Prevention and treatment of acute kidney injury after cardiac surgery

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2010

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ISBN 978-91-628-8081-1
http://hdl.handle.net/2077/21935

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Printed by Intellecta Infolog AB
Gothenburg, Sweden 2010

Prevention and treatment of acute kidney injury after cardiac surgery

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Abstract

Acute kidney injury (AKI) occurs frequently after cardiac surgery and is independently associated with increased mortality. The main cause of AKI in these patients is renal ischemia. However, data on the renal oxygenation, defined as the renal oxygen supply/demand relationship are lacking in clinical AKI, and the effects of various pharmacological interventions on renal oxygenation are not known.

Patients and methods: Detailed analyses on the effects of mannitol (n=10) and dopamine (n=12) on renal blood flow (RBF), glomerular filtration rate (GFR) and renal oxygenation were performed in post-cardiac surgery patients using the renal vein thermodilution technique. Furthermore, patients with AKI (n=12) were studied, with respect to their RBF, GFR and renal oxygenation, and compared to postoperative patients (n=37) with no renal impairment. Finally, the effects of norepinephrine-induced changes in mean arterial pressure (MAP) on renal variables were analysed in AKI patients (n=12) with vasodilatory chock.

Results: Mannitol increased GFR and the renal oxygen demand (RVO_2), while it had no effect on RBF. Mannitol, thus, pharmacologically improved the renal function at the cost of an impaired renal oxygenation. Dopamine, on the other hand, redistributed blood flow to the kidney and increased RBF, but had no effect on GFR or RVO_2. Consequently, dopamine improved renal oxygenation. AKI patients had a 40% lower RBF and a 60 % lower net-sodium reabsorption and GFR compared to control patients. However, contrary to previous hypothesis, this decrease in reabsorptive workload was not accompanied with a decrease in RVO_2. Thus, renal oxygenation was severely impaired in AKI. The high RVO_2 correlated directly to the sodium reabsorption, and 2.4 times more oxygen was consumed for a certain amount of reabsorbed sodium in AKI compared to control. Restoration of MAP from 60–75 mmHg with norepinephrine, improved renal oxygen delivery, GFR and renal oxygenation in AKI patients. Increasing MAP to 90 mmHg had no further beneficial effect.

Conclusions: While mannitol improves GFR at the cost of an impaired renal oxygenation, dopamine, in contrast, improves renal oxygenation, but has no effect on GFR. Furthermore, renal oxygenation is severely impaired in AKI, due to renal vasoconstriction and sodium reabsorption at a high oxygen cost. Finally, norepinephrine improves GFR and renal oxygenation when used for treatment of hypotension.

Key words: Kidney failure, acute; glomerular filtration rate; renal circulation; oxygen consumption; cardiac surgery; mannitol; dopamine; norepinephrine; autoregulation.

ISBN 978-91-628-8081-1 http://hdl.handle.net/2077/21935

List of original papers

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I Redfors B, Sward K, Sellgren J, Ricksten SE
Effects of mannitol alone and mannitol plus furosemide on renal oxygen consumption, blood flow and glomerular filtration after cardiac surgery.
Intensive Care Med 2009, 35(1):115-122.

II Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE
Dopamine increases renal oxygenation: a clinical study in post-cardiac surgery patients.
Acta Anaesthesiol Scand, 54(2):183-190.

III Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE
Acute renal failure is NOT an "acute renal success"- a clinical study on renal oxygen supply/demand in postoperative acute kidney injury
Submitted, Critical Care Med

IV Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE
Blood pressure restoration with norepinephrine improves renal function and oxygenation in post-cardiac surgery patients with vasodilatory shock and acute kidney injury
In manuscript

To Petra, Adrian, Alvin and Didrik

Contents

Abbreviations

Abbreviations used in the text

AKI	acute kidney injury
ANOVA	analysis of variance
CI	cardiac index, L/min/m^2
CVP	central venous pressure, mmHg
^{51}Cr-EDTA	chromium ethylene diamine tetraacetic acid
ERBF	effective renal blood flow, ml/min
FF	filtration fraction
GFR	glomerular filtration rate, ml/min
ICU	intensive care unit
K_{uf}	The ultrafiltration coefficient
MAP	mean arterial pressure, mmHg
NO	nitric oxide
OR	odds ratio
P_{Bow}	Hydrostatic pressure in the capsule of Bowman
P_{glom}	Hydrostatic pressure in the glomeruli
PAH	paraaminohippuric acid
PCWP	pulmonary capillary wedge pressure, mmHg
PVRI	pulmonary vascular resistance index, dynes·s/cm^5/m^2
π_{Bow}	Osmotic pressure in the capsule of Bowman
π_{glom}	Osmotic pressure in the glomeruli
RBF	renal blood flow, ml/min
RBF_{IC}	renal blood flow assessed by the infusion clearance technique, ml/min
RBF_{TD}	renal blood flow assessed by the thermodilution technique, ml/min
RPF	renal plasma flow, ml/min
RVO_2	renal oxygen consumption, ml/min
RVR	renal vascular resistance, mmHg/ml/min
SEM	standard error of mean
SPSS	statistical packages for the social sciences
SVI	stroke work index, ml/beat/m^2
SVRI	systemic vascular resistance index, dynes·s/cm^5/m^2

Introduction

Acute kidney injury – is it a problem?

Acute kidney injury (AKI) is defined as an abrupt reduction in kidney function, i.e. an increase in serum creatinine ≥ 26.4 μmol/l or ≥ 50%, or a reduction in urine output to less than 0.5 ml/kg/h for more than six hours (Table 1) (1). It is a complex disorder that occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure (1). Besides, it is often under-recognised and associated with severe consequences (2).

The incidence of AKI after cardiac surgery is 7 to 30% depending on type of surgery (3, 4), while the incidence of dialysis dependent AKI after cardiac surgery is one to three percent, with a mortality rate of 60-70% (5, 6). However, patients with postoperative AKI are often suffering from multiple-organ dysfunction and it has been difficult to determine the exact contribution of AKI itself to mortality. Chertow et al investigated this

Table 1. Classification/staging system for acute kidney injury[a]

Stage	Serum creatinine criteria	Urine output criteria
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% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 h
3[c]	Increase in serum creatinine to > 300% (> 3-fold) from baseline (or serum creatinine ≥ 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of > 0.5 mg/dl [44 μmol/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.

Mehta et al.,Critical Care 2007, **11**:R31 (1)

and found, in a multivariate analyse of 43 000 cardiac surgery patients, that patients with dialysis dependent AKI had an unadjusted odds ratio (OR) for death of 39 compared to patients without AKI. When the material was adjusted for eleven preoperative and seven postoperative factors, the OR for death was still 7.9 times higher in the AKI group (5).

Emerging evidence, yet, suggests that even minor changes in serum creatinine are associated with increased in-patient mortality (1). For example, Lassnigg et al found that cardiac surgery patients, whose postoperative creatinine level was 0 – 44 μmol/l higher than their preoperative value, had three times higher mortality than patients with a small decrease in serum creatinine after cardiac surgery (7). Furthermore, a larger increase in serum creatinine was associated with an > 18-fold increase in 30 day mortality. These relations were maintained also after including 20 pre- and per- operative risk indicators in a multivariate analysis (OR 1.9 and OR 5.8 respectively).

Renal anatomy and physiology

Renal blood flow

The renal blood flow (RBF) is 15 to 20 percent of cardiac output, the highest in the body in relation to organ weight. One fifth of this is filtrated in the 2 million glomeruli, producing a primary urine of approximately 180 litres per day. Ninety-nine percent of this filtrate is then actively reabsorbed, producing a daily urine of 1.5 to 2 litres. In order to possess this huge concentration ability, the blood flow in the kidney has to be unevenly distributed. Thus, cortex receives 80 % of the blood flow, while outer and inner medulla gets 20% and 1-2% of the RBF, respectively (19).

In the cortex, the renal artery divides into afferent arterioles, which turns into post glomerular efferent arterioles after the glomeruli and then divides into peritubular capillaries. The efferent arterioles of the juxtamedullary nephrons form the vasa recta reaching deep down in the renal medulla (8). The low blood flow of the medulla is necessary for maintaining the osmotic gradient intact, which makes an efficient reabsorption possible.

Glomerular filtration

The glomeruli are situated in the cortex and the glomerular ultrafiltration is a passive process that depends on the balance of Starling forces, regulating fluid flux from the glomerulus into Bowman's capsule. The glomerular filtration rate (GFR) depends on the permeability of the filtration barrier (indicated by the ultrafiltration coefficient (K_{uf})) and the filtration pressure (8). This filtration pressure is in turn dependent on the hydrostatic pressure in the glomerular capillary (P_{glom}), promoting filtration; the hydrostatic pressure in Bowman´s capsule (P_{Bow}), opposing filtration; and the mean colloid osmotic pressure in the glomerular capillary (π_{glom}), opposing filtration. The osmotic pressure in Bowman's capsule (π_{Bow}) is nearly absent in the normal kidney. Hence, the formula determining GFR is:

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

In renal transplant donors, P_{glom} – P_{Bow}

has been estimated to 50 mmHg, while π_{glom} has been calculated to 24 mmHg and K_{uf} to 3.2 ml/mmHg/min, giving a GFR of 83 ml/min (9).

Drugs or interventions can decrease the glomerular hydrostatic pressure and, thus, GFR by constricting the afferent arterioles. Substantial constriction of the efferent arterioles, on the other hand, increases the glomerular hydrostatic pressure, but not necessarily GFR.

Flow dependency of GFR: A decrease in RBF causes the plasma to remain for a longer time in the glomerulus. This will increase the proportion of plasma that is filtered, thus increasing mean colloid glomerular pressure (π_{glom}) and cause a decrease in GFR. A constriction of the efferent arteriole can, in that way, cause a paradoxical decrease in GFR despite an increase in glomerular hydrostatic pressure (P_{glom}). Conversely, an intervention that increases RBF will decrease mean colloid glomerular pressure and improve GFR, even if the glomerular hydrostatic pressure is unchanged.

Renal autoregulation: The protective mechanism of autoregulation normally

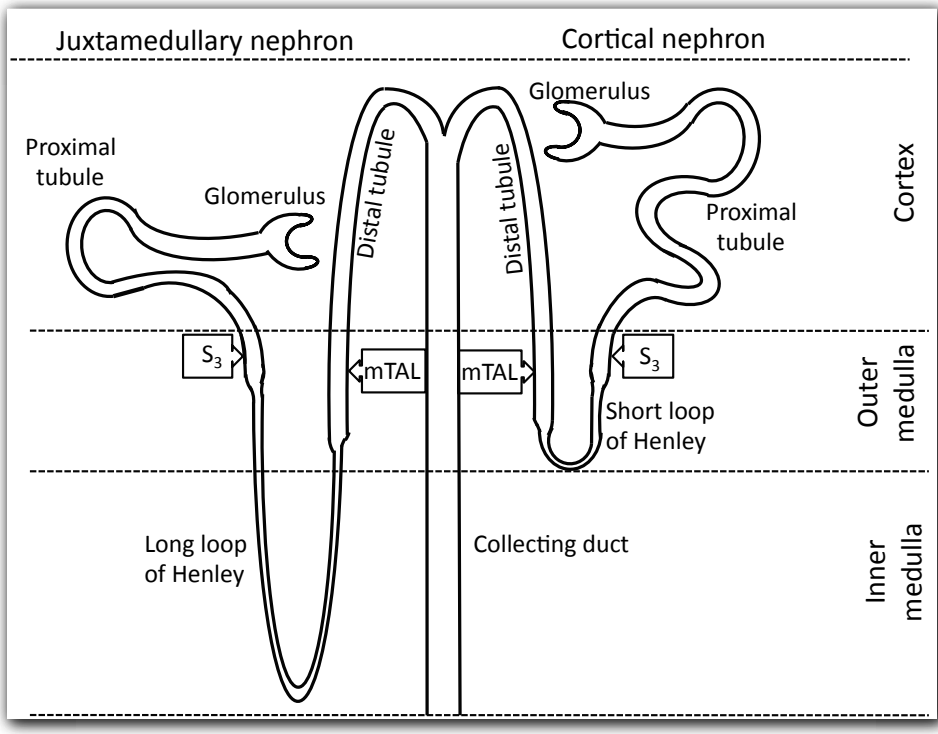

Figure 1. Schematic drawing of the tubules. Only the juxtamedullary nephrons have long loops of Henley. The medullary thick ascending limb (mTAL) and the S_3 part (or the straight part) of the proximal tubuli are booth situated in the outer medulla and are susceptible of ischemia.

maintains GFR and RBF constant over a wide range of pressures. It consists of a faster myogenic vasoconstrictive response of the afferent arterioles and a slower, superimposed, tubuloglomerular feedback mechanism, which acts in concert (10, 11). It has been shown that RBF is autoregulated between 65 mmHg and 180 mmHg in conscious dogs, whereas the lower threshold has been found to increase to 90 mmHg, both after sympathetic stimulation and after α_1-adrenoreceptor stimulation (12-14). The lower autoregulatory threshold for GFR was in the same studies found to be 10 – 15 mmHg higher, than the threshold for RBF, both with and without sympathetic stimulation. However, the autoregulatory limits for humans are not known.

Below the lower autoregulatory threshold, both RBF and GFR are pressure-dependent, i.e. as blood pressure decreases, blood flow decreases in an almost linear fashion (15) and GFR ceases at a higher pressure than RBF (12, 13).

Tubules and reabsorption

The anatomy of the nephrons is shown in Figure 1. While the cortical nephrons have short thin segments of Henley that only penetrate into the outer medulla, the juxtamedullary nephrons are located deeper in the cortex and have long loops of Henley that penetrate deep into the medulla (8). Between one third and one fifth of the nephrons are juxtamedullary. About 99% of the filtered load is reabsorbed from the tubules back to the circulation, during the passage through the nephron, and this is an active, energy consuming process (19). In fact, nearly all transport in the kidney (reabsorption and secretion) is coupled to active sodium reabsorption, by co-transport or by counter-transport. Sodium enters the tubuli cell passively though the apical membrane, due to a concentration gradient. It is then actively pumped by Na^+/K^+-ATPase out of the basolateral membrane to the interstitium from where it is absorbed into the peritubular capillaries (Figure 2) (16). Of interest is that the proximal tubules reabsorb approximately two thirds of the filtered sodium, while the thick ascending

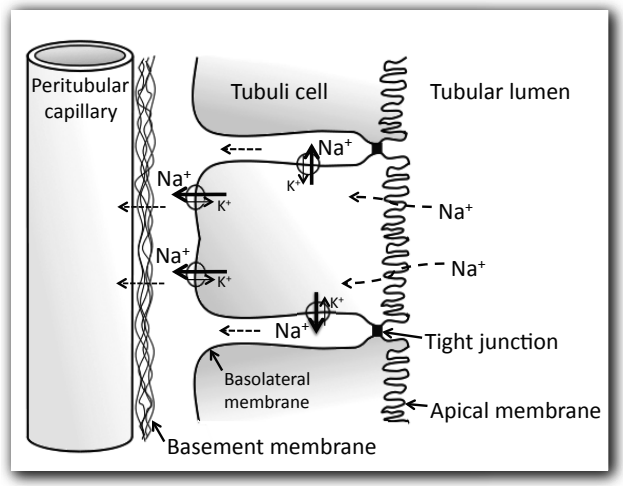

Figure 2. Sodium passively diffuses through the apical membrane in to the tubuli cells. It is then actively pumped by Na^+/K^+-ATPase through the basolateral membrane to the interstitium. From there it diffuses to the peritubular capillaries, drawn by the intra-vascular colloid osmotic pressure. The tight junctions hinder sodium leakage back to the tubuli, although some leakage occurs.

limb reabsorb 20 %.

