WHICH FLUIDS SHOULD BE USED IN THE CLINICAL SETTING?

- Big debate: crystalloids
  colloids
  crystalloids + colloids

My "personal strategy":

crystalloids + colloids

Why?

Jacob et al. Critical Care 2012, 16:R86
http://ccforum.com/content/16/3/R86

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

CRITICAL CARE

RESEARCH Open Access

The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans

Matthias Jacob[1*†], Daniel Chappell[1†], Klaus Hofmann-Kiefer[1], Tobias Helfen[1], Anna Schuelke[1], Barbara Jacob[1], Alexander Burges[2], Peter Conzen[1] and Markus Rehm[1]

Conclusions: Substitution of isolated intravascular deficits in cardiopulmonary healthy adults with the three-fold amount of Ringer's lactate impedes maintenance of intravascular normovolemia. The main side effect was an impressive interstitial fluid accumulation, which was partly restored by the intravenous infusion of 20% human albumin. We recommend to substitute the five-fold amount of crystalloids or to use an isooncotic preparation in the face of acute bleeding in patients where edema prevention might be advantageous.

Crystalloids + colloids end of the story?

Variables:

- Patients (comorbidities…)
- Surgery (type, duration..)

•Quantity:

vs

•Quality:

vs

We have different solutions…

- Crystalloids
  - Normal Saline
  - Lactate Ringer
  - Balanced Solutions
  - ……..
- Colloids
  - HES (NS or Balanced S.)
  - Gelatines (NS or Balanced S.)

Any relevance from the clinical point of view?

How much fluids should I give to my patients?

Early, very early!

E. Rivers, NEJM 2001

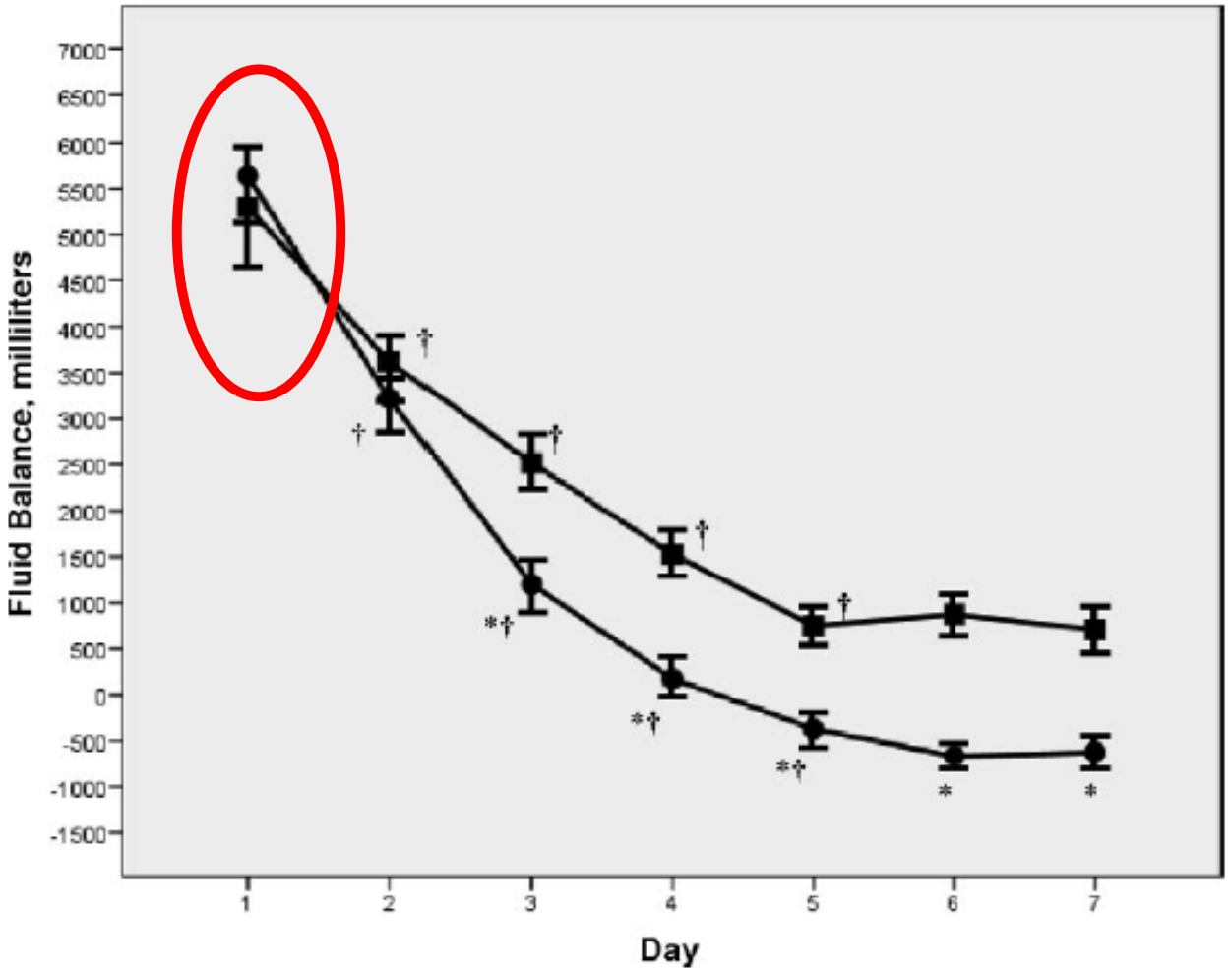

FIGURE 1. Mean (± SE) daily fluid balance (in milliliters) for days 1 through 7 following the onset of septic shock. Nonsurvivors are depicted by squares, and survivors by circles. * = $p < 0.05$ pairwise compared between survivors and nonsurvivors (ANOVA for repeated measures); † = $p < 0.05$ compared with the previous time point (ANOVA for repeated measures).

