17 Renal Perfusion During Aortic Surgery: Looking for the Ideal Substrate

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17.1 Pathogenesis of Ischemic Acute Tubular Necrosis During Aortic Surgery

The kidneys are the body's natural blood filters, eliminating around 1.5 l per day of urine [1–4]. The reabsorption of fluids after filtration in the renal tubule is the crucial process in maintaining body intravascular volume, in adjusting electrolytes and acid-base balance, and in concentrating toxic metabolites in the urine. Fluid reabsorption is mainly driven by Na^+ transport from the tubular lumen into the peritubular capillaries by the Na^+/K^+-ATPase pump in the basolateral membrane

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of the epithelial cells. This enzyme pumps three sodium ions out of the cell for every two potassium ions taken in. Both ions are moved against their concentration gradients, and since both have equal ionic charges, their movement creates an electrochemical gradient between the cell and its exterior. So this pumping is active and determines the essential energy consumption of the kidney because electrochemical gradient requires continuous energy supply from ATP to be maintained.

When surgical techniques require temporary interruption of renal blood flow, less Na^+ is transported within the tubular space, and Na^+/K^+-ATPase pump activity diminishes with a drop in ATP consumption. This process should lead to a theoretically high ischemic tolerance, but the range of safe ischemic time is largely variable. Laboratory studies indicate that most animals exhibit fatal renal failure for ischemic time longer than 2 h. Rats can survive after a thoracic aortic occlusion of 2 h [5]; dogs also tolerate 2 h of aortic occlusion with only a temporary and slight reduction in renal function [6], while rabbits did not survive with renal failure following 1 h of renal ischemia [7].

The safe duration of renal ischemia in humans is variable, even if, based on a study prospectively analyzing renal artery clamping in patients undergoing partial nephrectomy, human kidneys seem to safely tolerate 30–60 min of clamp ischemia if other nephrologic insults are not present [8]. It is however a common experience during aortic surgery that even suprarenal aortic clamping of less than 30 min is usually associated with some degree of renal damage in most patients. Hence, the crucial question is "why is a tissue with the energy consumption mainly related to Na^+ reabsorption so vulnerable to ischemia when the processes of reabsorption are inactivated?"

To answer this question, we have to keep in mind that, even if open TAAA repair is the most investigated clinical setting of renal ischemia/reperfusion injury, the pathophysiology of postoperative renal dysfunction is complex and still only partially known. Several intraoperative mechanisms typically affect tubular renal cells, among these, hemodynamic instability and anemia related to massive blood loss, embolism, vasospasm, increased myoglobin for lower limbs muscles ischemia, massive overall body fluid shifting, medications given, and hypoxia. Furthermore, many additional intraoperative nephrotoxic insults such as those related to the extracorporeal circulation may be involved, including activation of inflammatory mediators, oxygen free radicals systemic release, red blood cell damage, and activation of the coagulation cascade, fibrinolytic system, and complement chain.

We should also keep in mind that in the kidney, the workload is markedly inhomogeneous and fluid reabsorption occurs for approximately 70% of the total amount in the proximal convolute tubule. Hence, histology and cytological building of such an active tissue is complex with lush brush border carpets in the tubular lumen and lateral cellular processes largely interdigitating each other to expand the membrane surface. The surface of the basal tubular membrane is also amplified by extensive membrane infolding, creating numerous tiny feet. So, there is a non-negligible baseline ATP needed to preserve such an expanded and biologically active tubular epithelial surface, even when reabsorption processes are inactivated.