A modified portion of the early distal nephron is attached to the glomeruli, between the afferent and efferent arterioles and contains macula densa cells. Chemoreceptors, of these macula densa cells, sense the concentration of sodium in the nephron. When the concentration of sodium in the tubuli increases, e.g. when tubular sodium reabsorption is impaired, afferent arteriolar constriction is triggered causing a decrease in GFR and RBF. On the contrary, in a situation of a decrease in distal tubular sodium concentration, this tubuloglomerular feedback acts to increase GFR. Thus, the tubuloglomerular feedback regulates the renal filtration and circulation (10).

Renal oxygen supply/demand

Renal oxygen consumption is high in the renal cortex, due to the sodium reabsorption of the proximal tubules. However, renal cortex is generally well oxygenated with a high tissue pO_2 (6–8 kPa) due to the ample blood supply (17). The medulla, on the other hand, has a very limited blood flow and is, during normal conditions, on the border of hypoxia. While the inner medulla balances this with a minimal level of metabolic activity, the outer medulla has a high metabolic activity due to the sodium reabsorption of the S_3 segment of the proximal tubule and the medullary thick ascending limb (18, 19). Consequently, the tissue oxygen tension of the outer medulla is only 1.5–2.5 kPa during normal conditions, and the combination of low blood flow and high metabolic demand make it susceptible to ischemia (17).

However, not only hypoxia can injure the kidney. Hyperoxia has been shown to increase free oxygen radical production and this could cause kidney injury (20, 21). Renal arterio-venous shunting of oxygen, as a structural antioxidant mechanism, has been suggested as a defence mechanism against this hyperoxia. Arterio-venous shunting has, on the other hand, also been proposed to limit oxygen delivery to the medulla. Under conditions of reduced medullary perfusion or enhanced tubular oxygen consumption, oxygen shunting may exacerbate tubular hypoxia within the outer medullary region, especially in anemia (22, 23).

The rate of oxygen utilization by the kidney consists of an oxygen cost of active sodium reabsorption plus a smaller part of basal oxygen consumption. The oxygen utilization for reabsorbing sodium has been calculated to 0.8–1.0 ml O_2/mmol Na^+-reabsorbed, in dogs (24, 25). Thus, the kidney has been shown to reabsorb 20 – 25 molecules of sodium for each molecule of O_2 consumed, in animal experiments. The basal metabolism, on the other hand, has been calculated to 10 – 15 µl O_2/g kidney, in dogs (25). However, neither basal oxygen consumption nor oxygen consumption caused by sodium reabsorption has been studied in humans.

Renal sodium reabsorption is, thus, the main determinant of renal oxygen consumption (24, 26) and as 99 % of the filtered sodium is reabsorbed, GFR to a large extent determines the renal oxygen consumption (RVO_2) (26). Thus, all changes that increase GFR increase RVO_2 and vice versa. Consequently, if an interven-

tion increases GFR, the renal oxygen supply, i.e. RBF, must increase in proportion to maintain the oxygen supply/demand relationship.

The renal oxygen supply/demand relationship (the renal oxygenation) can be directly measured by the renal arteriovenous oxygen extraction. When the renal oxygen supply/demand is impaired, the renal oxygen extraction increases and vice versa.

Pathophysiology of AKI

Acute renal failure has classically been divided into three different types, depending on etiology: ischemic, nephrotoxic and mixed forms. However, the pathophysiology of AKI involves multiple pathways (6) and is to a large extent unknown (27). While ischemia is considered the most common cause of AKI (28), the pathophysiology of ischemic AKI is thought to involve a complex interplay between renal hemodynamics, tubular injury and inflammatory processes (29, 30). In addition, increasing evidence supports the view that regional renal hypoxia occurs in AKI irrespective of the underlying condition, even under circumstances basically believed to reflect "direct" tubulotoxity, e.g. sepsis or radiocontrast agents (31). AKI is, thus, multifactorial and the different mechanisms of injury are likely to be active at different times with different intensity and probably act synergistically (32). To describe this "time-factor", AKI has classically been divided in different phases.

The *"initiation phase"* of ischemic ARF begins with a vasomotor nephropathy in which there are associated alterations in vasoreactivity and renal perfusion. Under these pathological conditions, the delicate balance of oxygen supply, compared with demand, is easily disturbed owing to the unique arrangement of the renal microvasculature and its diffusive shunting pathways (28). RBF, thus, locally decreases to a level resulting in severe cellular ATP depletion, which in turn leads to acute cell injury and dysfunction (6, 29). This phase is followed by the *"extension phase",* where there is continued hypoxia and inflammation, both more pronounced in the outer medulla of the kidney (30). In this phase, regional blood is persistently decreased, affecting tissue oxygenation. This perceiving low blood flow has been attributed to endothelial dysfunction, probably involving nitric oxide) NO as a central mediator (28). Thereafter, the *"maintenance phase"* and the *"repair phase"* ensues, where cells undergo repair, migration, apoptosis and proliferation in an attempt to re-establish tubular integrity (29).

However, almost all our knowledge is based upon animal studies, because online recording of renal oxygenation and clear-cut dynamic detection of evolving pathology is lacking for the human kidney during AKI (31). Furthermore, the appropriateness of some of the animal models used for the simulation of the human disease is questionable, considering species-related morphological and functional differences (31). For example, the most used animal model, *the warm ischemia-reflow model* – with total renal artery obstruction for 20 to 75 minutes – causes extensive necrosis destroying the

proximal tubules of the outer stripe of the outer medulla. On the other hand, *the cold ischemia model* – with 12 to 16 hours of cold ischemia – causes extensive necrotic areas in the loops of Henley and collecting ducts. Finally, the *energy/oxygen depletion model* causes extensive medullary thick ascending limb damage (33). Thus, three of the most frequently used methods in recent years give totally different morphological findings and the relevance for human AKI can be questioned (33).

While animal models of AKI give extensive tubular necrosis, a distinct difference is that only very limited necrosis is present in biopsies of humans with AKI, in spite of severe organ failure (33, 34). Another difference is that tubular casts, which are one of the most important findings in animal models, are almost absent in the rare human biopsy data that exist (34). Olsen et al studied biopsies from twelve patients with ischemic AKI and compared those with biopsies from patients without renal disease, using electron microscopy. They found that both the straight part of the proximal tubule (S_3) and the thick ascending limb had significant reduction of the brush border, basolateral infoldings of the cell surface and a higher number of missing tubular cells (indicating sites of cellular desquamation). The convoluted tubules of the cortex were, on the other hand, less affected (35). Thus, AKI in humans affects primarily the outer medullary region with limited necrosis.

The knowledge of the renal physiology in clinical AKI is very scarce. By definition, GFR decreases. However, data on RBF during AKI in the critically ill is limited and it has been advocated that measurements in contemporary patients are required to further our understanding of this condition (36).

In addition, there is no knowledge on how renal oxygenation is affected in human AKI. One hypothesis that has frequently been put forward is that the reduction in GFR in AKI should lead to a reduction in reabsorptive workload and consequently to a reduction in RVO_2. This will in turn preserve renal oxygenation with a reduced risk of further aggravation of ischemia. Hence, the kidney protects itself during AKI, and it has accordingly, and rather provocatively, been stated that "acute renal failure is an acute renal success" (28, 31, 37-40).

Risk factors for AKI in cardiac surgery

Well validated risk factors associated with the development of AKI in post-cardiac surgery patients include: female gender, reduced left ventricular function or the presence of congestive heart failure, diabetes mellitus, peripheral vascular disease, use of an intra aortic balloon pump, chronic obstructive pulmonary disease, the need for emergent surgery and an elevated preoperative serum creatinine (6). Other more controversial risk factors are those specifically related to the bypass procedure, e.g. cross clamp time, duration of cardio pulmonary bypass and on-pump versus off pump coronary artery bypass surgery (6). While a substantial increase in preoperative creatinine can increase the risk for dialysis with up to 25% (6, 41), the other risk fac-

tors account for less than 10% of the variation in postoperative creatinine levels compared to baseline (41).

Prophylaxis/treatment of AKI after cardiac surgery and in general

Pharmacological interventions have been attempted following cardiac surgery, with inconsistent results, and at this time there are no drugs that have conclusively demonstrated a renal protection (6). This can be explained both by the fact that the patient populations studied have been at low risk for AKI, and that most clinical trials have enrolled a small number of patients, which in both cases make the studies inadequately powered to detect minor benefits (42). However, it could also be due to the complex pathogenesis of AKI, where hemodynamic, inflammatory and other mechanisms interact.

Nevertheless, renal parenchymal hypoxia plays a pivotal role under a variety of clinical conditions leading to AKI, and the knowledge of how the most commonly used renal drugs affect renal oxygen supply and demand in humans are to a large extent lacking (31). This knowledge, however, is of fundamental importance if future strategies shall be successful in the prevention/treatment of AKI.

Mannitol

Mannitol is a diuretic agent, commonly used in patients with acute renal dysfunction as well as in the pump prime of the heart lung machine, in the belief that it exerts renoprotective properties. It is a six-carbon non-metabolizable polyalcohol with a molecular weight of 182 (Figure 3). Mannitol is freely filterable and has a very limited reabsorption, thus creating an osmotic force in the tubular fluid sufficient to retard the reabsorption of fluids and solutes (notably NaCl) along

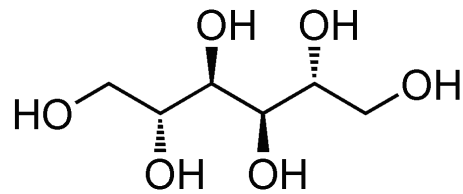

Figure 3. The molecular structure of mannitol.

the nephron (43).

It has been shown, in renal transplant patients, that mannitol given to a hydrated recipient just before renal artery cross-clamp removal, reduces the incidence of AKI after cadaveric kidney transplantation (44). Furthermore, mannitol increased GFR in patients after severe trauma (45). However, no clear cut benefit of mannitol has been found in the prevention of AKI (43, 46), and it has been suggested that high doses of mannitol may even cause acute renal failure (47). In addition, it has been shown that mannitol decreases the outer medullary oxygen tension in rats (48).

It is, thus, unclear if mannitol really has the potential to exert a protective renal effect, and data on the effects of mannitol on RBF, GFR, renal sodium handling and renal oxygenation in humans is very scarce.

Dopamine

Dopamine is a member of the cate-

cholamine family and a precursor to norepinephrine (Figure 4). In the belief that it increases RBF and thereby potentially decreases the risk for renal ischemia it has been used to prevent or treat AKI. However, the role of dopamine for prevention and treatment of AKI has been questioned (49-51), and one prospective randomised controlled trial comparing low-dose dopamine to placebo found no difference in renal outcome in patients with systemic inflammatory syndrome (SIRS) (52).

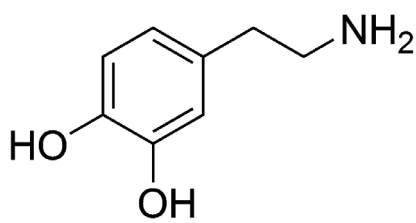

Figure 4. The molecular structure of dopamine.

A commonly held opinion, for this lack of effect, is that it could be due to a dopamine-induced increase in RVO_2, secondary to increases in GFR and sodium reabsorption (49, 52). Such an increase in RVO_2 might cause an oxygen debt of renal medullary nephrons, which are on the border of hypoxemia already under normal physiological conditions. It has also been speculated that dopamine-induced inhibition of proximal tubular sodium reabsorption might increase delivery of sodium to potentially ischemic distal tubular cells in the medulla, which would increase their oxygen demands (49).

Thus, a dopamine-induced increase in RVO_2 may have the potential to impair renal oxygenation, which could be detrimental in susceptible individuals. However, no study has assessed whether dopamine really increases sodium reabsorption and RVO_2 in postoperative patients.

Vasodilatory shock

Vasodilatory shock can be the final common pathway for severe shock of any cause and is due to failure of the vascular smooth muscle to constrict (53). This is, in turn, caused by extreme generation of endogenous vasodilators, such as NO and prostaglandins, and activation of the ATP-sensitive potassium channels in vascular smooth muscle cells (53). It is relatively common after cardiac surgery, especially after complicated surgery with a long cross-clamp time (54) and occurs often in conjunction with acute cardiac insufficiency that requires inotropic treatment (55).

Renal effects of norepinephrine in vasodiltatory chock

To counteract the vasodilatation and to restore blood pressure, in vasodilatory shock, potent vasopressors are given. Among these vasopressors, norepinephrine (Figure 5) is the recommended agent and most commonly used for treatment of hypotension in volume-resuscitated hyperdynamic shock (56).

The use of vasopressors in patients with AKI is controversial, as the vasoconstriction caused by these agents may potentially lead to a decrease in RBF and renal oxygen delivery, which could ag-

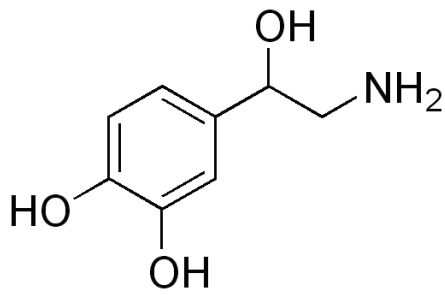

Figure 5. The molecular structure of norepinephrine.

gravate renal ischemia and thereby deteriorate renal function further. Indeed, intrarenal infusion of norepinephrine is an animal model of AKI (57) and norepinephrine has been shown to decrease RBF in healthy volunteers (58, 59). On the other hand, a too low dose of norepinephrine in patients with vasodilatory shock may result in an arterial blood pressure that is below the limit of the renal autoregulatory capacity, where RBF decreases almost linearly with blood pressure. Indeed, it has been shown that norepinephrine not only increases blood pressure, but also RBF in endotoxemic hypotensive dogs (60, 61).

The effect of norepinephrine on GFR is dependent on the balance between afferent and efferent arteriolar vasoconstriction and the resultant glomerular hydraulic pressure. An increase in creatinine clearance after norepinephrine treatment has been observed in three uncontrolled studies of patients with sepsis (62-64), while one controlled study found no significant increase in creatinine clearance, despite a numerical increase of 34% (65). However, if norepinephrine really improves GFR, this could lead to an increase in RVO_2, which could impair the renal oxygen supply/demand relationship, as GFR is the main determinant of RVO_2 (66-68).

Nevertheless, the effects of norepinephrine and renal perfusion pressure on renal circulation, filtration and oxygenation have previously not been studied in patients with AKI and vasodilatory shock.

Aims

- to analyse the effects of *mannitol* and *mannitol plus furosemide* on renal circulation, function and oxygenation in cardiac surgery patients.

- to study the effects of *dopamine* on renal circulation, function and oxygenation in cardiac surgery patients.

- to evaluate the disturbances in renal circulation, function and oxygenation in patients with *acute kidney injury*, after complicated cardiac surgery, by comparing them to postoperative patients with no renal impairment.

