CHAPTER 227

Hypothermia and the Kidney

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OBJECTIVES

This chapter will:

1. Detail the pathophysiology of ischemia/reperfusion injury and hypothermic protection described in experimental evidence.
2. Discuss the limitations of animal models.
3. Describe three clinical scenarios in which hypothermia is used in clinical settings of ischemia reperfusion injury: transplantation, deceased donors, and postcardiac arrest.

The effect of hypothermia on animal models and human physiology have been explored with clear evidence that it can protect organs at risk of ischemic injury either as preventive measure or as a therapy after the injury has occurred. Several studies have been performed with different models of ischemic damage in dogs, showing that hypothermia is protective against ischemic injury when applied during the reperfusion period. Indeed, although restoration of blood flow to an ischemic organ is essential to prevent irreversible cellular injury, reperfusion may amplify tissue damage exceeding that produced by ischemia alone (ischemia/reperfusion injury, IRI).[1] Acute ischemic renal injury is one of the most common causes of acute kidney injury (AKI) that occurs in many clinical situations with high morbidity and mortality. IRI is particularly important in kidney transplantation. Almost 30% of the delayed graft dysfunction after kidney transplantation is attributable to IRI, in which a significant damage occurs during and after the reperfusion. In this setting, hypothermia is able to decrease cellular metabolism and oxygen consumption preventing a rapid loss of mitochondrial activity through disruption of membrane permeability and consequent accumulation of calcium, sodium, and water within the cell.[2] However, if cooling the tissues can help to blunt some effects of ischemia, several drawbacks have to be counted when hypothermia is applied.[3] Although there is significant laboratory evidence supporting the efficacy of hypothermia in preserving organ function,[4,5] the cooling of whole body for neurologic protection is challenged by a series of trials showing no benefit in terms of improved neurologic outcomes.[6,7] Few studies investigated benefits on kidney outcomes so far. More recently encouraging results of a randomized controlled trial[8] suggested that mild hypothermia in deceased organ donors is a relatively safe and reliable intervention, with a meaningful impact on graft outcomes, particularly regarding kidneys from borderline donors.

PATHOPHYSIOLOGY OF ISCHEMIA/REPERFUSION INJURY AND HYPOTHERMIC PROTECTION

The most frequent cause of AKI in hospitalized patients is transient or prolonged renal hypoperfusion; in 55% of cases AKI may be considered a consequence of a significant decrease in mean arterial blood pressure (prerenal AKI). Prerenal AKI is generally reversible as long as the cause has been eliminated and the tissue has not been damaged at the cellular level.[9,10] During blood flow interruption, the reduction in medullary blood flow and the resultant decrease of glucose and oxygen delivery to the tubular structures cause an imbalance between delivery and demand.[11] Cells are forced to maintain adenosine 5′-triphosphate (ATP) production by anaerobic glycolysis using glycogen stores and the remaining glucose in the surrounding tissue fluid.[11] This leads to local tissue acidosis.[12] The ATP depletion is followed by the increase of cytoplasmic calcium load, which activates proteases, phospholipases, and caspases[13] and the cellular accumulation of hypoxanthine and reactive oxygen species (ROS).[13]

Hypoxia, glucose depletion, acidosis, and ROS production can contribute to cell death: apoptosis and active necrosis as well. An early structural manifestation of ischemia is the loss of cell polarity with decreased reabsorption of sodium and water from the tubular lumen.[14] Because of diminished sodium reabsorption, the macula densa releases signals that induce constriction of the vasa afferentia (tubuloglomerular feedback).[9] The terminology *acute tubular necrosis* is misleading because the dominant pattern of tubular cell damage is apoptosis and not necrosis. During the reperfusion phase in presence of an acidotic pH, the cell killing is abrogated. Acidosis (pH < or = 7.0) provides significant protection against cell death during ischemia. On the contrary, the rise of intracellular pH during reperfusion causes cell death. This phenomenon is defined as "pH paradox," and it is mediated by changes of intracellular pH in terms of rapidly increase more after reperfusion are responsible of acceleration of cell killing.[15] Reperfusion induces Ca^{2+} delivery by depleted cells, producing Ca^{2+} overload and postischemic injury through multiple pathways (e.g., mitochondrial dysfunction, increased ROS formation, and phospholipase activation).[16] The length of reperfusion is important for prevention or mitigation of ischemic AKI, and then for therapeutic implications. The delay of restoration of a normal renal function may be caused by an intense interstitial inflammation and microvasculopathy.