Additionally, the renal cortex, where proximal convoluted tubules are involved, in a normal condition is the most vascularized tissue of the entire human body in proportion to its weight. It receives far higher blood flow than would be required to nourish it, having 98–99% of the 1200 ml of oxygenated blood that every minute perfuses the kidneys in a subject of 70 kg. So, in the hypervascularized tissue of renal cortex, only oxygen-linked processes such as aerobic glycolysis and fatty acids beta-oxidation are used. But in ischemic tissues, the anaerobic glycolysis is the only cellular process able to produce the ATP providing energy enough for preparing sufficient postischemic function. Therefore, in the proximal tubule cells in case of poor oxygenation, block of cellular respiration, critical intracellular ATP reduction, and increase in lactate are early. At this point, a variety of factors can promote the development of cell injury, including the intracellular accumulation of calcium,

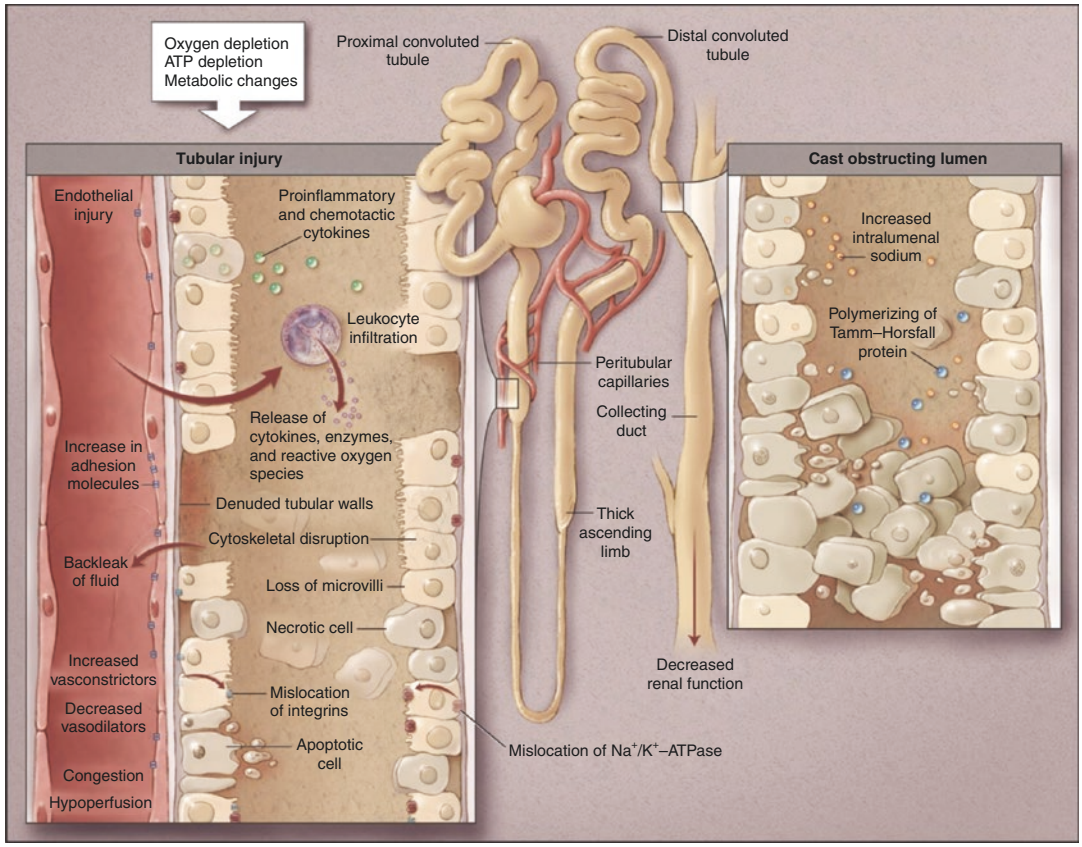

Fig. 17.1 Illustration showing the mechanisms of acute tubular necrosis. The major histologic changes are loss of proximal tubule brush border and patchy loss of proximal tubule cells by impairment of normal cell-to-basement membrane adhesion. This process leads to multiple areas of denudation of the basement membrane. Obstructing distal tubule casts of viable cells might also be observed and focal areas of proximal tubule dilatation appear. Intratubular obstruction by cells and cellular debris is an important component of acute tubular necrosis; the intraluminal casts are composed, in part, of Tamm-Horsfall protein, which is converted to a gel-like polymer in the setting of high local luminal sodium concentrations that is characteristic of acute tubular necrosis. Tubules from multiple nephrons drain into a single collecting tubule; as a result, obstruction in a relatively small number of collecting tubules may lead to failure of filtration in a large number of nephrons. In addition to observable tubule obstruction, complement activation is another early event underlying ischemic injury and influences the recruitment of neutrophils and directly damages the endothelium and surrounding cells. This process leads to back leak of filtered tubular fluid into the vascular space across the damaged tubule epithelium and peritubular capillaries congestion by leukocyte accumulation that impairs local renal blood flow. After revascularization, the combination of continued glomerular filtration and impaired proximal and loop reabsorptive function leads to increased sodium chloride delivery to the macula densa in individual nephrons. This activates the tubuloglomerular feedback mechanism, causing afferent arteriolar constriction, which lowers the GFR in an attempt to reduce tubule flow rate (Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007; 357(8):797–805. With permission of Massachusetts Medical Society. All rights reserved)

