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Acute Renal Failure (ARF) - "The Kopp Solution"

Acute Renal Failure (ARF) – "The Kopp Solution". Obviously the title of this paper offers a twofold interpretation. First, the author's clinical solution how to recognize, prevent and how to conservatively treat ARF is described. Second, the solution of the problem has also led to the development of a special intravenous solution which is basically needed to provide the ideal qualitative and quantitative substrate for the kidney to survive the toxic or ischemic injury leading to ARF. Finally, in our experience, the routine use of the newly developed protocol of Bicarbonate-Alkaline-Polyuria (BAP) for all the risk groups defined below has led to a significant decrease of ARF in need of dialysis resulting in a greater number of patients who survive ARF conservatively and lastly to an increased number of vital, polyuric kidneys useful for transplantation.

Keywords: Acute-Renal-Failure – "The Kopp Solution"

The clinical situation of Acute Renal Failure (ARF) is characterized by an unproportionate socio-economic burden and high costs which are due to the frequent development of ARF into the so-called Multi-Organ-Failure (MOF). The mortality rate of MOV is at minimum 50% (23, 24). To date, only artificial and highly cost intensive remedy is offered by extracorporeal blood-purification-techniques. The recent ARF-Satellite-Symposium of ISN in May 1999 in Chile has confirmed that the worldwide medical research and experimental efforts on the molecular and cellular level have as yet NOT led to a breakthrough (8). However, we were able to find a clinical solution to this problem on a clinical and patho-physiological basis. We developed and applied clinically on patients a special type of DIURESIS, the so called BICARBONATE-ALCALINE-POLYURIA (BAP) (9, 10, 11).

At first, It is very important to primarily evaluate the RISK of a patient to develop ARF. Unfortunately not only in Nephrology but also in many other disciplines the RISK regarding the occurrence of ARF with the need of dialysis is grossly underestimated, although it constitutes a life-threatening complication whatever the basic illness or trauma may be. Various examples may be mentioned e.g. interventional and surgical Cardiology, Oncology, Geriatric Surgery and many others (2, 12, 13). A RISK-Score of 10 Patient-Groups with highly increased RISK to develop ARF is therefore presented first.

1. Pre-existing Chronic Renal Insufficiency (**CRI**), Creatinine -> 1,6 mg/dl
2. Age over 60 Years
3. Dabetics I and II and Patients with Systemic Diseases
4. Patients with only ONE Kidney, either functional or anatomic

5. Nephrotoxins, exogen: e.g. Aethylenglycol, Tetracarbonchloride, Herbicides, Mushrooms etc.
6. Nephrotoxins, endogenous: eg. Sepsis, Rhabdomyolysis, Haemolysis, Hyperuricemia, Oxalosis etc.
7. Electrolyte-Fluid-Acid-Base-derangements, e.g. Dehydration, Drainages, Diarrhoe, etc.
8. Pregnancy with Risk of EPH, HELLP, and other Chronic Renal Insufficiency (**CRI**)
9. All Risks 1 – 8 pre- peri- and post-op large Interventions or pre- peri- post-interventions of intra-arterial or intra-venous Contrast-Media.
10. All Risks 1 - 8 pre- peri and post Nephrotoxic Pharmaceuticals, e.g NSAIDs, Antibiotics, Cytostatic or Immunsuppressive Drugs

Obviously, almost 70 % to 80 % of all patients of any large hospital will belong to those 10 categories. However, the most frequent cause of ARF is **the underestimation** of the risk of ARF to occur (5).

Therefore, the above list of RISKS is also the list of INDICATIONS requiring early and effective prophylactic and therapeutic measures. The introduction and maintenance of the so called Bicarbonate-Alcaline-Polyuria (BAP) regimen is therefore mandatory.

At first, the EMERGENCY-PROCEDURE to produce BAP will be described. It should always be applied in all cases where the RISK for the development of ARF may not clearly be identified initially, e.g. myocardial infarction, trauma, shock etc. The EMERGENCY-PROCEDURE must always be carried out according to the rules and regulations of intensive care. (16, 18). It should be started routinely as early as possible as a means of "RENAL RESURRECTION", together with a well trained nursing team, thus leading to favorable and encouraging results.

