Electrolyte imbalance and metabolic derangement

an unmet need for internists

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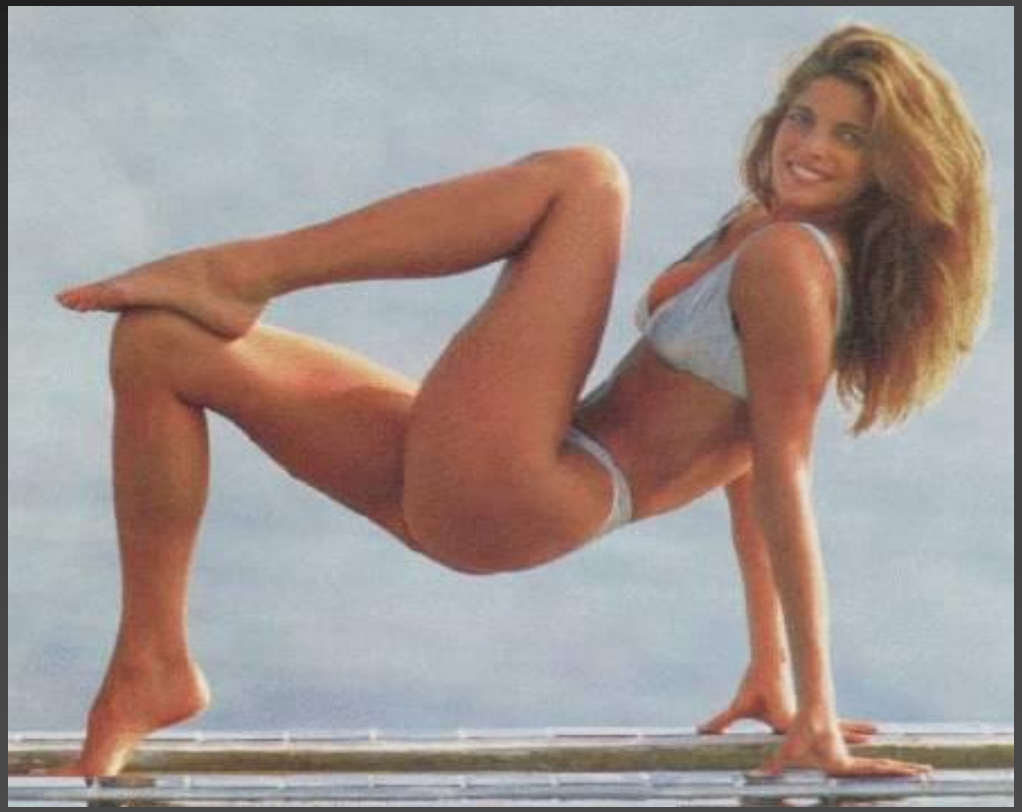
Electrolyte & metabolic derangement

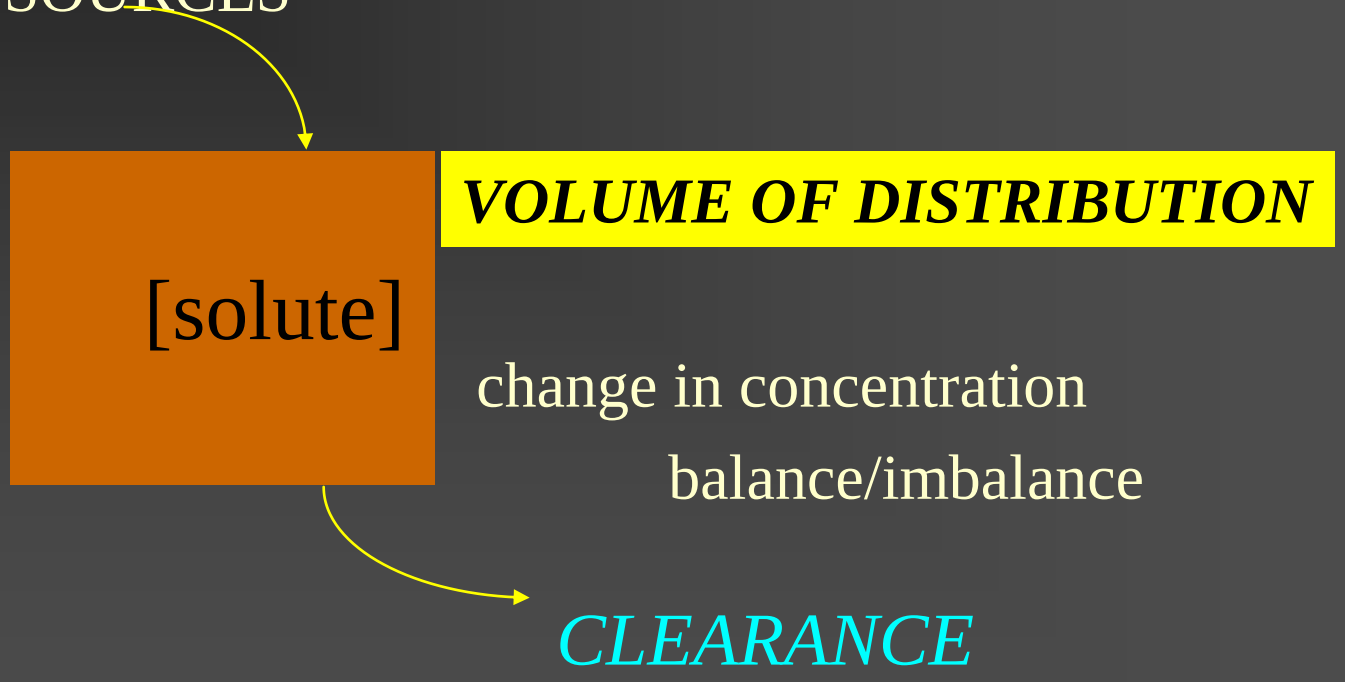
A need ...



Internists need more exercise

Mental exercise

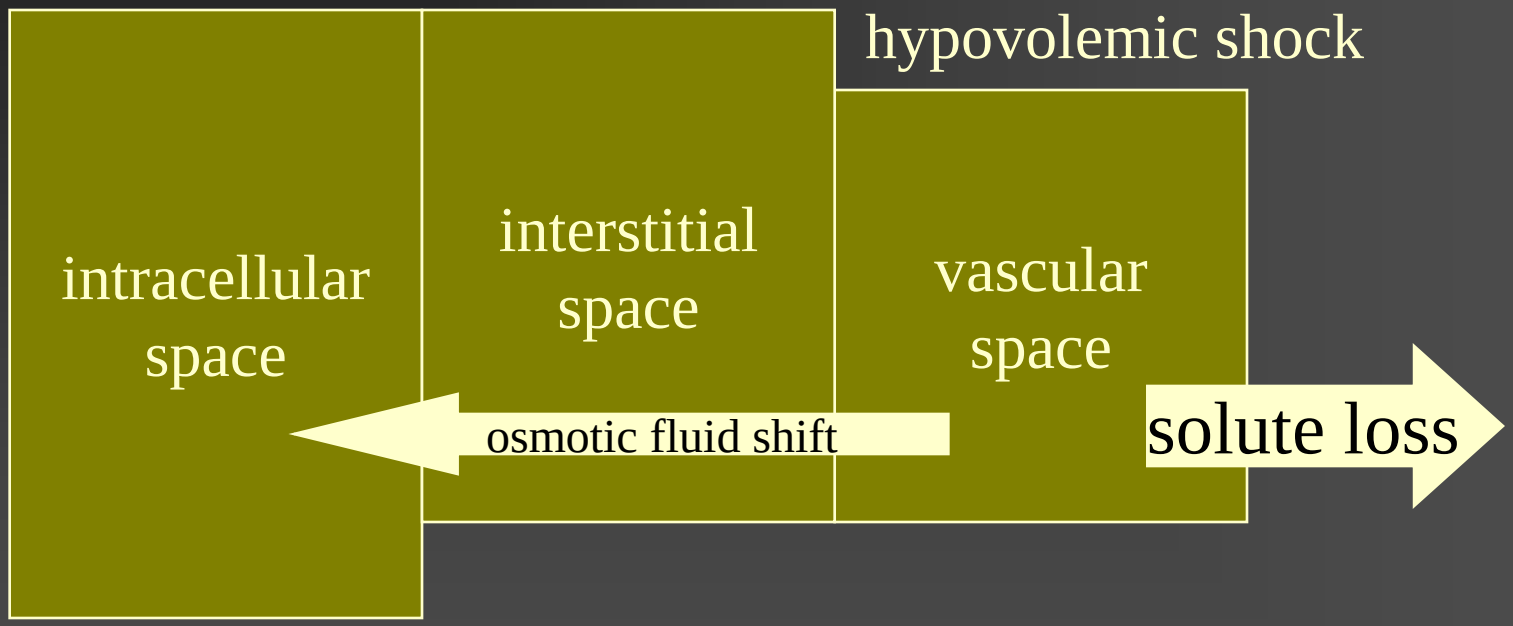
TOXIN, ELECTROLYTE, METABOLITE GENERATION
EXOGENOUS SOURCES



sodium (in water)

- important factor affecting ECF tonicity & volume
- Although Na distribution is ECF, the osmotic distribution is TBW
- OsmECF = OsmICF always balance
  - single-pool model is appropriate
- Na manipulation allows manipulation of haemodynamics

Sodium (and water)



cerebral edema
disequilibrium

high ICP + low BP = low CPP

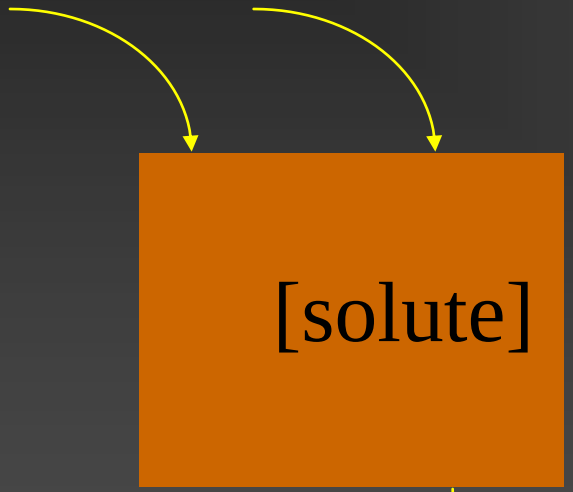
Na is the major factor affecting water volume

example

- 30y patient post pituitary tumor excision
  - polyuria 500 ml/h over 10h ie 5L H_2O loss
  - Osm_{urine} 120 mOsm/kg
  - Na_{plasma} 155 mM
  - Na_{urine} 50 mM
- what is going on?