- to explore the effects of *norepinephrine-induced changes in arterial blood pressure*, on renal circulation, function and oxygenation, in cardiac surgery patients with vasodilatory shock and acute kidney injury.

Patients and methods

Patients

The Human Ethics Committee of the University of Gothenburg approved the study protocols and the patients were included after written informed consent was obtained. However, due to critical illness and mechanical ventilation with sedation, informed consent was not possible from the patients with AKI in Paper III and IV; therefore, next to kin was informed, in accordance to the decision of the Ethics Committee.

Uncomplicated postoperative patients

Forty one patients with a normal preoperative serum creatinine <115 μmol/L and a left ventricular ejection fraction ≥45% were included in Paper I (10 patients), Paper II (14 patients) and in the control group of Paper III (all 41 patients) (Table 2). They were studied in the intensive care unit after elective uncomplicated cardiac surgery, sedated and mechanically ventilated.

Exclusion criteria were: need for inotropic or vasoactive support, or significant postoperative bleeding. Hence, three of the patients were excluded because of postoperative bleeding and one was excluded because of unsuccessful placement of the renal vein catheter (Paper II and III).

Table 2. Patient characteristics.

	Post op (n=37)	AKI (n=12)
Preoperative characteristics		
Gender, n (% men)	34 (92)	9 (75)
Age (year)	64.7 ± 1.8	68.8 ± 1.3
BSA (m^2)	2.0 ± 0.03	2.1 ± 0.07
Preop LVEF (%)	58.7 ± 1.2	43.1 ± 6.3
Diabetes, type 1/ type 2	0 / 6	0 / 2
Hypertension, n (%)	19 (51)	9 (75)
Preop s-creatinine (μmol/L)	83.2 ± 1.8	90.5 ± 3.9
Preop treatement:		
ACE inhibitor, n (%)	18 (49)	8 (67)
ß-blocker, n (%)	28 (76)	10 (83)
Ca^{2+}- antag, n (%)	6 (16)	1 (8)
Euroscore	2.8 ± 0.3	7.6 ± 0.9
Perioperative characteristics		
Type of surgery:		
CABG, n (%)	32 (86)	5 (42)
Valve, n (%)	4 (11)	2 (17)
Combined, n (%)	1 (3)	5 (42)
Other, n (%)	0	0
Non-elective, n (%)	0	3 (25)
CPB time (min)	75.3 ± 5.5	183 ± 24
Aortic cross-clamp time (min)	45.3 ± 3.1	104 ± 17
ICU Higgins	1.4 ± 0.2	12.3 ± 1.3

Preop, preoperative; LVEF, left ventricular ejection fraction; s-creatinine, serum creatinine; ACE, angiotensin converting enzyme; CABG, coronary artery bypass surgery; Non-elective, surgery performed within 24 hours after referral; CPB, cardiopulmonary by pass; ICU, intensive care unit.

Data are presented as mean ± SEM.

AKI patients

Fourteen patients with a normal preoperative serum creatinine (<115 µmol/L), who after complicated coronary artery and/or valve surgery developed AKI, were included in the AKI group of Paper III and in Paper IV (Table 2 and 3). Their inclusion criteria were: a) postoperative AKI, stage 1 or 2 according to the Acute Kidney Injury Network-classification, that is a 50-200% postoperative increase in serum creatinine from baseline (1), b) circulatory shock requiring significant vasoactive or inotropic support with or without intra-aortic balloon pump, and c) cardiac index ≥ 2.1 l/min/m^2. Patients were not included after heart transplantations, thoraco-abdominal aortic surgery or surgery for aortic dissection. Two patients were excluded, one due to ventricular fibrillation during the equilibration period, which was successfully converted, and one due to unsuccessful placement of the renal vein catheter.

Anaesthesia/ICU management

Uncomplicated postoperative patients

A standardised anaesthetic procedure, following clinical praxis, was used in all 37 "uncomplicated postoperative patients". The patients were premedicated with intramuscular morphine (5-10 mg), scopolamine (0.2-0.4 mg) and oral fluni-

Table 3. Patient characteristics at inclusion for patients in Paper IV and the AKI group in Paper III.

Pat nr	Study entry	Serum creatinine (µmol/L)			SOFA score	IABP	Norepi-nephrine	Milrinone	Furo-semide
		Pre-op	Inclusion	% increase					
	Day	*µmol/L*	*µmol/L*	*µmol/L*			*µg/kg/min*	*µg/kg/min*	*µg/kg/min*
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	112	200	79	9	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	2	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	2	82	135	65	10	No	0.33	0.26	3.21
Mean	*3.9*	*90.5*	*178.6*	*99.1*	*9.1*	*25%*	*0.23*	*0.31*$^+$	*1.95*$^+$
SEM	*0.5*	*3.9*	*10.1*	*11.3*	*0.4*		*0.03*	*0.05*$^+$	*0.35*$^+$

Pre-op, preoperative; IABP, intra aortic balloon pump; SOFA, sequential organ failure assessment; +, mean and SEM among patients treated with the drug.

trazepam (1mg). 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. During cardiopulmonary bypass, anaesthesia was maintained by propofol infusion and no mannitol was given in the heart lung machine. 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 (0.5-1.0 mg/h) with no addition of non-steroid anti-inflammatory drugs. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (Venofundin, Braun, Germany) and crystalloid fluids.

AKI patients

In the intensive care unit, the patients were sedated with propofol and mechanically ventilated to normocapnia. All patients received in addition a continuous infusion of morphine or fentanyl, with no addition of non-steroid anti-inflammatory drugs. The hemodynamic and renal management of the complicated patients with AKI were at the discretion of the attending intensive care physicians. The clinical treatment protocol includes inotropic support with milrinone and/or norepinephrine to maintain cardiac index ≥ 2.1 l/min/m^2, whole-body oxygen extraction < 40 % and a mean arterial pressure at 70-75 mm Hg with or without an intra-aortic balloon pump. To promote diuresis, a continuous infusion of furosemide (5-40 mg/hr) is used.

Measurements of systemic hemodynamics

In all patients a pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA) was inserted through the left subclavian vein and guided into the pulmonary artery. The mean arterial blood pressure (MAP), heart rate, pulmonary arterial pressure and central venous pressure (CVP) were continuously measured. Measurements of thermodilution cardiac output were performed in triplicate, and indexed to body surface area to get the cardiac index (CI). The pulmonary artery wedge pressure (PCWP) was measured intermittently. Systemic vascular resistance index (SVRI) was calculated as (MAP – CVP)/ CI x 80, while pulmonary vascular resistance index (PVRI) was calculated as mean pulmonary artery pressure (MPAP – PCWP)/ CI x 80 (Paper IV), and the left ventricular stroke volume index (SVI) was calculated as CI / HR.

Measurements of renal variables

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

Renal vein catheter placement

In all patients, a ball-ended 8-fr two-thermistor retrograde venous thermodilution catheter (Webster Laboratories, Baldwin Park, CA), originally designed for coronary sinus catheterisation, was used. It was introduced into the left renal vein, via the right femoral vein under fluoroscopic guidance and placed in the central portion of the renal vein (Figure

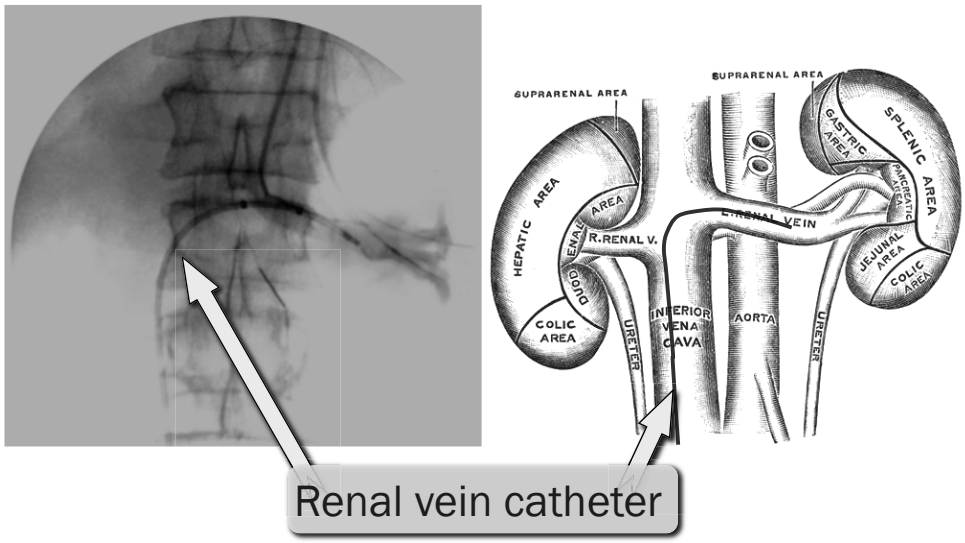

Figure 6. The renal vein catheter is guided via v cava inferior and positioned in the central portion of the renal vein. The position is verified with venography.

6). The position was verified by venography with ultralow doses of iohexol (Omnipaque® 300 mg I/ml, GE Healthcare, Stockholm, Sweden) (69) (uncomplicated postoperative patients: 30-60 mg Iodine/kg, AKI patients: 5-15 mg Iodine/kg).

Renal blood flow by continuous thermodilution

For measurements of RBF, an isotonic crystalloid solution, maintained at room temperature, was infused for 15-30 seconds at a constant rate of 53.7 ml/min. A two-channel Wheatstone bridge was connected to the catheter, measuring changes in resistance due to temperature variations of the indicator and external thermistors. The external thermistor is located 2.5 cm proximal to the catheter tip.

The analogue signals from the Wheatstone bridge, as well as arterial and venous pressure, were stored in a computer, using data acquisition software (AcqKnowledge Biopac, CA). The proportion of cooling between the indicator-thermistor and the external-thermistor was then used to calculate the left renal vein blood flow, as shown by Figure 7. Total renal vein blood flow was assumed to be twice the left renal vein blood flow, and urine flow was added to get the thermodilution measurement of total arterial renal blood flow (RBF_{TD}), see Formula 1. Mean of three measurements

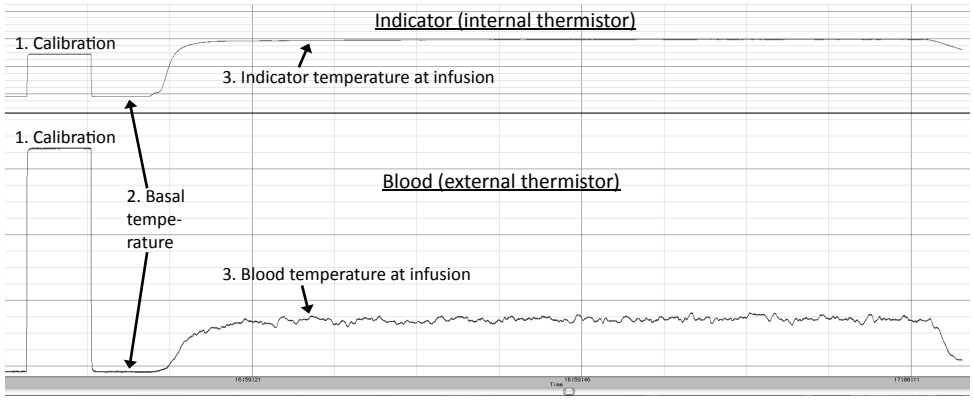

Figure 7. A recording of a continuous renal vein thermodilution blood flow measurement in AcqKnowledge. The upper graph reflects the temperature of the indicator (internal thermistor), while the lower reflects the temperature of the renal blood (external thermistor). A decrease in temperature induces an elevation of the graph. Three different measurements of booth graphs 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.

was used for estimation of RBF.

The correct position of the catheter was defined as one that yielded a variation in renal vein blood flow of no more than 10% in three consecutive measurements.

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

Formula 1. The formula 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 blood flow by infusion clearance of paraaminohippuric acid (PAH) in Papers II and III.

In Paper II and III we also measured RBF by infusion clearance of PAH (RBF_{IC}), corrected for the PAH-extraction by the renal vein catheter. Effective RBF (ERBF), approximating the PAH-extraction to 90% was also calculated. An intravenous priming dose of PAH, (8 mg/kg bodyweight) (Merck & Co., Inc., Whitehouse Station, NJ 08889, USA) was given, after blood and urine blanks were taken, followed by an infusion at a constant rate individualised to body weight and serum creatinine. The equilibration time before the start of the study was 60–90 minutes, and plasma from arterial and renal vein blood were analysed by a spectrophotometer (Beckman DU 530, Life Science UV/Vis, Fullerton, CA). Calculations of the renal plasma flows were as follows:

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

$$ERPF = \frac{1.73}{BSA} \times \frac{0.85 \times PAH_{amount/\min}}{[PAH_a] \times 0.9}$$

BSA is the body surface area and the subscript *a* and *rv* denotes arterial and renal vein, while $PAH_{amount/min}$ denotes the quantity of PAH infused per minute. The values were divided by (1–hematocrit) to get the renal blood flows.

Renal filtration fraction

The renal filtration fraction was defined as the renal extraction of chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA). An intravenous priming dose of ^{51}Cr-EDTA (GE Healthcare Limited, The Grove Center, Amhersham, England), (0,6 MegaBq/m^2 body surface area) was given, after blood and urine blanks were taken, followed by an infusion at a constant rate individualised to body weight and serum creatinine. Serum activity of ^{51}Cr-EDTA from arterial and renal vein blood were measured by a well counter (Wizard 3", 1480, Automatic Gamma Counter, Perkin Elma LAS, Turkuu, Finland). The formula of the filtration fraction was corrected taking the urine flow in account, in order to eliminate errors due to variations in RBF and urine flow (Formula 2) (70).

Urine flow

All patients had a Foley catheter for measurements of urine flow and measurements of the urine concentration of sodium.

Analysis of oxygen, sodium and hemoglobin

Arterial blood was analysed for the content of oxygen, hemoglobin and sodium, using an automated blood gas analyser, Radiometer ABL 700-series, Copenhagen. Furthermore, mixed venous blood and renal vein blood were analysed for oxygen content.

Additional calculations of renal data

For calculations, see Formula 2.

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

$$RDO_2 = RBF \times C_aO_2$$

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

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

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

$$GFR = RPF \times FF$$

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

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

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

$$PAH_{extr} = \frac{\left[PAH_a\right] - \left[PAH_{rv}\right]}{\left[PAH_a\right]}$$

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; RDO_2, renal delivery of oxygen; RVO_2, renal oxygen consumption; RO_2Ex, renal oxygen extraction; FF, filtration fraction; [$^{51}CrEDTA_a$], arterial concentration of Cr-EDTA; [$^{51}CrEDTA_{rv}$], renal vein concentration of 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; PAH_{extr}, PAH extraction; and [PAH_a] and [PAH_{rv}] the arterial and renal vein concentration of PAH.

