Delta T_{ind}^{cal} \times K_{ind}}\right)}{\left(\frac{1000 \times \Delta T_{blood}^{reg}}{\Delta T_{blood}^{cal} \times K_{blood}}\right)} - 1\right) + UF\right)$$

2. Calculations for renal data

$$RVR = \frac{MAP - CVP}{RBF}$$

$$RVO_2 = RBF\left(C_aO_2 - C_{rv}O_2\right)$$

$$RO_2Ex = \frac{C_aO_2 - C_{rv}O_2}{C_aO}$$

$$FF = \frac{RPF \times \left[{}^{51}CrEDTA_a\right] - \left(RPF - UF\right) \times \left[{}^{51}CrEDTA_{rv}\right]}{RPF \times \left[{}^{51}CrEDTA_a\right]}$$

$$GFR = RPF \times FF$$

$$Na^+ filtration = S_{Na} \times GFR$$

$$Na^+ reabsorption = S_{Na} \times GFR - UF \times U_{Na}$$

$$FE_{Na} = \frac{UF \times U_{Na}}{S_{Na} \times GFR}$$

3. The formula to calculate RPF by infusion clearance of PAH.

$$RPF_{IC} = \frac{1.73}{BSA} \times \frac{0.85 \times PAH_{amount/\min}}{\left[PAH_a\right] - \left[PAH_{rv}\right]}$$

FORMULAE ABBREVIATIONS

Abbreviations for additional renal calculations. RVR, renal vascular resistance; CaO_2, arterial oxygen content; $CrvO_2$, renal vein oxygen content; RVO_2, renal oxygen consumption; RO_2Ex, renal oxygen extraction; FF, filtration fraction, [^{51}CrEDTAa], arterial concentration of ^{51}CrEDTA; [^{51}CrEDTArv], renal vein concentration of ^{51}CrEDTA; Na^+filtration, renal sodium filtration; Na^+ reabsorption, renal sodium reabsorption; SNa, serum sodium concentration; UF, urine flow; UNa, urine sodium concentration; FENa, fractional excretion of sodium.

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PAPERS I-IV

PAPER I

J. Skytte Larsson, G. Bragadottir, V. Krumbholz, B. Redfors, J. Sellgren and S.-E. Ricksten.

Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid vs colloid.

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Clinical Practice

Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid *vs* colloid

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Abstract

Background: In the present randomized study, we evaluated the differential effects of a colloid and a crystalloid fluid on renal oxygen delivery (RD_{O_2}), glomerular filtration (GFR), renal oxygen consumption ($R\dot{V}O_2$), and the renal oxygen supply–demand relationship (i.e. renal oxygenation) after cardiac surgery with cardiopulmonary bypass.

Methods: Thirty patients with normal preoperative renal function, undergoing uncomplicated cardiac surgery, were studied in the intensive care unit in the early postoperative period. Patients were randomized to receive a bolus dose of either a crystalloid (Ringers-acetate® 20 ml kg^{-1}, *n*=15) or a colloid solution (Venofundin® 10 ml kg^{-1}, *n*=15). Systemic haemodynamics were measured via a pulmonary artery catheter. Renal blood flow and GFR were measured by the renal vein retrograde thermodilution technique and by renal extraction of ^{51}Cr-EDTA (=filtration fraction). Arterial and renal vein blood samples were obtained for measurements of renal oxygen delivery (RD_{O_2}) and $R\dot{V}O_2$. Renal oxygenation was estimated from the renal oxygen extraction.

Results: Despite an increase in cardiac index and renal blood flow with both fluids, neither of the fluids improved RD_{O_2}, because they both induced haemodilution. The GFR increased in the crystalloid (28%) but not in the colloid group. The crystalloid increased the filtration fraction (24%) and renal oxygen extraction (23%), indicating that the increase in GFR, the major determinant of $R\dot{V}O_2$, was not matched by a proportional increase in RD_{O_2}.

Conclusions: Neither the colloid nor the crystalloid improved RD_{O_2} when used for postoperative plasma volume expansion. The crystalloid-induced increase in GFR was associated with impaired renal oxygenation, which was not seen with the colloid.

Clinical trial registration: NCT01729364.

Key words: colloids; crystalloids; glomerular filtration rate; plasma volume expansion; postoperative treatment; renal blood flow; renal oxygen consumption and oxygenation

Acute kidney injury (AKI) after cardiac surgery with cardiopulmonary bypass continues to be a significant cause for morbidity and mortality. Depending on the complexity of the procedure, the incidence of postoperative AKI, defined as an increase of serum creatinine by >50%, ranges between 15 and 30%.[1–4] Dialysis-dependent AKI, occurring in 2–5% of cardiac surgery patients,

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Editor's key points

- Acute kidney injury is one major postoperative complication after cardiac surgery with cardiopulmonary bypass, and it is not known whether or not there are differences in renal oxygen delivery between plasma volume expansion with crystalloid and colloid.
- In a randomized design, effects on renal oxygen delivery and other renal factors were compared between plasma volume expansion with crystalloid and colloid.
- Neither colloid nor crystalloid improved renal oxygen delivery, but crystalloid, but not colloid, increased the GFR with impaired renal oxygenation.

carries a mortality between 50 and 80% and is associated with high hospital costs.[5–7] Furthermore, increasing evidence suggests that a minor elevation in serum creatinine after cardiac surgery is an independent risk factor for increased mortality and for prolonged stay in the intensive care unit and in hospital.[6 8 9]

The pathogenesis of cardiac surgery-associated AKI involves a variety of pathways.[10] Impaired renal oxygen delivery (RD_{O_2}), causing ischaemic tubular cell injury, has been considered to be one of the main mechanisms underlying postcardiac surgery AKI.[11] A decreased oxygen delivery may be caused by haemodilution-induced anaemia and intraoperative hypotension together with low postoperative cardiac output, in turn caused by heart failure or hypovolaemia.[3 12–14] The renal medulla, particularly the outer portion, is on the verge of hypoxia even in normal conditions. This is caused by the high utilization of oxygen of the medullary thick ascending limb and a relative medullary hypoperfusion, when compared with the cortex. The outer portion of the renal medulla is therefore particularly sensitive to impaired RD_{O_2}.[15]

I.V. fluids, such as colloids or crystalloids, are commonly used for treatment of postoperative hypovolaemia after cardiac or other major surgery, to prevent or ameliorate early AKI.[16] However, even though i.v. fluids may increase cardiac output and renal blood flow (RBF), they will also decrease arterial oxygen content by haemodilution, with potentially no or minor beneficial net effects on RD_{O_2}. Indeed, recent animal studies have shown that colloids or crystalloids do not increase RD_{O_2} despite increases in cardiac output and that crystalloids, in contrast to colloids, may impair regional renal microvascular oxygenation.[17 18]

To our knowledge, the effects of i.v. fluids on RD_{O_2} and renal oxygenation have not been studied in postoperative patients after major surgery. Furthermore, perioperative data on the differential effects of crystalloids *vs* colloids with respect to RBF, RD_{O_2}, glomerular filtration rate (GFR), renal oxygen consumption ($R\dot{V}O_2$), and renal oxygenation, defined as the renal oxygen supply–demand relationship, are lacking. We therefore performed a randomized study to evaluate the differential renal effects of bolus doses of a crystalloid and a colloid. In the present study, we tested the null hypothesis that there is no difference between a crystalloid and a colloid with respect to changes in RD_{O_2} and renal oxygenation after major surgery.

Methods

Patients

The study protocol was approved by the Gothenburg Regional Ethics Committee (www.epn.se). Written informed consent was obtained from each patient before the operation. The study was registered in ClinicalTrials.gov, identifier: NCT01729364. The inclusion criteria were as follows: (i) age >18 yr; (ii) elective coronary artery bypass surgery with cardiopulmonary bypass; (iii) preoperative normal serum creatinine; (iv) left ventricular ejection ≥40%; and (v) attainment of target levels of central venous pressure (5–10 mm Hg), mean arterial pressure (MAP; >70 mm Hg), and mixed venous oxygen saturation (Sv_{O_2}: >60%) before randomization, according to our local clinical treatment protocol. The exclusion criteria were as follows: (i) combined cardiac surgery procedures; (ii) excessive postoperative bleeding (>100 ml h^{-1}); (iii) intra- or postoperative need for inotropic or vasoactive support or diuretics (furosemide, mannitol); or (iv) hypotension because of arrhythmias.

Premedication consisted of oxazepam (10 mg) and oxycodone (10 mg). Anaesthesia was induced by fentanyl (5–10 μg kg^{-1}) and propofol (1–1.5 mg kg^{-1}). Before and after cardiopulmonary bypass, anaesthesia was maintained with sevoflurane (0.5–2.5%) in a 50% O_2–air mixture. During cardiopulmonary bypass, anaesthesia was maintained with an i.v. infusion of propofol (2–4 mg kg^{-1} h^{-1}). The pump was primed with acetated Ringer's solution (1300 ml) without mannitol. Normothermic, non-pulsatile cardiopulmonary bypass was performed at a flow of 2.4 litres min^{-1} m^{-2} and a target haematocrit of 20–25%. In the intensive care unit, the patients were sedated with propofol (1.5–3.6 mg kg^{-1} h^{-1}) and morphine (0.5–1 mg h^{-1}) and mechanically ventilated.

Systemic haemodynamics

Arterial blood pressure was measured continuously via a radial or femoral artery catheter. A pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was used for measurements of central venous pressure, pulmonary artery and wedge pressures and cardiac output. Bolus measurements of thermodilution cardiac output were performed in triplicate and indexed to the body surface area for cardiac index (CI). Systemic vascular resistance index, pulmonary vascular resistance index, and stroke volume index (SVI) were calculated according to standard formulae.

Measurements of renal variables

An 8 Fr catheter (Webster laboratories, Baldwin Park, CA, USA) was introduced into the left or right renal vein, via the right femoral vein under fluoroscopic guidance. The catheter was placed in the central portion of the renal vein, with the position being confirmed by venography using ultra-low doses of iohexol, 5–15 mg I kg^{-1} (Omnipaque 300 mg I ml^{-1}; GE Healthcare, Stockholm, Sweden). Renal blood flow was measured in duplicate by the continuous retrograde thermodilution technique.[19–22] At the end of each urine collection period, the bladder was rinsed with 100 ml of sterile water. After the collection of blood and urine blanks, an i.v. priming dose of chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA; GE Healthcare, Amersham, UK) was given, followed by an infusion at a constant rate, individualized to body surface area and preoperative serum creatinine. Serum ^{51}Cr-EDTA activity from arterial and renal vein blood was measured using a well counter (Wizard 3', 1480, Automatic gamma counter; Perkin Elma LAS, Turkuu, Finland).

Experimental procedure

The experimental procedure was performed 4–6 h after the end of cardiopulmonary bypass when the patients had a stable body

temperature >36°C. The patients were sedated and mechanically ventilated during the whole experimental procedure and were randomized to receive either a crystalloid (20 ml kg^{-1}, Ringer-acetate®; Fresenius Kabi, Uppsala, Sweden) or a colloid solution (10 ml kg^{-1}, hydroxyethylstarch 60 mg ml^{-1}, 130/0.62, Venofundin®; B. B. Braun, Melsungen, Germany). After an equilibration period of at least 60 min, two 30 min urine collection control periods (periods C1 and C2) were started. The investigational fluid was then administered during 20–30 min. Thermodilution measurements of RBF and CI were conducted, and blood and urine samples were obtained at 20, 40 and 60 min after the end of the fluid administration. Formulae for calculation of the various renal variables are shown in Table 1. All renal data were normalized to a body surface area of 1.73 m^2.

Statistical analysis

To detect a relative difference of 25% in RD_{O_2} or renal oxygen extraction with a power of 80% and a two-sided significance level of 0.05, at a standard deviation of 24 ml min^{-1} and 0.024, respectively, 30 patients would be required (15 patients in each group), based on data from a previous study.[23] To compensate for drop-outs, we aimed to include ~40 patients. Intragroup effects of the colloid and crystalloid solutions, respectively, were determined by one-way ANOVA for repeated measurements. Differences between groups were compared using an analysis of covariance (ANCOVA) for repeated mesurements, using the mean of the two baseline measurements (C1 and C2) as a covariate. This statistical approach adjusts for baseline differences between groups. Categorical data were compared using Fisher's exact test. A *P*-value <0.05 was considered significant. PASWStatistics 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Data are presented as mean and standard deviation (SD) of the mean.

Results

Informed consent was obtained from 39 patients the day before surgery. The clinical trial profile is shown in Figure 1. Thirty patients were randomized after renal vein catheterization to receive either a colloid (*n*=15) or a crystalloid solution (*n*=15). There were no significant differences between the two groups with respect to preoperative characteristics, as presented in Table 2. There were no significant differences between the groups at baseline (C1 and C2), before fluid administration, in any of the measured or calculated variables (Tables 3 and 4).

Table 1 Formulae for calculation of renal variables. Ca_{O_2} and Crv_{O_2}, arterial and renal vein oxygen contents; CVP, central venous pressure; MAP, mean arterial pressure; $[Na^+]_s$, serum sodium concentration; $[Na^+]_u$, urine sodium concentration

Variable	Formula
Renal blood flow (RBF)	(unilateral renal vein blood flow×2)+urine flow
Renal plasma flow (RPF)	RBF×(1−haematocrit)
Filtration fraction (FF)	{RPF×[^{51}Cr-EDTA arterial]−(RPF−urine flow)×[^{51}Cr-EDTA renal vein]}/(RPF×[^{51}Cr-EDTA arterial])
Glomerular filtration rate (GFR)	FF×RPF
Renal vascular resistance (RVR)	(MAP−CVP)/RBF
Arterial–renal vein (rv) oxygen content difference ($RAVO_2$-diff)	$(Ca_{O_2} - Crv_{O_2})$
Renal oxygen consumption ($R\dot{V}O_2$)	RBF×$(Ca_{O_2} - Crv_{O_2})$
Renal oxygen extraction	$(Ca_{O_2} - Crv_{O_2}/Ca_{O_2})$
Renal sodium filtration	GFR×$[Na^+]_s$
Renal sodium excretion	Urine flow×$[Na^+]_s$
Renal sodium reabsorption	(GFR×$[Na^+]_s$)−(Urine flow×$[Na^+]_u$)

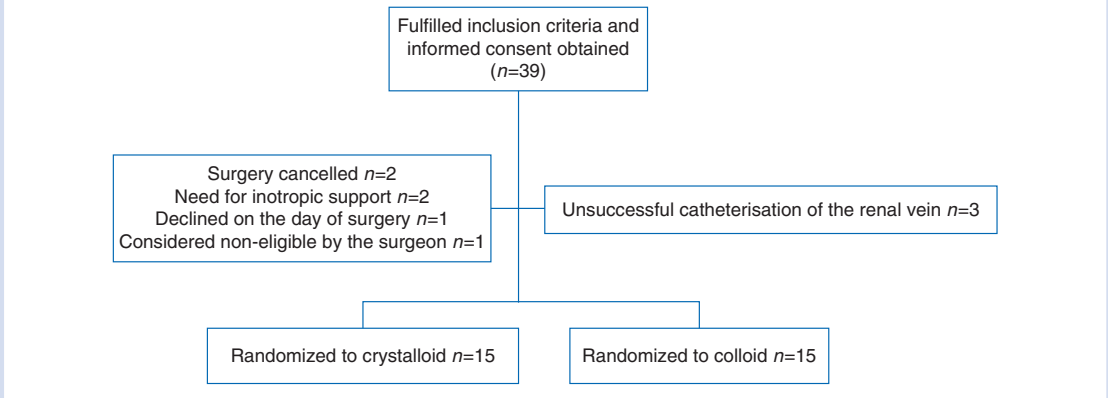

Fig 1 Clinical trial profile.