What is going on?

5L H_2O + 750 mmol Na



volume of distribution

change in concentration

5L H_2O + 250 mmol Na

What is going on?

Received 5L H_2O + 750 mmol Na

[Na]:
140 ->155

TBW no change: 30L

Change in conc
= 500/30 = 15 mmol/L

Lost 5L H_2O + 250 mmol Na

Great care is required

Hemofiltration replacement 3 - 12 L/h
isoNatremic 142 mmol/L

TBW
no change

Keep [Na]constant

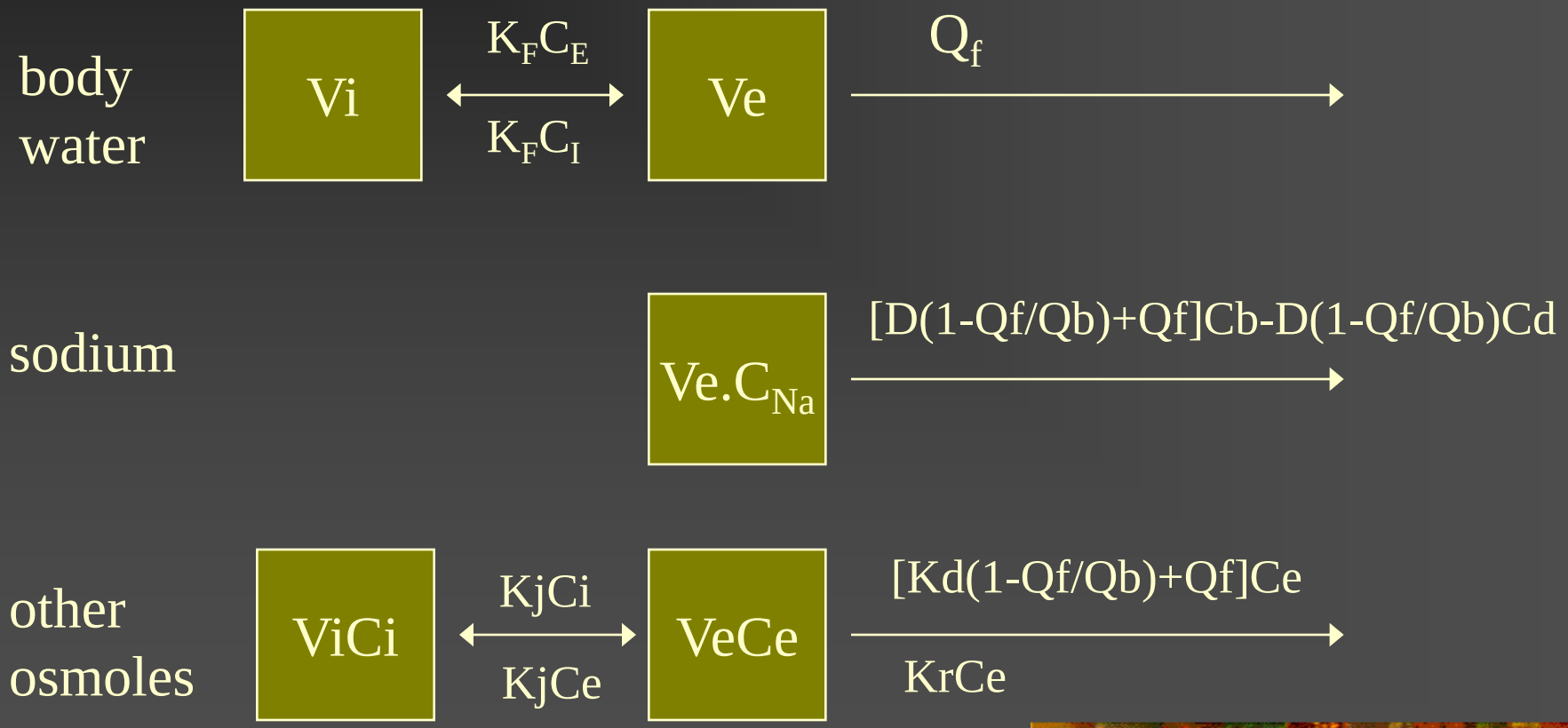
NaP	plasma (protein, lipid)	140
NaPW	plasma water	149
Na^+P	ionized plasma water	142

Hemofiltration effluent 3 - 12 L/h

NaUF (Gibb-Donnan effect)	142
Na^+UF	137

Locatelli F, et al. Int J Artif Organs 1982;5:17

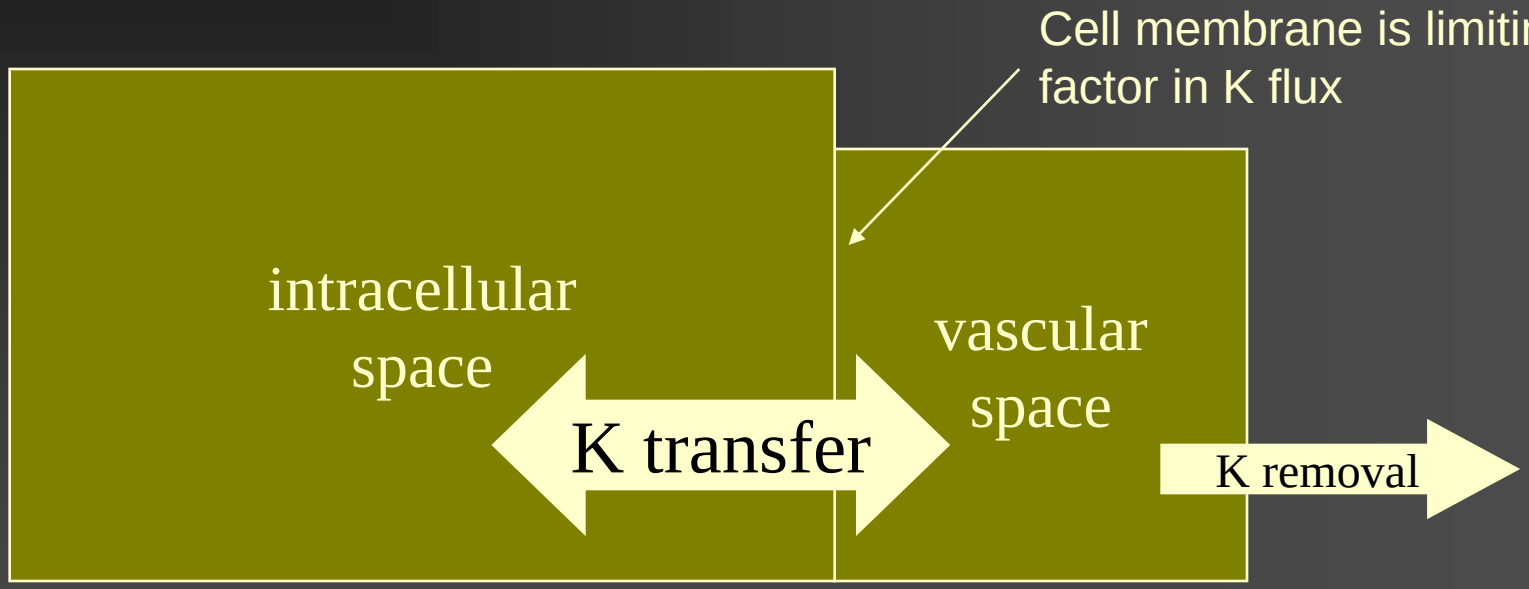
body water and osmole kinetic model



sodium & UF profiling

- ECF sodium-water modelling goals
  - target end-dialysis Na and TBW values
  - avoid fluid shift and vascular space dehydration; ie Vi~Ve
  - initial large first-order solute flux treated by delayed Na removal to maintain ECF volume: high Na with decreasing UF, or low UF decreasing Na, or both
    - “Na and UF profiling”
- cross-over RCT: n=10, haemodynamic stability
    - Paganini EP, et al. NDT 1996;11 suppl 8:32-37

Potassium: 2 compartments



- FACTORS AFFECTING K FLUX
  - hormonal milieu, catecholamine therapy
  - acid-base balance
  - tonicity, glycaemia

Potassium in the critically ill

- K balance poorly predicted from K removal efficacy
  - the ratio of ICF to ECF K is 30
  - plasma K reflects exposure to K in CEBP fluid
  - rebound of K occurs when RRT stops
- low K very common in the critically ill
  - higher $[K]_R$ is needed
- rapid changes in K causes arrhythmias
- K profiling: lower frequency of arrhythmias
  - Redaelli B, et al. Kidney Int 1996;50:609-17

