# Electrolyte imbalance and metabolic derangement

## an unmet need for internists

## IKS Tan

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## Mount Elizabeth Hospital
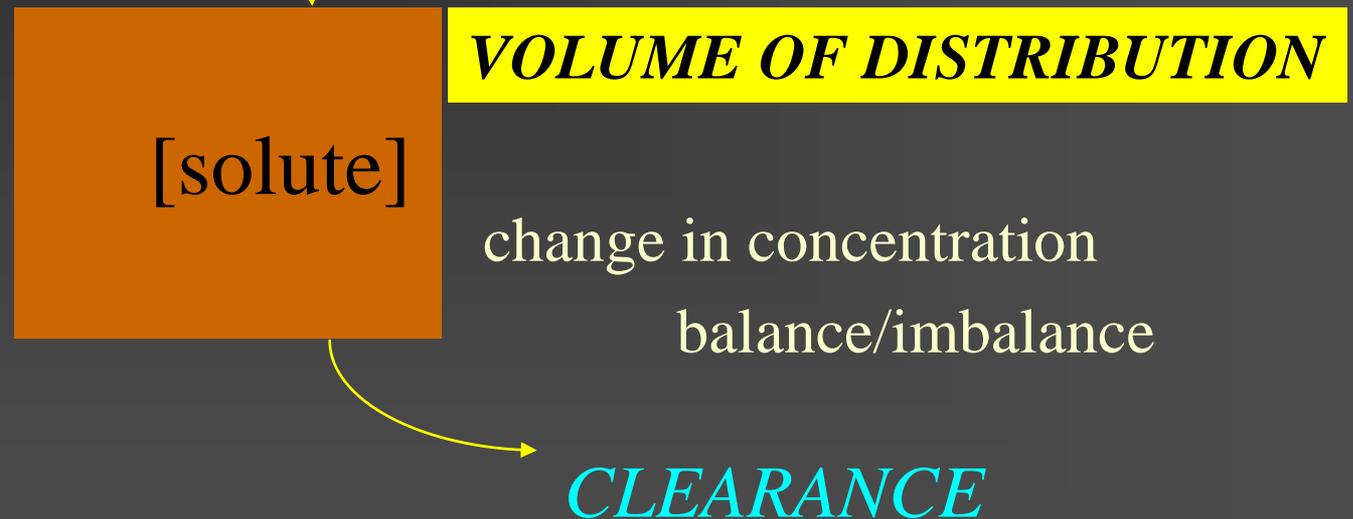
## Singapore

# Electrolyte & metabolic derangement

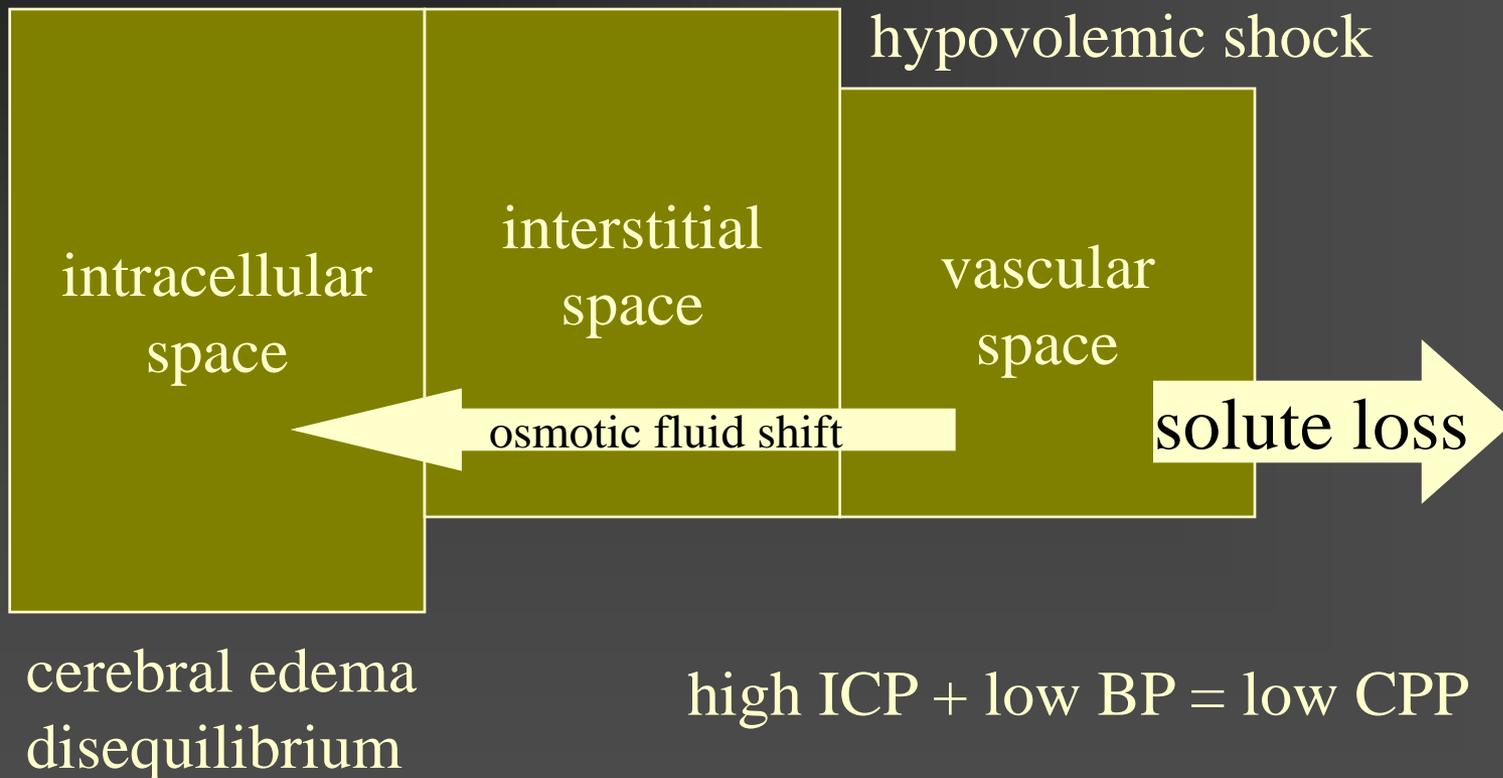# A need ...



