# Anaesthesia and peri-operative Care for Laparoscopic Donor Nephrectomy

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**Anesthesie en peri-operatieve zorg voor laparoscopische donor nefrectomie**

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Een leven in geschonken tijd
André Bek

Voor mijn ouders, Karel, Roos, Jan, Suske, Ben en mijn dierbare vrienden

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1

## Introduction

# Introduction

## Background

The kidney is a vital organ that may be involved in a great variety of diseases that can finally result in renal failure. Kidney replacement therapy consists of dialysis or kidney transplantation. Haemodialysis and peritoneal dialysis facilitate long-term survival of patients with end-stage renal disease and may bridge patients to kidney transplantation. However, dialysis has a substantial negative impact on the quality of life and is associated with an increased morbidity and mortality rate as compared to renal transplantation.
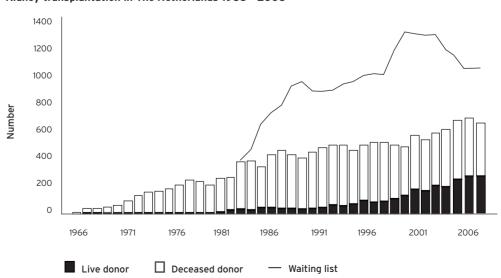
As early as the 18th century, researchers began to explore organ transplantation in animals and humans. A milestone was reached in 1954 when Dr. Joseph E. Murray, performed the first successful kidney transplantation. His team avoided the risk of graft rejection by using a genetically identical twin donor [1]. Thereafter, important medical breakthroughs, such as the introduction of immunosuppressant drugs, have legitimised the transplantation of a larger number of organs with a successful long-term survival for the recipients. The most notable development in this area was Jean Borel's discovery of an immunosuppressant drug, called Cyclosporine, in the mid-1970s [2].

The patients with end-stage renal disease are at risk for cardiac complications because of their underlying disease [3, 4]. A successful renal transplant reduces mortality rate (annual death rate per 100 patient years) by 40% to 60% when compared to patients who continue dialysis [5].

In the Netherlands, the first kidney transplantation was performed in 1966 and, up until today, more than 14,500 kidney transplantations have been performed. In our country there are eight kidney transplantation centres, which performed about 650 transplantations in year 2006. Of these transplants, 274 were achieved using living donors (Figure 1.1). Nowadays 1,084 dialysis patients are still on the waiting list for transplantation. The mean waiting time for patients who are already screened and appointed for kidney transplantation has increased to 4 years (it is important to realize that only patients who started dialysis are considered for this list). The number of Dutch people depending on dialysis is 5,600 and this number is increasing every day [6].

*Figure 1.1*

**Kidney transplantation in The Netherlands 1966 - 2006**

Because kidney donation is still the ultimate treatment for end-stage kidney failure, we are in desperate need for donors. Therefore, many centres have now implemented a living donation program, encouraging spouses and family members to donate their kidney. Currently, at the Erasmus MC Rotterdam more than half of all donated kidneys are from a living donor, and the number of unrelated living donors is increasing. Moreover, new initiatives like the "cross-over donation" program are stimulated to help patients awaiting kidney transplantation.

## Living kidney donors

In general, living donors are healthy and classified as American Society of Anaesthesiologists (ASA) grade I or II. One of the major concerns of living organ donation is the potential to cause harm to healthy individuals who undergo surgery for purely altruistic reasons. Morbidity after living kidney donation is low; Matas et al. (2003) reported two donor deaths and one donor who has remained in a persistent vegetative state in a series of 10,828 living kidney donations [7]. Beside mortality and morbidity, quality of life after organ donation is of great concern [8-10]. It is important that the benefits of living kidney donation outweigh the risk associated with the donation and transplantation of a living donor organ [11].

Organ donation from living donors has significant advantages over organ donation from deceased donors. The overall 3-year graft survival rate after deceased donor kidney transplant is >70% and after living donation >80% [12]. Obviously, a number of advantages can be mentioned that are responsible for the improved outcome. First, the procedure can be planned on an elective basis, providing the opportunity to optimise the conditions around the transplantation. Secondly, the cold ischemia time of the organ can be reduced significantly with living donation as compared with post-mortal donation. Thirdly, the living donors are hemodynamically stable. Fourthly, the time spent on the waiting list can be reduced significantly. Planning transplantation in an earlier stage of the disease can reduce the increase in morbidity and mortality of patients with end-stage renal disease. In a living donor program there is a tendency towards earlier transplantation, even as early as in the pre-dialysis period of the kidney patient, the so called "pre-emptive" transplantation. Finally, due to the above mentioned factors graft survival of kidneys coming from living donors is almost double that of kidneys from deceased donors.

## The laparoscopic donor nephrectomy
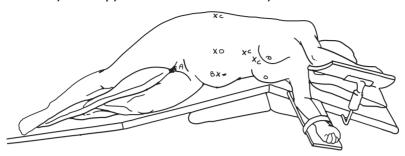
Traditionally the surgical approach for living donor nephrectomy was performed through a subcostal lateral incision, later the minimal-incision nephrectomy was adapted in our institution [13]. Now, laparoscopic donor nephrectomy (LDN) has become the method of choice to procure kidneys from living donors.

LDN is performed in lateral nephrectomy position by flexing the operation table to gain maximum access between the iliac crest and the ribs (Figure 1.2). Pneumoperitoneum (PP) is established by insufflation of carbon dioxide ($CO_2$) with an abdominal pressure of 12 mmHg. A video endoscope and three to four trocars are inserted. The kidney is freed from adjacent attachments and structures, after which the renal vein, the renal artery and later the urethra are identified and dissected. The left gonadal, lumbar and adrenal veins are clipped and divided, and the adrenal gland is released from the medial superior aspect of the renal capsule. A suprapubic incision is made through which an extraction device is inserted. Then the urethra, renal vein and artery (in this specific order) are clipped and divided; hereafter the kidney is placed in the extraction device and extracted via the suprapubic incision. Immediately

*Figure 1.2*

**Lateral nephrectomy position and location of trocar ports**



after the extraction the kidney is perfused with a cold preservation fluid.

LDN has become popular mainly because of the reduced procedure-related morbidity, shorter convalescence period, better cosmetic result and a superior quality of life compared with open surgery [10,14-22]. There are indications that these advances have increased the amount of living kidney donors and the willingness to donate. Kuo et al. reported that 47% of donors donated solely because of the availability of the LDN procedure [23].

Although LDN is beneficial to the donor, there are concerns about the transient function deterioration of the donor graft (called delayed graft function), compared to after the traditional open procedure. The creatinine concentration of recipients who received a kidney procured with the LDN procedure, decreases slower in the first weeks after transplantation compared to the open procedure [21,24,25]. Accordingly, the creatinine concentration of the donor with the LDN procedure is higher the first weeks after kidney donation [26].

Laparoscopic living donor nephrectomy for renal transplantation demands not only an operation that is safe and preferable for the donor but must also deliver a functionally intact kidney, providing graft function, comparable to open donor nephrectomy (ODN). It is supposed that $CO_2$ pneumoperitoneum ($CO_2PP$), necessary to create a working space for the surgeon, is the incrementing factor related to delayed graft function [26-28]. Since even moderate graft dysfunction can have a negative impact on graft rejection and long-term graft survival, it is of importance to minimize delayed graft function [29,30]. Thus, this should already start with optimisation of the donor kidney in the donor during the procedure of procurement.
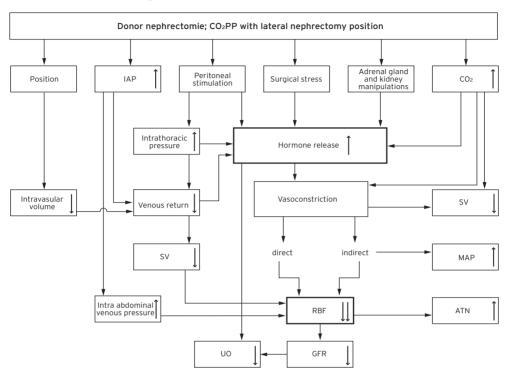
The causes and exact mechanisms of the altered hemodynamic parameters, renal blood flow and reduced urine output during LDN, and delayed graft function, after LDN are probably multifactorial. There is an ongoing debate over the causes of these induced changes during $CO_2PP$. Various mechanisms, such as venous compression caused by elevated IAP (with compression of abdominal vasculature and organs), and the pharmacological action of the absorbed $CO_2$, as well as activation of the sympathetic and neuro-humoral factors have all been suggested to explain these transient adverse renal effects [27,31-41]. Therefore, an understanding of the pathophysiologic consequences of increased intra-abdominal pressure (IAP) and elevated $CO_2$ is important. This is summarised in Figure 1.3.

The hemodynamic changes due to $CO_2PP$ consist of an increase in systemic vascular resistance (SVR) up to 65%, and a 20–59% decrease in cardiac output [42,43]. The decline in cardiac output parallels the decrease in venous return; the last is confirmed by a reduction in left ventricular end-diastolic volume and low atrial natriuretic peptide (ANP) concentrations. Cardiac filling pressures, however, rise during peritoneal insufflation. The increased intra-thoracic pressure associated with PP explains the paradoxical increase of cardiac pressure [44]. The increase in (SVR) with subsequent elevated mean arterial pressure (MAP) observed during $CO_2PP$ cannot only be explained by mechanical compression. $CO_2PP$ is associated with activation of endocrine vasoactive factors such as

*Figure 1.3*

**Schematic representation of the different mechanisms leading to decreased stroke volume, renal blood flow, glomerular filtration rate and urine output, and elevated MAP during living laparoscopic donor nephrectomy with CO$_2$PP**



IAP:   intra-abdominal pressure
SV:    stroke volume
MAP:  mean arterial pressure
RBF:   renal blood flow
ATN:   acute tubular necrosis
UO:    urine output
GFR:   glomerular filtration rate

catecholamines, vasopressin, and renin-angiotensin-aldosterone-system, which probably contribute to the rise in SVR [43,45-47].

In addition, CO$_2$PP causes a decrease in renal blood flow (RBF) up to 75% of baseline values, with subsequent temporary renal ischemia [27,38,40,41,46,48,49], which overall results in extra induction of acute tubular necrosis (ATN) [37,40,41,46,49-54]. Glomerular filtration rate (GFR) and urine output reduction can be up to 50%, despite well-maintained arterial blood pressure [28,37,40,41,50,51,53-59]. Onset of tubular damage usually occurs within 25 minutes of ischemia as the microvilli of the proximal tubular cell brush borders begin to change.

With every surgical procedure a certain degree of ATN occurs. The kind of surgical procedure, the baseline clinical condition of the patient, the anaesthetic management and the duration of the procedure, are all variables which play a role in the occurrence of ATN [60]. During LDN, which lasts around 220 minutes, the pathophysiologic situation of elevated IAP leaves abundant time for ATN to evolve.

## Fluid regime

Lateral nephrectomy position and PP, necessary for LDN, introduces relative hypovolemia. This position is known for its negative hemodynamic compromise, because of venous pooling in legs and upper body [61]. The decrease in cardiac output and increase in SVR during PP is affected by the patient's circulating volume before the induction of $CO_2$PP. The reduction in venous return and cardiac output can be attenuated: by fluid loading, tilting the patient to a slight head-down position, or by preventing pooling of blood with an intermittent sequential pneumatic compression device or by using anti-thrombosis stockings. The initial response to a contracted extracellular fluid volume is a decrease in RBF, the GFR and the filtered solute load. The presence of a low circulating blood volume leads to a series of vasoconstrictor, salt-retaining neuro-humoral systems being activated, i.e. the sympathoadrenal system, renin, angiotensin, aldosterone, and vasopressin.

In an animal model, London et al. have shown that PP resulted in a decrease in RBF during normal fluid management, whereas RBF did not decrease if volume expansion was given [27]. From these results, it has been advocated to use vigorous hydration up to 2 l.$^{-1}$h of crystalloids during LDN in patients [18,19,62-64]. However, it was shown that this vigorous hydration could not prevent the impaired creatinine clearance as observed after LDN [19,27,65,66]. Biancofiore et al. studied the effect of volume loading on graft function with a crystalloid infusion starting the night before surgery. In their study early graft function did not differ between ODN and LDN. However, with their regime, serum creatinine still declined earlier in those recipients receiving kidneys from ODN compared to the LDN procedure [67].

While under-hydration may contribute to renal dysfunction, perioperative fluid excess can cause problems, such as pulmonary oedema, ileus and cardiac failure, as well as impaired wound healing.

We hypothesized that volume loading after establishment of PP is too late in order to counterbalance the collapsed venal system. The goal is to compensate hypovolemia before PP is started; therefore, we designed a new fluid regimen with pre-hydration together with a bolus of colloids given just before the induction of PP. After prehydration, a relatively restrictive fluid regime can then be used during LDN, which may reduce the risk of fluid overloading, especially because during IAP elevation, urine output is diminished. In contrast with Biancofiore et al., we used colloids as part of the pre-emptive fluid loading [67].

## Stress response

Surgical procedures are associated with complex stress responses, mediated by neuroendocrine, immunologic and metabolic alterations, which are related to the magnitude of the inflicted injury [68,69]. Significant elevations are observed for catecholamines, cortisol, growth hormone, and anti-diuretic hormone (now called arginin vasopressin, AVP), due to surgical stress. Surgical stress and anaesthesia can affect renal function and body fluid regulation indirectly (as a reflection of overall circulatory responses) as well as directly [70]. The function of the kidney is modified directly by efferent sympathetic stimulation and/or circulating catecholamines and renin-angiotensin system (RAAS) via the receptors in the kidney. The vasoconstriction induced by these hormones might result in renal ischemia, with subsequent ATN [68]. Attenuating intra-operative stress is a key factor in improving general but also renal function outcome [71,72].

LDN is associated with a shorter and less intense recovery phase for the donor compared to ODN [10,22,73]. However, despite the improved conditions for recovery, the stress response is still shown to be significant [74,75]. Catecholamines, cortisol, RAAS, and especially AVP are all released during PP. The increase in SVR and the reduction in urine output during laparoscopic interventions are considered to be mediated by these neuro-humoral factors [44].

Several studies have reported elevated AVP levels during increased IAP [47,54,76-79]. AVP regulation is influenced by several mechanisms, e.g. osmotic receptors in the hypothalamus, pressure receptors in the atria (via ANP) and lung vessels, and high pressure receptors in the carotid sinus [80,81]. $CO_2$ and mechanical stimulation of peritoneal receptors also stimulates AVP release [82]. AVP is a potent vasopressor even at normal physiologic concentrations and promotes water retention and the production of concentrated urine by direct action on the kidney [83,84].

Pneumoperitoneum results also in stimulation of the RAAS, mainly because of the reduced RBF due to the elevated IAP and as a result of increased sympathetic efferent activation [39,43,78]. Renin is secreted as a reaction on a decrease in circulating blood volume from the juxtaglomerular cells of the kidney and stimulates the production of angiotensin II and aldosterone, which in turn leads to elevated MAP and sodium and water resorption from the distal tubules in the kidney [68,85].

Surgical stress itself increases plasma epinephrine and norepinephrine concentrations. Some publications report a higher increase during laparoscopic procedures compared to open procedures [81,86,87]. Epinephrine inevitably rises more during the procedure of LDN (which implicates handling of the adrenal gland, which is located next to the kidney) in comparison to other laparoscopic procedures.

The different hormones interact on different levels, cathecolamine release activates RAAS, AVP decreases RAAS activity, and ANP interacts with AVP [88]. RAAS, AVP and ANP changes can be prevented or modified by maintenance of normal or increased intravascular volume. Cathecholamine release can be prevented with high dosage of morphometica [89,90].

An increase in all the above-mentioned plasma hormones could be the result of reduced renal clearance, which is known to be reduced during PP [91].

Stress response during laparoscopic procedures in supine position (such as cholecystectomy) is moderate [69], whereas stress response in lateral nephrectomy position, in which donor nephrectomy is conducted, is significant (Table 1.1) [56,74-76]. For kidney donation, where preservation of kidney function is of paramount importance, these physiologic changes are undesirable. In literature we found one study that in our view had taken most of the necessary precautions to counteract biasing factors when comparing hemodynamic parameters and neuroendocrine release. Lentschener et al. 2001, described a strict protocol for anaesthesia and fluid therapy, and found that during gynecological laparoscopic surgery, intra-operative hemodynamic and neuroendocrine changes did not occur, provided that normovolemia, adequate depth of anaesthesia, and high plasma levels of opiates were maintained [92].

We hypothesized that if we would be able to alleviate the hormonal release associated with surgical stress and IAP elevation during the LDN procedure, this would have its effects on the hemodynamic compromise and on renal function. Therefore, we choose for administration of high dosage of morphometica, sufficient intravascular volume, and mechanical ventilation with a minimum of positive pressure. To study the mechanism and relation with renal function of elevated IAP in relation with hormone release and hemodynamics we evaluated the hormonal release in ODN and LDN.

Choice of anaesthetics may influence RBF, not only directly, but also by producing changes in cardiovascular function and in neuroendocrine activity. Propofol anaesthesia has been shown to attenuate surgical stress-induced adverse immune neuroendocrine hormone release better than other types of anaesthesia [89,93-100]. In addition some data suggest that the anti-oxidant action of propofol might be associated with a more favourable metabolic and immune responses [93,97]. In addition oxidative stress is likely to contribute to the impairment of renal function after PP [102]. Therefore we compared our standard isoflurane anaesthesia for the donor kidney procedures with propofol anaesthesia with regard to stress response during LDN and ODN procedures.

*Table 1.1*

**Hormone levels, comparing laparoscopic versus open surgery, or retroperitoneal surgery in lateral nephrectomy position, derived from literature**

| Author | Operation | Species | N | NE pg/ml | | E pg/ml | | RE ngAI ml-1.h | | ALD ngAI ml-1.h | | AVP pg/ml | | volume | extra |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | | |
| Mertens zB | LDN prop | Humans | 35 | 125 | 110 | 17 | 32 | 1,8 | 3,4 | 43 | 47 | 4 | 2,3 | 13 ml kg⁻¹ h⁻¹ | BIS equal and low |
| 2008 | ODN prop | | | 132 | 113 | 14 | 31 | 1.4 | 2,2 | 31 | 73 | 3.7 | 2.7 | with preload | PIP. High dose |
| Chapter 6 | LDN iso | | 43 | 197 | 243 | 26 | 66 | 1.5 | 8.3 | 36 | 82 | 3.5 | 3.2 | and colloids | sufentanil Compres- |
| | ODN iso | | | 164 | 183 | 23 | 76 | 1.7 | 6.7 | 28 | 68 | 3.3 | 5.2 | | sing stockings |
| Sunquist | LDN* | Humans | 4 | 288 | 474 | 27 | 183 | 35 | 65 | 44 | 128 | | | ? ml kg⁻¹ h⁻¹, | Compressing |
| 2004 [75] | ODN* | | 11 | 203 | 474 | 18 | 128 | 28 | 90 | 44 | 236 | | | with preload | stockings |
| Hazebroek | LDN* iso | Humans | 30 | | | | | | | | | 2 | 12 | ? ml kg⁻¹ h⁻¹ | |
| 2002 [76] | ODN* iso | | 6 | | | | | | | | | 1 | 3.5 | | |
| Mikami | Retro-PP÷ iso | Humans | 10 | 249 | 445 | 18 | 617 | | | | | | | ? ml kg⁻¹ h⁻¹ | |
| 1996 [74] | PP∅ iso | | 19 | 183 | 236 | 17 | 314 | | | | | | | | |

*All hormone concentrations are recalculated to the same units as used in this thesis.*

*Hormone concentration at time 1 is the control. This is not taken at the same moment in all articles, in our studies they are taken after induction of anaesthesia, but before intubation. Time 2 is when the operation is in proceeding, in our study this is after 2 hours of PP installation. The data from the literature are derived as much as possible around this duration.*

*\* data are derived from figures, ÷ Lateral decubitus position, ø Trendelenburg*

*LDN; laparoscopic donor nephrectomy, ODN; open donor nephrectomy, Prop; propofol, Iso; isoflurane. PIP; positive inspiratory pressure.*

## Epidural analgesia

The successful development of local anaesthesia began in the late 19th century. In abdominal surgery, thoracic epidural anaesthesia/analgesia (TEA) with local anaesthetic agents attenuates the stress response to surgery and improves postoperative outcome via beneficial effects on organ function [68,72,103-108]. Furthermore, transient thoracic sympathicolysis by TEA has been suggested to offer protective cardiac, pulmonary as well as positive immunologic and coagulation properties and thus decreases postoperative morbidity and mortality [105,109].

Patients treated with TEA have excellent pain relief, a prerequisite for accelerated recovery from surgery, and the patients experience better health-related quality of life.

Regional anaesthetics and the kidneys interact in a complex manner that varies according to the underlying cardiovascular, renal and fluid status of the patient [110]. After neuraxial block-induced sympathicolysis, total SVR decreases around 15% to 18% in normovolemic healthy patients. This vasodilatation can be easily augmented with supplemental intravenous fluids.

Spinal cord segments T4 through L1 contribute to the sympathetic innervation of the renal vasculature, which is innervated through sympathetic fibres from the celiac and renal plexus [111,112]. Regional anaesthesia above this level reduces sympathetic tone to the kidney and makes RBF and filtration directly dependent on perfusion pressure during sympathicolysis; consequently, RBF and GFR

directly depend on MAP and intravascular volume [112,113]. Provided that flow is maintained and perfusion pressure does not fall below the autoregulation range during epidural anaesthesia, there is little change in GFR or renal vascular resistance [114].

Pneumoperitoneum created during LDN negatively affects renal hemodynamics through renal vein compression and activation of the neuro-humoral stress response. This is why we consider a stress-free procedure during the procurement of a living donor kidney essential; to achieve that we used a relatively high dosage of sufentanil. However, the use of a high dosage of sufentanil has some side effects, like slow recovery. Inhibition of stress responses is known to be greatest with neural blockade mediated by local anaesthetics; in addition this technique offers several other advantages [72]. Therefore we implemented this technique in our research.

## Peri-operative protocol

Considering all the above-mentioned processes that potentially compromise the donor and the procured kidney, a protocol for peri-operative management of LDN was developed, that would ensure optimal function of the donor kidney. A comparison of the different components of the new and the previously used peri-operative protocol are shown in Table 1.2. In short, the new protocol addresses the following items: prevention of preload reduction, prevention of elevated $CO_2$ and of ventilation-induced elevated intrathoracic pressures, and prevention of stress-induced hormonal release.

In order to compare the effects of the various interventions, extra per-operative monitoring of

*Table 1.2*

**The old and new protocol**

|  | Old | New |
| --- | --- | --- |
| Stockings | Not | Compressing stockings |
| Positioning | Lateral nephrectomy position | Adapted lateral nephrectomy position |
| Preoperative fluid loading | Not | Overnight |
| Prehydration | Not | 3 ml.IBW-kg$^{-1}$.h$^{-1}$, eleven hours+ colloids before IAP elevation |
| Intra operative Crystalloids | 16 ml.kg$^{-1}$.h$^{-1}$ | 13 ml.IBW-kg$^{-1}$.h$^{-1}$ |
| Total colloids | 1000 ml | 950 ml |
| Ventilation mode | IPPV | PSV |
| Positive pressure | Mean PIP 30 kPa | Mean PIP 25 kPa |
| Sufentanil | Mean 45 µg | Mean 120 µg |
| Monitored guided titration of anaesthesia | Not | BIS mean 47 |
| Epidural analgesia | Not | TEA with Marcaine-sufentanil |

*IPPV        inspiratory positive pressure ventilation*
*PCV        pressure controlled ventilation*
*BIS        bispectral index*
*TEA        thoracic epidural anaesthesia/analgesia*

patients was mandatory. Because it was the intention to perform these studies with a minimal burden to the donors we used non-invasive techniques.

The BIS monitor (bispectral index monitor; Aspect Medical Systems, Newton, MA, USA) was used to measure depth of anaesthesia. An esophageal Doppler probe (HemoSonic 100; Arrow International, Reading, PA, USA) was used to measure stroke volume (SV) and left ventricular ejection time (LVET), which is a parameter for preload. The NICO monitor (Novametrix; Medical Systems, Wallingford, CT, USA) was used to measure $CO_2$ production per minute ($VCO_2$).

All three techniques have been extensively validated and have been used in previous studies in the field of anaesthesiology.

## Outline of this thesis

In **chapter 2** we performed a retrospective study comparing long-term kidney function in donors and recipients after laparoscopic versus open donor nephrectomy. Parallel to this study, a literature search was performed to develop the new peri-operative protocol for the LDN and ODN procedure. In **chapter 3**, two novel fluid regimens were evaluated and compared to the previous used fluid regimen. The most optimal intravenous fluid therapy was used in the studies presented in the following chapters. To improve knowledge of the pathophysiologic processes and to answer the question what is responsible for the reduced cardiac output and elevated MAP during LDN, we performed the study described in **chapter 4**. In **chapter 5** we evaluated whether the previously found increase in Delayed graft function in the LDN group compared to the ODN group was abrogated with this novel fluid regimen, and possible side effects of this regimen were studied. Since it is not clear from the literature whether previously described differences in stress response between ODN and LDN were due to the surgical procedure or to other factors, we performed the study described in **chapter 6**. In this chapter the stress response due to the surgical procedure (ODN and LDN) and choice of anaesthetic drug (propofol versus isoflurane) were compared. In **chapter 7** we studied whether epidural analgesia would improve patient recovery and satisfaction, without impairing the beneficial effects seen with the peri-operative protocol that used high dosage sufentanil.

Finally, in **chapter 8** the stress response was investigated in relation to high dosage of opioids and epidural analgesia during LDN.

## Aims of this thesis

The aim of the clinical studies described in this thesis was to develop and validate an anaesthesia and peri-operative care regimen, which prevents the deterioration of donor kidney function seen after LDN. We developed a protocol that focused on optimal hemodynamic function and low level of preoperative stress. Using this protocol as a basis, we searched for additional optimalization of outcome of the donor and donor kidney function. Secondly, the pathophysiological processes during LDN are studied.

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# CHAPTER

2

## The effect of laparoscopic and open donor nephrectomy on the long-term renal function in donor and recipient: a retrospective study

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## Abstract

*Background:* Pneumoperitoneum, as used in laparoscopic donor nephrectomy (LDN), may result in negative effects on renal function in donor and recipient. This study compares long-term serum creatinine in donor and recipient after laparoscopic and open donor nephrectomy (ODN).

*Methods:* A retrospective analysis of 120 LDN and 100 ODN donors and their recipients was performed. Serum creatinine of donor and recipient was recorded and analyzed. The follow-up period post-transplantation was 3 years.

*Results:* Serum creatinine in the recipients was significantly higher in the LDN groups the first week after transplantation. Serum creatinine in the donor was significantly higher in the LDN group at 1 day, 3 months, and 1 year posttransplant. Finally, creatinine levels remained 40% higher compared to preoperative values in both donor groups.

*Conclusion:* LDN results in higher short-term serum creatinine levels in donor and recipient. Long-term serum creatinine levels were comparable after LDN or ODN in donor and recipient.