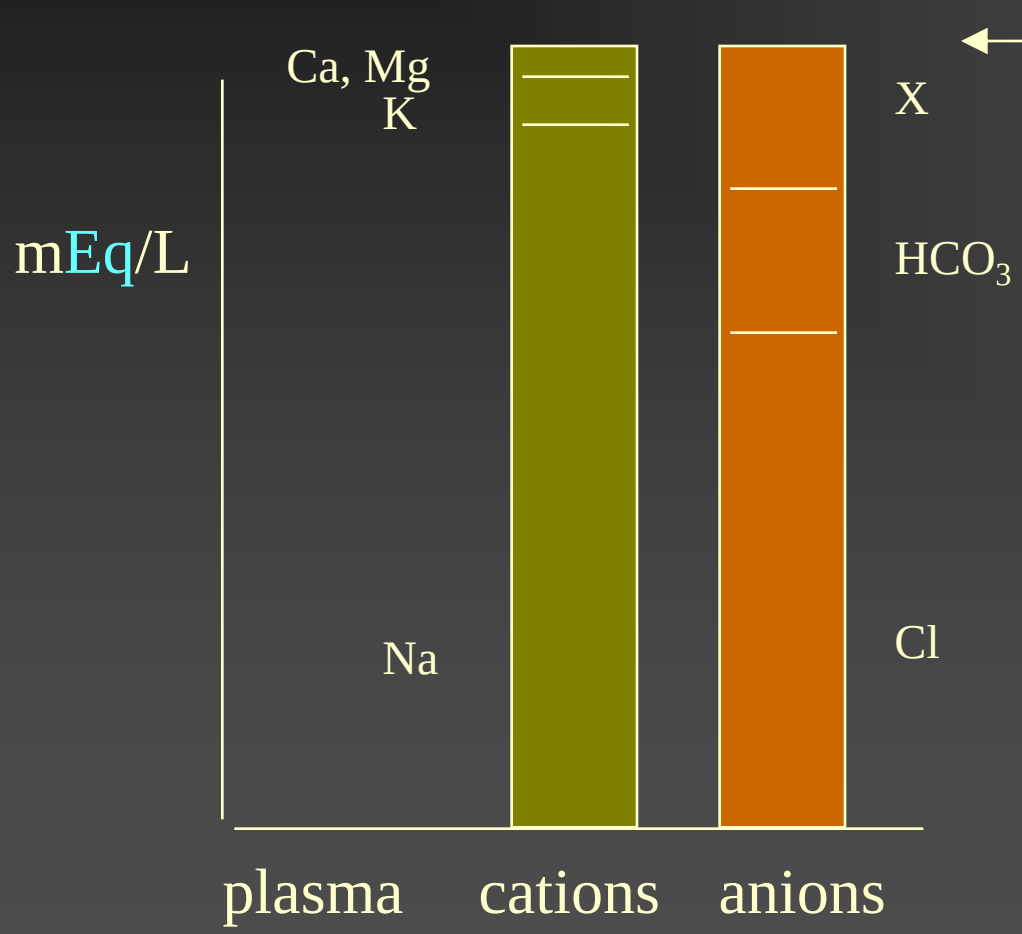
Magnesium in the critically ill

- intracellular cation
- “Type II” nutrient: deficiency may be associated with normal/high blood/tissue levels
- 65% of ICU patients are Mg deficient
  - Wong ET, et al. Am J Clin Path 1983;79:348-52
- Commercially
  - MgR 0.75 - 1.0 mmol/L
  - Mg (PD) 0.25 mmol/L

Some things always balance

System constraints

the ‘Gamblegram’ (Gamble JL 1939)



the law of electroneutrality

$\Sigma (+) = \Sigma (-)$

always balance

a ‘system constraint’

system constraints (aqueous solutions)

- electroneutrality
  - In aqueous solutions the sum of all positively charged ions equals the sum of all negatively charged ions
- dissociation equilibria
  - Incompletely dissociated ions are related by a dissociation constant
- mass conservation
  - The amount of a substance remains constant unless it is added or generated or removed or destroyed

Must always balance

- electroneutrality
  - Σ (+) = Σ (-)
- dissociation equilibria
  - Henderson-Hasselbach equation(s)
  - $[H^+] \times [A^-] = K_A \times [HA]$
  - water dissociation $[H^+] \times [OH^-] = K_W \times [H2O]$
- mass conservation
  - $[Atot]_n = [HA]_n + [A^-]_n$

Stewart PA. *Can J Physiol Pharmacol 1983; 61: 1444*

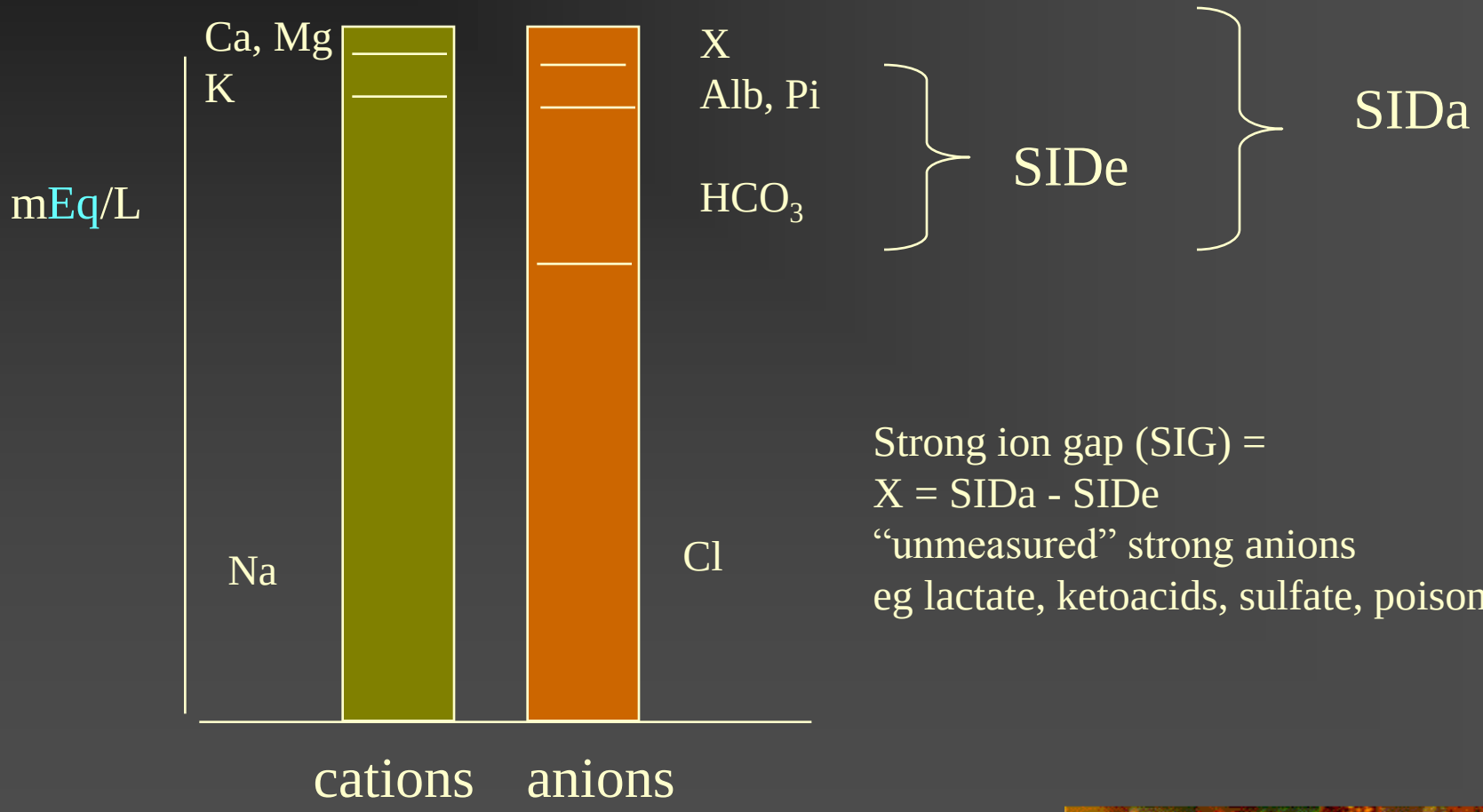
factors affecting pH

- to change $[H^+]$ in any body fluid, it is necessary to change the independent variables in that fluid
  - $PaCO_2$
  - SID (difference between strong cations and anions)
  - Atot (non-volatile weak ions: mainly albumin, Pi)
- adding or other dependent variables eg H^+ or HCO_3^-, will not change the pH (although this may be part of the mechanism eg proton pumps)
- $[H^+]$ changes result from *altered water dissociation* due to changes in the independent variables

Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow up. J Lab Clin Med 1992;120:713-9

