Implantation Warm Ischemia Time in Kidney Transplant Recipients: Defining Its Limits and Impact on Early Graft Function

Background: Prolonged cold ischemia is an established risk factor for poor early graft function (EGF). However, warm ischemia incurring during graft implantation has received little attention regarding its possible detrimental effect on EGF. The aim of our study was to examine the impact of recipient warm ischemia time on EGF.

Material/Methods: The data of 102 consecutive kidney transplants were analyzed to determine the association between duration of graft implantation time (IT) and EGF. Recipient IT groups were (GI) up to 45 min, (GII) 45–60 min, and (GIII) >60 min. EGF was categorized as immediate (IGF), slow (SGF), or delayed graft function (DGF). In recipients with IGF, graft function was further assessed by time needed for reduction in serum creatinine by 50% (SC50) of pre-transplant value, and serum creatinine on day 7 (SCD7).

Results: Of a total of 102 recipients, 55 (55%) were in GI, 33 (32%) were in GII, and 14 (13%) were in GIII. Factors prolonging IT were recipient body mass index (BMI) (p=0.02) and multiple arteries in donor kidneys (p<0.01). No recipients in GI had DGF or SGF, while 2 in GII had DGF, and 5 patients in GIII had poor EGF. SC50 was significantly longer in GIII and GII versus GI (40.8±42.4 and 32.8±20.4 vs. 22.2±17.2 [p=0.02, p£0.01]), respectively. Mean SCD7 was also significantly higher in GIII and GII versus GI. The mean last serum creatinine was comparable among all groups.

Conclusions: IT of more than 45 min was a risk factor for poor EGF, but achieved statistical significance only when it exceeded 60 min. Longer IT also significantly slowed the fall in SC50, and led to a higher SCD7. However, poor EGF and suboptimal early SC trends had little long-term effect on serum creatinine.

MeSH Keywords: Delayed Graft Function • Reperfusion Injury • Warm Ischemia

Abbreviations: ATG – antithymocyte globulin; CI – confidence interval; DGF – delayed graft function; EGF – early graft function; IGF – immediate graft function; IT – implantation time; OR – odds ratio; SGF – slow graft function; SC50 – serum creatinine on day 7; SCD7 – time taken for reduction in serum creatinine by 50% of pre-transplant level; DBD – donation after brain death; DCD – donation after cardiac death

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Background

Prolonged cold ischemia has been shown to have a strong association with delayed graft function (DGF) and inferior long-term outcomes in deceased donor kidney transplantation [1–3]. However, little data is available on the effects of recipient warm ischemia time on early graft function (EGF). Evidence is now emerging that warm ischemia incurring during implantation may also be a risk factor for DGF, with poor outcomes not only in deceased donor but also in living donor kidney transplantation [4–9]. In living donors, warm ischemia occurs either during recovery [10,11] or at implantation of the kidneys, and, if prolonged, can result in poor EGF [8,9]. The aim of this study was to analyze the impact of implantation time (IT) on EGF, and its effect on the trend of serum creatinine in the early post-transplant period.

Material and Methods

All recipients who received living or deceased donor kidneys between March 2014 and March 2018 carried out in King Salman Armed Forces Hospital, Tabuk in Saudi Arabia were included in this study. Clinical and laboratory data was retrieved from the transplant database after approval from the Institutional Review Board. All donor kidneys were perfused with cold histidine-tryptophan-ketoglutarate solution, and then stored in the same solution for the duration of cold ischemia. All serum creatinine values are reported in µmol/L.

Informed consent was obtained from all individual participants included in the study for use of retrospective patient data.

Immunosuppression

Induction

Antithymocyte globulin (ATG) was used in all recipients. Recipients with zero human leucocyte antigen mismatches (HLA) received 1 dose of 1.5 mg/Kg, while all others received a cumulative dose of 6 mg/Kg. Methylprednisolone (500 mg) was used intraoperatively in all cases, and 3 daily doses of 250 mg were administered postoperatively. Only patients identified not to receive oral glucocorticoids received 2 extra doses of methylprednisolone.

