Urol Res (1988) 16:57–62

Urological Research
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Metabolic, Energetic and Structural Changes in Protected and Unprotected Kidneys at Temperatures of 1 °C and 25 °C*

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Summary. In 110 canine kidneys, we examined the time course of energy rich phosphates, lactate, intrarenal ph and renal morphology with Euro-Collins- or with HTK-protection of Bretschneider and compared these findings with unprotected kidneys during complete ischemia at 1 °C and at 25 °C. Both kidney protective solutions prolonged energy-rich phosphate-decline by a factor of 3–4 compared with that of unprotected kidneys. The lactate increase was greater in Euro-Collins-protected kidneys than in HTK-protected and in unprotected kidneys, leading to pH values of 6.5 in Euro-Collins and to 6.4 in unprotected kidneys after 24 hours, in contrast to a pH-value of 7.3 with HTK-protection. This may be the reason for structural deterioration seen in unprotected and in Euro-Collins-protected kidneys after 12, and 48 h of ischemia at 1 °C, whereas in HTK-protected kidneys a sufficient preservation of structure can be seen. In one *human* kidney, protected with Euro-Collins-solution, we were able to show that at 1 °C intrarenal pH and lactate accumulation is similiar to the levels in canine kidneys. In Euro-Collins preserved kidneys lactate accumulation at 25 °C is even greater than at 1 °C, leading to inhibition of energy metabolism and to structural deterioration, whereas HTK-solution, because of its high buffer concentration, is able to maintain ischemic metabolism leading to sufficient protection of intrarenal pH and of adenine nucleotides as well as structural protection at 1 °C and at 25 °C.

Key words: Energy metabolism – Euro-Collins-solution – HTK-solution – Kidney preservation – Intrarenal pH – Renal ischemia – Structural preservation

* Supported by the Deutsche Forschungsgemeinschaft, SFB 330 – Organprotektion – Göttingen

Table 1. Composition of kidney protective solutions in mMol/l

	HTK-solution by Bretschneider	Euro-Collins solution
Na^+	15	10
K^+	10	115
Ca^{++}	–	–
Mg^{++}	4	–
Cl^-	50	15
HCO_3^-	–	10
HPO_4^{--}	–	43
$H_2PO_4^-$	–	15
Glucose	–	198
Tryptophan	2	–
K^+-α-Ketoglutarate	1	–
Histidine/Histidine-HCl	180/18	–
Mannitol	30	–
Osmolarity (mosmol/l)	310	406
pH (8 °C)	7.3	7.3
pO_2 (37 °C)	200	100

Introduction

During kidney preservation for transplantation there are several phases: 1) renal blood flow, depending on the circulation of the donor; 2) perfusion with the protective solution, for example Euro-Collins-solution [1, 9] or HTK-solution of Bretschneider [5–8, 14] (Table 1); 3) ischemia, when the ischemic stress depends on the duration and on the temperature during this period and 4) reperfusion with blood [25].

After short term perfusion with protective solutions [23], the kidney temperature falls to about 10 °C and it is then stored on ice at about 1 °C [9]. During retransplantation a so-called "second warm ischemia" may occur, as it is not always possible to keep the temperature of the kidney at 1 °C. This temperature may rise to 25 °C. Therefore we

examined dog kidneys at 1 °C over 96 hours and at 25 °C over 420 min under Euro-Collins- or HTK-protection and compared them to unperfused kidneys, over 24 h at 1 °C and over 240 min at 25 °C.

As a single cause for cell damage is difficult to establish [31], we examined kidneys with respect to several parameters: energy rich phosphates, lactate and intrarenal pH and morphology.

Material and Methods

Experiments were performed on 110 kidneys of mongrel dogs of both sexes with a body weight of 28–32 kg. A detailed description of the typical experimental procedure and especially of the perfusion technique with HTK- or Euro-Collins-solution has been published [23, 26].

