Tutto è già stato detto.

Grazie.

Un altro caso di malasanità.

Recatosi al PS del S.Maria della Misericordia per chiedere notizie di un congiunto vittima di un incidente, il signor XY è stato fatto entrare in un box e sottoposto a incannulamento di vena periferica, prelievi di sangue, **infusione di soluzioni endo-venose.**

La Magistratura indaga.

Il Messaggero Veneto

Cronaca di Udine

20 maggio 2012

Cardiopulmonary Bypass Priming Using a High Dose of a Balanced **Hydroxyethyl Starch** Versus an **Albumin-Based Priming Strategy**

Boldt J, Anesth Analg 2009;109:1752–62

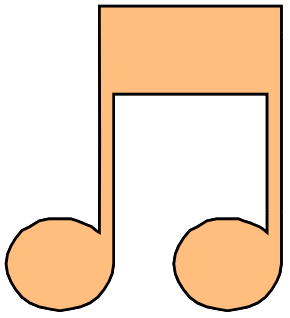
*…….**HESsolution** resulted in **reduced inflammation**, **less endothelial damage**, and **fewer alterations in renal tubular integrity** compared with an albumin-based priming.*

Riempi il paziente vuoto,

vuota il paziente pieno,

non lo lasciar mai vuoto,

non lo lasciar mai pieno.



Fluid Therapy Might Be More Difficult Than You Think

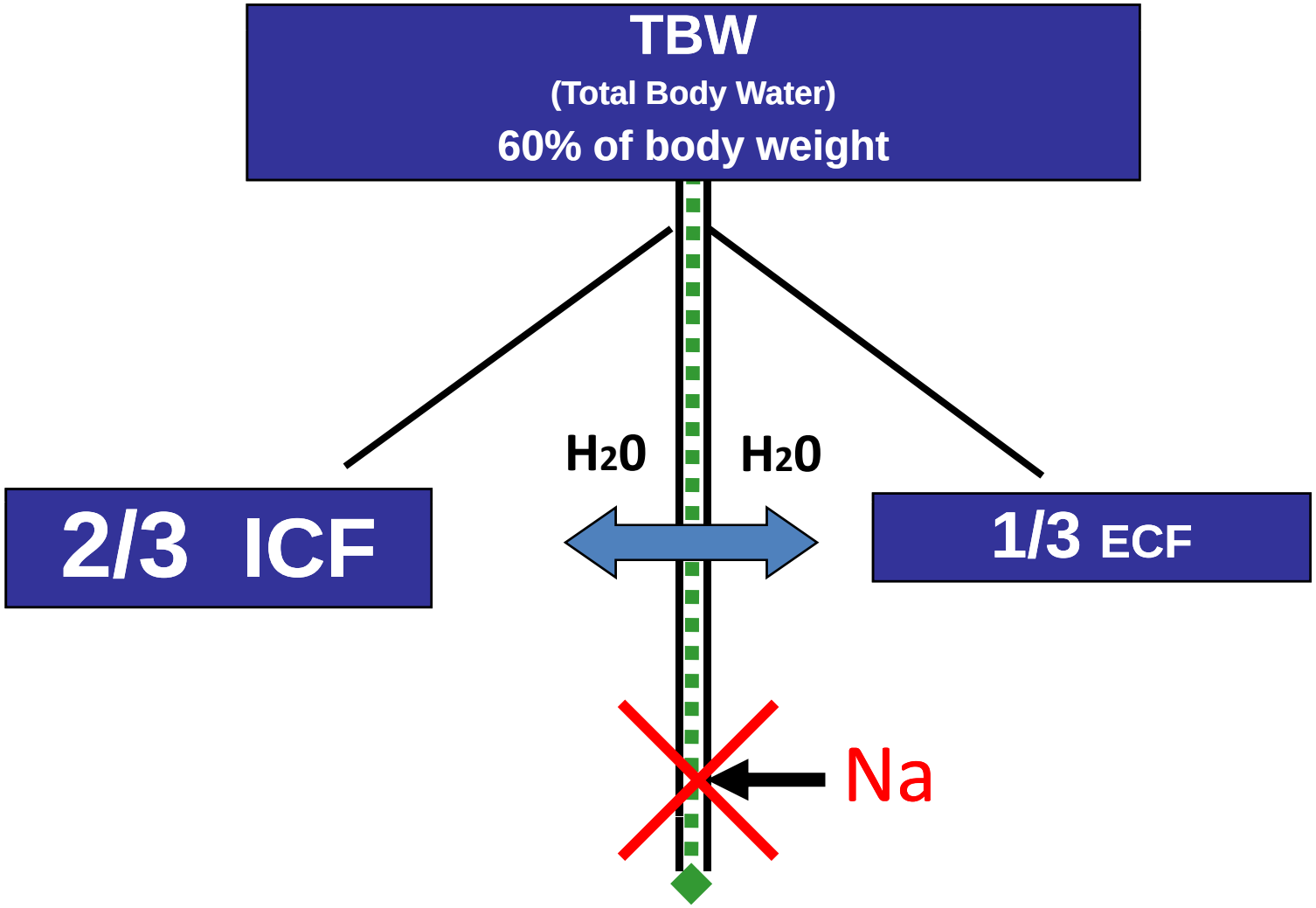
Hahn RG Anesthesia & Analgesia (2007) 105;2:304-5

