Update (2005) in Fluid, Electrolytes, and Acid-Base Disturbances

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Review

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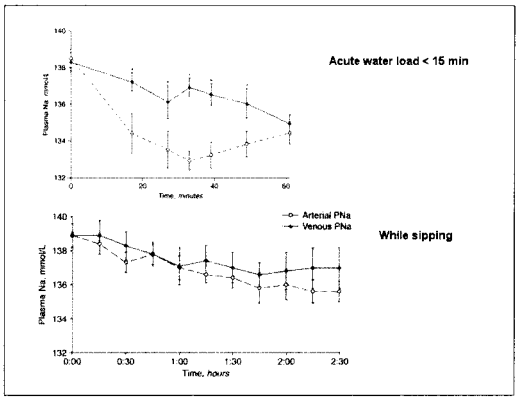
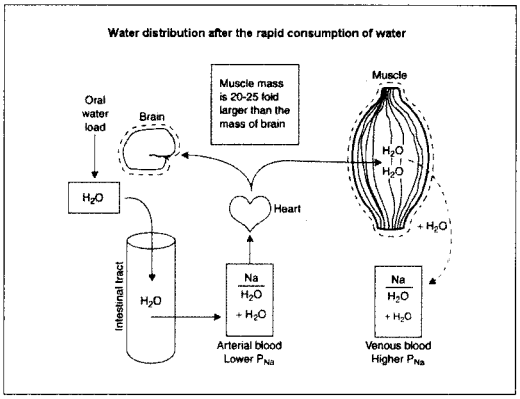
Defining conditions that lead to the retention of water: The importance of the arterial sodium concentration (*Kidney Int* 67: 613–621, 2005)

방법: To define conditions that permit the retention of ingested water, water loading was conducted after overnight food and water restriction in volunteers; paired arterialized and venous blood samples were analyzed.

결과: When 20 mL water/kg was consumed in <15 minutes, the peak urine flow rate was 11 ± 0.6 mL/min. The plasma sodium concentration (P_{Na}) was 4.0 ± 0.5 mmol/L lower in arterialized than paired venous blood 30 to 40 minutes after water ingestion began. The arterialized P_{Na} was not significantly lower than in paired venous samples when water was consumed slowly (sipping).

의의: When water absorption is rapid, the venous plasma sodium concentration is appreciably higher than in the arterial sodium plasma concentration (a measure of the sodium concentration to which the brain is exposed) in a simultaneous drawn sample.





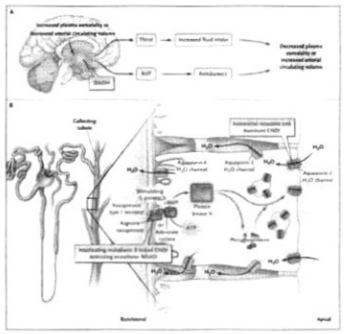
Hyponatremia among runners in the Boston Marathon
(*N Engl J Med* 352:1550-1556, 2005)

방법: Participants in the 2002 Boston Marathon were recruited one or two days before the race. After the race, runners provided a blood sample and completed a questionnaire detailing their fluid consumption and urine output during the race.

결과: Of 488 runners 13 percent had hyponatremia (≤ 135 mmol/L); 0.6 percent had critical hyponatremia (≤120 mmol/L). On multivariate analysis, hyponatremia was associated with weight gain, a racing time of >4 hours, and body-mass-index extremes.

의의: Hyponatremia occurs in a substantial fraction of nonelite marathon runners and can be severe. Excessive consumption of fluids, as evidenced by substantial weight gain while running, is the single most important factor associated with hyponatremia. Efforts to monitor and regulate fluid intake may lead to a reduction in the frequency and severity of this condition, which, in rare cases, can be fatal.

Physiology of Water Homeostasis in Humans (Panel A) and Pathway of AVP Signaling in Renal Collecting-Duct Cells Involved in Regulating Water Excretion (Panel B).



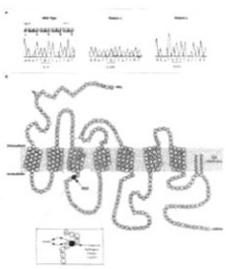
Nephrogenic syndrome of inappropriate antidiuresis
N Engl J Med 352:1884-1890, 2005

방법: DNA sequencing of V2R gene (*AVPR2*) in two infants whose clinical and laboratory evaluations were consistent with the presence of SIADH, yet who had undetectable arginine vasopressin (AVP) levels

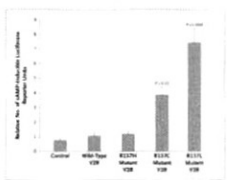
결과: Missense mutations of V2R gene, with resultant changes in codon 137 from arginine to cysteine or leucine

의의: The first demonstration of gain-of-function mutations in the V2 vasopressin receptor (V2R). These novel mutations cause constitutive activation of the receptor and are the likely cause of the patients' SIADH-like clinical picture. ..... termed "nephrogenic syndrome of inappropriate antidiuresis."