Maintenance

All patients received tacrolimus, mycophenolate mofetil, and glucocorticoids, except for recipients over age 50 years, those with zero HLA mismatches, diabetes, negative panel reactive antibody, cardiovascular and bony complications, who did not receive oral glucocorticoids. All patients received universal CMV, pneumocystis, and gastric ulcer prophylaxis. Mechanical devices were used for prevention of thromboembolism, and no patients received anticoagulation.

Definitions

DGF was defined as requiring dialysis in the first week after transplant, and a serum creatinine >300 on post-operative day 5 was regarded as SGF [12]. Poor EGF was the presence of SGF or DGF, and absence of poor EGF was considered intermediate graft function (IGF). All deceased donors were donors after brain death (DBD). Expanded-criteria donor kidneys were defined as any kidney recovered from a deceased donor over age 60 years, or aged 50–59 years with at least 2 of the following conditions: a history of hypertension, a pre-donation serum creatinine of 1.5 mg/dl, or death from a cerebrovascular accident. Minimum follow-up was 3 months and ranged between 3 and 45 months. Serum creatinine was categorized as post-transplant time (hours) needed to achieve 50% reduction in pre-transplant serum creatinine (SC50) and that on post-transplant day 7 (SCD7). Graft function on follow-up was assessed by serum creatinine recorded at the last out-patient visit. Donor warm ischemia time was the time from clamping of the aorta or renal artery to cold perfusion. Cold ischemia extended from cold perfusion of the kidney to the start of the venous anastomosis. IT was calculated from the start of venous anastomosis to removal of clamps after completion of the arterial anastomosis.

Surgical procedures

All open-donor nephrectomies were performed via a 15 cm flank incision with extraperitoneal access to the kidney. Following removal, the kidney was immersed in cold histidine-tryptophan-ketoglutarate solution and flushed with the same cold heparinized solution. Kidneys were typically placed extra-peritoneally in the recipient iliac fossae, or placed intraperitoneally on more proximal vessels. All vascular anastomoses were end-to-side to the external iliac or more proximal vessels using polypropylene 6/0. Multiple arteries were anastomosed independently to the external iliac artery, and, rarely, a single lumen was created. All ureters were implanted by the Lich-Gregoire extra-vesical technique over a double J stent.

Data collection and analysis

Clinical and laboratory data and inpatient and out-patient records were assessed individually, and records of dialysis in the first week were reviewed in all cases to determine incidence of DGF. Based on IT, recipients were grouped as GI
(up to 45 min), GII (45–60 min), or GIII (>60 min). Early graft outcome was categorized as IGF, DGF, and SGF. In recipients with IGF, graft function was further assessed by SC50 and SCD7. Graft function on follow-up was assessed by serum creatinine at the last follow-up.

**Statistical methods**

We used SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA) for all statistical analyses. All categorical variables were described as absolute values and percentages. Significance of differences (p value) among groups was determined by chi-square test and Fisher exact test. Numerical variables were described as mean ±SD, and analyzed by one-way ANOVA. Odds ratio (OR) calculation and 95% CI (confidence interval) were determined for the risk of graft dysfunction for varying IT, and p values of <0.05 were considered statistically significant.