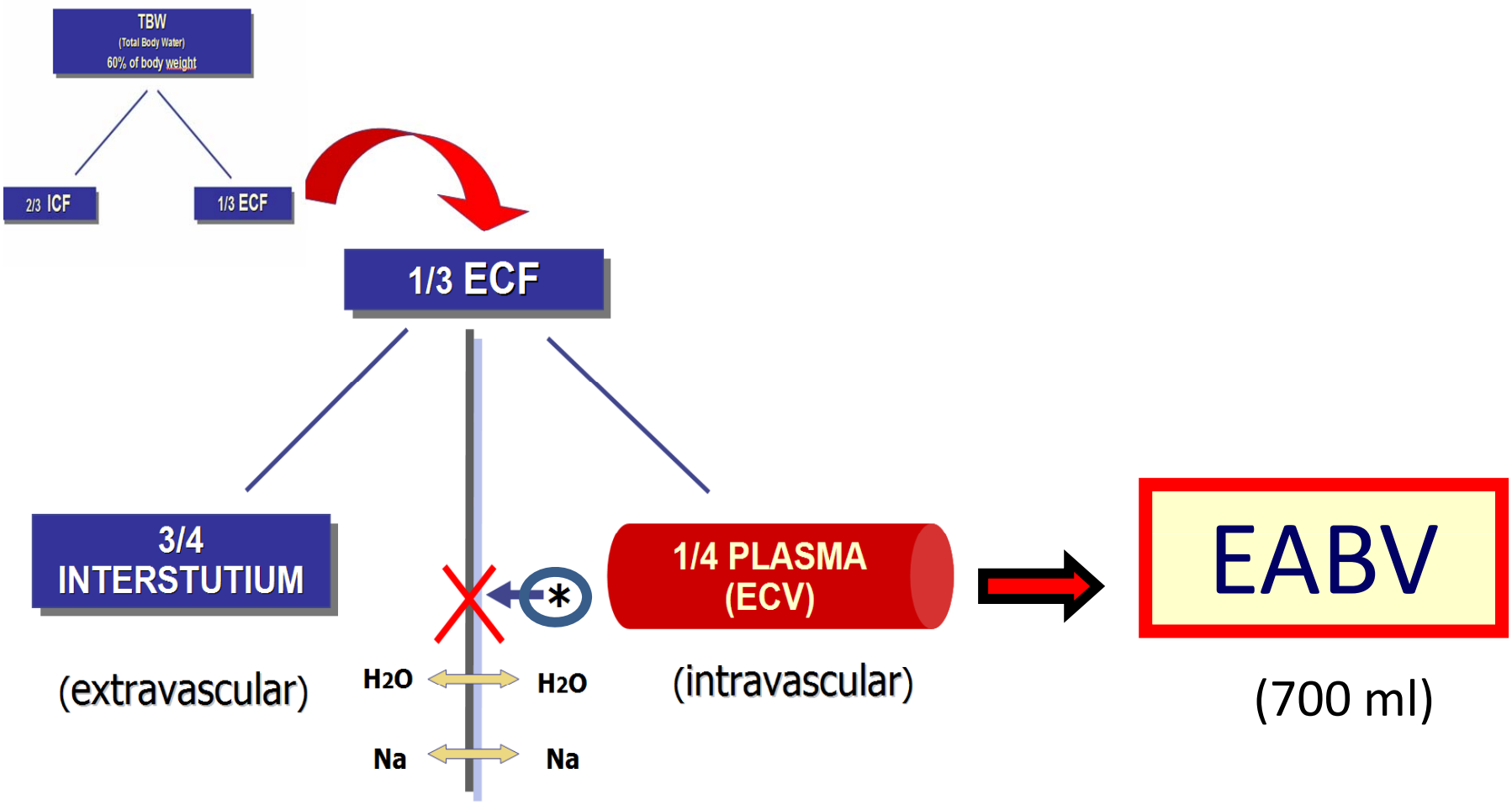
Manteinance of adequate body fluid volume

and of its distribution

is a critical part of **homeostasis**

1. **volume**
2. **tonicity (osmolality)**
3. **[H^+]**
4. **[electrolytes]**

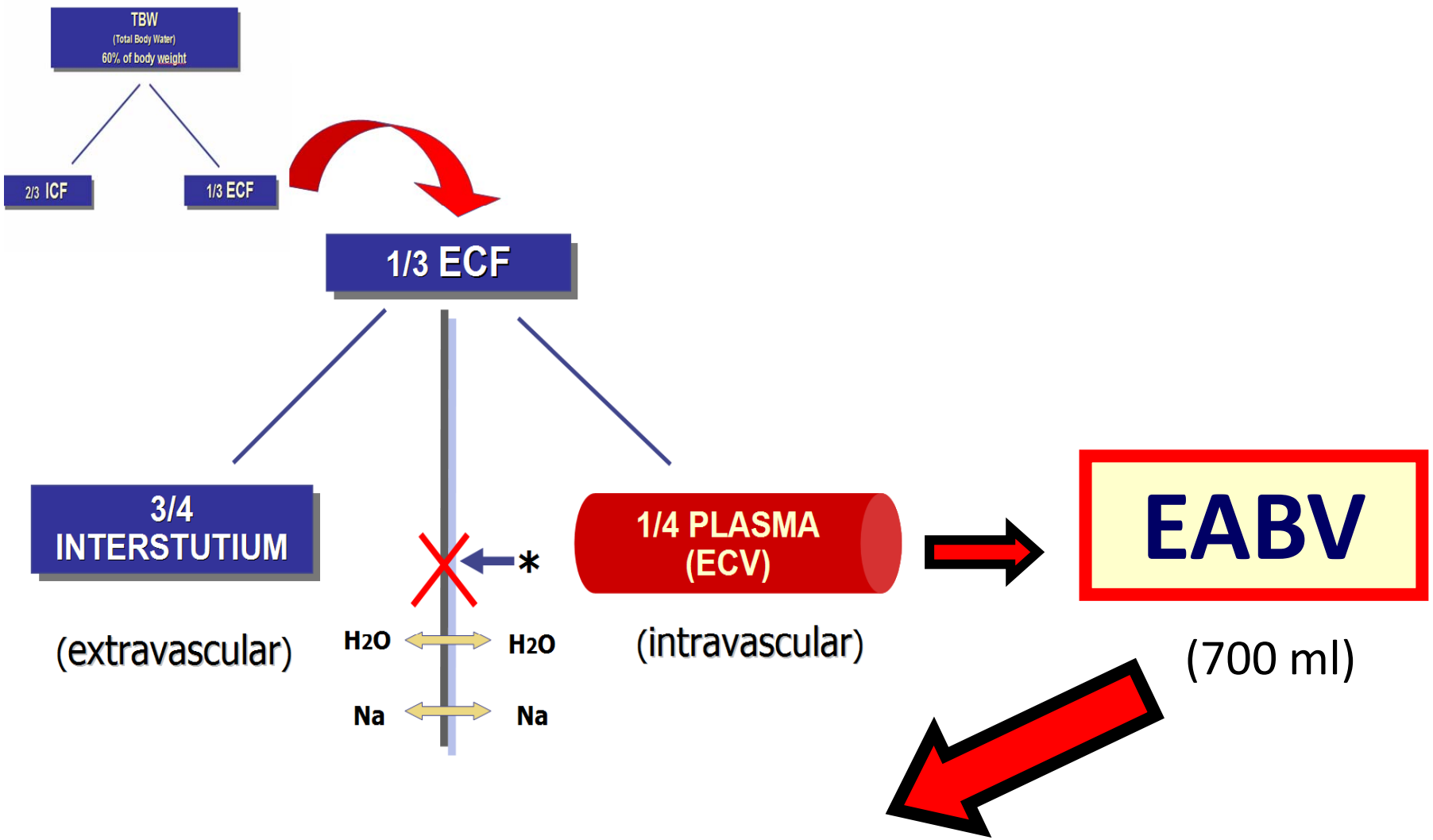

TBW
(Total Body Water)
60% of body weight
H20
H20
2/3 ICF
1/3 ECF
Na


TBW
(Total Body Water)
60% of body weight
2/3 ICF
1/3 ECF
1/3 ECF
3/4
INTERSTUTIUM
(extravascular)
H2O
H2O
Na
Na
*
1/4 PLASMA
(ECV)
(intravascular)
EABV
(700 ml)