Table 2 Patient characteristics. Values are means (SD). ACE inhibitor, angiotensin-converting enzyme inhibitor; CPB, cardiopulmonary bypass

Characteristic	Crystalloid	Colloid
Number of patients (*n*)	15	15
Female [*n* (%)]	3 (14)	1 (7)
Age (yr)	68 (43–80)	66 (48–83)
Weight (kg)	78.8 (11.2)	78.3 (9.4)
Body surface area (m^2)	2.08 (0.47)	1.94 (0.14)
Left ventricular ejection fraction (%)	57 (8)	57 (6)
Hypertension [*n* (%)]	6 (39)	11 (73)
Preoperative serum creatinine (μmol $litre^{-1}$)	80 (10)	81 (12)
Postoperative serum creatinine (μmol $litre^{-1}$)	72 (13)	76 (15)
β-Adrenergic blocker [*n* (%)]	11 (73)	14 (93)
ACE inhibitor [*n* (%)]	7 (47)	5 (33)
Calcium antagonist [*n* (%)]	4 (27)	3 (21)
Diuretics [*n* (%)]	2 (13)	2 (13)
CPB time (min)	66 (17)	75 (19)
Aortic cross-clamp time (min)	40 (17)	48 (15)

Effects of i.v. fluids on systemic haemodynamics, arterial oxygen content, and systemic oxygen delivery (Table 3)

As expected, both fluids induced haemodilution, with significant decreases in haematocrit and Ca_{O_2}. There was a peak 9% increase in MAP at 20 min after the end of fluid infusion in the crystalloid group, after which MAP declined towards baseline. In the colloid group, there was a consistent 12–15% increase in MAP. A 16–18% peak increase in CI and SVI were seen after 20 min in the crystalloid group, followed by a decline towards baseline. In the colloid group, there was a consistent 18–23% increase in CI and SVI. An increase in CI of >10% was seen in 12 of 15 patients in the crystalloid group and 13 of 15 patients and colloid group, and 11 of 15 patients in both groups increased their CI by >15%. Left- and right-sided filling pressures increased, systemic vascular resistance index decreased, and heart rate was unaffected by the two fluids. There was a transient 10% increase in systemic oxygen delivery index in the crystalloid group at 40 min, whereas systemic oxygen delivery index was not affected in the colloid group.

Crystalloid *vs* colloid

The decrease in haematocrit and arterial oxygen content was significantly greater after the fluid bolus administration in the colloid group. The increase in MAP was not significantly different between groups. The increase in CI was significantly higher in the colloid group, while changes in SVI or heart rate did not differ between groups. The increases in left- and right-sided filling pressures and mean pulmonary artery pressure were significantly higher in the colloid group during the experimental procedure. Increases in systemic oxygen delivery index and decreases in systemic vascular resistance index after fluid administration did not differ significantly between groups.

Effects of i.v. fluids on renal variables (Table 4)

There was a transient 9% increase in RBF at 20 min in the crystalloid group, whreas there was a more consistent 11–17% increase in RBF in the colloid group. The ratio between RBF and CI (RBF/CI)

Table 3 Systemic variables. Values are mean (SD). ANCOVA, between-groups analysis of variance with baseline as a covariate; ANOVA, within-group analysis of variance; Ca_{O_2}, arterial oxygen content; CI, cardiac index; CVP, central venous pressure; DO_2I, systemic oxygen delivery index; Hct, arterial haematocrit; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index (in dyn s cm^{-5} m^{-2})

Variable	Crystalloid				One-way ANOVA	Colloid				One-way ANOVA	ANCOVA crystalloid *vs* colloid
	Baseline	20 min	40 min	60 min	P-value	Baseline	20 min	40 min	60 min	P-value	P-value
MAP (mm Hg)	77.5 (10.1)	84.8 (13.0)	80.7 (10.7)	80.0 (10.3)	0.015	74.1 (13.2)	85.4 (12.0)	83.1 (14.2)	83.7 (14.3)	<0.001	0.112
CI (litres min^{-1} m^{2-1})	2.49 (0.53)	2.88 (0.64)	2.85 (0.67)	2.65 (0.61)	<0.001	2.63 (0.59)	3.24 (0.45)	3.21 (0.47)	3.17 (0.47)	<0.001	0.010
HR (beats min^{-1})	74.5 (10.5)	73.8 (10.6)	75.0 (10.9)	73.5 (10.3)	0.286	75.3 (11.8)	77.7 (9.5)	77.5 (9.1)	77.1 (10.0)	0.065	0.067
SVI (ml $beat^{-1}$ m^{-2})	33.6 (6.6)	39.5 (8.7)	38.3 (8.5)	36.3 (8.1)	<0.001	35.3 (7.5)	42.1 (6.5)	41.7 (5.6)	41.5 (5.8)	<0.001	0.103
SVRI (units)	2346 (759)	2189 (820)	2135 (841)	2246 (747)	0.028	2154 (741)	1875 (463)	1850 (513)	1892 (490)	<0.001	0.139
PCWP (mm Hg)	9.8 (2.8)	12.7 (3.2)	11.1 (3.4)	11.1 (2.9)	<0.001	9.5 (2.9)	14.9 (3.4)	14.3 (3.0)	13.9 (3.1)	<0.001	0.001
CVP (mm Hg)	8.7 (3.1)	11.0 (3.9)	10.3 (3.9)	10.2 (3.5)	<0.001	7.1 (2.1)	11.4 (2.5)	10.8 (2.4)	10.6 (2.3)	<0.001	0.001
MPAP (mm Hg)	18.1 (3.4)	20.9 (5.1)	21.2 (5.4)	19.8 (4.7)	<0.001	17.7 (3.1)	24.1 (4.1)	22.9 (4.0)	22.5 (3.8)	<0.001	0.001
Hct	0.337 (0.045)	0.314 (0.046)	0.325 (0.044)	0.321 (0.046)	<0.001	0.332 (0.041)	0.288 (0.039)	0.288 (0.039)	0.291 (0.039)	<0.001	0.000
Ca_{O_2} (ml $litre^{-1}$)	148 (21)	137 (22)	142 (22)	141 (22)	<0.001	147.6 (19)	127.3 (17)	126.8 (17)	128.5 (17)	<0.001	<0.001
DO_2I (ml min^{-1} m^{-2})	365 (73)	390 (82)	400 (89)	367 (84)	<0.001	387 (92)	411 (74)	406 (77)	405 (62)	0.144	0.786

Table 4 Renal variables. Values are mean (SD). ANCOVA, between-groups analysis of variance with baseline as a covariate; ANOVA, within-group analysis of variance; GFR, glomerular filtartion rate; $RAVO_2$-diff, arterial–renal vein oxygen content difference; RBF/CI, relationship between RBF and cardiac index; RD_{O_2}, renal oxygen delivery; RBF, renal blood flow; RO_2Ex, renal oxygen extraction; $R\dot{V}O_2$, renal oxygen consumption; RVR, renal vascular resistance; $SrvO_2$, renal vein oxygen saturation. All renal data were normalized to a body surface area of 1.73 m^2

Variable	Crystalloid				One-way ANOVA	Colloid				One-way ANOVA	ANCOVA crystalloid vs colloid
	Baseline	20 min	40 min	60 min	P-value	Baseline	20 min	40 min	60 min	P-value	P-value
RBF (ml min^{-1})	674 (170)	738 (178)	688 (226)	673 (201)	0.025	706 (199)	827 (164)	787 (207)	792 (184)	0.019	0.089
RVR (mm Hg ml^{-1} min^{-1})	0.108 (0.03)	0.107 (0.03)	0.112 (0.04)	0.112 (0.03)	0.625	0.104 (0.04)	0.093 (0.02)	0.098 (0.03)	0.098 (0.03)	0.394	0.165
RD_{O_2} (ml min^{-1})	99.2 (25.0)	99.7 (23.0)	95.9 (26.7)	93.1 (25.0)	0.176	102.5 (24.9)	105.4 (27.4)	99.7 (30.6)	101.6 (27.7)	0.750	0.582
GFR (ml min^{-1})	68.6 (14.3)	79.5 (21.1)	87.5 (22.7)	76.4 (16.0)	<0.001	70.9 (15.3)	85.7 (23.5)	78.3 (29.0)	83.9 (38.8)	0.291	0.989
Sodium filtration (mmol min^{-1})	9.42 (2.02)	10.88 (2.97)	12.00 (3.28)	10.44 (2.25)	<0.001	9.69 (2.03)	11.72 (3.27)	10.73 (4.05)	11.52 (5.41)	0.288	1.000
Sodium reabsorption (mmol min^{-1})	9.10 (2.01)	9.63 (3.00)	11.18 (3.21)	9.89 (2.14)	0.002	9.30 (2.05)	11.33 (3.22)	10.19 (4.01)	11.26 (5.20)	0.235	0.573
Fitration fraction	0.157 (0.031)	0.161 (0.046)	0.194 (0.052)	0.174 (0.045)	<0.001	0.154 (0.050)	0.148 (0.043)	0.142 (0.050)	0.146 (0.050)	0.773	0.030
Urine flow (ml min^{-1})	2.7 (1.2)	8.7 (4.9)	6.5 (4.3)	4.1 (1.9)	<0.001	2.5 (1.2)	2.4 (1.3)	3.5 (2.0)	3.9 (2.3)	0.003	0.002
$R\dot{V}O_2$ (ml min^{-1})	9.5 (2.4)	11.1 (2.3)	11.5 (2.9)	11.0 (3.4)	<0.001	10.1 (3.3)	10.6 (4.7)	10.1 (3.0)	10.3 (3.0)	0.964	0.085
$SrvO_2$ (%)	88.9 (3.2)	87.2 (3.3)	86.2 (3.6)	86.5 (3.9)	<0.001	88.4 (4.0)	88.0 (4.2)	87.5 (4.1)	87.8 (3.8)	0.452	0.019
RO_2Ex	0.099 (0.031)	0.113 (0.030)	0.121 (0.033)	0.120 (0.039)	<0.001	0.104 (0.039)	0.106 (0.043)	0.111 (0.039)	0.109 (0.039)	0.653	0.032
$RAVO_2$-diff (ml $litre^{-1}$)	14.3 (3.2)	15.4 (3.3)	17.3 (4.3)	16.8 (5.3)	0.004	15.3 (5.4)	13.4 (5.1)	13.8 (4.6)	13.8 (4.1)	0.169	0.002
RBF/CI	0.274 (0.054)	0.261 (0.056)	0.243 (0.055)	0.257 (0.055)	0.012	0.278 (0.090)	0.258 (0.055)	0.250 (0.073)	0.254 (0.069)	0.210	0.904

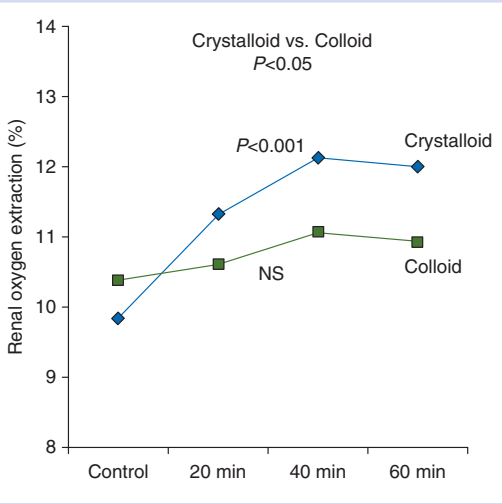

Fig 2 Effects of a crystalloid (10 ml kg^{-1}) and a colloid (20 ml kg^{-1}) bolus on renal oxygen extraction after cardiac surgery. The crystalloid increased renal oxygen extraction ($P<0.001$) 20, 40 and 60 min after the bolus, in contrast to the colloid (NS), suggesting impairment of renal oxygenation. The change in renal oxygen extraction was significantly ($P<0.05$) more pronounced in the crystalloid group compared with the colloid group.

decreased with the crystalloid but not with the colloid. Renal vascular resistance was not affected in any of the groups. Bolus fluid administration did not affect RD_{O_2} in any of the groups. The GFR and sodium filtration increased transiently with the crystalloid, with a peak 28% increase at 40 min. In the colloid group, GFR and sodium filtration were not significantly changed from baseline after fluid administration. In the crystalloid group, tubular sodium reabsorption increased transiently, with a peak increase of 23% at 40 min, whereas in the colloid group tubular sodium reabsorption did not change significantly from baseline. The filtration fraction (FF) increased transiently in the crystalloid group (24% at 40 min), with no changes in the colloid group. Urine flow increased in both groups. The $R\dot{V}O_2$ increased (by 16–21%) in the crystalloid group, with no changes in the colloid group. Renal vein oxygen saturation decreased and arterial–renal vein oxygen content difference increased in the crystalloid group, whereas these variables were not affected in the colloid group. Renal oxygen extraction, a direct measure of the renal oxygen supply–demand relationship, increased by 23% in the crystalloid group, whereas the colloid bolus did not affect renal oxygen extraction Figure 2.

Crystalloid *vs* colloid

The increase in urine flow was significantly higher in the crystalloid group. The increase in FF in the crystalloid group differed significantly from the change in the colloid group. In the crystalloid group, changes in renal vein oxygen saturation, renal oxygen extraction, and arterial–renal vein oxygen content difference were significantly higher than in the colloid group. There was a trend for a higher increase in $R\dot{V}O_2$ in the crystalloid group ($P=0.085$) and a higher increase in RBF in the colloid group ($P=0.089$). There were no significant intergroup differences in RD_{O_2}, GFR, renal vascular resistance, RBF/CI, sodium filtration, or sodium reabsorption.

Discussion

We studied the renal effects of acute plasma volume expansion with artificial solutions early after cardiac surgery. The main findings were that, despite apparent increases in cardiac index and RBF with both fluids, neither of the fluids increased RD_{O_2}. Furthermore, plasma volume expansion with the crystalloid impaired the renal oxygen supply–demand relationship, expressed as a more pronounced increase in renal oxygen extraction compared with the colloid.

The lack of effect on RD_{O_2}, despite the increase in RBF with both fluids, is explained by the fact that the arterial oxygen content decreased in both groups as a result of plasma volume expansion and haemodilution. In addition, the crystalloid bolus seemed to redistribute blood flow away from the kidneys, as reflected by the reduction in the RBF/CI ratio. Thus, the increase in RBF was not in proportion to the increase in CI with the crystalloid.

One important difference between the two fluids was their differential effects on the renal oxygen supply–demand relationship. The $R\dot{V}O_2$ increased in the crystalloid group, which was not matched by a proportional increase in RD_{O_2}, as indicated by the increase in renal oxygen extraction. In contrast, $R\dot{V}O_2$, RD_{O_2}, and renal oxygen extraction were not affected by the colloid. Our group has repeatedly shown in postoperative patients that the major determinant of $R\dot{V}O_2$ is GFR. An increase in glomerular sodium filtration will increase the sodium reabsorption, which, in turn, will increase $R\dot{V}O_2$.[19 20 24] Also in the present study, the increase in glomerular sodium filtration was associated with increases in sodium reabsorption and $R\dot{V}O_2$ in the crystalloid group. In the colloid group, however, this chain of events was not observed, as the colloid did not affect GFR.

Infusion of a bolus dose of an isotonic crystalloid, such as the acetated Ringer's solution used in the present study, redistributes within 20–30 min to the interstitial fluid space because of the short (8–10 min) distribution half-life.[25 26] Thus, a bolus dose of a crystalloid induces only a transient increase in plasma volume, as also demonstrated by a return towards baseline of haematocrit, cardiac filling pressures, and CI within 60 min in the present study, in contrast to the colloid group. Thus, to maintain the plasma volume in an expanded state in the treatment of postoperative hypovolaemia, repeated bolus doses of a crystalloid are required, with a potential for each of the crystalloid boluses to impair renal oxygenation in a hypovolaemic patient already subjected to impaired RD_{O_2} and potentially also renal medullary ischaemia.

In the present study, we measured the renal extraction of ^{51}Cr-EDTA, which is a direct measure of the renal FF (i.e. the GFR/RPF ratio). The FF increased with the crystalloid, suggesting that the increase in GFR (and $R\dot{V}O_2$) was not matched by a proportional increase in renal blood flow. We have previously shown in postoperative cardiac surgery patients that there is a close positive correlation (r^2>0.81) between the renal FF and renal oxygen extraction.[19 20] Thus, the crystalloid-induced increase in FF supports our finding of a renal oxygen supply–demand impairment with a crystalloid.[19 20 27]

Our data are in line with previous animal studies. Thus, in an experimental study on Merino cross-ewes, it was shown that both a crystalloid and a colloid infusion, if anything, reduced RD_{O_2}, because of haemodilution, despite increased cardiac output.[17] Furthermore, in a rat hypovolaemic shock model, saline for treatment of hypovolaemia did not improve RD_{O_2} or renal microvascular P_{O_2}.[28] In a recent experimental study, it was shown that acute normovolaemic haemodilution with a crystalloid decreased renal microvascular oxygenation in the cortex and outer medulla, in contrast to a colloid (hydroxethyl starch 6% 130/0.4), which maintained regional renal microvascular oxygenation.[18] Haemodilution with the crystalloid was also associated with highest formation of tissue oedema and highest expression of hypoxia-inducible factor-1α, in their study.