Nucleotide Sequence of the Wild-Type and Two Mutant *AVPR2* Genes in the Affected Region (Panel A) and Diagram of V2R (Panel B).



Basal Levels of cAMP Production in Cells Expressing Wild-Type and Mutant V2R



Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury (*Crit Care Med* 33: 196-202, 2005)

방법: To compare the effects of equimolar doses of hypertonic saline and dextran solution (HSD, Rescueflow) with 20% mannitol solution for reduction of increased intracranial pressure, 9 patients with an intracranial pressure of >20 mm Hg were recruited and received two treatments of each (Equimolar, rapid intravenous infusions of either 200 mL of 20% mannitol or 100 mL of 7.5% saline and 6% dextran-70 solution (HSD) over 5 mins).

결과: Treatments reduced intracranial pressure with both mannitol (median decrease, 7.5 mm Hg, 95% confidence interval, 5.8-11.8) and HSD (median decrease, 13 mm Hg; 95% confidence interval, 11.5-17.3). HSD caused a significantly greater decrease in intracranial pressure than mannitol (p = .044). HSD had a longer duration of effect than mannitol (p = .044).

의의: When given in an equimolar, rapid, intravenous infusion, HSD reduces intracranial pressure more effectively than mannitol. *cf. Nephrotoxicity*

Novel *CACNA1S* mutation causes autosomal dominant hypokalemic periodic paralysis in a Chinese family (*J Mol Med* 83:203-208, 2005)

배경: Hypokalemic periodic paralysis (HypoPP) is an autosomal dominant disorder. To date, only three mutations in the skeletal muscle calcium channel α-subunit gene *CACNA1S* (Arg528His, Arg1,239His and Arg1,239Gly) have been identified.

방법 및 결과: A four-generation Chinese family with HypoPP with 43 living members and 19 affected individuals was studied. DNA sequence analysis revealed a heterozygous C to G transition at nucleotide 1,582, resulting in a novel 1,582C G (Arg528Gly) mutation.

의의: HypoPP is due to abnormal muscle membrane excitability, commonly arising from mutations in the muscle calcium channel alpha1 subunit gene (*CACNA1S*) on chromosome1q3132 or in a smaller number of cases, from a mutation in the skeletal muscle sodium channel *SCN4A*. The alpha1 subunit of the calcium channel contains the dihydropyridine binding site (receptor) that acts as a pore for conducting calcium ions in the T tubule. The mutation results in a reduction of the calcium current in the T tubule. During attacks, there is an influx of potassium into muscle cells and the cells become electrically refractile.

A Korean family of hypokalemic periodic paralysis with mutation in a voltage-gated calcium channel (R1239G) (*J Korean Med Sci* 20:162-165, 2005)

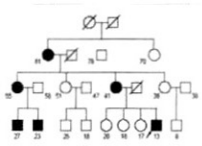


Fig. 1. Pedigree of the HOPP family. The dark symbols are affected individuals. The proband is indicated by an arrow. The age of the family members is designated by the number.

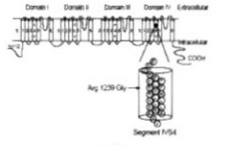


Fig. 2. Schematic diagram of the DHP receptor α_1-subunit composed of four domains of an internal homology (DI to DIV) connected by intracellular loops. The R1239G mutation substitutes a positively-charged arginine located within segment DIVS4 by a neutral glycine.

We report a 13-yr old boy with HypoPP from a family in which 6 members are affected in three generations. Genetic examination identified a nucleotide 3705 C to G mutation in exon 30 of the calcium channel gene, CACNA1S. This mutation predicts a codon change from arginine to glycine at the amino acid position #1239 (R1239G). This boy and the other family members who did not respond to **acetazolamide**, showed a marked improvement of the paralytic symptoms after **spironolactone** treatment.