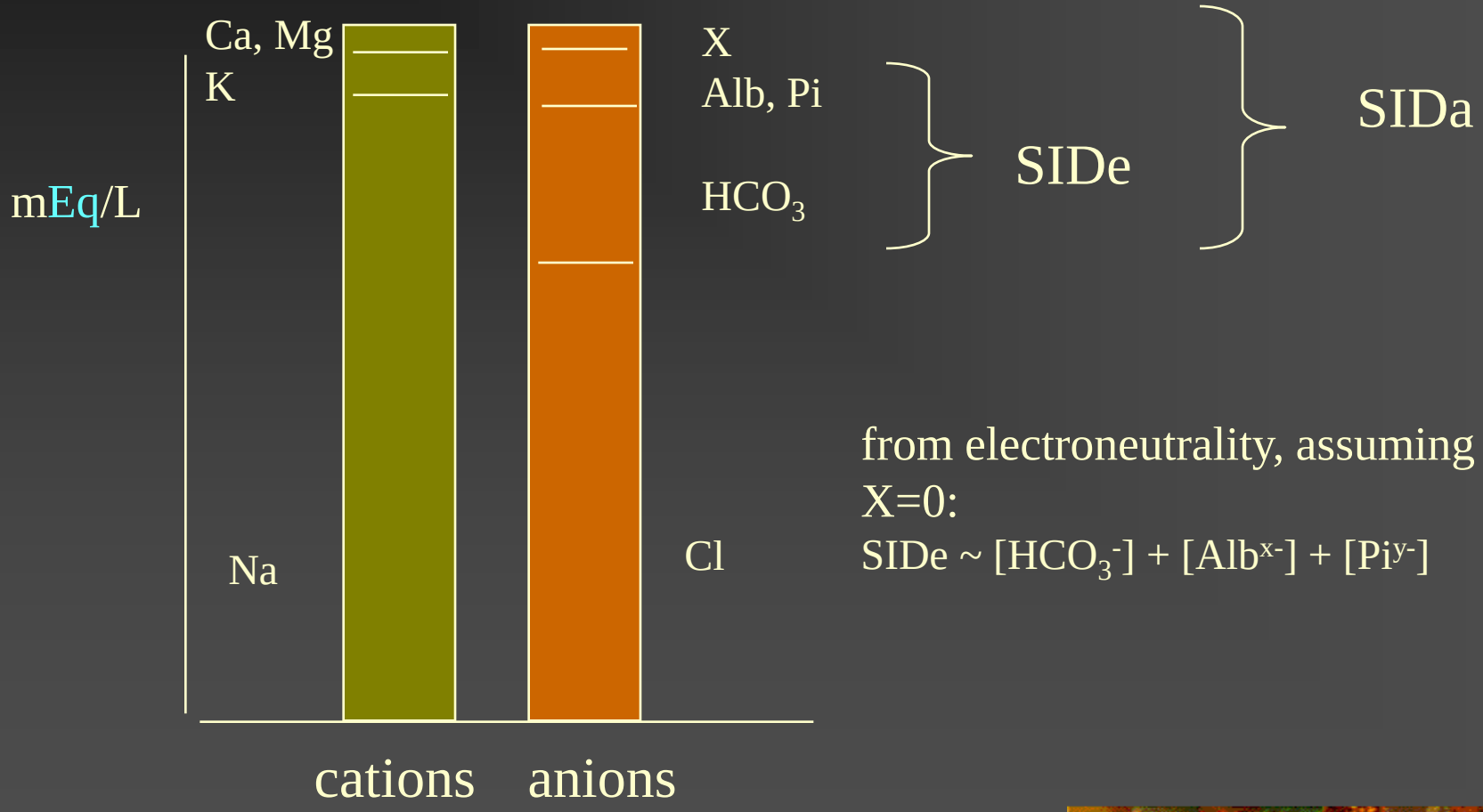
SID can be subdivided:

SIDa = SIDe + X



Strong ion gap (SIG) =
X = SIDa - SIDe
"unmeasured" strong anions
eg lactate, ketoacids, sulfate, poisons

SIDe measurement



from electroneutrality, assuming X=0:

$SIDe \sim [HCO_3^-] + [Alb^{x-}] + [Pi^{y-}]$

Acid-base evaluation

- $pH = f_{pH}(PaCO_2, SID, [alb], [Pi_{tot}])$
- $PaCO_2$, [alb], $[Pi_{tot}]$ is measured
- SID is calculated
  - $SIDa = [Na^+]+[K^+]+[Mg^{2+}]+[Ca^{2+}] - [Cl^-]$
  - $SIDe \sim [HCO_3^-] + 0.28[Alb\ g/L] + 1.8[P\ mM]$
    - Fencl V, et al. AJRCCM 2000; 162:2246-2251
  - SIG = SIDa - SIDe

acid-base disorders (SID model)

$pH = f_{pH}(PaCO_2, SID, [Atot])$

	acidosis	alkalosis
respiratory (PCO_2)	↑	↓
non-respiratory(metabolic)		
Abnormal SID	↓	↑
[water] (SID, Na)	(↓Na)	(↑Na)
abnormal SIDa (mainly Cl)	(↑Cl)	(↓Cl)
abnormal SIDe (ie presence of X)	(↑X = SIDa - SIDe)	
Abnormal Atot		
abnormal [albumin]	↑	↓
abnormal [phosphate]	↑	↓

Osmolality effects

- acid-base variables may change by significant amounts and cause osmotic fluid shifts, which cause secondary changes in [SID] and [Atot]

	Na	lact	HCO_3	Osm
acidosis		+10	-9	+1
alkalosis	+10		+9	+19

simplified correspondence between BE and SID

- SID and Atot (mEq/L) affect BE
- simplified:
  - sodium-chloride effect ~ $[Na^+]$ - $[Cl^-]$ - 38
  - sodium effect = 0.3 (Na - 140)
  - chloride effect = 102 - $[Cl^-]$. 140/$[Na^+]$
  - albumin effect ~ 0.25 . (42 - [alb]g/L)
  - minor effects (phosphate, etc)

Story DA, et al. Br J Anaes 2004; 92:54-60
Jabor A, et al. Acta Anaes Scand 1995; 39S107:119-122

typical ICU patient

- pH 7.37, PCO_2 4.7, BE -3.9, [HCO3] 21
  - [Na]135, [Ca] 5, [Mg] 1.8, [K]3.2, [Cl]105, [Alb]25, [Pi]0.5mEq/L
  - AG 9
- Diagnosis: metabolic acidosis
  - SIDa 40, SIDe 29, SIG 11: ‘unmeasured’ anion acidosis
  - hypoalbuminemic alkalosis
- despite ‘normal’ anion gap, the lactate in this example is 8 mmol/L

anhepatic phase OLTx

- [Na] 128, [Cl] 76, [K]4, [Alb] 30, [Pi] 0.5, pH 7.37, PCO_2 4.5, BE -5.7, bC 19, AG33
- Diagnosis: mixed
  - resp alkalosis
  - hypochloremic alkalosis }
  - hypoalbuminemic alkalosis } metabolic
  - lactic acidosis (lactate 29) }

anions

base:		MW	pK
bicarbonate	HCO_3^-	61	6.3, 9.8
acetate	$CH_3\text{-}COO^-$	136	4.7
lactate	$CH_3\text{-}CHOH\text{-}COO^-$	166	3.9
citrate	$COO^-\text{-}CH_2\text{-}COHCOO^-\text{-}CH_2\text{-}COO^-$	192	3.14, 4.77, 6.39

lactate-based fluids

- stable in solution, cheap, commonest ‘base’
- Hartmann’s solution
  - “isotonic solution for the correction of acidosis”: lactate 29 mmol/L
- commercial HF solutions
  - racemic L- & D-lactate
  - 24-55 mmol/L

Alexis F Hartmann
1898-1968

iv lactate without pyruvate

- promotes hepatic gluconeogenesis at the expense of amino acids, increasing protein catabolism
  - compared with HCO_3-based CAVH, higher [urea] & UGR
    - Olbricht CJ, et al. Int Soc Blood Purif 1992
- intracellular: increased ADP / ATP
  - myocardial depression
    - Nimmo GR, et al. Postgrad Med J 1991

lactate: more problems

- lactic acidosis worsened
  - rate of lactate to bicarbonate conversion less than bicarbonate loss in the diafiltrate
    - max lactate 2000 mmol/d
  - patients with hypoxia, liver impairment, preexisting lactic acidosis
- D-lactate accumulation
  - oxidation/utilization slower than L-lactate
  - encephalopathy — Thurn JR, et al. Am J Med 1985
  - increase ICP — Davenport A, et al. Renal Failure 1990

bicarbonate-based fluids

- bicarbonate treatment of
  - hyperchloremic acidosis: accepted
  - other acidoses: controversial
- data from cardiac arrest:
  - venous hypercarbia worsening intracellular & CSF acidosis
  - hyperosmolarity, volume load
    - these effects can be adjusted with CEBP

acetate-based fluids

- liver: $CH_3COO^- + H^+ + HS\text{-}CoA \leftrightarrow CH_3CO\text{-}SCoA + H_2O$
- acetate IHD in the critically ill
  - uptake 4.2 mmol/min > utilization 3.7 ; & HCO_3^- loss ~ 2.4 mmol/min
  - vasodilation, myocardial depression
  - Least effective in acid base control?
    - Herring et al Intensive Care Med 1999, Morgera et al Renal Failure 1997
  - 65% of AcetylCoA comes from IHD acetate, increasing FFA, ketone bodies
- less used in CEBP: Fr HF02, HF05
  - prospective cross-over CEBP trial
    - acetate-based: stable hemodynamics
    - bicarbonate-based: SVR, decr CI
      - Wakabayashi Y, et al. Jap Circ J 1994

citrate-based fluids

- Cleared by tricarboxylic pathway in liver, skeletal muscles, and renal cortex – levels return to normal within 30 mins
  - $Na_3citrate + 3H^+ \leftrightarrow 3Na^+ + 4H_2O + 6CO_2$
    - metabolism yields 3 strong cations/citrate
  - ACDA: 67% TSC & 33% citric acid
    - metabolism yields 2 strong cations/citrate
  - Effect is sodium and base loading
- anticoagulant, therefore given ‘pre-dilution’
  - Long filter life - better than heparin
    Kutsogiannis et al Am J Kidney Dis 2000
  - Avoid potential HIT, no systemic anticoagulation

The critically ill patient *inorganic* solute toxicities

	ESRD	ARF/MODS	
Na-H_2O	overload	under-resuscitation	
K	high	hypokalemia common	
Mg	high	65% low	Wong AmJClinPath 1983
P	high	28% low	Kruse JA CCM 1992