Experimental procedures

Paper I

Ten patients with a normal preoperative renal function were studied, after elective uncomplicated cardiac surgery, in the ICU, mechanically ventilated and sedated with propofol (57±13 μg/kg/min) and morphine (0.5-1 mg/h). Measurements started approximately four to six hours after end of cardiopulmonary bypass. All 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 the administration of

mannitol, 150 mg/ml, (Mannitol, Baxter Viaflo, Sweden). The patients received 225 mg mannitol/kg during 10 minutes as a bolus; thereafter, a continuous infusion at a rate of 75 mg/kg/h was given for three 30-min periods. Sixty minutes after the mannitol infusion was started, the patients also received a bolus dose of intravenous furosemide 0.25 mg/kg, (Furosemid, Recip, Sweden) followed by a continuous infusion of furosemide 0.25 mg/kg/h for one 30-min period (Figure 8). Urine was collected during all three 30-min periods. Cardiac output, thermodilution measurements of renal blood flow and blood samples were obtained at the end of each period.

During the experimental procedure, an isotonic crystalloid solution was continuously infused to substitute for fluid losses due to the diuretic response.

Paper II

Twelve patients with a normal preoperative renal function were studied, after elective uncomplicated cardiac surgery, in the ICU, mechanically ventilated and sedated with propofol (69±6.6 μg/kg/min) and morphine (0.5-1 mg/h). Measurements started approximately

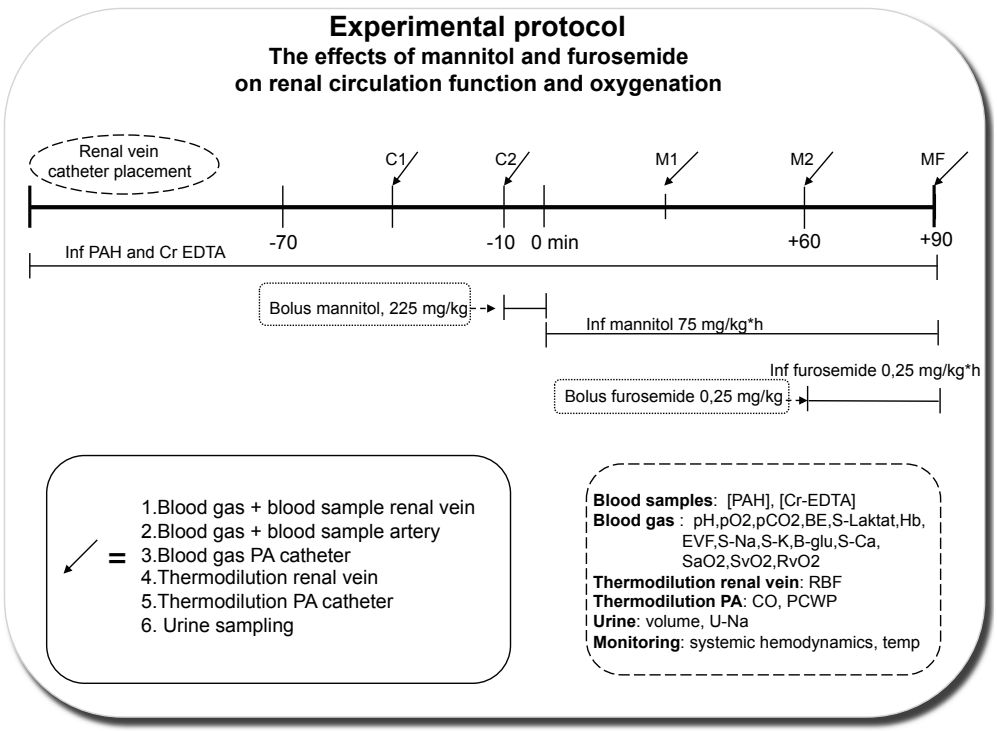

Figure 8. The experimental protocol for Paper I. Abbreviations: C, control; M, mannitol; MF, mannitol + furosemide.

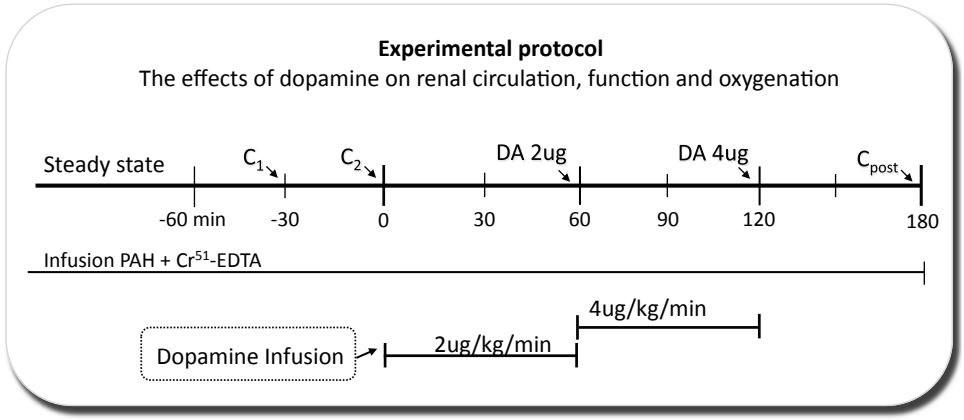

Figure 9. Experimental protocol, Paper II.

four to six hours after end of cardiopulmonary bypass. All 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 C_1 and C_2) were started followed by the administration of dopamine (Abbodop® 2 mg/ml, Hospira Enterprises, The Nederlands). The patients received a continuous infusion of dopamine at an infusion rate of 2 μg/kg/h followed by 4 μg/kg/h. Each dose was administered for 60 minutes and urine was collected at the second half of each hour of infusion (Figure 9). The highest acceptable systolic blood pressure level during dopamine infusion was 160 mmHg. After a washout period of 30 minutes, one 30-min post-drug urine collection control period ensued (C_{post}). Cardiac output, thermodilution measurements of RBF and blood samples for oxygen, PAH and ^{51}Cr-EDTA concentrations were obtained at the end of each urine collection period. During the experimental procedure, an isotonic crystalloid solution was continuously infused to substitute for fluid losses.

Paper III

In the control group, 37 patients with a normal preoperative renal function were studied after elective uncomplicated cardiac surgery, while in the AKI group, 12 patients with a normal preoperative renal function, who after cardiac surgery developed AKI, were studied. For patient characteristics, see Table 2 and 3. The patients were mechanically ventilated and sedated with propofol (control group: 63.8 ± 3.0 μg/kg/min, AKI group: 61.7 ± 4.2 μg/kg/min), and morphine or fentanyl. In all patients, a pulmonary artery catheter and a renal vein catheter were used for the measurements.

After an equilibration period of at least 60 minutes, two 30-min urine collection periods ensued (measurement period 1

and 2). At the end of each period, cardiac output and renal thermodilution measurements were performed and blood samples were taken from radial artery, pulmonary artery and renal vein for measurements of serum concentrations of sodium, ^{51}Cr-EDTA, PAH, hemoglobin as well as oxygen content. The inotropic medication and the fluid infusion rate were not changed during the experimental procedure. In the control group, serum creatinine was assessed on the first and second postoperative days.

Paper IV

12 patients with a normal preoperative renal function, who after cardiac surgery developed AKI, were studied. For patient characteristics, see Table 2 and 3. The patients were mechanically ventilated and sedated with propofol, and morphine or fentanyl. In all patients, a pulmonary artery catheter and a renal vein catheter were used for the measurements.

After an equilibration period of at least 60 minutes, two 30-min control periods ensued at a target MAP of 75 mmHg. The infusion rate of norepinephrine was then randomly increased or decreased to obtain a 60-min period at a MAP of 60 mmHg and a 60-min period at a MAP of 90 mmHg. A titration period of 15 to 30 min was needed for each new MAP level to obtain the target pressure. Thereafter, a post-intervention period of 60 minutes at a MAP of 75 mmHg was obtained (Figure 10). At each target MAP, urine was collected for 30 minutes. At the end of each such period cardiac output, renal thermodilution measurements and blood samples from artery, pulmonary artery and renal vein were taken, for oxygen, sodium and ^{51}Cr-EDTA estimations. The inotropic medication, the diuretic medication and the fluid infusion rate were not changed prior to or during the experimental procedure.

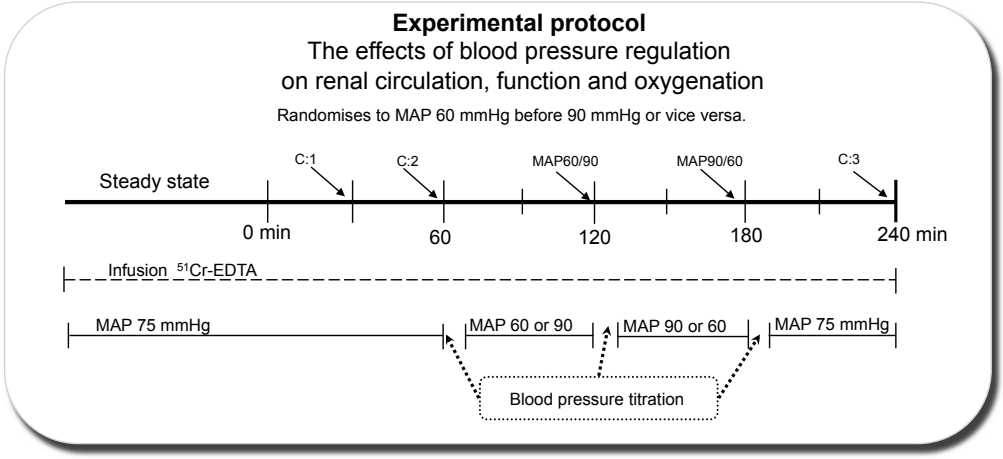

Figure 10. Experimental protocol Paper IV.

Statistical analyses

All statistical analyses have been made in Statistical Package Social Sciences (SPSS), version 12 –18. 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

Pre-drug control periods (C1 and C2) were compared in Paper I, II and IV. In Paper III the two measurement periods were compared, in both groups separately. In all studies, the control values (measurement values in Paper III) were then pooled ((C1 + C2)/2) before further comparisons were made. In paper II and IV the pooled pre-drug control values were also compared to post-drug control values.

The two mannitol periods (M1 and M2) were pooled in Paper I before evaluation of data.

All comparisons of the effects of study-drug/study-intervention were made against pre-drug control.

Kolmogorov-Smirnov

Kolmogorov-Smirnov test for goodness of fit to normal distribution was performed on all variables in study II - IV and normality was obtained for all measurements except for PCWP, in the control group, in Paper III.

Paired t-test

Paired t-test was used in all papers to compare control values (measurement values in Paper III) with each other.

Welch test

Independent samples t-test, in which equal variances were not assumed, (Welch test), was used in Paper III, to compare the control group with the AKI group. The test was chosen as the variances between the two groups differed in some variables, as shown by Levene's test.

Mann-Whitney U test

This non-parametric test was used for PCWP in Paper III, as the control group variable not was normally distributed.

Chi-Square test

To compare baseline categorical data in paper III, the Chi-Square test was used. 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 measures followed by Fisher's PLSD post hoc analysis was used in Paper I, II and IV to evaluate the effects of the interventions on renal data and systemic hemodynamics. To test the null hypothesis that the variance did not differ between groups, Mauchly's Test of Sphericity was used. When this test was significant, Greenhouse-Geisser was used instead of Sphericity Assumed, to test within subject effects.

Linear regression and correlations

To test correlations between numerical data, linear regression analyses using SPSS GLM univariate, were performed.

"Correlations within subject", with pa-

tient as a fixed factor, were calculated in Paper I and II (71). With this multiple regression, or analysis of covariance (ANCOVA), one can 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, thus, calculated. The program creates one regression-line for each patient, with different locations on the chart but with the same slopes, thereby eliminating the between-patient variance. For example, despite a substantial variation between patients in booth renal oxygen extraction and filtration fraction in Paper I, correlation within subject showed that the patients increased their oxygen extraction when the filtration fraction increased (Figure 11). Thus, it calculates the mean within-patient effect.

In Paper III, multiple regressions were calculated to correlate RVO_2 to GFR and RVO_2 to sodium reabsorption. The resultant regression lines are shown in Figure 14.

Results

Paper I – effects of mannitol and furosemide

To evaluate the renal effects of mannitol alone and the effects of combined infusion of mannitol and furosemide, we studied ten uncomplicated postoperative patients with preoperative normal renal function.

Data obtained during the two control periods, C1 and C2, did not differ significantly in any of the measured variables.

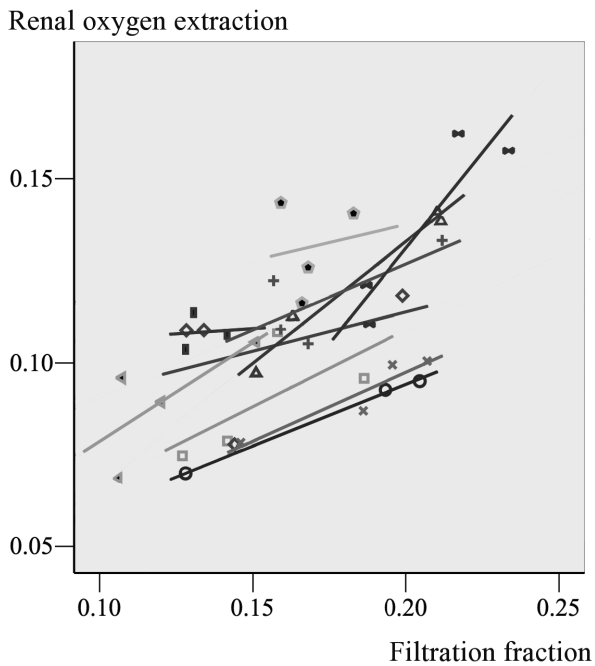

Figure 11. A close correlation between changes in filtration fraction and renal oxygen extraction was found. Thus, when the filtration fraction increases (= the quotient GFR/RBF increases) the renal oxygen supply/demand is impaired, as seen by the increase in renal oxygen extraction

Effects of mannitol alone

Mannitol did not change any of the systemic hemodynamic variables, RBF or RVR. However, it increased GFR by 20%, FF by 20%, the amount of filtered sodium by 18% and sodium reabsorption by 18%. Consequently, RVO_2 increased by 19% and renal oxygen extraction by 21%, (Figure 12). The urine flow was increased by 60%.

The mannitol-induced increase in RVO_2 correlated positively both to the increase in tubular sodium reabsorption (r^2 = 0.92, $p<0.001$) and the increase in GFR (r^2 = 0.90, $p<0.001$). The mannitol-induced increases in GFR and tubular sodium reabsorption also correlated positively to each other (r^2 = 0.99, $p<0.001$). Furthermore, there was a close correlation between filtration fraction and renal oxygen extraction (r^2 = 0.81, $p<0.001$), (Figure 11).

Effects of mannitol plus furosemide

Addition of furosemide increased SVR slightly (7%) but significantly ($p<0.05$), compared to control. However, all other systemic hemodynamic variables, RBF and RVR were unaffected by the addition of furosemide to mannitol. Nevertheless, FF and GFR were maintained at higher levels (14%, $p<0.05$ and 13%, $p=0.052$, respectively), while RVO_2, sodium reabsorption and renal oxygen extraction (Figure 12) returned to control accompanied by a 7-fold higher urine flow ($p<0.001$).

