Summary & Conclusions
Summary

Kidneys from living donors provide an increasing and important resource for transplantation. In general, kidney donation is safe and current follow-up data are reassuring in terms of long-term renal function of the donors. However, over the past decades, selection criteria for kidney donors have become more liberal, reflecting the need to increase the donor pool. Subjects with overweight, hypertension and older age are more easily accepted for donation. The prevalence of risk factors for future renal function impairment has thus increased and this may bear impact on the long-term outcome. It is therefore important to monitor donor outcome. Moreover, better understanding of the determinants of susceptibility of the healthy kidney to renal function loss is needed.

The vulnerability of a healthy kidney to damage may vary between healthy individuals, even in the absence of risk factors for renal damage. The normal biological variability between healthy individuals may thus be relevant to the susceptibility to renal damage once a trigger for damage occurs.

To test this concept, we studied the role of individual differences in the level of renal activity of the enzyme ACE in the kidney’s susceptibility to inflicted damage. Renal ACE activity was previously demonstrated to be higher in presence of renal damage, but it was not known whether ACE levels increase due to renal damage or precede it. In the study described in chapter 1, we measured renal ACE activity in a renal biopsy sample in healthy rats, prior to induction of renal damage. In rats with higher ACE activity, the severity of renal damage after administration of adriamycin was more pronounced. These data demonstrate that the normal biological variability between healthy individuals explains part of the variance in renal outcome after a standardized insult.

An important factor that affects renal function in healthy individuals is age. It is known from large cross-sectional studies in the general population that glomerular filtration rate (GFR) slowly declines with age. However, it has been challenged whether this also applies to a healthy subset of the population – such as kidney donors – and also whether this applies to both men and women. In chapter 2 we showed that in healthy kidney donors, GFR declined by approximately six to nine ml/min per decade in males as well as females. So even in a population that is preselected for good health, there is an association between increasing age and decreasing renal function. This was the case for GFR and effective renal plasma flow (ERPF). Unfortunately, we did not have longitudinal data at our disposal as it seems likely that there are large intra-individual differences in the amount of renal function loss with age.

Obviously, it is very important to be able to make an adequate pre-donation assessment of what the remnant renal function will be for a prospective donor after unilateral nephrectomy. Can post-donation renal outcome be predicted by pre-donation donor characteristics, such as gender, age, body mass index (BMI), renal function and renal reserve capacity? In chapter 3, we described that pre-donation GFR allows a reasonable and reliable prediction of post-donation renal function GFR, explaining 54% of the variation of post-donation renal function. Maximally stimulated GFR –as a measure of
renal reserve capacity--improved the prediction of post-donation renal function slightly and could account for 55% of the variation. When baseline GFR, donor age and BMI were also taken into account, predictive capacity was further enhanced, explaining 61% of the variation. It also became clear from this chapter that for a given pre-donation GFR, older donors and overweight donors have a slightly higher risk for post-donation impairment of renal function, defined as GFR <60 ml/min/1.73 m² early after donation.

Overweight is known to be a renal risk factor, not only in the general population, but in particular after nephrectomy. The mechanisms involved in the adverse effect of weight excess on renal damage are likely to be multiple, including associated conditions such as hypertension and insulin resistance. Renal hemodynamic factors are also assumed to be involved. Weight excess is associated with a so-called renal hyperfiltration pattern, i.e. an elevated glomerular filtration rate as well as an elevated filtration fraction. An increased filtration fraction reflects elevated intra-glomerular pressure, which is assumed to play a role in long-term renal damage. It is unknown, however, whether the well-established effect of weight excess on renal hemodynamics persists after donation, as pronounced changes occur in the remaining kidney as an adaptive response to the nephrectomy. In chapter 4, we confirmed this large adaptive response, showing that GFR in the single kidney increased by 28% and effective renal plasma flow by 32% early after nephrectomy. Despite these changes, BMI still modulated glomerular filtration and glomerular pressure. Filtration fraction was significantly higher with overweight and obesity, both before and early after nephrectomy. On long-term follow-up in a sub-group of this donor population, we found that an increase in body weight was associated with an increase in filtration fraction. In contrast, a decrease in body weight was associated with a decrease in filtration fraction. Weight excess thus remains a determinant of renal hemodynamics after nephrectomy, and could contribute to the renal risk profile in this population. Accordingly, it is a potential target for intervention. Renal hemodynamics can be modified by pharmacological intervention, such as blockade of the renin-angiotensin-aldosterone system. The finding of a rise in glomerular filtration pressure with an increase in body weight is important, as body weight is known to increase over the years. Post-donation weight gain may pose an extra burden on the remaining kidney. Weight loss is difficult to obtain but weight gain can possibly be prevented and this should be emphasized in donor screening, evaluation and follow-up.