Emergency-Procedure I.V.

Blood-Gas Controls. Initially arterial, later after exclusion of hypoxia and hypercapnia > **venous**.

In order to over-correct or elevate the blood-bicarbonate-level to approx. **28 mMol/l = BE ~ +7**
use 100 ml portions each of 1 Mol = 8,4 % NaHCO₃ via Central Venous Access under ICU supervision.

Formula: $0,3 \times \text{bodyweight (kg)} \times (\text{BE} + 7 \text{ minus BE measured}) = \text{mMol or ml 1-molar NaHCO}_3$

CAUTION: Cardio-pulmonary insufficiency, hypoxia, hypercapnia !!! Respirator therapy if indicated.

CAUTION: Alkaloses of other origin e.g. hypochloremia, hyperammonemia etc.

IMPORTANT: Na⁺, K⁺, Ca⁺⁺, Cl⁻ Correction to the normal !

Subsequent blood-gas-analyses may be venous.

AIM: Blood-BE > + 7 Then: loop-diuretic bolus I.V. : Dose: 40 mg Furosemide x Serum-Creatinine

AIM: Key-event: Urine pH > + 7.0 + Polyuria: > 125 ml/h = 2000 to 3000 ml/24h = BAP

Mandatory controls initially hourly, then 6 to 3 times daily: Urine-pH, Urine output, fluid balance, blood-gas-analysis, Electrolytes, Creatinine, BUN, Glucose (CAVE Diabetics); etc.

MAINTENANCE OF BAP is necessary until the kidney fully recovers > days or weeks !! (KOPP's Solution if available)

LEADING PARAMETER is Urine-pH above +7.0

Note: The **Kidney threshold for bicarbonate** is variable and depends on numerous factors such as Volume,

Potassium, Aldosterone etc. for any given patient. It can be as low as BE + 2 mMol/L. Therefore, repeated blood-gas and urine-pH-controls are needed in order to:

1. To identify the lowest possible Blood-BE at which alkaline Urine-pH > +7.0 can be maintained.
2. To prevent undesired systemic alkalosis.

Loop-diuretic Dose per 24 hrs: = identical to starting bolus = 40 mg Furosemide x Serum-Creatinine by continuous infusion, or alternatively Torasemide approx. $\frac{1}{2}$ Dose of Furosemide

For a ~ 70 kg man Polyuria of 3000 to 4000 ml/ 24 hr/ is required in order

1. **to obtain adequate uremic waste clearances (diluted urine only)**
2. **to obtain negative fluid balance, if required (e.g. fluid load by intravenous nutrition)**
3. **to maintain normal serum levels Fluid and Electrolytes have to be precisely substituted**

Note: Urine volumes of more than 6000 ml/24 hrs are possible and have to be managed

Elevated Serum-Creatinine will decrease by approx. 1 mg/dl daily after 1 or 2 days

Following the Emergency-Procedure I.V. practical clinical problems arise from the multitude of the many different I.V.-Infusions in different bottles which have to be administered at differing infusion-rates and with different compositions, thereby requiring multiple infusion-pumps.

In order to avoid these problems we were able to develop a single I.V.-Infusion-fluid the so-called Kopp's-Solution which was prepared in the University- hospital pharmacy (TUM) on demand.

Its composition was as follows: Na⁺ 146 mMol/l; K⁺ 4 mMol/l; HCO⁻³ 60mMol/l; Cl⁻ 90 mMol/l.

With the use of this solution the continuous maintenance of the Bicarbonate-Alcaline-Polyuria was made simple and safe for the routine clinical practice. In preterminal, chronic renal

insufficiency, the retention of uremic waste-products was effectively treatable. Most likely, the efficacy of the Kopp's Solution is based on its similarity with the physiological environment of sea-water in the DEVON-CARBON period.

