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Electrolyte equilibration of human kidneys during perfusion with HTK-solution according to Bretschneider

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Abstract Twelve surgically removed human kidneys (mainly tumor kidneys) were investigated. The investigations comprised perfusion criteria (perfusion flow, perfusion pressure, perfusion resistance, electrolyte equilibration). During perfusion of the kidneys with HTK solution, the perfusion resistance was nearly three times as high in human kidneys as in canine kidneys perfused under the same conditions in previous studies. Beside possible species differences the raised perfusion resistance may be explained by the greater trauma to the human kidneys due to the surgery, the primary ischemic stress which cannot be avoided clinically and the often nonoptimal initial diuresis. Nevertheless definitive perfusion is possible under clinical conditions although pronounced increases of perfusion resistance may occur. As indicated by the raised perfusion resistance of human kidneys under clinical conditions as compared with canine kidneys in an experimental model, electrolyte equilibration of human kidneys was protracted. For this reason, a duration of perfusion of at least 10 min is necessary in clinical application of HTK solution, i.e., longer than in animal experiments.

Key words HTK solution · Kidney perfusion · Electrolyte equilibration · Kidney preservation

Introduction

HTK solution according to Bretschneider [6–8], originally developed for myocardial protection, has also proved effective for kidney protection under clinical conditions. This applies both to in situ protection in organ-preserving operations on the renal parenchyma [2–5, 9, 15] and its use in the context of transplantation surgery [11]. Its use in extracorporeal kidney surgery ("workbench surgery") is also conceivable.

The protective efficacy of HTK solution after a single hypothermal organ perfusion is based on a lowering of renal energy requirements by sodium reduction, freedom from calcium as well as a slight elevation of potassium and magnesium levels compared with the serum. Moreover, critical tissue acidosis is prevented by a buffering with histidine/histidine-HCl. Structural protection is improved by tryptophan and ketoglutarate [17]. An important prerequisite for the protective efficacy of HTK solution is as rapid and complete as possible an equilibration of the electrolyte composition in the renal extracellular space to the electrolyte content of the protective solution. The process of electrolyte equilibration in turn depends on the perfusion resistance [16]. We investigated the duration of perfusion necessary under clinical conditions in human kidneys to attain as complete an electrolyte equilibration (Na^+, K^+) as possible in the kidneys.

Materials and methods

The investigations were performed on 12 human kidneys which had been removed surgically. The nephrectomies were performed because of small kidney cell cancer with an average tumor diameter of 3 cm ($n = 7$), renal pelvis carcinomas ($n = 2$), ureteral carcinoma ($n = 1$) and a complicated urogenital fistula ($n = 1$). The weight of functioning renal parenchyma averaged 150 g. Owing to the differences in the surgical conditions, the primary warm ischemia times from the time of ligature of the renal artery up to the beginning of perfusion varied from 36 s to 8.5 min, averaging 3 min 14 s.

After removal of the kidney, a perfusion catheter with integrated pressure lead [19] was introduced into the renal artery. The renal perfusion was commenced simultaneously with the introduction of the perfusion catheter. The perfusion was carried out with HTK solution cooled to 6–8°C (Table 1). The perfusate was propelled by means of a calibrated peristaltic pump via a tube system and a perfusion catheter connected to it. The perfusion flow

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Table 1 HTK solution according to Bretschneider

Na^+	15 mmol/l
K^+	10 mmol/l
Mg^{2+}	4 mmol/l
Cl^-	50 mmol/l
Tryptophan	2 mmol/l
Ketoglutarate	1 mmol/l
Histidine	180 mmol/l
Histidine-HCl	18 mmol/l
Mannitol	30 mmol/l
Osmolarity:	310 mosmol/l
pH (8°C):	7.3
pO_2 (37°C):	200 mmHg

was variable and could be registered. The perfusion pressure was measured continuously. The perfusion lasted 10 min. In this period, two to four samples were taken from the perfusate and investigated for their sodium and potassium content.

