A Study on Endoscopic Live Donor Nephrectomy and Elevated Intraperitoneal Pressure

BY

PERNILLA LINDSTRÖM
Live donor nephrectomy (LDN) is a unique surgical challenge where surgery is performed on healthy individuals. It is of great importance to keep the morbidity of donors as low as possible, as well as harvesting a kidney in optimal condition. Lowering morbidity is the motive for introducing the endoscopic technique in LDN. Oliguria and impaired kidney function can, however, be seen during pneumoperitoneum and endoscopic LDN have been criticized for not yet being proven safe enough.

The aims of this study were to investigate the changes in renal function during elevated intraabdominal pressure (IAP) in donors and rats and to evaluate donor morbidity and safety of the new endoscopic techniques compared to the open LDN.

In two studies, a rat model was used. It was found that elevation of IAP diminished glomerular filtration rate (GFR). Cardiac output (CO) and renal blood flow decreased as well. Elevation of IAP activates the renin system and aldosterone was increased. Acute angiotensin II receptor 1 blockade (candesartan) treatment lowered blood pressure significantly and impaired renal function during elevated IAP. Volume expansion prior to, and during, pneumoperitoneum reduces the deleterious effects on renal function.

Three studies on kidney live donors show that traditional laparoscopic surgery (TLS) takes longer time to perform than open LDN. Hand-assistance facilitates the operation and increases the safety margin as well as shortens the operation by 27% compared to TLS. Evaluation of a hand-assisted retroperitoneoscopy (HARS), performed for the first time ever in Uppsala 2001, show that the operation is short and safe, the donors experience little pain and the renal function is favourable compared to open surgery, TLS and hand-assisted transperitoneal laparoscopic approaches.

In conclusion, the results indicate that elevated IAP decreases GFR due to decreased CO and activation of the RAAS, which can be avoided with adequate hydration. Endoscopy can be facilitated if hand-assistance is applied and in particular hand-assisted retroperitoneoscopic nephrectomy shows advantages for the donor.

Keywords: Candesartan, cardiac output, glomerular filtration rate, hand-assisted laparoscopy, hand-assisted retroperitoneoscopy, kidney, living donor nephrectomy, morbidity, pneumoperitoneum, rat, renal transplantation.

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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>Ang II</td>
<td>Angiotensin II</td>
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<tr>
<td>BF</td>
<td>Blood flow</td>
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<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
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<tr>
<td>BW</td>
<td>Body weight</td>
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<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HALS</td>
<td>Hand-assisted laparoscopy</td>
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<td>HARS</td>
<td>Hand-assisted retroperitoneoscopy</td>
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<tr>
<td>IAP</td>
<td>Intra-abdominal pressure</td>
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<tr>
<td>i.v.</td>
<td>Intra-venous</td>
</tr>
<tr>
<td>KW</td>
<td>Kidney weight</td>
</tr>
<tr>
<td>LD</td>
<td>Living donor</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>N-ANP</td>
<td>N-terminal natriuretic peptide</td>
</tr>
<tr>
<td>PP</td>
<td>Pneumoperitoneum</td>
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<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>TLS</td>
<td>Traditional laparoscopy</td>
</tr>
<tr>
<td>VE</td>
<td>Volume expansion</td>
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<td>WIT</td>
<td>Warm ischemia time</td>
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INTRODUCTION

Renal transplantation is the optimal treatment for end stage renal disease. It is associated with a lower morbidity and mortality than dialysis treatment (Meier-Kriesche, 2001, Meier-Kriesche, 2000) and it is also more cost effective (Johnsson, 2002, Laupacis, 1996). A requirement for transplantation is donation. There are two sources of renal donors; cadaveric and living donors. Despite big efforts, the source of cadaveric donors diminishes in many countries (Scandiatransplant, Registry Data 2002). At the same time, the number of patients treated for end stage renal disease is increasing with about 4% per year (USRDS, Registry Data 2002, Schön, 2001) As a result the waiting list for a kidney transplantation is steadily increasing (UNOS, Annual Data Report 2001, Scandiatransplant, Registry Data 2002). The increasing waiting list for cadaveric kidneys and the superior results of kidney transplantation from live donors (Cecka, 1998, Lindholm, 1993, Medin, 2000, Terasaki, 1995) have brought living donor issues to the forefront of the transplantation arena, with a development of new and better surgical techniques for donor nephrectomy. This thesis examines new surgical techniques in living renal donation and their influence on kidney function as well as donor morbidity. Furthermore, the thesis investigates the changes in renal function during elevated intra-abdominal pressure.

Historical landmarks

The first renal transplantation on a dog was reported in 1902 by Ullman (Ullman, 1902), but renal transplantations first became clinical praxis in the 1950’s, when the first successful transplantation was performed between a pair of identical twins by Murray in 1954 (Murray, 1955). When effective immunosuppression was introduced by Starzl and Calne (Calne, 1960, Starzl, 1963), successful transplantation between non-identical individuals (allotransplantation) became clinical reality in the 1960’s. Curt Franksson performed the first renal transplantation in Sweden in 1964 (Jepsson, 2001).

Laparoscopy, minimal invasive or keyhole surgery, became widely used in the early 70’s by gynaecologists. As improved light systems and the videoscope were introduced, the general surgeons followed in the late 80’s with laparoscopic procedures. The minimally invasive surgery was spread all over the world extremely fast, though there was a lack of
scientific evidence to prove its safety. There was a growing demand from patients for laparoscopic surgery both for cosmetic and economic reasons. The development was also driven by surgeons, as both hospital stay and convalescence were shortened.

The feasibility of laparoscopic transperitoneal nephrectomy was reported in 1991 by Clayman. The laparoscopic operation was accomplished in an elderly male using a stapler device to divide the renal vessels. The diseased kidney was morcellated and retrieved by an endoscopic retrieval bag (Clayman, 1991). Gill reported of a technically reproducible pig model for laparoscopic harvest of kidneys assigned for renal donation (Gill, 1994). Only a year later, Ratner et al (Ratner, 1995) gave a case report on the first laparoscopic nephrectomy from a 40-year old male for living donor transplantation, that was successfully transplanted to the donor’s sister.

The living donor

As the number of transplantations increased and better methods to preserve the graft without circulation developed, as well as a more distinct legislation concerning donations and brain death, the cadaveric donors became the main source of organs for kidney transplantation. However, due to the increasing waiting times for cadaveric transplantation and the significant better results with living donor transplants the interest for transplantations from living donors is increasing again. This interest has grown rapidly in later years as there is no longer any need for HLA matching with modern immunosuppression and more importantly, it has recently been shown that not only morbidity but also patient and graft survival is significantly improved with shorter time on dialysis prior to transplantation (Meier-Kriesche et al., 2001). Living donor transplantation is really the only alternative if you want to shorten the time on the waiting list or even to perform the transplantation before starting dialysis.

Almost 40% (118 of 305) of renal transplantations are performed with grafts from living donors in Sweden today (OFO, Registry Data 2002). The donors volunteer to donate to a loved one and do not have to be genetically related to the recipient. Spouses, close friends and step-parents, for example, are nowadays considered for donation as well as siblings and parents.

The donor visits the doctor and social worker several times for information and discussions. Potential donors are extensively examined before they are accepted. The purpose of the examination is to test the suitability of the donor for a specific recipient with a check
for blood group compatibility and negative cross match. A further purpose is to rule out renal, systemic and contagious diseases and to assess and minimise the short and long term risks of donor nephrectomy. About two thirds of the potential donors are not accepted (Trevitt, 2001).

Grafts from living donors actually show better results than cadaveric kidneys (Cecka, 1998, Lindholm, 1993, Medin, 2000, Terasaki, 1995) and the recipients prefer a kidney from a close relative (Sanner, 1998). There are several advantages with the living donor transplantations. First of all, the donor is healthy. Furthermore, the procedure is performed as an elective operation, which means that the recipient can be in optimal condition and the immunosuppression can be initiated before the transplantation. The recipient also avoids a prolonged time on dialysis. Finally, the ischemia time can be kept at a minimum, as the nephrectomy and transplantation operations can be performed simultaneously in neighbouring operating rooms.

Several long-term studies on renal donors have been made. Perioperative mortality is approximately 0.03%-0.06% (Najarian, 1992, Bay, 1987). The glomerular filtration rate (GFR) is reduced by half during the nephrectomy, but within a few weeks, GFR is increased and reaches 66-75% of the preoperative value (Fehrman-Ekholm, 2001, Blohme, 1992, Mathillas, 1988). There is no accelerated loss of renal function after donation. Hypertension (in 15-38-%) and proteinuria (in 9-38%) develop in long-term follow-ups, but there is no evidence that donation is a long-term risk for the donors’ health, though a careful selection of donors is necessary (Fehrman-Ekholm, 2001, Mathillas, 1988, Goldfarb, 2001, Talseth, 1986). Donors are proud of their act and their quality of life is increased compared to the rest of the population (de Graaf Olson, 2001, Corley, 2000, Johnson, 1999, Johnson, 1997, Westlie, 1993, Jacobs, 1998).

The kidney

A primary function of the kidney is the regulation of the extracellular fluid volume and composition. The kidney achieves a constant composition of the extracellular fluid by regulating the concentrations of sodium, potassium and hydrogen ions and excreting end-products of metabolism. Hormones, such as renin, erythropoietin and the active form of D-vitamin, calcitriol, are produced in the kidney.

The kidney consists of 1 million nephrons, each capable of producing urine itself. The nephron consists of a glomerulus, a spool of branching capillaries, through which fluid is
filtered from the blood. The fluid, or ultrafiltrate, is passed into Bowman’s capsule and flows through the different parts of the tubule and finally into the collecting duct and empties into the renal hilus.

