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The Impact of Warm Ischemia Time on Kidney Function in Experiment

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Abstract

Background: The main difficulty with donation after circulatory death is the inevitable period of warm ischemia, which may adversely affect tissue viability and graft function after transplantation. The aim of this study was to evaluate dynamic changes in the functional parameters of the kidneys because of renal warm ischemia (RWI) in the experiment.

Methods and Results: The experiments were carried out on 78 white male rats weighing 214.5±31.8g. To achieve the study's aim, we applied a method of modeling the intraoperative RWI by clamping renal arteries from both sides through a median laparotomy under ether anesthesia. Vascular clamping lasted 12, 24, 36, or 48 minutes in four experimental groups of rats, each containing 18 rats. The intact group of rats became the control group (n=6). In each of the 4 experimental groups, rats were euthanized by decapitation on Days 3, 7, and 14 of the experiment. Before euthanasia, a 24-hour urine collection was performed in metabolic chambers. Laboratory tests included the determination of blood urea nitrogen (BUN), serum creatinine (sCR), serum potassium (SP), and urinary creatinine (uCr); glomerular filtration rate (GFR) was calculated using the Rehberg-Tareev method.

Warm ischemia time (WIT) for no more than 12 minutes did not lead to significant negative changes in most of the studied parameters of renal function at all time stages of the experiment, with the exception of a significant decrease in GFR, as well as an increase in SP levels on Days 3 and 7 of the experiment. The WIT up to 24 minutes led to a more pronounced drop in GFR at all time stages of the experiment (P<0.05 in all cases), as well as a moderate increase in the levels of BUN and SP and a decrease in uCr levels on Days 3 and 7 (P<0.05 in all cases). The WIT up to 36 minutes led to a drop in GFR by 84% and 86% on Days 3 and 7 of the experiment, as well as a decrease in diuresis, an increase in levels of BUN and SP, as well as a twofold decrease in uCr, compared to the control at the specified time intervals (P<0.05 in all cases). The WIT up to 48 minutes led to a drop in GFR by 95%, 97%, and 100% on Days 3, 7, and 14 of the experiment, respectively (P<0.05 in all cases). The drop in diuresis worsened on Days 3 and 7 to anuria on Day 14 (P<0.05 in all cases). The levels of BUN and SP increased from Day 3 to Day 14, and uCr dropped significantly to zero on Day 14 (P<0.05 in all cases).

Conclusion: Among all parameters analyzed, GFR was the early and most sensitive indicator of renal dysfunction in RWI. A 12-minute WIT leads to a slight decrease in renal function on Days 3 and 7, which is relatively restored by Day 14. The 24-minute and 36-minute WIT leads to a noticeable decrease in renal function with a tendency to recover on Day 14. The 48-minute WIT leads to a sharp decline in renal function, progressing on Day 7 and reaching critical changes by Day 14 of the experiment. **(International Journal of Biomedicine. 2024;14(2):295-299.)**

Keywords: kidney transplantation • donation after circulatory death • warm ischemia time • glomerular filtration rate

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Abbreviations

BUN, blood urea nitrogen; **sCr**, serum creatinine; **uCr**, urinary creatinine; **DGF**, delayed graft function; **DCD**, donation after circulatory death; **GFR**, glomerular filtration rate; **HR**, hazard ratio; **RWI**, renal warm ischemia; **SP**, serum potassium; **WIT**, warm ischemia time.

Introduction

Kidney transplantation has a history of more than half a century and is still developing. In terms of a patient's lifespan and quality of life, the effectiveness of alternative renal replacement therapies other than kidney transplantation has been shown to be comparably low.[1] Kidney transplantation is accepted as alone the most optimal radical therapy for end-stage renal disease.[2,3] However, there is a chronic shortage of cadaveric organ donors for renal transplantation,[4] which might be solved using donation after circulatory death (non-heart-beating donation).[5-9] In contrast, a conventional heart-beating donor is one who sustains an irreversible brain injury, and death is based on neurologic criteria.[10]

Donation after circulatory death (DCD) can be categorized into 2 groups: controlled (cDCD) and uncontrolled (uDCD).[8] cDCD takes place when the death occurs within an intensive care unit/hospital setting, and cDCD occurs in a controlled fashion with surgical team assembly before a planned withdrawal of life-sustaining therapy. uDCD takes place when death occurs outside the hospital or within the emergency room after an unexpected cardiac arrest and resuscitative efforts fail. uDCD is identified as a significant potential source of organ donors in the out-of-hospital cardiac arrest population, but significant operational, ethical, logistical, and legal barriers exist across most jurisdictions.[11]

It is well established that living donor kidney transplants are associated with superior post-transplant outcomes, compared with deceased donor transplants.[12] According to the Scientific Registry of Transplant Recipients (SRTR) report, from 2010 to 2014, the unadjusted one-year allograft survival rate for recipients of a first deceased donor kidney transplant was 93.4%. The five-year unadjusted allograft survival rate for a primary deceased donor transplant was 72.4% among transplant recipients from 2005 to 2009. In recipients undergoing a primary living donor kidney transplant, the one-year unadjusted allograft survival rate was 97.2%. The five-year unadjusted allograft survival rate for a first living donor kidney transplant was 84.6%.