At the same time as the beginning of perfusion, a catheter was introduced into the stump of the renal vein from which 5-ml samples of the "venous" perfusate were taken at intervals of 1 min. The "venous" perfusate was investigated for its sodium and potassium concentration. A ureteral catheter was also introduced into the ureter at the beginning of perfusion. This enabled corresponding analyses in the "perfusion urine". The experimental design is shown schematically in Fig. 1.

Results

During perfusion, the perfusion flow averaged 279 ml/min and the perfusion pressure averaged 123 mmHg. The perfusion resistance was relatively constant between 0.5 and 0.6 mmHg/ml per minute (Fig. 2). For methodological reasons the perfusion resistance was not related to the kidney weight. The difference in the sodium content between the perfusion solution and the venous effluent fluid was 7.18 mmol/l after 1 min (Fig. 3). There was a marked reduction of the difference to 1.54 mmol/l in the third minute. The further fall was then delayed and reached a value of about 0.36 mmol/l after 10 min. This curve is a manifestation of the almost complete "equilibration process".

After 4 min of perfusion, the difference between the sodium concentration in the perfusion solution and the perfusion urine was 5.66 mmol/l (Fig. 4). There was a steep fall of the curve up to the sixth minute, which then became flatter. After 10 min, the difference was 0.35 mmol/l. In a corresponding comparison of the potassium concentration between the perfusion solution and the venous effluence, an almost complete equilibration was attained after 1 min (Fig. 5).

After 4 min of perfusion, the difference in the potassium concentration between the perfusion solution and the perfusion urine was 1.52 mmol/l (Fig. 6). The course of curve was very steep up to the fifth minute. After 10 min, the value was 0.30 mmol/l.

Discussion

Our investigations were carried out on human kidneys which had to be removed surgically for various reasons. Despite the availability of such surgical preparations, there are problems which limit the use of human kidneys for experimental purposes [20, 21]. The supreme maxim is that the patient may not be endangered in any case, nor may other disadvantages ensue for the patient. Hence longer primary warm ischemia times up to the