Oral Prophylaxis

Early recognition of the risk of ARF, e.g. in planned interventions with antibiotics, contrast-media or cytotoxic drugs etc. will allow the oral introduction of Bicarbonate Alcaline Polyuria (BAP) within one or two days, using oral dosage forms, e.g. Tablets of Sodium-Bicarbonate and the oral administration of adequate amounts of fluids.

If POSSIBLE or AVAILABLE: BLOOD-GAS-ANALYSIS: Venous, Arterial in case of Hypoxia and/or Hypercapnia)
Oral Use of Gastro-resistant 100 mg Tablets Sodium hydrogen carbonate bicaNorm® (Fresenius Medical Care), Alka-Seltzer-Gold-effervescent-tablets, Sodium-hydrogen-carbonate tablets (Walgreen), Kaiser-Natron or any other NaHCO₃ - Preparation available at drugstores either tablets or powder.

LEADING PARAMETER IS Urine-pH Optimum pH = 7,5 - 8,0

If Urine-pH is **lower than pH 7.5** immediately take 3 tablets or 3 Gramms of NaHCO₃ repeatedly until Urine-pH- Optimum is reached and continuously maintained.

There is no fixed Dose of NaHCO₃ per day

If Creatinine is above 1,9 mg/dl (Patient 70 +/- 20 kg B.W.) use FUROSEMIDE- tablet 40 mg

Dose/ day = 40 mg x Serum Creatinine (or TORASEMIDE half of the Furosemide Dose) in order to enhance Urine-Flow up to >>125 ml/h = 2000 to 3000 ml per 24 hours = Bicarbonate-Alcaline-POLYURIA (BAP)

Avoid low Blood NaCl-levels = Salt Depletion. Therefore, NO LOW-SALT-DIET

MAINTENANCE of BAP: Continue intake of NaHCO₃ until Optimum Kidney Function is reached and maintained according to the lowering of Serum-Creatinine. Use Minimum Diuretic-Dosis/24 hr

CONTROLS:

Depending on Clinical Condition e.g. Inpatient / Outpatient:

Blood-Gases, Serum-Electrolytes including Chloride !

Blood-Pressure: CAVE Hypotension. In Case of HYPER-Tension, lowering of RR !

Blood-Glucose: CAVE Hypoglycemia especially in Diabetics

URINE-Volumes: ml /12 h, ml /24h CAVE: Urine volumes up to 6000 ml/24 h are possible! Therefore:

Daily Control of BODY-WEIGHT, FLUID-BALANCE

URINE-pH-Testing: Use pH-Indicator-paper Range: pH 5,6 – 8.0 (Uralyt-UR MADAUS)

At best every time at Urine-passage. At least: 3 times daily !

Keep PATIENT-RECORD !

Results

In view of the the high 24 hour Urine-Output negative fluid-balance (if desired) may easily be achieved and will also permit full parenteral nutrition even with high I.V.- fluid volumes (6). Creatinine-decrement daily will be 1 to 2 mg/dl with respect to the general clinical condition of the patient, Age, preexisting renal damage, Cardio-Circulatory-Condition etc.

The total number of ARF-patients, who thus have been treated during the past 20 years cannot be given precisely. The various Divisions where the patients belonged performed the Renal Resurrection Therapy on there own, after initial consultation with us. Seven Doctoral Theses about the use of BAP in ARF were written in various medical Departments of the Technical University of Munich (TUM). Two experimental animal studies on rats, using a gentamicin-toxic and an ischemic ARF-model also confirmed the efficacy of BAP-procedure to prevent ARF (3, 14).

Discussion

The basic patho-physiological efficacy of the Bicarbonate-Alcaline-Polyuria- regimen can be explained is as follows: The KIDNEY, after a renal insult which led to significant renal insufficiency, is unable to perform its three main tasks:

1. The Kidney can no longer CONCENTRATE
2. The Kidney can no longer DILUTE
3. The Kidney can no longer ACIDIFY

The FETAL KIDNEY gradually develops these abilities to produce urine step by step until birth. Therefore, the ontogenetic development of the kidney to produce concentrated urine represents the abbreviated repetition of Phylogenesis. During the phase of Evolution, approximately 200 Million Years ago, the identical development of Kidney Organs took place in the first land-inhabiting mammals. They preserved their original External Environment within their circulation as their Internal Environment which enabled them to take the step from Sea-Water on to the dry land. (See Fig. 1). The principles of these fundamental physiological data can therefore still to date be applied clinically.

