General Introduction
Figure 1. The first successful kidney transplantation was performed in Boston, in 1954.

Front row: the Herrick twin brothers (left, recipient; right, donor); back row: the surgical team (left, Dr. Murray).
Historic perspective

*Boston, 1954.* Dr. Joseph Murray transplanted a kidney between the Herrick identical twin brothers [figure 1]. It would be the first successful living kidney donation procedure in the world and a milestone in the history of renal transplantation [1]. Previous attempts of organ transplantation –even since the beginning of the twentieth century– had failed due to rejection of the transplanted graft.

In the second part of the twentieth century, immunosuppressive therapies were developed to overcome rejection, making it possible to perform transplantation to non-identical recipients, and to use post-mortem organs. Further development and refinement of immunosuppressive therapy and introduction of new drugs led to a tremendous improvement of graft survival, in particular in the first year after transplantation [2,3].

Ever since, transplantation has become the preferred treatment for end stage renal failure. It is preferred over dialysis because survival rates after renal transplantation are much higher than during dialysis [4,5]. Furthermore, quality of life improves for patients with end stage renal disease when they receive a renal transplant [6,7].

The waiting list for kidney transplantation has grown expansively over the past decades [figure 2]. This is mainly attributable to the increase of patients on dialysis, a large part of whom are elderly [8]. Not only the general population is becoming more and more senescent, the average age of the dialysis population is also increasing. Elderly patients are the fastest growing group requiring renal replacement therapy [8,9]. Furthermore, diabetes and hypertension are increasingly prevalent, also contributing to the increasing number of patients that progress to end stage renal disease [10,11].

The shortage of organs from deceased donors persists and efforts to increase the number of deceased donors have not been successful. In the Netherlands, as of January 2008, a thousand people are awaiting kidney transplantation and average time on the waiting list for patients on dialysis is currently 4½ years. Even though dialysis is a lifesaving treatment, with the high mortality rate for patients on dialysis, one in five patients die while waiting for transplantation [8].

Kidneys from a living donor provide an increasingly important resource for transplantation that not only helps to reduce the shortage in donor organs, but also leads to better outcome for the recipient [12,13]. Graft function and survival are superior compared to a kidney from a post-mortem donor [3,14]. Furthermore, it is possible to transplant prior to the onset of dialysis, so-called pre-emptive transplantation, which is

![Figure 2. Dynamics of the Eurotransplant waiting list from 1969 to 2006.](image)

The grey area under the curve shows the number of patients on the waiting list. Bars show the number of transplantations. While the number of transplants from a post-mortem donor has been stable for several years, the number of transplants from a living donor is steadily increasing.
also beneficial for the recipient. Longer waiting list time has negative impact on renal transplant outcome, in living as well as deceased donor transplantation [15,16]. Therefore, it is important to transplant as soon as possible when a patient reaches end stage renal disease.

The introduction of laparoscopic techniques for donor nephrectomy in the nineties has further contributed to the increase in living donor transplantations. It has made kidney donation more appealing than with open procedures, because post-operative recovery for the donor is quicker, hospital stay is shorter and the duration of getting back to work is shorter too [17-19].

Groningen, 2008. It has been 40 years since the first (post-mortem) kidney transplantation was performed in our centre. Today, renal transplantation from a living kidney donor has become a common procedure, with 358 living donor procedures performed in the Netherlands in 2007 [20]. In Groningen, nearly 50% of the annually transplanted kidneys comes from a living donor. Whereas in 1997 merely 6 living kidney donor transplantations were performed in Groningen, just a decade later this had increased almost tenfold to 58 living kidney donor transplantations in 2007 [figure 3], by virtue of a dedicated, multidisciplinary living donation program.

Living donor safety
Obviously, risks for donors should be minimal. After all, whereas benefits for the recipient are large, for the healthy donor there is no direct medical benefit to undergo major surgery with potential severe complications. Fortunately, kidney donation in general is safe. Mortality rates for the surgical procedure are currently around 0.03% [21-23].

Previous studies have shown that donor nephrectomy usually does not lead to clinically significant short or long-term renal damage in the remaining kidney [24-26]. In 1997, a Swedish epidemiological study by Fehrman-Ekholm et al. showed that life expectancy of living kidney donors was not compromised. In fact, the opposite seemed to be true, as living kidney donors lived longer than age-matched controls [27]. In figure 4, observed survival curves for these Swedish kidney donors are presented as well as the expected survival based on the general population, matched for age. It shows that the pattern of mortality was similar to that in the general population, but overall survival of donors was superior compared to the general population. This is generally attributed to the fact that kidney donors represent a very healthy subset of the population with less risk factors for renal and cardiovascular morbidity and mortality, otherwise they would not have been eligible to donate in the first place.

