Research Square

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Prolonged Ex Vivo Normothermic Machine Perfusion of an Uncontrolled Donation After Circulatory Death Kidney Graft Using a Hemoglobin-Based Oxygen Carrier beyond 53 Hours

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Abstract

Background: Normothermic machine perfusion (NMP) has emerged as a promising technology in organ transplantation by enabling physiological preservation, real-time viability assessment, and therapeutic intervention during ex vivo organ maintenance. Although prolonged ex vivo preservation has been successfully achieved in liver transplantation, the application of NMP in kidney grafts remains limited, particularly for marginal kidneys from uncontrolled donation after circulatory death (uDCD) donors. Extending kidney preservation time may facilitate long-distance organ transportation, improve the utilization of marginal grafts, and provide a platform for graft repair and pre-transplant therapeutic interventions.

Methods: We developed a portable normothermic kidney perfusion system using a hemoglobin-based oxygen carrier (HBOC) instead of human red blood cells and performed prolonged ex vivo preservation of a discarded left kidney graft from a uDCD donor. Hemodynamic parameters, biochemical profiles, urine production, and histological changes associated with kidney injury and inflammation were continuously evaluated during perfusion. The contralateral kidney preserved with University of Wisconsin (UW) solution at 4°C served as a cold storage control.

Results: The kidney graft was successfully maintained under NMP for 53 hours with stable perfusion conditions. Mean perfusion pressure and flow were maintained at 62.38 ± 7.51 mmHg and 125.13 ± 20.40 mL/min, respectively, with perfusate temperature maintained between 32.5°C and 33.5°C. The renal vascular resistance index remained stable (0.50 ± 0.12 mmHg/mL/min). The HBOC-based oxygen delivery system maintained adequate oxygenation throughout perfusion. Perfusate creatinine levels remained relatively stable, while lactate levels initially increased and subsequently returned to normal levels after prolonged perfusion, suggesting recovery of renal metabolic activity. Cumulative urine output reached 1267 mL by the end of perfusion.

Histological evaluation demonstrated no significant progression of glomerulosclerosis, tubular atrophy, or interstitial fibrosis. Compared with cold storage, NMP was associated with reduced progression of tubular injury, although mild tubular degeneration and inflammatory changes developed during prolonged perfusion. After approximately 32 hours of perfusion, renal resistance, blood flow, biochemical parameters, and histological findings demonstrated progressive improvement, whereas deterioration was observed with further extension of perfusion duration. however, they gradually deteriorated after 32 hours.

Conclusion: This study demonstrates the feasibility of prolonged blood-free normothermic machine perfusion for maintaining the viability of a marginal uDCD kidney graft for more than 53 hours ex vivo. HBOC-based NMP may provide a promising platform for extended kidney preservation, real-time graft assessment, and future development of organ repair strategies. Further studies using larger cohorts and transplantation models are required to validate its clinical applicability. it is recommended that the perfusion preservation time of ex vivo kidneys should not exceed 32 hours.

1. Introduction

Kidney transplantation remains the optimal treatment for patients with end-stage kidney disease; however, the persistent shortage of donor organs continues to limit access to transplantation worldwide. To expand the donor pool, increasing attention has been directed toward the utilization of marginal kidney grafts, including organs from extended criteria donors (ECDs) and donors after circulatory death (DCD)[1]. Nevertheless, these grafts are associated with more serious ischemic injury, increased susceptibility to delayed graft function (DGF), and a higher risk of primary non-function, which restricts their broader clinical application[2–4].

Currently, static cold storage (SCS) remains the most widely used method for kidney preservation due to its simplicity and reliability[5–7]. However, hypothermic conditions substantially suppress cellular metabolism and do not adequately reproduce the physiological environment required for maintaining organ function[8]. Consequently, SCS provides limited opportunities for real-time assessment of graft viability or therapeutic intervention before transplantation[9]. Although hypothermic machine perfusion (HMP) has improved outcomes in kidney transplantation, particularly among marginal grafts, it remains limited by reduced metabolic activity and restricted capacity for active organ repair[10–12].