In the present study, both fluids increased cardiac index. In the colloid group, the increase in CI was more pronounced and consistent during the experimental procedure. One could therefore argue that a larger bolus dose of the crystalloid, e.g. 30 ml kg^{-1}, would have induced a more pronounced increase in CI, RBF, and renal oxygen delivery, with less or no impairment of the renal oxygen demand–supply relationship. On the contrary, a higher dose of the crystalloid would have induced a more pronounced haemodilution, which would have counteracted a beneficial increase in RBF, with potentially no net increase in RD_{O_2}. Furthermore, a higher dose of the crystalloid would decrease the oncotic pressure further, potentially increasing GFR and $R\dot{V}O_2$ to a greater extent than with a lower dose of crystalloid. Thus, it is not immediately evident that a higher dose (e.g. 30 ml kg^{-1}) of a crystalloid than the one used in the present study would have had a less negative effect on the renal oxygen demand–supply relationship.

One limitation of the present study was that we included patients who were considered haemodynamically stable, according to our local postoperative treatment protocol. Thus, we did not measure arterial pulse pressure or stroke volume variation to assess fluid responsiveness.[28 29] The reason for this approach is that we considered it unethical to include patients with obvious haemodynamic signs of hypovolaemia, defined by our clinical protocol, without treating this condition during the preparation for the experimental procedure, including time to reach a body temperature >36°C, time needed for serum ^{51}Cr-EDTA to reach steady state (at least 60 min), and baseline measurements (60 min) before start of the plasma volume expansion. However, 80–90% of the patients in both groups responded to the plasma volume by an increase in CI.[29 30] We therefore strongly believe that our results on the renal effects of colloid and crystalloid solutions are valid for a group of patients undergoing major surgery, responding to plasma volume expansion with an increase in CI in the early postoperative period.

In conclusion, we evaluated the differential renal effects of a colloid and a crystalloid early after cardiac surgery. Although both fluids increased CI and RBF, neither of the fluids improved renal oxygen delivery. The crystalloid-induced increase in GFR was associated with impaired renal oxygen demand–supply relationship, not seen with the colloid. Treatment of hypovolaemia with a bolus dose of a crystalloid therefore has the potential to impair renal oxygenation in postoperative patients.

Authors' contributions

Planned and designed the study: B.R., J.S., S.-E.R.
Conducted the experiments: J.S.L., G.B., V.K.
Analysed data: J.S.L., G.B.
Carried out statistical analysis: J.S.L.
Interpreted data: G.B., B.R., J.S., S.-E.R.
Wrote up the first draft: J.S.L.
Revised the manuscript: G.B., B.R., S.-E.R.
All authors gave final approval of the submitted version.

Declaration of interests

None declared.

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PAPER II

Jenny Skytte Larsson, Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten.

Renal function and oxygenation are impaired early after liver transplantation despite hyperdynamic systemic circulation.

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Critical Care

RESEARCH Open Access

Renal function and oxygenation are impaired early after liver transplantation despite hyperdynamic systemic circulation

Jenny Skytte Larsson*, Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten

Abstract

Background: Acute kidney injury (AKI) occurs frequently after liver transplantation and is associated with the development of chronic kidney disease and increased mortality. There is a lack of data on renal blood flow (RBF), oxygen consumption, glomerular filtration rate (GFR) and renal oxygenation, i.e. the renal oxygen supply/demand relationship, early after liver transplantation. Increased insight into the renal pathophysiology after liver transplantation is needed to improve the prevention and treatment of postoperative AKI. We have therefore studied renal hemodynamics, function and oxygenation early after liver transplantation in humans.

Methods: Systemic hemodynamic and renal variables were measured during two 30-min periods in liver transplant recipients ($n = 12$) and post-cardiac surgery patients (controls, $n = 73$). RBF and GFR were measured by the renal vein retrograde thermodilution technique and by renal extraction of Cr-EDTA (= filtration fraction), respectively. Renal oxygenation was estimated from the renal oxygen extraction.

Results: In the liver transplant group, GFR decreased by 40% ($p < 0.05$), compared to the preoperative value. Cardiac index and systemic vascular resistance index were 65% higher ($p < 0.001$) and 36% lower ($p < 0.001$), respectively, in the liver transplant recipients compared to the control group. GFR was 27% ($p < 0.05$) and filtration fraction 40% ($p < 0.01$) lower in the liver transplant group. Renal vascular resistance was 15% lower ($p < 0.05$) and RBF was 18% higher ($p < 0.05$) in liver transplant recipients, but the ratio between RBF and cardiac index was 27% lower ($p < 0.001$) among the liver-transplanted patients compared to the control group. Renal oxygen consumption and extraction were both higher in the liver transplants, 44% ($p < 0.01$) and 24% ($p < 0.05$) respectively.

Conclusions: Despite the hyperdynamic systemic circulation and renal vasodilation, there is a severe decline in renal function directly after liver transplantation. This decline is accompanied by an impaired renal oxygenation, as the pronounced elevation of renal oxygen consumption is not met by a proportional increase in renal oxygen delivery. This information may provide new insights into renal pathophysiology as a basis for future strategies to prevent/treat AKI after liver transplantation.

Trial registration: ClinicalTrials.gov, NCT02455115. Registered on 23 April 2015.

Keywords: Liver transplantation, Acute kidney injury, Renal blood flow, Glomerular filtration rate, Renal oxygen consumption, Renal oxygenation

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Background

Acute kidney injury (AKI) is a common complication after liver transplantation, with a reported incidence of 11–57% [1–4]. Even a minimal increase in serum creatinine of 0.3 mg/dl (26.4 μmol/L) is associated with higher mortality and shorter graft survival after liver transplantation [5, 6]. Mortality after liver transplantation is reported to be 2–6% in patients not developing AKI, compared to a 47–55% mortality in patients who do develop AKI after liver transplantation [3, 4].

The etiology of AKI after liver transplantation is unknown, but is most likely multifactorial. Hypotension caused by intra-operative blood loss and reperfusion injury is presumably of importance. Furthermore, renal dysfunction may be present prior to transplantation as seen in patients with hepatorenal syndrome (HRS). In patients with HRS, a splanchnic vasodilatation is seen. This vasodilation is accompanied by an activation of the renin-angiotensin and of the sympathetic nervous system, resulting in increased renal vascular resistance. As a result, blood flow will be distributed away from the kidneys and hence the kidneys will receive a decreased oxygen delivery [7, 8]. This could be considered as a potential mechanism causing AKI after liver transplantation.

The diagnosis of AKI is based on an increase in serum creatinine according to Kidney Disease Improving Global Outcomes (KDIGO) criteria [9, 10]. Patients with hepatic failure usually have low levels of serum creatinine because of a low skeletal muscle mass, a lower creatine production and lower conversion of creatine to creatinine [11, 12]. Thus, creatinine-based methods for calculation of glomerular filtration rate (GFR) will overestimate measured GFR in this population.

To our knowledge, there is no data on the effects of liver transplantation on measured GFR, renal hemodynamics or renal oxygenation early after liver transplantation. Thus, to improve the prevention and treatment of postoperative AKI, it is of great importance to get more insights into the renal pathophysiology after liver transplantation. Indeed, in the most recent practice-based recommendations from the American Society of Transplantation Liver and Intestine Community of Practice, Levitsky et al. stress that nephro-protective strategies are needed to improve renal outcome after liver transplantation [13].

In the present study, we measured GFR, renal blood flow, renal oxygen consumption and renal oxygenation early after liver transplantation by using the retrograde renal vein thermodilution technique and by measuring the renal extraction of the filtration marker chromium ethylenediaminetetraaceticacid (^{51}Cr-EDTA). Patients undergoing uneventful major cardiac surgery served as controls. We believe that the comparison between these two groups is relevant since both groups have been exposed to major surgery, both groups have had contact with material that is not endogenous, with a consequent systemic inflammation. Furthermore, both groups were sedated and mechanically ventilated during the experimental procedure, which was performed early after arrival in the intensive care unit (ICU). Hence, differences between the two groups with respect to renal function can be viewed as results-specific for liver recipients. Our primary end point was the change in measured GFR from baseline after liver transplantation. Our null hypothesis was that measured GFR is not affected in the immediate postoperative period after liver transplantation.

Methods

The Gothenburg Regional Ethics Committee approved the study protocol and written informed consent was obtained from all patients within the 24 hours before surgery. The group of liver-transplanted patients was compared to a group of post-cardiac surgery patients after uncomplicated cardiac surgery, at a numerical ratio of 1:6. Patients in both groups were studied in the early postoperative period in the intensive care unit during sedation and mechanical ventilation.

Liver transplant recipients

Twelve adult patients undergoing liver transplantation were prospectively included during the period of January 2015 to February 2016 with the following inclusion criteria: (a) age >18 years and (b) measured GFR > 60 ml/min. The exclusion criteria were: (a) intra-operative need for veno-venous bypass, (b) clinically significant postoperative bleeding, (c) unsuccessful catheterization of the renal vein, and (d) contraindication to radio-contrast agents. In all patients, GFR was measured within 3 months prior to transplantation by the plasma clearance of either ^{51}Cr-EDTA or iohexol.

Anesthesia was induced by propofol and fentanyl or remifentanil, and maintained with sevoflurane and either of the opiates used for induction. Intra-operative blood salvage was performed with the Cell Saver® 5+ device (Haemonetics Corporation, Braintree, MA, USA). Packed red blood cells were given to maintain hemoglobin ≥ 80 g/liter and plasma and blood platelets were administered at the discretion of the attending anesthesiologist. Immediately before reperfusion, all patients obtained methylprednisolone at a dose of 0.5–1 gram and mannitol at a dose of 200–300 ml. A bolus dose of epinephrine (0.01–0.15 mg) was administered in reperfusion-induced hemodynamic instability. Norepinephrine was administered intra-operatively to maintain a mean arterial pressure > 65 mmHg.

On arrival to the intensive care unit (ICU), the patients were mechanically ventilated and sedated with propofol (2.7 ± 0.6 mg/kg/h) and either fentanyl or remifentanil. Postoperative targets were pulse pressure variation < 12%

and a mean arterial pressure of 70–80 mmHg. Postoperative hypovolemia was treated according to routine clinical practice with albumin (Albumin Baxalta® 200 g/l) and/or crystalloid fluid (Ringer–Acetate®, Baxter Viaflo, Baxter Healthcare Corporation, Irvine, CA, USA). Hypotensive normovolemic patients were treated with norepinephrine according to the attending intensivist.

Cardiac surgery group (control group)

Seventy-three post-cardiac surgery patients served as controls. These patients participated in pharmacological intervention trials performed by our research group in 2006–2014 [14–17]. The inclusion criteria were: (a) age >18 years, (b) elective cardiac surgery with cardiopulmonary bypass, (c) preoperative left ventricular ejection fraction ≥ 40%, and (d) preoperative serum creatinine within normal range. The exclusion criteria were: (a) postoperative need for inotropic support, (b) postoperative arrhythmias requiring treatment, (c) significant postoperative bleeding, (d) unsuccessful catheterization of the renal vein, and (e) postoperative AKI according to the AKIN criteria [18]. The baseline renal and systemic data of these patients, i.e. before pharmacological intervention, were used for comparison with those of the liver-transplanted group. Preoperative estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula in all patients.

Anesthesia was induced by fentanyl and propofol. Before and after cardiopulmonary bypass, anesthesia was maintained with sevoflurane. During cardiopulmonary bypass, anesthesia was maintained with propofol. In the intensive care unit, the patients were sedated with propofol (3.8 ± 0.18 mg/kg/min) and morphine or fentanyl, and mechanically ventilated. Target central venous pressure (CVP) and target mean arterial pressure (MAP) were 5–10 mmHg and 70–80 mmHg, respectively. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethyl starch (Venofundin, Braun, Germany) and crystalloid fluids (Ringer–Acetate®, Baxter Viaflo).

Measurements of systemic hemodynamics

Arterial blood pressure was measured continuously via a femoral or radial artery catheter. CVP was measured continuously via a central venous catheter inserted through the right jugular vein. Cardiac output (CO) was measured by the transthoracic thermodilution pulse contour technique using the PiCCO™ device (Pulsion Ltd, Munich, Germany) in the liver-transplanted group, and in the cardiac surgery group by a pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA, USA). CO was measured in triplicate and indexed to the body surface area. Systemic vascular resistance index (SVRI) and stroke volume index (SVI) were calculated according to standard formulae. In the liver transplant recipients, cardiac index was recorded before, during and after the anhepatic phase.

Measurements of renal variables

An 8 Fr catheter (Webster Laboratories, Baldwin Park, CA, USA) was postoperatively introduced into the left or right renal vein, via the right femoral vein, under fluoroscopic guidance. The catheter was placed in the central portion of the renal vein, the position being confirmed by venography using ultra-low doses of iohexol, 5–15 mg I kg – 1 (Omnipaque 300 mg I ml – 1; GE Healthcare, Stockholm, Sweden). Renal blood flow (RBF) was measured in triplicate by the continuous retrograde thermodilution technique [14, 17, 19, 20]. After the collection of blood and urine blanks, an intravenous priming dose of ^{51}Cr-EDTA (GE Healthcare, Amersham, UK) was given, followed by an infusion at a constant rate, individualized to body surface area and to preoperative serum creatinine. Serum ^{51}Cr-EDTA activity from arterial and renal vein blood was measured using a well counter (Wizard 3', 1480, Automatic gamma counter; PerkinElmer LAS, Turku, Finland). Formulae for calculation of renal variables are described in Table 1. All renal data were normalized to a body surface area of 1.73 m^2. Serum creatinine was measured in all patients within 24 hours before surgery and on the first and second postoperative days. In addition, serum creatinine was measured on admission to the ICU in the liver recipients.

Experimental procedure

After an equilibration period of at least 60 min, two 30-min urine collection control periods were started.

Table 1 Formulae for calculation of renal variables

Variable	Formulae
Renal blood flow (RBF)	(Unilateral renal vein blood flow × 2) + urine flow
Renal plasma flow (RPF)	RBF × (1 – hematocrit)
Filtration fraction (FF)	(RPF × [^{51}Cr-EDTA arterial] – (RPF – urine flow) × [^{51}Cr-EDTA renal vein])/(RPF × [^{51}Cr-EDTA arterial])
Glomerular filtration rate (GFR)	FF x RPF
Renal vascular resistance (RVR)	(MAP-CVP)/RBF
Arterial-renal vein (rv) oxygen content difference ($RAVO_2$-diff)	(CaO_2-$CrvO_2$)
Renal oxygen consumption (RVO_2)	RBF × (CaO_2-$CrvO_2$)
Renal oxygen extraction	(CaO_2-$CrvO_2$/CaO_2)
Renal sodium filtration	GFR × $[Na^+]_s$
Renal sodium excretion	Urine flow × $[Na^+]_s$
Renal sodium reabsorption	(GFR × $[Na^+]_s$) – (urine flow × $[Na^+]_u$)

^{51}Cr-EDTA, chromium ethylenediaminetetraaceticacid, *MAP* mean arterial pressure, *CVP* central venous pressure, *CaO_2* arterial oxygen content, $CrvO_2$ renal vein oxygen content, *$[Na^+]_s$* serum sodium concentration, *$[Na^+]_u$* urine sodium concentration

Thermodilution measurements of RBF and measurements of cardiac index (CI) were conducted at the end of each of the urine collection periods followed by blood and urine sampling. Infusion rates of fluids and of norepinephrine (liver-transplanted group) were not changed during the experimental procedure.