Figure 3. Annual number of kidney transplantations in the UMCG.
Grey bars represent transplantations from a living donor; white bars represent post-mortem transplantations.
Can we simply state that—judging from results from the past—living kidney donation is currently safe on the long-term? Unfortunately, as yet, we do not know. Donors from the past differ from donors nowadays in a number of aspects. With the persistent shortage of kidneys for transplantation, several efforts have been undertaken to expand the potential kidney donor pool. Among this, selection criteria for living kidney donors have been extended over the past decade. Reluctance towards accepting so-called marginal donors is declining and it has become more and more common to accept donors with advanced age, hypertension or obesity, as addressed in more detail below. These factors could possibly influence eventual donor health and future risks may be higher than in historical populations [28]. This asks for continuous re-assessment of short-term and long-term donor safety, thus keeping up with the changes in kidney donation practice.

Mean donor age in our centre has increased over the last twenty years, from an average of forty in the eighties to fifty nowadays, notably since elderly donors are now more easily accepted for kidney donation. This is in line with donor practice in other countries, as shown for instance by a recent survey from the USA, revealing that most centres do not have an upper age limit for donation any more [29]. The rise in donor age may have several implications, both for outcome of the recipient and for possible health risks of the donor. First, renal function slowly declines with age, as will be discussed below. Accordingly, renal function of the transplanted graft may be compromised. Reports on whether higher donor age is associated with higher rejection rates and unfavourable graft survival are conflicting [30-32]. Currently, conclusions regarding influence of living kidney donor age on outcome for the recipient cannot be made. Nonetheless, it is clear that transplantation from an elderly living donor source is superior to both dialysis and transplantation from a deceased donor [33-35]. As to long-term safety for the elderly donor, less is known, but several issues are relevant. As mentioned before, renal function in elderly is lower due to age-related decline in glomerular filtration rate and renal perfusion. Second, risk factors for renal and cardiovascular damage, such as hypertension and overweight, are more prevalent with advanced age. On the other hand, the expected life span of an elderly donor is shorter than for a young donor. The need for long-term safety may thus be of more importance for younger donors.

The general population is becoming more and more overweight, which also affects our kidney donors, all the more so because overweight is more prevalent in older subjects. Figure 5 illustrates the...
growing prevalence of overweight in the general population in the Netherlands [36]. It is nowadays well recognized that excess body weight is associated with an unfavourable risk profile for cardiovascular as well as renal disease [37]. Furthermore, overweight in general and obesity in particular are associated with both hypertension and diabetes, the two leading causes of end stage renal disease. Despite this association, obesity is not an absolute contra-indication for kidney donation [28,29]. In our own centre, the proportion of overweight and obese donors has gradually increased as well, as shown in figure 6.

In the eighties, it was unthinkable that a potential donor with hypertension would be accepted to complete the donation procedure. Nowadays, donors with pre-hypertensive blood pressure [38] or with hypertension which is well-regulated by one or two antihypertensive drugs are eligible to donate. In a group of hypertensive donors, renal function was found to be adequate at one year post-donation and it appears to be safe to accept subjects with regulated hypertension [39]. In our centre, we started to accept donors who used anti-hypertensive medication in the year 2002. Since then, the percentage of hypertensive donors gradually increased to 24% in the year 2007.

As pointed out, the risk profile within the donor population has gradually changed and will presumably continue to change. Historical data on donor safety cannot simply be extrapolated to estimate risks for our current and future donors. Changes in our practice are set out towards a less favourable cardiovascular and renal risk profile. Possible long-term effects of accepting elderly, overweight and/or hypertensive kidney donors may not yet be clear, but more pronounced vulnerability to renal damage is plausible. We need to monitor donor outcome so that we can work towards maintenance of long-term donor safety. A better understanding of renal safety and vulnerability will hopefully contribute to individual renal risk assessment of prospective donors, so that we can optimize the potential donor pool.
Renal adaptive capacity & vulnerability to damage after kidney donation

In the clinical context of renal disease, the mechanisms of renal function loss have been extensively studied, and risk factors for future renal function loss have been well-documented and validated. In the context of kidney donation, however, the challenge is to identify the determinants of renal outcome after contra-lateral nephrectomy in a healthy kidney, prior to nephrectomy and thus during the healthy condition. The well-established markers for renal prognosis, such as proteinuria, are by definition absent, and if not, the subject under consideration will not be eligible to donate. So, risk profiling of the kidney donor requires a specific approach, aimed at identifying the determinants of renal vulnerability in the healthy kidney.