the generation of reactive oxygen species, and activation of phospholipases and proteases.

In the hypoxic areas, the net effect is the *so-called* acute tubular necrosis with either necrotic or apoptotic processes leading to cell death that is usually restricted to the proximal tubule and thick ascending limb of the loop of Henle.

The acute tubular necrosis is a direct consequence of metabolic pathways activated by ischemia, but it is potentiated by inflammation with a wide variety of pro-inflammatory molecules released in response to ischemic injury. This disorder is initially characterized by a decline in the glomerular filtration rate that is usually more

prominent than the severity of the histologic changes (Fig. 17.1).

The urine volume may be reduced, and the early rising of plasma creatinine concentration is usually associated to a characteristic set of laboratory changes including elevation in specific urine and serum biomarkers that are indicative of tubular injury.

Eventually, according to the severity and duration of ischemia, histologic changes might recover with restored areas of cellular regeneration. In particular when preoperative renal function is good and kidneys are not exposed to adjunctive nephrotoxic agents and harmful conditions, renal function might stabilize back to baseline.

17.2 Surgical Strategies for Renal Perfusion

The most encouraging approaches in renal protection are currently based on surgical techniques focused on the reduction of ischemic time, together with renal artery perfusion.

Over the last 50 years, several strategies have been developed for selective renal artery perfusion during the repair of the visceral aorta, including blood perfusion with passive shunts and extracorporeal circulation (Fig. 17.2).

Warm selective blood perfusion of the renal arteries is, in theory, the nearest approach to physiology preventing cell membrane injury and intracellular swelling, thanks to a continuous delivery of oxygen and buffers.

However, the protective effects of local renal cooling against ischemia/reperfusion injury have been established as well for almost six decades [4]. In the randomized trial of Köksoy, acute renal dysfunction in patients who underwent TAAA repair under renal artery selective perfusion with cold crystalloid was 21%, compared to the 63% reported for warm blood [9].

Cold blood, combining the benefits of hypothermia and blood substrates, has also been used in clinical settings. However, in the retrospective study of Hassoun, in which 359 patients underwent open TAAA repair with either warm or cold visceral perfusion, cold blood did not provide any significant advantage in postoperative renal