Murphy et al: Chest 2009; 136:102-109

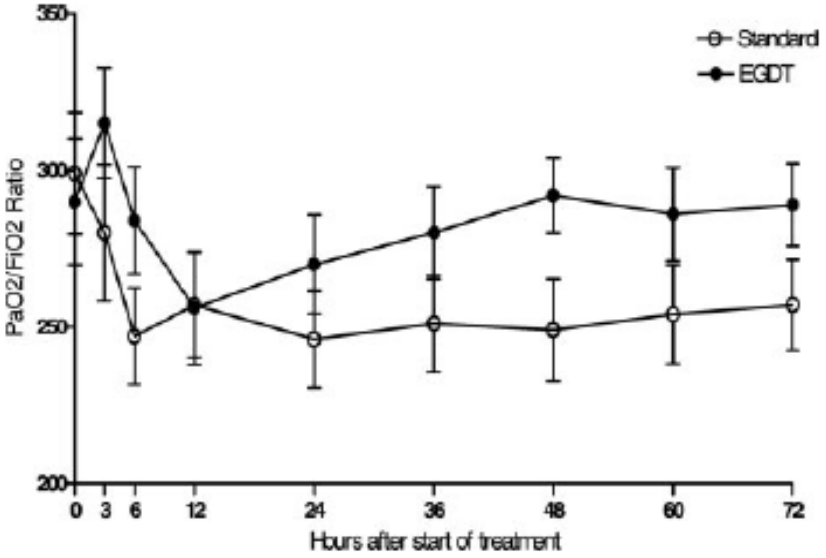

FIGURE 4. Comparing the PaO_2/fraction of inspired oxygen (FIO_2) ratios between the EGDT and standard-care groups. Despite more volume resuscitation in the EGDT group during initial 6 h, there was no net difference in PaO_2/FIO_2 ratio ($p = 0.34$).

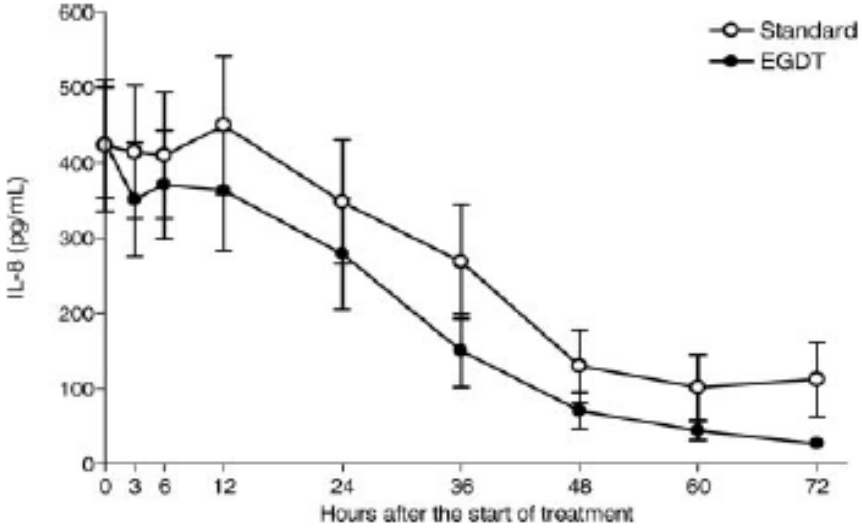

FIGURE 5. The effect of EGDT on inflammation. EGDT effects on inflammation (IL-8) associated with ALI. EGDT patients had a corresponding lower level of IL-8 and a decreased rate of mechanical ventilation in the subsequent 7 to 72 h time period ($p = 0.045$).

(CHEST 2006; 130:1579–1595)

Critical Care Medicine
Society of Critical Care Medicine
Wolters Kluwer Health | Lippincott Williams & Wilkins
S.B.A. Universita' di Ferrara 13086

Interaction Between Fluids and Vasoactive Agents on Mortality in Septic Shock: A Multicenter, Observational Study*

Waechter, Jason MD[1]; Kumar, Anand MD[2]; Lapinsky, Stephen E. MB, MSc[3]; Marshall, John MD[3]; Dodek, Peter MD, MHSc[4]; Arabi, Yaseen MD[5]; Parrillo, Joseph E. MD[6]; Dellinger, R. Phillip MD[7]; Garland, Allan MD, MA[2]; for the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group

Measurements and Main Results: Fluids and vasoactive agents had strong, interacting associations with mortality ($p < 0.0001$). Mortality was lowest when vasoactive agents were begun 1–6 hours after onset, with more than 1 L of fluids in the initial hour after shock onset, more than 2.4 L from hours 1–6, and 1.6–3.5 L from 6 to 24 hours. The lowest mortality rates were associated with starting vasoactive agents 1–6 hours after onset.

Conclusions: The focus during the first hour of resuscitation for septic shock should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration. Starting vasoactive agents in the initial hour may be detrimental, and not all of that association is due to less fluids being given with such early initiation of vasoactive agents.

CHEST

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality

A Retrospective Cohort Study

Sarah J. Lee, MD, MPH; Kannan Ramar, MBBS, MD; John G. Park, MD, FCCP; Ognjen Gajic, MD, FCCP; Guangxi Li, MD; and Rahul Kashyap, MBBS

CONCLUSIONS: Earlier fluid resuscitation (within the first 3 h) is associated with a greater number of survivors with severe sepsis and septic shock. CHEST 2014; 146(4):908-915

Fluid received in hours 0-3, mL	1,600 (600 to 3,010)	2,085 (940 to 4,080)	.007[a]
Fluid received in hours 3.1-6, mL	880 (360 to 1,680)	660 (290 to 1,485)	.09
Total fluid received in 6 h, mL	2,875 (1,390 to 47,20)	3,150 (1,630 to 5,665)	.10

TABLE 2] Clinical Hemodynamic Outcomes

Variable	Nonsurvivors	Survivors	*P* Value
CVP in hour 6, cm H_2O	10 (5-16) (n = 88)	10 (5-14) (n = 279)	.52
MAP in hour 6, mm Hg	64.5 (59-72) (n = 142)	68.5 (62-77) (n = 452)	< .01[a]
$Scvo_2$ in hour 6	68.5 (61-78) (n = 75)	73 (68-78) (n = 252)	< .01[a]
Vasopressor use in first 24 h, %	76 (n = 108)	54 (n = 242)	< .01[a]
Oliguria in hour 6, %	71 (n = 101)	41 (n = 186)	< .01[a]
SOFA score day 1	8 (6-12) (n = 142)	6 (4-9) (n = 452)	< .01[a]

We have different solutions…

- Crystalloids

  Normal Saline

  Lactate Ringer

  Balanced Solutions

  ……..

Any relevance from the clinical point of view?

Normal saline…….

