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A new method for conservative renal surgery – experimental and first clinical results *

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Eine neue Methode der konservativen Nierenchirurgie – experimentelle und erste klinische Ergebnisse

Zusammenfassung. Zur Verlängerung der renalen Ischämie stehen bisher zwei Verfahren zur Verfügung: 1) eine Oberflächenkühlung mit Eis und 2) eine Perfusionskühlung mit einer extrazellulären Lösung. Beide Methoden nutzen nur das Prinzip der Stoffwechselsenkung durch Kühlung. Während der Wiedererwärmung bei der Operation geht der Ischämieschutz verloren oder die Niere muß erneut gekühlt werden. Deshalb sollte eine neue Protektionslösung den Energieverbrauch zusätzlich zur Kühlung auch durch ihre Zusammensetzung senken. Bei offenen Herzoperationen wird die HTK-Lösung nach Bretschneider bereits klinisch angewendet. In 71 Experimenten an Hundenieren wurde die Ischämiezeit durch diese Lösung von 15 auf 120 min bei 35 °C und von 45 auf 360 min bei 25 °C verlängert. Nach 120 min Ischämie bei 30 °C betrug die glomeruläre Filtrationsrate ca. 20 ml/min 100 g_{FG} innerhalb von 3 h Reperfusion. Nach 6 Tagen postoperativ war die GFR wieder 40 ml/min 100 g_{FG}. Es konnte kein ischämischer Schaden durch histologische Untersuchungen mehr festgestellt werden. Der klinische Nutzen dieser Methode konnte in 7 klinischen Anwendungen gezeigt werden. Die Ischämiezeit betrug bis zu 113 min und das Kreatinin lag zwischen 0,8 und 2,4 mg% am 6. postoperativen Tag. Dieses Protektionsverfahren führt also zu einer verbesserten Nierenfunktion in der postoperativen Phase. Eine längere Ischämiezeit wird von der Niere vertragen, und unter Anwendung dieser Technik wird eine ausgezeichnete Übersichtlichkeit während der Nierenoperation erreicht, was eine radikale Tumorexzision erleichtert.

Schlüsselwörter: Nierenperfusion – Renale Ischämie – HTK-Protektion – Tumorexzision – Nierenfunktion – Intrarenaler pH

Summary. So far two methods for prolonging the tolerance of renal ischemia are available: 1) surface cooling with crushed ice and 2) perfusion cooling with an extracellular-like solution. Both methods use only the principle of reducing metabolism through cooling. While rewarming during surgery the ischemic protection is lost, or the kidney must be cooled once again. Therefore, a new preservation solution should reduce energy consumption due to its composition in addition to cooling. For open heart surgery, the HTK solution by Bretschneider is already used clinically. In 71 dog *kidney* experiments, the ischemic time kidneys could tolerate was prolonged by this solution from 15 to 120 min at 35 °C and from 45 to 360 min at 25 °C. After 2 h of ischemia at 30 °C glomerular filtration rate was about 20 ml/min · 100 g_{ww} within 3 h of reperfusion. After six postoperative days the filtration rate was 40 ml/min · 100 g_{ww}. No ischemic damage could be recognized by histological investigations. The clinical effectiveness of this method was shown in 7 clinical applications. Ischemic duration lasted up to 113 min, and blood creatinine was between 0.8 and 2.4 mg% at the 6th postoperative day. Use of this preservation technique thus leads to improved kidney function immediately following operation. Longer ischemia can be tolerated by a kidney thus protected, and using this technique excellent visibility can be achieved during intrarenal surgery, simplifying, for example, tumor extirpation.

So far, two procedures have been available for in situ kidney protection during longer periods of ischemia: a) superficial cooling with ice, and b) perfusion cooling with either Ringer lactate or Sacks solution [1, 32, 43]. Both procedures have not been satisfactory, as the temperature dependence of ischemic metabolism of the kidney is great. Reducing of temperature from 35 to 25 °C prolongs a critical renal tissue acidosis by the factor of 4, from 25 to 15 °C by the factor of 3.5 and from 15 to 5 °C by the factor of 2.8 (Fig. 1). Thereby it is understandable that simple cooling may be very effective and would allow

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Table 1. HTK solution of Bretschneider (Custodiol®)

NaCl	15 mM
KCl	9 mM
$MgCl_2$	4 mM
K-α-Ketoglutarate	1 mM
Tryptophane	2 mM
Histidine	180 mM
Histidine-HCl	18 mM
Mannit	30 mM
pH at 8 °C	7.3
pO_2 at 37 °C	200 mm Hg
Osmolarity	310 mosmol/l

ischemia up to 1 h, but thereby it is also explained that the ischemic protection is getting lost by rewarming during in situ operation. Therefore – in our opinion – an organ protective solution should be effective due to its composition in addition to cooling [6, 13, 14, 19, 20, 26, 27, 34].