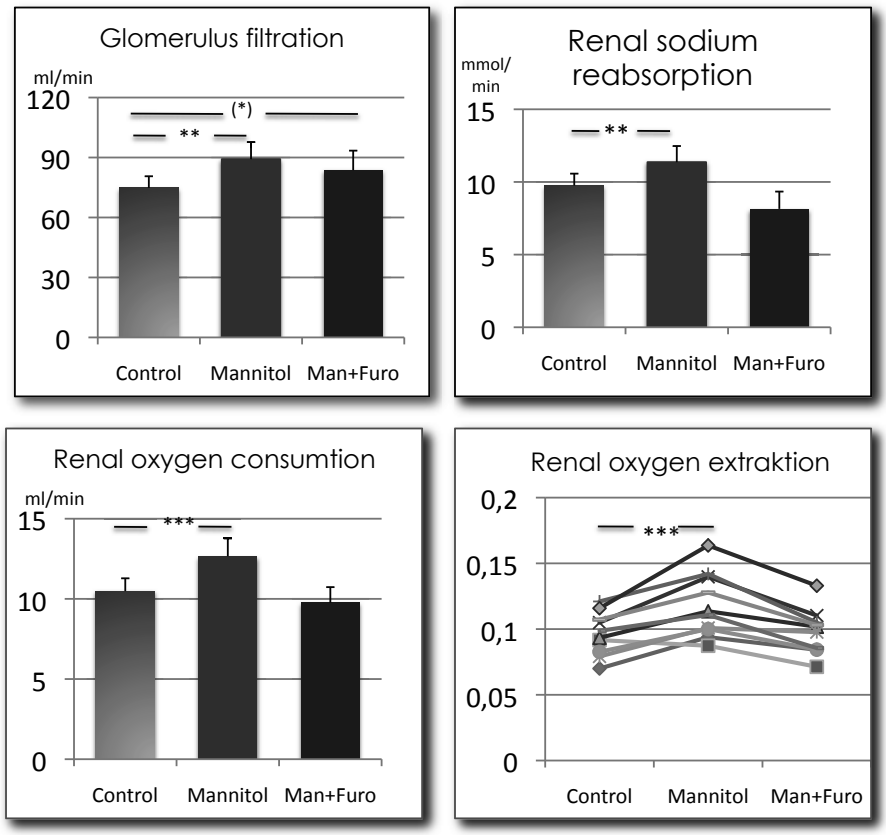

Figure 12. Mannitol increased GFR and thereby the reabsorptive workload. Consequently, mannitol also increased the sodium reabsorption, which led to an increase in renal oxygen consumption. Since RBF and the renal oxygen supply were unaffected by mannitol, this increase in oxygen consumption caused a deterioration of renal oxygen supply/demand, as seen by the increase in renal oxygen extraction (individual data). Addition of furosemide maintained GFR higher than control, while renal oxygen consumption and extraction returned to control value. (*)=$p<0.052$ **=$p<0.01$ ***=$p<0.001$.

Paper II – effects of dopamine

To evaluate the effects of dopamine on renal perfusion, filtration and oxygenation, we studied twelve uncomplicated postoperative patients with normal preoperative creatinine.

Data obtained during the two control periods, C1 and C2, did not differ significantly in any of the measured renal or hemodynamic variables.

Effects of dopamine on systemic variables

Dopamine, at an infusion rate of 2 and 4 µg/kg/min, induced no changes in MAP or cardiac filling pressures (CVP, PCWP). SVRI decreased by 20% and 24%, respectively, while CI increased by 20–30%. The increase in CI was caused by an increase in HR (9% and 17%, respec-

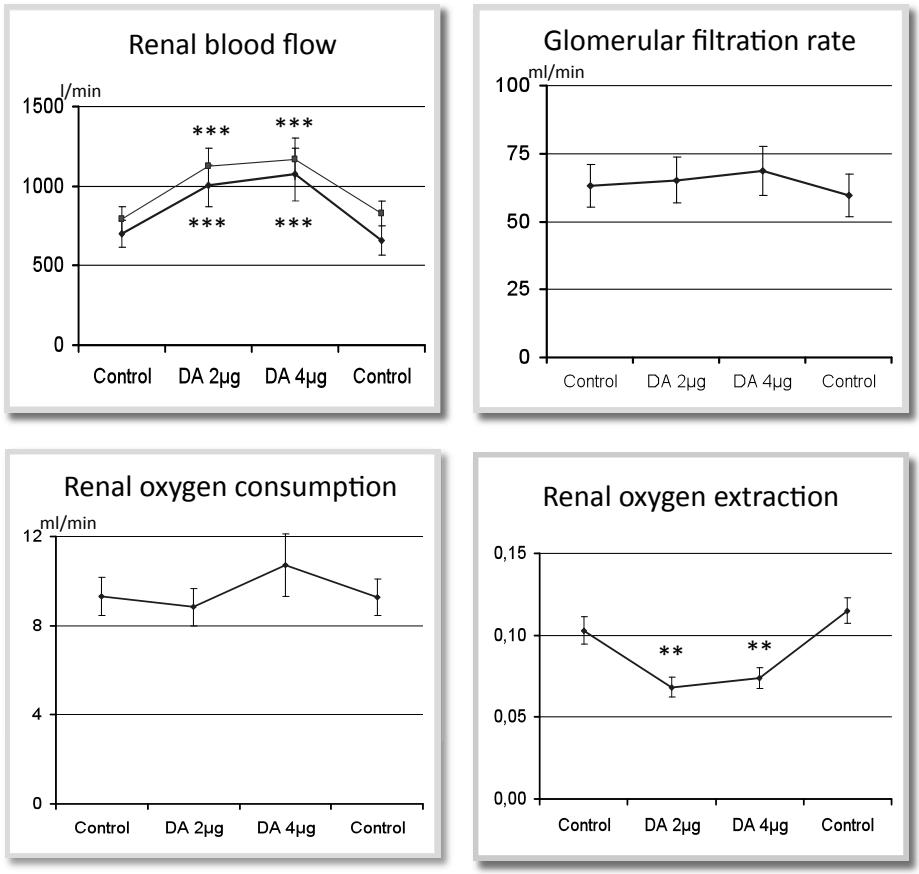

Figure 13. The renal effects of dopamine 2 and 4 µg/kg/min. While dopamine increased RBF, it had no effect on GFR or renal oxygen consumption. Consequently, dopamine improved total renal oxygenation, as seen by the decrease in renal oxygen extraction. Renal blood flow: upper line, RBF by infusion clearance; lower line, RBF by thermodilution. **=p<0.01 ***=p<0.001.

tively) and SVI (9% and 12%, respectively).

In the post-dopamine control period, CI (-6%), SVI (-10%) and MAP (-10%), were significantly lower compared to the pre-drug control periods. Post-drug control values of all other hemodynamic variables did not differ significantly from pre-drug control values.

Effects of dopamine on renal variables

Dopamine infusion at a rate of 2 and 4 ug/kg/min induced a fall in RVR by 30-35%. This fall in resistance produced an increase in RBF by approximately 45-55%, as estimated by the two independent techniques. Furthermore, dopamine redistributed blood flow to the kidney, as the RBF/CI ratio increased significantly (24% in relative terms, $p<0.05$). The dopamine-induced increase in RBF was not accompanied by a significant increase in GFR; thus, the filtration fraction decreased by -26% and -21%, respectively, at the two infusion rates. As dopamine had no effect on GFR, it had neither any effect on renal sodium filtration, reabsorption, sodium excretion or RVO_2. Renal oxygen supply/demand was improved significantly, secondary to the increase in RBF, as shown by the decrease (28–34%) in renal oxygen extraction (Figure 13). There was a trend for an increase in urine flow at the highest dose of dopamine ($p=0.069$).

ERBF was calculated for comparison and it underestimated RBF_{IC} by approximately 10% at baseline. Furthermore, ERBF only increased by 27–31 % when dopamine was given, thus underestimating the dopamine-induced relative increase in RBF by 40-45%. This was due to a dopamine-induced decrease in PAH extraction of 10 %. In the post-dopamine control period, urine flow was significantly lower compared to pre-drug control. Post-drug control values of all other renal variables did not differ significantly from pre-drug control values. The dopamine-induced decrease in FF correlated positively to the decrease in renal oxygen extraction ($r^2 = 0.70$, $p<0.001$).

Paper III – control versus AKI

Thirty-seven uncomplicated postoperative patients were compared with twelve patients with postoperative AKI, to evaluate the effects of AKI on renal circulation and oxygenation.

The patients in the AKI group had a lower preoperative ejection fraction, longer cardiopulmonary bypass and cross-clamp times and a higher Higgins ICU admission score. For detailed baseline characteristics see Table 2 and 3 on page 23 and 24. Neither systemic, nor renal data obtained during the two 30-min periods differed significantly from each other in either group.

Systemic variables

There were no differences in MAP, SVI, HR or CI between the groups. The AKI patients had higher cardiac filling pressures and arterial lactate, while SVRI was lower (-11%) compared to the control group. There were no differences in serum hemoglobin, arterial oxygen saturation, systemic delivery of oxygen or systemic oxygen extraction, but mixed venous oxygen saturation was lower

Table 4. Renal variables obtained from the thermodilution and the infusion clearance techniques.

	Control (n= 37)	AKI (n=12)	*p* Value
RO_2Ex	0.097 ± 0.004	0.163 ± 0.009	<0.001
Urine flow (ml/min)	3.73 ± 0.39	4.04 ± 0.48	ns
Thermodilution			
RBF_{TD} (ml/min)	758 ± 40	477 ± 54	<0.001
RVR (mmHg/ml/min)	0.097 ± 0.005	0.146 ± 0.015	0.01
GFR (ml/min)	74.7 ± 4.7	32.3 ± 3.6	<0.001
FF	0.148 ± 0.006	0.109 ± 0.014	0.022
Na^+-filtration (mmol/min)	10.2 ± 0.7	4.4 ± 0.4	<0.001
Na^+-reabsorption (mmol/min)	9.7 ± 0.7	4.0 ± 0.4	<0.001
FE_{Na}	0.050 ± 0.007	0.099 ± 0.019	0.028
RDO_2 (ml/min)	110.0 ± 6.2	68.0 ± 7.2	<0.001
RVO_2 (ml/min)	10.4 ± 0.6	11.0 ± 1.1	ns
Infusion clearance of PAH			
RBF_{IC} (ml/min)	822 ± 40	496 ± 34	<0.001
ERBF (ml/min)	779 ± 37	375 ± 35	<0.001
RVR (mmHg/ml/min)	0.086 ± 0.004	0.131 ± 0.095	<0.001
GFR (ml/min)	80.3 ± 4.2	33.6 ± 3.4	<0.001
FF	0.148 ± 0.005	0.107 ± 0.014	0.017
Na+-filtration (mmol/min)	11.0 ± 0.6	4.6 ± 0.5	<0.001
Na+-reabsorption (mmol/min)	10.5 ± 0.6	4.2 ± 0.5	<0.001
FENa	0.042 ± 0.004	0.093 ± 0.015	0.008
RDO_2 (ml/min)	120,1 ± 6.6	70.9 ± 4.5	<0.001
RVO_2 (ml/min)	11.4 ± 0.5	11.8 ± 0.8	ns
PAH extraction	0.85 ± 0.01	0.68 ± 0.04	0.002

Values are means±SEM. RO_2Ex, renal oxygen extraction; RBF_{IC}, renal blood flow assessed by infusion clearance; RBF_{TD}, renal blood flow assessed by the thermodilution technique; ERBF, effective renal blood flow; RVR, renal vascular resistance; GFR, glomerular filtration rate; FF, filtration fraction; FE_{Na}, fractional excretion of sodium; RDO_2, renal oxygen delivery; RVO_2, renal oxygen consumption.

(-7%) due to an increase in systemic oxygen consumption (18%) in the AKI group. Body temperature was slightly, but significantly, higher in the AKI group.

Renal variables

Measured and derived renal variables obtained from the two independent methods, renal thermodilution (TD) and PAH-infusion clearance (IC), are pre-

sented in Table 4. The AKI patients had significantly lower RBF (TD: -37%, IC: -40%) and renal delivery of oxygen (TD: -38%, IC: -41%). GFR (TD: -57%, IC: -58%), sodium filtration (TD: -57%, IC: -58%) and sodium reabsorption (TD: -59%, IC: -60%) were decreased to the same extent, compared to the control patients, while RVR was higher in the AKI group (TD: 51%, IC: 52%). Renal oxygen extraction was 68% higher in the AKI group, whereas there was no difference in RVO_2 between the groups. PAH extraction was 20% lower in AKI group. There were no differences in urine flow between groups.

In the control group, mean serum creatinine values preoperatively and on the first and second postoperative days were 83±2, 78±5 and 85±5 μmol/l, respectively. The postoperative serum creatinine values did not differ significantly from the preoperative value. None of the patients in the AKI group died or required renal replacement therapy during their stay in ICU.

RVO_2 correlated to GFR in both controls ($p<0.001$, $r^2 = 0.82$) and the AKI patients ($p=0.016$, $r^2 = 0.50$), but the slope of the AKI group was significantly steeper ($p=0.04$) (Figure 14). Furthermore, RVO_2 correlated to sodium reabsorption in both the control ($p<0.001$, $r^2 = 0.85$) and the AKI group ($p=0.005$, $r^2 = 0.61$). The slopes in this regression, which indicates the oxygen

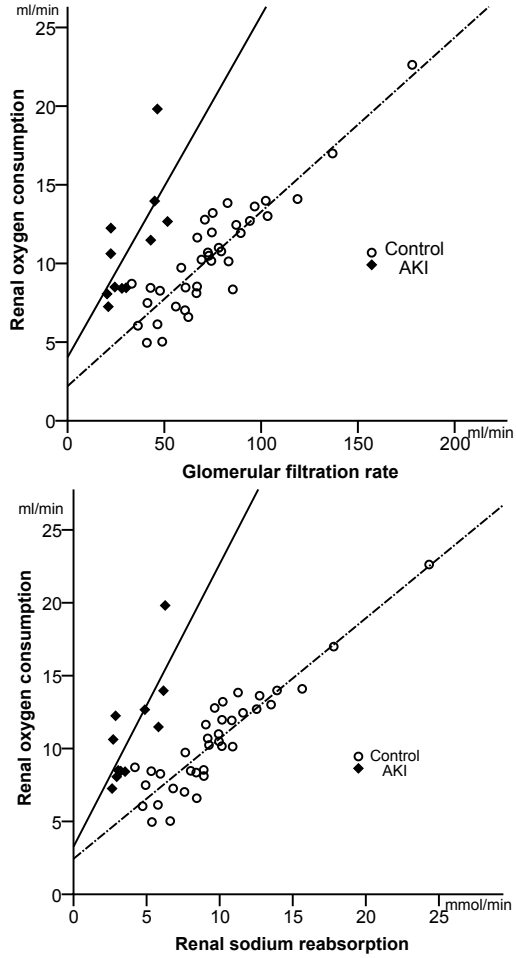

Figure 14. *Upper* shows the individual data on the relationship between renal oxygen consumption and glomerular filtration rate for the control group and patients with acute kidney injury (AKI). Note that the slope of the regression line was significantly ($p<0.04$) steeper in the AKI group compared to control.
Lower shows the individual data on the relationship between renal oxygen consumption (RVO_2) and renal sodium reabsorption (Na^+-reab) for the control group ($RVO_2 = 2.43 + 0.82 \times Na^+$-reab) and patients with acute kidney injury (AKI) ($RVO_2 = 3.27 + 1.94 \times Na^+$-reab). Note that the slope of the regression line was significantly ($p<0.004$) steeper in the AKI group compared to control, while the intercepts of the regression lines did not differ significantly.

consumption per sodium reabsorbed, differed, as the regression line in the AKI group was significantly steeper (p=0.004). Thus, oxygen consumption per mmol reabsorbed sodium (O_2/Na^+) were 1.94±0.36 in AKI and 0.82±0.071 in the control group (Figure 14). The slope intercepts on the abscissa differed significantly from origin (p=0.002) in both groups (control: 2.4±0.65 ml O_2/min and AKI: 3.3±2.29 ml O_2/min), but the slope intercepts, indicating basal renal oxygen consumption, did not differ between groups.

