FLUID THERAPY IN SEPTIC PATIENTS - 2014

CRYSTALLOIDS or COLLOIDS

Which-What-When-Why-How ?

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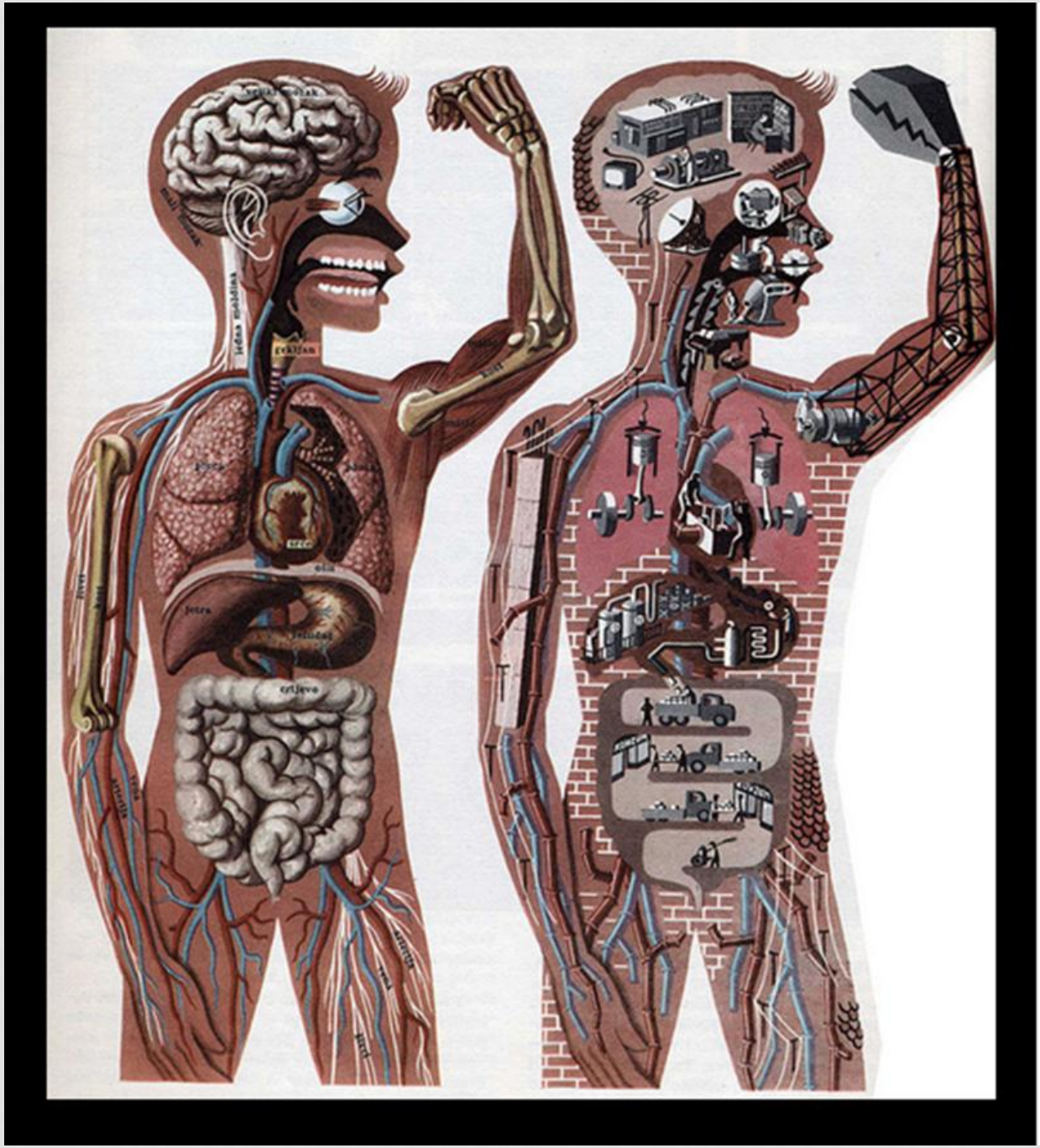
TEN POINTS TO PONDER

1. Fluid therapy = DRUG therapy
2. The Crystalloid-Colloid controversy DOES NOT EXIST
3. TOTAL Fluid management - balance chart, fluid creep
4. Pathophysiology, fluid therapy and the 3rd space
5. Oedema, DO2/VO2, Convection & Diffusion, the micro-circulation, capillary density, extravascular lung water, compartment Sx
6. Acute volume therapy. Fluid requirements by assessing preload. Static vs dynamic measures and endpoints in resuscitation - Starling and Guyton!
7. CVP change to CVL – use the line NOT the pressure
8. Physiological Monitoring = Driving with your lights on
9. The kidney – AKI, ATN and polyuric renal failure
10. Acid base homeostasis, SID; Electrolyte disturbances



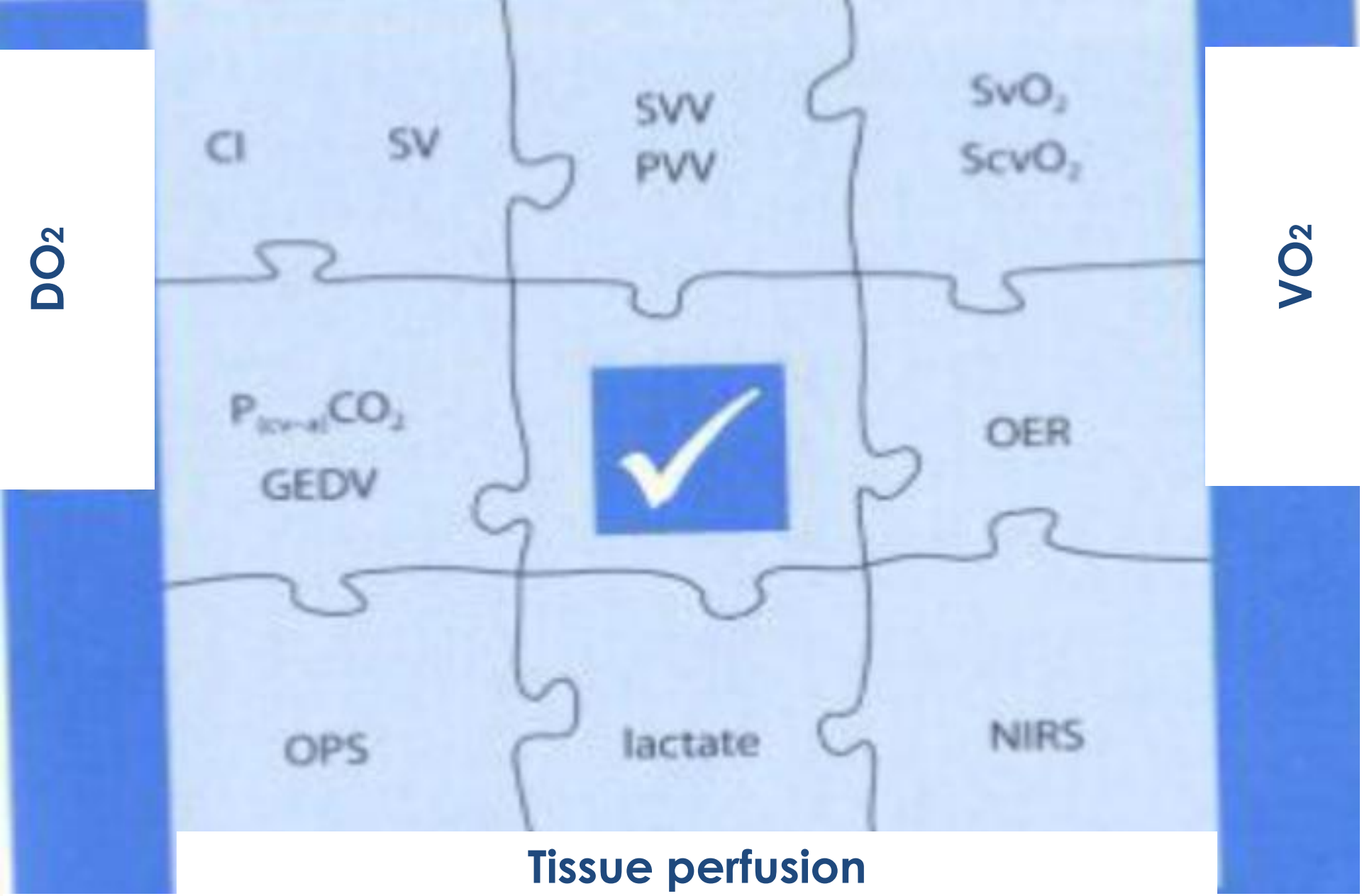
A SYSTEMS APPROACH

THE HEALTHY HUMAN BODY
Homeostasis
ISO ? - ISO9090 !
Perfect harmony
Excellent communi-cation systems
Maximum performance

SEPTIC SHOCK
Communication failure
Disrupted CVS
- CO ↓
- Hypotension
- Vasodilatation

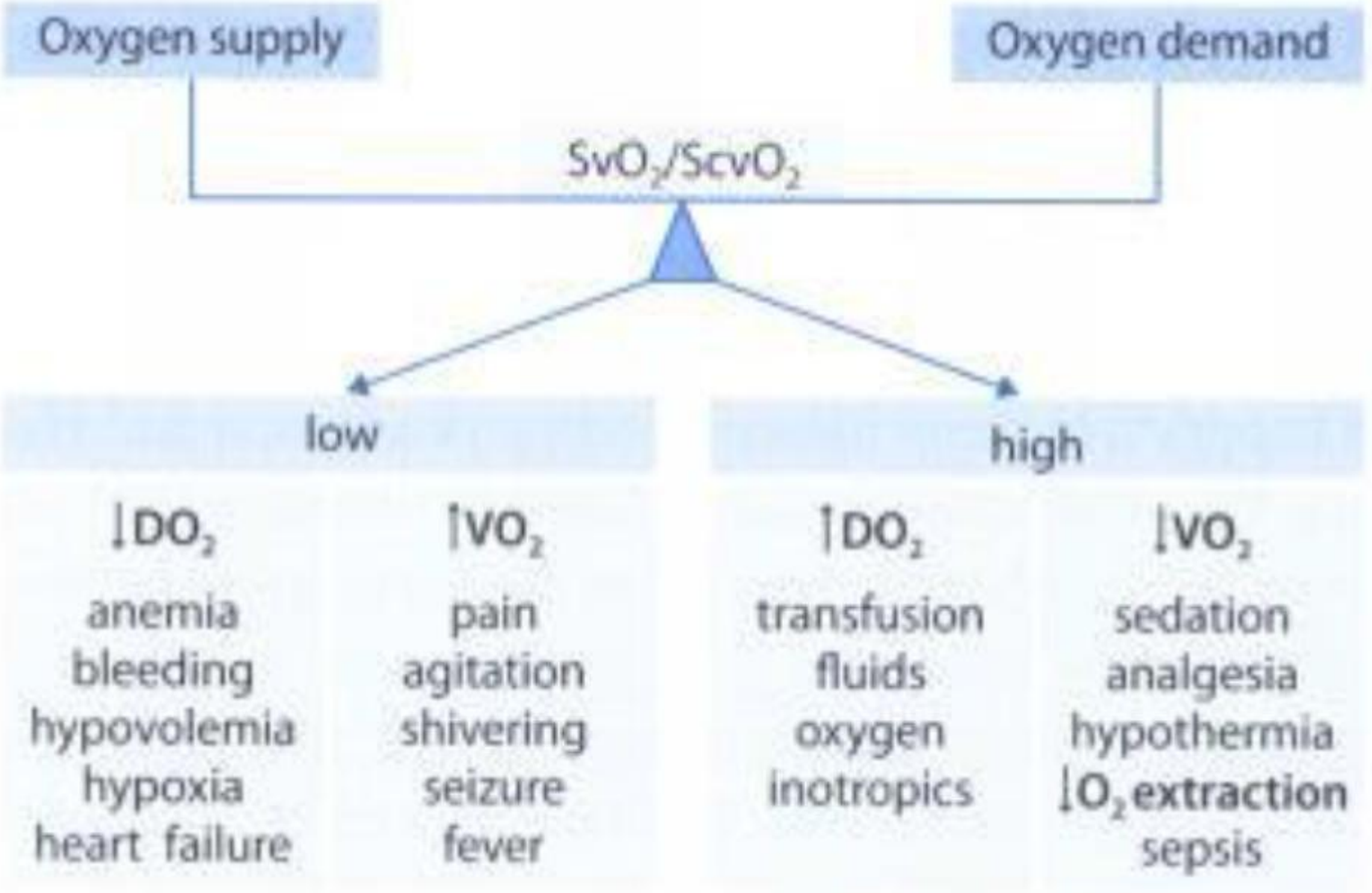
Chaos-MOFS-Death

Resuscitation is more complicated …..than filling empty buckets with water !



Tissue perfusion

Solving the Haemodynamic Puzzle



A Physiological Balancing Act !!!

WHY AND HOW TO RESUSCITATE
OR, WHY AND HOW TO USE FLUIDS IN SHOCK

- **The aim of resuscitation is to …**
  - Improve the peripheral perfusion to …
  - Restore the microcirculation in order to …
  - Provide adequate or appropriate DO2 to the tissues or cells
- Fluid therapy is only **one element** in the complex therapeutic bundle to treat distributive shock
- Stop chasing / optimizing the static CVP only. *This pressure does NOT reflect preload or preload sensitivity*.
- Move towards optimizing the performance of the **cardiovascular system** in total.
- This is the only safe, realistic way to increase peripheral perfusion.

Marik *Annals of Intensive Care* 2014, **4**:21
http://www.annalsofintensivecare.com/content/4/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Iatrogenic salt water drowning and the hazards of a high central venous pressure

Paul E Marik

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

Protocols are OUT - Individualization is IN

PERSPECTIVE

The Challenge: improving the microcirculation and tissue oxygenation *without inducing fluid overload…or further dehydration*

- **Resuscitation:**
  - GDT = **EARLY** institution of **INDIVIDUALIZED (NOT** protocolized) treatment guided by haemodynamic **MONITORING** to optimize oxygen flow goals of high-risk surgical and septic patients
- **Maintenance:**
  - "Restrictive" = adequate substitution of fluid needs ?Deliberated or Reasoned fluid policy
  - Actual losses
- **Macrocirculation vs Microcirculation**
  - Rheology, Viscosity, Capillary density, Vascular resistance, Haemoglobin all play a role
  - Visualizing the microcirculation: OPS, NIRS, SDF, IDF We need tools!
  - Not only increase microcirculatory flow velocity, but rather fill empty capillaries with oxygen rich RBC's to reduce the oxygen diffusion distance to tissue cells.
  - Microcirculatory dose response to fluid differs from the Macrocirculatory or haemodynamic response.

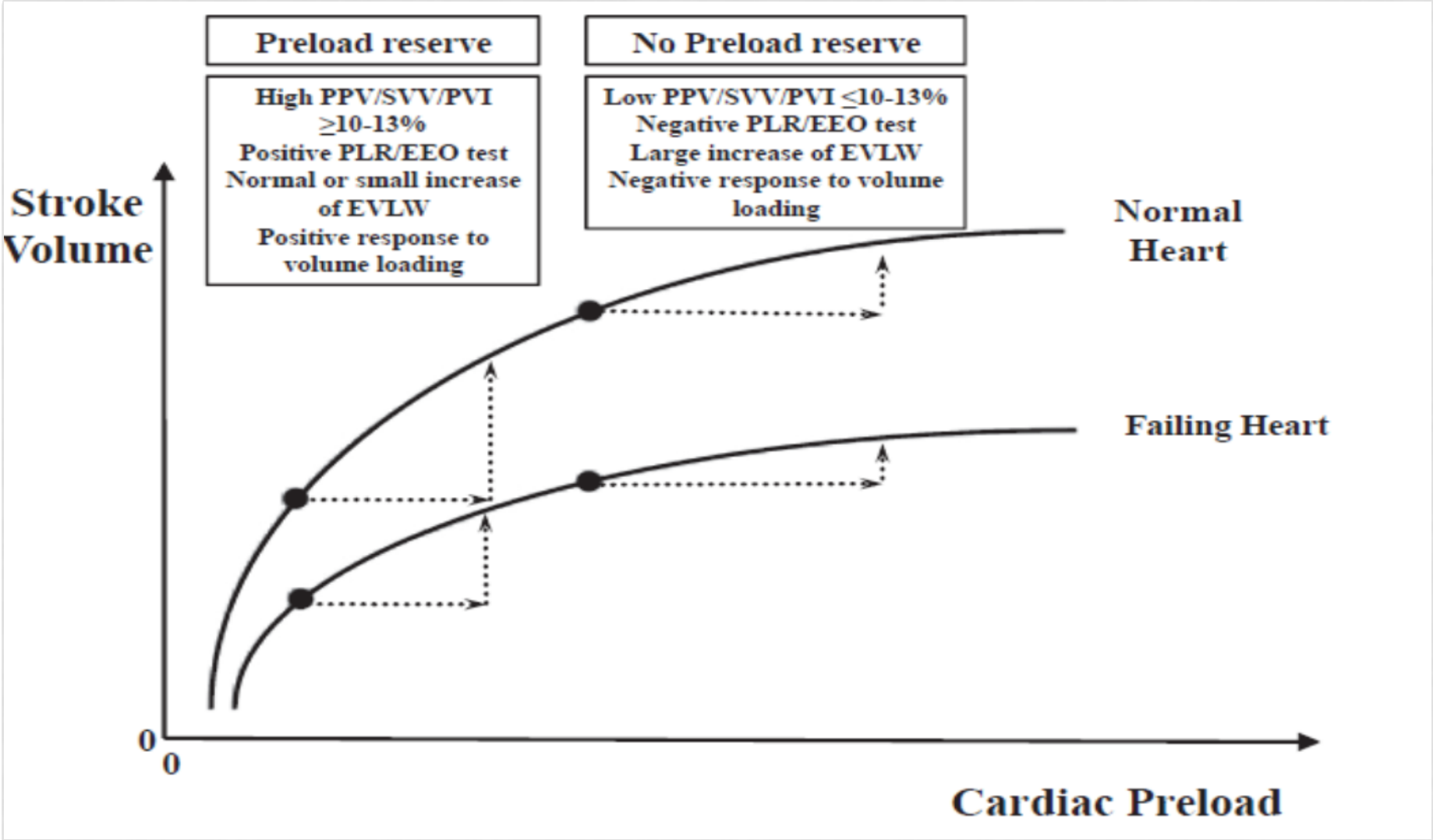
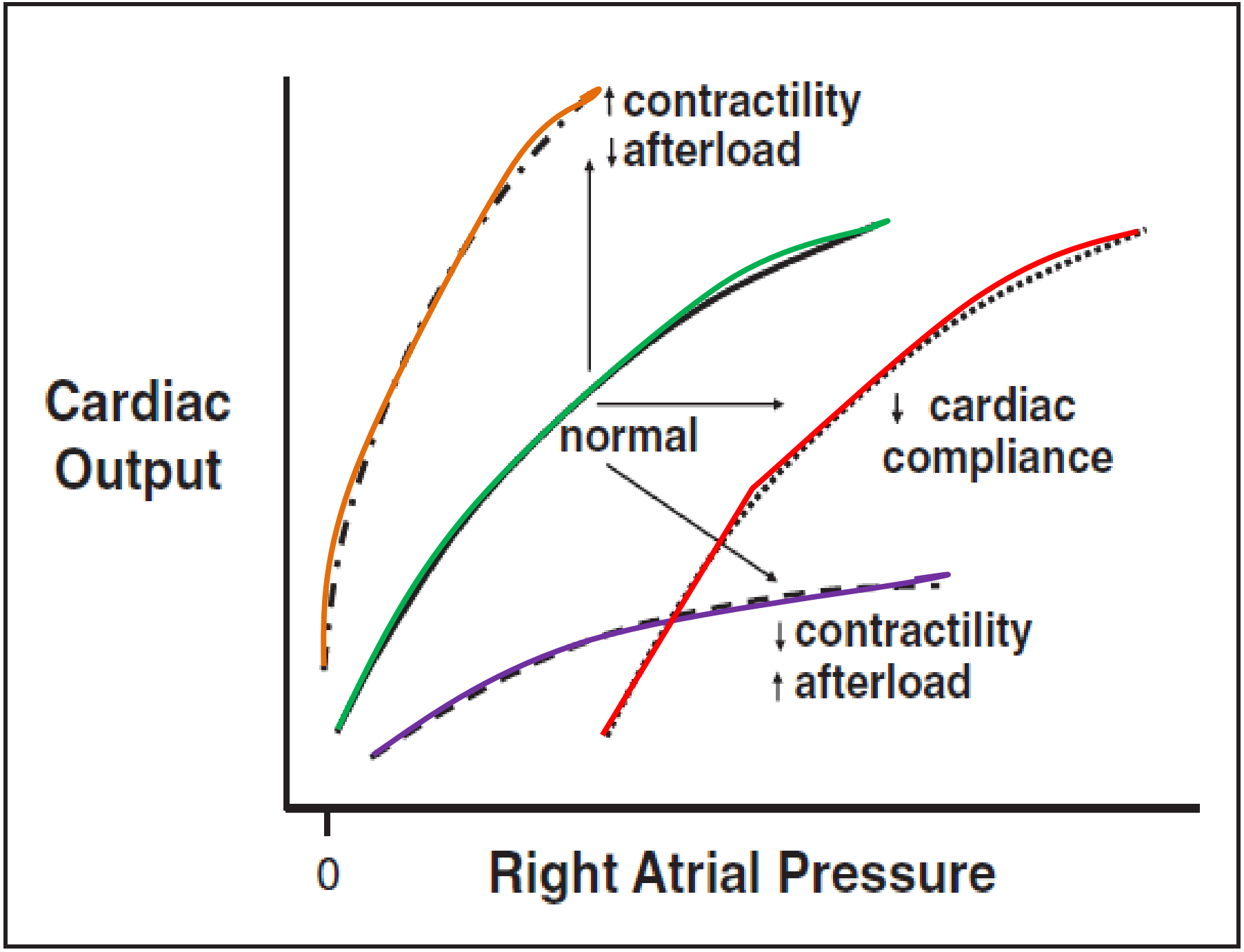
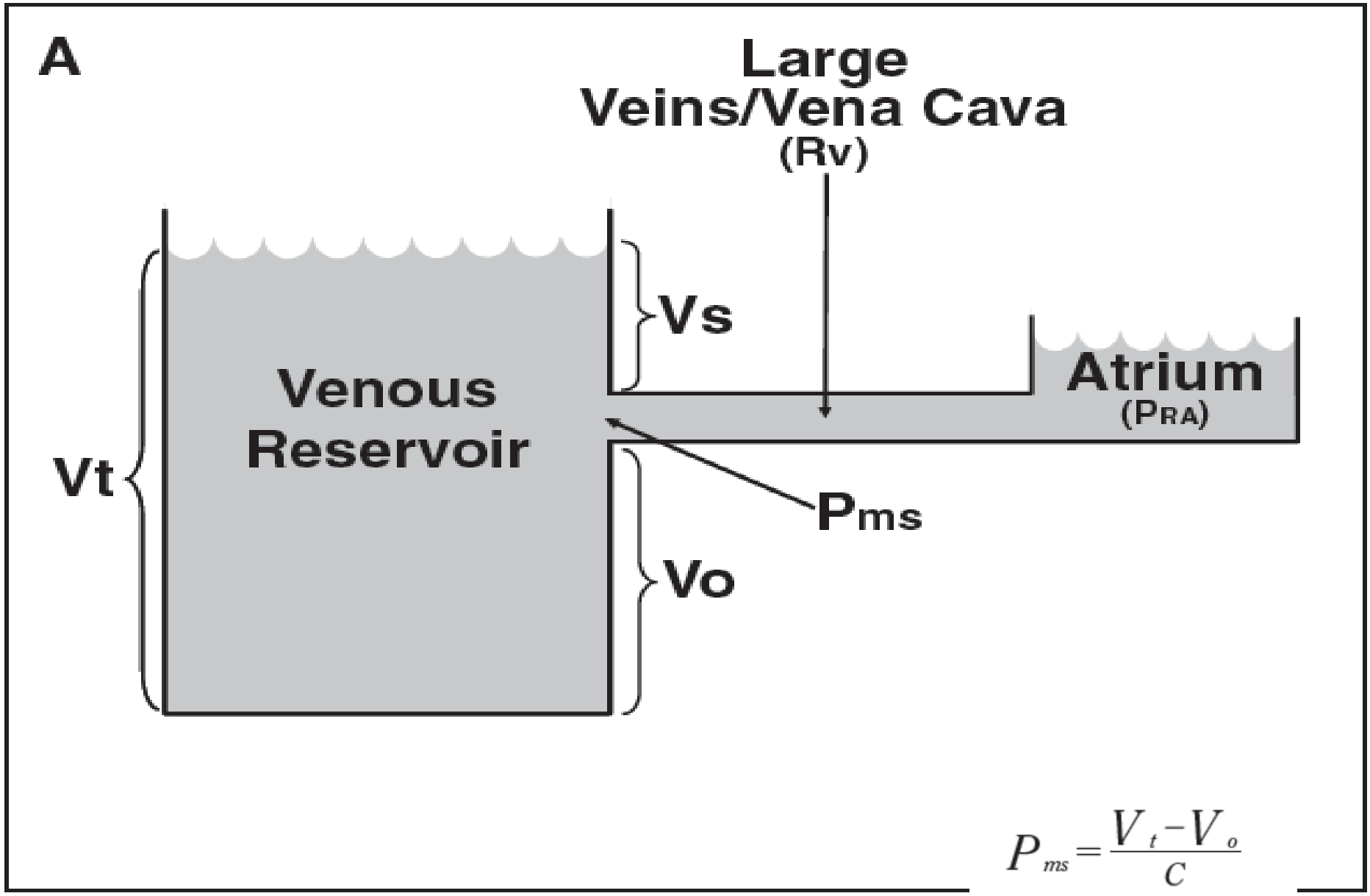