The kidneys receive about 20% of the cardiac output during resting conditions. The kidneys autoregulate renal blood flow to achieve a relatively constant renal blood flow despite changes in systemic blood pressure. About 20% of renal plasma flow is filtered in the glomeruli as primary urine or ultrafiltrate. The fraction of plasma that is not filtered in the glomeruli continues to the renal vein. The production rate of ultrafiltrate is called the glomerular filtration rate, GFR. The composition of the ultrafiltrate is changed passing through the tubular system on its way to the bladder; this allows the kidney to adjust the amount of water and electrolytes excreted in the urine, according to the current situation in the body. (Guyton, 1991)

**Hormonal regulation**

Renin is formed in the kidney, released in response to decreases in renal blood flow and acts as an enzyme, converting angiotensinogen into angiotensin I. Angiotensin I has weak vasoconstrictor properties, but its main function is to be a pro-hormone that is broken down by angiotensin converting enzyme (ACE) to angiotensin II (Ang II). Angiotensin II is a strong vasoconstrictor. Vasoconstriction leads to an increase in vascular resistance and a rise in blood pressure. Aldosterone is secreted from the adrenals by stimulation of angiotensin II. Aldosterone increases reabsorption of sodium in the distal part of the tubules and collecting ducts. (Guyton, 1991)

Atrial natriuretic peptide (N-ANP) is produced by the myocytes of the cardiac atrium and is secreted when the myocytes are stretched as a result of volume expansion and pressure overload. ANP stimulates the kidneys to excrete sodium and water. (Guyton, 1991)

B-Type natriuretic peptide (BNP) is a neurohormone secreted from the cardiac ventricles in response to the same stimuli as ANP (Suzuki, 2001).

Anti-diuretic hormone (ADH) or vasopressin is a peptide produced in the hypothalamus and is released when serum osmolality increases. Urine is concentrated in the presence of vasopressin, as the collecting ducts become more permeable for water to exit the ducts. (Guyton, 1991)
Noradrenaline is secreted in nerve endings of sympathetic nerves. On sympathetic activation of the adrenals, noradrenaline and adrenaline are secreted into the blood and act as vasoconstrictors. The sympathetic effects on the kidney are vasoconstriction and subsequently a decrease in GFR and renin release. (Guyton, 1991).

Endothelin is released from vascular endothelium in response to several stimuli, for instance; blood pressure changes and angiotensin II. Endothelin acts as an vasoconstrictor and constricts renal vascular endothelium, thereby reducing GFR. Sodium absorption is enhanced and aldosterone released (Simonson, 1993, Simonson, 1991).

**Laparoscopy**

During laparoscopic surgery, access to the abdominal cavity is achieved by using a Veress needle or by a mini laparotomy. Carbon dioxide gas is then insufflated into the abdominal cavity creating pneumoperitoneum. By insufflation of CO2 working space is created. A trocar is then inserted through the abdominal incision. The trocars or ports are furnished with valves, which make it possible to easily take instruments in and out without loosing pneumoperitoneum. To be able to see, a videoscope is inserted to the cavity through the port and the image is shown on TV monitors. Additional working ports, with a diameter of 5-15 mm are introduced for the surgical instruments. HandPort™ is a hand-assistance device. It is a large port with a sleeve, which allows the surgeon’s hand to enter the abdominal cavity without loosing pneumoperitoneum. The incision that has to be made for the HandPort™ has the size of the width of the surgeon’s hand.

**Pneumoperitoneum**

Elevated intra-abdominal pressure (IAP) is seen in a variety of situations; natural variations in intra-abdominal pressures are seen in different body positions and when a person is laughing, coughing, vomiting or carrying things (Chevrel, 1998). Prolonged intra-abdominal hypertension is seen for example during peritoneal dialysis, ascites, intra-abdominal bleeding after surgery or trauma and during laparoscopic surgery (Richards, 1983, Harman, 1982, Zakaria, 1995).
During laparoscopy, pneumoperitoneum is created by insufflation of carbon dioxide into the abdominal cavity. The pressure used to be up to 40 mmHg, but the pressure level has decreased over time and is now generally below 15 mmHg.

Different insufflation gases have been investigated. Room air, because of its oxygen content is not used, as electrocoagulation cannot be utilized due to the risk of explosion. Nitrogen carries a greater risk of gas embolism than carbon dioxide without showing any benefits over CO₂. It is therefore not used in clinical praxis. (Aneman, 2000). Argon and helium reduces renal blood flow equally compared to carbon dioxide, though argon reduces liver blood flow more than CO₂ and helium. Both are, however, expensive gases and still carry the risk of gas embolism (Junghans, 1997, McDougall, 1996). The carbon dioxide gas is chosen in the clinical situation because of the low price, it is easy to handle, does not burn or explode, can be eliminated easily through ventilation and carries a low risk of gas embolism (Fahy, 1999).

**Effects of pneumoperitoneum**

During laparoscopic procedures and pneumoperitoneum, several pathophysiologic changes are seen. There are two major causes for these changes: the elevated intraperitoneal pressure and the insufflated gas.

The carbon dioxide is absorbed into the tissues and hypercarbia develops, unless the ventilation is increased.

Pneumoperitoneum leads to a decrease in renal blood flow, GFR and oliguria. (Razvi, 1996, Hamilton, 1998, Dolgor, 1998). The oliguria is transient, and after desufflation, the diuresis is normalized or elevated (Nishio, 1999, Chang, 1994, Chiu, 1996, Lindberg, 2002). There are no reported cases of renal failure after laparoscopic procedures, though one graft failure after laparoscopic harvest is thought to be an effect of intraoperative ischemia (Nakache, 2000). In an early report comparing laparoscopic and open nephrectomies for renal transplantations, the creatinine clearances of the recipients were higher during the first month post transplantation in the laparoscopic groups compared to the recipients of the open group (Nogueira, 1999). Histological examination of rat kidneys, two weeks and three months after pneumoperitoneum did, however, not show any morphological changes (Hazebroek, 2002a, Lee, 1999).

The pressure of pneumoperitoneum is transmitted to the large central veins. It is shown that blood flow is slower and the veins are enlarged in the lower extremities (Wazz, 2000), which could result in an increased risk of thrombosis. There is also an activation of the coagulation system during laparoscopic procedures (Lindberg, 2000). The frequency of phlebography-verified deep vein thrombosis seen in a screening study was however low (0-6%) (Lindberg, 2002).

The increased pressure in the large veins thus impairs venous return. There are reports of both increased and reduced cardiac output (Elliott, 1998, Andersson, 1999, Cisek, 1998, Dexter, 1999, McDougall, 1996, Ortega, 1996). An increase in systemic vascular resistance is often seen (Walder, 1997, Mikami, 1998, Agusti et al., 2001, Harman et al., 1982) and could be associated with a hormonal response, such as hormones of the renin-angiotensin-aldosterone system, anti-diuretic hormone (ADH) and/or endothelin.

Angiotensin II could be formed upon an increase of intra-abdominal pressure with CO₂, when renal blood flow is decreased. Angiotensin II production gives rise to the formation of aldosterone. An increase in serum-aldosterone levels has been shown in a pig pneumoperitoneum model (Chiu, 1996). The up-regulation of hormonal output of the renin-angiotensin-aldosterone system has been studied during elevated intra-abdominal pressure created by fluid instillation. Both renin activity and aldosterone levels are increased by elevated intra-abdominal pressure, but return towards baseline levels with intra-venous volume expansion (Bloomfield, 1997).

An important factor in laparoscopic surgery is the position of the patient. In gynaecological procedures, the patient is placed in a head-down tilt (Trendelenburg), whereas during surgery in the upper part of the abdomen the patient has a head-up tilt (reverse Trendelenburg). During live donor nephrectomy the donors are placed horizontal, in a flank position. Venous return is increased in a head-down position, with an increase in pulmonary wedge pressure and decreased pulmonary compliance. In the reverse Trendelenburg position, venous return is diminished not only by pneumoperitoneum, but also by gravity (Hirvonen, 1997, Junghans, 1997, Odeberg, 1994).
During retroperitoneoscopy, the gas is insufflated outside the peritoneum. This has been shown to have less cardiovascular and pulmonary effects compared to pneumoperitoneum (Chiu, 1995, Giebler, 1997), though there are no differences in urinary output between pneumoretroperitoneum and pneumoperitoneum (McDougall, 1996).

**Live donor nephrectomy**

Nephrectomy (kidney removal) for donation demands a functionally and structurally intact kidney. The incision and surgical dissection down to the kidney can be made with several different techniques, where basically the route to the kidney differs (see Methods), but the main features of the surgery are the same.

The donor is generally anaesthetised. The surgeon gains access to the retroperitoneal space, where the kidney is situated, through open surgery (flank or anterior incision with transperitoneal or retroperitoneal approach) or by endoscopic techniques (laparoscopy, hand-assisted laparoscopy, retroperitoneoscopy, hand-assisted retroperitoneoscopy or video-assisted open nephrectomy). Gerota’s fascia that surrounds the kidney is opened. The artery and vein are carefully dissected free from the surrounding tissue all the way to the aorta and caval vein on the right side and proximal to the gonadal and supra-renal veins on the left side. The right renal vein is rather short, as the caval vein runs close to the kidney. The purpose of this dissection is to achieve vessels long enough to anastomose them to the recipient’s iliac vessels. The ureter is carefully dissected with preservation of the vascular supply of the ureter to avoid ureteral complications and necrosis of the distal ureter in the transplanted kidney. When the kidney is loosened from its attachments, the ureter is cut between clips or ligatures. The artery is then clamped or cut between staples, which means that the warm ischemia time (WIT) has started. The renal vein is ligated and cut as well and the kidney is retrieved. An awaiting surgeon takes the harvested kidney to a back table where the kidney is put on iced saline and perfusion of the kidney with a cold solution is started with a cannula placed in the cut renal artery. When the perfusion is established, the warm ischemia time stops and the cold ischemia time starts. The harvested kidney is prepared and the transplantation is continued in the room next door, where the operation of the recipient has already started in order to keep the cold ischemia time as short as possible.
**Surgical approaches**

The donor nephrectomy has been done with a flank incision for many years and the technique has been proven to be safe with a mortality of about 0.03-0.06 % (Najarian, 1992, Bay, 1987). The procedure is well documented and is the gold standard to which we can compare newer surgical techniques. Drawbacks of the flank incision are a sometimes poor cosmetic result and a relatively long convalescence (Blohme, 1992). There is also a risk of herniation or muscle relaxation due to nerve injury. This complication is often associated with neuralgia. Both conditions are difficult to treat. The most common surgical complication with flank incision is pneumothorax (Waples, 1995, Taghavi, 2001).