Normothermic machine perfusion (NMP) has emerged as a promising strategy that maintains organs under physiological conditions, allowing continuous metabolic support[13], functional evaluation[14], and potential therapeutic manipulation during ex vivo preservation[15]. In liver transplantation, NMP has already demonstrated clinical feasibility and has substantially extended preservation duration, while also enabling objective assessment of marginal graft quality[16]. However, compared with liver grafts, the application of prolonged NMP in kidney transplantation has progressed more slowly, largely due to the complex renal microvascular structure, limited regenerative capacity, and challenges associated with maintaining long-term ex vivo renal function[17].

Prolonging the ex vivo preservation period of kidney grafts may provide several important clinical advantages. First, extended preservation could facilitate long-distance organ transportation and improve donor-recipient matching[18]. Second, it may create a therapeutic window for repairing marginal grafts through pharmacological intervention[19], cell-based therapy[20], gene delivery[21], or other regenerative approaches before transplantation[22]. Therefore, developing reliable long-term kidney NMP platforms represents an important step toward transforming organ preservation from a passive storage process into an active organ assessment and repair strategy.

A major challenge for prolonged normothermic perfusion is the requirement for an effective oxygen delivery system[23]. Conventional NMP protocols frequently rely on human red blood cells as oxygen carriers; however, long-term ex vivo perfusion using blood products carries potential limitations, including hemolysis, electrolyte imbalance, inflammatory responses, infection risks, and logistical constraints related to blood availability. Hemoglobin-based oxygen carriers (HBOCs) provide a potential alternative by enabling oxygen delivery without dependence on human blood products, which may improve the feasibility and safety of prolonged organ perfusion[24–27].

In this study, we developed a portable normothermic kidney perfusion system using an HBOC-based oxygen carrier and evaluated the feasibility of prolonged ex vivo preservation of a discarded uncontrolled DCD (uDCD) kidney graft. Through continuous monitoring of hemodynamic parameters, biochemical changes, urine production, and histological alterations, we aimed to determine whether blood-free NMP could maintain kidney graft viability during extended preservation and provide a potential platform for future organ repair and translational therapeutic strategies.

2. Materials and Methods

2.1 Study design and ethical approval

This single-center prospective study evaluated the feasibility of prolonged ex vivo normothermic machine perfusion (NMP) of a discarded uncontrolled donation after circulatory death (uDCD) kidney graft. The study protocol was reviewed and approved by the Research Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University. Written informed consent was obtained from the donor's family for the use of the discarded kidney graft for research purposes.

During the perfusion process, continuous assessments were performed, including hemodynamic parameters, biochemical profiles, urine production, histological changes, and markers associated with renal injury and inflammation. The contralateral kidney preserved using University of Wisconsin (UW) solution at 4°C was used as a cold storage control.

2.2 Normothermic machine perfusion system and perfusion protocol

A portable kidney normothermic machine perfusion system (TH-LS KID100, True Health Medical Technology Development Co., Ltd.) was used for ex vivo kidney preservation (Fig. 1). The device was designed with a compact portable structure and incorporated an active magnetic levitation pump, automated temperature regulation, pressure maintenance control, and closed kidney storage chamber.

The renal artery was connected to the perfusion circuit through a clamp-type connector. Venous effluent drained continuously into the reservoir within the organ chamber and was subsequently returned to the circulation through the oxygenator and pump system. Urine was collected through an 8-Fr ureteral catheter and was not recirculated into the perfusion circuit.

The perfusion system continuously monitored oxygen saturation, mean perfusion pressure, arterial flow rate, renal vascular resistance index (RVRI), and perfusate temperature.Perfusion was performed under a pressure-controlled mode. Perfusion pressure was gradually increased until the mean arterial pressure reached approximately 60 mmHg. The target perfusion temperature was set at 34°C.

2.3 Perfusate composition and oxygen delivery strategy

The perfusion solution consisted of two units of a hemoglobin-based oxygen carrier (HBOC, XY-101), 500 mL balanced crystalloid solution, 12,500 IU heparin, Sulbactam and Cefoperazone 1.5g, 20 mL of 8.4% sodium bicarbonate, and 40 mg methylprednisolone, with a total perfusate volume of approximately 1000 mL.

Oxygenation was achieved using an oxygenator (Weigao Medical Technology Co., Ltd.; model not specified). Room air containing 21% oxygen was manually supplied at a flow rate of 1 L/min, maintaining perfusate oxygen saturation above 95%.

