Minimizing Risks and Morbidity in Live Kidney Donors

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Abstract

Live kidney donors are healthy volunteers who are exposed to major surgical procedure and physical harms with no direct therapeutic benefits. Efforts to minimize their risks and morbidity are therefore of utmost importance. The current thesis describes studies on donor evaluation, surgical procedure and postoperative management of live kidney donors. The overall purpose is to evaluate and possibly improve routines and treatments in order to reduce risks and the overall morbidity of live kidney donors.

In Study I, we evaluated the assessment of kidney function during donor evaluation and found that the accuracy of iohexol glomerular filtration rate (GFR) is compromised by large variations in repeated measurements in presumably healthy donors. We proposed that there is a need for improvement of GFR measurements and that the assessment of predonation kidney function should be more comprehensive, involving GFR, laboratory investigations, functional and morphological examinations and sound clinical judgment. In Study II, we addressed the risk of perioperative venous thromboembolism (VTE) and concluded that expanding the standard screening protocol for VTE to include perioperative venous duplex can potentially decrease the VTE-related morbidity. In studies III and IV, we investigated the impact of hand-assisted retroperitoneoscopic (HARS) nephrectomy on donor safety and perioperative morbidity. The HARS nephrectomy uses the hand-assisted approach, which enables immediate manual compression for hemostasis in case of sudden and severe bleeding. Additionally, the pure retroperitoneal access further increases the safety margin of laparoscopic donor nephrectomy by 1) minimizing the risk of intestinal injury, and 2) exposure of the retroperitoneal nerves, making HARS suitable for continuous infusion of local anesthetics (CILA). CILA effectively reduces the need for opioid consumption and has the potential to totally obviate opiate analgesics postoperatively. Consequently, CILA in combination with HARS reduces morphine-related morbidity and promotes postoperative recovery.

In accordance with these data, we recommend improvement and modification of the donor evaluation process as well as a broad introduction of HARS nephrectomy in combination with CILA to increase the safety margin for live kidney donors.

Keywords: live donors, morbidity, GFR, donor nephrectomy, postoperative pain treatment, venous thromboembolism, HARS

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In living-donor transplantation, ethics involves not only the philosophy behind the program, but also the professionalism to enact it.

Vitto Bonomini, 1990
List of Papers

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


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“From within me this picture appeared, 8 days after I, at the age of 77, was accepted as a donor. My daughter (the recipient) and I share a deep gratitude to Dr. Alireza Biglarnia and the team who took part in the transplantation.”

Gunnar Lundkvist
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CG</td>
<td>Cockcroft-Gault</td>
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<tr>
<td>CCME</td>
<td>Cumulative consumption of morphine equivalent</td>
</tr>
<tr>
<td>CDC</td>
<td>Complement-dependent cytotoxicity</td>
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<tr>
<td>CILA</td>
<td>Continuous infusion of local anesthetics</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HALS nephrectomy</td>
<td>Hand-assisted transperitoneal nephrectomy</td>
</tr>
<tr>
<td>HARS nephrectomy</td>
<td>Hand-assisted retroperitoneoscopic nephrectomy</td>
</tr>
<tr>
<td>LDN</td>
<td>Laparoscopic donor nephrectomy</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of diet in renal disease</td>
</tr>
<tr>
<td>SFKK</td>
<td>Swedish Association for Clinical Chemistry</td>
</tr>
<tr>
<td>OT</td>
<td>Operating time</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>WIT</td>
<td>Warm ischemic time</td>
</tr>
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</table>
Introduction

Historical Overview

The origins of solid organ transplantation in its modern sense in medicine can be traced back to 1902 and the pioneering work of Emerich Ullmann (1861-1937), who was the first to perform a successful kidney auto-transplantation in a dog with a functioning kidney graft anastomized to the collar vessels. Soon thereafter, he also performed the first renal xenotransplantation between a goat and a dog, which, however, resulted in a fatal outcome. Being unaware of the immunological barrier, Ullmann continued his work and performed the first human kidney transplant using a pig kidney, which he implanted into the cubital region of a woman with end-stage renal disease (1). But even this second attempt of xeno-transplantation was doomed to fail. After Ullmann’s death, the first technical era of solid organ transplantation came to an end.

In 1923, Carlos Williamson described for the first time the underlying mechanism in organ failure after transplantation, establishing the basic biological principles of rejection. The following year, in 1924, Emile Holman performed skin grafts in volunteer donors, described donor-specific sensitization to “proteins”, and discovered that rejection was a result of antibodies (2). With the newfound awareness of the biological barrier, the modern era of solid organ transplantation emerged on December 23, 1954, when Josef Murray performed the first successful kidney transplant between the identical twins Ronald and Richard Herrick, the latter of whom suffered from glomerulonephritis and end-stage renal failure. The transplant was successful and Richard went on to live another 9 years, marry his attending nurse, and father two children (3).

In the years that followed, several more successful kidney transplantations were performed between identical twins (4). However, it became more obvious that there was a need to overcome the immunological barriers in order to extend the indication for kidney transplantation to non-HLA identical individuals. Early immunosuppressive protocols included sublethal total body irradiation, which induced profound bone marrow aplasia. However, many patients developed severe infectious complications and rejection episodes were still frequent (3, 5). Consequently, total body irradiation was aban-
The modern era of immunosuppression began with the clinical use of 6-mercaptopurine and its pro-drug azathioprine (6, 7), and evolved to the discovery of calcineurin inhibitors (8-10), which are still the cornerstone of the current immunosuppressive treatment after organ transplantation.

A half-century has now elapsed and kidney transplantation has become the treatment of choice for patients with end-stage renal disease (ESRD), with excellent short- and long-term results. However, transplantation has paradoxically become the victim of its own success. In the United States and Europe, the number of patients on the waiting list with end-stage renal disease is increasing (11, 12). The number of organs available from deceased donors, on the other hand, has remained fairly constant. This phenomenon is also observed in Sweden, where the number of deceased donors remains unchanged since 1981 (13). Hence, there is a growing discrepancy between the number of transplantations performed and the number of patients awaiting transplantation (14). It is evident that the annual number of available organs from deceased donors will not resolve the organ shortage. Living donors have thus emerged as an ever more important donor category.

The superior outcome of living donor kidney transplantation (Figures 1a and 1b), the increased willingness of living donors to help their loved ones, and the recent advances in laparoscopic donor nephrectomy have to some degree helped to meet the growing demand for kidney allograft. The price we certainly pay is a growing dependency on healthy individuals who undergo a major surgical procedure with no direct therapeutic benefit. In the next half century to come, history will judge the medical community by its responsibility and constant efforts to reduce the morbidity and risks of these heroic individuals.
Ethical considerations

The practice of living donation violates a very fundamental principle of medical ethics *primum non nocere* (First, do no harm). While it is generally accepted to inflict harm (such as surgery) on an individual if there is a therapeutic benefit from the procedure, live organ donors are healthy volunteers, who are exposed to major surgical procedures and physical harms with no direct therapeutic benefits. This dilemma has raised a wide range of ethical issues since the inception of living donation in the 1950s. In 1990, Bonomini proposed the term “moral ethics” in transplantation, which rests on two assumptions: 1) individual knowledge acquired through experience; and 2) avoidance of all dogmatism and a spirit of flexibility towards proven realities (15). In other words, a pure denial of living donation in the context of the Hippocratic notion would hardly fulfill the criteria of moral acting in itself, since it ignores the perspectives of the donor and promotes dogmatism.

Autonomy is another fundamental ethical principle, defined as an individual’s right to make personal decisions regarding his/her own health (16). Hence, the practice of living donation can be ethically legitimate when carried out with the freely given informed consent of the donor. However, freely given informed consent assumes also the responsibility of the medical community to identify and quantify all potential risks to the best of their ability and to make this information available and understandable for each living donor. Under these circumstances, it is possible for living donors to freely give informed consent, as is re-stated in “The Consensus on the Care of the Living Kidney Donors” (17).

Ethics in transplantation is an ongoing process involving our understanding of the principles of philosophy and the professionalism of the medical community (15). It is therefore important to understand that new developments in the field of medical care or surgical techniques will undoubtedly influence our ethics. Living donors should thus be placed in the forefront of medical progress in an aim to minimize their risks and maximize their safety during and after nephrectomy.
The importance of living donation from the patient’s perspective

Advancements in immunosuppressive treatment have markedly narrowed the difference in outcome between perfectly HLA-matched and unmatched living donor kidney grafts (18, 19). Based on this development, living donor kidney transplantation has progressed from the limitations of requiring an identical twin, to the current reality where anyone, including genetically, emotionally and unemotionally related persons, can donate a kidney. At the University Hospital in Uppsala, the annual number of living donor kidney transplantations increased from 20 to almost 50 within a 10-year period, while the number of deceased donor transplantations remains constant. Today, living donation, not only in Uppsala but around the world, has increasingly become the treatment of choice because it offers the best chance for patient and graft survival and improvement of quality of life for patients with ESRD (Figures 1a and 1b).