Internists need more exercise

# Mental exercise

TOXIN, ELECTROLYTE, METABOLITE GENERATION
EXOGENOUS SOURCES

[solute]

**VOLUME OF DISTRIBUTION**

change in concentration

balance/imbalance

*CLEARANCE*

# 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)

intracellular space

interstitial space

hypovolemic shock

vascular space

← osmotic fluid shift

solute loss →

cerebral edema disequilibrium

high ICP + low BP = low CPP
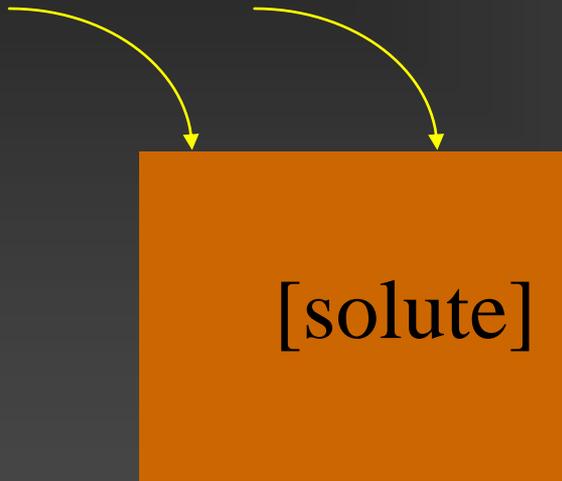
Na is the major factor affecting water volume

# 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**

[solute]

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
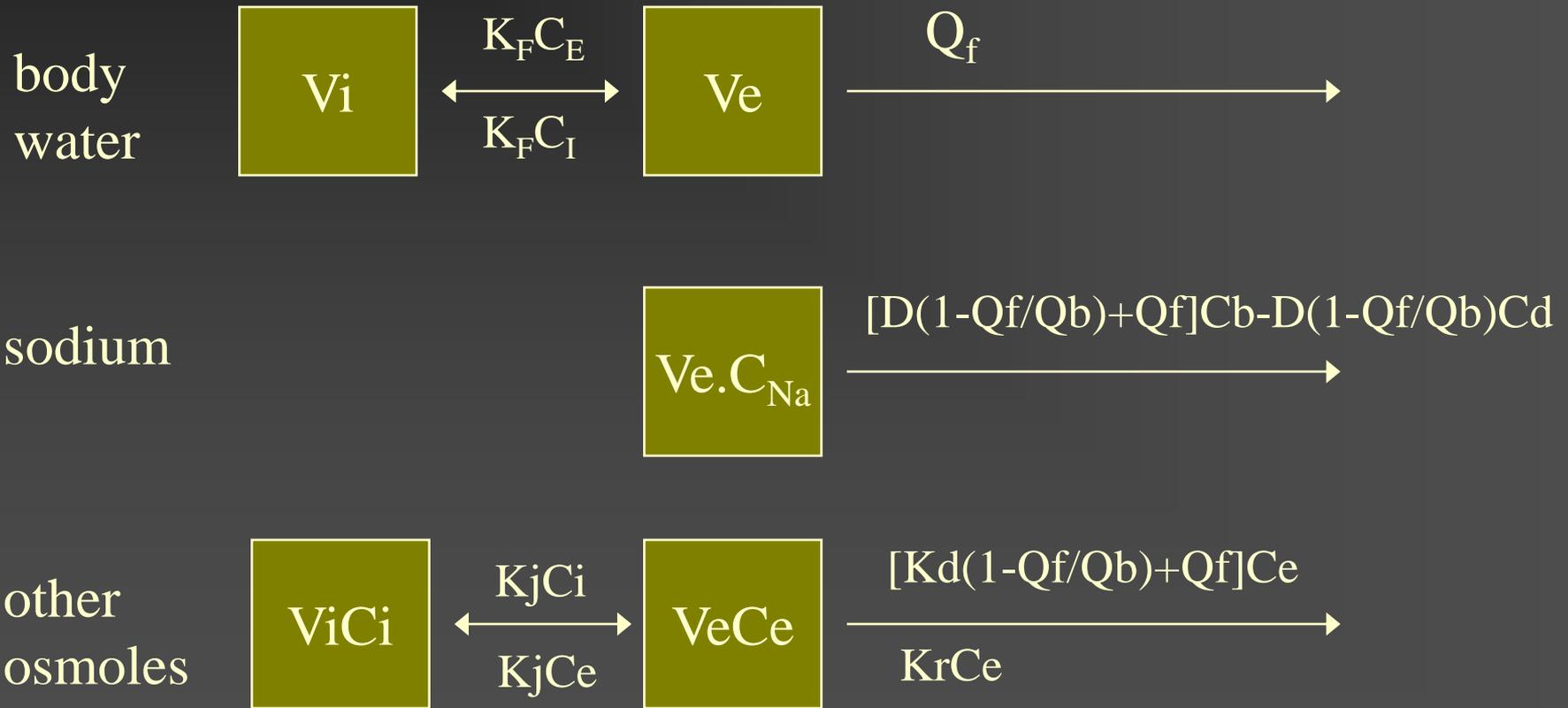isoNatremic 142 mmol/L

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

body water

$$V_i \xrightleftharpoons[K_F C_I]{K_F C_E} V_e \xrightarrow{Q_f}$$

sodium

$$V_e . C_{Na} \xrightarrow{[D(1-Q_f/Q_b)+Q_f]C_b - D(1-Q_f/Q_b)C_d}$$

other osmoles

$$V_i C_i \xrightleftharpoons[K_j C_e]{K_j C_i} V_e C_e \xrightarrow[K_r C_e]{[K_d(1-Q_f/Q_b)+Q_f]C_e}$$