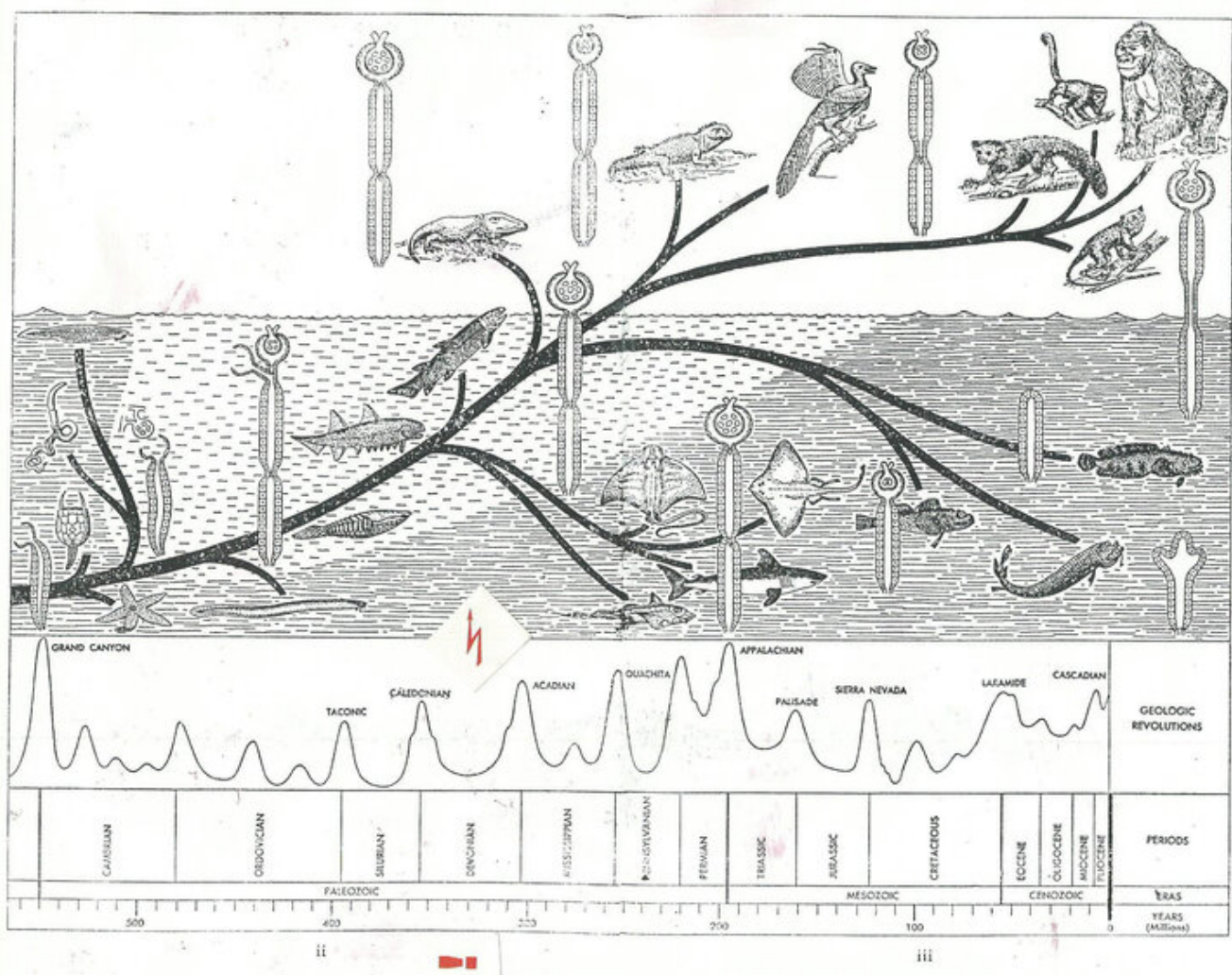


Fig. 1

The "Kopp's Solution", is therefore identical to the composition of the Sea-Water at the time of DEVON-CARBON in which at that time Amphibia and early Mammals lived.