Tubular epithelial and vascular endothelial cells release a diverse range of proinflammatory cytokines, inducing and perpetuating inflammation.[17] Postischemic renal inflammation may contribute to microvasculopathy characterized by endothelial cell swelling that can lead to prolonged ischemia and then a slower reperfusion, even if the primary cause has been eliminated; this is defined as *no reflow-phenomenon*.[18] Postischemic microvasculopathy has been associated with the risk of developing chronic renal failure in the long term, and it is therefore a meaningful therapeutic target.[19]

Advances in renal hypothermia to prevent ischemic damage were not introduced until the 1950s and 1960s. Experimental examinations performed in dogs, analyzing the effects of hypothermic renal ischemia, showed a reduction of perfusion probably because of cold-induced vasoconstriction with intact tubular function because of the

TABLE 227.1

Effect of Hypothermia on Ischemia

ISCHEMIC EFFECTS	HYPOTHERMIA EFFECTS
Suppression of reaction rates	Slowdown of metabolism Reduction in oxygen demand Reduction in energy depletion
Metabolic changes	Displacement of joined biochemical pathways Shifts from aerobic to anaerobic
Proton activity, ion transport, and cell swelling	pH regulation changes Passive redistribution of ions and water across cell membranes
Generation of oxygen-derived free radicals (ODFR)	Increased susceptibility of cells to generate ODFR and attenuates natural defense mechanisms
Structural changes	Membrane phase changes and loss of phospholipids Thermal shock Induction of stress proteins Cytoskeletal changes
Cell death	Apoptosis or necrosis

protective mechanism of hypothermia. In 1964, Shirmer and Walton investigated kidney ischemia in a dog model, and showed the renal effects of hypothermia conducted with local cooling: renal function was depressed only temporarily, and irreversible damage was limited (Table 227.1).[20]

A recent animal model of ischemia/reperfusion in the kidney was performed to evaluate the role of different temperature applications (normothermia [±37°C], mild hypothermia [26°C], moderate hypothermia [15°C], and deep hypothermia [4°C]) on the production of oxidative-stress markers. The results showed an increased catalase expression during deep hypothermia, suggesting the association of this level of temperature with higher antioxidative effects with a decreased free radical production.[6] However, tissue protection was not observed. Experimental studies also have investigated the effect of body temperature on renal susceptibility to ischemic injury showing that an elevated body temperature dramatically accentuates hypoxic injury, having a profound impact on renal ATP losses during hemorrhagic shock. In addition, hyperthermia is correlated significantly to ischemic renal injury, whereas hypothermia confers protection.[21] Minimal temperature changes during renal ischemia alter functional and morphologic outcome.[22] These findings in literature showed that in animals hypothermia is able to reduce the risk of renal failure after renal IRI.[23]

DECEASED DONORS

IRI is one of the most important nonimmunologic factors causing delayed graft function (DGF) and late allograft dysfunction in kidney transplantation because of activation of different programs of cell death. Several factors participate in the ischemic process: (1) clamping of renal artery in the allograft deriving from living related donor, (2) cold ischemia during allograft kidney storage, and (3) hemodynamic disturbances with impairment of blood flow in the allograft deriving from deceased donor before renal artery clamping.[24] As a result, IRI can affect the kidney at various stages of kidney transplantation. However, hypothermic solutions flushing the kidneys after allograft withdrawal are administered to cool the organ and minimize the negative effects of ischemia and hypothermia (Fig. 227.1 and Table 227.2). An alternative to cold storage is the hypothermic machine perfusion (HMP),[25] which allows a continual flush of the microcirculation, preventing the accumulation of waste products, sustaining a normal metabolic rate, and reducing free radical production and renal cell apoptosis.[26] Typically, transplanted kidneys derive from living donors or after brainstem death (standard-criteria donor, SCD) in which the heart is still beating and general blood flow is preserved.[27] The number of organs available from these donors is always inferior with respect to the demand. To increase the number of available organs, the novel expanded criteria donors (ECDs)[28] and donation after cardiac death (DCD)[29] recently have been applied. ECDs are normally aged 60 years or older, or over 50 years with at least two of the following conditions: hypertension history, serum creatinine > 1.5 mg/dL, and cause of death from cerebrovascular accident.[28] ECD transplantation is associated with an increased risk of graft loss compared with transplants from an SCD.[30]