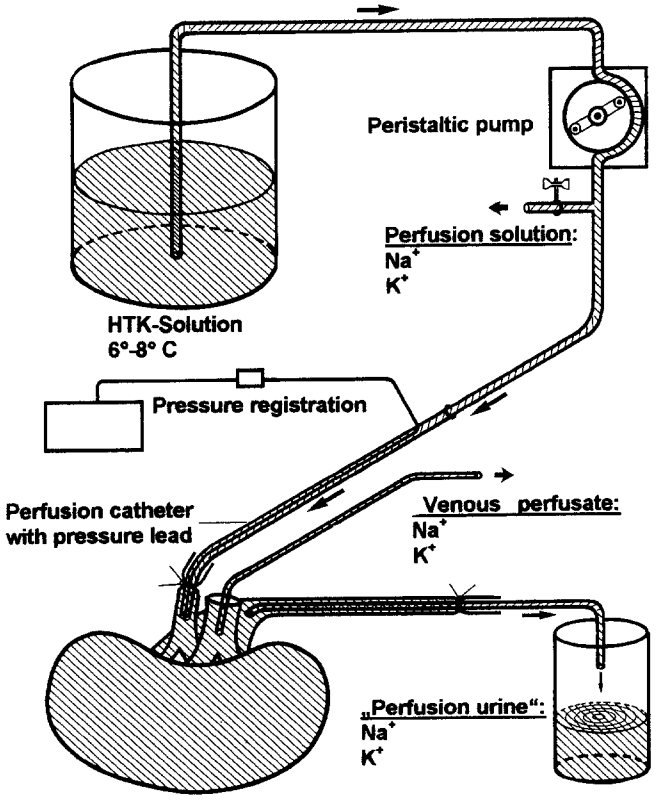

Fig. 1 Experimental design

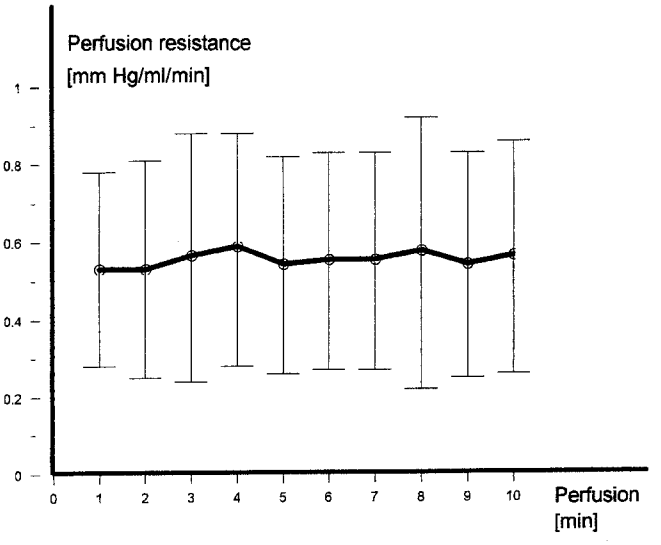

Fig. 2 Perfusion resistance during protective perfusion

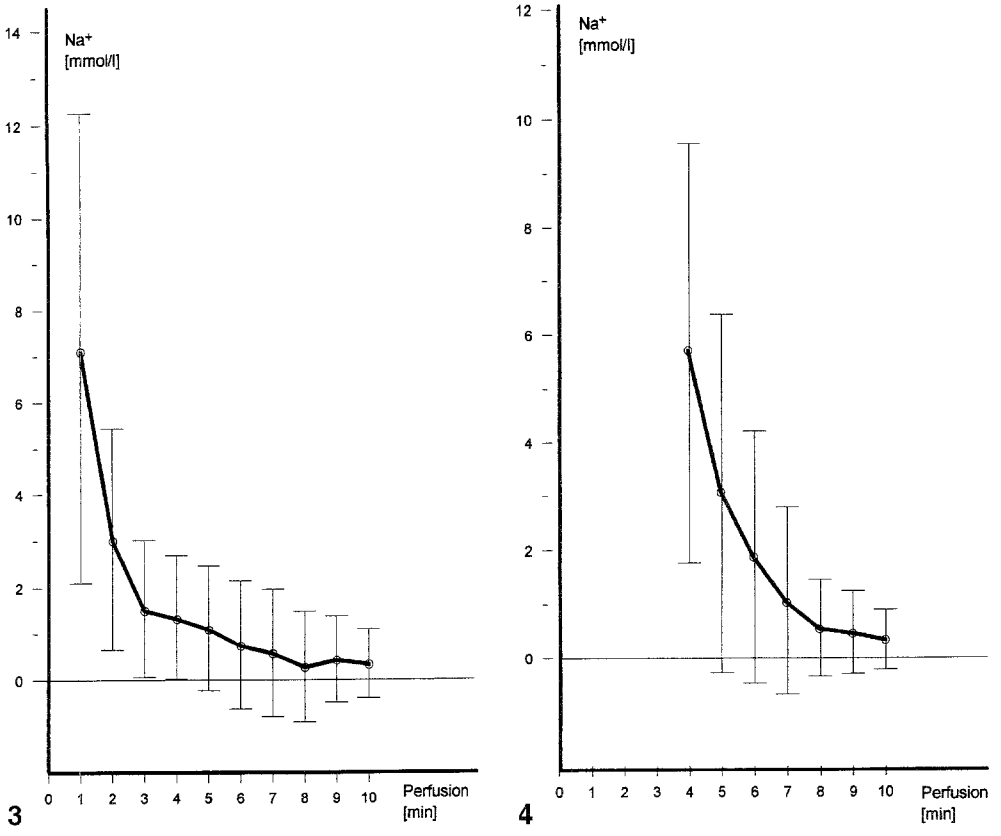

Fig. 3 Difference in the sodium concentration between the perfusion solution and the venous effluence during perfusion

Fig. 4 Difference in sodium concentration between perfusion solution and perfusion urine during perfusion

beginning of protective perfusion cannot be avoided, especially in tumor nephrectomies.

The drawbacks of an inhomogeneous investigation material conversely present advantages from a clinical point of view. The different primary ischemia times and possible prior damage to the kidneys investigated correspond to the clinical situation. This enables practice-related investigations to be carried out.