Figure 1a. CTS analysis. Patient survival after living and deceased donor kidney transplantation at Uppsala University Hospital – A 10-year follow-up survey. (Source: http://www.ctstransplant.org)
For patients with ESRD, there are a number of potential benefits to receiving a kidney from a living donor:

**Living donor transplantation - an elective procedure**

The availability of a living donor allows flexibility in timing and planning of the procedure with the following consequences:

- Both donors and recipients can be evaluated and prepared, to achieve an optimal medical and psychological condition before surgery.
- Radiological evaluation of the vascular anatomy of the donor allows the selection of the kidney with the more favorable anatomy, which reduces the risks for vascular complications during the transplantation. It is also a valuable tool for examining the functional quality of the kidney, as well as ruling out transmission of diseases such as malignancy.
- Cold ischemic time (CIT) is associated with graft injury and delayed function (20). The availability of a living donor helps to keep CIT as short as possible, since the surgical procedures in the donor and the recipient are started simultaneously. Indeed, delayed graft function is a rare event after living donor transplant (21).
Meticulous immunological screening enables optimal HLA-matching in cases where a recipient has more than one potential donor. This option is very useful among the siblings, where there is a substantial probability of finding an HLA-identical donor.

Avoidance of brain death
An inevitable event of deceased donation is brain death. The massive cerebral trauma and infarction causes hemodynamic (22), hormonal (23), immunological (24) and pathophysiological changes to the human body, which influence the renal function and cause structure changes such as vacuolization, atrophy and necrosis of the renal proximal and distal tubules (25). It is therefore conceivable that kidney grafts from living donors have better quality and are less exposed to functional and structural damage. This assumption is supported by the observation that kidney grafts from deceased donors have worse survival in every age group, even among donors 25-36 years of age (26).

Preemptive transplantation
Patients with chronic renal failure suffer from the progression of cardiovascular disease, which seems to accelerate once the patient is maintained on regular dialysis (27-29). Successful kidney transplantation provides survival benefits and long-term rehabilitation because it reduces the incidence of cardiac mortality (30). Interestingly, the time on dialysis prior to transplantation is an independent risk factor for both patient death (31) and graft failure (32) after transplantation. The availability of living donors provides the possibility of performing kidney transplantation before patients are exposed to chronic dialysis, which is described as preemptive transplantation. The advantages of such a procedure are manifold: most importantly, it offers best outcomes by avoiding dialysis-associated morbidity (32-34), obviates the need for access surgery for hemo- or peritoneal dialysis, and is cost-effective because it promotes post-transplant employment (35) and eliminates the cost of chronic dialysis treatment (36). Furthermore, patients undergoing preemptive transplantation never end up on the waiting list, which theoretically increases the likelihood of transplantation for patients waiting for a deceased donor transplant.

Expansion of donor pool
It is evident that the annual number of available deceased donors will not resolve the growing organ shortage and the prolonged waiting time for transplantation. Many centers have therefore placed greater emphasis on
living kidney donation to meet the growing demand for kidney transplantation in patients with ESRD.

**Living unrelated kidney transplantation**

Transplantation from genetically unrelated donors (friends, spouses and even unknown individuals) provides excellent short- and long-term graft survival rates that are similar to results from living related donors and superior to those from deceased donors (37, 38). By extending the inclusion criteria for living donors beyond genetically related family members, the pool of potential donors becomes unlimited, because any person who is medically and psychologically eligible can donate. Hence, unrelated kidney transplantation could be a definite solution to the growing shortage of organs. This has been demonstrated by the Iranian model of a compensated and regulated transplant program adopted in 1988. In only 10 years, the dramatic increase of annual living unrelated transplantations has eliminated the renal transplant waiting list in the country (39, 40). The practice of the Iranian model is considered unethical in most countries, however, since it creates and allows financial incentives for unrelated donors. Hence, the donor pool in most countries remains limited to emotionally related (spouses and friends) or altruistic donors. Nevertheless, also in these countries, living unrelated kidney transplantation has contributed markedly to expansion of the donor pool, with the largest increase of available kidney grafts coming from living donors (41, 42).

**Transplantation across immunological barriers**

In the United States and Scandinavian countries, there is a 36% probability of two unrelated individuals having incompatible blood groups (43, 44). ABO-incompatibility has previously been a contraindication to transplantation because of the risk for severe hyper-acute rejection and immediate graft loss (45). However, the availability of a living donor and the development of effective desensitization protocols provide the possibility of overcoming the ABO barrier and increasing the number of transplantations. The results, in addition, are impressive: in Uppsala, 35 ABO-incompatible kidney transplantations were performed between 2004 and 2009. At a median follow-up of 36 months (range 3-60 months), median creatinine and glomerular filtration rate (GFR) were 112 µmol/L and 78 mL/minute, respectively (Abstract presented at the 2010 Scandinavian Transplant Society Congress in Helsinki, Finland).

A more challenging immunological barrier is transplantation across positive T-cell complement-dependent cytotoxicity (CDC) crossmatch. Usually, patients who are highly sensitized with widespread HLA antibodies (panel reactive antibody >50%) are doomed to remain on the waiting list because of the extreme low probability of finding a cross-match negative graft. In some
cases, sensitized patients never receive a transplant. However, the implementation of newer desensitization protocols, involving high-dose IVIG and antibody depletion treatment (plasmapheresis, immunoadsorption) has been shown to reduce the level of HLA antibodies and to increase the probability for such a patient to receive a transplant with excellent results (46). Similarly to ABO incompatibility, these protocols require planning and timing of the procedure and are therefore mainly feasible only in connection with living donor kidney transplantation.

**Paired kidney exchanges**

Kidney pair exchange is a new concept developed to help patients to find a suitable donor when their own willing donors are not eligible due to immunological reasons (47). For instance, patient A has donor B, but donor B is immunologically incompatible with patient A; and the same situation is also observed between patient C and his/her incompatible donor D. If, however, there is compatibility between patient A and donor D, as well as between patient C and donor B, the concept of paired kidney exchange makes it possible for both patients to receive a compatible kidney from a non-directed living donor. This simple example describes a balanced 2-way paired kidney exchange. The concept can be extended by using a more complicated algorithm, such as 3-way or higher exchanges (48). There are also algorithms for a chain or domino effect of transplants for incompatible pairs, triggered by non-directed (altruistic) donors (49). The concept of paired kidney exchange has the potential to expand the pool of donors and potential matches.
The importance of living donation from the donor’s perspective

Psychological aspects
Live donors undergo major surgical trauma for the good of another individual. Despite the fact that there are no direct therapeutic benefits for these healthy volunteers, the psychological impact of live donation should not be underestimated. In a large survey, living related donors had a better quality of life as compared to the general population (50). These results are confirmed by large Scandinavian studies showing that quality of life of living related donors was higher than that of age-matched control populations (51, 52) — a finding that could be explained by the increased self-esteem (53) after the donation and by the satisfaction of helping a beloved relative. In light of these observations, the low rate (1-5%) of donors who regretted donating a kidney (51, 52, 54, 55) is understandable.

Medical short- and long-term consequences of living donation
Apart from psychological benefits, live donor nephrectomy harbors risks for morbidity, mortality and long-term complications. In a large survey from 1992, Najarian et al. reported a surgical mortality of 0.03% or 3 per 10,000 cases for donors undergoing unilateral nephrectomy (56). This compares with a surgical mortality of 18 per 10,000 cases for patients undergoing laparoscopic cholecystectomy (57). Although the portion of elderly (>50 years) and obese (BMI >30) donors has increased over the past decades, the death rate has not changed over time (58).

The surgical morbidity is difficult to determine, both from a qualitative and quantitative aspect, because it is very much dependent on the technique used for donor nephrectomy. The reported morbidity varies substantially from center to center (59). Kasiske et al. analyzed a large number of surveys and single-center studies, finding that the rate of major surgical complications varied between 0% and 13%. The overall surgical morbidity rate in this analysis ranged from 12% to 63% (60). Table 1 gives an overview of the incidence of surgical donor complications. It is important, however, to emphasize that more than 90% of these studies were published between 1970 and 1989. It is therefore conceivable that the current “true” risk of morbidity associated with kidney donation varies substantially from these reports.

There is a general consensus that unilateral nephrectomy in living donors is associated with few long-term medical risks. Hypertension and albuminuria are considered risk factors for cardiovascular disease (61), and both risk
factors are observed in live kidney donors. In an analysis of Swiss Organ Donor Health Registry (SOL-DHR) data on 631 donors, the incidence of albuminuria and hypertension at 7-year follow-up was 9% and 34%, respectively (62). In a more recent analysis, Ibrahim et al. report an incidence of 32.1% for hypertension and 12.7% for albuminuria in 255 donors at a mean follow-up of 12.2 years (63). However, in this survey, the prevalence of albuminuria and hypertension was similar to the control population, matched for sex, BMI, age, race and ethnic group. Regardless of all the physical changes that may occur after unilateral nephrectomy, there is evidence to suggest that the survival rate and the risk for ESRD in live kidney donors are similar to both the general population (63, 64) and matched cohorts (58) even decades after donation. In accordance with these data, it is conceivable that live donor nephrectomy is a safe procedure in these selected and well-screened populations.

Table 1. Kasiske’s report on donor morbidity from 27 studies published between 1970 and 1994 (60).