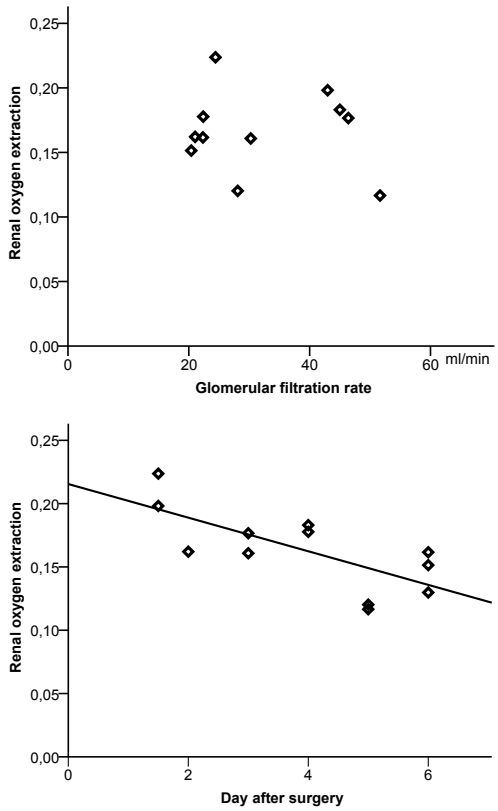

Figure 15. There were no correlation between renal oxygen extraction and GFR in the AKI group, but renal oxygen extraction was higher in the patients studied early after surgery. This indicates that renal oxygen supply/demand is most affected in the early phases of AKI.

Renal oxygen extraction did not correlate to GFR. However, in the AKI group, the high renal oxygen extraction decreased with time after surgery, as shown by the linear regression in Figure 15, (p=0.008, r^2=0.47).

Dose norepinephrine did not correlate to RVR and treatment with furosemide did not correlate to RVO_2, urine flow or fractional excretion of sodium in the AKI group.

Paper IV – effects of norepinephrine in AKI

We studied the effects of titrating the norepinephrine infusion rates to reach target MAP of 60, 75 and 90 mmHg, to establish the optimal blood pressure, in terms of renal perfusion, filtration and oxygenation, in norepinephrine-dependent patients with AKI.

Neither the two pre-75 mmHg nor the pooled pre versus post-75 mmHg differed significantly from each other in any measured hemodynamic or renal value, indicating stable baseline conditions.

Systemic variables

The infusion rate of norepinephrine was increased by 38% to raise MAP from 60 mmHg to 75 mmHg. This norepinephrine-induced elevation in MAP was accompanied by significant increases in SVRI (13%), CI

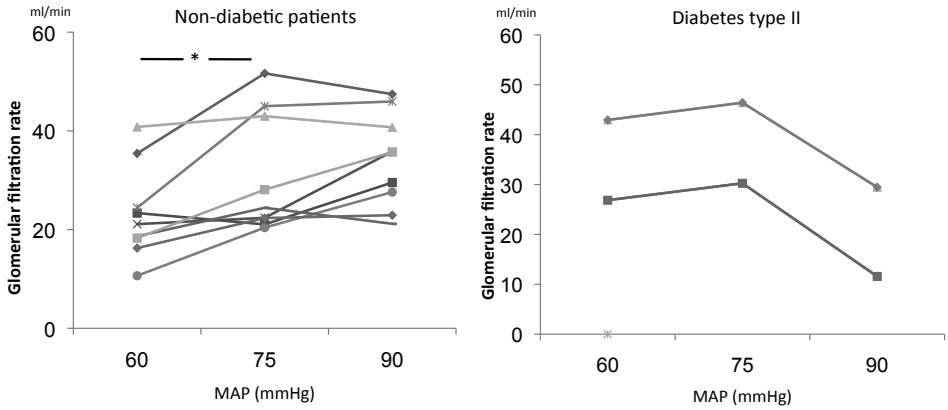

Figure 16. Individual data on GFR in patients with and without diabetes mellitus. GFR was significantly higher at MAP 75 than MAP 60 in the non-diabetic patients. When MAP was raised from 75 to 90 mmHg, this induced a small numerical increase in GFR in non-diabetic patients, while GFR numerically decreased 46 % in the two diabetic patients.

(11%), systemic delivery of oxygen (17%), CVP (11%) and PCWP (14%), while systemic oxygen extraction decreased (13%).

A further increase in norepinephrine-infusion rate of 34 % increased MAP from 75 to 90 mmHg, SVRI (18%), CI (8%), systemic delivery of oxygen (10%), CVP (7%) and PCWP (11%), but systemic oxygen extraction was not influenced further. Thus, norepinephrine affected the systemic variables almost linearly throughout the ranges MAP 60 – 75 mmHg and 75 – 90 mmHg.

Renal variables

Renal variables were, however, not affected uniformly throughout the range of 60 to 90 mmHg. When MAP was increased from 60 – 75 mmHg, concomitant increases in RVR (16%), renal delivery of oxygen (13%), FF (19%), GFR (27%), sodium filtration (31%), sodium reabsorption (25%), fractional excretion of sodium (114%) and urine flow (115%) were found. At the same time, renal oxygen supply/demand was improved slightly but significantly, since renal oxygen extraction decreased 6.4 %.

When MAP was augmented further, from 75 – 90 mmHg, with norepinephrine, RVR increased another 25 %, but no other significant changes were found in renal variables.

Patients with and without diabetes mellitus

Two patients in the study had diabetes mellitus type II. A hypothesis-generating finding was that these diabetic patients responded totally different to the increase in norepinephrine and MAP compared to the non-diabetic patients. When MAP was raised from 60 to 90 mmHg, RVR increased 134% in the diabetic patients, whereas RVR only increased 40 % in the patients without diabetes.

In the subgroup of patients without

diabetes, RBF, but not RVR, increased significantly (+12%) when MAP was raised from 60 – 75 mmHg. In addition, GFR increased by 47% when MAP was raised from 60 – 90 mmHg in the patients without diabetes, while it decreased by 41 % in the two diabetes patients (Figure 16).

Discussion

Methodological and experimental considerations

Study population

The population of "uncomplicated postoperative patients" could not be compared to a population of healthy volunteers. Indeed, they were all sedated and mechanically ventilated and all had been subjected to a major surgical trauma. It can be argued that cardiac surgery with cardiopulmonary bypass caused renal injury in these uncomplicated postoperative patients and the possibility of a tubular injury cannot be ruled out, as urinary markers of tubular damage were not measure postoperatively (6). However, it is not likely that this group had experienced a major ischemic renal insult at the time of the study, as serum creatinine values the first and second postoperative days did not differ from preoperative serum creatinine.

Study design

One major limitation in this thesis is that we did not include time-control groups in Paper I, II and IV. One could, therefore, argue that changes in the measured renal or hemodynamic variables were not entirely caused by the study-drug itself, but also, to some extent, by spontaneous fluctuations or time-dependent effects on these variables. On the other hand, neither systemic hemodynamics, nor renal variables differed significantly between the two pre-drug control periods in any of the studies, indicating a stable baseline. Additionally, in Paper IV, the patients were randomised to target MAP of 60 or 90 mmHg. Finally, nearly no post-control value differed significantly from pre-control value. It is, therefore, most likely that the effects of study-drug on measured variables are caused by the study-drug itself and not by spontaneous fluctuations or time-dependent changes of these variables.

RBF by infusion clearance of PAH

The infusion clearance technique yields an estimation of RBF without the need for urine collection. However, there are some requirements that should be met by the clearance substance. First, it should not be metabolised, instead it should be eliminated almost exclusively by the kidneys. Second, it should have an extraction close to 100%. Third, in order get an equilibration between infused and excreted substance in a reasonable time, the volume of distribution should not be too large and the RBF, studied, should not be to low. Finally, the intervention/treatment studied should not

change any of these conditions.

PAH is eliminated to approximately 90% during the passage through the kidney (72) and have been found to have an extra-renal elimination of 15% in postoperative ICU patients (73). However, as a renal vein catheter was inserted in all patients, the infusion clearance of PAH was individually corrected for the PAH-extraction. Furthermore, RBF_{IC} was corrected for its extra-renal elimination, by multiplying the RBF-value with 0.85. Thus, the measurements of RBF_{IC} were compensated for these two aberrations from the optimal condition. The range of PAH extraction was 0.67 to 0.95 in the patients without renal failure. To determine the importance of individual correction for PAH-extraction, ERBF was calculated, assuming that PAH-extraction was 0.90 in all patients.

Dopamine decreased the PAH extraction, from 0.82 to 0.71, in Paper II, which was corrected for when estimating RBF_{IC}. This phenomenon has previously been described in healthy volunteers (74). As a consequence, ERBF underestimated the dopamine-induced increase in RBF by 40%. Former studies of the renal effects of dopamine on RBF have most often measured ERBF, and there is, thus, a risk that the renal effect dopamine has been underestimation in those studies (75-79).

The mean PAH extraction was found to be 0.85 in the uncomplicated post-operative patients. However, in the AKI group, mean PAH extraction was only 0.68, with a range from 0.48 to 0.84, due to the tubular damage. Hence, without correction for renal PAH extraction, RBF will be seriously underestimated in patients with AKI, as demonstrated by the 25% lower mean ERBF compared to RBF_{IC}, with a potential error of 7% to 47% at the most extreme deviations of PAH extraction from 0.9. These results are in accordance with the results from Brenner et al., who found the PAH extraction to be 0.56, with a range from 0.28 to 0.90 in eight septic patients (80). Thus, ERBF underestimates RBF in AKI and during dopamine infusion.

Infusion clearance of PAH requires steady state for adequate measurement of RBF. However, own unpublished data shows that, after discontinuing the PAH infusion, the half time (t ½) of the PAH concentration is 19±12 min (mean±SD) in postoperative patients, while it is 76±30 minutes in critically ill patients. This discrepancy is due to a lower RBF and a larger volume of distribution of PAH (26±12 L) in the critically ill patients. Thus, the infusion clearance of PAH-technique is inappropriate for estimations of dynamic changes in RBF in intensive care patients.

RBF by thermodilution

The renal vein thermodilution technique has been described and validated using either bolus or a continuous infusion technique (73, 80, 81). The obvious advantages with the renal vein thermodilution technique are that rapid and repeated estimations of RBF can be performed at bedside with short intervals. Recently, the continuous renal vein thermodilution method was validated against the gold standard technique, which is the urinary clearance of PAH

corrected for by renal extraction-fraction of PAH (73). The coefficient of variation for repeated estimations of RBF was similar (10%) for the thermodilution and the urinary clearance techniques, suggesting that the reproducibility of the thermodilution technique is comparable to the gold standard technique. The coefficient of variation for repeated estimations of RBF by thermodilution was also calculated on the material used in this thesis. It was found to be 8.0 % in the uncomplicated postoperative patents and 6.2 % in the patients with AKI. The repeatability was thus better than previously reported in both groups independently. However, correct and stable position of the renal vein catheter thermistor is the most critical factor for the estimation of RBF.

Consequently, the thermodilution technique is validated and measures RBF instantly. It is neither dependent on a steady state, nor affected by extra renal elimination, nor changes in renal extraction. The thermodilution technique can, hence, be used in intensive care patients detecting dynamic changes in RBF.

Filtration fraction by ^{51}Cr-EDTA

^{51}Cr-EDTA is freely filtered in the glomeruli and not reabsorbed by the tubules. It has good correlation to inulin clearance, although renal clearance of ^{51}Cr-EDTA tends to be 5-15% lower at high values (82). The extra-renal elimination of approximately 3-5% is of no importance as the renal extraction of ^{51}Cr-EDTA has been measured in Paper I-IV. ^{51}Cr-EDTA has been judged as the method of choice for assessment of GFR in the clinic (83).

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 where RBF is low and/or the urine flow is high (70). However, the renal extraction of ^{51}Cr-EDTA has been corrected for the differences in renal vein hemoconcentration, in all Papers.

Renal physiology after cardiac surgery

The uncomplicated postoperative patients evaluated in this thesis, were studied after cardiac surgery with cardio pulmonary bypass, which is known to increase the risk for AKI. However, there is no previous evaluation of how uncomplicated cardiac surgery affects renal perfusion, filtration or oxygenation.

In uncomplicated cardiac surgery patients RBF and GFR were decreased in proportion (20–30%) compared to healthy controls in other studies (8, 84, 85) (Table 5). Most likely, the former group, which were sedated and mechanically ventilated, had a lower cardiac output. RVO_2 was also lower in the post-cardiac patients, probably due to the lower GFR, compared to healthy controls in other studies. However, the renal oxygenation was not affected in the postoperative patients, due to the fact that they had proportional declines in renal oxygen supply and demand (84, 85).

Table 5. Renal physiology after cardiac surgery.

	After uncomplicated cardiac surgery		Healthy controls
	PAH clearance	Thermodilution	
RBF ml/min	822 ± 239	758 ± 240	1000 – 1300
GFR ml/min	80 ± 26	75 ± 29	100 – 125
RVO_2 ml/min	11.4 ± 3.2	10.4 ± 3.5	15 – 19
$RO_2A\text{-}V_{diff}$ ml/min	14.1 ± 3.1	14.1 ± 3.1	14 – 15

Healthy controls, adult subjects without renal disease; $RO_2A\text{-}V_{diff}$, the difference between arterial and renal vein oxygen content. Values are mean ± SD, in "healthy controls" range.

Renal effects of mannitol after cardiac surgery (Paper I)

Mannitol induced an increase in GFR, which was accompanied by increases in tubular sodium reabsorption and RVO_2. This increase in RVO_2 was not accompanied by an increase in RBF. Thus, infusion of mannitol impaired renal oxygenation (renal oxygen supply/demand relationship).

In most animal studies, mannitol has been shown to increase RBF by renal vasodilatation, both during normotensive} and hypotensive conditions (43, 86). Data on the effects of mannitol on RBF in man are scarce. However, three small clinical studies found no or a minimal effect of mannitol on RBF (84, 87, 88). Those clinical data are supported by Paper I in which mannitol induced no effects on either RBF or RVR.

Reports on the effects of mannitol on GFR are conflicting. In normotensive animals, as well as in healthy volunteers, mannitol does not seem to have any effect on GFR (43, 84). Clark et al. studied the effects of mannitol on five male healthy volunteers, age 17 to 58 years, and found no effect on RBF, GFR or RVO_2 (84). On the other hand, in hypotensive animals, as well as in critically ill humans, mannitol seems to increase GFR (45, 89, 90). These findings also cohere with Paper I, where a mannitol-induced increase in GFR was found after cardiac surgery with cardio-pulmonary bypass. Indeed, experimental data have shown that mannitol infusion tends to restore GFR towards normal levels, in hypoperfused kidneys, both when given prior to and after the hypotension has been induced (89, 90). It has been suggested that it is the osmotic effect of mannitol that restores GFR, by reducing endothelial cell swelling and tubular cell swelling, thus opening up collapsed tubular segments, increasing tubular flow and restoring GFR (91-95). One could, thus, speculate that hypotensive episodes during cardiopulmonary bypass might induce cell swelling and derecruitment of functional nephrons, which are opened up by mannitol after surgery.