# 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

Cell membrane is limiting factor in K flux

intracellular space

vascular space

K transfer
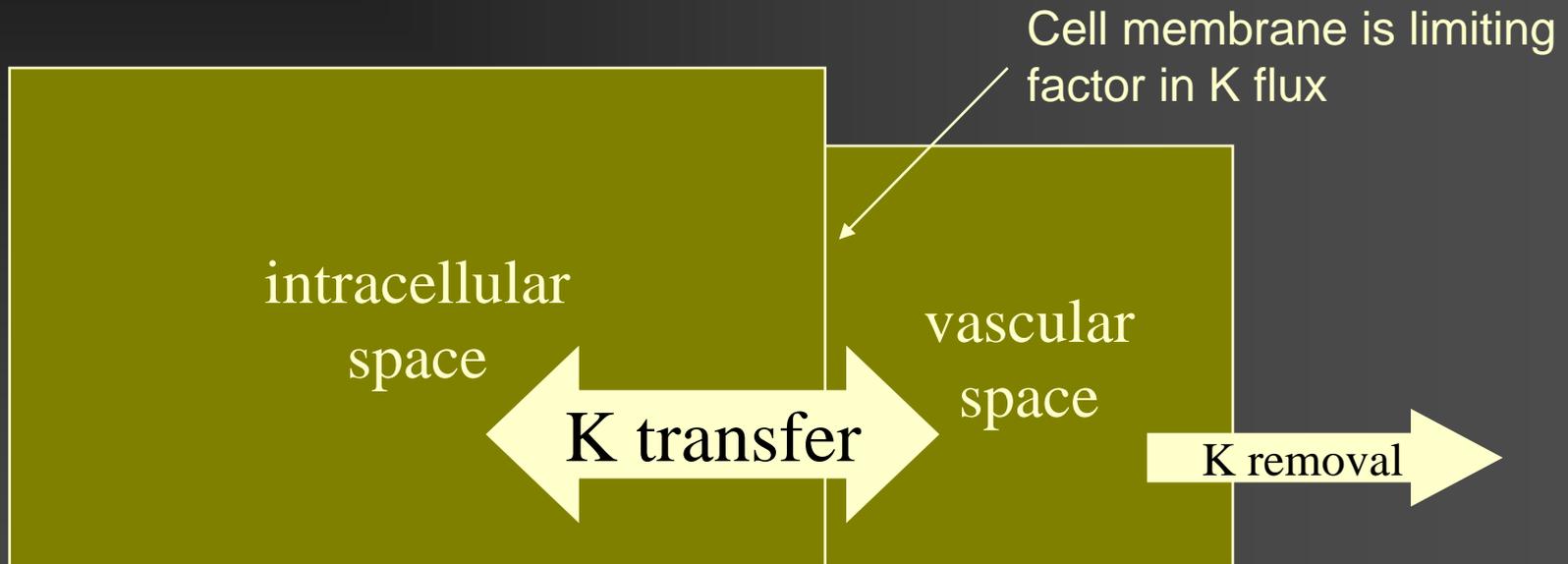
K removal

- 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
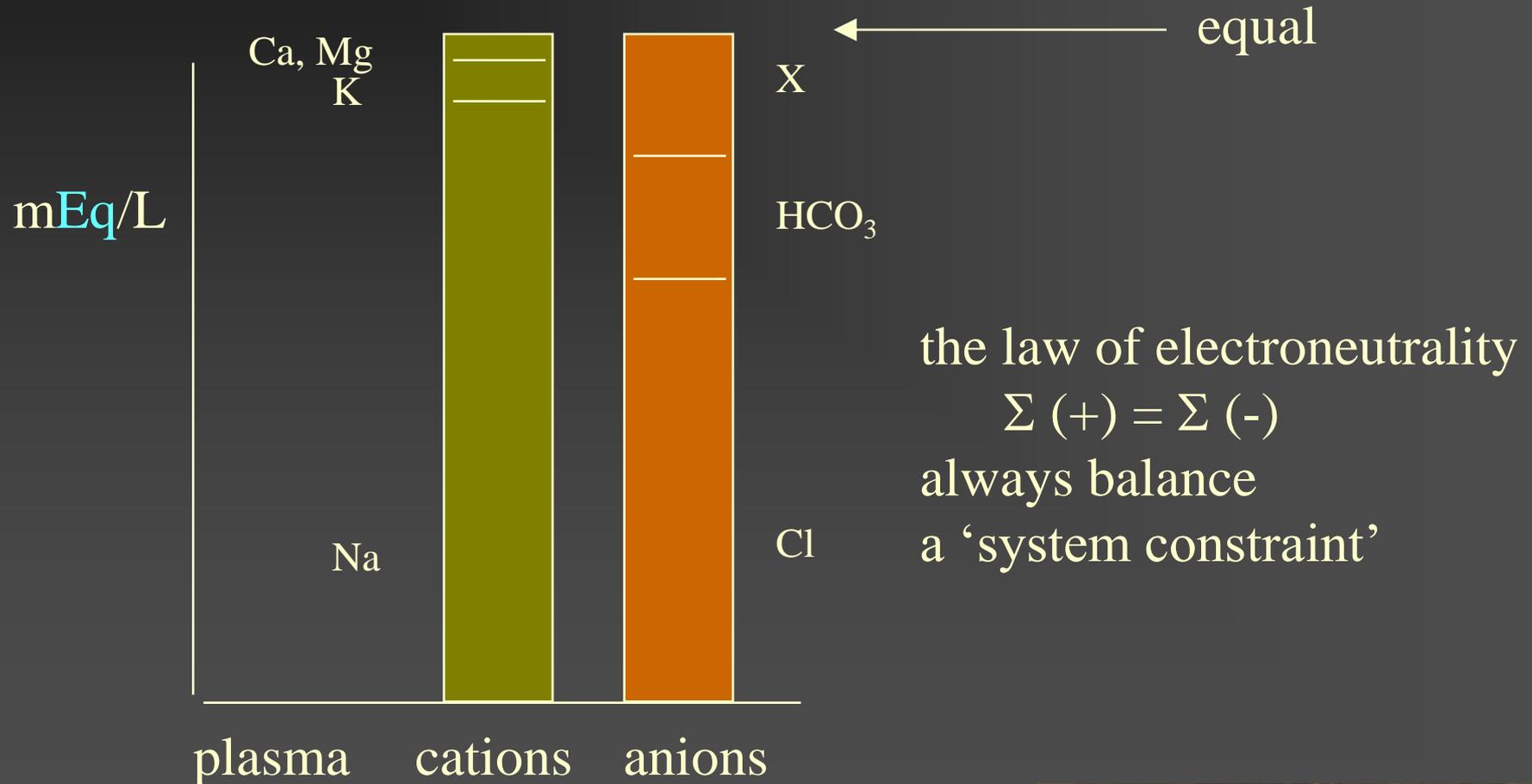
# Magnesium in the critically ill

- 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)

← equal

mEq/L

Ca, Mg
K

X

HCO₃

the law of electroneutrality
$$\Sigma\ (+) = \Sigma\ (-)$$
always balance
a 'system constraint'