The cardioplegic solution HTK by Bretschneider has successfully been applied in cardiac surgery during operations on the arrested heart for many years as a routine method [6, 11, 35, 38]. This led to the question whether the working principle of this solution can also be applied to an organ as different as the kidney. The aerobic myocardial metabolism is distinctly different from the metabolism and function of the kidney. For the ischemic metabolism there are similiar principles: glycolysis is the only known way of anaerobic energy gain [15]. But this energy is only enough for preparing sufficient postischemic function if ischemia does not last too long and if it comes to a decline of adenosinetriphosphate (ATP) and pH and an increase in lactate [5, 17, 18, 21]. The essential energy consumption of the kidney is – according to investigations of Deetjen and Kramer [9] – the sodium reabsorption. The organ protective solution HTK contains therefore only a sodium concentration of 15 mM. Beside this the solution is nearly calcium-free and magnesium is enriched to 4 mM. This composition reduces the ischemic energy consumption. An ischemic tissue acidosis is prohibited by an effective buffer such as histidine/histidine-hydrochlorid in a concentration of nearly 200 mM [7, 22] (Table 1).

Materials and methods

Experiments

For our *experiments* we used 71 kidneys of German shepherd bastard dogs of both sexes, with an average body weight of 32 kg. Thirty minutes following premedication with 90 mg dipidolor and 0.5 mg atropin, the animals were anaesthesized with thiopental. Anaesthesia was maintained with a combination of fentanyl, halothane, and a 3:1 mixture of N_2O and oxygen (for further details see [24]). Following median laparotomy, the kidneys were isolated from the surrounding tissue under ligation of all capsule vessels; then the renal artery, the renal vein, and the ureter were dissected. For the experimental perfusion of the kidneys with the HTK solution, the renal perfusion catheter with its terminal pressure lead and 4 lateral openings was inserted into the abdominal aorta distal to the branching of the external iliac artery. To avoid any preperfusion ischemia, the flow of HTK-solution (Custodiol®, Dr. Franz Köhler Chemie GmbH, W-6141 Alsbach-Hähnlein 1, FRG), cooled to 4 °C, was initiated at a flow rate of 100 ml/min while the catheter was advanced into the renal artery, where it was fixated by means of a torniquet string. Then the renal artery was clamped, the perfusion catheter removed, and the renal vein incision closed by means of atraumatic suture material. The kidney remained in situ without any further cooling, resulting in a median temperature of 30 °C during 120 min of ischemia (group 2). After returning to blood perfusion urine was collected in 15-min fractions, and the glomerular filtration rate (GFR) was calculated by endogenous creatinine clearance. At the end of a 2-h postischemic recovery period, the kidney was extirpated, weighed, analyzed as to high-energy phosphate and lactate content and was prepared for morphological evaluation by perfusion fixation immediately thereafter. In the experiments of group 1 the kidneys were exstirpated after protective perfusion and analysed for ATP, lactate (Boehringer Mannheim GmbH, FRG) and intrarenal pH (pH electrode, Dr. Ingold KG, FRG).

The experiments consisted of three groups:

1) In vitro studies ($n=36$ kidneys) For measuring intrarenal pH, ATP and lactate the kidneys were extirpated without any protection and incubated at approx. 30 °C. This unprotected group was used as a control group and compared to HTK-protected kidneys. Intrarenal pH was measured continuously, ATP and lactate were measured during 2 h of ischemia every 15 or 30 min (described in detail in [26]).

2) In situ reperfusion studies ($n=30$ kidneys) The kidneys were perfused with the HTK solution, left in situ at a mean ambient temperature of 30 °C and were reperfused for 3 h after closing of the renal vein. The contralateral kidney of each experiment served as control; it was not perfused and was left in situ untreated.

3) Survival studies ($n=5$ dogs) This group was treated like the second group, but the contralateral kidney was nephrectomized immediately and the abdomen was closed for survival of the animals.