Fig. 1. Franke Starling curves are influenced by ventricular contractility. There is preload reserve when the ventricle is functioning on the steep part of the curve. This indicates preload responsiveness, where pulse pressure variation (PPV), stroke volume variation (SVV) and pulse variability index (PVI) are high, and end-expiratory occlusion (EEO) and passive leg raise (PLR) tests are positive. Volume loading induces a significant increase in stroke volume, and results in a small increase in extravascular lung water (EVLW). When the ventricle is functioning near the flat part of the curve, there is no preload reserve. This indicates preload unrespon- siveness, where PPV, SVV and PVI are low, and EEO and PLR tests are negative. Volume loading has little effect on stroke volume and leads to a large increase in EVLW. (Reproduced with Permission from Ref. [65]) [70].


↑ contractility
↓ afterload
Cardiac Output
normal
↓ cardiac compliance
↓ contractility
↑ afterload
0
Right Atrial Pressure



$$P_{ms} = \frac{V_t - V_o}{C}$$

The Venous Return Concept

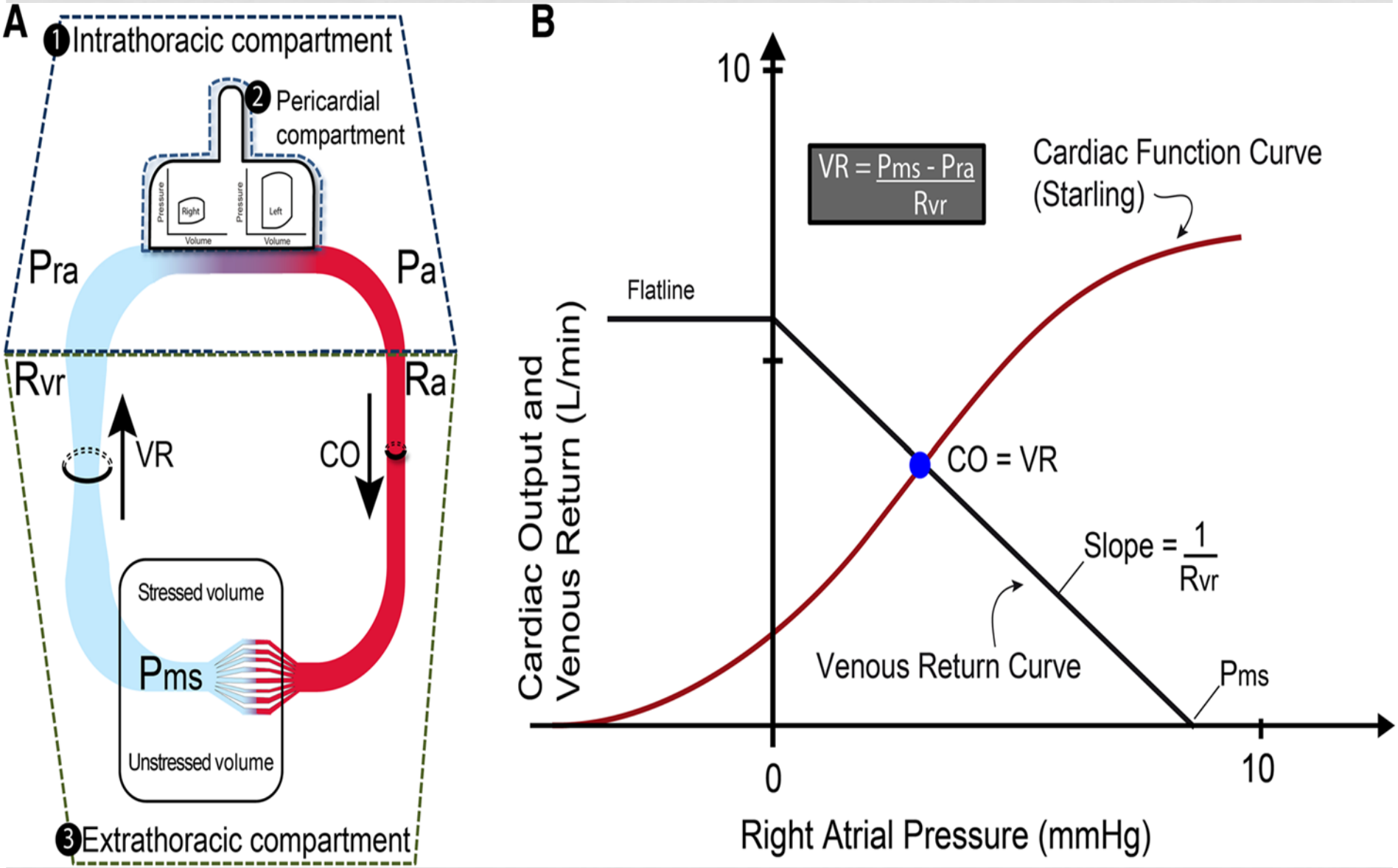
$$VR = \frac{Pms - Pra}{Rvr}$$

TABLE 1. Distribution of Blood in the Various Components of the Circulatory System

Structure	Percentage of Total Blood Volume
Systemic venous system	64
Systemic arterial system	13
Capillaries	7
Pulmonary circuit	9
Heart	7

Reprinted with permission from Milnor W: Cardiovascular Physiology. New York, NY, Oxford University Press, 1990.

Funk et al, 2013



Denault et al Can J Anaesth 2014

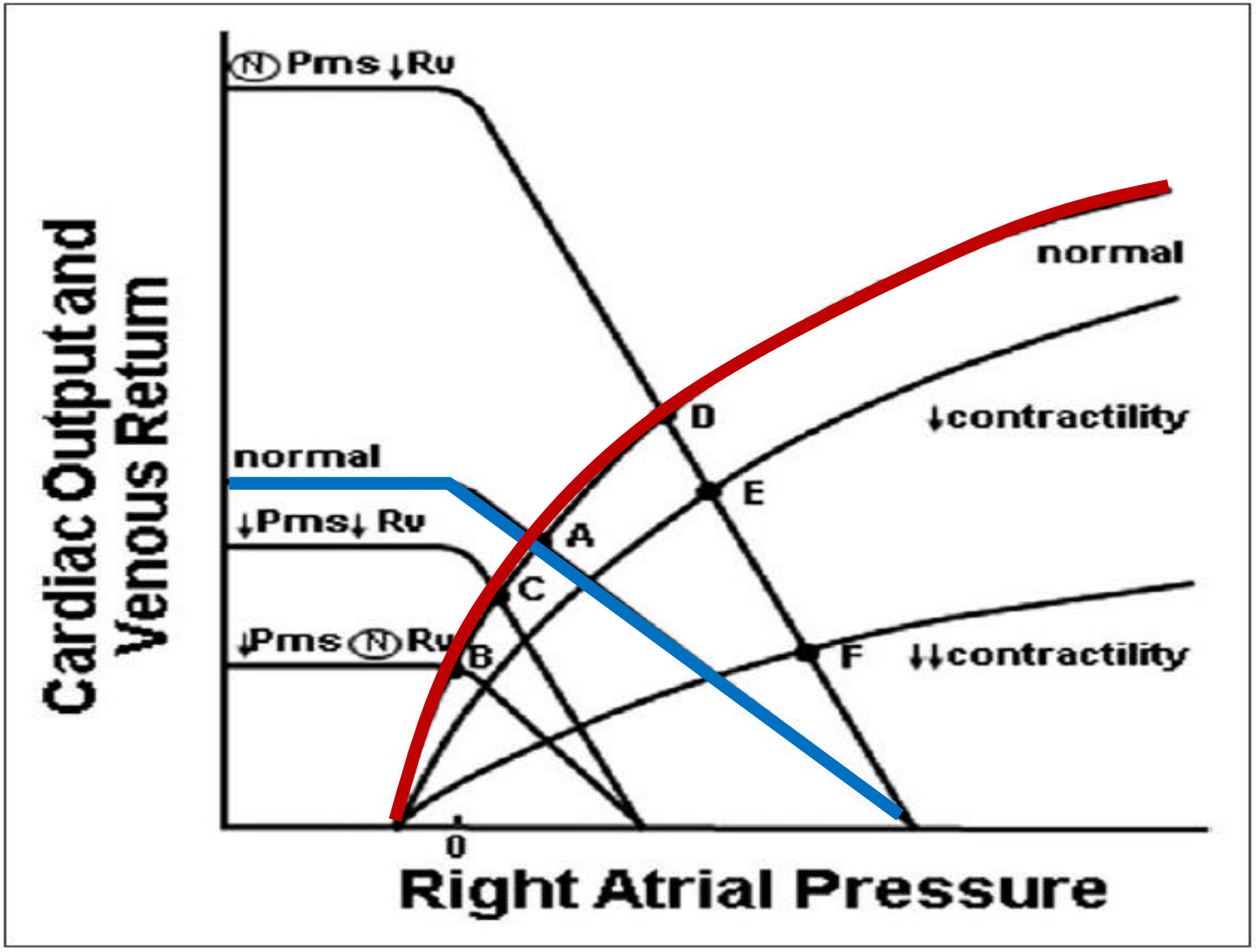
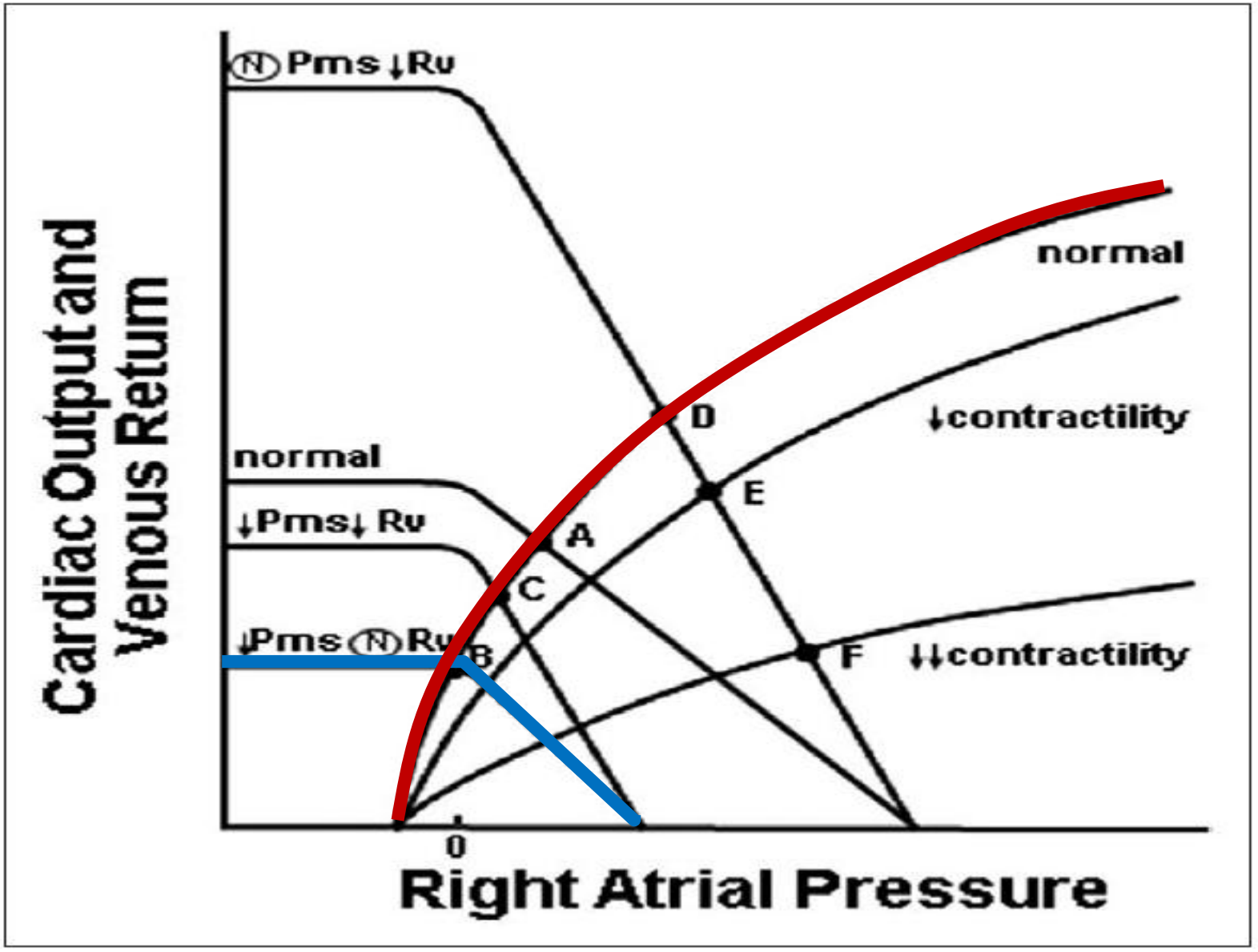


Figure 3. **Septic shock.** Arrows indicate increase or decrease in parameter as appropriate. Circled "N" indicates "normal" (see text for explanation). Pms = mean systemic pressure; Rv = venous resistance.