Na

Cl

plasma    cations    anions

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

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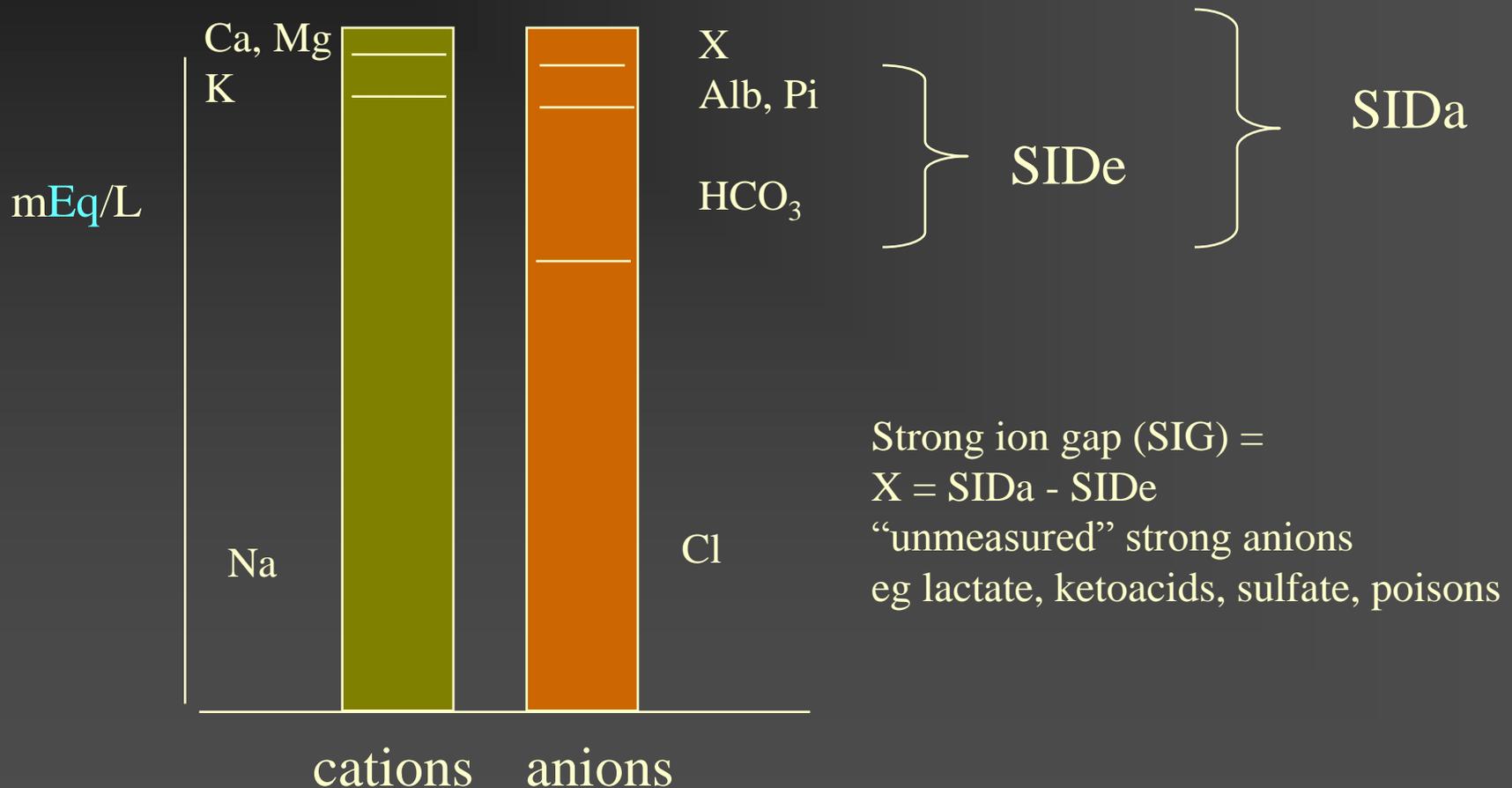
- **mass conservation**
  - $[Atot]_n = [HA]_n + [A^-]_n$
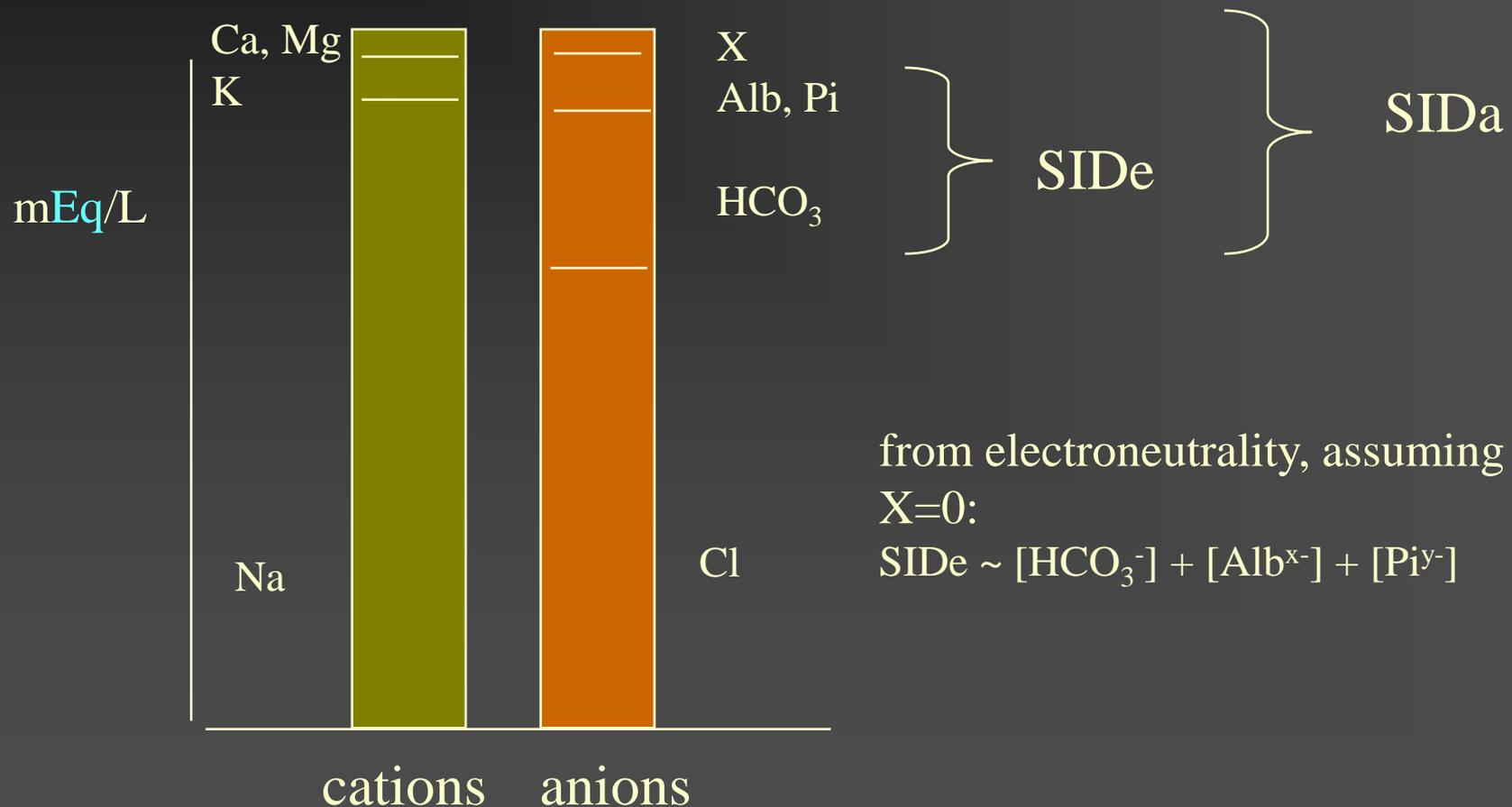
# factors affecting pH

- 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

mEq/L

Ca, Mg
K

Na

cations

X
Alb, Pi

HCO$_3$

Cl

anions

SIDe

SIDa

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

# SIDe measurement

Ca, Mg

K

mEq/L

Na

cations

X

Alb, Pi

$HCO_3$

Cl

anions

SIDe

SIDa

from electroneutrality, assuming X=0:
SIDe ~ $[HCO_3^-] + [Alb^{x-}] + [Pi^{y-}]$

# 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 ~ [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$_2$O | 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**
    - $\beta2-\mu$globulin, 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**
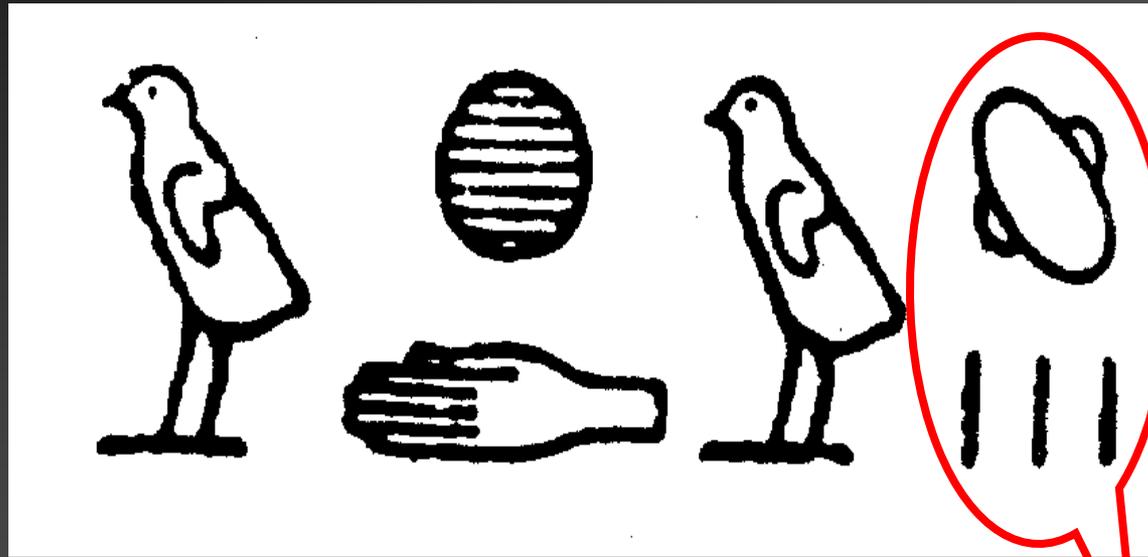
# WHDW: pathogenesis