Another approach for the open surgery is the somewhat smaller anterior subcostal incision, which can be made trans- or retroperitonealy (Ruiz, 1980, Blohme, 1981). The working space can be quite narrow and deep, especially in obese donors. There is no need for resection of a rib and the postoperative discomfort is thereby less than with the flank incision. The transperitoneal technique carries a greater risk of splenic injury and splenectomy (Ruiz., 1980).

To lessen the discomfort and morbidity, but also in an attempt to increase the number of donors, laparoscopic live donor nephrectomy was introduced as described above. Although no large prospective randomised trails have been performed comparing open and live donor nephrectomies there is now good evidence that endoscopic nephrectomy does reduce pain and discomfort (Wolf, 2000, Jacobs, 2000, Stifelman, 2001, Ratner, 1999).

However, there are some drawbacks of the procedure. The most common reason reported for converting a laparoscopic operation into open surgery is vascular injury (Ratner, 1997b) (Jacobs et al., 2000). Major bleeding is difficult to handle with laparoscopic instruments alone. With the aim to improve the safety of the technique, and to make use of the incision that has to be made for harvesting the kidney, hand-assisted transperitoneal laparoscopy (HALS) was introduced (Wolf, 1998).

The first retroperitoneoscopic nephrectomy was reported by Gaur (Gaur, 1993), followed by other reports of retroperitoneal approaches. Yang (Yang, 1994) reported the first retroperitoneal video-assisted live donor nephrectomy.

Visceral injury is the second most frequent complication encountered in urologic laparoscopy (Fahlenkamp, 1999). These injuries can be difficult to detect during pneumoperitoneum and are often discovered postoperatively (Deziel, 1993).
The retroperitoneal technique does not insult the viscera. Thus, the benefits of the two techniques, i.e., hand-assistance – for increased control and confidence with the endoscopic technique, and the retroperitoneal approach – to minimize the risk of short- and long-term complications associated with the transabdominal approach, were combined as hand-assisted retroperitoneoscopy (HARS) (*study V*).

The endoscopic technique has now found widespread acceptance in live donor nephrectomies, though some concerns still remain, mainly concerning the operative technique and its safety, but also the renal function of both donor and recipient. In this study we have focused on issues concerning kidney function in connection with elevated intra-abdominal pressure and endoscopic live donor nephrectomy as well as questions regarding safety and morbidity of the donor.
AIMS

The general purpose of this study was to gain more knowledge about renal function during elevated intra-abdominal pressure, in particular during endoscopic live donor nephrectomies. The purpose was also to assess the potential benefits of endoscopic live donor nephrectomy in terms of lowering morbidity.

Studies were undertaken with these specific objectives:

I To investigate changes in renal function in connection with increased intra-abdominal pressure in a rat model. In particular, we wanted to investigate whether the renin-angiotensin-aldosterone system is significantly involved. This was done by administration of an angiotensin II receptor I antagonist. In addition, volume expansion was performed during elevation of intra-abdominal pressure.

II To examine the hemodynamic changes and alterations in organ blood flow occurring during elevation of intraperitoneal pressure in a rat model.

III To study the different surgical techniques of living donor nephrectomy and their impact on donor peri- and postoperative morbidity, as well as the effects of the different surgical techniques in regard to renal function.

IV To evaluate the hand-assisted laparoscopic technique in live donor nephrectomies in comparison to traditional laparoscopic nephrectomies.

V To examine and report of the first ten endoscopic live donor nephrectomy by combining hand-assistance and retroperitoneoscopy.
MATERIAL AND METHODS

Two of the studies (*study I and II*) are experimental *in-vivo* studies and three are clinical studies (*study III, IV and V*). To simplify the presentation, the methods are presented separately.

**Experimental studies (study I and II)**

**Animals**

The independent Local ethics committee approved the experiments. A total number of 82 male inbred Dark Agouti rats were used. They were bred at B&K International, Sollentuna, Sweden, weighing 200-293 g. Animals were stabled at Laboratory Animal Department, Biomedical Centre, Uppsala, for ten days to acclimatise prior to the day of the experiment, with free access to tap water and standard rat chow.

**Anaesthesia**

The animals were anaesthetised by gas anaesthesia with halothane (Fluothane®, AstraZeneca, Macclesfield Cheshire, UK). The rats were placed in a box and anaesthesia was induced and maintained by 3% and 1.75% halothane, respectively. The gas was delivered through a breathing mask while cannulating the trachea and then the rats were ventilated in a small animal ventilator (Rodent Ventilator Model 683, Harvard Apparatus Inc, MA, USA) with 33% oxygen in air. The acid-base balance (Compact 3, AVL Scientific Corp, Roswell, GA, USA) was measured and the respiration rate adjusted accordingly to keep arterial pCO₂ within normal range. The rats were placed on a servo-regulated heating pad with a rectal probe to maintain their body temperature at 37.5° C.

**Preparatory surgery**

Polyethylene catheters were placed in the left jugular vein for maintenance infusion and drug administration and in the left carotid artery for blood sampling and monitoring of mean
arterial pressure (MAP). For study II, the catheter in the carotid artery was inserted under pressure monitoring to immediately above the aortic valves for blood sampling and injection of microspheres. Additional catheters were introduced into the femoral arteries; in study II, the left artery for withdrawal of blood during cardiac output measurements and the right artery for blood pressure monitoring.

In both studies I and II, the abdomen was opened by a small low midline incision and the urinary bladder was catheterised for urine collection. Two polyethylene catheters were put through the abdominal wall guided by a 20G needle. One of the catheters was connected to the carbon dioxide supply and the other to an overflow valve to keep the intraperitoneal pressure at the desired level. The muscle and skin layers of the abdominal wall were closed separately by silk sutures in an airtight manner. The animal was then placed in a horizontal flank position.

Following a 0.5 ml primary bolus injection of 2.5 µCi/ml (3H) methoxy-inulin (NEN, Boston, Mass, USA) in saline solution, a continuous infusion (study I: 0.9 % saline infusion, 5 ml/kg/h, study II: Ringer solution, 8 ml/kg/h, Fresenius Kabi, Halden, Norway) with inulin (1.25 µCi/ml) was given until the end of experiment. One hour of equilibration time followed the preparatory surgery.

**Experimental protocols**

**Study I**

This investigation examined the changes in renal function during elevated intra-abdominal pressure. The study was divided into three series consisting of three groups each.

**Series 1.** Established the model and studied changes in renal function as an effect of capnoperitoneum;

- C_{N}; control group with normal intra-abdominal pressure, n=8,
- C_{IAP 5}; elevated intra-abdominal pressure to 5 mmHg, n=6,
- C_{IAP 10}; elevated intra-abdominal pressure to 10 mmHg, n=6.

**Series 2.** Studied the influence of acute candesartan treatment on renal function during capnoperitoneum;

- Cand_{N}; normal intra-abdominal pressure, n=5,
- Cand\textsubscript{IAP 5}; candesartan treatment and 5 mmHg intra-abdominal pressure, n=5,
- Cand\textsubscript{IAP 10}; candesartan treatment and 10 mmHg intra-abdominal pressure, n=5.

Series 3, studied the influence of volume expansion (VE; 5% of BW/h) and acute candesartan CV 11974 treatment on renal function during capnoperitoneum;
- VEcand\textsubscript{N}; VE and candesartan treatment with normal intra-abdominal pressure, n=6,
- VEcand\textsubscript{IAP 5}; VE and candesartan treatment with 5 mmHg intra-abdominal pressure, n=5,
- V\textsubscript{E}\textsubscript{IAP 5}; VE with 5 mmHg intra-abdominal pressure, n=5.

The protocol consisted of two 60-minutes study-periods. Urine was collected. MAP was recorded throughout the experiment and blood samples were taken at the midpoint of the two periods for acid-base balances and inulin concentrations. Candesartan was given in series 2 and 3 as a slow bolus intra-venous (i.v.) injection, 0.1 mg/kg BW in 250µl saline 30 minutes before induction of capnoperitoneum.

Study II

Study II examined changes in renal function and systemic blood flow in connection with elevation of intra-abdominal pressure. The rats were divided into three groups; one in which the intra-abdominal pressure was not manipulated (BF\textsubscript{N}, n=7), one with intra-abdominal pressure elevated to 5 mmHg (BF\textsubscript{IAP 5}, n=6) and one with intra-abdominal pressure elevated to 10 mmHg (BF\textsubscript{IAP 10}, n=6) by insufflation of CO\textsubscript{2} intraperitoneally.

After surgical preparation and an equilibration period, a pre-insufflation period (P0) started. Three insufflation periods (P1-3) and one post-insufflation period (P4) followed. Each period consisted of 30 minutes. Urine was collected during all periods and blood samples (50-60 µl) were withdrawn at the midpoint of each period for measuring haematocrit, acid-base balance and for determining plasma concentrations of inulin. Blood flow measurements was conducted at three time points, at the midpoint of P0, P1 and P3. At the end of the experiment the animals were euthanized with saturated KCl i.v. and organs (kidneys, adrenals, pancreas, stomach, duodenum, colon, testis, diaphragm muscle, heart, lungs and brain) were excised and weighed.
Urine analysis (studies I and II)

The urine volumes were determined gravimetrically. The urinary concentrations of sodium and potassium were obtained by flame photometry (FLM3, Radiometer, Copenhagen, Denmark). Osmolality in the urine was measured by depression of the freezing point (Model 3MO, Advanced Instruments Inc, Needham Heights, MA, USA). The amounts of inulin in samples of urine and plasma were determined in a scintillation counter (PW4700, Phillips, Eindhoven, Holland). The GFR was estimated as the clearance of inulin, according to:

\[
GFR = \frac{\text{inulin}_{\text{urine}} \times \text{UV}}{\text{inulin}_{\text{plasma}}} \quad \text{Equation 1}
\]

where UV denotes urine flow.

Candesartan treatment (study I)

The purpose was to choose a drug blocking the renin-angiotensin system. This was done by administration of captopril and candesartan. To decide drug and dose to administer in this series, pilot series were performed.