Human kidney perfusion

For the *human* kidney perfusion we used an 7 Charrier angiography catheter and in the last 2 cases we placed the catheter in the renal artery via the a. mesenterica inferior and aorta abdominalis using a Charrier 9 catheter (Angiomed GmbH, FRG). The flow was immediately increased in order to reach a perfusion pressure of 100 mm Hg at the end of the first minute of protective perfusion. The rate of perfusion then amounted to about 400 ml/min/100 g_{kidney} in our animal experiments and to about 250 ml/min in our human cases. Within the first minute of perfusion an incision into the renal vein was performed to drain the perfusate, and the renal vein was clamped. The renoprotective perfusion was continued for 6 min in the animal experiments and to 10 minutes in human cases. This is a total amount of ≈2000 ml in animal experiments and 2500 ml in human cases.

Experimental results

In unprotected kidneys the intrarenal pH drops from 7.3 to 6.4 within approx. 10 min at 35 °C. At 25 °C a pH of 6.4 is reached after approx. 40 min, at 15 °C an intrarenal pH of 6.4 is reached after nearly 3 h and at 5 °C after about 12 h (Fig. 1). During HTK perfusion of kidneys the intrarenal pH is not altered. During ischemia of 2 h at about 30 °C the tissue pH is not below 6.7 and a normal pH is reached at least within 3 h of reperfusion with

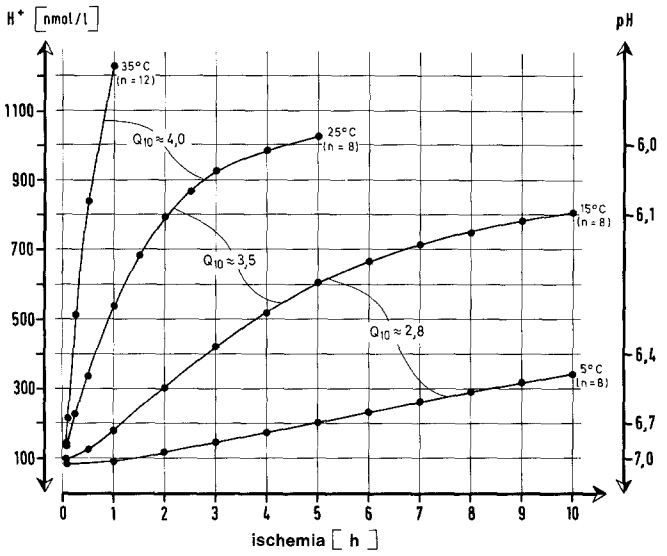


Fig. 1. Intrarenal pH in unprotected kidneys during ischemia at different temperatures