## Introduction

The therapy of choice for end-stage renal failure is kidney transplantation. Unfortunately, the number of cadaveric kidneys required for transplantation is exceeding the number of available kidneys. The use of kidneys from living donors might reduce the shortage of donor kidneys. Living (un)related donor kidney transplantation is associated with advantages such as reduced waiting-list period, elective nature of the operation and better graft and patient survival compared to cadaveric kidney donation [1]. Open donor nephrectomy (ODN) is associated with a mortality of 0.03% and considerable morbidity [2]. In order to reduce morbidity and potentially increase the number of living donors, various alternative techniques were introduced. Ratner et al. performed the first laparoscopic donor nephrectomy (LDN) in 1995 [3]. Several studies show a reduction in hospital stay, pain and return to work comparing laparoscopic to open donor nephrectomy [4-8]. Other techniques currently applied are thehand-assisted and retroperitoneal approach.

Establishing a pneumoperitoneum is necessary when performing a transperitoneal laparoscopic donor nephrectomy to provide sufficient working space and overview of the operating area to the surgeon. This pneumoperitoneum is, however, accompanied with important negative hemodynamic effects. Intra-abdominal pressure due to gas insufflation results in decreased renal flow and subsequent renal ischemia in the graft and the remaining kidney in the donor [9]. The impact of pneumoperitoneum on the kidney function in donor and recipient remains controversial. Some studies show a decreased short-term graft function in recipients of laparoscopically procured kidneys [10,11], whereas other studies show no difference [12-14].

Studies investigating long-term renal function in kidney donors after open donornephrectomy show a deterioration in renal function of about 30% [2,15]. Considering the potentially increased renal ischemia during laparoscopic donor nephrectomy compared to open kidney donation, we were interested in determining whether long term serum creatinine would be significantly higher after laparoscopic donor nephrectomy compared to open donor nephrectomy in both the donor and the recipient.

## Patients and methods

A retrospective analysis of all living (un)related kidney donors and their recipients, operated between 04-01-1994 and 12-03-2002, was performed. In this period, a total of 220 donor nephrectomies were carried out; 120 were laparoscopic, of which eight were hand-assisted (16). All removed kidneys were transplanted.

Because the first LDN at our institute was performed in December 1997, the follow-up period of the LDN group was shorter than that of the ODN group. Analysis was performed until 3 years follow-up for both groups.

 Data from donors were collected from medical records and consisted of age, sex, and operating technique. Serum creatinine levels were available preoperatively and on days 1, 2, 21, 90, 365, 730, and 1095 postoperatively. These serum creatinine levels were statistically analyzed as discussed below. Data collected from recipients consisted of age and sex. Serum creatinine levels were available preoperatively and on days 1, 2, 3, 4, 5, 7, 14, 28, 180, 365, 730, and 1095.

### Statistics

Statistical analysis was performed using the SPSS 10.0 (SPSS, Chicago, IL) statistical software package on an intention-to-treat basis. Analysis of serum creatinine levels of donor and recipient was done after log-transformation to approximate normal distribution. Repeated measurements ANOVA

using the PROCMIXED procedure from SAS showed that the differences of donors and recipients depended on the day for serum creatinine levels. Therefore, a univariate analysis of variance was performed per day. Preoperative serum creatinine levels were determined as baseline values and analyzed as covariate into the univariate analysis. Using regression analysis, we adjusted for differences between the two groups (age and origin).

Analysis of donor and recipient age was done using the Mann-Whitney test. Categorical data such as sex and origin were reported as absolute numbers of patients and/or percentages and were compared using the chi-square test.

A $p$ value of 0.05 was considered to be statistically significant.

## Results

There were no significant differences between LDN and ODN donor-groups for age and sex (Table 2.1). Operating times were significantly longer in the LDN group (Table 2.1).Comparing log serum creatinine, LDN donors had significantly higher serum creatinine levels on postoperative day 1 ($p < 0.034$), day 90 ($p < 0.008$) and 1 year ($p < 0.031$) compared to ODN donors (Fig. 2.1). In both groups serum creatinine remained approximately 40% higher than preoperative values (Fig. 2.2).

In recipients, sex was not significantly different between the ODN and LDN groups. The LDN recipients, however, were significantly older than the ODN group. Also, the percentage of living unrelated donations was significantly

higher in the LDN recipients. With regard to log serum creatinine, we found significantly higher values in recipients of LDN kidneys compared to ODN kidneys in the first week posttransplant (Fig. 2.3).

*Table 2.1.*

**Donor and recipients characteristics are given as number of patients (percentage) or mean (range).**

|  | LDN (122) | ODN (100) | $p$-value |
|---|---|---|---|
| Donor |  |  |  |
| Gender |  |  |  |
| Male | 56 (47%) | 43 (43%) | 0.68 |
| Female | 64 (53%) | 57 (57%) |  |
| Age (years) | 47 (20-76) | 48 (20-77) | 0.70 |
| Body mass index | 25.5 (17-35) | 25.8 (16-37) | 0.76 |
| Operating time (min) | 236 (105-420) | 157 (75-310) | < 0.001 |
| Warm ischemia time (min) | 7.7 (2-17) | # |  |
| Recipient |  |  |  |
| Gender |  |  |  |
| Male | 74 (62%) | 52 (52%) | 0.15 |
| Female | 46 (38%) | 48 (48%) |  |
| Age (years) | 45 (16-73) | 40 (18-71) | 0.002 |
| Origin donor |  |  |  |
| Related | 68% | 88% | 0.001 |
| Un-related | 32% | 12% |  |

*Figure 2.1.*

**Geometric mean of serum creatinine (μmol/L) with 95% CI of living kidney donors in time**

(open squares, LDN; closed triangles, ODN). *p < 0.05 after correction for the difference in baseline values.



| DAY : | 0 | 1 | 2 | 21 | 90 | 365 | 730 | 1095 |
|---|---|---|---|---|---|---|---|---|
| LDN # | 120 | 99 | 103 | 98 | 113 | 94 | 62 | 33 |
| ODN# | 99 | 73 | 81 | 88 | 94 | 83 | 69 | 66 |
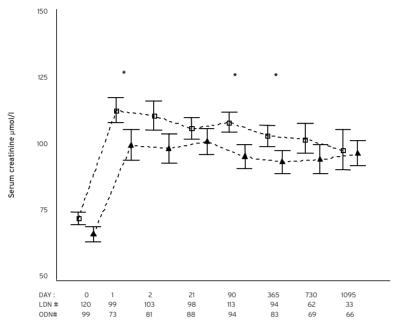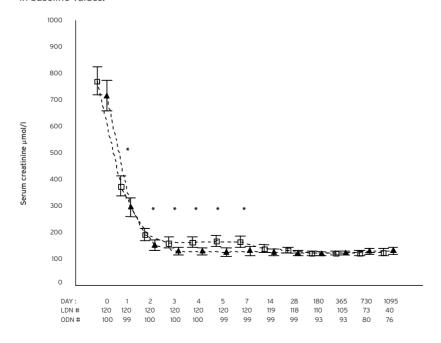
*Figure 2.2.*

**Geometric mean of serum creatinine (μmol/L) with 95% CI of recipients in time**

(open squares, LDN; closed triangles, ODN). *p < value 0.05 after correction for the difference in baseline values.



| DAY : | 0 | 1 | 2 | 3 | 4 | 5 | 7 | 14 | 28 | 180 | 365 | 730 | 1095 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDN # | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 119 | 118 | 110 | 105 | 73 | 40 |
| ODN # | 100 | 99 | 100 | 100 | 100 | 99 | 99 | 99 | 99 | 93 | 93 | 80 | 76 |

# Discussion

Ever since the first successful laparoscopic donor nephrectomy, the safety of this procedure for donor and recipient has been questioned. It is commonly known that pneumoperitoneum, necessary for the laparoscopic technique may cause intraoperative adverse cardiovascular and renal effects [9]. This study was conducted to investigate renal function (serum creatinine) in donor and recipient after ODN

*Figure 2.3.*

**Bar chart representing serum creatinine**

Grey represents LDN, Black represents ODN



and LDN. We found a significantly higher serum creatinine in LDN donors on day 1, 3 months, and 1 year after donation. Also, serum creatinine postdonation remained 40% higher than preoperative values. In recipients, serum creatinine was significantly higher in the LDN group during the first week after transplantation.

A clinical study by Ratner et al., comparing graft function in recipients after ODN and LDN, showed a higher serum creatinine on day 2 and 3 in the laparoscopic group [11]. Also, Nogueira et al. found a significant higher serum creatinine during the first week after transplantation in recipients of laparoscopically procured kidneys [10]. In accordance with their findings, we also found higher serum creatinine levels in recipients of laparoscopically procured kidneys in the first week after transplantation. After the first week, however, serum creatinine levels were comparable until three years posttransplant. There seems to be a short-term graft dysfunction in kidneys after laparoscopic donor nephrectomy compared to the kidneys from open donor nephrectomy. The laparoscopic and open groups in this study differ significantly with respect to the origin of the donor (living related or unrelated) and age. It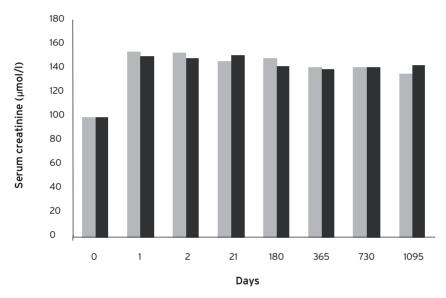 is, however, not very likely that this difference is the main causal factor for the short-term graft dysfunction. Terasaki et al. reported similar graft survival rates of unrelated kidney grafts compared to related kidney grafts [1]. With respect to the age, studies show a decreased graft survival in younger recipients compared to older recipients. The higher serum creatinine levels in the LDN group can not be explained by the age difference since the ODN group was younger [17,18]. Finally, after

adjusting for the differences between the two groups for age and origin, serum creatinine levels remained significantly higher the first week posttransplantation in the LDN group.

One very important discriminating factor between ODN and LDN is the pneumoperitoneum. This may explain the higher serum creatinine levels we found in the first week posttransplantation. In an animal model, Kirsch et al. showed that with an intra abdominal pressure (IAP) of 10 mmHg the blood flow in the caval vein was decreased by 54% and the aortic blood flow by 7%. Also, urine output was decreased and creatinine levels were elevated [19]. McDougall et al. demonstrated a significant decrease in renal vein flow concomitant with a drop in urine output at a pressure of 15 mmHg [20]. These effects persisted for several hours after desufflation. This transient renal dysfunction has been well documented and various mechanisms have been described to explain these changes, which are probably multi factorial. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression and systemic and regional hormonal effects. Cisek et al., in an animal model, performed renal reductive surgery and applied 20 mmHg IAP for 6 hr [21]. Dramatic drops in urine output (80%), GFR (63%), and renal blood flow (20%) were noted with concomitant acute renal failure related to tubular cell injury, without chronic renal failure. These observed blood flow changes suggested the possibility of renal tubular damage secondary to ischemia as a cause of oliguria during pneumoperitoneum. Altintas et al. showed significant histologic changes in rabbit kidneys after only 1 hr of pneumoperitoneum with pressures up to 15 mmHg [22]. Several authors, however, report reduced urine output and GFR without chronic damage to the tubula. Lee et al. found no histologic damage after 5 hr of pneumoperitoneum in a rat study, McDougall et al. confirmed a lack of histologic abnormality in kidneys rendered oliguric at pressures of 15 mmHg [23,20]. To counteract the effects of pneumoperitoneum expert anaesthesiologists and intense volume management are of major importance [24]. Also, it should be noted that intra-abdominal pressures must be as low as possible; keeping in mind that retroperitoneal donor nephrectomy does not require pneumoperitoneum, avoiding any negative effects of increased intra-abdominal pressure.

A decreased renal flow due to increased intra abdominal pressure might not only have a negative effect on the graft, but also on the remaining kidney in the donor. Serum creatinine levels in donors were significantly higher after LDN. Renal clearance is determined by renal blood flow and GFR, ($\mu$mol/L) of the donor in comparison to predonation values in time (light grey bars, LDN; dark grey bars, ODN). both are deprived during pneumoperitoneum up to 75% [25]. This so called prerenal azotemia (insufficient renal blood flow) leads to hormone release, which enhances hormonal directed tubular reabsorption and induces systemic and renal afferent artery vasoconstriction. Normally, prerenal azotemia leads predominantly to tubular ischemia and could lead to acute renal failure [26]. Interestingly, it has been demonstrated that the autoregulatory behavior of renal circulation is lost in laboratory animals with postischemic acute renal failure [27]. Of interest is that in both groups serum creatinine levels remained 40% higher than preoperative levels for both groups, comparable to Goldfarb et al. who found an increase of approximately 30% [15]. After unilateral nephrectomy, in literature creatinine clearance decreases by approximately 35% [2,15].

We acknowledge the fact that this is a retrospective study with significant differences in cohorts. Although, after adjusting for these differences with regression analysis the higher levels serum creatinine in LDN recipient the first week remained. We are currently monitoring LDN and ODN renal function in donor and recipient in a prospective fashion.

In conclusion, this retrospective study shows higher serum creatinine levels in recipients of laparoscopically procured kidneys in the first week after transplantation. It is reassuring that these levels normalize to comparable levels in ODNrecipients, until 3 years posttransplantation. Serum creatinine was found to be higher in the first year after donation in LDNdonors compared toODNdonors. Although serum creatinine from 1 year until 3 years posttransplant are comparable for LDN and ODN groups, serum creatinine levels remain approximately 40% higher than preoperative values.

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# CHAPTER

3

**Comparison of three perioperative fluid regimens for laparoscopic donor nephrectomy: a dose finding study**

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# Abstract

*Background:* Pneumoperitoneum (PP) as used for laparoscopic procedures, impairs stroke volume, renal blood flow, glomerular filtration rate and urine output. This study investigated whether peri-operative fluid management can abolish these negative effects of PP on hemodynamics.

*Methods:* Twenty-one patients undergoing laparoscopic donor nephrectomy (LDN) were randomized into three groups: group 1 received overnight infusion and received a bolus of colloid before induction of anesthesia, followed by a bolus just before PP; group 2 received overnight infusion and a colloid bolus before anesthesia; group 3 served as controls and received only infusion during operation. All three groups received the same total amount of crystalloids and colloids until nephrectomy. Data analysis of the donor included: mean arterial pressure (MAP), stroke volume (SV), left ventricular ejection time (LVETc), peri-operative urine output and renal function measured as the creatinine clearance (CrCl) until one-year post-transplantation.

*Results:* SV was significantly higher in group 1 compared to controls for all measurements. In the control group SV significantly decreased after changing from supine to lateral position whereas there was no change in SV in both pre-hydrated groups. In all groups, MAP decreased after induction of anesthesia, and restored to pre-anesthetic values during PP. CrCl decreased in the control group during PP, but not in the other groups. From 2 days postoperative, CrCl was comparable between the three study groups.

*Conclusion:* Overnight infusion and a bolus of colloid just before induction of PP attenuate hemodynamic compromise from PP.

## Introduction

Laparoscopic donor nephrectomy (LDN) has become the method of choice to procure kidneys from living donors, mainly because of the reduced procedure-related morbidity and faster convalescence period [1-3]. Despite the benefits to the donor, there are concerns over the transient deterioration of renal function in the recipient of the kidney procured by the laparoscopic technique, compared with open donor nephrectomy (ODN) [2,4-6]. The exact mechanism of delayed graft function after LDN is not fully understood.

Pneumoperitoneum (PP) elevates intra-abdominal pressure (IAP), causing a decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) resulting in oliguria [7-10]. In an animal model, London et al. have shown that PP resulted in a decrease in RBF during normal saline infusion, whereas RBF did not decrease if volume expansion was given [11]. From these results vigorous hydration up to 2 l/h of crystalloids during LDN in patients has nowadays been advocated [1,12-15].

In 52 patients, Bergman et al. [16] found, however, no difference in graft function after LDN between aggressive (> 10 ml.kg$^{-1}$.h$^{-1}$) and conservative (< 10 ml.kg$^{-1}$.h$^{-1}$) intra-operative fluid management. Volume loading after establishment of PP is perhaps too late in order to counterbalance the collapsed venal system. Biancofiore et al. [17] studied the effect of volume loading on graft function with a crystalloid infusion starting the night before surgery. Early graft function did not differ between ODN and LDN, although the serum creatinine declined earlier, but not significantly, in those receiving kidneys from ODN procedure.

Fasting before operation and induction of anesthesia leads to relative hypovolemia and the goal is therefore to compensate this before PP is started. In this study, we compared three different fluid regimes in LDN patients, in which the effect of pre-hydration together with a bolus of colloids given just before induction of anesthesia and a second one just before inflation of PP on hemodynamics was of special interest.

## Patients and methods

Patients undergoing LDN from June 2001 to November 2001 (N=21) were included in the study. The anesthetic procedure was performed according to a strict protocol for medication, ventilation and fluid regimen. In our hospital the donor patients are admitted the day before the operation, they are fasted during the night from 0.00 o'clock and operated on at 8.00 O'clock the next morning. Patients were randomized the day before operation by sealed envelopes by the responsible anesthetist to three different fluid regimens (Table 3.1): in Group 1 fluid administration was started at 10 pm the day before operation with 3 ml.ideal body weight $(IBW)^{-1}.h^1$ Ringers Lactate (RL) until operation. Before induction of

*Table 3.1*

**Infusion protocol used in the three groups**

| Group | n | ml RL.IBW-1.h-1 prehydration | ml RL.IBW$^{-1}$.h$^{-1}$ peroperative | ml HES.IBW$^{-1}$ before induction | ml HES.IBW$^{-1}$ before PP | ml HES.IBW.$^{-1}$h$^{-1}$ after PP | ml HES.IBW-1 total |
|---|---|---|---|---|---|---|---|
| 1 | 7 | 3 | 13 | 6 | 6 | | 12 |
| 2 | 7 | 2 | 13 | 6 | | 3x2 | 12 |
| 3 | 7 | | 16 | | | 3x4 | 12 |

*Column 2   n = number of patients*

*Column 3   Prehydration from 10.00 pm the day before laparoscopic donor nephrectomy, until operation.*

*Column 4   The amount of Ringer's Lactate given during operation, until nephrectomy in ml.IBW-1.h-1.*

*Column 5   Amount of 6% HES 130/0.4 given before induction of anesthesia.*

*Column 6   Amount of 6% HES 130/0.4 given before installation of pneumoperitoneum.*

*Column 7   Amount of 6% HES 130/0.4 given per hour after installation of pneumoperitoneum.*

*IBW = ideal body weight*

*HES = 6% HES 130/0.4*

*RL = ringers lactate*

anesthesia, the patients received 6 ml.IBW$^{-1}$ of colloid (6% HES 130/0.4), thereafter 13 ml.BW$^{-1}$.h$^{-1}$ RL was started until nephrectomy, before installation of PP another bolus of 6 ml.IBW$^{-1}$ colloid was given. Group 2 received overnight infusion in the same way as in group 1 and a bolus of 6 ml.IBW$^{-1}$ colloid just before induction. During operation, an infusion was started with 13 ml.IBW$^{-1}$.h$^{-1}$ RL and 2 ml/IBW/h of colloid was given for three hours. Group 3 was fasted from 0.00 o'clock on day of operation and received only an infusion during operation with 13 ml. IBW$^{-1}$.h$^{-1}$ RL and 4 ml.IBW$^{-1}$.h$^{-1}$ of colloid for three hours. After nephrectomy infusion protocol was adjusted, so that exactly six hours after start of operation all the patients had received in total 9 ml.IBW$^{-1}$.h$^{-1}$ RL. Patients were fitted with anti-thrombosis stockings.

Induction of anesthesia was performed with propofol (2 mg.kg$^{-1}$) after a bolus of sufentanil (0.3 µg.kg$^{-1}$). Muscle relaxation was achieved with rocuronium (0.8 mg.kg$^{-1}$) and monitored by train-of-four (TOF) guard, a bolus of rocuronium (0.3 mg.kg$^{-1}$) was given by 3 or more twitches. Anesthesia was maintained with propofol by continuous infusion (4-11 mg.kg$^{-1}$.h$^{-1}$), aiming at a bispectral index between 45 and 55 (BIS monitor; Aspect Medical Systems, Newton, MA, USA), and analgesia was achieved by continuous infusion of sufentanil (0.4 µg.kg $^{-1}$.h$^{-1}$) until nephrectomy. One hour after the start of operation 20 g mannitol was given intravenously.

After intubation all patients were ventilated in a pressure-controlled mode using a closed-loop ventilator (Physioflex®, Dräger, Lübeck, Germany) with the following initial settings: FiO$_2$ of 0.4, positive end-expiratory pressure (PEEP) of 7 cm H$_2$O and peak inspiratory pressure (PIP) of 22 cm

H$_2$O. Ventilation frequency was adjusted to keep PetCO$_2$ between 4 and 5.5 kPa. After induction of anesthesia and before positioning of the patient, an esophageal Doppler probe (HemoSonicTM 100, Arrow International Inc., Reading, PA, USA) was positioned for measuring stroke volume (SV) and left ventricular ejection time, corrected for heart rate (LVETc) [18-20].

After positioning the patient in full lateral nephrectomy position, PP was installed with an IAP of 12 mmHg, which was constantly maintained at this level. The same team of anesthesiologists and surgeons did all operations. The surgical techniques have been described in detail elsewhere [21].

Mean arterial pressure (MAP) and SV (available after induction of anesthesia) were monitored non-invasively every 5 minutes. Urine output was measured from 22.00 the day before until the introduction of PP (T0), then urine output was measured every hour up to 6 hours hereafter (T1-6). Blood samples of the donors were collected to determine creatinine levels the day before operation, after induction of anesthesia, 6 hours after installation of PP, two days, one month, and 1 year after operation. Creatinine clearance (CrCl) was determined using the Cockcroft-Gault formula [22].

### Statistics

Data analysis was performed using SPSS for Windows (version 14.0, SPSS Inc., Chicago, USA). Data are presented as means with standard deviation (SD). Differences between the groups were analyzed using the independent t-test, depending on the Levene's test, pooled or not pooled. Repeated measures with a general linear model from SPSS were used to assess significance for CrCl. A $p$-value <0.05 (two-sided) was considered statistically significant.


## Results

Baseline characteristics are shown in Table 3.2 and were comparable between the three groups. After induction of anesthesia, SV was significantly higher in both pre-hydrated groups compared to the control group (Fig. 3.1). After repositioning from supine to lateral, SV decreased significantly in the control group whereas not in groups 1 and 2 (Fig. 3.1). After instillation of PP, SV remained stable in group 1 but not in groups 2 and 3 (Fig. 3.1).

After induction, LVETc was higher in group 1 compared to the control group during the whole procedure and remained stable (Table 3.3). In all groups MAP decreased after induction of anesthesia; in the control group MAP decreased significantly more compared to group 1 ($p$ = 0.03). HR was comparable between the 3 groups (Table 3.3).


*Table 3.2*

**Demographic data on the three groups**

|                      | group 1   | group 2   | group 3   |
| -------------------- | --------- | --------- | --------- |
| Age (yrs)            | 56 (11)   | 53 (9)    | 55 (12)   |
| Weight (kg)          | 72 (9)    | 82 (8)    | 74 (7)    |
| IBW (kg)             | 70 (8)    | 78 (8)    | 71 (6)    |
| Male/female          | 2/5       | 4/3       | 3/4       |
| Operation time (min) | 237 (37)  | 251 (46)  | 226 (31)  |

*IBW = ideal body weight*

*Data are mean (SD)*

*Table 3.3*
**Data on hemodynamic parameters**

| | preop | supine | lateral | PP30 | PP60 | PP90 | PP120 |
|---|---|---|---|---|---|---|---|
| **HR** | | | | | | | |
| group 1 | 65 (6) | 65 (13) | 63 (20) | 60 (9) | 61 (8) | 60 (10) | 61 (9) |
| group 2 | 63 (11) | 60 (9) | 61 (14) | 62 (11) | 61 (9) | 63 (6) | 63 (8) |
| group 3/control | 73 (9) | 69 (14) | 61 (6) | 65 (10) | 63 (6) | 60 (7) | 61 (6) |
| **MAP** | | | | | | | |
| group 1 | 102 (11) | 85 (13)* # | 81 (19)* | 93 (14) | 96 (15) | 94 (17) | 98 (20) |
| group 2 | 102 (14) | 73 (10)* | 81 (15)* | 107 (10) | 107 (18) | 104 (8) | 102 (12) |
| group 3/control | 105 (12) | 70 (11)* | 79 (7)* | 103 (9) | 98 (11) | 95 (12) | 95 (15) |
| **LVETc** | | | | | | | |
| group 1 | | 336 (19)# | 339 (20)# | 355 (26)# | 345 (31) | 335 (30) | 336 (33) |
| group 2 | | 313 (29) | 308 (39) | 295 (58)° | 311 (20)° | 308 (27) | 300 (28) |
| group 3/control | | 294 (26) | 284 (31) | 292 (26) | 307 (18) | 309 (18) | 311 (25) |

*\* p < 0.05 versus preoperative values*

*# p < 0.05 group 1 and 2 versus control group*

*° p < 0.05 group 1 versus group 2*

*Data are mean (SD)*

*Column 1;  HR=heart rate, MAP=mean arterial pressure, LVETc=left ventricular ejection time*

*Column 2; preop;   before anesthesia*

*Column 3; supine;  after induction of anesthesia, supine position*

*Column 4; lateral;  full lateral position*
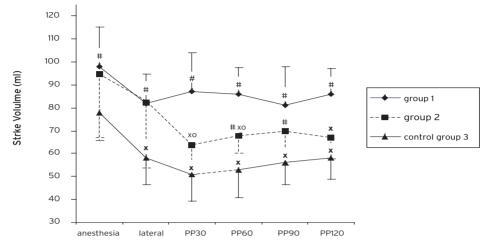
*Column 5; PP30;   mean measurement the first 30 minutes after installation of pneumoperitoneum*

*Column 6; PP60;   mean measurement the second 30 minutes after installation of pneumoperitoneum*

*Column 7; PP90;   mean measurement the third 30 minutes after installation of pneumoperitoneum*

*Column 8; PP120;  mean measurement the fourth 30 minutes after installation of pneumoperitoneum*

Urine output, measured from the start of operation until the moment of kidney extraction, was 1.9  ml.kg$^{-1}$.h$^{-1}$ (range 1.2-3.2) for group 1, 1.4 ml.kg$^{-1}$.h$^{-1}$ (range 0.8-2.3) for group 2, and 1.1 ml.kg$^{-1}$.h$^{-1}$ (range 0.6-1.6) for group 3. In controls, the urine production was significantly lower compared to group 1 ($p$=0.01). CrCl decreased in the control group directly after PP, but not in the other groups (Table 3.4). From 2 days postoperative, CrCl was comparable between the 3 study groups (Table 3.4).

CHAPTER

3

*Figure 3.1*

**Stroke volume changes during laparoscopic donor nephrectomy, comparing three different fluid regimens**



# *p < 0.05 group 1 and 2 versus control group*

° *p < 0.05 group 1 versus group 2*

x *p < 0.05 versus supine position*

*Data are mean (two times standard deviation)*

## Discussion

This study showed that during LDN preoperative hydration together with a bolus of colloid given before induction of anesthesia and before installation of PP resulted in higher SV and more urine output compared to a fluid regimen with only an intra-operative aggressive fluid infusion. Also the second group, that received no bolus of colloid before PP compared to group 1, showed a significant reduction in SV after installation of PP. In the control group, LVETc and urine output at the moment of kidney extraction showed significantly lower values compared to both pre-hydration groups. CrCl values six hours after start of the operation was significantly reduced in the control group compared to pre-operative values but not in the both pre-hydrated groups; this difference was reduced two days postoperatively.