- 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
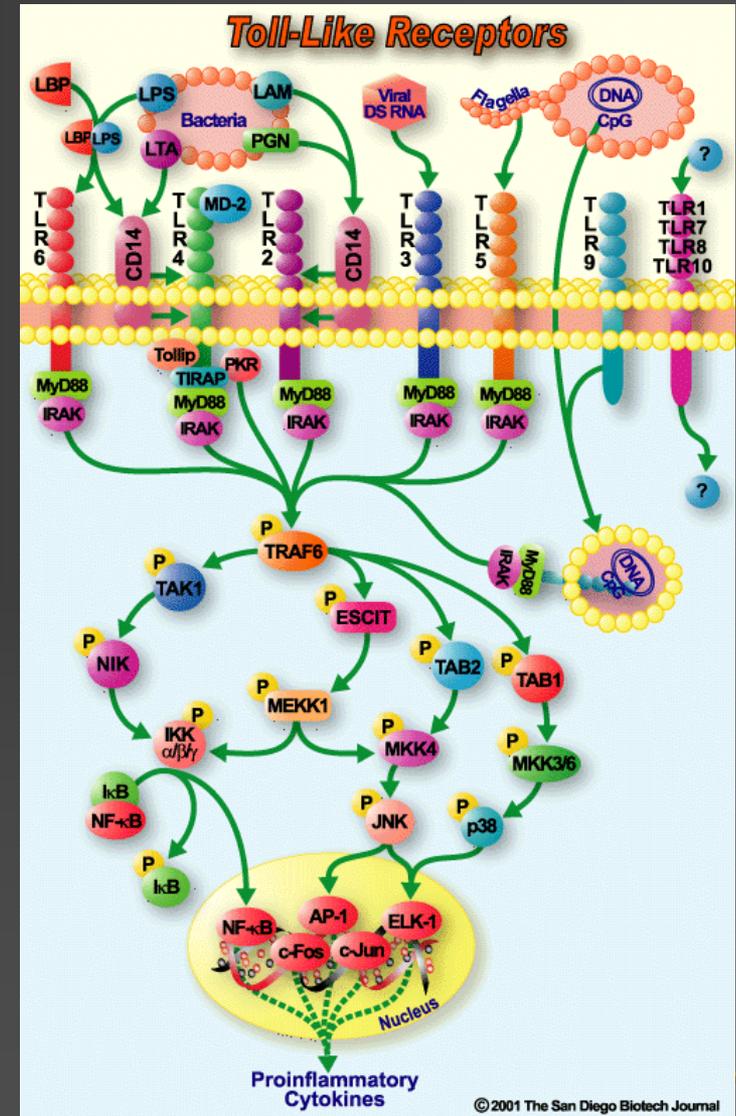
# but cytokine-directed 'ancillary' therapies have been disappointing