<table>
<thead>
<tr>
<th>Surgical complication after kidney donation</th>
<th>Mean (%)</th>
<th>Standard deviation</th>
<th>Range (%)</th>
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</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>0.2</td>
<td>0.5</td>
<td>0-2.3</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.2</td>
<td>0.6</td>
<td>0-3</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
<td>0.2</td>
<td>0.7</td>
<td>0-3.3</td>
</tr>
<tr>
<td>Wound hematoma</td>
<td>0.3</td>
<td>0.7</td>
<td>0-3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.4</td>
<td>0.8</td>
<td>0-3</td>
</tr>
<tr>
<td>Intraabdominal hematoma</td>
<td>0.5</td>
<td>1.2</td>
<td>0-5.9</td>
</tr>
<tr>
<td>Pleura effusion</td>
<td>0.9</td>
<td>1.8</td>
<td>0-5.6</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1</td>
<td>2.2</td>
<td>0-9.3</td>
</tr>
<tr>
<td>Ileus</td>
<td>1</td>
<td>2.1</td>
<td>0-10</td>
</tr>
<tr>
<td>Pneumonia or atelectasis</td>
<td>9.3</td>
<td>10.8</td>
<td>0-35.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5.3</td>
<td>6.3</td>
<td>0-25</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4.3</td>
<td>5.5</td>
<td>0-26.7</td>
</tr>
<tr>
<td>Hernia</td>
<td>0.3</td>
<td>0.7</td>
<td>0-3</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5.3</td>
<td>6.8</td>
<td>0-27.8</td>
</tr>
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Donor evaluation

The algorithm for the donor evaluation process is well defined (60, 65-67). In Sweden, there are guidelines for donor evaluation issued by the Swedish Transplantation Society (13). In agreement with these guidelines, all potential donors undergo a comprehensive, mandatory evaluation process, which includes:

- Education of the donor about the donation process
- Preliminary informed consent
- Basic donor evaluation
  - Relation to the recipient
  - Age
  - Ongoing medical treatment
  - Psychological and social status
  - History of smoking and alcohol consumption
  - History of abuse
  - History or heredity of venous thromboembolism (VTE)
  - Estrogen medication in female donors
- Evaluation of somatic status (blood pressure, heart rate, BMI, etc.)
- Laboratory investigations
  - Blood group, electrolytes, creatinine, hemoglobin, leukocytes, thrombocytes, liver function test
  - Evaluation of HLA type
  - CDC and FACS crossmatch
  - Screening for coagulopathy
    - Activated partial thromboplastin time (APTT)
    - International normalized ratio (INR)
    - Antithrombin
    - Protein C and protein S
    - Resistance to activated protein C (factor V Leiden)
    - Prothrombin gene mutation
    - Anticardiolipin antibody screening
    - Antiphospholipid antibody screening
  - Cholesterol and triglycerides
  - Oral glucose tolerance test, HbA1c
  - Plasma and urine electrophoresis
  - Iohexol clearance (4-point measurement) or $^{51}$Cr-EDTA
  - Virological screening
- Psychosocial evaluation
- Renal ultrasound
- Spiral CT scan to assess vascular anatomy
- Radioactive renogram to assess split renal function
- Cardiac evaluation
One of the purposes of the evaluation process is to ensure medical and psychological suitability of the potential donor in order to minimize risks for short- and long-term consequences after unilateral nephrectomy. The other is to ensure that the kidney is of good quality and anatomically suitable for transplantation and that there is no risk of transmitting disease (infection, malignancies) to the patient. In a survey of 430 donors, Fehrman-Ekholm et al. showed that living donors had a better survival after 20 years than the general population. This motivated the authors to choose the title “Living donors live longer” for their publication. However, as the authors mentioned, the better survival of the donors was not because of unilateral nephrectomy but rather because of fact that living donors are both selected and well-screened compared to general population.

The degree of risk a kidney donor is allowed to accept is an issue of intense debate and there is discussion that even marginally increased medical risks are not acceptable (68, 69). However, such debate is often more esoteric than related to the current clinical reality. Over the past decade, the portion of donors over 50 years of age nearly doubled, and more obese donors (BMI >30) as well as donors with manifest hypertension are increasingly accepted (37, 70). Other transplant programs even accept individuals with diabetes mellitus as kidney donors (71). It is obvious that there is a clear trend toward extending the risk profile of kidney donors. We can abnegate this trend but we must also face the possibility that this development may continue to evolve in the future. Consequently, the major purpose of donor evaluation must shift from selection of young and “perfectly” healthy donors to a more accurate assessment of individual risk profiles. The process must further communicate these risks to the prospective donor and enable a balanced discussion, which should sometimes involve the recipient, of whether it is reasonable to accept short- and long-term consequences of living donation. The evaluation process must therefore be constantly revised and improved. To do this, the accuracy and consistency of the methods used during the evaluation process need to be challenged and scrutinized.

In the evaluation of a live donor, assessment of kidney function is, for obvious reasons, one such issue.
Assessment of renal function

The biological consequence of unilateral nephrectomy is a 50% reduction of renal mass and functioning nephrons (72). Hence, all potential donors are required to have sufficient renal function prior to donation, in order to ensure adequate residual capacity after the procedure.

Glomerular filtration rate (GFR) is generally considered to be the best overall index of renal function (73) and, according to the US National Kidney Disease Education Program and National Institute of Health (NIH), GFR should be the method of choice to assess kidney function (www.nkdep.nih.gov).

The questions that however, are: 1) What implies normal kidney function? And: 2) How can kidney function be accurately measured? As trivial as these questions might sound, they are equally difficult to answer in clinical reality. The Swedish Association for Clinical Chemistry (SFKK) founded a workshop consisting of nephrologists, transplant surgeons, general physicians and experts from clinical laboratory, in order to define a consensus on optimal assessment of kidney function. In 2008, this workshop published recommended guidelines for GFR in healthy individuals, which are summarized in Table 2. However, the workshop further stated that consistent databases for the values and confidence limits of recommended GFR in healthy individuals are lacking, especially for elderly persons (>60 years) (74). It is therefore conceivable to assume that determination of “normal” kidney function in healthy individuals may be difficult, which in turn challenges the recommendation of a universal cut-off value for baseline GFR in live kidney donors.

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>GFR, mL/min (1.73 m2)</th>
</tr>
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<tbody>
<tr>
<td>&lt; 2</td>
<td>unknown</td>
</tr>
<tr>
<td>2-17</td>
<td>86-134</td>
</tr>
<tr>
<td>18-50</td>
<td>80-125</td>
</tr>
<tr>
<td>51-65</td>
<td>60-110</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>should be &gt;60</td>
</tr>
</tbody>
</table>

An even more challenging aspect is the accurate measurement of kidney function. Early GFR measurements were originally performed using creatinine as a marker (75) and, still, serum and plasma creatinine continue to be the most commonly used parameter for GFR estimations due to simplicity and widespread availability (76). However, the accuracy of creatinine clearance is often questioned because it is influenced by factors such as age, gen-
der muscle mass, physical activities and diet (77, 78). Furthermore, creatine clearance is insensitive to small changes in GFR in the so-called creatinine-blind GFR area, which is caused by the non-linear relationship between plasma concentration and GFR (79). GFR is often calculated from plasma creatinine using the Cockcroft-Gault (CG) (80) and modification of diet in renal disease (MDRD) study equations (81). The use of MDRD to estimate GFR in donors is inadequate because the formula was originally developed in patients with a GFR <60 mL/min per 1.73 m² (63). Furthermore, there is a clear difference in interaction of GFR and serum creatinine in living donors as compared to patients with chronic renal disease. While differences in serum creatinine between two healthy individuals predominantly reflect measurement error and/or non-renal factors, the same variations are more likely to reflect true differences of kidney function among patients with chronic renal disease. Hence, both, CG and MDRD equations may overestimate the strength of correlation between GFR and serum creatinine in healthy individuals (82).

More accurate assessment of GFR can be achieved by exogenous markers, which fulfill the following criteria: 1) exclusive filtration in the glomeruli, 2) no secretion, metabolization or reabsorption in the tubuli, and 3) no impact on kidney function. Exogenous markers that to a large extent meet these criteria are inulin, iohexol and ⁵¹Cr-EDTA (83-85). Inulin was the first exogenous marker to be described, in the 1930s (86). The classic method of measuring inulin clearance included the steady-state renal clearance technique (87). Following intravenous administration of a priming dose, inulin is given continuously in order to reach equal levels in arterial and venous blood. After an equilibration period, sequential urine samples are collected to measure the inulin level (U). Inulin clearance is calculated from the measurement of plasma inulin level (P) and urine flow rate (V) using following equation: GFR=UxV/P. However, inulin clearance is not widely used, because it is expensive, difficult to execute and time-consuming.

In Europe iohexol and ⁵¹Cr-EDTA are widely used, while in Sweden iohexol is the predominant marker, and is considered to have a low coefficient of variation and a high reproducibility (88, 89). It also has an advantage over ⁵¹Cr-EDTA in that it eliminates the use of radioactive substances.