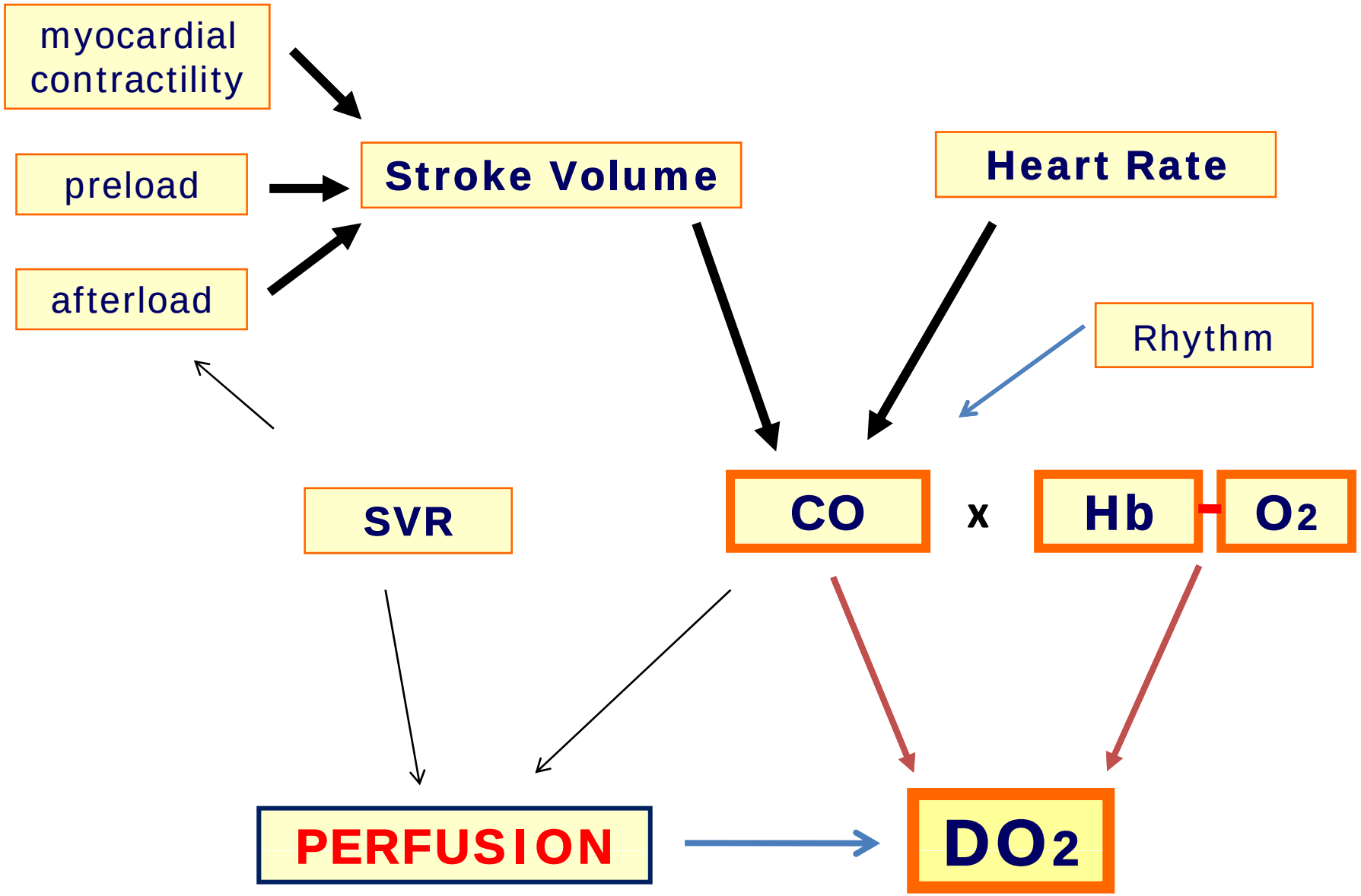
Evaluate volume status

ECF volume

EABV


TBW
(Total Body Water)
60% of body weight
2/3 ICF
1/3 ECF
1/3 ECF
3/4
INTERSTUTIUM
(extravascular)
1/4 PLASMA
(ECV)
(intravascular)
*
H2O
H2O
Na
Na
EABV
(700 ml)
Tissues Perfusion

$$DO_2 = CO \times CaO_2$$


myocardial contractility
preload
afterload
Stroke Volume
Heart Rate
Rhythm
SVR
CO
x
Hb
O2
PERFUSION
DO2

Perfusione e DO_2 non bastano

The **microcirculation is a key** (if not the most important**) target organ** for injury in **the sepsis syndrome.**

Manaker, Sexton

Microcirculatory alterations have been repeatedly observed in patients with severe **sepsis**, but recent findings show that these also occur in patients with **severe heart failure** and in those submitted to **high-risk surgery**.

More severe and more persistent alterations are observed in patients with a poor outcome.

Current Opinion in Critical Care 2010, 16:250–254

Perfusione, DO2, microcircolo non bastano

Interstitium: The next diagnostic and therapeutic platform in critical illness

Venkatesh B et al
Crit Care Med 2010; 38[Suppl.]:S630 –S636

ISF and Critical Illness

In **sepsis** there are well-documented **increases in the extracellular body water** **during the acute phase of the inflammatory response**.

Elderly patients with sepsis demonstrate increases in extracellular water compared with younger patients, and **increasesing extracellular water are associated with worse outcome.**

Patients with **major blunt trauma** display similar pathophysiologic changes.