- 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
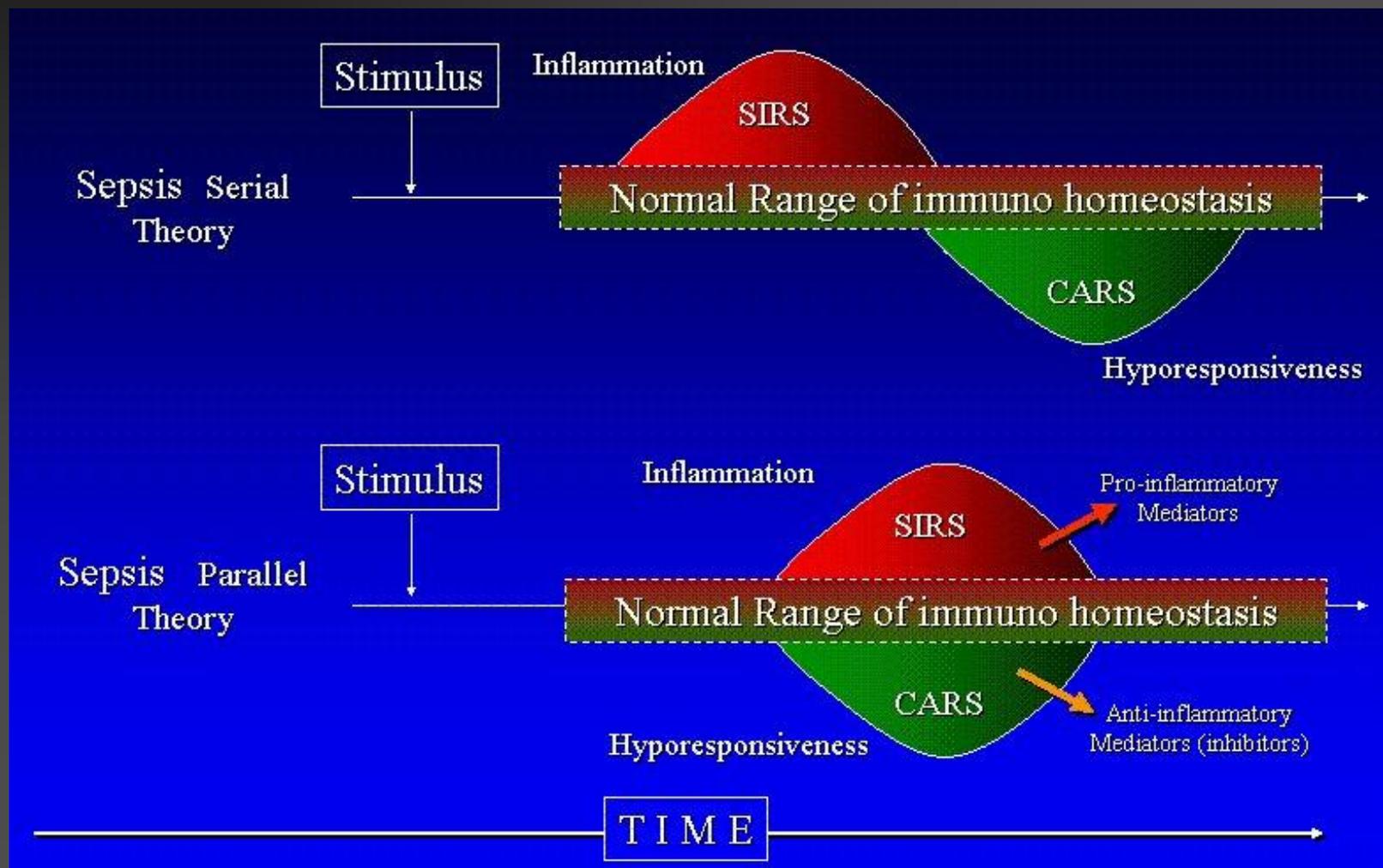
# non-specific anti-inflammation and anti-anti-inflammation
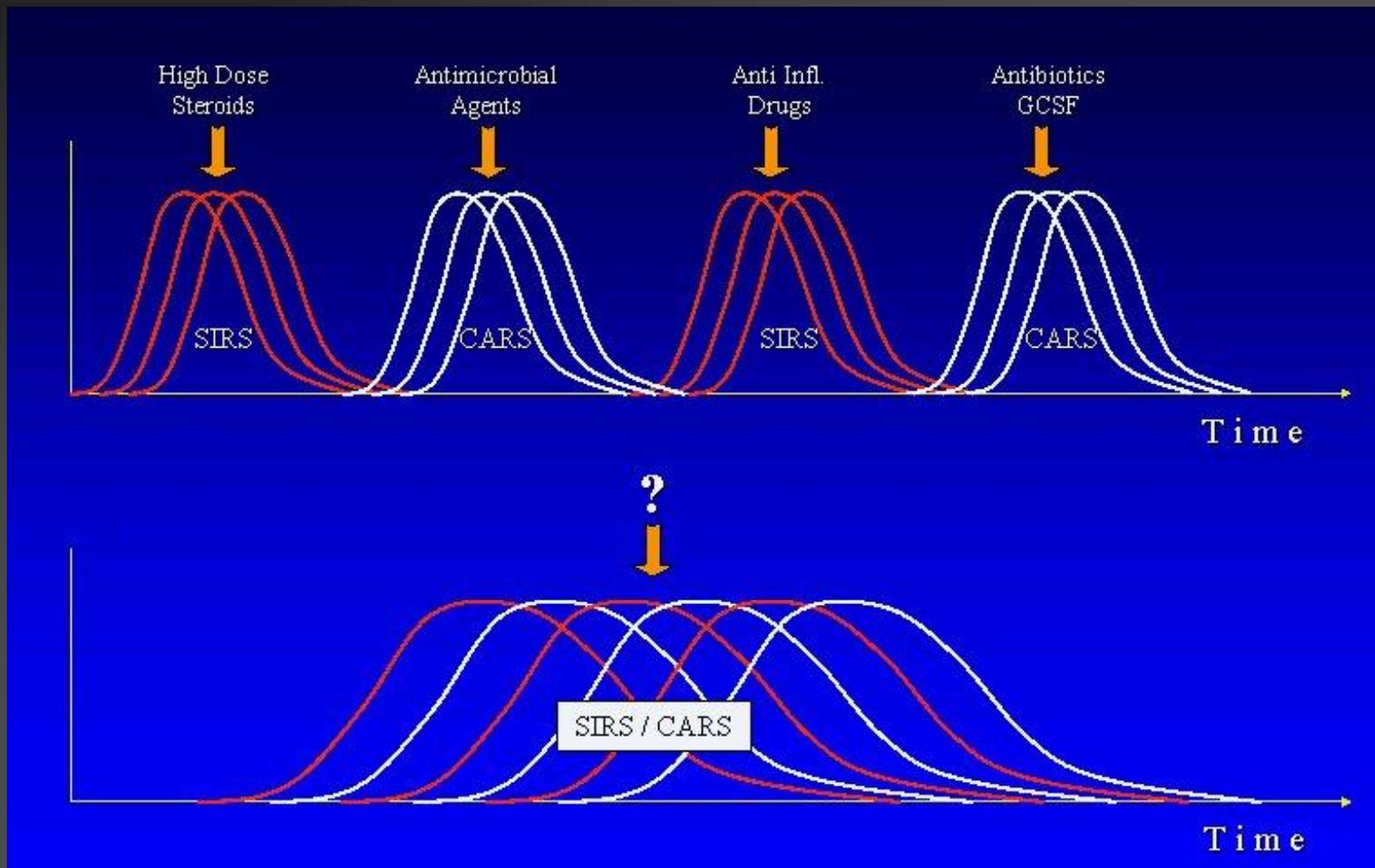
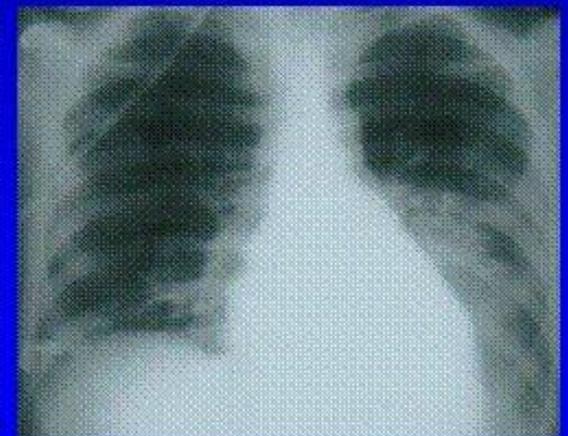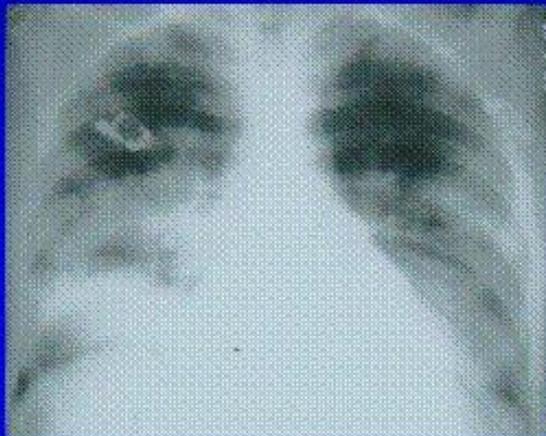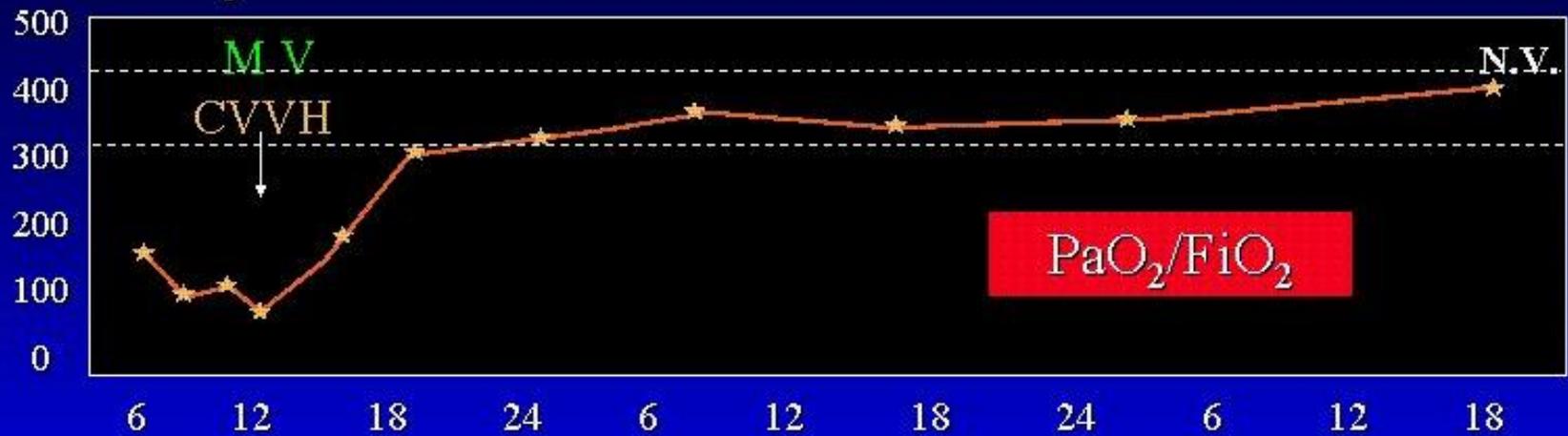# Electrolyte & metabolic derangement