In chapter 5, we investigated the influence of age and BMI on renal reserve capacity. It was known from previous studies that renal reserve was significantly decreased after living kidney donation. It was unknown whether age and BMI could have impact on the decline in renal reserve after nephrectomy. In chapter 5, we showed in a large cohort of kidney donors that older age and higher BMI did not affect reserve capacity before donation, but were determinants of post-donation renal hemodynamic reserve, tested as the renal hemodynamic response to infusion of low-dose dopamine. With increasing age and BMI, post-donation reserve capacity was lower. For obese donors, renal reserve was no longer demonstrable after donation. Loss of renal reserve was most pronounced in young donors with overweight and obesity. This is of importance, since these subjects may be exposed to an increased renal risk for a long period of time. Absence of reserve capacity might be an unfavourable prognostic sign, indicating hyperfiltration that could potentially be harmful in the long-run, but obviously, this needs substantiation by long-term follow-up data.
As mentioned in chapters 3 and 5, a pronounced adaptive response occurs in the remaining kidney after living kidney donation. This adaptive response was slightly less in older donors, as apparent from a somewhat increased risk for post-donation renal function impairment and decreased renal function reserve. These changes, however, were subtle, and it would be important to see whether they herald a worse renal outcome on the long-term. Therefore, in chapter 6, we investigated renal function (GFR, ERPF) in a sub-group of living kidney donors in whom follow-up data approximately six years after donation were available. Fortunately and remarkably, in this subgroup, older age did not compromise the long-term renal adaptive response after living kidney donation. Older donors had the same long-term increase in single kidney GFR and ERPF as younger donors. The donation-induced increase in GFR and ERPF seemed to overcome the age-related decline that could have been anticipated from the normal course of renal function with age. These data support the safety of the living donor program. It is important to extend this long-term monitoring along with the gradual changes in donor selection policy and the consequent changes in the donor population.

In our centre, renal function measurements are performed as the clearance of iothalamate and hippuran, which provide the gold standard for GFR and ERPF. Many centres depend on creatinine clearance or renal function equations to estimate renal function. Even more so, it is currently common practice for many laboratories to provide a renal function estimate by the MDRD equation as a so-called estimated GFR (eGFR) when a blood sample is sent in for creatinine measurement. The eGFR estimates GFR based on serum creatinine, age and gender. The equation was developed in a population with renal disease and is known to underestimate true GFR, in particular in subjects with normal renal function. In chapter 7, we analysed eGFR in relation to true GFR in subjects screened for kidney donation. Adapting the commonly used threshold for donation of 80 ml/min/1.73 m², we found that the vast majority of potential kidney donors would have been declined to donate when their renal function would have been estimated as eGFR. Despite an eGFR below the required threshold of 80 ml/min/1.73 m², donation was nonetheless safe on the short-term, provided that true GFR did meet the required threshold. Applying a Bayesian approach, the probability that a healthy subject with eGFR below 80 ml/min/1.73 m² indeed has a true GFR below 80 ml/min/1.73 m² was merely 7.5%. Use of eGFR in donor screening would lead to unnecessary reduction of the living kidney donor pool. Fortunately, most centres where no gold standard GFR measurement is available use creatinine clearance rather than eGFR. However, due to the increasing use of eGFR by laboratories serving general practitioners, eGFR data are available for many healthy individuals, giving the enormous impression of sub-optimal renal function. This may discourage them to enter screening for kidney donation. Use of a Bayesian approach, that takes into account the low prevalence of renal function impairment in the general population, can help to limit this unwanted side effect of using eGFR in populations without renal disease.
In conclusion,

In this thesis, we provided insights into determinants of renal vulnerability and renal outcome of living kidney donors. We presented further evidence for a permissive role of individual differences in renal RAAS activity in the development of renal damage. Overweight and older age were identified as post-donation renal risk factors, as they were associated with slightly larger early renal function loss and loss of renal reserve capacity early after nephrectomy. Also, younger donors with overweight displayed loss of renal reserve after donor nephrectomy. It would be important to determine the long-term prognostic impact of these changes in the near future.

So far, the long-term follow-up data that were available in a subgroup of our living donor cohort are encouraging. In donors who lost weight over several years after nephrectomy, the renal hemodynamic profile improved, which supports the importance of weight control, in particular after kidney donation. Furthermore, in elderly donors, long-term post-donation adaptation of renal function was not compromised and paralleled that in younger donors. The long-term adaptive increase in GFR and ERPF after nephrectomy appeared to overcome the anticipated age-related renal function decline in this population.

Finally, we showed that healthy subjects have a very low chance of a true GFR below 80 ml/min/1.73 m² even though estimated GFR by MDRD suggests otherwise. In particular female subjects and older subjects are likely to present with an MDRD below 80 whilst true GFR is above 80 ml/min/1.73 m². The MDRD equation is not suitable for donor screening.

These data support the safety of our living donor program. The donor selection policy gradually changes, which consequently changes the donor population. It would be important to extend long-term monitoring along with these changes. This will contribute to optimizing the available donor pool, along with optimizing living kidney donor safety.