**Results**

There were 102 recipients in this cohort, mean age (years) was 40.2±16.7 (range: 2–75), and male to female sex ratio was 1.3: 1. Donor mean age (years) was 29±7.3 years (range: 18–53) and the male to female ratio was 12: 1. Of the donors, 73% (n=72) were living related, 16% (n=16) were unrelated, and 11% (n=12) were deceased donors (DBD). Eight percent (n=8) were re-transplants. Among all the recipients, 55% (n=56) were overweight [BMI >24.9], 25% (n=26) were obese [BMI >29.9], and 5% (5) had morbid obesity [BMI >34.9]. Multiple donor arteries were present in 16% (n=16). Seven recipients had poor EGF (6.8%), manifesting as DGF in 5 and SGF in 2. Thirty-three recipients (33%) received a steroid-sparing immunosuppressive regimen with 2 extra doses of 250 mg Methylprednisolone. There were 55 (55%) recipients in GI, 33 (32%) in GII, and 14 (13%) in GIII, and detailed demographics are given in Table 1. Factors significantly prolonging IT were recipient BMI (p=0.02) and multiple donor arteries (p<0.01). Two recipients in GI and 3 in GII had DGF, and SGF occurred in 2 recipients in GIII. No SGF or DGF was observed in GI (Table 2). A statistically insignificant number had poor EGF in GII (OR 0.35, 95% CI: 0.26 to 0.47, p=0.36). In GII, however, a statistically significant number had poor EGF [OR 0.13, 95% CI: 0.07 to 0.25, p<0.01]. The SC50 was significantly longer in GII and GI vs. GIII (40.8±42.4, 32.8±20.4, and 22.2±17.2 h, respectively, [p<0.01]) (Table 3). The mean SCD7 was also significantly higher in GII and GI vs. GI (111.7±58.1, 102.9±23.1, and 90.4±27.3 µmol/L), respectively [p<0.01] (Table 4). The mean last serum creatinine in the 3 groups was comparable, (GI – 84.3±21.3, GII – 96.2±28.5, and GIII – 93.4±31.0 µmol/L, respectively [p=0.80]) (Table 5). The table also shows the difference among groups in proportion of higher than normal values of last serum creatinine [GI vs. GII or GIII [p=0.19]]. Mean last serum creatinine in recipients with early graft dysfunction versus those with IGF was significantly higher (p=0.02), but the proportion of recipients with higher than normal last serum creatinine was comparable (p=0.19) (Table 5).

Two of the 3 deceased donor kidneys that developed DGF were expanded-criteria donor kidneys, 1 of which was lost 11 months after transplant. The second kidney recovered, and 21 months later, the serum creatinine was 159. The third, a standard-criteria kidney functioned well despite a cold ischemia time of 20 h and IT of 70 min, with last serum creatinine of 119 after 40 months. Four living donor recipients developed poor EGF; 2 had DGF and 2 SGF, and 3 of these were over age 60 years, with diabetes, body mass index (BMI) over 30, and with a history of cardiac revascularization. The 2 that developed DGF (right kidneys) had widespread atherosclerosis and calcification; the first, with IT of 65 min, suffered prolonged post-operative hypotension from an acute coronary event requiring early stenting, and the second, which had thrombosed external iliac veins, had IT of 97 min because the donor right kidney with 2 arteries was placed intraperitoneally on the proximal left common iliac vessels. Both kidneys were functioning well with last serum creatinine of 115 and 91 µmol/L after 8 and 7 months, respectively. Of the 2 living donor recipients with SGF, one had widespread atherosclerosis and received a small kidney, while the other had a BMI of 35, received a donor kidney with 3 arteries, and had an IT of 79 min, and 21 and 25 months later, their last serum creatinine was 170 and 61 µmol/L, respectively.