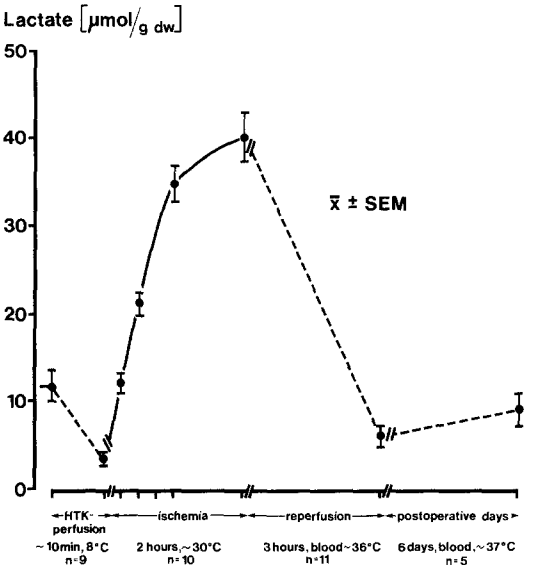


Fig. 3. Renal lacatate during HTK perfusion, ischemia and reperfusion

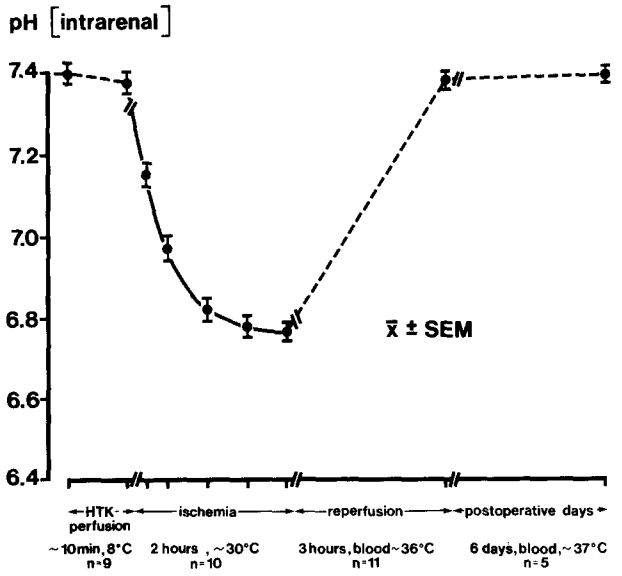


Fig. 2. Intrarenal pH during HTK perfusion, ischemia and reperfusion

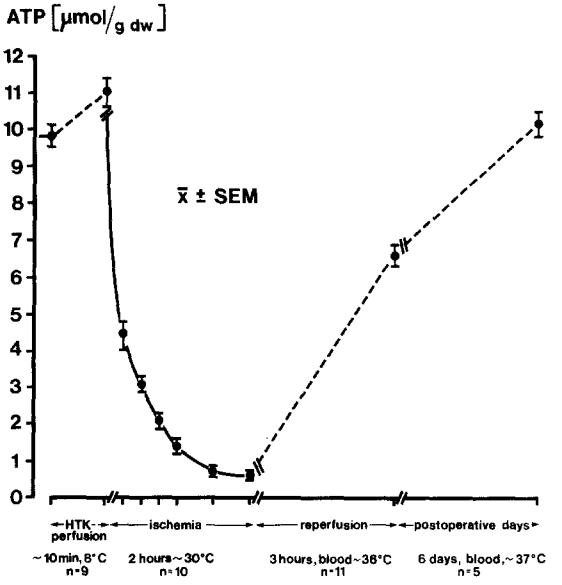


Fig. 4. *A*denosine-*tri*-*p*hosphate (ATP) during HTK perfusion, ischemia and reperfusion

blood (Fig. 2). The lactate content of the kidneys is reduced by perfusion with the HTK solution from 12 µmol/g_{dw} to 2–3 µmol/g_{dw}. During ischemia it climbs up to about 40 µmol/g_{dw}, but is washed out within 3 h of reperfusion (Fig. 3). The ATP content rises from 10 to 11 µmol/g_{dw} during HTK perfusion and is metabolized during ischemia to nearly 0.5 µmol/g_{dw}. After 3 h of reperfusion the ATP is about 7 µmol/g_{dw} and is normal after 6 postoperative days (Fig. 4). The glomerular filtration rate is during HTK perfusion about 10 ml/min · 100 g_{ww}, during ischemia sero and goes up to nearly 20 ml/min · 100 g_{ww} during 3 h of reperfusion. After 6 postoperative days it is within the normal range of 40–50 ml/min · 100 g_{ww} (Fig. 5). The structure of glomerula as well as proximal and distal tubules is well preserved after 2 h of ischemia and 3 h of reperfusion (Fig. 6).

Clinical results

The operated clinical cases are listed in Table 2. Five patients had a renal cell carcinoma, one an angiomyolipom and one a staghorn calculus. The ischemic time of the operated kidneys lasted from 36 to 113 min in situ (about 30 °C in the mean). The postoperative creatinine value at the 6th day ranged from 0.8 to 2.4 mg% and the isotope clearance was 183 to 347 ml/min at this day.

The preoperative angiogramm of the patient S. A., female, shows the tumors in both kidneys (Fig. 7). The operative situs is shown in Fig. 8 with the perfused and protected kidney and the tumor excised. The morphology of the surrounding tissue of the tumor after about 70 min of ischemia at approx. 30 °C shows normal glomerular capillaries and well preserved tubular epithelia (Fig. 9).

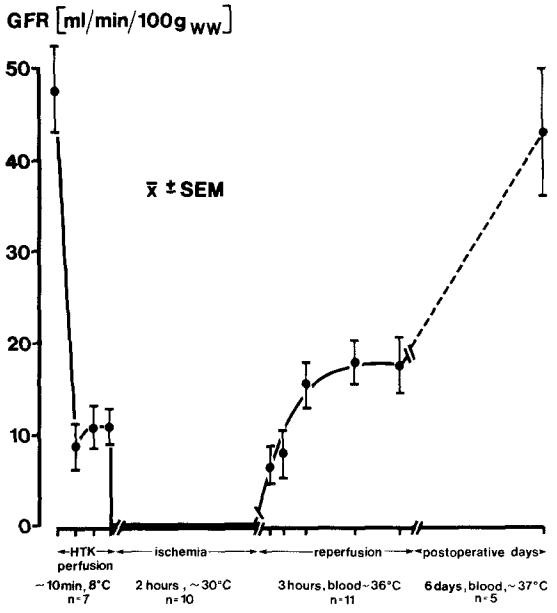


Fig. 5. Glomerular filtration rate (GFR) during HTK perfusion, ischemia and reperfusion