The perfusate was continuously supplemented according to urine output. Verapamil was continuously infused as a vasodilator at a rate of 0.2 mg/h. Sodium bicarbonate was administered when required to maintain perfusate pH above 7.30, and 5% glucose was supplemented when necessary to maintain perfusate glucose concentrations above 100 mg/dL.Blood gas analyses of the perfusate were performed using the epoc® blood analysis system (Siemens Healthineers).

2.4 Sample collection and biochemical assessment

Perfusate samples were collected hourly during the first 6 hours of perfusion and subsequently every 2 hours thereafter. Biochemical parameters, including pH, oxygen partial pressure, carbon dioxide partial pressure, lactate, electrolytes, creatinine, and urea concentrations, were monitored throughout the perfusion period.

Renal tissue samples were collected at the following time points:baseline (T0), 1 h, 3h, 6 h, 12h, 24h, 48h, and 72 h after initiation of NMP. Cortical tissue samples measuring approximately 1 × 1 × 1 mm were collected and immediately preserved in RNAprotect® reagent (Qiagen) for 24 hours before storage at − 80°C for subsequent analysis.When biopsy sampling resulted in bleeding, the sampling site was carefully sutured to prevent leakage and minimize interference with renal perfusion.

2.5 Histological evaluation

To evaluate the severity of acute tubular necrosis (ATN), renal tissue injury was graded using a five-level scoring system:

- ATN grade 0: normal renal tissue without evidence of tubular necrosis;
- ATN grade 1: rare necrotic tubules identified within the renal cortex;
- ATN grade 2: scattered and focal tubular necrosis involving a small number of tubules;
- ATN grade 3: easily identifiable clusters of necrotic tubules within the renal cortex;
- ATN grade 4: extensive and widespread tubular necrosis.

Additional histological parameters, including glomerulosclerosis, tubular atrophy, interstitial fibrosis, tubular degeneration, inflammatory infiltration, and microthrombus formation, were evaluated during the perfusion period.

2.3 Statistical Analysis

Data are presented as mean ± standard deviation (SD). Graphical analyses were performed using GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1 Donor characteristics and initiation of normothermic machine perfusion

The donor was a 51-year-old male with a history of hypertension. According to the uncontrolled donation after circulatory death (uDCD) protocol, the functional warm ischemia time was 30 minutes before kidney procurement. No implantation biopsy was performed; however, pre-existing pathological abnormalities, including glomerulosclerosis, tubular atrophy, and interstitial fibrosis, were identified, resulting in rejection of both kidneys for transplantation. After procurement, the left kidney was flushed and stored in University of Wisconsin (UW) solution at 4°C until initiation of normothermic machine perfusion (NMP). The total cold ischemia time before NMP was 18 hours. The right kidney remained under cold storage and was used as the control kidney during the extended preservation period.

3.2 Hemodynamic stability during prolonged normothermic machine perfusion

The kidney was successfully perfused using a pressure-controlled NMP protocol. Perfusion pressure was gradually increased until reaching a target mean arterial pressure of approximately 60 mmHg. During the 53-hour perfusion period, the mean perfusion pressure and renal blood flow were maintained at 62.38 ± 7.51 mmHg and 125.13 ± 20.40 mL/min(Figure 2), respectively. Perfusion temperature remained stable between 32.5°C and 33.5°C throughout the experiment.

The renal vascular resistance index remained relatively stable, with an average value of 0.50 ± 0.12 mmHg/mL/min, indicating preserved renal vascular responsiveness during prolonged ex vivo perfusion.

3.3 Oxygen delivery and metabolic recovery during NMP

The HBOC-based oxygen delivery system provided stable oxygenation throughout the perfusion period. The perfusate oxygen partial pressure remained adequate during NMP, with a mean value of 250.24 ± 28.62 mmHg.

Perfusate creatinine concentration remained relatively stable throughout the preservation period, with an average concentration of 40.24 ± 7.92 μmol/L(Figure 3). Lactate levels increased during the initial phase of perfusion, reaching a peak concentration of approximately 205–213 mg/dL within the first several hours. Subsequently, lactate levels progressively decreased and returned to near-normal levels after approximately 34 hours of perfusion, reaching a minimum value of 7.34 mg/dL.The reduction in lactate concentration was accompanied by increased urine production, suggesting recovery of renal metabolic activity during prolonged NMP. At the end of perfusion, cumulative urine output reached approximately 1260–1267 mL. Potassium concentration in the perfusate gradually decreased during the early phase of perfusion. However, after prolonged perfusion beyond 53 hours, hyperkalemia developed.