The mannitol-induced increase in GFR, after cardiac surgery in Paper II, was closely correlated to increases in renal sodium reabsorption and RVO_2. Thus, mannitol increased renal oxygen

demand but had no effect on renal oxygen supply, as RBF was unaffected. Consequently, mannitol decreased renal oxygen supply/demand. These findings are consistent with animal data, which have shown that mannitol decreases outer medullary oxygen tension while cortical oxygen tension is unaffected (48, 96). Zager et al found that mannitol caused a 3-fold acute increase in RVO_2 in the post-ischemic kidney of the renal ischemia/reperfusion model (92). Additionally, in glycerol-induced experimental ARF it has been observed that mannitol worsens cellular energetics by a pronounced acute reduction in ATP content, which was explained by a mannitol-induced increase in GFR, tubular sodium reabsorption and RVO_2 (97).

Mannitol remains in common use in cardiac surgery today, usually in the pump prime (98). Evidence for its use as a renal protective agent in the setting of cardiac surgery is controversial (98) and there is, to our knowledge, no study showing that mannitol improves renal outcome in cardiac surgery with cardiopulmonary bypass.

Mannitol also exhibits hydroxyl radical (·OH) scavenging properties and this could possibly protect the kidney. However, mannitol has limited reactivity with other free oxygen radicals than ·OH, and ·OH is so reactive that it damage the first molecule it meet within a few Ångstroms of its formation (99). Furthermore, mannitol has a very limited transport into cells and it has, consequently, been concluded that there is no realistic possibility that mannitol can protect against tissue damage in biological systems by scavenging ·OH (99).

In conclusion, mannitol improves GFR and, hence, the renal function, in patients after cardiac surgery, probably by decreasing pathological cell swelling. However, as mannitol improves renal function without improving renal perfusion, it impairs renal oxygenation.

Renal effects of mannitol plus furosemide after cardiac surgery (Paper I)

The addition of furosemide to mannitol infusion, in paper I, induced a fourfold increase in urine flow, due to an inhibition of tubular reabsorption of sodium. This was accompanied by a return of both RVO_2 and renal oxygen extraction back to control levels. Consequently, one could speculate that the potential beneficial effects of mannitol in renal ischaemia could be reinforced by combined treatment with furosemide, which would counteract mannitol-induced impairment of renal oxygenation.

Furosemide inhibits the Na-K-Cl cotransporter and thereby active sodium reabsorption in the medullary thick ascending limb (96). It has previously been shown that it decreases RVO_2 in patients after cardiac surgery (26) and furosemide could, thus, ameliorate the risk for renal hypoxia (31). However, furosemide also increases the sodium delivery to the distal tubuli and decreases GFR, due to the activation of the tubulo-glomerular feedback mechanism (26). Consequently, furosemide, as an indirect pharmacological effect, may increase the serum creatinine level. Indeed,

it has been shown that furosemide increases the serum creatinine level 12 - 24 hours after cardiac surgery, compared to control (100). Even though this could be due to a pure pharmacological effect, it could also be due to negative effects of furosemide, for example secondary to hypovolemia.

Renal effects of dopamine after cardiac surgery (Paper II)

The main finding of Paper II was that dopamine, at the infusion rates of 2 and 4 μg/kg/min, does not affect RVO_2 or GFR in cardiac surgery patients. Instead, it showed that dopamine increases RBF and, thus, increases the renal oxygenation, as reflected by the decrease in renal oxygen extraction.

In Paper II, dopamine induced an increase in RBF of 45-55%, as assessed by two independent techniques, and these results are in accordance with most clinical studies (75, 78, 101). It has been argued that the increase in RBF, by dopamine, is not necessarily caused by a more or less selective decrease in renal vascular resistance, but could as well be attributed to a dopamine-induced increase in cardiac output (49). Data from the present study does not support this view, as the RBF/CI ratio increased significantly with dopamine, suggesting that dopamine induces a more pronounced decrease in renal vascular resistance compared to systemic vascular resistance.

There is a controversy in the literature regarding the effects of dopamine on GFR in man, as assessed by the use of isotope or inulin clearances. Some studies have shown an increase in GFR (75, 78), whereas some have found no effect of dopamine on GFR (59, 76). To our knowledge, there is no previous study on the effects of dopamine on RBF and GFR in post-cardiac surgery patients. In Paper II it was shown that dopamine did not affect GFR, indicating that dopamine had a balanced effect on afferent and efferent arterioles, maintaining the filtration pressure constant.

Dopamine had no effect on the filtered load of sodium, sodium reabsorption or RVO_2, which is explained by the lack of effect on GFR. Similarly, low dose dopamine had no effect on RVO_2, in patients with malaria sepsis (101). However, dopamine has been shown to induce natriuresis, due to its inhibitory action on sodium reabsorption of the proximal tubules (77). It has been proposed that this inhibition may increase the delivery of sodium to the medullary nephrons, which will increase their sodium reabsorption and, consequently, their oxygen consumption. This may, in turn, have the potential to impair renal oxygenation of the medulla, which has low oxygen tension during normal conditions (49). However, this is unlikely to occur, according to the findings of Paper II, as dopamine improved total renal oxygen supply/demand by 50%. In addition, experimental studies have shown that dopamine causes a relatively higher increase in blood flow to the inner cortex and the medulla than to the outer cortex (102) and that this vasodilatory effect of dopamine alleviates medullary hypoxia when medullary blood flow is already

compromised (103). The dopamine-induced decrease in PAH extraction also indicates a redistribution of blood flow from outer cortex to inner cortex and medulla in Paper II, as the PAH extraction has been found to be lower in juxtamedullary nephrons than in the cortical nephrons (104).

Some small studies have assessed the effects of dopamine on serum creatinine levels after elective coronary artery bypass surgery in low risk patients and found no difference in serum creatinine or creatinine clearance compared to control (100, 105-107). It can provocatively be argued that that is not surprising, if dopamine has no effect on GFR and the risk for AKI in this category of patients is low. In any case, these studies incline that routine prophylactic "renal-dose" dopamine in low risk cardiac surgery is not recommended.

Dopamine has been shown to induce tachyphylaxis after a short period of infusion (24 hours) (108-110). It is, therefore, questionable whether any renal protective effect of long-term infusion (days) of dopamine could be expected, in ongoing AKI. Hence, there was no beneficial effect on peak creatinine in patients with SIRS and AKI, who were treated with dopamine (2μg/kg/min) for a mean of five days (52).

On the other hand, low dose dopamine may have the potential to exert beneficial renal effects when used prophylactically in high-risk patients, exposed to well-defined episodes of renal ischemia, as e.g. in patients undergoing major cardiac or vascular surgery. So far, the preventive effects of dopamine have not been tested in such a clinical setting.

In conclusion, we have shown, in post-cardiac surgery patients, that dopamine (2 and 4μg/kg/min) improves renal oxygenation, as it causes a renal vasodilatation of both afferent and efferent arterioles, with a 45-55% increase in RBF and no apparent effect on GFR or RVO_2. However, further studies are needed to determine whether dopamine is of value, as a renal protective agent, in selected populations.

Acute kidney injury after cardiac surgery (Paper III)

Patients with AKI had a GFR and a sodium reabsorption that were only 40% of the values of the control group. Despite this, their RVO_2 was not significantly different from the control patients, who had no renal impairment. In addition, RBF was 35 - 40% lower than control patients, in turn caused by renal vasoconstriction. Consequently, the renal oxygen supply/demand relationship was severely impaired in AKI, as demonstrated by the almost 70% increase in renal oxygen extraction.

Acute renal failure is not an "acute renal success"

Data on RVO_2 and renal oxygenation clinical AKI has been lacking. Nevertheless, many authors have advocated a hypothesis, in which acute renal failure has been described as an "acute renal success"(28, 31, 37-40). The rationale is that a reduction in GFR, in AKI, should lead to a reduction of the renal reabsorptive workload and a reduction of RVO_2. The

decreased RVO_2 should, thus, preserve medullary oxygenation and reduce the risk of further aggravation of ischemia.

However, our findings do not support that hypothesis. Instead, the AKI-patients had a high oxygen consumption despite the decrease in GFR and sodium reabsorption. Acute renal failure can, therefore, not be described as an acute renal success.

Renal vascular resistance and renal blood flow

Previous reports on RBF in acute renal failure, particularly in the critical care setting, are scarce (36). In Paper III it was found that RBF was decreased by 35 – 40%, caused by a 52% higher renal vascular resistance in the AKI group, compared to control. These findings are in line with the limited previous data on patients with clinical AKI (36). The decrease in RBF in AKI has been attributed to afferent arteriolar vasoconstriction caused by e.g. circulatory vasoconstrictors (catecholamines, angiotensin II, endothelin), NO-deficiency, tubuloglomerular feedback mechanism and/or ischemic endothelial cell injury (18, 29, 111).

Renal oxygen consumption (and sodium reabsorption)

It is well established that the rate of oxygen utilization by the kidney consists of an oxygen cost of active sodium reabsorption plus a basal oxygen consumption. The AKI-patients had a high oxygen consumption despite the decrease in GFR and sodium reabsorption and this could, thus, be due to an increase in basal renal oxygen consumption, e.g. due to renal inflammation or increased oxygen stress (18, 112). On the other hand, it could also be coupled to the oxygen consuming sodium reabsorption. A linear regression gives an estimate of the relative contributions of these two components on RVO_2 (Figure 14, lower; page 40).

Basal renal oxygen consumption: Although one should be cautious when extrapolating regression lines, the intercept between the regression line and the y-axis indicates the basal RVO_2 of the studied subjects. In the control group, the estimated basal renal oxygen consumption was 8.3 µl/min/gram kidney, about ¼ of mean oxygen consumption. This is a somewhat lower than previously found in dogs (25). To calculate this, an assumption of a kidney-weight of 300 gram/1.73 m^2 was made. The AKI group had a calculated basal oxygen consumption that did not differ significantly from the basal oxygen consumption of the control group. Hence, it cannot be concluded that the high RVO_2 in AKI was caused by an increase in basal renal oxygen consumption.

Oxygen consumption coupled to sodium reabsorption: The control group consumed a mean of 0,82 (±0,06) ml oxygen per mmol sodium reabsorbed, which is in line with previous animal experiments (24, 25). However, in distinct contrast to this, the AKI group consumed a mean of 1.94 (±0.36) ml oxygen per mmol sodium reabsorbed. Thus, net-reabsorbing a certain amount of sodium, consumed 2.4 times more oxygen in the AKI group than in the control group. In other words,

our data indicates that the relatively high RVO_2 in AKI was linked to the sodium reabsorption.

One can only speculate on the exact mechanism behind this. However, two different potential explanations for the pathologically high oxygen consumption for sodium reabsorption are: ischemia-induced loss of epithelial cell-polarisation (113, 114), and intra renal NO-deficiency (115, 116).

Ischemia-induced loss of epithelial cell-polarisation and loss of tight junction integrity: Normally sodium enters the tubular cell passively though the apical membrane, due to concentration gradient. It is then actively pumped by Na^+/K^+-ATPase out of the basolateral membrane to the interstitium from where it is absorbed into the peritubular capillaries (Fig. 17) (16). To retain this efficient vectorised reabsorption of sodium and solutes from the tubuli to the peritubular circulation, it is mandatory that the epithelial cells are polarised and that the integrity of the tight junctions are maintained(117,118).
However, it has been

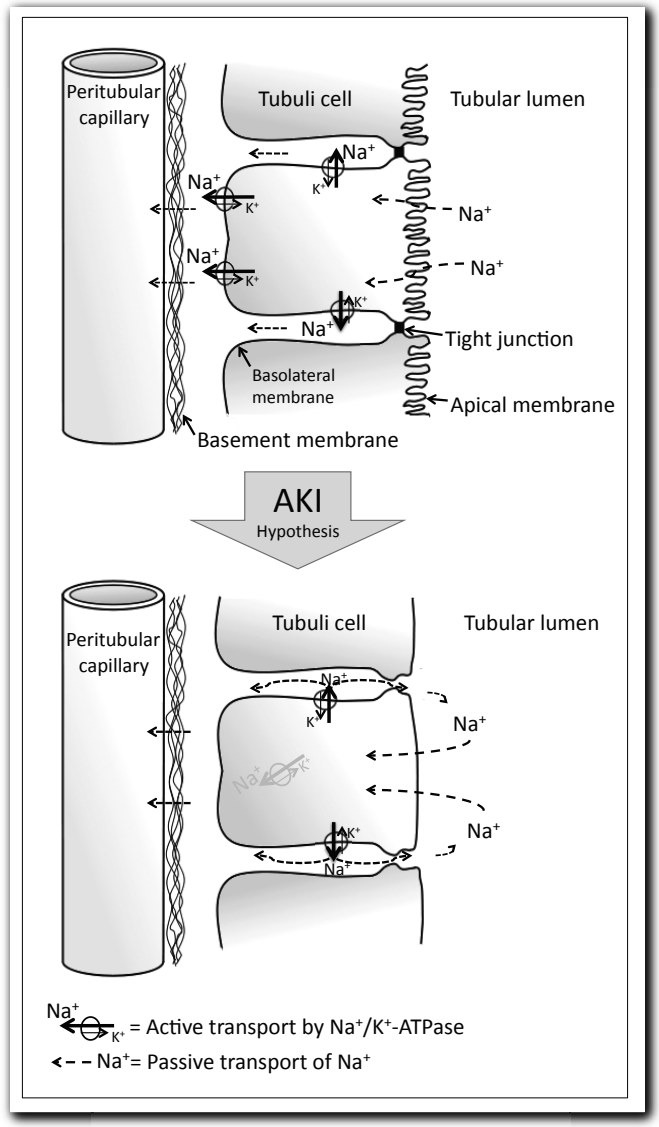

Figure 17. Efficient vectorised sodium reabsorption is dependent on polarised epithelial cells and intact tight junctions. Tubular damage in AKI has been shown to depolarise tubular cells and disrupt tight junctions. A vicious circle, where reabsorbed sodium-ions leak back to the tubuli to be reabsorbed again, might explain the high oxygen utilization in AKI.

shown, both in experimental studies and after human renal transplantation, that proximal tubular cells lose their polarity and the tight junction integrity in AKI, secondary to cytoskeletal disruption (113, 114, 119, 120). Thus, with their loss of polarity, the tubular cells lose their ability to efficiently pump in a specific direction, from one compartment to another (121, 122). Despite this loss of direction, Na^+/K^+-ATPase has been found to retain its Na^+ pumping activity (122) and it has been proposed that this could result in a futile cycle, with vectorised transport of sodium uncoupled from ATP utilization and oxygen consumption (Figure 17, lower) (118).