The accuracy of GFR estimation based on these markers can, however, be compromised by the human factor. Iohexol clearance, for instance, is often estimated by a single-shot plasma clearance technique. Following an injection of 2-5 ml iohexol, clearance is calculated as the iohexol dose divided by the area under curve (AUC) of iohexol plasma levels (90). Accurate determination of AUC is however challenging, and requires, in theory, numerous blood samples, which is not feasible in the clinical setting. The final slope of
the plasma decay curve of iohexol after the single-shot injection is therefore reproduced by different approaches. The easiest way to estimate AUC is by a single sample taken 3-4 hours after the injection (91). This simplification, however, assumes that the distribution volume can be accurately calculated from height, weight, sex and age of the donor. The calculated concentration at time 0 and the measured concentration of iohexol define the final slope of the plasma decay curve and through this the AUC. While some authors favor the single-sample investigation (92), others claim that this technique should be discouraged in favor of repeated sampling for a more accurate estimation of iohexol AUC (93). Irrespective of the method of measurement of AUC, erroneous injection and imprecise sampling can also compromise the accuracy of iohexol estimates and other exogenous markers. Another important aspect in the evaluation of kidney function is the differentiation between absolute and relative GFR. Absolute, non-corrected GFR (e.g. Cockcroft-Gault equation) is expressed as mL/min and defines the total filtration capacity of the patient, which is important for drug dose adjustment. Indexing GFR for body surface area (mL/min/1.73 m²), however, is influenced less by the anthropometric data (weight and height) and has a narrower reference window, making it easier to use in clinical practice (94). Table 3 shows differences in variation of relative and absolute GFR in relation to body surface area.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body surface area (DuBois)</th>
<th>Absolute GFR (mL/min)</th>
<th>Relative GFR (mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>90</td>
<td>13</td>
<td>0.56</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>115</td>
<td>20</td>
<td>0.8</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>140</td>
<td>40</td>
<td>1.24</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>adult</td>
<td>150</td>
<td>50</td>
<td>1.43</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td><strong>adult</strong></td>
<td><strong>170</strong></td>
<td><strong>63</strong></td>
<td><strong>1.73</strong></td>
<td><strong>40</strong></td>
<td><strong>40</strong></td>
</tr>
<tr>
<td>adult</td>
<td>180</td>
<td>80</td>
<td>2</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>adult</td>
<td>190</td>
<td>90</td>
<td>2.18</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>adult</td>
<td>200</td>
<td>100</td>
<td>2.37</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>adult</td>
<td>210</td>
<td>120</td>
<td>2.65</td>
<td>61</td>
<td>40</td>
</tr>
</tbody>
</table>
Assessment of risks for venous thromboembolism

Pulmonary embolism is one of the most common causes of perioperative mortality and accounts for approximately 40% of donor death (56). Non-fatal venous thromboembolism (VTE) is also a cause of long-term morbidity and a severe life-threatening complication as reported in larger series of donor follow-ups (95-97). In Sweden, an extensive screening protocol for VTE has therefore been implemented in all transplant centers (13). This screening protocol involves history or heredity of VTE, estrogen medication, blood analysis including activated partial thromboplastin time (APTT), international normalized ratio (INR), antithrombin, protein C, protein S, resistance to activated protein C (factor V Leiden), prothrombin gene mutation, lupus anticoagulant, and anticardiolipin antibodies. Table 4 summarizes the most important risk factors and their corresponding relative risk for VTE (98-101).

Table 4. Risk factors with corresponding relative risk for VTE.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Relative risk for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
<td>*</td>
</tr>
<tr>
<td>Obesity (defined as BMI &gt;30)</td>
<td>3</td>
</tr>
<tr>
<td>History of idiopathic VTE</td>
<td>5-10</td>
</tr>
<tr>
<td>Estrogen (≥50 µg per day)</td>
<td>2-4</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>1-2</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>10-20</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>5-10</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>5-10</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>3-6</td>
</tr>
<tr>
<td>Homozygous factor V Leiden</td>
<td>30-50</td>
</tr>
<tr>
<td>Heterozygous prothrombin gene mutation</td>
<td>2-5</td>
</tr>
<tr>
<td>Homocysteinemia</td>
<td>5-10</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>10</td>
</tr>
<tr>
<td>Cardiolipin antibodies</td>
<td>10</td>
</tr>
</tbody>
</table>

* Risk for VTE is 10 x higher for donors >60 compared to individuals <40 years of age.

At our institution, all prospective donors undergo prophylactic treatment for VTE, which is adjusted to the individual risk profile. Donors who have no risk factors for VTE are given thromboprophylaxis with low molecular weight heparin (LMWH) at 20 mg daily and antiembolic compression stockings. Donors with risk factors for VTE (based on history or thrombophilia screening) receive an increased dose of 40 mg LMWH daily and continue with the prophylaxis for 6 weeks. Individuals with high risks for VTE are advised not to donate.
Donor nephrectomy

Live donor nephrectomy is an important and critical moment for donors, as the invasiveness of the procedure is the main cause of morbidity and even mortality. It is therefore of utmost importance that the donor nephrectomy per se be at the forefront of all efforts and developments to minimize morbidity and mortality related to the surgical procedure.

Evolution of live donor nephrectomy

Since the introduction of live donor nephrectomy, the open surgical approach through a lumbotomy has for decades been the classical method for retrieval of the kidney. For this approach, the donor is positioned in a lateral decubitus position on a broken operating table. The retrieval of the kidney is carried out retroperitoneally through a flank incision. Often the distal part of the first rib is resected for optimal access to the kidney. This approach has been shown to be very safe, with a calculated mortality of 0.03% (97), and with the retroperitoneal access there is limited risk for intraabdominal complications such as intestinal perforation, bowel obstruction and splenic injuries. However, major disadvantages of the flank incision are significant injury to the abdominothoracic wall and a high incidence of perioperative morbidity, in up to 48% of patients (62). These complications include iatrogenic pneumothorax (102), wound complications (103), chronic neuralgia (103, 104), and nerve lesions causing bulging of the flank (105). Consequently, there was a demand for a less invasive technique for donor nephrectomy.

In 1995, Ratner performed the first laparoscopic donor nephrectomy (106), which was a logical step towards minimizing morbidity associated with the open approach. The technique has been introduced as pure laparoscopic, transperitoneal approach and has shown to cause less postoperative pain, and to promote recovery and earlier return to employment (107-109). However, the safety of pure laparoscopic donor nephrectomy has been questioned (110, 111), the surgeon’s ability to control the surgical field in a manner equivalent to open surgery. A major life-threatening complication with pure laparoscopy is severe sudden bleeding, which can be difficult to manage using laparoscopic instruments alone (112-114). Indeed, bleeding is the most common reason for conversion from laparoscopic to open surgery and has been the cause of death in kidney donors (95, 114, 115). In 1993, Boland described the technique of manual manipulation through a fascial incision during laparoscopic surgery, which afforded speed and facility. The procedure started with a 5-10 cm incision early in the operation, followed by insertion of the hand inside the intraperitoneal cavity. Pneumoperitoneum was preserved by occluding residual spaces around the arm with wet laparotomy pad and high insufflation of gas (116). This technique was initially used to
minimize the learning curve of pure laparoscopy (117). However, in 1998, Wolf described the first hand-assisted laparoscopic nephrectomy (HALS) in living donors using a modern hand port, which allowed insertion of the hand without losing the pneumoperitoneum (118).

Today, HALS has evolved from a complementary tool for surgical training to an established procedure for live kidney donors that provides the following advantages over pure laparoscopy:

- The tactile feedback and better spatial orientation, as well as less traumatic handling of the tissue.
- It thus allows better control of the kidney, which reduces the risk for torsion of the kidney around the vessels (62).
- The hand-assisted approach shortens operation time by facilitating the surgical procedure (119, 120).
- Shorter operating time leads to reduction of costs and potentially to reduced morbidity such as wound infection, postoperative pain, and even rhabdomyolysis (62, 95, 121-124).
- After the dissection of the vessels, the kidney is retrieved immediately with the inserted hand, which minimizes the warm ischemic time as compared to pure laparoscopic donor nephrectomy (119, 120, 125).
- The procedure obviates the use of a retrieval bag, which can malfunction and lead to extended WIT and injury to the kidney, and thereby reduces costs (119, 120, 124).
- The most important advantage of HALS is the increased safety margin for live donor nephrectomy through (115, 126-128):
  - Safe placement of trocars with the hand under the entry site, preventing the risk for laceration of vascular structure and other tissues.
  - Immediate manual compression for hemostasis in case of sudden and severe bleeding.

The two major life-threatening complications after transperitoneal pure laparoscopic surgery are bleeding and intestinal injury (114, 115, 129-132). The HALS technique addresses the risk of sudden bleeding by providing the possibility of immediate and sufficient hemostasis. However, since HALS is performed transperitoneally, there is an inherent risk for intestinal injury. Intestinal injuries are often not detected intraoperatively, which means that delayed diagnosis can aggravate their severity. Ileus, nausea, vomiting and dehydration are the most common causes of readmission after transperitoneal laparoscopic nephrectomy (95, 114, 130, 132). Hence, intestinal injuries compromise donor safety and in the worst case can progress to life-threatening complications (128, 130, 132, 133).
In 2002, Wadström introduced the hand-assisted retroperitoneoscopic (HARS) technique, which was a further step in development of endoscopic live donor nephrectomy (134). Like HALS, the HARS technique uses the advantages of hand-assisted approach to rapidly achieve hemostasis in case of sudden and severe bleeding. However, by choosing a pure retroperitoneal access to the kidney, HARS virtually eliminates the risk of intraabdominal complications. In following with these aspects, the HARS method optimizes the safety margin of live donor nephrectomy by addressing the two major life-threatening complications of the transperitoneal, pure laparoscopic approach. This could explain the growing interest in the technique, as demonstrated by the large number of participants at a recent course given under the auspices of the European Society of Organ Transplantation (ESOT).