3.4 Histological assessment of renal injury during prolonged perfusion

Histological evaluation demonstrated no significant progression of pre-existing glomerulosclerosis, tubular atrophy, or interstitial fibrosis during prolonged NMP. In the NMP-treated kidney, tubular vacuolar degeneration showed mild progression over time. Minimal tubular necrosis was first observed after approximately 30 hours of perfusion, with tubular necrosis involving approximately 10% of evaluated tissue areas at 52 hours. Mild progression of interstitial inflammatory changes was also observed.Microthrombus formation was detected during the later phase of perfusion. Small amounts of microthrombi appeared after 24 hours, with increased severity at later time points, which was considered potentially associated with infection-related changes. Mild inflammatory alterations were observed in the ureter and renal artery(Figure 4)Table 1.

Table 1
Comparison of pathology scores between the two groups

serial number	Glomerulosclerosis score	Renal tubular atrophy score	Renal interstitial fibrosis score	Small artery stenosis	renal tubular vacuolar degeneration	Renal tubular necrosis	Interstitial inflammation	TMA	other	ureter
A12h	1	0	0	0	Mild	none	1%	none	none	
A24h	1	0	0	0	moderate	none	10%	small amount		
A48h	2	0	0	0	moderate	1%	1%	small amount	tubular	
A53h	0	0	0	0	moderate	10%	5%	Large amount	Infection (fungal ?)	Mild inflammation
B12h	1	0	0	0	Mild	1%	1%	none	none	
B24h	0	0	0	0	Mild	5%	2%	none	Predominantly renal medull fungal infections?	
B48h	1	1	0	0	moderate	10%	10%	none	none	
B53h	1	1	0	0	moderate	10%	10%	none	none	

In comparison, the cold-stored control kidney demonstrated earlier progression of tubular injury. Tubular necrosis increased after 8 hours, reaching approximately 10% involvement at 30 hours, accompanied by increased interstitial inflammation. Focal medullary infection-like changes were observed after 8 hours of cold storage.

3.5 Perfusate biochemical changes during extended NMP

The mean perfusate pH was maintained at 7.29 ± 0.15 during perfusion. A total of 50 mL of 8.4% sodium bicarbonate was administered to maintain acid-base balance. Perfusate sodium concentration demonstrated a gradual decline during prolonged perfusion, with a more pronounced decrease after approximately 50 hours. In contrast, potassium levels remained within or below the normal range during the first 40 hours but increased significantly after completion of the 53-hour perfusion period.

However, deterioration in metabolic and biochemical parameters was observed during the late phase of prolonged perfusion, suggesting that optimization of oxygen carriers, perfusate management, and long-term perfusion strategies will be required for further extension of preservation duration.

4. Discussion

In this study, we demonstrated the feasibility of prolonged ex vivo normothermic machine perfusion (NMP) of a discarded uncontrolled donation after circulatory death (uDCD) kidney graft using a hemoglobin-based oxygen carrier (HBOC)-based perfusion strategy. The kidney was maintained under normothermic conditions for 53 hours with stable hemodynamic parameters, progressive metabolic recovery, increasing urine production, and limited progression of structural injury. Compared with static cold storage, NMP attenuated the progression of tubular injury, although pre-existing chronic pathological changes were not reversed. These findings suggest that prolonged blood-free NMP may represent a promising approach for maintaining marginal kidney graft viability and establishing a platform for future organ repair strategies.

The clinical application of kidney NMP remains considerably less developed than liver NMP[28–29], largely due to the complex renal microvascular architecture and the limited regenerative capacity of kidney tissue. Previous studies have demonstrated the feasibility of short-term NMP in discarded human kidneys. Weissenbacher et al. reported 24-hour NMP of discarded human kidneys, showing modest histological improvement, although kidney injury markers such as KIM-1 did not significantly decrease over time[30]. Subsequently, prolonged perfusion of a discarded donation after brain death (DBD) kidney for 48 hours was reported, with improved tubular structural preservation and lower lactate levels. In comparison, our study extended ex vivo preservation of a marginal uDCD kidney graft to 53 hours, suggesting that prolonged NMP may be feasible even in kidneys with significant pre-existing injury and extended ischemic exposure.