Captopril inhibits the angiotensin converting enzyme (ACE). Rats were treated with a bolus dose 3mg/kg of captopril followed by an continuous infusion of 3 mg/kg/h. Three animals were given captopril and otherwise treated according to the protocol described for Cand\textsubscript{N} above. Four rats were given captopril and then subjected to an elevated intra-abdominal pressure of 10mmHg.

Candesartan is a selective angiotensin II receptor 1 antagonist. Candesartan cilexetil CV 11974 (AstraZeneca, Macclesfield Cheshire, UK) denotes an administration form for experimental i.v. use. The substance was dissolved, in accordance with the manufacturer’s instructions, in saline and NaHCO\textsubscript{3}, to a candesartan concentration of 1mg/ml. pH was corrected to 7.4.

The dose of candesartan to use in study I, was established by treating animals with an acute bolus i.v. injection with a low dose (n=5, 0.1 mg/kg BW) or a high dose (n=5, 1.0 mg/kg BW). The low and high doses were selected according to the instructions manual of candesartan. There was no difference in GFR between high and low dose treatment or compared to C\textsubscript{N} (series 1) and the lower dose was chosen to be used in study I.
It was found that GFR did not differ between the animals with normal intra-abdominal pressure and candesartan or captopril treatment compared to control in series 1. Urine production and blood pressures were equal as well. Furthermore, there was no difference between candesartan and captopril treated animals in response to elevation of intra-abdominal pressure. Both treatments showed MAP of about 50 mmHg during pneumoperitoneum. There was no urine production in either group. Due to the simpler administration of cand, this drug was chosen in our protocol of series 2 and 3.

**Aldosterone measurements (study I)**

Additional experiments were performed to measure serum aldosterone. Rats were subjected to; normal intra-abdominal pressure (n=3); 5 mmHg elevation of intra-abdominal pressure (n=3); 10 mmHg elevation of intra-abdominal pressure (n=3); volume expansion and an intra-abdominal pressure of 5 mmHg (n=3). Elevation of intra-abdominal pressure by carbon dioxide was maintained for 90 minutes before withdrawal of blood for aldosterone measurement. Analyses of aldosterone were performed at the Clinical Chemistry routine laboratory, Uppsala University Hospital, Sweden, using a commercial radioimmunoassay (DPC, Los Angeles, Ca, USA).

**Microsphere technique (study II)**

Blood flow and cardiac output measurements were conducted with microsphere technique. By injecting microspheres small enough to be able to penetrate into the tissues but large enough to get caught in the capillaries, it is possible to get a good picture of tissue blood flow distribution. NEN-TRAC™ microspheres (NEN, Boston, MA, USA) with a diameter of 15±0.1 µm and labelled with 141Cerium, 103Ruthenium or 113Tin were delivered as a suspension in 0.01% TWEEN buffer. About 200,000 spheres were precounted in a multi-channel gamma counter (1282 Compugamma CS, Perkin Elmer Life Science Wallac AB, Upplands Väsby, Sweden) for the total count.

To minimize aggregation of the microspheres, they were treated with ultrasonic agitation for a few minutes on the day of the experiment. Just prior to injection, the spheres were vortexed and suspended in Ringer solution with a total volume of 300µl. Injection of the spheres was done via the catheter in the carotid artery. To achieve a good mix between blood
and microspheres, the tip of the catheter was positioned just above the aortic valves. The microspheres blend with the blood and behave similarly to the blood cells. The number of spheres is measured as the level of radioactivity in a sample. Blood was simultaneously withdrawn at a constant speed (0.76 ml/min) from the left femoral artery during the time of injection of spheres. The suction was begun just before the injection and disrupted 15 seconds after the completion of the microsphere injection. The injection lasted for about 20 seconds.

After the experiment was completed, the number of microspheres in the syringes and organs were counted in a multi-channel gamma counter and cardiac output as well as organ blood flows were calculated. Organ blood flows were calculated by the equation:

\[
\frac{F}{F_s} = \frac{M}{M_s}
\]

Equation 2

Where \( F_s \) and \( M_s \) are, respectively, flow and activity as sampled from the femoral artery; \( M \) is the activity found in the tissue and \( F \) is the flow to be calculated.

Cardiac output was determined by the same equation, but the factor \( M \) will denote the total amount of activity injected and \( F \) will represent the cardiac output.

**Statistics**

All data are given as means ± standard error of the mean (SEM). Two-way analysis of variance (ANOVA, Statview, SAS Institute, Inc., Cary, NC, USA) was performed for comparison between groups. Scheffe’s multiple comparison test was applied. A \( P \) value <0.05 was considered to be statistically significant.
Clinical studies (studies III, IV and V)

Donors and recipients

The local ethics committee approved the present study. Donors who were accepted for live kidney donation and their respective recipients were asked to participate in the study. When it was appropriate to harvest the left kidney, donors were allowed to choose between open or laparoscopic surgery. The right kidneys were harvested with the open technique. The first eleven laparoscopic live donor nephrectomies performed after the introduction of this surgical procedure were not included in the study in an attempt to avoid the effect of the learning curve.

In study III, donors were divided into three groups, according to the surgical method; the HARS-group, nephrectomized by hand-assisted retroperitoneoscopic surgery; the LAP group, consisting of traditional laparoscopic (TLS) and hand-assisted laparoscopic (HALS) nephrectomies and the open group nephrectomized by the flank or open approaches. Demographics of the three groups are shown in table 1.

<table>
<thead>
<tr>
<th></th>
<th>HARS group</th>
<th>LAP group</th>
<th>OPEN group</th>
</tr>
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<tbody>
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<td>14</td>
<td>11</td>
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<td>25.6 (range 22-29)</td>
<td>24.6 (range 17-31)</td>
</tr>
</tbody>
</table>

Table 1. Demographics of donors in study III. BMI: body mass index.

In study IV the first eleven consecutive hand-assisted laparoscopic (HALS) nephrectomies were compared retrospectively to donor nephrectomies performed with traditional laparoscopic surgery (TLS). The mean age of the TLS group was 53 and 48 years for the HALS group. Nine of eleven in the TLS group and four of eleven in the HALS group were women. One of the TLS donors was excluded from the study as the operation was converted to open nephrectomy due to bleeding.
In study V all hand-assisted retroperitoneoscopic (HARS) live donor nephrectomies performed at our centre from April to October 2001 were included consecutively and followed prospectively. The mean age of these donors was 44 years; six were women and four men. Their mean BMI was 25, hence not significantly different from the TLS or HALS groups.

Operative techniques (study III, IV and V)

Donors were given intra-venous fluid during the night prior to operation to ensure a good hydration state. The nephrectomy was performed under general endotracheal anaesthesia and the donors received an arterial line in the radial artery to be able to record blood pressure and to take blood samples for acid-base balance measurements and hormone analysis. Bladder catheterisation, antibiotic prophylaxis intraoperatively and antithrombosis prophylaxis (low molecular weight heparin and compression stockings) were used. All donors were carefully padded and secured to the surgical table to ensure a comfortable position for the donor. The endoscopic procedures are performed with attention to the recommendations of Fahlenkamp et al. for increased safety in urologic surgery (Fahlenkamp et al., 1999).

Open surgery, flank incision

The donor is placed in a full flank position and an incision is made at the site of the twelfth rib. The musculature is split, and the 12th rib is resected. Gerota’s fascia is opened and the kidney is dissected from the perirenal fat. The renal vein is dissected free and veins from the gonads and adrenal gland are divided. The ureter is identified and freed down to the iliac vessels. The renal artery is dissected free. The ureter is ligated distally and divided. The vessels are clamped and cut, after which the kidney is perfused with cold perfusion solution at a back table. The donor’s renal vein is sutured and the artery ligated. Thorough haemostasis is achieved. The muscle layers and skin are sutured separately and a drainage tube is occasionally placed in the wound.

Open surgery, anterior subcostal incision

The supine position is used and a subcostal incision is made. The abdominal muscles are divided and a retroperitoneal space is created. The operation is then performed in the same manner as the open nephrectomy with the flank incision.
Traditional laparoscopic surgery (TLS)

During laparoscopic donor nephrectomy, the donor is positioned in a full flank position, with the right side down. In TLS the Veress needle is introduced into the abdominal cavity and CO₂ is insufflated. One port is then introduced just inferior to the umbilicus and two additional ports are introduced along the costal margin. The video laparoscope is introduced through the infra-umbilical port. The descending colon is dissected and moved medially and the lateral attachments of the spleen are dissected. The medioanterior portion of Gerota's fascia is opened, leaving most of the perirenal fatty tissue and Gerota's fascia along with the kidney. The upper pole of the kidney is dissected free. The vascular pedicle is dissected starting with the vein. The gonadal, lumbar and adrenal veins are cut between double clips. The artery is freed down to the aorta. The ureter is then dissected together with the gonadal vein down to the iliac vessels. Finally, the lateral attachments of the kidney are divided. To facilitate a safe dissection of the renal vessels and its branches, in most of the operations here, an additional port was placed in the flank. This allows the introduction of a Babcock clamp, which can grasp the perirenal fat and pull the kidney in a lateral direction to stretch the vessels. After stapling of the vessels the kidney is harvested through an extended midline incision using a laparoscopic retrieval bag (Endocatch, AutoSutures, US Surgical, USA).

Hand-assisted laparoscopic surgery (HALS)

The operation starts with an infra-umbilical midline laparotomy, with the donor in a full flank position. A HandPort™ (Smith and Nephew, Inc. Andover MA, USA) is introduced through the incision, in accordance with the instructions manual in all cases. The HandPort™ system allows the surgeon to have his or her hand in the abdominal cavity without loosing pneumoperitoneum. The surgeon’s left hand (the non-dominant hand) is placed through the HandPort™ in the abdomen and a working port is placed immediately to the left of the hand port. Pneumoperitoneum is established and an additional port is introduced high on the subcostal margin. This port allows access for a 30°-video laparoscope. An additional working port is introduced in the flank to pull the kidney laterally. The surgeon and the assistant are comfortably seated throughout the procedure. The operation is performed in essentially the same manner as the TLS technique. Removal of the kidney is made by manual extraction.
Hand-assisted retroperitoneoscopic surgery (HARS)

The donor is placed with the right side down in a flank position. The operation starts with an infra-umbilical midline incision, though the peritoneum is left intact. The HandPort™ is introduced into the wound, through which the surgeon’s left hand is inserted and a pre-peritoneal space is created through blind manual dissection. A port is then placed immediately to the left of the HandPort™, through which the pre/retro-peritoneal space is inflated with CO₂ to a retroperitoneal pressure of 12 mmHg. The peritoneum is then loosened from the abdominal wall further medially and in a cranial direction to a level above the kidney by manual dissection. A second port, for the 30°-video laparoscope, is introduced high on the subcostal margin in the anterior axillary line. Finally, a third port is placed in the flank below the costal margin in the posterior axillary line. The surgeon and the assistant are comfortably seated throughout the procedure. The operation is performed in essentially the same manner as the HALS technique. The kidney is retrieved by hand. Note that there is no need for loosening colon or the splenocolic ligament.