In the area of donor management, a recent RCT investigated the effect of mild cooling from 37°C (±0.5°C) to 34.5°C (±0.5°C) in organ donors after brain death on delayed graft function (DGF) versus donors subjected to conventional normothermia before organ retrieval. Results showed that

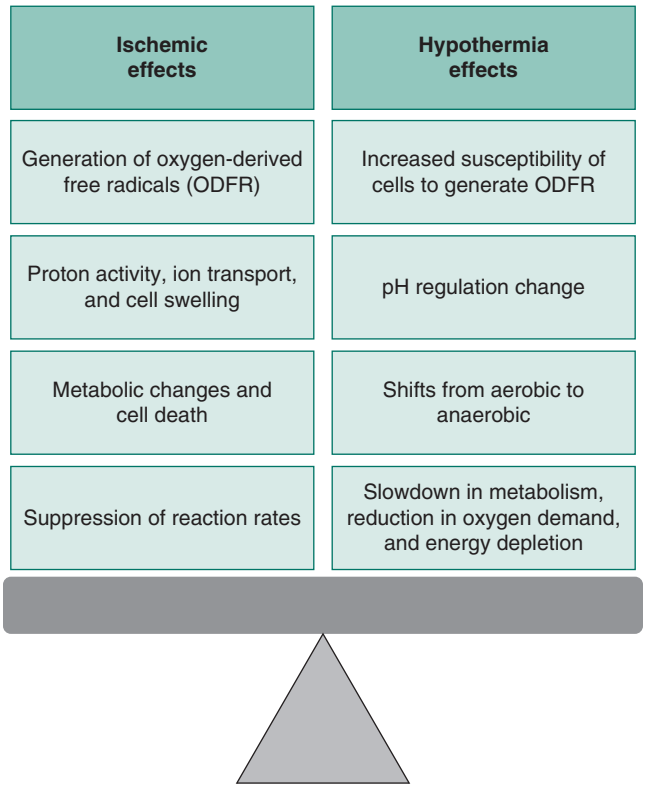

FIGURE 227.1 Ischemia/reperfusion injury. The blood flow interruption causes an imbalance between O_2 delivery and demand; the consequent hypoxia, glucose depletion, acidosis, and ROS production contribute to cell death. In addition, tubular epithelial and vascular endothelial cells release proinflammatory cytokines (interstitial inflammation) that are also responsible for endothelia cell swelling with a consequent prolonged ischemia and slower reperfusion (interstitial microvasculopathy). During reperfusion, the restoration of pH induces Ca^{2+} delivery by depleted cells producing Ca^{2+} overload and increased oxygen free radical formation that contribute to inflammatory cascade and cell injury.

TABLE 227.2

Preservation Solutions Components

COMPONENTS	FUNCTION	EXAMPLES
Impermeant	Minimize swelling and provide stability	Glucose, lactobionate, mannitol, raffinose, sucrose
Colloid	Reduction of interstitial edema and endothelial cell swelling	Hydroxyethyl starch (HES) Polyethylene glycol (PEG)
Buffers	Maintain pH in the physiologically range and combat acidosis at low temperatures	Citrate, histidine, phosphate
Electrolytes	Maintain intracellular electrolyte concentrations	Calcium, chloride, magnesium, magnesium sulphate, potassium, sodium
Antioxidants	Reduction of oxygen free radicals	Scavenge oxygen free radicals (glutathione) Inhibit the activity of xanthine oxidase (allopurinol) Stabilize cellular membranes and prevent oxidant damage (tryptophan)
Additives		Restore high-energy phosphate (adenosine) Support anaerobic metabolism (ketoglutarate)