- The use of 0.9% saline originated from the ***in vitro*** studies of Hartold Jacob Hamburger, who, in the 1890s, found that the freezing point of 0.9% saline was the same as that of human serum (ie, iso-osmolar) and that erythrocytes were least likely to lyse in it. Hamburger called this solution "indifferent" saline, indicating that it had no effect on red blood cells.

- It is uncertain when 0.9% saline was first used intravenously in patients

- The side effects of administering large amounts of it were recognized as early as 1911 when Evans commented,

"*One cannot fail to be impressed with the danger . . . (of) the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period . . . " and observed that " . . . the disastrous role played by the salt solution is often lost in light of the serious conditions that call forth its use."*

[Evans GH. The abuse of normal salt solution. *JAMA. 1911]*

"Normal (?) saline"

- Na^+ 154 mmol/L; Cl^- 154 mmol/L

  [n.v.: Na^+: 140 mmol/L; Cl^- 100 mmol/L]

- It is chloride that induce acidosis

  The trouble is to see Cl^- as an acid (NaCl is a salt)!

- Water is not only H_2O, but also H^+ and OH^-! If we add NaCl to pure water → no effects on pH

- Cl^- → H^+ = HCl (acid)

- Na^+ → OH^- = NaOH (base)

- However, blood plasma is not pure water, is not neutral solution, but an alkaline one!

- Normal saline alters more [Cl^-] than [Na^+]

Volta et al. Journal of Inflammation 2013, 10:29
http://www.journal-inflammation.com/content/10/1/29

JOURNAL OF INFLAMMATION

RESEARCH Open Access

Effects of two different strategies of fluid administration on inflammatory mediators, plasma electrolytes and acid/base disorders in patients undergoing major abdominal surgery: a randomized double blind study

Carlo Alberto Volta[1*], Alessandro Trentini[2], Lucia Farabegoli[1], Maria Cristina Manfrinato[2], Valentina Alvisi[1], Franco Dallocchio[2], Elisabetta Marangoni[1], Raffaele Alvisi[1] and Tiziana Bellini[2]

Primary outcome:
to verify if the use of normal saline can be responsible for ***alteration of electrolytes plasmatic levels*** associated with hyperchloremic acidosis

Secondary outcomes:
the influence of balanced solutions on

a) renal function;
b) inflammatory cascade.

Acid – base disorders

Volta et al. Journal of Inflammation 2013, 10:29
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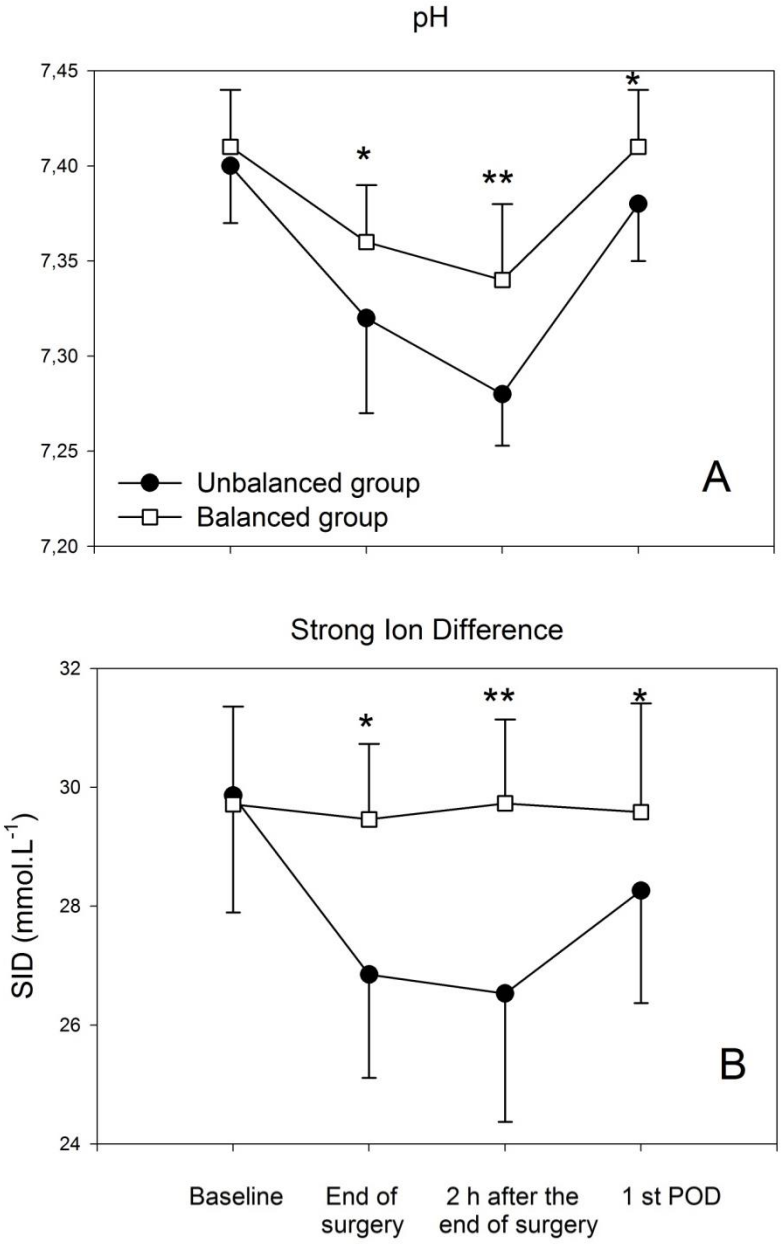

