CARDIAC SURGERY AND THE KIDNEY
- STUDIES ON THE EFFECTS OF PHARMACOLOGICAL INTERVENTIONS ON RENAL PERFUSION, FILTRATION AND OXYGENATION

GUDRUN BRAGADOTTIR

DEPARTMENT OF ANAESTHESIOLOGY AND INTENSIVE CARE
INSTITUTE OF CLINICAL SCIENCES
SAHLGRENSKA ACADEMY

UNIVERSITY OF GOTHENBURG

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Cardiac surgery and the kidney - studies on the effects of pharmacological interventions on renal perfusion, filtration and oxygenation

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Cardiac surgery and the kidney
– studies on the effects of pharmacological interventions on renal perfusion, filtration and oxygenation

Gudrun Bragadottir

Department of Anaesthesiology and Intensive Care, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Acute kidney injury (AKI) commonly complicates cardiac surgery and is associated with high mortality. Renal ischemia is considered to be the major cause. There is a close association between glomerular filtration rate (GFR), tubular sodium reabsorption and renal oxygen consumption (RVO_2) in humans. The filtered load of sodium is an important determinant of RVO_2 and any agent that increases GFR has the potential to increase RVO_2. An ideal agent to treat patients with AKI would be one that increases both renal blood flow (RBF) and GFR, with no impairment in renal oxygenation, defined as the renal oxygen supply/demand relationship, the inverse of this relationship being the renal extraction of O_2 (RO_2Ex). Data on the effects of pharmacological interventions on RBF, GFR and renal oxygenation, are scarce.

Patients and methods: The renal vein thermodilution technique was used to analyse the effects of vasopressin (n=12) and the effects of levosimendan vs placebo (n=30), on RBF, GFR and renal oxygenation in post-cardiac surgery patients. The effects of mannitol on RBF, GFR and renal oxygenation were studied in patients (n=11) with AKI after cardiac surgery. The agreement of urinary creatinine clearance (CrCl) and three commonly used estimating equations, in comparison to GFR, measured by the infusion clearance of ^{51}Cr-EDTA, were evaluated in critically ill patients with AKI.

Results: Vasopressin increased renal vascular resistance (RVR) and decreased RBF, while GFR, RVO_2 and RO_2Ex increased. Mannitol in AKI, increased urine flow, decreased RVR and increased RBF. Mannitol tended to increase GFR and RVO_2 but did not change RO_2Ex. Compared to placebo, levosimendan decreased RVR and increased RBF and GFR, while RVO_2 and RO_2Ex were not affected. Finally, the within-group error was higher for the urinary CrCl method than the ^{51}Cr-EDTA clearance method. The urinary CrCl method and the estimating equations had high biases and high errors compared to GFR measured by ^{51}Cr-EDTA.

Conclusion: The vasopressin-induced increase in GFR was caused by post-glomerular renal vasoconstriction, accompanied by an increase in RVO_2 and RO_2Ex. Thus, vasopressin impaired renal oxygenation. Mannitol treatment of AKI induced a renal vasodilation and increased RBF. Mannitol did neither affect filtration fraction nor renal oxygenation, suggestive of balanced increases in perfusion/filtration and oxygen demand/supply. Levosimendan induced a vasodilation, preferentially of pre-glomerular resistance vessels, increasing both RBF and GFR without jeopardizing renal oxygenation. Levosimendan could therefore be a potentially useful agent for treatment of AKI in patients with heart failure. Assessment of GFR by the urinary CrCl method, had a poor precision in critically ill patients with AKI, and should not be used as a reference method, when validating new methods for assessing kidney function in this patient population. All the estimating equations performed poorly, when estimating GFR in these patients.

Key words: Kidney failure, acute; glomerular filtration rate; renal circulation; oxygen consumption; cardiac surgery; vasopressin; mannitol; levosimendan; estimating equations.
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List of original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Bragadottir G, Redfors B, Nygren A, Sellgren J, Ricksten SE
Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients.
Acta Anaesthesiol Scand 2009; 53: 1052 -1059

II. Bragadottir G, Redfors B, Ricksten SE
Mannitol increases renal blood flow and maintains filtration fraction and oxygenation in postoperative acute kidney injury; a prospective interventional study.
Crit Care 2012; Aug17;16(4):R159

III. Bragadottir G, Redfors B, Ricksten SE
Effects of levosimendan on glomerular filtration rate and renal blood flow and renal oxygenation after cardiac surgery with cardiopulmonary bypass - a randomized placebo-controlled study.
Accepted for publication in Critical Care Medicine

IV. Bragadottir G, Redfors B, Ricksten SE
Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury (AKI) - true GFR versus urinary creatinine clearance and estimating equations.
Manuscript submitted

To Jökull and Anna Maria

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Abbreviations

Abbreviations used in the text

ACE	angiotensin converting enzyme
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ANOVA	analysis of variance
BSA	body surface area
Bw	body weight
CABG	coronary artery bypass grafting
CG	The Cockcroft-Gault equation
CI	cardiac index
CKD-EPI	The Chronic Kidney Disease Epidemiology Collaboration equation
CO	cardiac output
CPB	cardiopulmonary bypass
CrCl	creatinine clearance
^{51}Cr-EDTA	^{51}Chromium-ethylene diamine tetraacetic acid
CVP	central venous pressure
eGFR	estimated GFR
$eGFR_{CG}$	GFR estimated with the CG equation
$eGFR_{CKD-EPI}$	GFR estimated with CKD-EPI equation
$eGFR_{CrCl}$	GFR estimated with urinary CrCl
$eGFR_{MDRD}$	GFR estimated with the MDRD equation
FE_{Na}	fractional excretion of sodium
FF	filtration fraction
GF_{Na}	sodium filtration
GFR	glomerular filtration rate
$GFR_{51Cr-EDTA}$	GFR measured with ^{51}Cr-EDTA infusion clearance
Hct	hematocrit
HR	heart rate
IABP	intraaortic balloon pump
IBW	ideal body weight
ICU	intensive care unit
K*uf*	ultrafiltration coefficient
LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MDRD	The Modification of Diet in Renal Disease (MDRD) equation
MPAP	mean pulmonary artery pressure

P_{Bow}	hydrostatic pressure in the capsule of Bowman
P_{glom}	hydrostatic pressure in the glomeruli
PCWP	pulmonary capillary wedge pressure
π_{Bow}	osmotic pressure in the glomeruli
π_{glom}	osmotic pressure in the capsule of Bowman
postop	postoperative
preop	preoperative
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
RBF	renal blood flow
RBF_{TD}	renal blood flow assessed by the 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
SD	standard deviation
se-crea	serum creatinine
SEM	standard error of mean
SOFA	sequential organ-failure assessment
SPSS	statistical packages for the social sciences
SV	stroke volume
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TR_{Na}	tubular sodium reabsorption.
U-crea	urine creatinine
U-volume	urine volume

Introduction

The problem of acute kidney injury after cardiac surgery

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at high risk for developing postoperative acute kidney injury (AKI). The reported incidence of AKI after cardiac surgery is 5–30%, depending on the definition of AKI and type of surgery [1-5]. The lowest incidence of AKI is seen in coronary artery bypass grafting (CABG), followed by valvular surgery and the combined CABG/valvular surgery [6]. The incidence of dialysis dependent AKI after cardiac surgery is 1-5% [2, 6-8]. AKI after cardiac surgery increases morbidity, mortality and costs [1-4, 9]. The mortality rate in cardiac surgery patients with AKI increases with the degree of renal impairment [4]. Patients with dialysis dependent AKI have the highest mortality, and in some studies the mortality in this patient group is reported to be 60 – 80% [6, 7, 10]. 2.2-4.7% of patients who survive dialysis dependent AKI after cardiac surgery with CPB have been reported to remain dialysis dependent [10-12]. As patients with postoperative AKI are often suffering from multiple-organ dysfunction, the exact contribution of AKI to mortality, has been difficult to determine. Chertow *et al.* showed in a multivariate analysis, adjusted for comorbid factors, that the occurrence of dialysis dependent AKI is an independent factor for risk of death, with an odds ratio of 7.9 [7].

Evidence suggests that even minor changes in serum creatinine are associated with increased in-patient mortality [9]. Cardiac surgery patients, whose postoperative creatinine was 0-0.5 mg/dL (0-44 μmol/l) higher than the preoperative value, had three times higher mortality than patients with a small decrease in serum creatinine after cardiac surgery in a study by Lassnigg *et al* [5]. In the same study a larger increase in serum creatinine (≥ 0.5mg/dL), was associated with more than 18-fold inrease in 30-day mortality and after adjustment for comorbid factors in a multivariate analysis it was shown that AKI is an independent predictor of mortality after cardiac surgery, with odds ratio of 5.8 [5].

Definition and classification/staging of AKI

AKI is a complex disorder. It occurs in a variety of settings with clinical manifestations ranging from only a minimal elevation in serum creatinine to anuric renal failure [9]. AKI is often under-recognized [13].

In the literature, AKI has been described by using several definitions and diagnostic criteria, ranging from a 25% increase in baseline serum creatinine to the need for hemodialysis [14]. Because of the variation in the definitions of AKI, making comparisons of results between populations and studies difficult, the AKIN and RIFLE classification criteria have been developed [9, 15]. The RIFLE (risk, injury, failure, loss, end-stage kidney disease) classification criteria, defines three grades of severity (risk, injury, failure) and two outcome classes (loss of kidney function and end-stage kidney disease)[15]. The AKIN (Acute Kidney Injury Network) classification criteria, defines three AKI stages, with no outcome classes [9]. These two systems differ. (1) In RIFLE the diagnosis is based on changes over a one-week period, while AKIN requires only changes within a 48-hour period. (2) Estimated glomerular filtration rate (eGFR) criteria, using various estimating equations, are not included in AKIN. (3) The percentage change in serum creatinine from baseline is identical in both definitions, except for additional criteria of an absolute serum creatinine increment of ≥ 0.3 mg/dL (26.5 μmol/L) within the AKIN stage 1 category. The reason for this, is the evidence that even minor increases in serum creatinine are associated with adverse outcomes. (4) Outcome classes are not included in the AKIN classification criteria. Patients with RRT are placed in stage 3 in AKIN [4].

Studies have shown that both systems are valuable tools to evaluate AKI. However, in a study by Englberger *et al*. on 4836 patients undergoing cardiac surgery with cardiopulmonary bypass, significantly more patients were diagnosed with AKI by AKIN (26.3%) than by RIFLE (18.9%) criteria[4]. Both RIFLE and AKIN criteria have been shown to be accurate early predictors of mortality after cardiac surgery [3]. However, these classification systems have limitations, i.e. both systems relay on serum creatinine concentration. Creatinine is not an ideal biomarker for AKI [14]. The concentration of serum creatinine lags behind the decline and recovery in glomerular filtration rate, and it is affected by factors other than kidney function [16].

Table 1 and 2 represents the diagnostic criteria for acute kidney injury and the AKIN classification/staging system, for acute kidney injury used in papers II and IV of this thesis.

Table 1. Diagnostic criteria for acute kidney injury

An abrupt (within 48 hours) reduction in kidney function currently defined as absolute increase in serum creatinine of more than or equal to 0.3 mg/dL (≥ 26.4 μmol/L), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours

From Methta et al, Critical Care 2007, 11:R31 [9]

Table 2. Classification/staging system for acute renal failure

Stage	Serum creatinine criteria	Urine output
1	Increase in serum creatinine of ≥ 0.3 mg/dL (≥26.4 μmol/L) or increase to ≥ 150% to 200% (1.5- to 2- fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2[b]	Increase in serum creatinine to > 200% - 300% (>2- to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3[c]	Increase in serum creatinine to > 300% (> 3-fold) from baseline (or serum creatinine ≥ 4.0 mg/dL [≥ 354μmol/L] with an acute increase of 0.5 mg/dL [44μmol/L)	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

[a]*Modified from RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria. The staging system proposed is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum creatinine influences outcome. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.* [b]*200% to 300% increase = 2- to 3-fold increase.* [c]*Given wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT. From Methta et al, Critical Care 2007, 11:R31 [9]*

Renal anatomy and physiology

Renal blood flow and filtration

Normal renal blood flow (RBF), is extraordinarily large, 1-2% of the body mass receives 20-25% of cardiac output [17, 18]. The blood supply to the kidney is from the renal artery, which divides into a number of interlobar arteries. These further divide into the arquate arteries and supply the small interlobular arteries, from which the glomerular vessels arise. Each glomerulus is supplied by a single afferent arteriole, which branch into the glomerular capillaries that drain into the efferent arteriole. The efferent arteriole forms the peritubular capillaries (pars recta around the proximal tubule and the vasa recta around the loop of Henle). The capillaries drain into the interlobular veins and then into the

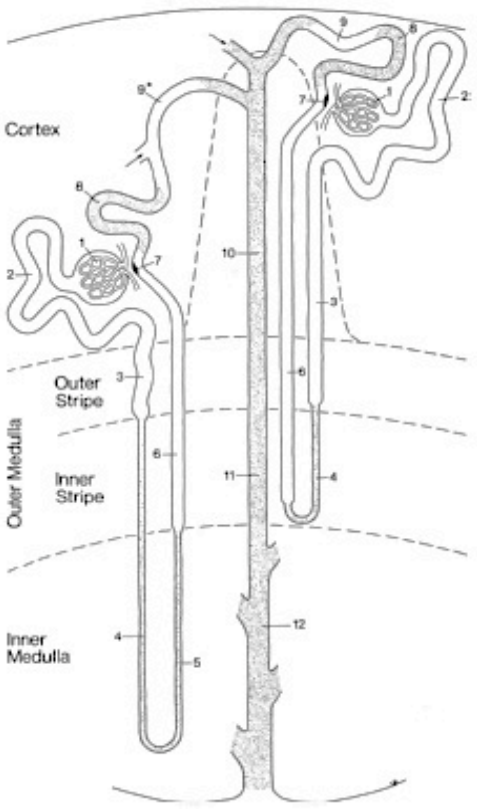


Figure 1. *Schematic illustration of superficial (right) and juxtamedullary (left) nephrons in the kidney. 1) The renal glomerulus with Bowman's capsule 2) Proximal convoluted tubule 3) S_3 segment of the proximal convoluted tubule 4) Descending thin limb 5) Ascending thin limb 6) Medullary thick ascending limb (mTAL) 7) Macula densa 8) Distal convoluted tubule 9) Connecting tubule 10) Cortical collecting duct 11) Outer medullary collecting duct 12) Inner medulary collecting duct. From [19] with permission.*

renal vein. Each afferent artery has a region of renin-secreting granular cells, which form a part of the juxtaglomerular apparatus of the nephron. This specialized apparatus consists also of the extraglomerular mesangial cells and the macula densa region of the thick ascending limb [17].

The functional unit of the kidney is the nephron (1 000 000 in each kidney), composed of the glomerulus and its renal tubule (Figure 1)[19]. There are two populations of nephrons in the kidney. (1) Cortical (85%), which have glomeruli that lie close to the surface of the kidney. These have short loops of Henley, which dip only into the outer medulla. (2) Juxtamedullary (15%), with glomeruli that lie in the juxtamedullary area

of the cortex. These have long loops of Henley, which dip into the inner medulla [17].

The blood is filtered in the glomeruli, into the Bowmans capsule, producing 180L of primary urine per day (125mL/min). The glomerular filtration is a passive process. The same forces that cause fluid to filter from any high pressure capillary also apply to filtration from the glomerulus into the Bowman's capsule (the Starling forces). The glomerular filtration rate (GFR) depends on the permeability of the filtration barrier, assessed as the ultrafiltration coefficient (K_{UF}), the forces *driving* filtration and the forces *opposing* filtration. Forces *driving* filtration are the hydrostatic pressure inside the glomerular capillaries (P_{glom}), and the mean colloid osmotic pressure in the Bowman's capsule (π_{Bow}), which under normal conditions contains no proteins and has no significant effect. The forces *opposing filtration* are the hydrostatic pressure in the Bowman's capsule (P_{Bow}) and the mean colloid osmotic pressure in the glomerular capillaries (π_{glom}). The formula for GFR may be expressed as:

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

GFR is to some extent flow dependent. If RBF decreases, the plasma remains for a longer time in the glomerulus. The proportion of plasma that is filtered is increased, causing the mean colloid glomerular pressure to increase and this will cause a decrease in GFR. The opposite is seen if RBF increases [17].

The tubule is made up of a number of sections, the proximal tubule, the medullary loop (loop of Henle), and the distal tubule, which finally empties into the collecting duct (Figure 1). The role of the renal tubule is to modify the volume and composition of the glomerular filtrate according to the needs of the organism. This is an enormous task, 180 L of filtrate produced daily needs to be reduced by 99% to achieve a final 24 h urine volume of approximately 1.8 L. Similarly, approximately 25000 mmol of Na are filtered per day, the vast majority of this being reabsorbed to provide a urinary output of 100 -200 mmol/24h [17].

The sodium reabsorption is an active, energy consuming process and nearly all the transport in the kidney is coupled to sodium reabsorption by co- or counter transport. Due to a concentration gradient, sodium enters the tubular cell passively, through the apical membrane. It is then actively pumped by Na+/K+-ATP ase out of the basolateral membrane to the interstitium from where it is absorbed into the peritubular

capillaries (Figure 2). Two thirds of the filtered sodium is absorbed in the proximal tubule, the thick ascending limb reabsorbs 20% [17, 20].

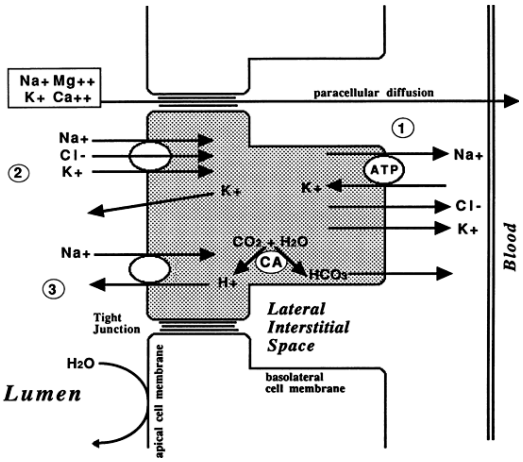


***Figure 2**. The sodium reabsorption is an active, energy consuming process and nearly all the transport in the kidney is coupled to sodium reabsorption by co- or counter-transport. Due to a concentration gradient, sodium enters the tubular cell passively, through the apical membrane. It is then actively pumped by Na+/K+-ATP ase out of the basolateral membrane to the interstitium from where it is absorbed into the peritubular capillaries.*

Regulation of renal perfusion, filtration and oxygenation

Renal perfusion, filtration and oxygenation is regulated by systemic mechanisms, autoregulation and the exact matching of renal oxygen supply (RBF) and demand (tubular solute reabsorption). Besides, a number of paracrine mediators regulate renal oxygen homeostasis and the cortico-medullary distribution of blood flow in the kidney.

Systemic mechanisms

These include the endocrine renin-angiotensin system, efferent sympathetic nerve activity, vasopressin and the family of natriuretic peptides[18].

Renal autoregulation

The kidney autoregulation maintains RBF and GFR constant over a wide range of pressures. Autoregulation is important for the regulation of the salt content and the fluid balance of the body and for the preservation of the glomerular structure [18, 21].

Autoregulation occurs in the preglomerular microcirculation and is mediated by two mechanisms, the faster myogenic mechanism and the slower tubuloglomerular feedback mechanism (TGF) [18]. The myogenic response involves vasoconstriction of the afferent arteriole when this vessel is presented with increase in transmural pressure. The TGF mechanism leads to vasoconstriction of the afferent arteriole in response to an increase in the luminal concentration of NaCl, sensed by

chemoreceptors in the macula densa in the early distal tubule. The concentration of NaCl in the macula densa is dependent on the rate of tubular flow. Increased tubular flow results in a higher distal tubular NaCl concentration. An increase in arterial pressure will, due to enhanced GFR and sodium filtration, raise the NaCl concentration in the macula densa, leading to constriction of the afferent arteriole and restoration of RBF and GFR [18].