**Discussion**

Warm ischemia occurring during kidney recovery is termed donor warm ischemia, and that occurring during graft implantation is termed recipient warm ischemia. The latter is the subject of this study, which is also variously referred to as second warm ischemia, ex-vivo warm ischemia, re-warming ischemia, or anastomosis time. We have termed it implantation time, as it relates to this specific phase of the recipient procedure. Donor warm ischemia time is the time from clamping the vascular pedicle of the donor kidney to placing it in cold storage; it is generally short and of little consequence in open-donor nephrectomy. Kidneys recovered by laparoscopic procedure, however, have been shown to be an independent risk factor for DGF in many studies [10,11]. Donor warm ischemia is considered more damaging than recipient warm ischemia, as the donor kidney is warm in the former, while it is cold in the latter, and has a window of time before re-warming injury sets in [13]. The duration of IT extends from the time of removal of the kidney from cold storage to its reperfusion after un-clamping of recipient vessels. The realization that warm ischemia occurring during graft implantation has
| Number of patients in each group | GI (up to 45) | GII (45–60) | GII (60) | Significance of difference between means & percentages |
|---------------------------------|---------------|-------------|----------|-------------------------------------------------------|
| Recipient age (years)           |               |             |          | P=0.35                                               |
| Up to 25                         | 15 (27.3%)    | 6 (18.8%)   | 2 (13.3%)| P=0.54                                               |
| 26–59                            | 32 (58.2%)    | 22 (68.8%)  | 9 (60%)  |                                                       |
| >60                              | 8 (14.5%)     | 4 (12.5%)   | 4 (26.7%)|                                                       |
| Recipient gender                 |               |             |          | P=0.58                                               |
| Male                             | 34 (61.8%)    | 22 (66.7%)  | 8 (57.1%)|                                                       |
| Female                           | 21 (38.2%)    | 11 (33.3%)  | 6 (42.9%)|                                                       |
| Donor age (years)                |               |             |          | P=0.08                                               |
| Male                             | 30.6±7.3      | 28.4±6.1    | 25.8±8.9 |                                                       |
| Female                           |               |             |          |                                                       |
| Donor gender                     |               |             |          | P=0.11                                               |
| Male                             | 52 (94.5%)    | 27 (84.8%)  | 13 (93%) |                                                       |
| Female                           | 3 (5.5%)      | 5 (15.6%)   | 1 (7)    |                                                       |
| Recipient BMI                    | 24.6±5.2      | 28.4±5.4    | 25.1±5.3 | P=0.01                                               |
| Donor type                       |               |             |          |                                                       |
| LRD                              | 37 (68.3%)    | 26 (81.3%)  | 11 (73.3%)|                                                       |
| DD                               | 5 (9.1%)      | 5 (15.6%)   | 2 (13.3%)| P=0.15                                               |
| LURD                             | 13 (23.6%)    | 1 (3.1%)    | 2 (13.3%)|                                                       |
| Donor kidney side                |               |             |          | P=0.94                                               |
| Right                            | 23 (41.8%)    | 14 (43.8%)  | 7 (46.7%)|                                                       |
| Left                             | 32 (58.2%)    | 18 (56.3%)  | 8 (53.3%)|                                                       |
| Donor arteries No                |               |             |          | P=0.01                                               |
| Single                           | 54 (98.2%)    | 27 (84.4%)  | 5 (33.3%)|                                                       |
| Multiple                         | 1 (1.8%)      | 5 (15.6%)   | 10 (66.7%)|                                                       |
| HLA typing                       |               |             |          | P=0.84                                               |
| Zero mismatch                    | 3 (5.7%)      | 5 (16.1%)   | 1 (7.1%) |                                                       |
| Zero match                       | 1 (1.9%)      | 1 (3.2%)    | 0        |                                                       |
| Up to 6 mismatches               | 33 (62.3%)    | 21 (67.7%)  | 9 (64.3%)|                                                       |
| 6–11 mismatches                  | 16 (30.2%)    | 4 (12.9%)   | 4 (28.6%)|                                                       |
| PRA                              |               |             |          | P=0.43                                               |
| Negative                         | 6 (11.1%)     | 3 (9.7%)    | 0        |                                                       |
| Positive                         | 48 (88.9%)    | 28 (90.3%)  | 14 (100%)|                                                       |
| DSA                              |               |             |          | P=0.28                                               |
| Negative                         | 24 (63.0%)    | 24 (77.4%)  | 11 (78.6%)|                                                       |
| Positive                         | 20 (37.0%)    | 7 (22.6%)   | 3 (21.4%)|                                                       |
| Cold Ischemia (minute)           | 98.25±193.86  | 216.97±371.40 | 194.64±338.61 |                                                       |
| Donor Warm Ischemia(minutes)     | 2.83±1.15     | 2.86±1.9    | 4.13±3.1 | P=0.43                                               |
| Split function (donor kidney DTPA)|               |             |          |                                                       |
| Up to 43%                        | 6 (11.5%)     | 4 (14.8%)   | 4 (30.8%)| P=0.25                                               |
| >43%                             | 46 (88.5%)    | 23 (85.2%)  | 9 (69.2%)|                                                       |
| Immunosuppression                |               |             |          | P=0.20                                               |
| Steroid based                    | 39 (70.9%)    | 18 (56.3%)  | 12 (80.0%)|                                                       |
| Steroid sparing                  | 16 (29.1%)    | 14 (43.8%)  | 3 (20.0%)|                                                       |
| Follow up (months)               | 11.6±10.9     | 11.1±10.3   | 9.1±7.5  | P=0.69                                               |
a deleterious effect on EGF and long-term graft outcomes is recent [4–9], inspired by lessons learned in urology during partial nephrectomies in solitary kidneys [14]. There is a consensus in the transplant community about keeping graft IT to a minimum, but there is debate concerning its safe upper limit [4–9]. In a study by Marzouk, IT of less than 29 min was considered safe [4], while 30 and 34 min were deemed safe in 2 European studies [5,6]. In a recent large Dutch living-donor study, poor EGF was found in 13% with IT <30, 11% in IT of 30–45 min, and a 3-fold increased risk of graft loss when IT