The unperfused, i.e. unprotected, control-kidneys were removed under the same conditions as the protected kidneys and stored immediately in ice-cold (≈ 1 °C) or 25 °C warm electrolyte-solution (Tutofusin; Pfrimmer & Co. GmbH, Erlangen, FRG). Protected kidneys were stored in the same solution, which was used for perfusion: Euro-Collins- (Dr. E. Fresenius, Bad Homburg v.d.H., FRG) or cardioplegic-solution HTK by Bretschneider (Dr. Franz Köhler Chemie GmbH, Alsbach, FRG).

In the cold ischemic group (≈ 1 °C) tissue samples were taken from each kidney at specific times, i.e. 0, 6, 12, 18, 24, 48, 72 and 96 h. In addition intrarenal pH was measured continuously in 8 kidneys without protection, in 3 kidneys with Euro-Collins-protection and in 4 kidneys with HTK-protection by a implanted electrode (pH-Elektrode, Typ LOT 403-M6; Dr. Ingold KG, Frankfurt/Main, FRG) [20].

In the 25 °C group 10 tissue samples were taken over 420 min of ischemia from each kidney (0, 15, 30, 60, 120, 180, 240, 300, 360 and 420 min and intrarenal pH was measured continuously.

Tissue samples of about 2 g – consisting of about 2/3 cortex and 1/3 medulla – were homogenized in cold perchloric acid and ATP (Testkombination ATP, Boehringer Mannheim GmbH, Mannheim, FRG), ADP, AMP (Testkombination ADP/AMP, Boehringer Mannheim GmbH, Mannheim, FRG) and lactate [16] were analysed enzymatically. In addition to biochemical analysis, the 71 kidneys were morphologically investigated during ischemia at 1 °C in the three groups (unprotected, Euro-Collins- and HTK-protected). From these data we compare kidneys of 12 h of ischemia at 1 °C without protection with kidneys of 48 h either under Euro-Collins- or under HTK-protection, as these times are relevant to the clinical situation, and can be related to energy and pH levels.

Morphological studies were performed on 1–2 g kidney slices from all parts of the kidney. The tissue was fixed in 1.5% glutaraldehyde and paraffin embedded.

Results

Normal canine kidneys had an ATP-content of about 10 $\mu mol/g_{dw}$, the ADP was about 4.0 $\mu mol/g_{dw}$ and the AMP-content was 1,5 $\mu mol/g_{dw}$; the *T*otal *A*denine *N*ucleotides (TAN) were approx. 15 $\mu mol/g_{dw}$.

After six hours of ischemia at *1 °C* the ATP was in the *unprotected kidneys* 1,5 $\mu mol/g_{dw}$ and after 24 h it was 0.5 $\mu mol/g_{dw}$. The ADP-content was after 6 h 1.8 $\mu mol/g_{dw}$ and after 24 h it fell to 1 $\mu mol/g_{dw}$. The AMP rose to 6 $\mu mol/g_{dw}$ after six hours of ischemia and fell to about 5 $\mu mol/g_{dw}$ during the 24 h. In unprotected kidneys the lactate-content was 11 $\mu mol/g_{dw}$ initially which rose to 50 $\mu mol/g_{dw}$ during 24 hours at this temperature. Intrarenal pH fell from 7.2 to 6.4 within 24 h (Fig. 1).

After 60 min of ischemia at *25 °C* the ATP-content in unprotected kidneys fell from 10 $\mu mol/g_{dw}$ to 1.5 $\mu mol/g_{dw}$. The ADP-content fell from 4 $\mu mol/g_{dw}$ to about 1 $\mu mol/g_{dw}$ within this time, while AMP rose from 1.5 $\mu mol/g_{dw}$ to about 8 $\mu mol/g_{dw}$ during 30 min and then declined to 5 $\mu mol/g_{dw}$ within 120 min of ischemia at 25 °C. Renal lactate content rose to 90 $\mu mol/g_{dw}$ during 240 minutes of complete ischemia. Intrarenal pH changes from 7.4 to 6.0 during this time (Fig. 4).