Ciao, Starling

Revised Starling equation and the **glycocalyx model of transvascular fluid exchange**: an improved paradigm for prescribing intravenous fluid therapy

WoodcockTE, Woodcock TM British Journal of Anaesthesia 108 (3): 384–94 (2012)

L’equazione di Starling stabilisce che il movimento di un liquido attraverso la parete di un capillare è determinato dalla pressione netta attraverso la parete, che è data dalla somma delle pressioni idrauliche ed oncotiche.

Legge di Starling: la quantità di liquido che filtra all’esterno all’estremità arteriolare dei capillari equivale all’incirca alla quantità di liquido che viene riassorbita all’estremità venulare.

- pressione idrostatica intravasale
- pressione osmotica del liquido interstiziale

vs

- pressione oncotica

In condizioni fisiologiche ***a livello dell’estremità arteriosa si ha filtrazione netta, a livello dell’estremità venosa assorbimento netto***

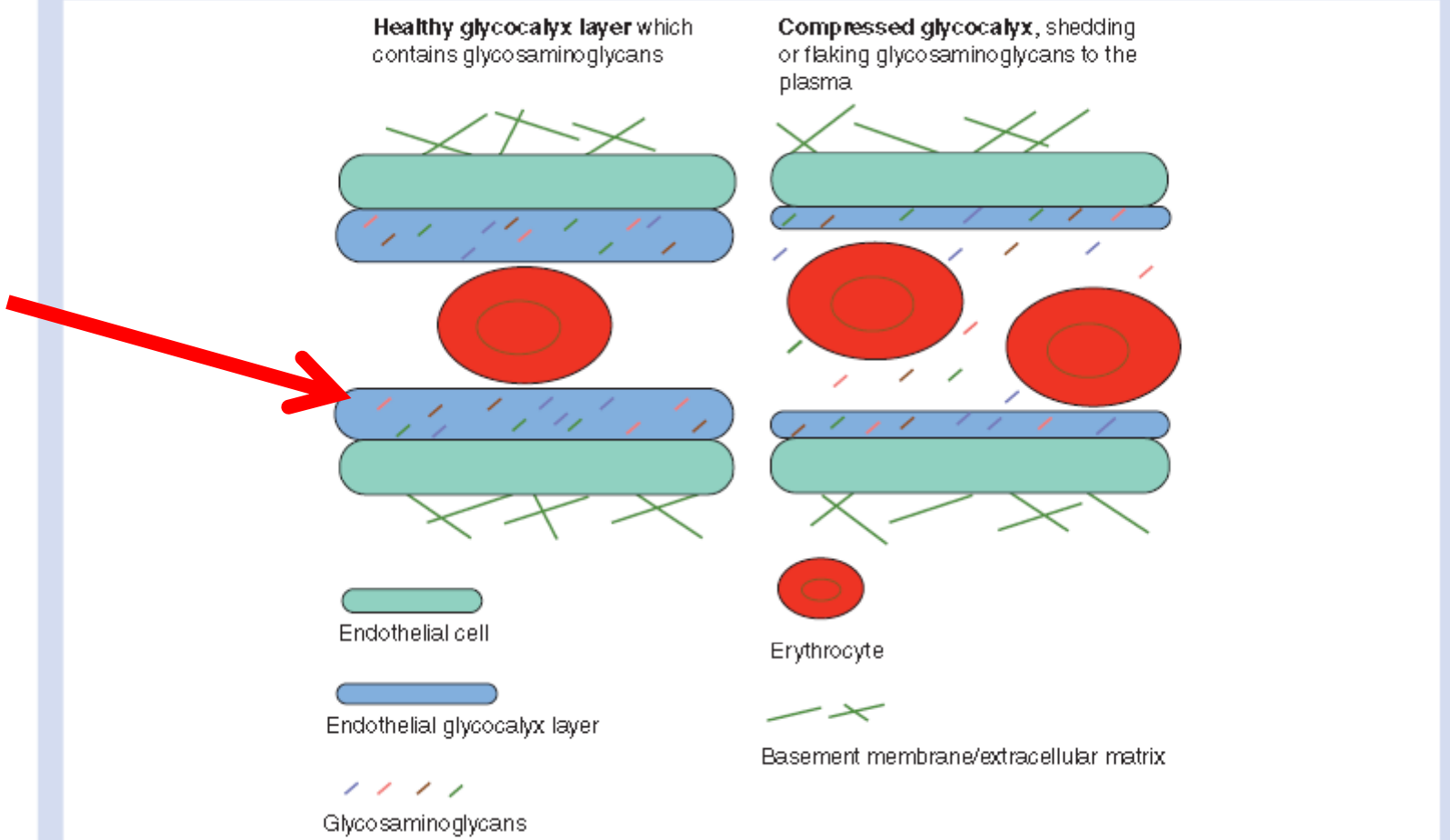


Fig 1 A cartoon illustrating that the intravascular volume contains the non-circulating glycocalyx fluid volume and the circulating plasma volume. Red blood cells are excluded from the glycocalyx layer. Compaction of the glycocalyx layer increases plasma volume and the red cell dilution volume independently of changes in intravascular volume.