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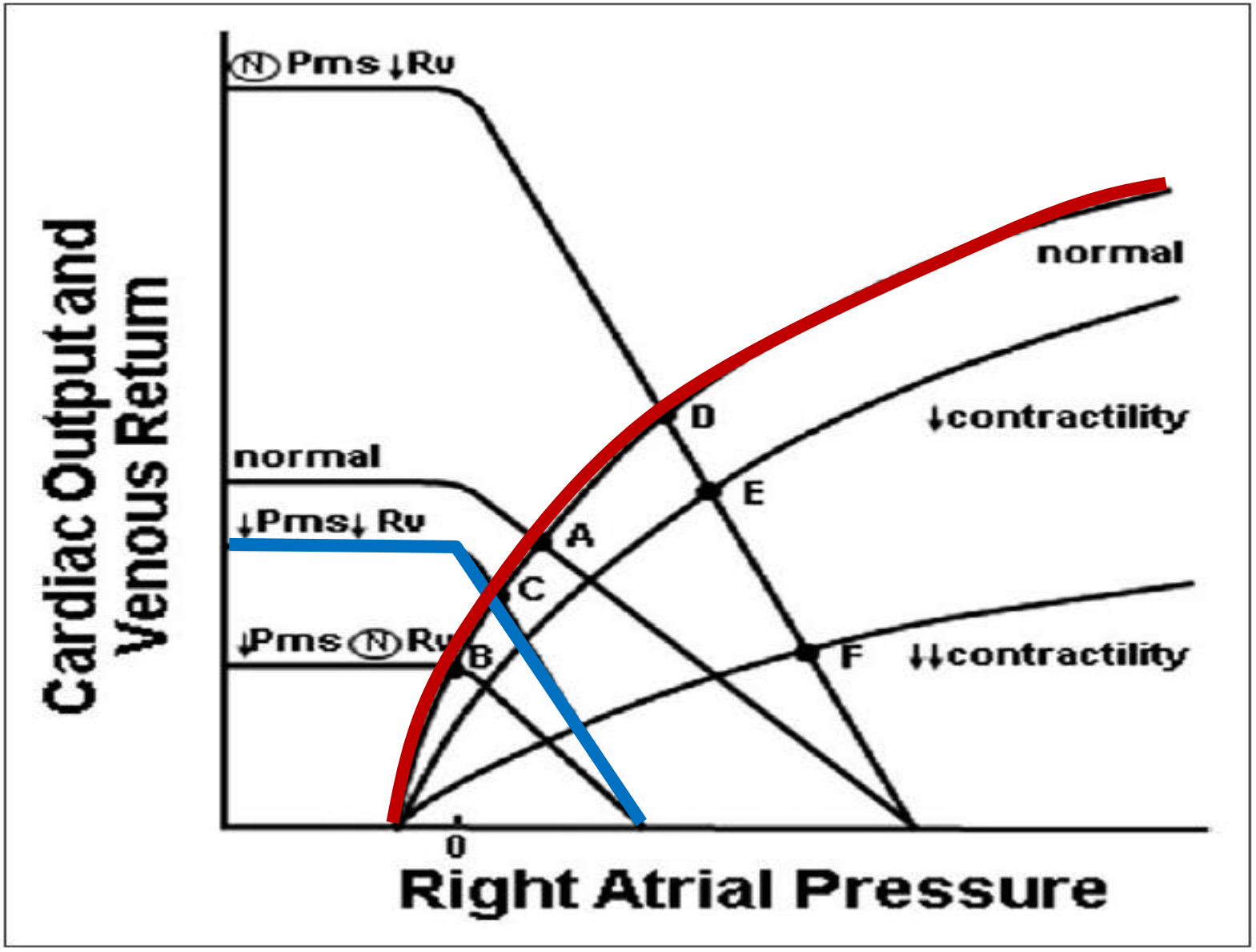

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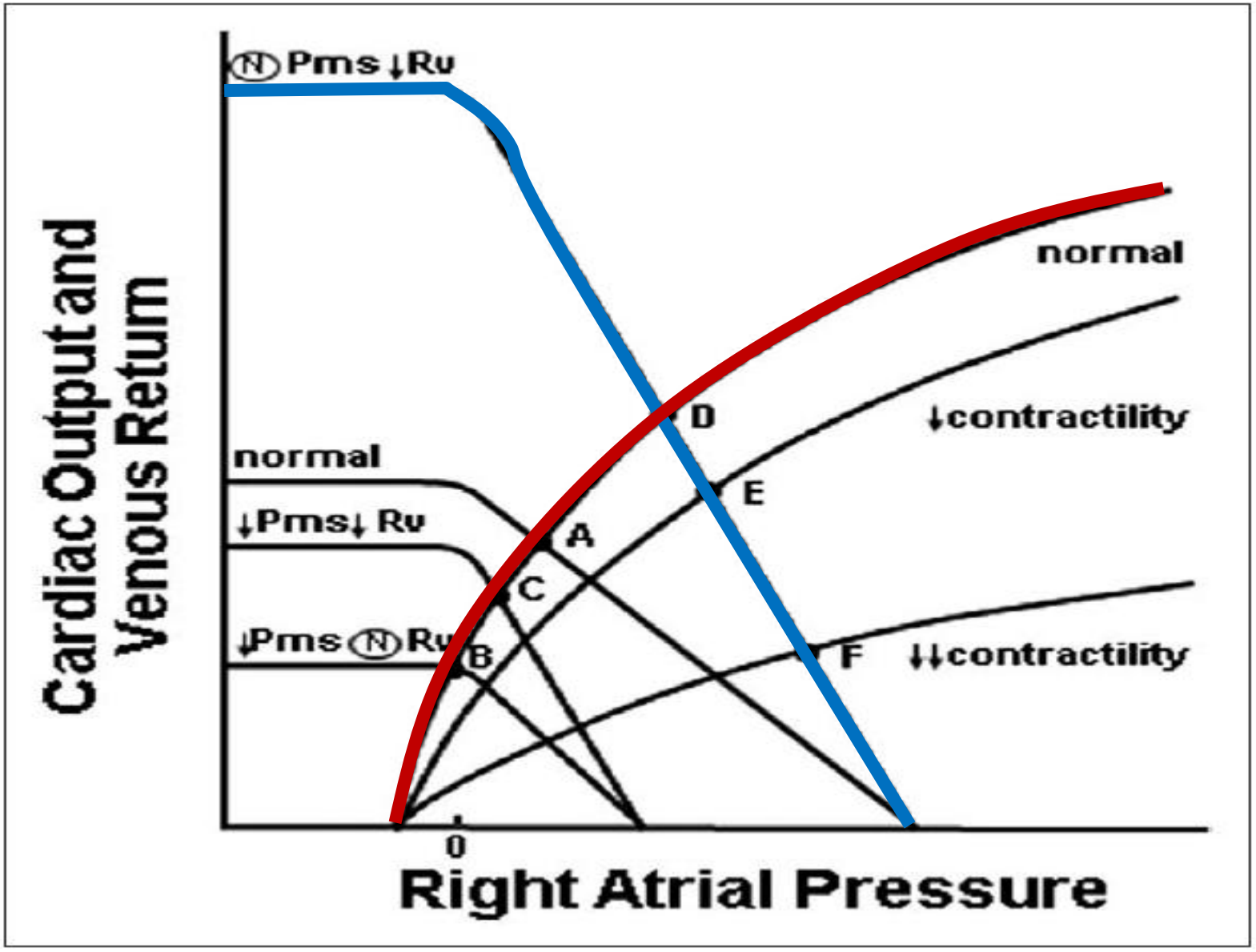

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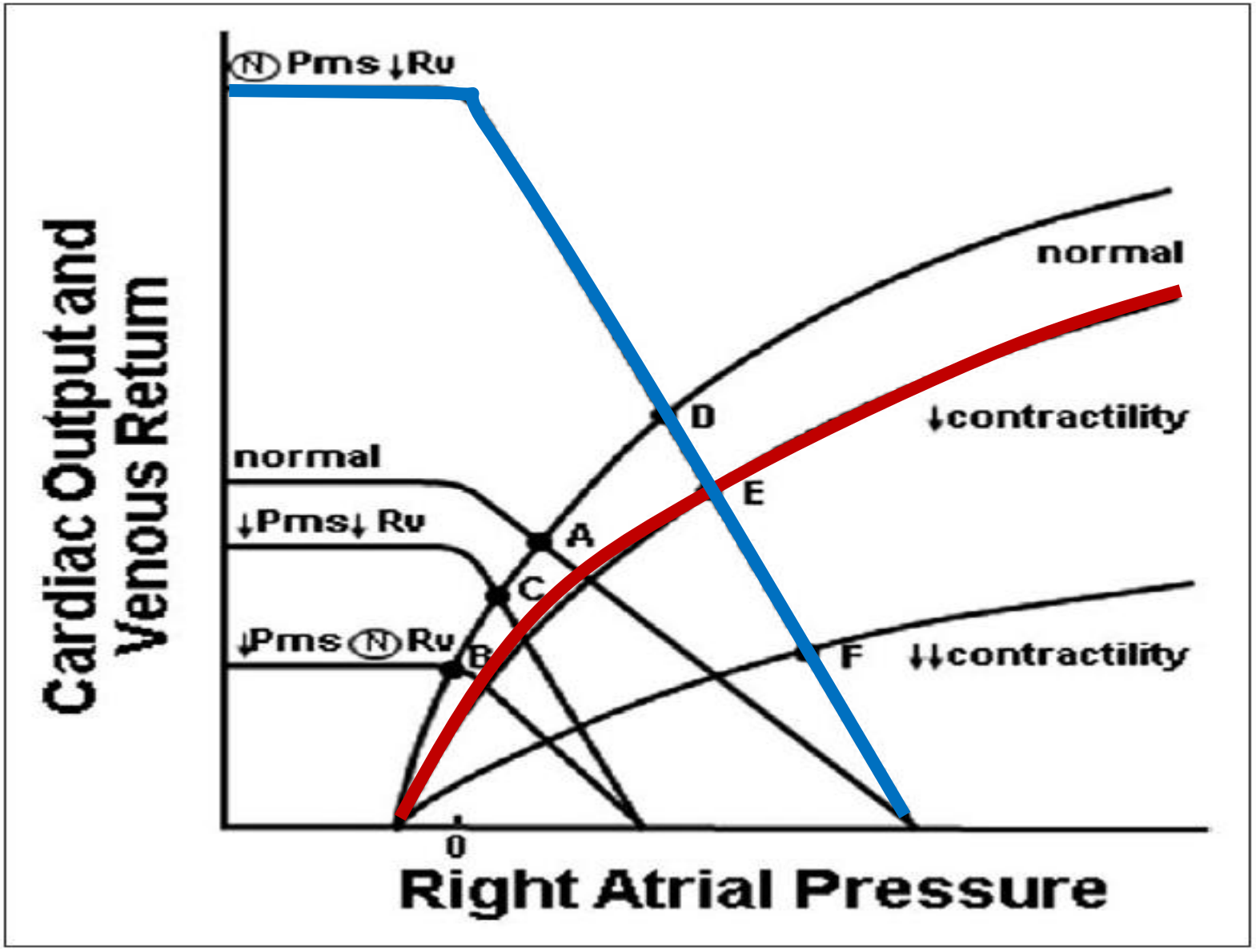

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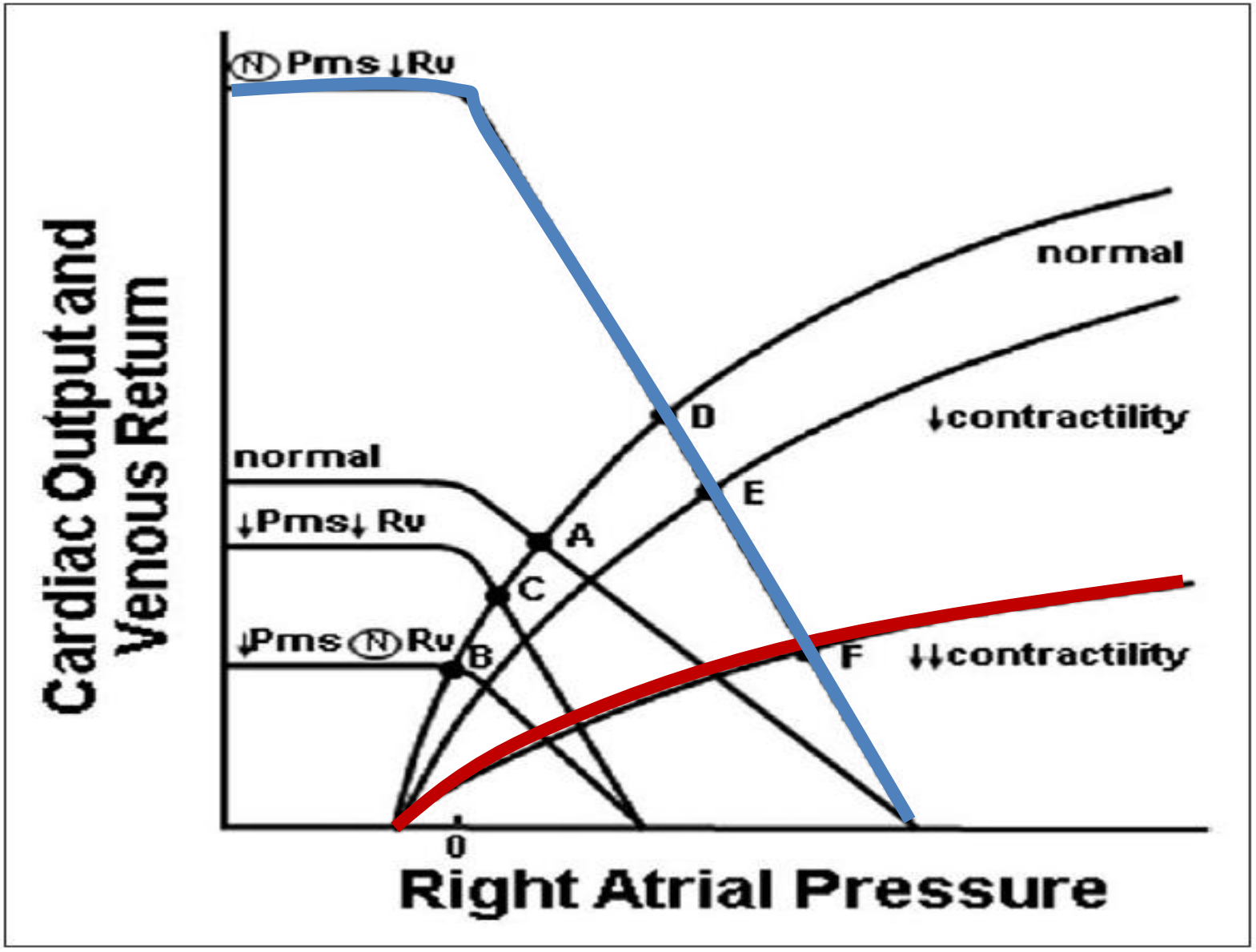

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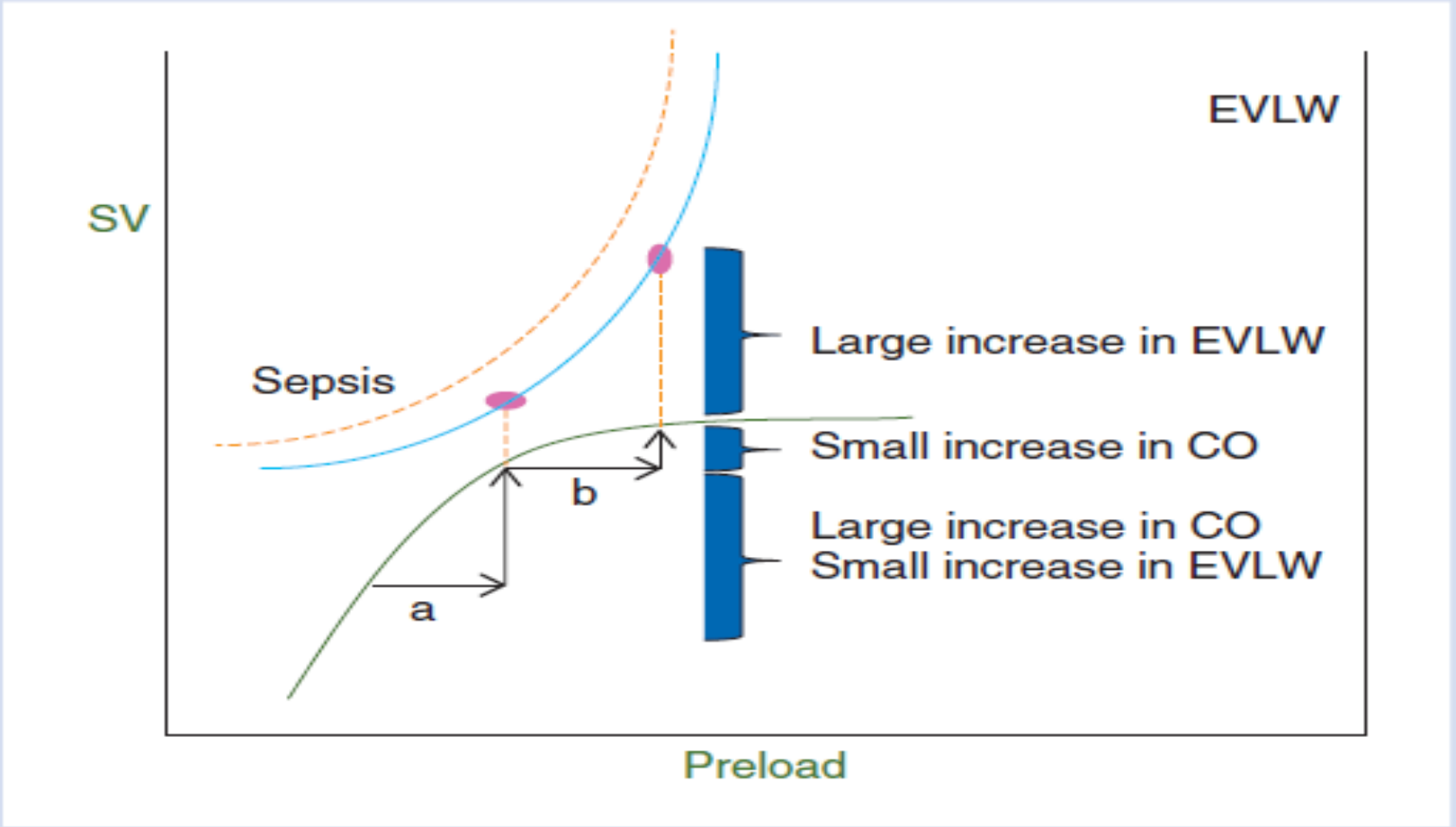


Fig 1 Superimposition of the Frank–Starling and Marik-Phillips curves demonstrating the effects of increasing preload on SV and lung water in a patient who is preload responsive (a) and non-responsive (b). With sepsis, the EVLW curve is shifted to the left. EVLW, extra-vascular lung water; CO, cardiac output; SV, stroke volume.

Martin Westphal…

"Since infusion therapy should be –
goal-directed,
individualised and
procedure specific,
it is time …

stop talking about 'wet' and 'dry'!

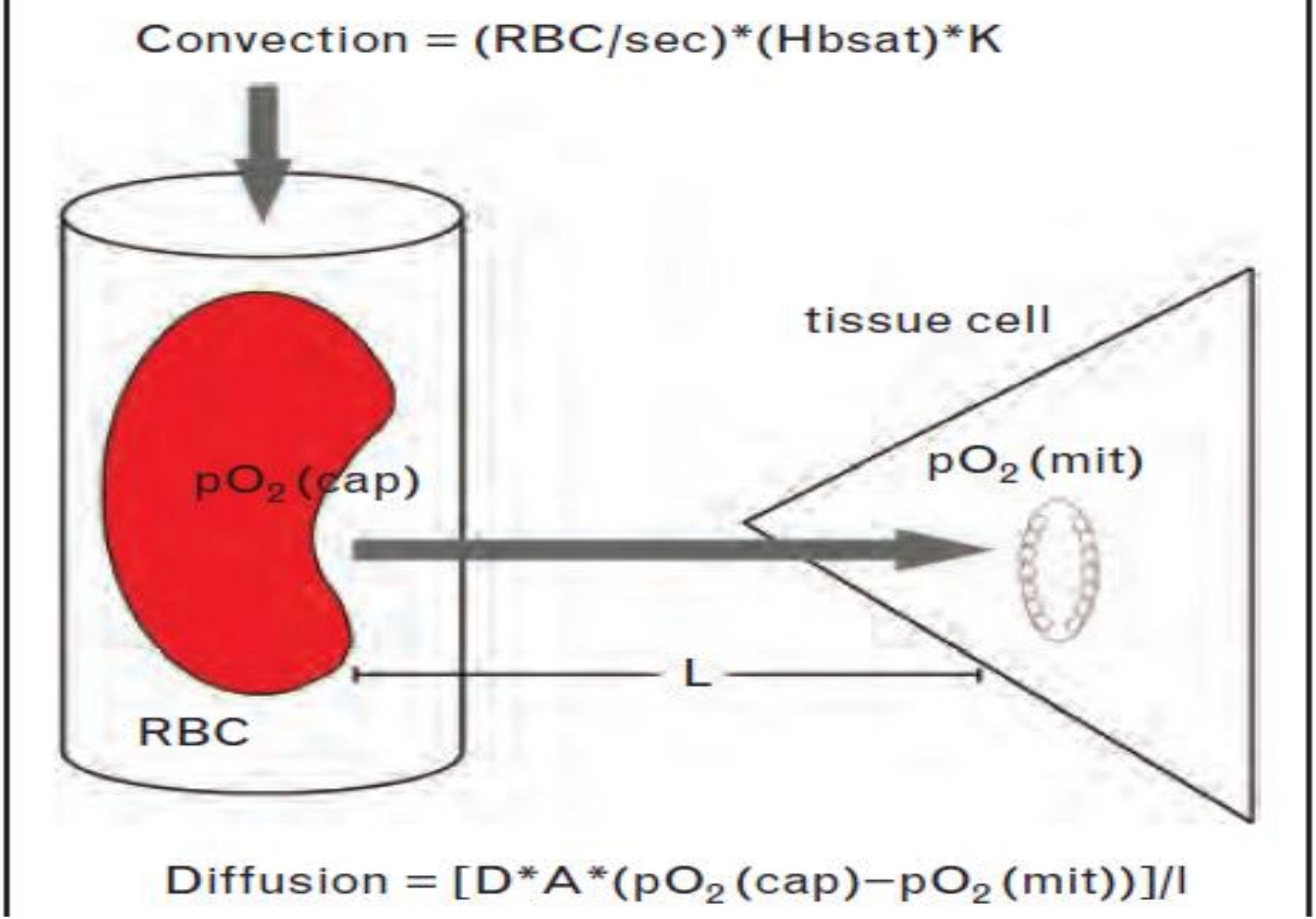


FIGURE 1. The convective and diffusive determinants of oxygen transport from the microcirculation to the tissue cell. The convective flow is defined by the product of the oxygencarrying saturation of the red blood cells and the rate at which red blood cells enter the capillary and the oxygencarrying
capacity of a red blood cell at 100% saturation (0.0362 pl O2/red blood cell). The diffusive movement of oxygen from the red blood cells to the mitochondria is defined by Fick's law of diffusion where the flux of oxygen shown above is the product of the oxygen gradient from RBC to mitochondria and the diffusion distance times the exchange surface divided by the diffusion distance from the RBC to the mitochondria.