Early identification and treatment of surgical complications are critical for patient and graft survival.[13] The main difficulty with DCD is the inevitable period of warm ischemia, which may adversely affect tissue viability and graft function after transplantation.[14]

The aim of this study was to evaluate dynamic changes in the functional parameters of the kidneys because of renal warm ischemia (RWI) in the experiment.

Materials and Methods

The experiments were carried out on 78 white male rats weighing 214.5±31.8g. The experiments were performed in accordance with the norms for the humane treatment of animals, which are regulated by the International Guidelines of the Association for the Assessment and Accreditation of Laboratory Animal Care, following the protocol approved by the Institutional Animal Care and Use Committee at the Republican Research Center of Emergency Medicine (Tashkent, Uzbekistan).

The rats were allowed free access to standard rat chow and water. To achieve the study's aim, we applied a method of modeling the intraoperative RWI by clamping renal arteries from both sides through a median laparotomy under ether anesthesia. Vascular clamping lasted 12, 24, 36, or 48 minutes in four experimental groups of rats, each containing 18 rats (Group 1, Group 2, Group 3, and Group 4). Clamping of the arteries was carried out by temporarily ligating with a special loop (like an end-loop) of the renal hilum. Surgical procedures were performed on a heated pad to avoid cold-induced hemodynamic alterations. After the laparotomy, the wound was sutured tightly. The intact group of rats became the control group (n=6). There was no significant difference in age and weight between all groups. The rats' condition was monitored daily, with a qualitative determination of the presence of diuresis and recording changes in body weight. In each of the 4 experimental groups, rats were euthanized by decapitation on Days 3, 7, and 14 of the experiment. Thus, 3 subgroups (Subgroup A, Subgroup B, and Subgroup C, with 6 rats in each subgroup) were formed for each experimental group. Before euthanasia, a 24-hour urine collection was performed in metabolic chambers. Laboratory blood tests included the determination of BUN, sCR, and SP; uCr was also measured; GFR was calculated using the Rehberg-Tareev method.

Statistical analysis was performed using the statistical software package SPSS version 23.0 (SPSS Inc, Armonk, NY: IBM Corp). The Mann-Whitney U Test was used to compare the differences between the two independent groups A probability value of $P<0.05$ was considered statistically significant.

Results

During the experiment, all rats from Groups 1 and 2 survived until the planned date of euthanasia. In Group 3, 2(11.1%) rats died on Days 7 and 8. In Group 4, death was observed in 5(27.8%) cases on Days 7, 8, 10, 11 and 12 of the experiment. Autopsy of dead rats on Days 7 and 8 revealed the presence of thrombosis of the inferior vena cava, starting from the right renal vein and reaching the chambers of the heart and pulmonary artery. Congestion and an increase in the size of the liver and right kidney were noted. This was due to the short right renal vein and increasing thrombosis of the inferior vena cava as a result of prolonged ligation of the right renal hilum. After autopsying dead rats on Days 10-12, a decrease in and pallor of kidney parenchyma, dilation of the heart chambers, swelling of the lung tissue, and ascitic fluid in the abdominal cavity were noted to varying degrees.

Table 1 presents the functional parameters of the kidney on different days of the experiment. In Group 1, daily diuresis showed a significant increase in Subgroups B and C, compared to the control group ($P=0.048$ and $P=0.042$, respectively). In Group 2, a decrease in diuresis in all subgroups was insignificant ($P>0.05$ in all cases). In Group 3, a significant reduction in daily diuresis was found in Subgroups A and

B (P=0.048 and P=0.023, respectively); this reduction was without statistical significance in Subgroup C, compared to the control group (P=0.077). In Group 4, there was a sharp decrease in daily diuresis in Subgroups A and B, and we found anuria in Subgroup C (P=0.047, P=0.038, and P=0.031, respectively).

The BUN level did not change significantly in all subgroups of Group 1 (P>0.05 in all cases). In Group 2, we found a significant increase in BUN level in Subgroups A (P<0.05) and B (P<0.05), but in Subgroup C, BUN level returned to control value (P=0.275). In the subgroups of Group 3, we found changes like Group 2. In subgroups of Group 4, the increase in the BUN level was the most significant, and in Subgroup C, the BUN level increased almost 7 times, compared to the control (P=0.038).