The physiological laws of renal function were described in the textbooks on the Physiology of the Kidney written by HOMER SMITH (22), ROBERT F. PITTS (17), KLAUS THURAU (25), JÜRGEN SCNERMANN (19), O. MATHISEN (15), ROBERT SCHRIER (20), R. GREGER (7) and many others.

Homer W. SMITH already described the important fact that in all mammals living on land the arterial blood supply

of the Nephron is controlled and regulated by the Vas afferens and Vas efferens of the glomerulum. Thereby, the metabolic activity of the Nephron depends on and is warranted by the magnitude of the glomerular bloodflow.

Robert F. PITTS, based on his self-experiment, first described the principles of the renal excretion of bicarbonate, which depends on the constancy of tubular reabsorption of bicarbonate when the maximum concentration of bicarbonate in the blood exceeds 28 mMol/dl (See Fig 2).

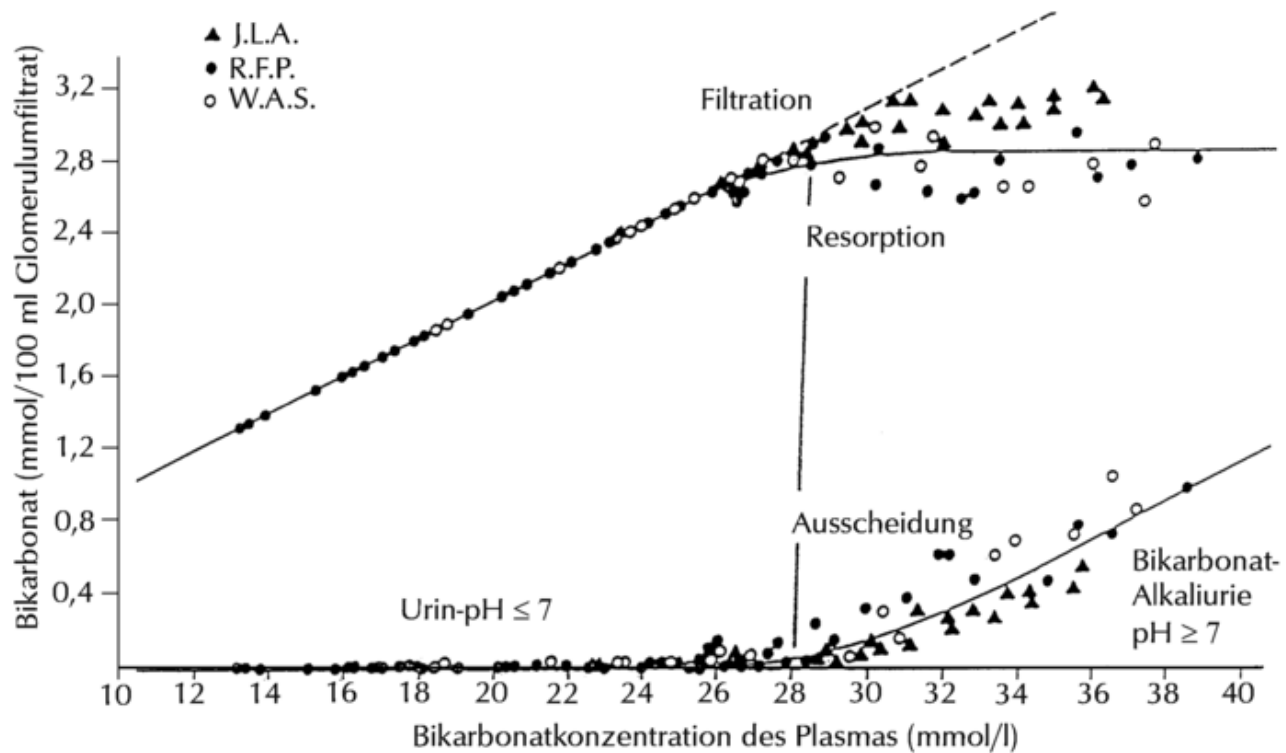


Fig. 2

Filtration, reabsorption and excretion of bicarbonate as functions of plasma-concentration In normal man. (From Pitts, R.F.;

Ayer and Schiess, W.A.: J. Clin. Invest. 28:35, 1949), modified by K.F. Kopp: At bicarbonate- plasma-concentrations of 28 mmol/l and above ($\sim BE > 7$) Bicarbonate-Alcaline-diuresis is present.

J. Schnermann and K. Thureau first described the regulation of the Glomerul-Tubular-Balance (GTB) and of the Glomerular-Filtration-Rate (GFR) via Vasoconstriction or Vasodilation of the glomerular Vas Afferens and Vas Efferens.

J. Schnermann (19) discovered **the unique vasodilating** property of NaHCO_3 .

O. Mathisen et al. (15) were able to confirm, NaHCO_3 to be the "KEY-MEDIATOR" of the Glomerulo-Tubular Balance (GTB).

R. Greger (7) described the energy-lowering effect of loop-diuretics in the Thin Ascending Loop (TAL) of the Kidney on the $\text{Na}^2 \text{CL}^- \text{K}^+$ Cotransporter and the Enhancement of Diuresis due to this effect.