Clinical studies yield conflicting data concerning the effect of LDN on recipient graft function compared to ODN. The largest study to date compared more than 5000 kidney transplants from a database and found that LDN was associated with slower early graft function compared to ODN. However, renal function and graft survival at 1 year was similar between both groups. This was confirmed by retrospective analysis of 120 LDN and 100 ODN in our own institution in which serum creatinine in the recipients was significantly higher in the LDN group only in the first week after transplantation [4]. One very important discriminating factor between ODN and LDN is the pneumoperitoneum. From experimental studies it has become clear that PP decreases RBF and that the magnitude of this decrease is affected by the IAP used, the volume status, and positioning. To counterbalance the increased IAP, vigorous intravenous hydration during LDN has nowadays been recommended in an attempt to optimize preload and promote diuresis but randomized clinical data are missing. In a porcine model, Demyttenaere et al. [23] showed that the decrease in SV and renal cortical perfusion could be prevented by a simple hydration of 15 ml.kg.$^{-1}$h$^{-1}$ saline combined with a bolus 20

*Table 3.4*

**Data on creatinine clearance in the three groups**

|  | group 1 | group 2 | Control group 3 |
| --- | --- | --- | --- |
| CrCl preop (ml.min-1) | 89 (19) | 101 (25) | 102 (34) |
| CrCl after induction (ml.min-1) | 104 (18) | 109 (20) | 96 (31) |
| CrCl after the operation (ml.min-1) | 87 (17) | 94 (14) | 73 (23)[a] |
| CrCl D2 (ml.min-1) | 63 (10)* | 65 (11)* | 64 (19)* |
| CrCl 1 month (ml.min-1) | 63 (12)* | 67 (11)* | 63 (24)* |
| CrCl 1 year (ml.min-1) | 71 (13) | 71 (13)* | 66 (25)* |

*\* p < 0.05 versus preoperative values*

*[a] p < 0.05 difference between CrCl preop and CrCl after operation, control group versus group 1 and 2*

*Data are mean (SD)*

*CrCl preop;           creatinine clearance one day before operation*

*CrCl after induction;      creatinine clearance just after induction of anesthesia*

*CrCl after the operation; creatinine clearance at around 14.30 pm, 6 hours after installation of pneumoperitoneum T6*

*CrClD2;            creatinine clearance two days after operation*

*CrCl1month;          creatinine clearance one month after operation*

*CrCl1year;           creatinine clearance one year after operation*

ml.kg^{-1} saline, in accordance with the findings of London et al. [11] This was also seen in the present study in which pre-hydration with a normal infusion with crystalloids during operation combined with a bolus of colloids just before PP did not decrease SV and improved diuresis. Besides PP, the kidney lateral decubitus position, which is an anti-Trendelenburg position, contributes to hemodynamic alterations by decreasing preload through the effect of gravity on venous return [24]. Yokoyama et al. [25] found no significant change in hemodynamic values after postural change of their patients from supine to lateral but a significant reduction in SV after postural change to kidney position; these patients received a fluid regime of 20 ml.kg^{-1}.h[-1] of crystalloids. This was confirmed by our study in which the control group showed a significant reduction in SV after postural change from supine to kidney position whereas there was no reduction in both pre-hydrated groups which received a bolus of colloid just before induction (Fig. 3.1).

After prehydration with crystalloids we infused colloids to achieve optimal plasma expansion just before installation of PP [26]. In our hospital we use 6% HES 130/0.4 for fluid expansion, because the rate for anaphylactic reactions is considerably lower than for gelatin products [27]. However, there are concerns that infusion of certain HES types may influence kidney function [28]. As long adequate hydration using sufficient amounts of crystalloids are used, the latest generation of HES products (6% HES 130/0.4) does not increase the risk for renal dysfunction even when used in large amounts [29-30]. Lang et al. [31] even demonstrated that 6% HES 130/0.4 improved tissue oxygenation during and after major surgical procedures, compared with a crystalloid-based volume strategy.

In this study, we used the HemoSonic[TM], a Transoesophageal Doppler ultrasonography (TOD) device, to measure blood flow in the descending aorta. Several studies have confirmed a good correlation with cardiac output measured by the thermodilution technique [18-32]. It is shown that the accuracy of the device is somewhat operator-dependent [20] and therefore the same 2 persons did all the measurements with this device in the present study. Feldman et al., used LVET to guide their fluid management in LDN patients [33]. In the present study it was shown that LVETc was significantly lower in the control group that did not received pre-hydration and increased over time (Table 3.2). It should,

however, be taken into account that the blood flow with this device is measured in the descending aorta, which is around 70% of the total cardiac output. This could be of influence on our measurements if redistribution of flow away from the descending aorta occurs because of elevated IAP and this is more pronounced in hypovolemic patients.

Some other limitations of this study should be noted. In only 4 patients a MAG3 scan was performed which provides the distribution of the function from the two kidneys of the donor. In the four measured patients the harvested kidney contributed 43- 48% of the total kidney function, these four patients were divided over all three study groups. However because we do not have the data on the other patients, this could have biased our data on postoperative CrCl. Prehydration of the donor patients conform our protocol, started the night before operation, which contradicts fast track surgery were kidney donor patients are admitted to hospital on the day of surgery. Also these patients can receive adequate prehydration, but further research should be done.

In this study we focused on intraoperative hemodynamic changes, our data show that preoperative hydration together with a colloid bolus given before induction of anesthesia and before installation of PP resulted in higher SV and more urine output during LDN, compared to controls that received only an aggressive intra-operative infusion. While under-hydration may contribute to renal dysfunction, perioperative fluid excess can also cause problems, such as pulmonary edema, ileus and increased risk of cardiopulmonary and wound healing complications, which might results in longer hospital stay [34]. However, there is a need to ensure adequate hydration status during PP without being over-aggressive. First, our fluid regime will be tested in a large prospective study in order to prevent the negative effect of PP on early graft function in the recipient, and to study the possible side effects in the donor.

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CHAPTER

3

# CHAPTER

4

**Effects of intra-abdominal pressure elevation and positioning on hemodynamic responses during carbon dioxide pneumoperitoneum for laparoscopic donor nephrectomy**

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# Abstract

*Background:* Carbon dioxide ($CO_2$) pneumoperitoneum (PP) increases mean arterial blood pressure (MAP) and systemic vascular resistance (SVR) but decreases stroke volume (SV) and cardiac output (CO). This study evaluated the hemodynamic effects of elevated intra-abdominal pressure (IAP), occurring during laparoscopic donor nephrectomy (LDN).

*Methods:* Twenty-two patients undergoing LDN were investigated and hemodynamic parameters, $P_vCO_2$ (carbon dioxide partial pressure), and $VCO_2$ (carbon dioxide production) were monitored during the procedure. Before and after PP, IAP was raised from 12 to 20 mmHg and the hemodynamic effects were measured every 30 seconds.

*Results:* During IAP of 12mmHg and stable serum $CO_2$, there was no change in SV, compared to preinsufflation levels. When IAP was elevated from 12 to 20 mmHg, SV initially decreased ($p < 0.05$), followed by an increase in MAP and SVR ($p < 0.05$).

*Conclusion:* This study shows that with the fluid and ventilation protocol used, PP has no significant effect on SV at an IAP of 12 mmHg, whereas increasing IAP to 20 mmHg does. In this study the hemodynamic effects induced by $CO_2$ PP of 12 mmHg are not due to changes in serum $CO_2$. Compression of the venous system during PP of 20 mmHg reduces preload with a subsequent increase in SVR.

## Introduction

There has been a dramatic increase in laparoscopic procedures, mainly because of the consequent reduction in procedure-related morbidity. Advances in laparoscopic techniques have made procedures such as laparoscopic donor nephrectomy (LDN) possible. It has been shown, that increased intra-abdominal pressure (IAP) during carbon dioxide pneumoperitoneum ($CO_2$ PP) is associated with increased mean arterial blood pressure (MAP) and systemic vascular resistance (SVR), together with decreased stroke volume (SV) [1,2]. In addition, impaired renal blood flow (RBF) and glomerular filtration rate (GFR), with oliguria and anuria have been reported [3-6]. Various mechanisms, such as venous compression caused by elevated IAP (with compression of abdominal vasculature and organs), and the pharmacological action of the absorbed $CO_2$, have been proposed to explain these transient adverse hemodynamic and renal effects [7-11].

To analyze the mechanisms occurring perioperatively during PP, we studied the hemodynamic changes on line with new Doppler techniques. This technology enables SV, left ventricular contraction and preload to be measured on a beat-to-beat basis [12].

The aim of the study was to determine the effect of IAP elevation on hemodynamic parameters during $CO_2$ PP for LDN.

## Patients and methods

The local ethical committee of the Erasmus Medical Center approved this study. From November 2001 to November 2002, twenty-two patients undergoing LDN were included in the study. Exclusion criteria were the use of β-blockers and Ca antagonists. All patients were classified as ASA 1 or 2. Patients received 1000 mg paracetamol 1 h before operation and were fitted with anti-embolic stockings.

The anesthetic procedure was performed according to a strict protocol for medication, ventilation and fluid regimen. Ideal body weight (IBW) was calculated according to body height, gender and age.

Peri-operative fluid management was as follows: the day before operation intravenous fluid administration was started at 10 PM, with 3 ml. $IBW^{-1}.h^{-1}$ Ringer's lactate (RL) until the operation. Before induction of anesthesia, the patients received 6 ml.$IBW^{-1}$ of 6% hetastarch 130/0.4, thereafter ml. $IBW^{-1}.h^{-1}$ RL was started, and before initiating PP another bolus of 6 ml.$IBW^{-1}$ 6% hetastarch 130/0.4 was given. Induction of anesthesia was performed with 2 mg.$IBW^{-1}$ propofol 1% after 0.3 μg.$IBW^{-1}$ of sufentanil. Muscle relaxation was achieved with 0.8 mg.$IBW^{-1}$ of rocuronium. Anesthesia was continued with propofol 1% with 40% oxygen aiming at a bispectral index between 45 and 55 (BIS monitor; Aspect Medical Systems, Newton, MA,USA), and analgesia was given by continuous infusion of 0.4-μg.$IBW^{-1}.h^{-1}$ sufentanil. Muscle relaxation was monitored by train of four (TOF) ulna nerve stimulation guard, and kept under 3 twitches at 60 mA stimulation. Rocuronium 10 to 20 mg was given when necessary. One hour after the start of operation 20 g mannitol (100 cc, 20%) was given. Lungs were ventilated with a closed-loop ventilator (Physioflex®, Dräger, Lübeck, Germany). Initially, the same ventilator settings were used in all patients: pressure controlled ventilation (PCV), positive end-expiratory pressure (PEEP) 7 cm $H_2O$ and peak inspiratory pressure (PIP) of 22 cm $H_2O$, with first ventilation frequency and (where necessary) PIP were adjusted as required to keep $PetCO_2$ between 4 and 5.5 kPa.

After induction of anesthesia, a NICO monitor (Novametrix, Medical Systems Inc., Wallingford, CT, USA), and an esophageal Doppler probe (HemoSonic™ 100, Arrow International Inc., Reading, PA, USA) were installed. The NICO monitor was used to measure $CO_2$ output per minute ($VCO_2$). The HemoSonic device was used to measure SV, and left ventricular ejection time (LVET), which is a parameter for preload and acceleration (Acc), which is a parameter for contractility of the left ventricle measured in

the aorta descendens [13]; cardiac output (CO) and SVR were calculated using the HemoSonic device.

MAP was monitored non-invasively every 5 min; HemoSonic parameters (available after induction of anesthesia and intubation) were monitored every 15 s. After induction of anesthesia a venous blood sample was collected to determine pH and $PvCO_2$. After the patient was positioned in the lateral decubitus position, PP was installed with an IAP of 12 mmHg. Data were recorded in the supine position before and after induction of anesthesia: directly after lateral positioning; and in the 1st, 2nd and 3rd hour of PP.

Two additional periods of separate measurement were made at the beginning of PP (period A) and at the end of PP (period B), in which the IAP was raised from 12 to 20 mmHg.

During period A, data collection was started after stabilization of hemodynamic parameters for 10 min, with an IAP of 12 mmHg. Venous blood samples were collected to determine pH and PvCO2, and two sets of data ($VCO_2$, CO, SV, LVET, Acc, MAP, SVR) were recorded at an IAP of 12 mmHg (level 1). Hereafter, an IAP of 20 mmHg was installed in 30 sec (level 2); for 3 min hereafter, six sets of data were recorded. Then IAP was lowered again to 12 mmHg in 30 sec (level 1) and four sets of data were recorded, in the following 2 min. During this procedure the ventilator setting and the anesthesia protocol remained unchanged. The surgical procedure was then started. During period B, after nephrectomy, the same data were collected in the same way as in period A.

### Statistics

Data were analyzed using SPSS for Windows (version 10). Data are presented as means and SD. Differences measured during PP over time were analyzed with repeated-measures analysis of variance (ANOVA). Differences between period A and B were analyzed using paired sample t-tests.

Statistical significance was accepted at $p < 0.05$.

# Results

Table 4.1 gives the demographic data for the 22 patients included in the study. Mean propofol infusion during the study period was 7 mg.kg. -1h-1. After induction of anesthesia and positioning of the patient in the lateral position mean MAP decreased from 99 mmHg to 78 mmHg ($p < 0.001$), but then increased significantly during the 1st to 3rd hour of PP (91 mmHg; range, 65-125) (Table 2). After lateral positioning, SV decreased (15%; $p = 0.044$), but induction of an IAP of 12 mmHg had no significant effect on SV (Table 4.2). There was no significant change in heart rate (mean, 68 b/min) during the entire procedure.

Between period A and B the mean duration of PP was 190 (range, 112-249) min. During this period

*Table 4.1*

**Demographic data on the 22 study patients, undergoing laparoscopic donor nephrectomy.**

|  | N = 22 |
| --- | --- |
| Age in years, mean (range) | 47 (21-70) |
| Sex  Males | 12 |
|     Females | 10 |
| Weight in kg, mean (range) | 82 (50-118) |
| IBW in kg, mean (range) | 76 (55-100) |
| Operated side  Left | 14 |
|     Right | 8 |

*IBW; ideal body weight*

*Table 4.2*

**Data on mean arterial pressure (MAP) and cardiac output (CO) during laparoscopic donor nephrectomy.**

|  | MAP (mmHg) | p-value | SV (ml) | *p*-value |
|---|---|---|---|---|
| Time 1<br>Before anesthesia | 99 (17.1) |  |  |  |
| Time 2<br>Supine position after induction of anesthesia | 82 (17.6) | 0.0017 | 93 (20) |  |
| Time 3<br>Lateral nephrectomy position | 78 (17.8) | n.s. | 79 (21) | 0.044 |
| Time 4<br>First hour of pneumoperitoneum | 91 (17.8) | 0.006 | 84 (23) | n.s. |
| Time 5<br>Second hour of pneumoperitoneum | 90 (17.7) | n.s. | 82 (19) | n.s. |
| Time 6<br>Third hour of pneumoperitoneum | 94 (19.5) | n.s. |  |  |

*Data are mean (standard deviation); n.s. = nonsignificant*

*MAP and SV were compared with the previous outcome*

$VCO_2$ rose significantly from 182 (range, 82-250) to 218 ml.min-1 (range, 134-310); ($p$ = 0.014). Minute ventilation was raised with 8%, mainly by an increase in frequency from 11 to 14 times per min (27%); PIP was reased from 23 to 25 kPa (9%).

A comparison of LVETc before period A and before period B showed no significant change. Venous pH and $PvCO_2$ did not change during ventilation and between period A and B, and it stayed within physiologic limits (Table 4.3). After IAP was increased from 12 to 20 mmHg in period A and B, there was a significant and immediate (within 90 sec) reduction in SV and CO. There was a significant increase in MAP and SVR, within 120 s (figure 4.1a and 4.1b). Ventricular contraction measured with acceleration did not change (mean13 ± 4) during the increase in IAP from 12 to 20 mmHg.

Mean changes in SV and MAP during period A and B are given in Table 4.4. Mean blood loss was 283 ml.

*Table 4.3*

**Data on $VCO_2$, pH and $PvCO_2$ at the beginning of period A and B.**

|  | Period A | Period B | p-value |
|---|---|---|---|
| $VCO_2$ | 182 (46.2) | 218 (42.3) | 0.014 |
| pH | 7.37 (0.04) | 7.35 (0.04) | n.s. |
| $PvCO_2$ | 5.82 (0.69) | 5.84 (0.69) | n.s. |

*Data are mean (standard deviation); n.s. = nonsignificant*

*Values for Period A and B were compared with each other.*

**Figure 4.1a**
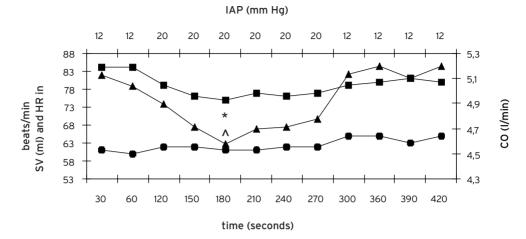


**Figure 4.1b**
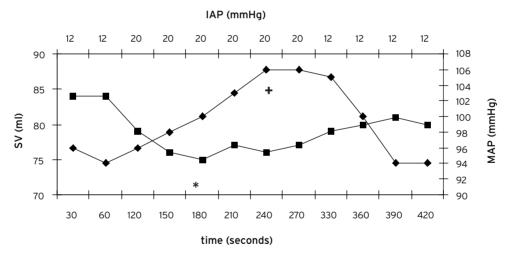


*Figure 4.1a Stroke volume ■ , cardiac output ▲ , and heart rate ■ every 30 seconds at 12 and 20 mmHg intra-abdominal pressure (IAP), in period A and B.*

*Figure 4.1b Stroke volume ■ and Mean arterial blood pressure ◆ every 30 seconds at 12 and 20 mmHg intra-abdominal pressure (IAP), in period A and B.*

*Between two IAP levels 30 seconds were needed to achieve the desired IAP.*

*\* Significant difference for SV, time 180s vs. 30 and 60s*

*^ Significant difference for CO, time 180s vs. 30 and 60s*

*+ Significant difference for MAP, time 180s vs. 30 and 60s*

*(T test, p- value< 0.05)*

*Table 4.4*

**Data on stroke volume (SV), mean arterial pressure (MAP) and systemic vascular resistance (SVR) in laparoscopic donor nephrectomy, during a period of elevated IAP (from 12 to 20 mmHg),**

**Period A**

|  | IAP 12 mmHg | IAP 20 mmHg | p-value | IAP 20 mmHg | p-value |
|---|---|---|---|---|---|
| SV ml (SD) | 84 (24) | 78 (21) | 0.016* | 80 (21) | 0.018* |
| MAP mmHg (SD) | 91 (16) | 101 (15) | 0.001* | 98 (14) | 0.011* |
| SVR (SD) | 1581 (634) | 1874 (795) | 0.001* | 1753 (797) | 0.006* |

**Period B**

|  | IAP 12 mmHg | IAP 20 mmHg | p-value | IAP 20 mmHg | p-value |
|---|---|---|---|---|---|
| SV ml (SD) | 83 (19) | 76 (20) | 0.001* | 80 (20) | 0.001* |
| MAP mmHg (SD) | 98 (21) | 103 (21) | 0.001* | 98 (19) | 0.001* |
| SVR (SD) | 1529 (540) | 1763 (631) | 0.001* | 1530 (453) | 0.001* |

*\* Significant IAP 12 vs. IAP 20 and IAP 20 vs. IAP 12*
*Mean data of SV, MAP and TSVR during IAP 12 mmHg were compared with mean data of SV, MAP and TSVR during IAP elevation of 3 min to 20 mmHg. After pressure decrease back to 12 mmHg, data were compared again. Data were gathered every 30 sec.*

## Discussion

Laparoscopy requires the establishment of pneumoperitoneum to obtain adequate surgical exposure, and $CO_2$ is still the most commonly used gas. The clinical importance of renal and cardiovascular changes has been tempered by the fact that most laparoscopic procedures are short and generally performed in relatively healthy subjects. However, with the rapid expansion of indications for laparoscopic surgery, more advanced and longer procedures, such as LDN, are now performed.

In our study group, PP was induced with a mean duration of 190 min. During such a time period, in case of insufficient renal blood flow (pre-renal azotemia), ischemic renal injury can result in acute tubular necrosis in both the kidney for donation and the remaining kidney [1]. The impaired postoperative short-term function of human LDN kidney transplants may be caused by the same mechanism [15,16]; thus, prevention of PP-induced pre-renal azotemia is important. However, direct assessment of renal hemodynamic and renal tubular function is not easily obtained in the clinical setting. Instead as in this study, indirect variables such as MAP, SV, CVP and urine output (UO) are useful parameters.

Both systemic $CO_2$ accumulation and compression of vessels and organs due to increased IAP have been proposed as mechanisms that cause the negative effects on hemodynamics during $CO_2$ PP [3, 7-10]. If the main cause is $CO_2$ accumulation, then, because of the elevated $PCO_2$, primarily systemic vascular resistance will increase and contractility of the left ventricle will be impaired. If the main cause is the increased IAP, then a decrease in preload will be expected because of vascular compression, followed by compensatory systemic vascular resistance increase.

This study was performed with the idea that the mechanical compression of organs and vessels is the main cause of the change in hemodynamics. Other studies have shown that the amount of hemodynamic reaction due to PP is greatly affected by intravascular volume, and changes in SV are

variable and often reflect changes in intravascular volume loading. In those studies augmentation of circulating intravascular blood volume attenuates these hemodynamic changes as well as the renal response during increased IAP. Therefore vigorous intra-operative hydration is now advised [16,18].

In our study, an optimal intravascular volume was achieved, as confirmed by an optimal LVET. Due to our fluid management, SV did not change significantly after installation of an IAP of 12 mmHg; however it did change when the patient was positioned in the kidney rest lateral decubitus position (with legs are in the Trendelenburg position). Yokoyama et al.[19] found comparable results when changing to the kidney rest lateral decubitus position; in this position, there was a reduction in MAP and SV, and SVR increased. Our study shows that intravascular volume shift after the position change is of primary importance for SV during the LDN procedure, whereas an increase in IAP to12 mmHg on its own did not suppress SV any further.

During period A and B, when IAP was elevated from 12 to 20 mmHg for 3 min, an immediate and significant reduction of SV was observed within 90 s (Fig. 4.1a and b) followed by MAP and SVR elevation, which was significant after 120 s (Fig. 4.1b). Thus, with an increase in IAP from 12 to 20 mmHg, preload reduction is evident and this precedes afterload elevation; contractility of the heart measured during this procedure did not change. Changing IAP from 20 back to12 mmHg reversed the observed hemodynamic changes.

At the start of periods A and B, we had expected a difference in $PvCO_2$, because of the intraabdominal inflated $CO_2$. There was a significant increase in VCO2 from the start of period A to B, but adjustment of the pressure-controlled ventilation enabled the maintenance of Pet $CO_2$ and $PvCO_2$ at preinsufflation levels. First, we raised minute ventilation as necessary to maintain a stable Pet $CO_2$, using frequency alone; this was done to ensure a minimum elevation in intrathoracal pressures. We needed to elevate PIP with only 9%. Our study in ASA I and II patients demonstrates that with sufficient alveolar ventilation and SV, it is possible to remove $CO_2$ adequately. No hypercarbia or respiratory acidosis were observed during the 190 min of PP, despite a significant increase in $VCO_2$. Thus, the elevation of SVR and MAP during an IAP of 12 mmHg, cannot be explained by hypercarbia. During the elevation in IAP from 12 to 20 mmHg (period A and B) ventilation was not adapted, and it is likely that $PCO_2$ increased. However the hemodynamic changes occurred after only 30 seconds. We think it unlikely that changes in $PCO_2$ or hormones are responsible for this quick change in hemodynamics. And ventricular contraction was not impaired during this procedure, probably indicating no substantial increase in $PCO_2$.

Catecholamines, the renin-angiotensin-aldosteron system, and vasopressin are all released during PP, contributing to increased afterload [1,20-23]. It is possible that hormone induction caused by increased IAP explains the increase in SVR and MAP that we observed during IAP of 12 mmHg. However because we did not measure hormones we are unable to draw conclusions about their influence.

In conclusion, appropriate ventilation and adequate volume status during LDN with an IAP of 12 mmHg is sufficient to prevent SV reduction. With a higher IAP level MAP, SV and SVR change considerably, and a primary reduction in preload is observed followed by an increase in afterload. This study demonstrates that hemodynamic stress due to PP during LDN is due to the reduction in preload that occurs as a result of caval and/or renal vein compression and elevated venous resistance.

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# Beneficial effects of a new fluid regime on kidney function of donor and recipient during laparoscopic versus open donor nephrectomy

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## Abstract

*Background*. Laparoscopic donor nephrectomy (LDN) has been associated with delayed graft function compared with open donor nephrectomy (ODN). We have recently shown that the adverse effect of pneumoperitoneum (PP) on hemodynamics could be prevented by a new fluid regime. The aim of this study was to test the effect of this fluid regime on the kidney function of the donor and recipient after LDN and ODN.

*Methods*. We prospectively collected data of 51 donors undergoing ODN and 59 donors undergoing LDN as well as data from the corresponding recipients. Baseline characteristics of the two groups were comparable. All donors and recipients were treated with a standardized anesthesia and fluid regime. This fluid regime consisted of preoperative overnight hydration together with a bolus of colloid given before induction of anesthesia and before introduction of PP.  Follow-up was two years.

*Results*. Hemodynamics and urine output until nephrectomy were comparable between both groups. Donor kidney function did not differ after ODN and LDN. Estimated glomerular filtration rate, graft survival and recipient survival did not differ between open and laparoscopic procured transplants. No adverse effects of the novel fluid regime (eg, pulmonary edema, or additional oxygen supply) were observed in the donors.

*Conclusion*. In contrast to our earlier findings, the kidney function of the donor and recipient is comparable between ODN and LDN after introduction of a new fluid regime.

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## Introduction

Kidney transplantation from live donors has become the preferred treatment for end-stage renal disease in many Western countries because of short waiting lists, excellent initial transplant function, and long average graft survival compared with transplantation from deceased donors [1].

Laparoscopic donor nephrectomy (LDN) has become the gold standard to procure the transplant in live donors because this approach is associated with a less intense recovery phase and a superior quality of life compared with open surgery [2-5]. However, serum creatinine values of the donor and recipient appeared to be temporarily higher after LDN and delayed graft function occurred more often [6-11]. Until the prognostic value of these findings on long-term renal function in donor and recipient is established, it is necessary to optimize short-term renal function of donor and recipient after LDN.

The pneumoperitoneum (PP), which has to be established during LDN, is considered one of the causative factors affecting renal function [6,12,13]. Clinical and experimental studies have demonstrated that increased intra-abdominal pressure (IAP) may disturb hemodynamics. This can result in oliguria and transient renal dysfunction because of impaired renal blood flow (RBF), which is, in turn caused by compression of the renal parenchyma and venous system [14-18]. In an effort to minimize renal blunting, vigorous intra-operative hydration has been shown to prevent RBF decrease caused by PP [12,19-21]. However, this did not correct the impaired creatinine clearance as observed during PP [12,19-21]. In contrast, we have shown that preoperative hydration together with a bolus of colloid given before induction of anesthesia and before installation of PP resulted in higher stroke volume and more urine output during LDN, compared with controls, who received only an aggressive intra-operative infusion [22].