Statistical analysis

Data on renal and systemic hemodynamic variables from the two 30-min measurement periods were pooled. The primary end-point of the present study was the change in GFR after liver transplantation compared to the preoperatively measured GFR. To detect a fall in GFR by 30%, ten patients were needed at a power of 0.80, a significance level of 0.05 and a standard deviation of 20 ml/min. Continuous variables were checked for normal distribution. Intergroup differences where compared using independent-samples *t* test or Mann-Whitney *U* test when appropriate. Categorical data were compared using Fisher's exact test. Linear regression analyses were performed to correlate renal oxygen consumption to renal sodium reabsorption and GFR, respectively. PASW Statistics Version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Within- and inter-group repeated measurements of serum creatinine were calculated using mixed model in SAS (SAS version 9.3, SAS Institute Inc., Cary, NC, USA). An unstructured covariance structure was assumed for the inter-group analysis.

Data are presented as mean ± SD throughout the text. A p value < 0.05 was considered significant.

Results

Liver transplant recipients

In the liver-transplanted group, informed consent was obtained from 14 patients. One patient was excluded because of postoperative bleeding and another patient was excluded because of unsuccessful placement of the renal vein catheter. Individual preoperative and intra-operative data on the liver-transplanted group are shown in Tables 2 and 3, respectively. Primary sclerotic cholangitis was the most common liver-related diagnosis, followed by cirrhosis due to viral infection. The mean Model For End-Stage Liver Disease (MELD) and Child-Pugh scores were 14.0 ± 5.7 and 9.3 ± 1.7, respectively. Mean preoperative measured GFR (mGFR), estimated GFR (eGFR) and serum creatinine were 85.5 ± 18.7 ml/min, 86.9 ± 19.8 ml/min and 70.8 ± 13.9 μmol/l, respectively. The duration of the surgical procedure was 5.9 ± 1.4 hours and mean intra-operative bleeding was 2.3 ± 1.3 liters.

Liver transplant recipients versus post-cardiac surgery (control) group

Data on the characteristics of the two study groups are shown in Table 4. In the liver-transplanted group, the proportion of female gender was higher, the patients were younger, and they had a lower preoperative serum creatinine compared to the post-cardiac surgery group. The difference in preoperative estimated GFR between the groups was not statistically significant. Hypertension and treatment with angiotensin-converting enzyme inhibitor (ACE inhibitor) were less frequent in liver transplant recipients. A greater proportion of patients in the liver-transplanted group were treated with diuretics, while there were no statistical differences between the groups with respect to the use of beta-adrenergic blockers or calcium channel antagonists.

Systemic variables (Table 5)

All liver-transplanted patients required norepinephrine infusion at a mean dose of 0.28 ± 0.17 μg/kg/min to maintain a MAP of between 70 and 80 mmHg. There were no statistically significant differences between the liver-transplanted group and the control group regarding MAP, heart rate, CVP, serum hemoglobin or systemic oxygen consumption index. CI (65%), SVI (69%) and systemic oxygen delivery index (60%) and venous saturation were all significantly higher (all $p < 0.001$), while SVRI was significantly lower (−36%, $p < 0.001$), in the liver-transplanted group compared to the control group. In liver transplant recipients, CI increased by 33% after reperfusion ($p < 0.01$) (Table 3).

Renal variables (Figs. 1, 2, 3 and Table 6)

In the immediate postoperative period, mGFR decreased from 85.5 ± 18.7 to 51.5 ± 30.4 (−40%, $p < 0.01$) in liver transplant recipients. This decline in mGFR measured directly after liver transplantation was accompanied by a statistically significant increase in serum creatinine by 24%, from 70.8 ± 13.9 to 87.7 ± 18.7 μmol/l ($p < 0.05$) (Fig. 1).

RBF was higher (18%, $p < 0.05$) and renal vascular resistance was lower (15%, $p = 0.051$) in liver transplant recipients compared to the control group. The ratio between RBF and CI (RBF/CI) was 27% lower ($p < 0.001$) in the liver-transplanted compared to the control group. GFR and filtration fraction were 27% ($p < 0.05$) and 40% ($p < 0.01$) lower in liver transplant recipients. Renal oxygen consumption was 44% higher ($p < 0.001$) in liver transplant recipients despite a 19% lower renal sodium reabsorption compared to the control group. In both groups, there was a close correlation between renal oxygen consumption and renal sodium reabsorption, (control group: $r^2 = 0.728$, p <0.001, liver recipients: $r^2 = 0.587$ $p < 0.05$), and between renal oxygen consumption and GFR (control group: $r^2 = 0.708$, $p < 0.001$, liver recipients: $r^2 = 0.395$, p <0.05) (Fig. 2). However, the renal oxygen consumption per mmol/min of reabsorbed sodium was 2.7 times higher in the liver-transplanted compared to

Table 2 Preoperative individual data, liver transplant recipients

Patient number	Diagnosis	MELD score	Child-Pugh score	Serum bilirubin (mmol/l)	mGFR (ml/min/1.73 m^2)	Serum creatinine (μmol/l)	ASA
1	Primary biliary cirrhosis	15	10	36	75	67	3
2	Hepatitis C virus, cirrhosis	17	10	32	95	109	2
3	Primary sclerosing cholangitis	6	9	8	72	60	2
4	Primary sclerosing cholangitis, cirrhosis	22	11	110	62	59	3
5	Hepatitis C virus, hepatocellular carcinoma, cirrhosis	8	7	10	105	74	2
6	Alpha-1 antitrypsin deficiency, cirrhosis	16	11	43	94	75	3
7	Alcoholic liver cirrhosis	24	12	150	72	62	3
8	Primary sclerosing cholangitis, cirrhosis	13	9	60	102	73	2
9	Primary sclerosing cholangitis, cirrhosis	9	6	32	89	76	2
10	Hepatitis C virus, hepatocellular carcinoma, cirrhosis	9	9	14	122	60	3
11	Primary sclerosing cholangitis, hepatitis B virus	18	10	340	77	60	2
12	Hepatitis C virus, hepatocellular carcinoma, cirrhosis	11	8	24	61	75	3
Mean		14.0	9.3	71.6	85.5	70.8	2.50
SD		5.7	1.7	94.6	18.7	13.9	0.52

Data presented as mean ± SD
MELD Model For End-Stage Liver Disease, *mGFR* measured glomerular filtration rate, *ASA* American Society of Anesthesiologists

the control group. This increase in renal oxygen consumption was not met by a proportional increase in renal oxygen delivery, as demonstrated by the higher renal oxygen extraction in liver transplant recipients compared to the control group ($p < 0.05$). Serum creatinine increased in the liver-transplanted group by 41% ($p < 0.01$) and 48% ($p < 0.01$) on the first and second postoperative day, respectively, compared to the preoperative baseline value. This was not seen in the control group, and as shown in Fig. 3, there was a statistically significant difference in serum creatinine between the groups over time. Eight patients in the liver-transplanted group (67%) developed acute kidney injury, as defined by the KDIGO criteria, during the two first postoperative days.

Table 3 Intra-operative data of liver transplant recipients

Duration of surgery (min)	357 ± 86
Duration of anhepatic phase (min)	73 ± 30
Bleeding (ml)	2270 ± 1290
Packed red blood cells (units)	2.5 (0–4)
Platelets (units)	2.5 (0–4)
Plasma (units)	4.0 (0–6)
Fibrinogen (g)	2.0 (0–11)
Albumin (ml)	300 (0–600)
Cellsaver (ml)	400 (0–980)
Intra-operative crystalloid (L)	2.5 ± 0.9
Epinephrine, n (%)	9 (75)
Diuresis (ml/procedure hour)	118 ± 47
CI prior to anhepatic phase (l/min/m^2)	3.3 ± 0.9
CI during anhepatic phase (l/min/m^2)	3.9 ± 1.6
CI after reperfusion (l/min/m^2)	4.4 ± 0.9
SVRI (ml/min/min^2)	1413 ± 290
CVP (mmHg)	8 ± 2
Intra-operative fluid balance (ml)	665 ± 1540

Data are presented as median (min-max), mean ± SD, n = number of patients (%)
CI cardiac index, *SVRI* systemic vascular resistance index, *CVP* central venous pressure

Discussion

The main finding of the present study was that there was an early and substantial decline in renal function after liver transplantation. In spite of this decline in GFR, and the lower renal sodium reabsorption, renal oxygen consumption was considerably elevated in liver recipients compared to after uncomplicated cardiac surgery. Furthermore, the renal oxygen supply/demand relationship (i.e. oxygenation) was impaired in liver transplant recipients, as the increase in renal oxygen consumption was not met by a proportional increase in renal oxygen delivery, despite the hyperdynamic circulation seen in this group.

The physiological control of GFR is mediated by the balance between the tone of the afferent and efferent arterioles. A fall in GFR may be caused either by vasoconstriction of the afferent arterioles, with reduced RBF as a consequence, or a vasodilation of the efferent arterioles, which will be accompanied by an increase in RBF. An activation of the tubulo-glomerular feedback mechanism, caused by tubular dysfunction, would induce an afferent arteriolar vasoconstriction with a decrease in both RBF and GFR [21, 22]. Our findings of a fall in GFR combined with an increased RBF, is thus best explained by vasodilation preferentially of the efferent arterioles.

Table 4 Patient characteristics

Variable	Control group ($n = 73$)	Liver transplant recipients ($n = 12$)	p value
Gender, n (% female)	8 (11)	7 (58)	0.001
Age, mean (SD)	66.6 ± 10.1	56.7 ± 10.7	0.005
Body surface area (m2)	1.96 ± 0.2	1.92 ± 0.2	0.509
Body mass index (kg/m2)	26.4 ± 3.4	21.9 ± 1.1	<0.001
Hypertension, n (%)	40 (54.8)	1 (8.3)	0.004
Diabetes, n (%)	3 (4.1)	1 (8.3)	0.462
Beta-adrenergic blocker, n (%)	58 (79.5)	7 (58.3)	0.143
ACE inhibitor, n (%)	37 (50.7)	2 (16.7)	0.033
Calcium antagonist, n (%)	12 (16.4)	0 (0)	0.201
Diuretics, n (%)	3 (4.1)	8 (66.7)	<0.001
- Aldosterone antagonists, n (%)		6 (50%)	
Preoperative serum creatinine (μmol/l)	82.7 ± 11.4	70.8 ± 13.9	0.001
Preoperative estimated GFR (mL/min)	84.5 ± 14.5	86.9 ± 19.8	0.690
Preoperative measured GFR (mL/min)	-	85.5 ± 18.7	-

Values are means ± SD, n = number of patients (%). Estimated GFR; using MDRD (Modification of Diet in Renal Disease) formula
ACE inhibitor angiotensin-converting enzyme inhibitor, *GFR* glomerular filtration rate

Another tentative explanation to the fall in GFR after liver transplantation, as an alternative to the "vascular abnormality" described above, would be tubular cell dysfunction ("tubular abnormality") manifested as a decrease in tubular sodium reabsorption. This would increase the sodium delivery to the macula densa, activating the tubulo-glomerular feedback mechanism causing an afferent arteriolar vasoconstriction with a decrease in both RBF and GFR [21, 22]. This mechanism, however, is unlikely to explain the fall in GFR after liver transplantation, as renal vascular resistance in the present study was lower compared to the control group. Furthermore, we find the early fall in GFR in this study unlikely to be caused by shedding of tubular cells causing tubular obstruction, as this has been described to occur only in later phases of ischemic AKI [22].

Our group has repeatedly shown that there is a close correlation between GFR, tubular sodium reabsorption and renal oxygen consumption in postoperative patients [14, 19, 23, 24]. This was also demonstrated in the present study in patients early after liver transplantation (Fig. 2). The major difference between liver recipients and the control group was that renal oxygen consumption was higher at a certain level of tubular sodium reabsorption or GFR in the liver transplant group. This is demonstrated by the upward displacement of the curves relating renal oxygen consumption to tubular sodium reabsorption and GFR in Fig 2. Furthermore, the renal

Table 5 Systemic data in the immediate postoperative period

Variable	Control group ($n = 73$)	Liver transplant recipients ($n = 12$)	p value
Mean arterial pressure (mmHg)	74.0 ± 8.7	75.1 ± 1.1	0.338
Cardiac index (l/min/m^2)	2.6 ± 0.5	4.3 ± 1.0	<0.001
Heart rate (beats/min)	76 ± 11	73 ± 17	0.522
Stroke volume index (ml/m^2)	35.4 ± 7.1	60.0 ± 12.0	<0.001
Central venous pressure (mmHg)	7.9 ± 2.5	7.4 ± 3.0	0.639
Systemic vascular resistance index (dynes x sec/cm^3/m^2)	2081 ± 577	1337 ± 392	<0.001
Mixed/central venous oxygen saturation (%)	72.5 ± 4.4	81.2 ± 6.7	0.001
Serum hemoglobin (g/l)	106.2 ± 13	104.7 ± 15	0.730
Systemic oxygen delivery index (ml/min/min2)	381 ± 74	608 ± 142	<0.001
Systemic oxygen consumption index (ml/min/min2)	100.1 ± 15.1	94.5 ± 19.3	0.357

Data are presented as mean ± SD

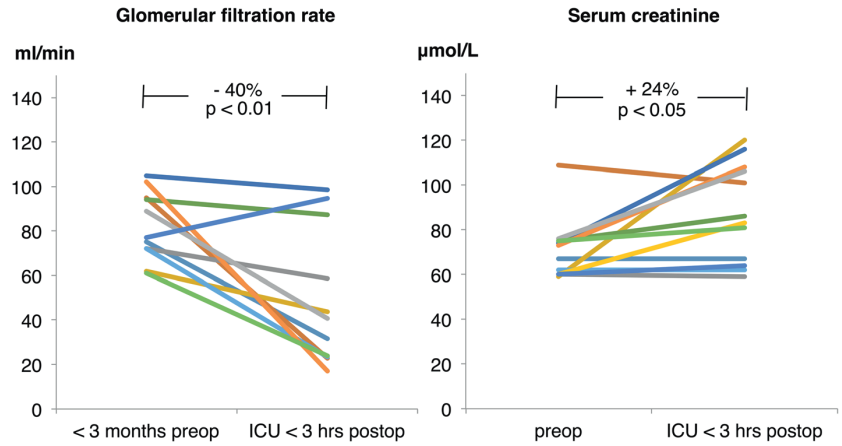

Fig. 1 Individual data on measured glomerular filtration rate (GFR) and serum creatinine before (preoperative) and early after liver transplantation (intensive care unit [*ICU*] ≤ 3 hours) ($n = 12$)

oxygen consumption per millimole reabsorbed sodium was 2.7 times higher in the liver-transplanted group compared to the control group. This could either be caused by tubular injury and an energy-inefficient tubular sodium transport, as demonstrated by our group in patients with early ischemic AKI [24], or by an increase in oxygen demand for basal renal metabolism. Extrapolation of the regression lines in Fig. 2 to the y-axis indicates the renal oxygen consumption in a non-filtering, non-reabsorbing kidney, i.e. the basal renal metabolism. Thus, the major explanation for the higher renal oxygen consumption after liver transplantation, despite the lower GFR and sodium reabsorption, seems to be an elevation of basal renal oxygen requirements. The mechanism behind this finding is, so far, unclear. It is not likely to be explained by a generalized increase in organ oxygen consumption, as the systemic oxygen consumption index did not differ between groups. One could speculate that the production and release of reactive oxygen species (ROS) from the liver graft, as a consequence of the ischemia/reperfusion injury [25], may contribute to the increased renal oxygen consumption, as it has been shown that oxidative stress increases mitochondrial oxygen consumption [26].