C Ince Curr Opin CC 2014 20:301-8

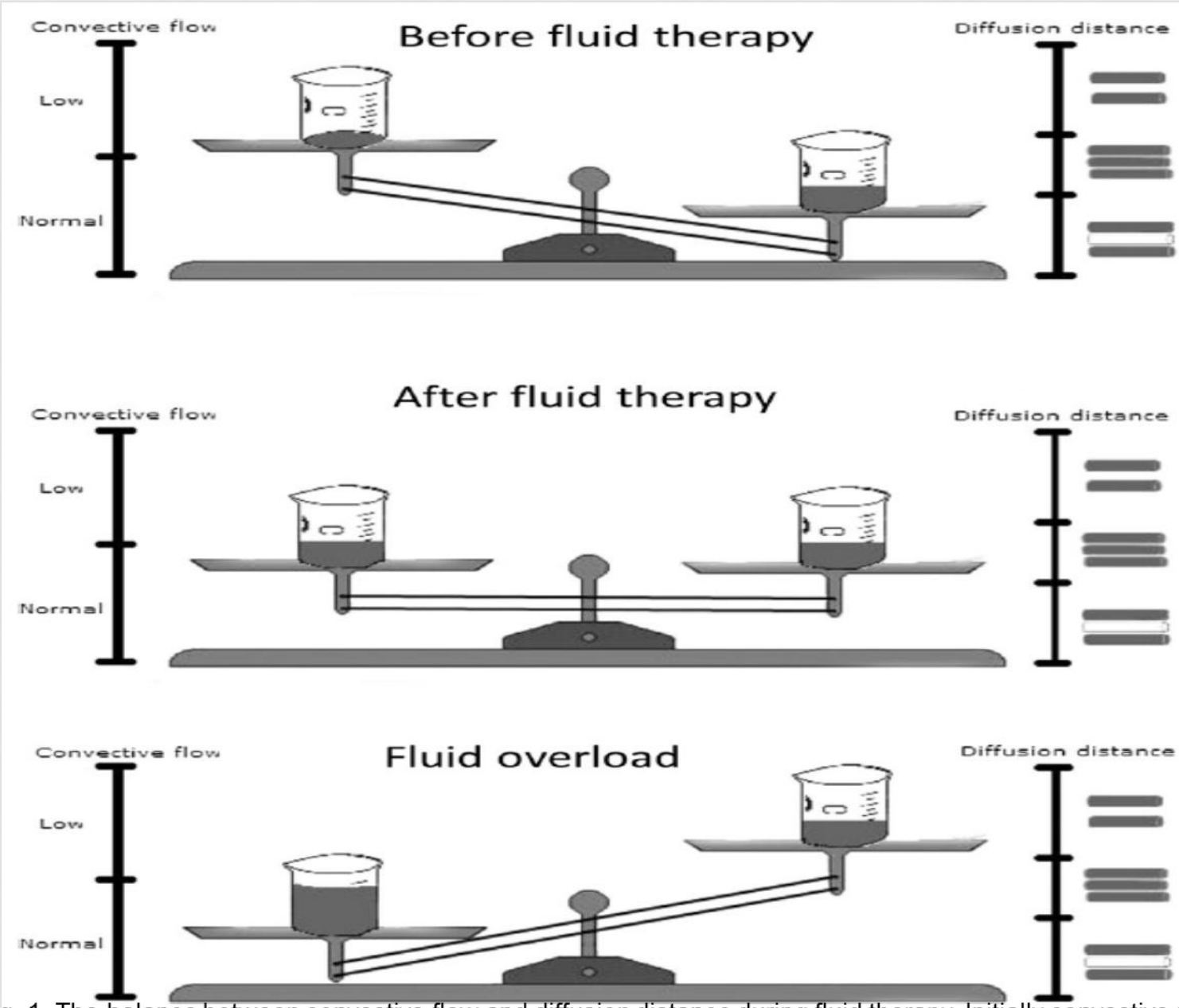
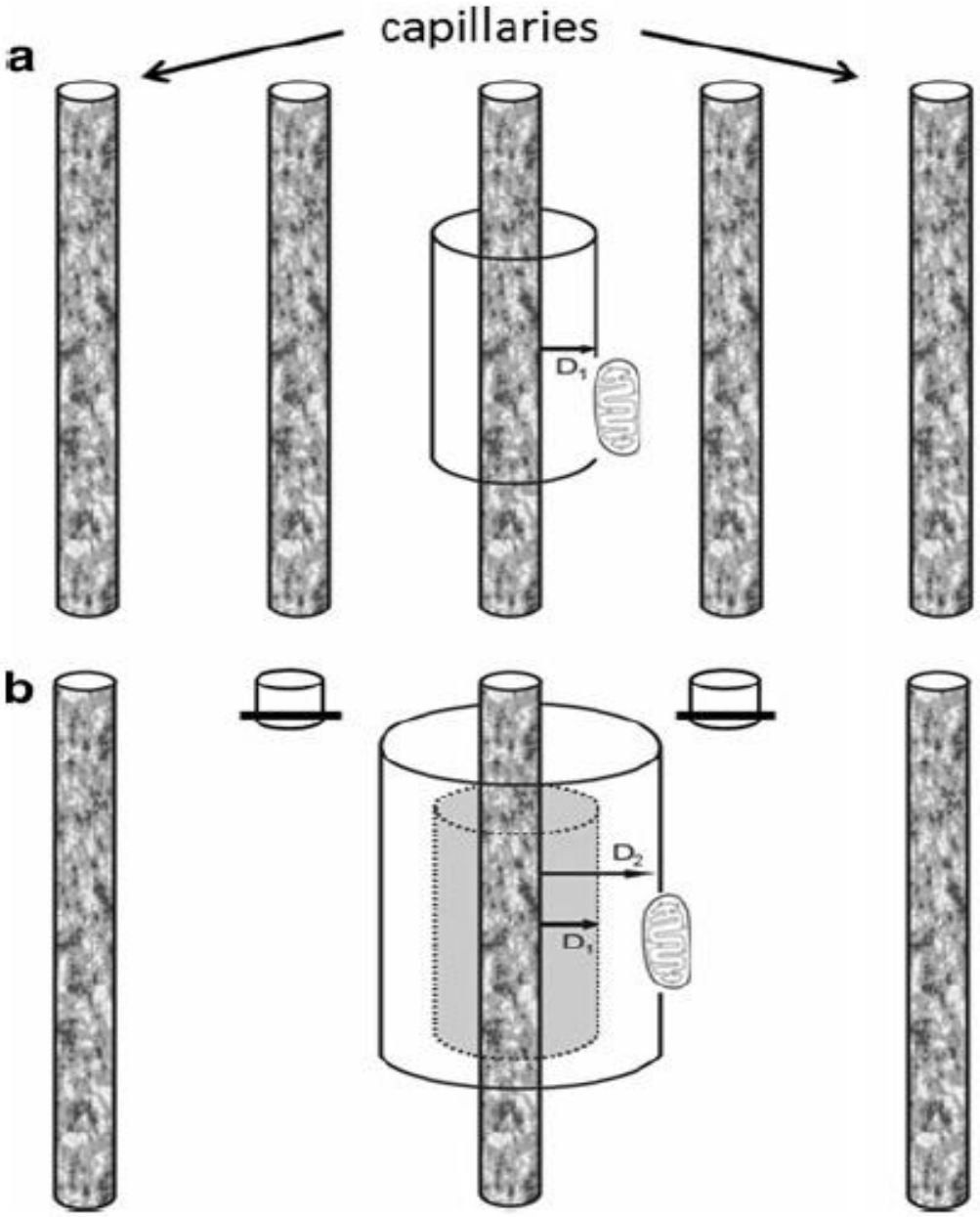


Fig. 1. The balance between convective flow and diffusion distance during fluid therapy. Initially convective flow will normalize after the initiation of fluid therapy and diffusion distance will reduce as a result of reflow of previously non-perfused vessels. However, after restoration of convective flow and diffusion distance further fluid administration will remain convective oxygen transport unaffected but diffusion distance will increase as a result of edema formation.



$$VO_2 = \frac{C \times A\,(cappO_2 - mitpO_2)}{D}$$

VO_2	oxygen volume transported by diffusion
C	diffusion constant
A	capillary surface area
$cappO_2$	capillary pO_2
$mitpO_2$	mitochondrial pO2

Fig. 2 Convective transport of oxygen through the capillaries depends on red blood cell velocity, capillary hematocrit and oxygen saturation.
Oxygen transport from the capillary to the cell via diffusion is inversely related to the diffusion distance (D1 and D2) according to Fick's law

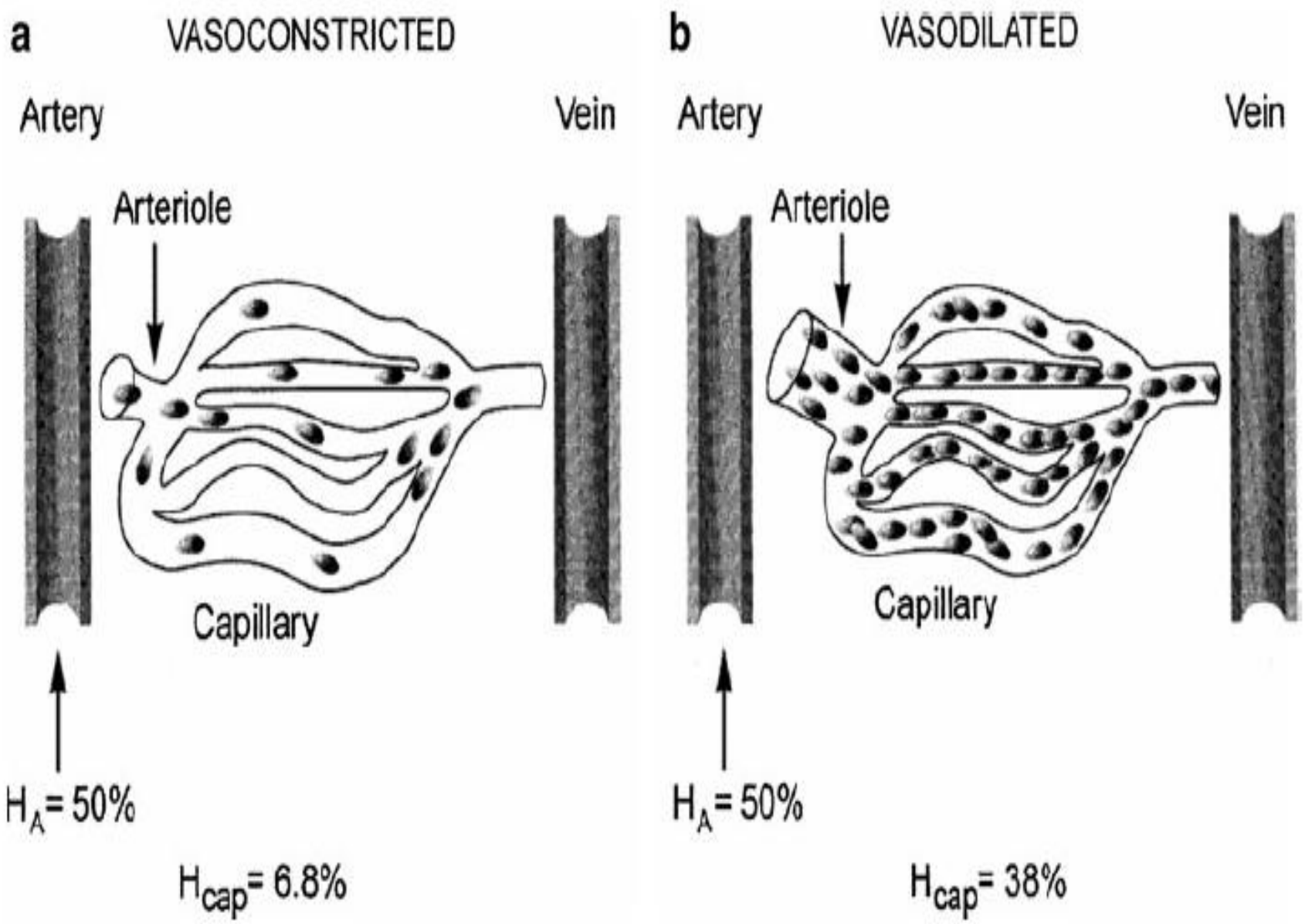


Fig. 3 Under experimental conditions with a systemic hematocrit (HA) of 50%, capillary hematocrit (Hcap) ranges from 6.8% under vasoconstriction to 38% under vasodilation.

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Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D.,

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doi: 10.1111/j.1399-6576.2012.02750.x

Viscoelastic and aggregometric point-of-care testing in patients with septic shock – cross-links between inflammation and haemostasis

T. Brenner[1], K. Schmidt[1], M. Delang[1], A. Mehrabi[2], T. Bruckner[3], C. Lichtenstern[4], E. Martin[1], M. A. Weigand[4] and S. Hofer[1]

[1]*Department of Anaesthesiology, University of Heidelberg, Heidelberg, Germany,* [2]*Department of General and Transplant Surgery, University of Heidelberg, Heidelberg, Germany,* [3]*Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany and* [4]*Department of Anaesthesiology and Intensive Care Medicine, University of Gießen, Gießen, Germany*

DIC HISTORICALLY……..

- **Early literature**……
  - consumptive coagulopathy
- **Later**……..
  - defribination syndrome
- **Recent past**……
  - disseminated intravascular coagulation
- **Future**……..
  - thrombo-haemorrhagic consumptive disorder

THCD ?

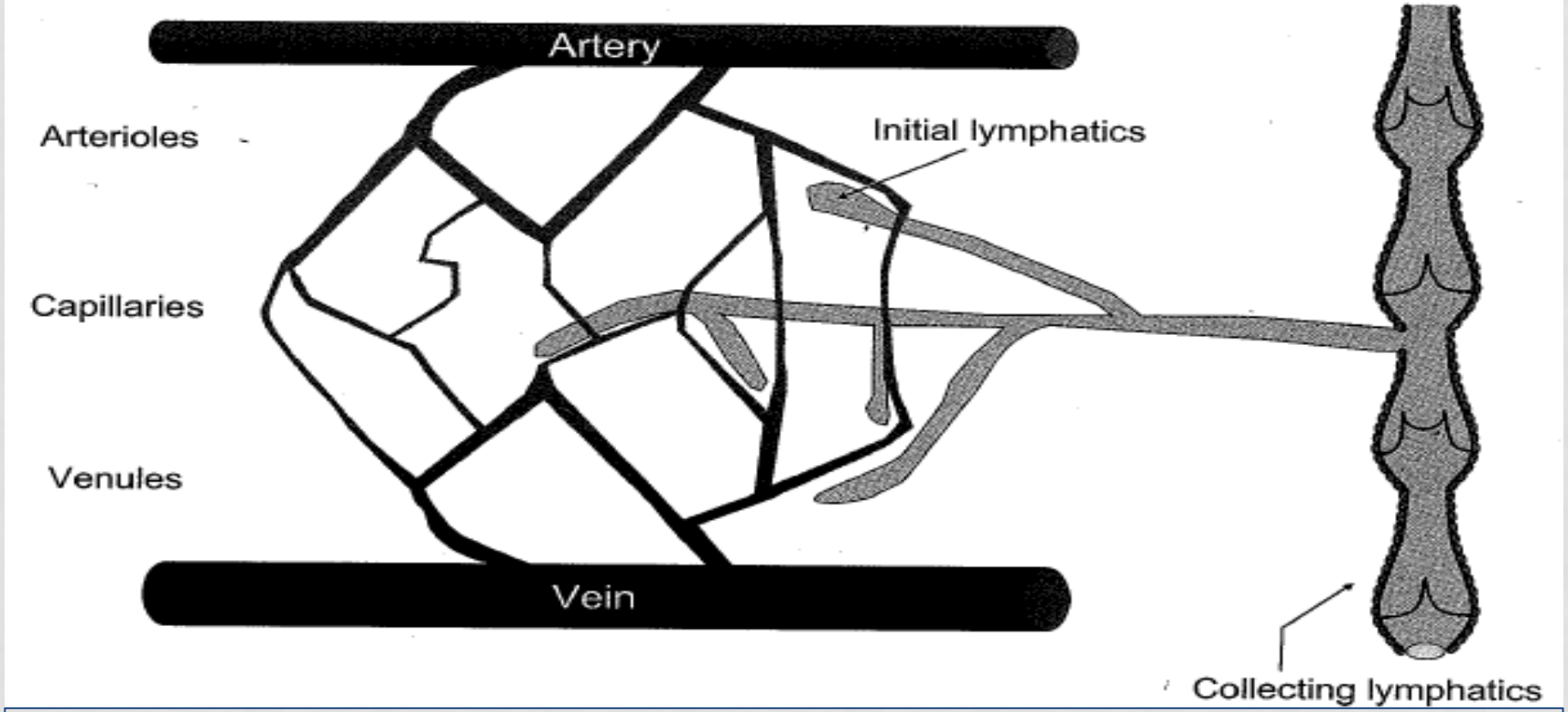
TREATMENT

- Source control
- Replacement of platelets and coagulation factors (pts for surgery or with bleeding)
- Non specific for the rest
- Low or Mini-dose Heparin
  - Can at least partly, but specifically control the thromboplastic onslaught. Evidence for:
    - bolus of 25U/kg
    - Followed by infusion of 5 -10U/kg/hr
  - …..***IF…..***titrated by the Trombelastographic Transfer Test

***IN THE PAST:* too large doses of Heparin caused anxiety related to bleeding!!!**

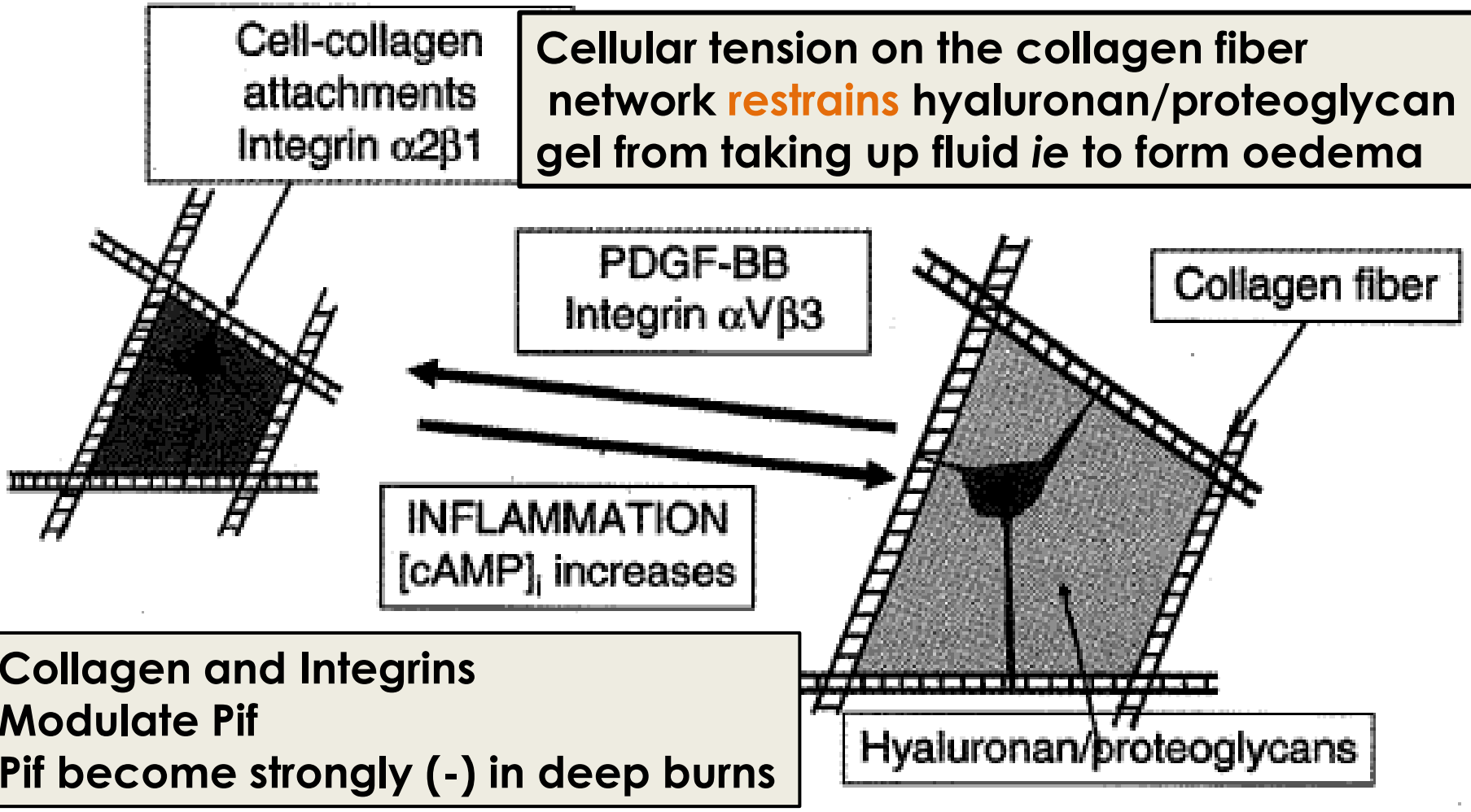
BLOOD VESSELS & LYMPHATICS

Lymphatics – The hidden circulation
They are permeable – and PARTICIPATE in microvascular exchange.
Permeability is increased by disease, leading to oedema (ANP)