In humans, the lower autoregulatory threshold is not exactly known. In other mammalians it is situated around 60-80 mmHg. Below the lower autoregulatory threshold, RBF and GFR become pressure-limited, as blood pressure decreases, RBF decreases in an almost linear fashion. Sympathetic stimulation results in upward shift of the lower limit of autoregulation, resulting in pressure-dependent perfusion at MAPs above the normal autoregulatory threshold [22, 23]. It has been shown in experimental studies that renal autoregulation is impaired in acute ischemic renal failure [24].

Renal oxygen supply/demand

Tight regulation of tissue oxygenation is critical for survival [25]. Renal oxygenation is defined as the relationship between renal oxygen delivery (RDO_2) (renal oxygen supply) and renal oxygen consumption (RVO_2) (renal oxygen demand). The inverse of this relationship is equivalent to the renal extraction of O_2 (RO_2Ex). An increase in RO_2Ex means that RDO_2 has decreased in relation to RVO_2, i.e. renal oxygenation has impaired, and vice versa.

Normal renal blood flow is, as already described, extraordinarily high. One reason for the high renal blood flow is the high oxygen consumption of the kidneys. They rank second to the heart in oxygen consumption. However, because of the high blood flow, the oxygen extraction in the healthy kidney is low, approximately 10-15%, compared to other organs e.g. the heart in which oxygen extraction is 45% [26]. Despite the low RO_2Ex, the kidneys are particularly susceptible to hypoxia.

Experimental studies have shown that tubular sodium reabsorption is the major determinant of RVO_2 [27]. Brezis *et al*. have shown in an experimental study, that inhibition of sodium reabsorption in the mTAL and proximal tubule by diuretics increases pO_2 in the medulla and cortex [28]. Up to 80% of the oxygen consumption of the kidneys drives, under normal conditions, the Na^+-K^+-ATPase, which drives active tubular transport of sodium [17, 20]. Tubular transport processes are load-dependent. It has been shown both in experimental studies [29] and in

patients [30-32], that there is a linear correlation between glomerular filtration rate (GFR), renal sodium reabsorption and RVO_2 (Figure 3). The filtered load of sodium is an important determinant of RVO_2 and strategies that decrease GFR and the tubular sodium load, act to decrease tubular sodium reabsorption and RVO_2, and vice versa [26].

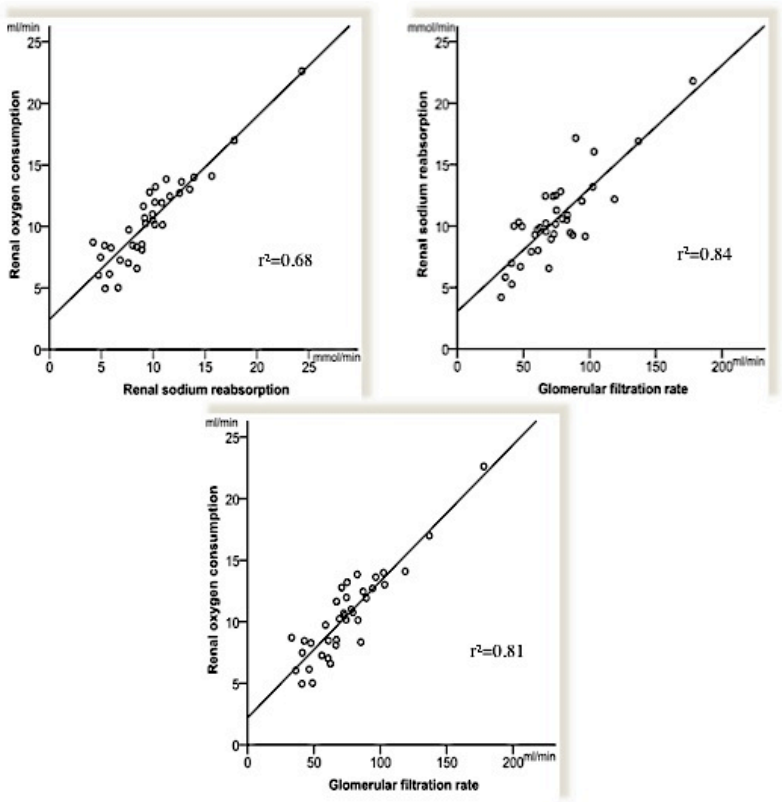


Figure 3. *Shows the correlation between renal sodium reabsorption, GFR and RVO_2, in 37 post-cardiac surgery patients with normal preoperative renal function. Modified from Redfors et al [30] with permission*

RVO_2 is flow-dependent. It has been shown that RO_2Ex remains stable over a wide range of RBF, which means that changes in RDO_2, caused by changes in RBF, are offset by changes in RVO_2 [33]. Unlike other organs where increases in blood flow will improve oxygenation, increased RBF augments GFR and the filtered load of sodium, which increases RVO_2. Because of the flow-dependency of RVO_2 (increased oxygen supply, simultaneously increases oxygen demand), renal oxygenation will remain constant, unless changes in RBF and GFR are

dissociated [25]. However, the relationship between RBF and RVO_2 is complex and studies on humans have shown that RBF and GFR (and so total tubular sodium reabsorption) do not always change in parallel as evidenced by changes in filtration fraction (FF) in response to both vasodilator and vasoconstrictor agents [25, 31, 34, 35].

The blood supply to the kidney, is very inhomogenous [36]. To optimise the filtration process and solute reabsorption, the RBF is directed preferentially to the cortex. In contrast, the blood flow in the outer medulla is low, less than 50% of the blood flow in the cortex [37]. The low blood flow in the medulla is necessary to preserve osmotic gradients and to enhance urinary concentration. The combination of low medullary perfusion, high oxygen consumption of the S3 segment of the proximal tubule and the medullary thick ascending limb (mTAL) (Figure 1) and the countercurrent exchange of oxygen within the vasa recta, results in a poorly oxygenated outer medulla, which has an oxygen tissue partial pressure (PO_2) of 10-20 mmHg, compared to 50 mmHg in the cortex [36]. The outer medulla is therefore, under normal conditions on the border of hypoxia, and therefore particularly sensitive low RDO_2 (Figure 4) [36].

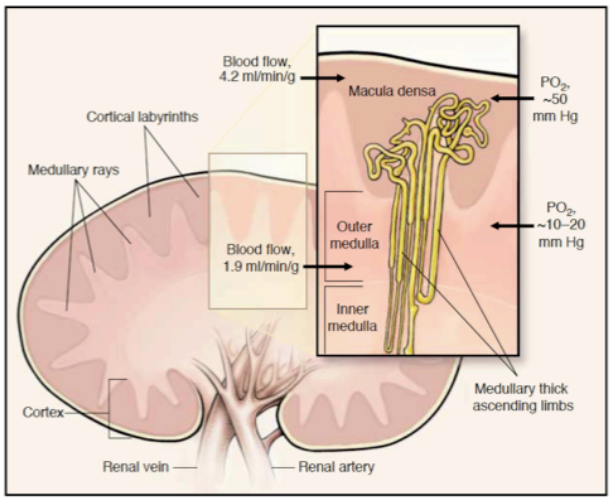


Figure 4. *The blood supply of the renal cortex and medulla. PO_2, partial pressure of oxygen. From [36], reproduced with permission, Copyright Massachusetts Medical.*

The rate of oxygen consumption by the kidney consists of oxygen used for active sodium reabsorption plus a small amount of oxygen used for basal metabolism. In a study on sedated mechanically ventilated postoperative cardiac surgery patients with normal preoperative kidney function, Redfors *et al*. found that RVO_2 was 10-12 mL/min, values that

are slightly lower than reported in conscious healthy volunteers. The individuals in the study by Redfors *et al.* consumed a mean of 0.82 mL of oxygen per mmol of reabsorbed sodium [30].

Not only hypoxia can injure the kidney. Hyperoxia has been shown to increase free radical production that could cause kidney injury [25, 38]. Shunting of oxygen between arteries and veins in the kidney limits oxygen delivery to the renal tissue. Arterio-venous-oxygen shunting has been suggested as a mechanism that protects the kidney from potentially damaging consequenses of tissue hyperoxia [38]. On the other hand, under conditions of reduced medullary perfusion or enhanced tubular oxygen consumption, areterio-venous-oxygen shunting is proposed to exacerbate tubular hypoxia within the outer medullary region [38]. Renal arterial-venous-oxygen shunting has also been suggested to contribute to development of renal hypoxia during anemia [26, 39], and acute hemodilution [40], presumably because the high affinity of hemoglobin for oxygen retards oxygen shunting.

Paracrine mediators

A number of paracrine mediators regulate renal oxygen homeostasis and the cortico-medullary distribution of blood flow in the kidney. The balance of vasodilators and vasoconstrictors is important for the precise regulation of the blood flow. The paracrine mediators include the intrarenal renin-angiotensin system, prostaglandins, kinins, endothelin and NO that transfer information from one part of the kidney to another [18]. Prostaglandins, NO and adenosine oppose neurohormonal vasoconstriction mediated by sympathetic stimuli, vasopressin, and angiotensin II [41]. Adenosine has different effects on the vasculature in the cortex and medulla, mediating vasoconstriction in the cortex and vasodilation in the medulla [36].

Pathophysiology of AKI

Acute kidney injury is most frequently caused by ischemia, sepsis or nephrotoxic insults to the kidney. In patients with hospital-acquired AKI the cause is frequently multi-factorial, with concomitant ischemic, septic and nephrotoxic components and overlapping pathogenetic mechanisms that are complex and incompletely understood [42].

Our understanding of the pathogenesis of human ischemic AKI, is affected by the lack of non-invasive methods to measure RBF and oxygenation and lack of histopathological information. Renal biopsy is an invasive procedure and not without risks, making it ethically unjustifiable to obtain tissue from patients with no suspected

parenchymal disorders which can be treated, such as vasculitis or primary glomerulonephritis [43, 44]. Therefore, much of our knowledge of the pathophysiology of ischemic AKI is derived from animal studies. Animal models of acute ischemia, induced by occlusion of the renal artery are commonly used and have shown the many pathways that are involved in the mechanism of AKI [44]. However, in patients with AKI induced by the most common causes of AKI, i. e. sepsis, cardiac surgery or heart failure, the renal artery is not occluded, and in addition, because of species-related morphological and functional differences, the appropriateness of some of these animal models can be questioned [41, 44]. Furthermore, kidney biopsies from animal models of AKI show extensive tubular necrosis, while biopsies from patients with AKI have shown very limited necrosis in spite of severe organ failure [45]. In ischemic AKI in humans, the prominent morphologic features include effacement of and loss of proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubular dilatation and distal tubular casts, and areas of regeneration. Necrosis is inconsiderable and restricted to the highly susceptible outer medullary region [42].

Renal parenchymal hypoxia plays a central role in a variety of clinical conditions leading to AKI, even in conditions basically believed to reflect direct tubulotoxicity [41]. Altered renal perfusion, hypoxia and inflammatory processes contribute to tubular epithelial cell injury, that plays a central role in the pathogenesis of ischemic AKI [46]. In addition, there is evidence indicating that additional mechanisms, including renal microvascular endothelial injury and dysfunction, also play a part in extending the renal tubular epithelial injury [46, 47].

Ischemic AKI has been divided into 5 clinical phases, the *early*, *initiation*, *extension*, *maintenance* and the *repair* phase [48].

In the *early phase,* decreased renal perfusion, due to intrarenal vasoconstriction, is associated with reduced GFR, leading to prerenal azotemia (accumulation of wastes such as urea and creatinine). Vascular and cellular adaptive responses maintain cellular integrity [46, 48].

The *initiation phase* occurs when RBF decreases to a level resulting in severe cellular ATP depletion, leading to acute cell injury and dysfunction [46, 48].

The *extension phase* is characterized by two events, continued hypoxia and an inflammatory response, both events more pronounced in the outer medullary region of the kidney. Blood flow is severely reduced. Accumulation of inflammatory cells has been noted. Production and release of chemokines and cytokines enhance the inflammatory cascade. Cells, predominantly in the outer medulla continue to undergo injury

and death, with both necrosis and apoptosis. In the peritubular capillaries of the outer medulla, the inflammatory cells adhere to the activated endothelium, leading to medullary congestion and further hypoxic injury to the S3 segment of the proximal tubule and to the medullary thick ascending limb (mTAL). Renal endothelial cell damage and swelling, as well as the inflammatory response, probably play a key role in maintaining ischemia of the renal tubular epithelium, during this phase [46-48].

Tubular cells then begin the process of proliferation and redifferentiation (the *maintenance phase*). RBF returns to normal. Finally, epithelial cell polarity and function is reconstituted (the *repair phase*).

Hypoxia inducible factor (HIF), is a factor that has recently been found to be involved in the regulation of the adaptive responses to hypoxia. It induces several target proteins that have an impact on O_2 delivery and consumption. The significance of the regulation of renal oxygenation by HIF under pathophysiological conditions is under investigation [49, 50].

The effect of the cardiopulmonary bypass (CPB)

The CPB contributes to the pathogenesis of AKI after cardiac surgery. The contribution of CPB to AKI is supported by the decreased overall incidence of AKI in patients undergoing cardiac surgery by the off-pump technique [14, 51, 52].

The contact of blood components with the artificial surface of the bypass circuit, triggers the CPB induced systemic inflammatory response syndrome (SIRS)[14]. This inflammatory reaction contributes to the development of postoperative complications, i.e. myocardial dysfunction, respiratory failure, renal and neurologic dysfunction, bleeding disorders, altered liver function, and multiple organ failure (MOF) [53]. Furthermore, during CPB, the blood cells are exposed to nonphysiologic surfaces and shear forces, leading to cell lysis. Free hemoglobin is released which can cause tubular injury [6, 14, 54].

Hemodilution during CPB theoretically improves organ perfusion by a decrease in blood viscosity and improved microcirculatory flow. However, four studies have demonstrated that hemodilution, down to hematocrits lower than 21-24% during CPB, is associated with significant increase in the incidence of AKI [14, 55-58]. Early on-pump transfusions aimed at reversing the hemodilution, however, worsened renal outcome in one of these studies [56]. The susceptibility of the kidney to hemodilution likely arises from multiple factors, including

reduced renal oxygen delivery [59], diminished renal autoregulatory function and arterio-venous oxygen shunting in the kidney [60].

Finally, microemboli are formed during CPB and smaller emboli not effectively filtered by the CPB system can damage renal capillaries [14]. Sreeram *et al.* recorded transcranial doppler signals and emboli counts during CABG and found that emboli counts were independently associated with postoperative AKI [61].

Renal perfusion, filtration and oxygenation in ischemic AKI after cardiac surgery

As a reduction in GFR in AKI should lead to a reduction of the renal reabsorptive workload, thereby preserving medullary oxygenation with a reduced risk of further aggravation of ischemia, it has provocatively been stated that "acute renal failure is an acute renal success" [30, 41, 62]. Redfors *et al*. recently studied renal perfusion, filtration and oxygenation in patients with preoperative normal renal function, developing early AKI (50-200% increase in serum creatinine) after complicated cardiac surgery [30]. It was shown in that study that renal oxygenation was severely impaired in patients with early AKI, demonstrated by a 70% relative increase in RO_2Ex, compared with uncomplicated post-cardiac surgery patients with normal renal function. This was caused by a pronounced renal vasoconstriction and a 40% lower RBF, in combination with RVO_2 that was not significantly different from the control group, despite the 60% decrease in GFR and renal tubular sodium reabsorption. The RVO_2 of the AKI patients was 1.9 ml/mmol reabsorbed sodium, i.e. 2.4 times higher than in the uncomplicated control group (0.82 ml/mmol reabsorbed sodium). A decrease in RDO_2 by 40% in combination with a tubular sodium reabsorption at a high oxygen demand, suggests that renal oxygenation is severely impaired after the initiation phase of ischemic AKI [30].

Redfors *et al*. suggested that the following mechanisms might explain the increased oxygen utilization for sodium transport in patients with AKI [30]; (1) Loss of epithelial cell-polarisation and tight junction integrity in AKI, making tubular sodium reabsorption less efficient. This has been shown in studies on experimental renal ischemia and after human renal transplantation [30, 63, 64]. (2) Diminished renal nitric oxide (NO) generation because of endothelial damage and down-regulation of endothelial nitric oxide synthase (eNOS/NOS-3). NO is a major regulator of microvascular oxygen supply and RVO_2 [30, 65]. NO increases RBF and hence oxygen delivery, through vasodilation. (3) NO

has been suggested to act as a "brake" on oxidative metabolism at various sites, including direct competition of NO with oxygen for mitochondrial respiration and inhibition of cytochrome c oxidase [30, 66].

The 40% decrease in RBF in the AKI patients, shown in the study by Redfors *et al*, was caused by a 52% higher RVR compared to patients with no renal impairment [30]. The decrease in RBF in AKI has been attributed to constriction of the afferent arteriole, in turn caused by the tubuloglomerular feedback mechanism, circulatory vasoconstrictors (catecholamines, angiotensin-II, endothelin), and outer medullary congestion. Furthermore, endothelial injury and dysfunction, causes imbalance in the production of mediators of vasoconstriction and renal vasodilators, i.e, imbalance in the production of endothelin and nitric oxide (NO). In support of this, antagonists to endogenous vasoconstrictors have been shown to ameliorate renal ischemic injury in animal models. In addition, contributing to the NO deficiency in AKI is the angiotensin II-induced activation of reactive oxygen species, that inactivate NO [24, 30, 42, 46, 47, 67].

Risk factors for AKI in cardiac surgery

Certain risk factors have repeatedly been associated with an increased risk for AKI after cardiac surgery. These factors are; female gender, reduced left ventricular function or the presence of congestive heart failure, diabetes mellitus, peripheral vascular disease, preoperative use of an intra aortic balloon pump (IABP), chronic obstructive pulmonary disease, the need for emergent surgery and an elevated preoperative serum creatinine [6]. The most important predictive risk factor for AKI after CPB is preoperative serum creatinine [14]. The risk of AKI requiring dialysis approaches 10-20% in patients with a baseline creatinine concentration of 2.0-4.0 mg/dL (175-350μmoL/L), and approximately 25% when the baseline creatinine concentration is greater than 4.0 mg/dL (350μmol/L)[6, 14].

Other more controversial risk factors are those specifically related to the bypass procedure such as, aortic cross-clamp time and the duration of CPB (especially longer than 100-120 minutes) and on pump vs off pump coronay artery bypass surgery (see The effect of the CPB)[6, 68].

Few studies have investigated the effect of perioperative BP control on the pathogenesis of AKI, after cardiac surgery. Moreover, the effect of different BP targets on the incidence of AKI has never been investigated in a controlled prospective study [69]. Thus, there is insufficient evidence to suggest MAP parameters or minimum flow rates for patients

undergoing CPB to specifically prevent renal injury [14, 70]. However, Kanji *et al*. recently showed in a study on high-risk cardiac surgery patients, that a large delta MAP, ≥ 26mmHg (defined as the preoperative MAP, minus average MAP on CPB), and lower CPB flow during cardiac surgery, was independently associated with early postoperative AKI [71]. In a recent study it was shown that excursions of MAP below the lower limit of cerebral autoregulation, as determined with NIRS monitor, during CPB, was independently associated with AKI. The lower limit of autoregulation was higher in patients with AKI than in those without AKI. In the same study, a preoperative pulse-pressure of > 60 mmHg was also independently associated with AKI [72]. Elevated pulse pressure indicates central vascular stiffnes, which may lead to arteriolar narrowing that necessitates higher blood pressure for renal perfusion during cardiac surgery [72].