The renal oxygen/supply demand relationship, i.e. renal oxygenation, was impaired early after liver transplantation, expressed as the higher renal oxygen extraction compared to the control group. It is reasonable to assume that this impairment in renal oxygenation may induce tubular injury

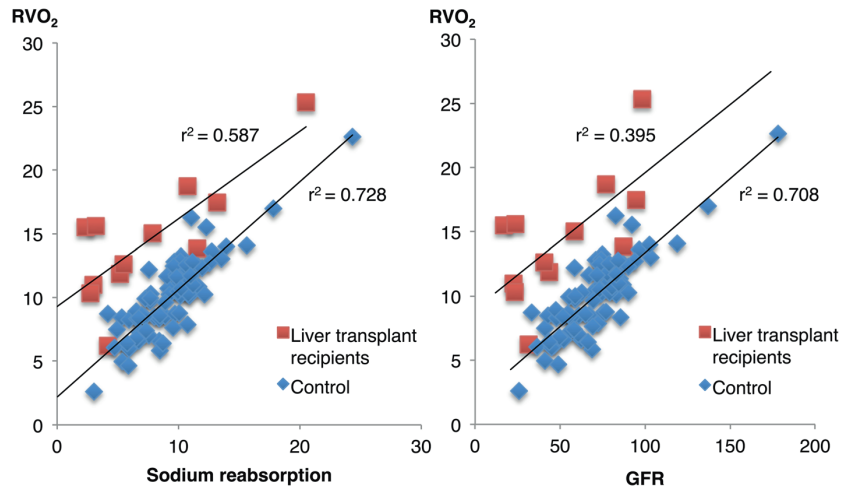

Fig. 2 Relationship between renal oxygen consumption (RVO_2) and renal sodium reabsorption, and between renal oxygen consumption and glomerular filtration rate (*GFR*), in the early postoperative period in liver recipients and after uncomplicated cardiac surgery (controls)

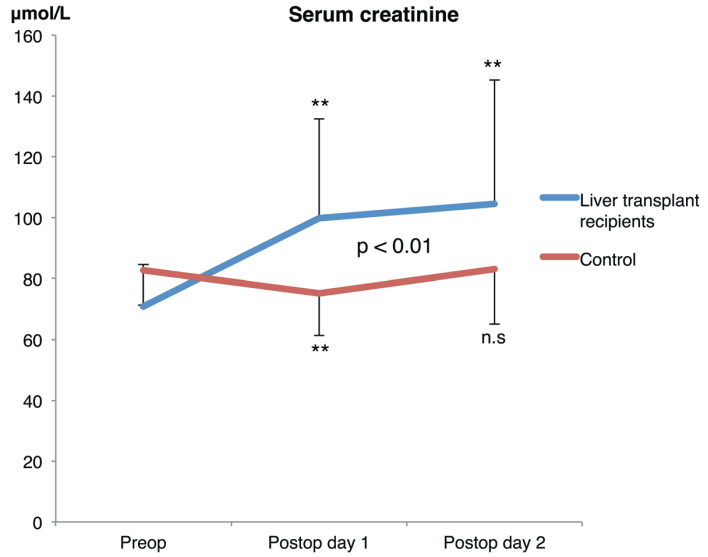

Fig. 3 Changes in serum creatinine in liver recipients and after uncomplicated cardiac surgery (controls). $^{**}p < 0.01$

in the postoperative period, particularly so in the renal medulla, which is sensitive to ischemia. Medullary tissue oxygen tension is low already under normal conditions, because of the high oxygen utilization of the medullary thick ascending limb [27]. It has been shown that tubular injury markers, such as neutrophil gelatinase-associated lipocalin, are released in the urine within hours after liver transplantation and that this may predict AKI [28–30]. An early release of tubular injury markers early after liver transplantation could be explained by the impaired renal oxygenation demonstrated in the present study.

In this group of patients, with advanced or moderately advanced chronic liver disease, a hyperdynamic circulation was seen, with a profound systemic vasodilation and a high cardiac index. Such a hyperdynamic circulation in patients with advanced cirrhosis has been suggested to be caused by a splanchnic vasodilation [31] in turn caused by augmented levels of nitric oxide [32]. Furthermore, there is a post-reperfusion increase in cytokines and complement factors, which also contributes to the systemic vasodilation resulting in a perioperative need for vasopressor treatment during liver transplantation

Table 6 Renal data in the immediate postoperative period

Variable	Control group ($n = 73$)	Liver transplant recipients ($n = 12$)	p value
Renal oxygen extraction	0.100 ± 0.03	0.124 ± 0.04	0.042
Urine flow (ml/min)	3.13 ± 1.7	2.54 ± 2.2	0.065
Renal blood flow (ml/min)	716 ± 209	843 ± 197	0.024
Renal blood flow/cardiac index	0.277 ± 0.08	0.202 ± 0.05	<0.001
Renal vascular resistance (mmHg/ml/min)	0.100 ± 0.03	0.085 ± 0.02	0.051
Glomerular filtration rate (ml/min)	70.9 ± 23.3	51.5 ± 30.4	0.043
Filtration fraction	0.15 ± 0.04	0.09 ± 0.06	0.006
Renal sodium filtration (mmol/min)	9.67 ± 3.2	7.63 ± 5.6	0.052
Renal sodium reabsorption (mmol/min)	9.28 ± 3.2	7. 50 ± 5.5	0.065
Fractional sodium excretion (%)	5.0 ± 4.0	2.5 ± 3.5	0.002
Renal oxygen delivery (ml/min)	103.5 ± 32.1	119.7 ± 29.7	0.048
Renal oxygen consumption (ml/min)	10.0 ± 3.2	14.4 ± 4.8	0.001
Renal oxygen consumption/renal sodium reabsorption (ml/mmol)	1.15 ± 0.3	3.13 ± 2.4	<0.001
Serum creatinine day 1 (µmol/l)	75.1 ± 13.9	99.8 ± 32.7	0.025

Data are presented as mean ± SD

[25]. In the present study, the hyperdynamic circulation was accompanied by a redistribution of RBF away from the kidneys, as illustrated by the 27% lower RBF to CI ratio. The systemic vasodilation in the liver-transplanted group was treated with norepinephrine. As norepinephrine has been shown to decrease renal blood flow in volunteers [33, 34], one could argue that this might have mitigated an even more profound renal vasodilation and renal hyperemia that would otherwise have occurred. We believe that this is less likely, as we have shown that restoration of mean arterial pressure from 60 to 75 mmHg by increasing the dose of norepinephrine, improves renal oxygen delivery, GFR and renal oxygenation in postoperative patients with norepinephrine-dependent systemic vasodilation and AKI [35].

An alternative approach to treat systemic vasodilation during and after liver transplantation would be to use the vasopressin-analogue terlipressin, which is metabolized to vasopressin. In a randomized, controlled study, Mukhtar et al. studied the effects of terlipressin versus saline on splanchnic hemodynamics and postoperative renal function in patients undergoing liver transplantation [36]. Terlipressin improved renal function, as serum levels of creatinine and cystatin C were significantly lower in the terlipressin group during the two first postoperative days. Bragadottir et al. analysed in a pharmacodynamic study the renal effects of vasopressin in uncomplicated postcardiac surgery patients and found that vasopressin induces a vasoconstriction of the efferent arterioles causing an increase in GFR and renal oxygen consumption but a decrease in renal blood flow [14]. Thus, vasopressin caused an impairment of renal oxygenation, as demonstrated by an increase in renal oxygen extraction, suggesting that the use of vasopressin in liver transplantation might be a two-edged sword.

One limitation of the present study is the relatively low number of included liver transplant recipients. Furthermore, we did not assess whether or not there was a structural tubular cell injury in the early postoperative period in this group, as we did not measure tubular injury markers. However, the incidence of AKI in the present study was high (67%), when compared to previous studies on tubular injury markers after liver transplantation (38–46%) [28, 29], and it is likely that release of tubular injury markers occurred also in the present study. The strength of the present study is that it provides new information on renal function and oxygenation in the early period after liver transplantation.

Conclusions

There is a substantial decline in renal function early after liver transplantation despite hyperdynamic circulation and renal vasodilation. This early decline in renal function is accompanied by an impaired renal oxygenation, as the pronounced elevation of renal oxygen consumption is not met by a proportional increase in renal oxygen delivery.

Key messages

After liver transplantation:

- there is an early and substantial fall in GFR caused by a vasodilation of the efferent arterioles
- renal oxygen consumption is considerably increased
- renal oxygen delivery does not meet the increased renal metabolic demand despite renal vasodilation
- renal oxygenation is impaired

Abbreviations

$[Na^+]_s$: Serum sodium concentration; $[Na^+]_u$: Urine sodium concentration; ^{51}Cr-EDTA: Chromium ethylenediaminetetraaceticacid; ACE inhibitor: Angiotensin-converting enzyme inhibitor; AKI: Acute kidney injury; ASA: American Society of Anesthesiologists; CaO_2: Arterial oxygen content; CO: Cardiac output; $CrvO_2$: Renal vein oxygen content; CVP: Central venous pressure; GFR: Glomerular filtration rate; HRS: Hepatorenal syndrome; ICU: Intensive care unit; MAP: Mean arterial pressure; MDRD: Modification of Diet in Renal Disease; MELD: Model For End-Stage Liver Disease; mGFR: Measured glomerular filtration rate; RBF: Renal blood flow; SVI: Stroke volume index; SVRI: Systemic vascular resistance index

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Availability of data and materials

The dataset generated and/or analysed during the current study is not publicly available due to patient-related confidentiality, but is available from the corresponding author on reasonable request.

Authors' contributions

JSL contributed to conception and design, patient recruitment, renal vein catheterization and experimental procedure, compilation of data, statistical analysis, writing and drafting of the manuscript. GB contributed to critical intellectual review of the manuscript, and language editing. BR contributed to conception and design, statistical advice, critical intellectual review of the manuscript, and language editing. SER contributed to conception and design, statistical analysis, critical intellectual review of the manuscript, language editing, and was responsible for the approval of the final manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The Gothenburg Regional Ethics Committee (Sweden) approved the study protocol, reference number 1026-13. Written informed consent was obtained from all patients within the 24 hours before surgery.

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PAPER III

Jenny Skytte Larsson, Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten.

Renal effects of norepinephrine-induced variations in mean arterial pressure after liver transplantation: a randomised cross-over trial.

Submitted

Renal effects of norepinephrine-induced variations in mean arterial pressure after liver transplantation: a randomised cross-over trial

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Abstract

Background: Acute kidney injury is commonly seen after liver transplantation. The optimal perioperative target mean arterial pressure (MAP) for renal filtration, perfusion and oxygenation in liver recipients is not known. The effects of norepinephrine-induced changes in MAP on renal blood flow (RBF), oxygen delivery (RDO_2), glomerular filtration rate (GFR) and renal oxygenation (= renal oxygen extraction, RO_2Ex) were therefore studied early after liver transplantation.

Methods: Ten patients with an intra- and postoperative vasopressor-dependent systemic vasodilation were studied early after liver transplantation during sedation and mechanical ventilation. To achieve target MAP levels of 60, 75 and 90 mmHg, the norepinephrine infusion rate was randomly and sequentially titrated. At each target MAP, data on cardiac index (CI), RBF and GFR were obtained by transpulmonary thermodilution (PiCCO), the renal vein thermodilution technique and renal extraction of chromium ethylenediaminetetraaceticacid (^{51}Cr-EDTA), respectively. Renal oxygen consumption (RVO_2) and extraction (RO_2Ex) were calculated according to standard formulas.

Results: At a target MAP of 75 mmHg, CI (13%), RBF (18%), RDO_2 (24%), GFR (31%) and RVO_2 (20%) were higher while RO_2Ex was unchanged compared to a target MAP of 60 mmHg. Increasing MAP from 75 up to 90 mmHg increased RVR by 38% but had no further effects on CI, RBF, RDO_2 or GFR.

Conclusions: In patients undergoing liver transplantation, RBF and GFR are pressure-dependent at MAP levels below 75 mmHg, reflecting an exhausted renal autoregulatory reserve. The optimal perioperative target MAP for renal function, perfusion and oxygenation in liver transplant recipients is approximately 75 mmHg.

Keywords: liver transplantation, renal blood flow, glomerular filtration rate, renal oxygen consumption and oxygenation, mean arterial pressure, norepinephrine

Introduction

Acute kidney injury (AKI) is commonly seen after liver transplantation with an incidence of over 50% [1, 2]. Morbidity, e.g. chronic kidney disease with a lifelong need for haemodialysis, and mortality rates are several times higher in liver recipients developing AKI compared to those who do not [1-3]. Moreover, graft survival is shortened among liver recipients who develop AKI with vast consequences for individuals and society [4].

Risk factors for the development of AKI after liver transplantation have been identified as pre-transplant renal dysfunction caused by the hepatorenal syndrome [5-9], liver graft dysfunction [7] and hypoperfusion caused by intra-operative blood loss [5]. The post reperfusion syndrome (PRS) is also a potential risk factor for postoperative AKI [10]. PRS is an intra-operative serious complication causing hemodynamic derangement due to severe systemic vasodilation combined with an increased or decreased cardiac output [11]. The systemic vasodilation is usually treated with norepinephrine to uphold a mean arterial pressure (MAP) ≥ 65 mmHg [11, 12]. Norepinephrine may on the one hand cause a renal vasoconstriction, as shown in healthy volunteers [12, 13]. On the other hand, leaving the systemic vasodilation insufficiently treated, may result in a blood pressure-dependent renal blood flow (RBF) since the arterial blood pressure, in this situation is left below the limit of the renal autoregulatory capacity. The renal effects of norepinephrine in patients undergoing liver transplantation are not well studied. Particularly, the optimal MAP for renal filtration, perfusion and oxygenation in patients undergoing liver transplantation is not known.

In the present investigation, we aimed to study the effects of three various target levels of MAP, i.e. 60, 75 and 90 mmHg, on renal function, perfusion and oxygenation early after liver transplantation. These target levels of MAP were randomly set and achieved by changes in norepinephrine infusion rates. RBF, GFR, renal oxygen consumption (RVO_2) and renal oxygenation, were studied using the retrograde renal vein thermodilution technique and

by the measurement of the extraction of the renal filtration marker chromium ethylenediaminetetraaceticacid (^{51}Cr-EDTA) in patients early after liver transplantation.

Patients and methods

The study protocol of this prospective randomised cross-over clinical trial was approved by the Gothenburg Regional Ethics Committee (www.epn.se/goeteborg/) on the 30th of January 2014 (No. 1026-13). The study was registered in ClinicalTrials.gov Identifier: NCT02455115, 23 April 2015. All patients gave their written informed consent within 24 hours before surgery. In a recent descriptive article, we compared the data on renal filtration, perfusion and oxygenation after liver transplantation (n=12) to the results from a large population (n=73) of uncomplicated major cardiac surgery patients [14]. A subgroup of these liver transplant recipients (n=10) was subjected to an interventional procedure, in which perioperative target MAP was randomly changed, as described below.

In this prospective trial, fourteen adult patients accepted for liver transplantation were included from January 2015 to January 2017. The inclusion criteria were: a) age >18 years, and b) a preoperative measured GFR (mGFR) > 60 ml/min and the exclusion criteria were: a) the use of veno-venous bypass intra-operatively, b) significant postoperative blood loss, c) failed catheterization of the renal vein, d) re-transplantation, and e) contraindication to radio-contrast agents.

Agents for anaesthesia induction were propofol and fentanyl/remifentanil, and anaesthesia was maintained by sevoflurane and an either of the opiates. Norepinephrine was administered intra-operatively to maintain a MAP > 65 mmHg. To reduce transfusion requirements, intra-operative fluid replacement was kept restrictive and central venous pressure (CVP) was aimed < 5 mmHg using nitroglycerine when needed [15]. The Cell Saver® 5+ device (Haemonetics®, USA) was used for blood salvage. Target haemoglobin was maintained at ≥ 80 g/liter. Plasma and blood platelets were administered at the discretion of the anaesthetist in charge. Methylprednisolone at a dose of 0.5-1 gram and mannitol at a dose of 200-300 ml was administered to all patients before reperfusion of the transplant. In reperfusion-induced hemodynamic instability, epinephrine (0.01 - 0.15 mg) was administered

The patients were mechanically ventilated and sedated with propofol and fentanyl/ remifentanil in the intensive care unit. Target postoperative MAP target was 70-80 mmHg. A pulse pressure variation of >12% was considered as postoperative hypovolemia and was treated with albumin (Albumin Baxalta® 200g/l) and/or a crystalloid (Ringer–Acetate®, Baxter Viaflo). Norepinephrine was used as vasoconstrictor to reach the postoperative target MAP in hypotensive, normovolemic, vasodilated patients.

Systemic haemodynamics

Arterial blood pressure was measured via a femoral artery catheter. A central venous catheter was used to measure CVP and central venous oxygen saturation ($ScvO_2$). The PiCCO ™ device (Pulsion Ltd, Munich, Germany) was used to measure (in triplicate) cardiac output (CO) by transpulmonary thermodilution, which was indexed to the body surface area (BSA). Cardiac index (CI), systemic vascular resistance index (SVRI) and stroke volume index (SVI) were calculated according to standard formulae.