The ATP-content in *Euro-Collins-kidneys* was 8 $\mu mol/g_{dw}$ at the beginning of ischemia. It fell to about 1 $\mu mol/g_{dw}$ within 24 h of ischemia at *1 °C*. The ADP was 4 $\mu mol/g_{dw}$ initially and fell to 2 $\mu mol/g_{dw}$ within 24 h; thereafter little change ensued. The AMP-content was 7.5 $\mu mol/g_{dw}$, falling to 6.3 $\mu mol/g_{dw}$ after 24 h and to 6.0 to 4.3 and to 4.6 $\mu mol/g_{dw}$ after 48, 72 and 96 h of ischemia at 1 °C. The renal lactate-content was 15 $\mu mol/g_{dw}$ and rose to 130 $\mu mol/g_{dw}$ during 96 h of ischemia. Intrarenal pH falls from 7.3 to 6.0 during ischemia of 96 h at 1 °C (Fig. 2).

During ischemia at *25 °C* under Euro-Collins-protection the ATP-content fell from 8 $\mu mol/g_{dw}$ to 3 $\mu mol/g_{dw}$ in 180 min. The ADP-content was initially 4 $\mu mol/g_{dw}$, which was reduced slightly to 2.5 $\mu mol/g_{dw}$ during ischemia at 25 °C. The AMP-content fell from 7.5 $\mu mol/g_{dw}$ to about 5 $\mu mol/g_{dw}$ within 240 min. Intrarenal lactate-content rose to 330 $\mu mol/g_{dw}$ within 7 h and intrarenal pH declined from 7.1 to 5.1 (Fig. 5).

The ATP-content approached 12 $\mu mol/gdw$ after protective perfusion with the *HTK-solution.* After 24 h of ischemia at *1 °C* it was below 0.5 $\mu mol/g_{dw}$. The ADP-content was about 4 $\mu mol/g_{dw}$ at the start of ischemia and 1.5 after 24 h. The AMP was 7 $\mu mol/g_{dw}$ and fell to 4.8 $\mu mol/g_{dw}$ within 72 h of ischemia. Renal lactate-content was 5 $\mu mol/g_{dw}$ rising to 40 $\mu mol/g_{dw}$ within 72 h. Intrarenal pH remained at 7.3 during 96 h under this protection at 1 °C (Fig. 3).

The ATP-content fell from about 10 $\mu mol/g_{dw}$ to 1 $\mu mol/g_{dw}$ within 120 min of ischemia at *25 °C* with HTK-protection. The ADP-content was also 1 $\mu mol/g_{dw}$ after 120 min. The AMP rose to nearly 10 $\mu mol/g_{dw}$ during 30 min of ischemia and then fell to 5 $\mu mol/g_{dw}$ during the ensuring 300–360 min of ischemia at this temperature. The renal lactate-content reached 90 $\mu mol/g_{dw}$ after 300 min and the intrarenal pH fell from 7.2 to 6.8 during the 420 min of ischemia (Fig. 6).

In one *human* kidney, protected with *Euro-Collins-solution,* which was not possible to transplant because of contralateral renal artery stenosis and hypertension (Goldblatt) of the donor, we were able to determine the same parameters as in our canine investigations at 1 °C. The lactate-content-increase and the intrarenal pH were almost the same as in canine kidneys under the same conditions, but energy rich phosphates declined faster in this human kidney than in the canine kidneys (Fig. 7).