The main pre- and intraoperative risk factors for AKI after cardiac surgery have been mentioned above. There are also less well defined postoperative risk factors, mainly involving complications of surgery and a prolonged postoperative course [59]. In a study by Slogoff *et al*. postoperative blood loss, excessive postoperative transfusion, postoperative myocardial infarction and need for emergent reoperation were reported as postoperative risk factors independently associated with AKI after cardiac surgery [73].

Prevention/treatment of AKI after cardiac surgery

Renal parenchymal hypoxia plays an important role under a variety of clinical conditions that lead to AKI [41]. Prevention/treatment should focus on maintenance of intrarenal oxygenation, minimizing the potential for mismatching of tubular oxygen delivery and demand [25]. If future strategies shall be successful in the prevention/treatment of AKI, *further* knowledge of how the most common pharmacological interventions, used in the treatment of critically ill patients with AKI, affect renal perfusion, filtration and oxygenation, is needed. Here is a brief summary of the known effects of few pharmacological interventions, used in the prevention/treatment of AKI, on renal perfusion, filtration and oxygenation.

Prevention

There are no known drugs that have conclusively and repeatedly demonstrated renal protection in cardiac surgery with CPB[6, 74]. Rosner *et al.* have suggested a number of factors that might be related to the failure of these drugs to prevent AKI [6]. (1) The pathogenesis of AKI

after CPB is complex, involving hemodynamic, inflammatory and other interacting mechanisms. Interventions that target one single pathway are therefore unlikely to succeed. (2) The patient populations that have been studied are often at low risk for AKI after cardiac surgery, potentially masking small beneficial effects of therapies. (3) Most clinical trials have enrolled a small number of patients, and are therefore not adequately powered to detect small benefits [6].

Diuretics

It has been shown in an experimental study that furosemid and other loop diuretics, inhibit sodium reabsorption and oxygen consumption in the mTAL, leading to increased oxygen availability and consequently increased tissue PO_2 of the medulla [28]. In post-cardiac surgery patients, Swärd *et al*. showed, using the retrograde renal vein thermodilution technique and renal extraction of ^{51}Cr-EDTA, that furosemid improved renal oxygenation by decreasing sodium reabsorption, RvO_2 and RO_2Ex by 20-30%, with no change in RBF [31]. In healthy individuals, Prasad *et al.* demonstrated that furosemid increased medullary oxygenation, using the blood oxygen level-dependent magnetic resonance imaging technique (BOLD MRI) [75]. There are several reports demonstrating that furosemid has renoprotective effect in experimental ischemic AKI [49]. Studies have so far not been able to show that furosemid has a renoprotective effect in cardiac surgery patients [6], but its potential preventive effect has not been studied in a population of high-risk cardiac surgery patients in a prospective randomized controlled trial.

Dopaminergic agents

In post-cardiac surgery patients, Redfors *et al*. showed, using the retrograde renal vein thermodilution technique and renal extraction of ^{51}Cr-EDTA, that low-dose dopamine induced a 45-55% increase in RBF. GFR and RVO_2 were not affected and consequently renal oxygenation was improved[34].

The capacity of dopamine to improve renal oxygenation, as seen in postoperative cardiac surgery patients, would make it a suitable agent for prevention of AKI, as it would increase the tolerance to renal ischemia during perioperative renal hypoperfusion[49]. The potential preventive effect of dopamine has not been confirmed in earlier studies, but it has not been evaluated in high-risk cardiovascular surgery. On the other hand, fenoldopam, which exerts the same renal effects as dopamine, has been shown to improve creatinine clearance in high-risk cardiac surgery patients, in a randomized controlled trial [76]. In

addition, Bove *et al*. compared the preventive effects of fenoldopam and dopamine (2.5μg/kg/min) on renal excretory function, in a prospective double blind randomized clinical trial on high risk cardiac surgery patients and found no difference in percent increase in postoperative serum creatinine, between these two dopaminergic agents [77]. Finally, Ranucci *et al.* showed in a prospective double blind, randomized, placebo controlled study on patients undergoing complex cardiac surgical operations, requiring a predictable CPB time over 90- minutes, that the rate of AKI in the first three days after the operation was significantly lower in the fenoldopam-treated patients. In the same study, a subgroup analysis on patients receiving inotropic drugs to treat low cardiac output state immediately after the operation, showed, that fenoldopam treatment resulted in better kidney function and reduced the rate of AKI [78].

Treatment

Among the available pharmacological options for the treatment of AKI after cardiac surgery, there is still a lack of definitive evidence supporting specific therapy in any setting. The major goal in the management of AKI is to increase glomerular filtration rate (GFR). However, there is a close association between GFR, tubular sodium reabsorption and renal oxygen consumption (RVO_2) in humans [31, 32]. A pharmacologically induced increase in GFR will therefore increase RVO_2 and potentially further impair renal oxygenation in patients with AKI. Thus, an ideal agent to treat AKI, would be one that increases both RBF and GFR, i.e. an agent that induces a vasodilation of preferentially the preglomerular resistance vessels. Such an agent will not only increase GFR but also meet the increased renal metabolic demand of the medulla by increased renal oxygen delivery [49].

ANP

It has been shown that ANP induces a selective dilation of renal afferent arterioles with an increase in both RBF and GFR by approximately 40% in patients with ischemic AKI after complicated cardiac surgery [79]. In addition, in a prospective, randomized, blind trial, Swärd *et al*. showed that infusion of ANP at an infusion rate of 50 ng/kg/min, enhances renal excretory function, decreases the probability of dialysis and improves dialysis-free survival in early, ischemic AKI after complicated cardiac surgery [80].

Dopaminergic agents

In a randomized, double blind placebo-controlled clinical trial in 155 ICU patients with early AKI, fenoldopam did not reduce the incidence of death or dialysis therapy at 21 days, compared to placeo. However, in a subgroup analysis on patients with early AKI after cardio-thoracic surgery (n=70), it was found that a 72 hours infusion of fenoldopam, significantly reduced the incidence of dialysis therapy or death at 21 days [81].

Noradrenaline

In a recent study on post-cardiac surgery patients with NE-dependent vasoplegia and concomitant AKI, the effects of NE on renal perfusion, filtration and oxygenation were evaluated [35]. Restoration of MAP from 60 to 75 mmHg improved renal oxygen delivery (RDO_2), GFR and renal oxygenation in these patients.

Vasopressin

Vasodilatory shock can be the final common pathway for long lasting and severe shock of any cause [82]. It is not uncommon after complicated cardiac surgery with cardiopulmonary bypass with a long cross-clamp time, and occurs often in conjunction with postoperative heart failure that requires inotropic treatment [83, 84]. Clinical septic shock and the vasodilatory shock syndrome after cardiac surgery, are characterized by a profound arteriolar vasodilation resulting in a low systemic vascular resistance and hypotension, in turn caused by extreme generation of endogenous vasodilators or activation of the ATP-sensitive potassium channels in vascular smooth muscle cells [82, 85]. The recommended vasopressor to counteract the vasodilation is norepinephrine, and it is commonly used for treatment of hypotension in volume-resuscitated hyperdynamic septic shock [86] and to correct hypotension in the vasodilatory shock syndrome after cardiac surgery with cardiopulmonary bypass [83, 87, 88]. However, resistance to norepinephrine and other catecholamines may develop in vasodilatory shock because of adrenergic receptor downregulation and endogenous vasodilators [89].

Vasopressin (antidiuretic hormone), is essential for cardiovascular homeostasis. It is a nonapeptide hormone released from the axonal terminals of magnocellular neurons in the hypothalamus [90]. It is both a vasopressor and an antidiuretic hormone. It also has hemostatic, GI and thermoregulatory effects, and it stimulates ACTH release. Vasopressin mediates vasoconstriction via V1-receptor activation on

vascular smooth muscle and antidiuretic effect via V2-receptor activation in the renal collecting duct system. At low concentration, vasopressin mediates vasodilation in coronary, cerebral and pulmonary arterial circulations. Vasopressin is rapidly metabolized by liver and kidney vasopressinases and has a half-life of 10-35 min [90]. Under normal conditions the serum concentration of vasopressin is around 2pg/mL. In healthy individuals, secretion is regulated by changes in serum osmolarity (osmoregulation). Two percent increase in serum osmolarity is reversed by an increase in serum vasopressin to around 5 pg/mL [91, 92]. Baroregulation only plays a significant role if blood pressure decreases by more than 10%. Hormone levels can then increase more than ten-fold to help restore normal blood pressure, mainly by vasoconstriction [91, 92].

It has been shown that plasma levels of vasopressin are low in post-cardiotomy vasodilatory shock [93, 94] and in septic shock [95] in contrast to hypovolemic and cardiogenic shock. This vasopressin deficiency might contribute to the vasodilatory shock syndrome after cardiac surgery and in sepsis [93-95]. Furthermore, there is an enhanced sensitivity to vasopressin in septic shock [96]. Vasopressin has therefore been suggested as an additional or alternative therapy in catecholamine-dependent vasodilatory shock [90, 96-98].

Several studies have shown that low- to moderate doses of vasopressin increase urine output in septic shock [97-100]. It has also been reported that vasopressin increases creatinine clearance, a surrogate variable of glomerular filtration rate (GFR), in these patients [98, 100]. The mechanisms behind these potentially beneficial renal effects of vasopressin in vasodilatory shock are not known. Increased urine output and creatinine clearance do not necessarily reflect increased renal blood flow. The effects of low to moderate doses of vasopressin on renal circulation, filtration and oxygenation have previously not been studied in humans.

Mannitol in AKI

Oliguria is a poor prognostic indicator in patients with AKI [101, 102], and diuretic agents are frequently used to improve urine output and to facilitate fluid management in these patients.

Mannitol is an osmotic diuretic, commonly used in patients with acute renal dysfunction. It is a six-carbon non-metabolizable polyalcohol with a molecular weight of 182. Mannitol is freely filterable and has a very limited reabsorption, thus creating an osmotic force in the tubular fluid that retards the reabsorption of fluids and solutes (NaCl) along the

nephron [103]. It has been used in patients undergoing surgery as well as in the pump prime of the heart lung machine, in the belief that it exerts renoprotective properties. Experimental studies have shown that mannitol may decrease ischemia-induced swelling of tubular cells, which might obstruct tubular lumen [104]. Results from studies in which mannitol has been evaluated in the perioperative setting, for prevention or treatment of AKI, are divergent. Although mannitol has failed to show a prophylactic effect in patients undergoing abdominal aortic or cardiac surgery [105, 106], mannitol has been shown to reduce the incidence of postoperative AKI in the setting of renal transplantation, along with volume expansion [107, 108]. Furthermore, mannitol treatment has been shown to increase the glomerular filtration rate (GFR) in patients after severe trauma or surgery [109]. In addition, in a recent study it was shown that mannitol increases GFR in postoperative cardiac surgery patients, with normal preoperative renal function, possibly by a deswelling effect on tubular cells [32].

Data on the effects of mannitol treatment on renal perfusion, filtration and oxygenation in patients with early ischemic AKI are lacking.

Levosimendan

Heart failure is a common cause of renal ischemia. Levosimendan is an agent that has successfully been used for the treatment of heart failure after cardiac surgery with CPB [110-112]. It is an agent that exerts positive inotropic effects on the failing heart mediated by calcium sensitisation of contractile proteins and systemic as well as pulmonary vasodilatory effects mediated by opening of ATP-sensitive potassium channels in vascular smooth-muscle cells [113, 114]. Both improved cardiac output and vasodilatation, could lead to better renal perfusion and improved kidney function.

Levosimendan has previously been evaluated for the treatment of congestive heart failure and impaired renal function [115-118]. In those studies it was shown that levosimendan improved renal function, as assessed by measurements of serum creatinine and estimated values of creatinine clearance from serum creatinine (eGFR). However, the specific pharmacodynamic effects of levosimendan on RBF or GFR were not studied and it was not evident whether or not the beneficial effect of levosimendan on renal function, in those studies, was caused by a specific renal vasodilatory action of levosimendan or by the levosimendan induced increase in renal perfusion pressure, in turn

caused by the increase in cardiac output in combination with a decreased central venous pressure.

No studies have assessed the effects of levosimendan on renal perfusion, filtration and oxygenation in patients that have undergone a stressful procedure as cardiac surgery with CPB.

Assessing GFR in critically ill patients with AKI

The marker used daily for the assessment of kidney function in the critically ill patient, is the concentration of creatinine in serum. However, it may not be suitable for this purpose as it is affected by factors other than kidney function. Creatinine is metabolized from creatine, which is released by the muscles, therefore muscle mass and metabolic transformation of creatine have an impact on serum creatinine concentration [16]. In addition, age, gender and race, all affect muscle mass and, in turn, serum creatinine concentrations [119, 120].

In critically ill patients with AKI, three main factors influence the evaluation of kidney function using serum creatinine; true kidney function, fluctuations in creatinine production and fluid balance [121]. In these patients, the creatinine production may be decreased because of immobilization and malnutrition or increased due to catabolic illness. Increases in total body water, commonly seen in these patients, increases the distribution volume of creatinine, and attenuates the increase in serum creatinine concentration caused by AKI [16, 122-124]. Furthermore, various drugs used to treat critically ill patients, e.g. cimetidine and trimethoprim-sulfamethoxazole, are known to compete with the active tubular secretion of creatinine, and therefore to affect the serum creatinine concentration [125, 126]. Thus, daily changes in serum creatinine poorly reflect changes in kidney function, in this patient population [122].

Glomerular filtration rate (GFR), measured by using exogenous substances as filtration markers, such as ^{51}Cr-EDTA, is considered as the *gold standard* for assessment of renal function [127, 128]. Unfortunately, measuring GFR with the use of these markers is expensive and complex, making them unsuitable for routine use in the intensive care setting.

The second best method for assessment of renal function is the urinary creatinine clearance (CrCl), computed from a timed urine collection (e.g. a 24-hour urine collection) and blood sampling for serum creatinine [129]. However, clearance methods require a steady state situation, a criteria not always met in critically ill patients, where changes in the hemodynamic status can result in dramatic changes in

renal function over a 24 hour urine collection period. Furthermore, accurate timed collection of urine is both cumbersome and the main source of error [130]. The serum level of endogenous filtration markers is also affected by factors other than the GFR, as discussed above, and urinary CrCl may considerably overestimate GFR because of tubular secretion and extrarenal elimination of creatinine [16, 123].

Finally, GFR can be assessed by using estimating equations, that include variables such as age, sex, race and body weight in addition to serum creatinine, as a substitute for muscle mass and therefore they can overcome some of the limitations with the use of serum creatinine alone [127, 131-133]. Estimating equations for GFR have been developed in study populations consisting of patients with chronic stable kidney disease and stable serum creatinine concentrations [131-133]. These equations are poorly evaluated in critically ill patients with AKI and most often they have been validated against urinary CrCl, instead of a gold standard reference method. Furthermore, data on the agreement between urinary CrCl and gold standard GFR in critically ill patients with early AKI are lacking.

Aims

- To study the effects of vasopressin on renal circulation, function and oxygenation in post - cardiac surgery patients.

- To study the effects of mannitol on renal circulation, function and oxygenation in critically ill patients with early acute kidney injury, after complicated cardiac surgery

- To study the effects of levosimendan versus placebo on renal circulation, function and oxygenation in post - cardiac surgery patients.

- To evaluate the agreement of urinary creatinine clearance (CrCl) and three commonly used estimating equations, the Cockcroft Gault (CG), the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, in comparison to GFR measured by the infusion clearance of ^{51}Cr-EDTA, in critically ill patients with early acute kidney injury after complicated cardiac surgery.

Patients and methods

Patients

The study protocols were approved by the Human Ethics Committee of the University of Gothenburg. In Paper I and in Paper III, written informed consent was obtained from the patients, at the pre-operative evaluation, before enrolment in the studies. All the patients with AKI in Paper II and 23 of 30 patients with AKI in Paper IV, were due to critical illness, sedated and mechanically ventilated. Informed consent was not possible from these patients and therefore, the patient's next of kin were informed, before inclusion in the studies, in accordance to the decision of the Ethics Committee.

Paper I and III - patients after uncomplicated cardiac surgery

Forty-six patients with normal preoperative serum creatinine (< 105 μmol/L) and LVEF > 45 % where included after uncomplicated cardiac surgery in Paper I (14 patients) and Paper III (34 patients). The preoperative and the intraoperative characteristics of the patients are shown in Table 3. The exclusion criteria were: (a) need for inotropic and vasoactive support, with or without intra-aortic balloon pump after surgery, b) clinically significant postoperative bleeding, c) postoperative hypotension because of arrhythmias. Six patients were excluded from the studies, four because of significant post-operative bleeding (two in Paper I and two in Paper III) and two because of unsuccessful placement of the renal vein catheter (Paper III).

Paper II and IV - patients with AKI after complicated cardiac surgery

Thirty-two patients with normal preoperative serum creatinine, who developed AKI after complicated heart surgery were included in Paper II (13 patients) and in Paper IV (30 patients). All the patients in Paper II were also included in Paper IV. The following inclusion criteria were used: a) cardiac surgery with cardiopulmonary bypass, b) normal preoperative renal function (serum creatinine ≤ 105 μmol/L), c) development of early AKI, stage 1 or 2, according to the Acute Kidney Injury Network (AKIN) criteria, defined as a 50-300% postoperative increase in serum creatinine from baseline [9]. The following exclusion criteria were used: a) heart transplantation, b) thoraco-abdominal aortic

surgery, c) aortic dissection, d) use of nephrotoxic drugs such as radiocontrast agents, aminoglycoside antibiotics or NSAID analgesics, e) need of dialysis. In Paper II, two patients were excluded because of unsuccessful placement of the renal vein catheter. Table 3 shows the preoperative and the perioperative characteristics of the patients in Paper II and IV and Table 4 and Table 5 the characteristics of the patients at inclusion to the studies.

Table 3. Baseline patient characteristics

	Post op (n=42)	AKI (n=30)
Preoperative characteristics		
Gender, n (% men)	39 (93)	24 (80)
Age (years)	65.6 ± 1.78	68.0 ± 1.71
BSA (m^2)	1.98 ± 0.03	2.0 ± 0.04
Preop LVEF (%)	57.0 ± 0.99	0.43 ± 0.03
Diabetes, type 2 (%)	1 (2)	7 (23)
Hypertension, n (%)	26 (62)	15 (50)
Preop serum creatinine (µmol/L)	81.31 ± 1.98	86.5 ± 3.00
Preop Higgins risk score	0.98 ± 0.15	3.6 ± 0.46
Preop treatment		
ACE inhibitor, n (%)	24 (57)	18 (60)
β-Adrenergic blocker, n (%)	33 (79)	24 (80)
Calcium antagonists, n (%)	4 (10)	3 (10)
Perioperative characteristics		
Type of surgery:		
CABG, n (%)	39 (93)	12 (40)
Valve, n (%)	3 (7)	5 (17)
Combined, n (%)	3 (27)	7 (23)
Other, n (%)	1 (9)	4 (13)
Redo CABG/Valve	0 (0)	2 (7)
Nonelective, n (%)	0 (0)	9 (30)
CPB time (minutes)	68.43 ± 2.76	145.9 ± 12.65
Aortic cross-clamp time (min)	42.60 ± 2.05	81.8 ± 8.88
ICU Higgins risk score	2.29 ± 0.41	9.1 ± 0.93
Postop serum creatinine (µmol/L)	75.12 ± 2.55	119.2 ± 5.59

Data are presented as mean ± SEM. ACE, angiotensin-converting enzyme; BSA, body surface area; CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; ICU, intensive care unit; LVEF, left ventricular ejection fraction; nonelective, surgery performed within 24 hours after referral; preop, preoperative; postop, postoperative (day 1)

Table 4. Patient characteristics at inclusion for patients in Paper IV.