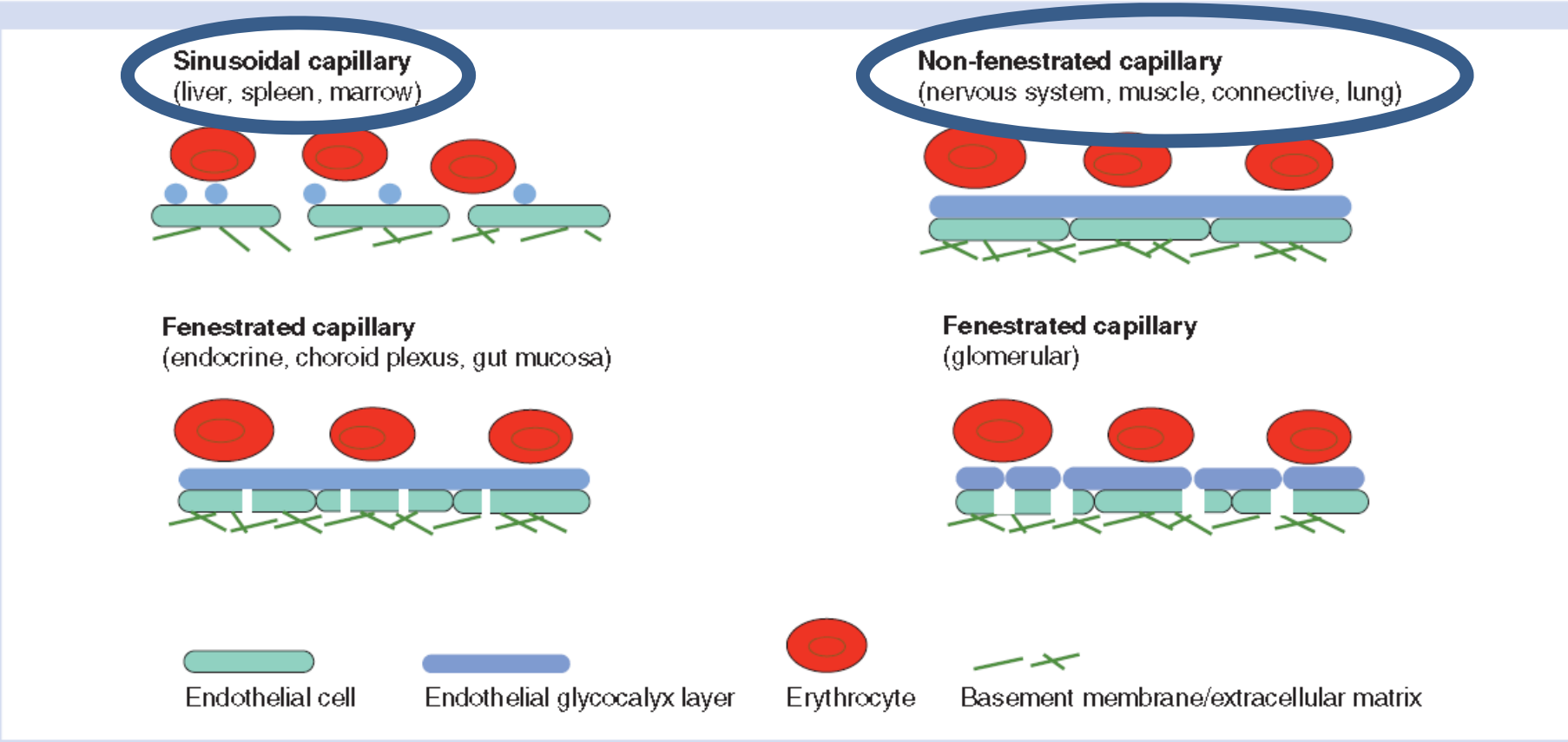


Fig 2 A cartoon illustrating some anatomic differences between four capillary phenotypes.

It is now established that

- *nonfenestrated capillaries* normally filter fluid to the ISF throughout their length.
- *Absorption* through venous capillaries and venules *does not occur.*
- *COP opposes, but does not reverse, filtration*.
- Most of the filtered fluid returns to the circulation as *lymph*.

British Journal of Anaesthesia 108 (3): 384–94 (2012)

Plasma proteins, including albumin, escape to the interstitial space by a relatively small number of large pores, which are responsible for the **increased transcapillary flow (Jv**) observed in the early stage of **inflammation**.

British Journal of Anaesthesia 108 (3): 384–94 (2012)

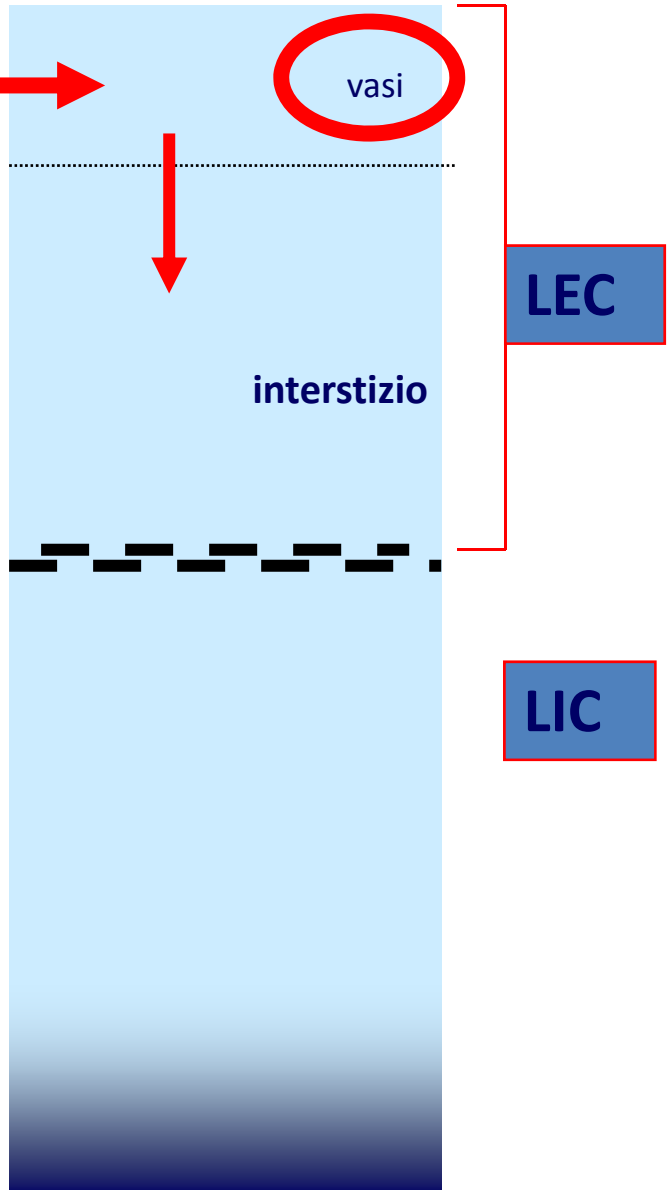
Colloids or crystalloid solutions?

Is this (still) the question?

- capacità di espansione volemica
- persistenza in circolo
- effetti sulla cascata di attivazione della SIRS
- influenza sul microcircolo
- sicurezza
- reazioni avverse
- costo

Fisiologica

1 litro



Bilancio dopo la infusione di 1 litro di soluzione:

Intravasale	**=**	**250**
Interstiziale	**=**	**750**
Intracellulare	**=**	**0**

Currently, there is no consensus on the clinical definition of **hypovolemia**.

In broad terms, ***patients who improve with fluid therapy are hypovolemic***.

Static indices of preload have no predictive power in hypovolemia.