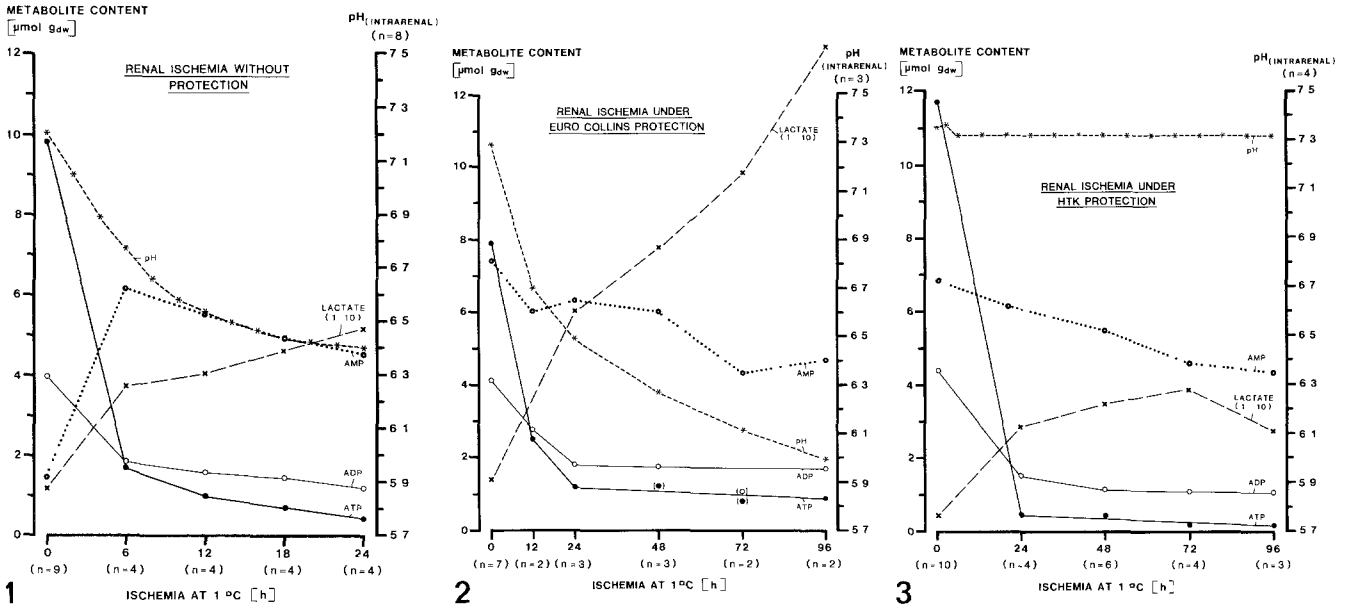

Fig. 1. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 1 °C over 24 h in unprotected kidneys

Fig. 2. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 1 °C over 96 h under Euro-Collins-protection

Fig. 3. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 1 °C over 96 h under HTK-protection according to Bretschneider

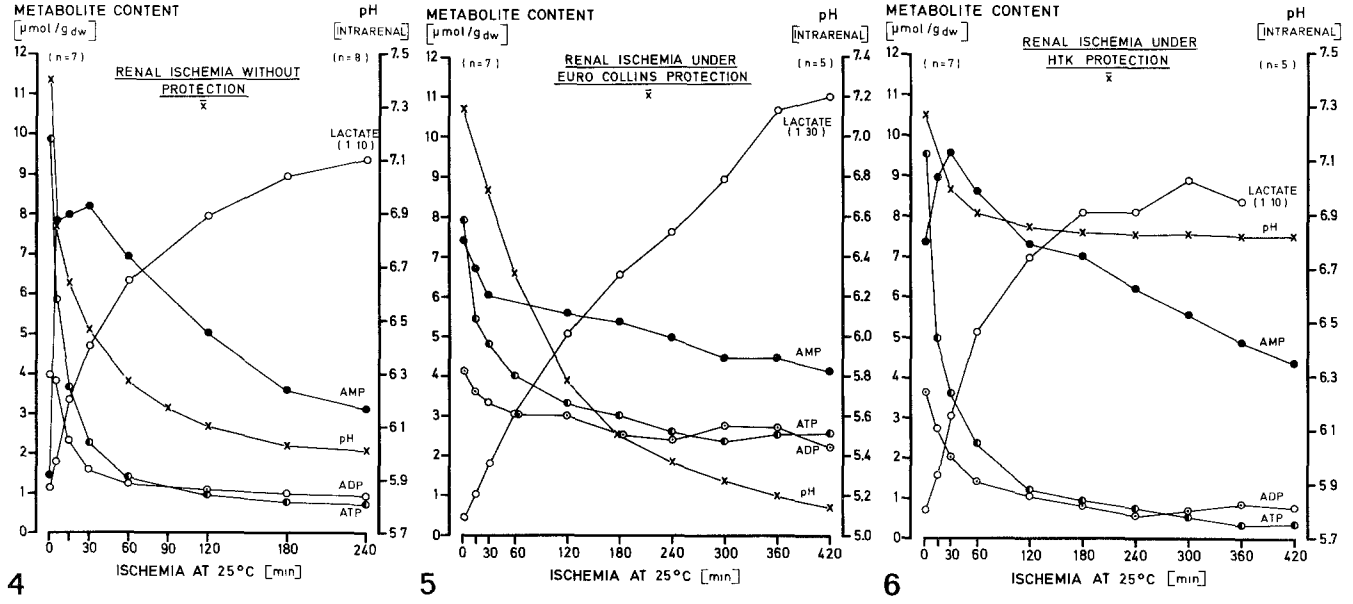

Fig. 4. Renal mebabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 25 °C over 240 min in unprotected kidneys