Pat no.	Study entry (day)	Preop crea (µ*M)*	Crea incl (µ*M)*	Crea increase (%)	SOFA score	IABP	NE µg/ kg/m	Milr µg/ kg/m	Furo µg/ kg/m
1	5	65	136	109	9	No	0.25	0	2.53
2	2	107	209	95	10	Yes	0.16	0.24	1.02
3	3	109	200	83	8	Yes	0.12	0.13	0.80
4	4	91	151	66	12	No	0.14	0.18	0
5	4	102	170	67	7	No	0.09	0	0.99
6	6	78	145	86	9	No	0.43	0.43	0
7	6	101	194	92	7	No	0.22	0	2.22
8	1.5	90	146	62	10	Yes	0.33	0.44	3.70
9	3	81	230	184	10	No	0.11	0.52	3.06
10	6	93	210	126	7	No	0.32	0.25	1.05
11	5	84	217	158	9	No	0.27	0	0.95
12	1.5	82	135	65	10	No	0.33	0.26	3.21
13	2	102	155	52	10	Yes	0.92	0.26	7.41
14+	4	83	182	119	10	No	0.95	0.20	6.53
15	2	81	127	57	6	Yes	0.39	0.40	2.22
16#	2	129	233	81	11	No	0.54	0.30	7.58
17	2	79	131	66	8	No	0.10	0	3.06
18	1	80	150	88	7	No	0.10	0	4.76
19+	4	62	134	116	10	Yes	0.21	0.50	1.14
20	6	105	184	75	4	No	0	0.25	0
21#+	8	105	362	245	9	No	0.02	0.35	5.34
22	12	84	187	123	9	No	0.05	0	1.75
23	12	63	108	71	8	No	0.47	0	4.14
24+	1	67	127	90	8	No	0.92	0.50	3.47
25	3	69	162	135	6	No	0.02	0	6.67
26	5	79	163	106	8	No	0.40	0	5.55
27	6	64	119	86	7	No	0.15	0	4.63
28	4	99	156	58	13	No	0.40	0.50	9.44
29	8	93	156	68	5	No	0	0	2.53
30	8	69	173	151	12	No	0.55	0.20	8.58
Mean	4.6	86.5	172	99.3	8.6		0.32*	0.33*	3.86*
SEM	0.53	3.0	8.96	7.81	0.38		0.05*	0.03*	0.49*

*Abbreviations: pat, patient; no,number; preop crea, preoperative creatinine, crea incl, creatinine at inclusion; µM, µmol; SOFA, sequential organ-failure assessment; NE, norepinephrine; milr, milrinone; dopa, dopamine; furo, furosemide; + dialysis later in ICU; # treatment with dopamine 2.0 µg/kg/min *Mean and SEM among treated.*

Table 5. Patient characteristics at inclusion for patients in Paper II.

Pat no	Study entry (day)	Preop crea (µ*M)*	Incl crea (µ*M*)	Crea incr (%)	SOFA score	IABP	NE µg/ kg/m	Milr µg/ kg/m	Furo µg/ kg/m
1	4	91	151	66	12	No	0.14	0.18	0
2	4	102	170	67	7	No	0.09	0	0.99
3	2	90	146	62	10	Yes	0.33	0.44	3.70
4	6	93	210	126	7	No	0.32	0.25	1.05
5	5	84	217	158	9	No	0.27	0	0.95
6	2	82	135	65	10	No	0.33	0.26	3.21
7	2	102	155	52	10	Yes	0.92	0.26	7.41
8	4	83	182	119	10	No	0.95	0.20	6.53
9	2	81	127	57	6	Yes	0.39	0.40	2.22
10	4	62	150	141	10	Yes	0.21	0.50	1.14
11	5	79	163	107	8	No	0.40	0	5.55
Mean	3.83	90.3	164	93	9.0	36%	0.39	0.31*	1.98*
SEM	0.43	3.41	8.67	11.55	0.54		0.09	0.04*	0.78*

Abbreviations: Pat no, patient number; preop crea, preoperative creatinine; µ*M, µmol/L; incl crea, creatinine at inclusion; crea incr, creatinine increase at inclusion; IABP, intraaortic balloon pump; SOFA, sequential organ-failure assessment. *Mean and SEM among treated.*

Anaesthesia/ICU management

Paper I and III - patients after uncomplicated cardiac surgery

In all the 42 uncomplicated postoperative patients in Paper I and III, a standardised anaesthetic procedure was used. The patients were premedicated with intramuscular morphine (5-10mg) and scopolamine (0.2-0.4mg) and oral flunitrazepam (0.5-1.0 mg). Anaesthesia was induced with thiopentone 2–4 mg/kg, fentanyl 5–7 µg/kg followed by pancuronium 0,1 mg/kg and maintained by sevoflurane. Anaesthesia was maintained by propofol infusion, during CPB. Mannitol was not used in the pump prime. In the intensive care unit (ICU), the patients were sedated with propofol and mechanically ventilated to normocapnia. All patients received a continuous infusion of morphine 1.0 mg/h during the experimental procedure, with no addition of acetaminophene or NSAID:s. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (Venofundin, Braun, Germany) and crystalloid fluids (Ringer –Acetate, Baxter, Viaflo).

Paper II and IV - patients with AKI after complicated cardiac surgery

In the intensive care unit (ICU), patients who were mechanically ventilated, were sedated with propofol. All the patients in Paper II and 23 of 30 patients in Paper IV, were mechanically ventilated. Seven patients in Paper IV were unsedated and spontaneously breathing. All the patients received morphine or fentanyl for treatment of postoperative pain. The hemodynamic and renal management of the patients were at the discretion of the attending intensive care physician. The treatment protocol included inotropic support with milrinone, dopamine and/or norepinephrine to maintain cardiac index ≥ 2.1 L/min/m^2, whole body oxygen extraction ≤ 40% and mean arterial pressure (MAP) at 70-80 mmHg with or without an intra-aortic balloon pump. A continuous infusion of furosemid (5-40 mg/h) was used, if needed, to promote diuresis.

Measurements of systemic hemodynamics

In all patients in papers I–III and in 21 of 30 patients in Paper IV, a pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was inserted through the right internal jugular vein or the left subclavian vein and guided into the pulmonary artery. The heart rate (HR), mean arterial blood pressure (MAP), mean pulmonary arterial pressure (MPAP) and central venous pressure (CVP) were continuously measured and stored in a computer, using data acquisition software (AcqKnowlegde Biopac, Goleta, CA, USA). Measurements of thermodilution cardiac output (CO) were performed in triplicate. CO was indexed to body surface area to get the cardiac index (CI) in Paper II and Paper III. The pulmonary artery wedge pressure (PCWP) was measured intermittently. Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left ventricular stroke volume (SV), were calculated according to standard formulas (SVR = (MAP – CVP) / CO, PVR = (MPAP – PCWP) / CO, SV = CO/HR). SVR, PVR and SV were indexed in Paper II and Paper III, systemic vascular resistance index was calculated as (MAP – CVP) / CI x 80, the pulmonary vascular resistance index was calculated as (MPAP – PCWP) / CI x 80 and the left ventricular stroke volume index was calculated as CI / HR.

Measurements of renal variables

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

Renal vein catheter placement

In all the patients in papers I–III, a ball-ended 8-Fr catheter (Webster Laboratories, Baldwin Park, CA), originally designed for coronary sinus catheterisation, was used. The catheter was introduced into the left renal vein via the right femoral vein, under fluoroscopic guidance (Figure 5)[134]. The catheter was placed in the central portion of the renal vein and its position was verified by venography, using ultralow doses of iohexol (Omnipaque® 300 mg I/mL, GE Healthcare, Stockholm, Sweden) [135]. The uncomplicated postoperative patients received 30–60 mg Iodine/kg, and the patients with AKI 5–15 mg Iodine/kg.

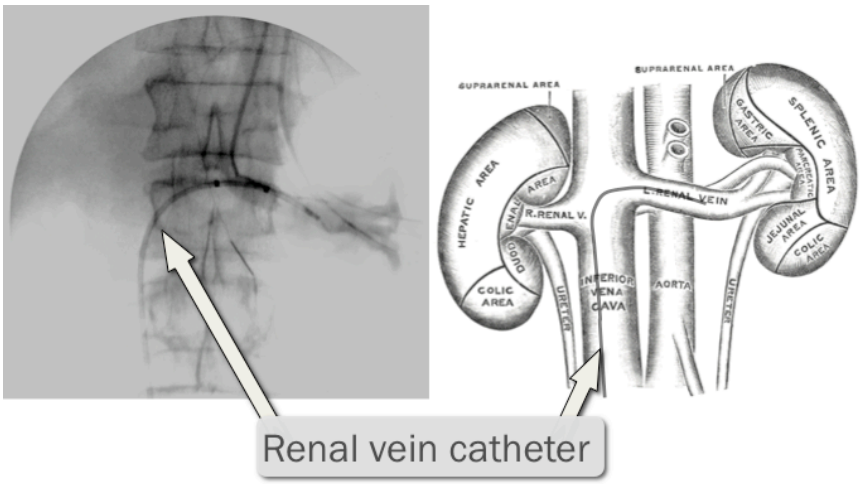


Figure 5*. The renal vein catheter is guided via v. cava inferior and positioned in the central portion of the left renal vein. The position is verified by venography. From [134], with permission.*

Renal blood flow by continuous thermodilution

To measure the RBF in papers I-III, a room tempered isotonic crystalloid solution was infused in the renal vein catheter for 15-30 seconds, at a constant rate of 53.7ml/min. A two-channel Wheatstone bridge was connected to the catheter and used to measure changes in resistance due to temperature variations of the indicator and the external thermistor located 2.5 cm proximal to the catheter tip.

The analogue signals from the Wheatstone bridge were stored in a computer, using data acquisition software (AcqKnowlegde Biopac, Goleta, CA, USA). The proportion of cooling between the indicator-thermistor and the external-thermistor was used to calculate the left renal vein blood flow (Figure 6) [134]. The correct position of the catheter was defined as one that yielded a variation in renal blood flow of no more than 10% in three consecutive measurements. The total renal blood flow was assumed to be twice the left renal blood flow and urine flow was added to get the total thermodilution measurement of total arterial renal blood flow (RBF_{TD}) (Formula 1). For the estimation of RBF, the mean of three measurements was used.

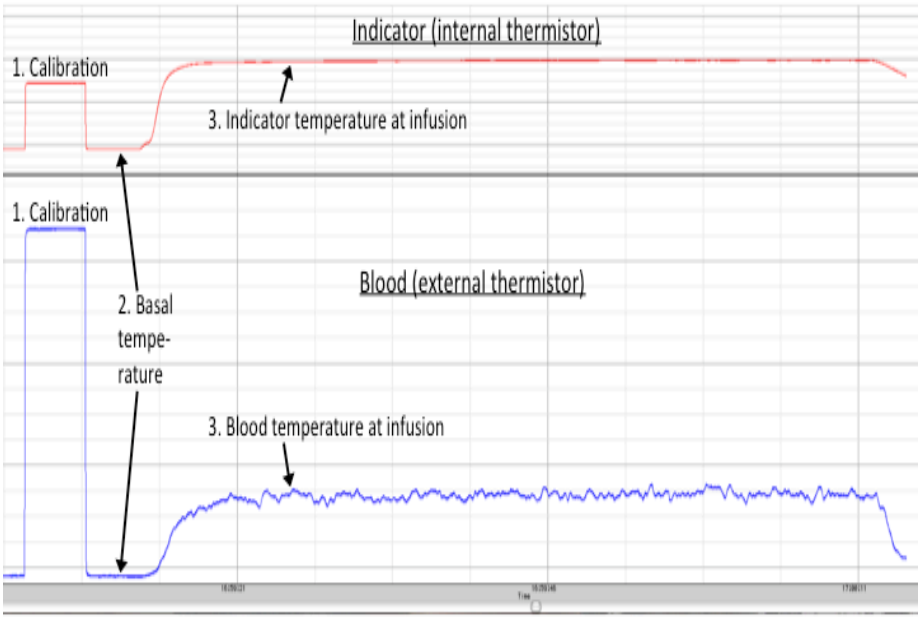


Figure 6. *A recording of a continuous renal vein thermodilution blood flow measurement in AcqKnowledge. The upper graph reflects the temperature of the indicator (internal thermistor), while the lower reflects the temperature of the renal blood (external thermistor). A decrease in temperature induces an elevation of the graph. Three different measurements were used to calculate the RBF: 1. Calibration signal strength. 2. Basal blood temperature. 3. Temperatures at infusion of crystalloid solution. The three different measurement periods were defined manually and the program then calculated the mean signal strength for each period and each channel separately. From [134] with permission.*

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

Formula 1. *The formula used 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 signal (cal) or registration signal (reg). ΔT, change in temperature; K, catheter constants; UF, urine flow.*

Renal filtration fraction by ^{51}Cr-EDTA

In papers I-III, the renal filtration fraction (FF) was defined as the renal extraction of chromium ethylenediamine-tetraacetic acid (^{51}CrEDTA). After blood and urine blanks were taken, an intravenous priming dose of ^{51}CrEDTA (GE Healthcare Limited, The Grove Center, Amhersham, England), (0,6 MegaBq/m^2 body surface area), was given, 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 by a well counter (Wizard 3", 1480, Automatic Gamma Counter, Perkin Elma LAS, Turkuu, Finland). In order to eliminate errors due to variations in RBF and urine flow, the formula for the calculation of FF was corrected taking the urine flow in account (Formula 2) [136].

Urine flow

All the patients had a Foley catheter that drained the bladder for measurements of urine flow and measurements of the urine concentration of sodium and in Paper IV urine concentration of creatinine.

Analysis of oxygen, sodium and hemoglobin

Arterial blood was analyzed for the content of oxygen, hemoglobin and sodium, using an automated blood gas analyzer, ABL800 FLEX analyzer (Radiometer Medical ApS, Brønshøj, Denmark). Furthermore, mixed venous blood and renal vein blood were analyzed for oxygen content, with the same analyzer.

Analysis of plasma vasopressin

Blood samples for subsequent determination of plasma concentrations of vasopressin were obtained at the end of the second control period (C2), at the end of each of the vasopressin infusion periods and at the end of the second post drug control period (C4) in Paper I. The plasma concentration of vasopressin was measured by radioimmunoassay.

Formulas used to calculate renal data

For calculation of additional renal data in Paper I-III, see Formula 2.

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

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

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

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

$$GFR = RPF \times FF$$

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

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

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

Formula 2. *Abbreviations for additional renal calculations. RVR, renal vascular resistance; C_aO_2, arterial oxygen content; $C_{rv}O_2$, renal vein oxygen content; RVO_2 , renal oxygen consumption; RO_2Ex, renal oxygen extraction; FF, filtration fraction, [^{51}Cr-EDTA$_a$], arterial concentration of ^{51}Cr-EDTA; [^{51}Cr-EDTA$_{rv}$], renal vein concentration of ^{51}Cr-EDTA; Na^+filtration, renal sodium filtration; Na^+ reabsorption, renal sodium reabsorption; S_{Na}, serum sodium concentration; UF, urine flow; U_{Na}, urine sodium concentration; FE_{Na}, fractional excretion of sodium.*

Infusion clearance of ^{51}Cr-EDTA

Infusion clearance for ^{51}Cr-EDTA was obtained as a measure of glomerular filtration rate in all patients in Paper IV. This method does not require urine sampling, but requires equilibrium between the rate of infusion and excretion of the filtration marker. After blood and urine blanks were taken, an intravenous priming dose of ^{51}Cr–EDTA (0.6MBq/m^2 body surface area) was given, followed by an infusion at a constant rate individualized to body weight and serum creatinine. Serum ^{51}Cr–EDTA activities from arterial blood were measured by a well counter (Wizard 300, 1480, Automatic Gamma Counter, Perkin Elma LAS, Turku, Finland). Glomerular filtration rate was calculated from the formula; GFR (mL/min/1.73m^2) = ^{51}Cr-EDTA infusion rate x 1.73 / arterial ^{51}Cr-EDTA x BSA.

Estimation of GFR

Urinary creatinine clearance

The GFR was estimated in Paper IV, using the urinary creatinine clearance method. Urine was collected in two 30-min periods to measure urine flow and urine creatinine (period A and period B). Urinary CrCl, was calculated for period A and B from the formula; CrCl (mL/min/1.73m^2) = Urine-volume x Urine-creatinine x 1.73 / serum creatinine x 30min x BSA (Formula 3).

Estimating equations

GFR was estimated in all patients in Paper IV, by the use of three frequently used equations: the Cockcroft-Gault (CG) equation [131], the simplified refitted Modification of Diet in Renal Disease (MDRD) equation [137] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [133]. The CG equation was calculated with the actual body weight, the preoperative body weight and the preoperative ideal body weight, calculated according to a standard formula (Formula 3). To allow comparison to the results of other estimating equations, the estimated GFR (eGFR), from the CG equation was normalized to body surface area (BSA) 1.73m^2. All the equations used for eGFR are summarised in Formula 3.

Formula 3. Formulae for estimating glomerular filtration rate

Measured 30 min urinary creatinine clearance:
CrCl (mL/min/1.73m^2) = (U-vol x U-crea x 1.73) / (S-crea x 30min x BSA)
BSA (m^2) = weight (kg)$^{0.425}$ x height (cm)$^{0.725}$ x 71.84 / 10000
The Cockcroft-Gault equation:
CrCl (mL/min/1.73 m^2) = ([140-age] x weight) x 1.73 /
(S-creat x 72) x BSA (x 0.85 if female)
Cockcroft-Gault adjusted for ideal body weight (IBW):
CrCl (mL/min/1.73 m^2) = ([140-age] x IBW) x 1.73 /
(S-creat x 72) x BSA (x 0.85 if female)
IBW (male) = 50 kg + 0.9 kg for each cm > 150 cm in height
IBW (female) = 45 kg + 0.9 kg for each cm > 150 cm in height
The simplified refitted MDRD equation:
GFR (mL/min/1.73 m^2) = 175 x S-creat $^{-1.154}$ x Age$^{-0.203}$ (x 0.742 if female)
(x 1.212 if black)
The CKD-EPI equation:
Women:
GFR (mL/min/1.73 m^2) = 144 x (S-creat/0.7)$^{-0.329}$ x 0.993^{age}
(x 1.15 if black) if S-creat ≤ 0.7 mg/dL
GFR (mL/min/1.73 m^2) = 144 x (S-creat/0.7)$^{-1.209}$ x 0.993^{age}
(x 1.15 if black) if S-creat > 0.7 mg/dL
Men:
GFR (mL/min/1.73 m^2) = 141 x (S-creat/0.9)$^{-0.411}$ x 0.993^{age}
(x 1.16 if black) if S-creat ≤ 0.9 mg/dL
GFR (mL/min/1.73 m^2) = 141 x (S-creat/0.9)$^{-1.209}$ x 0.993^{age}
(x 1.16 if black) if S-creat > 0.9 mg/dL

CrCl; urinary creatinine clearance, U-vol; urine volume; U-crea; urinary creatinine concentration, S-creat; serum creatinine concentration in mg/dL, BSA; body surface area, IBW; ideal body weight, MDRD; modification in diet in renal disease, GFR; glomerular filtration rate, CKD-EPI; chronic kidney disease epidemiology collaboration.