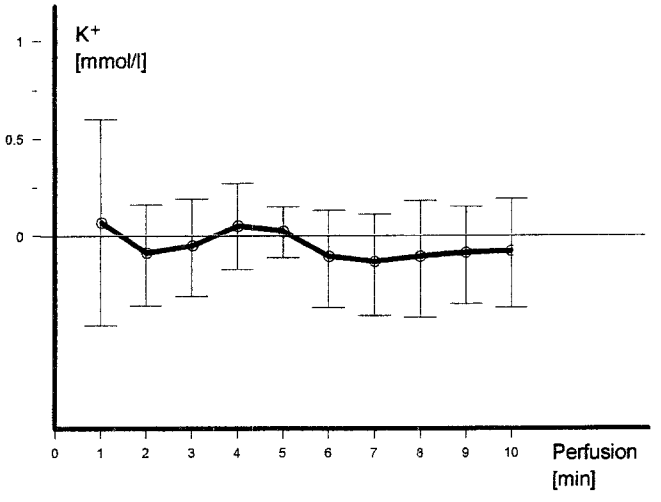

Fig. 5 Difference in potassium concentration between the perfusion solution and the venous effluence during perfusion

After protective perfusion of the kidneys and subsequent ischemic stress, the postischemic kidney function essentially depends on the perfusion characteristics [18]. The renal perfusion resistance plays a central role [1]: with a low perfusion resistance there is an enhanced "perfusion diuresis" with more rapid and complete equilibration of the electrolyte composition of the venous effluence and the perfusion urine with the perfusion solution and thus with electrolyte composition of the extracellular space. Conversely a high perfusion resistance is an unfavorable sign for the effectiveness of protective perfusion, resulting in poorer postoperative function parameters [1].

In the human kidneys perfused with HTK solution the perfusion resistance was 0.55 mmHg/ml per minute at a mean perfusion pressure of 123 mmHg and an average perfusion flow of 279 ml/min. Thus with 150 g functioning renal parenchyma, without considering the tumor, there is a renal perfusion resistance of 0.83 mm Hg/ml per minute × 100 g wet weight.

Compared with canine kidneys which were perfused with the same technique, the same solution and the same pressure, and showed a medium perfusion resistance of 0.3 mmHg/ml per minute × 100 g wet weight in previous studies [12, 14], the perfusion resistance of the human kidneys was almost 2.8 times higher. However, perfusion resistances of up to 0.6 mmHg/ml per minute × 100 g wet weight also occurred occasionally in animal experiments [18]. Nevertheless, even taking into consideration possible imprecisions in the investigation model with

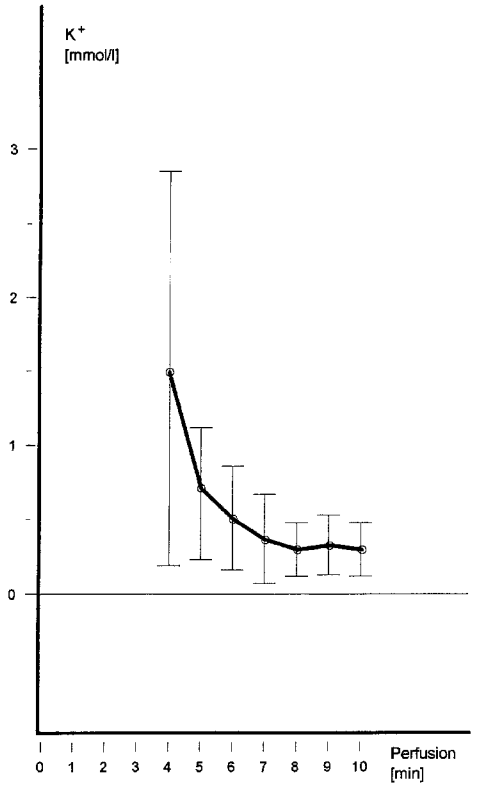

Fig. 6 Difference in potassium concentration between the perfusion solution and the perfusion urine during perfusion

human kidneys, it must be assumed that higher perfusion resistances are present than in corresponding animal experimental investigations. The following factors are likely to be the cause of this: in operations to remove human kidneys, both the surgical and the anesthesiological procedure take account of clinical considerations. In contrast to animal experiments, an enhanced initial diuresis cannot always be attained before the protective perfusion. On the other hand, optimal preconditions to obtain as low a perfusion resistance as possible can be established by intense diuresis before the beginning of the protective perfusion, possibly supported by diuretics [19].