Likely, the normal biological variability between individuals, due to both genetic and environmental factors, is relevant in this respect. Among healthy individuals, there is a relatively wide range in renal function and in renal responsiveness to (patho-)physiological stimuli. The impact of this variation for susceptibility to renal damage in general, and to the risk for renal damage after kidney donation in particular, is largely unknown. For kidney donation, it is important to identify mechanisms that contribute to renal adaptive capacity, or, conversely, the risk for renal damage after nephrectomy and find ways to test these before donor nephrectomy.

Renal hemodynamic response to a reduction of renal mass

Loss of a large amount of functioning nephrons by contra-lateral nephrectomy elicits an adaptive response in the remaining kidney to ensure maintenance of renal excretory capacity with the reduced number of nephrons. This adaptive response consists of an immediate and a long-term component. The immediate renal hemodynamic component includes vasodilation that leads to a considerable increase in renal blood flow and glomerular filtration rate in the remaining kidney. The long-term component also includes compensatory renal growth [40-42].

In the absence of other triggers for damage, unilateral nephrectomy does not usually lead to progressive renal damage, neither in experimental models nor in human. This provides the justification of the living donation practice. However, loss of a larger proportion of nephrons, as induced by subtotal (5/6) nephrectomy has been extensively shown to be a potent trigger for progressive damage in the remnant nephrons.

![Figure 6. The distribution of normal weight, overweight and obese living kidney donors over time in the University Medical Center Groningen from 1984 to 2006.](image)

Five groups of approximately 50 donors each were created in chronological order of date of donor nephrectomy. Normal weight was defined as a BMI≤24.9; overweight as a BMI 25-29.9 and obesity as a BMI≥30 kg/m². The percentage donors with normal weight declined from 64% in the first cohort to 33% in the last cohort.
In the early eighties, Brenner elaborated the so-called remnant nephron hypothesis, focussing on the role of glomerular hypertension in the remaining nephrons as the main pathway for progressive renal damage [43]. In animal models, his group showed that loss of renal mass, if sufficient large, was a trigger for extensive and irreversible renal damage. Micropuncture data documented the pathogenetic role for glomerular hypertension in this setting. Glomerular hyperfiltration is the effect of the compensatory response that increases the single nephron glomerular filtration rate in the remnant nephrons in order to maintain renal excretion. However, the exposure of the glomerular capillary bed to the elevated pressure eventually induces glomerular capillary damage and glomerular protein leakage. This contributes to a vicious circle of ongoing renal damage and progressive renal function loss.

Glomerular hypertension can be reduced by dietary protein restriction, antihypertensive therapy, or specific reduction of glomerular pressure by blockade of the Renin Angiotensin Aldosterone System (RAAS). These interventions reduce glomerular damage in experimental models of kidney disease [44-48]. Moreover, the renoprotective effect of RAAS-blockade has extensively been shown in human renal patients, and in particular in proteinuric renal disease [49], where the antiproteinuric effect is assumed to be a main contributor to the renoprotective effects. A contribution of the renal hemodynamic effects to long-term renoprotection is likely [50-52], but has not been proven. Remarkably, it was not until recently that the prognostic impact of renal hemodynamic profile for long-term renal function has been substantiated in patients. A study from our department found that for a given glomerular filtration rate, a higher filtration fraction was associated with worse renal and overall outcome of transplant recipients, which was independent of blood pressure and proteinuria [53].

It should be noted that glomerular hypertension cannot be measured directly in man. However, the filtration fraction (FF) can be used as a non-invasive surrogate marker. When glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) are measured simultaneously, the filtration fraction (FF) can be derived as follows: FF=GFR/ERPF. The FF represents the proportion of plasma that is actually filtered by the glomerulus and reflects intra-glomerular pressure. The scarcity of evidence for a pathogenetic role of renal hemodynamic factors, as opposed to the abundance of experimental data, is due to the fact that measurement of renal hemodynamics in man is relatively laborious and expensive. As a result, the number of studies with large series of patients with well-documented renal hemodynamics is very sparse, especially in combination with data on long-term follow-up.