The sCr level remained within the normal range in Groups 1-3 in all subgroups. At the same time, in Group 4, there was a gradual increase in the sCr level in Subgroups A and B, with a sharp rise in Subgroup C, compared to the control (P=0.031).

The SP increased significantly, compared to the control group in Subgroups A and B of all groups (P<0.05 in all cases). By Day 14 of the experiment, we found a decrease to normal levels in Groups 1-3, except for Group 4, where SP was 10.10±1.04 mmol/L vs. 5.1±0.16 mmol/L in the control (P=0.044).

The uCr level was within the normal limits in all subgroups of Group 1. At the same time, it decreased significantly in Subgroups A and B of Group 2, and this decrease was more pronounced in Subgroups A and B of Group 3. We found the most pronounced decrease in uCr levels in Group 4 to complete absence in Subgroup C.

During RWI, a decrease in GFR was observed in all subgroups of all 4 experimental groups, and the degree of decline increased from Group 1 to Group 4 to zero in Subgroup C of Group 4 (P<0.05 in all cases).

Table 1.

The functional parameters of the kidney on different days of RWI in the experiment.

	Control group (0)	Group 1 (1)	Group 2 (2)	Group 3 (3)	Group 4 (4)	P-value
Diuresis, ml/day						
Day 3 (Subgroup A)	5.30±1.10	5.08±0.24	4.73±0.38	3.31±0.32	1.50±0.40	P_{0-1}=0.827; P_{0-2}=0.513; P_{0-3}=0.048; P_{0-4}=0.047;
Day 7 (Subgroup B)		6.70±0.14	3.78±0.63	2.80±0.09	1.30±0.05	P_{0-1}=0.048; P_{0-2}=0.127; P_{0-3}=0.023; P_{0-4}=0.038;
Day 14 (Subgroup C)		6.80±0.39	4.83±0.12	3.63±0.58	0.00±0.00	P_{0-1}=0.042; P_{0-2}=0.827; P_{0-3}=0.077; P_{0-4}=0.031;
BUN, µmol/L						
Day 3 (Subgroup A)	6.08±0.54	5.79±1.03	8.09±0.36	8.5±0.04	15.2±2.37	P_{0-1}=0.827; P_{0-2}=0.049; P_{0-3}=0.023; P_{0-4}=0.047;
Day 7 (Subgroup B)		5.22±0.68	9.07±2.06	9.6±0.92	15.3±4.72	P_{0-1}=0.121; P_{0-2}=0.045; P_{0-3}=0.042; P_{0-4}=0.033;
Day 14 (Subgroup C)		4.92±0.23	6.5±0.20	6.8±1.12	42.3±0.03	P_{0-1}=0.055; P_{0-2}=0.275; P_{0-3}=0.509; P_{0-4}=0.038;
sCr, µmol/L,						
Day 3 (Subgroup A)	59.07±5.15	51.40±0.60	57.03±2.76	59.60±8.07	66.35±3.65	P_{0-1}=0.055; P_{0-2}=0.412; P_{0-3}=0.827; P_{0-4}=0.127;
Day 7 (Subgroup B)		49.93±5.44	58.55±4.15	62.80±2.87	70.2±14.25	P_{0-1}=0.227; P_{0-2}=1.000; P_{0-3}=0.487; P_{0-4}=0.275;
Day 14 (Subgroup C)		45.00±4.12	55.70±6.75	58.35±2.25	225.0±20.64	P_{0-1}=0.055; P_{0-2}=0.273; P_{0-3}=0.787; P_{0-4}=0.031;
SP, mmol/L						
Day 3 (Subgroup A)	5.1±0.16	6.37±0.32	6.62±0.83	7.04±0.63	7.60±1.18	P_{0-1}=0.041; P_{0-2}=0.045; P_{0-3}=0.049; P_{0-4}=0.047;
Day 7 (Subgroup B)		5.99±0.09	7.07±0.12	7.08±0.81	8.39±0.87	P_{0-1}=0.038; P_{0-2}=0.045; P_{0-3}=0.044; P_{0-4}=0.046;
Day 14 (Subgroup C)		5.50±0.92	6.42±0.64	6.89±1.15	10.10±1.04	P_{0-1}=0.529; P_{0-2}=0.052; P_{0-3}=0.058; P_{0-4}=0.044;
uCr, µmol/L						
Day 3(Subgroup A)	504.51±67	437.01±0.98	313.57±52.52	236.37±69.49	186.30±39.24	P_{0-1}=0.513; P_{0-2}=0.049; P_{0-3}=0.047; P_{0-4}=0.037;
Day 7(Subgroup B)		502.20±0.33	284.35±11.85	246.15±11.05	122.50±0.48	P_{0-1}=0.487; P_{0-2}=0.041; P_{0-3}=0.036; P_{0-4}=0.042;
Day 14 (Subgroup C)		512.40±0.28	445.20±13.90	402.10±66.40	0.0±0.0	P_{0-1}=0.474; P_{0-2}=0.431; P_{0-3}=0.127; P_{0-4}=0.036;
GFR, µl/min						
Day 3 (Subgroup A)	55.97±1.20	30.01±2.38	18.04±0.99	9.10±0.09	2.9±0.07	P_{0-1}=0.033; P_{0-2}=0.023; P_{0-3}=0.041; P_{0-4}=0.029;
Day 7 (Subgroup B)		46.79±1.15	12.70±0.31	7.6±0.03	1.6±0.1	P_{0-1}=0.028; P_{0-2}=0.034; P_{0-3}=0.042; P_{0-4}=0.038;
Day 14 (Subgroup C)		53.77±3.11	26.80±0.11	17.3±1.28	0.0±0.0	P_{0-1}=0.044; P_{0-2}=0.024; P_{0-3}=0.043; P_{0-4}=0.034;