Fig. 5. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 25 °C over 420 min under Euro-Collins-protection

Fig. 6. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH during a complete ischemia at 25 °C over 420 min under HTK-protection according to Bretschneider

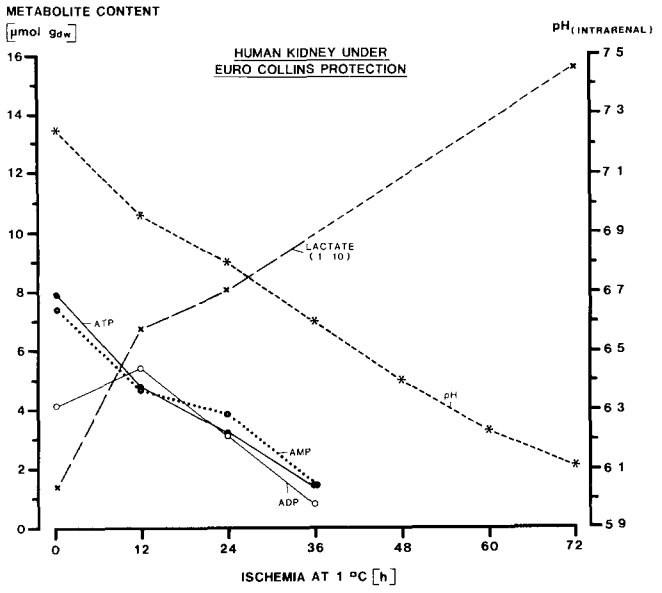

Fig. 7. Renal metabolite content of ATP, ADP, AMP and lactate and intrarenal pH in a human kidney during a complete ischemia at 1 °C over 76 h under Euro-Collins-protection

The *unprotected* kidneys (Fig. 8) after 12 h of ischemia at 1 °C revealed collapsed proximal tubular epithelium with preponderant vacuolation of the apical parts of the cytoplasma and the development of brush border membrane defects; pycnosis in distal tubular epithelium was evident. Kidneys with *Euro-Collins-protection* (Fig. 9) after 48 h of ischemia at 1 °C demonstrated a glomerulum with collapsed capillary tufts and an enlarged capsule: marked vacuolation of apical and basal parts of cytoplasma of the proximal epithelium and a flattened distal tubuli epithelium with condensed nuclei was evident also. Under *HTK-protection* (Fig. 10) after 48 h of ischemia at 1 °C a normal glomerulum, with dilated proximal tubuli and a well preserved brush border with compact cytoplasma were found.

Discussion

A preservation method must protect kidneys against damaging intrarenal acidosis [4, 20, 27], against unsufficient energy reserves [2, 3, 10, 13, 15, 19, 28, 32–34] and against structural deterioration [30] not only at reduced temperatures but also during the period of retransplantation. Therefore we examined canine kidneys under two preservation conditions, at about 1 °C and at 25 °C, with respect to