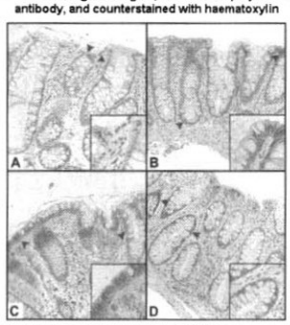
Enhanced large intestinal potassium permeability in end-stage renal disease (*J Pathol* 206:46-51, 2005)

방법 : The capacity of the colon for K^+ secretion may increase in ESRD. This hypothesis was tested in patients with normal renal function or ESRD, by evaluating the effect of barium ions on rectal K^+ secretion using a rectal dialysis technique, and the expression of high conductance (BK) K^+ channel protein in colonic mucosa by immunohistochemistry.

결과: Under basal conditions, rectal K^+ secretion was almost 3-fold greater in ESRD patients (n = 8) than in patients with normal renal function (n = 10). Intraluminal barium (5 mmol/l) decreased K^+ secretion in the ESRD patients by 45%, but had no effect on K^+ transport in patients with normal renal function. Immunostaining using a specific antibody to the BK channel α-subunit revealed greater levels of BK channel protein expression in surface colonocytes and crypt cells in ESRD patients (n = 9) than in patients with normal renal function (n = 9).

의의: Enhanced colonic K^+ secretion in ESRD may involve an increase in the apical K^+ permeability of the large intestinal epithelium, which most likely reflects increased expression of apical BK channels.

Mucosa taken from the rectosigmoid region, stained with polyclonal anti-BK channel antibody, and counterstained with haematoxylin



The figure shows faint staining indicating low levels of BK channel expression in surface cells in patients with normal renal function (A), and different patterns of generally enhanced BK channel expression along the surface cell-crypt cell axis in patients with ESRD (B, C, and D).

Reversal of life-threatening, drug-related potassium-channel syndrome by glibenclamide (*Lancet* 365:1873-1875, 2005)

증례: The authors describe three critically ill patients who received drugs with K_{ATP} channel-opening properties and subsequently developed severe life-threatening complications, including hyperkalemia and cardiovascular disturbances. Administration of the sulfonylurea-receptor inhibitor glibenclamide promptly reversed these abnormalities.

의의: Over the past 3 years, they have seen this syndrome and response in five patients taking nicorandil, cyclosporine, or isoflurane, which suggests that this disorder arises more frequently than is currently realized.
Nevertheless, while the cases reported here are novel and look plausible, we should bear in mind that the evidence remains anecdotal.

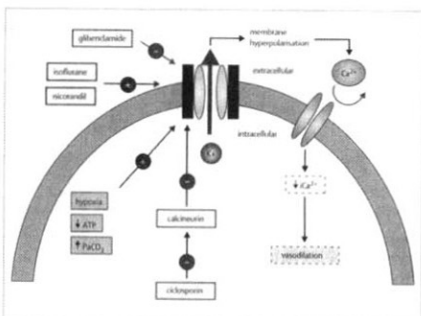


Figure 2: Schematic of how K^+ channels can affect vascular smooth-muscle tone
The ATP-sensitive K^+ channel can be activated with metabolic and/or respiratory acidosis, which, in turn, causes K^+ ions to leave the cell, leading to membrane hyperpolarisation, closure of voltage-gated Ca^{2+} channels and, ultimately, vasodilation. Opening can be potentiated by inhibition of calcineurin or by drugs acting directly on the channel.

The anion gap (AG): studies in the nephrotic syndrome and diabetic ketoacidosis (*J LabClin Med* 147:121–125, 2006)

배경: The serum anion gap (AG) is not only a function of "unmeasured" anions, but also it is a function of plasma non-carbonate buffers (albumin and phosphate), the plasma pH, and the method of measurement.

방법 및 결과: To clarify the contribution of non-carbonate buffers to the AG, the Figge–Fencl–Waston model of human plasma was applied to laboratory values obtained from two novel populations, patients with nephrotic syndrome and patients with diabetic ketoacidosis (DKA). The model performed adequately, justifying the common clinical practice of correcting the AG for the net protein charge.

A^- = {[albumin g/dl](1.2×pH - 6.15) + [phosphate mg/dl](0.097 × pH - 0.13)}
where A^- is the charge of the non-carbonate buffer species, in mM.
Omitting the relatively small contribution of divalent cations to electroneutrality, A^- in the absence of unmeasured anions accounts for a significant portion of the AG:
Unmeasured anions ≥ strong ion gap (SIG);
$AG - A^- = AG - \{[albumin] \times (1.2 \times pH - 6.15) + [phosphate](0.097 \times pH - 0.13)\}$

의의: We may surmise that SIG should be superior to AG in the detection of unmeasured anions.