Experimental procedures

Paper I - effects of vasopressin

Twelve patients with normal preoperative serum creatinine were studied, after elective uncomplicated cardiac surgery. The patients were studied in the ICU, sedated with propofol (64±6μg/kg/min) and morphine (0.5-1.0 mg/h) and mechanically ventilated to normocapnia. Measurements started when the patients had a stable body temperature > 36,0 ^{0}C, approximately 4-6 hours after end of cardiopulmonary bypass. All the patients received a pulmonary artery catheter and a renal vein catheter.

After an equilibration period of at least 60 minutes, two 30-min urine collection control periods (period C1 and C2) were started followed by a continuous infusion of vasopressin (Pitressin®, Goldshield Pharmaceuticals, UK) at infusion rates of 1.2, 2.4, and 4.8 U/h. Each dose was administered for 60 minutes and urine was collected at the second half of each hour of infusion. The highest acceptable systolic blood pressure (SAP) was 150 mmHg. After a washout period of 30 minutes, two 30-min post drug urine collection control periods ensued (C3, C4). Cardiac output, thermodilution measurements of renal blood flow and blood samples were obtained at the end of each period. Blood samples for subsequent determination of serum concentrations of vasopressin were obtained at the end of the second control period (C2), at the end of each of the vasopressin infusion periods and at the end of the second post drug control period (C4). Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (Venofundin, Braun, Germany) and crystalloid fluids (Ringer –Acetate, Baxter, Viaflo), with a target central venous pressure of 5-10 mmHg and target mean arterial pressure of 70-80 mmHg (Figure 7).

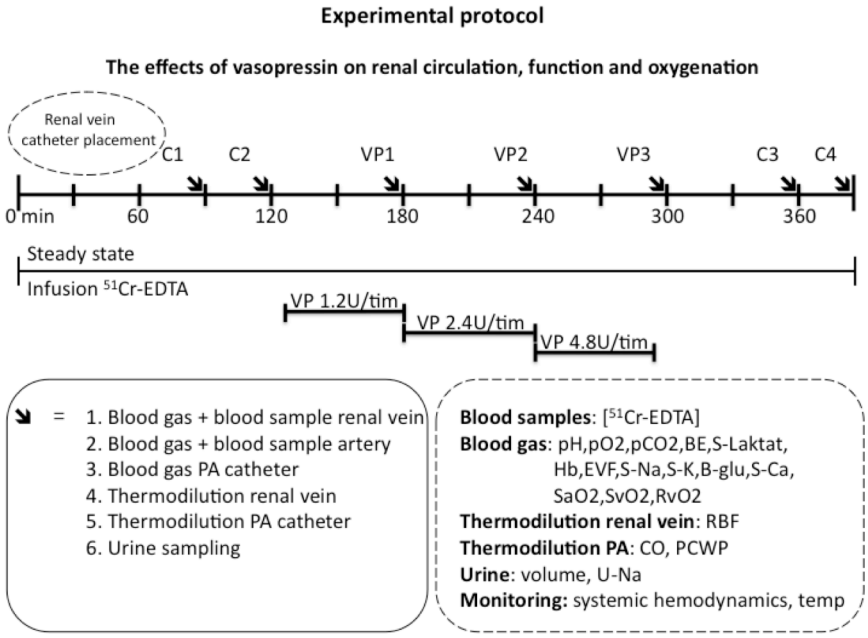


Figure 7. *The experimental protocol for Paper I. Abbreviations; C, control; VP, vasopressin.*

Paper II - effects of mannitol in AKI

Eleven patients with normal preoperative serum creatinine, who developed AKI after complicated cardiac surgery were studied, in the intensive care unit (ICU), where they were sedated with propofol (50.1 ± 3.3 μg/kg/min) and morphine or fentanyl, and mechanically ventilated to normocapnia. All the patients received a pulmonary artery catheter and a renal vein catheter.

The patients were included in the study from 2 to 6 days after the cardiac surgery. After an equilibration period of at least 60 minutes, two 30-minute urine-collection control periods were started, followed by the administration of mannitol, 150 mg/ml (Mannitol; Baxter Viaflo, Baxter Medical AB, Kista, Sweden). The patients received a bolus dose of mannitol, 225 mg/kg, followed by a continuous infusion of mannitol at a rate of 75 mg/kg/h, for two 30-minute urine collection periods. Thermodilution measurements of RBF, hemodynamic variables, as well as blood and urine samples, were obtained at the end of each urine-collection period. During the experimental procedure, the blood pressure was kept constant, and an isotonic crystalloid solution was continuously infused to substitute for fluid losses due to the diuretic response (Figure 8).

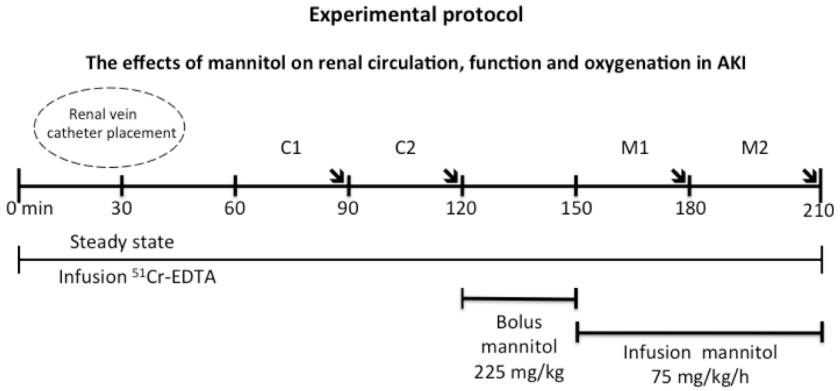


Figure 8. *The experimental protocol for Paper II. Abbreviations; C, control; M, mannitol.*

Paper III - effects of levosimendan versus placebo

Thirty patients with normal preoperative serum creatinine were studied after elective uncomplicated cardiac surgery, in the ICU. The patients were sedated with propofol (43.2 ± 2.23 μg/kg/min) and morphine (0.5-1.0 ml/h) and mechanically ventilated to normocapnia. Patients were randomized (closed envelopes) to receive either levosimendan (n=15) or placebo (n= 15). Measurements started when the patients had a stable body temperature > 36^0C; approximately 4–6 h after the end of cardiopulmonary bypass.

After an equilibration period of at least 60 min, two 30-min urine collection control periods were started, followed by the administration of a bolus dose of levosimendan, 12 μg/kg (Simdax®, Orion Corporation, Orion Pharma, Espoo, Finland) or placebo. This bolus dose was given to achieve steady state plasma concentrations within a short time period, as recommended by the manufacturer. Thereafter, a continuous infusion of levosimendan, 0,1μg/kg/min, or placebo was given for two additional 30-min urine collection periods. Thermodilution measurements of RBF, CO as well as blood and urine samples were obtained at the end of each period. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (Venofundin, Braun, Germany)

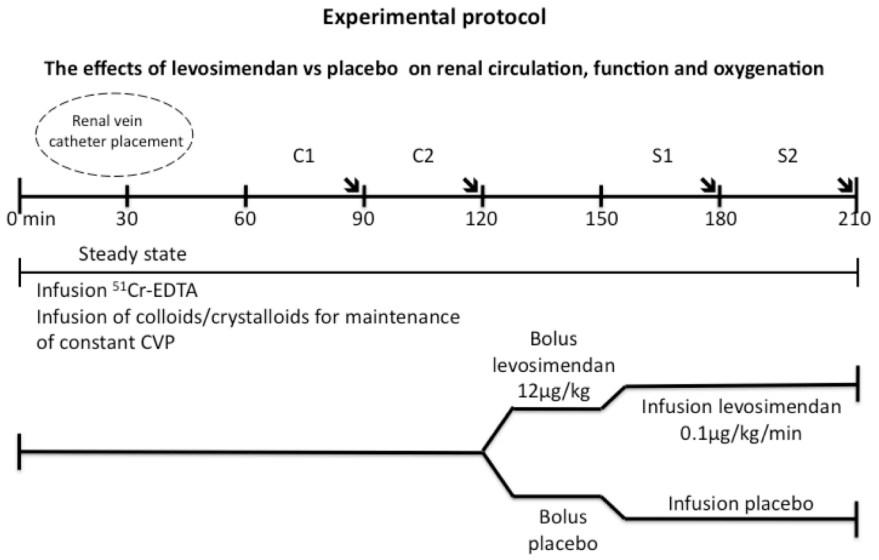


Figure 9. *The experimental protocol for Paper lll. Abbreviations; C, control; S, Simdax® (levosimendan).*

and crystalloid fluids (Ringer –Acetate Baxter Viaflo), keeping CVP constant during the experimental procedure (Figure 9).

Paper IV - true GFR versus urinary creatinine clearance and estimating equations in critically ill patients with AKI

30 patients with normal preoperative serum creatinine, were studied 2-12 days after complicated cardiac surgery. In the intensive care unit (ICU), patients who were mechanically ventilated, were sedated with propofol. Morphine or fentanyl was used for treatment of postoperative pain.

After blood and urine blanks were taken, an intravenous priming dose of ^{51}Cr–EDTA (0.6MBq/m^2 body surface area) was given, followed by an infusion at a constant rate individualized to body weight and serum creatinine. After an equilibration period of at least 60 min, urine was collected in two 30-min periods to measure urine flow and urine creatinine (period A and period B). An indwelling Foley catheter drained the urine bladder. The levels of ^{51}Cr-EDTA were obtained from arterial blood at the end of each urine collection period. The mean of the two ^{51}Cr-EDTA clearances (period A and B) was used for subsequent comparison with the urinary CrCl and the estimating equations. Hemodynamic measurements were obtained at the end of each period (Figure 10).

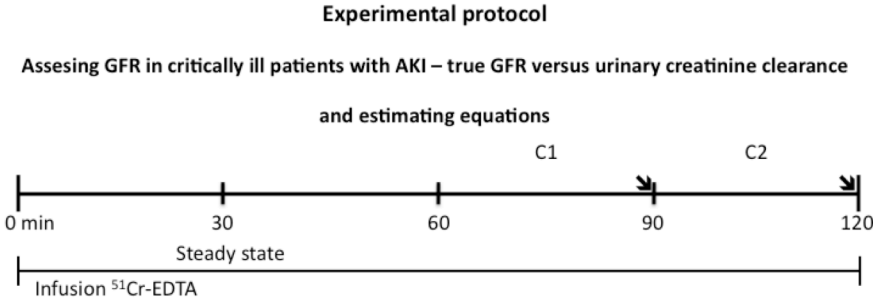


Figure 10. *The experimental protocol for Paper lV. Abbreviations; C1, urine collection period A; C2, urine collection period B.*

Statistical analysis

Statistical analyses have been made in SPSS (Statistical Package Social Sciences) version 16.0. Values are presented as mean ± SEM. A probability level (p-value) of less than 0.05 has been considered to indicate statistical significance.

Data Management

Predrug control periods (C1 and C2) in Paper I-III were pooled ((C1+C2)/2) before further comparisons were made. In Paper IV the mean of the two ^{51}Cr-EDTA clearances (period A and B) was used for subsequent comparison with the mean of the two urinary creatinine clearances (period A and B) and the estimating equations. In Paper II the two mannitol treatment periods (M1 and M2) were pooled ((M1+M2)/2) and in Paper III the data from the two intervention periods (treatment) were pooled. The second postdrug control period in Paper I (C4) was compared to pooled predrug control periods.

Kolmogorow-Smirnov

Kolmogorov-Smirnov test for goodness of fit to normal distribution was performed on all variables in Paper I and normality was obtained for all measurements.

Paired t-test

Predrug control values (C1 and C2), were compared using a paired T-test (Paper I-III). In Paper I pre- and postdrug control values were compared using a paired t-test. In Paper II, the renal and hemodynamic effects of mannitol, compared with pooled control, were assessed with a paired t-test. In Paper IV, data on hemodynamic and renal variables from periods A and B were compared using a paired t-test.

Unpaired t-test

Baseline data in Paper III, were compared using independent samples T-test.

Chi-Square test

Categorical baseline data in Paper III, were compared using a Chi-square test. However, when there were less than 5 observations in one of the populations, Fisher's exact test was used.

Repeated measures ANOVA

Analyses of variance (ANOVA) for repeated measurements followed by Fisher's PLSD post hoc analysis were used to compare the renal and haemodynamic effects of the different doses of vasopressin to the pooled control period (Paper I).

Two-way repeated measures ANOVA

To compare the differential effects of levosimendan and placebo on the measured variables in Paper III, a two-way repeated measures analysis of variance (ANOVA) was used.

Within-subject correlation analyses

Within-subject correlation analyses were also performed to correlate RVO_2 to tubular sodium reabsorption, tubular sodium reabsorption and RVO_2 to GFR and RO_2Ex to FF before and during vasopressin infusion in Paper I [138]. With this multiple regression, or analysis of covariance (ANCOVA), it is possible to evaluate whether a change in one numeric variable is associated with a change in another variable, within the individual. The within-patient variation for repeated measures is calculated. One regression-line is created for each patient, with different locations on the chart but with the same slopes, thereby eliminating the between-patient variance. As an example we can see that despite substantial variation between patients in both renal oxygen extraction and filtration fraction in Paper I, correlation within subject showed that there was a close correlation between vasopressin-induced changes in RO_2Ex and FF, thus the patients increased their oxygen extraction when the filtration fraction increased. The mean with-in patient effect is calculated.

Assessment of repeatability and agreement

Descriptive data analyses on the ^{51}Cr-EDTA infusion clearance method and the urinary CrCl method for measurement of GFR were performed according to Bland and Altman, in Paper IV [139]. The (within-method) repeatability of each of these two methods, were assessed by the error (double standard deviation of the absolute differences divided by the mean of the repeated measurements), the repeatability coefficient (the double standard deviation of the absolute differences) and the mean coefficient of variation (standard deviation of the mean divided by the mean of the repeated measurements).

The agreements between the "gold standard" ^{51}Cr-EDTA infusion clearance method, and the urinary CrCl method, as well as the estimating equations used for eGFR (the CG equation, the MDRD equation and the CKD-EPI equation), were assessed according to Bland and Altman, in Paper IV [139]. The mean difference between two methods (bias) and the standard deviation of the differences were calculated as well as the error (double standard deviation divided by the mean of the measurements from the two methods) and the limits of agreement (mean difference ± two standard deviations). According to Critchley and Critchley, an acceptable within-method error was defined as 20% or less and between-method error as 30% or less [140].

Results

The repeatability of methods used for measurements of renal variables in the present thesis

The repeatability of methods used for measurements of renal variables in Paper I and III of the present thesis, can be seen in Table 6.

Table 6. Repeatability of methods used for measurements of renal variables in the present thesis.

				Limits of agreement	
	Bias	COV	Error	Upper	Lower
RBF (ml/min)	10.8	5.2 ± 5.6	19.9	-134	156
FF	-0.002	12.2 ± 8.0	40.6	-0.06	0.05
GFR (ml/min)	1.29	14.0 ± 8.4	44.1	-27.8	30.4
RO_2Ex	-0.01	7.8 ± 5.8	23.4	-0.03	0.017
RVO_2 (ml/min)	-0.28	9.8 ± 9.3	32.0	-3.82	2.73

RBF, renal blood flow; FF, filtration fraction; GFR, glomerular filtration rate; RO_2Ex, renal oxygen extraction; RVO_2, renal oxygen consumption; COV, mean coefficient of variation ±SD.

Paper I- effects of vasopressin

To evaluate the renal effects of vasopressin, we studied 12 uncomplicated postoperative patients, with normal preoperative renal function. Data obtained during the two control periods, C1 and C2, did not differ significantly in any of the measured systemic hemodynamic or renal variables. Serum vasopressin concentrations increased dose-dependently. Concentration of vasopressin at the end of the second postdrug control period was significantly higher when compared to the predrug control period. All patients were discharged from the ICU the day after surgery and postoperative creatinine was lower in all patients compared to the respective preoperative value (74±3 vs. 82±3, $p<0.01$).

Effects of vasopressin on systemic hemodynamic variables

In none of the patients did vasopressin cause an increase in SAP greater than 150 mmHg. SVR, CVP and pulmonary capillary wedge pressure increased, heart rate, CO, mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance decreased, while MAP and stroke volume (SV) were unchanged with vasopressin. Postdrug control values of SV, MPAP, and cardiac filling pressures were significantly

elevated when compared to predrug control values. Postdrug control values of all other haemodynamic variables did not differ significantly from predrug control values.

Effects of vasopressin on renal variables

Vasopressin induced an increase in RVR and a decrease in RBF already at the lowest dose of vasopressin. GFR increased at the highest dose of vasopressin. FF, RVO_2 and RO_2Ex increased dose-dependently with vasopressin (Figure 11). Tubular sodium reabsorption increased with vasopressin at the highest dose, while urine flow and renal sodium excretion decreased dose-dependently with vasopressin. Urine osmolarity increased with vasopressin. Postdrug control values of RO_2Ex and urine flow were higher and lower, respectively, when compared to predrug control values. Postdrug control values of all other renal variables did not differ significantly from predrug control values. The vasopressin-induced increase in RVO_2 correlated positively to the increase in tubular sodium reabsorption (r^2 = 0.94, $p<0.01$) and the

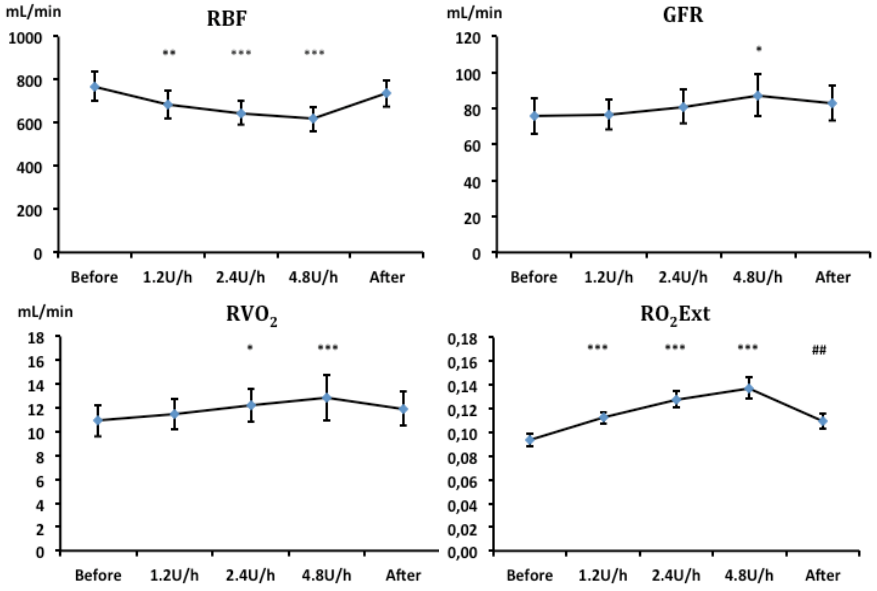


Figure 11. *The effects of incremental infusion rates of vasopressin (1.2, 2.4 and 4.8U/h) on renal blood flow (RBF), glomerular filtration rate (GFR), renal oxygen consumption (RVO_2) and extraction (RO_2Ex). Vasopressin causes a constriction of renal efferent arterioles with a fall in RBF and an increase in GFR and RVO_2. Vasopressin impairs the renal oxygen demand/supply relationship as reflected by the increase in RO_2Ex. *P<0.05, **P<0.01 and ***P<0.001 compared with predrug control; ##, post-control drug control vs. pre-drug control.*

vasopressin-induced increase in GFR correlated positively to increases in both tubular sodium reabsorption and RVO_2 ($r^2 = 0.98$, $p<0.001$ and $r^2 = 0.93$, $p<0.001$, respectively). Finally, there was a close correlation between vasopressin-induced changes in FF and RO_2Ex ($r^2 = 0.86$, $p<0.001$) (Figure 12).