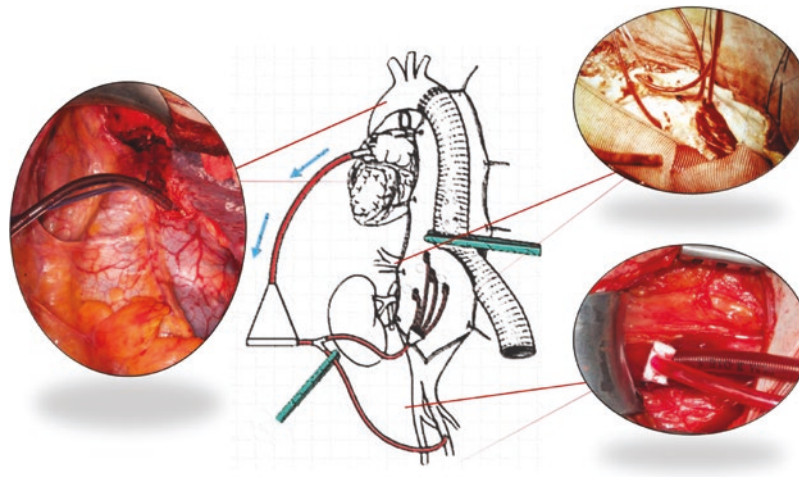

Fig. 17.2 Schematic drawing and surgical pictures showing an open TAAA repair performed with sequential clamping and distal aortic perfusion with a centrifugal pump. The circuit in-flow site is usually the left atrium, and intraoperative picture on the left shows left atrium cannulation through the left superior pulmonary vein. After proximal aortic anastomosis and reattachment of the intercostal arteries, the visceral segment of the aorta is opened, and coeliac trunk, superior mesenteric artery, and renal arteries are cannulated with occlusion-perfusion balloon catheters for selective hematic perfusion. Intraoperative picture in the upper right corner shows hematic visceral artery perfusion during repair of visceral aorta. Intraoperative picture in the lower right corner shows nonocclusive cannulation of the left common femoral artery for distal lower limbs and visceral perfusion during proximal aortic clamping

dysfunction and recovery compared to warm blood [10].

Even compared to cold crystalloid, cold blood failed to provide any significant superiority. In the prospective trial from Lemaire, 155 patients were randomized, receiving intermittent renal perfusion with 4 °C lactated Ringer's solution or 4 °C blood. No significant difference was reported in postoperative renal dysfunction score or in subclinical injury, measured with changes of specific renal biomarkers [11].

Cold blood properties have not been fully studied at 4 °C, and several arguments may justify the reported lack of superiority, including oxyhemoglobin dissociation curve shift to the left that reduces its ability to release oxygen. Cold blood perfusion also requires adjunctive lines and issues in extracorporeal blood circuits. Some authors advocated that the concept of selective blood renal perfusion technique should be questioned because non-pulsatile hypotensive perfusion is not effective [12, 13]. Kalder has recently focused on the effectiveness and safety of selective renal artery blood perfusion in porcine model, thus in animals with similar vascular vessel diameters and hemodynamic parameters compared to humans [13]. In his study, despite an acceptable blood pressure in the target vessels, the selective roller pump failed to supply sufficient perfusion volume to the renal arteries. Elevated NGAL levels were also measured in renovenous blood and in urinary samples together with significantly increased serum free hemoglobin. The study concluded that selective organ perfusion system induces kidney tubule injury and erythrocyte damage [13]. However, these disappointing results with roller pump are in contrast with those reported by Idu, again in a porcine model, with selective renal blood perfusion instituted with a centrifugal pump [14]. In this study, adequate renal perfusion volumes without significant hemolysis and effective renal tissue oxygenation were reported during supraceliac aortic cross-clamping [14].

In the debated area of selective blood perfusion, the concept proposed by Jacobs in the clinical setting is of special interest [15]. The author states that selective renal blood perfusion is an effective measure to protect renal function during open TAAA repair, but only if perfusion is provided with adequate volume and pressure. In a series of 279 consecutive TAAA repairs, selective visceral perfusion was instituted with centrifugal pump and renal volume flow was assessed with ultrasound. Pressure channels were placed in the perfusion catheters, enabling real-time-controlled perfusion of the kidneys. Repeated adjustments of renal artery perfusion pressure were performed as a dynamic process increasing arterial pressure in the renal catheters by diminishing flow and pressure to the femoral or the visceral arteries based on urinary output. The volume flow in the catheters for the renal arteries varied between 80 and 500 ml/min; intrarenal mean arterial pressure is between 60 and 112 mmHg. Uninterrupted urine output during aortic cross-clamping, irrespective of clamp time, and good postoperative renal outcomes were reported. Unfortunately, we are not allowed to consider these results as evidence because the article has been retracted for unresolvable issues in data collection [16].

The dispute regarding the effectiveness of blood perfusion is still unsolved; however, until today, both warm and cold blood have failed to support the hypothesis that blood perfusion is undoubtedly more effective in renal protection than cold crystalloid [9, 11]. Due to debated results and technical troubles and drawbacks issued with blood, current clinical practice has been mainly addressed to crystalloid perfusion, an easier and effective strategy based on an independent roller pump or even a simple dripping chamber (Fig. 17.3).