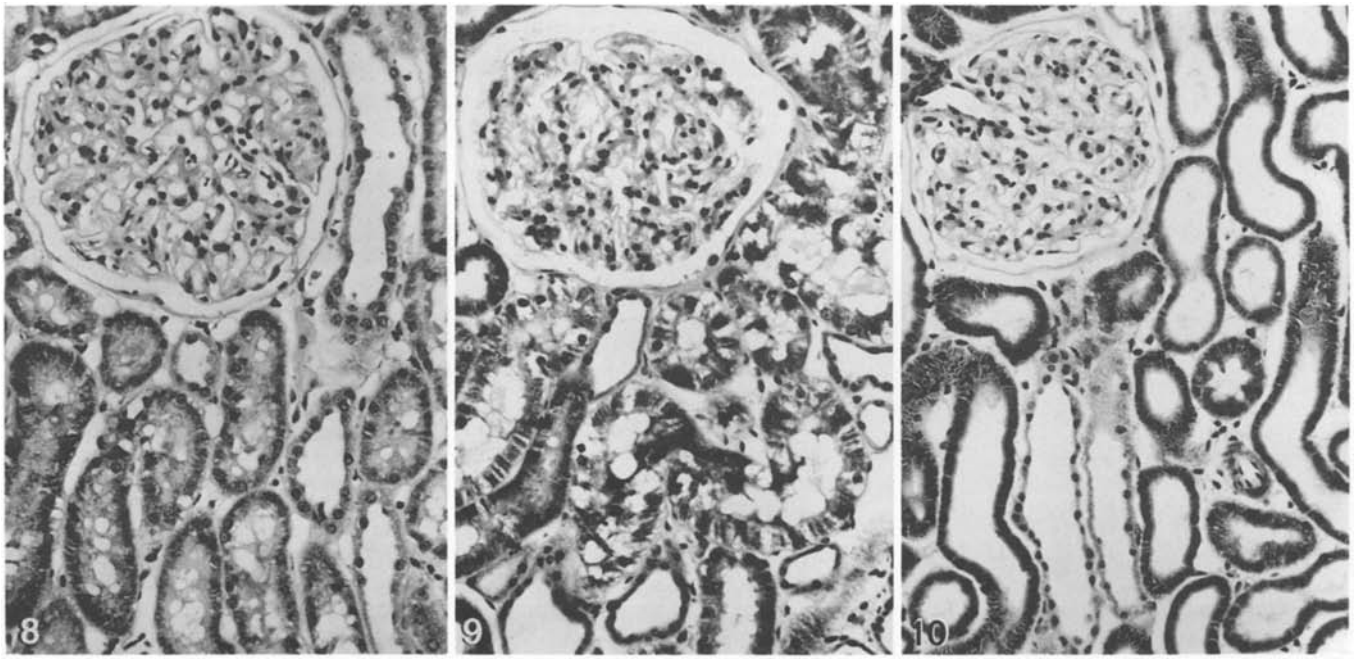

Fig. 8. Experiment 354, left kidney, renal ischemia of 12 h at 1 °C without protection: Collapsed proximale tubuli with preponderant vacuolation of apical cytoplasma parts with development of brush border membrane defects; pyknosis in distal tubuli-epithelia-layer. Goldner-Masson, x 420

Fig. 9. Experiment 406, left kidney, renal ischemia of 48 h at 1 °C under Euro-Collins-protection: Glomerulum with collapsed tuft of capillaries and enlarged glomerular capsule (Bowmann's space). A high degree of vacuolisation of apical and basal parts of cytoplasma of the proximal epithelia. Flattend distal tubulus epithelia with condensed (pyknotic) nuclei. Goldner-Masson, x 420

Fig. 10. Experiment 347, right kidney, renal ischemia of 48 h at 1 °C under HTK-protection: normal glomerulum; dilated proximal tubuli with well preserved brush border and compact (tight), not vacuolisated cytoplasma. Goldner-Masson, x 420

energy-rich-phosphates, lactate and intrarenal pH as well as morphological features.

At 1 °C ATP-, ADP- and AMP-decline were not very different in Euro-Collins- and in HTK-protected kidneys and both preservation techniques prolonged depletion of energy-rich-phosphates in comparison with unprotected ischemic kidneys by a factor of 3–4, if the time until 5 $\mu mol/g_{dw}$ AMP is reached [21], is taken as parameter. This result may be explained by similarly low sodium-concentrations in both solutions and by the absence of Ca^{++} in both solutions, as sodium transport is the main energy consuming process [11] and Ca^{++} stimulates energy turnover. During protective perfusion of the kidneys with the Euro-Collins- or the HTK-solution, it was shown [23] that renal oxygen consumption was the same.