An important, perhaps decisive factor for increasing renal vascular resistance is likely to be vasoconstrictions caused by surgical manipulations on the kidneys and on the renal vessels [1]. As shown by clinical experience, such vasoconstrictions already occur in slight traumatizations which cannot be avoided surgically. On the other hand, there are almost always more favorable preconditions for dissections with minimum tissue damage in animal experiments, so that vascular spasms are of less significance.

A possible further reason for the increase of the perfusion resistance in human kidneys are the vasoconstrictions due to ischemia. In previous animal experiments [14], there was practically no warm ischemia before the beginning of the perfusion. However, warm ischemia times cannot be avoided in our investigation model. They are on average well over 3 min. In our investigation model with possible imprecisions we could not find a significant difference in the perfusion resistance depending on the duration of warm ischemia. On the other hand Grupp and Heimpel [10] could show that marked increases of perfusion resistance occur after phases of ischemia lasting between 1 and 7 min.

From the investigations presented here, which showed a higher perfusion resistance of human kidneys under HTK perfusion as compared with canine kidneys, the extent of possible species differences (e.g., a result of different organ sizes) cannot be inferred in view of what has been said concerning initial diuresis, vasoconstriction due to surgical manipulations, and vasoconstrictions due to ischemia. It is not known to what extent the renal tumors which were also perfused have an effect on the perfusion characteristics. Investigations on this question have not been reported. The specific features of this investigation model are likely to be essentially responsible for the raised perfusion resistance of the human kidneys.

At a low perfusion resistance, a rapid and complete electrolyte equilibration was shown in animal experiments, i.e., an equilibration of the electrolyte content of the extracellular cavity of the perfused kidneys with the protective solution [16]. At a high perfusion resistance, on the other hand, the equilibration is delayed. However, complete equilibration is a crucial prerequisite for successful protection, since only in this way can the protective solution be completely effective [14, 16]. Since the human kidneys showed a higher perfusion resistance in this investigation model compared with canine kidneys in previous studies, delayed and/or incomplete equilibration may also occur.

Canine kidneys perfused with the HTK solution still showed a difference in the sodium concentration between the perfusion solution and the venous effluence of 0.35 mmol/l [13] after 4 min, whereas the corresponding value in the investigations here was attained after 8 min. On the other hand, there was complete equilibration for potassium both in animal experiments and in human kidneys [14]. The equilibration in the perfusion urine was slower than in the venous effluence. In canine kidneys, the concentration of sodium in the perfusion urine had largely equilibrated with the concentration in the perfusion solution after 6 min of perfusion, whereas there was still a difference of 0.3 mmol/l in the human kidneys after perfusion for 10 min. In the animal experiments, there was complete equilibration of the potassium concentration after 3 min [14], whereas there was still a difference of 0.30 mmol/l after 10 min of perfusion in human kidneys. The raised perfusion resistance in human kidneys must be regarded as the cause for the delayed, and in part incomplete, electrolyte equilibration of these kidneys perfused with HTK solution.

These investigations and the data from previous animal experiments imply various criteria for the clinical application of the method of kidney protection with HTK solution. According to the results reported here

the perfusion resistance also plays a crucial role in the quality of the protective perfusion in respect of electrolyte equilibration. Since this has repercussions for postischemic kidney function [18], the perfusion resistance must be kept as low as possible in clinical use of the protection procedure. A high initial diuresis, dissection of the kidneys and the renal vessel with minimum tissue damage and as short a phase of warm ischemia before the beginning of perfusion as possible is favorable. On the other hand, the investigations on human kidneys showed that protective perfusions can be carried out with higher perfusion resistances than in animal experiments even under more unfavorable conditions such as those which occur clinically. Consequently, adequate postischemic kidney function can be reckoned on in view of the results of animal experiments. However, longer perfusion times of at least 10 min are necessary in order to attain definitive equilibration.

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