Study protocol

Study III

This study evaluates different surgical techniques with regard to renal function, convalescence and complications. The donors are divided into three groups according to the surgical technique applied;

- HARS; hand-assisted retroperitoneoscopic surgery, n=11,
- LAP; hand-assisted laparoscopic and traditional laparoscopic surgery; n=14,
- OPEN; open surgery with flank and anterior subcostal approaches, n=11.

The three groups were all examined prospectively according to the same study protocol. Demographic parameters of the donors were; age, sex and body mass index (BMI). Clearances of iohexol and serum creatinine as well as blood pressure and peak expiratory flow (PEF) were documented prior to the nephrectomy. During the procedure the following parameters were measured: acid-base balance, ventilatory status, plasma concentrations of: active renin, noradrenaline, adrenalin, N-terminal pro-atrial natriuretic peptide (N-ANP), B-type natriuretic peptide (BNP), creatinine and urea. Serum concentrations of aldosterone were
determined as well as urine flow rate (UV) and renal excretion products such as: osmolality, sodium, potassium and albumin in the urine. Glomerular filtration rate (GFR) was estimated as endogenous creatinine clearance (standard calculation, adjusted to 1.73 m² body surface). These parameters were taken at several time points during the procedure;

A. In the generally anaesthetised donor preoperatively,
B. At the beginning of surgery,
C. After 60 minutes of surgery,
D. Prior to clamping of the renal artery,
E. In the morning of the first postoperative day and
F. In the morning of the second postoperative day.

Additional parameters obtained were: length of operation, warm ischemia time (WIT), estimated blood loss and length of harvested renal vessels (artery, vein and ureter). WIT is defined as the time from clamping of the renal artery until the kidney is harvested and the cold perfusion (Sach’s modified solution) has been established at a back table.

Postoperatively, notes were made of the time spent in the recovery room, when oral intake and bowel function were resumed, amount of analgesics used and length of hospital stay for the donors. All complications were recorded.

Donors were examined at three and 12 months postoperatively, where blood pressure and serum creatinine, together with objective and subjective disabilities were documented. Endogenous creatinine clearance was determined at the three-months visit. The donors were asked to estimate their pain on a visual analogue scale (VAS), once a day during the first week postoperatively and subsequently once a week for the first three months after the operation. The amounts of analgesics consumed were also noted. The time of sick leave was documented. Also, the graft function of the recipient was recorded; GFR, creatinine, number and degree of rejection episodes as well as other complications.

**Study IV**

Consecutive donors operated with TLS and HALS techniques were compared. The following parameters were monitored: age, sex, BMI, length of operation, WIT, estimated blood loss, the economy of the surgery and length of hospital stay for the donors. The WIT is defined as the time from clamping of the renal artery to the time when the kidney is harvested and the
cold perfusion (Sach’s modified solution) has started at a back table. Complications were noted as well. The serum creatinine levels of the recipients were measured at release from the hospital and at three months postoperatively.

**Study V**

Consecutive donors nephrectomized with the HARS technique are reported. The first ten living donor nephrectomies are described with regard to demographic parameters, length of operation, WIT, estimated blood loss and serum creatinine of the donors preoperatively, postoperatively, on release from hospital and three months later. WIT is defined as the time from clamping of the renal artery until the kidney is perfused with cold perfusion (Sach’s modified solution) at a back table.

**Statistics**

The Mann-Whitney U-test was applied (*study IV*). Two-way analysis of variance (ANOVA, Statview, SAS Institute, Inc., Cary, NC, USA) was performed for comparison between groups (*study III*). Fischer’s multiple comparison test was applied. A p-value less than 0.05 was considered to be statistically significant.
RESULTS AND COMMENTS

Study I

Effects of increased intra-abdominal pressure and volume expansion on renal function in the rat.

This investigation looks into the changes in renal function during increased intra-abdominal pressure. The effects of angiotensin II blockade (candesartan and captopril) and volume expansion during pneumoperitoneum were studied as well.

The GFR deteriorated by 70% during pneumoperitoneum of 10 mmHg. There was a dramatic drop in Na+ excretion (88–97%). With candesartan and elevated intra-abdominal pressure, there was a drop in mean arterial pressure (from 90 to 55 mmHg) and there was almost no urine production. Treatment with captopril gave the same results as treatment with candesartan. Renal function was better preserved during elevated intra-abdominal pressure when the animals were well hydrated; the GFR and urine production were kept at a normal level. Volume expansion and candesartan treatment showed preserved renal function during pneumoperitoneum. Increased amounts of aldosterone were obtained after 90 minutes of intra-abdominal hypertension. Volume expanded animals had lower levels of aldosterone than control animals.

In conclusion, these results indicate that capnoperitoneum suppresses renal function, especially in combination with angiotensin II blockade. Volume expansion prior to, and during, pneumoperitoneum reduces the deleterious effects on renal function during elevated intra-abdominal pressure. The results suggest that the renin-angiotensin-aldosterone system is important during pneumoperitoneum and patients should not receive pharmaceuticals that block this system prior to endoscopic operations with elevated intra-abdominal pressure. It may be beneficial also to reduce angiotensin II formation by volume expansion.
Study II

Blood flow distribution during elevated intraperitoneal pressure in the rat.
This study was designed to investigate changes in blood flow and renal function during elevated intraperitoneal pressure. Glomerular filtration rate decreased from 0.7 to 0.1 ml/min/g KW with elevated intra-abdominal pressure and the urine output was reduced as well, from 8.5 to 0.6 µl/min/g KW. Dramatic decreases were seen in renal excretion of sodium (by 97%), potassium (by 94%) and osmotically active substances (by 93%).

During pneumoperitoneum, the blood flow to the kidneys, as well as to other organs, such as the brain, parts of the gastrointestinal tract, pancreas, spleen and testes was reduced. Cardiac output was diminished by 54% at 5 and by 65% at 10 mmHg intraperitoneal pressures, respectively, and there was a three-fold increase in systemic vascular resistance in the groups subjected to capnoperitoneum, while the resistance of the control group was unchanged. Thus, the differences in electrolyte excretion rate exist despite the relatively similar central hemodynamic effects and reduction of renal blood flow in the two different pressure groups. These findings indicate the importance of hormonal effects and would be in line with an activation of the renin-angiotensin-aldosterone-system.

In conclusion, cardiac output, measured by microsphere technique, decreased during elevated intraperitoneal pressure by carbon dioxide in anaesthetized rats, while systemic vascular resistance was elevated and renal excretory functions were decreased to a large extent.

Study III

Hand-assisted retroperitoneoscopic live donor nephrectomy in comparison to the open and laparoscopic procedures. A prospective study on donor morbidity and kidney function.
In this study, renal donors were included and followed prospectively for one year in an attempt to evaluate the laparoscopic and hand-assisted retroperitoneoscopic living donor nephrectomies in comparison to the open technique with regard to renal function, hormonal output during surgery, donor morbidity and safety of the technique.
All surgical techniques showed decreases in GFR and urine output during the course of surgery. Aldosterone was more elevated during the open operations compared to the endoscopic techniques, while endoscopy increased catecholamines more than open surgery. Comparing the two endoscopic techniques, HARS seems to be a simpler and easier operation demonstrated as a shorter operating time. HARS also seems to have the advantage of causing less surgical trauma resulting in a quicker normalisation of peak expiratory flow postoperatively, as well as causing less and shorter periods of experienced pain. Kidney function also seems to be less compromised in HARS compared to the laparoscopic technique, demonstrated as lower rise in creatinine. The recipients had a better creatinine clearance than the recipients of kidneys retrieved by laparoscopy and open surgery up to three months postoperatively. There was no difference between groups at one year posttransplantation.

In conclusion, the new hand-assisted retroperitoneoscopic technique seems to be a safe method with shorter operating times and warm ischemia times than the laparoscopic nephrectomies. The method shows good results with regard to kidney function and morbidity of the donor.

Study IV

Hand-assisted laparoscopic surgery (HALS) for live donor nephrectomy is more time- and cost-effective than standard laparoscopic nephrectomy.

This study evaluated the HALS technique in live donor nephrectomies in comparison with TLS. The mean donor BMI was the same in both groups. All operations were performed on the left side. Two donors in the TLS group and one in the HALS group had two left renal arteries; all of the other donors had one artery.

In the TLS group, mean operating time was 270 (210-350) minutes compared to 197 (120-255) minutes for the HALS group. This is a reduction of 27%. The warm ischemia time was also significantly reduced, from 297 (138-525) seconds in the TLS-group to 213 (100-300) seconds in the HALS group, a reduction of 28%. There was no difference in operating time or warm ischemia time between the two operating surgeons. There was no difference in estimated blood loss. In the TLS group one laparoscopic retrieval bag did not manage to trap the kidney and the surgeon had to insert his hand into the abdominal cavity to retrieve the kidney. On two occasions during TLS, the kidney was rotated around its own vessels. In one
case, it was quickly rotated back into place, but the other was accidentally turned another 180 degrees before finally being untwisted. Both kidneys produced urine immediately on revascularization. Serum creatinine three months post-transplantation was 163 mmol/l in the group of patients receiving kidneys from the TLS group and 154 mmol/l for the recipients receiving kidneys from the HALS group.

In conclusion, hand-assisted laparoscopic nephrectomy in living donor kidney transplantation can be recommended, as it increases confidence and the safety margin of the procedure. In addition to shorter operating time and warm ischemia time, HALS presents safety advantages, in particular during trochar placement, prevention of torsion of the kidney, control of potential bleedings and in the final stages of vascular stapling and kidney removal.