![Intraoperative picture of HARS nephrectomy. The patient is placed in a 90° oblique position. The table is not broken in order to maximize the retroperitoneal space and to not stretch the peritoneum. A hand-assist device is placed in a Pfannenstiel incision. The surgeon’s left hand is placed in the retroperitoneal space. A blunt 12-mm working port is placed to the left of the hand port (or to the right in the case of right-sided nephrectomy). A second 12-mm blunt port is placed high on the subcostal margin, allowing access for a 30°-video laparoscope. A third 5, 10 or 12-mm blunt port is placed in the flank below the costal margin. For right-sided nephrectomy, the camera is often introduced through this port.](image)

**Pain as a major risk for postoperative morbidity**

Sufficient postoperative pain treatment is important and promotes postoperative recovery (135-137). Laparoscopic donor nephrectomy (LDN) has been demonstrated to reduce the amount of postoperative analgesic...
required, hospital stay and convalescence time as compared to open donor nephrectomy (138-141). However, LDN still represents a major surgical trauma that causes postoperative pain and discomfort. Inadequate pain management is one obvious factor that increases morbidity (136, 137, 142). Thus, the development of safe and well-tolerated analgesic techniques that provide optimal postoperative pain relief is of utmost importance. At present, opiate analgesics are the mainstay of postoperative pain relief (143). At the University Hospital in Uppsala, kidney donors routinely receive a multimodal analgesia combining acetaminophen and nurse-controlled opioid treatment based on the individual needs of the donor. In a small number of cases, donors have been treated with morphine-based patient-controlled analgesia (PCA). Opioid side-effects such as postoperative nausea, vomiting (144) and decreased gastrointestinal motility (145, 146) are, however, often encountered. The impact of postoperative nausea and vomiting on patient’s comfort and postoperative recovery is substantial. With an incidence of up to 80% (147), postoperative nausea and vomiting has been reported to be the major concern of patients, resulting in poor satisfaction, increased nursing care and delayed discharge (147, 148). Opiate analgesics can cause far more severe adverse events. Excessive sedation and severe respiratory depression are life-threatening consequences of postoperative opioid use, causing considerable morbidity and even mortality (149-156). At our department, one donor experienced a serious life-threatening respiratory depression while maintained on morphine-based PCA. Hence, the risk for opioid-related mortality in live kidney donors should not be trivialized. There is a need for alternative non-opioid analgesic methods that provide safe and sufficient analgesia. One solution could be the infiltration of local anesthetics to the surgical site, in order to decrease the need for opioid analgesics and occurrence of opioid side-effects post donation. Local anesthetics modulate pain at the peripheral level by inhibiting transmission of nociceptive signals from the site of the injury. However, the analgesic duration of most local anesthetics is brief, which means that single infiltrations would not provide long-term benefits or any substantial opioid-sparing effect. A simple and effective solution to this is the use of the On-Q system to maintain continuous delivery of local anesthetics to the surgical site. The On-Q system consists of a portable multilayer elastomeric pump reservoir and two delivery catheters. The pump continuously delivers local anesthetics via the flexible catheters to the site of tissue injury.
Aims of the Investigations

The medical care of a live kidney donor is a process involving donor evaluation, surgical procedure and perioperative management. The purpose of the studies behind this thesis was to evaluate and possibly improve routines and treatments in the care of live kidney donors in order to reduce risks and the overall morbidity.

The specific aims were:

- To assess the reliability and accuracy in measuring kidney function in live kidney donors (Study I).
- To evaluate an extensive screening protocol for venous thromboembolism (Study II).
- To evaluate the learning experience and outcomes when implementing the HARS technique for live donor nephrectomy (Study III).
- To investigate whether continuous infusion of local anesthetics can provide sufficient anagesia and opioid-sparing effect in order to minimize opioid-related morbidity in connection with HARS nephrectomy (Study IV).
Patients and Methods

The studies performed for this thesis are based exclusively on live kidney donors who underwent donor nephrectomy during the period 2000 to 2010. The number of donors, period of inclusion and design of each study are summarized in Table 5.

Table 5. Overview of study designs and donor cohorts.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study I</strong></td>
<td>116 consecutive donors 2000-2004</td>
<td>Retrospective analysis of GFR measurement</td>
</tr>
<tr>
<td><strong>Study II</strong></td>
<td>130 consecutive donors 2003-2007 (HARS 105, open 25)</td>
<td>Prospective analysis of the incidence of thromboembolism</td>
</tr>
<tr>
<td><strong>Study III</strong></td>
<td>Total of 413 consecutive donors in 4 centers 2001-2008 Center I (n=97) Center II (n=138) Center III (n=65) Center IV (n=113)</td>
<td>Retrospective analysis of the four centers’ experience, development and learning curves of HARS</td>
</tr>
<tr>
<td><strong>Study IV</strong></td>
<td>Total of 80 donors in 2 groups 1. Study group (n=40 consecutive donors; 2009-2010) 2. Matched case-control (n=40 donors 2005-2007)</td>
<td>Case control analysis to evaluate safety and efficacy of continuous infusion of local anesthetics</td>
</tr>
</tbody>
</table>
Surgical procedure

**Hand-assisted retroperitoneoscopic (HARS) nephrectomy**
Donors were placed in a 90° oblique position. A 5-7 cm Pfannenstiel incision was made and a hand port placed in the wound. The peritoneum was loosened from the anterior and posterior abdominal wall, creating a retroperitoneal space by blunt manual dissection. Two 12-mm ports and a 5-mm port were placed lateral to the hand port, high on the subcostal margin and in the flank, respectively. After dissection of the kidney and ligation of the vessels and ureter, the kidney was retrieved through the Pfannenstiel incision. All donors in studies III and IV and the majority of donors in studies I and II underwent HARS procedure.

**Anterior retroperitoneal open nephrectomy**
In studies I and II, a small portion of donors underwent open donor nephrectomy performed using an anterior retroperitoneal approach. Flank incision technique was completely avoided. These donors were placed supine with the ipsilateral side elevated 20-30 degrees and supported in this position by a roll placed under and parallel to the sacrospinalis muscle. After a horizontal skin incision from the tip of the 12th rib to the mid-axillary line, the abdominal muscle was divided leaving the rectus muscle intact. The peritoneum was then loosened from the abdominal wall without entering the intraabdominal cavity. After a medial reflection of the peritoneum, the retroperitoneal cavity and the kidney were exposed. The kidney was retrieved after dissection of the vessels and ureter.

**Study I**
Data were collected retrospectively from routine preoperative donor evaluations. The following parameters were recorded for all donors: age, gender, weight, height, s-creatinine, and GFR estimates (iohexol, $^{51}$Cr-EDTA or endogenous clearance). Iohexol clearance (157) was performed in 109 donors (94%), $^{51}$Cr-EDTA in 16 donors (13.7%), and endogenous clearance in 13 donors (11.2%). In addition, creatinine clearance was calculated in 116 donors (100%) according to Cockcroft-Gault and MDRD equation. Iohexol, $^{51}$Cr-EDTA and endogenous clearance were performed according to local laboratory routines. A simple linear regression analysis was performed to analyze how well the different methods for estimated GFR correlate. The analysis was performed with SPSS statistical software, version 13.0. Values are given as mean ±SD.
Study II

The study cohort was made up of 75 females and 55 males. Median age and BMI (with range) were 51 (20-72) years and 25 (17-33) kg/m², respectively. The donor nephrectomy was performed using HARS in 105 donors and through open surgery in 25 donors. Donors undergoing the two types of surgery were of similar age, sex and BMI. All donors were fit and healthy at the time of the operation, and had undergone thorough preoperative evaluation according to Swedish protocol for donor evaluation. The screening includes history or heredity of VTE, estrogen medication, blood analysis, including APTT, INR, antithrombin, protein C, protein S, resistance to activated protein C (factor V Leiden), prothrombin gene mutation and anticardiolipin antibodies. All donors were examined with venous duplex of the legs, preoperatively and postoperatively before leaving the hospital.

The donors were followed up at 3 months for the occurrence of any clinical VTE. Thromboprophylaxis was given in the form of enoxaparin (20 mg the evening before surgery, 20 mg preoperatively the day of surgery, and then 20 mg every morning during hospitalization) in combination with antiembolic compression stockings. Donors with risk factors for VTE (based on history or thrombophilia screening) received an increased dose of 40 mg daily and continued with the prophylaxis for 6 weeks. Any donor who showed signs of thrombus formation in the legs on the postoperative venous duplex also received the higher dose of enoxaparin for 6 weeks postoperatively.