DGF occurred in 79/280 (28.2%) of recipients in the intervention arm versus 112/286 (39.2%) in the standard arm ($p = .008$), with an impressive difference of about 11% of absolute risk reduction. The beneficial effect of hypothermia was particularly notable in the ECD group (30% in the intervention vs. more than 50% in the standard arm). In the SCD group, although hypothermia reduced DGF, this did not reach statistical significance. Nevertheless, the authors did not consider in their study long-term outcomes such as acute rejection or graft survival nor outcomes of the other organs transplanted, such as livers and pancreases.[4] DCD is defined as organ donation from patients with irremediable brain injuries who do not meet the criteria for brain death testing and who experience cardiopulmonary arrest after withdrawal of ventilator support; it has been investigated as a method to increase the number of organs available for donation.[29]

The ways in which organ retrieval can take place after circulatory death are described in the modified Maastricht Classification. The first two types are composed of patients who died suddenly on arrival at the emergency department (type I) and after an unsuccessful resuscitation (type II). After death declaration, an aortic cannula is placed through the femoral artery and the perfusion is started for kidney preservation. The maintenance of circulation before the cooling could be performed through the extracorporeal membrane oxygenator and also combined with a cooler to provide cold oxygenated blood to the abdominal visceral organs. Concerning patients awaiting from cardiac arrest (CA) (type III) or with CA while brain death (type IV), after the cessation of the heart beat, the patient is transferred to the operating room and the kidney is retrieved after in situ cooling. In the case of the unexpected CA in a critically ill patient (type V), the management will be the same of types II and I.[31] DCD renal transplants are accompanied by a greater release of free radicals at reperfusion more than SCD and ECD, with an increase in tissue injury markers at reperfusion.[32] DCD organs receive a warm ischemic insult before the onset of preservation but also a different degree of injury on the basis of the length of ischemia. For this reason, uncontrolled DCD kidneys are exposed to more prolonged warm ischemia injury compared with the warm ischemic time in controlled DCD (15 minutes).[29] In addition, the combination of warm ischemia and cold reperfusion may exacerbate the injury. Although experimental data suggested that the duration of cooling has a strong influence on graft outcome,[33] the direct impact of cold ischemia on long-term graft survival is less clear.

POSTCARDIAC ARREST

The restoration of spontaneous circulation (ROSC) after prolonged, complete, whole-body ischemia is a peculiar pathophysiologic state created by successful cardiopulmonary resuscitation (CPR). The ischemia and reperfusion during circulatory arrest (CA), resuscitation, and postresuscitation phases can affect the kidney; the alterations of epithelial cells, the interstitial inflammation, and the interstitial microvasculopathy cause an abnormal repair process, including incomplete repair of tubular cells and fibrosis. The effects of whole-body ischemia followed by reperfusion activate a systemic inflammatory response, and the injury occurs simultaneously in multiple organs through the release of injury products into the circulation associated with defective clearance function after shock.[34] Indeed, after ROSC, AKI is a common complication with an increase in mortality risk, dialysis requirement, and prolonged hospital stay.[35] There is limited information on the epidemiology of AKI after CA, particularly because most studies were performed before the development of consensus definitions of AKI. Bellomo et al. investigated retrospectively the AKI from CA in isolation and AKI secondary to post-CA cardiogenic shock on 105 adult patients who survived for more than 48 hours after successful resuscitation after CA. Although baseline serum creatinine (SCr) levels were not always available, results showed that CA in absence of postresuscitation cardiogenic shock is associated uncommonly with significant AKI.[36] Geri et al. assessed retrospectively the prevalence of AKI (defined with Acute Kidney Injury Network [AKIN] classification AKIN) in 580 CA patients to identify risk factors and to evaluate the impact of AKI on outcome after CA. Results showed that AKIN stage 3 was present in 280 (48.3%) patients after CA with a significantly higher association with 30-day mortality. However, the urine output was collected within the first 24 hours, and the urine output criteria were evaluated only on the basis of this data. The admission SCr level was used as a surrogate of baseline renal function and the estimation of glomerular filtration rate (GFR) was performed using the Modification of Diet in Renal Disease equation to assess day-30 GFR leading to a potential misevaluation of renal recovery.[37] The decrease in whole-body temperature performed through physical means for therapeutic purposes, defined therapeutic hypothermia (TH), could limit the ischemic injuries.