![Box-plots showing operating and warm ischemia times of TLS (n=11), HALS (n=11) and HARS (n=10) groups in studies IV and V.](image)

**Figure 1.** Box-plots showing operating and warm ischemia times of TLS (n=11), HALS (n=11) and HARS (n=10) groups in studies IV and V.

**Study V**

**Hand-assisted retroperitoneoscopic living donor nephrectomy: initial ten cases.**

This is a report of the first hand-assisted retroperitoneal live donor nephrectomies. All donors gave their left kidney. Two donors had a retro-aortic renal vein and one donor had two renal arteries. Mean operating time was 155 minutes, which is significantly shorter than both TLS and HALS. The mean warm ischemia time was 181 seconds and mean estimated blood loss 225 ml. All donors demonstrated rapid recovery, though one developed left lower lobe pneumonia that was treated with oral antibiotics. The mean serum creatinine levels on
admission, discharge from hospital and three months postoperatively, were 85 (73-104), 112 (91-124) and 112 (102-124), respectively. The average length of hospital stay was 6.3 days. All transplanted kidneys demonstrated immediate onset of function.

In conclusion, hand-assisted retroperitoneoscopy in living donor nephrectomy could reduce risks associated with traditional transperitoneal laparoscopy. It is a promising new method and should be further evaluated.
Live donor nephrectomy is a major and surgically challenging procedure, where health and well being of the donor is the primary concern, though function of the procured kidney is also of major importance. Lowering morbidity is the motive for introducing the endoscopic technique in live donor nephrectomy. Oliguria and impaired kidney function can, however, be seen during pneumoperitoneum. Furthermore, endoscopic live donor nephrectomy has been criticized for not yet being proven safe enough. The aims of this study were to investigate the changes in renal function during elevated intra-abdominal pressure in donor nephrectomies and in an experimental rat model. Further aims were to evaluate donor morbidity and safety of the new endoscopic techniques compared to the open live donor nephrectomy.

**Effects of pneumoperitoneum**

Urine production is the most common way in the clinical situation to monitor renal function during surgery. This does not, however, truly reflect the renal status. London et al showed that large amounts of intra-venous fluids during pneumoperitoneum restored urinary and cardiac outputs, but glomerular filtration rate (GFR) did not recover in a porcine model (London, 2000). This is in line with Harman et al, who subjected dogs to high intra-abdominal pressure and found that GFR diminished. After 40 minutes, the dogs were subjected to volume expansion until cardiac output was back to baseline; however, GFR was still reduced (Harman, 1982).

In the present studies, kidney function, seen as GFR, deteriorates by approximately 70% during elevated intra-abdominal pressure of 10 mmHg *(study I and II)*. When the animals were volume expanded with saline (5% BW/h) prior to and during pneumoperitoneum, this reduction in GFR was not seen. There are methodological differences though. Both London and Harman began volume expansion after elevation of intra-abdominal pressure, while we began the high infusion rate prior to pneumoperitoneum. GFR reduction during pneumoperitoneum could thus be prevented by volume expansion in the present studies.

At initiation of pneumoperitoneum, there was a transient drop in arterial blood pressure *(study I and II)*. The effect on blood pressure is immediate and could be the result of impaired venous return. However, the blood pressure is restored in 30 minutes, but a
decreased GFR is still seen. The reduction in GFR in normovolemic animals is much larger than can be explained only by the initial drop in arterial blood pressure and that suggests effects of local factors within the kidney. Angiotensin II is likely the major cause for the large increase in systemic vascular resistance and is known to increase the sensitivity of the tubuloglomerular feedback (Schnermann, 1990, Selen, 1983). This mechanism would act to reduce GFR.

Angiotensin II has a major vasoconstrictive effect. Many of the effects of angiotensin II can be prevented by the blockade of the angiotensin II receptor 1 by candesartan. Renal function in rats with candesartan treatment only did not alter GFR or urine output compared with the control group in study I. However, the blood pressure decreased slightly during the course of the experiment in the candesartan treated group, but not in the controls. The control animals thus have continuous vasoconstriction in this setting, which might be due to a rather low intra-venous infusion rate. The vasoconstrictor responsible is most likely angiotensin II, as is blocked by candesartan.

In the groups treated with candesartan and subjected to pneumoperitoneum (study I), blood pressure was decreased at insufflation to the extent that the renal autoregulation diminished or disappeared. Blood pressure was not restored after the initial drop. GFR was decreased and small amounts of urine (or no urine at all) were produced. This is in contrast to the rats subjected to elevation of intra-abdominal pressure only where a transient drop and restoration of arterial blood pressure were shown.

Angiotensin converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to angiotensin II. ACE inhibitors thus exhibit a less specific action than angiotensin II blockade. Nevertheless, the same pattern was seen in rats treated with the ACE inhibitor captopril. Blood pressure was significantly reduced throughout the protocol. There was no urine production and GFR could thus not be calculated (study I). Like candesartan, captopril treatment prior to pneumoperitoneum thus prevented vasoconstriction from restoring blood pressure back to normal.

During elevated intra-abdominal pressure in study I and II, oliguria was seen. The most dramatic finding is that very little sodium is excreted. The sodium excretion rate is actually decreased by 93-97%. Potassium excretion is reduced by 75-90% and osmolality is decreased by 13-27%. Diluted oliguria was thus seen.

Antinatriuretic oliguria suits well with the effects of aldosterone, as the main effect of aldosterone is antinatriuretic. Aldosterone is released by angiotensin II. In study I and II,
small amounts of diluted urine were seen during pneumoperitoneum. Blocking the actions of angiotensin were deleterious to renal function (study I). This would suit well with actions of the renin-angiotensin-aldosterone system. To find out, we measured the serum aldosterone in rats subjected to pneumoperitoneum. Indeed aldosterone was elevated more than two-fold. These results are consistent with those shown by Chiu et al in a pig pneumoperitoneum model (Chiu, 1996).

According to our measurements in the superior and inferior caval veins (study II), the intra-abdominal pressure seems to be transmitted fully to the central venous system. An increased central venous pressure impairs venous return of blood from the periphery to the heart. This is probably the cause of the decrease in cardiac output that we observed both in the 5 and 10 mm Hg groups (study II). The inferior vena caval pressure has been measured to increase in other studies as well (Lindberg, 1997, 1996, Kirsch, 1994, Kashtan, 1981). Lindberg et al found the resistance of the inferior vena cava in pig to be increased, with maintained flow. The increased resistance remained after desufflation as well, suggesting a vasoconstrictive humoral factor. Ortega et al reported of an increased inferior vena caval flow in pig at lower intra-abdominal pressure levels, but a decreased flow at intra-abdominal pressure at 20 mmHg and higher (Ortega, 1996). When a decreased cardiac output is found, as in the present study, it is reasonable to believe that the venous return is impaired. The driving pressure for venous return is the difference in pressure in the venules and the pressure in the right atrium. When an increased intra-abdominal pressure is applied, there is a compression of the vena cava, and the resistance in inferior vena cava is increased. By increasing the pressure in the venules by volume expansion, the venous return is augmented. The vena cava is thus less prone to collapse by elevation of the intra-abdominal pressure. The preload to the right atrium is therefore not diminished and the cardiac output is preserved, or even elevated, as was shown by Kashtan et al, when they increased intra-peritoneal pressure by fluid instillation intraperitoneally in dogs and intravascular volume expansion was given.

In the present studies, there is no significant difference in blood pressure between the groups subjected to an intra-abdominal pressure of 5 and 10 mmHg, nor is there a difference in cardiac output between the groups. Based on these two findings, systemic vascular resistance is increased to about the same extent in the two groups (study II).

Despite the relatively similar central hemodynamic effects and reduction of renal blood flow in the two different pressure groups, there are differences in renal function. The decrease in GFR is rather large in the 10 mm Hg pressure group and small in the 5 mm Hg
group. Even more striking differences exists in electrolyte excretion rates, in particular for sodium, where the excretion rate is close to zero in the 10 mm Hg group while the 5 mm Hg group has a 10 fold greater sodium excretion. One conceivable explanation for the graded antinatriuretic oliguria and GFR reduction is due to reduced renal blood flow and renin release due to decreased cardiac output by pneumoperitoneum. Angiotensin and subsequently aldosterone is released in a dose-response fashion. The hormonal output is greater in the rats subjected to the higher intra-abdominal pressure, and therefore a greater effect on the renal function is seen. It thus seems important in the clinical situation to apply an intra-abdominal pressure as low as possible.

With saline volume expansion, we could reduce the production of renin, angiotensin II and aldosterone. Aldosterone levels in the volume-expanded animals were even lower than in the control rats (study I). In the volume-expanded animals, no effect on arterial blood pressure and only small effects on excretory functions were seen during increased intra-abdominal pressure, even after blockade with candesartan. Blood pressure was kept high by the volume expansion and there was no stimulus for angiotensin II production.

From the above findings, it seems reasonable to state, with regard to humans, that treatment with angiotensin II receptor 1 blockers as well as ACE inhibitors should be avoided in patients in whom intra-abdominal pressure is increased during surgery. Patients subjected to surgery involving increased intra-abdominal pressure may gain from a mild volume expansion to prevent blood pressure drop, angiotensin II release, and loss of renal function. In cases where patients are already on such medication, volume expansion is an advantageous tool to prevent oliguria and reduction of GFR.

The donors were not on anti-hypertensive medication. They were well hydrated prior to surgery and GFR was rather high (as was the urine output) prior to surgery (study III). The filtration rate was suppressed during surgery, but there was no difference between the open and endoscopic techniques (study III). Donors were given loop diuretics during surgery (in about 50% of the cases), when urine output decreased. This leads to difficulties in interpreting both urine output results as well as GFR, as the filtration rate is calculated using urine output.