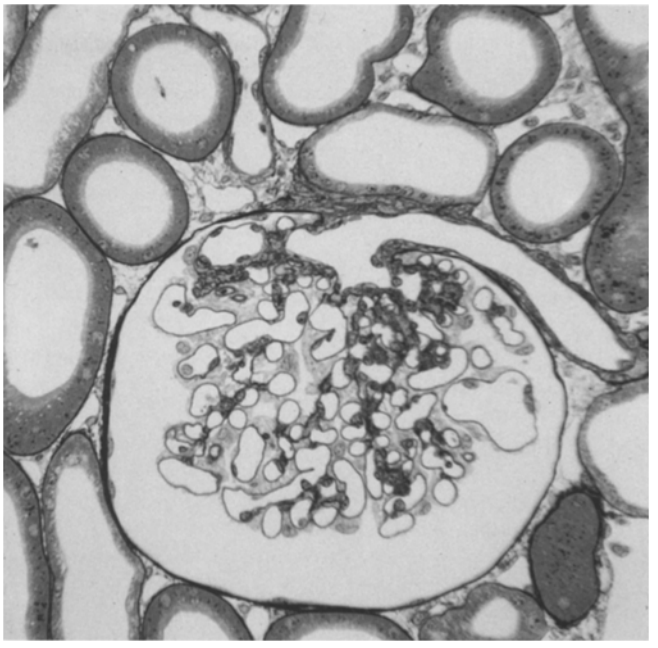
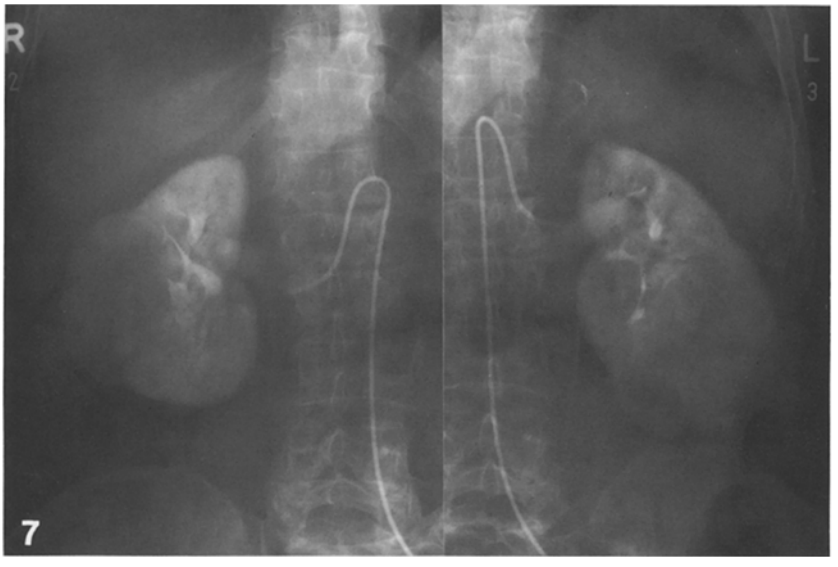
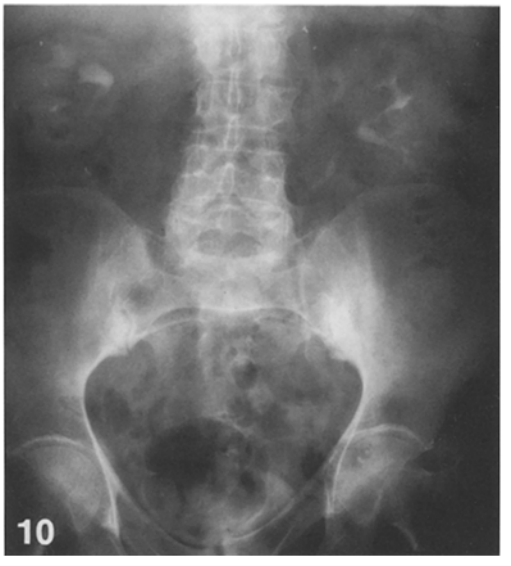