While under hydration may contribute to renal dysfunction, perioperative fluid excess can also cause problems, such as pulmonary edema, ileus and increased risk of cardiopulmonary, and wound-healing complications.

In a prospective study investigating donor-experienced benefits after LDN versus ODN initiated by our surgeons, we studied whether this fluid regime, that combines aggressive preoperative and standardized intra-operative hydration, could solve the delayed graft function seen after LDN, but without side-effects for the donor after laparoscopic live kidney donation.

## Patients and methods

A total of 116 donors were scheduled for LDN between November 2001 and January 2004. Six donors were excluded from the present analysis because a different fluid regime was applied (n=4) or because the open surgical approach was different (n=2). Data of all the donors and the corresponding recipients were prospectively collected. These patients also participated in another study that investigated donor-experienced benefits after LDN versus ODN [2,23]. The local medical ethics committee approved the study protocol.

Overnight infusion with lactate Ringer's solution (RL, 3 ml.kg$^{-1}$.h$^{-1}$) was started 10 hours before the operation. Before induction of anesthesia, the donor received a bolus of colloids (6 ml.kg$^{-1}$; 6% Hetastarch 130/0.4-HES). During the operation, RL (13 ml.kg$^{-1}$.h$^{-1}$) was administered. Before inflation of the peritoneal cavity, a second bolus of colloids (6 ml.kg$^{-1}$; 6% Hetastarch 130/0.4-HES) was administered. Each ml blood loss was replaced with HES (ratio 1:1). One hour after the start of surgery, 20 g mannitol was administered intravenously. After nephrectomy the infusion protocol was adjusted, so that exactly six hours after start of operation all the patients had received in total 9 ml.kg$^{-1}$.h$^{-1}$ RL. Intra-operatively, anti-thrombotic stockings were routinely used to improve venous return.

Induction of general anesthesia was performed with propofol (2 mg.kg$^{-1}$); sufentanil (0.3 μg.kg$^{-1}$) was also administered, and muscle relaxation was achieved with rocuronium (0.8 mg.kg$^{-1}$).

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Anesthesia was maintained with continuous infusion of propofol (3-12 mg.kg$^{-1}$.h$^{-1}$) or isoflurane (0.5-1.2%) maintaining the bispectral index between 40 and 60 (BIS monitor; Aspect Medical Systems, Newton, MA, USA). Analgesia was maintained by continuous infusion of sufentanil (0.4-$\mu$g.kg$^{-1}$.h$^{-1}$) until nephrectomy. At the end of the operation donors received an intravenous bolus of morphine (0.06 mg.kg$^{-1}$).

For postoperative pain management, all donors received an intravenous patient-controlled analgesia (PCA) pump with morphine (1 mg.ml$^{-1}$, bolus 1 ml; lock-out time 5 minutes) and 1000 mg acetaminophen four times daily. The PCA device was removed when morphine had not been required for six hours.

After intubation, all patients were ventilated in a pressure-controlled mode using a closed-loop ventilator (Physioflex, Dräger, Lübeck, Germany) with the following initial settings: FiO$_2$ of 0.4, positive end-expiratory pressure of 7 cm H$_2$O, peak inspiratory pressure of 22 cm H$_2$O. Ventilation frequency was adjusted to keep PetCO$_2$ between 4 and 6 kPa.

After positioning the donor in a lateral decubitus position, an esophageal Doppler probe (HemoSonicTM 100, Arrow International Inc., Reading, PA, USA) was installed to measure stroke volume. The NICO (Novametrix, Medical Systems Inc., Wallingford, CT, USA) was placed between the patient and the ventilator, and was used to measure VCO$_2$.

After extubation, administration of oxygen was stopped if the oxygen saturation remained within 2% of the preoperative values. Adverse effects of the fluid regime (such as pulmonary edema) were postoperatively checked by bilateral auscultation, and by non-invasive oxygen saturation monitoring during the first two hours after extubation.

The surgical techniques have been described in detail elsewhere [23]. Both techniques were performed with the donor in a lateral decubitus position. Briefly, mini-incision ODN was performed with an 8 to 15 cm skin incision (depending on the body mass index) anterior to the eleventh intercostal space. The muscles of the abdominal wall were carefully split to access the retroperitoneal space. The abdomen was insufflated with CO$_2$ to a pressure of 12 mmHg. The kidney was extracted through a Pfannenstiel incision with an endobag (Endocatch, US Surgical, Norwalk, USA).

Urine output was measured from 10 hours before the operation (start of fluid infusion) until the introduction of PP (T0), urine output was then measured hourly until 6 hours thereafter (T1-6). Extubation time was documented from the last suture to the moment of extubation. Oxygen saturation was documented preoperatively and during the recovery period, which was planned to be two hours.

Blood samples of the donors were collected preoperatively and at 1, 2, and 21 days, 2 and 3 months and 1 and 2 years postoperatively. Blood samples of the recipients were collected preoperatively, daily until discharge (usually 10-14 days following transplantation), 1, 3, 6, and 9 months, and 1 and 2 years postoperatively. Creatinine clearance was estimated using the Cockcroft-Gault formula [24]. Urine output during donor nephrectomy was quantified. Mean arterial pressure (MAP) and stroke volume (SV) were monitored non-invasively every 5 minutes during operation.

All recipients also received a prehydration infusion with normal saline (2 ml.kg$^{-1}$h; 0.9% NaCl) from 5 hours preoperatively until the start of operation. Before induction of anesthesia, patients received a bolus of colloids (5 ml.kg$^{-1}$ of HES) during one hour. During the operation, saline was administered at 15 ml.kg$^{-1}$.h$^{-1}$. A second bolus of colloids was given (5 ml.kg$^{-1}$) before incision of the skin. Each ml blood loss was replaced with colloids (ratio 1:1). All patients received antibiotics, prednisolone 50 mg, and 50 g mannitol before reperfusion of the kidney. Postoperatively, all recipients received a calcineurin inhibitor based on the immunosuppressive regime.

**Statistics**

Main outcomes were estimated creatinine clearance of donors and recipients during follow-up. Donors whose laparoscopic procedure was converted to an open procedure were analyzed in the

LDN group according to the intention-to-treat principle. Categorical variables were compared with the chi-square test, continuous variables were compared with the Mann-Whitney U test, and repeated measurements were compared by repeated measurement of analysis of variance using SPSS mixed models; this allowed adjustment for baseline characteristics, including baseline creatinine clearance, the donor's gender and age, and whether or not a transplantation was pre-emptive. All analyses were conducted with SPSS (version 11.5, SPSS Inc., Chicago, USA). A $p$-value <0.05 (two-sided) was considered statistically significant.

## Results

There were no significant differences in baseline characteristics between the two groups (Table 5.1). Two laparoscopic procedures were converted (Table 5.2). One conversion was needed due to uncontrolled bleeding from a lumbar branch of the renal vein and one conversion was elective and performed immediately after introduction of the camera because of massive adhesions.

Estimated creatinine clearance of recipients of open and laparoscopic procured kidneys was comparable during the 2-year follow-up (Fig. 5.1a and 5.1b). The estimated creatinine clearance of the donors was comparable between both groups and remained 35% lower during the 2-year follow-up compared with the preoperative values (Fig.5.2).

Extubation times were similar between donors who underwent ODN and LDN (Table 3). No reintubations were necessary. There was no difference in additional oxygen therapy between groups during the 2-hour recovery period (Table 5.3). One patient in the LDN group received physostigmine (2 mg) for treatment of a central anticholinergic syndrome. In the ODN group, two patients were treated with

*Table 5.1.*
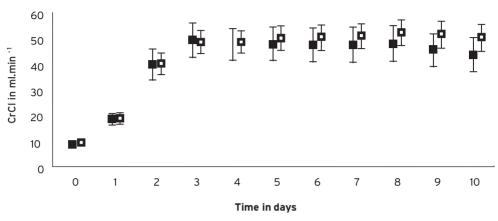
**Baseline characteristics of the donors and recipients**

|  | ODN (N=51) | LDN (N=59) |
|---|---|---|
| **Donor** | | |
| Male gender | 19 (37%) | 32 (54%) |
| Age  (years) | 50 (21-75) | 49 (20-77) |
| Left kidney | 27 (53%) | 27 (46%) |
| ASA classification >I | 15 (29%) | 11 (19%) |
| Weight (kg) | 75 (48-114) | 80 (46-118) |
| Ideal body weight (kg) | 70 (54-98) | 75 (55-100) |
| >1 renal artery | 11 (22%) | 16 (27%) |
| >1 renal veins | 3 (6%) | 5 (9%) |
| **Recipient** | | |
| Male gender | 32 (63%) | 32 (54%) |
| Age   (years) | 43 (11-77) | 48 (13-73) |
| Living unrelated recipient | 15 (29%) | 15 (25%) |
| Pre-emptive transplantation | 11 (22%) | 11 (19%) |

*Data are expressed as number (%) and continuous data as median (range).*

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*Figure 5.1a.*
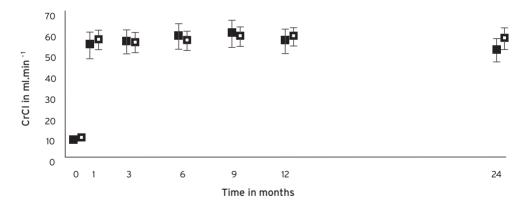
**Estimated creatinine clearance (ml.min$^{-1}$) with 95% CI of recipients
the first ten days postoperatively**



*(open squares, LDN; solid squares, ODN).*

*Figure 5.1b.*

**Estimated creatinine clearance (ml.min$^{-1}$) with 95% CI of recipients up to
two years after donation**



*(open squares, LDN; solid squares, ODN).*

naloxone (0.2 mg) because of respiratory depression caused by sufentanil.

There were no differences in the complication rates of donors who underwent ODN or LDN (Table 5.4). Major complications included an infected wound hematoma in the ODN group requiring re-admission and intravenous treatment with antibiotics, and two re-operations in the LDN group. Splenectomy was performed in one donor because of persistent bleeding from a tear of the splenic capsule, and re-laparoscopy was performed in another donor suspected with continuous bleeding, but no bleeding was identified.

Of all the grafts, 88% produced urine within one hour after re-circulation of the kidney in the ODN group, and 95% in the LDN group (Table 5.2). One recipient in each group required dialysis in the first
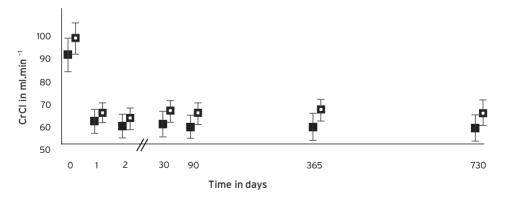
**Intra-operative data of ODN versus LDN**

| | ODN (N=51) | LDN (N=59) |
|---|---|---|
| **Donor** | | |
| Conversion to open | - | 2 (3%) |
| Time until nephrectomy  (min) | 108 (60-201) | 192 (107-339)# |
| Operation time (min) | 151 (84-298) | 240 (135-390)# |
| Blood loss  (ml) | 200 (20-1400) | 110 (10-2700) |
| Urine production  (ml/kg) | | |
|   Pre-operative | 1.5 (0.2-3.0) | 1.6 (0.3-3.6) |
|   Intra-operative until nephrectomy | 1.8 (0.5-8.7) | 1.7 (0.4-5.8) |
| **Recipient** | | |
| Warm ischemia time (min) | 25 (13-165) | 27 (12-55) |
| Urine within one hour | 45 (88%) | 56 (95%) |

*Data are expressed as number (%) and continuous data as median (range).*

*# p < 0.05 between ODN and LDN*

*Figure 5.2.*

**Estimated creatinine clearance (ml.min$^{-1}$) with 95% CI of living kidney donors over time**



*(open squares, LDN; solid squares, ODN).*

postoperative week (Table 5.4). In the LDN group, one recipient lost the graft due to arterial thrombosis, and another recipient lost the graft due to a severe gynecological infection that was locally spread to the transplant. Two grafts were lost in the ODN group due to severe vascular rejections (Table 5.4). Biopsy-proven acute rejection occurred more frequently after ODN: 18 versus 10 recipients (Table 5.4).

*Table 5.3.*

**Peri-operative data of ODN versus LDN of the donor**

| | ODN (N=51) | LDN (N=59) |
|---|---|---|
| **Intra-operative data** | | |
| Sufentanil total (μg/h) | 21 (13-36) | 23 (13-39) |
| BIS first 2 hours | 44 (35-53) | 44 (30-54) |
| HR first 2 hours | 63 (42-90) | 63 (86-37) |
| MAP first 2 hours (mmHg) | 89 (64-123) | 94 (52-133) |
| SV pre (ml) | 81 (38-128) | 85 (42-130) |
| SV first 2 hours (ml) | 84 (35-160) | 86 (84-140) |
| PetCO$_2$ first 2 hours (kPa) | 4.9 (4.2-5.7) | 5.2 (4.3-6.2) |
| Ventilation frequency | 12 | 15 |
| Tidal volume | 599 | 584 |
| PIP | 24 | 26 |
| VCO$_2$ first 2 hours (min/kg) | 1.8 (0.9-2.7) | 2.5 (1.2-3.6) |
| PvCO$_2$ after 2 hours (kPa) | 5.6 (3.9-7.1) | 5.8 (3.9-7) |
| VO2 first 2 hours (min/kg) | 3.1 (2.0-6.2) | 3.4 (2.1-6.3) |
| SaO$_2$ pre | 97% (95-100) | 97% (94-100) |
| **Postoperative data** | | |
| Time extubation (min) | 24 (2-105) | 22 (2-80) |
| SaO2 postoperative 2 hours | 96% (93-100) | 95% (92-100) |
| Auscultation; number of patients with repitation (%) | 0 | 0 |
| Number of patients needing additional oxygen (%) | 4 (8%) | 6 (10%) |

*Data are expressed as number (%) and continuous*

*data as median (range).*

*# p < 0.05 between ODN and LDN*

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*Table 5.4.*

**Postoperative data of ODN versus LDN**

|  | ODN (N=51) | LDN (N=59) |
|---|---|---|
| **Donor** | | |
| Complications | 4 (8%) | 3 (5%) |
| Hospital stay (days) | 3 (2-6) | 3 (1-10) |
| **Recipient** | | |
| Dialysis in first week | 1 (2%) | 1 (2%) |
| Acute rejection | 18 (35%) | 10 (17%) |
| One-year graft survival* | 48 (96%) | 55 (97%) |
| One-year recipient survival | 50 (98%) | 56 (95%) |
| Two-year graft survival* | 48 (96%) | 55 (97%) |
| Two-year recipient survival | 49 (96%) | 56 (95%) |

*Data are expressed as number (%) and continuous data as median (range).*

*\* one- and two-year graft survival censored for death.*

*# p < 0.05 between ODN and LDN*

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## Discussion

Although LDN is the preferred method for live kidney donation from the perspective of the donor, the results of laparoscopic procurement on early graft function have remained controversial.

Retrospective analyses of our patient data (patients from 1994 to 2000) [10,11] have shown that the estimated glomerular filtration rate (GFR) of donors and recipients was significantly less after LDN despite a liberal fluid management (16.2 ml.kg $^{-1}$.h $^{-1}$ crystalloids and 3.4 ml.kg $^{-1}$.h $^{-1}$ colloids only peroperatively). In the donors who underwent laparoscopy, this adverse effect was present up to one year, and in the recipients this effect lasted up to 7 days compared with ODN [10,11]. Therefore, we performed a pilot study in which three different fluid regimes were compared during LDN, including the old regime that served as control [22].

The first group was exposed to overnight fluid infusion and a bolus of colloid before induction of anesthesia and before inflation of PP, a second group was exposed to overnight infusion and only a bolus of colloid before induction of anesthesia, and a control group that received only fluid peroperatively (i.e., the old regime). It was shown that the pre-emptive fluid delivery in combination with a fluid bolus given before installation of pneumoperitoneum resulted in less reduction of stroke volume and urine output during LDN compared with the control group [22]. Fluids administered after the installation of PP did not prevent the decrease of stroke volume and decline in urine output during LDN.

These results emphasize that the total amount of fluid is less important than the timing of hydration. Intravascular volume should be expanded before the donor is positioned in the lateral position and before installation of PP in order to prevent collapse of the renal veins.

To investigate whether timed hydration would reduce the clinically experienced differences between ODN and LDN, in the present study we applied this new fluid régime in ODN and LDN. With adequate prehydration, PP did not cause delayed graft function and did not affect postoperative GFR

in the donor. Some have reported slower initial graft function after LDN [4,7,9,10,25] whereas others found comparable graft function between LDN and ODN [21,26-28].

Studies that reported no differences were either comparing hand-assisted laparoscopy with the traditional LDN [26] or with ODN [27]. Further, these studies did not repeatedly assess renal function during the first weeks [21,28,29] or did not adjust serum creatinine values for possible confounders at baseline [21,28,29]. Most of these studies were retrospectively designed and did not investigate concurrent groups [21,26-28]. None of these studies had a strict anesthetic protocol or mentioned the fluid regime used.

Troppmann et al. retrospectively compared 2734 LDN patients with 2576 ODN patients to explore the impact of LDN on early graft function; they observed significantly slower early post-transplant graft function after LDN [8]. Delayed graft function is associated with a higher incidence of acute rejection and has been reported to occur more frequently after LDN; even mild to moderate graft dysfunction post-transplant can have a negative impact on long-term graft survival [8,30,31].

Proposed mechanisms of delayed graft function after LDN include mechanical injury to the graft, longer operation time, longer first warm ischemia time, variable immunosuppression and increased abdominal pressure because of PP leading to decreased SV, RBF and GFR [6,12,13,32-34]. The predictive value of these findings on graft survival remains unclear [35].

The association between more affected kidney function in donors after LDN, suggests that pneumoperitoneum is at least partly responsible for this phenomenon [6]. Fluid management is known to abolish these changes and could therefore affect kidney function in donor and recipient. Mainly based on experimental studies, vigorous hydration up to 2 $L.h^{-1}$ of crystalloids has been suggested to improve preload and diuresis [12].

Retrospectively, Bergman et al. did not assess differences between groups that received more than 10 $ml.kg^{-1}.h^{-1}$ of fluid intraoperatively and less than 10 $ml.kg^{-1}.h^{-1}$ crystalloids during LDN. Both groups had similar postoperative donor serum creatinine levels, and similar rates of delayed graft function and acute rejection in the recipients. The authors concluded that lower intra-operative fluid administration did not worsen recipient outcome. However, the delayed graft function was 18% in the restrictive fluid group versus 10% in the liberal group [36]. In the present study, more fluid was administered intra-operatively (13 $ml.kg^{-1}.h^{-1}$) crystalloids, and 12 $ml.kg^{-1}.h^{-1}$ colloids in total) but the delayed graft function occurred in only 2% after LDN.

Our fluid protocol with overnight infusion prehydration may hinder fast-track kidney donation and definitely influences the cost of the donation procedure. Perhaps fluids may be given in a shorter period and before insufflation of the pneumoperitoneum but further studies needed to investigate this. In addition, costs related to additional nights in the hospital by the donor will easily be offset by lower rates of delayed graft function.

In conclusion, we found no difference in hemodynamics, urine output and postoperative kidney function in donors and recipients between LDN and ODN. This is in contrast to our earlier findings. In order to establish that our new fluid regime is responsible for the absence of the delayed graft function, a new study is needed in which the old and new fluid regimes are compared directly during LDN.

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# Neuroendocrine stress responses in laparoscopic and open donor nephrectomy are equal: propofol ensures more stress response reduction than isoflurane

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# Abstract

*Background:* Several studies have compared laparoscopic with open abdominal surgery regarding the effects on stress responses. Most studies showed lower concentrations of stress hormones after the laparoscopic procedure compared to open surgery; however intra-operatively, conflicting results were found. It is known that volume status and type of anaesthesia can influence these hormonal changes during surgery. Therefore, we studied neuroendocrine stress responses in laparoscopic donor nephrectomy (LDN) and open donor nephrectomy (ODN) under propofol anaesthesia compared with isoflurane anaesthesia, and using a strict protocol for analgesia and fluid management.

*Methods:* A total of 41 LDN patients and 41 ODN patients were included in this prospective randomized study. Patients received randomly either propofol or isoflurane anaesthesia. Depth of anaesthesia was monitored by the bispectral index. Blood samples for measurement of norepinephrine (NE), epinephrine (E), dopamine (DA), vasopressin (AVP), renin (REN), aldosterone (ALD), and glucose (GL) were taken before intubation (T1) and before nephrectomy (T2).

*Results:* Intra-operatively there were no differences in stress hormone levels between the LDN and ODN procedures. During propofol anaesthesia, however, the levels of E (31.7 versus 73.3 pg.ml$^{-1}$), DA (9.3 versus 15 pg.ml$^{-1}$), AVP (2.5 versus 4.2 pg.ml$^{-1}$) and REN (2.8 versus 7.5 ngAl.ml$^{-1}$.h$^{-1}$) were statistically significantly lower compared to those during isoflurane anaesthesia.

*Conclusion*: The anaesthetics protocol used resulted in an equal neuroendocrine stress response in both LDN and ODN. In addition, in these procedures anaesthesia with propofol resulted in a significantly lower level of stress response compared with isoflurane anaesthesia.

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## Introduction

Surgical procedures are associated with complex stress responses, characterized by neuroendocrine, immunologic and metabolic alterations, which are related to the magnitude of the inflicted injury [1]. Stress response during laparoscopic procedures in supine position (such as cholecystectomy) is moderate [2], whereas stress response in lateral decubitus position, in which donor nephrectomy is conducted, is significant [3-5].

Stress response can affect renal function and regulation of body fluid indirectly (as a reflection of overall circulatory responses) as well as directly (via intra-renal receptors) [6]. $CO_2$ pneumoperitoneum ($CO_2$PP) causes a decrease in renal blood flow (RBF) up to 75% of baseline values, with subsequent temporary renal ischaemia [7-14], which overall results in extra induction of acute tubular necrosis (ATN) [11-17]. For kidney donation, where preservation of kidney function is of paramount importance, these physiologic changes are undesirable. It has been suggested that kidneys derived with the laparoscopic procedure have a higher incidence of delayed graft function in the recipient compared with the open procedure [18-20]. Moreover Attenuating intra-operative stress is a key factor in improving outcome [21-22].

Lentschener et al. found that during gynaecological laparoscopic surgery, intra-operative haemodynamic and humeral changes did not occur if normovolaemia, adequate depth of anaesthesia, and high plasma levels of opiates were maintained [23]. Therefore, we were interested in the stress response during laparoscopic (LDN) and open (ODN) donor nephrectomy, with the use of our new fluid management together with a high dose of opioids. In addition, isoflurane anaesthesia was compared with propofol anaesthesia with regard to stress response during these two procedures.

## Patients and methods

The local human Ethics Committee approved this prospective randomized trial. All patients scheduled for donor nephrectomy by the nephrologists and surgeons were eligible for this study, and all of them gave written consent. All donors also participated in a study that aimed to determine whether LDN or ODN was the preferred operation technique for the living donor [24].

Randomization was carried out according to a computer-generated list using a hidden block size of four. The next numbered sealed opaque envelope provided by the trial statistician was opened when informed consent had been confirmed the day before operation. Randomization of the anaesthesia group was performed hereafter by the anaesthetists, conducted in similar way. Each operation was attended by the same anaesthetist (I.MzB) and surgeons (J.IJ and I.A.); the surgical techniques have been described earlier [25]. Medication was given according to ideal body weight (IBW), which was calculated from a table provided by the local dietician and corresponded to the upper level of normal weight as determined by the body mass index. Anti-thrombosis stockings were used routinely to improve the venous return peri-operatively.

We used a newly developed fluid regimen, which was equal for all groups [26,27]. Pre-operative fluid administration was started at 10 p.m. on the day before the operation with Ringer's Lactate (RL; 3 ml. kg-IBW$^{-1}$ h$^{-1}$) and continued until the operation. Before induction of anaesthesia, the patients received a bolus of colloids (6 ml kg$^{-1}$BW$^{-1}$ of 6% Hetastarch 130/0.4), followed by crystalloids (13 ml kg-IBW$^{-1}$ h$^{-1}$ RL). Before initiation of the laparoscopic procedure (or the open procedure), another bolus of colloids was given (6 ml kg-IBW$^{-1}$ 6% Hetastarch 130/0.4). One hour after the start of surgery 20 g mannitol was administered. Blood loss was replaced with 6% Hetastarch 130/0.4

Anaesthesia was induced with propofol (2 mg.kg-IBW$^{-1}$) and sufentanil (0.3 μg.kg-IBW$^{-1}$). Muscle relaxation was achieved with rocuronium (0.8 mg.kg-IBW$^{-1}$) and monitored by train-of-four (TOF) guard, and a bolus of rocuronium (0.3 of mg.kg-IBW$^{-1}$) was given to keep the TOF under three twitches.

Anaesthesia was maintained with propofol by continuous infusion (4–12 mg.kg-IBW$^{-1}$.h$^{-1}$), or isoflurane (0.5-1.2 % end tidal) maintaining the bispectral index between 40 and 55 (BIS, bispectral index, monitor; Aspect Medical Systems, Newton, MA, USA). Analgesia was maintained by continuous infusion of sufentanil 0.4µg.kg-IBW$^{-1}$. h-1 until the kidney was removed. If MAP declined by more than 30% from preoperative levels, dopamine was started. These patients were than excluded for the statistical analysis of the hormones; norepinephrine (NE), epinephrine (E) and dopamine (DA).

After intubation, all patients were ventilated in a pressure-controlled mode using a closed-loop ventilator (Physioflex®, Dräger, Lübeck, Germany) with the following initial settings: FiO$_2$ of 0.4, positive end-expiratory pressure 7 cm H$_2$O, and a peak inspiratory pressure of 22 cm H$_2$O . Ventilation was adjusted to keep PetCO$_2$ between 4 and 5.5 kPa, primarily with enhancement of frequency.

All patients were operated in the lateral decubitus position. Pneumoperitoneum (PP) was achieved by insufflation of CO$_2$ with an intra-abdominal pressure of 12 mmHg, which was maintained at this level during the operation.

After positioning of the patient the NICO monitor (Novametrix, Medical Systems Inc., Wallingford, CT, USA) was placed between the patient and the ventilator, and an oesophageal Doppler probe (HemoSonicTM 100, Arrow International Inc., Reading, PA, USA) was installed. The NICO monitor was used to measure the amount of CO$_2$ produced per minute (VCO$_2$); the HemoSonicTM device was used to measure stroke volume (SV) every three minutes. Mean arterial pressure (MAP) (measured non-invasively) and heart rate were extracted every 5 minutes.

Urine output during the donor procedure was quantified. Blood samples of the donors were collected to determine creatinine levels the day before operation (Crpre), after induction of anaesthesia (CrT1), 6 hours after installation of PP (CrT6), and one day (CrD1) after operation.

Venous blood samples for measurement of norepinephrine (NE), epinephrine (E), dopamine (DA), vasopressin (AVP), renin (REN), aldosterone (ALD), glucose (GL) and PvCO$_2$ were taken after induction of anaesthesia but before intubation (sample T1) and two hours after start of the procedure and before nephrectomy (sample T2). These samples were collected in chilled heparinized polystyrene tubes. All samples were immediately centrifuged at 4ºC, and plasma was stored at minus 80ºC until analysis. NE, E and DA were measured with fluorimetric detection after HPLC separation. Active plasma renin activity was measured by radioimmunoassay of angiotensin I formed during incubation in the presence of excess exogenous angiotensinogen. AVP and ALD were analyzed by radioimmunoassay using commercial kits (DiaSorin, Stillwater, MN, USA and and Diagnostic Products Corporation, Los Angeles, CA, USA respectively). Glucose was determined by a standard technique in the Clinical Chemistry Laboratory.