An important observation in our study was the gradual recovery of metabolic activity during prolonged perfusion. Lactate concentration initially increased during the early phase of NMP, reflecting the metabolic burden associated with ischemia-reperfusion injury. However, lactate levels subsequently declined to near-normal values after approximately 34 hours, accompanied by increasing urine output and macroscopic improvement of the graft. These findings suggest that severely injured kidneys may require prolonged physiological support before achieving metabolic stabilization. Unlike conventional preservation techniques, NMP provides an active physiological environment in which renal function can be monitored dynamically and therapeutic interventions can be performed.

Beyond preservation, NMP may serve as an ex vivo biological platform for organ repair and therapeutic evaluation. The ability to maintain organs under near-physiological conditions creates a unique opportunity to test interventions that are difficult to evaluate in vivo, including pharmacological therapies, cell-based approaches, gene delivery strategies, and regenerative treatments[31]. However, renal repair is considerably slower and more complex than hepatic regeneration, indicating that extended perfusion durations may be necessary before clinically meaningful recovery can be achieved[32].

A critical challenge for long-duration normothermic perfusion is the selection of an appropriate oxygen carrier. Conventional NMP protocols frequently rely on human red blood cells; however, prolonged exposure to ex vivo perfusion conditions may lead to hemolysis, electrolyte disturbances, inflammatory activation, and reduced perfusate stability. In this study, HBOC was used as an alternative oxygen carrier[33–36], avoiding dependence on human blood products and enabling extended perfusion. Nevertheless, deterioration during the late phase of perfusion suggested that oxygen carrier stability remains a key limitation for further extension of preservation time. The increase in perfusate potassium concentration after prolonged perfusion and the accelerated decline in hemoglobin levels suggested that hemolysis-related effects may contribute to late-stage graft deterioration. Future strategies may include maintaining higher oxygen carrier concentrations, periodic perfusate replacement, or further development of non-hemoglobin-based oxygen delivery systems[37].

We also observed progressive changes in perfusate electrolyte composition during prolonged perfusion. The decline in sodium concentration, particularly after 50 hours, may have been associated with the absence of urine recirculation in our system. Previous studies have suggested that urine recirculation may improve electrolyte and fluid balance during kidney NMP. In our system, continuous supplementation with crystalloid solutions and blood-derived components[38], combined with the lack of urine recycling, may have contributed to the development of hyponatremia during extended perfusion. Optimization of perfusate management and integration of urine recycling systems may therefore be important for future long-term kidney preservation protocols.

Several limitations should be acknowledged. First, this study represents a single-center single-graft experimental report, and the findings require validation in larger studies. Second, the kidney evaluated in this study had significant baseline pathological injury and prolonged cold ischemia before NMP, which may limit direct extrapolation to other donor categories. Third, the perfused kidney was not transplanted into a recipient; therefore, post-transplant graft function and long-term outcomes could not be assessed. Nevertheless, the primary objective of this study was to evaluate the feasibility of prolonged ex vivo kidney preservation and establish a platform for future therapeutic interventions rather than to demonstrate immediate clinical transplantation outcomes.

5. Conclusion

In conclusion, our findings demonstrate that HBOC-based normothermic machine perfusion can maintain a marginal uDCD kidney graft in a viable ex vivo state for more than 50 hours. This approach extends the potential application of kidney NMP beyond preservation alone, toward dynamic graft assessment, organ repair, and translational therapeutic development. Further studies incorporating transplantation models and larger cohorts are required to determine whether prolonged NMP can improve clinical outcomes in kidney transplantation.

Declarations

Funding Declaration

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Conflict of Interest Statement

The authors declare that they have no competing interests.

