Immediate and early renal function after living donor transplantation

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Abstract

Background. In order to assess the immediate renal function after living donor transplantation, renal function was compared in eight renal allograft recipients and their living related kidney donors during the first 24 h after transplantation.

Methods. Substantial and comparable intraoperative volume loading with Ringer’s acetate and mannitol was performed together with the administration of frusemide. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by the clearances of inulin and $p$-aminohippurane, respectively. Tubular reabsorptive function and injury were estimated from the clearance of lithium, the fractional excretion of sodium and the urinary excretion of $N$-acetyl-$\beta$-glucosaminidase.

Results. One hour after completion of surgery, GFR ($54 \pm 7 \text{ ml/min}$) and ERPF ($294 \pm 35 \text{ ml/min}$) were only $30\%$ lower in the grafts than in the remaining donor kidneys, increasing to similar levels within $3 \text{ h}$. Only minor tubular dysfunction and injury were revealed in the grafted kidneys, and these tended to normalize within $24 \text{ h}$.

Conclusions. By the present transplantation procedure comprising short ischaemia time and substantial volume expansion combined with mannitol and frusemide administration, kidneys from living donors regain nearly normal function within a few hours after transplantation.

Key words: living donor transplantation; renal allograft function

Introduction

Living donor renal allografts yield superior results as compared with cadaveric grafts, and the use of living donors also keeps the waiting list for cadaveric donor transplantation short enough to make renal transplantation a realistic alternative for most patients suffering from end-stage renal disease. Immediate function in transplanted kidneys is related to the cold ischaemia time, and the frequency of delayed graft function may increase by as much as $23\%$ for every $6 \text{ h}$ of cold ischaemia [1]. Living donor transplantation represents an optimal setting whereby duration of ischaemia is minimized, and it also gives the opportunity to compare graft function with the paired, remaining and presumptive equal kidney in the donor. It is well known that primary function in living donor grafts is generally achieved, but the immediate and early function in the graft as compared with the remaining kidney function has not been examined previously. The purpose of the present study was to assess the renal allograft function during the first $24 \text{ h}$ after transplantation in comparison with the remaining donor kidney in order to evaluate the effects of the transplantation procedure itself on renal allograft function.

Subjects and methods

Eight consecutive living donor renal transplant recipients and their donors were asked to participate in the study. Informed written consent was given, and the protocol was approved by the Regional Ethics Committee. All recipients were stable in dialysis, and only biocompatible membranes were used. To avoid an influence of remaining kidney function, only recipients undergoing a planned simultaneous bilateral nephrectomy were included. Of these, six were nephrectomized due to polycystic kidney disease, and two because of severe hypertension.

The mean age was $40 \text{ years for both recipients (range 30–48)}$ and their living related donors (range 21–60).

On the evening before transplantation/nephrectomy, three tablets ($18 \text{ mmol}$) of lithium citrate (Lithionit®) were given to obtain plasma concentrations of lithium of $0.2–0.3 \text{ mmol/l}$ at the start of the study.

Anaesthesia was performed according to our standard procedures, including thiopental, fentanyl, pancuronium, $\text{N}_2\text{O}$ and isoflurane. During surgery, before nephrectomy, donors received $3000 \text{ ml}$ of Ringer’s acetate and $200 \text{ ml}$ of $15\%$ mannitol as a standard procedure. Further volume was given according to individual judgement, ranging from $300$ to $2000 \text{ ml}$. Recipients received Ringer’s acetate to keep a central venous pressure of $12–14 \text{ mmHg}$ (range $3000–7000 \text{ ml}$), and $200 \text{ ml}$ of $15\%$ mannitol was given when the transplanted kidney started to produce urine. Both donors and recipients were given a bolus of $40 \text{ mg}$ frusemide.
(when the surgical wound was closed in donors; just before opening of the artery to the transplanted kidney in recipients) followed by an infusion of 5 mg/h until the investigation was finished. During the investigation, urine volume was substituted successively with Ringer’s acetate intravenously in such a way that the hourly measured volume was infused the following hour. After nephrectomy, the harvested kidney was submerged immediately in a basin of iced Ringer’s acetate and the renal artery flushed with Euro-Collins solution until the venous effluent was clear. Thereafter, the kidney remained in cold storage until the transplantation 30–60 min later.