Although there is significant laboratory evidence supporting the efficacy of hypothermia in preserving organ function, the cooling of whole body for neurologic protection

in CA patients is challenged by a series of trials that show no benefit,[7,8] and it remains unclear what therapeutic or harmful effect on renal function could result because of confounding perturbations in cardiovascular and renal physiology in the post-CA setting.[38] Clinical guidelines suggest that TH increases urine output particularly in the induction phase, and this phenomenon is called cold-induced diuresis (CID).[39] Debate exists with regard to the significance or impact of CID, the nature of diuresis, and the physiologic mechanism responsible for CID. A school of thought suggests that CID is a renal autoregulatory response to a relative central hypervolemia induced by the peripheral vasoconstriction with increase in cardiac output and renal blood flow (RBF). Other authors think that CID may be due to osmotic alteration (tubular dysfunction) and incapability to appropriately concentrate the urine.[39] Renal function is depressed progressively during TH; a progressive fall in systemic blood pressure causes a decrease in RBF with a consequent rise in renal vascular resistance, promoting a further decrease in RBF and GFR.[40] Limited human data are available on this issue, given that the type of resuscitation fluids, cardiogenic shock, or AKI could influence the urine production.[41]

Raper et al. performed a secondary analysis of prospective study on patients receiving TH post-CA observing a modest increase in urine output rates during TH induction compared with the rewarming period. However, they included only a portion of total TH cases because of the incomplete reporting of urine output. Limited by numerous clinical confounding factors such as body mass index and AKI, the preliminary study supported the evidence of potential CID, but not a rewarm antidiuresis during TH.[39] Previous trials comparing the effect of TH versus normothermia on kidney end points showed conflicting results resulting from small sample size and low study quality. In the Hypothermia After Clinical Arrest clinical trial, an increased need for volume replacement resulting from high urinary output during the cooling period was observed in all patients. Results showed no impairment of renal function and no need of hemofiltration, but also no benefits.[42] A meta-analysis[43] including 19 trials suggested that TH, applied in different population settings including brain injury, out-of-hospital CA, and major cardiovascular surgery with cardiopulmonary bypass, has no impact on prevention of AKI (odds ratio [OR] 1.01, 95% confidence interval [CI] 0.68, 1.51; $p = .95$) and dialysis requirement (OR 0.81; 95% CI 0.30, 2.19; $p = .68$), but it was associated with a lower mortality (OR 0.69; 95% CI 0.51, 0.92; $p = .01$). Only one study showed a protective effect of hypothermia against AKI.[38] Unfortunately, most of the trials included were not designed originally to examine the effect of TH on kidney end points as their primary end point, and the sample size is small. In addition, it is evident the variability or lack of definition of AKI.

CONCLUSION

The application of hypothermia for kidney protection during IRI has a biologic rationale that has not been confirmed consistently, so far. Much of the evidence currently available relies on animal models. Unfortunately, the clinical transfer of experimental results to complex human pathophysiology has several inherent limitations. In kidney transplantation, hypothermia is a double-edged sword: cold preservation can help to combat the deleterious effects of ischemia; a prolonged hypothermia can be associated with worse recovery of renal function. The relationship between warm ischemia, cold ischemia, and graft survival is still not clear. In the area of donor management, results from an RCT on application of hypothermia in heart-beating deceased donors showed improvement of short graft outcomes. However, the application of temperature decrease for preserving renal function during the donation process could be really helpful also in DCD, in whom there is a greater release of ROS at reperfusion than in a heart-beating donor and living donor, with an increase in tissue injury markers at reperfusion. Data on renal outcomes from TH studies performed to assess neuroprotection in post-ROSC patients demonstrated variable or absent renal impact. Future studies will have to address the best strategy for rewarming, possibly assessing a gentle temperature normalization. The possible application of TH to DCD to preserve renal function during the donation process also should be evaluated in large trials.