Crit Care Med 2009 Vol. 37, No. 9

Fluid Challenge Test

Test di espansione volemica

Increasing the infusion rate of an

oliguric patient from

100 ml/h to 200 or 300

provides no answer to the question of

etiology of oliguria nor does it

adequately treat volume depletion.

Chernow

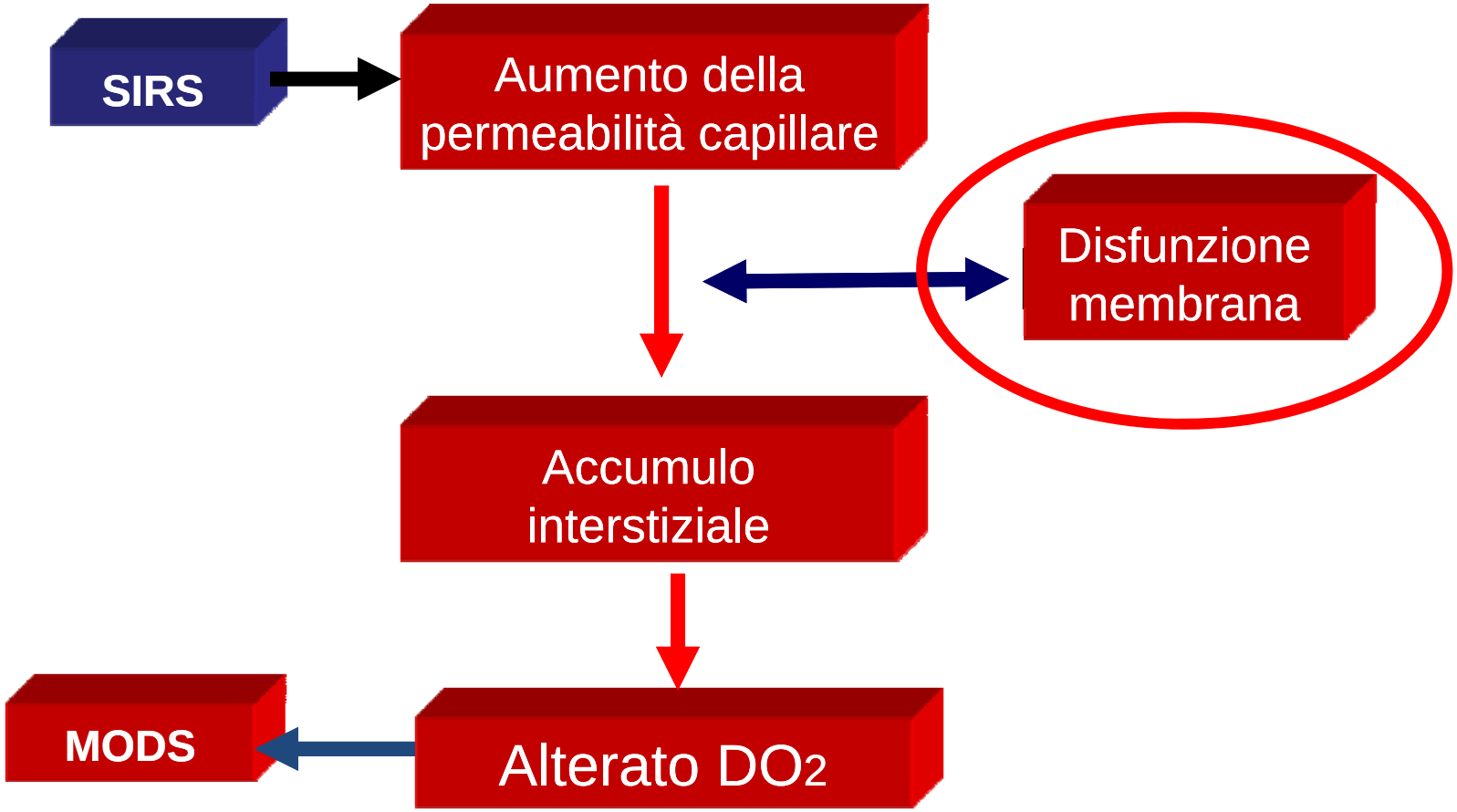
- capacità di espansione volemica
- **persistenza in circolo**
- effetti sulla cascata di attivazione della SIRS
- influenza sul microcircolo
- sicurezza
- reazioni avverse

Distribuzione relativa di colloidi e cristalloidi a 30-60 minuti dalla infusione

da Haljmae e Lindgren, 2000

	INTRAVASCOLARE	EXTRAVASCOLARE
	Normale permeabilità capillare (PC)	
CRISTALLOIDI	**25%**	**75%**
COLLOIDI	**70%**	30%
	Aumentata PC	
CRISTALLOIDI	15-20%	80-85%
COLLOIDI	60-70%	30-40%
	Aumentata PC + disfunzione di membrana	
CRISTALLOIDI	10-15%	85-90%
COLLOIDI	**50-60%**	**40-50%**

I pazienti critici hanno frequentemente importanti disordini della omeostasi dei fluidi.



There is **no evidence from RCTs that resuscitation with colloids reduces the risk of death**, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery.

As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, **it is hard to see how their continued use in these patients can be justified outside the context of RCTs.**

Colloids versus crystalloids for fluid resuscitation in critically ill patients

Perel P, Roberts I

Cochrane Database of Systematic Reviews. 3, 2011

No clinical differences were found between colloids and crystalloids in most of the studies analyzed.

Given the ***significant difference in costs*** between both groups of expanders and in light of the currently available evidence, **crystalloids should be used as first-choice expanders.**

Health Technology Assessment Database. 2010 Issue 4,

SAFE (Saline *vs* Albumin Fluid Evaluation) Study.

N Engl J Med 2004; 350: 2247–56

Human serum albumin as a resuscitation fluid: Less SAFE than presumed?

most likely depending on the dosing and timing, in some patients, HSA ***may not only lack therapeutic efficacy, but may even be harmful.***

Crit Care Med 2011 Vol. 39, No. 6:1584-85

Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (**VISEP**) trial

The **VISEP** trial was ***stopped early for safety reasons***.

…patients receiving pentastarch were approximately 50% more likely to have ***acute renal failure*** *develop and were also more likely to require renal replacement therapy*.

N Engl J Med. 2008;358:125-139

For patients with **hypovolaemia**, **there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline**.

There is **no evidence that albumin reduces mortality** in critically ill patients with burns and hypoalbuminaemia.