- metabolic acidosis/anions
  - ESRD: responds to bicarbonate/acetate
  - ARF/MODS: bicarbonate not useful
    - Cooper DJ. Ann Int Med 1990

Organic solute toxicities

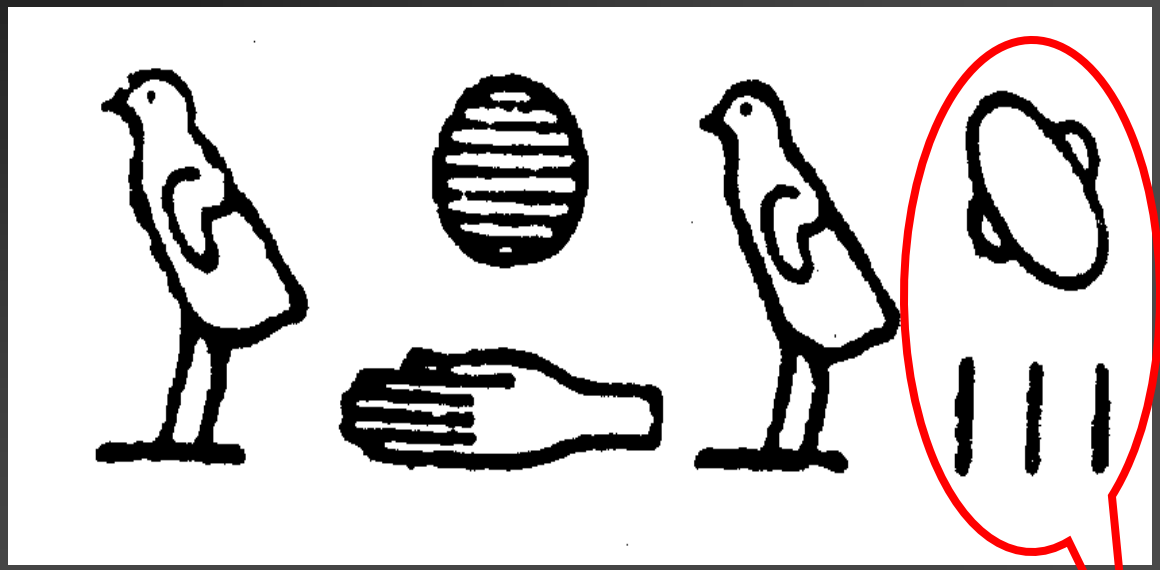
- ESRD toxins

  Vanholder R. Sem Neph 1994

  - small water-soluble
    - guanidines, purines, oxalate
  - middle molecules
    - β2-μglobulin, AGE-products, oxidation products, leptin, Clara cell protein, cystatin C, peptides, PTH
  - protein-bound compounds
    - indoles, CMPF, hippurate, P-cresol, polyamines
- sepsis/ARF toxins
  - inflammatory mediators / cytokines

Egyptian concepts of sepsis

2000 BCE



W H D W

dangerous thing

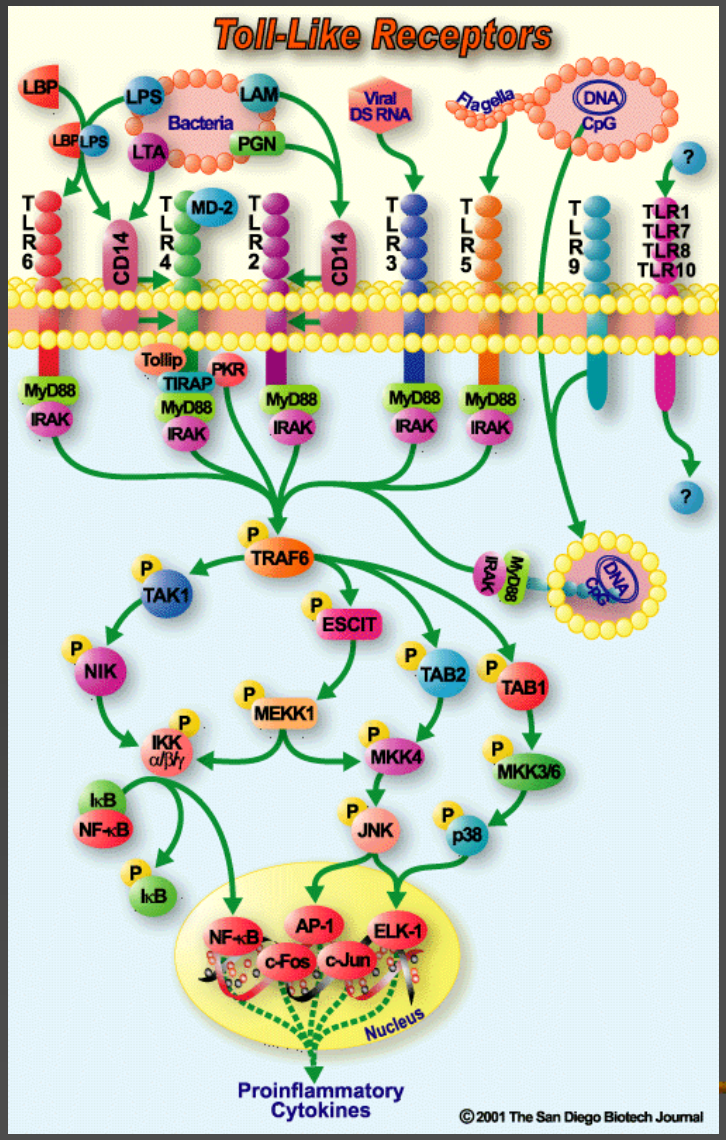
disgusting thing

WHDW: pathogenesis

- Found in *the gut*
- *Translocates* into the blood
  - 4 blood vessels open into the anus, and blood vessels are connected to the heart
- Becomes *systemic*
- Can ‘rise to the heart’ and KILL

The idea still lives on

- Marshall JC, et al. The gastrointestinal tract: The ‘undrained’ abscess of multiple organ failure. Ann Surg 1993; 218:111-9
- Williams DL, et al. Modulation of tissue Toll-like receptor 2 and 4 during the early phases of polymicrobial sepsis correlates with mortality. Crit Care Med 2003; 31:1808-1818



but cytokine-directed ‘ancillary’ therapies have been disappointing

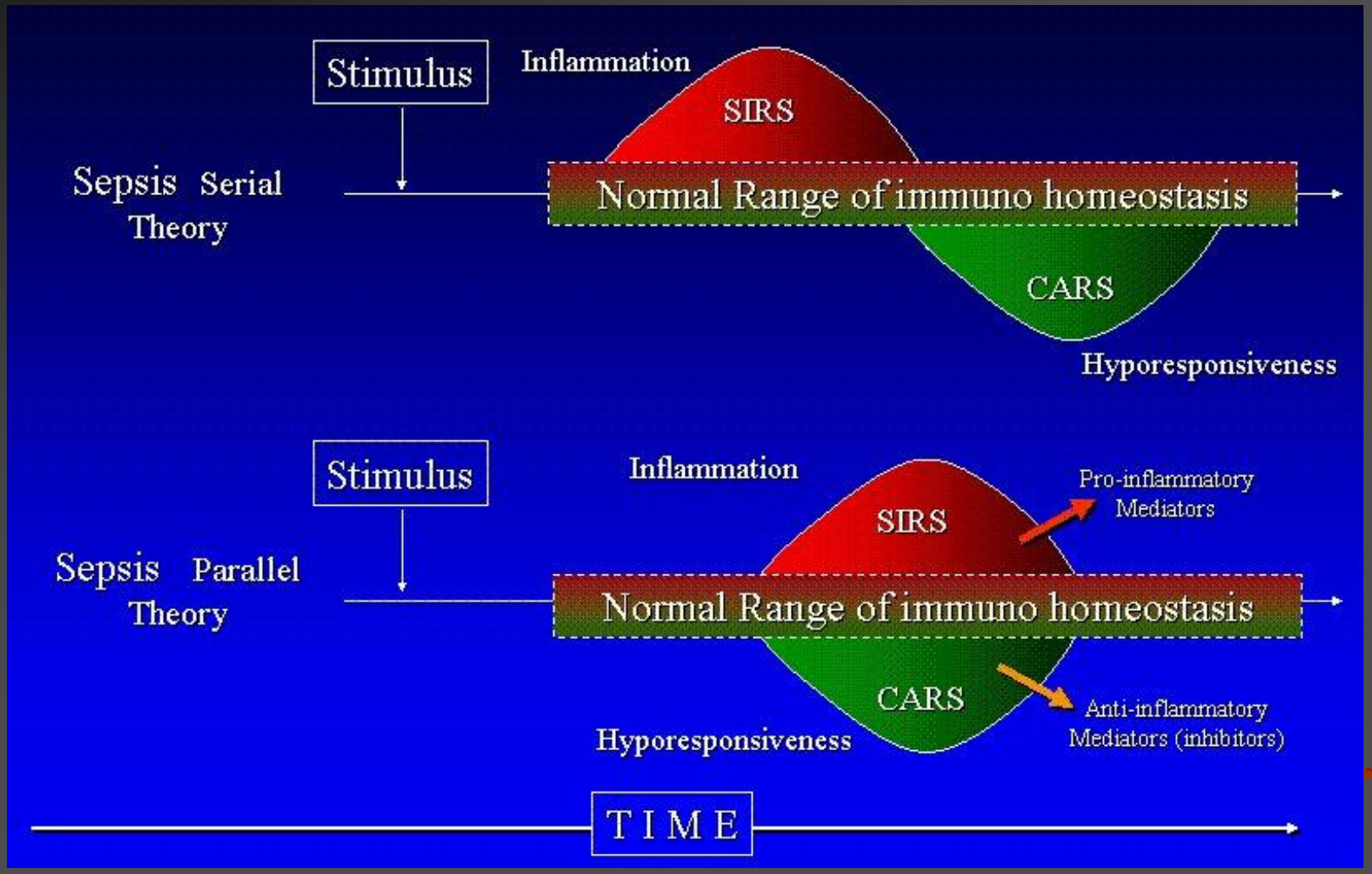
- Multiple anti-inflammatory drugs have failed
  - Antiendotoxin antibodies, BPI
  - anti-TNF, sTNF-r, IL-1ra
  - anti-thrombin III, TFPI
  - iNOS inhibition, antioxidants, N-Acetylcysteine
  - ibuprofen, PG E1, interferon
  - immunonutrition, growth hormone
  - ... and the list goes on
- and on! Newer agents under investigation
  - thrombomodulin, PAF acetylhydrolase, anti-GPIIbIIIa, 7E3 F(ab')2, Triflavin, PAI-1 inhibitors