$$SID = [HCO_3^-]+[Alb^-]+[Pi^-]$$

Volta et al. Journal of Inflammation 2013, 10:29
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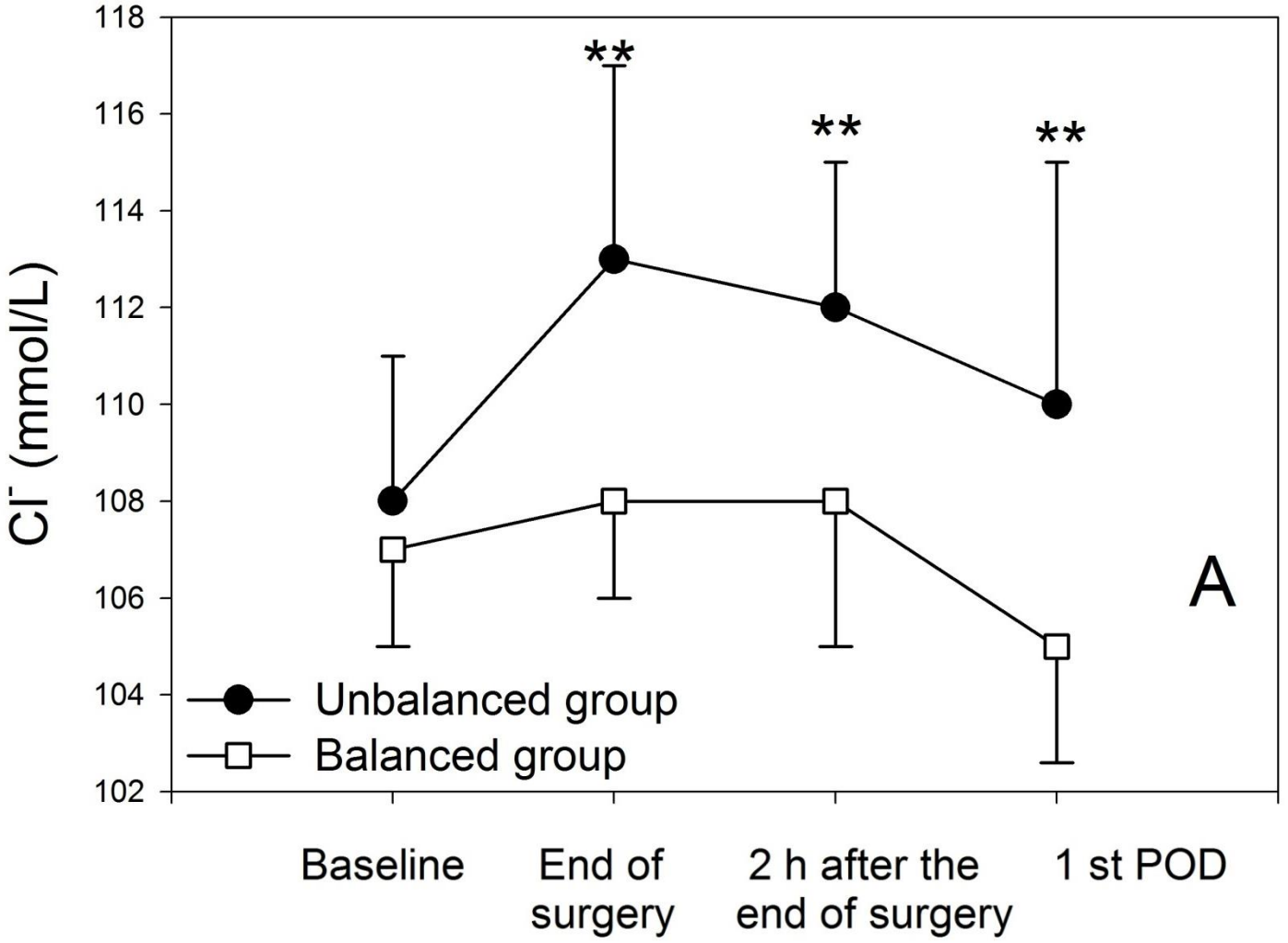
Chloride (mEq/l)



Hyperchloremic acidosis

- intramucosal acidosis (gastrointestinal tract)
- prolongation of gastric emptying time
- paralytic ileus and decreased smooth muscle contractility
- oedema in the gastrointestinal tract (anastomotic swelling)
- an increase in abdominal pressure (renal perfusion!)
- reduced splanchnic blood flow

➢ *"Hypercloremic acidosis was associated with higher mortality and postoperative morbidity in patients undergoing open abdominal surgery"*

[Ann Surg, 2012]

References :
Wilkes NJ, et al. Anesth Analg. 2001; 93:811–6
Lobo DN, et al. Lancet. 2002;3 59:1812–8
Tournadre JP, et al. Anesth Analg. 2000; 90:74–9
Chowdhury AH, Lobo DN. Curr Opin Clin Nutr Metab Care. 2011; 14:469–76
Shaw AD, et al. Ann Surg 2012; 255:821-9

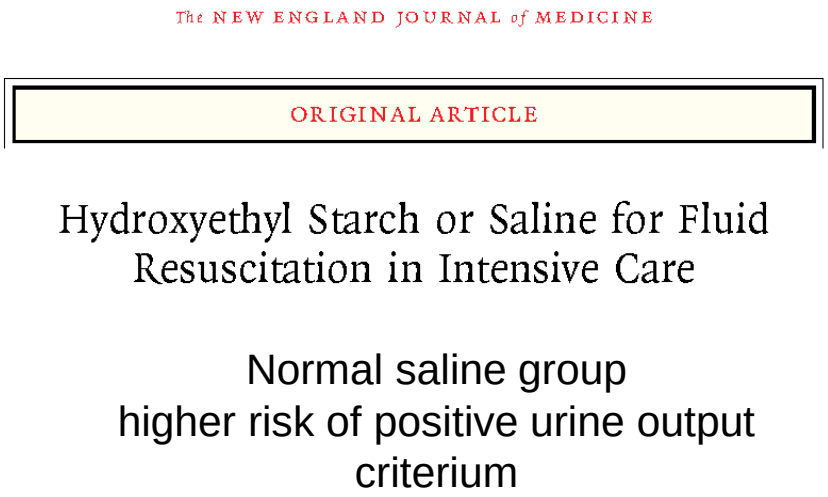
Hyperchloremia

- renal vasoconstriction
- increase in renal vascular resistance (approx. 35%)
- decrease of GFR (approx. 20%), reduction in diuresis
- suppression of renin activity (NaCl and not $NaHCO_3$)
- reduction in blood pressure

References

Animal experiments:
Wilcox CS: J Clin Invest 1983; 71: 726-735;
Wilcox CS et al.: Am J Physiol 1987; 253: F734-F741;
Quilley CP et al.: Br J Pharmacol 1993; 108: 106-110

Human experiments
Chowdhury AH, et al. Ann Surg. 2012; 256:18-24
Waters JH, et al. Anesth Analg 2001; 93: 817–22
Kotchen TA, et al. Ann Intern Med 1983; 98:817–22