Study III

For this study, the following data were collected: age, sex, BMI, relation to recipient, operative time (OT), side of operation, perioperative bleeding, number of arteries, other anatomical variants, warm ischemic time (WIT), intraoperative complications, conversion, reason for conversion, postoperative complications, hospital stay and recipient outcome. The median follow-up was 365 days. The OT was from skin to skin. WIT was recorded and documented in the operating theater by a co-ordinator or nursing staff. The time recorded was from when the artery was clamped and stapled until the kidney was immersed in ice sludge on the back table and flushing of the artery with cold perfusion solution began. Postoperative hospital stay is from the first postoperative day until discharge. Mean, minimum and maximum values were calculated for OT and WIT. ANOVA was performed for OT, with center, sequence number with separate slopes for each center (“center-wise learning”), age of donor, conversion, number of arteries, sex/BMI and side of operation as independent variables. F-tests were used to analyze whether these independent variables had an effect on OT.
Study IV

The study group (n=40) was compared to a retrospective case-matched control cohort (n=40), matched with regard to sex, age, BMI and surgical technique. The cumulative consumption of morphine equivalents (morphine, oxycodone, ketobemidone), incidence of postoperative nausea and vomiting, as well as visual analogue scale (VAS) scores, were analyzed. All donors (in both groups) underwent HARS nephrectomy and were maintained postoperatively on standardized multimodal analgesia that combined nurse-controlled oxycodone treatment and acetaminophen. The study group was, in addition, treated with continuous infusion of local anesthetics (CILA). In this group, CILA was provided by the On-Q system (I-Flow Corp., Lake Forest, CA, USA), consisting of a portable multilayer elastomeric pump, a filter, and two flow restrictors attached to two 12.5-cm silver-ionized delivery soaker catheters (SilvaGard®, AcryMed Inc., Beaverton, OR, USA). During the operation, the On-Q system was assembled by a scrub nurse. First the pump reservoir was filled with ropivacaine 0.5% (Narop®, AstraZeneca PLC, London, Great Britain) at a total volume of 450 mL and then the filter, flow restrictors and soaker catheters were attached to the pump reservoir. After the retrieval of the kidney, the first catheter was placed in the retroperitoneal cavity and the second catheter in the pre-peritoneal position under the rectus fascia. The total infusion rate was 96 mL/24 h, allowing a CILA treatment for approximately 4 days. Oxycodone and ketobemidone were normalized to morphine equivalents by following an equianalgesic dose ratio of: IV oxycodone to IV morphine 1:1 (158); oral oxycodone to IV morphine 3:1 (159); IV ketobemidone to IV morphine 1:1 (160, 161). Data are shown as median and range. Statistical analysis was performed using a two-tailed Wilcoxon rank test. Assuming a 25% difference in CCME between the CILA group and the control group, a sample size of at least 22 patients per group was required to detect a difference at $\alpha=0.05$ and 80% power. A sample size of 40 for each group was chosen to enable detection of a difference of less than 25% in CCME and to compensate for potential outliers and dropouts. A p-value less than 0.05 was considered significant.
Results

Study I

Description of the study population
The mean age of the kidney donors was 48 ± 9.1 (mean ± SD) years and 41% were males (Table 6). The study group had a normal mean BMI (26 ± 3.4) and serum creatinine (78 µmol/L ± 14.1). Of the 116 donors, 8 (6.9%) had an iohexol clearance below 75 mL/min/1.73 m² at the first measurement. In these cases, a repeat measurement was performed using the same method (Iohexol, n=5) or ⁵¹Cr-EDTA clearance (n=4).

Table 6. Clinical and biochemical characteristics of individual donors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (±SD)</td>
<td>48.2 (±9.1)</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>47/69</td>
</tr>
<tr>
<td>Body mass index (±SD)</td>
<td>26 (±3.4)</td>
</tr>
<tr>
<td>Mean serum creatinine µmol/L (±SD)</td>
<td>78.4 (±14.1)</td>
</tr>
<tr>
<td>Donors with iohexol estimates</td>
<td>109 (94%)</td>
</tr>
<tr>
<td>Donors with Cockcroft-Gault estimates</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>Donors with MDRD estimates</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>Donors with ⁵¹Cr-EDTA estimates</td>
<td>16 (13.7%)</td>
</tr>
<tr>
<td>Donors with endogenous clearance</td>
<td>13 (11.2%)</td>
</tr>
<tr>
<td>Donors with repeated iohexol estimates</td>
<td>13 (11.2%)</td>
</tr>
<tr>
<td>Donors with initial iohexol clearance &lt;75 mL/min/1.73 m²</td>
<td>8 (6.9%)</td>
</tr>
</tbody>
</table>

Correlation between repeated iohexol measurements in individual patients
In 13 donors (11.2%), more than one iohexol clearance was conducted. Repeated iohexol determinations showed a high degree of variation in several patients (Figure 3). In 4 of the donors, the difference between repeated measurements was approximately 50% or more (individual donors 2, 3, 9 and 12).
Correlation between iohexol clearance and Cockcroft-Gault or MDRD in individual patients
For 109 kidney donors (94%), it was possible to compare iohexol with Cockcroft-Gault or MDRD-calculated clearance. There was a very poor correlation between iohexol clearance and Cockcroft-Gault ($R^2=0.046$) or MDRD-calculated creatinine clearance ($R^2=0.045$) (Figure 4). There was, however, a moderate positive correlation between MDRD and Cockcroft-Gault calculated clearance ($R^2=0.396$).
Study II

The most common type of thrombophilia was factor V Leiden, found in four donors (three female and one male) or 3%, and all were heterozygous. There was one donor with heterozygous prothrombin gene mutation. Deficiency of protein S was found in one, and one had anticardiolipin antibodies. None had protein C or antithrombin deficiency. Ten of the 75 females had been on estrogen treatment (contraceptive pills or hormone replacement therapy), but this medication was stopped 1 month before surgery. Possible heredity was seen in two donors (mother with multiple thrombi in one, and pulmonary embolism in the other). There were no postoperative deaths within 3 months. One donor died after 3 years, of a glioblastoma stage IV. The preoperative duplex investigation was normal in all donors. Postoperatively, the duplex investigation was missed in one donor and showed signs of thrombosis in three (2.3%). One donor, a 50-year-old male with no risk factors, but with a history of leg trauma and intermittent swelling of the leg, underwent laparoscopic nephrectomy. The venous duplex at discharge showed a deep vein thrombosis localized to the distal part of the superficial femoral vein and the fibular vein (non-occlusive). There were no local signs of thrombosis or clinical signs of pulmonary embolism. In two donors (one open and one laparoscopic) it was not possible postoperatively to compress the vein cusps:
the left popliteal vein in a 39-year-old male donor, and the proximal femoral vein on both sides in a 60-year-old female donor, respectively. The cusp contents were interpreted as small thrombi. There were no symptoms but these donors received prolonged prophylaxis. Twelve donors in total received intensified and prolonged prophylaxis due to patient history, laboratory screening, or findings on the postoperative venous duplex. This represents 9.2% of the donors. The results are summarized in Table 7. Three donors required blood transfusions, one perioperatively due to surgical bleeding and two postoperatively. Apart from that, there were no bleeding complications.

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Postop venous thrombosis on duplex</td>
<td>3</td>
<td>2.3</td>
</tr>
<tr>
<td>Pt-prothrombin gene mutation</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Heredity</td>
<td>2</td>
<td>1.5</td>
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<tr>
<td>Total</td>
<td>12</td>
<td>9.2</td>
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</table>

Study III

**Preoperative characteristics**
In 284 cases the donor was related, in 124 unrelated, and in 5 cases non-directed. In 59 cases the donor and the recipient were incompatible, 53 ABO and 6 cross-match positive, necessitating desensitization. Centers differed significantly with respect to selection of side of nephrectomy, age of donors, BMI and number of arteries, but gender ratio did not significantly differ by center.

**Operative characteristics**
The mean OT was 170.2 (range 65-428) minutes, with substantial differences between the centers. Center 1: 278 (175-428) min; Center 2: 145 (80-305) min; Center 3: 149 (103-275) min; and Center 4: 120 (65-240) min. ANOVA demonstrated significance for OT for center, center-wise learning, conversions, sex/BMI, and side of nephrectomy, while number of arteries did not quite reach significance (p<0.05) and age of donor was not significant. The sex/BMI variable demonstrated that OT was longer for normal and overweight male donors than for female donors of corresponding weight.
category – 13 and 31 minutes, respectively. OT was 21 minutes longer in overweight males compared to normal weight males.

The mean bleeding was 155 (range 0-1325) ml. Major bleeding was relatively rare, with 5 cases over 1000 ml. Bleeding (4 arterial and 2 venous) and adhesions (3) were the most common cause for conversions. In one case, it was due to stapler malfunction. The overall conversion rate was 2.4%. The frequency of conversion differed significantly (p<0.001) between centers. Center 1 had the highest rate with 9 (9.3%) conversions, Center 4 had one (0.9 %), and centers 2 and 3 had no conversions.

**Postoperative characteristics**

The mean postoperative hospital stay was 5.7 (range 2-18) days. There were statistically significant differences between centers, p<0.001. Postoperative stays were 7.8 (5-18), 6.3 (4-15), 5.7 (4-12) and 3.1 (2-8) for centers 1, 2, 3 and 4, respectively. None of the donors experienced any postoperative ileus. The complications that did occur are summarized in Table 8.