The renal clearance study started at the end of surgery, 1 h after the priming doses of inulin and p-aminohippurane (PAH) were given, followed by a sustaining infusion to keep a steady-state inulin concentration of ~200–300 mg/l and a PAH concentration of 20–40 mg/l.

Glomerular filtration rate (GFR) was calculated as inulin clearance measured by the resorcinol method, and effective renal plasma flow (ERPF) was calculated from the clearance of PAH. Lithium was measured by flame photometry of serum and by atomic absorption of urine specimens. Urinary N-acetyl-β-glucosaminidase (NAG) was measured by a fluorometric method as described by Price et al. [2].

Immunosuppressive protocol

The recipients received a triple immunosuppressive regimen consisting of cyclosporin A (CsA), azathioprine and prednisolone. Prednisolone was given at 1 mg/kg, azathioprine at 4 mg/kg and CsA at 10 mg/kg as a daily preoperative dose for 2 days including the morning of the operation. After the first 8 h of clearance measurements, CsA was infused i.v. at a dose of 5 mg/kg over the course of 4 h.

Calculations

Standard clearance formulae were used for the clearance data. Lithium was used to estimate proximal reabsorption as previously described [3]. The formula used for the calculation of fractional proximal reabsorption (FPR) based on the lithium clearance data is:

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FPR = \frac{AR_{Li}}{F_{Li}} = 1 - \frac{C_{Li}}{C_{inulin}}
\]

where \(AR_{Li}\) is absolute reabsorption of lithium, \(F_{Li}\) is filtered lithium, \(C_{inulin}\) is the inulin clearance and \(C_{Li}\) is the lithium clearance.

Statistics

Results are given as mean ± SEM. Differences between periods within each group were tested by Friedman’s non-parametric test for repeated measurements, and differences between the two groups by Kruskal–Wallis’ non-parametric ANOVA test followed by Dunn’s multiple comparisons test. A value of \(P \leq 0.05\) was considered significant.

Results

Duration of graft ischaemia ranged from 58 to 178 min (mean = 121 ± 15 min), and all allografts had immediate onset of function. During the first hour after surgery, GFR and ERPF were significantly lower in the recipients than in their living related donors (Figure 1). GFR averaged 54 ± 7 vs 77 ± 9 ml/min and ERPF averaged 294 ± 35 vs 355 ± 26 ml/min, \(P \leq 0.05\).

In the donors, GFR and ERPF remained stable at these levels without significant changes throughout the
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study and averaged 70 ± 9 and 349 ± 19 ml/min, respectively, 24 h after surgery (Figure 1). In the recipients, GFR and ERPF successively increased during the first 3 h and then stabilized at the same levels as measured in the donors (Figure 1). At 24 h after surgery, GFR and ERPF averaged 66 ± 11 and 342 ± 20 ml/min, respectively. Blood pressure (Figure 1) tended to be higher in the recipients than in the donors, but the difference was only statistically significant during the last sampling period 20–24 h after the end of surgery.

Urine flow is shown in Figure 2. One hour after surgery, urine flow constituted 45 ± 5% of GFR in recipients and 32 ± 2% in donors, demonstrating low tubular reabsorption in both groups. Low tubular reabsorption is also demonstrated by high fractional excretion of sodium (FE Na); 0.38 ± 0.06 and 0.28 ± 0.02 during the first hour after surgery in recipients and donors, respectively. Compared with the donors, FE Na was higher in the recipients throughout the study, but the difference declined with time, and at 20–24 h after surgery it was no longer statistically significant. The values of FE Na successively decreased in both groups, and from the first to the last measurements they were reduced by approximately two-thirds in both recipients and donors.