**Renal hemodynamic reserve capacity**

The healthy kidney has a considerable functional renal hemodynamic reserve, as apparent from the changes in renal function after kidney donation. After unilateral nephrectomy, GFR and ERPF usually considerably exceed the 50% of pre-nephrectomy values that would be expected in the absence of reserve capacity. As this occurs almost immediately after contra-lateral nephrectomy, a hemodynamic mechanism is likely. Reserve capacity can be tested by measuring the renal hemodynamic response to different stimuli, such as a protein load or dopamine infusion [54-58]. In our centre, we use low-dose dopamine, an amino-acid solution and their combination [59]. In the healthy
kidney, dopamine predominantly induces efferent vasodilation, infusion of amino-acids leads to predominantly afferent stimulation and the combination of both substances induces a large increase in both GFR and ERPF. After donor nephrectomy, renal reserve capacity is reduced, indicating that the kidney addressed its reserve capacity to maintain excretory function [60]. It could be hypothesized that other factors that reduce reserve capacity can bear impact on renal adaptive capacity after donation, and may thus be relevant for long-term renal prognosis. Theoretically, ageing –by loss of nephrons– and weight excess –by inducing hyperfiltration– could reduce reserve capacity. These are factors that occur in a healthy population, such as kidney donors.

**Effects of ageing on the kidney**
With ageing, structural and functional changes occur within the kidney and renal function slowly declines. Nephrons are lost, which are the functional units of the kidneys. This could theoretically lead to compensatory hyperfiltration in the remaining nephrons. Several cross-sectional studies in the general population have shown that the decline in GFR on average amounts to 5-10 ml/min per decade [61,62]. Simultaneously, effective renal plasma flow (ERPF) decreases. However, ERPF proportionally decreases more than GFR. Consequently, filtration fraction, which is the ratio between ERPF and GFR, increases with ageing, suggesting that (single nephron) hyperfiltration is a characteristic of renal ageing. Compared to young healthy subjects, the filtration fraction (FF) was higher in elderly subjects and still higher in elderly subjects with hypertension, whereas GFR was similar in both elderly groups [63]. It has been stated, however, that an age-related increase in FF is not part of the physiology of healthy ageing, but rather reflects concomitant cardiovascular disease.

Arteriosclerosis builds up during a lifetime, not only in the larger blood vessels, but also in the smaller, arcuate arteries within the kidney [64]. These changes contribute to the decrease in ERPF and GFR and are associated with reduced renal responsiveness to vasodilatory stimuli. Accordingly, older age has been associated with a reduced renal hemodynamic reserve, albeit not invariably so [58,64-66]. Even more so, the ageing kidney might be more vulnerable to renal damage, possibly due to blunted adaptive capacity.

Despite the fact that kidney donors represent a group that is in very good health, cross-sectional analyses do show a negative relation between age and renal function [67,68] though not invariably so [69,70]. A major drawback in the knowledge on the effects of the normal ageing process on the kidney is the lack of properly documented longitudinal data on renal hemodynamics. Further studies on renal hemodynamics and renal adaptive capacity in healthy older subjects are therefore warranted.

**Overweight**
Overweight is an independent risk factor for progressive renal damage [37,71,72]. In the general population, overweight, defined as a body mass index (BMI) between 25 and 30 kg/m², nearly doubles the risk for end stage renal disease and with a BMI over 30 kg/m², which signifies obesity, the risk is more than tripled [37]. Obesity has been associated with onset of proteinuria and histologic changes in the kidney and with idiopathic focal glomerular sclerosis [73]. Even in biopsies taken at donor nephrectomy, and thus from healthy kidneys, differences were found between non-obese and obese
Kidney samples from obese donors displayed subtle but structural changes, such as enlargement of glomeruli and tubular dilation [74]. Even more so, Praga et al. demonstrated that after nephrectomy, overweight was an important risk factor for proteinuria and progressive renal damage [75].

The mechanisms through which excess body weight leads to structural renal changes and even renal damage have not been fully elucidated. Co-morbid conditions such as hypertension and insulin resistance are assumed to play a role. Furthermore, hyperfiltration may play a role [53]. Of note, not only morbid obesity, but also modest weight excess is associated with an elevated filtration fraction, consistent with the epidemiological observations that the renal risks of weight excess are not limited to morbid obesity [76]. As mentioned before, hyperfiltration is a reflection of higher intra-glomerular pressure. If this exists for a prolonged time, the glomeruli can become damaged, as has been shown in animal models of renal mass reduction [46,77,78]. The presence of glomerular hyperfiltration in conditions of weight excess can be independent from hypertension or insulin resistance. Hyperfiltration may partly explain why the kidney is more vulnerable when excess body weight is present. It would be logical to expect that renal hemodynamic reserve would be reduced in subjects with weight excess, but so far, no data are available to substantiate this assumption.