NO-deficiency: The high oxygen cost for sodium reabsorption could also be due to decreased NO-availability in AKI (16, 18). This lack of NO has been attributed both to ischemic endothelial cell injury causing an imbalance in the production of endothelin and endothelial NO, and angiotensin II-induced reactive oxygen species (ROS) that inactivates NO (18, 28, 116). Thus, it has been shown, in dogs, that NO-synthase blockade decreased RBF, GFR and sodium reabsorption, but increased RVO_2 (115). In fact, inhibition of NO synthesis more than doubled the ratio of oxygen consumption per sodium reabsorbed, suggesting a reduction in renal efficiency for transporting sodium, similar to the finding in Paper III. The exact mechanism behind this inefficient utilization of oxygen for chemical work, in NO deficiency, is not clear. However, NO regulates the mitochondrial respiratory chain, binding to the oxygen binding sites, and NO-synthase blockade also enhances oxygen usage at a given level of work in other tissues (116). Furthermore, in the previously mentioned study (115), RVR increased significantly after the NO-synthase blockade, a finding in accordance to Paper III.

Renal oxygenation

The decreased renal oxygen delivery together with the high oxygen cost for sodium reabsorption, in the AKI group, induced a severe impairment of the renal oxygenation. The, renal oxygenation was most affected in patients studied early after surgery, as shown by the significant correlation between renal oxygen extraction and day after surgery (Figure 15, page 41). Moreover, three patients, in the AKI group, were studied two days after surgery. They all had lower RBF than any of the patients studied later. Together this supports the opinion, from the animal models of AKI, that RBF and renal oxygenation is most affected in the initiation and extension phases, early in AKI.

The level of GFR, on the other hand, had no significant effect on renal oxygen supply/demand in the AKI subgroup (Figure 15, page 41), due to decreases in RBF, proportional to the decreases in GFR. There was, thus, no difference in renal oxygen supply/demand relationship, between those with the highest GFR and those with the lowest GFR in AKI, which could indicate that renal oxygenation is equally affected in mild and severe AKI.

In conclusion, in this study on hemodynamically resuscitated high-risk patients with postoperative AKI, renal oxy-

genation was severely impaired. This was caused by a combination of renal vasoconstriction and a tubular sodium reabsorption at a high oxygen demand. This indicates that renal hypoxia may be present also after the initiation phase of AKI.

Renal effects of norepinephrine in acute kidney injury (Paper IV)

In Paper IV, the effects of norepinephrine-induced variations in MAP on RBF, GFR, RVO_2 and renal oxygenation, were evaluated in patients with norepinephrine-dependent vasodilatory shock and AKI after cardiac surgery. The main findings of the study were that restoring MAP from 60 to 75 mmHg increased renal delivery of oxygen, GFR and renal oxygenation. In contrast, a further norepinephrine-induced increase in MAP to 90 mmHg only increased RVR with no additional changes in renal perfusion, filtration or oxygenation.

Norepinephrine-induced elevation of renal perfusion pressure increases RVR in two ways: by α_1-mediated direct vasoconstriction and by pressure-dependent renal autoregulation, i.e. provided that the blood pressure is within autoregulatory limits (123). It has been shown that autoregulation is responsible for more than 90 % of the increase in RVR after α_1-stimulation in dogs (123). Thus, it might be expected that norepinephrine should decrease RBF and GFR, only to a minor extent, when the blood pressure is raised within the autoregulatory limits. However, when the blood pressure is below the lower limit, the conclusion could be drawn that norepinephrine should increase RBF and GFR, as the positive effect of an increase in blood pressure should outweigh the α_1-mediated direct vasoconstriction. However, the autoregulatory limits are not known in humans, and these limits most certainly differ between subjects depending on e.g. age, the presence and extensiveness of vascular disease, as seen in hypertension or diabetes, and the level of sympathetic stimulation.

Indeed, at a MAP of 75 mmHg, a higher GFR and RVO_2 was seen when compared to a MAP of 60 mmHg, implying that this pressure-interval at least partly is below the lower autoregulatory limit, and that the increase in perfusion pressure outweighed the increase in renal vascular resistance. In contrast, the increase in MAP from 75 to 90 mmHg did not further increase GFR or renal delivery of oxygen, probably as a consequence of an autoregulatory 25% increase in RVR.

The increase in GFR, from 60 to 75 mmHg, was due to an increase in filtration fraction and accompanied by increases in renal sodium filtration and reabsorption. However, despite this increase in GFR and renal sodium reabsorption, the renal oxygen consumption did not increase. The explanation for this disparity is not obvious, but it has been shown that norepinephrine causes an α_1 -mediated increase in proximal tubular sodium transport (124) with no effect on cellular oxygen consumption (125).

Renal delivery of oxygen was lower at MAP 60 mmHg than at MAP 75mmHg, while there were no difference in RVO_2,

Consequently, renal oxygen extraction increased when blood pressure was decreased from 75 to 60 mmHg, suggesting that renal oxygenation, might be further impaired in AKI when blood pressure is maintained below the lower limit of renal autoregulation. Increasing blood pressure from 75 to 90 mmHg did not affect renal oxygen extraction. This finding is in line with a recent study on healthy volunteers, in which it was shown that norepinephrine does not affect renal oxygenation, as assessed by the renal blood oxygenation level-dependent (BOLD) MRI signal (126).

Patients with and without diabetes mellitus

Two patients in the study had diabetes mellitus and they responded totally different to the increase in norepinephrine and MAP, compared to the non-diabetic patients. In fact, their GFR decreased by 41% and their renal vascular resistance increased by 134%, when MAP was increased from 60 to 90 mmHg (compared to GFR increasing 47% and RVR increasing 40% in the non-diabetic patients). However, this difference in response to norepinephrine might be explained by the known changes in vascular reactivity and renal physiology that occur in early diabetes (127). It has been shown that patients with diabetes mellitus have an exaggerated pressor responsiveness to norepinephrine and angiotensin II (127, 128) and diabetes has been considered to alter autoregulation of RBF and GFR (129). Thus, diabetes per se could explain the diverging renal response to norepinephrine, a finding which deserve further studies.

If the patients with diabetes were excluded from the analysis, RBF increased significantly while RVR did not, when MAP was increased from 60 to 75 mmHg.

In conclusion, we have shown that restoration of MAP from 60 to 75 mmHg improved renal oxygen delivery, GFR and renal oxygenation in post-cardiac surgery patients with vasodilatory shock and AKI. However, a further increase in MAP to 90 mmHg with norepinephrine did not influence these variables further. Thus, renal perfusion and filtration seems partly pressure-dependent at levels of MAP below 75 mmHg, reflecting a more or less exhausted renal autoregulatory reserve.

Conclusions

- After cardiac surgery, *mannitol* improves the glomerular filtration rate (GFR). This improvement is accompanied by increases in renal sodium reabsorption and renal oxygen consumption (RVO_2). As mannitol has no effect on renal blood flow (RBF) it impairs the renal oxygen supply/demand relationship.

- Low dose *dopamine* causes a 45-55% increase in RBF after cardiac surgery. This is caused by a pre and post-glomerular vasodilatation, with no increases in GFR, renal sodium reabsorption or RVO_2. Thus dopamine improves the renal oxygen supply/demand relationship.

- The renal oxygen supply/demand relationship is severely impaired in *acute kidney injury* (AKI) after cardiac surgery. This is caused by renal vasoconstriction and an abnormally high oxygen utilization for sodium reabsorption

- In patients with vasodilatory shock and AKI, a *norepinephrine*-induced increase in mean arterial pressure, from 60 mmHg to 75 mmHg, improves renal oxygen supply, GFR and renal oxygen supply/demand relationship. A further increase in mean arterial pressure, to 90 mmHg, does not improve renal variables further

Acknowledgements

This thesis could never have been accomplished without a substantial contribution from others. I would, therefore, like to express my warmest gratitude and appreciation to all of you, who, in one way or the other, made this thesis possible.

Sven-Erik Ricksten, my supervisor and tutor, who has always been accessible, guiding the project with careful and skilful hands. We have had many rewarding discussions, exploring the truth of acute kidney injury. Your great knowledge and catching enthusiasm is admirable. I especially remember the moment, when we found out that we could instantly measure the effects of an aortic balloon pump on RBF, your happiness beaming, filling the room and all of us with imminent excitement, not far from the excitement of a Christmas Eve from childhood. It is a pleasure to have had you as a supervisor.

Marita Ahlqvist, with whom I have spent many long days and evenings, reaching the night, trying to bring science forth. Some days, the data was easy caught, some days it was not. But you always held your temper up and I think that we managed to have a joyful time even when it really felt like we were walking in glue. I also must thank you for your willingness to work, whatever time of day or day of year; for analysing all data and spending loathes of time with excel; and for so happily taking on new tasks, completing them in no time.

Kristina Swärd, my predecessor in renal research. Thank you for being my co-supervisor.

Gudrun Bragadottir, my co-postgraduate mate and co-author. Thank you for the extensive work you have done on the patients in this thesis, for always being ready to help me and for the joy when we have cooperated in data collection lately.

Johan Sellgren, my co-author, for making the data collection devices up to date and for helping when problems have occurred.

Klaus Kirnö, former Head of Department of Cardiothoracic Anaesthesia and Intensive Care, who employed me and first gave me the opportunity to start this thesis. *Per Nellgård,* who was the last Head of Department of Cardiothoracic Anaesthesia and Intensive Care, and made it possible for me to continue my research. *Monica Hyllner*, who is my current Head in the line-organisation and has put an effort on optimising the conditions these last months. *Lars Wiklund*, who is my current Head of Department. *Björn Biber*, who is Head of Department of Anaesthesiology and Intensive Care, at the Sahlgrenska Academy. Thank you all for giving me the opportunity to work on this thesis.

Susanne Wilson, for all the work you are doing taking care of the renal vein catheters and keeping track of them both at Sahlgrenska and back and forth to Holland. Without your work, there would be no renal research in our department.

My *colleagues, the anaesthesiologists, cardiac surgeons, nurses, assistant nurses and perfusionists,* for always being helpful and supportive and for showing patience during the long sometimes difficult study procedures.

I also want to thank my *friends*, at this moment especially *Mathias Holm* (who really have other things to do right now) and *Berndt Johansson* for their contribution.

Last but not least I want to thank my family: my parents *Åsa* and *Arne*, for endless love and support, and an upbringing with and atmosphere of knowledge being fun; my sisters *Maria* and *Ylva*, my idols from youth and very close friends, and their families for days and weeks of fun. I especially want to thank *Petra*, my love and my wife, for love and for being the one you are, for putting up with nights of research without any complaint, for small things and large things and in the end for making my life a good and happy life, together with our children *Adrian, Alvin* and *Didrik*, who are the meaning of everything, really. Thank you boys for that! *Adrian*, you knew more about mannitol when you were seven, than most people learn in a lifetime. *Alvin*, you love words and this leads to funny jokes and a lot of writing. Before I wrote this story, I think you had written more stories than I had, but now we may be even. *Didrik*, you have so much love in your little body, keep on in that way.

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Populärvetenskaplig sammanfattning

Förebyggande åtgärder och behandling av akut njursvikt efter hjärtkirurgi

Njurens funktion är att rena kroppen från slaggprodukter. Detta gör den genom att blodet filtreras i njuren (ca 180 l/dygn). Slaggprodukterna lämnar kroppen via urinen medan 99 % av den filtrerade vätskevolymen återabsorberas till blodet. Denna återabsorption kräver mycket energi och förbrukar därmed mycket syre.

Akut njursvikt definieras som en relativt snabb nedsättning av njurens filtrerande förmåga. Sjukdomen är vanlig efter hjärtkirurgi och är associerad med hög dödlighet. Orsaken till akut njursvikt anses huvudsakligen vara minskat blodflöde till njuren med syrebrist som följd. Kunskapen om hur njurens syresättning påverkas av de läkemedel som oftast ges till dessa patienter saknas. Dessutom vet man inte hur njurens syresättning påverkas av njursvikten i sig. Detta har vi undersökt hos patienter efter hjärtkirurgi.

Mannitol: Mannitol används bland annat för att öka urinproduktionen vid akut njursvikt och i hjärt-lung maskinen vid hjärtoperationer. Man har dock inte kunnat visa att mannitol minskar risken för njursvikt. Vi studerade tio njurfriska patienter efter hjärtoperationen och fann att mannitol förbättrade njurens filtrerande förmåga. Denna förbättring skedde dock till priset av en försämring av njurens syresättning.

Dopamin: Dopamin har använts länge vid behandling av njursvikt eftersom dopamin ökar njurblodflödet och urinproduktionen. Man har dock inte kunnat visa att dopamin minskar risken för akut njursvikt och man har trott att detta beror på att dopamin eventuellt skulle kunna öka njurens syreförbrukning. Vi fann dock, hos tolv njurfriska patienter, att dopamin inte ökade njurens syreförbrukning, istället förbättrade dopamin njuren syresättning.

Akut njursvikt: Trots att man anser att akut njursvikt sätts igång av syrebrist så är inte njurens blodcirkulation eller syresättning vid akut njursvikt undersökt hos människa.

Normalt återabsorberar njuren nästan 180 liter/dag men vid akut njursvikt endast 10 – 90 liter per dag. Eftersom njurens arbete alltså minskar drastiskt vid akut njursvikt har man bedömt att njurens syreförbrukning troligen också minskar, vilket gör att njurens syresättning borde vara relativt god vid akut njursvikt.

Trettiosju patienter med normal njurfunktion jämfördes med tolv patienter med akut njursvikt efter hjärtkirurgi. Fynden visade, tvärt emot tidigare hypoteser, att njurens syresättning är ordentligt påverkad vid akut njursvikt. Detta beror både på att njurblodflödet är kraftigt sänkt och på att njuren arbetar väldigt ineffektivt och därmed konsumerar mycket syre trots litet återabsorptionsarbete.

Noradrenalin vid cirkulatorisk chock och samtidig akut njursvikt: Noradrenalin ges i dropp för att höja blodtrycket hos patienter som är i cirkulatorisk chock pga utvidgning av blodkärlen (vasodilatatorisk chock). Dessa patienter har spontant ett så lågt blodtryck att det inte är förenligt med liv. Olika doser noradrenalin höjer blodtycket olika mycket och man kan alltså ställa in vilket blodtryck en specifik patient skall ha. Ett högre blodtryck borde ge mer njurgenomblödning. Å andra sidan så verkar noradrenalin genom att dra ihop blodkärlen och mer noradrenalin kan således istället strypa njurblodflödet. Ingen har dock undersökt vilket blodtryck man skall sträva efter hos patienter i cirkulatorisk chock.

Tolv patienter, som efter hjärtkirurgi behandlades pga vasodilatatorisk chock med noradrenalin och som samtidigt hade akut njursvikt, undersöktes. Fynden visade att ett noradrenalin inställt medelartär tryck på 75 mmHg gav signifikant bättre syretillförsel till njuren, bättre syresättning av njuren och bättre filtration än vid ett medelartärtryck på 60 mmHg. När vi höjde medelartärtrycket till 90 mmHg förbättrades dock inte dessa variabler ytterligare.

Sammanfattningsvis har studierna alltså visat, på hjärtkirurgiska patienter, att mannitol förbättrar njurens filtration till priset av försämrad njursyresättning. Dopamin å andra sidan påverkar inte filtrationen men förbättrar njurens syresättning. Vidare har studierna visat att patienter i cirkulatorisk chock med akut njursvikt får en kraftig försämring av njurens syresättning, som blir ännu sämre om man inte håller uppe blodtrycket tillräckligt med noradrenalin. Den dåliga syresättningen beror på sänkt syretillförsel och hög syrgasförbrukning trots litet njurarbete.