Fig. 6. Glomerular and tubular structure after HTK protection, ischemia and reperfusion





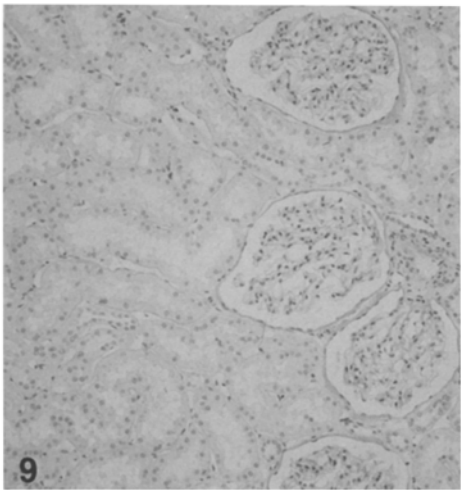


Fig. 7. S.A., female, kidney cell carcinoma in both kidneys, preoperative angiogram

Fig. 8. S.A., female, intraoperative situs after HTK protection and tumor excision

Fig. 9. Glomerular and tubular structure of healthy renal tissue after HTK protection and 70 min of ischemia at 30 °C

Fig. 10. S.A., female, i.v. urogram about 7 weeks postoperatively

Table 2. Clinical use of in situ protection against renal ischemia with the HTK solution by Bretschneider

Patient	Diagnosis	Ischemia (min)	Plasma-creatinine at 6th POP day (mg %)	Isotope clearance (%)
S.L.	Angiomyolipom Left Kidney	48	0,8	TBCL = 347 (ml/min) R. = 56% L. = 44%
P.A.	Staghorn calculus Right Kidney	113	1,1	TBCL = 207 (ml/min) R. = 37% L. = 63%
S.A.	Renal cell Carcinoma Bilateral	1) L: 36 2) R: 70	1,1 1,9	TBCL = 341 35/65 TBCL = 227 41/59
F.G.	Renal cell Carcinoma Left kidney	54	1,2	TBCL = 287 (ml/min) R. = 100% L. = 0%
V.E.	Renal cell carcinoma left Cystic kidney Right	55	2,4	TBCL = 183 (ml/min) R. = 41% L. = 59%
L.H.	Renal cell carcinoma left Renal pelvic Carcinoma right	55	1,6	TBCL = 338 (ml/min) R. = 65% L. = 35%

TBCL = total body clearance
Isotope-clearance = ^{131}J-hippuran-clearance
POP = postoperative

The postoperative i.v. urogramm shows adequate contrast media secretion approx. 7 weeks after the operation (Fig. 10).

Discussion

Kidney protection includes 4 periods: 1) the preischemic period, 2) the protective perfusion, 3) the ischemic period and 4) the postischemic recovery [27].

The preischemic period includes initiating and stabilizing an appropriate anaesthesia, which prevents vasospastic reactions of the kidney as well as achieving a sufficient diuresis to wash out different osmotic gradients existing from renal cortex to medulla prior to protective perfusion [24], as the protective solution has only one osmolarity (HTK solution: approx. 300 mosmol/kg_{H_2O}). This also reduces the energy demand for tubular reabsorption, as filtration is essentially passive requiring little expenditure of energy which diminishes renal oxygen consumption. In kidney preservation for transplantation there is normally no need for additional diuresis, as the donor is diuretic because of diabetes insipidus. For in situ protection with the HTK solution 500 ml glucose 5% and furosemide (0.1 mg/kg body weight) should be given about 30 min before protective perfusion; this was also done in our experimental experiments and in human cases [23, 25].

The protective perfusion of the kidney with HTK solution results in rapid, homogeneous cooling of the organ – from approx. 35 °C to 10 °C within 2 min – together with a reduction of renal oxygen consumption from 6–7 ml/min/100 g_{ww} before protective perfusion to approx. 0.2 ml/min/100 g_{ww} after 2–3 min, which is possible because of the temperature and, in addition, the electrolyte composition of the solution: by sodium reduction to 15 mM, by calcium washout and magnesium elevation (see Table 1) [8, 31]. During this period the intrarenal pH is kept constant, the lactate is washed out like other substances e.g. BUN, Na^+ and Ca^{++} and ATP is not lowered (see Fig. 2–4). Histidine has a concentration of 200 mM in the solution. There could be an influx into the cell during perfusion or ischemia, but the transport of histidine is Na-depending [16], and sodium is reduced to 15 mM in the solution.