As a result, a new form of diuresis, namely the Bicarbonate-Alcaline-Polyuria (BAP) could be developed which up to now has been unknown. BAP eliminates most efficiently all uremic retention-products, endogenous and exogenous toxins, it also relieves Nephron-ischemia due to the vasodilating effect of NaHCO_3 . The so-called "Re-trafficking" of nephrotoxic substances is efficiently reduced and thereby provides the nephro-**protective** effect of BAP (1).

The clinical combination of all these synergistic effects led to the clinical protocol of the Bicarbonate-Alcaline-Polyuria (BAP) regimen, as a prerequisite to produce extremely efficacious renal diuresis and urinary volumes so far unknown. The prophylactic use in incipient ARF is therefore most promising.

Normally, the glomerular filtrate is reabsorbed in the proximal tubule up to 70 %. In the case of supersaturation of the glomerular filtrate with bicarbonate, the excessive bicarbonate, together with its filtrate will not be reabsorbed and an **increased** filtered flow thereby reaches the distal tubules and the collecting duct to be excreted in polyuric urine- volumes including all uremic waste-products. This explains the efficient elimination of uremic toxins by BAP.

Various controlled studies did show that the application of diuretics in various amounts and its combination with the infusion of electrolyte-solutions produced Polyuria, but this type of enhanced diuresis was not able to lower or to inhibit the retention of uremic substances neither in ARF nor in CRF. However, clinical attempts with failing results are still being made worldwide (4, 21).

Figure 3 and Fig 4 demonstrate the principle of the Bicarbonate-Alcaline-Polyuria (BAP)-regimen. In Fig 3 the situation of Oligo-Anuria which is hardly influenced by Furosemide is represented. Fig 4 shows the contrasting effect of Bicarbonate to produce Polyuria.