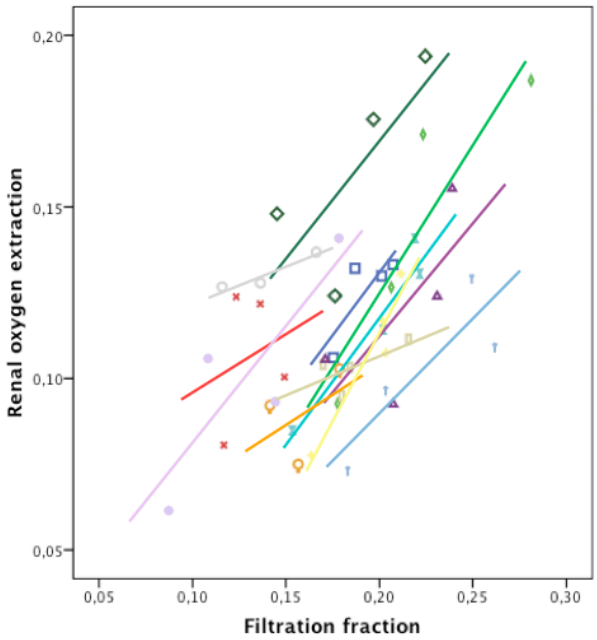


Figure 12. *Shows the individual data on the correlation between the vasopressin-induced increase in renal filtration fraction, and renal oxygen extraction ($r^2 = 0.86$, $P < 0.001$).*

Paper II - effects of mannitol in AKI

To evaluate the renal effects of mannitol in AKI, we studied 11 patients with > 50 % increase in serum creatinine after complicated cardiac surgery. Data obtained during the two control periods, C1 and C2, did not differ significantly in any of the measured systemic hemodynamic or renal variables. Patient characteristics at inclusion are presented in Table 5.

Effects of mannitol on systemic hemodynamic variables

Mannitol induced a significant increase in SVI (4%) and significantly decreased Hct (2%). Mannitol caused no significant changes in MAP, MPAP, CI, HR, SVRI, or PVRI and had no effects on filling pressures (CVP, PCWP). The body temperature did not change during the experimental procedure.

Effects of mannitol on renal variables

Mannitol induced a significant increase in RBF (12%) and significantly decreased RVR (-13%). Mannitol increased the RBF/CO relation (P = 0.040). Mannitol also caused significant increases in urine output (61%) and FE_{Na} (58%). Although mannitol tended to increase GFR (16%, P = 0.16), sodium filtration (18 %, P = 0.14), tubular sodium reabsorption (14%, P = 0.28), and RVO_2 (10%, P = 0.14), none of these changes reached statistical significance. Mannitol affected neither FF nor RO_2Ext (Figure 13).

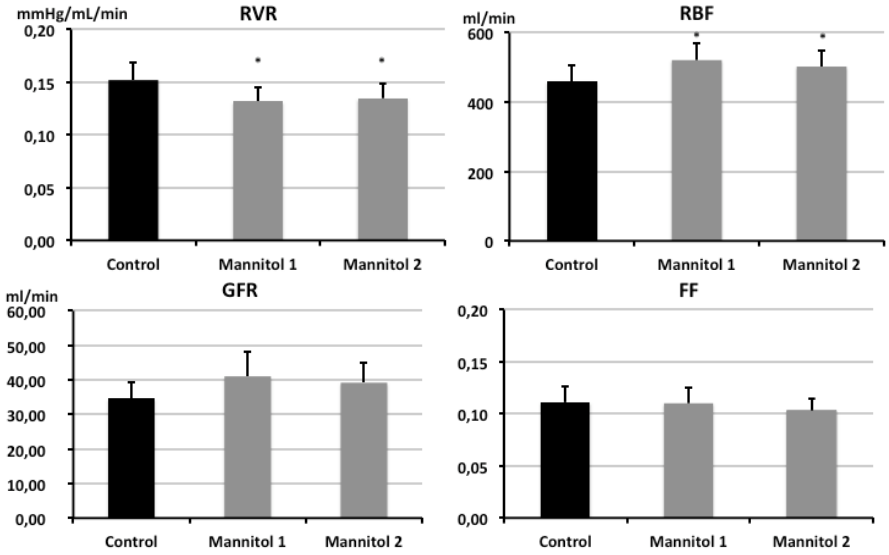


Figure 13. *Effects of mannitol on renal vascular resistance (RVR), renal blood flow (RBF), glomerular filtration rate (GFR) and renal filtration fraction (FF). *P < 0.05.*

Paper III - effects of levosimendan versus placebo

To evaluate the renal effects of levosimendan, we studied 30 uncomplicated postoperative patients, with normal preoperative creatinine. The patients were randomized to receive either levosimendan (n=15) or placebo (n=15). The two groups did not differ in baseline patient characteristics and there were no baseline differences (before treatment) between the placebo group and the levosimendan group in any of the measured systemic hemodynamic variables or renal variables.

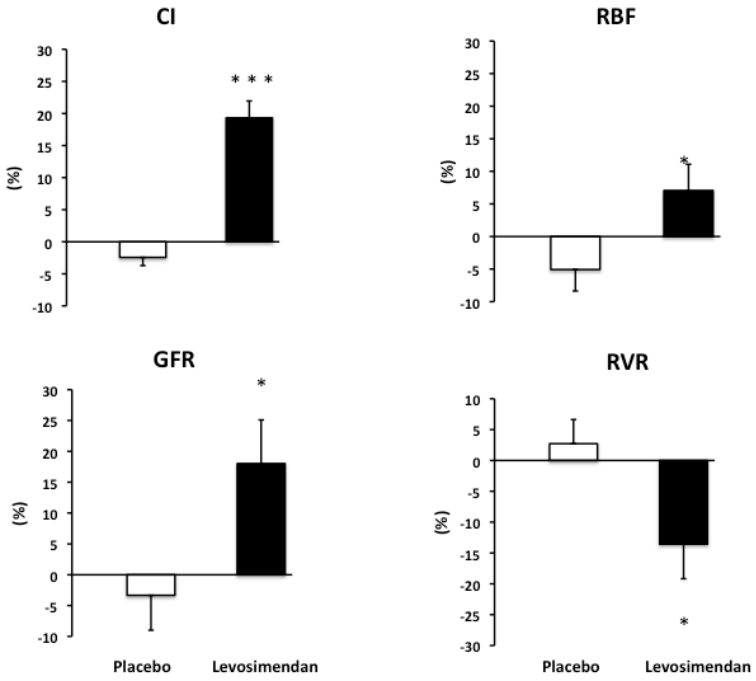
Effects of levosimendan on systemic hemodynamic variables

Levosimendan increased CI (22%), stroke volume index (15%) and heart rate (7%), decreased SVRI (21%), PVRI (15%), while MAP, PCWP and MPAP were not significantly affected by levosimendan when compared to placebo. Hematocrit decreased significantly (6%) in the levosimendan group compared to placebo. There was no significant difference in body temperature between the groups during the experimental procedure.

Effects of levosimendan on renal variables

Levosimendan induced significant increases in RBF (12%, $p<0.05$), GFR (21%, $p<0.05$), GF_{Na} (21%, $p<0.05$), and TR_{Na} (21%, $p<0.05$), while RVR decreased (18%, $p<0.05$) significantly, compared to placebo (Figure 14). Levosimendan caused no significant changes in FF, FE_{Na}, RvO_2, RO_2Ext and urine flow compared to placebo.

Figure 14. *Shows the effects of levosimendan vs. placebo on cardiac index (CI), renal blood flow (RBF), glomerular filtration rate (GFR) and renal vascular resistance (RVR). *=p<0.05 ***=p<0.001*



Paper IV- true GFR versus urinary creatinine clearance and estimating equations in critically ill patients with AKI

To evaluate the agreement of urinary CrCl, and three commonly used estimation equations, the Cockcroft-Gault, MDRD and CKD-EPI, for estimating GFR, in comparison to GFR measured by the infusion clearance of ^{51}Cr-EDTA in critically ill patients with early AKI, we studied 30 patients 2-12 days after complicated cardiac surgery. There were no statistically significant differences in plasma ^{51}Cr-EDTA concentrations, GFR measured by ^{51}Cr-EDTA infusion clearance and eGFR measured by creatinine clearance, between period A and B.

Repeatability within methods

The mean values for $GFR_{51Cr\text{-}EDTA}$ and for $eGFR_{CrCl}$ were 47.0 ± 18.0 and 43.8 ± 21.9 ml/min/1.73m^2, respectively. The within-group error was lower for $GFR_{51Cr\text{-}EDTA}$ than $eGFR_{CrCl}$, 7.2%. vs. 55.0%, respectively. The repeatability coefficient for $GFR_{51Cr\text{-}EDTA}$ and the $eGFR_{CrCl}$ were 3.3 and 23.9, respectively and the mean coefficient of variation for $GFR_{51Cr\text{-}EDTA}$ was lower than the mean coefficient of variation for $eGFR_{CrCl}$, 1.73 ± 1.38 vs. 13.4 ± 11.3%, respectively (Figure 15).

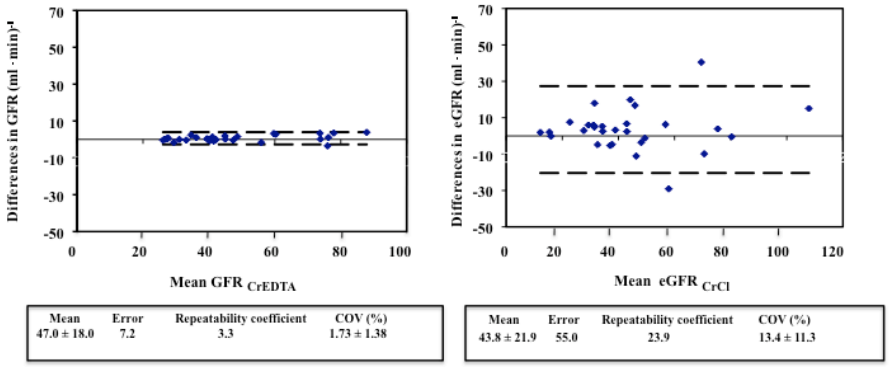


Figure 15*. Repeated estimations of GFR by a) the ^{51}Cr-EDTA infusion clearance method and b) the urinary CrCl method. The within group error, the repeating coefficient and the coefficient of variation, is lower for $GFR_{51Cr\text{-}EDTA}$ than $eGFR_{CrCl}$*

Agreement between methods

The agreements between measured GFR ($GFR_{51Cr\text{-}EDTA}$) and the urinary CrCl method and the prediction equations used to estimate GFR ($eGFR_{CrCl}$, $eGFR_{CG}$, $eGFR_{MDRD}$, $eGFR_{CKD\text{-}EPI}$) are described in Figure 16 and 17. The between-method bias was 2.6, 11.6 and 11.1 ml/min, for $eGFR_{CrCl,}$ $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$, respectively, when compared to $GFR_{51Cr\text{-}EDTA}$. The between-method bias was 7.39, 7.43 and 11.5 ml/min, respectively, for $eGFR_{CG\ actual\ bw}$, $eGFR_{CG\ preop\ bw}$ and $eGFR_{CG\ preop\ ideal\ bw}$, when compared to $GFR_{51Cr\text{-}EDTA}$.

The error was 103, 68.7 and 67.7% for $eGFR_{CrCl}$, $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$, respectively, when compared to $GFR_{51Cr\text{-}EDTA}$ (Fig 3). The limits of agreement were -43.9 to 49.1, -16.7 to 39.9 and -17.0 to 39.2 ml/min, respectively, when compared to $GFR_{51Cr\text{-}EDTA}$. The error was 68.0, 66.8 and 67.7%, respectively, and the limits of agreement were -21.7 to 36.5, -21.5 to 36.3 and -17.0 to 39.1 ml/min for $eGFR_{CG\ actual\ bw}$, $eGFR_{CG\ preop\ bw}$ and $eGFR_{CG\ preop\ ideal\ bw}$, when compared to $GFR_{51Cr\text{-}EDTA}$ (Figure 16 and 17).

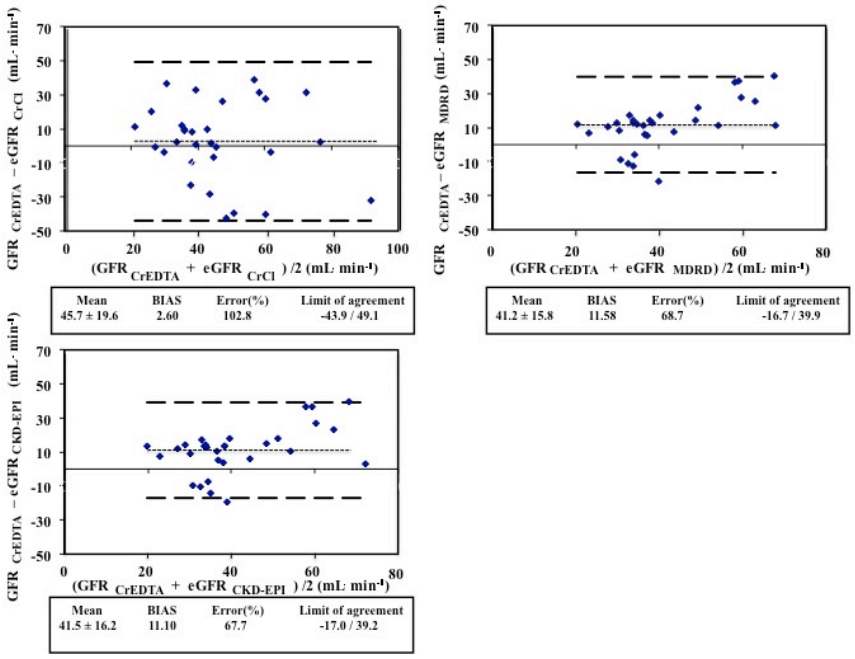


***Figure 16**. Agreement between a) $GFR_{51Cr\text{-}EDTA}$ and $eGFR_{CrCl}$ b) $GFR_{51Cr\text{-}EDTA}$ and $eGFR_{MDRD}$ c) $GFR_{51Cr\text{-}EDTA}$ and $eGFR_{CKD\text{-}EPI}$*

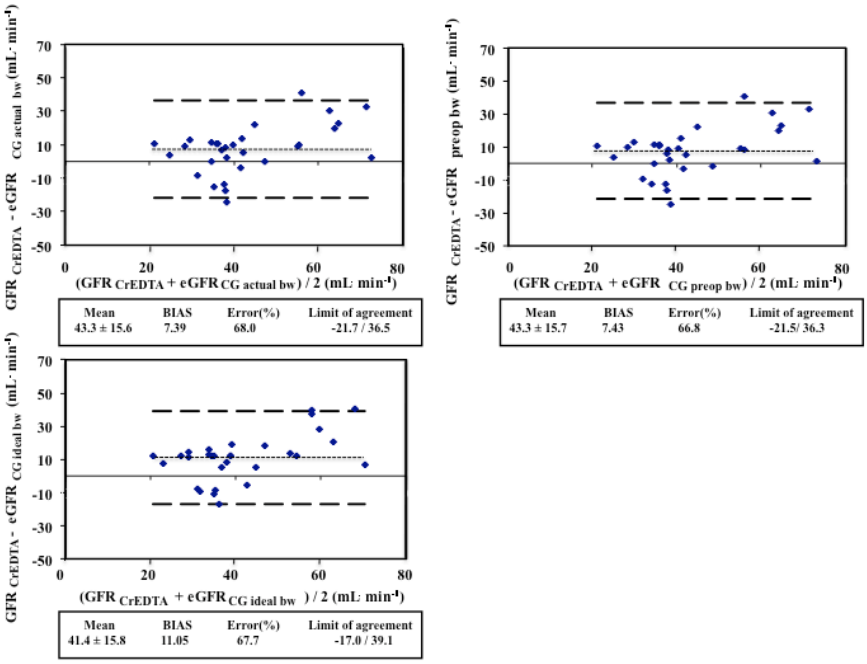


Figure 17. *Agreement between a) $GFR_{51\ Cr\text{-}EDTA}$ and $eGFR_{CG\ actual\ bw}$ b) $GFR_{51\ Cr\text{-}EDTA}$ and $eGFR_{CG\ preop\ bw}$ c) $GFR_{51\ Cr\text{-}EDTA}$ and $eGFR_{CG\ preop\ ideal\ bw}$ Abbreviations; bw, body weight.*

Discussion

Methodological and experimental considerations

Ethical issues

Paper I is a pharmacological study on the effects of vasopressin on RBF, GFR and RVO_2 in patients undergoing routine cardiac surgery. Thus, the patients did not receive vasopressin because of a clinical need. One could argue that we exposed our patients to a significant risk as we administered a vasopressor to uncomplicated post-cardiac surgery patients, with normal SVR, thereby increasing the risk for hypertension and the risk of bleeding and reoperation. However, systemic "overconstriction" was avoided by the use of low- to moderate, non-hypertensive (SAP < 150 mmHg) doses of vasopressin. These doses increased SVR by only 5-10%, did not affect MAP, and none of the patients were subjected to reoperation, because of bleeding, induced by high MAP. This was not an unexpected finding, as it is known that exogenous vasopressin has negligible vasopressor activity in individuals that are not in shock [91, 92]. The chosen infusion rates of vasopressin were in the lower range (1.2, 2.4 and 4.8 U/h), of those previously used for treatment of septic, vasodilatory or cardiogenic shock [141]. Furthermore, in Paper I, serum concentrations of vasopressin reached levels between 80-90 pg/ml at the highest infusion rate, which are slightly lower than those found in e.g. the recent VASST trial [141], in which infusion of vasopressin (1.8 U/h) was compared to low-dose norepinephrine in septic shock.

In Paper I, the short-term infusion of vasopressin induced a 10-20% decrease in RBF, which could have triggered renal damage. On the other hand, RBF returned to baseline after discontinuation of vasopressin infusion and this short-lasting (3 hours) decrease in RBF was not severe enough to cause a detectable decline in renal function, as, in all patients, the postoperative serum creatinine values were, lower compared to their respective preoperative levels. However, a prolonged infusion of vasopressin at these infusion rates could potentially be detrimental to the kidneys.

Study population

The populations of patients studied in the papers of this theses were biased with regard to gender. In Paper I, 92% of the patients were men and in Paper III, 93% of the patients in both study groups were men. The

most common type of cardiac surgery procedure in these 2 papers was CABG, (93%). The patients were recruited from the list of elective cardiac surgical procedures at our center. The reason why we included more men than women reflects the fact that fewer women than men undergo CABG surgery. Of all patients in western Sweden who underwent CABG surgery between June 1988 and June 1991 only 20% were women [142], and in an outcome study by Risum *et al.* on all patients submitted to CABG surgery at Rikshospitalet in Oslo, between August 1982 and December 1986 only 11% were women [143].

The fact that Paper I investigated the effect of an intervention where the patients served as theirs own controls (paired design), reduces the probability that the statistical results were biased by the low percentage of female patients. In Paper III, the number of women in the two groups that were compared was the same, reducing the probability that the statistical results were biased by the low percentage of female patients. In Paper II, we included patients with early AKI after complicated cardiac surgery. 27% of the included patients were women. The fact that Paper II investigated the effect of an intervention where the patients served as theirs own controls (paired design), reduces the probability that the statistical results were biased by the low percentage of female patients.