| IT (minutes) | Upto 45 (GI) | 46–60 (GII) | >60 (GIII) |
|-------------|-------------|-------------|------------|
| No of cases | 55          | 33          | 14         |
| IGF         | 55 (100%)   | 31 (93.9%)  | 9 (64.3%)  |
| DGF         | 0           | 2 (6.1%)    | 0          |
| SGF         | 0           | 0           | 2          |
| Graft dysfunction (DGF+SGF) | 0 | 2 (6.1%) | 0 |

| Odd ratio for graft dysfunction: GI vs. GII | 0.3 | 95% Confidence interval [CI]: 0.27–0.47 | Significance P=0.35* |
| Odd ratio for graft dysfunction: GI vs. GIII | 0.14 | 95% Confidence interval [CI]: 0.08–0.425 | Significance P<.001** |

Table 2. Association between IT duration and graft dysfunction.

| Measured serum creatinine (Umol/L) | GI (Up to 45) | GII (45–60) | GIII (>60) | Significance |
|-------------------------------------|---------------|-------------|------------|--------------|
| Post-transplant time (hours) for 50% drop in pre-transplant level | No of cases 55 | 30 | 10 | Amongs all groups* Gl vs. GII** Gl vs. GIII** Gl vs. rest** |
| Mean ±STD | 22.2±17.2 | 32.8±20.4 | 40.8±42.4 | P=0.04 | P=0.01 | P=0.02 | P=0.04 |
| Post-transplant day 7 level | No of cases | 55 | 30 | 10 | P=0.01 | P=0.01 | P=0.01 | P=0.01 |
| Mean ±STD | 90.4±27.3 | 102.9±23.1 | 111.7±58.1 | |

* One-way Anova; ** Independent T-Test.

Table 3. Mean serum creatinine trends in early post-transplant period in all IT groups.

| Categories of recipients | IT time (minutes) | SC up to 115 µmol/L | Significance* | Odd ratio for SC >115 µmol/L | 95% confidence interval [CI] |
|--------------------------|------------------|---------------------|---------------|-------------------|-----------------------------|
| GI vs. rest              | 45 or less       | 47                  | 64%           | P=0.02            | 3.1                         | 1.1 | 8.2 |
|                         | >45              | 26                  | 36%           |                   |                             |
| GI vs. GII              | 45-60            | 21                  | 31%           | P=0.05            | 2.9                         | 1.0 | 8.3 |
|                         | 45 or less       | 47                  | 90%           |                   |                             |
|                         | >60              | 5                   | 10%           | P=0.03            | 5.2                         | 1.2 | 21.8 |

* Fisher Exact Test.

Table 4. Proportion of recipients with IGF normal vs. high post-transplant day 7 serum creatinine.
was >45 min [8]. This indicates that even IT <30 min may not be entirely safe and could compromise EGF, which suggests that there may be other factors besides IT that influence EGF. The safe upper limit of IT in our study was 45 min, which is longer than that reported in the literature. This favorable outcome in our cohort could be due to several factors, including the very short donor warm ischemia of open nephrectomy, the universal use of ATG, which is known to preserve the microcirculation and reduce ischemia reperfusion injury [15], and the cooling measures taken during graft implantation to delay rewarming. Separate anastomoses that we performed for multiple donor arteries and a higher BMI likely contributed to the longer IT in our study, and it may be that our IT was different because calculating IT is not standardized.

Surprisingly, lowering donor kidney temperature during implantation has not been given due importance, despite its significant bearing on making prolonged IT safer. Following its removal from ice at 4°C, the kidney re-warms at a rate of 0.5°C per minute and would take about 60 min to reach 34°C [16], and delaying re-warming could help make longer IT safer. During implantation, we wrapped kidneys in slush-filled swabs along with irrigation with cold saline. Using customized polythene bags with crushed ice, Pupka et al. compared outcomes in kidneys from the same deceased donor, cooling one and using standard technique for the other [17]. Their mean IT was 23.6±8.1 min, the cooled kidney had a lower incidence of DGF (26% vs. 61%, p=0.015), and a 40% higher day 14 eGFR (p=0.026), and they concluded that reducing warm ischemia by cooling during IT had better outcomes. This is in line with our findings that IT up to 45 min, or even beyond, is safe, provided there is an efficient method of cooling during implantation. Clearly, an unhurried and meticulously performed anastomosis is the most critical step in obtaining optimal graft perfusion and function.