The lactate-content increased in Euro-Collins-kidneys to 130 $\mu mol/g_{dw}$, to 40 $\mu mol/g_{dw}$ in HTK-kidneys and to 50 $\mu mol/g_{dw}$ during 24 h in unprotected kidneys at 1 °C. Thus intrarenal pH decreased to *lowest* values in Euro-Collins kidneys, because the buffer capacity was insufficient [20]; a pH of 6.2 after 48 h and of 6.0 after 96 h, were recorded.

The energy consumption or turnover, measured as lactate increase, was marginally stimulated during cold (1 °C) Euro-Collins-preservation in comparison to unprotected and to HTK-protected kidneys, as this temperature reduced ischemic metabolism [17]. The low intrarenal pH in the Euro-Collins-kidneys was therefore related to the lower buffer capacity of this solution. But at 25 °C lactate accumulation and H^+-production was increased in comparison to the unprotected and to the HTK-protected kidneys, leading to structural deterioration [24].

Our results also indicate the protective effect of the Euro-Collins-solution in comparison to unprotected kidneys at 1 °C, seen in clinical kidney transplantation.

ATP-content was about 3 $\mu mol/g_{dw}$ after 120 min of ischemia using Euro-Collins-protection at 25 °C and was higher than in unprotected kidneys and in those with HTK-protection. But the Euro-Collins-kidneys were anuric after 120 min of ischemia [25]. Therefore we conclude that the ATP is not "usuable", because of to low intrarenal pH, inhibiting enzyme dependant energy metabolism [18, 29]. The AMP-content was higher in Euro-Collins-protected kidneys than in unprotected kidneys, but in HTK protected kidneys AMP was 7.5 $\mu mol/g_{dw}$ after 120 min and in Euro-Collins-kidneys it was 6 $\mu mol/g_{dw}$. AMP remained constant after 30–60 min of ischemia with Euro-Collins-protection, indicating possible metabolic inhibition by low intrarenal pH of about 6.3 after 60 min of ischemia. In HTK-protected kidneys the pH was constant at pH 6.8 also at 25 °C and lactate accumulation rose after 300 min of ischemia reflecting ischemic metabolism. Even after 120 min of ischemia at 30–34 °C kidneys show a good postischemic function [22] providing a sufficient protection, while kidneys under Euro-Collins-protection are anuric after the same ischemic stress [25].

In one human kidney with Euro-Collins-protection at about 1 °C, we were able to measure the same parameters as in the canine kidneys. The time course of intrarenal pH and lactate is very similar to canine kidneys. Therefore we pressume that human kidneys would show the same behaviour at 25 °C as canine kidneys, and would therefore suffer additional damage in the second ischemic period during retransplantation.

The HTK-solution prevented a decrease in pH by histidine/histidine-HCl-buffering, and did not stimulate glycolysis – measured as lactate-increase – in comparison to unprotected kidneys. Thus the solution maintains "physiological energy turnover" during ischemia and protects structure as well at 1 °C as it does at 25 °C [24].

Structural alterations, investigated after 12 h of ischemia at 1 °C in unprotected and after 48 h in Euro-Collins- or in HTK-protected kidneys, corresponded more to the intrarenal pH at this time than to the content of energy rich phosphates. The pH was after 12 h of ischemia in unprotected kidneys and after 48 h under Euro-Collins-protection about 6.5, whereas in HTK-protected kidneys the intrarenal pH was constantly above 7.3. ATP and ADP were below 2 $\mu mol/g_{dw}$ and AMP was about 6 $\mu mol/g_{dw}$ in all three groups after this ischemia. Therefore an improvement of membrane and structural preservation can only be achieved with stability of intrarenal pH [24].

The HTK-solution allows immediate renal function after 2 h of ischemia at about 30–32 °C [21, 22], whereas Euro-Collins-protected kidneys are anuric after the same ischemic stress [25], an improvement in kidney preservation may be derived from the HTK-solution at 1 °C.

Acknowledgements. We thank Mrs. R. Dohrmann and Mr. E. Burger for their perfect operative and technical assistance during the experiments, Mrs. G. Dallmeyer and Mrs. B. Riekhoff for biochemical analyses, Mrs. E. Neumeyer for preparation of the figures, Mrs. U. Kneissler and Mrs. W. Gebauer for preparation of the morphological features.

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