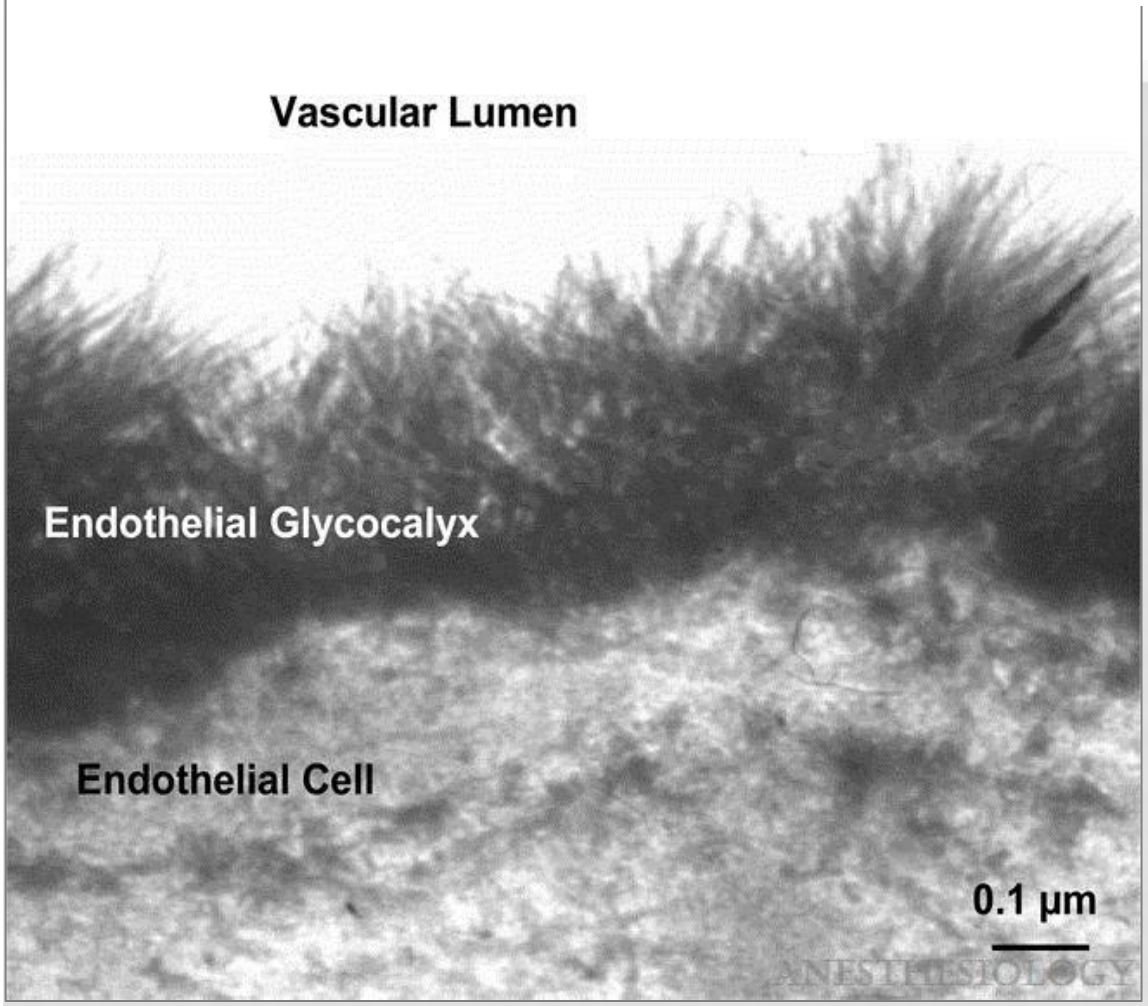
Sepsis : Lymphatic insufficiency = < pumping
< contraction frequency
Effect: contribute to maintain oedema, rather than reducing ECF

A tissue has an inherent ability to "autoregulate" its volume and thereby counteract oedema formation.



Collagen and Integrins
Modulate Pif
Pif become strongly (-) in deep burns

The Endothelial Glycocalyx : Gateway to the Interstitial space



Double barrier concept of vascular permeability

Endothelial permeability barrier
Prevent - leukocyte adhesion
- platelet aggregation
NO production
Modulate capillary RBC filling
Repulse red blood cells

A Rational Approach to Perioperative Fluid Management

Chappell, Daniel; Jacob, Matthias; Hofmann-Kiefer, Klaus; Conzen, Peter; Rehm, Markus

Anesthesiology. 109(4):723-740, October 2008.

doi: 10.1097/ALN.0b013e3181863117

Another myth.....

3RD SPACE OR ONLY INTERSTITIAL OEDEMA?

fECF

- Anatomical
- Physiologic phenomenon
- Intact vascular barrier
- Lymphatic system
- Can overwhelm lymphatics
- Redistribution & urinary output

nfECF

- Nonanatomical
- Post tissue trauma
- Fluid consuming
- Spaces where there is normally no fluid
- Trapped – increase at expense of fECF
- Total body water unchanged

It does not exist !

Do Not Rx Deficits Which Do Not Exist !

Another myth...

CRYSTALLOID VS COLLOID: TIME TO END AN ERRONEOUS DISCUSSION

Infusion solutions are generally not considered for what they are: drugs with indications, contraindications and side effects.

Crystalloids – replacement of fluid losses:
1. Insensible perspiration
2. Urinary losses

Colloids – replace plasma deficits:
1. Acute blood loss
2. Protein fluid shifts to the interstitial space

Use the right kind of fluid in appropriate amounts at the right time!

It is erroneous to compare 2 classes of drugs with different indications regarding their impact on patient outcome.

D Chappell

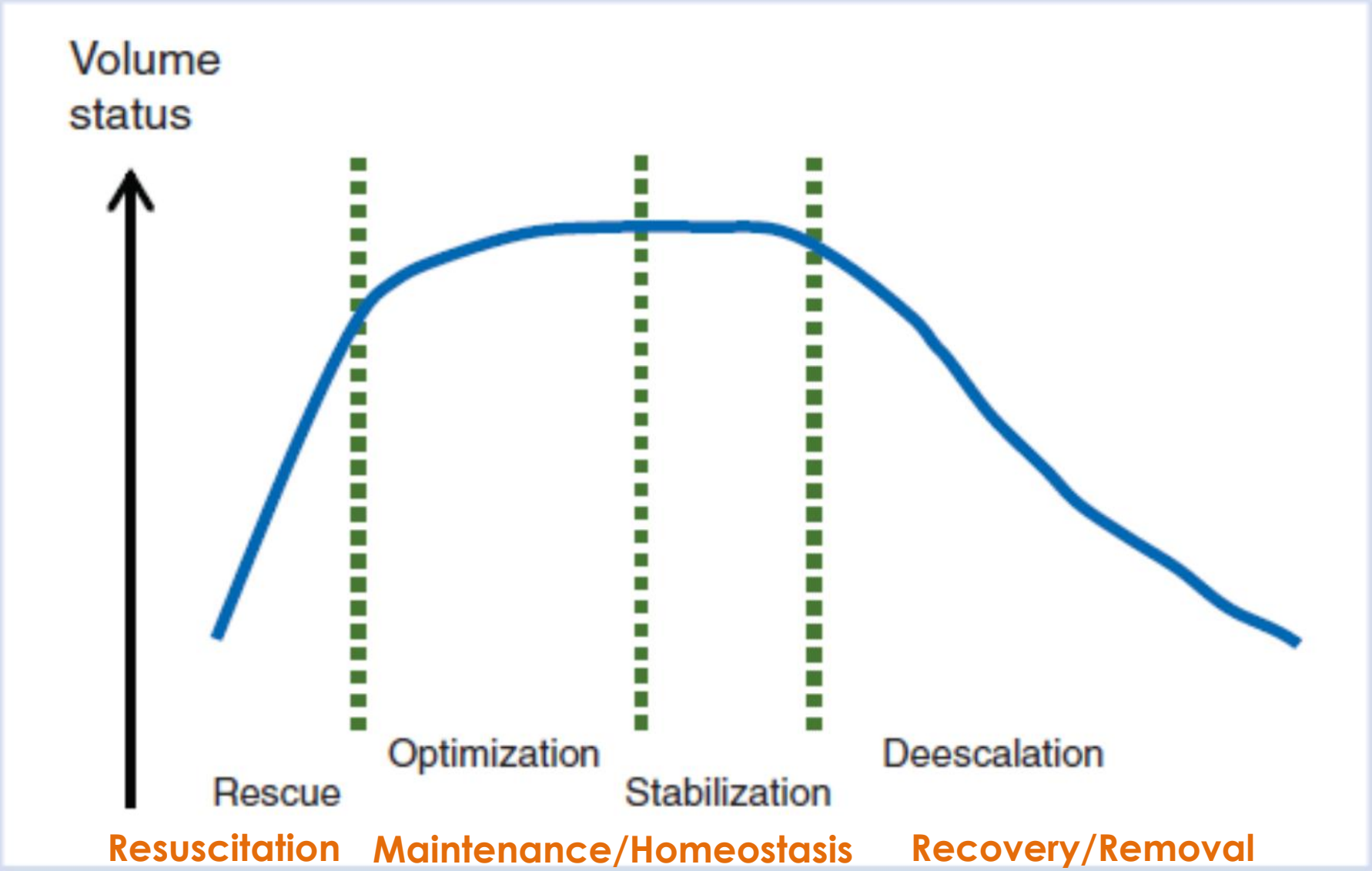


Fig 2 Patients' volume status at different stages of resuscitation. Reproduced with permission from ADQI (www.ADQI.org).

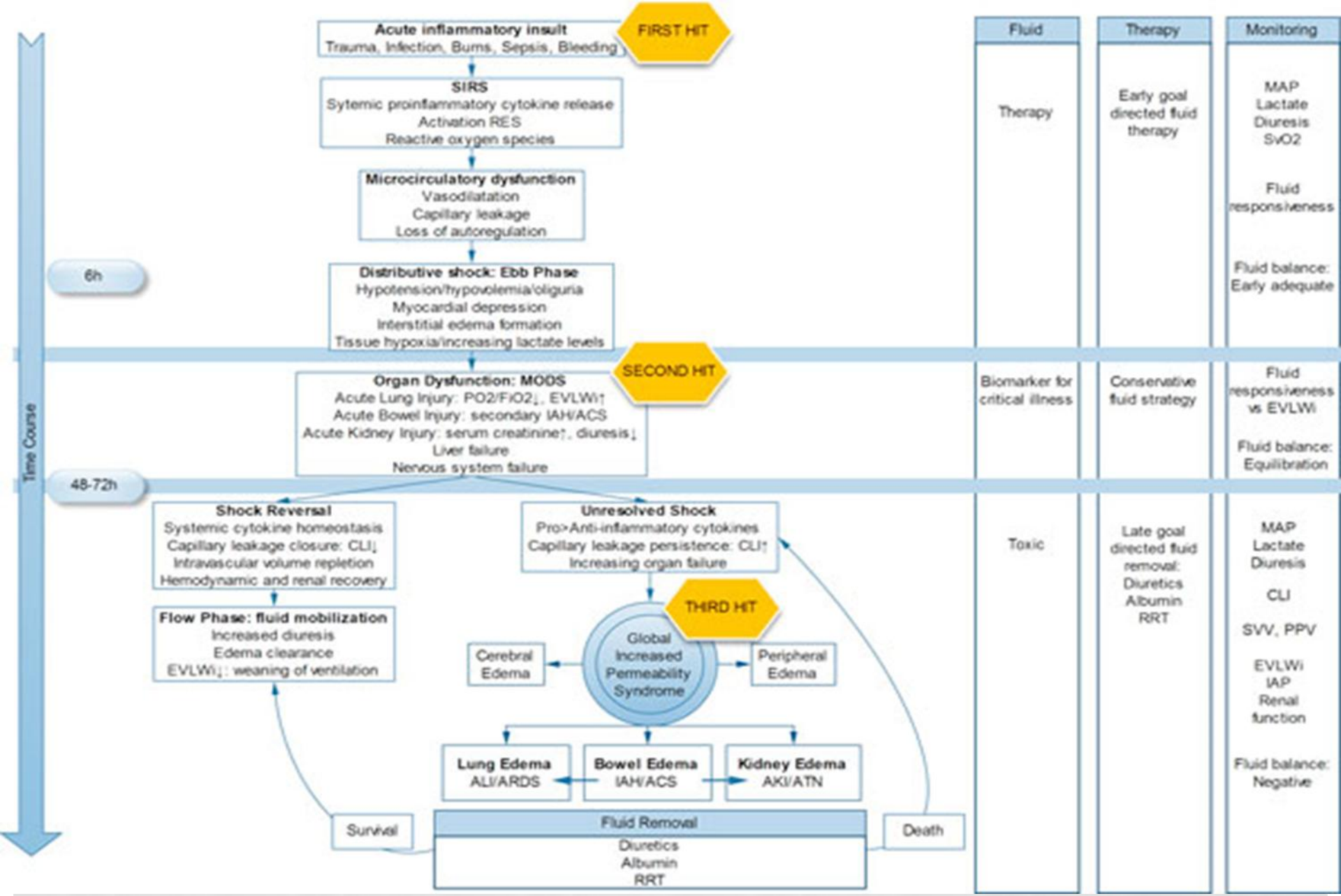


Figure 5.

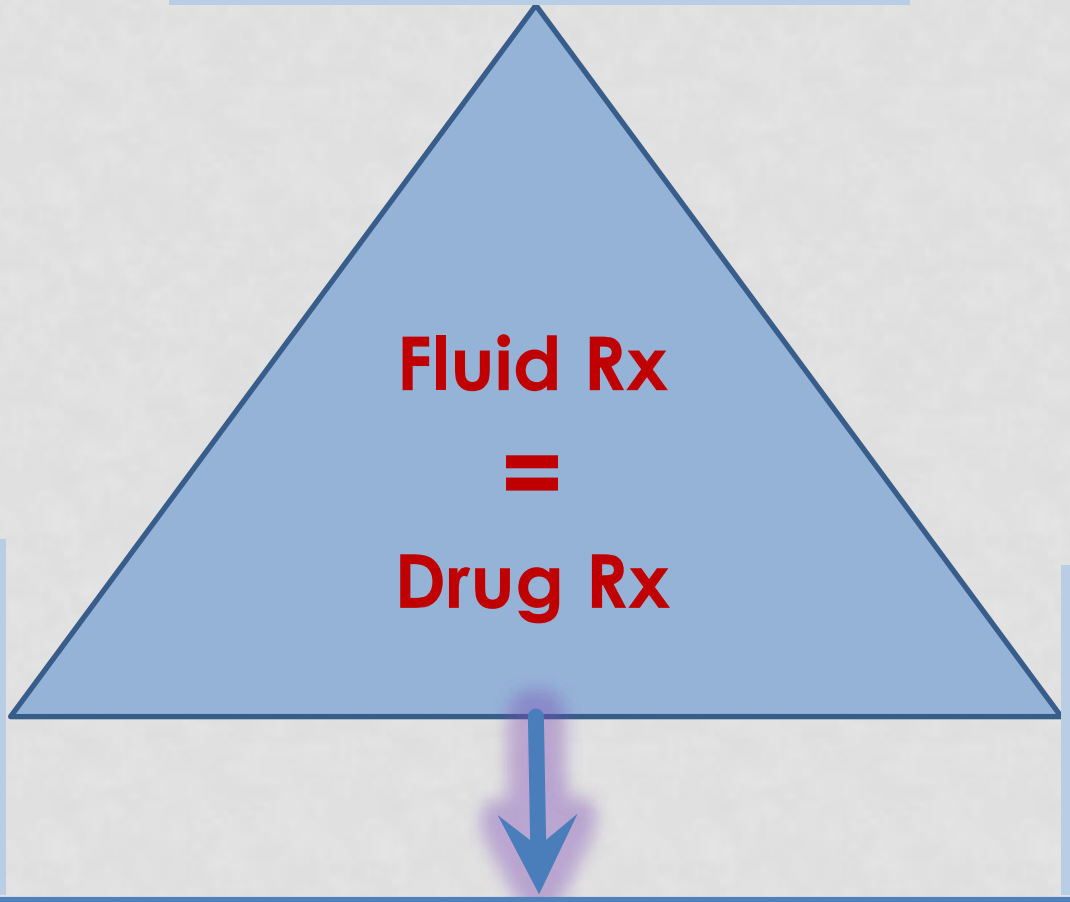
Proposed time course in shock, introducing a three-hit model and global increased permeability syndrome.

Cordemans *et al. Annals of Intensive Care* 2012 **2**(Suppl 1):S1 doi:10.1186/2110-5820-2-S1-S1

- "F&E Rx ….something benign…just something that goes on…now very clear that it is a very, very important issue.
- …evidence that type of fluid used affects outcome…
- Fluids need to be given in a much more considered scientific approach
- …2nd most common intervention after oxygen…evidence quite limited…
- …NaCl used most commonly…no evidence for its use…
- …ubiquitous intervention…choice depends on where you live…random fashion…junior staff…middle of the night…a convenience???!!!
- Need paradigm shift to regard fluids like we do drugs …toxicity ???"

PERI-OPERATIVE FLUID MANAGEMENT - 2014

Indications for IV Fluid Rx



Fluid
Properties,
Contra-indications,
Complications

Dose
Volume
Duration
Toxicity

The basis of physiological support of surgical patients

GDT = Individualized Haemodynamic Rx to ensure adequate tissue perfusion and cellular oxygenation.

CALCULATION OF BASAL DAILY FLUID REQUIREMENTS

- Conservative formula
- Based on BW

Adult patient of 80kg		>50yr	<50yr
1st 10kg body mass	- 100ml/kg/d=	1000ml	=1000ml
2nd 10kg body mass	- 50ml/kg/d=	500ml	= 500ml
Above 20kg: > 50yr	- 15ml/kg/d=	900ml	
< 50yr	- 20ml/kg/d		=1200ml
		= 2400ml	=2700ml

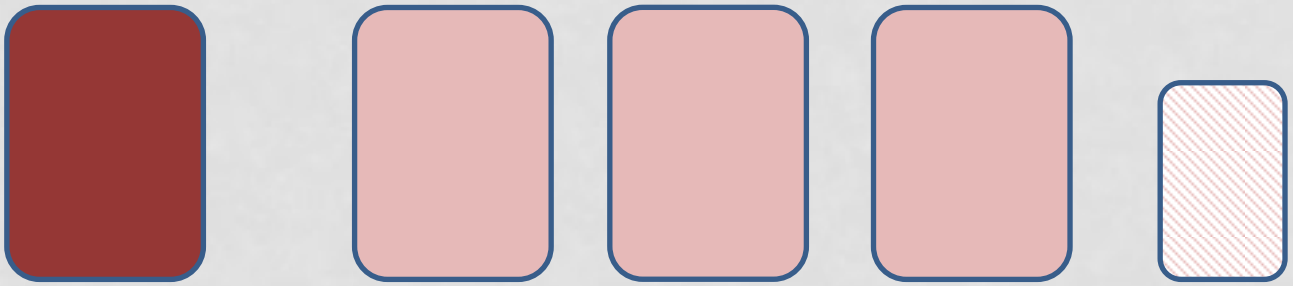
TFM = staying within this limit with ALL fluids: Maintenance/Nutrition + Medications!