Donors received almost three litres of fluid during surgery. This did not have any adverse effects, as the donors are cardiopulmonary fit. In patients with cardiac insufficiency, attempts to correct the oliguria during pneumoperitoneum by fluid administration, might however lead to pulmonary oedemas.
In study III, there was no significant difference in renin release between the groups, though it was elevated intraoperatively in all groups. Aldosterone was more elevated in the open compared to the endoscopic groups. In contrast, in study I, aldosterone was elevated during pneumoperitoneum. Explanations for this difference between studies I and III might be several. Rats with normal intra-abdominal pressure were not surgically manipulated, as opposed to donors in open surgery. Another reason for the differing results between rats and humans might be that, the pressure used in rats (up to 10 mmHg) might be comparably higher than the 12 mmHg-level used in the clinical study. Donors were well hydrated and this could be a reflection of the findings in study I, where volume-expanded rats showed decreased levels of aldosterone during pneumoperitoneum.

Catecholamines were more elevated in the endoscopic groups than in the open group (study III). Donors in the hand-assisted retroperitoneoscopic group had a larger increase of noradrenaline than the other groups. The overspill of noradrenaline in our samples taken does not tell whether the activation is a moderate general activation of the sympathetic nervous system, or a strong local activation. The endoscopic groups had a higher output of adrenaline (though not significant) than the open group. Output of adrenaline is an indicator of general sympathetic activation. Shauer et al showed that open cholecystectomy elevated catecholamines more than the laparoscopic procedure (Schauer, 1995). Myre et al and Donald et al, on the other hand, found increased levels of noradrenaline during pneumoperitoneum, but no increased adrenaline levels (Myre, 1998, Donald, 1993). Both Myre and the present study show an early activation of the sympathetic nervous system. In our study, blood pressure is not significantly altered, though somewhat elevated, at induction of pneumoperitoneum. It is conceivably that either the insufflated pressure or gas activates the sympathetic nervous system. Pneumoretroperitoneum seems to increase sympathetic tone slightly more than pneumoperitoneum.

There was no difference in the levels of atrial or B-type natriuretic peptides (N-ANP; BNP) between the different study groups (study III). Both peptides showed the same pattern; no changes during surgery but an increase postoperatively. Both peptides are secreted in response to fluid overload. Intraoperatively, donors are given great amounts of fluid but there are no signs of fluid overload, maybe because of pneumoperitoneum and effects of the anaesthesia. After the nephrectomy the situation is different. Elevated intra-abdominal pressure and anaesthesia are no longer present but still, brisk hydration is given (close to seven litres per 24 h, no difference between groups) and their renal function have literary been
cut by half (as one kidney is taken away). Both N-NANP and BNP were elevated postoperatively. Bloomfield did not find any changes in N-ANP during elevated intra-abdominal pressure (Bloomfield et al., 1997).

Contradicting results are seen in release of vasopressin and endothelin in combination with pneumoperitoneum that could contribute to the oliguria seen in connection with pneumoperitoneum (Donald, 1993, Hamilton, 1998, Joris, 1998, Koivusalo, 1996, Odeberg, 1998). Vasopressin was measured in study III, but was, unfortunately, not analysed successfully. Vasopressin is released to a number of stimuli, not only increased plasma osmolality and hypotension. The results of the different studies are thus difficult to interpret. Odeberg et al did not see any changes in vasopressin in patients with either intra-venous or inhalation anaesthesia, where the intraperitoneal pressure was elevated without surgical stimuli. Koivosalo et al observed increased levels of vasopressin and renin, during capnoperitoneum during laparoscopic cholecystectomy. Hamilton et al found an increase in endothelin, but only in the measurement made after 20 minutes of pneumoperitoneum. In their study, urine output and urine osmolality diminished during capnoperitoneum, but when a renal compression device was applied in another group of dogs, urine output was reduced but with an increase of osmolality. GFR was more reduced in their pneumoperitoneum group compared to the renal compression-group.

Clavell et al utilize a model in dogs mimicking cardiac failure by a chronic thoracic inferior vena caval constriction (Clavell, 1996). This model also resembles the effects of elevated intraperitoneal pressure. The study demonstrated elevated endothelin levels on the fourth day of cardiac failure, while the renin-angiotensin-aldosterone system was activated immediately. Furthermore, endothelin levels were reduced with angiotensin converting enzyme inhibition. This suggests that endothelin might be activated by the renin-angiotensin system.

The rat model in the present studies (II) showed, as a result of elevated intra-abdominal pressure, marked decreases in cardiac output and mean arterial blood pressure leading to renal functional impairment. The pressures used in our model are in the same range as other rat pneumoperitoneum models (Kirsch, 1994, Sandoval, 1996, Giuffrida, 1997, Berguer, 1997, Berguer, 1993). However, in humans and other larger animals the effect is not equally large at the same intraperitoneal pressure level (Aneman , 2000, Blobner, 1998, Ortega, 1996, Shuto, 1995, Joris, 1998, Schafer, 2001, Berguer, 1997). At higher intra-abdominal pressures, the effects on larger species are the same seen in rats at five and ten
mmHg. The present study has not investigated the basis for these observed differences. One might speculate that small animals with thin abdominal muscle layer and loose skin would present more pronounced physiological changes at lower intraperitoneal pressures than humans because of a more pronounced transmission of the induced pressure. Arterial and venous blood pressure levels are about the same in different species, but larger animals have a better buffering capacity, as organs and abdominal walls are larger. The pressure elicited on the surface is equal, but the pressure effect might fade with distance from the surface under pressure. Humans generally have more retroperitoneal fat than the rats. Another explanation might be that a smaller circulating blood volume, seen in small animals, might be more easily affected. Furthermore, the vena cava in rat has a relatively long abdominal course, which might increase the effect of pressure changes intraperitoneally.

Several studies have been made, with a great variation in results regarding the hemodynamic response to pneumoperitoneum. The wide range of results can be the result of the wide range of study designs, but it also shows the complex physio-pathophysiological situation of pneumoperitoneum (Yavuz, 2001, Shuto, 1995, Schafer, 2001, Reed, 1998, Marshall, 2000, Myre, 1997, Elliott, 1998, Hachenberg, 1998, Ho, 1992). The extent of hemodynamic changes associated with intra-operative pneumoperitoneum, is not only species dependent, but will also depend on several additional factors.

The position of the patient (horizontal/head-up/head-down) is important. The head-down position increases venous return and a reduction in cardiac output is not seen. In clinical studies, head-up and head-down positions are the best-studied postures, as these are frequently used in cholecystectomies and gynaecological procedures, respectively. However, many articles have not stated the position used.

The ventilatory technique used is another important factor influencing the hemodynamics. It is reasonable to believe that hypercarbia would result in different hemodynamic effects than normocarbia. Many studies have not specified the ventilatory status of their subjects. Nor is the ventilatory technique (spontaneous breathing or mechanical ventilation) always stated, which makes it difficult to compare studies.

As discussed elsewhere in the present study, intravascular volume is an important factor on the effects of elevated intra-abdominal pressure. Pastor et al suggests in an experimental study that trauma patients should be carefully monitored, especially with regard to renal function, when subjected to laparoscopy (Pastor, 2001). Trauma patients might suffer from hypovolemia due to haemorrhage.
The pre-existing cardiac and pulmonary function of the subjects is also of great importance. As discussed above, the donors of our studies are extensively examined prior to surgery and they are healthy. Pneumoperitoneum increases the workload for the heart, and decreases in cardiac output have been seen (Gebhardt, 1997). It is further known that anaesthetic agents have different cardio depressive characteristics that might lead to different study results. Finally surgical manipulations can elicit differences as well.

**Surgical techniques**

The most important experience gained with hand-assisted endoscopy is the increased safety, but we have also shown reduced operating time and warm ischemia time compared to traditional laparoscopy (*studies III and IV*). In a time where economics has become increasingly important, shorter times in the operating and recovery rooms, are valuable, not only to the patient, but also to the hospital.

There are other reasons to keep operation times short as well, as there are case reports of ischemic complications of the kidney (Nakache, 2000) and intestines (Klugewitz, 1998, Sternberg, 1998, Andrei, 1999) after laparoscopic surgery. They all report complications to laparoscopic surgery, believed to be due to prolonged capnoperitoneum.

Hand-assistance presents advantages during stapling of the vessels. Dissection and stapling of the vessels are the most hazardous part of the operation and carry risk of massive bleeding. With hand-assistance the stapler is put in place in a rapid and secure manner, under tactile control, even when the vessels are of complex anatomy. In our early experience of laparoscopic nephrectomy (prior to the donors in the present studies), one donor bled profusely when an ovarian vein was torn off. Bleeding is difficult to deal with using laparoscopic instruments only and is the most common reason for conversion to open surgery (Jacobs et al., 2000). When hand-assisted techniques are used, the surgeon’s finger can compress a bleeding vessel immediately. Since hand-assistance was introduced at our centre, no patient has been converted to open surgery, neither before nor after the present investigations.

Yang *et al* reported the first retroperitoneal video-assisted live donor nephrectomy (Yang et al., 1994). The operation was performed with so-called lift technique and without pneumoperitoneum. The incisions used in these operations were 5-7 cm, which is not large enough to insert a hand in the event of a large vascular injury. If a major bleeding does occur,
the incision must be extended before control over the bleeding can be achieved. The HandPort™ obviates this drawback, as the surgeon can compress the bleeding vessel immediately with his or her hand. Though the incision used in our technique is only marginally longer, it improves the safety of the procedure. Also, the skin incision of Yang’s operation has to be made at the site of the kidney, which is less appealing from a cosmetic standpoint and carries a greater risk of nerve injury, which is further increased by lifting and pulling retractors. With hand-assisted retroperitoneoscopy, the hand port can be a lower midline incision or, for petite donors, a Pfannenstiel incision.

One reason for introducing the retroperitoneoscopic approach was to minimize the risk of injuring the bowel and other internal organs (Fahlenkamp, 1999). Such injuries can be difficult to detect during pneumoperitoneum, as an elevated pressure is applied that masques venous or capillary bleedings and the field of vision is restricted to the image of the videoscope. Injuries of the bowel or other viscera are instead discovered in the postoperative period and can progress into life-threatening complications such as sepsis and multiple organ failure (Fahlenkamp, 1999, Deziel, 1993).

The retroperitoneal approach also has other surgical advantages since there is no need for mobilizing the colon or the spleen. The splenocolic ligament is left intact, which obviates the risk of internal herniation (Knoepp, 1999).