As far as the substrate is concerned, crystalloid has come to mean lactated Ringer's solution because most of the studies in this area are Ringer's solution-based. Whynn recently reported a retrospective analysis of postoperative renal function in 55 patients treated for TAAA with simple cross-clamp technique and profound renal cooling with crystalloid perfusion [12]. The renal perfusion was done by infusing 300 ml of lactated Ringer's solution at 4 °C containing mannitol 12.5 g and heparin 1000 units/l under moderate pressure into each renal artery. Very low rates of renal complications were reported with acute kidney injury in 7.6% of patients, acute renal failure in 4%, temporary dialysis in 2%, and permanent dialysis in 0.66% .

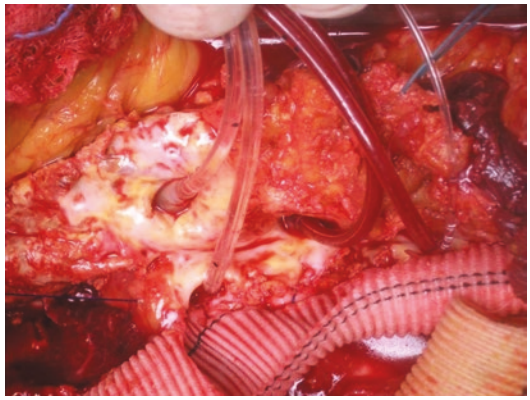

Fig. 17.3 Intraoperative image showing visceral artery reattachment in a visceral patch during an open TAAA repair. Of note, occlusion-perfusion balloon catheters into coeliac trunk, superior mesenteric artery for selective hematic perfusion, and occlusion-perfusion balloon catheters into renal arteries for selective cold crystalloid perfusion

However, we must be aware that renal damage with lactated Ringer's solution is still non-negligible and acute kidney injury may be found in the majority of patients [9, 11, 12].

Alternative crystalloids should be evaluated, and those developed over time for cardioplegia and organ preservation during transplantation are especially appealing in this research area.

17.3 Custodiol Solution: The Rationale, Results, and Future Perspectives

Custodiol or histidine-tryptophan-ketoglutarate (HTK) or Bretschneider's solution is a buffered crystalloid solution produced by Dr. Franz-Kohler Chemie GmbH, Bensheim, Germany. It was originally developed as cardioplegic agent by the German surgical research pioneer Hans Jürgen Bretschneider in 1964, with histidine added in 1975. It was soon registered as drug/medical product in several European countries.

The solution was developed with the aim of protecting the heart through the inactivation of organ function by withdrawal of extracellular sodium and calcium, together with intensive buffering of the extracellular space by means of histidine. Custodiol also contains high concentrations of the amino acids tryptophan and α-ketoglutarate that support membrane integrity and the osmotic agent mannitol. As far as the effectiveness of Custodiol as cardioplegic agent is concerned, the solution has successfully been applied for many years worldwide as a routine method, and it has been shown that even high doses (25 ml/kg) perfused in the heart are safe [17].

Furthermore, Custodiol was found to have the potential to exert its protective effect not only in the heart, but it has also become a standard perfusion/preservation solution of several organs during donor transplantation including the liver, kidney, pancreas, and lungs (Fig. 17.4). This indication has been approved by many countries, with the inclusion of the United States (FDA 510(k) approval).

In ex vivo application during renal transplant surgery, particularly encouraging results have been reported in renal function preservation. The donor kidney perfusion with Custodiol has been shown to maintain organ vitality during cold ischemic times of longer than 20 h, and the reduced rate of delayed graft function even compared to other solutions has been confirmed in meta-analysis, systematic review, and randomized trials [18–20].

This led to the question of whether the working principles of Custodiol can also be applied for direct in vivo perfusion in an organ as different from the heart as the kidney, where the aerobic metabolism and function are distinctly different.

The most used and investigated solution for in vivo direct renal perfusion is lactated Ringer's solution that is considered the benchmark substrate for the comparison of any other and that is totally different in concept and composition compared to Custodiol (Table 17.1).