Author Contributions

Z.C. conceived and designed the study, and supervised the project. J.F. and W.G. contributed equally to this work; they performed the perfusion experiments, collected and analyzed the data, and drafted the manuscript. G.L., W.Y., Jialin W., L.L., Y.G., W.Z., Jiao W., and X.X. participated in the perfusion procedures, sample collection, biochemical and histological assessments, and data interpretation. Z.C. critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figures

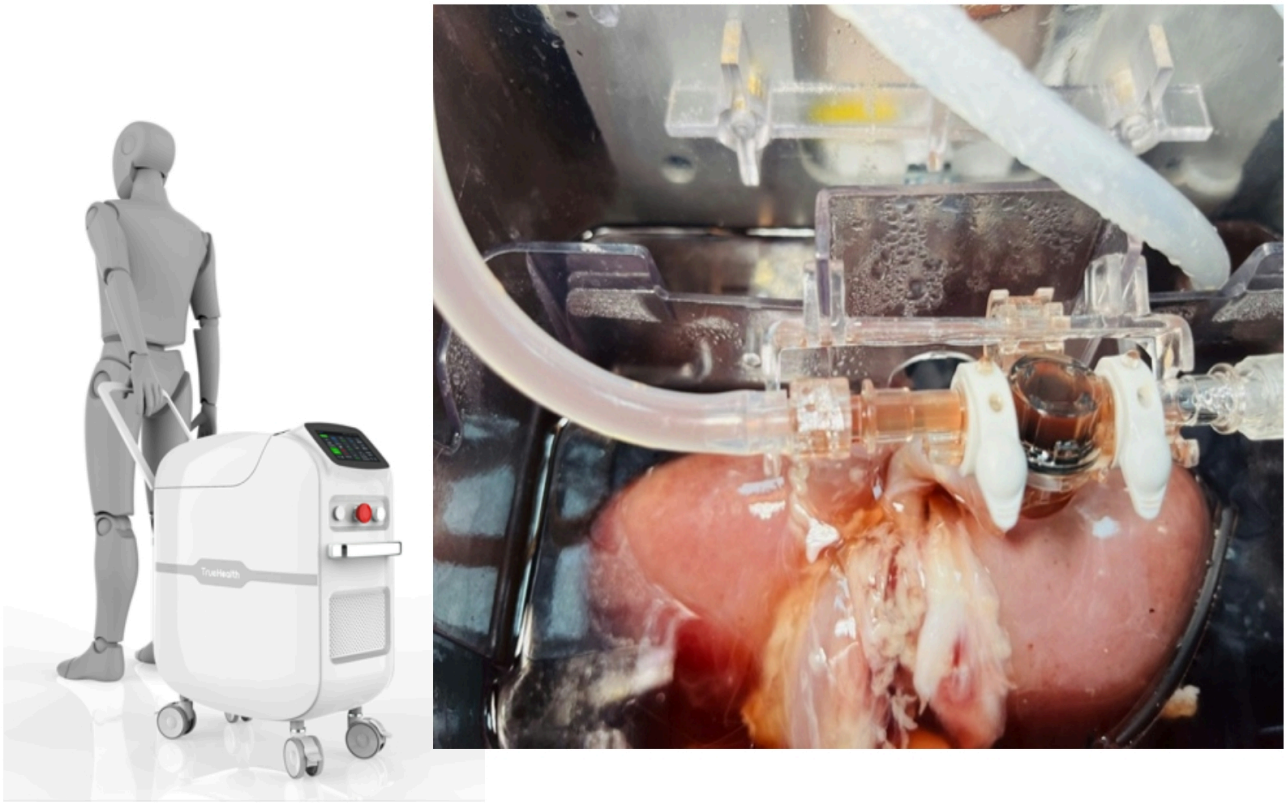


Figure 1

TH-LS KID100 Portable Kidney Mechanical Perfusion Preservation Device