Surface cooling is inhomogenous and may be harmful to the renal cortex, protective to the outer medulla, but insufficient to the inner medulla. Ringer lactate solution is effective by homogenous cooling, but does not use the protective effect of reducing energy demand by electrolyte composition (reduction of Na^+ and Ca^{++}, elevation of Mg^{++}).

Following perfusion, the period of ischemia begins. Temperature and duration influence the degree of ischemic stress. Three parameters – intrarenal pH, tissue content of lactate and of ATP – are used to demonstrate the anaerobiosis in protected ischemic kidneys. Intrarenal pH drops from initially pH 7.4 to about 6.7 after 2 h at about 30 °C in HTK protected kidneys. After this ischemic stress in unprotected kidneys the intrarenal pH would be below 6.0 (see Fig. 1) [2, 22]. Lactate climbs up to 40 µmol/g_{dw}, but is washed out already within 3 h of reperfusion. As lactate transport depends on pH [17], it is of importance to keep intrarenal acidosis above 6.8–6.7 by buffering (histidine/histidine-HCl, 200 mM), otherwise cellular volume dysregulation would follow [10]. During perfusion of the kidney with HTK solution, ATP content is about 11 µmol/g_{dw} and after 120 min at 30 °C it is below 1 µmol/g_{dw}. After 3 h of reperfusion it is 2/3 again. This is possible if intracellular metabolism is not irreversibly destroyed during ischemia, but is sufficient to cover energy demand during ischemia. Therefore a high ATP-content at the end of ischemia may be due to insufficient ischemic metabolism by low intrarenal pH inhibition (12, 29, 41]. This is probably followed by structural deterioration, leading for example to failed "reflow" [10]. On the other side a low ATP-content at the end of ischemia can be due to a high and unnecessary energy turnover during ischemia, for example by glucose addition to the solution, leading probably to an unsufficient structural preservation [12]. Thus, only intact structure of the kidney in combination with successful postischemic reperfusion demonstrates sufficient protection [28, 30].

Postischemic aerobic recovery: The kidneys were perfused with the HTK solution as described, then exposed to a

120 min ischemia at body temperature, resulting in a mean kidney temperature of 30 °C, and finally reperfused in situ. The renal glomerular filtration rate is nearly 20 ml/min · 100 g_{ww} after 3 h of reperfusion and is within a normal range after six days postoperatively (Fig. 5) [23, 25]. The morphology shows well preserved glomerular and tubular structures. From these experimental results we started clinical use of this new preservation method.

Different solutions have been used for renal preservation, e.g. Ringer lactate, Euro Collins [42] and more recently U.W. solution. We compared our results with the results gained by Euro Collins protection. For in situ protection at an ambient temperature of 30 °C the Euro Collins solution is worse than without any protection [25, 26]. Ringer lactate uses only the cooling effect, as the extracellular sodium concentration in this solution does not reduce energy demand additionally. For clinical use external cooling should be not necessary, as it prevents preparation in detail on the kidney. The Euro Collins and the U.W. solution are in our opinion dangerous for in situ protection, as the potassium content in both is about 115 mM and the U.W. solution contains adenosine, a strong vasoconstrictor to the kidney.

The application of the protective solution was performed in the first 5 clinical cases with a preoperatively placed catheter via the A. femoralis in so-called Seldinger technique with a 7 Charrier (1 Charr. = 1/3 mm) angiography catheter [4]. As function was lost in one kidney because of occlusion of renal artery by this technique prior to protective perfusion, we placed the catheter in the last two cases intraoperatively via the A. mesenterica inferior and could use even a 9 Charrier catheter, which is of advantage because of the high flow rate during protective perfusion. Beside this an intraoperative last decision is possible whether to use this organ-protective measurement or not and to avoid a reduced blood perfusion of the kidney during its preparation by the catheter. This new in situ preservation technique is of advantage for partial nephrectomy as the operation field is blood and ice free and the tumor can be excised precisely and totally, and a fresh frozen biopsy can be taken from the tumor ground during excellent visibility conditions (see Fig. 8). Radical tumor extirpation is of importance for prognosis [3, 33, 36, 37, 39, 44]. Tumor enucleation should be avoided [36].

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