INDICATIONS FOR FLUID AND ELECTROLYTE THERAPY IN SURGICAL PATIENTS

JP Pretorius Unpublished data

TOTAL FLUID MANAGEMENT: TFM	*MAINTENANCE*	*RESUSCITATION*	*REPLACEMENT*
1. Indication:	Daily requirements	Hypovolaemia	Abnormal or continuing losses.
2. Intention:	According to a *formula* based on body mass	"Aggressively" according to *endpoints*	Collect drainage for 4 hours, *replace a %* during next 4 hours, while collecting again.....
3. Infusion rate:	Continuously per 24 hours = 24 equal doses	Bolus	Continuously according to losses.
4. Type of fluid:	*Maintenance:* Maintelyte 5%, Electrolyte No2 10% Sustenance 5%	*Volume expander:* Ringers Lactate (Modified), Plasmalyte B, Saline, Colloids	*According to fluid lost:* Rehydration solution, 5% Dextrose in water, 0,45% NaCl, 0,9% NaCl, Ringers Lactate
5. Monitor	Serum and urine electrolytes & osmol. Fluid balance chart.	Central haemodynamics, Stroke Volume Variation, Urine flow, SvO_2, Lactate, pH, BE	Serum and urine electrolytes & osmol

VOLUME COMPARISON



Past:

1000ml Colloids = **3000ml Crystalloids** = **250ml Hypertonic Saline**

Present: **1000ml** **1500ml**

Why?

- Goal-directed individualized optimization.
- More physiological endpoints for resuscitation.
- More appropriate and physiological monitoring.

Grocott, Chappell, Kehlet, Myburgh

RATIO OF COLLOIDS : CRYSTALLOIDS 1:3 OR 1:1.4 ?

- "The **transience of this colloid effect** may explain why only short-term volume challenge studies (2, 5) showed a requirement of **three- to four-fold more** volume of crystalloid than colloid fluid…. whereas we found a volume ratio of only **1.4 to 1 and 1.1 to 1 for 6% HES and 4% gelatin, respectively**, which is similar to findings in other studies with longer observation periods (12, 13)"
- Experimental design????

Bayer et al CCM 2012 (40):9, 2543

WHAT MATTERS WHEN CHOOSING A RESUSCITATION FLUID?

- The type of disease – ***understand*** the pathophysiology
- The time/stage of the disease when fluid therapy is started
- The duration of use
- The type of colloid or crystalloid used
- The severity of illness = The urgency to complete the resuscitation or to reach haemodynamic stability.

Best practice: * **Achieve "source" control** (sepsis/bleeding)
* **Resuscitate promptly**
* **Understand pathophysiology and adapt**

THINK….DELIBERATE….REASON….INDIVIDUALIZE

BALANCED vs UNBALANCED CRYSTALLOIDS

1. From an evolutionary and physiological perspective there is little doubt that serum chloride concentrations much above 100 are normal
2. The question remains, do they have significant impact?
3. Animal studies indicate harm under septic conditions but it is less clear that there is a problem in non-septic animals (42 – 44).
4. Three large observational studies indicate greater morbidity and even mortality in one study, but this only indicates an association and not causality.
5. Unfortunately, the randomized trials are far too insufficient to make any statement of causality, even with a meta-analysis.
6. A further fundamental question arises as to whether it is the total burden of C1 that is important or is it the concentration in the serum and interstitial space that counts.
7. This has important implications for therapy

Albumin: Therapeutic Role in the Current Era

•A. Farrugia,

The pendulum has now swung to the virtual exclusion of these compounds because of their adverse effects, and a renewed interest in albumin.

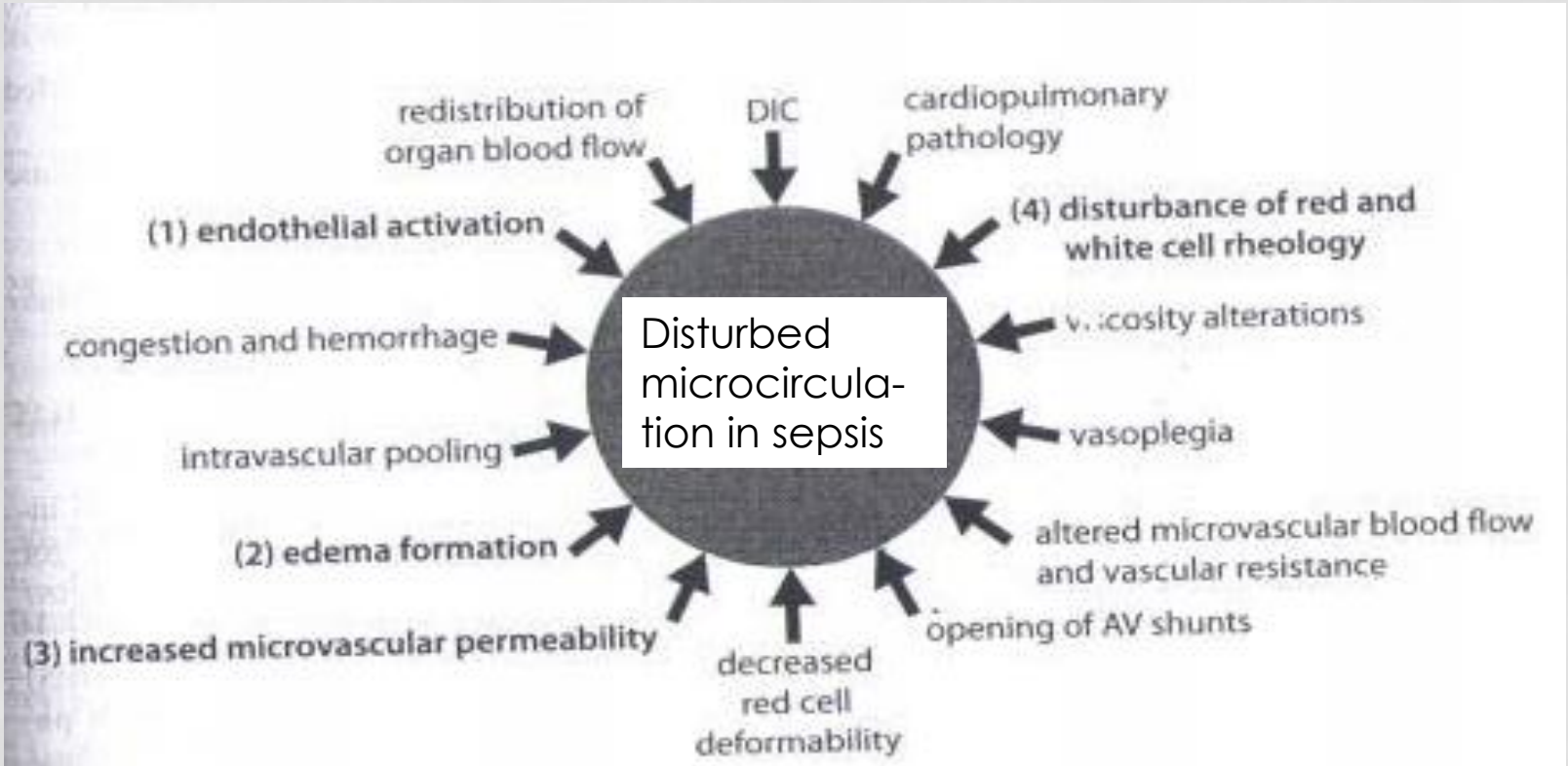


Fig. 8 Microcirculatory pathology in sepsis showing areas (1–4) of possible moderation by albumin. DIC: disseminated intravascular coagulation. From [41]

HETASTARCH - RECOMMENDATIONS FOR HEALTH PROFESSIONALS

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to ICU.
- Avoid use in patients with pre-existing renal dysfunction
- Discontinue use of HES at the first sign of renal injury
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy

So you can still use HES provided you don't use it in ICU patients, septic patients or cardiac surgery, and provided you monitor renal function for 90 days each time you use it.

Key messages

- The safety of HES has been questioned in recent trials, although full adherence to 'presumably correct indication', defined by short time interval from shock to randomisation, restricted use for initial volume resuscitation, use of any consistent algorithm for haemodynamic stabilisation, reproducible indicators of hypovolaemia, maximum dose of HES, and exclusion of patients with pre-existing renal failure or RRT, could not be found in any of these trials.
- The question, whether or not HES may be harmful when it is limited to immediate haemodynamic stabilisation, cannot be answered yet. We suggest an algorithm for clinical management emphasising the strict indication of HES.
- Further, we suggest a safety checklist for future prospective randomised controlled trials that might be important in the field of acute volume resuscitation in critically ill patients.
- The PRAC recommendation is viewed with concern, since it extrapolates not only from long-term use in septic patients to acute haemodynamic stabilisation in this cohort of patients but also to all licensed and not licensed (off-label) use of HES.

EFFECT OF HYPERCHLORAEMIC ACIDOSIS

Lactate and HCl induce different patterns of inflammatory response in LPS stimulated cells.

- Hyperchloraemic metabolic acidosis
- Renal impairment
- HCl is pro-inflammatory as evidenced by increased:
  - NO production
  - IL-6 to IL-10 ratio
  - and NF-ḰB DNA binding
- Lactic acid is anti-inflammatory in that NO, IL-6 and IL-10 were reduced

Physiological means of predicting response to fluid administration

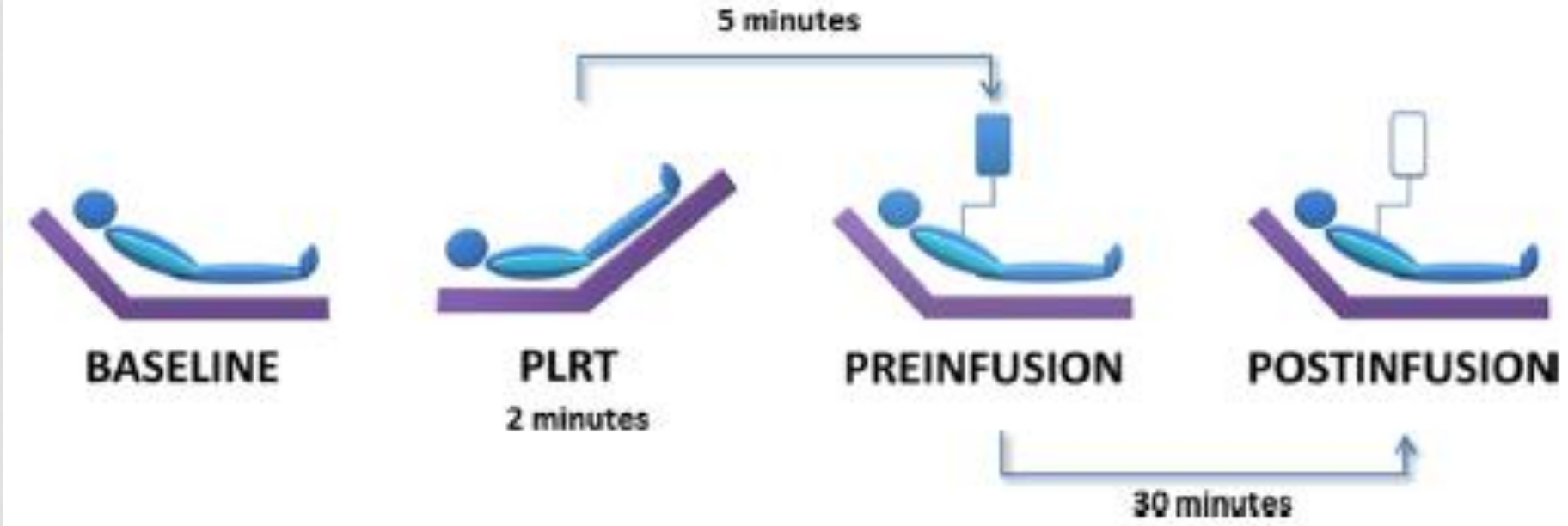
(To ID hypovolaemia & optimise IV fluid volume)

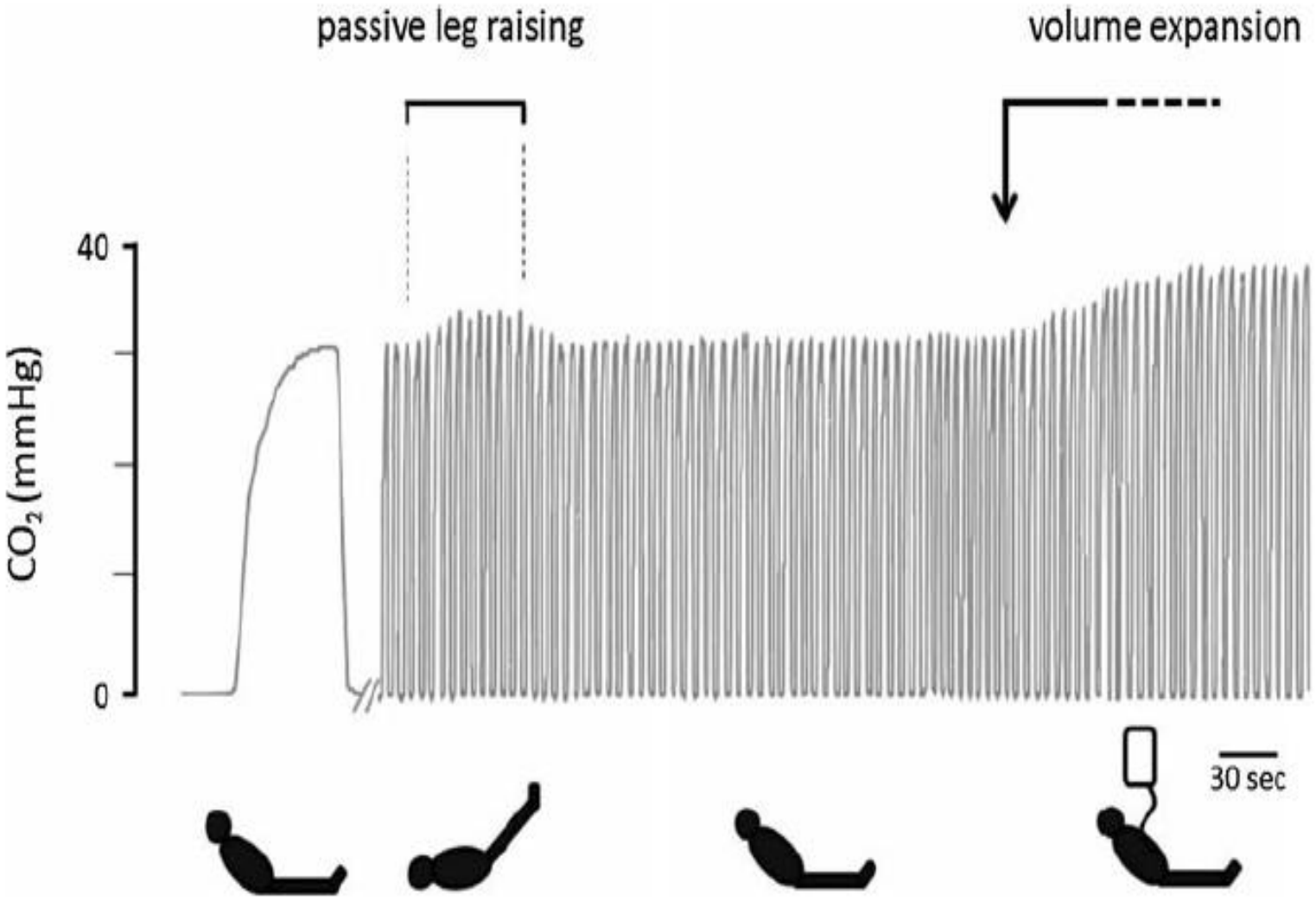
Passive leg raising

(reversible auto-transfusion from capacitance vessels)

for 4 minutes identifies patients with hypovolemia

1. Change in radial artery pulse pressure correlate with changes in stroke volume during PLR. ($r = 0.77$; $p<0.001$)
2. Change in stroke volume correlate with fluid loading (300ml over 24hrs) ($r = 0.89$; $p<001$)
3. Change in radial artery pulse pressure with PLR correlate with change in stroke volume induced by fluid ($r = 0.84$; $p<0.001$)
4. PET CO2….Cardiac Output


5 minutes
BASELINE
PLRT
2 minutes
PREINFUSION
POSTINFUSION
30 minutes


passive leg raising
volume expansion
40
0
CO_2 (mmHg)
30 sec

Physiological means of predicting response to fluid administration

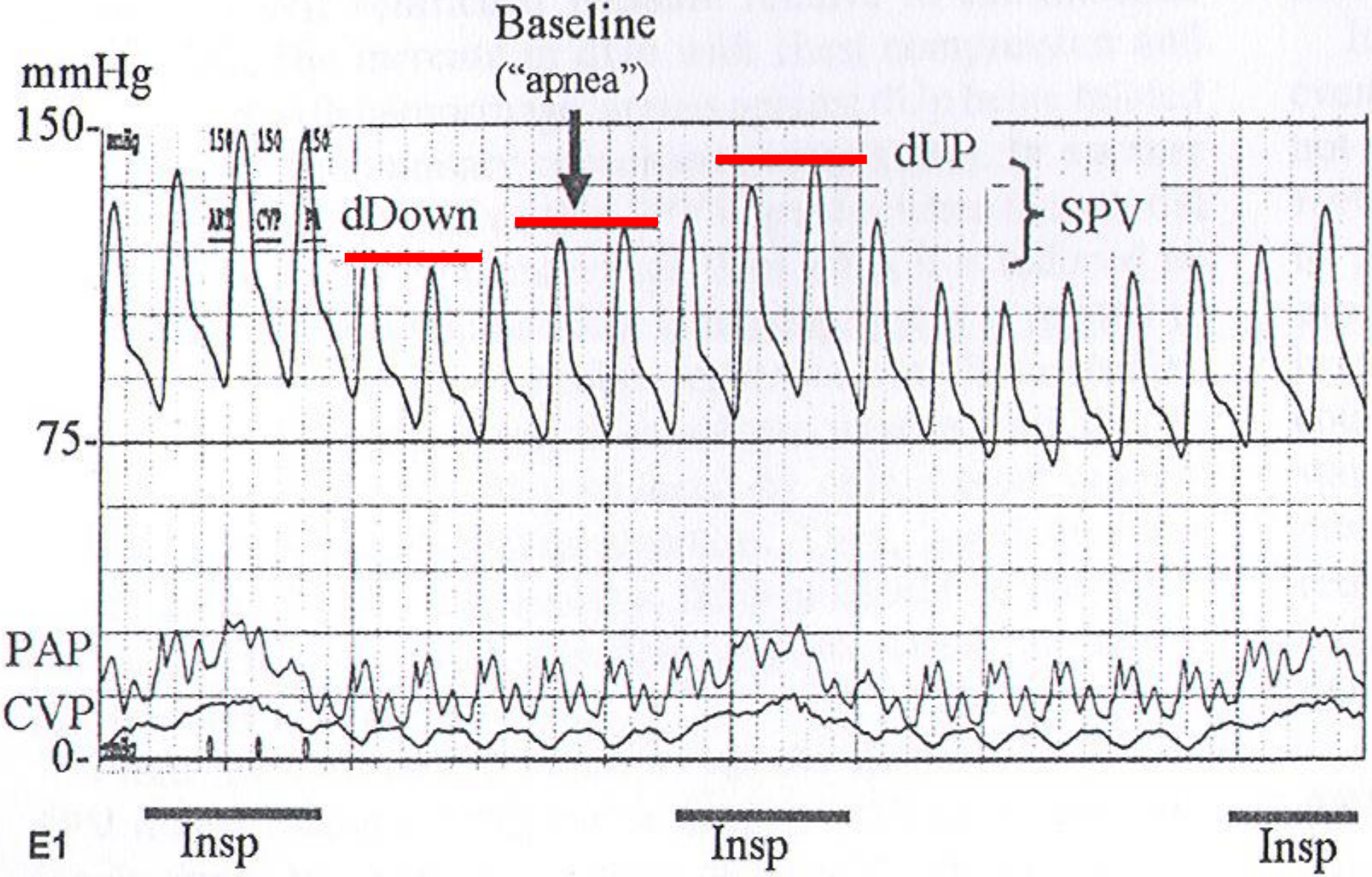
(To ID hypovolaemia & optimise IV fluid volume)

Assessment of systolic - and pulse pressure variation

(BP & CO variations caused by heart-lung interactions during ventilation)

1. Useful during positive pressure ventilation to predict response to volume replacement
2. Assessment of fluctuation in arterial pressure during the ventilatory cycle (>5mm Hg decrease in SAP during one positive pressure mechanical breath, predicts positive response to colloid bolus)
3. Pulse pressure variation most reliable

Consider volume, flow and pressure


Baseline
("apnea")
mmHg
150-
75-
0-
dDown
dUP
SPV
PAP
CVP
E1
Insp
Insp
Insp

Optimising fluid loading & IV volume

The spontaneously breathing patient:

- In euvolaemia: CVP close to zero / slightly negative = optimal CO for venous return
- CVP can detect fluid overload or CCF but not hypovolaemia during spontaneous breathing
- Pressures measured are valid *BUT errors lie in deductions made* from changes in CVP
- Greater filling pressures *are not necessarily* associated with greater SV or CO
  - Greater filling pressure indicates RV diastolic dis-fx
  - CVP & PCWP do not reflect RVEDV

Optimising fluid loading & IV volume

The mechanically ventilated patient

- Neither absolute CVP values nor "trend tracking" the response to bolus or challenge fluid Rx is valid or reproducible
- The higher CVP & PCWP values here, indicate intrathoracic pressures rather than cardiac filling or IV fluid status
- Again - low pressures indicate good cardiac Fx. - very high pressures indicate overload

Table 1 Clinical indices of the adequacy of tissue/organ perfusion

- Mean arterial pressure

Cerebral and abdominal perfusion pressures

- Urine output
- Mentation
- Capillary refill
- Skin perfusion/mottling
- Cold extremities (and cold knees)
- Blood lactate
- Arterial pH, BE, and HCO3
- Mixed venous oxygen saturation $SmvO_2$ (or $ScvO_2$)
- Mixed venous pCO_2
- Tissue pCO_2
- Skeletal muscle tissue oxygenation (StO_2)

RECOMMENDATIONS FOR FLUID RESUSCITATION IN ACUTELY ILL PATIENTS - 1

Fluids should be administered with the same caution that is used with any intravenous drug.