(Abraham E: Why immunomodulatory therapies have not worked in sepsis. ICM 1999; 25:556-66
Eichacker PQ, et al.: Risk and the efficacy of anti-inflammatory agents. AJRCCM 2002; 166:1197-1205

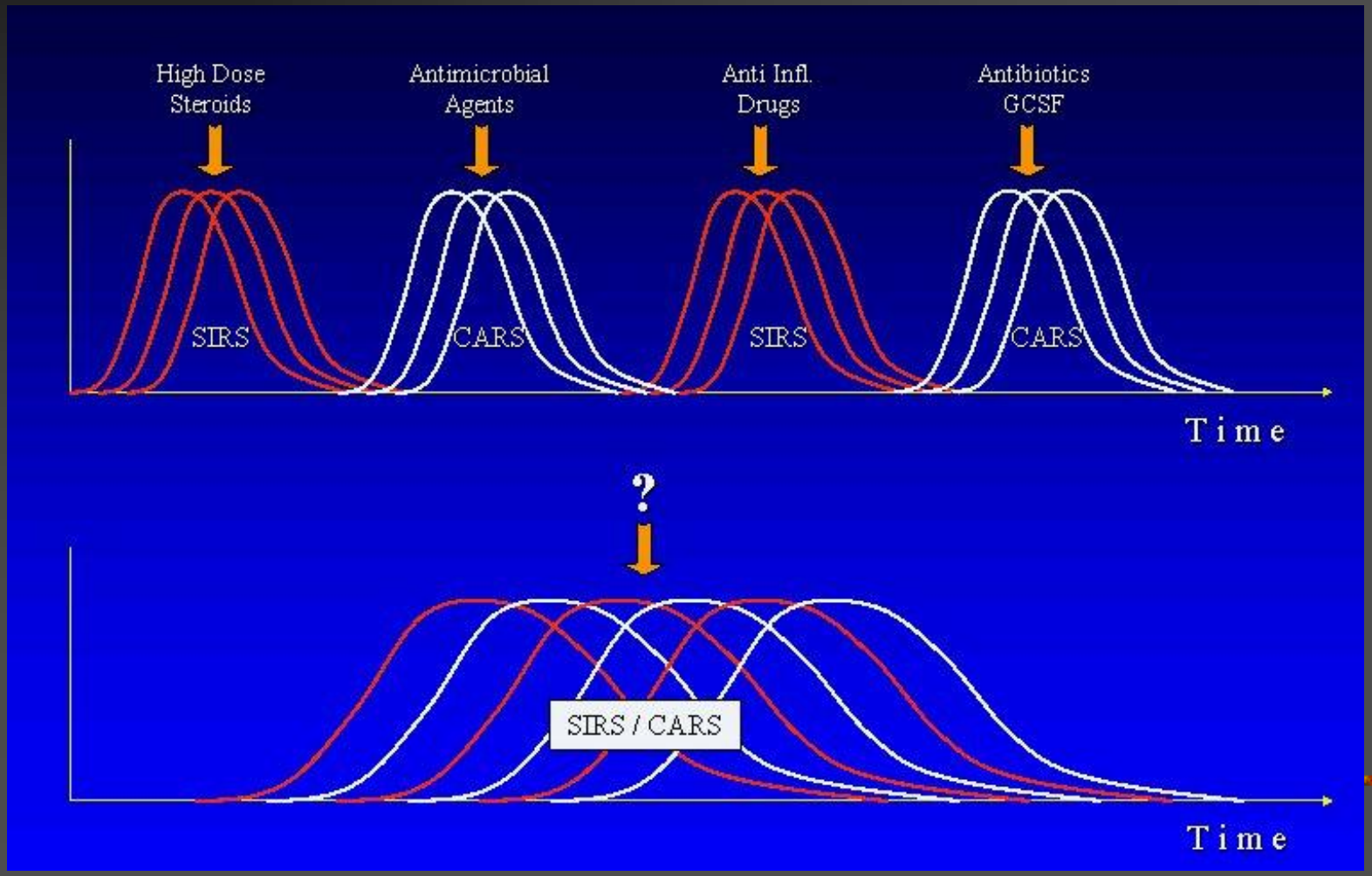
non-specific therapy more effective?

- meta-analysis 27 trials
  - Alejandra MM, et al. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane review). In: the Cochrane library 2004
- monoclonal Ig does not reduce mortality
  - anti-endotoxin RR 0.97 (8 trials, n=2826, 95%CI 0.88-1.07)
  - anti-cytokine RR 0.93 (8 trials, n=4318, 95%CI 0.86-1.01)
- Polyclonal Ig reduces mortality
  - RR 0.64 (11 trials, n=492, 95% CI 0.51-0.8)
  - “However, all the trials were small and the totality of evidence insufficient to support a conclusion of benefit”

it's not just inflammation



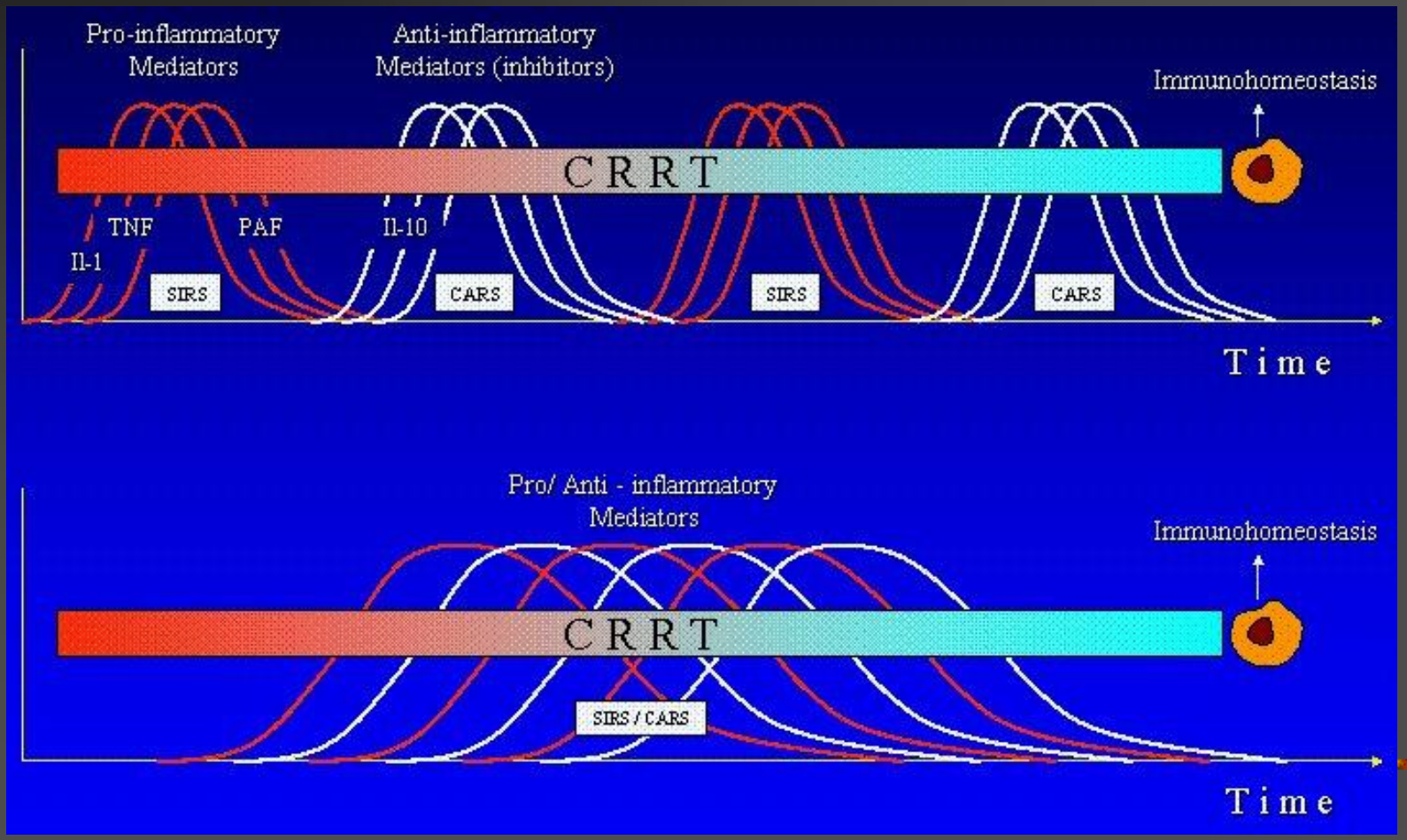
non-specific anti-inflammation and anti-anti-inflammation