Discussion

It is assumed that ischemic damage and DGF lead to a decrease in the number of functioning nephrons, and an inadequate "amount" of nephrons causes graft dysfunction in the late period.[15] According to Weight et al.,[16] the rat model demonstrated different renal changes depending on the RWI time: mild morphological changes (15-30 minutes), which became moderate (45 minutes) and severe with the presence of impaired glomerular perfusion, apoptosis, and pyknotic nuclei (60 minutes). In a study by Arefjev et al.,[17] ischemic damage to the donor kidney is morphologically manifested by acute tubular necrosis. The main target in ischemic damage to the donor kidney is tubular epithelial cells, because of which acute kidney injury develops.[18] Most of the studies indicated that WIT longer than 30 minutes should be considered as a major, potentially modifiable risk factor for inferior long-term results after kidney transplantation.[19]

Tennankore et al.,[20] in a study on 131,677 kidney transplant recipients, found that WIT >30 minutes was associated with a statistically higher adjusted relative hazard for the composite event of death or graft failure. In the case of WIT >60 minutes, a 23% increase in the adjusted relative hazard for death or graft failure was observed. Donor WIT >20 minutes was also found to correlate with increased delayed graft function.[21]

Donation after circulatory death (DCD) donors are an important source of kidneys for transplantation. In a study by Gill et al.,[22] among the 12,831 DCD kidneys transplanted, kidneys with WIT ≤48 minutes had survival like that of kidney transplants from brain-dead donors. DCD kidneys with WIT > 48 minutes had a higher risk of allograft failure (HR = 1.23; 95% CI: 1.07 - 1.41).

A study by Chen et al.[23] included 11,907 DCD kidney transplants. Compared to kidneys with WIT <60 minutes, kidneys with WIT 60-79 minutes had similar rates of graft failure (HR = 0.95, 95% CI: 0.67-1.37), whereas those with WIT ≥80 minutes had 1.66 times more failure (HR = 1.66, 95% CI: 1.16-2.38, P<0.05). One-year (90±0.3%, 87±2.7% vs. 82.1±4.2%) and 5-year (69.4±0.6%, 79.0±4% vs. 62.0±6.8%) survival were greater in kidneys with WIT <60 minutes and 60-79 minutes, compared to those with WIT ≥80 minutes, respectively.

In our study, WIT for no more than 12 minutes did not lead to significant negative changes in most of the studied parameters of renal function at all time stages of the experiment, with the exception of a significant decrease in GFR, as well as an increase in SP levels on Days 3 and 7 of the experiment.

The WIT up to 24 minutes led to a more pronounced drop in GFR at all time stages of the experiment, as well as a moderate increase in the levels of BUN and SP and a decrease in uCr levels on Days 3 and 7.

The WIT up to 36 minutes led to a drop in GFR by 84% and 86% on Days 3 and 7 of the experiment, as well as a decrease in diuresis, an increase in levels of BUN and SP, as well as a twofold decrease in uCr, compared to the control at the specified time intervals.

The WIT up to 48 minutes led to a drop in GFR by 95%, 97%, and 100% on Days 3, 7, and 14 of the experiment, respectively. The drop in diuresis worsened on Days 3 and 7 to anuria on Day 14. The levels of BUN and SP increased from Day 3 to Day 14, and uCr dropped significantly to zero on Day 14.

Conclusion

Among all parameters analyzed, GFR was the early and most sensitive indicator of renal dysfunction in RWI. A 12-minute WIT leads to a slight decrease in renal function on Days 3 and 7, which is relatively restored by Day 14. The 24-minute and 36-minute WIT leads to a noticeable decrease in renal function with a tendency to recover on Day 14. The 48-minute WIT leads to a sharp decline in renal function, progressing on Day 7 and reaching critical changes by Day 14 of the experiment.

Competing Interests

The authors declare that they have no competing interests.

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