Renal variables

Postoperatively, an 8 Fr catheter (Webster laboratories, Baldwin Park, CA, USA) was introduced into the left or right renal vein, via punction of the right femoral vein. The central position of the catheter in the renal vein was confirmed by venography using ultra-low doses of iohexol, 5–15 mg I kg^{-1} (Omnipaque 300 mg I ml−1; GE Healthcare, Stockholm, Sweden). The continuous retrograde thermodilution technique was used to measure RBF (in triplicate). [16-19]. An i.v. priming dose of chromium ethylenediamine tetraacetic acid (^{51}Cr-EDTA) (GE Healthcare, Amersham, UK) was given after the collection of blood and urine blanks. This bolus dose was followed by constant rate infusion, individualized to BSA and to preoperative serum creatinine. Serum ^{51}Cr-EDTA activity from arterial and renal vein blood was measured using a well counter (Wizard 3', 1480, Automatic gamma counter; Perkin Elma

LAS, Turkuu, Finland). Renal data were normalised to a BSA of 1.73m^2. In Table 1, formulas for calculation of renal variables are described.

Experimental protocol

The experimental procedure was performed shortly after arrival to the intensive care unit. Two 30 min urine collection control periods were started at a target MAP of 75 mmHg (C1 and C2) following a period of equilibration of at least 60 min. At the end of each 30 min period, urine was collected and measurements of CO and RBF were performed. Arterial, central and renal venous blood samples were drawn for measurements of serum concentrations of sodium, ^{51}Cr-EDTA, haemoglobin and oxygen content. Using a cross-over design, the infusion rate of norepinephrine was changed in a random fashion to reach target MAP:s of 60 mmHg and 90 mmHg, respectively. Randomisation was accomplished using sealed envelopes in two blocks. The titration period of the norepinephrine infusion rate lasted for approximately 15 minutes. MAP was then kept at the new target MAP for 30 min. Measurements of CO, RBF and blood- and urine samples were conducted at the end of each 30 min period. Infusion rates of fluids and drugs were unchanged during the experimental procedure.

Statistical analysis.

The change in GFR at a MAP of 60, 75 and 90 mmHg, respectively, was the primary end-point of this investigation study. To detect GFR change by 30%, 9 patients were needed at a power of 0.80, a significance level of 0.05 and a standard deviation of the mean difference of paired measurements of 15 ml/min. Changes in other renal and systemic variables were secondary outcome variables. Data from the first (C1) and second (C2) control measurements were pooled. The Shapiro-Wilks analysis was used to check for normal distribution of continuous variables. . A repeated measures analysis of variance (ANOVA) and a least

significant difference (LSD) post-hoc test were used to evaluate the effects of variations in MAP on normally distributed data, while Friedman's test was used followed by Wilcoxon summed rank test for non-parametric data. PASWStatistics 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Statistical significance was indicated at a probability level (p value) of less than 0.05. Data is presented as mean ± standard deviation (SD).

Results

Fourteen patients were included in this investigation. One patient was excluded before measurements due to significant postoperative bleeding and another patient was excluded due to failed placement of the renal catheter. In two patients, catheterization and control measurements were completed, but the renal vein catheter was occluded after randomization, excluding also these patients. Thus, this study includes data from 10 patients. Data on patient characteristics are presented in Table 2 and 3, and intraoperative data are presented in Table 4.

The experimental procedure started when the patient was considered normovolemic by the attending intensivist, 83 ± 69 minutes after arrival to the ICU. Sedation was maintained by propofol 3.3 ± 0.9 mg/kg/hour and fentanyl (n=7) 0.02 ± 0.005 µg/kg/min or remifentanil 0.12 ± 0.02 µg/kg/min (n=3) and the patients were mechanically ventilated to normocarbia at a FiO_2 0.35 ± 0.06 and with a PEEP of 6.6 ± 1.7 cmH_2O.

Systemic variables (Table 5)

The mean norepinephrine infusion rates at the target MAP:s of 60 mmHg, 75 mmHg and 90 mmHg were 0.13 ± 0.11, 0.25 ± 0.16 and 0.38 ± 0.28 µg/kg/min, respectively. At a target MAP of 75 mmHg, CI (13%), SVI (13%) SVRI (14%), $ScvO_2$ (4%), haemoglobin (4%) and global oxygen delivery index (DO_2I) (18%) were all significantly higher than at MAP 60 mmHg. CVP, global oxygen consumption index (VO_2I) and heart rate were, however, not affected. The dose of norepinephrine had to be increased by 52% to increase MAP from 75 mmHg to 90 mmHg. This caused significant increases in SVI (7%), SVRI (26%), serum haemoglobin (3%), and a decrease in heart rate (-10%) with no changes in CI, CVP, $ScvO_2$, DOI_2, VO_2I or temperature.

Renal variables (Table 6)

GFR was 31% higher at target MAP of 75 mmHg than at a target MAP of 60 mmHg. This GFR increase was accompanied by increases in sodium filtration (31%) and sodium reabsorption (29%). Increasing MAP from 60 to 75 mmHg increased RBF (18%), renal oxygen delivery (RDO_2) (25%), and renal oxygen consumption (RVO_2) (20%), but had no effect on renal vascular resistance (RVR), filtration fraction (FF), urine flow (UF) or renal oxygen extraction (RO_2Ex). A further increase in MAP from 75 mmHg to 90 mmHg increased RVR (38%), but caused no other changes in renal variables. Six patients (60%) developed acute kidney injury, as defined by the KDIGO criteria [20], during the two first postoperative days.

Discussion

In the present investigation, the effects of various target levels of MAP on GFR, RBF, RVO_2 and renal oxygenation were studied early after liver transplantation. The main findings were that increasing MAP from 60 mmHg to 75 mmHg caused an increase in both GFR and in RVO_2. Renal oxygenation was preserved by the proportional increase in RDO_2, leaving the renal oxygen extraction and hence the oxygen supply/demand relationship unaffected. No additional beneficial renal effects were seen when further increasing target MAP to 90 mmHg. Thus, the perioperative MAP for optimal renal perfusion, filtration and oxygenation in normovolemic patients early after liver transplantation should be kept at approximately 75 mmHg, as lower levels may be suboptimal in this respect.

Our results are compatible with a recent investigation by Mizota et al, evaluating the relationship between the level of intraoperative blood pressure reduction and the risk of developing postoperative AKI in patients undergoing liver transplantation [21]. They found that the lowest intraoperative MAP was an independent predictor of AKI and that even a short period of severe hypotension was significantly related to the development of postoperative AKI. Thus, one way to evade development of postoperative AKI is to avoid hypotension, i.e. a MAP < 75 mmHg, by the use of an adequate dose of norepinephrine, to optimize renal perfusion, function and oxygenation perioperatively, in liver transplantation, as shown in this study.

Increasing renal perfusion pressure by norepinephrine increases renal vascular resistance (RVR) partly by a direct α-mediated vasoconstriction, but also, and to a much greater extent, by pressure-dependent renal autoregulation [22]. In experimental studies, it has been shown that the renal autoregulatory mechanism accounted for approximately 90% of the RVR increase when MAP was elevated by 20-40 mmHg using norepinephrine [22]. This renal autoregulatory mechanism controls the tone of the afferent arterioles to maintain both RBF and GFR virtually unchanged despite changes in MAP [23, 24]. Renal autoregulation is

mediated by the faster myogenic vasoconstrictory mechanism and the slower superimposed tubuloglomerular feed-back mechanism, both acting in concert to control the afferent arteriolar tone. In the present study, both RBF and GFR increased when MAP was increased from 60 mmHg to 75 mmHg, but there was no change in RVR. These results suggest that both RBF and GFR are pressure-dependent, perioperatively, at a target MAP of approximately 60 mmHg in liver transplants, and hence that renal autoregulation of GFR and RBF has been lost due to a too low pressure. On the other hand, when MAP was increased to 90 mmHg, there was an increase in RVR without any effect on filtration fraction (i.e. the GFR/renal plasma flow ratio) and without any further increase in RBF or GFR. This together suggests that the increase in RVR to a great extent is mediated by renal autoregulation causing afferent arteriolar vasoconstriction, although we cannot exclude the possibility of an additional α-mediated renal vasoconstriction. These results are in line with our previous study, in which an elevation of MAP from 60 to 75 mmHg improved GFR and RDO_2 in patients suffering from AKI and norepinephrine-treated vasodilatory shock after cardiac surgery [25].

We have repeatedly shown in postoperative patients that the major determinant of RVO_2 is GFR [14, 16, 17, 26]. An improved renal function, i.e. an increase in GFR, will enhance the filtered amount of sodium. This will increase the delivery of sodium to the tubules and the tubular sodium reabsorption increasing RVO_2. Thus, any intervention that increases GFR will also increase renal oxygen demand. In this investigation, the norepinephrine-induced increase in MAP from 60 to 75 mmHg increased GFR by 31%, which induced an elevation of both tubular sodium reabsorption and RVO_2. Such an increase in RVO_2 could potentially impair renal oxygenation, provided that the increase in renal oxygen requirements is not accompanied by a similar increase in RDO_2. This is of particular importance as the outer portion of the renal medulla is on the border of hypoxia under normal conditions, due to a relative hypoperfusion and elevated oxygen utilization of the medullary

thick ascending limbs when compared to the renal cortex [27]. In this investigation, RDO_2 increased by 25%, an increase that was sufficient enough to match the 20% increase in RVO_2, resulting in a unaffected RO_2Ex upon the induced changes in MAP. Thus, norepinephrine did not jeopardise renal oxygenation at the target MAP:s investigated in the present study, i.e. the renal O_2 demand/supply relationship was preserved.

Splanchnic vasodilation caused by increased levels of nitric oxide [29] has been suggested to contribute to the hyperdynamic vasodilated circulation in patients with advanced cirrhosis [28]. An intraoperative post-reperfusion rise in cytokines and complement factors adds further to a systemic vasodilation, resulting in a perioperative need for vasopressor treatment during and after liver transplantation [11]. In the present study, the patients presented with a vasodilatory hyperdynamic state both intra- and postoperatively, with a high cardiac index and a low systemic vascular resistance resulting in a need for vasoconstrictory norepinephrine treatment to obtain adequate systemic perfusion pressures. One could argue that norepinephrine would induce a renal vasoconstriction redistributing CI from the kidneys. In this study, the RBF/CI ratio was ≈ 20%, which is somewhat lower than previously described in uncomplicated postoperative patients, in whom the RBF/CI ratio was 27% [19]. This redistribution is, however, unlikely to be explained by a norepinephrine-induced renal vasoconstriction, as RBF and GFR improved while RVR was unchanged when MAP was changed from 60 to 75 mmHg, as shown in this study. This is in line with previous results in postoperative patients with AKI norepinephrine-dependent systemic vasodilation [25].

Cardiac index increased by 8% when increasing MAP from 60 mmHg to 90 mmHg, most likely explained by the norepinephrine-induced, $ß_1$-mediated increase in myocardial contractility. This finding is compatible with previous studies on septic [25, 30] and post-cardiotomy vasodilatory shock patients [25, 30]. It has previously been shown that norepinephrine induces a decrease in plasma volume dependent on blood pressure, attributed to a transcapillary fluid extravasation, which will increase serum haemoglobin and arterial

oxygen content [31]. In the present study, both systemic and renal oxygen delivery were increased partly as a consequence of the norepinephrine-induced increase in serum haemoglobin.

One limitation of this investigation is the low sample size, which may limit the generalisibility of our results. The finding of an optimal target MAP between 70-80 mmHg for renal function, perfusion and oxygenation needs, described here, needs to be confirmed in a larger study involving several centers, evaluating the role of postoperative MAP for renal outcome after liver transplantation. Another limitation of the present study is the lack of a time-control group, resulting in a possibility that the observed changes in systemic and renal variables could be due to time-dependent or spontaneous fluctuations in MAP, and not to norepinephrine or the target MAP per se. One way to circumvent this problem was to change the infusion rates of norepinephrine to achieve the target MAP:s in a random fashion.

In conclusion, at MAP levels below 75 mmHg, renal blood flow and GFR are pressure-dependent, reflecting an exhausted renal autoregulatory reserve early after liver transplantation. These results suggest that MAP should be targeted to approximately 75 mmHg for optimal perioperative renal filtration, perfusion and oxygenation in patients undergoing liver transplantation.

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Table 1. Formulas for calculation of renal variables

Variable	Formulae
Renal blood flow (RBF)	(unilateral renal vein blood flow × 2) + urine flow
Renal plasma flow (RPF)	RBF × (1 – hematocrit)
Filtration fraction (FF)	(RPF × [^{51}Cr-EDTA arterial] – (RPF – urine flow) × [^{51}Cr-EDTA renal vein])/(RPF × [^{51}Cr-EDTA arterial])
Glomerular filtration rate (GFR)	FF x RPF
Renal vascular resistance (RVR)	(MAP-CVP)/RBF
Arterial-renal vein (rv) oxygen content difference ($RAVO_2$-diff)	(CaO_2-$CrvO_2$)
Renal oxygen consumption (RVO_2)	RBF × (CaO_2-$CrvO_2$)
Renal oxygen extraction	(CaO_2-$CrvO_2$/CaO_2)
Renal sodium filtration	GFR x $[Na^+]_s$
Renal sodium excretion	Urine flow x $[Na^+]_s$
Renal sodium reabsorption	(GFR x $[Na^+]_s$) – (Urine flow x $[Na^+]_u$)

MAP; mean arterial pressure, CVP; central venous pressure, CaO_2 and $CrvO_2$; arterial and renal vein oxygen contents, $[Na^+]_s$; serum sodium concentration, $[Na^+]_s$; urine sodium concentration

Table 2. Patient characteristics

Gender, n (% female)	5 (50)
Age, mean (SD)	57 ± 12
Height (cm)	172.0 ± 7.0
Body surface area (m2)	1.93 ± 0.2
Body mass index (kg/m2)	22.0 ± 1.2
Diabetes, n (%)	1 (10)
Beta-adrenergic blocker, n (%)	6 (60)
ACE-inhibitor, n (%)	2 (20)
Diuretics, n (%)	7 (70)

Values are means ± SD, n = number of patients (%)
ACE-inhibitor; angiotensin converting enzyme-inhibitor

Table 3. Preoperative individual data

Patient	Diagnosis	MELD score	Child-Pugh score	Serum bilirubin (mmol/l)	mGF (ml/min/1.73m$^{2)}$	Serum creatinine (µmol/l)	ASA
1	Primary biliary cirrhosis	15	10	36	75	67	3
2	Hepatitis C virus, cirrhosis	17	10	32	95	109	2
3	Primary sclerosing cholanigitis	6	9	8	72	60	2
4	Primary sclerosing cholanigitis	22	11	110	62	59	3
5	Alpha-1 antitrypsin deficiency	16	11	43	94	75	3
6	Alcoholic liver cirrhosis	24	12	150	72	62	3
7	Primary sclerosing cholanigitis	13	9	60	102	73	2
8	Primary sclerosing cholanigitis	9	6	32	89	76	2
9	Hepatitis C virus,	9	9	14	122	60	3
10	Hepatocellular carcinoma, Primary sclerosing cholanigitis , Hepatitis B virus, ulcerative colitis	18	10	340	77	60	2
Mean		**14.9**	**9.7**	**86.0**	**87.7**	**70.1**	**2.5**
SD		**5.8**	**1.6**	**101.0**	**17.9**	**15.2**	**0.5**

MELD; Model For End-Stage Liver Disease**,** mGFR; measured glomerular filtration rate, ASA; American Society of Anesthesiologists

Table 4. Intra-operative data of liver transplant recipients (n=10)

Cold Ischaemia Time (min)	466 ± 131
Duration of surgery (min)	363 ± 86
Bleeding (L)	2.4 ± 1.3
Packed red blood cells (n=8, units)	2.5 (1-4)
Platelets (n=4, units)	2.5 (2-3.25)
Plasma (n=6, units)	4.5 (1-6)
Fibrinogen (n=7, g)	2.0 (1-11)
Albumin (n=5, ml)	300 (200-600)
Cellsaver (n=8, ml)	525 (215-980)
Intra-operative crystalloid (L)	2.4 ± 1.0
Epinephrine, n (%)	7 (80)
Diuresis (ml/procedure hour)	123 ± 49
CI prior to anhepatic phase (l/min/m^2)	3.4 ± 0.9
CI during anhepatic phase (l/min/m^2)	4.1 ± 1.8
CI after reperfusion (l/min/m^2)	4.6 ± 0.9
SVRI (ml/min/min^2)	1380 ± 307
CVP (mmHg)	7 ± 2
Intra-operative fluid balance (ml)	583 ± 1620