<table>
<thead>
<tr>
<th>Table 8. Donor complications. Major complications are defined as those requiring further intervention or that were potentially life-threatening.</th>
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<tbody>
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<td>Major complications</td>
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<td>Minor complications</td>
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<td>Overall complication rate</td>
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</tbody>
</table>

DVT: deep vein thrombosis, PE: pulmonary embolism

**Study IV**

The groups in this study did not differ with respect to age, sex, BMI, conversion rate and side of the donor nephrectomy. The CILA and case control groups differed with respect to median operating time (150 min vs. 130 min; p=0.014), median estimated blood loss (100 mL vs. 175 mL; p<0.001), me-
median time in PACU (160 min vs. 242.5; p<0.001), and median hospital stay (4 [4-7] vs. 6 [4-11] days; p<0.001).

**Adverse events**
In the CILA group, leakage of fluid, particularly from the Pfannenstiel incision, was observed and required an increased number of dressing changes. The leakage occurred early post donation and had no impact on the analgesic effect nor on the incidence of wound infection. An effective way to stop leakage without affecting device functionality was by using skin adhesive to seal the wound. In one donor, an asymptomatic serous subcutaneous fluid collection from the Pfannenstiel incision (25 mL) was evacuated through a percutaneous puncture.

**Overall cumulative consumption of morphine equivalents (CCME)**
Compared to the CILA group, the control population was more prone to require supplemental CR oxycodone since iterative IR oxycodone in combination with acetaminophen failed to achieve pain relief (VAS score ≤3). The CCME was lower in the CILA group compared to the case control group (7 mg [0-56] vs. 42 mg [15-127]; p<0.0000001) (Figure 5). Thirteen donors (32.5%) in the CILA group did not require morphine equivalents postoperatively and 70% had a CCME of less than 10 mg for the entire hospitalization (0% in case control; p<0.001).

**Supplemental parenteral pain and nausea treatment**
In the case of refractory breakthrough pain (no response to iterative oral IR/CR oxycodone administered), either IV oxycodone or IV morphine was titrated in 1- to 2-mg increments as supplemental treatment. In the CILA group no donor (0%) received supplemental IV opioid treatment compared to 22 donors in the control group (55%) (p<0.001). There was also a difference in the number of donors treated for nausea between the CILA group and the control population (18 [45%] v. 35 [87.5%]; p<0.001).
Figure 5. Forty consecutive live kidney donors underwent HARS and were treated with the On-Q system, providing CILA with 0.5% ropivacaine through 2 Silvagard® catheters placed in retroperitoneal cavity and in the rectus sheath, respectively. The case control group consisted of 40 matched donors. The figure illustrates differences in CCME for each matched pair and indicates a higher overall consumption of morphine equivalent in all matched control donors as compared to the corresponding CILA donors. Matched pairs are ranked from top to bottom according to the magnitude of difference in CCME. The difference in CCME between the groups was still significant when a constant of 25 mg or less morphine equivalents was subtracted from every control donor (p<0.05).
Discussions

The medical care of living donors is a dynamic process that involves donor evaluation, surgical procedure, perioperative management and long-term follow-up of the donor. This process starts with assessment of the donor’s baseline kidney function, which is essential for evaluating whether the functional capacity of the remaining kidney will be sufficient to prevent renal failure in the long-term post donation. Some current recommendations suggest that all potential donors should have a GFR >80 mL/min/1.73 m$^2$ irrespective of age, gender or race (59, 162, 163). Other recommendations consider the physiological decline of GFR with age (164) and suggest a kidney function within 2 standard deviations of “normal” value for age and gender (98). It is important to recognize that the assessment of kidney function in living donors and formulation of these recommendations are founded on two important assumptions: first, that the “normal” renal function is well-defined and, second, that there are reliable means to measure it. Two legitimate questions are, however, do we really know what “normal” kidney function implies and, more importantly, do we have accurate methods to measure kidney function in healthy individuals?

In 2008, SFKK published recommendations for GFR in healthy individuals (summarized in Table 2). In these recommendations, SFKK clearly notes that consistent databases for the values and confidence limits of recommended GFR in healthy individuals are lacking, especially for elderly persons (>60 years) (74). In plain language, “normal” kidney function in healthy individuals is not well-defined or well-known. The dilemma is instead overcome by specifying values and confidence limits of GFR within which the “true” value might reside. This is a very important aspect to be aware of when the suitability of a potential donor is assessed by a single GFR value.

A far more important aspect in the assessment of kidney function is the reliability of the methods used to measure GFR. To date, there is no ubiquitous consensus specifying the optimal method for assessment of kidney function in live kidney donors. Most centers rely either on estimated GFR (Cockcroft-Gault, MDRD equation) or on creatinine clearance despite the shortcomings and inaccuracies of these methods, as described in detail in the introduction, above (82, 165-170). Other centers measure GFR by exogenous markers for
more accurate and precise assessment of kidney function. In Sweden, io-
hexol clearance is considered the golden standard. At the University Hospital
in Uppsala, all prospective donors used to be required to have a GFR >80
mL/min/1.73 m². In some cases, we observed, however, that the io-
hexol clearance was below the acceptable limit in otherwise healthy prospective
donors. Instead of rejecting these donors, we decided to repeat the io-
exhol measurement and found normal repeat GFR values in most of the donors.

These cases prompted us to perform Study I and to analyze retrospectively
all io-hexol estimates from the routine preoperative donor evaluation from the
period 2000 to 2004. In all donors GFR was assessed by one-point plasma
clearance determination of injected io-hexol. We were surprised to find more
than 50% variation in repeated measurements of io-hexol-calculated GFR in
three donors, and one individual with a 68% variation between repeated
measurements (Figure 3). Scientific reports usually report low variability in
repeated io-hexol measurements in the same individual, but these studies are
generally performed at a single laboratory under well-controlled conditions.
In Study I, io-hexol was analyzed at different laboratories and interlaboratory
variation may thus contribute to the variability. The demonstrated variability
is probably not limited to kidney donors and probably gives a true picture of
the quality and accuracy of GFR measurement in Sweden today, since the
measurements were performed in 11 laboratories with different creatinine
methods over a period of 4 years.

In a recent unpublished analysis, by Dr. Mats Flodin from the department of
clinical chemistry at Uppsala University Hospital, the plasma io-hexol of 43
prospective donors was measured at 4 time points after a single injection.
Subsequently, four different 1-point GFRs and one 4-point GFR were deter-
mined from the same sequential measurements in each prospective donor
(Figure 6). It was very surprising to observe that 10 donors (23%) had a 10-
50% variation between the estimates within a sampling time of 240 minutes,
an observation that further underlined the findings of our initial study.

In well-controlled study designs io-hexol clearance has been shown to have a
low coefficient of variation and high reproducibility (88, 89). The purpose of
the current thesis is not to question these data, but rather to emphasize that in
clinical reality the reliability of io-hexol clearance is compromised, most
likely by preanalytical problems such as erroneous times for io-hexol admin-
istration, blood sampling time, or erroneous registration of administered io-
exhol.
Figure 6. Variations between one-point iohexol plasma estimates (1p-GFR) and four-point iohexol clearance (4p-GFR) obtained from 4 sequential iohexol measurements: 180, 200, 220 and 240 minutes after a single injection of iohexol in each prospective donor.

According to our data, it is conceivable to argue that a single GFR value should not be the dominant marker defining the fate of the prospective donor. Instead, GFR should be considered as one piece of the process in assessment of kidney function. Prospective donors usually undergo extensive laboratory testing for analysis of urea, serum creatinine, cystatin C clearance, and urinary protein excretion. Today’s computer tomography (CT) scans deliver information about the size, blood circulation and even split function of the kidneys (171, 172). If all these examinations reveal no abnormalities, is it justifiable to turn down a prospective donor solely due to a single, low single GFR value? The answer is a definitely no! Considering the large variation in iohexol estimates in uncontrolled clinical reality, the proper approach should be to repeat the GFR measurements to define a range, wherein the “true” GFR might reside. The decision for acceptance or rejection of a prospective donor should be based on the interpretation of the true GFR value within the range of the repeated measurements and findings from the CT scan, laboratory investigations and sound clinical judgment.

Far more severe than the presumable risk for insufficient renal capacity post donation is the risk for VTE, which is one of the most common causes of perioperative mortality (56) and long-term morbidity (95-97). In Sweden, all centers have implemented an extensive screening protocol for VTE according to Swedish guidelines for evaluation of kidney donors (13). The prophylactic treatment for VTE is adjusted to the individual’s risk profile. Donors with no risk factors are given prophylaxis with low molecular weight heparin (LMWH) at 20 mg daily and antiembolic compression stockings. Donors
with moderately elevated risk factors for VTE receive an increased and prolonged dose of LMWH.

In 2001, a 48-year-old male donor, at Uppsala University Hospital, developed a severe bilateral multiple pulmonary emboli 3 months after a retroperitoneoscopic live-donor nephrectomy. The preoperative screening did not indicate increased risk of VTE, and he had received standard prophylaxis with LMWH and compression stockings as well as early mobilization.