Blood purification meets the need

# blood purification and the peak concentration hypothesis
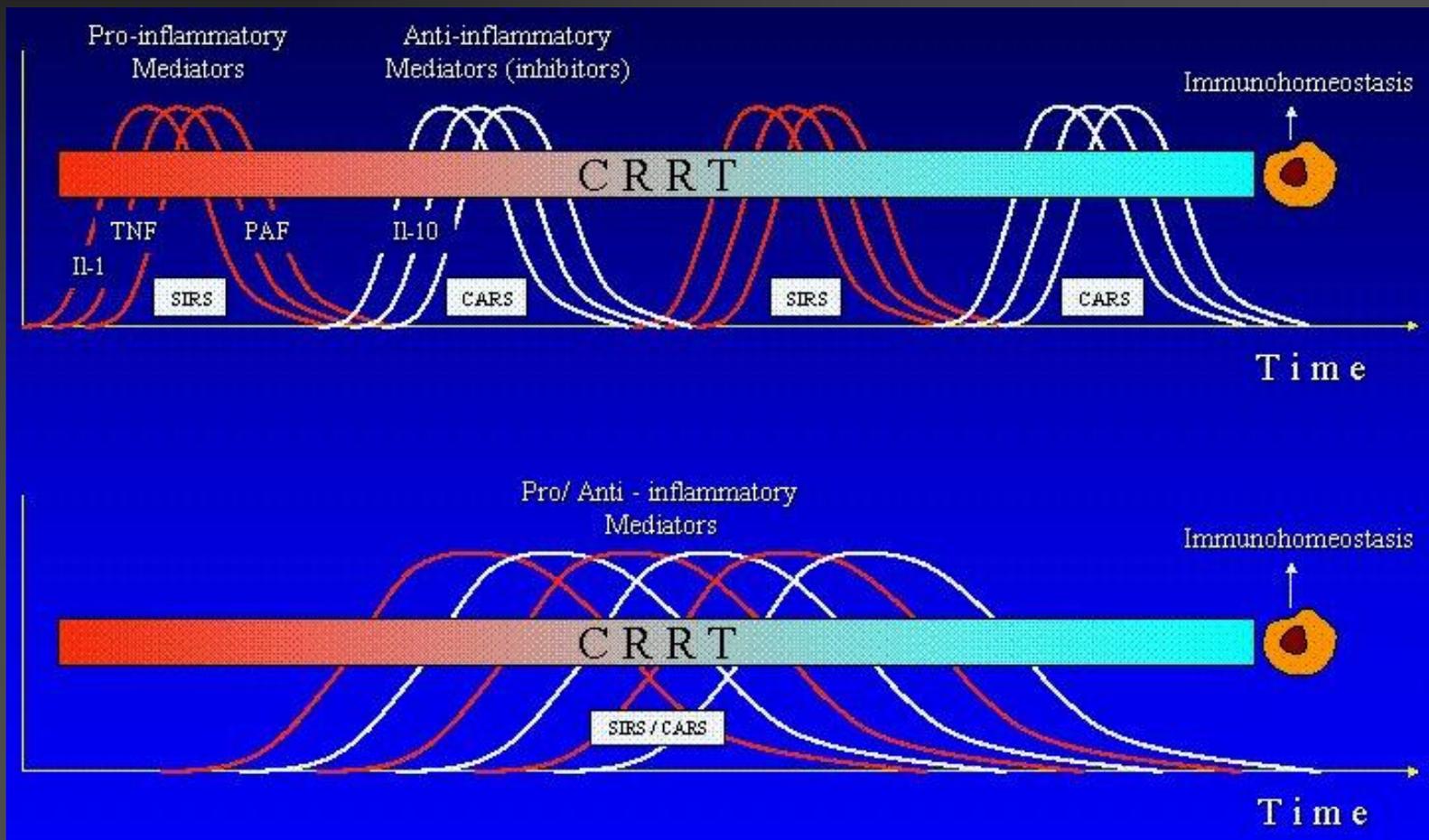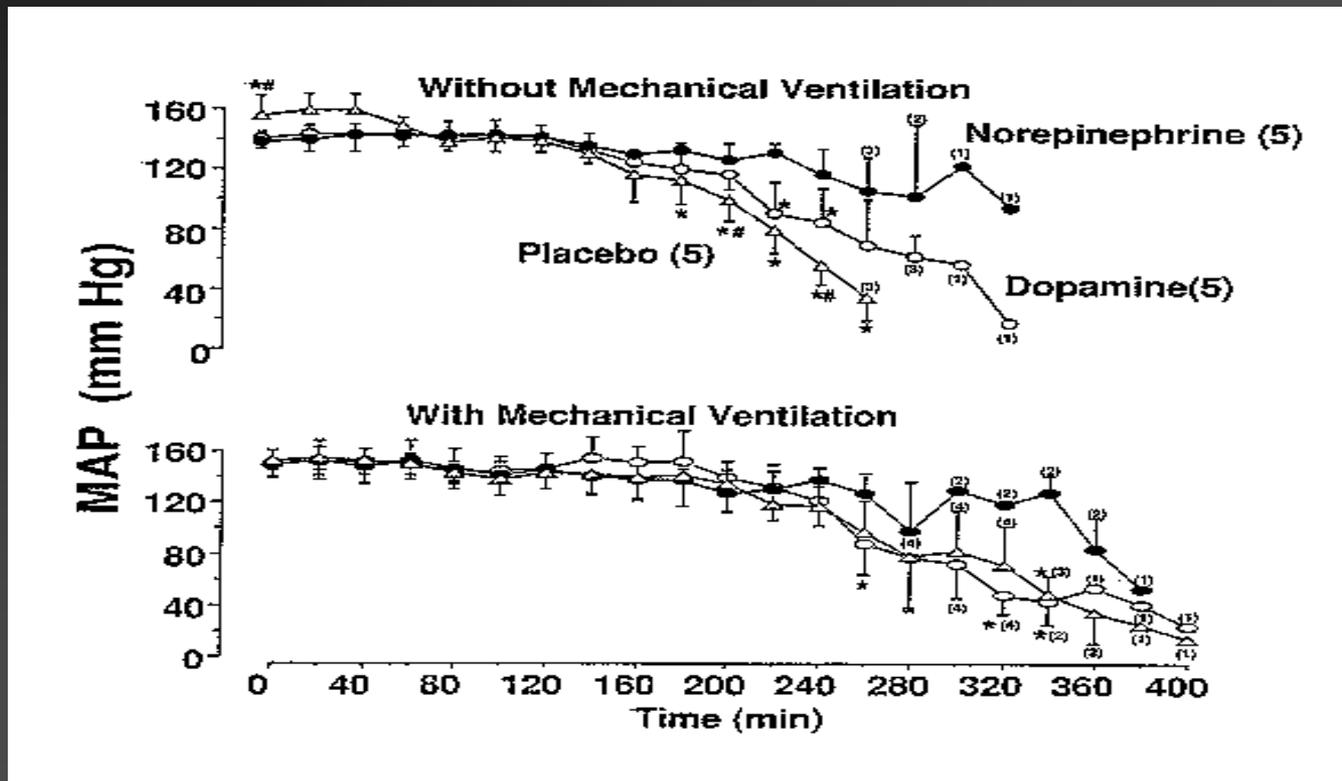
# CVVH and the heart
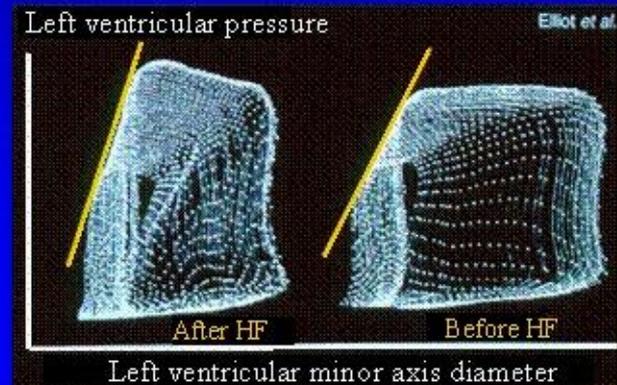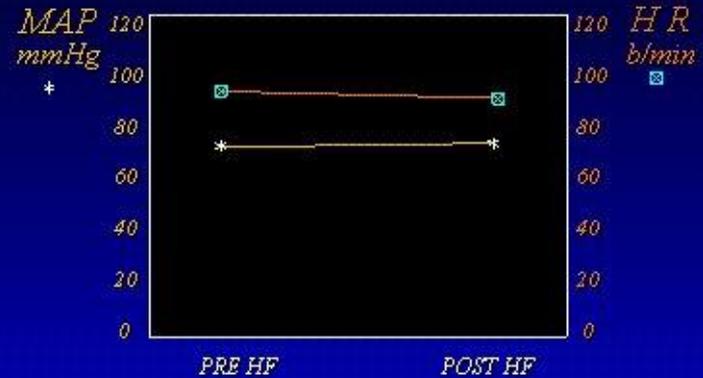