FPR estimated from Cli was low (range 0.23–0.39) and without significant differences between recipients and donors, and with no significant changes throughout the study in either group (P = 0.94) (Figure 2).

The urinary excretion of NAG is shown in Figure 3. The NAG excretion was lower in the donors and did not change significantly throughout the study (P = 0.39). In the recipients, the initial NAG excretion was 4-fold higher, but decreased significantly during the first 8 h. Compared with the donors, NAG excretion was significantly higher during the first 6 h.

Discussion

This study demonstrates that during optimal conditions, including short duration of ischaemia, transplanted kidneys from living donors reach 70% of the function of the remaining kidney already within 1 h after completion of surgery. No differences in filtration or blood flow between the two kidneys could be revealed later than 3 h following surgery.

The results were somewhat surprising, and the grafted kidneys regained function more quickly than expected. In a study by Kamper et al. [4], the first comparisons between recipients and donors were made after 5 days, and GFR was at that time 20% lower in

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**Fig. 2.** Urine flow, fractional excretion of sodium (FE Na) and fractional proximal reabsorption (FPR) in the recipients (■) and their living related kidney donors (○) during the first 24 h after transplantation. The asterisks denote a significant difference between groups (P ≤ 0.05).

**Fig. 3.** Urinary NAG excretion in the recipients (■) and their living related kidney donors (○) during the first 24 h after transplantation. The asterisks denote a significant difference between groups (P ≤ 0.05).
the grafts compared with the remaining kidneys. Few details from the perioperative regimen are described in that study, and a comparison with the present study is not easy to make. Alejandro et al. [5] concluded that in renal transplantation, ischaemic damage to the allograft invariably was present. Even in kidneys with immediate urine production, GFR did not reach normal values until 2 days postoperatively. The transient ischaemic injury was characterized by extensive reduction in apical brush border and patchy necrosis of tubular cells, notably those of the proximal tubule. It was associated with transient impairment of sodium reabsorption, urinary concentrating ability and glomerular ultrafiltration [5].

Due to heavy volume loading and frusemide administration, tubular reabsorptive function is difficult to evaluate from the present study. Nevertheless, there were significant differences in FE_{Na}, demonstrating lower tubular reabsorption in recipients as compared with donors. The variations in FPR estimated from C_{Li} were not greater than expected by chance (P = 0.94) with no significant differences between the groups, indicating that the differences in reabsorption were located distal to the proximal tubule. One may, however, question the validity of C_{Li} as a proximal marker [6], but during the combined influence of volume expansion and loop diuretics, lithium reabsorption in more distal parts of the nephron is low and constant [7], and variations in C_{Li} are therefore likely to reflect variations in FPR. The presence of tubular injury to the transplanted kidney is supported by the increased excretion of NAG compared with the donors. NAG is a lysosomal enzyme found in high concentrations in renal tubules, especially in the S_{1} segment of the proximal tubule, but also in distal tubular cells [8,9]. Its relative molecular mass precludes its filtration by the glomerulus, and makes urinary NAG excretion a very sensitive marker of renal tubular injury [8]. A 4-fold higher level of NAG excretion in the recipients compared with the donors, falling to a 2-fold higher level in 6 h, indicates minimal tubular damage which was reversed rapidly. This is in agreement with the small differences in tubular reabsorption, but one may question whether these differences really were due to tubular dysfunction induced by the transplantation procedure or merely reflected small differences in volume loading or blood pressure (pressure natriureses) between the two groups.

Alejandro et al. [5] demonstrated in their study that the predominant cause of hypofiltration in this form of post-ischaemic injury is due to a reduction in transcapillary glomerular pressure (ΔP), and that afferent vasoconstriction rather than tubular obstruction is the proximate cause of ΔP reduction. Obviously, GFR and thus ΔP were well maintained in the recipients of the present study. One may only speculate about the factors contributing to this preservation of GFR and ΔP. Besides a short ischaemia time, intraoperative volume expansion is shown to reduce the frequency of delayed graft function [10], and it is generally accepted to hydrate the recipients to a central venous pressure of 12–15 mmHg or a mean pulmonary artery pressure ≥ 20 mmHg. The mechanism of volume expansion in preventing ischaemic damage is not known, but volume expansion may prevent afferent renal vasoconstriction by reducing activity in the renin—angiotensin system [11], by increasing plasma levels of atrial natriuretic factor, and by reducing the sensitivity of the tubulo-glomerular feedback (TGF) mechanism [12].