Off-label in vivo Custodiol perfusion was reported in 1995 in a series of 11 patients undergoing renal tumor resection [21]. Continuous Custodiol perfusion was performed in all patients, the mean cold ischemia time was 62.1 min (range 18–88), and mean perfusion volume was 2875 cm^3. The kidneys resumed excretion within an average of 16.8 min (range 0–60) and no patient required dialysis. Postoperative renal function was unimpaired in all patients without changes in serum electrolyte levels and no disorders of cardiac conduction.

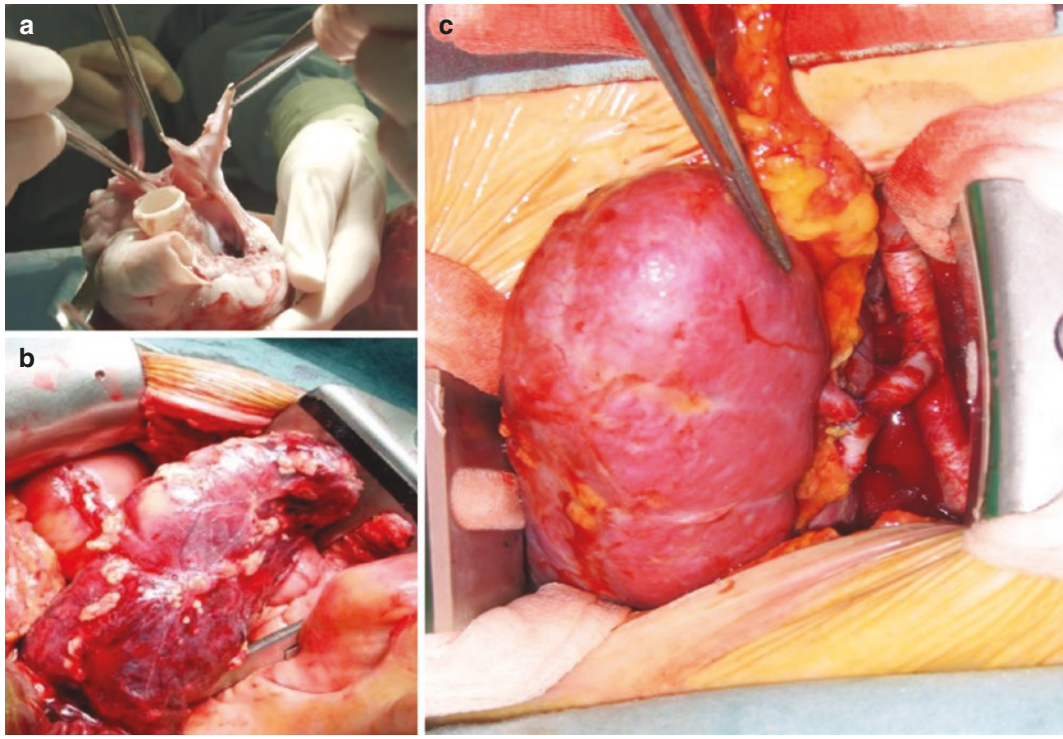

Fig. 17.4 Custodiol solution is a crystalloid solution approved for cardioplegia in open heart surgical procedures (**a**) as well as for the preservation of several organs in non-heart-beating donor transplantation including the pancreas (**b**) and kidney (**c**). During hypothermic storage and transportation to the recipient, the solution is left in the organ vasculature and is not currently indicated for continuous perfusion. The solution is ready to use, and the low potassium content makes preflushing from the organ unnecessary prior to implantation (courtesy of Dr. Carlo Socci)

Furthermore, several series with off-label use of Custodiol with direct renal arteries perfusion during suprarenal aortic clamping were reported, but, until 2014, no comparative studies were performed.

In 2014, Tshomba and Chiesa reported a retrospective comparative study to assess effectiveness in renal protection of Custodiol when compared with lactated Ringer's solution [22].