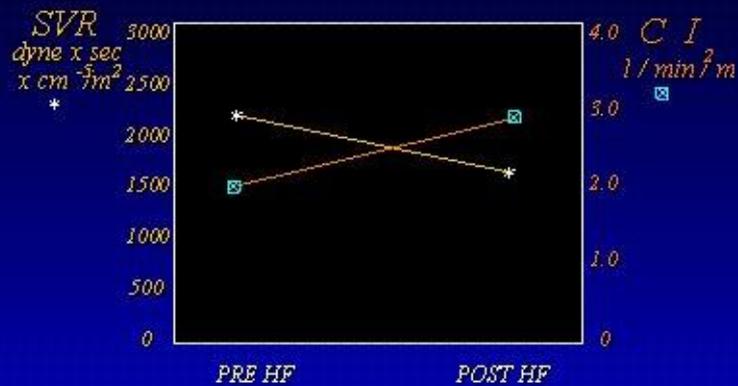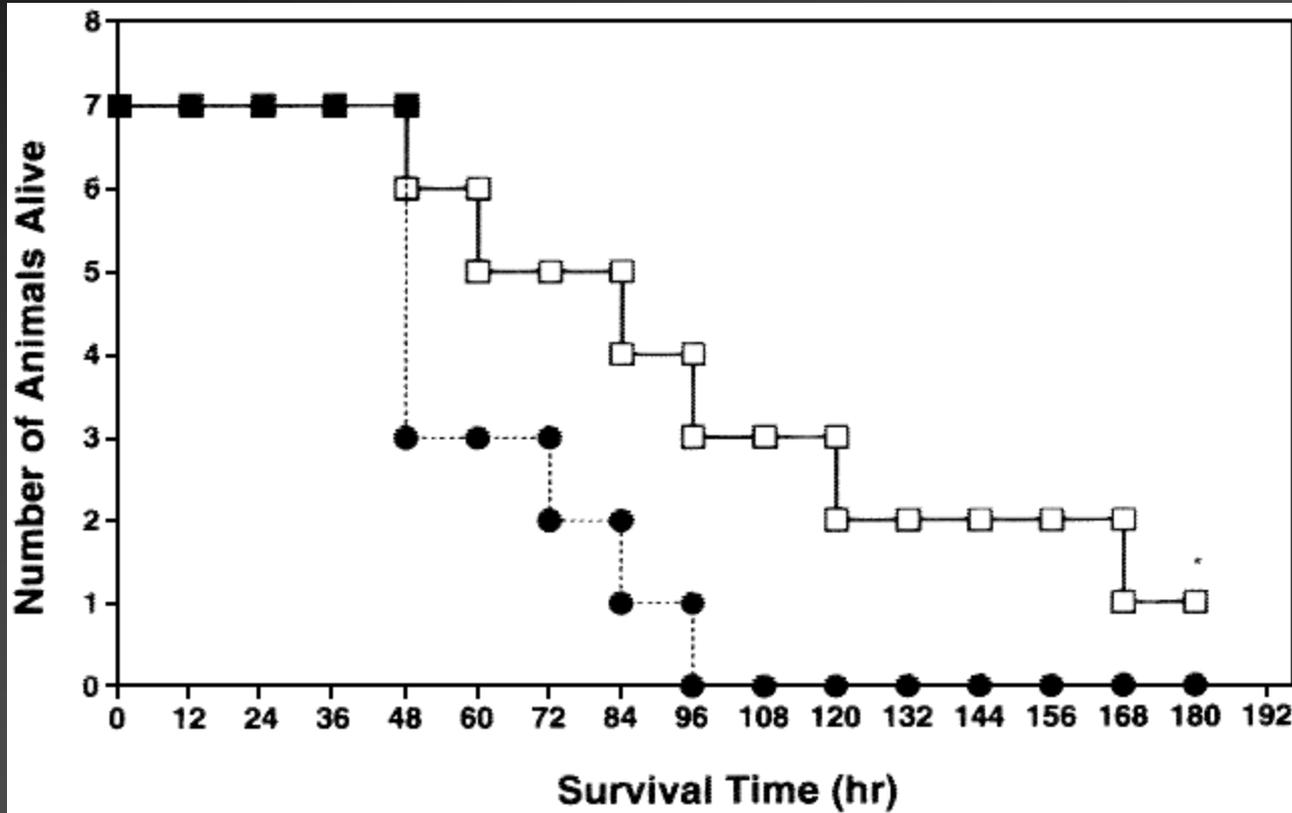
# CVVH and the lung

# 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

% survival

**CVVH**



Legend:
- 20 ml /h/kg
- 35 ml /h/kg
- 45 ml /h/kg

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 |