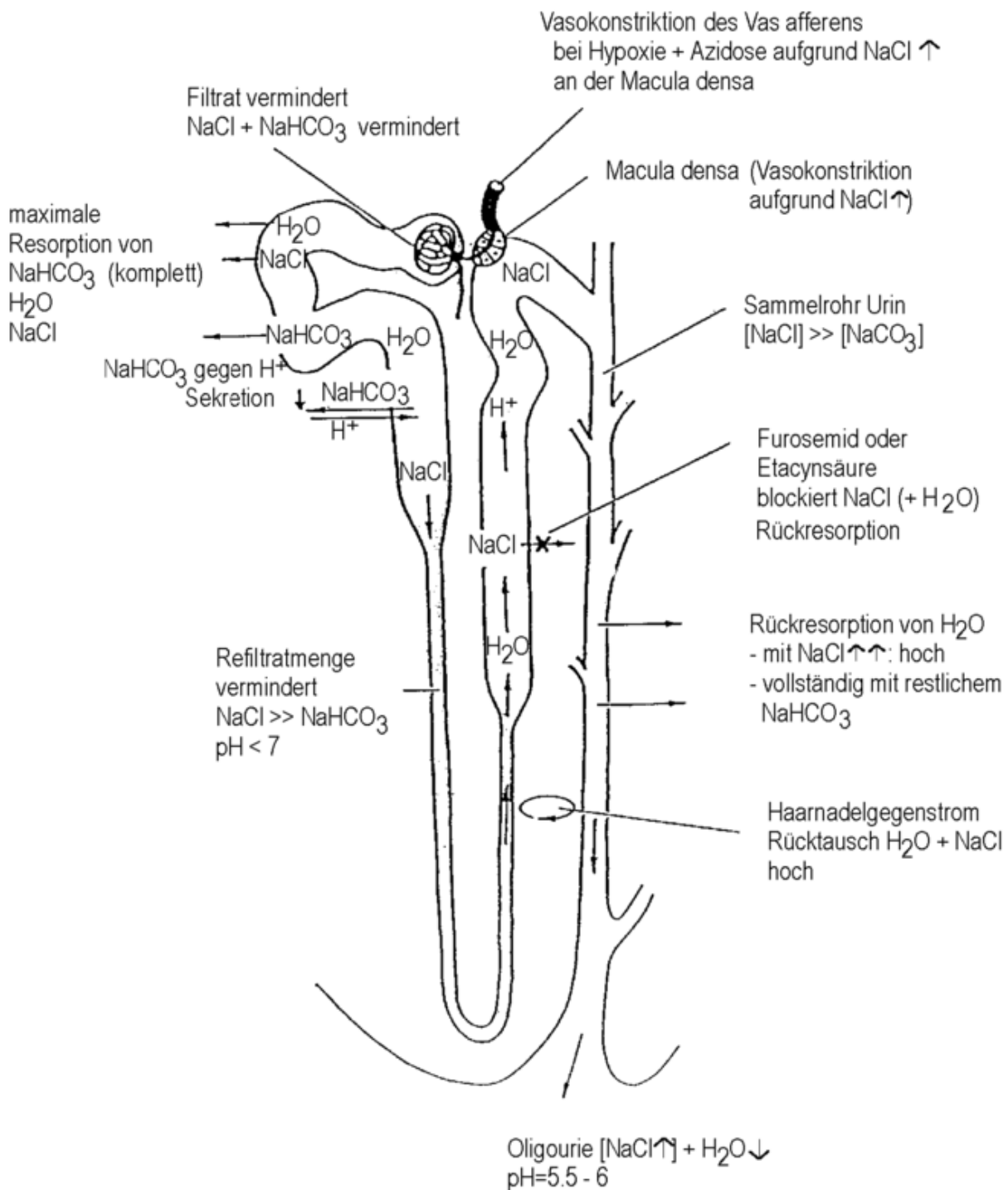


Fig. 3
Salt-Water-Diuresis at $\text{pH} < 6$ + Loop-Diuretic resulting only in a moderate diuresis of Salt and Water (Oliguria)