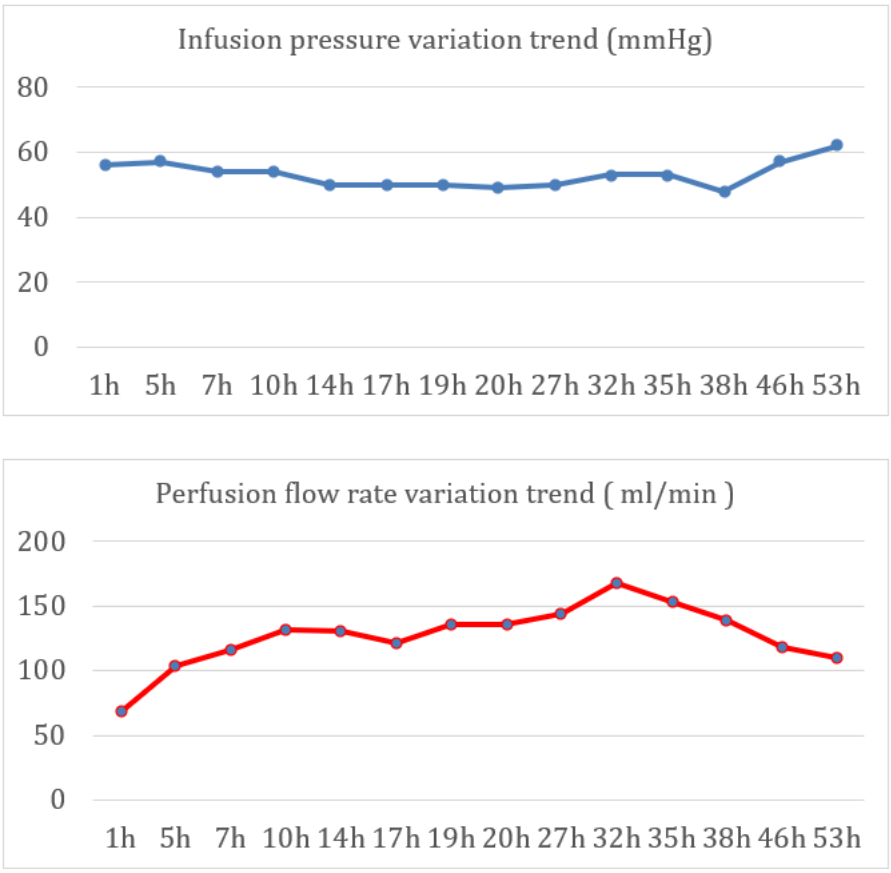


Figure 2

Changes in mechanical infusion pressure and flow rate in the experimental group

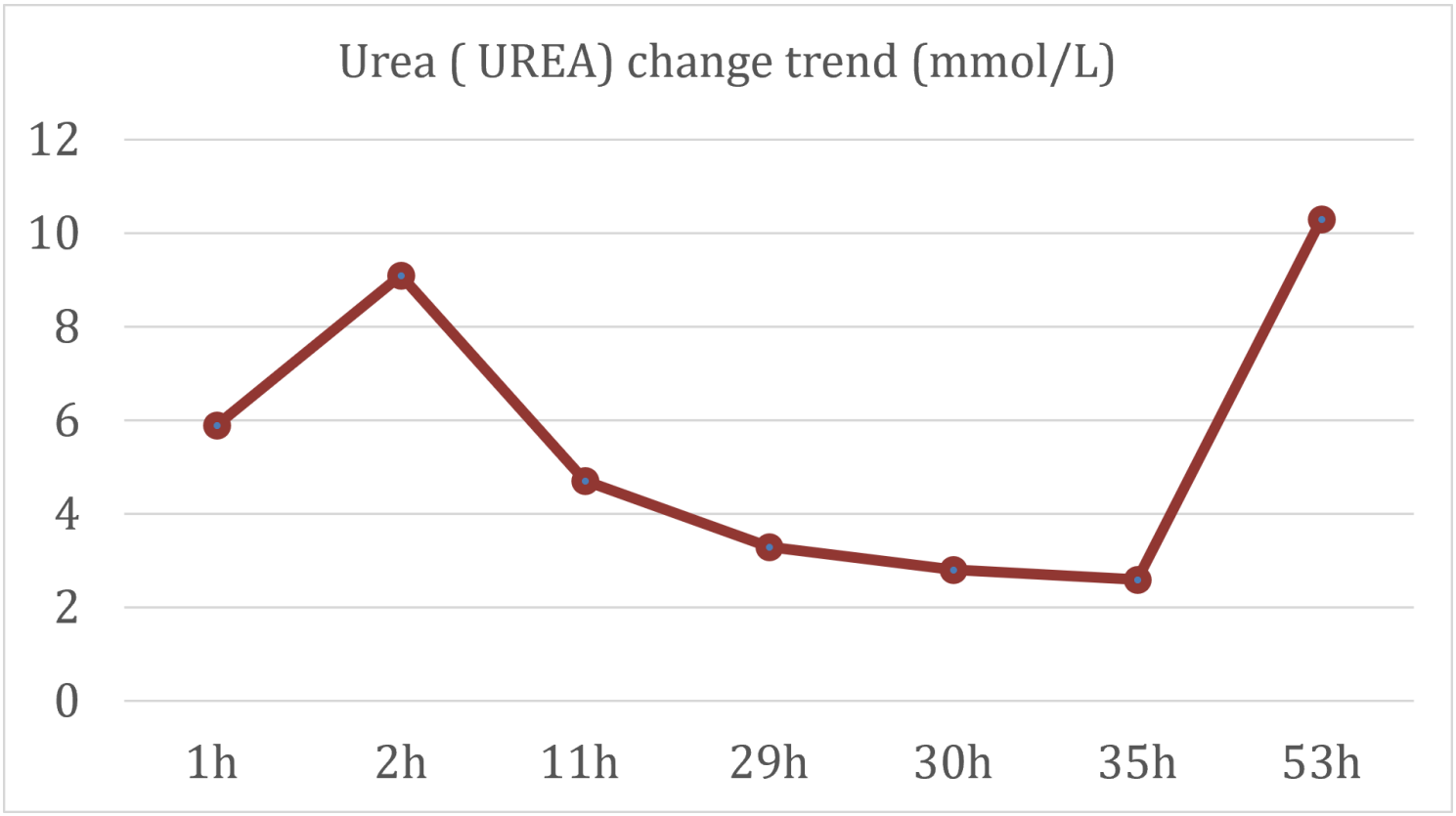


Figure 3

Trend of creatinine changes in perfusion fluid

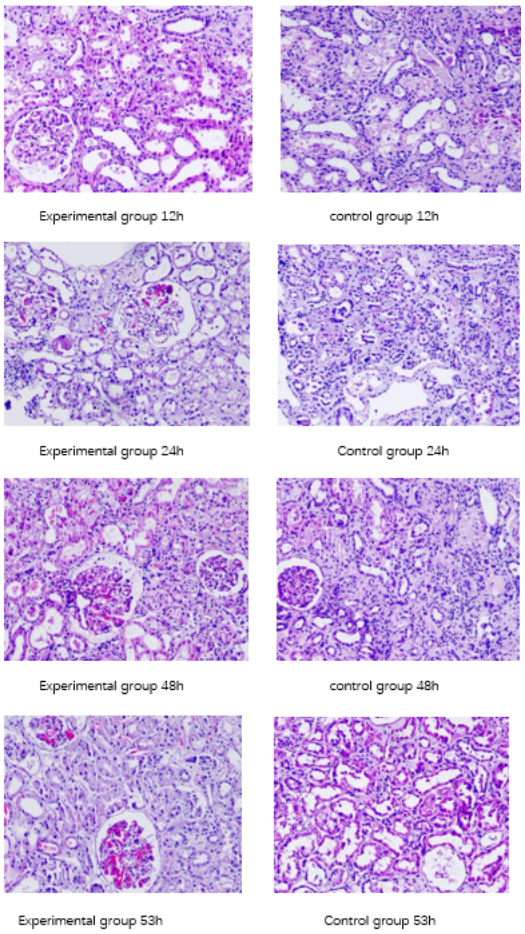


Figure 4

Pathological results : Experimental Group (A): With prolonged perfusion time: glomerular sclerosis, tubular atrophy, and interstitial fibrosis showed no progression, while the degree of tubular vacuolar degeneration slightly worsened. A small amount of tubular necrosis began to appear at 30 hours, with the necrosis rate reaching approximately 10% at 52 hours. Interstitial inflammation slightly worsened. Microthrombi appeared at 12 hours, and the degree of microthrombi was more severe at 52 hours, considered to be related to infection. Mild inflammation was observed in the ureters and arteries. **Control Group** (B): With prolonged perfusion time: glomerular sclerosis, tubular atrophy, and interstitial fibrosis showed no progression, while the degree of tubular vacuolar degeneration slightly worsened. Tubular necrosis worsened at 8 hours, with the necrosis rate reaching approximately 10% and interstitial inflammation worsening at 30 hours. Focal infection in the medulla was observed at 8 hours.