Key Points

1. Acute ischemic renal injury is one of the most common causes of acute kidney injury, particularly important in kidney transplantation. Hypothermia is able to decrease cellular metabolism and oxygen consumption, preventing a rapid loss of mitochondrial activity through disruption of membrane permeability and consequent accumulation of calcium, sodium, and water within the cell.
2. Experimental studies investigated the effect of body temperature on renal susceptibility to ischemic injury, showing that hyperthermia is correlated significantly to ischemic renal injury, whereas hypothermia confers protection. The clinical transfer of experimental results to complex human pathophysiology has several inherent limitations.
3. In kidney transplantation, cold preservation can help to combat the deleterious effects of ischemia; a prolonged hypothermia can be associated with worse recovery of renal function. In the area of donor management, the application of temperature decrease for preserving renal function during the donation process could be really helpful also in donation after cardiac death, in whom there is a greater release of reactive oxygen species at reperfusion than in a heart-beating donor and living donor.

Key References

1. Collard CD, Gelman S Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology*. 2001;94(6):1133-1138.
2. Kosieradzki M, Rowinski W. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. *Transplant Proc*. 2008;40(10):3279-3288.
7. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. 2013. *N Engl J Med*. 2013;369:2197-2206.
8. Niemann CU, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med*. 2015;373:405-414.
43. Susantitaphong P, Alfayez M, Cohen-Bucay A, et al. Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials. *Resuscitation*. 2012;83:159-167.

A complete reference list can be found online at ExpertConsult.com.