- Consider the type, dose, indications, contraindications, potential for toxicity, and cost.

Fluid resuscitation is a component of a complex physiological process.

- Identify the fluid that is most likely to be lost and replace the fluid lost in equivalent volumes.
- Consider serum sodium, osmolarity, and acid–base status when selecting a resuscitation fluid.
- Consider cumulative fluid balance and actual body weight when selecting the dose of resuscitation fluid.
- Consider the early use of catecholamines as concomitant treatment of shock.

RECOMMENDATIONS FOR FLUID RESUSCITATION IN ACUTELY ILL PATIENTS - 2

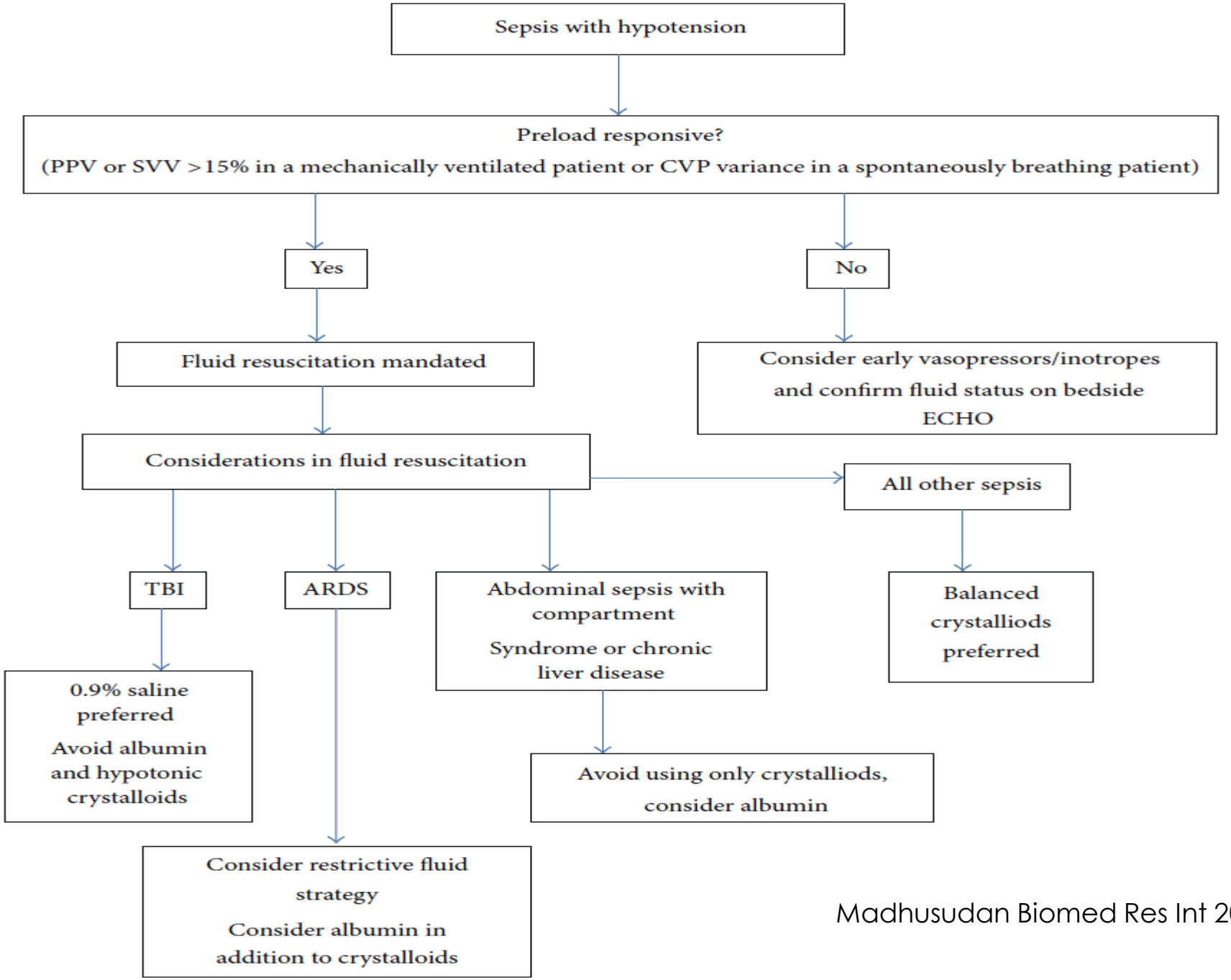
Fluid requirements change over time in critically ill patients.

- The **cumulative dose** of resuscitation and maintenance fluids is associated with interstitial edema.
- **Pathological edema** is associated with an adverse outcome.
- **Oliguria** is a normal response to hypovolemia and should not be used solely as a trigger or end point for fluid resuscitation, particularly in the post-resuscitation period.
- The use of a **fluid challenge in the post-resuscitation** period (≥24 hours) is questionable.
- The use of hypotonic maintenance fluids is questionable once dehydration has been corrected.

RECOMMENDATIONS FOR FLUID RESUSCITATION IN ACUTELY ILL PATIENTS - 3

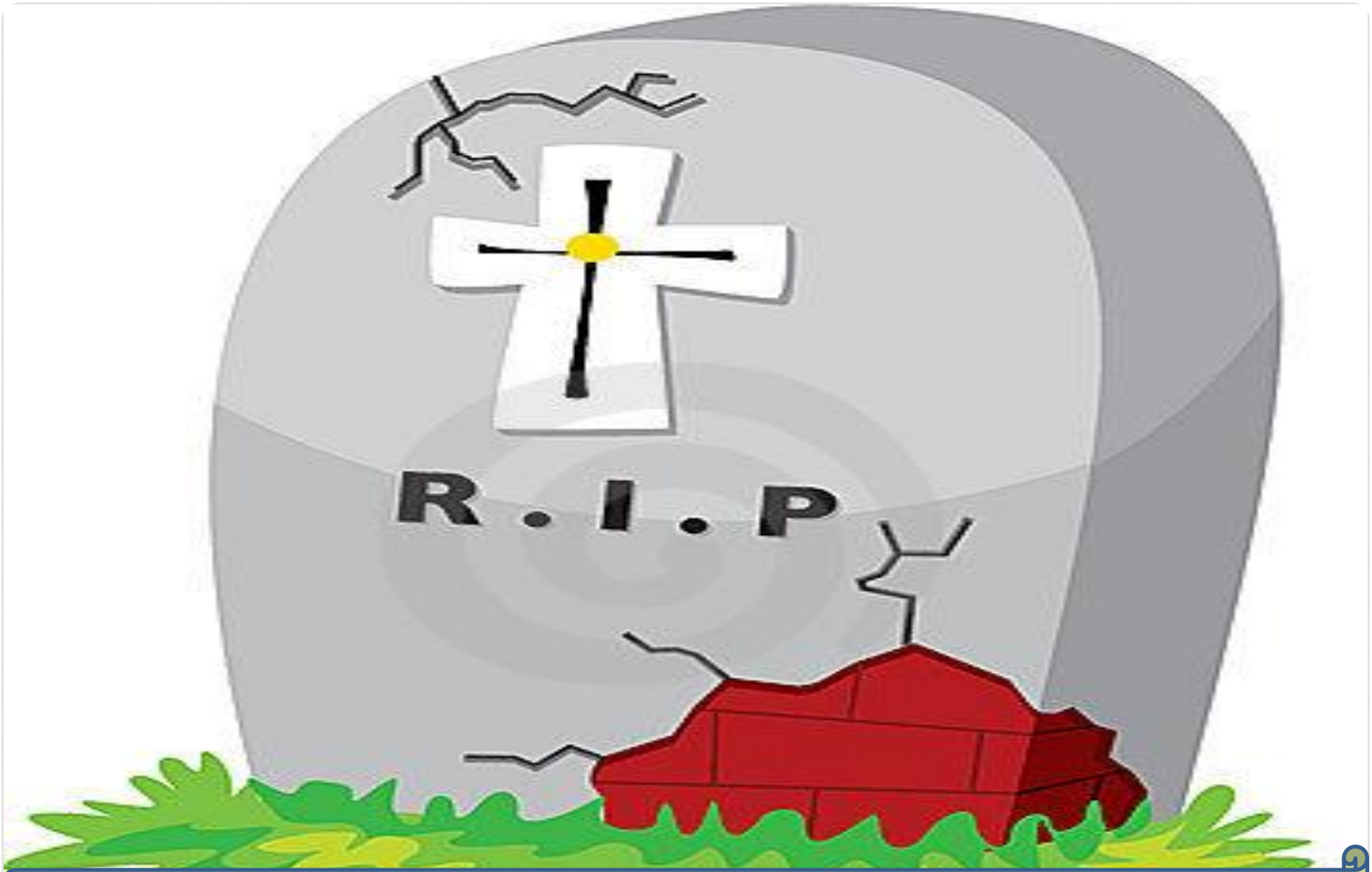
Specific considerations apply to different categories of patients.

- **Bleeding patients** require control of hemorrhage and transfusion with red cells and blood components as indicated.
- Isotonic, balanced salt solutions are a pragmatic initial resuscitation fluid for the majority of **acutely ill patients.**
- Consider saline in patients with **hypovolemia and alkalosis**.
- Consider albumin during the early resuscitation of patients with **severe sepsis.**
- Saline or isotonic crystalloids are indicated in patients with **traumatic brain injury.**
- Albumin is not indicated in patients with **traumatic brain injury**.
- Hydroxyethyl starch is not indicated in patients with **sepsis** or those at risk for **acute kidney injury**.
- The safety of **other semisynthetic colloids** has not been established, so the use of these solutions is not recommended.
- The safety of **hypertonic saline** has not been established. The appropriate type and dose of resuscitation fluid in patients with burns has not been determined.



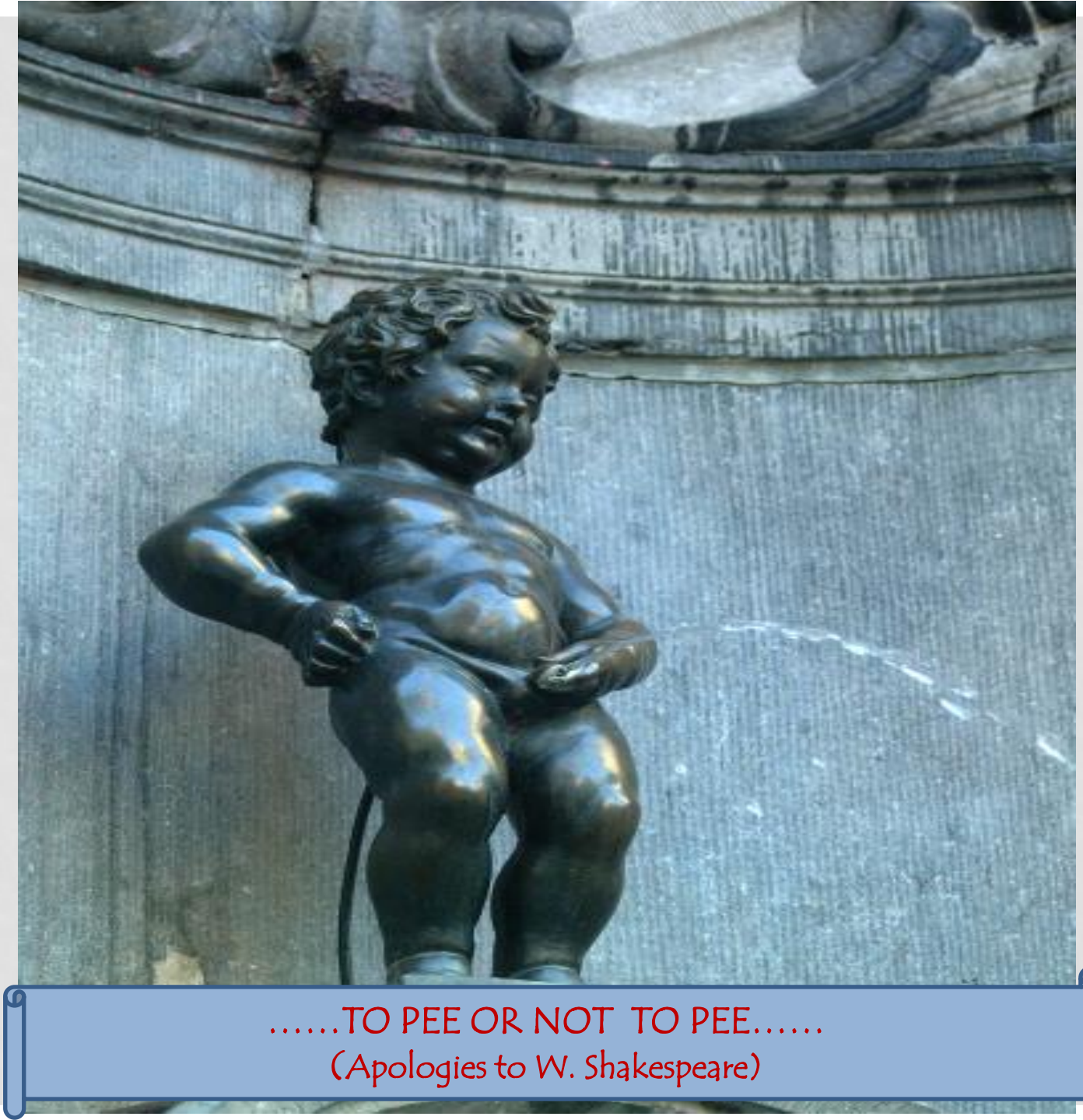
Madhusudan Biomed Res Int 2014

FIGURE 1: Algorithm to guide fluid therapy in the septic patient.



Run them dry & watch them die.....

Run them right & watch them fly!.....



……TO PEE OR NOT TO PEE……

(Apologies to W. Shakespeare)

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ALSO: 6S-, CHEST-, CRISTAL- and BASIS study results.

THE CURRENT LITERATURE

- Extremely frustrating and confusing
- Opposing
- Contradictory
- Flaws and design faults in trials
- New plans and suggestions for better studies.