Data are presented as median (min-max), mean ± SD, n = number of patients (%).
CVP; central venous pressure, SVRI; systemic vascular resistance index, CI; cardiac index

Table 5. Effects of varying doses of norepinephrine on systemic variables (n=10)

	60 mmHg	75 mmHg	90 mmHg
Norepinephrine (μg/kg/min)	0.13 ± 0.11	0.25 ± 0.16***	0.38 ± 0.28##
Cardiac index (l/min/m^2)	3.8 ± 1.0	4.3 ± 1.1***	4.1 ± 1.1
Heart rate (beats/min) ¶	72 ± 15	72 ± 16	65 ± 19##
Stroke volume index (ml/m^2)	53.2 ±11.7	59.9 ± 11.6**	63.9 ± 10.9##
Central venous pressure (mmHg)	7.1 ± 3.0	7.9 ± 2.8	8.4 ± 3.1
SVRI (dynes x sec/cm^3/m^2)	1183 ± 374	1352 ± 431**	1707 ± 474###
$ScvO_2$ (%)	78.0 ± 6.4	81.5 ± 7.4***	81.3 ± 7.2
Serum haemoglobin (g/l)	102.4 ± 14.2	106.6 ± 16.2***	109.5 ± 14.5##
DO_2I (ml/min/min2)	521 ± 122	614 ± 156***	604 ± 150
VO_2I (ml/min/min2)	97 ± 14	92 ± 19	93 ± 19
Body temperature	36.7 ± 0.4	36.9 ± 0.4*	36.8 ± 0.3

Data are presented as mean ± SD. 75 mmHg versus 60 mmHg *p <0.05, ** p < 0.01, *** p < 0.001; 90 mmHg versus 75 mmHg # p <0.05, ## p < 0.01, ### p < 0.001
SVRI, systemic vascular resistance index; $ScvO_2$, central venous oxygen saturation
DO_2I, systemic oxygen delivery index; VO_2I, systemic oxygen consumption index.
¶, indicates a variable not normally distributed

Table 6. Effects of varying doses of norepinephrine on renal variables (n=10)

	60 mmHg	75 mmHg	90 mmHg
Renal oxygen extraction	0.121 ± 0.05	0.120 ± 0.04	0.125 ± 0.05
Urine flow (ml/min) ¶	1.27 ± 0.7	2.74 ± 2.5	2.52 ± 2.9
Renal blood flow (ml/min)	694 ± 243	820 ± 208*	767 ± 272
Renal blood flow /cardiac index	0.185 ± 0.06	0.200 ± 0.06	0.190 ± 0.06
Renal vascular resistance (mmHg/ml/min)	0.083 ± 0.03	0.087 ± 0.02	0.120 ± 0.04##
Glomerular filtration rate (ml/min)	42.6 ± 44.4	55.9 ± 38.3**	58.8 ± 58.8
Filtration fraction	0.08 ± 0.07	0.10 ± 0.05	0.11 ± 0.09
Renal sodium filtration (mmol/min)	5.84 ± 6.2	7.64 ± 5.4**	8.02 ± 8.2
Renal sodium reabsorption (mmol/min)	5.80 ± 6.2	7. 51 ± 5.4**	7.93 ± 8.2
Fractional sodium excretion (%) ¶	2.4 ± 3.2	2.7 ± 3.8	1.6 ± 2.5#
Renal oxygen delivery (ml/min)	95.1 ± 33.8	119.0 ± 34.1**	114.3 ± 41.7
Renal oxygen consumption (ml/min)	11.4 ± 5.8	13.7 ± 4.5*	14.1 ± 7.4

Data are presented as mean ± SD. 75 mmHg versus 60 mmHg *p <0.05, ** p < 0.01, *** p < 0.001;
90 mmHg versus 75 mmHg # p <0.05, ## p < 0.01, ### p < 0.001.
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PAPER IV

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Renal blood flow, glomerular filtration rate and renal oxygenation in early clinical septic shock.

Submitted

Renal blood flow, glomerular filtration rate and renal oxygenation in early clinical septic shock

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Abstract

Objective: Current views on renal hemodynamics, function and oxygenation in clinical acute kidney injury (AKI) are largely based on experimental studies and clinical data are lacking. We therefore measured renal blood flow (RBF), glomerular filtration rate (GFR), renal oxygen consumption and oxygenation in patients with early septic shock.

Design: Prospective, two-group comparative study

Setting: General and cardiothoracic intensive care units

Intervention: None

Methods: Patients with norepinephrine-dependent early septic shock (n=8) were studied within 24 hours after arrival in the ICU and compared with post-cardiac surgery patients without AKI (n=58, controls). Data on systemic hemodynamics and renal variables were obtained during two 30-minute periods. Systemic hemodynamics were obtained by pulmonary artery- or transpulmonary thermodilution techniques, respectively. RBF was measured by the infusion clearance of para-aminohippuric acid (PAH), corrected for renal extraction of PAH by the use of a renal vein catheter. The filtration fraction was measured by renal extraction of ^{51}Cr-EDTA. Renal oxygenation was estimated from the renal oxygen extraction, directly reflecting the renal oxygen supply/demand relationship.

Results: RBF and renal oxygen delivery were significantly lower in the septic group (-19%, p=0.068 and -24%, p=0.037, respectively). The RBF/cardiac index ratio was significantly lower (-30%, p=0.003), while renal vascular resistance was higher (20%, p=0.069) the septic shock group. GFR (-32%, p=0.006) and renal sodium reabsorption (-29%, p=0.014) were both lower, in the septic group. Filtration fraction did not differ between groups., while there was no difference in renal oxygen consumption between groups. Renal oxygen extraction was significantly higher in the septic group (28%, p=0.022). In the septic group, markers of tubular injury were elevated.

Conclusions: In early clinical septic shock, a reduced renal function is accompanied by an impaired renal oxygenation, caused by a combination of renal vasoconstriction, reduced renal oxygen delivery and tubular sodium reabsorption at a high oxygen cost.

Introduction

Severe sepsis and septic shock continues to be a common cause of ICU admission and is responsible for acute kidney injury (septic AKI) in approximately 40-50% of the population of critically ill patients. Furthermore, septic AKI is associated with high risk of early hospital mortality [1-4].

The pathophysiology of AKI in septic shock is not well known. In 2004, Schrier and Wang proposed, based on experimental models, that the predominant early pathogenetic factor is renal vasoconstriction [5]. Thus, endotoxinemia induces a systemic vaso- and venodilation, causing a reflex activation of renal sympathetic activity and the renin-angiotensin system together with an increased secretion of the renal vasoconstrictor arginine vasopressin. This stimulation of the neurohormonal axis will cause a renal vasoconstriction and renal ischemia with a predisposition to acute renal failure [5].

This hypothesis was challenged by Langenberg et al who, in a conscious septic sheep model, found in that the endotoxinemia-induced hypotension and systemic vasodilation was accompanied by a high cardiac output, increased renal blood flow (RBF) and a fall in creatinine clearance, a surrogate for glomerular filtration rate (GFR) [6]. In that hyperdynamic sepsis model, the fall in creatinine clearance was explained by a renal vasodilation of preferentially the efferent arterioles, which will increase RBF but decrease the upstream glomerular filtration pressure [6].

Data on renal hemodynamics and GFR in clinical sepsis is scarce. Prowle et al measured RBF non-invasively by magnetic resonance imaging in 10 patients with established septic AKI (90% of the patients were on continuous renal replacement therapy) [7]. They found that the renal vascular bed was severely constricted with a RBF being only half of that seen in healthy volunteers.

To our knowledge there is a lack of reports on RBF, GFR and renal oxygenation in *early* clinical sepsis. In the present study, we have therefore measured renal perfusion, filtration and oxygenation in patients submitted to the intensive care unit (ICU) due to early norepinephrine-dependent septic shock requiring mechanical ventilation. RBF was measured using the infusion clearance technique for para-aminohippurate (PAH), corrected by renal extraction of PAH by a renal vein catheter. Filtration fraction was measured by renal extraction of chromium ethylenediamine tetraaceticacid (^{51}Cr-EDTA). Mechanically ventilated and sedated post-cardiac surgery patients with no pre- or postoperative renal impairment served as controls. We tested the hypothesis that in early norepinephrine-dependent clinical septic shock, a reduced GFR is accompanied with an increased RBF and increased renal oxygen delivery.

Material and methods

The study protocol was approved by the Gothenburg Regional Ethics Committee, and written informed consent was obtained from the next of kin. The study was registered in ClinicalTrials.gov (identifier NCT02453425). Patients in septic shock were compared to a group of post-cardiac surgery patients early after uncomplicated cardiac surgery, at a numerical ratio of 1:7. Patients in both groups were studied in the intensive care unit during sedation and mechanical ventilation.

Septic patients

Eight septic patients were prospectively included in the study with the following inclusion criteria a) > 18 years of age, b) normal premorbid serum creatinine, c) norepinephrine-dependent septic shock as defined by the International Surviving Sepsis Campaign Guidelines [8, 9], d) normovolemia as indicated by a pulse pressure variation < 12%, e) mechanical ventilation and f) inclusion within 24 hours after arrival in the ICU. The exclusion criteria were: a) severe circulatory instability refractory to treatment b) renal impairment due to other causes than septic shock, c) unsuccessful catheterization of the renal vein, and d) contraindication to radio-contrast agents. The patients were mechanically ventilated and sedated with propofol (2.23 ± 0.53mg/kg/h) and fentanyl (0.021 ± 0.014 μg/kg/min). Postoperative targets were pulse pressure variation < 12% and a mean arterial pressure of 70-80 mmHg. Postoperative hypovolemia was treated according to routine clinical practice with albumin (Albumin Baxalta® 200g/l) and/or crystalloid fluid (Ringer–Acetate®, Baxter Viaflo) at the discretion of the attending intensivist.

Control group

Fifty-eight patients served as a control group. These patients had earlier been included in pharmacological studies performed by our study group [10-13]. Inclusion criteria for this group were: a) age >18 years, b) elective cardiac surgery, c) left ventricular ejection fraction ≥ 40%, and d) normal preoperative serum creatinine. The exclusion criteria were postoperative a) inotropic support, b) arrhythmias requiring treatment, c) significant bleeding, d) unsuccessful catheterization of the renal vein, and e) postoperative AKI according to the AKIN criteria. The baseline renal and systemic data of these patients, i.e. before pharmacological intervention, were used for comparison with those of the septic shock group. The studies were performed postoperatively in the intensive care unit, where the patients were sedated with propofol (3.8 ± 0.18 mg/kg/min) and morphine (0.5-1.0 mg/hour), and mechanically ventilated. Target central venous pressure (CVP) and target mean arterial pressure (MAP) were 5-10 mmHg and 70-80 mmHg, respectively. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (Venofundin, Braun, Germany) and crystalloid fluids (Ringer–Acetate®, Baxter Viaflo).

Measurements of systemic variables

Arterial blood pressure and heart rate were continuously measured using a catheter in either the radial or the femoral artery. Cardiac output was measured by the transthoracic thermodilution pulse contour technique using the PiCCO ™ device (Pulsion Ltd, Munich, Germany) and by a pulmonary artery thermodilution catheter (Baxter Healthcare Corporation. Irvine CA) in the septic shock group, and in the cardiac surgery group, respectively. Cardiac index, stroke volume index, systemic oxygen delivery index, systemic oxygen consumption index and systemic vascular resistance index were calculated according to standard formulae.

Measurements of renal variables

A 8-Fr catheter (Webster laboratories, Baldwin Park, CA, USA) was introduced via the femoral vein centrally into the left or right renal vein, guided by fluoroscopy. An intravenous priming dose of PAH (8mg/kg bodyweight) and ^{51}Cr- EDTA (0.6 MBq/m2 BSA), (GE Healthcare Limited, The Grove Center, Amersham, UK), were given. This was followed by an infusion at a constant rate individualized to body weight and serum creatinine. Serum concentrations of PAH and serum ^{51}Cr-EDTA activity from arterial and renal vein blood were measured using a spectrophotometer (Beckman DU 530, Life Science UV/Vis, Fullerton, CA) and a well counter (Wizard 300, 1480, Automatic Gamma Counter, Perkin Elma LAS, Turkuu, Finland), respectively. Renal plasma flow was calculated and measured using the infusion clearance technique as the amount of infused PAH divided by the difference in arterial- renal vein PAH concentrations [14]. Formulae for calculation of the various renal variables are described in table 1. All renal data were normalized to a BSA of 1.73 m^2.

Urine in the septic group was assayed for N-acetyl- β -d-glucosaminidase (NAG*)* by a spectrophotometric method (ABX Pentra 400, Horiba Medical, CA, USA) using a commercially available kit (Roche Diagnostics GmbH, Mannheim, Germany). The urinary NAG/creatinine ratio was calculated.

Experimental procedure

In both the septic and the control group, two 30-minutes urine collection periods were conducted after an equilibration period of at least 60 minutes. Cardiac index was measured at the end of each of the urine collection periods, followed by arterial, renal vein and mixed venous blood sampling and urine sampling for measurements of systemic and renal variables. The infusion rates of on-going infusions were not changed during the experimental procedure.

Statistical analysis

The primary end-points of this study were RBF and renal oxygen delivery (RDO_2). To detect a 30% difference in RBF or RDO_2 between the control and the septic group, 8-9 patients were needed in the septic group and 56-63 patients were needed in the control group at an enrolment ratio of 7 and a standard deviation of 250 ml/min (RBF) and 40 ml/min (RDO_2) at a power of 0.05 and alpha of 0.8 [15]. Intra-group data on renal and systemic variables from the two 30- minute periods were pooled. Continuous variables were checked for normal distribution using Shapiro-Wilk test. Intergroup differences where compared using independent-samples t-test and Mann-Whitney U test when appropriate. Categorical data were compared using Fisher's exact test. PASWStatistics 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Data are presented as mean ± SD throughout the text. A p-value < 0.05 was considered significant.

Results

Patient characteristics for the septic group are presented in Table 2. Five patients had abdominal sepsis and three had septic pneumonia. The mean SOFA score was 7.9 ± 2.6 at the time of the study. The mean serum creatinine at study entry was 91 ± 22 µmol/l (range 73-139 µmol/l). The mean dose of norepinephrine was 0.23 ± 0.17 µg/kg/min. One patient was treated with an infusion of furosemide (20 mg/hour).

There was a larger portion of females in the study group than in the control group, and the study group had a smaller body surface area. Premorbid renal function was higher in the septic group, while there was no difference in age or in the prevalence of diabetes between groups. Hypertension, as well as, anti-hypertensive medication was more frequent in the control group (Table Supplemental Digital Content).

Systemic variables (Table 3)

The mean arterial pressure in the control group was slightly (-3.4%) but significantly lower, while central venous pressure was significantly higher in the septic group compared to control. There was a trend for a lower systemic vascular resistance index in the septic group (p=0.059) There were no statistically significant differences between the groups with respect to cardiac index, stroke volume index, heart rate, systemic oxygen delivery index, systemic oxygen consumption index, serum hemoglobin or arterial oxygen content.

Renal variables (Table 4, Fig. 1)

Serum PAH concentration from the two measurement periods did not differ significantly in neither of the groups, suggesting that steady state was achieved. The RBF/cardiac index ratio was significantly lower in the septic shock group (p=0.003). In the septic group, GFR (-32%, p=0.006), renal sodium filtration (-31%, p=0.008), renal sodium reabsorption (-29%, p=0.014) and urine flow (-52%, p=0.007) were significantly lower compared to controls.

There was a trend for a higher renal vascular resistance (20%, p=0.069) and a lower RBF (-19%, p=0.068) in the septic group compared to controls. Renal oxygen delivery was significantly lower in the septic group (-24%, p=0.037), while there was no difference in renal oxygen consumption (RVO_2) between the two groups. Renal oxygen extraction, a direct measurement of the renal oxygen supply/demand relationship, was significantly higher in the septic group (p=0.022). RVO_2 per mmol of reabsorbed sodium was higher in the septic group (31%, p=0.057) compared to the control group. In the septic group, the urinary N-acetyl- β -D-glucosaminidase (NAG) / creatinine ratio was 5.4 ± 3.4 units/ µmol creatinine (range 1.9 - 11.4).