Study primary endpoints were acute kidney injury (AKI) according to the KDIGO guidelines criteria and postoperative eGFR calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [23]. Study provided statistical evidence of reduction of AKI incidence of almost 25% in the Custodiol group compared to Ringer, with a reduction of AKI rate in each AKI class, with a halved rate of AKI class II (Fig. 17.5). Furthermore, Custodiol renal perfusion resulted as the only independent intraoperative predictor of freedom from AKI and was associated with a significantly improved perioperative trend of eGFR. Interestingly, these improved renal outcomes were reported despite longer total renal ischemic time and increased transfusion requirements in Custodiol group.

Study findings support the hypothesis that Custodiol perfusion has the potential to be more effective than lactated Ringer's solution in preserving renal function. However, several limitations affect the study, including its retrospective nature and temporal bias related to the different periods in which the patients of the two study groups were treated.

A prospective trial has been designed specifically to resolve these issues. "CUstodiol and Ringer: whaT Is the Best Agent?" (CURITIBA) trial (ClinicalTrials.gov Identifier: NCT02327611) is a monocentric phase IV double-blinded randomized trial with parallel groups

Table 17.1 Different electrolyte concentrations in Custodiol and Ringer's lactated solutions

	Ringer (mmol/l)	Custodiol (mmol/l)
Sodium chloride	130.0	15.0
Potassium chloride	4.0	9.0
Magnesium chloride $6H_2O$	0.0	4.0
Histidine hydrochloride H_2O	0.0	18.0
Potassium hydrogen 2-Ketoglutarate	0.0	1.0
Histidine	0.0	180.0
Tryptophan	0.0	2.0
Mannitol	0.0	30.0
Calcium chloride $2H_2O$	2.7	0.015
Sodium lactate	28.0	0.0

Custodiol is a crystalloid solution with electrolyte concentrations similar to the intracellular environment, containing lower levels of sodium, calcium, potassium, and magnesium compared to a standard isotonic solution used for intravenous systemic infusion, such as Ringer, in which several salts are dissolved

Compared to extracellular solutions, organ perfusion with Custodiol should reduce the cellular swelling, toxicity, and damage caused by the ischemic insults. Custodiol solution also contains a high hydrogen ion buffer level that reduces acidosis associated with ongoing anaerobic metabolism. Custodiol solution is also enriched with three main factors: histidine/histidine hydrochloride (an amino acid buffering agent), tryptophan, and α-ketoglutarate enhancing the buffering and protecting capacity of the solution during the ischemic-induced acidosis

Alpha-ketoglutarate is also a key intermediate in the Krebs cycle, coming after isocitrate and before succinyl CoA and contributing in immediate intracellular ATP production, that is, the ultimate determinant of respiratory pathways, when oxygen is still available after ischemic time

aimed at comparing the effects of selective renal perfusion with Custodiol versus lactated Ringer's solution in patients undergoing open TAAA repair with renal artery crystalloid perfusion. The primary endpoint is the incidence of AKI; secondary endpoints are the eGFR trend during the hospital stays, together with the mortality rate at 30 days from the surgery and at 1 year. Also, serum cystatine C and urinary submarkers of renal injury including albumin (uALB), retinol-binding protein (uRBP), and neutrophil gelatinase-associated lipocalin (uNGAL) will be measured in order to evaluate more precisely filtration failure, protein reabsorption failure, and proximal and distal tubular injury. The trial results are still unpublished but, when available, will contribute to bridging the gap of our current knowledge about the real safety and effectiveness of Custodiol in vivo renal perfusion.

Currently, several new research lines and horizons might be imagined, among these, solutions specifically aimed at protecting hypothermic tissues from reperfusion damage. An interesting mechanism of cell damage after cardiac arrest in heart surgery has been found to be induced by hypothermia leading to cold-induced increase of iron-dependent formation of highly reactive oxygen species [24]. Custodiol-N, is a chloride- and histidine-poor cardioplegic solution based on Custodiol and supplemented by cytoprotective amino acids: LK614 and deferoxamine. LK614 is a lipophilic, membrane-permeable intracellular free iron chelator. Deferoxamine is a well-known extracellular iron chelator. Histidine has proven to be an excellent buffer and has therefore been introduced into Custodiol, but this protective buffer itself can be the origin of cytotoxity, and its concentration is reduced in Custodiol-N [25]. A study comparing the efficacy and safety of Custodiol-N with Custodiol in a model of heterotopic heart transplantation in the rat reported improved myocardial and endothelial function during the critical phase of reperfusion after heart transplantation, and this solution could also be assessed in hypothermic renal protection [26].