**Statistics**

The main outcome was the neuroendocrine stress response of the donors between the LDN and ODN procedure and secondarily, propofol compared with isoflurane anaesthesia during both procedures. Sample size was determined based on literature [23,28]. Power calculation had indicated that at least 32 patients would be required per group to detect a difference of 20% in plasma concentration of NE with an error of 0.05 and a power of 80%.

Differences between the two operation techniques and between the two anaesthesia techniques, demographic data and creatinine levels were compared with two-sided independent Student's *t*-test, pooled or not pooled, depending on results of Levene's test, after data were tested for normal distribution. Categorical variables were compared with Fisher's exact two-sided test. Differences between neuroendocrine levels were assessed with paired t-tests, and repeated measurements of the hormone samples were analyzed by means of SPSS mixed models, which allowed adjustment for baseline characteristics. Correlations were determined for BIS value, with MAP and hormone plasma levels and for urine output and hormone plasma levels using Pearson's correlation coefficients.
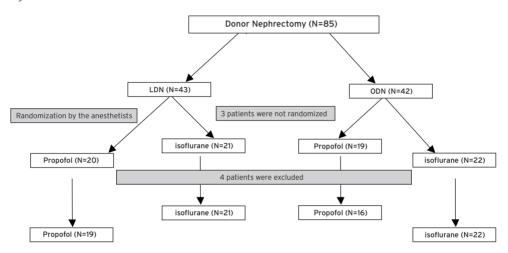
Data are presented as mean values with standard deviation (SD). Statistical analysis was performed using SPSS (version 14 SPSS Inc., Chicago, USA). A *p*-value < 0.05 (two-sided) was considered statistically significant.

## Results

Randomization of the patients scheduled for donor nephrectomy is shown in Figure 6.1. Data of the donors were prospectively collected, but for statistical analyses of NE, E and DA, additionally 5 donors from the LDN group and 2 donors from the ODN group were excluded because these donors were given dopamine intravenously. Significantly more DA was used in the isoflurane group (*p*= 0.03).

Baseline characteristics of the patients are given in Table 6.1; there were no significant differences between the subgroups.

*Figure 6.1.*

*A total of 85 patients scheduled for donor nephrectomy, were randomly assigned to the LDN group or the ODN group. After this, the patients were stratified to the propofol or isoflurane group. Three patients were excluded because the research team was not available, and 4 donors were excluded because the blood collection for neuroendocrine hormones failed.*

After correction for the baseline levels (T1) of the tested hormones, no differences were found between the LDN and ODN group (Table 6.2). In contrast, the hormone levels of E, DA, AVP and REN were significantly lower in the propofol group compared to the isoflurane group (Table 6.2).

Intra-operative data are given in Table 6.3. HR and SV were comparable in all situations, whereas MAP was higher in the propofol group. BIS was significantly higher in the isoflurane group (*p* < 0.001) (Table 6.2). No correlation was found between BIS value and MAP and stress hormone plasma levels.

Until nephrectomy, there was no significant differences in urine output for all groups, except for the urine output in the ODN-isoflurane group which was lower the second hour (T2) of operation (*p* = 0.017)(Table 6.3). AVP in the ODN-isoflurane group was significantly higher compared with the ODN-propofol group (*p* = 0.03) (Table 6.2) and correlated with less urine output (*p* < 0.01).

Creatinine levels of the donors were comparable for all groups during the observation period.

*Tabel 6.1.*

**Characteristics of the patient population (n=77) by subgroup**

| | LDN prop | iso | ODN prop | iso | *p*-value LDN-ODN | *p*-value prop-iso |
|---|---|---|---|---|---|---|
| Gender; male/female | 11/8 | 11/10 | 4/12 | 11/11 | 0.18 | 0.50 |
| Side kidney; left/right | 12/7 | 11/10 | 6/10 | 18/4 | 0.65 | 0.17 |
| Weight in kg | 78 (16) | 80 (17) | 73 (17) | 79 (16) | 0.52 | 0.33 |
| IBW in kg | 74 (10) | 74 (13) | 70 (11) | 75 (13) | 0.57 | 0.50 |
| Age in years | 50 (12) | 46 (13) | 51 (12) | 50 (15) | 0.43 | 0.39 |

Data are given as mean (SD)

LDN; laparoscopic donor nephrectomy, ODN; open donor nephrectomy, Prop; propofol,

Iso; isoflurane, IBW; ideal body weight

*Tabel 6.2.*

**Data on hormone levels in the four subgroups.**

| | LDN prop | iso | ODN prop | iso | interaction effect LDN-ODN *p*-value | interaction effect prop-iso *p*-value |
|---|---|---|---|---|---|---|
| $DA_{T1 pg.ml^{-1}}$ | 5.7 (2.6) | 6.5 (4.4) | 8.3 (15.6) | 6.3 (2.8) | | |
| $DA_{T2 pg.ml^{-1}}$ | 11.4 (7.1)* | 15.5 (13.2)* | 7.1 (3.5) | 12 (4.5)* | 0.056 | **0.047** |
| $NE_{T1 pg.ml^{-1}}$ | 125 (50) | 197 (109) | 132 (87) | 164 (91) | | |
| $NE_{T2 pg.ml^{-1}}$ | 110 (60) | 243 (200) | 113 (92) | 183 (154) | 0.71 | 0.081 |
| $E_{T1 pg.ml^{-1}}$ | 17 (7) | 26 (13) | 14 (8) | 23 (18) | | |
| $E_{T2 pg.ml^{-1}}$ | 32 (41) | 66 (88)* | 31 (32)* | 76 (69) * | 0.057 | **0.042** |
| $AVP_{T1 pg.ml^{-1}}$ | 4.0 (2.2) | 3.5 (1.5) | 3.7 (2.2) | 3.3 (2.0) | | |
| $AVP_{T2pg.ml^{-1}}$ | 2.3 (1.6)* | 3.2 (2.5) | 2.7 (1.7) | 5.2 (4.0) | 0.054 | **0.008** |
| $REN_{T1 ngAl.ml^{-1}.h^{-1}}$ | 1.8 (1.3) | 1.4 (0.6) | 1.5 (0.6) | 1.7 (0.8) | | |
| $REN_{T2 ngAl.ml^{-1}.h^{-1}}$ | 3.4 (4.2) | 8.3 (8.1) * | 2.2 (1.0)* | 6.7 (5.8) * | 0.22 | **<0.001** |
| $ALD_{T1 pg. ml^{-1}}$ | 43 (41) | 36 (29) | 31 (27) | 28 (28) | | |
| $ALD_{T2 pg. ml^{-1}}$ | 47 (35) | 82 (60) * | 73 (68)* | 68 (50) * | 0.26 | 0.135 |
| $Glucose_{T1 mmol. L^{-1}}$ | 5.6 (1.0) | 5.5 (0.9) | 5.5 (0.6) | 5.6 (1.0) | | |
| $Glucose_{T2 mmol. L^{-1}}$ | 5.7 (1.2) | 5.8 (0.8) | 5.5 (0.6) | 6.2 (1.0) | 0.65 | 0.091 |

Data are given as mean (SD)

* ; p-value < 0.05, for T1 and T2

LDN; laparoscopic donor nephrectomy, ODN; open donor nephrectomy, Prop; propofol, Iso; isoflurane.

DA; dopamine, NE; norepinephrine, E; epinephrine, AVP; vasopressin, REN; renin, ALD; aldosterone

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*Tabel 6.3.*

**Intra-operative data on the four subgroups.**

| | LDN | | ODN | | p-value LDN-ODN | p-value prop-iso |
| | Prop | iso | prop | iso | | |
|---|---|---|---|---|---|---|
| Prop T0-T2 in mg. kg$^{-1}$.h$^{-1}$ | 6.5 (1.9) | | 6.5 (1.6) | | 1.00 | |
| Iso$_{et}$ T0-T2 % | | 0.85 (0.19) | | 0.86 (0.19) | 0.50 | |
| Total Suf in ug | 122 (29) | 131 (27) | 98 (19) | 107 (27) | **< 0.001** | 0.88 |
| Dopamine | 0 | 5 | 0 | 2 | 0.32 | **0.03** |
| BIS T0-T2 | 43 (4) | 47 (4) | 43 (4) | 47 (4) | 0.40 | **< 0.001** |
| Blood loss in ml | 283 (228) | 106 (175) | 201 (149) | 231 (199) | 0.57 | 0.08 |
| Ext. time in min | 22 (20) | 24 (19) | 21 (31) | 31 (27) | 0.56 | 0.30 |
| **Haemodynamic parameters** | | | | | | |
| Hr T0-T2 in beats. min$^{-1}$ | 63 (9) | 62 (13) | 62 (11) | 64 (10) | 0.42 | 0.38 |
| MAP T0-T2 in mmHg | 95 (18) | 86 (16) | 93 (13) | 81 (11)O | 0.14 | **0.001** |
| SV T0-T2 in ml.stroke$^{-1}$ | 86 (23) | 90 (21) | 83 (18) | 78 (22) | 0.07 | 0.84 |
| **Ventilatory parameters** | | | | | | |
| Vent. Freq T0-T2.per min | 15 (3) | 16 (3) | 11 (3) | 13 (3) | **< 0.001** | 0.49 |
| Tidal volume T0-T2 in ml | 592 (127) | 562 (136) | 587 (117) | 599 (105) | 0.52 | 0.74 |
| PIP T0-T2 in kPa | 26 (3) | 26 (4) | 23 (2) | 22 (2) | **< 0.001** | 0.86 |
| VO$_2$ T0-T2 in ml. min$^{-1}$. kg$^{-1}$ | 3.3 (0.8) | 2.8 (0.4) | 2.9 (0.6) | 3.2 (1.0) | 0.89 | 0.42 |
| PVCO$_2$T0 in kPa | 6.1 (0.6) | 6.0 (0.7) | 5.8 (0.9) | 6.1 (0.7) | 0.63 | 0.59 |
| PVCO$_2$T2 in kPa | 5.6 (0.7) | 5.9 (0.6) | 5.7 (0.9) | 5.6 (0.6) | 0.34 | 0.64 |
| VCO$_2$ T0-T2 in ml. min$^{-1}$. kg$^{-1}$ | 2.6 (0.5) | 2.5 (0.6) | 1.9 (0.3) | 1.8 (0.4) | **< 0.001** | 0.24 |
| **Urine output** | | | | | | |
| UOT1 in kg.h $^{-1}$ | 2.0 (1.4) | 1.6 (1.9) | 2.4 (2.1) | 1.6 (1.3) | 0.77 | 0.11 |
| UOT2 in kg.h $^{-1}$ | 2.3 (1.2) | 2.6 (2.1) | 2.7 (2.0) | 1.4 (0.8) | 0.21 | 0.24 |
| UOTK in kg.h $^{-1}$ | 2.2 (1.1) | 2.1 (1.8) | 2.2 (1.9) | 1.6 (0.9) | 0.36 | 0.26 |

*Data are given as mean (SD)*

*T0-T2; in the first two hours of operation, Prop$_{T0-T2}$; mean use of propofol, Iso$_{et\,T0-T2}$; mean use of isoflurane (in %), Total Suf ; total use of sufentanil in ug (including induction dosage), Dopamine; amount of patients requiring dopamine infusion during the operation, BIS $_{T0-T2}$; mean bispectral index, $T_\kappa$; Operation time, from skin incision until kidney extraction, Blood loss; the amount of blood loss until kidney extraction, Ext. time; extubation time, measured from the last suture to extubation, Hr$_{T0-T2}$; mean heart rate, MAP$_{T0-T}$2 ; mean arterial pressure, SV$_{T0-T2}$; mean stroke volume, PIP$_{T0-T2}$; mean positive inspiratory pressure, VO$_2$; mean oxygen delivery, PvCO$_{2T0}$; venous CO$_2$ just before operation, PvCO$_{2T2}$; venous CO$_2$ after two hours of operation, VCO$_2$; mean CO$_2$ extraction, UO$_{T1\,kg.h}$ $^{-1}$; mean urine output, the first hour of operation, UO$_{T2\,kg.h}$ $^{-1}$; mean urine output, the second hour of operation, UO$_{TK\,in\,kg.h}$ $^{-1}$; amount of intra-operative urine output until extraction of the kidney.*

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## Discussion

In the present study, intra-operatively there were no differences in stress hormone levels between the LDN and ODN procedures. During propofol anaesthesia, however, the levels of epinephrine, dopamine, AVP and REN were significantly lower compared with those during isoflurane anaesthesia.

The present study shows increases during both surgical procedures (although not significant) in epinephrine (LDN 22 to 49 pg.ml^{-1}, ODN 18 to 53 pg.ml^{-1}), but not in norepinephrine plasma levels. We speculate that the rise in epinephrine in this study is caused by the surgical procedure of nephrectomy, which implicates handling of the adrenal gland, which is located next to the kidney.

No difference in REN and ALD was observed between the LDN and ODN group. This is in contrast to earlier findings in which PP resulted in stimulation of the renin-angiotensin-aldosterone system [29-31]. However, also for REN and ALD there was a moderate and significant rise during both surgical procedures (REN; ODN 1.6 to 4.7, LDN 1.6 to 6 ngAI.ml^{-1}.h[-1])( ALD; ODN 30 to 70, LDN 39 to 65 pg.ml^{-1}). Renal blood flow influences the production of REN and ALD and increases with hypovolaemia, but could also be induced through manipulation of the kidney during the procedure, with consequent renal vasoconstriction [26,27,32].

Several studies have reported elevated AVP levels during increased IAP [3,9,16,31,33]. AVP regulation is influenced by several mechanisms, e.g. osmotic receptors in the hypothalamus, low pressure receptors in the atria (via the atrial natriuretic factor) and lung vessels, and high pressure receptors in the carotid sinus [34,35]. $CO_2$ and mechanical stimulation of peritoneal receptors probably initiate a pathophysiologic process that also stimulates AVP release [36]. AVP is a potent vasopressor even at normal physiologic concentrations [37] and induces reabsorption of water in the distal tubuli resulting in less urine production. It has been suggested that increased plasma AVP levels contribute to the observed oliguria and elevated MAP during PP [38]. In the present study, with the use of our protocol, AVP did not increase during either LDN or ODN, it even decreased during the LDN procedure. This might implicate that the patients were sufficiently hydrated, that too much elevated intrathoracic pressures was sufficiently avoided and that the intra-abdominal pressure elevation of 12 mmHg was not enough to release AVP.

An increase in plasma hormones could also be the result of reduced renal clearance and glomerular filtration rate, which is known to be reduced during PP [9]. In the present study there was an equivalent creatinin and urine output during the procedure in all four subgroups, except for the urine output in the ODN-isoflurane group. However this only correlated with the AVP plasma level.

In our study epinephrine plasma level in the propofol group during the two procedures was less than half of the epinephrine level in the isoflurane group. Also REN and AVP plasma levels were significantly lower in the propofol group.

The impact of propofol on the metabolic hormonal response during surgery has received little attention. Our findings of less stress response in the propofol group are supported by the results of Ledowski et al. [39]. These authors found a higher sympathetic outflow using propofol with remifentanil versus sevoflurane with remifentanil during ear-nose-throat surgery; MAP was equal between their two anaesthesia groups and the bispectral index was higher in their propofol group. In our study, however, MAP was higher in the propofol group and the bispectral index was lower in the propofol group. In concordance with Ledowski et al. we found no significant correlation between the bispectral index and the release of stress hormones or MAP. In our study a difference in BIS of [43] versus [47] can not explain the higher MAP or the lower release in hormones in the propofol group. The lower MAP in the isoflurane group might be the reason for compensatory release of hormones.

Propofol anaesthesia has been shown to attenuate surgical stress-induced adverse immune and oxidative stress responses better than other types of anaesthesia [40-43]. Although clinical evidence is still lacking, some indirect data suggest that the anti-oxidant action of propofol [41,44] might be

associated with a more favourable metabolic and immune responses. There is evidence for bidirectional communication between the neuroendocrine and immune systems: cytokine production seems to be responsible for the development of the stress response of the hypothalamo-pituitary-adrenal axis during surgery [45].

Some limitations of our study should be noted. Firstly, as we focused on intra-operative changes of neuroendocrine stress hormones we cannot comment on the outcome of our patients. Secondly, this study does not clarify whether the derived benefit is due only to the new fluid regimen or to a combination of the type of anaesthesia used together with the fluid management.

The effect of the operation technique on plasma concentrations of epinephrine, dopamine and AVP showed no differences with a *p*-value of < 0.06, suggesting the possibility of a type II error. This study was powered for norepinephrine and not for epinephrine, dopamine and AVP. Therefore, retrospectively we performed a calculated power analysis based on the assumption that mean and SD remains equal and that 20% difference would be of clinical significance. This calculation revealed that, if we would have tripled our study groups, still no differences between the two operations techniques for plasma concentrations of epinephrine, dopamine and AVP would have been found, with a power of 80%.

We conclude that in both the LDN and ODN group, patients treated with a preload of fluids, under general (and monitored) anaesthesia and supplemented with a high dosage of sufentanil, there is only a moderate intra-operative stress response, without any differences between operation technique (LDN and ODN). Additionally, the choice of anaesthetic drug modifies this response: propofol anaesthesia resulted in lower levels of epinephrine, dopamine, AVP and REN for both the LDN and the ODN group, compared with isoflurane anaesthesia in donor nephrectomy.

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# CHAPTER

7

## Epidural anaesthesia for laparoscopic donor nephrectomy is beneficial for the donor without affecting kidney function: a randomised controlled clinical study

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# Abstract

*Background*: Laparoscopic surgery for donor nephrectomy is associated with advantages such as lower morbidity and shorter convalescent period, advantages that epidural anaesthesia also confers. The objective of this study was to evaluate whether epidural analgesia (combined with general anaesthesia) would similarly benefit patients undergoing laparoscopic donor nephrectomy (LDN). The primary goal was reduced postoperative pain and improved recovery, and the secondary goal was kidney function of donor and recipient.

*Methods:* Seventy-four patients undergoing LDN were randomised to receive either general anaesthesia with sufentanil (GA + Suf) or general anaesthesia in combination with thoracic epidural analgesia (GA + TEA). At the end of the operation, a bolus of morphine was administered and the epidural catheter was removed. Patients in both groups received patient-controlled (PCA) iv. morphine. Postoperative VAS scores for pain, nausea, discomfort and tiredness were recorded. Recovery and satisfaction of the donor were evaluated and kidney function by creatinine clearance (CrCl) and urine output, were evaluated.

*Results:* The patients with epidural analgesia had less pain, experienced less nausea, and were more comfortable and satisfied the first hour after extubation. Furthermore, these patients were extubated faster and discharged from the recovery room earlier and used less morphine postoperatively. Postoperative donor and recipient CrCl values were comparable in both groups.

*Conclusion*: Epidural analgesia has postoperative advantages for patients undergoing laparoscopic kidney donation. These patients benefit from better analgesia, a quicker and smoother recovery without influencing postoperative kidney function of the donor and the recipient.

CHAPTER

7

## Introduction

A smooth perioperative and short convalescent period may motivate more people to consider living kidney donation. Kuo et al. reported that 47% of donors donated solely because of the availability of the laparoscopic donor nephrectomy procedure and would not have otherwise donated their kidney [1]. Laparoscopic donor nephrectomy (LDN) is associated with several advantages, such as shorter hospitalisation and more rapid convalescence, compared to open donor nephrectomy (ODN) [2,3].

In abdominal surgery, thoracic epidural analgesia (TEA) improves postoperative outcome and attenuates the physiologic response to surgery [4-6]. Patients treated with TEA have excellent pain relief, a prerequisite for accelerated recovery from surgery, and experience better health-related quality of life [5,6]. However mid-TEA (Th 6–7) results in a sympathetic block, affecting the autoregulation of the kidney; consequently, renal blood flow (RBF) and glomerular filtration rate (GFR) directly depend on mean arterial pressure (MAP) and intravascular volume [7]. Renal blood flow is already compromised during laparoscopic surgery because of increased abdominal pressure during pneumoperitoneum (PP) [8-10].

In this prospective study, by comparing LDN under general anaesthesia with or without the combination of epidural analgesia, we investigated whether epidural analgesia benefits direct postoperative recovery of living donors. We evaluated remaining donor kidney function and recipient kidney allograft function to review the possible renal effects of the epidural technique during LDN.

## Patients and methods

The local human ethical committee approved this prospective randomized trial. Written informed consent was obtained from all patients. Patients were excluded from the study when the laparoscopic approach had to be converted to an open approach, or if the patient wanted to abort the procedure, before they arrived in theatre.

Patients were randomly assigned to general anaesthesia alone (GA + Suf) or to general anaesthesia combined with mid-thoracic epidural analgesia (GA + TEA). The night before the operation, patients were randomised using sealed opaque envelopes, which the anaesthesiologist opened in the presence of the patient.

Because we chose not to give an epidural to the GA + Suf group, the patients were not blinded to the choice of anaesthetic, but they were unaware of the study hypothesis. Blinded observers collected postoperative data. Each operation was attended by the same anaesthetist (I.MzB) and surgeons (J.IJ and I.A.); the surgical techniques have been described in detail earlier [11]. Briefly, the abdomen was insufflated with $CO_2$ to a pressure of 12 mmHg. The kidney was extracted through a Pfannenstiel incision with an endobag (Endocatch, US Surgical, Norwalk, USA).

Anaesthesia was induced with propofol (2 mg. kg-IBW[-1]) and sufentanil (0.3 µg.kg-IBW[-1]). Ideal body weight (IBW) was calculated according to body height, gender, and age. Muscle relaxation was achieved with rocuronium (0. 8 mg.kg-IBW[-1]) and monitored by train of four (TOF) guard, and a bolus of rocuronium (0. 3 of mg.kg-IBW[-1]) was given when necessary to keep the TOF under 3 twitches. Anaesthesia was maintained with propofol by continuous infusion (4–12 mg kg-IBW[-1]. h[-1]), maintaining the bispectral index between 45 and 55 (BIS monitor; Aspect Medical Systems, Newton, MA, USA). In the GA + Suf group, analgesia was maintained by continuous infusion of sufentanil 0.4 µg.kg-IBW-1.h[-1] until the kidney was removed. In the GA +EA group, epidural catheter was inserted after locating the epidural space with the loss of resistance technique with air at T6-T8 level. This was achieved under iv. slight sedation analgesia. A bolus of 8–12 ml (depending on the height of the patient, and our clinical experience) of a mixture of 0.25% bupivacaïne with sufentanil (2 µg.ml^{-1}) was given through the epidural catheter; after 2 hours an extra bolus of 5–7 ml of the same mixture was given. One hour

after the start of operation, 20 g mannitol was administered. At the end of the operation, the GA + Suf group received intravenous morphine (0.06 mg.kg-IBW⁻1), while the GA + TEA group received morphine through the epidural catheter (0.03 mg.kg-IBW$^{-1}$), after which the catheter was removed.

Epidural analgesia was considered insufficient if heart rate and MAP increased by more than 10% after the start of the operation, and an extra bolus of 5–7 ml of a mixture of 0.25% bupivacaïne with sufentanil (2 μg.ml$^{-1}$) did not result in a return to preoperative levels for heart rate and MAP. In this case, a continuous infusion of sufentanil was administered (like the GA + Suf group), these patients remained in the study group.

For postoperative pain, both patient groups received intravenous patient control analgesia (PCA) with iv. morphine (1mg.ml-1, bolus 1 ml, lock out 5 min). The PCA device was discontinued when the patients were tolerating a regular diet or when the patient had not used it the previous 6 hours. In both groups, patients started with acetaminophen 1000 mg 4 times a day orally, begun preoperatively. Patients received morphine only via the PCA device, and no additional rescue pain medication was administered.

After intubation, all patients were ventilated in a pressure-controlled mode using a closed-loop ventilator (Physioflex®, Dräger, Lübeck, Germany) with the following initial settings: 40% oxygen, and 60% air, positive end-expiratory pressure 7cm $H_2O$, and a peak inspiratory pressure of 22cm $H_2O$. Ventilation frequency was adjusted to keep PetCO$_2$ between 4 and 5.5 kPa. All patients were operated in the lateral decubitus position. Pneumoperitoneum (PP) was installed with $CO_2$ with a constant intra-abdominal pressure of 12 mmHg.

A strict perioperative fluid management protocol was followed; which consisted of prehydration with Ringer's Lactate (RL) and a bolus of colloids (12 ml.kg-IBW$^{-1}$ of 6% Hetastarch 130/0.4), before initiation of the laparoscopic procedure. Intra operatively crystalloids (13 ml.kg-IBW-1.h-1 RL) were administered until nephrectomy, hereafter fluid infusion was adjusted to ensure that exactly 6 hours after start of the operation all patients had received in total

9 ml.kg-IBW$^{-1}$ h$^{-1}$ RL. Blood loss was replaced with 6% Hetastarch 130/0.4. This fluid regime was investigated in prior studies [12,13]. If MAP declined by more than 30% from preoperative levels, dopamine was started.

Blood samples were taken from the donor patient to determine creatinine and blood gases at T0 (before surgery), T2 (2 hours after incision), T6 (6 hours after incision), D1 (first postoperative day), and D28 (1 month postoperatively). Creatinine clearance (CrCl) was determined using the Cockcroft-Gault formula, which corrects for age, weight and gender [14]. Urine output was measured from 10 p.m. the day before operation until 6 hours postoperatively. In the recipient, CrCl elevation was measured until one month postoperatively.

A visual analogue score (VAS) concerning pain, fatigue, nausea, and discomfort, and a questionnaire consisting of a Mini Mental State Examination (MMSE), was taken preoperatively, and at 30 and 60 minutes after extubation. VAS was assessed using the 10-cm chiroscience gauge, ranging from 0 (indicating no pain, no fatigue, no nausea, or no discomfort at all) to 10 (indicating worst possible pain, fatigue, nausea, or discomfort).

The MMSE, the VAS scores, and the need for supplemental oxygen dictated official discharge from the recovery room; this was tested 30 minutes and 60 minutes after extubation. The MMSE score should be more than 25, the VAS score for pain and nausea should be less than 4, the VAS score for tiredness and discomfort should be less than 6, and oxygen saturation should be more than 95% with no more than 2 l.min$^{-1}$ oxygen supply. A member of the research team blinded to the patient's group assignment conducted interviews.

Finally, patient satisfaction with the postoperative pain management (using a verbal rating scale with 0 = poor to 100 = excellent) was assessed at the patient's departure from the recovery room [15]. Use of morphine by the donor patient, VAS for pain and nausea postoperatively.