Study design

One major limitation of the studies of this thesis is that we did not include a time-control group in Paper I and II. One could, therefore, argue that changes in the measured haemodynamic or renal variables were not entirely caused by vasopressin or mannitol itself, but also, to some extent, by spontaneous fluctuations or time-dependent effects on these variables. On the other hand, data on renal and systemic haemodynamics, as well as on renal function and oxygen metabolism, obtained during the two predrug control periods in both papers, did not differ significantly. We therefore believe that the effects of vasopressin and mannitol on the measured haemodynamic and renal variables in Paper I and II were caused by vasopressin and mannitol, respectively, and not by spontaneous fluctuations or time-dependent changes of these variables. Furthermore, in Paper I almost all renal variables returned towards baseline after discontinuation of vasopressin infusion. Postdrug control values of RO_2Ex and urine flow were elevated and reduced, respectively, compared to predrug control values. This could at least to some extent be explained by a carry-over effect of vasopressin on renal variables to the postdrug control periods as the half-life of vasopressin is

estimated to be 10-35 minutes [90, 144]. This was also reflected by the fact that serum vasopressin was significantly elevated even at the second postdrug control period.

RBF by thermodilution

The renal vein thermodilution technique has been described and validated using either a bolus or a continuous infusion technique [145-147]. Thermodilution derived absolute values of RBF assume that a single vein is present on the site of measurement, that there is equal blood flow to both the kidneys, that there is minimal admixture of non-renal blood flow (spermatic, adrenal and ovarian) into the renal vein and that there is complete mixing of the injectat solution with the blood. Correct and stable position of the renal vein catheter termistor is the most critical factor for the estimation of RBF.

Swärd *et al*. recently validated the continuous renal vein thermodilution technique against the gold-standard technique, which is the urinary clearance of PAH, corrected for the renal extraction-fraction of PAH [145]. The coefficient of variation for repeated estimations of RBF was similar (10%) for the thermodilution and the urinary clearance techniques, suggesting that the repeatability of the thermodilution technique is comparable to the gold standard technique. When calculated on the material used in this thesis, the coefficient of variation for repeated estimations of RBF by thermodilution, was found to be better than that reported by Swärd *et al*. It was found to be 5.2% in the patients after uncomplicated cardiac surgery (Paper I and III), indicating that the repeatability of the technique has improved over the past 10 years (Table 6).

The obvious advantages with the continuous renal vein thermodilution technique are that rapid and repeated estimations of RBF can be performed at the bedside with short intervals. It is neither dependent on a steady state, nor the need for urine collection. The thermodilution technique can, hence, be used in intensive care patients to detect dynamic changes in RBF.

Filtration fraction by ^{51}Cr-EDTA and GFR by infusion clearance of ^{51}Cr-EDTA

^{51}Cr-EDTA is freely filtered in the glomeruli and not reabsorbed by the tubules. It has a good correlation to inulin clearance, although renal clearance of ^{51}Cr-EDTA tends to be 5-15% lower at high values [148]. The extra-renal elimination of 3-5% is of no importance, as the renal extraction of ^{51}Cr-EDTA has been measured in papers I-III. Plasma

clearance of ^{51}Cr-EDTA is the method of choice for assessment of GFR in clinical routine work [149]. The formation of urine induces a hemoconcentration in the renal vein. The renal vein concentration of ^{51}Cr-EDTA, thus, becomes inappropriately high, leading to an underestimation of the filtration fraction and the GFR, if the formula for renal extraction of ^{51}Cr-EDTA is not corrected. This is especially evident in situations were RBF is low and/or the urine flow is high [136]. In papers I-III, the renal extraction of ^{51}Cr-EDTA has, however, been corrected for the differences in renal vein hemoconcentration, in turn caused by differences in urine output (Formula 2).

The coefficient of variation for repeated estimations of FF, was found to be 12.2% in the patients after uncomplicated cardiac surgery (Paper I and III).

In Paper IV, infusion clearance for ^{51}Cr-EDTA was obtained as a measure of GFR. This method does not require urine sampling but requires equilibrium between the rate of infusion and excretion of the filtration marker. Swärd *et al*. have previously compared the within-method error of the *infusion* clearance of ^{51}Cr-EDTA to that of the *urinary* clearance of ^{51}Cr-EDTA measured simultaneously in ICU patients [145]. It was shown that the within-method error was lower for the *infusion* clearance method than the *urinary* clearance method, 11% vs 33%, respectively [145]. The collection of urine is probably the main source of error in the case of the *urinary* clearance of ^{51}Cr-EDTA, despite the use of urine catheters for the urine collection. In Paper IV, the repeatability of *infusion* clearance of ^{51}Cr-EDTA method is high, the with-in method error is only 7.2% and the mean coefficient of variation is low, 1.73%.

Renal physiology after cardiac surgery

The patients in papers I and III, were included after uncomplicated cardiac surgery. They were all on CPB, which is known to increase the risk for AKI.

As can be seen in Table 7, RBF and GFR is 30-40% lower in the uncomplicated postoperative patients, compared to healthy controls from other studies [17, 150, 151]. Serum creatinine was not significantly higher on the first and second postoperative day in the uncomplicated postoperative patients. It is therefore unlikely that the CPB did have major negative effect on the kidney function in this group of patients. One explanation for lower RBF and GFR in the uncomplicated postoperative patients, compared to the healthy controls, might be that the patients were sedated and mechanically ventilated and they therefore had lower cardiac output than the healthy controls. Lower

RVO_2 in the postoperative uncomplicated patients, probably reflects the lower GFR in this group of patients compared to healthy controls. Renal oxygenation is not affected in the study group because the renal oxygen supply declines in proportion to the decline in renal oxygen demand.

Normal aging is associated with changes in renal structure and function and in creatinine metabolism that influence the serum creatinine concentration. In patients over 60 years of age, renal pathological features include arterial medial sclerosis and global glomerular sclerosis, that is probably a consequence of generalized arteriosclerosis observed in older populations [16]. Renal plasma flow and GFR normally decrease with aging. Studies in healthy men show that the average decline in the GFR is 10mL/min per 1.73m^2 per decade after the age of 30 years [152]. From age 30 – 80 years, GFR declines from 130 – 80 mL/min. Renal plasma flow decreases by a similar proportion so that the filtration fraction (the ratio of GFR to RPF) remains unchanged [152]. The decline in GFR, decreases creatinine clearance in older people. As the reduction in clearance and production of creatinine is proportionate, serum creatinine concentration is relatively normal in older individuals [16]. The mean age of the patients in papers I and III was 65.5 ± 1.8 years. All had normal preoperative serum creatinine at inclusion but we did not measure GFR before enrolment to the studies. Age-related reduction in GFR and RPF could explain, in addition to mechanical ventilation and sedation, why GFR and RBF is decreased in the uncomplicated postoperative patients compared to healthy controls from other studies.

Table 7. Renal physiology after cardiac surgery.

	Patients after uncomplicated cardiac surgery	**Healthy controls**
RBF mL/min	757 ±214	1000-1300
GFR mL/min	69 ± 27	100-125
RVO_2 mL/min	10.0 ± 3.3	15-19
RO_2A-Vdiff mL	13.5 ± 4.5	14-15

Healthy controls, adults without renal disease; RO_2A-Vdiff, the difference between arterial and renal vein oxygen content. Values are mean ± SD.

Interpretation of results

Paper I - renal effects of vasopressin

The main findings of Paper I were that short-term infusion of low- to moderate, non-hypertensive doses of vasopressin induced an increase in RVR and a decrease in RBF. This was accompanied by an increase in GFR, which increased RVO_2 as a consequence of an increase in filtered load of sodium and tubular sodium reabsorption. Because the increase in RVO_2 was not accompanied by an increase in RBF, vasopressin impaired the renal oxygen demand/supply relationship as reflected by the increase in renal oxygen extraction.

The beneficial effects of vasopressin on urine flow and creatinine clearance in patients with vasodilatory shock [90, 97-100], has been attributed to the positive effect of vasopressin on blood pressure, which by itself would increase urine output, combined with the relatively small renal vasoconstricting effect, providing a better preservation of renal blood flow (RBF) when compared to adrenergic agents [97]. It has also been speculated, that the vasopressin induced increase in creatinine clearance in vasodilatory shock, is caused by a constriction of preferentially the efferent arterioles, which would increase glomerular perfusion pressure and GFR [99, 100]. In Paper I, vasopressin induced renal vasoconstriction in parallel with an increase in filtration fraction and GFR, strongly suggesting that low- to moderate doses of vasopressin causes a constriction of mainly the post-glomerular resistance vessels. These data are in line with a previous experimental in vitro study showing that vasopressin causes a concentration-dependent constriction of efferent arterioles with virtually no effect on afferent arterioles [153].

In Paper I, close associations were found between vasopressin-induced increases in GFR, tubular sodium reabsorption and RVO_2. The renal medulla is, due to the concentration mechanisms, already under normal conditions on the border of hypoxia [36]. A vasopressin-induced increase in GFR and RVO_2 might therefore jeopardise renal oxygenation, as the increase in renal oxygen requirement is not met by an increase in RBF.

Vasopressin decreased urine flow and increased osmolarity, due to an activation of V_2 receptors on the convoluted tubule and collecting ducts, which is responsible for vasopressin's antidiuretic effect by increasing water reabsorption and decreasing inner medullary blood flow [92, 154]. Besides, vasopressin exerted an anti-natriuretic effect, as renal sodium excretion decreased by 50-60%. This finding is in agreement with data from a recent study in healthy humans

demonstrating a potent V_2-dependent antinatriuretic effect of vasopressin in the collecting duct [155]. These antidiuretic and antinatriuretic effects of vasopressin are in contrast to previous studies on patients with vasodilatory or septic shock in which vasopressin increased urine flow. The beneficial effect of vasopressin on blood pressure in these patients would by itself increase urine flow as has been demonstrated with norepinephrine for the treatment of septic shock [156, 157]. This vasopressor-induced diuretic/natriuretic response may be attributed to the well-known phenomenon of "pressure natriuresis" mediated by a decrease in tubular sodium reabsorption as a response to acute blood pressure elevation [158]. Furthermore, pharmacological doses of vasopressin producing high serum levels of vasopressin (>100 pg/ml), as seen in the treatment of septic shock [97, 159, 160], have a well-documented natriuretic action independent of the systemic blood pressure [161].

In conclusion, in post-cardiac surgery patients, with normal renal function, low-to moderate doses of vasopressin cause a renal vasoconstriction and a fall in RBF, which is accompanied by an increase in GFR. This suggests that vasopressin mainly constricts efferent arterioles, which could explain why vasopressin increases creatinine clearance in patients with vasodilatory shock. RVO_2 increases as a consequence of the elevated filtered load of sodium and vasopressin thus impairs the renal, oxygen demand/supply relationship. A future study devoted to a detailed analysis of the renal effects of vasopressin in patients with vasodilatory shock is, warranted.

Paper II - renal effects of mannitol in AKI

The main findings of Paper II, were that mannitol treatment of early AKI after cardiac surgery, induced a renal vasodilatation and increased RBF with no changes in filtration fraction or the renal oxygen supply/demand relationship, as assessed by the lack of effect on RO_2Ex.

In animal studies, it has been shown that mannitol increases RBF by renal vasodilation during both normotensive [162-164] and hypotensive conditions [165-167]. However, there is not much data in the literature on the effects of mannitol on RBF in humans. With the xenon^{133} washout technique, Castaneda-Zuniga *et al.* [35] studied the effects of mannitol (20%) infusion on RBF in humans with no renal impairment and demonstrated only a minimal increase in RBF. With the same methods as in Paper II, Kurnik *et al.* [36] studied the effect of mannitol (15%) on RBF in patients with moderate chronic renal failure and found that mannitol did not affect RBF. These results are supported by a study, recently

published by Redfors *et al*, demonstrating no effect of mannitol on RBF, in postoperative uncomplicated cardiac surgery patients with normal renal function [32].

What are the potential mechanisms behind the mannitol-induced decrease in RVR in early clinical, ischemic AKI, demonstrated in Paper II? It has been suggested that the mannitol-induced renal vasodilatory response to experimental renal ischemia is mediated directly by increased synthesis of prostacyclin, or indirectly by augmenting plasma levels of ANP because of the plasma volume expansion [167, 168]. In Paper II, plasma volume expansion with mannitol was not large enough to cause increased cardiac filling pressures at the time of RBF measurements. However, we cannot rule out the possibility that mannitol bolus plus infusion induced a transient increase in cardiac filling pressures and distension, causing a release of natriuretic peptides. In the study by Redfors *et al*. on postoperative uncomplicated cardiac patients with normal renal function, RBF was not affected by mannitol [32]. Redfors *et al*. used the same study protocol as in Paper II and it can therefore be suggested that mannitol-induced plasma volume expansion and the consequent cardiac release of renal vasodilatory cardiac peptides is not the main mechanism behind the renal vasodilation, demonstrated in Paper II.

It has been shown in experimental studies that renal ischemia causes endothelial cell injury and dysfunction followed by endothelial cell edema [47]. Flores *et al*. [169], showed in an animal study that ischemia-induced endothelial cell swelling can be reversed and prevented by mannitol. It was suggested that the failure of blood flow to return to the kidney after transient ischemia, the so-called “no reflow” phenomenon, was due to swollen endothelial cells, and that the no-reflow could be corrected by mannitol. Based on those experimental studies, one could therefore speculate that mannitol might exert its beneficial effect on renal perfusion in patients with AKI by a deswelling effect on injured endothelial cells.

Data on the effects of mannitol on the GFR are divergent. In animal studies, mannitol has been shown to decrease [170], increase [171], or to have no effect on the GFR [162]. In hypoperfused animal kidneys, mannitol infusion tends to restore the GFR toward normal levels [165, 166, 172], when given both before and after the induction of hypotension [166, 172]. Flores *et al*. suggested that mannitol maintains the GFR in renal ischemia primarily by an osmotic effect that reduces vascular endothelial cell swelling, which would reduce RVR and increase RBF [169]. A study on healthy human volunteers showed no effect of

mannitol on GFR [173], whereas mannitol increased creatinine clearance in patients with severe trauma/surgery, as shown in a study by Valdes *et al*. [109]. In a recent study on uncomplicated postcardiac-surgery patients with normal renal function, by using a protocol identical to that used in Paper II, it was shown that mannitol induced a 20% increase in GFR and filtration fraction with no change in RBF [32]. These findings were interpreted as deswelling effect on tubular cells, subjected to intraoperative hypotensive episodes, and recruitment of functional nephrons that are opened up by mannitol, which will increase tubular flow and restore GFR [174]. In Paper II, mannitol tended to increase GFR (16%), but the increase in GFR did not reach statistical significance (P = 0.16). This study was powered to detect a 20% increase in GFR, based on the study by Redfors *et al* [32]. In a *post hoc* power analysis, it was found that the sample size would have to be increased to 30 patients to detect a 16% increase in GFR, at a power of 0.8 in Paper II. The fact that filtration fraction was not altered with mannitol, however, suggests that GFR increased in proportion to the increase in renal plasma flow. If mannitol affected only RBF, one would have expected a decrease in the filtration fraction, which was seen in a similar group of patients receiving low-dose dopamine, which was found to increase RBF with no effects on the GFR [34]. Thus, it can be suggested that mannitol treatment in early AKI results in both vascular endothelial and tubular epithelial deswelling, which will improve both renal perfusion and filtration.

Treatment of patients with AKI with mannitol did not affect the renal oxygen supply/demand relation, as assessed by no changes in renal oxygen extraction. Thus, the mannitol-induced increase in RBF was matched by a proportional increase in RVO_2. If mannitol only affected RBF, with no increase in GFR or RVO_2, one would have expected a decrease in renal oxygen extraction, as was seen with low-dose dopamine, which increased RBF with neither effects on the GFR nor the RVO_2 [34].

In conclusion, treatment with the osmotic diuretic mannitol, in patients with AKI after cardiac surgery, caused by severe heart failure, requiring inotropic and mechanical support, induces a renal vasodilation and increases RBF, with maintained filtration fraction (i.e. causes a balanced increase in GFR and renal plasma flow) and renal oxygenation/demand supply relationship, as assessed by the lack of effect on RO_2Ex (i.e. the increase in renal blood flow was matched by aproportional increase in renal oxygen consumption). A larger population of patients must be studied to evaluate whether mannitol may improve renal outcome in AKI.

Paper III - renal effects of levosimendan versus placebo

The main finding of Paper III, was that levosimendan induced a renal vasodilatation, increasing *both* RBF and GFR, suggesting a dilatation of predominantly the preglomerular resistance vessels with no change in filtration fraction. Furthermore, the renal oxygen demand/supply relationship was not impaired by levosimendan as demonstrated by the lack of significant effect on renal oxygen extraction.

The finding, that levosimendan increases GFR, most likely, by a preglomerular vasodilation, expands the knowledge on the regional circulatory effects of levosimendan in humans and suggests that the beneficial renal effects of levosimendan in patients with heart failure and impaired renal function [115-117], may not only be caused by an increase in cardiac output, but also by a specific renal vasodilatory action.

Using the same methodology as used in Paper III, on a similar group of post-cardiac surgery patients, Redfors *et al*. have recently shown that 2 - 4 μg/kg/min dopamine causes a pronounced (45-55%) increase in RBF [34]. Thus, low-dose dopamine induces a much more pronounced renal vasodilation (30-35% decrease in RVR) when compared to levosimendan, which increased RBF by 12% and decreased RVR by 18%.

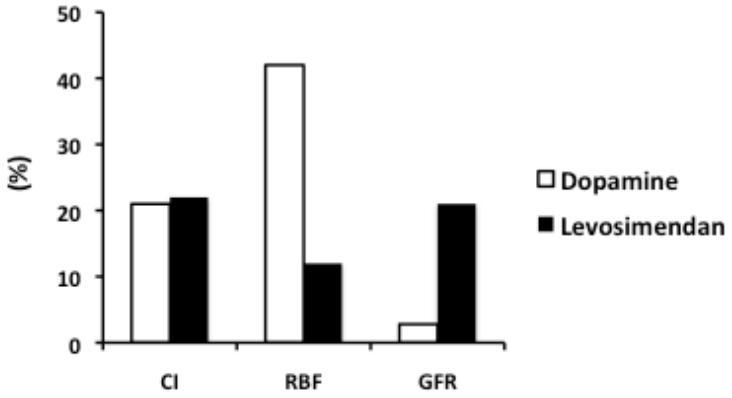


Figure 18. *Shows the differential effects of levosimendan (0.1 μg/kg/min) and dopamine (2μg/kg/min) on renal blood flow (RBF) and glomerular filtration rate (GFR) in post-cardiac surgery patients. Cardiac index (CI) was increased by approximately 20% with the two agents. Dopamine data from Redfors et al [34].*

However, in contrast to levosimendan, low-dose dopamine does not increase GFR (Figure 18). The differential renal effects of the two inodilators, dopamine and levosimendan, could be explained by a predominant preglomerular renal vasodilation with levosimendan, which will increase RBF but also enhance downstream glomerular hydraulic pressure and thus GFR. Dopamine, on the other hand seems to induce an unspecific dilation of *both* pre- and postglomerular resistance vessels with a pronounced effect on total RVR and RBF but with no effect on glomerular hydraulic pressure and GFR. This could explain why low-dose dopamine (2 μg/kg/min) does not improve renal outcome in ICU patients with early AKI [175]. Thus, levosimendan might have the potential to prevent or treat clinical ischemic AKI, caused by e.g. post-cardiac surgical heart failure, as it is probably, the only inodilator studied in patients, which will increase GFR. This is supported by the finding that the renal vasodilator, atrial natriuretic peptide (ANP), which increases both RBF and GFR in early postoperative AKI [176], by a preglomerular vasodilation, decreases the need for dialysis and improves dialysis-free survival in early post-cardiac surgery AKI [80].