Cochrane Database of Systematic Reviews. 11, 2011

However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that **albumin should only be used within the context of well concealed and adequately powered randomised controlled trials.**

Cochrane Database of Systematic Reviews. 11, 2011

The Boldt debacle

Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy

Joachim Boldt, MD

Stephan Suttner, MD

Christian Brosch, MD

Andreas Lehmann, MD

Kerstin Röhm, MD

Andinet Mengistu, MD

BACKGROUND: The optimal priming solution for cardiopulmonary bypass (CPB) is unclear. In this study, we evaluated the influence of high-volume priming with a modern balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with an albumin-based CPB priming regimen.

METHODS: In 50 patients undergoing coronary artery bypass grafting, the CPB circuit was prospectively and randomly primed with either 1500 mL of 6% HES 130/0.42 in a balanced electrolyte solution (Na^+ 140 mmol/L, Cl^- 118 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, acetate$^-$ 24 mmol/L, malate$^-$ 5 mmol/L) (n = 25) or with 500 mL of 5% human albumin plus 1000 mL 0.9% saline solution (n = 25). Inflammation (interleukins [IL]-6, -10), endothelial damage (soluble intercellular adhesion molecule-1), kidney function (kidney-specific proteins α-glutathione *S*-transferase, neutrophil gelatinase-associated lipocalin), coagulation (measured by thrombelastometry [ROTEM®, Pentapharm, Munich, Germany]), and platelet function (measured by whole blood aggregometry [Multiplate® analyzer, Dynabyte Medical, Munich, Germany]) were assessed after induction of anesthesia, immediately after surgery, 5 h after surgery, and on the morning of first and second postoperative days.

RESULTS: Total volume given during and after CPB was 3090 ± 540 mL of balanced HES and 3110 ± 450 mL of albumin. Base excess after surgery was lower in the albumin-based priming group than in the balanced HES priming group (−5.9 ± 1.2 mmol/L vs +0.2 ± 0.2 mmol/L, P = 0.0003). Plasma levels of IL-6, IL-10, and intercellular adhesion molecule-1 were higher after CPB in the albumin-based priming group compared with the HES priming group at all time periods (P = 0.0002). Urinary concentrations of α-glutathione *S*-transferase and neutrophil gelatinase-associated lipocalin were higher after CPB through the end of the study in the albumin group compared with the balanced HES group (P = 0.00004). After surgery through the first postoperative day, thrombelastometry data (clotting time and clot formation time) revealed more impaired coagulation in the albumin-based priming group compared with the HES priming group (P = 0.004). Compared with baseline, platelet function was unchanged in the high-dose balanced HES priming group after CPB and 5 h after surgery, but it was significantly reduced in the albumin-based priming group.

CONCLUSION: High-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming.

(Anesth Analg 2009;109:1752–62)

The ideal strategy for priming of the cardiopulmonary bypass (CPB) circuit in adult cardiac surgery is still a matter of debate.[1–6] In many institutions, either albumin or nonprotein synthetic colloids (gelatins, dextrans, hydroxyethyl starch [HES]) are added to the crystalloid-based prime. HES preparations are classified based on their mean molecular weight (MW; low MW HES: 70 kD; medium MW HES: from 130 to 260 kD; high MW [HMW] HES: >450 kD), their molar substitution (MS; high MS: >0.7; medium MS: >0.5; low MS: >0.5), and their ratio of the C_2/C_6 hydroxyethylation. The importance of the diluent solution of HES has been recently emphasized.[7,8] Most colloids (including albumin) are diluted in 0.9% normal saline that contains nonphysiologically high concentrations of sodium (154 mmol/L) and chloride (154 mmol/L) that might contribute to hyperchloremic acidosis.[9] Modern HES preparations are dissolved in an electrolyte solution closer in composition to plasma ("balanced" or "plasma adapted" solutions). The purpose

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Accepted for publication June 12, 2009.

Supported by a hospital grant.

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DOI: 10.1213/ANE.0b013e3181[illegible]

Crystalloids versus colloids: the end of an old debate?

JOACHIM BOLDT, MD, PhD

Transfusion Alternatives in Transfusion Medicine © 2010 Medical Education Global Solutions • 11, 118–126

Consensus statement of the **ESICM** task force on colloid volume therapy in critically ill patients

Intensive Care Med (2012) 38:368–383

We **recommend not to use HES** with molecular weight C200 kDa and/or degree of substitution[0.4 in patients with severe sepsis or risk of acute kidney injury and **suggest not to use 6% HES 130/0.4 or gelatin** in these populations.

We **recommend not to use colloids in patients with head injury** and not to administer gelatins and HES in organ donors.

We suggest not to use hyperoncotic solutions for fluid resuscitation.

We conclude and recommend that any new colloid should introduced into clinical practice only after its patient-important safety parameters are established.

Intensive Care Med (2012) 38:368–383

Whereas

inadequate volume resuscitation is well recognized to result in organ failure and death, ***excessive resuscitation places the patient at risk*** *for increased* **IAP**, worsening **visceral edema**, and **cardiopulmonary dysfunction**.

Cheatham M Crit Care Med 2008 36(3):1012-1014

Fluid resuscitation in septic shock:

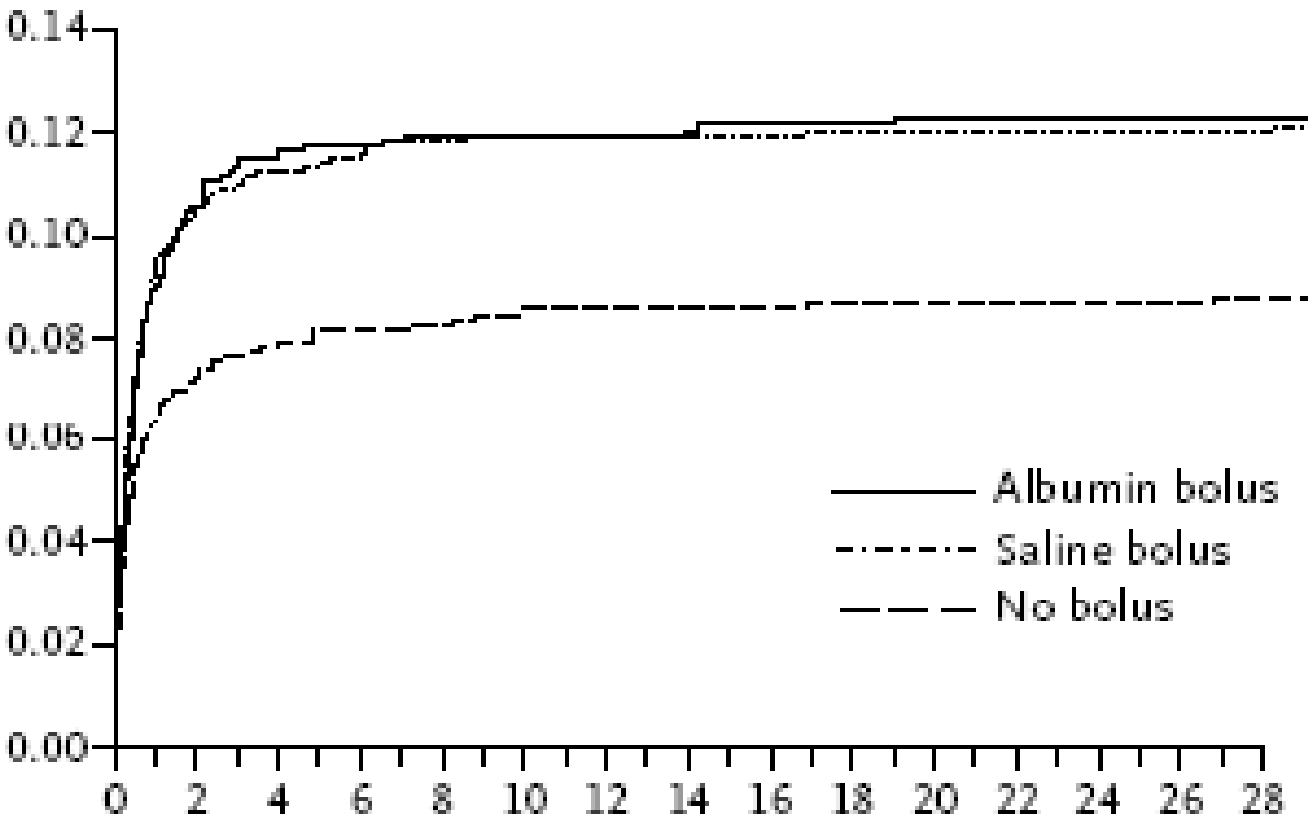
A positive fluid balance and elevated central venous pressure are associated with increased mortality

Crit Care Med 2011; 39:259 –265

ED crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and nonelderly trauma patients.

ED volume replacement of 1.5 L or more was an independent risk factor for mortality. High-volume resuscitations were associated with high-mortality particularly in the elderly trauma patient

Ley EJ et al J Trauma 2011 Feb;70(2):398-400


0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Albumin bolus
Saline bolus
No bolus

Fluid Expansion as Supportive Therapy **(FEAST) trial**

Maitland K, Kiguli S, Opoka RO, et al.
Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011. DOI: 10.1056/NEJMoa1101549

May 26, 2011

the trial was stopped after **the recruitment of 3141 patients when bolus-fluid resuscitation with albumin or saline was shown to increase the absolute risk of death** at 48 hours by 3.3 percentage points and the risk of death, neurologic sequelae, or both at 4 weeks by 4 percentage points.

The excess mortality associated with bolus-fluid resuscitation was consistent across all prespecified subgroups, which included subgroups according to age, lactate level, base deficit, presence or absence of severe anemia, and status with respect to coma and malaria.

Fluid Resuscitation in Acute Illness

Time to Reappraise the Basics

John A. Myburgh, M.B., B.Ch., Ph.D.

...discontinuation of the practice of bolus-fluid resuscitation in patients with febrile illness due to medical causes and impaired perfusion or compensated shock must be recommended.

Given that 2 million children die from this condition each year in sub-Saharan Africa, the potential impact is enormous.

Myburgh

Potential mechanisms may include **the interruption of genetically determined catecholamine-mediated host defense** responses by the rapid increase in plasma volume, which might result in a ***reperfusion injury.***

Similarly, transient hypervolemia or hyperosmolality **might exacerbate capillary leak** in patients who are susceptible to intracranial hypertension or pulmonary edema, with fatal consequences.

Myburgh

A critique of fluid bolus resuscitation in severe sepsis

Hilton and Bellomo *Critical Care 2012*, ***16:302***

Such recommendations are only based on expert opinion and lack adequate experimental or controlled human evidence.

Despite these limitations, **fluid bolus therapy (20 to 40 ml/ kg)** is widely practiced and is currently considered a cornerstone of the management of sepsis.

….we will argue that such therapy **has *weak physiological support, has limited experimental support,* ….**

Does fluid bolus resuscitation in patients with severe sepsis actually increase vital organ blood flow or even cardiac output?

If it does, what is the magnitude of its effect on both the blood flow and cardiac output for a given dose?

How long does this effect last?

What is the physiological price (positive fluid balance, worse gas exchange, organ edema, acid–base changes) paid to achieve this effect?

What evidence do we have to answer some of these questions in man?

Hilton and Bellomo *Critical Care 2012,* ***16:302***

Until recently, no study had asked the **ultimate question**:

Are the physiological gains (if they exist) worth the physiological costs ?

We now know that the answer in children in resource-poor countries is **a resounding 'no'.**

Hilton and Bellomo *Critical Care 2012,* ***16:302***

Quanto costa una fisiologica?

	ml	€
NaCl 0,9%	1000	0.72
NaCl 0,9%	500	**0.42**
Ringer Ac	500	0.77
Voluven	500	**6.24**
Alb 20%	20	20.42
Emagel	500	3.69

St.Mary Mercy's, Udine, 2011

	ml	N	€
NaCl 0,9%	1000	65.290	47.182
NaCl 0,9%	500	65.010	25.278
Voluven	500	**15.100**	94.360
Alb 20%	20	862	17.608
Emagel	500	476	1759

St.Mary Mercy's, Udine, 2011

	ml	N	€
NaCl 0,9%	1000	3160	2.238
NaCl 0,9%	500	1300	513
Voluven	500	**180**	1.125
Alb 20%	20	-	-
Emagel	500	-	-

Pronto Soccorso, St.Mary Mercy's, Udine, 2011

Fluid Therapy Might Be More Difficult Than You Think

Hahn RG Anesthesia & Analgesia (2007) 105;2:304-5

The difficulty lies, not in new ideas, but in escaping old ones, which ramify, for those brought up with them, as most of us have been, into every corner of our minds.

John Maynard Keynes