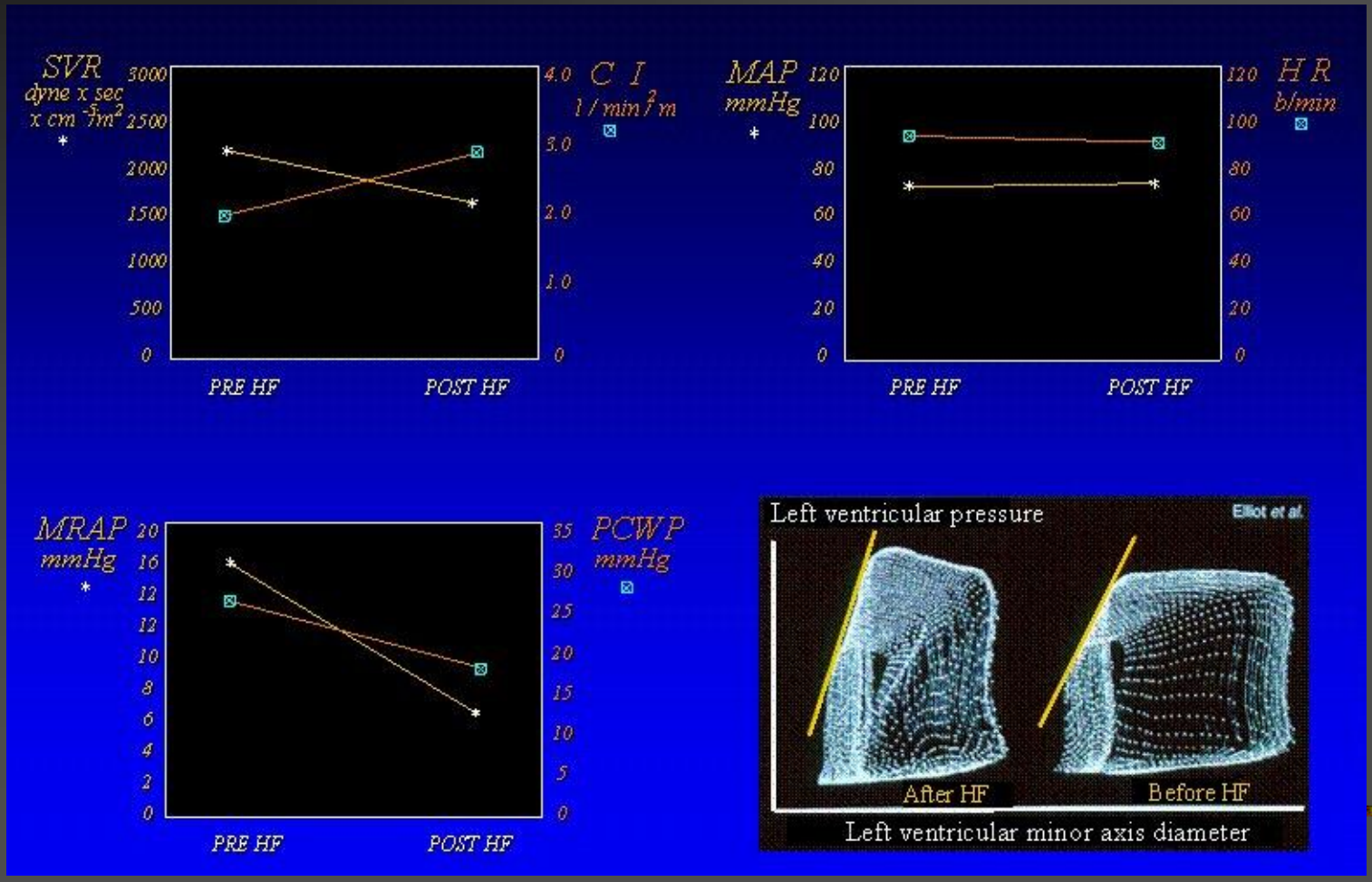
Electrolyte & metabolic derangement

Blood purification meets the need

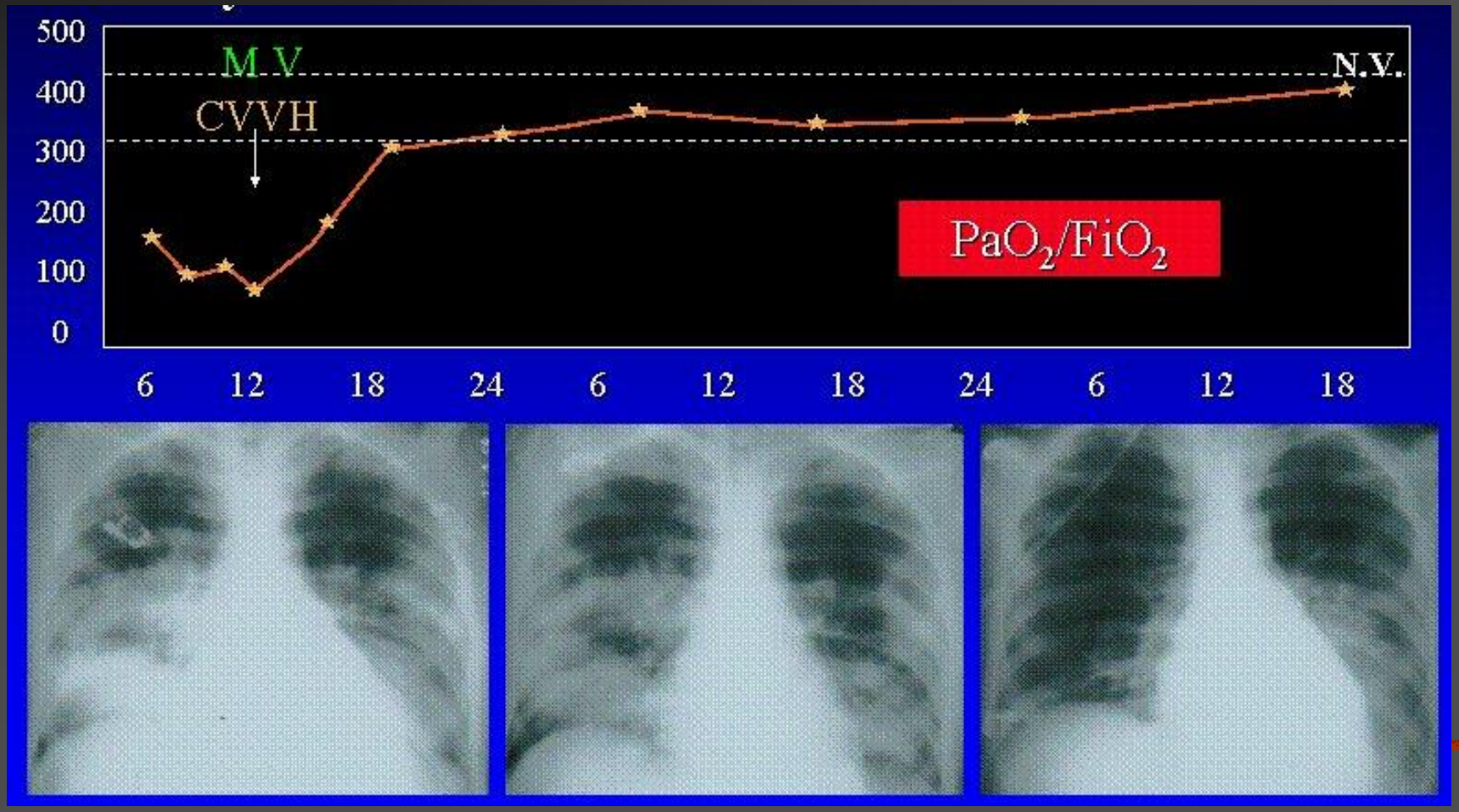
blood purification and the peak concentration hypothesis