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

Normal saline group
higher risk of positive urine output criterium

PRELIMINARY
COMMUNICATION

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

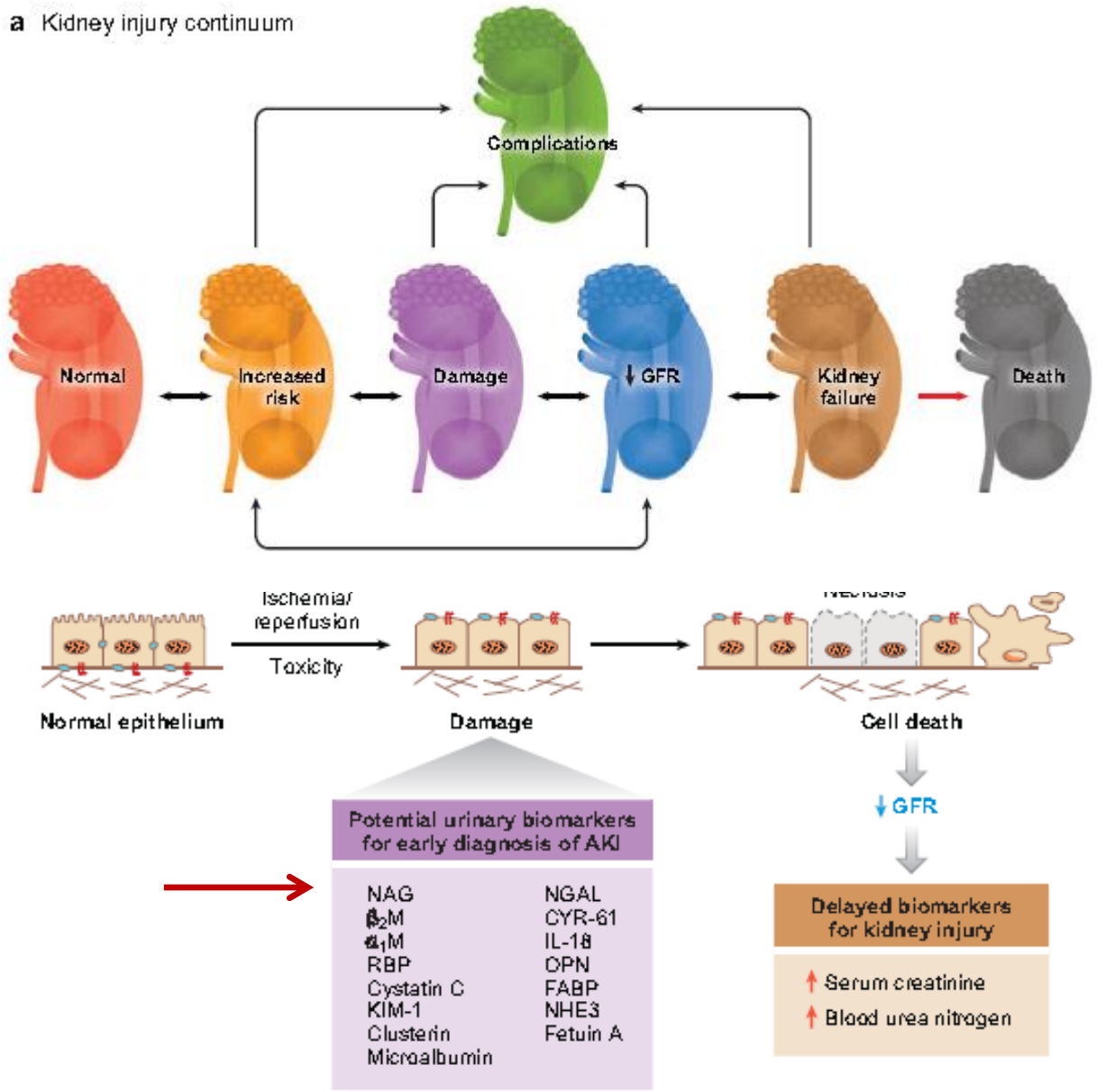
Conclusion The implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and use of RRT.

Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

	No. (%) [95% CI] of Patients[a]		
	Control Period (n = 760)	Intervention Period (n = 773)	*P* Value
RIFLE class			
Risk	71 (9.0) [7.2-11.0]	57 (7.4) [5.5-9.0]	.16
Injury	48 (6.3) [4.5-8.1]	23 (3.0) [1.8-4.2]	.002
Failure	57 (7.5) [5.6-9.0]	42 (5.4) [3.8-7.1]	.10
Injury and failure	105 (14) [11-16]	65 (8.4) [6.4-10.0]	<.001

[a] The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.

Renal function



Renal function and NGAL

NGAL is upregulated by ischemia in several segments of the nephron, predominantly in proximal tubules and it is suggested to be an early marker of acute renal injury

This gelatinase significantly and rapidly (about two hours) increases in presence of kidney cellular damage

The 2-hour NGAL a reliable predictor of severity and duration of AKI, length of hospital stay, renal replacement therapy requirement and mortality

Urinary NGAL value should be : < 100 ng/mL.

Mishra J, et al. J Am Soc Nephrol 2003; 14:2534–43
Han WK, et al. Curr Opin Crit Care 2004;10:476–82
Dent CL, et al.Crit Care 2007; 11:R127
Bennett M, et al. Clin J Am Soc Nephrol 2008; 3: 665–73.

Renal function : NGAL (ng/ml)

Volta et al. Journal of Inflammation 2013, 10:29
http://www.journal-inflammation.com/content/10/1/29