### Statistics

Main outcome was the quality of the direct postoperative period. Power calculation revealed that at least 13 donors should be included in each group to detect a difference of 50% in direct postoperative pain, with an error of 0,05 and a power of 95% [16]. In the computer-generated randomisation sequence, 20% extra patients were anticipated in the study group to provide an equal number of patients despite expected epidural failures [17]. The study was designed as intension to treat. Data were analysed using SPSS for Windows (version 14.0) and are presented as means with standard deviations (SD). Differences in means between the control and study groups were analysed using independent samples t-test, pooled or not pooled depending on results of Levene's test, this after data were tested for normal distribution. Relations between interval- and ratio-levelled variables were analysed using Pearson's correlation coefficient. A $p$ value < 0.05 was considered statistically significant.
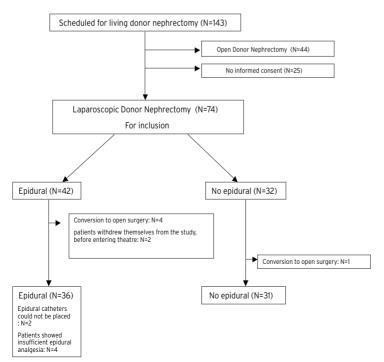
## Results

From August 2004 until January 2006, 143 living-donor nephrectomies were performed in our hospital. The donor nephrectomy was performed either by a laparoscopic (N= 99) or by an open procedure (N= 44). Of the 99 LDN patients, [18] either were not informed properly during the preoperative evaluation (which occurred around 3 months preoperatively) or the complete research team was not present during the operation. Another 7 patients refused to take part in the study.

Finally seventy-four LDN patients gave written consent en were enrolled in the study, of these seven patients were excluded, according to our exclusion criteria (Fig. 7.1). All patients were classified as ASA I or II. The characteristics of the two groups were comparable (Table 7.1).

Operation time (skin-to-skin) and blood loss were significantly shorter in the GA + TEA group

*Figure 7.1*

**Overview of the study population**

(Table 7.2). Haemodynamic- and ventilation parameters, sedation level, and amount of propofol used were comparable between the groups (Table 7.3). As a result of low blood pressure, four patients received dopamine infusion (3-6 $\mu$g.kg$^{-1}$.min$^{-1}$) as did two patients in the GA + Suf group. Because these six patients exhibited significantly higher ($r = 0.30$; $p = 0.014$) urine output compared to the group not receiving dopamine, these six patients were excluded from statistics for urine output.

Patients in the GA + TEA group were extubated faster, had less pain, were less nauseated, and were more comfortable postoperatively compared to patients in the GA + Suf group; they also had an MMSE score 30 minutes after extubation that was similar to their score before the operation, and they left the recovery room ($p < 0.001$) sooner. Fourteen patients in the GA + Suf group indicated to have shoulder-tip pain, compared to 2 patients in the GA + TEA group. Patients were tested the moment they left the recovery room, and the GA + TEA patients were more satisfied than the GA + Suf patients, with their pain management ($p < 0.03$). In contrast, the GA + Suf patients took longer to wake up and used more morphine postoperatively, until two days after the operation (Table 7.4).

Urine output between groups was comparable from the start of the operation until six hours hereafter (mean 1.9 ml.kg1.h$^{-1}$). In the GA + TEA group, intraoperative and preoperative urine outputs were correlated ($r = 0.46$; $p = 0.021$), as were intraoperative urine output and MAP ($r = 0.43$; $p = 0.008$), but not in the GA + Suf group. During PP, CrCl did not decrease. After nephrectomy, CrCl decreased equally in both groups (Table 7.5).

More than 90% of transplanted kidneys from both groups produced urine immediately after recirculation. Although the CrCl values of the recipients in the GA + TEA group were higher overall, they did not differ significantly between groups at any point in time up to 1 month postoperatively.

*Tabel 7.1*

**Patient characteristics**

| | GA + TEA (N=36) | GA + Suf N=31 |
|---|---|---|
| Age (yrs) | 50 (17) | 52 (13) |
| Weight (kg) | 71 (10) | 74 (11) |
| IBW (kg) | 69 (8) | 71 (9) |
| BMI (kg.m$^{-2}$) | 24 (4) | 26 (5) |
| ASA I | 27 | 24 |
| ASA II | 9 | 7 |
| Gender  Male | 13 | 7 |
| Female | 23 | 24 |
| Donor side Left | 14 | 10 |
| Right | 23 | 21 |
| Antihypertensive drugs | 4 | 3 |

*IBW: ideal body weight, calculated according to body height, gender and age*
*BMI: body mass index*
*number of patients using antihypertensive drugs (all b blockers)*
*Data are given as; mean (SD), no significant differences between groups.*

*Tabel 7.2*

**Perioperative data: surgery**

| | GA + TEA (N=36) | GA + Suf (N=31) | *p* value |
|---|---|---|---|
| Warm ischemia (min) | 5.5 (3.0) | 5.8 (2.9) | NS |
| Blood loss (ml) | 101 (101) | 174 (164) | 0.02 |
| Difference between operation time and time in theatre (min) | 73 (19) | 62 (14) | 0.01 |
| Operation time (min) | 210 (50) | 231 (52) | 0.02 |
| Time for kidney extraction (min) | 173 (51) | 186 (50) | NS |

*Warm ischemia time: the time of renal artery occlusion, before the kidney is extracted and*

*flushed with iced perfusion fluid*

*Blood loss: the amount of blood loss until kidney extraction*

*Operation time: the skin-to-skin operation time in minutes*

*The time in minutes needed to extract the kidney, from the start of the operation*

*NS: non-significant*

*Data are given as mean (SD)*

*Tabel 7.3*

**Perioperative data: anaesthesiology**

| | GA + TEA (N=36) | GA + Suf (N=31) | | GA + TEA (N=36) | GA + Suf (N=31) |
|---|---|---|---|---|---|
| $Hr_{T0-T2}$ | 66 (10) | 64 (10) | $BIS_{T0-T2}$ | 41 (4.5) | 40 (4.7) |
| $MAP_{pre}$ | 104 (11) | 103 (13) | $PvCO_2 T0$ | 5.7 (0.7) | 5.7 (0.7) |
| $MAP_{T0-T2}$ | 94 (18) | 100 (17) | $PvCO_2 T2$ | 6.6 (1.4) | 6.3 (0.9) |
| $SV_{T0-T2}$ | 97 (27) | 99 (25) | $Prop_{T0-T2}$ | 7.7 (2.0) | 7.4 (2.7) |
| $PetCO_2 T0-T2$ | 5.3 (0.4) | 5.3 (0.5) | Total Suf | 33 (6) | 122 (29) |
| $UO_{T0-2}$ | 2.4 (1.6) | 2.1 (1.3) | | | |
| $UO_{T3-6}$ | 1.7 (0.9) | 1.7 (0.7) | | | |

$Hr_{T0-T2}$:     *mean heart rate during the first two hours of operation*

$MAP_{T0-T2}$:   *mean arterial pressure during the first two hours of operation in mmHg*

$SV_{T0-T2}$:     *mean stroke volume during the first two hours of operation in ml*

$Pet_{CO2T0-T2}$:  *mean end tidal $CO_2$ during the first two hours of operation in kPa*

*UO:*       *urine output in the first two hours (T0-2) or in the third till sixth hour (T3-6) after the incision, in ml $kg^{-1} h^{-1}$.*

$BIS_{T0-T2}$:   *bispectral index during the first two hours of operation*

*Above parameters were all measured every 5 minutes*

$Pv_{CO2T0}$:    *venous $CO_2$ in kPa, just before operation*

$Pv_{CO2T2}$:    *venous $CO_2$ in kPa, after two hours of operation*

$Prop_{T0-T2}$:   *use of propofol in $mg.kg-IBW^{-1}$ during the first two hours of operation*

*Total Suf :  total dose of sufentanil given during the procedure in $\mu g$*

*Data are given as mean (SD), if p-value is not given it is non significant*

*Tabel 7.4*

**Postoperative results**

| | GA + TEA (N=36) | GA + Suf (N=31) | *p* value |
|---|---|---|---|
| **VAS for pain (0–10)** | | | |
| Preoperative | 0 (0.1) | 0.2 (0.4) | NS |
| Postoperative | | | |
| 30 min | 2.3 (2.5) | 3.2 (1.4) | NS |
| 60 min | 2.7 (2.6) | 4.5 (2.4) | 0.005 |
| day 1 | 2.9 (1.9) | 3.2 (2.5) | NS |
| **VAS for tiredness (0–10)** | | | |
| Preoperative | 1.0 (1.7) | 1.3 (1.6) | NS |
| Postoperative | | | |
| 30 min | 3.0 (3.0) | 6.8 (2.3) | < 0.001 |
| 60 min | 3.0 (3.1) | 5.0 (2.3) | 0.032 |
| **VAS for nausea (0–10)** | | | |
| Preoperative | 0.1 (0.3) | 0.2 (0.5) | NS |
| Postoperative | | | |
| 30 min | 0.3 (0.1) | 1.9 (2.0) | < 0.001 |
| 60 min | 0.7 (1.3) | 1.8 (1.7) | < 0.001 |
| day 1 | 2 (2.9) | 3.8 (3.4) | 0.007 |
| **VAS for discomfort (0–10)** | | | |
| Preoperative | 1.0 (2.0) | 1.5 (2.4) | NS |
| Postoperative | | | |
| 30 min | 2.3 (2.7) | 4.7 (2.4) | 0.001 |
| 60 min | 2.4 (2.6) | 4.2 (2.0) | 0.007 |
| **MMSE (0-30)** | | | |
| Preoperative | 28.9 (0.9) | 28.5 (1.6) | NS |
| Postoperative | | | |
| 30 min | 26.8 (5.2) | 22.7 (6.5) | < 0.001 |
| 60 min | 28.3 (3.6) | 27.0 (3.9) | 0.019 |
| Postoperative | | | |
| Extubation time in min. | 15.8 (22.3) | 26.2 (26.7) | 0.002 |
| Number donors 30 min post-extubation who could not be discharged from the recovery care | 8 | 29 | < 0.001 |
| Patient satisfaction with pain management (0-100) on the moment of recovery discharge | 96 | 85 (15) | 0.01 |
| Morfine (mg) used by PCA, day 1 | 10 (10) | 19.7 (14.1) | 0.003 |
| Morfine (mg) used by PCA, day 2 | 0 | 9.3 (9) | |

*VAS: Visual analogue scale rating from 0-10; MMSE: Mini Mental State Examination*

*Data are given as mean (SD)*

*NS: nonsignificant*

*Tabel 7.5*

**Perioperative CrCl values, from the donors**

|  | GA + TEA (N=36 | GA + Suf (N=31) |
| --- | --- | --- |
| CrCl pre | 98 (30) | 102 (24) |
| CrCl T0 | 116 (39) | 114 (30) |
| CrCl T2 | 120 (40) | 122 (28) |
| CrCl T6 | 90 (28) | 94 (20) |
| CrCl D1 | 67 (20) | 71 (15) |

*CrCl calculated with the Cockroft-Gault formula*

*pre: preoperative CrCl*

*T0: CrCl just before surgery*

*T2: CrCl two hours after start of surgery*

*T6: CrCl six hours after start of surgery, which is about 2.5 hours after the end of surgery*

*D1: CrCl one day after surgery*

*Data are given as mean (SD); there were no significant differences between groups.*

## Discussion

This study shows that patients for donor nephrectomy benefit from epidural analgesia in the postoperative period (reduced pain, improved and faster patient recovery). Laparoscopic surgery has become popular because of its smooth and fast recovery; however, in the immediate postoperative period, pain in the laparoscopic patient can be as severe as for laparotomy [18,19], and nausea is a primary complaint. Our observations confirmed these findings: the patients in the GA + Suf group had a mean VAS of 4.5 one hour after extubation, although relative high dosage of sufentanil was given during the operation.

Epidural analgesia has been reported to significantly reduce perioperative morbidity, including ileus, acute renal failure (approximately 30%), and blood loss (approximately 30%). Epidural analgesia not only improves analgesic efficacy but also reduces opioid demand and side effects such as nausea, vomiting, and sedation [5,6,20]. The results of the present study confirm this finding.

Combined spinal–epidural anaesthesia for traditional open donor nephrectomy, compared to general anaesthesia, results in lower morbidity and shorter hospitalisation, with similar effects on kidney graft function in recipients and the remaining kidney function of the donors [21,22].

The use of TEA for laparoscopic procedures is becoming more common. However for the laparoscopic cholecystectomy TEA was not recommended in a recent review from Bisgaard et al. [23]. In colon surgery, TEA significantly improves early analgesia and favourably affects dietary tolerance and duration of stay [24,25]. However, in other studies, epidural analgesia is one item in a multimodal rehabilitation program [26,27], and it is not clear that epidural analgesia is the sole reason for the success. To decide whether GA+TEA with single shot morphine is the better treatment for the LDN procedure, a risk benefit analysis should be done. Risks (in a general population) are e.g.; spinal haematoma (incidence 1:150.000), serious infections (1:10.000), late respiratory depression (5:1000), nausea (3:10) and purities (6:10) [28]. Most of these risks are related to morphine dosage, duration of catheter insertion and underlying health of the patients [28]. The incidence of these risks will be much lower in the healthy donor population, and with the low dosage of morphine as we used. Besides in this study none of these side effects were encountered. In addition the procedure of catheter insertion can be painful and bothersome, however this was done under sedation and our protocol dictated that the procedure

for epidural placement should be swift and smooth; if not the procedure was boarded. In the end the patients scored satisfaction with pain management and they scored all the maximum of 100, except for the group who had to be converted intra-operatively to the sufentanil regime. We used in the GA+Suf group high dosage of sufentanil (mean 122 μg), this to assure stress free anaesthesia. If we had used lower amounts of sufentanil the differences in postoperative pain and discomfort would presumably be greater.

Than the risk of renal function impairment due to TEA should be addressed. Regional anaesthesia and the kidney interact in a complex manner, renal blood flow and filtration fraction can be influenced both directly and indirectly by underlying cardiovascular function, fluid status and the level of induced sympatholysis in the patient. Regional anaesthesia from level T4 reduces or even abolishes sympathetic tone to the kidney, accordingly auto-regulation of renal blood flow (RBF) and glomerular filtration rate (GFR) is lost (mainly the efferent vasoconstriction is blocked which results in a lower filtration fraction), this makes RBF and filtration directly dependent on mean arterial pressure (MAP) and intravascular volume [7,29]. Laparoscopic surgery is normally associated with reduced RBF and GFR. A series of systemic and renal compensatory responses during elevated intra-abdominal pressure are activated to preserve ultrafiltration and renal clearance. Normally cortical-to-medullary redistribution of RBF protects the vulnerable medullary oxygen balance [30]. Iwase et al. determined the serial changes in renal function occurring during laparoscopic cholecystectomy; they showed that the decrease in GFR during pneumoperitoneum (PP) was less pronounced than that in RBF, which means that the filtration fraction was enhanced [31]. In the present study, we observed a MAP of 100 mmHg in the GA + Suf group and a MAP of 94 mmHg in the GA + TEA group. Urine output was closely related with MAP in the GA + TEA group, and the intraoperative urine output correlated with preoperative urine output, an association not seen in the GA + Suf group. In this study, CrCl did not decline during PP in either group, not even in the GA + TEA group where sympatholysis blocked autoregulation and the filtration fraction could not be enhanced, implying that MAP and intravascular volume were sufficient. In a study of healthy volunteers from Suleiman et.al., renal blood flow was unchanged during epidural anaesthesia with a T6 sensory block as long as MAP remained higher than 70 mmHg and did not decrease more than 6% below baseline level [32]. If GFR and urine output do not decrease, as in the present study, the cautious implication can be, that RBF was not compromised during PP or because of TEA.

We chose to remove the epidural catheter at the end of the operation in this study, after administration of a bolus of morphine (0.03 mg.kg-IBW$^{-1}$) via the catheter. Viscusi et al. concluded in their review that a single epidural injection of morphine for postoperative analgesia can be a favourable technique [33]. For practical reasons (e.g., no experience on the ward with this regime and reduction of side effects), in our previous pilot study we started with a low dosage of epidural morphine bolus. This dosage of (0.03 mg.kg-IBW$^{-1}$) proved to be sufficient in reducing the specific postoperative pain (shoulder-tip pain) after laparoscopy. Our previous clinical experience had shown that continuous epidural analgesia postoperatively, did not improve VAS scores for pain and nausea one day after LDN, but it did delay removal of the urine catheter and mobilization of the patient.

Our study had some limitations. Epidural analgesic function was not tested before operation, but failure was anticipated based on hemodynamic data. In addition, the GA+Suf group did not receive a sham epidural catheter. Although the widely used Cockcroft-Gault formula for estimation of CrCl is a crude measure of renal function, we chose to use this approach instead of more advanced methods (like inulin clearance for GFR and para-aminohippurate clearance for RBF). This because we were mainly interested in the trend and the comparison between the two groups, not in the absolute values, and as long the patients are not too old or too obese it is an acceptable estimation [34]. These were chooses the study team made, because the study should not be unnecessary demanding to the donor. Another limitation associated with a study involving epidural analgesia is the procedure for placing the epidural catheter. The anaesthetist residents who were part of the research team placed most of the catheters,

and although under close supervision, our epidural failure rate was 15%. Still the failure rate in the current study is in line with the 12 to 13% reported overall, and the up to 22% reported for teaching hospitals [17,35].

The epidural approach as used in this study showed advantages for patients undergoing laparoscopic kidney donation in the postoperative period: the patients benefit from a quicker and smoother recovery and were more satisfied with their pain management. With the perioperative fluid management protocol used in this study, TEA did not result in a compromised postoperative kidney function in the donor or the recipient. Use of TEA for patients in whom renal performance is of utmost importance (as it is in this study group) should be done with special care to maintain adequate intravascular volume and MAP, especially because laparoscopic surgery is normally associated with reduced renal blood flow and GFR. These results are particularly interesting because a quicker and smoother recovery for kidney donors may be paramount in motivating eligible donors.

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CHAPTER

7

# CHAPTER

8

# Effect of epidural analgesia on inflammatory and stress response in laparoscopic donor nephrectomy: a randomised controlled clinical study

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# Abstract

*Introduction:* Pneumoperitoneum created during laparoscopic donor nephrectomy (LDN) negatively affects renal hemodynamics through renal vein compression and activation of the neuro-humoral stress response. We hypothesized that the thoracic epidural blockade attenuates hormone responses in donors undergoing LDN.

*Patients and Methods:* Between 2004 and 2006, we randomised 61 LDN patients into two groups: 31 patients received general anaesthesia (GA + Suf), while 30 patients received general anaesthesia combined with an epidural analgesia (GA + TEA). Fluid regime, ventilation, and anaesthetic management were standardized. Venous blood was sampled for measurements of epinephrine, norepinephrine, dopamine, renin, aldosterone, cortisol, C-reactive protein and creatinine, before, during and after operation.

*Results:* Norepinephrine ($p$= 0.004), cortisol ($p$ = 0.02) and C-reactive protein ($p$= 0.007) responses were significantly lower in the study group compared to control. Creatinine concentration did not differ between both donor groups or the donor recipients of these groups.

*Conclusion*: Thoracic epidural analgesia depresses the neuroendocrine stress and the postoperative inflammatory response more than high dosage of sufentanil during LDN.

CHAPTER

8

## Introduction:

Surgical procedures are associated with a complex stress response mediated by endocrine metabolic changes and biological cascades that include the C-reactive protein (CRP) [1].

Compared to open donor nephrectomy (ODN), laparoscopic donor nephrectomy (LDN) is associated with a shorter and less intense recovery phase for the donor [2-3]. However, despite the improved conditions for recovery, the stress response during LDN is still shown to be significant [4,5].

The pneumoperitoneum (PP) necessary for LDN is known for its adverse hemodynamic and renal physiology. The increased intra-abdominal pressure (IAP) causes a decrease in renal blood flow (RBF), glomerular filtration rate (GFR), and urine output conducted through compression of the renal veins, as well as activation of the sympathetic and humoral vasoactive system [6-8]. Literature shows that kidneys derived with the laparoscopic procedure show a higher incidence of delayed graft function in the recipient compared with those obtained from the open procedure [9-11].

In abdominal surgery, thoracic epidural anaesthesia/analgesia (TEA) with local anaesthetic agents improves postoperative outcome via beneficial effects on organ function [1,12-14]. Epidural local anaesthetics providing an effective afferent blockade results in inhibition of the classical stress and inflammatory response normally induced by surgery such as; catecholamines, cortisol, glucose and CRP [13]. This stress response also affect the kidney and its blood flow.

For kidney donation, preservation of kidney function and smooth recovery of the donor are of paramount importance. In a prior study we already proved that the use of TEA has postoperative advantages for patients undergoing LDN [15]. These patients benefit from a quicker and smoother recovery without influencing postoperative kidney function of the donor and the recipient.

In this prospective study, our objective was to compare the effects of our previous high dosage sufentanil regime to TEA in relation to neuroendocrine stress and systemic inflammatory response in LDN.

## Patients and methods

This study was approved by the local human ethics committee, and written informed consent was obtained from all patients. Data of the same patient group were used in a parallel study [15]. Patients were excluded from the study if the laparoscopic approach had to be converted to an open approach, if the patient chose to abort the procedure, and when epidural analgesia failed.

Patients were randomly assigned either to general anaesthesia (GA + Suf) or to general anaesthesia combined with mid-thoracic epidural analgesia TEA (GA + TEA). The night before the operation, patients were randomised using sealed opaque envelopes, which the anaesthesiologist opened in the presence of the patient. Because we chose not to give an epidural to the control group, the patients were not blinded to the choice of anaesthetic, but they were unaware of the study hypothesis. Blood samples for analyses were not labelled according to treatment group and were analysed by a blinded technician; the results of the tests were revealed only after the last patient was included.

In the GA +TEA group, epidural catheter was inserted after locating the epidural space with the loss of resistance technique with normal saline at T6-T8 level. This was performed, according to standard procedures from our hospital. To ensure a comfortable and stress-free situation for the patients, the donors were allowed to stop the procedure on their own accord, and the duration of the procedure was restricted.

Ideal body weight (IBW) was calculated according to body height, gender, and age.

Anaesthesia was induced with propofol (2 $mg.kg-IBW^{-1}$) and sufentanil (0.3 $\mu g.kg-IBW^{-1}$). Muscle relaxation was achieved with rocuronium (0.8 $mg.kg-IBW^{-1}$) and monitored by train of four (TOF) guard, and a bolus of rocuronium (0.3 of mg. $kg-IBW^{-1}$) was given when necessary to keep the TOF under three twitches.

Anaesthesia was maintained with propofol by continuous infusion (4–12 mg.kg-IBW$^{-1}$.h$^{-1}$), maintaining the bispectral index between 45 and 55 (BIS monitor; Aspect Medical Systems, Newton, MA, USA). In the GA + Suf group, analgesia was maintained by continuous infusion of sufentanil (0.4 µg.kg-IBW$^{-1}$.h$^{-1}$) until the kidney was removed. In the GA + TEA group, a bolus of 8–12 ml (depending on the height of the patient, and our clinical experience) of a mixture of bupivacaïne (0.25%) with sufentanil (2 µg.ml$^{-1}$) was given through the epidural catheter; after two hours, an extra bolus of 5–7 ml of the same mixture was administered. At the end of the operation, the GA + Suf group received intravenous morphine (0.06 mg.kg-IBW$^{-1}$), while the GA + TEA group received morphine through the epidural catheter (0.03 mg.kg-IBW$^{-1}$), after which the catheter was removed. Epidural analgesia was considered insufficient if heart rate and MAP increased by more than 10% after the start of the operation, and an extra bolus of 5–7 ml of a mixture of 0.25% bupivacaïne with sufentanil (2 µg.ml$^{-1}$) did not result in a return to preoperative levels for heart rate and MAP. In this case, a continuous infusion of sufentanil was administered (like the GA + Suf group) and the patient was excluded from the study. For postoperative pain, both patient groups received intravenous patient control analgesia (PCA) with morphine (1mg.ml$^{-1}$, bolus 1 ml, lock out 5 min). In both groups, patients started with acetaminophen (1000 mg, 4 times a day orally), which begun before the operation.

After intubation, all patients were ventilated in a pressure-controlled mode using a closed-loop ventilator (Physioflex®, Dräger, Lübeck, Germany) with the following initial settings: 40% oxygen and 60% air, positive end-expiratory pressure of 7 cm $H_2O$, and a peak inspiratory pressure of 22 cm $H_2O$. Ventilation frequency was adjusted to keep PetCO$_2$ between 4 and 5.5 kPa. The closed-loop ventilator provided the oxygen delivery in ml.min.kg-1 (VO$_2$ kg$^{-1}$): All patients were operated in the lateral nephrectomy position. After positioning of the patient an oesophageal Doppler probe (HemoSonicTM 100, Arrow International Inc., Reading, PA, USA) was placed this device was used to measure stroke volume (SV) every three minutes. Mean arterial pressure (MAP) and heart rate were extracted every three minutes.

PP was installed with CO$_2$ with a constant intra-abdominal pressure of 12 mmHg.

Peri-operative fluid management was as follows: pre-operative fluid administration of 3 ml.kg-IBW$^{-1}$.h$^{-1}$ Ringer's Lactate (RL) was initiated at 10 p.m. on the day before the operation until the operation, 11 hours later. Prior to induction of anaesthesia, the patients received a bolus of colloids (6 ml.kg-IBW$^{-1}$ of 6% Hetastarch 130/0.4), followed by crystalloids (13 ml.kg-IBW$^{-1}$ h$^{-1}$ RL). Before initiation of the laparoscopic procedure and after the first blood sample (T0), another bolus of colloids was given (6 ml.kg-IBW$^{-1}$ 6% Hetastarch 130/0.4). Blood loss was replaced with 6% Hetastarch 130/0.4. After nephrectomy, the infusion protocol was adjusted to ensure that exactly 6 hours after the start of the operation all patients had received a total of 9 ml.kg-IBW$^{-1}$.h$^{-1}$ RL. This fluid regime was investigated in prior studies [16,17]. If MAP declined by more than 30% from preoperative levels, dopamine infusion was initiated. One hour after the start of the operation, 20 g mannitol was administered.

Venous blood samples were taken from the donor patient to determine creatinine and hormone concentrations (epinephrine (E), norepinephrine (NE), dopamine (DA), renin (REN), aldosterone (ALD), cortisol (COR)) at T0 (after induction of anaesthesia but before intubation and surgery), T2 (2 hours after incision), T6 (6 hours after incision), D1 (first postoperative day) and D28 (1 month postoperative). These samples were collected in chilled heparinized polystyrene tubes. All samples were immediately centrifuged at 4ºC, and plasma was stored at minus 80ºC until analysis. NE, E and DA, were measured by fluorimetric detection after HPLC separation. Active plasma renin activity was measured by radioimmunoassay of angiotensin I formed during incubation in the presence of excess exogenous angiotensinogen. The serum concentration of cortisol was determined by competitive luminescence immunoassay (ACS: centauer, Bayer Diagnostics, Mijdrecht, the Netherlands). C-reactive protein (CRP) was measured at D-1 (one day before operation) and on days 1 to 3 after operation (D1-D3). Serum CRP

was measured using an immunoturbidimetric assay (Boehringer, Mannheim, Germany) with a minimum detectable concentration of 0.3 mg.dl$^{-1}$.

Urine output was measured from 10 p.m. the day before operation until 6 hours after operation. Creatinine concentrations were measured till 3 days postoperative in de donors and till one month postoperative in the recipients of the donor kidneys.