There is always a risk of injuries when a blind access through the abdominal wall is achieved. When a laparoscopic procedure is commenced, either a Veress needle is used, or a mini-laparotomy is performed. The hand-assisted procedures (either transperitoneal or retroperitoneal) are started with a midline incision and the trocars can then be placed with the surgeons’ hand inside the abdomen. All trocars are introduced guided by visual- or tactile control, which should lower the risk of injuring organs or perforating the pleural cavity, which is sometimes seen, especially in the retroperitoneal routes (McDougall, 1994). Eleven of endoscopic donors, and three of the open, in the present study went through postoperative chest X-rays to verify the position of the central venous catheter. None had pneumothorax. One pure laparoscopic operation was converted to open nephrectomy due to bleeding caused by a Veress needle (study IV). The needle damaged the liver that was adherent to the ventral abdominal wall. We believe that this could have been avoided if hand-assistance had been used.

Our retroperitoneoscopic method commences with manual creation of the retroperitoneal working space and thereby avoids the risk of musculofascial defects due to
improper balloon dilation in the abdominal wall musculature when the working space is created by a dilation balloon (Gill, 1995).

There was a significant difference in postoperative pain and analgesics consumption between the open nephrectomies and those operated by endoscopy (study III). This is well known, but the new hand-assisted retroperitoneoscopic technique also inflicted less pain and a shorter period of postoperative pain. These donors did not complain of shoulder pain, which is sometimes seen after capnoperitoneum. Peak expiratory flow measurements were conducted and showed that the donors operated on with the retroperitoneoscopic technique did not reduce their ability to forced expiration as much as the other techniques. This might be a reflection of less pain and operative trauma. Ability to ventilate the lung parenchyma and early mobilisation could be important factors in preventing donor morbidity in pneumonias and thromboembolic complications.

The nephrectomy is more rapidly performed with hand-assisted retroperitoneoscopic and open techniques compared to the laparoscopic approach (study III) and hand-assisted laparoscopy is more rapid than traditional laparoscopy (study IV). Introduction of the hand-assisted technique is the most important factor influencing operation times but the retroperitoneal hand-assisted approach has brought further simplifications that speeds up the operation. There is no need for taking down the left colon and the spleen and there is no conflict with intestines during surgery.

The warm ischemia time has been reported to be longer when traditional laparoscopy is performed compared to open (Nogueira, 1999) and to hand-assisted methods (Ravizzini, 1999, Slakey, 1999). The warm ischemia time was shorter for the open group (study III). When comparing traditional laparoscopy with the hand-assisted ones (HALS), the latter group has a significant (28%) shorter warm ischemia time (study IV). The lengths of graft vessels are similar with the different techniques.

In the early laparoscopic experience, reports showed that grafts from laparoscopic donor nephrectomies more often had delayed graft function and complications of the ureter (Nogueira, 1999, Kavoussi, 2000, Ratner, 2000, Novick, 1999). Some technical improvements together with increased experience have diminished these problems (Novotny, 2001, Odland, 1999, Ratner, 1997a, Philosophe, 1999, Ratner, 1999). Dissecting the ureter together with the gonadal vein and using a harmonic scalpel instead of cautery preserves optimal circulation to the ureter and can thereby reduce the number of ureteral complications. Still there are reports of higher creatinine in the first postoperative days after laparoscopic
nephrectomy compared to open (Hazebroek, 2002b, Buell, 2001), which is seen also in our study. The rise in donor creatinine postoperatively in the hand-assisted retroperitoneoscopic group does not differ from the open surgery. The laparoscopic nephrectomies showed a larger rise in creatinine postoperatively, but the series is too small to draw the conclusion that laparoscopic nephrectomy is inferior to the other techniques with regard to donor renal function.

The present study (III) shows that the recipient creatinine clearance is better for the retroperitoneoscopic approach than the open and transperitoneal routes two weeks postoperatively, but there was no difference in regard to glomerular filtration rate one year post-transplantation. There are no studies that show a prolonged negative effect of endoscopic donor nephrectomy.
CONCLUSION

Taken together the results from the present studies support the view that elevated intra-abdominal pressure decreases GFR due to decreased cardiac output and activation of the renin-angiotensin-aldosterone system, which can be avoided with adequate hydration. Endoscopy in live donor nephrectomy can be facilitated if hand-assistance is applied and in particular hand-assisted retroperitoneoscopic nephrectomy shows advantages for the donor.

We can also conclude that:

I  Capnoperitoneum suppresses renal function, especially in combination with blockade of the renin-angiotensin-aldosterone system. Volume expansion prior to, and during, pneumoperitoneum reduces the deleterious effects of pneumoperitoneum on renal function during elevated intra-abdominal pressure.

II Cardiac output, measured by microsphere technique, decreased during elevated intraperitoneal pressure by carbon dioxide in anaesthetized rats, while systemic vascular resistance was elevated and renal excretory functions were decreased to a large extent.

III The new hand-assisted retroperitoneoscopic technique compares favourably to open and transperitoneal laparoscopic techniques, in an overall assessment of living donor nephrectomies. Kidney function also seem to be less compromised, demonstrated as lower rise in creatinine at time of discharge.

IV In addition to shorter operating time and warm ischemia time, hand-assisted laparoscopic nephrectomy presents advantages compared to traditional laparoscopic nephrectomy, in particular during trochar placement, prevention of torsion of the kidney, control of potential bleedings, and in the final stages of vascular stapling and kidney removal.

V Hand-assisted retroperitoneoscopy in living donor nephrectomy could reduce risks associated with traditional transperitoneal laparoscopy. It is a promising new method and should be further evaluated.
SUMMARY IN SWEDISH/SAMMANFATTNING PÅ SVENSKA


Laparoskopisk nefrektomi har däremot fördelar för donatorn i samband med levande givarnefrektomi då den ger mindre postoperativ smärta, kortare sjukskrivning och minskar risken för bestående besvär från operationssåret. Det är därför viktigt att visa att denna operationsmetod är lika säker som den vanliga öppna kirurgin och att förstå orsakerna till att njurfunktionen påverkas och hur denna påverkan i så fall kan minskas. Det kan då leda till att fler personer är villiga att utsätta sig för detta altruistiska ingrepp och därigenom kunna hjälpa fler personer med kronisk njursvikt.


Syftet med denna studie var att utveckla en stabil och reproducerbar modell på rätta för att kunna studera effekten av förhöjt intraperitonealt tryck på njurfunktionen. Vi fann att den glomerulära filtrationen (GFR) gick ned, liksom urinproduktionen, vid förhöjda buktryck om 5 och 10 mmHg. Det var också en tydlig minskning av natrium och osmolärt aktiva substanser i urinen. Blodtrycket sjönk vid induktionen av pneumoperitoneum. Injektion av angiotensin II receptor 1 blockad förvärrade njurpåverkan och sänkte blodtrycket ytterligare. Om djuret istället volymexpanderades med fysiologisk koksaltlösning, minskade det förhöjda
buktryckets effekter på njuren och blodtrycket. Detta talar för att renin-angiotensin-aldosteronsystemet spelar en viktig roll vid pneumoperitoneum.

**Delarbete II. Blood flow distribution during elevated intraperitoneal pressure in the rat.**

För att vidare studera de fynd vi fick i delarbete I, använde vi radioaktivt märkta mikrosfärer i syfte att studera hur blodflödet förändrades under pneumoperitoneum. Mikrosfärerna injicerades strax ovan klaffplanet i aorta och de följer sedan blodflödet på liknande sätt som blodkropparna. Mikrosfärerna fastnar i de allra minsta blodkärlen och vi kunde efter försöket slut mäta hur blodflödet fördelat sig i de olika organen. Återigen fann vi hur GFR och urinproduktion minskade samt att koncentrationen av natrium i urinen gick ned. Blodflödet minskade i de flesta organen vid förhöjt intraperitonealt tryck. Vi fann vidare att hjärtminutvolymen minskade samt att den totala perifera resistensen ökade trefalt. Detta stödjer fynden i delarbete I.

**Delarbete III. Hand-assisted retroperitoneoscopic live donor nephrectomy in comparison to the open and laparoscopic procedures.**

Syftet med denna studie var att utvärdera endoskopisk levande givarnefrektomi mot den traditionella öppna tekniken. Fokus är njurfunktionen per- och postoperativt, säkerhetsmarginalen under ingreppet samt om operationsmetoderna påverkar hormonsystemen. Vidare studerades det postoperativa förloppet hos donatorn med avseende på medicinska samt psykosociala parametrar och graftfunktionen hos mottagaren följes. Donatorerna delades in i tre grupper efter operationsmetod; öppen kirurgi (OPEN), laparoskopisk teknik (LAP) samt handassisterad retroperitoneoskopisk teknik (HARS).

Den öppna gruppen hade högre koncentrationer av aldosteron under operationen än den laparoskopiska gruppen. LAP gruppen hade högre halter av adrenalin och HARS gruppen hade högre nivåer av noradrenalin peroperativt än den öppna gruppen. Hos alla donatorer minskade urinproduktionen under operationen. Stegningen i serumkreatinin var högre hos LAP gruppen jämfört med den öppna gruppen. HARS och OPEN donatorer skilde sig inte åt i kreatininstegring. Donatorer opererade med endoskopisk teknik hade mindre ont under första veckan postoperativt, och HARS-gruppen blev snabbast smärtfria. Sjukskrivningstiden var...


Det är viktigt att levande givarnefrektomier (LD nefrektomier) har så låg morbiditet som möjligt, samtidigt som njurens anatomi och funktion måste vara optimal inför transplantationen. En s.k. handport vid laparoskopiska nefrektomier kan öka säkerheten, då operatören under hela operationen har en hand inne i bukhålan. Delarbete IV utfördes med utvärdering av användandet av handport vid LD nefrektomier som mål, genom att jämföra icke handassisterade laparoskopiska nefrektomier med handassisterade laparoskopiska nefrektomier. Handport vid laparoskopiska LD nefrektomier förkortar operationstiden och den tid njuren är kroppstempererad och utan blodtillförsel, varm ischemitid. Handporten ökar säkerheten och underlättar vid flera kritiska moment av operationen samt vid uttagande av njuren efter delning av kärlen.


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