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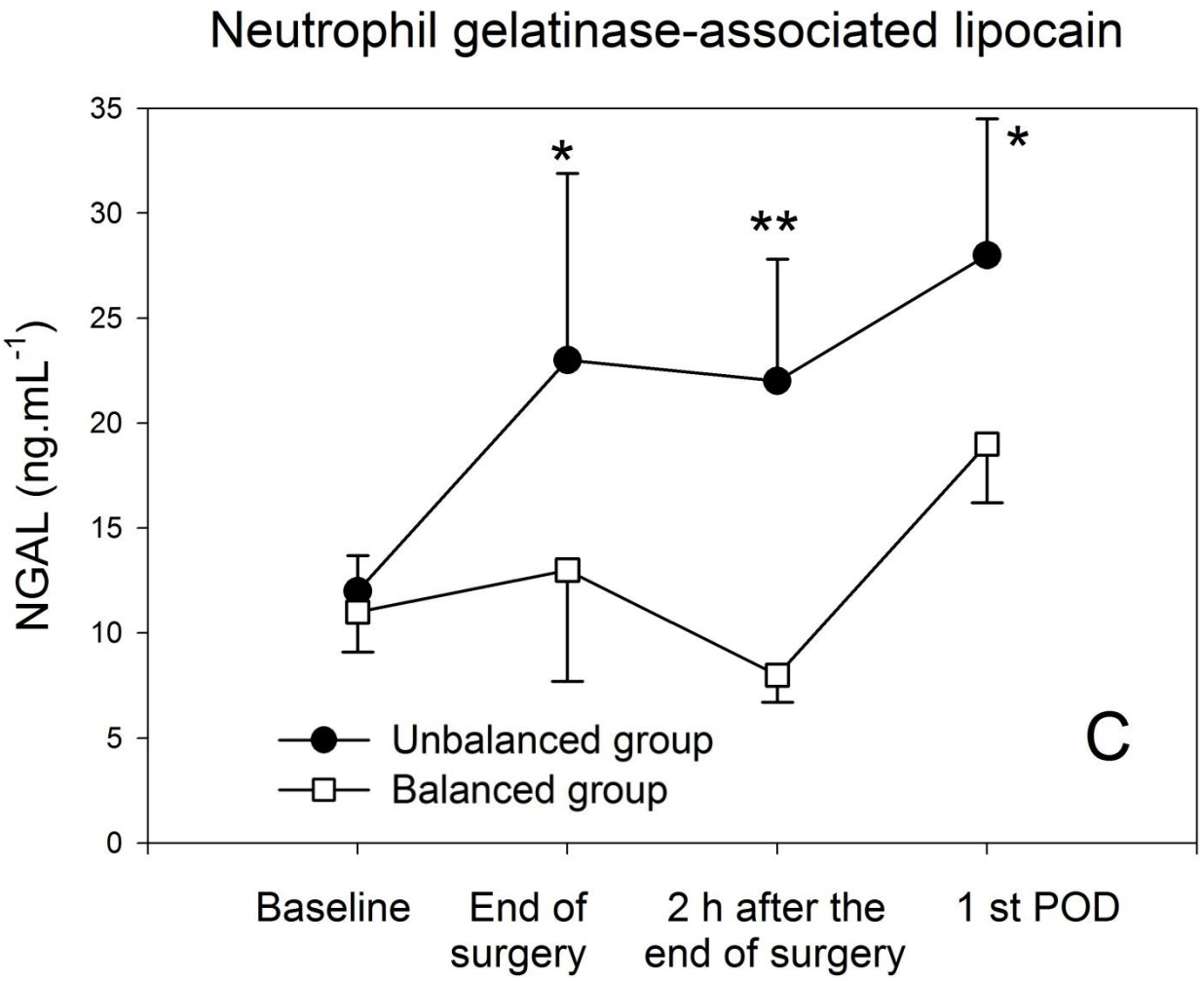

Calcium

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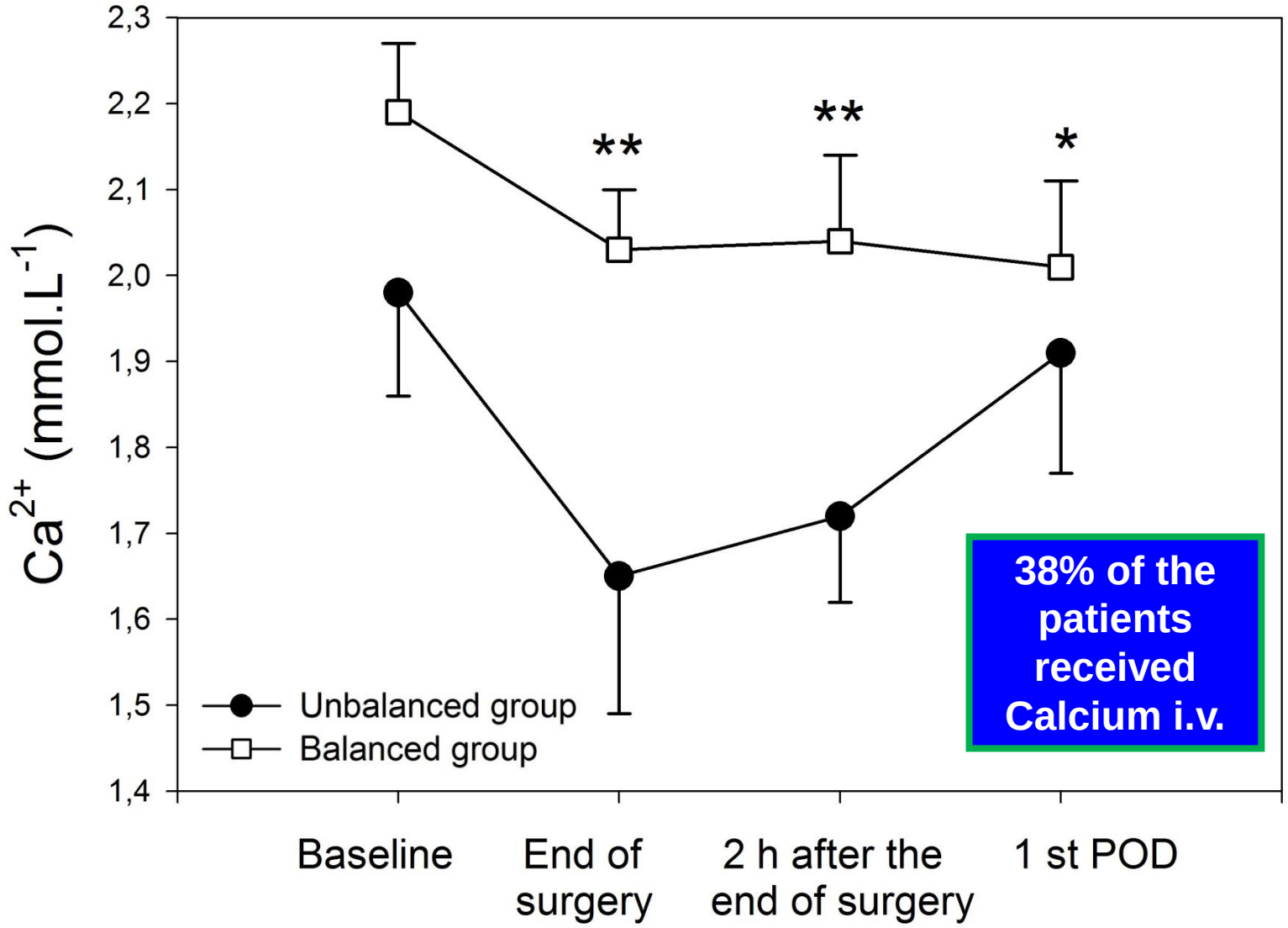

38% of the patients received Calcium i.v.