### Statistics

The main outcome was the neuroendocrine stress response during LDN with two different anaesthesia techniques. Sample size was determined based on literature 18. Power calculation had indicated that at least 29 patients would be required per group to detect a difference of 25% in plasma concentration of Cortisol with an error of 0.05 and a power of 80%.In the computer-generated randomization sequence, 20% extra patients were anticipated in the study group to provide an equal number of patients despite expected epidural failures [19]. Data were analyzed using SPSS for Windows (version 14.0 Inc., Chicago, USA) and are presented as means with standard deviations (SD). After data were tested for normal distribution, differences in means between the GA + Suf and GA + TEA groups were analysed using independent samples t-test, pooled or not pooled depending on the results of Levene's test. Categorical variables were compared with Fischer's exact two-sided test. Differences between the stress hormone concentrations over time and between the two different anaesthesia techniques were assessed using SPSS linear mixed models with Bonferroni correction. This allowed for adjustment of baseline characteristics at T0, and the ''drop out hormone levels'' of certain time points (T2, T6 or D1) did not result in the deletion of the hormone data for T0, T2, T6 or D1. Hormone pair-wise comparison was performed between the control group and study group, and over time. A *p* value < 0.05 was considered statistically significant.
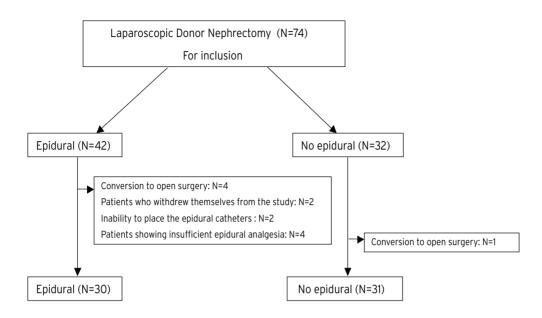
## Results

From August 2004 until January 2006, 143 living related kidney donations were performed at our institution. Donor nephrectomy was performed either by a laparoscopic (N= 99) or by an open procedure (N= 44). Of the 74 LDN patients who gave informed consent to participate in the study, two patients later withdrew their consent, and 11 patients were excluded, according to our exclusion criteria (Fig 8.1), leaving a total study population of 61 patients. Thirty patients were randomized to the GA + TEA group, and 31 patients to the GA + Suf group. All patients were classified as ASA I or II. The patient characteristics of the two groups were comparable (Table 8.1).

Four patients in the study group and 2 patients in the control group required dopamine infusion (3-6 μg.kg$^{-1}$.min$^{-1}$) to maintain an adequate MAP. In these patients, data regarding hormone concentrations of NE, E, DA and urine output were excluded, as these variables are directly influenced by dopamine.

Norepinephrine and cortisol responses to LDN were significantly lower in the GA + TEA group compared to the GA + Suf group. Also, the C-reactive protein response was suppressed in the GA + TEA group compared to GA + Suf group (Figs. 8.2, 8.3, 8.4). Epinephrine, dopamine, renin, and aldosterone concentrations were comparable between both groups (Table 8.4). Hemodynamic and ventilatory variables, were comparable between both groups (Table 8.3). Intra-operative urine output was slightly higher in the GA + TEA group, though not to a significant degree, and creatinine concentrations for the donors and the recipients were comparable.

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┌─────────────────────────────────────────────┐
│   Laparoscopic Donor Nephrectomy  (N=74)     │
│              For inclusion                   │
└─────────────────────────────────────────────┘
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Epidural (N=42)          No epidural (N=32)

Conversion to open surgery: N=4
Patients who withdrew themselves from the study: N=2
Inability to place the epidural catheters : N=2
Patients showing insufficient epidural analgesia: N=4

Conversion to open surgery: N=1

Epidural (N=30)          No epidural (N=31)

*Tabel 8.1*

**Patient characteristics**

|  | GA +TEA (N=30) | GA +Suf (N=31) |
|---|---|---|
| Age (yrs) | 49 (17) | 52 (13) |
| Weight (kg) | 71 (11) | 74 (11) |
| IBW (kg) | 69 (8) | 71 (9) |
| BMI (kg.m$^{-2}$) | 24 (3) | 26 (5) |
| Male | 10 | 7 |
| Female | 20 | 24 |
| Donor side left | 11 | 10 |
| Donor side right | 19 | 21 |
| Antihypertensive drugs | 0 | 3 |

*IBW: ideal body weight, calculated according to body height, gender and age*

*BMI: body mass index*

*number of patients using antihypertensive drugs (all β blockers)*

*Data are given as mean (SD). No significant differences were detected between groups.*

*Tabel 8.2*

**Intra operative data**

| | GA +TEA (N=30) | GA +Suf (N=31) | *p* value |
|---|---|---|---|
| Warm ischemia (min) | 5.7 (3.2) | 5.8 (2.9) | NS |
| Blood loss (ml) | 94 (97) | 174 (164) | 0.016 |
| Time before incision (min) | 61 (13) | 50 (11) | 0.002 |
| Operation time (min) | 202 (40) | 231 (52) | 0.017 |
| Time for kidney extraction (min) | 165 (43) | 186 (50) | NS |

*Warm ischemia time: the time of renal artery occlusion before the kidney is extracted and*

*flushed with iced perfusion fluid*

*Blood loss: the amount of blood loss until kidney extraction*

*Operation time: the skin-to-skin operation time in minutes*

*Time for kidney extraction: The time in minutes needed to extract the kidney from the start of the operation.*

*NS: nonsignificant*

*Data are given as mean (SD).*

*Tabel 8.3*

**Perioperative data: anaesthesiology**

| | GA +TEA (N=30) | GA +Suf (N=31) | | GA +TEA (N=30) | GA +Suf (N=31) |
|---|---|---|---|---|---|
| $Hr_{T0-T2}$ | 66 (11) | 64 (10) | pHT0 | 7.38 (0.04) | 7.39 (0.04) |
| MAPpre | 102 (10) | 103 (13) | pHT2 | 7.33 (0.04) | 7.32 (0.05) |
| MAPT0-T2 | 92 (19) | 100 (17) | PvCO2T0 | 5.7 (0.7) | 5.7 (0.7) |
| SVT0-T2 | 96 (28) | 97 (25) | PvCO2T2 | 6.7 (1.5) | 6.3 (0.9) |
| PetCO2T0-T2 | 5.3 (0.4) | 5.3 (0.5) | BIST0-T2 | 41 (4.4) | 40 (4.7) |
| VF | 18 (3.3) | 18 (3.5) | PropT0-T2 | 7.7 (2.1) | 7.4 (2.7) |
| PIP | 24 (3) | 25 (2) | Dopamine | 4 | 2 |
| VO2 kg-1 | 3.5 (1.1) | 3.8 (1.3) | Lactate T0 | 1.4 | 1.2 |
| UOT0-2 | 2.42 (1.6) | 2.14 (1.34) | Lactate T2 | 1.3 | 1.2 |
| UOT3-6 | 1.7 (0.9) | 1.7 (0.7) | | | |

*$Hr_{T0-T2}$: mean heart rate during the first two hours of operation; $MAP_{T0-T2}$: mean arterial pressure during the first two*

*hours of operation in mmHg; $SV_{T0-T2}$: mean stroke volume during the first two hours of operation in ml; $PetCO_{2T0-T2}$: mean*

*end tidal $CO_2$ during the first two hours of operation in kPa; VF: ventilation frequency; PIP: positive inspiratory pressure;*

*$VO_2 kg^{-1}$: oxygen delivery in ml.min $kg^{-1}$; pH, just before operation (T0) or after two hours of operation (T2); PvCO:*

*venous $CO_2$ in kPa, just before operation (2T0) or after two hours of operation (2T2); $BIS_{T0-T2}$: bispectral index during the*

*first two hours of operation; $Prop_{T0-T2}$: use of propofol in mg.kg-IBW$^{-1}$ during the first two hours of operation; UO: urine*

*output in the first two hours (T0-2) or in the third till sixth hour (T3-6) after the incision, in ml.kg$^{-1}$ h$^{-1}$; Dopamine the*

*number of patients who were supplemented with dopamine infusion as dictated by our protocol; Lactate in mmol.L$^{-1}$*

*Data are given as mean (SD). No significant differences were detected between groups.*

*Tabel 8.4*

**Hormone concentrations**

| | GA +TEA (N=30) | GA +Suf (N=31) | 1 | 2 |
|---|---|---|---|---|
| NE pg/ml T0 | 152 (105) | 177 (79) | 0.61 | |
| NE pg/ml T2 | 143 (133) | 208 (148) | 0.21 | |
| NE pg/ml T6 | 278 (202)* | 507 (364)** | < 0.001 | |
| NE pg/ml D1 | 186 (76) | 260 (107)* | 0.23 | |
| NE pg/ml total | 191 | 294 | | 0.004 |
| E pg/ml T0 | 22 (14) | 18 (8) | 0.84 | |
| E pg/ml T2 | 76 (116)* | 66 (107)* | 0.61 | |
| E pg/ml T6 | 76 (69)** | 99 (63)** | 0.26 | |
| E pg/ml D1 | 33 (16) | 52 (29)** | 0.54 | |
| E pg/ml total | 52 | 59 | | 0.6 |
| DA pg/ml T0 | 21 (30) | 15 (16) | 0.59 | |
| DA pg/ml T2 | 39 (74) | 27 (22)* | 0.31 | |
| DA pg/ml T6 | 21 (19) | 28 (30)* | 0.49 | |
| DA pg/ml D1 | 34 (46) | 12 (5) | 0.11 | |
| DA pg/ml total | 28 | 21 | | 0.091 |
| Re ngAl/ml.h T0 | 270 (212) | 192 (97) | 0.18 | |
| Re ngAl/ml.h T2 | 458 (354)* | 317 (352) | 0.017 | |
| Re ngAl/ml.h T6 | 195 (90) | 177 (96) | 0.77 | |
| Re ngAl/ml.h D1 | 156 (104) | 161 (79) | 0.95 | |
| Re ngAl/ml.h total | 270 | 212 | | 0.089 |
| Ald pg/ml T0 | 21 (24) | 21 (17) | 0.99 | |
| Ald  pg/ml T2 | 70 (65)** | 51 (49)* | 0.1 | |
| Ald  pg/ml T6 | 59 (60)* | 50 (43)* | 0.44 | |
| Ald pg/ml D1 | 28 (29) | 42 (41)* | 0.27 | |
| Ald pg/ml total | 44 | 42 | | 0.72 |
| Cort nmol/L T0 | 430 (170) | 481 (132) | 0.093 | |
| Cort nmol/L T2 | 361 (268) | 485 (235) | 0.059 | |
| Cort nmol/L T6 | 607 (323)* | 689 (320)* | 0.82 | |
| Cort nmol/L D1 | 495 (231) | 651 (209) | 0.087 | |
| Cort nmol/L total | 483 | 580 | | 0.02 |
| CRP mg/ml D-1 | 3 (2) | 11 (5) | 0.5 | |
| CRP mg/ml D1 | 53 (23)** | 66 (38)** | 0.29 | |
| CRP mg/ml D2 | 74 (35)** | 125 (86)** | < 0.001 | |
| CRP mg/ml D3 | 60 (31)** | 96 (65)** | 0.006 | |
| CRP mg/ml total | 47 | 75 | | 0.007 |

*1. p-value linear mixed models with Bonferroni correction*

*2. Differences in groups, pair wise comparison.*

*epinephrine (E), norepinephrine (NE), dopamine (DA), renin (REN), aldosterone (ALD), cortisol (COR) and C-reactive protein (CRP); T0: just after induction of anaesthesia, but before intubation and surgery; T2: 2 hours after start of the operation; T6: 6 hours after start of the operation; D-1: day before the operation; D1: day 1 after the operation Data listed as mean (SD).*

*\* p < 0.05 compared with T0, or D-1; \*\* p < 0.001 compared with T0, or D-1*

*Fig. 8.2*
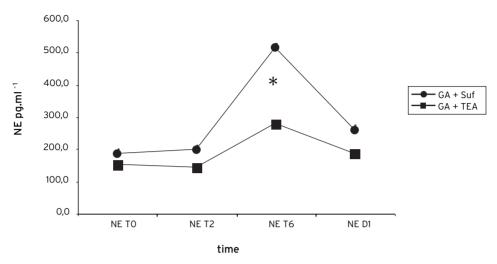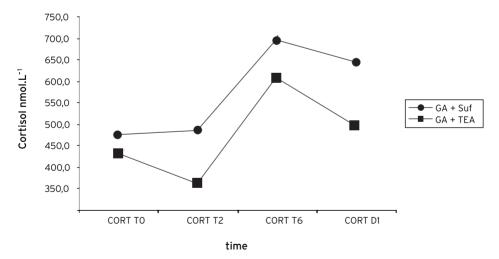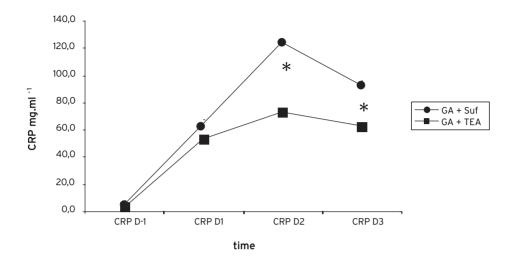**Norepinephrine concentrations**



*Fig. 8.3*
**Cortisol concentrations**

*Fig. 8.4*
**CRP concentrations**



## Discussion

In this clinical study, we demonstrated that additional use of TEA did suppress plasma concentrations of norepinephrine and cortisol in donors undergoing laparoscopic donor nephrectomy (LDN); in contrast, epinephrine, dopamine, renin, and aldosterone release remained unaffected. The reduced plasma norepinephrine concentrations, probably is a direct result of the sympaticolythic effect of the local anaesthetics. But the GA + TEA group also exhibited suppressed plasma cortisol concentrations, indicating an overall stress reduction. In addition C-reactive protein, an inflammatory marker, was significantly reduced in the GA + TEA group from the second postoperative day and onwards.

The use of additional TEA for laparoscopic procedures is becoming more common, particularly in colon surgery in which TEA significantly improves early analgesia and favourably affects dietary tolerance and duration of stay [20,21]. The impact of the addition of TEA analgesia to general anaesthesia on the metabolic hormonal response during laparoscopic surgery however has received little attention. The few publications on this topic are performed for laparoscopic cholecystectomy, they describe a reduction in AVP, epinephrine, norepinephrine and cortisol on account of the usage of additional epidural analgesia [18,22,23].

The endocrine metabolic response during and after laparoscopic surgery compared to open surgery has been studied by several authors, most of them have been unable to detect an endocrine metabolic response increase during PP compared to open surgery, these concerned cholecystectomy or gynaecological surgery [13]. However, laparoscopic procedures with low amounts of fluid administration (< 6 ml kg$^{-1}$ h$^{-1}$) or laparoscopic procedures performed in lateral nephrectomy position (in which LDN is conducted) have shown increased concentrations of stress hormones [4,5,8,24-28].

Previously, we demonstrated that the LDN procedure handled with an explicit protocol for anaesthesia, with adequate depth of anaesthesia, high dose of opioids and preoperative hydration before installation of PP, attenuated the hemodynamic compromise from this PP [16,17]. However, the high dose of opioids (as part of our multimodal approach) resulted also in longer recovery time.

In abdominal surgery, TEA improves postoperative outcome with less perioperative morbidity, resulting in swifter recovery, and attenuates the physiologic response to surgery [12-14,29]. Furthermore, effective afferent neural blockade with epidural local anaesthetic techniques inhibits a major part of the endocrine metabolic response, leading to improved protein economy [13]. Combined spinal–epidural anaesthesia for traditional ODN, compared to general anaesthesia, also resulted in lower morbidity and shorter hospitalisation, with similar effects on kidney graft function in recipients and the remaining kidney function of the donors [30,31].

When using TEA with local anaesthetic, it has to be considered that the induced sympathicolysis, might result in relative hypovolemia. The LDN procedure is already prone for relative intra-abdominal hypovolemia through the lateral nephrectomy position and the mechanical compression during PP. Hypovolemia with a reduction in renal blood flow (RBF), will cause stimulation of the RAAS (renin-angiotensin-aldosterone system) [6,8,26]. We used a fluid regime with the aim of preventing RBF reduction based on PP [16,17]. In addition we aimed with our sympathiclysis at the operation area only, by placing the epidural catheter between Th 6 and 7, and by administration of a relative small amount of local anaesthetic. In the present study SV and urine output were equal between the two groups, however the plasma concentration of REN was significantly higher at T2 (when the laparoscopic procedure was 2 hours in progress). This might indicate that although several precautions were taken, renal blood flow was lower in the GA + TEA group compared to the GA + suf group. Plasma concentration of ALD was not higher, which indicates that the elevation was not major, however this shows that sufficient hydration is necessary when sympaticolysis is enforced in this type of surgery.

An increase in plasma hormones could also be the result of reduced renal clearance and glomerular filtration rate, which is known to be reduced during PP [6]. In this study, however, an equivalent creatinine and urine output during and after the procedure in both study groups was observed.

Evidence is mounting that patients benefit from diminished surgical trauma and maintained immune function after laparoscopic surgery [13,32,33]. After laparoscopic surgery, the increase in serum CRP values was found to be significantly less pronounced over the first 3 postoperative days, which implies a certain benefit for the minimally invasive procedure [13]. The effects of epidural blockade with local anaesthetics on the pro-inflammatory response to surgery are however controversial [13, 34-36]. In the current study, CRP increased considerably after LDN, but epidural anaesthesia could suppress this CRP increase. C-reactive protein (CRP) is a liver-derived acute phase protein that serves as a non-specific marker of an acute-phase reaction caused by trauma or inflammation. The maximum increase of CRP is delayed until day 2 after operation, this delay is caused by protein biosynthesis of the acute-phase protein after stimulation. In this study, CRP was indeed at its highest level at the second post-operative day.

To minimize confounding factors that may lead to neuroendocrine stress release, we monitored and regulated the depth of anaesthesia and ventilator settings between preset values. BIS (monitoring depth of anaesthesia); usage of propofol, $PetCO_2$ and $PvCO_2$ all were comparable between the two study groups.

Our study had some limitations. Statistic analysis was not performed on an intention-to-treat basis, conversion to the open technique and insufficient epidural analgesia were excluded from the study. Our mean interest was in the effects of epidural analgesia on stress response during LDN. Secondly, although in this study no significant differences for postoperative plasma creatinine concentrations were found in the donor and the recipient groups, this significance is under-powered. To conclude on this important item in living kidney donor procedures, at least 260 patients would be required per group to detect a significant difference with an error of 0.05 and a power of 80%. This because with our anaesthesia and fluid regime we already provided excellent conditions for postoperative kidney function.

CHAPTER

8

In conclusion, our study shows that thoracic epidural has a beneficial effect on the classic neuroendocrine stress response in patients undergoing LDN, and that the postoperative inflammatory response was significantly suppressed. If this effect is also beneficial in preventing the moderate delayed graft dysfunction in the recipient as seen after LDN needs further research.
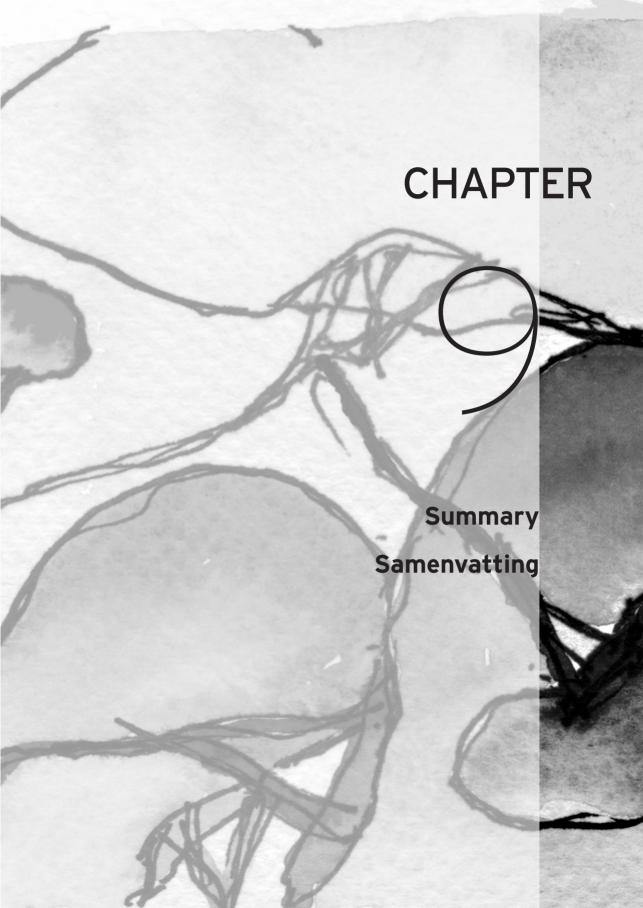
CHAPTER

8

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CHAPTER
8

# CHAPTER

9

**Summary**

**Samenvatting**

# Summary

**Chapter 1** provides a general introduction to living laparoscopic donor nephrectomy. Laparoscopic donor nephrectomy (LDN) has become popular mainly because of the better quality of life compared to open surgery (ODN) after the procudure. Although LDN is beneficial to the donor, there are concerns about the transient early delayed graft function compared to the open procedure. Therefore, we developed and validated an anaesthesia and peri-operative care protocol in order to prevent this delayed graft function. This protocol is discussed.

**Chapter 2** gives a retrospective view of our study population before we started our trial. We compared long-term serum creatinine levels in donors and recipients after LDN and ODN. In the first week, higher levels of serum creatinine levels are found in recipients of the laparoscopic group. Thereafter, serum creatinine levels are comparable for both groups up to 3 years after donation. Additionally higher serum creatinine levels are found in the donors after LDN.

**In Chapter 3** we prospectively compare three different peri-operative fluid regimes for laparoscopic donor nephrectomy. Two study groups are compared to one control group. The two study groups received an overnight infusion and a bolus of colloid before induction of anaesthesia and one of the groups received another bolus of colloid before the induction of pneumoperitoneum (PP). The control group only received intravenous infusion during the operation, conform our old protocol. The total amount of fluids used in these three groups is equal, but the timing of administration is different. Although this pilot study includes only a small number of patients, we found that overnight infusion and a bolus of colloids before PP attenuates the hemodynamic compromise from PP, and that the immediate postoperative creatinine clearance is higher in the two study groups compared to the control group. Therefore, this optimal fluid regimen is used in the next studies.

**Chapter 4** evaluates the mechanisms leading to negative hemodynamic effects during $CO_2$PP. These mechanisms can be either the influence of elevated $CO_2$, or compression of the vessels and organs due to elevated intra-abdominal pressure (IAP). We found that the decrease in stroke volume during $CO_2$PP is due to compression of the intra-abdominal vasculature and/or organs (caused by elevated IAP), with subsequent reduction of venous return, and not due to elevated $CO_2$.

**In Chapter 5** we evaluate our newly developed protocol for anaesthesia and fluid management in respect to the kidney function of the donor and recipient in LDN vs. ODN. Also, the side effects of this new fluid regime are monitored. Hemodynamics, urine output and creatinine clearance are comparable in both the LDN and ODN groups up to 2 years after donation. Furthermore, no side effects of the new fluid regime are noted.

**In Chapter 6** we study the neuroendocrine stress response after ODN and LDN and also investigate the effect of the type of anaesthesia on the stress response in both procedures. No differences are found between LDN and ODN for norepinephrine, epinephrine, dopamine, renin, aldosterone, vasopressin and glucose. However, significantly lower concentrations of epinephrine, dopamine, renin and vasopressin are found in favour of the propofol group compared to the isoflurane group.

**In Chapter 7** we investigate whether epidural anaesthesia offers any advantages for LDN donors. We randomised LDN donors either for general anaesthesia with high dosage of opioids (as used in our prior research), or for general anaesthesia with epidural analgesia. Again, we used the same fluid protocol and ventilator settings and we titrated anaesthesia to achieve an equal depth of anaesthesia. Preservation of kidney function in this patient group is important. Because epidural analgesia with local anaesthetics and elevated IAP both (directly or indirectly) influence kidney function, we additionally tracked urine output and creatinine clearance during and immediately after the procedure. The epidural approach resulted in a quicker and smoother recovery. Postoperatively these patients are extubated

faster, have less pain, experience less nausea, and are more comfortable and satisfied than the patients with general anaesthesia alone. Additionally, kidney function is comparable in both groups.

In **Chapter 8**, we use the same study population as in **chapter 7**, but this time the effect on the neuroendocrine stress response is studied. The addition of epidural analgesia results in lower norepinephrine and cortisol levels during LDN, and lower CRP levels after the LDN procedure.

## Samenvatting

**Hoofdstuk 1** geeft een algemene introductie over het onderwerp "laparoscopische nierdonatie bij leven". De laparoscopische benadering (LDN) is vooral populair geworden door de betere kwaliteit van leven direkt na de operatie, vergeleken met de (klassieke) open benadering (ODN). Hoewel LDN voordelen voor de donor oplevert zijn er zorgen over de tijdelijk verminderde functie van het transplantaat in vergelijking met ODN. Daarom hebben we een peri-operatief protocol ontwikkeld en gevalideerd waarmee deze tijdelijk verminderde nierfunctie na LDN kan worden voorkomen. Dit protocol wordt besproken.

**Hoofdstuk 2** geeft een retrospectieve analyse van de studiepopulatie, voor de start van ons onderzoek. We vergelijken daarbij de serum kreatinineconcentraties bij donoren en ontvangers na LDN en ODN over een langere periode. In de eerste week na LDN werden bij de ontvangers hogere serum kreatininewaarden gevonden dan na ODN. Daarna waren deze waarden vergelijkbaar voor LDN en ODN tot 3 jaar na de procedure. Ook bij de donoren werden hogere serum kreatininewaarden gevonden na LDN.

In **hoofdstuk 3** vergelijken we prospectief drie varianten in peri-operatief vloeistofbeleid tijdens LDN. Twee studiegroepen worden vergeleken met een controle groep. De twee studiegroepen worden behandeld met prehydratie vanaf de avond voor operatie en krijgen voor de inleiding van de anesthesie een bolus colloïden toegediend. Eén studiegroep krijgt bovendien een bolus colloïden toegediend voordat het pneumoperitoneum (PP) wordt aangelegd. De controlegroep krijgt intraveneus vloeistoffen toegediend conform ons oude protocol, namelijk alleen tijdens de ingreep. Het totaal aan intraveneus toegediende vloeistoffen is gelijk in alle drie groepen, alleen het tijdstip van toediening van de vloeistoffen verschilt. Alhoewel deze pilot studie slechts een klein aantal donoren betreft, kunnen we concluderen dat prehydratie in combinatie met een bolus colloïden voordat PP wordt aangelegd, zorgt voor minder hemodynamische veranderingen in vergelijking met de controlegroep. Daarnaast is ook de post-operatieve kreatinineklaring beter in de twee studiegroepen. We passen vervolgens het meest optimale intraveneuze vochtbeleid uit dit onderzoek toe bij de volgende studies.

**Hoofdstuk 4** evalueert de verschillende mechanismen die tot hemodynamisch negatieve effecten leiden gedurende $CO_2$PP. De oorzaak daarvan is òf de verhoogde $CO_2$-concentratie òf de mechanische druk op de vaten en organen ten gevolge van de verhoogde intra-abdominale druk (IAP). Uit deze studie blijkt dat het verminderde slagvolume tijdens $CO_2$PP veroorzaakt wordt door compressie van de intra-abdominale vasculatuur en/of organen door de verhoogde IAP, met als gevolg een verminderde veneuze return, en niet door een verhoogde $CO_2$-concentratie.

In **hoofdstuk 5** evalueren we ons nieuw ontwikkelde protocol voor anesthesie en intravenues vloeistofbeleid bij nierdonatie. De nierfuncties van de nierdonoren en de ontvangers worden vervolgd na de ingreep. Daarnaast worden de eventuele bijwerkingen van dit nieuwe beleid bekeken. De hemodynamiek, de urineproductie en de kreatinineklaring tot 2 jaar van de LDN- en ODN-groep zijn vergelijkbaar. Er worden geen bijwerkingen geobserveerd in de direct post-operatieve fase.