In the fascinating research area of organ protection during reperfusion, and especially in the area of renal protection, it has been also shown that several adhesion molecules, such as ICAM-1, may participate in the development of ischemic acute tubular necrosis [27]. The administration of anti-ICAM-1 antibodies preserves renal function and mitigates cell injury in experimental models of acute tubular necrosis, even if given as long as 2 h after the ischemic insult. In addition, mutant mice without ICAM-1 are almost completely protected against ischemic renal injury [28]. However, in human trials, the administration of anti-ICAM-1 monoclonal antibody did not prevent acute tubular necrosis in deceased-donor kidney transplant recipients following ischemia [29].

Several studies have also suggested a role for other adhesion molecules, such as E- and

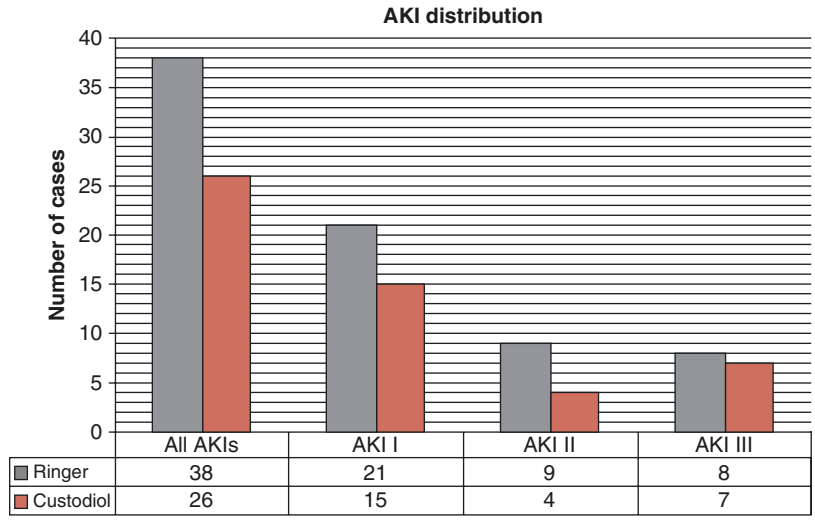

Fig. 17.5 Acute kidney injury (AKI) distribution in two groups of patients who underwent open TAAA repair with direct renal artery perfusion either with Custodiol or lactated Ringer's solution [22]

P-selectins and integrins, and in an animal model, the use of specific monoclonal antibody reduced ischemia/reperfusion injury [30].

17.4 Conclusions

The prognostic value of reduction of any class of postoperative AKI is priceless because acute kidney injury, even if often temporary and totally reversible, is a strong postoperative determinant of mortality after open TAAA repair. Patients with AKI type I have more than three times the in-hospital mortality rate of patients without AKI. Similarly, patients with AKI type II have close to twice the mortality rate of patients with AKI type I, and patients with AKI type III have 10 times the mortality rate of patients without AKI [31].

Every effort and research focused on full understanding of mechanisms of postoperative AKI and on the development of strategies specifically addressed to reduce both its occurrence and severity should be strongly supported.

Various molecules with the potential to contrast harmful processes of renal ischemia/reperfusion injury may be investigated for a direct in vivo perfusion. Furthermore, the efficacy of different strategies of arterial perfusion together with the effects of different temperatures of perfusion substrates should be carefully evaluated.

In this research area, 4 °C Custodiol renal perfusion, even if currently considered off-label, is simple and provides excellent protection, even in prolonged times of renal ischemia and during complex operations.

Larger comparative series, randomized trials, and the use of new biomarkers able to detect even subclinical renal injury together with continuous evaluation of new substrates are needed for an incessant renal outcomes improvement.

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