Calcium is essential for:

Excitation-contraction coupling (cardiac arhythmias)

Ciliary movments

Neurotransmitters release

Enzyme secretion

Hormonal secretion

Coagulation

Acidosis, Calcium and Coagulation status

- Clotting activity is affected not only by temperature, but also by pH
- Hypocalcemia can affect clotting activity
- Lactate produces a linear decrease of Ca^{2+} concentration

  (*attention to Ringer's lactate administration*)

Magnesium

Volta et al. Journal of Inflammation 2013, 10:29
http://www.journal-inflammation.com/content/10/1/29

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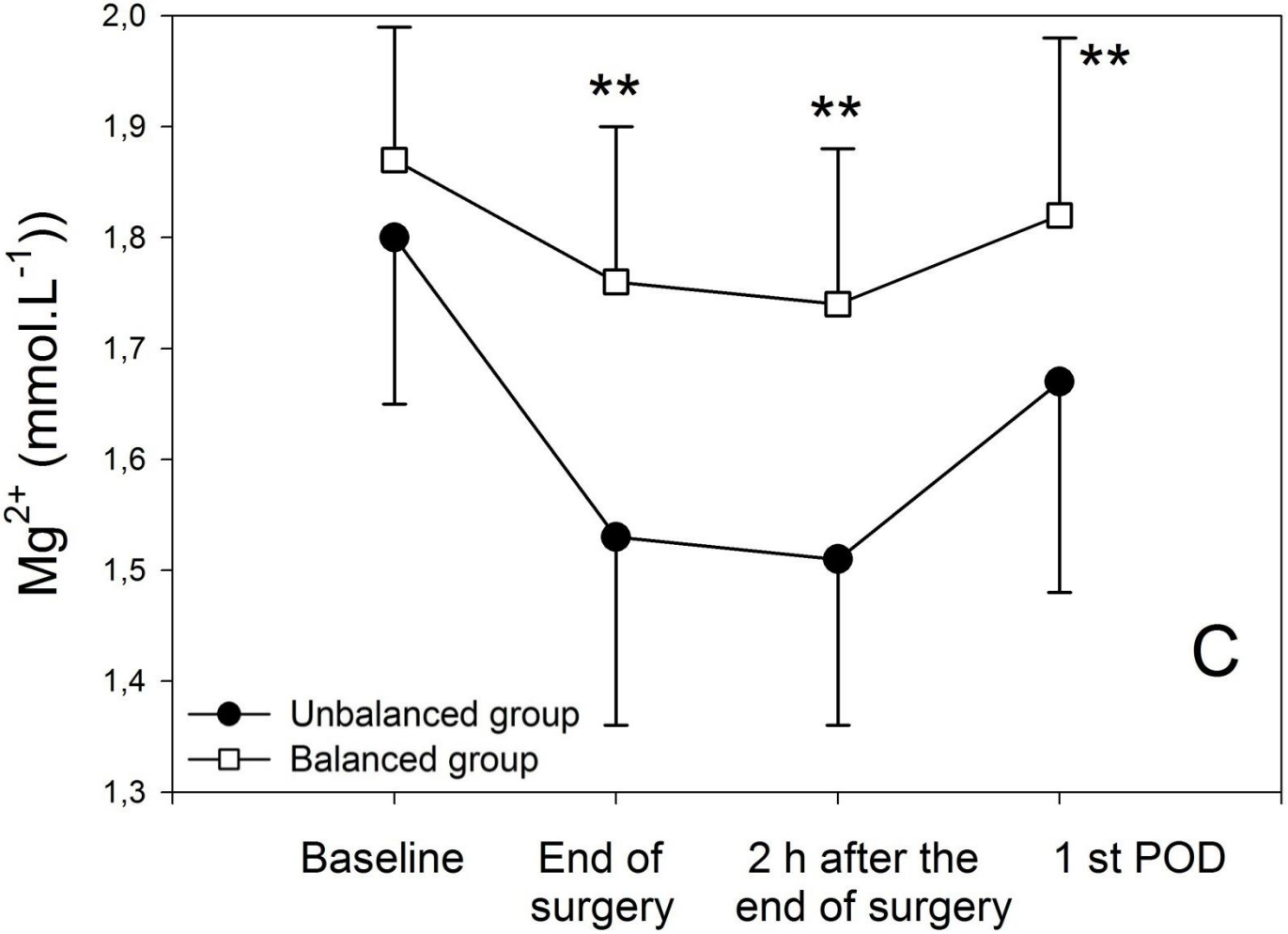


Mg^{2+} deficiency

- Magnesium reduces the catecholamine release during the stressful manouvres.
- Magnesium has anti-nociceptive effects (it reduces the need for intraoperative anesthetics and relaxant drugs and reduces the amount of morphine for the treatment of pospoperative pain).
- The role of magnesium has been extensively studied in cardiology especially during **myocardial infarction**, **arrhythmia** and **cardiac surgery**.