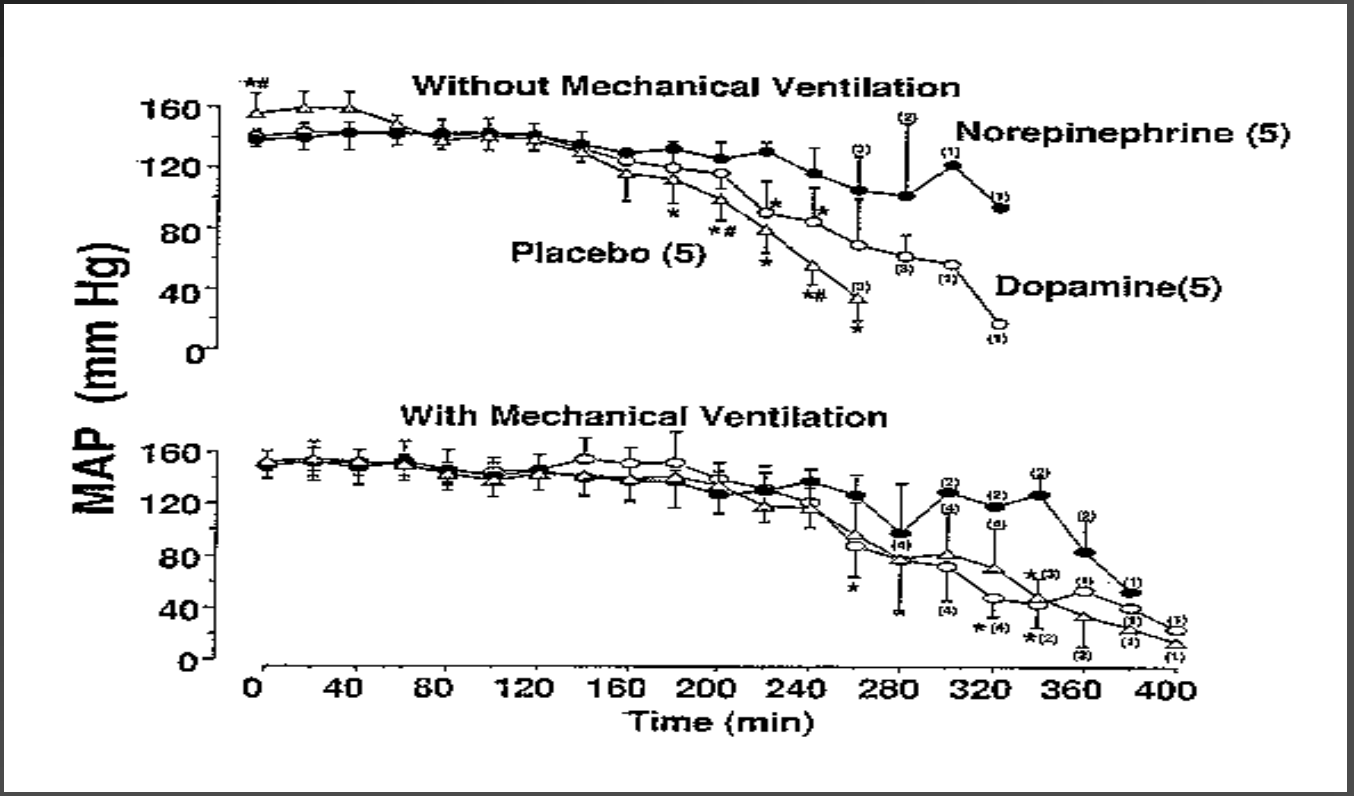
CVVH and the heart



CVVH and the lung

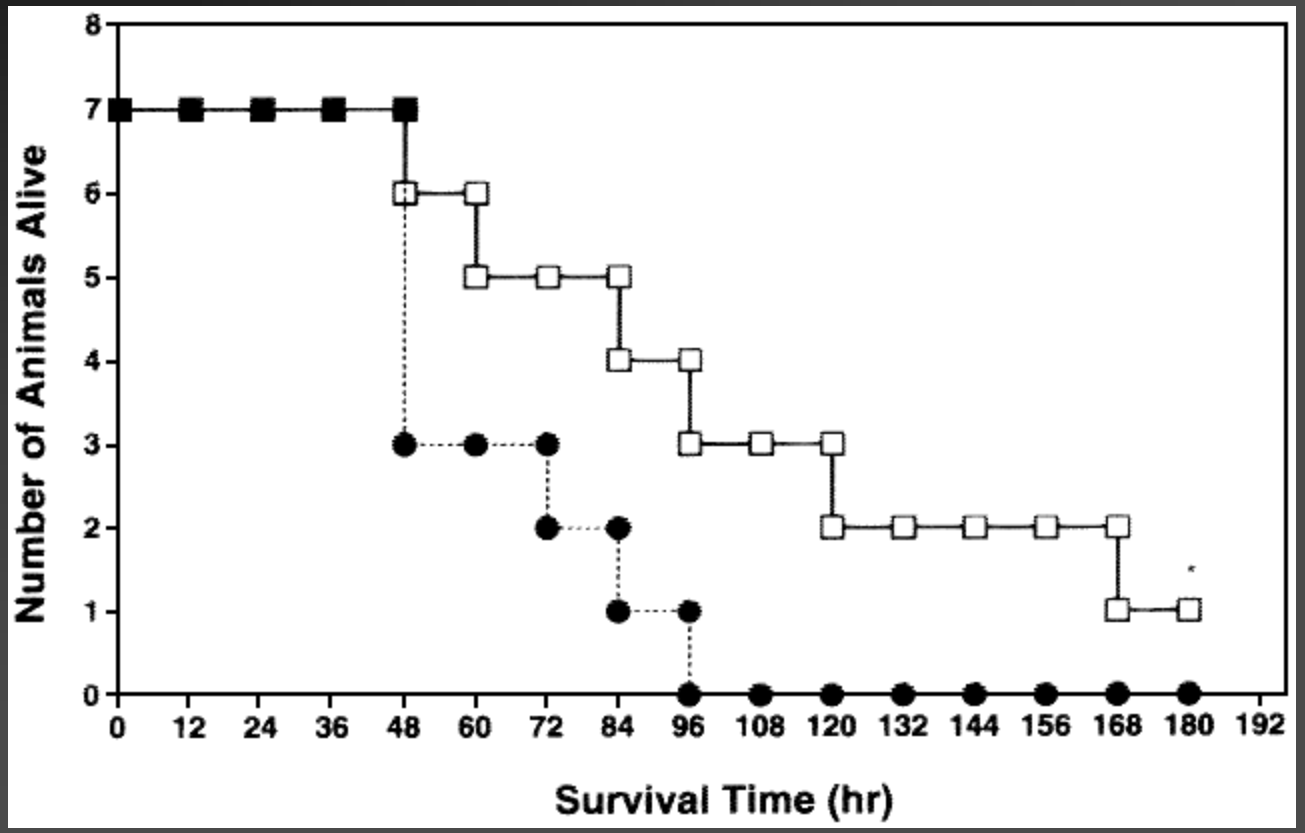


organ system support



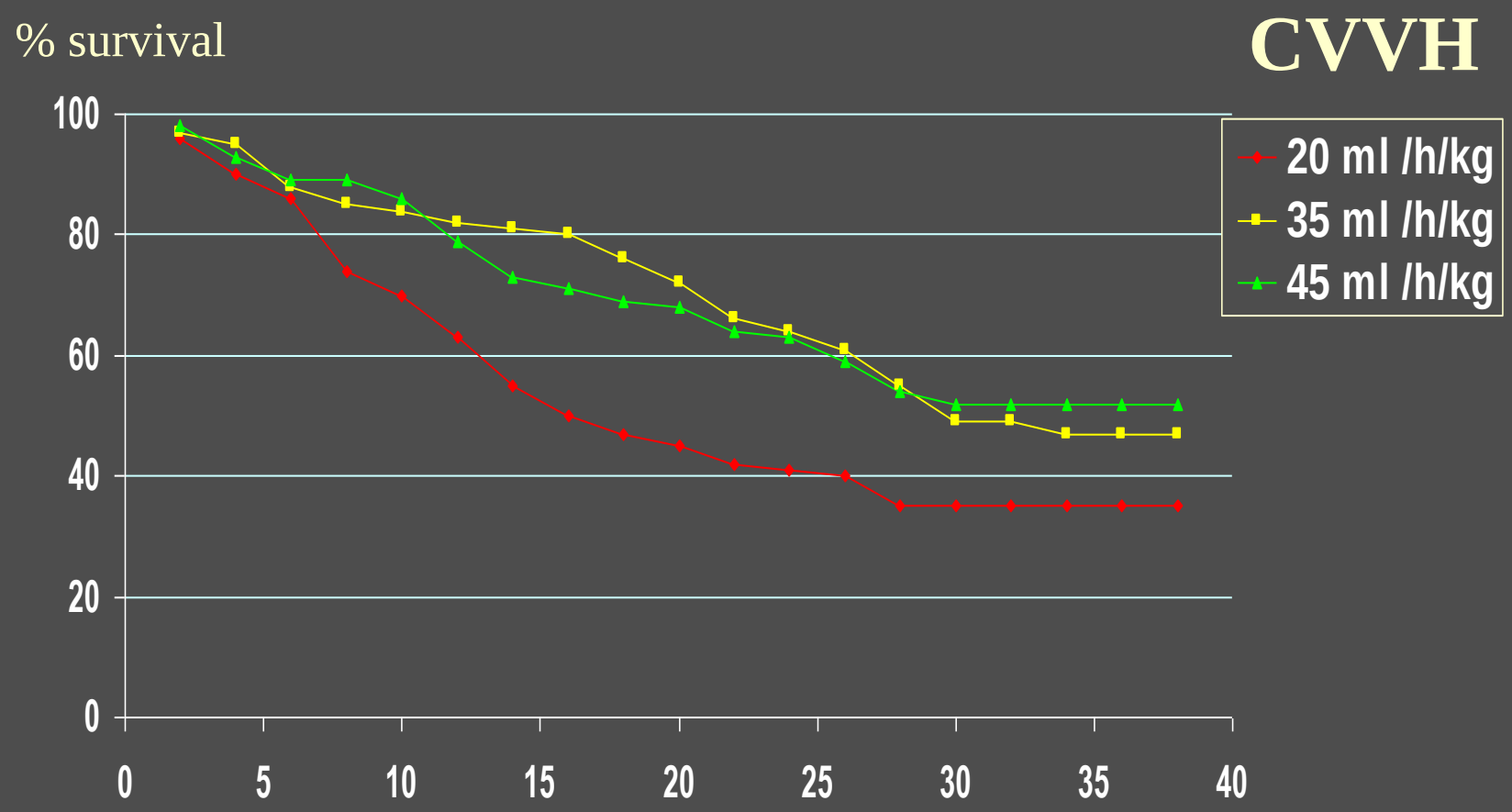
Tang W, Pakula JL, Weil MH, et al. Adrenergic vasopressor agents and mechanical ventilation for the treatment of experimental septic shock. Crit Care Med 1996;24:125-130

Blood purification



Lee PA, et al. Effects of filter pore size on efficacy of continuous arteriovenous hemofiltration therapy for Staphylococcus aureus-induced septicemia in immature swine. CCM 1998;26:730-737

CVVH dose n=425, AP2 23, lactate, PS, urea 18



Ronco C, et al. Lancet 2000;3566:26-30

Some NNTs

Intervention	***NNT***
Adequate dialysis dose	***5.5***
Early goal directed resus	***6-8***
Low dose steroids?!	***7***
aPC (APACHE2>25)	***8***
aPC (entry criteria)	***16*** (whole trial)
Intensive insulin therapy	***29***