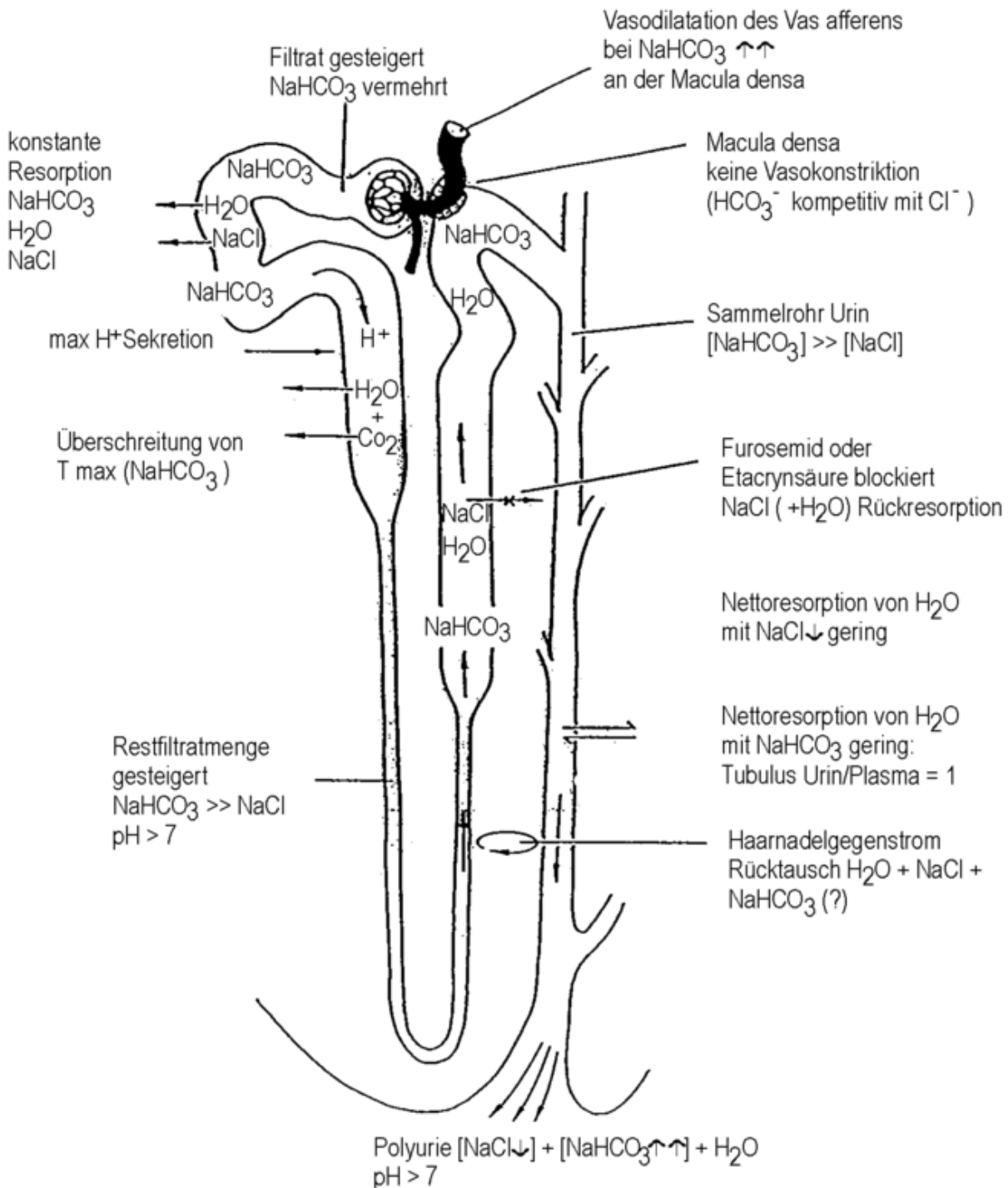


Fig. 4
Tubular transport conditions together with an enhanced glomerular flowrate eventually result in Bicarbonate-Alcaline-Polyuria; $\text{pH} > 7.0$

Summary

The routine use of the Bicarbonate-Alcaline-Polyuria (BAP) protocol for the conservative Prophylaxis and Therapy of ARF of all 10 RISK-Groups mentioned before, will lead to

1. a significantly reduced number of cases in need of Acute Dialysis for ARF,

2. a significantly greater number of surviving patients due to the conservative management of ARF
3. a significantly greater number of vital and polyuric Kidneys suitable for TRANSPLANTATION

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