References

1. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology*. 2001;94(6):1133-1138.
2. Kosieradzki M, Rowinski W. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. *Transplant Proc*. 2008;40(10):3279-3288.
3. Devarajan P. Update on mechanisms of ischemic acute kidney injury. *J Am Soc Nephrol*. 2006;17(6):1503-1520.
4. Gotberg M, van der Pals J, Olivecrona GK, et al. Optimal timing of hypothermia in relation to myocardial reperfusion. *Basic Res Cardiol*. 2011;106(5):697-708.
5. Santos EB, Koff WJ, Grezzana Filho Tde J, et al. Oxidative stress evaluation of ischemia and reperfusion in kidneys under various degrees of hypothermia in rats. *Acta Cir Bras*. 2013;28(8):568-573.
6. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med*. 2005;33(2):414-418.
7. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197-2206.
8. Niemann CU, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med*. 2015;373(5):405-414.
9. Singh P, Okusa MD. The role of tubuloglomerular feedback in the pathogenesis of acute kidney injury. *Contrib Nephrol*. 2011;174:12-21.
10. Patschan D, Muller GA. Acute kidney injury. *J Inj Violence Res*. 2015;7(1):19-26.
11. Dennis SC, Gevers W, Opie LH. Protons in ischemia: where do they come from; where do they go to? *J Mol Cell Cardiol*. 1991;23(9):1077-1086.
12. Gottlieb RA, Gruol DL, Zhu JY, et al. Preconditioning rabbit cardiomyocytes: role of pH, vacuolar proton ATPase, and apoptosis. *J Clin Invest*. 1996;97(10):2391-2398.
13. Devarajan P. Cellular and molecular derangements in acute tubular necrosis. *Curr Opin Pediatr*. 2005;17(2):193-199.
14. Lee DB, Huang E, Ward HJ. Tight junction biology and kidney dysfunction. *Am J Physiol Renal Physiol*. 2006;290(1): F20-F34.
15. Kalogeris T, Baines CP, Krenz M, et al. Cell biology of ischemia/reperfusion injury. *Int Rev Cell Mol Biol*. 2012;298: 229-317.
16. Schrier RW, Arnold PE, Van Putten VJ, et al. Cellular calcium in ischemic acute renal failure: role of calcium entry blockers. *Kidney Int*. 1987;32(3):313-321.
17. Segerer S, Nelson PJ, Schlondorff D. Chemokines, chemokine receptors, and renal disease: from basic science to pathophysiologic and therapeutic studies. *J Am Soc Nephrol*. 2000;11(1):152-176.
18. Vrints CJ. Pathophysiology of the no-reflow phenomenon. *Acute Card Care*. 2009;11(2):69-76.
19. Patschan D, Patschan S, Muller GA. Inflammation and microvasculopathy in renal ischemia reperfusion injury. *J Transplant*. 2012;2012:764154.
20. Schirmer HKA, Walton KN. The effect of hypothermia upon respiration and anaerobic glycolysis of dog kidney. *Invest Urol*. 1964;1:604-609.
21. Zager RA, Altschuld R. Body temperature: an important determinant of severity of ischemic renal injury. *Am J Physiol*. 1986;251(1 Pt 2):F87-F93.
22. Pelkey TJ, Frank RS, Stanley JJ, et al. Minimal physiologic temperature variations during renal ischemia alter functional and morphologic outcome. *J Vasc Surg*. 1992;15(4):619-625.
23. Delbridge MS, Shrestha BM, Raftery AT, et al. The effect of body temperature in a rat model of renal ischemia-reperfusion injury. *Transplant Proc*. 2007;39(10):2983-2985.
24. Guibert EE, Petrenko AY, Balaban CL, et al. Organ preservation: current concepts and new strategies for the next decade. *Transfus Med Hemother*. 2011;38(2):125-142.
25. Lee CY, Mangino MJ. Preservation methods for kidney and liver. *Organogenesis*. 2009;5(3):105-112.
26. Zhang Y, Fu Z, Zhong Z, et al. Hypothermic machine perfusion decreases renal cell apoptosis during ischemia/reperfusion injury via the ezrin/AKT pathway. *Artif Organs*. 2015.
27. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725-1730.
28. O'Connor KJ, Delmonico FL. Increasing the supply of kidneys for transplantation. *Semin Dial*. 2005;18(6):460-462.
29. Akoh JA. Kidney donation after cardiac death. *World J Nephrol*. 2012;1(3):79-91.
30. Aubert O, Kamar N, Vernerey D, et al. Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. *BMJ*. 2015;351:h3557.
31. Evrard P. Belgian modified classification of Maastricht for donors after circulatory death. *Transplant Proc*. 2014;46(9):3138-3142.
32. Gok MA, Shenton BK, Pelsers M, et al. Ischemia-reperfusion injury in cadaveric nonheart beating, cadaveric heart beating and live donor renal transplants. *J Urol*. 2006;175(2):641-647.
33. Dragun D, Hoff U, Park JK, et al. Prolonged cold preservation augments vascular injury independent of renal transplant immunogenicity and function. *Kidney Int*. 2001;60(3):1173-1181.
34. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation*. 2008;79(3):350-379.
35. Mattana J, Singhal PC. Prevalence and determinants of acute renal failure following cardiopulmonary resuscitation. *Arch Intern Med*. 1993;153(2):235-239.
36. Chua HR, Glassford N, Bellomo R. Acute kidney injury after cardiac arrest. *Resuscitation*. 2012;83(6):721-727.
37. Geri G, Guillemet L, Dumas F, et al. Acute kidney injury after out-of-hospital cardiac arrest: risk factors and prognosis in a large cohort. *Intensive Care Med*. 2015;41(7):1273-1280.
38. Guluma KZ, Liu L, Hemmen TM, et al. Therapeutic hypothermia is associated with a decrease in urine output in acute stroke patients. *Resuscitation*. 2010;81(12):1642-1647.
39. Raper JD, Wang HE. Urine output changes during postcardiac arrest therapeutic hypothermia. *Ther Hypothermia Temp Manag*. 2013;3(4):173-177.
40. Wong KC. Physiology and pharmacology of hypothermia. *West J Med*. 1983;138(2):227-232.
41. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37(7 suppl):S186-S202.
42. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke*. 2000;31(1):86-94.
43. Susantitaphong P, Alfayez M, Cohen-Bucay A, et al. Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials. *Resuscitation*. 2012;83(2):159-167.