Previous studies have shown that central venous pressure is an important and independent predictor of estimated GFR in patients with congestive heart failure [177]. It has been suggested that venodilation is the main mechanism behind the beneficial effects of levosimendan on renal function [178]. Venodilatation would decrease renal congestion and increase renal perfusion pressure. In Paper III, levosimendan increased, as expected, cardiac output by an increase in stroke volume and heart rate and induced a systemic and pulmonary vasodilation, as has been described repeatedly in the literature. Systemic venodilation was, according to the study protocol used, counteracted by infusion of crystalloids and colloids to maintain filling pressures constant. The levosimendan group received more fluids compared to the placebo group, which was reflected by a slight but significant fall in hematocrit. GFR increased, in spite of maintained filling pressures, suggesting that levosimendan-induced improved renal function in patients with congestive heart failure may be caused by a preglomerular vasodilation, in addition to relief of venous congestion [178].

Levosimendan did not affect fractional excretion of sodium, suggesting that levosimendan did not exert a direct tubular diuretic effect. This could also explain why levosimendan did not affect diuresis when compared to placebo, which is in contrast to the results of the studies by both Yilmas and Morelli, where levosimendan induced an increase in urine output [115, 179]. In Paper III, levosimendan tended to

decrease MAP, and that might be the explanation for the lack of a diuretic response.

Levosimendan induced a significant increase in GFR, resulting in a significant increase in tubular sodium reabsorption compared to placebo. This increase in metabolic requirements was, however, matched by increased RBF with no significant impairment of renal oxygenation.

In conclusion, in Paper III, it has been shown in post-cardiac surgery patients, that levosimendan-induced increase in cardiac output, is accompanied by a renal vasodilatation, and an increase in RBF. Levosimendan also increases GFR, suggesting a preferential dilatation of the pre-glomerular resistance vessels. Levosimendan does not impair renal oxygenation. The findings of Paper III, provide new information regarding the potentially beneficial specific renal actions of levosimendan, as demonstrated in a group of patients that have undergone a stressful, high-risk procedure such as cardiac surgery with cardiopulmonary bypass. Future studies are needed to explore the possibility that levosimendan might have beneficial effects on renal perfusion, filtration and oxygenation in postoperative AKI and in heart failure patients with the cardiorenal syndrome.

Paper IV - true GFR versus urinary creatinine clearance and estimating equations in critically ill patients with AKI

In Paper IV, the performance of urinary creatinine clearance (CrCl) and various estimation equations for assessment of GFR (eGFR), were compared to one of the gold standard techniques for measurement of GFR, the ^{51}Cr-EDTA infusion clearance technique, in critically ill patients with early AKI. The main findings were that urinary CrCl, that has been used as a reference method, had an unacceptably low repeatability and that all methods showed a poor agreement with the gold standard technique and can therefore not be considered as reliable methods to assess GFR in critically ill patients with early AKI.

Although commonly used in the ICU, data on the performance of the urinary CrCl method for assessment of GFR in critically ill patients with early AKI, when compared to gold standard GFR measurements, is limited. Robert *et al*. compared urinary CrCl to inulin clearance in twenty mechanically ventilated, hemodynamically stable patients, not requiring inotropic support and in whom a minority had acute renal dysfunction [180]. They found that there was a poor correlation between both 30-min and 24-hr urinary CrCl and inulin clearance. However, agreement between the two methods was not tested according to Bland and Altman

[139]. Erley *et al*. validated 24-hr urinary CrCl to inulin clearance in thirty-one ICU patients with a stable (three days) but wide range of renal (dys)function (serum creatinine: 53 to 590 μmol/l) [130]. Although they did not calculate the bias or error, they found a mean ratio of CrCl over inulin clearance of 1.03 with a 95% confidence interval between 0.54 and 1.92, suggesting a low bias but a high error, i.e. 95% of the CrCl values could be up to 92% higher and 44% lower than the inulin clearance values. The results of Paper IV, are in line with the data from Erley *et al*.[130].

Assessment of within-method repeatability is important in a study of method comparison, because the repeatability of each of two methods limits the amount of agreement, which is possible [139, 181]. Clearly defined criteria for an acceptable agreement between two methods have been lacking since the publication of Bland and Altman [139]. In an attempt to clarify the criteria for acceptable agreement between two methods, Critchley and Critchley suggested that acceptance of a new method should relay on a between-method error of up to 30% [140]. They could also demonstrate that the limits of within-group error of both the test and the reference method should be 20% or less to achieve a between-group error of 30% or less. In Paper IV, the repeatability for ^{51}Cr-EDTA infusion clearance was high, with a within-method error of only 7.2%. However, urinary CrCl had an unacceptably low repeatability, with a within-method error of 55%. It is therefore not surprising that the agreement between the ^{51}Cr-EDTA clearance and urinary CrCl is very low, with an unacceptably high between-method error of 103%.

In the case of urinary CrCl, the collection of urine is probably the main source of the error, demonstrated by Erley et al [130], and in Paper IV, despite the fact that bladder catheters were used. Swärd *et al*. have previously compared the within-method error of the *urinary* clearance of ^{51}Cr-EDTA to that of the *infusion* clearance of ^{51}Cr-EDTA measured simultaneously in ICU patients [145]. The latter method, which was used in Paper IV, does not require urine sampling but requires equilibrium between the rate of infusion and excretion of the filtration marker. It was shown that the within-method error was 33% and 11% for the *urinary* and *infusion* clearance of ^{51}Cr-EDTA, respectively [145]. This illustrates the inherent limitations of urinary clearance methods for the assessment of GFR, irrespective of the filtration marker used.

Urinary CrCl may grossly overestimate GFR due to creatinine secretion at the tubular level. The magnitude of this overestimation increases as GFR declines, and may be as great as 141% for patients with GFR of < 40 mL/min/1.73m^2 [182]. Robert *et al*.[180] compared urinary

CrCl to inulin clearance, and showed that urinary CrCl overpredicted GFR at GFR:s < 40 ml/min, but underpredicted GFR at GFR:s > 40 ml/min. In Paper IV, the mean GFR, assessed by ^{51}Cr-EDTA clearance, was approximately 45-50 ml/min, which could explain the low bias (2.6 ml/min) comparing urinary CrCl to ^{51}Cr-EDTA clearance.

Discrepancies between measured GFR and urinary CrCl in critically ill patients may result from factors that are difficult to control in the intensive care setting. Clearance methods require a steady state situation, a criteria not always met in critically ill patients. Variations in urine output values, due to changes in hormonal regulation of renal perfusion, changes in systemic hemodynamics, as well as alterations in creatinine production, secretion and metabolism, secondary to rapidly evolving underlying disease states, influence the accuracy of estimated CrCl in critically ill patients. Inaccurate 24-hour urine collection is also a major pitfall in the determination of CrCl. A majority of comparative studies conducted in ICU patients have used 24-hour CrCl as a reference method [121, 183-186]. To improve clinical utility and diminish procedural error, shorter timed urine collection for calculating urinary CrCl is now proposed. Instead of 24-hour urine collection period, 2 times 30 min urine collection periods, were used in Paper IV. Previous studies on critically ill patients have demonstrated that urinary CrCl, calculated from shorter urine collection periods, show good correlation with those values calculated from longer urine collection periods [180, 183, 187-189].

All the GFR estimating equations used in Paper IV, the CG, MDRD and CKD-EPI equations, performed poorly when compared to infusion clearance of ^{51}Cr-EDTA in this group of critically ill patients with early AKI. The biases ranged from 7.39 ml/min ($eGFR_{CG\ actual\ bw}$) to 11.58 ml/min ($eGFR_{MDRD}$). The between-group errors were unacceptably large, ranging from 66.8 – 68.7% and with wide limits of agreement for all the equations. The poor performance of the estimating equations in critically ill patients with early AKI may be explained in part by the methods and populations used to develop these equations. All equations were developed and validated in populations of non-ICU patients with chronic kidney dysfunction. The CG equation was originally designed to estimate 24-hour CrCl, and not GFR, in hospitalised patients with mild renal dysfunction [131]. The MDRD equation was developed using urinary ^{125}I-iothalamate clearance as a reference in 1628 patients with chronic-kidney disease [132], and finally the CKD-EPI equation was developed using data from 8254 people with and without chronic kidney failure, using iothalamate clearance as a reference [133].

Another explanation for the poor performance of the estimating equations is depressed production of creatinine, in turn caused by rapid muscle loss, in ICU patients. Hoste *et al*. [190], studied recently admitted critically ill patients with serum creatinine levels within the normal range and found that 25% of these patients had a urinary CrCl below 60 ml/min/1.73m^2. Urinary creatinine excretion was low in patients with low CrCl, suggesting a pronounced muscle loss and depressed production of creatinine. This can explain why the estimating equations, based on serum creatinine, overestimated GFR in Paper IV.

The estimating equations used in Paper IV, have not been validated in critically ill patients with early AKI. Two studies have compared the CG formula to "gold standard reference method" in critically ill patients. In the study by Robert *et al*. [180], the performance of the CG equation was compared to inulin clearance, in 20 critically ill patients *not* needing inotropic support. They found that there was a good correlation between inulin clearance and the CG equation, using the ideal body weight, and that CG equation can better predict GFR than urinary CrCl. However, the precision of the CG equation to predict GFR, i.e the error, was not estimated. In the second study, Erley *et al*. [130] compared the CG formula to inulin clearance, in 31 critically ill patients with *stable* renal function for at least 3 days before inclusion, and found that the results of the CG formula were not sufficiently accurate to predict GFR. The third estimating equation used in Paper IV, (CKD-EPI), has not been evaluated against true measures of GFR, in any population of critically ill patients.

An issue regarding the use of the CG equation, is which patient weight should be used (actual, preoperative or preoperative ideal body weight), as creatinine generation is a function of musle mass, not body mass. Recalculating the CG equation with the preoperative body weight (to correct for the weight increase due to edema) and preoperative ideal body weight (to correct for overweight), instead of using the actual body weight of the patient, did not improve the agreement between the CG equation and the $GFR_{^{51}Cr\text{-}EDTA}$ in Paper IV.

In conclusion, the commonly utilized urinary creatinine clearance method, for assessment of GFR in critically ill patients with early AKI, shows a poor precision. Therefore, it should not be used as a reference method when validating new methods for assessing kidney function in this particular patient population. Furthermore, the commonly used estimating equations (CG, MDRD and CKD-EPI equations) perform poorly, when estimating GFR, with high biases and unacceptably high errors.

Conclusions

- Short-term infusion of low- to moderate, non-hypertensive doses of vasopressin induces a post-glomerular renal vasoconstriction with a decrease in RBF and an increase in GFR in post-cardiac surgery patients. This is accompanied by an increase in RVO_2, as a consequence of the increases in filtered sodium and tubular sodium reabsorption. Vasopressin, thus, impairs the renal oxygen demand/supply relationship.

- Mannitol treatment of postoperative AKI induces a renal vasodilation and redistributes systemic blood flow to the kidneys. Mannitol does not affect filtration fraction or renal oxygenation, suggestive of balanced increases in perfusion/filtration and oxygen demand/supply.

- After cardiac surgery with CPB, levosimendan induces a vasodilation, preferentially of preglomerular resistance vessels, increasing both RBF and GFR without jeopardizing renal oxygenation. Due to its renal pharmacodynamic profile, levosimendan might be an interesting alternative for treatment of postoperative heart failure complicated by AKI in post-cardiac surgery patients.

- The commonly utilized urinary CrCl method for assessment of GFR has a poor precision in critically ill patients with early AKI and should not be used as a reference method when validating new methods for assessing kidney function in this patient population. The frequently used estimating equations perform poorly, when estimating GFR, with high biases and unacceptably high errors.

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Populärvetenskaplig sammanfattning

Hjärtkirurgi och njuren – effekterna av olika läkemedel som används vid behandling av kritiskt sjuka hjärtkirurgiska patienter, på njurens blodflöde, filtrationsförmåga och syresättning.

Njurarnas huvuduppgift är att rena blodet från slaggprodukter som uppkommer vid metabolismen i cellerna. Reningen av blodet sker genom att vätska med slaggprodukter (180L/dygn) filtreras ut i njurarnas urinkanaler för vidare transport till urinblåsan. För att åstadkomma detta, distribueras 15-20% av kroppens totala blodflöde till njurarna som bara väger några hekto. En annan uppgift som njurarna har är att under transporten genom urinkanalerna koncentrera urinen, för att undvika att för stora vätskeförluster uppstår. 99% av den filtrerade vätskevolymen återreabsorberas till blodet. Resterande 1%, ca 1-2L, lämnar kroppen som urin. Koncentrationen av urinen sker huvudsakligen i njurmärgen och är en mycket energikrävande process som kräver mycket syrgas (O_2).

Akut njursvikt definierar man som en relativ snabb nedsättning av njurens filtrerande förmåga. Akut njursvikt är vanlig efter hjärtkirurgi och är associerad med hög dödlighet. En av huvudorsakerna till akut njursvikt anses vara nedsatt blodflöde till njurarna och därmed nedsatt O_2 transport, som leder till O_2 brist i njuren, fr. a i njurmärgen som har högst O_2 behov och är därmed mycket känslig för lågt blodflöde och O_2 brist. En viktig terapeutisk strategi för att förhindra/behandla uppkomsten av akut njursvikt är därför att öka tillförseln av O_2, genom att öka blodflödet och/eller minska njur(märgens) O_2 behov, dvs. förbättra förhållandet mellan tillgång och efterfrågan på O_2 i njuren.

Kunskap om hur njurens blodflöde, funktion och syresättning påverkas av olika läkemedel som används vid behandling av svårt sjuka patienter med akut njursvikt behövs. Vår unika metod med njurvenskateter och retrograd thermodilutionsteknik gör det möjligt att mäta njurens perfusion, filtrationsförmåga, och syresättning hos människor.

Vasopressin används för att höja blodtrycket på intensivvårdspatienter i cirkulatorisk chock pga paralys av blodkärlen. Vasopressin drar ihop blodkärlen. Patienter i cirkulatorisk chock löper en stor risk att drabbas av njursvikt. Det är visat att vasopressin ökar urinproduktionen samt uppskattad filtrationsförmåga hos patienter i septisk chock och i cirkulatorisk chock efter hjärtkirurgi. Det är dock ingen som har studerat

effekten av vasopressin på njurens blodflöde, filtrationsförmåga och syresättning. Vi studerade 12 njurfriska patienter efter hjärtoperation och fann att vasopressin förbättrade njurens filtrationsförmåga, som ökade njurens O_2 behov. Samtidigt minskade vasopressin njurens blodflöde och därmed O_2 tillförseln. Förhållandet mellan tillgång och efterfrågan på O_2 i njuren försämrades, dvs. syresättningen i njuren blev sämre.

Levosimendan: Efter hjärtkirurgi drabbas många av hjärtsvikt som kan leda till nedsatt genomblödning av njuren och njursvikt. Hjärtsvikt kräver behandling med hjärtstimulerande läkemedel. Levosimendan är ett läkemedel som har hjärtstimulerande och kärlvidgande effekt. Studier har visat att levosimendan förbättrar uppskattad filtrationsförmåga hos patienter med hjärtsvikt och njursvikt och ökar urinproduktionen. Ingen har studerat vilka mekanismer ligger bakom dessa fynd. Vi studerade 30 patienter efter hjärtoperation och jämförde effekterna av placebo (n=15) och levosimendan (n=15) på njurens blodflöde, filtrationsförmåga och syresättning och fann att levosimendan jämfört med placebo ökade njurens blodflöde och filtrationsförmåga. Förhållandet mellan tillgång och efterfrågan på O_2 i njuren förändrades inte, dvs. syresättningen i njuren påverkades inte negativt av levosimendan.

Mannitol vid akut njursvikt: Mannitol används för att öka urinproduktionen vid akut njursvikt och i hjärt-lungmaskinen vid hjärtoperationer. I en studie på 10 njurfriska hjärtopererade patienter fann man att mannitol förbättrade njurens filtrationsförmåga. Vi studerade 11 patienter som efter komplicerad hjärtoperation hade utvecklat akut njursvikt och fann att behandling med mannitol vid akut njursvikt, förbättrade diuresen, ökade renala blodflödet och tenderade att öka njurens filtrationsförmåga. Mannitol påverkade inte förhållandet mellan tillgång och efterfrågan på O_2 i njuren, dvs syresättningen påverkades inte. Mekanismen bakom mannitols gynnsamma effekter på njurfunktionen kan vara dess avsvällande effekt på njurkärlens och urinkanalernas celler.

Bedömning av njurens filtrationsförmåga vid akut njursvikt: Det finns olika metoder för att bedöma njurens filtrationsförmåga. Clearance är ett mått på den blodvolymen som helt renas från en viss substans per tidsenhet. Bestämning av njurarnas clearance av en lämplig substans till exempel ^{51}Cr-EDTA kan användas för att mäta njurens filtrationsförmåga som kallas glomerulära filtrationshastigheten (GFR) (standard metod).

Man kan också mäta urin clearance av kreatinin och på så sätt uppskatta njurens filtrationsförmåga (estimerad GFR). Kreatinin är en

restprodukt som bildas när kroppen frigör energi ur kreatinfosfat som finns lagrat i musklerna och som kroppen gör sig av med genom njurarna. Om njurarnas förmåga att filtrera bort ämnen i blodet är försämrat stiger halten av kreatinin i blodet. Men halten av kreatinin i blodet är inte enbart beroende av njurfunktionen, utan också av patientens muskelmassa. Därför kan uppskattning av filtrations-förmågan som bygger på mätning av halten av kreatinin i blodet, så som mätning av kreatinin clearance och beräkning med olika formler i vissa situationer visa felaktiga värden.

Estimerad GFR (eGFR) används mycket i kliniken för att bedöma njurens filtrationsförmåga. Vi undersökte hur väl det korrelerar till GFR mätt med standard metod, hos svårt sjuka patienter med akut njursvikt. Vi studerade 30 kritiskt sjuka patienter med tidig akut njursvikt efter hjärtkirurgi. Vi mätte GFR med ^{51}Cr-EDTA, samtidigt som vi mätte eGFR med urin clearance av kreatinin metoden och kalkylerade eGFR med 3 vanligen använda formler. Vi fann att jämfört med GFR, mätt med standard metod, har eGFR mätt med kreatinin clearance metoden dålig precision för bedömning av GFR och att formler för bedömning av GFR fungerar dåligt, hos svårt sjuka patienter med akut njursvikt.

Sammanfattning: *Vasopressin* förbättrar njurens filtrationsförmåga, vilket ökar njurens O_2 behov, samtidigt som det minskar njurens blodflöde och därmed O_2 tillförseln. Syresättning i njuren blir sämre. Jämfört med placebo ökar *levosimendan* njurens blodflöde och filtrationsförmåga. Förhållandet mellan tillgång och efterfrågan på O_2 ändras inte, dvs. levosimendan påverkar inte syresättningen i njuren negativt. Behandling med *mannitol* vid akut njursvikt, förbättrar diuresen, ökar renala blodflödet och tenderar att öka njurens filtrationsförmåga. Mannitol påverkar inte förhållandet mellan tillgång och efterfrågan på O_2, dvs. mannitol påverkar inte syresättningen i njuren negativt. Mekanismen bakom mannitols gynnsamma effekter på njurfunktionen kan vara dess avsvällande effekt på njurkärlens eller urinkanalernas celler. eGFR mätt med kreatinin clearance metoden har dålig precision för bedömning av GFR jämfört med GFR mätt med standard metod och formler för bedömning av GFR fungerar dåligt, hos svårt sjuka patienter med akut njursvikt, jämfört med GFR mätt med standardmetod