In **hoofdstuk 6** wordt de stress respons tijdens ODN en LDN vergeleken. Ook wordt gekeken naar de vorm van anesthesie. Er blijkt geen verschil te zijn tussen de twee operatietechnieken voor wat betreft serumconcentraties noradrenaline, adrenaline, dopamine, renine, aldosteron, vasopressine en glucose.
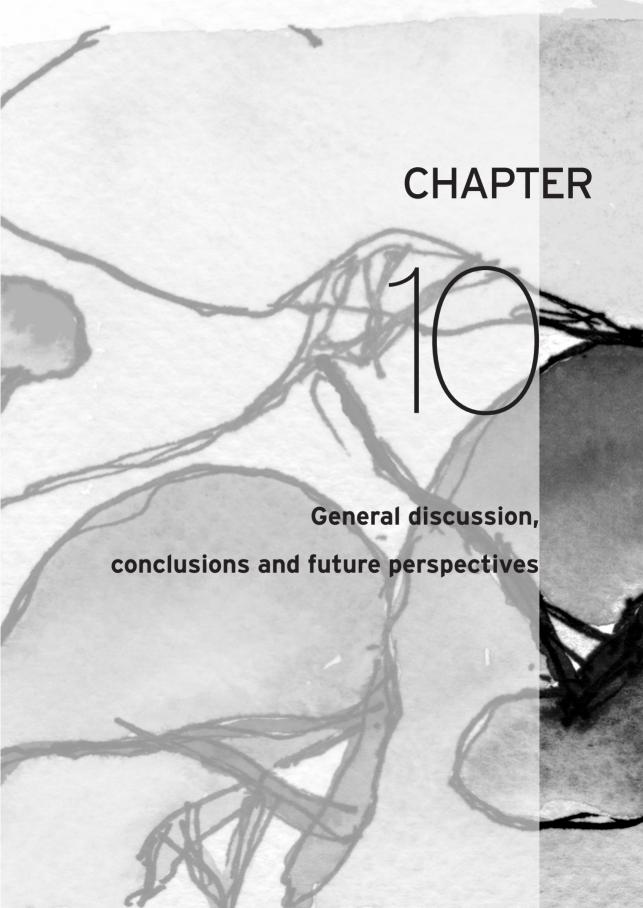
We zien echter wel duidelijk lagere serumconcentraties van adrenaline, dopamine, renine en vasopressine in de groep die propofol als anestheticum heeft gehad, in vergelijking met de isoflurane groep.

In **hoofdstuk 7** onderzoeken we of epiduraal analgesie voordelen oplevert voor de donor. Daartoe worden LDN donoren gerandomiseerd. De ene groep krijgt algemene anesthesie met hooggedoseerd sufentanil (gelijk aan onze vorige studies) en de andere groep krijgt algemene anesthesie in combinatie met epiduraal analgesie. Ook nu weer worden hetzelfde vloeistofbeleid en dezelfde ventilatieinstellingen gebruikt en wordt de anesthesie getitreerd op basis van de anesthesiediepte, conform voorgaande studies. Aangezien de nierfunctie in deze groep patiënten zo belangrijk is en epiduraal analgesie met locaal anesthetica en verhoogde IAP beide (direct of indirect) invloed hebben op de nierdoorbloeding en nierfunctie, worden ook de urineproductie en kreatinineklaring tijdens en net na de ingreep gemeten.

Postoperatief kunnen de patiënten uit de epiduraal groep eerder geëxtubeerd worden en is er sprake van minder pijn. Ook is er bij hen in de direct postoperatieve fase minder sprake van misselijkheid, ongemak en vermoeidheid dan bij de sufentanil groep en zijn de donoren met de epiduraal aanpak meer tevreden. We concluderen dat de post-operatieve fase sneller en aangenamer verloopt voor de donoren met epiduraal analgesie, zonder dat de nierfunctie verschil laat zien tussen beide studiegroepen.

In **hoofdstuk 8**, wordt dezelfde studiepopulatie gebruikt als in hoofdstuk 7, echter in dit hoofdstuk wordt de stress respons van de sufentanil groep en de epiduraal analgesie groep vergeleken. Het toevoegen van epiduraal analgesie leidt tot lagere serumconcentraties noradrenaline en cortisol tijdens LDN, en een lagere CRP-concentratie na LDN.

# CHAPTER

# 10

**General discussion,
conclusions and future perspectives**

# General discussion

In our university, M. Lind (2005) and N.F. Kok (2007) have both demonstrated in their thesis that laparoscopic kidney donation (LDN) is the procedure of choice, that it is safe for the donor and acceptor, and that it offers the best outcome to the donor with regard to quality of life.

However, Hazebroek et al. (2002) showed already that, in recipients, mean serum creatinine was higher after LDN compared with open donor nephrectomy (ODN) shortly after surgery [1]. They emphasized that this was caused by the pathophysiologic changes due to $CO_2PP$. Our goal was to develop a peri-operative care regimen that prevents the delayed graft function as seen after LDN by focusing on fluid management and low levels of stress.

In an effort to combat the cardiovascular, endocrine and renal effects of laparoscopic surgery, we first introduced some simple adjustments. The problem of blood pooling in legs und upper trunk because of the lateral nephrectomy position, was dealt with by adjustment of position (adapted lateral nephrectomy position) and anti-thrombosis stockings [2]. In a (unpublished) trial with 6 patients we demonstrated that these actions are able to alleviate the reduction in cardiac output with a mean of 530 ml.min$^{-1}$.

To ensure low levels of stress during operation, we used relatively high levels of sufentanil. The mean usage of sufentanil until nephrectomy was 124 microg sufentanil for the LDN group and 103 microg for the ODN group; this latter procedure was shorter in time. To study hemodynamics and neuroendocrine stress response changes during operation it is mandatory to standardise the depth of anaesthesia. This was achieved by monitoring the depth of anaesthesia with a BIS monitor. The mean BIS values were between 40 and 50 units.

In addition, high intrathoracic pressure reduces venous return and consequently will depress the release of atrial natriuretic factor, which is known to interact with AVP. In turn, AVP is known for its vasoconstriction and antidiuretic effect. Therefore ventilation settings were directed toward comparable (for LDN and ODN) and low peak pressure levels. To achieve this we chose for the pressure-controlled ventilation mode, and adequate ventilation was achieved primarily with elevation in ventilation frequency and not in ventilation pressure. Although, because of elevated IAP during PP, it is not always possible to keep the ventilatory positive pressures at the primary fixed level of 22 kPa, we only had to enhance this towards a mean of 25 kPa, with a subsequent PetCO$_2$ mean of 5.3 kPa, for all studies together in this thesis.

As described by London et al. $CO_2PP$ results in a relatively hypovolemic state leading to decreased intra-abdominal blood flow and urine output [3]. The pressure exerted on the inferior vena cava during pneumoperitoneum (PP) in volume-depleted animals results in partial caval compression, thereby decreasing preload and stroke volume [4]. In an attempt to ameliorate the decrease in venous return and urine output, vigorous hydration intra-operatively was advocated [3,5]. This view has enforced a widely used high-volume fluid regimen for the LDN procedures, up to 2 L.h$^{-1}$ of crystalloids [6-10], but this has never been investigated in a prospective study in humans. However, we believed that volume loading after establishment of PP is too late in order to counterbalance the pathophysiologic compromise of $CO_2PP$ during living kidney procurement. We emphasized that the fluid regime should focus on prophylactic volume expansion. The relative hypovolemia induced by position and elevated IAP due to PP should be compensated before these are established, thereafter the fluid load can be restricted. This is shown in chapter 3 in which we found that prehydration with crystalloids and colloids before installation of PP resulted in less hemodynamic and renal function compromise.

To draw the conclusion that the reduced incidence of delayed graft function following the LDN procedure was resolved as result of our new peri-operative regimen is tempting. However, several

confounding factors should be considered. The retrospective study from chapter 2 comparing kidney function after the ODN and LDN procedure with our previous anaesthetic peri-operative regiem and the prospective study from chapter 5 comparing kidney function after the ODN and LDN procedure with our new anaesthetic peri-operative regiem are not completely comparable.

The experience of the surgeons with the LDN procedure has improved over the years. Besides the surgical approach for ODN has changed; the formerly used ODN procedure was done with the traditional lumbotomy approach, the ODN procedure in the prospective trial was performed with the mini-incision technique, developed in our clinic (the Erasmus MC muscle-split technique) [11].

In addition, the donor population has changed; less healthy people are willing to donate a kidney and inclusion criteria seem to have slightly adapted. In our prospective studies 76% of the donors were classified as ASA I in the LDN group, compared to 82% in the retrospective study (The American Society Anaesthesiologists, ASA Class II, beholds patients with mild systemic diseases i.e. hypertension, smoking, thyroid disease and others). Also, the mean preoperative serum creatinine of the donors and recipients has increased over the years. In addition, the mean percentage of unrelated living donations has increased from 12% to 27%, which all may have had an impact on the graft function in the recipient. The recipients can be divided into three groups; the peritoneal dialysis group, the hemodialysis group and the pre-dialysis group. However, we do not have an overview of the hemodynamic response to anaesthesia of these three groups. It seems that the hemodialysis patients react with more hypotension and have lower stroke volume after induction of anaesthesia than the patients from the other two groups. This could have a direct effect on the graft function of the newly received kidney in the recipient. We will use all the collected data of the recipients to deal with this issue in a future retrospective study.

It is arguable as to whether the donor groups were comparable in view of the chosen kidney for donation. The two kidneys from the donor can differ in function, so the choice of which kidney is harvested for donation can bias the outcome in graft function outcome. An MAG3 scan provides the distribution of the function from the two kidneys of the donor; however, in our institution only a minority of the donors was scanned and therefore we were not able to include this factor in our comparison.

Finally, in this thesis we did not take into account the progression over the years in the field of the nephrologists. The improvement in immunostatic therapy after kidney transplantation for the recipient must certainly have had a considerable influence on the outcome of renal graft function. Because the recipients are a very inhomogeneous group (different ASA classification, different morbidity, and different forms of dialysis) and because over the years postoperative treatment by the nephrologists has changed, comparing renal function in the acceptors is bound to be a subject to these confounding factors. Therefore we focused on the postoperative renal function outcome of the donors; this was based on the assumption that if the anaesthesia regimen matters to the donated kidney then it also matters for the kidney that was donated.

We cannot rule out that above mentioned improvements over the years have had their impact on the difference in postoperative kidney function between LDN and ODN.

In most studies postoperative pain is significantly reduced by the laparoscopic approach as compared with open techniques. However, in the immediate postoperative period, pain in the laparoscopic patient, which is mainly identified as subcostal pain or shoulder tip pain, can be as severe as after laparotomy, [12-14]. In their prospective study comparing laparoscopy with laparotomy with comparable peri-operative pain management, Ekstein et al. showed that the pain VAS of the laparotomy patients was 4.1 compared with 6.1 in the laparoscopy patients[12]. We confirmed in Chapter 7 that the laparoscopic approach in the direct postoperative period can be rather painful; in spite of administration of high dosage of sufentanil during the LDN procedure, the patients indicated one hour after extubation a VAS score of 4.5 for pain. Thoracic epidural analgesia (TEA) is known for its

favourable profile for postoperative outcome. Moreover, in an unpublished pilot study of 5 patients, we found that epidural administered low dosage of morphine was effective in reducing the typical postoperative laparoscopic pain.

Because epidural administered local anaesthetics induce a sympathicolysis in the target area, the kidney will partly loose its ability to autoregulate its blood flow. Therefore, if epidural anaesthesia is chosen extra care should be given to the fluid balance. With the novel fluid regime used in this study no differences in urine output or creatinine clearance are observed in the donor patient. Also the renal function of the recipient, monitored up to one month after the transplantation, did not show any differences between the sufentanil and epidural group. Our epidural failure rate was 15%; one can argue, however, that this failure rate is too high for the benefit which epidural analgesia is producing.

## Conclusions and Future perspectives

Adequate fluid loading before installation of PP, together with prevention of blood pooling with anti-thrombosis stockings and adjustment of the position, adequate ventilation with the aim to minimize elevated intrathoracic pressures, high dose of sufentanil and adequate depth of anaesthesia resulted in the prevention of the hemodynamic and renal compromise encountered due to elevated IAP, during LDN. Moreover, the differences in stress response between ODN and LDN have disappeared with this regimen. The use of propofol anaesthesia and the addition of epidural analgesia further reduced the stress response and provided a faster and qualitatively better direct postoperative recovery.

In conclusion, the work presented in this thesis shows that the anaesthetist is able to improve the outcome for the donor patient, as well as for the donor kidney.

Future directions include addressing the tendency of accepting more donors with morbidity (such as older age, hypertension and obesity), and increasing the number of live kidney donors without compromising safety to the donors or the graft. The complex pathophysiological state induced by CO2PP, i.e. an increase in afterload with a drop in cardiac output, and reduced renal blood flow was tackled with our new anaesthesia regime. However, we did not prove that these precautions were sufficient for the increasing number of donors with minor diseases. Struther emphasized that pharmacological treatment could prevent the negative pathophysiological reaction towards PP [15]. Studying pharmacological options (like selective renin and AVP inhibitors) could result in a protective treatment as well as a further insight in the pathophysiologic procedures during elevated IAP. As yet, no one has explored peri-operative use of these drugs as a means to prevent the harmful cardiovascular and renal effects of positive-pressure PP.

The main issue of this thesis was reduction of delayed graft function due to $CO_2$PP during LDN compared to ODN. To confirm that our newly developed anaesthesia regime does indeed eliminate the delayed graft function after the LDN procedure, a sufficiently powered multi-center trial should be initiated. However, most of the transplantation centers have already adapted the LDN procedure as the favorable approach for living donor nephrectomy.

Until now we proved with indirect measurements (i.e. stroke volume, urine output, creatinine clearance, hormones) that we might have reduced the compromised RBF associated with LDN. In our next study we will measure RBF and GFR with more advanced methods like para-aminohippurate clearance and inulin clearance. We will record the changes in RBF and GFR when PP is installed, and probably confirm with this direct method that our peri-operative care regime does indeed have a positive effect on RBF during elevated IAP.

The hand assistant approach for donor nephrectomy is now being adapted in our hospital; this

procedure also includes $CO_2PP$, but is a faster procedure compared with LDN.  A new trial will be started in the near future for comparison of the hand assitant technique with LDN. Additionally we will study the effect of our anaesthesia regimen on RBF during these two procedures.

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CHAPTER

10

# Abbreviations

| | |
|---|---|
| Acc | Acceleration |
| ADH | Anti Diuretic Hormone |
| ADL | Aldosteron |
| ASA | American Society of Anaesthesiologists |
| ATN | Acute Tubular Necrosis |
| AVP | arginin Vasopressin |
| BIS | Bispectral index |
| CO | Cardiac Output |
| $CO_2PP$ | $CO_2$ Pneumoperitoneum |
| DGF | Delayed Graft function |
| E | Epinephrine |
| ESRD | End stage renal disease |
| GFR | Glomerular Filtration Rate |
| IAP | Intra Abdominal Pressure |
| IBW | Ideal Body Weight |
| IPPV | inspiratory positive pressure ventilation |
| LDN | Laparoscopic Donor Nephrectomy |
| LVET | Left Ventricular Ejection Time |
| MAP | Mean Arterial Pressure |
| NE | Nonepinephrine |
| ODN | Open Donor Nephrectomy |
| PCV | Pressure controlled ventilation |
| PEEP | Positive end exspiratory pressure |
| PIP | Positive inspiratory pressure |
| PP | Pneumoperitoneum |
| RAAS | Renin-Anginotensin-Aldosteron System |
| RBF | Renal Blood Flow |
| REN | Renin |
| SV | Stroke Volume |
| SVR | Systemic Vascular Resistance |
| TEA | Thoracic Epidural Analgesia |
| TOF | Train of Four |
| $VCO_2$ | $CO_2$ production per minute |
| $VO_2$ | $O_2$ production per minute |

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Buwe!!! Hik hou van huwlie...Betere en lievere buren kunnen we ons niet wensen.

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Lieve Pa en Ma, een ieder zou mogen wensen ouders te hebben zoals jullie. Nog steeds ben ik gelukkig als ik zie hoeveel jullie van elkaar en ons houden. Jullie waren en zijn een warme en stevige basis voor ons leven. Nog steeds kunnen we onvoorwaardelijk op jullie een beroep doen. Pap je levenslust, je gedreven plannen, je betrokkenheid en vrolijke humor zijn altijd een goed voorbeeld voor mij geweest. Enne bedankt voor de prachtige website! Ma, Moes, Sidonia naast deze bijnamen had je er nog een en deze is zeer treffend, nl. het Parlement. Deze naam geeft aan dat jij de spil bent in ons gezinnetje, met je sterke karakter en niet aflatende liefde was je altijd en altijd voor ons aanwezig. Dank jullie!

Ben.... wat ben je toch enorm veel voor mij/ons gaan betekenen, je bent al vele jaren een deel van ons gezin en zonder jou zijn we niet compleet. Karel of ik kunnen weken weg zijn zonder enig probleem. Als jij een week weg bent dan hebben wij, en met name de dieren een slechte tijd. Ik kan gerust stellen

dat zonder jou dit boekje nooit gerealiseerd zou zijn. Het is niet mogelijk op papier te zeggen hoe dankbaar ik ben met je betrokkenheid voor ons gezin. Daarnaast bewonder ik je moed en eigenheid.

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Lieverd ik dank je en ben gelukkig dat we samen op zaterdag 31 mei 2008 ons huwelijk in combinatie met mijn promotiefeest  gaan vieren.

# Nawoord

Narcose beschouw ik als een beademde dood, een artificiële dood, een verzwakt en vervalst beeld van de eeuwigheid. Voor een patiënt is niets leger dan een narcose. Niets is er alles, er wordt niet geleden en de wetten van de tijd zijn slechts spaties tussen woorden van leegheid. Een heerlijkheid. Want als de dood is als een narcose, dan is er niets om bang voor te zijn. Toch? En mocht er meer zijn, dan is dat dus mooi meegenomen. En dit alles - of moet ik zeggen 'niets' - vindt plaats in de gevaarlijkste ruimte op aarde, de OK, waar medisch specialisten goden zijn, of zich als zodanig gedragen.

Mijn naam is André Bek. Ik beschouw mezelf, zonder enige valse bescheidenheid, na vier niertransplantaties van levende donoren binnen 20 jaar, als 'gepromoveerd' ontvanger. Over mijn leven, belevenissen en zieleroerselen schreef ik een boek: 'Dansen in het zand - *Een leven in geschonken tijd'*. Ingrid Mertens zur Borg speelt daarin een essentiële rol. Deze 'godin' hielp mijn dierbare donor en mij, nagenoeg vrij van lijden, over de kloof die de werelden van onbenoembaar gezamenlijk sukkelen en gezamenlijke wedergeboorte van elkaar scheidt.

*'Het is het laatste wat ik me van haar herinner. Er brandt iets in mijn aderen, het stijgt vanuit mijn linkerarm zwaar naar mijn hoofd. Vormen vervagen. Gedaanten verdwijnen in een dikke mist. Stilte overstemt ieder geluid.*

*Het licht gaat uit. Een val in een volkomen tijdloos, droomloos gat. En toen was er niets meer. Geen waarnemingen, geen gedachten, geen verwachtingen, geen herinneringen, geen dromen, geen duisternis, geen licht, geen pijn, geen zorgen, geen ziekte, geen leegte, geen José, geen ik. Helemaal niets. De totale afwezigheid van iets. Mijn bewustzijn en zeggenschap zijn niet meer.' (citaat uit: 'Dansen in het zand')*

Later ontmoette ik niet zozeer de gewaardeerde anesthesioloog dokter Mertens zur Borg, maar Ingrid, een enthousiaste lezeres van 'Dansen in het zand', de kwetsbare mens achter de dokter. Een lieve en gedreven vrouw. Mijn boek sloeg een brug tussen betrokkenheid en professionele distantie. Een zeldzaam genoegen.

De afgelopen 20 jaar ben ik als niertransplantatiepatiënt getuige geweest van nauwelijks bij te houden ontwikkelingen op de gebieden van anesthesie, medicatie, operatietechnieken en verpleging. De synergie van deze deelontwikkelingen heeft de drempel voor nierdonatie bij leven vanuit medisch-ethisch oogpunt en vanuit het (potentiële) donorenperspectief verlaagd. Het is tot op heden ook verreweg de beste niervervangende therapie. De resultaten van transplantaties met een nier van een levende donor zijn duidelijk beter dan die waarbij een postmortale nier wordt getransplanteerd en in alle opzichten onvergelijkbaar met de zwaar belastende dialyse. Bovendien is het de enige mogelijkheid om pre-emptief te transplanteren.

Zelfs bij aanname van een rechtvaardiger geen-bezwaarsysteem, een utopie vrees ik, zal er schaarste aan organen blijven bestaan. Ook dan zullen er patiënten op de wachtlijst sterven voordat ze een levensreddend orgaan ontvangen. Nierdonatie bij leven is om al die redenen een niet meer weg te denken fenomeen.

Het is een moedige daad, de nierdonor stelt zichzelf bloot aan risico's en is een periode onttrokken aan het maatschappelijke leven. Des te meer verdienen deze donoren uitmuntende zorg en het profijt van voortschrijdend medisch inzicht.

De laparoscopische operatietechniek gecombineerd met epidurale anesthesie is zo'n meer dan fantastische vooruitgang. Zowel nierdonoren als ontvangers zijn er in meerdere opzichten direct bij gebaat. Het voordeel van een beduidend minder belastende ingreep voor de donor en het overbrengen van een optimaal werkende donornier naar de ontvanger is onbetwistbaar. Het verlagen van de drempel om bij leven een nier te doneren levert zelfs indirect een positief effect op de wachtlijst. Ik complimenteer en feliciteer Ingrid met dit geweldige resultaat, waarbij ze haar eigen ontwikkeling in dienst heeft gesteld van de lijdende medemens. Een ware arts, een arts naar mijn hart en donornier.

Door André Bek, Auteur van 'Dansen In Het Zand - Een Leven In Geschonken Tijd'
Barendrecht, februari 2008.

# Publications

## Publications related to this thesis

Effect of intra-abdominal pressure elevation and positioning on hemodynamic responses during carbon dioxide pneumoperitoneum for laparoscopic donor nephrectomy: a prospective controlled clinical study.
Mertens zur Borg IR, Lim A, Verbrugge SJ, IJzermans JN, Klein J
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## Chapters

In; Abdominal Compartment syndrome
Editors; Rao Ivatury, Michael Chetham, Manu Malbrain and Michael Sugrue

Chapter 6 Intra-abdominal Hypertension and the respiratory system
Ingrid Mertens zur Borg, Serge Verbrugge, Claudia Olvera

Chapter 21 Anesthetic considerations in Abdominal compartment syndrome
Ingrid Mertens zur Borg, Serge Verbrugge, Karel Kolkman

## Abstracts

Effect of intra-abdominal pressure elevation and positioning on hemodynamic responses during carbon dioxide pneumoperitoneum for laparoscopic donor nephrectomy
I. Mertens zur Borg
SAGES congress, USA

Comparing neuroendocrine stress response during conventional open and laparoscopic donor nephrectomy
I. Mertens zur Borg, F. Boomsma, J. Bergsma, S. Verbrugge , J. IJzermans, J. Klein
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D. Jonsson, I. Mertens zur Borg, G. Lambrou, M. di Biase, J. Klein
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I. Mertens zur Borg, T. Lim, J. IJzermans, J. Klein
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G. Lambrou, I. Mertens zur Borg, J. Klein
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M. Doornaar, I. Mertens zur Borg,
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# Curriculum Vitae

Ingrid Mertens zur Borg was born on January 18 1961, in Nijmegen. In 1980 she graduated from Walburg College, Zwijndrecht; this was followed by medical studies at Erasmus University Rotterdam (EUR) where she received her medical degree in 1989.

As a student, her research experience started in the Ear-Nose-Throat department where she worked for 6 years in the histologic/audiometric experimental division. Here she learned to micro dissect cochlea´s from rats and guinea pigs. Besides during evening hours, she worked for four years as a student assistant on the psychiatric ward, and for two years as a free-lancer (mainly at nights) in the 24-hour Psychiatric Crisis centre in Rotterdam. In addition she taught gynaecology and anatomy at the Rotterdam teaching school for nurses for two years. At the end of her study she did her extra internship in Indonesia, where she worked in the internal nephrology department of the Cikini Hospital, Djakarta

She started work as an AGNIO Anaesthesiology in Delft, and thereafter worked as locum House Officer (Surgery) in the Princess Royal Hospital, Telford, England. In 1990 she moved back to the Netherlands to start working as an AGNIO Gynaecology in Delft.

In 1991 she started working in her beloved specialization, Anaesthesiology, first in Nijmegen and later in Rotterdam. In 1994 she started her tracking for Anaesthesiology at the University Hospital-Dijkzigt of the EUR, under the inspiring leadership of Prof. Dr. W. Erdmann. In 1999 she was registered as anaesthesiologist. During her specialization she worked for four years as a free-lancer - repatriating diseased patients from abroad, and for five years she was secretary of the Dijkzigt resident organization.

Before she started work as staff member at the Department of Anaesthesiology, EUR, she worked for one year in Australia at the Department of Neonatology, Liverpool Hospital, Sydney.

On her return from Australia her research focused on non-invasive cardiac output measurement, specializing in different methods to measure cardiac output and other hemodynamic parameters. At that time the surgeons initiated a multicenter trial on donor nephrectomy, and were aware that differences in anaesthesia could influence the kidney function of the donor and the recipient, as well as the quality of recovery of the donor. Therefore, Dr. Diederik Gommers (her co-promotor) introduced the author to the surgeons with the aim to produce an optimal anaesthesia protocol for use in the two study groups (i.e. the open donor nephrectomy and the laparoscopic donor nephrectomy). The non-invasive hemodynamic measurements introduced a reliable way to optimize hemodynamics, and thus renal blood flow, during the procedure without any burden to the donor.

A protocol was developed mainly to counteract the negative hemodynamic and renal effects induced during laparoscopic surgery. This protocol formed the basis for the work presented in this thesis.

Currently, as an anaesthesiologist, she has become a military reservist (lieutenant colonel) in the Dutch army and in this function has been sent on several missions. Furthermore, she has been several times to Africa, to work there as an anaesthesiologist.

Karel Kolkman her partner and soon, her husband is trauma surgeon, and they have two beautiful kids, Roos (1997) and Jan (1999). Besides, together with the help of Ben they run their small farm, and have also started riding and breeding Islandic horses.

Adequate fluid loading before installation of Pneumoperithoneum, together with prevention of blood pooling with anti-thrombosis stockings and adjustment of the position, adequate ventilation with the aim to minimize elevated intrathoracic pressures, high dose of sufentanil and adequate depth of anaesthesia results in the prevention of the hemodynamic and renal compromise encountered due to elevated intra-abdominal pressure, during laparoscopic donor nephrectomy.

Moreover, the differences in stress response between open donor nephrectomy and laparoscopic donor nephrectomy have disappeared with this regimen. The use of propofol anaesthesia and the addition of epidural analgesia further reduced the stress response and provided a faster and qualitatively better direct postoperative recovery.

In conclusion, the work presented in this thesis shows that the anaesthetist is able to improve the outcome for the donor patient, as well as for the donor kidney.