To draw valid inferences when studying the impact of IT on graft outcome, consideration should also be given to other variables like donor type and kidney quality. Thus, kidneys from donors after circulatory death may have poorer outcomes than kidneys from donors after brain death because of the considerably longer donor warm ischemia in the former, and the fact that living donor kidneys can better tolerate longer IT than deceased donor kidneys because of the shorter cold ischemia and better kidney quality. Our study aimed to detect both overt and subtle detrimental effects of recipient warm ischemia on the graft. We considered such a detailed analysis necessary because even minor graft injury can have grave consequences in the recipient. In that context, the significance of our results, calculated by the available statistical tools, needs cautious interpretation because even those reported as statistically insignificant could still have significant clinical importance. In assessing EGF, we did not rely on traditional statistical tests, but rather on the raw data and their clinical relevance. An additional limitation is the variable use of postoperative protocol therapy, which could have influenced our results. To overcome this, we performed an analysis of variance (ANOVA) to compare the mean serum creatinine (SC) levels among different groups of patients, and found significant differences between the groups. The results are presented in Table 5.

### Table 5. Mean serum creatinine and frequency of normal/high values on last follow-up.

| Cohort          | GI (Up to 45) | GII (45–60) | GIII (>60) | Significance |
|-----------------|---------------|-------------|------------|--------------|
| No of cases     | 55            | 32          | 14         | One-way Anova |
| Mean SC µmol/L  | 84.3±21.3     | 96.1±28.4   | 93.3±30.8  | P=0.09       |
| SC within normal range (115 µmol/L or less) | | | | |
| 50 (91%)        | 26 (81%)      | 11 (79%)    |            | Gi vs. GII   |
| SC above normal range (>115 µmol/L) | 5 (9%) | 6 (19%) | 3 (21%) | Gi vs. rest |

### IGF vs. graft dysfunction (DGF or SGF)

| IGF | DGF | Significance | Risk estimates |
|-----|-----|--------------|----------------|
| Total No of cases | 95 | 6 | |
| Mean SC µmol/L | 87.8±23.7 | 112.8±41.7 | P=0.02 | 95% CI |
| SC within normal range (115 µmol/L or less) | 83 (87%) | 4 (67%) | P=.19 | Odd ratio |
| SC above normal range (>115 µmol/L) | 12 (13%) | 2 (33%) | |

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solely on the incidence of SGF and DGF, but also examined IGF, comparing the effect of varying durations of IT on SC50 and SCD7. Similarly, for longer-term graft function, we used mean last serum creatinine and compared the number with normal or higher than normal values. Details of all the above parameters are given in Tables 2–4. In cases with IGF, we found that longer IT slowed the fall in SC50, led to a higher SCD7, and had a lower number with normal serum creatinine on day 7. Similarly, the mean last serum creatinine was also higher with longer IT, and in those with poor EGF, with a greater number of cases with values above normal, but this difference was not statistically significant.

This study has the limitations of a single-center retrospective analysis, and smaller numbers in GIII may have affected statistical analysis. The risk of selection bias was low because cases were consecutive and all data were recorded. Since our primary objective was to examine the impact of IT on poor EGF, the follow-up may not have been long enough to document its longer-term consequences. The issues raised in the study need to be validated by examination of a larger multicenter cohort. However, the inferences drawn from our study are worth considering for practicing surgeons, developing strategies to minimize warm ischemia and make longer IT safe, and seeking to improve graft function and outcomes.

**Conclusions**

IT of more than 45 min was a risk factor for poor EGF, which achieved statistical significance only when it exceeded 60 min. Longer IT also significantly slowed the fall in SC50, and led to a higher SCD7. However, poor EGF and suboptimal early SC trends had little long-term effect on serum creatinine.

**Conflict of interest**

None.

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