Discussion

In the present study, RBF, GFR and renal oxygenation were measured in an early norepinephrine-dependent septic shock. The main findings were that renal oxygen delivery was impaired caused by renal vasoconstriction and a redistribution of blood flow away from the kidneys when compared to controls. This redistribution of RBF in septic shock impaired the renal oxygen supply/demand relationship as evidenced by an increased renal oxygen extraction. Thus, these results do not support the concept derived from studies on large animals, that AKI in early septic shock is accompanied by renal vasodilation and an increase in RBF [6]. On the contrary, the results presented here are in line with the previously presented hypothesis that RBF is low due to a renal vasoconstriction resulting in a reduction of renal oxygen delivery [5].

The redistributon of RBF away from the kidneys could be explained by an increase in the tone of the renal afferent arterioles, as there was a decrease in both RBF and GFR in the present study. This explanation is supported by the finding that renal filtration fraction (GFR/RPF) was unchanged suggestive of a balanced decrease in both GFR and RBF. Such an increase of the tone of the afferent arterioles in sepsis has been demonstrated before in endotoxemic animals [16].

An increased production of nitric oxide (NO) has been demonstrated to result in a systemic vasodilation and hypotension in both clinical and experimental sepsis [17, 18] [19, 20]. Hypotension in sepsis elicits a baroreflex-mediated increase in renal sympathetic nerve activity, as demonstrated in animal models of sepsis [21, 22] and in clinical sepsis as an elevated plasma norepinephrine level [23]. Thus, a NO-mediated renal vasodilation may be antagonised by the increase in renal sympathetic activity in sepsis. Ramchandra et al demonstrated, in conscious septic sheep, that the previously described renal vasodilatation [6] was accompanied by an increase in renal sympathetic nerve activity, which would promote

renal vasoconstriction [22] . They suggested that the profound increase in NO in septic shock will override this sympathetically-mediated renal vasoconstriction causing a net renal vasodilation. Based on the results of the present study, on the other hand, one could speculate that in clinical sepsis, the neuro-hormonal activation dominates over the release of NO, causing a renal distribution of RBF away from the kidneys decreasing renal oxygen delivery. Thus, the host response to septicemia in terms of renal hemodynamics seem to vary between species.

The fall in GFR in the septic group could be explained by the increased renal sympathetic nerve activity, as discussed above. Activation of the renal sympathetic nerve activity will cause a reduction in both RBF and GFR, suggesting an effect on preferentially the afferent arterioles [24]. Another explanation could be an activation of the tubulo-glomerular feedback (TGF) mechanism, caused by tubular dysfunction. This would reduce sodium reabsorption of individual tubules, increasing the sodium delivery to the macula densa, activating the TGF response, inducing afferent arteriolar vasoconstriction with a decrease in both RBF and GFR [5, 25]. This hypothesis is supported by the finding that renal extraction of PAH was significantly lower in septic shock patients, which is an indicator of tubular dysfunction in early clinical sepsis. We find the early fall in GFR, in this study, unlikely to be caused by shedding of tubular cells causing tubular obstruction[5], as postmortal histopathological findings in septic AKI shows limited tubular injury [26], suggesting that the early fall in GFR in clinical sepsis is functional rather than structural in nature.

We have repeatedly shown that there is a close correlation between GFR, tubular sodium reabsorption and RVO_2 in postoperative patients [10, 12, 14, 15]. Thus, the major determinant of RVO_2 is the GFR. In the septic shock group, the lower GFR was accompanied by a lower tubular sodium reabsorption compared to controls, as expected. However, there

was no difference in RVO_2 between groups, suggesting that in early clinical septic shock there is an increase in oxygen utilization for a certain level of sodium transport. This indicates an impaired tubular oxygen utilization, as reflected by the higher oxygen consumption per mmol reabsorbed sodium. Such an impairment of tubular oxygen utilization has previously been described by us in established AKI after cardiac surgery [15], in patients with tubular injury after cardiac surgery with cardiopulmonary bypass [27] and in patients with renal dysfunction early after liver transplantation [28]. One explanation for this impaired renal oxygen utilization in clinical acute renal dysfunction could be hypoxia-induced loss of epithelial cell-polarisation and tight junction integrity [29, 30], or reduced renal production of NO which will cause an increase in RVO_2 [31, 32]. Finally, the impaired renal oxygen utilization could be explained by oxidative stress, which will increase renal mitochondrial oxygen consumption [33].

N-acetyl- β -D-glucosaminidase (NAG) is an enzyme that is originating mainly from the proximal tubules in the kidneys. As NAG does not undergo glomerular filtration, urinary excretion of NAG is a marker of tubular damage [34]. We have recently shown in anesthetized mechanically ventilated patients with normal renal function that baseline, presurgical urinary NAG/creatinine is < 3 units/ µmol [27]. In the present study, mean urinary NAG/creatinine was found to be approximately 5 units/µmol creatinine and NAG/creatinine was > 3 units/µmol in 5 patients, suggesting a tubular injury in this group of patients with early clinical septic shock. This could be explained by renal hypoxia due to the impairment of the renal oxygen supply/demand relationship, as reflected by the lower renal oxygen delivery with a normal RVO_2, also expressed as a higher renal oxygen extraction compared to controls.

One could argue that the lower renal oxygen delivery in the septic shock group was caused by the fact norepinephrine was used for treatment of vasodilatory shock. We believe

that this is less likely, as we have shown that restoration of mean arterial pressure from 60 to 75 mmHg by increasing the dose of norepinephrine, improves renal oxygen delivery, GFR and renal oxygenation in postoperative patients with norepinephrine-dependent systemic vasodilation and AKI [35].

Previous data on RBF and GFR in patients with septic shock are controversial. Brenner et al studied seven hyperdynamic (CI: 5.5 l/min) septic patients, all being treated with dopamine and found that the RBF/cardiac output (CO) ratio was reduced below 10%, suggesting a renal vasoconstriction [36]. Rector et al found that the RBF/CO ratio was essentially normal in six patients with septic shock [37] There are no data on concomitant medication or management of those patients in the study by Rector et al. Furthermore, none of those studies presented data from a non-septic mechanically ventilated and sedated control group with normal renal function and none demonstrated data on renal oxygenation.

One limitation of the present study is the low number of included patients with septic shock. The strength of our study is that we, for the first time, measured RBF, GFR and renal oxygenation in the early phase of clinical septic shock in patients with premorbid normal renal function. Furthermore, we included a large group of control patients with uncompromised renal function, all being mechanically ventilated and sedated postoperatively in the ICU after cardiac surgery, a procedure known to induce a pronounced systemic inflammatory response syndrome (SIRS) [38, 39].

Conclusions

We have shown that in patients with early septic shock, there is a fall in GFR and a redistribution of RBF away from the kidneys due to renal vasoconstriction, most likely caused by a constriction of afferent arterioles when compared to controls. The consequent impairment in renal oxygen delivery may explain early signs of tubular dysfunction/injury

expressed as a pathological elevation of the tubular injury marker NAG.

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Conflicts of interest:

The authors declare that they have no conflict of interest.

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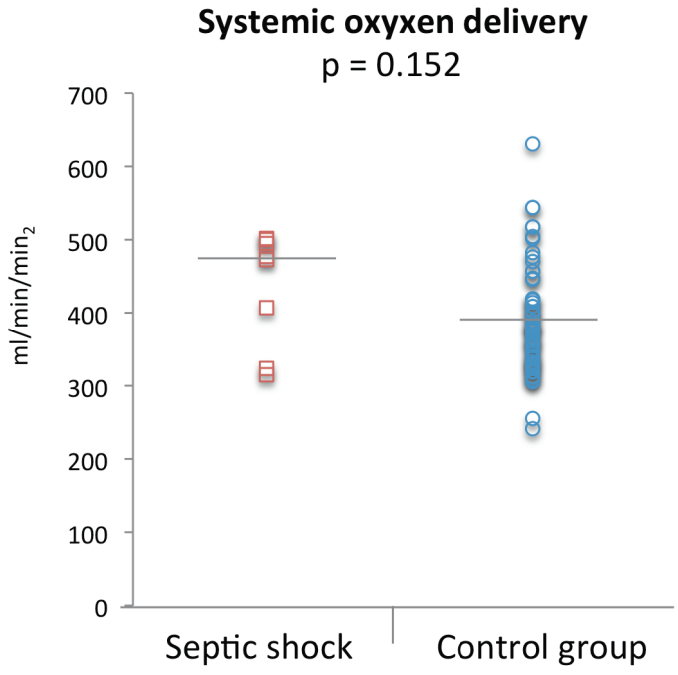
Legend

Figure 1: Shows the individual data on systemic and renal oxygen delivery in patients with early septic shock and in uncomplicated post-cardiac surgery patients with no renal impairment. Both groups were sedated and mechanically ventilated in the intensive care unit.

Figure


Systemic oxyxen delivery
p = 0.152
ml/min/min2
700
600
500
400
300
200
100
0
Septic shock
Control group

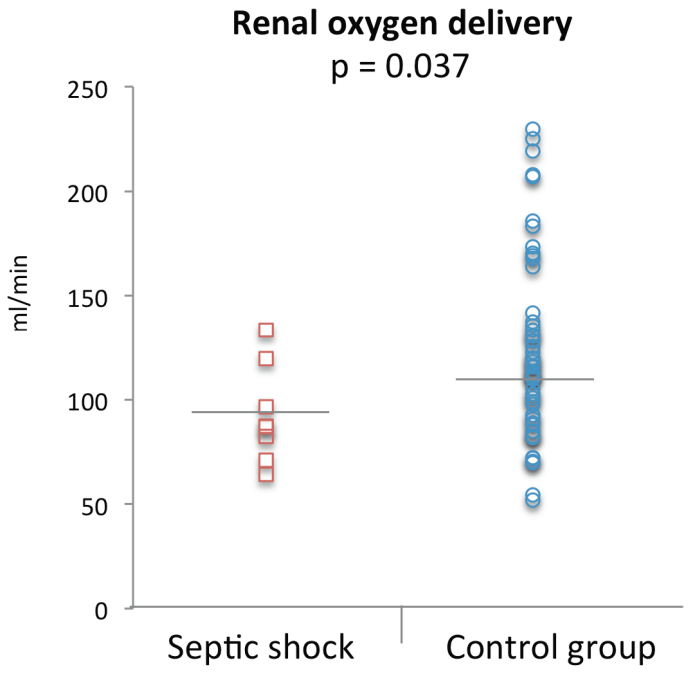

Renal oxygen delivery
p = 0.037
ml/min
250
200
150
100
50
0
Septic shock
Control group

Table 1 Formulas for calculation of renal variables

Variable	Formula
Renal plasma flow (RPF)	Amount of PAH infused/([PAH arterial] − [PAH renal vein])
Renal blood flow (RBF)	RPF/ (1 − hematocrit)
Filtration fraction (FF)	(RPF × [^{51}Cr-EDTA arterial] – (RPF – urine flow) × [^{51}Cr-EDTA renal vein])/(RPF × [^{51}Cr-EDTA arterial])
Glomerular filtration rate (GFR)	FF x RPF
Renal vascular resistance (RVR)	(MAP-CVP)/RBF
Arterial-renal vein (rv) oxygen content difference ($RAVO_2$-diff)	(CaO_2-$CrvO_2$)
Renal oxygen consumption (RVO_2)	RBF × (CaO_2-$CrvO_2$)
Renal oxygen extraction	(CaO_2-$CrvO_2$/CaO_2)
Renal sodium filtration	GFR x $[Na^+]_S$
Renal sodium excretion	Urine flow x $[Na^+]_U$
Renal sodium reabsorption	(GFR x $[Na^+]_S$) – (Urine flow x $[Na^+]_U$)

MAP; mean arterial pressure, CVP; central venous pressure, CaO_2 and $CrvO_2$; arterial and renal vein oxygen contents, $[Na^+]_S$; serum sodium concentration, $[Na^+]_U$; urine sodium concentration

Table 2. Individual data on the septic shock patients

Patient no.	Age	Sex	Diagnosis	Comorbidity	SOFA	Premorbid S-creatinine	Study entry S-creatinine	Norepi-nephrine
						μ mol/L	μ mol/L	μg /kg/min
1	71	f	Perforated diverticulitis	CAD treated with PCI	7	60	95	0.42
2	83	m	Perforated colon	CAD treated with PCI. Atrial fibrillation.	6	87	90	0.15
3	22	f	Pneumonia	Partus 3 weeks before	10	53	139	0.03
4	72	f	Pneumonia	Pancoast tumour	6	56	77	0.55
5	73	f	Rupture of esophagus	COPD	5	48	78	0.10
6	72	m	Pneumonia	Stroke	9	80	97	0.16
7	69	f	Intestinal perforation	Esophageal cancer	7	66	73	0.20
8	48	f	Intestinal anastomosis insufficiency	Ovarial cancer	13	61	76	0.27
Mean ± SD	**64 ±20**				**7.9 ±2.6**	**64 ±13**	**91 ±22**	**0.23 ±0.17**

CAD; coronary artery disease, PCI; percutaneous coronary intervention, COPD; chronic obstructive pulmonary disease, SOFA; sequential organ failure score, S-creatinine; serum creatinine

Table 3. Systemic hemodynamics

Variable	Control group (n=58)	Septic shock (n=8)	p-value
Mean arterial pressure (mmHg)	73.2 ± 7.1	76.0 ± 1.3	0.011
Cardiac index (l/min/m^2)	2.8 ± 0.5	3.3 ± 0.6	0.502
Heart rate (beats/min)	76 ± 11	86 ± 17	0.522
Stroke volume index (ml/m^2)	37.5 ± 7.6	39.8 ± 11.2	0.127
Central venous pressure (mmHg)	7.8 ± 2.5	10.9 ± 3.0	0.003
Systemic vascular resistance index (dynes x sec/cm^3/m^2)	1943 ± 445	1630 ± 305	0.059
Mixed/central venous oxygen saturation (%)	73.0 ± 4.7	74.8 ± 4.9	0.293
Serum hemoglobin (g/l)	104.8 ± 12.0	98.8 ± 9.1	0.181
Systemic oxygen delivery index (ml/min/min^2)	392 ± 75	437 ± 78	0.152
Systemic oxygen consumption index (ml/min/min^2)	100.6 ± 14.5	99.6 ± 16.2	0.753
Arterial oxygen content (ml O_2/l)	142.9 ± 16.4	133.0 ± 10.9	0.103

Values are means ± SD

Table 4. Renal variables

Variable	Control group (n=58)	Septic shock (n=8)	p-value
Renal oxygen extraction	0.097 ± 0.027	0.124 ± 0.039	0.022
Urine flow (ml/min)	3.84 ± 2.34	1.85 ± 1.05	0.007
Renal blood flow (ml/min)	858 ± 261	696 ± 166	0.068
Renal blood flow/cardiac index	0.31 ± 0.79	0.22 ± 0.67	0.003
Renal blood flow/cardiac output	0.16 ± 0.42	0.12 ± 0.43	0.028
Renal vascular resistance (mmHg/ml/min)	0.082 ± 0.023	0.098 ± 0.023	0.069
Glomerular filtration rate (ml/min)	79.8 ± 24.3	54.4 ± 17.6	0.006
Filtration fraction	0.140 ± 0.033	0.120 ± 0.052	0.306
Renal sodium filtration (mmol/min)	11.0 ± 3.4	7.6 ± 2.5	0.008
Renal sodium reabsorption (mmol/min)	10.5 ± 3.3	7.5 ± 2.5	0.014
Renal oxygen delivery (ml/min)	122.3 ± 42.4	92.7 ± 23.5	0.037
Renal oxygen consumption (ml/min)	11.4 ± 3.1	11.4 ± 4.0	0.956
Renal oxygen consumption / renal sodium reabsorption (ml/mmol)	1.12 ± 0.25	1.62 ± 0.71	0.057
Renal extraction of para-aminohippurate	0.84 ± 0.07	0.66 ± 0.22	0.005

Values are means ± SD