Table II. Accuracy of acid–base parameters for the detection of plasma acetoacetate in patients hospitalized for treatment of type I diabetes

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Area under receiver operating curve ± SEM	Correlation (r value) with plasma acetoacetate (mM)
BE < 2 mM	77.8	94.7	98	56.0	0.928 ± 0.042	−0.767
AG > 14 mM	74.8	89.5	95	51.3	0.893 ± 0.035	−0.771
TCO_2 ≤ 24 mM	82.5	89.5	96	60.0	0.923 ± 0.044	−0.771
SIG > 4 mM	88.9	84.2	95	69.4	0.917 ± 0.037	0.815
Urine ketones[a]	96.0	80.0	63	98.0	–	–

*P < 0.05 vs. AG.
†P < 0.05.
[a]Data from Schwab et al.[28]

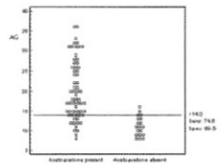


Fig 2. Sensitivity and specificity of AG > 14 mM for the detection of plasma acetoacetate in children hospitalized for treatment of type I diabetes. The area under the ROC is 0.893 ± 0.035 (standard error). The optimal threshold was determined by post hoc analysis.

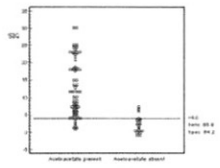


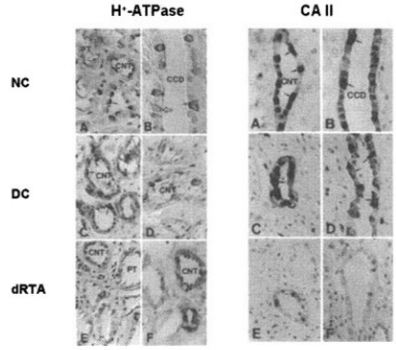
Fig 3. Sensitivity and specificity of SIG > 4 mM for the detection of plasma acetoacetate in children hospitalized for treatment of type I diabetes. The area under the ROC is 0.917 ± 0.037 for SIG, $P < 0.05$ versus AG. The optimal threshold was determined by post hoc analysis.

Autoantibodies against carbonic anhydrase II are increased in renal tubular acidosis associated with Sjögren syndrome (*Am J Med* 118:181-184, 2005)

배경: Serum samples from patients with Sjogren syndrome contain several autoantibodies, including anti-carbonic anhydrase II antibody. Mice immunized with carbonic anhydrase II develop systemic exocrine gland inflammation that mimics Sjogren syndrome in humans.

방법 및 결과: The authors measured autoantibodies against carbonic anhydrase II in 46 patients with Sjogren syndrome. In this sample, 6 patients with complete distal RTA and 7 with incomplete distal RTA (urine pH after acid loading 5.5) were identified. Levels of serum anti-carbonic anhydrase II antibody levels were higher in patients with defective urine acidification that in those without this defect, although there was some overlap in antibody levels.

의의: Antibody may be produced in response to tubular damage that exposes the circulation to intracellular carbonic anhydrase II. It is not known how autoantibodies against carbonic anhydrase II arise or whether they alter the function of the enzyme in cortical collecting duct cells.



J Am Soc Nephrol 13: 1425–1432, 2002

Effects of Induced Metabolic Alkalosis on Prolonged Intermittent-Sprint Performance (*Medicine & Science in Sports & Exercise* 37:759-767, 2005)

방법: Seven female team-sport athletes volunteered for the study. The athletes ingested two doses of either 0.2 g/kg of $NaHCO_3$ or 0.138 g/kg of NaCl (placebo), in a double-blind, random, counterbalanced order, 90 and 20 min before performing the IST on a cycle ergometer.

결과: Resting plasma bicarbonate concentration ($[HCO_3^-]$) averaged 22.6 ± 0.9 mmol/L, and at 90 min postingestion was 21.4 ± 1.5 and 28.9 ± 2.8 mmol/L for the placebo and $NaHCO_3$ conditions, respectively. Plasma $[HCO_3^-]$ during the $NaHCO_3$ condition remained significantly higher throughout the IST compared with both placebo and preingestion. There was a trend toward improved total work in the second, but not first, half of the IST after the ingestion of $NaHCO_3$. Furthermore, subjects completed significantly more work in 7 of 18 second-half, 4-s sprints after $NaHCO_3$ ingestion.

의의: $NaHCO_3$ ingestion may improve intermittent-sprint performance and may be a useful supplement for team-sport athletes.

Metabolic alkalosis reduces exercise-induced acidosis and potassium accumulation in human skeletal muscle interstitium (*J Physiol* 566:481-489, 2005)