Deep vein thrombosis most commonly occurs in the femoral and popliteal veins of the legs and is associated with a 3% pulmonary embolism-related mortality (173). This raises the question of how and why venous thrombosis is initiated predominantly in the lower extremity. Examination of thrombi in humans revealed no significant evidence of preceding damage in the wall of the veins (174). Venous valvular sinus has frequently been associated with location of thrombosis initiation (174-177). It is therefore conceivable that venous thrombosis is predominantly initiated at the level of venous valves. Hence, we implemented a pre- and postoperative venous duplex investigation in the screening protocol for VTE, in order to identify pre-existing and/or new-onset thrombi in the lower extremity veins, especially at the level of venous valves. Additionally, all donors, irrespective of their risk profile for VTE, were followed up at 3 months with special focus on clinical assessment of asymptomatic deep vein thrombosis in the lower extremity.

In Study II, data on 130 consecutive live kidney donors were prospectively collected and analyzed. The frequency of postoperative deep vein thrombosis in this cohort was 2.3%, which is comparable to the frequencies after open and laparoscopic cholecystectomy (178, 179). In 12 of the 130 donors (9.2%), there was an indication for intensified and prolonged prophylactic treatment. Three donors developed subclinical venous thrombosis in the perioperative period, which was detected by venous duplex investigation. This finding was the second most common cause, after heterogeneity of factor V Leiden, for intensifying and prolonging the prophylaxis. In accordance with these data, we concluded that venous duplex could be used to identify donors for whom intensified and prolonged prophylaxis is indicated. Since these donors are not identified by the standard screening protocol, implementation of perioperative venous duplex might decrease VTE-related morbidity.

In living donation, the overall morbidity and mortality are a direct consequence of the invasiveness of the surgical procedure. With the introduction of pure laparoscopic donor nephrectomy in 1995 (106), the morbidity of open donor nephrectomy through a flank incision was addressed. However, the safety of the pure laparoscopic technique has been questioned due to
limited ability of the surgeon to control the surgical field in the case of sudden and severe bleeding (110, 111). The introduction of the hand-assisted approach (HALS) addressed the safety concerns of the pure laparoscopic technique by enabling immediate manual compression for hemostasis in case of bleeding (115, 126-128). However, HALS is performed transperitoneally, which harbours risks for intestinal complications such as bowel obstruction, ileus and intestinal injury. In the worst case, these complications can progress into life-threatening situations (128, 130, 132, 133). In 2002, Wadström introduced the HARS donor nephrectomy (134), which uses the advantages of hand-assisted technique combined with a pure retroperitoneal access to the kidney, which in theory should decrease the risk for intraabdominal complications.

In order to verify this hypothesis, we performed Study III and reported on the largest compiled experience with the HARS technique. The retrospective analysis of 413 donors from 4 different centers revealed that the HARS technique virtually eliminates the risk for intraabdominal morbidity, since in this large series there were no visceral injuries or postoperative ileus. Furthermore, in Study III, where hand-assistance and a retroperitoneal approach were combined, the mean operative time was substantially shorter than reported in the three largest single-center publications citing over 500 cases operated with the pure laparoscopic approach (114, 121, 132). HARS thus seems to be quicker, potentially adding a further safety advantage. Furthermore, HARS preserves optimal kidney function and integrity. In the current series, there was only one case of primary non-function and one case of delayed graft function that was not directly related to difficulties during the recipient operation. This low frequency can possibly be attributed to the hand-assisted technique, which is associated with shorter warm ischemic time (120, 133, 180).

Another safety aspect of HARS technique is the opportunity for sufficient pain management, which is founded on two circumstances: 1) in a comparative prospective study, Sundqvist et al. demonstrated that donors undergoing HARS experienced less pain compared to donors undergoing HALS nephrectomy (181), indicating less traumatic injury to the tissue; and 2) the pure retroperitoneal access during HARS nephrectomy exposes the intercostal, ilioinguinal, and genitofemoral nerves within a fairly limited space. This makes HARS technique notably suitable for nerve blockade with local anesthetics.

At present, opiate analgesics are the mainstay of postoperative pain relief (143). At the University Hospital in Uppsala, donors were usually treated with a multimodal analgesia combining acetaminophen and a nurse-controlled opioid treatment based on the individual needs of the donor. Opioid side-effects such as nausea, vomiting (144) and decreased gastroin-
testinal motility (145, 146) are, however, often encountered. In one case, we even observed a serious life-threatening respiratory depression in a donor being treated with morphine-based PCA. Excessive sedation and severe respiratory depression are life-threatening consequences of postoperative opioid use causing considerable morbidity and even mortality (149-156). With the HARS technique, we sought an alternative non-opioid analgesic method that would provide safe and sufficient analgesia. In this regard, we hypothesized that CILA could provide sufficient pain control while minimizing risks related to opiate analgesics in live kidney donors. In Study IV, we performed a matched case-control analysis with a series of 40 consecutive live kidney donors who were treated with a standardized multimodal analgesia combining acetaminophen, nurse-controlled opioid delivery and CILA. The historic case-matched controls consisted of 40 donors who had received the same standardized multimodal analgesia with the exception of CILA. We found that CILA with 0.5% ropivacaine was a very effective and safe technique for postoperative pain relief in live donors undergoing HARS. In fact, median CCME differed considerably between the donors who received CILA and the matched case-control group. The efficacy of CILA was furthermore highlighted by the observation that the median opioid consumption in the postoperative care unit and on the ward between postoperative day 0 and 4 was 0 mg, indicating that the majority of the donors in the CILA group received no morphine equivalents on a daily basis. Further donor-experienced benefit in the CILA group was lower incidence of postoperative nausea and vomiting. We assume this to be a consequence of lower CCME, as has been shown in previous studies (182, 183). Ultimately, the biggest improvement in postoperative pain management was reflected by an accelerated recovery in terms of shorter time in the postoperative care unit and earlier discharge.
Conclusions

The current thesis is based on four studies with the purpose of evaluating and possibly improving routines and treatments in the care of live kidney donors in order to reduce risks and the overall morbidity.

In the first study (Study I), we demonstrated large variations in repeated iohexol GFR measurements, which compromises the accuracy of this golden standard. We made clear the need for improvement of GFR measurements and that the assessment of predonation kidney function should be more comprehensive, involving GFR, laboratory investigations, functional and morphological examinations, and our clinical judgment. In the second study (Study II), we concluded that the extension of standard screening protocol for VTE with perioperative venous duplex could potentially decrease VTE-related morbidity. In study III, we demonstrated that HARS technique can be implemented with excellent donor and recipient outcomes despite different population, demographics, centre/surgeon-related traditions, and experiences. Furthermore, the study indicated that HARS increases the safety margin of laparoscopic donor nephrectomy by virtually eliminating the risk of intestinal injury. In study IV, we demonstrated that the pure retroperitoneal access to the kidney exposes the retroperitoneal nerves making HARS suitable for CILA. CILA effectively reduces the need for opioid consumption and has the potential to totally obviate opiate analgesics postoperatively. Consequently, CILA in combination with HARS reduces morphine-related morbidity and promotes postoperative recovery.

In accordance with these data, we recommend the improvement and modification of the donor evaluation process as well as a broad introduction of the HARS technique to increase the safety margin of live donor nephrectomy.
Future Perspectives

The continuously growing demand for organs and the remarkable success of living donor kidney transplantation expands the criteria for donor acceptance. In only 10 years, the portion of donors >50 years nearly doubled. Today, donors with isolated hypertension and obesity are accepted (37, 70).

The growing liberality in donor acceptance and risk-taking has obviously no significant effect in the short term. However, there is some uncertainty regarding whether the morbidity or even mortality of donors with isolated risks might be affected in the long term.

In 2010, Dr. Tomoyuki Suzuki presented, at the American Transplant Congress in San Diego, 20 years of follow-up data on 71 live kidney donors with either impaired glucose tolerance pattern or diabetes. The analysis showed that there was no difference in survival or in incidence of ESRD between diabetic and healthy donors after a follow-up of more than 20 years (71). In following with this report, it is conceivable that not all diabetic donors will develop chronic nephropathy. The same might be true for other risk profiles like hypertension.

The trend towards accepting donors with a specific risk profile is already a clinical reality and will evolve further. Hence, it is conceivable that the purpose of donor evaluation must evolve from choosing the “perfect” donor to a more sophisticated evaluation of long-term morbidity in donors with a specific risk profile.

In the future, we will also increasingly encounter new categories of live donors who donate more than only one tissue. This scenario is already a reality for those donating a kidney combined with either a liver- or pancreas segment. We might also see an upcoming indication for isolated pancreatic segment resection in live donors as the treatment of choice for patients with diabetes, which will be exceedingly attractive with the realization of allogeneic tolerance. Today, laparoscopic pancreatic tail resection in live donors is an established procedure in some centers, with promising short-term results but uncertain long-term morbidity.

The success of living donation and the advancements in minimally invasive surgery will certainly create new challenges and perspectives. As long as
live donors are constantly kept at the forefront of medical progress, with the aim of minimizing their risk and morbidity, live donation might keep its legitimacy in the future.
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