Mannitol reduces the frequency of acute renal failure after renal transplantation [13], and has become an indispensable constituent of intraoperative hydration protocols. The combination of volume expansion and mannitol administration gives better protection than volume expansion alone [13], but the mechanism for this protective effect is not known. By its osmotic activity, mannitol induces plasma volume expansion, decreases both systemic and renal vascular resistance, and counteracts swelling of tubular cells. All these properties of mannitol may contribute to its protective effect against ischaemic renal injury. However, the mechanism(s) behind the protective effects of mannitol cannot be deduced from our study, but the results support the assumption that mannitol may protect against ischaemic injury by preventing reperfusion damage.

Frusemide is often included in the transplantation protocol, but studies on the protective effects of loop diuretics on ischaemic renal injury have produced contradictory results [14]. One reason may be that the haemodynamic events following administration of loop diuretics may vary depending on the individual’s volume status. Extracellular volume expansion with saline reduces the stimulatory effect of loop diuretics on renin release [15], and may thus reduce medullary ischaemia caused by angiotensin II [16]. Frusemide reduces NaCl reabsorption and oxygen consumption in the thick ascending limb of Henle’s loop (TALH), and may thus protect this segment against hypoxic injury. Simultaneously, it increases the oxygen availability for the S_{1} segment of the proximal tubule which normally competes with the TALH for a sparse supply of oxygen [17]. Heyman et al. [17] demonstrated in their study on isolated perfused rat kidneys that frusemide protected the S_{1} segment from hypoxic damage, and those results are in agreement with those of the present study showing small and short lasting increases in the excretion of NAG in the transplanted kidneys. The S_{1} segment is the main site for urinary NAG excretion [9].

One difference between the two types of kidney was that the transplanted kidney was denervated. Uninephrectomy increases diuresis and sodium excretion in the remaining kidney, and this effect is fast and reflex-mediated through reduced efferent sympathetic renal nerve activity to the remaining kidney [18]. Volume expansion has a similar effect on renal nerve activity [19], and the additional effect of uninephrectomy during volume expansion is probably negligible. Uninephrectomy also increases GFR and ERPF, but those are not acute effects [18] but develop over time. Maintained innervation in the remaining kidney is
therefore not likely to account for the differences in GFR and ERPF observed between the two kidneys during the first 3 h after surgery.

More surprising is the apparent lack of effect of the administration of CsA. CsA may cause acute renal vasoconstriction, renal hypoperfusion, and a fall in GFR and ERPF [20]. Furthermore, mannitol and frusemide may increase these adverse renal effects of CsA [21,22]. Angiotensin II augments CsA-induced renal vasoconstriction, and the effect of frusemide in this coherence is probably by activating the renin–angiotensin system [22]. Plasma volume expansion reduces both intrarenal levels of angiotensin II [11] and the stimulatory effect of loop diuretics on renin release [15], and thus reduces the vasoconstrictive effect of CsA on the renal vasculature. Despite high doses of CsA from 2 days before transplantation, we could not demonstrate any significant acute effects due to the administration of CsA. Although GFR and ERPF were not measured in connection with the CsA infusion 8 h postoperatively, neither GFR nor ERPF were changed 8–12 h post-infusion. Therefore, CsA administration seems to play a minor role, if any, in early transplant function in well-hydrated living donor recipients.

In conclusion, by the present transplantation procedure comprising short ischaemia time and substantial volume expansion combined with mannitol and frusemide administration, kidneys from living related donors regain nearly normal function within a few hours after transplantation.

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