CLINICAL MANIFESTATION:

Tetany

Seizures

Arrythmias

Neuromuscolar irritability

Hypocalcemia

Hypokalemia

ANESTHESIA & ANALGESIA

A Randomized, Double-Blind Comparison of Lactated Ringer's Solution and 0.9% NaCl During Renal Transplantation

Catherine M. N. O'Malley, FFARCSI*, Robert J. Frumento, MPH*, Mark A. Hardy, MD, Alan I. Benvenisty, MD, Tricia E. Brentjens, MD*, John S. Mercer, MD, and Elliott Bennett-Guerrero, MD*

2005

AIM OF THE STUDY:

to explore the effects of NS administration on graft function as reflected by:

- **intraoperative acid-base balance**
- **intraoperative K concentration**
- **serum creatinine concentration on postoperative day 3**
- **postoperative urine output**
- **blood loss and transfusions**
- **postoperative hospital length of stay**

METHODS:

- **Randomized NS or LR for intraoperative fluid replacement during surgery for kidney transplantation**
- **No algorithm for fluid administration or treatment of acidosis and hyperkalemia**
- **Blood samples at baseline and every 30 min for the duration of surgery, then once a day**

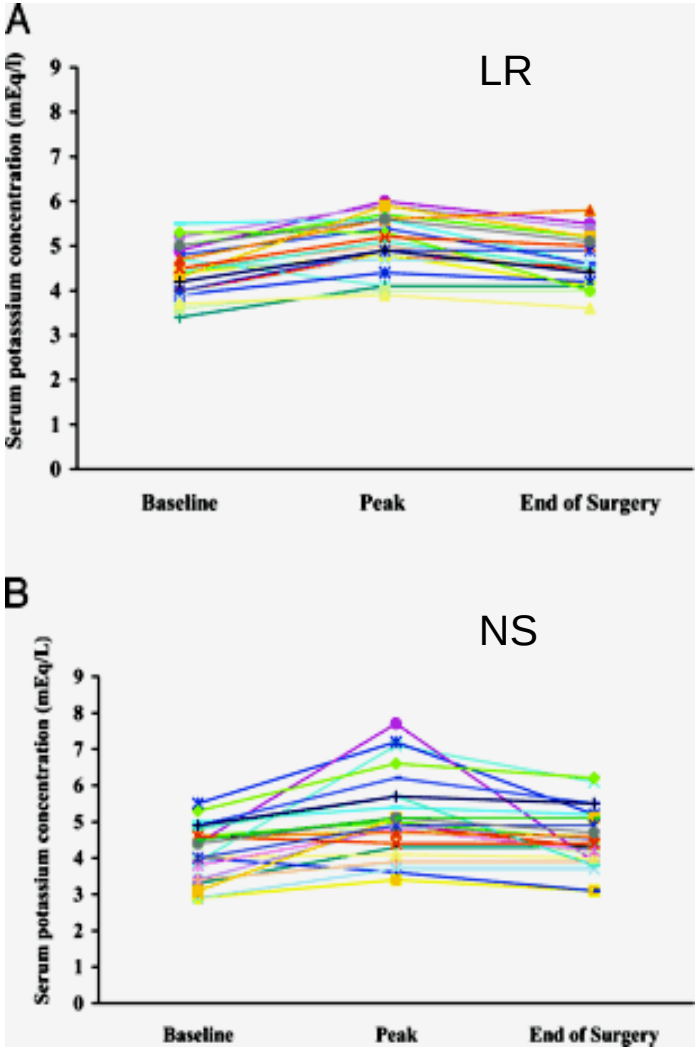
Table 1. Demographic and Perioperative Variables

	NS (n = 26)	LR (n = 25)	P-value
Age, y	44 ± 13	44 ± 11	ns
Sex, No. (%) men	17 (65)	15 (60)	ns
Weight, kg	72 ± 14	75 ± 18	ns
Living donor, No. (%)	25 (96)	23 (92)	ns
Patients requiring preoperative hemodialysis, No. (%)	18 (69)	13 (52)	ns
Volume of study fluid, L	6.1 ± 1.2	5.6 ± 1.4	ns
Operating room time, h	5.6 ± 1.1	5.6 ± 1.3	ns
Warm ischemia time, min	34 ± 13	34 ± 9	ns
Patients receiving intraoperative dopamine, No. (%)	23 (85)	20 (80)	ns
Blood loss, mL	309 ± 162	310 ± 190	ns
Patients transfused, No. (%)	3 (11)	2 (8)	ns
Baseline serum creatinine, mg/dL	7.0 ± 2.7	8.0 ± 2.6	ns
Baseline serum potassium, mEq/L	4.2 ± 0.7	4.5 ± 0.5	ns
Peak intraoperative serum potassium, mEq/L	5.1 ± 1.1	5.1 ± 0.6	ns
End of surgery serum potassium, mEq/L	4.5 ± 0.8	4.6 ± 0.6	ns
Baseline pH	7.39 ± 0.05	7.36 ± 0.08	ns
Lowest intraoperative pH	7.26 ± 0.08	7.33 ± 0.07	0.001
End of surgery pH	7.28 ± 0.07	7.37 ± 0.07	<0.0001
End of surgery serum chloride, mEq/L	111 ± 4	106 ± 4	<0.0001
Baseline serum bicarbonate, mEq/L	22 ± 5	22 ± 6	ns
Lowest intraoperative serum bicarbonate, mEq/L	16 ± 3	19 ± 4	0.004
End of surgery serum bicarbonate, mEq/L	18 ± 3	21 ± 4	0.007

Data are mean ± SD unless otherwise stated.
NS = 0.9% NaCl (normal saline) group; LR = lactated Ringer's solution group.

Metabolic acidosis, hypercloremia in NS group vs LR group

Figure 1. Perioperative potassium concentrations in (A) LR- and (B) NS-treated patients



The study was stopped prematurely because, compared with ***none*** in those receiving Ringer's lactate, 19% of patients in the saline group had to be treated for hyperkalemia and 31% for metabolic acidosis.

"…hyperkalemia in NS-treated patients is presumably through an extracellular shift of potassium caused by hyperchloremic metabolic acidosis.."

Fluids and "potential elevated ICP"

- However, RL is an hypotonic solution
- Intracranical compartment responses to changes in plasma osmolality. A decrease from 288 to 280 mosml/Kg/H_2O results in an increase in brain volume by 3%, causing a decrease in blood and / or cerebrospinal fluid volume by 30%!
- A decrease from 288 to 287 (!) is able to incraese the ICP by 10 mmHg

NS or balanced solution?

- NS: acidosis, arythmias, hypocoagulability, iperK^+ hypocalcemia, …. (+ hypothermia..)

Balanced versus chloride-rich solutions for fluid resuscitation in brain-injured patients: a randomized double-blind pilot study
(Critical Care, 2013)

This study provides evidences that balanced solutions *reduce the incidence of hyperchloraemic acidosis in brain-injured patients* as compared with saline solutions….. *intracranial pressure did not appear different between groups*.