In overweight and obesity, the Renin Angiotensin Aldosterone System (RAAS) is upregulated. This happens through several pathways, not only through direct upregulation of the RAAS, but also indirectly, for instance through higher sympathetic activity. The increased RAAS activation with overweight contributes to higher blood pressure, which in its turn can lead to chronic renal damage [79]. Moreover, the RAAS may contribute to obesity-related renal damage—indeed from hypertension—through pathways of cell proliferation and fibrosis, as will be discussed below.

It is nowadays more and more recognized that adipose tissue may well be the body’s largest endocrine organ. Excess body fat does not just “sit there”, but is highly active, for instance by secreting adipocytes and contributing to a low-grade inflammatory state [80,81]. In addition to above-mentioned systemic and renal RAAS activation with excess body weight, adipose tissue has its own RAAS, which contributes to overweight-associated cardiovascular and renal risks [80,82].

Sodium status may also be relevant to the adverse effects of weight excess on renal hemodynamics and on renal risk profile [81,83]. In the general population, sodium intake was shown to affect urinary albumin excretion in particular in subjects with higher BMI [84]. Remarkably, in mildly overweight healthy young man high sodium intake elicited hyperfiltration, which was not the case in the lean subjects [85].

Thus, the mechanisms through which overweight leads to renal damage are complex and entangled. Even though living kidney donors are selected for their good health, they incur long-term renal and cardiovascular risks when overweight is present, too. Intervention in the RAAS has been shown to modify renal hemodynamics in diabetic and non-diabetic overweight subjects particularly [86,87], and may prevent onset or progression of cardiovascular or renal disease. Still, weight loss should always be emphasized.
**Renin Angiotensin Aldosterone System**

The Renin Angiotensin Aldosterone System (RAAS) is a key regulator of blood pressure and renal hemodynamics. By its hemodynamics effects as well as by direct effects on tissue remodelling, it is involved in the pathophysiology of renal damage in many renal disorders [88]. Accordingly and as mentioned above, blockade of the RAAS by pharmacological intervention with ACE-inhibitors or AT1-receptor antagonists is a major tool for renoprotection.

The RAAS is an intricate system with many components, of which a simplified scheme is shown in figure 7. Part of the complexity of the RAAS is due to the fact that there are circulating systemic RAAS and local tissue RAAS that interact. Blood pressure, sodium and volume equilibrium are thus regulated through a complex interplay between sympathetic nerve activity, circulating RAAS, local tissue RAAS and other mediators and effectors. Angiotensin II (ang-II) is the main active component of the RAAS that directly increases blood pressure through vasoconstriction. Ang-II stimulates contraction and hypertrophy of smooth muscle cells and stimulates aldosterone synthesis. In the kidney, ang-II causes...

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**Figure 7. The Renin Angiotensin Aldosterone System (RAAS).**

A simplified scheme of the RAAS. The RAAS is involved in the regulation of blood pressure as well as water and sodium balance in the body. Renin is produced by the kidney when blood pressure is low. Renin stimulates the formation of angiotensin, which is cleaved to angiotensin II by the angiotensin converting enzyme (ACE). Angiotensin II has vasoconstrictive effects. Furthermore, angiotensin stimulates the production of aldosterone from the adrenal cortex. Aldosterone causes the tubules to retain sodium and water.
Ang-II is a renal growth factor and has (pro-)fibrotic properties. It has direct effects on renal cells, for instance by promoting the phenotype change that can occur in fibroblasts, transforming them to active myofibroblasts, which contributes to matrix deposition and thus fibrosis [89,90]. Ang-II can also contribute to renal damage indirectly, by enhancing inflammatory responses, inducing growth factors like TGF-β and cytokines like IL-6 and TNF-α, promoting chemotaxis, inflammation, proteinuria and so on [91]. Pharmacological intervention in the RAAS can ameliorate the effects of these pathways and has beneficial effects on renal hemodynamics, reduces protein excretion and blood pressure and reduces fibrotic and inflammatory processes in the tissue [92-94].

vasoconstriction of the efferent arteriole and vasa rectae, which reduces renal blood flow and increases post-glomerular and total renal vascular resistance. ERPF thus decreases; the filtration fraction, however, increases and accordingly GFR is preserved or increases.

Renin release from the kidney, elicited by low renal perfusion pressure, volume depletion or sympathetic nerve stimulation, has long been considered the (only) rate limited step in the RAAS. However, the level of local tissue ACE activity has been forwarded as being pathophysiological relevant as well [88]. This might in particular be relevant for the non-hemodynamic effects, exerted by locally generated ang-II.
References