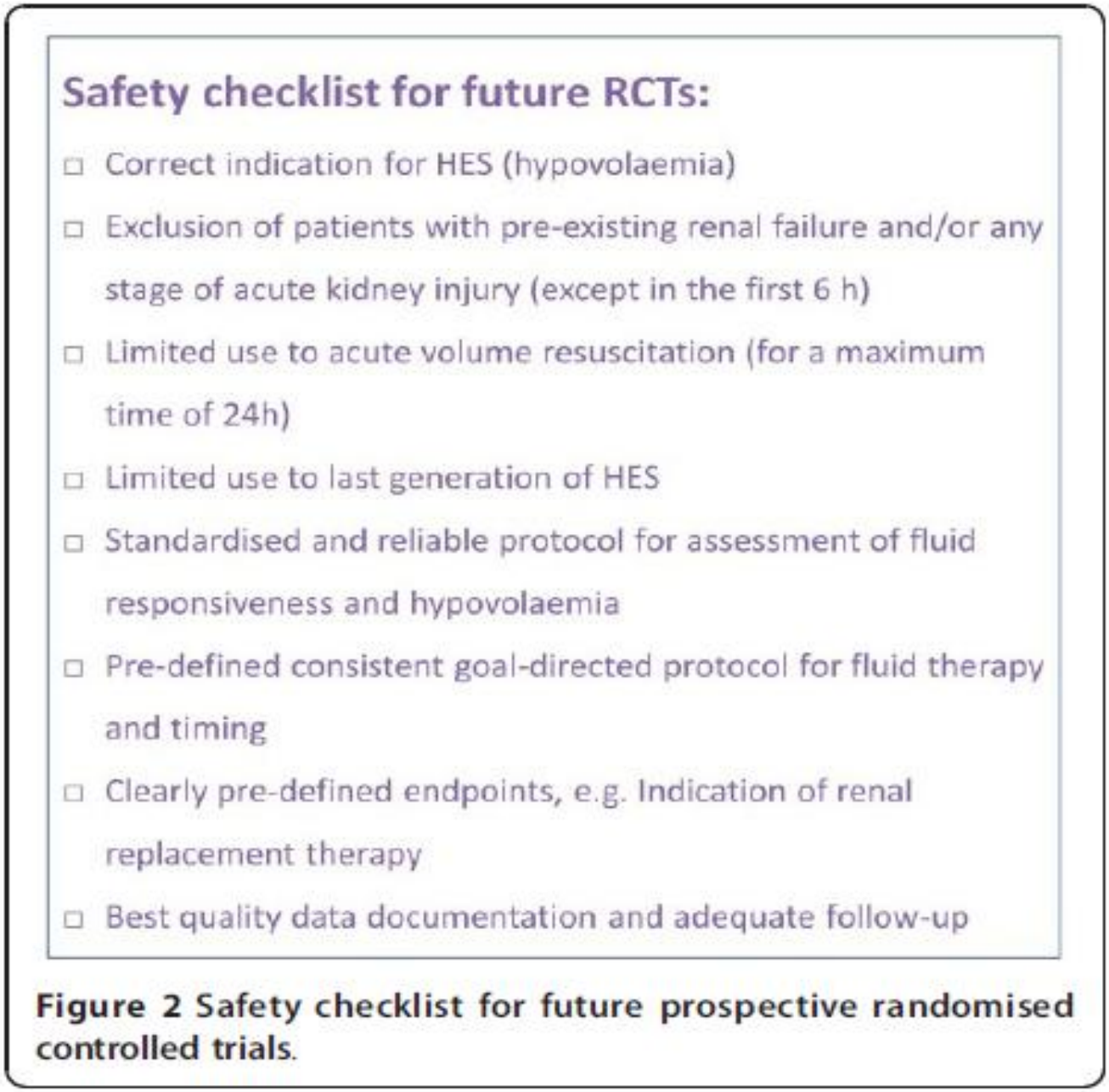
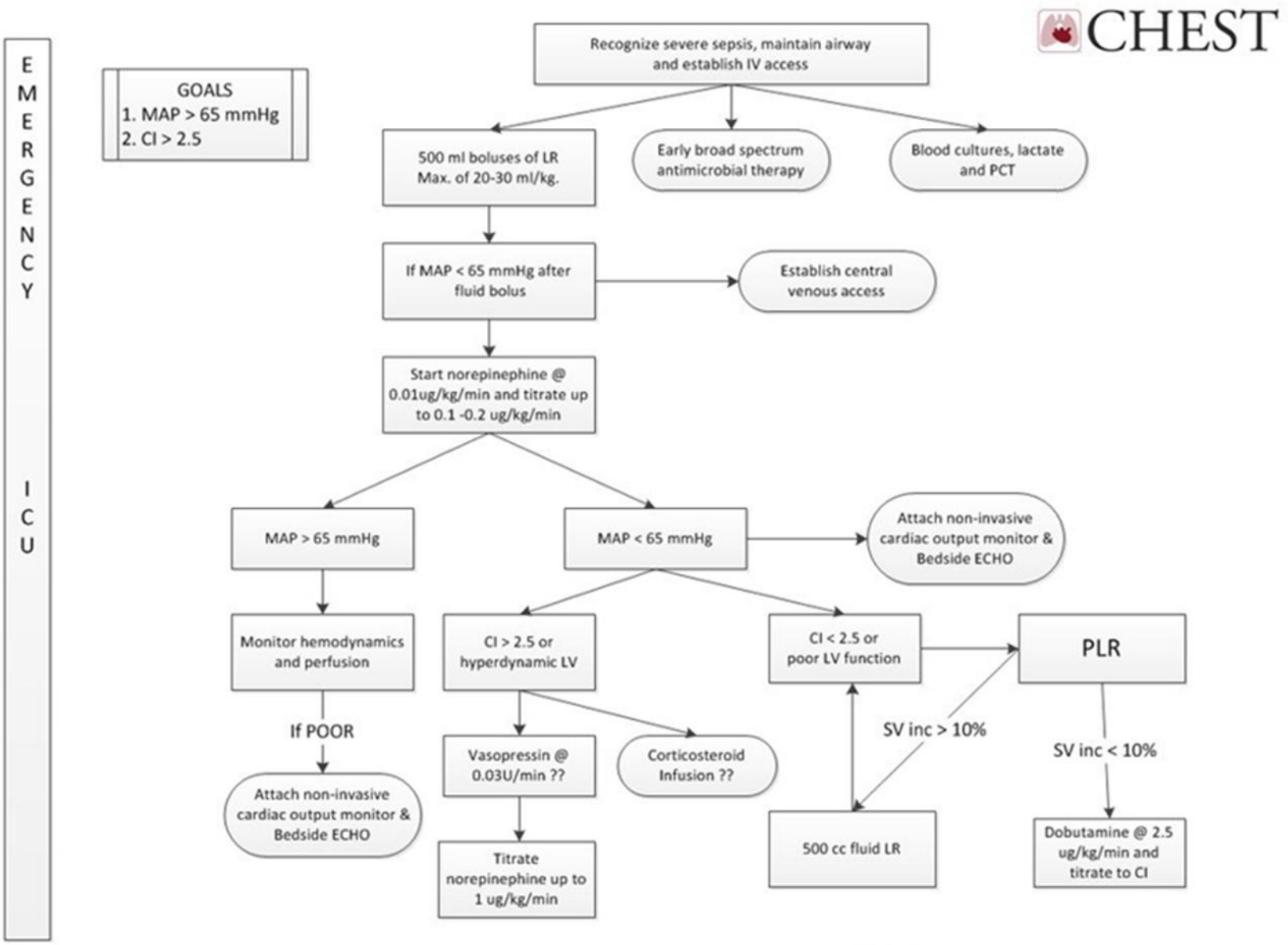
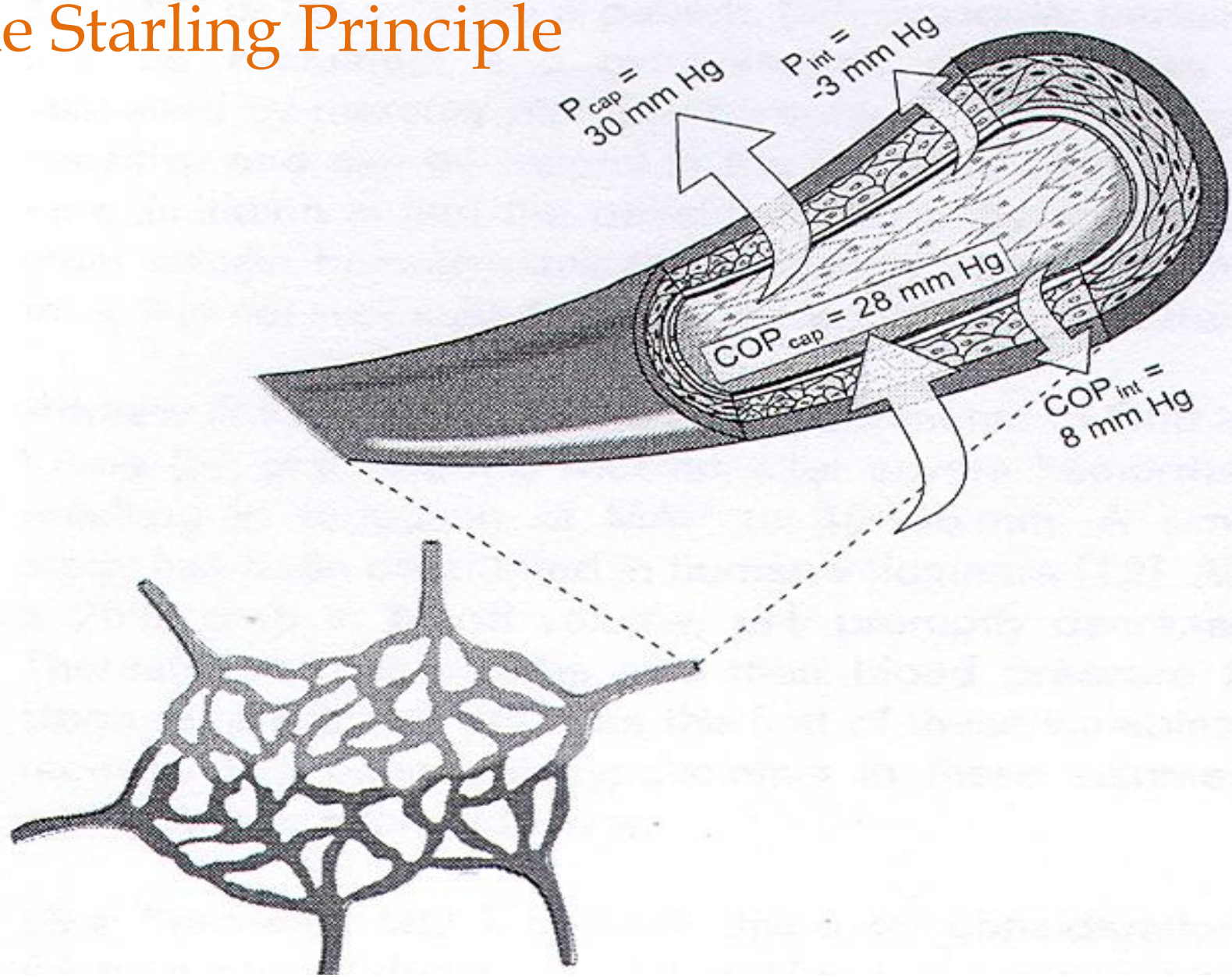


Figure 2 Safety checklist for future prospective randomised controlled trials.



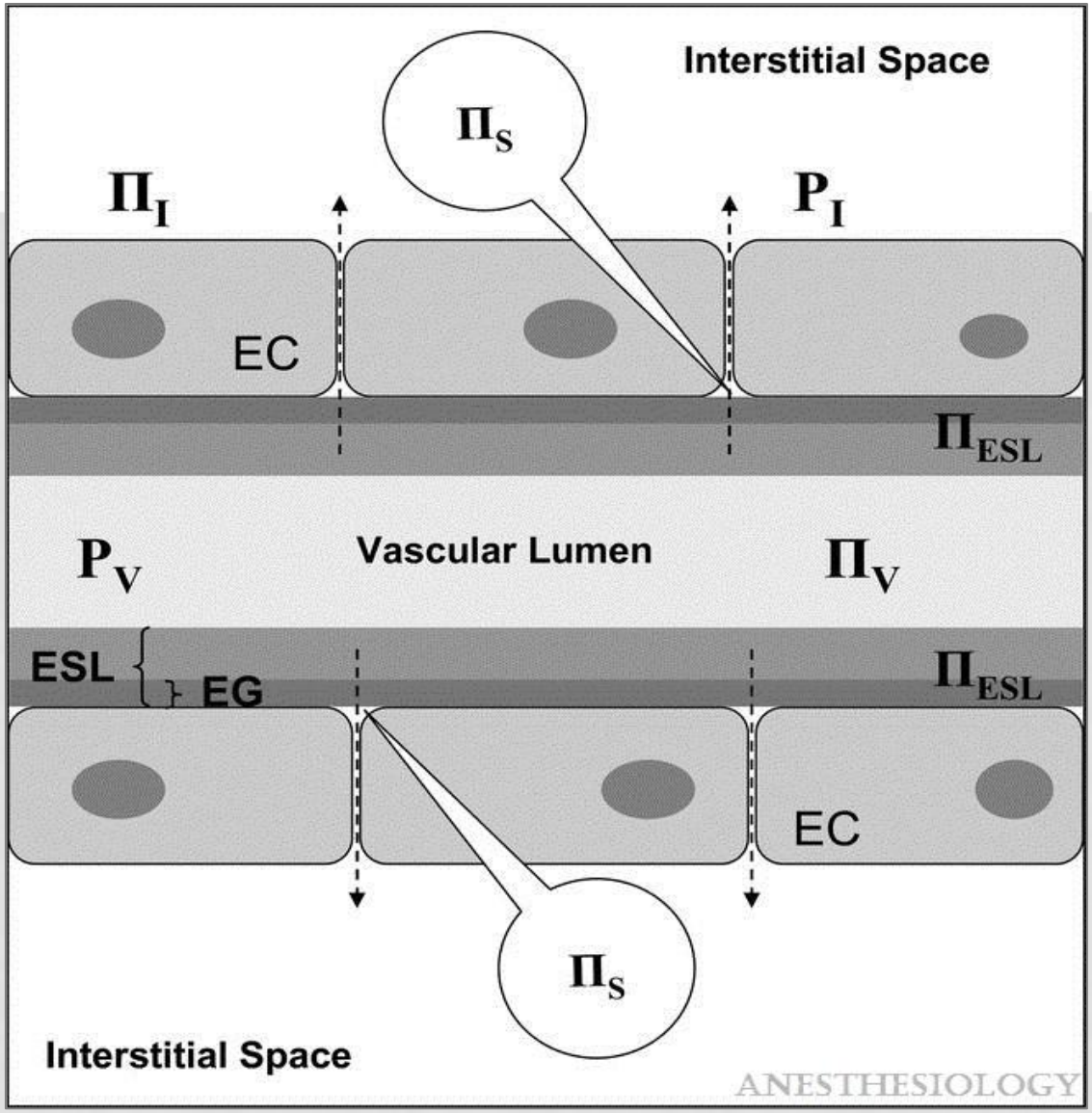
Marik Chest 2014

The Starling Principle



$$J_V = L_P S[(P_C - P_{if}) - \sigma(COP_C - COP_{if})]$$

Starling principle meets the Endothelial Glycocalyx



A Rational Approach to Perioperative Fluid Management

Chappell, Daniel; Jacob, Matthias; Hofmann-Kiefer, Klaus; Conzen, Peter; Rehm, Markus

Anesthesiology. 109(4):723-740, October 2008.
doi: 10.1097/ALN.0b013e3181863117

Fig. 7. The revised Starling principle.176,178The hydrostatic pressure in the vascular lumen (PV), which largely exceeds the interstitial pressure (PI), forces fluid outward. The endothelial glycocalyx (EG) binds plasma proteins, forming the endothelial surface layer (ESL) with a high internal oncotic pressure. The low net flux passing through the EG (arrows) has a sparse protein concentration; the oncotic pressure underneath the EG is low. Accordingly, an inward-directed oncotic pressure gradient develops just across the EG, while the proteins in the small space underneath the EG are continuously cleared toward the interstitial spaceviathe remaining net flux. The extremely simplified illustration does not consider the venular site of the revised model, suggesting free and easy access of plasma proteins toward the interstitial space.176Because the hydrostatic force is low there, this should be no problem. ΠESL = oncotic pressure within the endothelial surface layer; ΠI = oncotic pressure in the interstitial space; ΠS = oncotic pressure below the endothelial glycocalyx (subglyceal); ΠV = oncotic pressure in the vascular lumen; EC = endothelial cell.

$$J_v = K_f\left([P_c - P_i] - \sigma[\pi_c - \pi_i]\right),$$

$$J_v = K_f\left([P_c - P_i] - \sigma[\pi_{esl} - \pi_b]\right),$$

Original Starling principle	Revised Starling equation and glycocalyx model
Intravascular volume consists of plasma and cellular elements	Intravascular volume consists of glycocalyx volume, plasma volume, and red cell distribution volume
Capillaries separate plasma with high protein concentration from ISF with low protein concentration	Sinusoidal tissues (marrow, spleen, and liver) have discontinuous capillaries and their ISF is essentially part of the plasma volume Open fenestrated capillaries produce the renal glomerular filtrate Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma Continuous capillaries exhibit 'no absorption' The EGL is semi-permeable to anionic proteins and their concentration in the intercellular clefts below the glycocalyx is very low
The important Starling forces are the transendothelial pressure difference and the plasma–interstitial COP difference	The important Starling forces are the transendothelial pressure difference and the plasma–subglycocalyx COP difference. ISF COP is not a direct determinant of J_v
Fluid is filtered from the arterial end of capillaries and absorbed from the venous end. Small proportion returns to the circulation as lymph	J_v is much less than predicted by Starling's principle, and the major route for return to the circulation is as lymph
Raising plasma COP enhances absorption and shifts fluid from ISF to plasma	Raising plasma COP reduces J_v but does not cause absorption
At subnormal capillary pressure, net absorption increases plasma volume	At subnormal capillary pressure, J_v approaches zero. Auto transfusion is acute, transient, and limited to about 500 ml
At supranormal capillary pressure, net filtration increases ISF volume	At supranormal capillary pressure, when the COP difference is maximal, J_v is proportional to transendothelial pressure difference
Infused colloid solution is distributed through the plasma volume, and infused ISS through the extracellular volume	Infused colloid solution is initially distributed through the plasma volume, and infused ISS through the intravascular volume At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases J_v At supranormal capillary pressure, infusion of ISS also raises capillary pressure, but it lowers COP and so increases J_v more than the same colloid solution volume At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of ISS increases intravascular volume, but J_v remains close to zero in both cases

Jv = net filtration

Pathophysiology and fluid therapy

Fluids available

* Maintenance
*Resuscitation
*Replacement

Cells 2L

Plasma 3L

Interstitial compartment 12 L

Intracellular compartment 30 L

Colloid

Saline

Glucose

Where does the fluid go?

Starling forces
Blood vessels
Endothelial glycocalyx
Lymphatics
The interstitium
The tissue

Influence of disease

Maintenance for elective surgery
Trauma/Burns
Sepsis
MODS

HOW SHOULD FLUID BE ADMINISTERED?

CURRENT OPINION:

- **PAST:**
  Fluids were administered without **adequate monitoring** to guide dosage (volume) and this might have resulted in adverse outcomes relating to either inadequate or excess fluid administration.
- **FUTURE:**
  Strategies of fluid administration by titration of dosage (volume) to rational physiological endpoints by using appropriate monitoring (flow-based, alternatively clinical judgment) can improve clinical outcome.
- **PATHOPHYSIOLOGY!!!!!!! Use the appropriate DRUG!!!!!**
  Crystalloids: fasting+insensible loss+urine
  Colloids: IV loss : bleeding+fluid shifting
- **FLUID RESPONSIVENESS:**

• Systolic pressure variation • Passive leg raise • Stroke volume (SV) • Cardiac output (CO)	vs	Pulse Peripheral perfusion/capillary refill JVP/CVP, GCS Acid-base, Lactate

- Adverse outcomes may be associated with **inadequate** OR **excessive** fluid administration.

Grocott et al Anesth Analg2005:100:1093-106

A RATIONAL APPROACH TO PERIOPERATIVE FLUID MANAGEMENT

- The 3rd space does not exist
- Crystalloid overload & iatrogenic injury to the vascular permeability barrier leads to major fluid and protein shifts to the interstitium
- Get source control (sepsis, bleeding)
- Adequate and timely (EARLY) replacement of actual losses
- Use appropriate preparations
- Replace plasma losses with a goal-directed approach via physiological circulatory surrogates
- The extracellular compartment cannot currently be monitored
- Replace ECF on a protocol basis = demand related
  - Fasting affects the ECF minimally
  - Clear fluids up to 2h pre-op
  - Basal fluid losses 0.5 – 1.0 ml/kg/h during major surgery – this should represent adequate substitution of fluid needs

JL Vincent: "All Fluids are good & bad"

D Chappell

HOW SHOULD FLUID BE ADMINISTERED ?

- Cautiously
- After due deliberation
- Progressively, titrating smaller boluses
- According to physiological dynamic end points
- Appropriate, adequate monitoring:
  - Maintenance
  - Resuscitation
  - Replacement

BAN: Blind fluid "challenges"

"Restrictive policies"

"Run them dry"

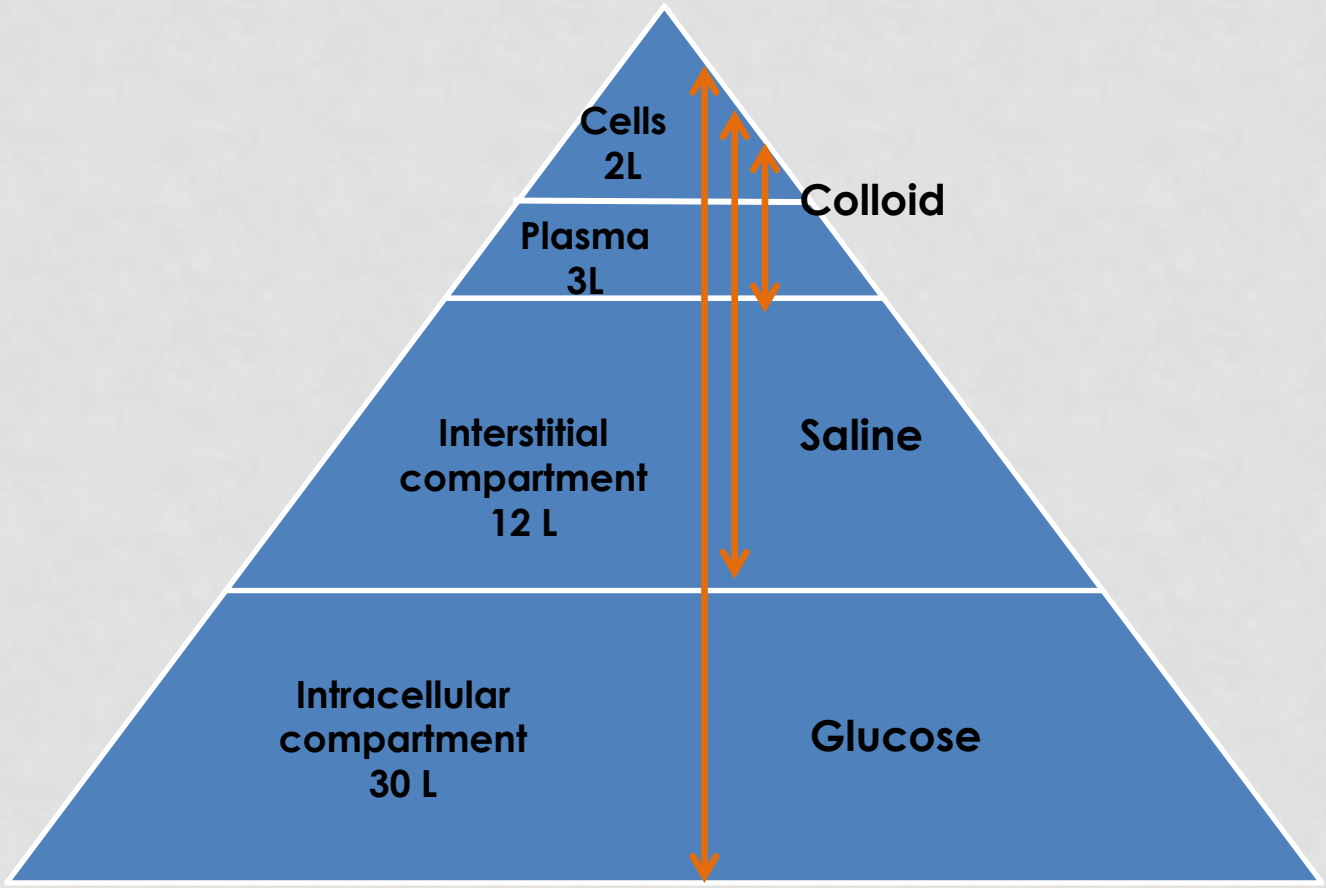
Both *excessive & inadequate* fluid therapy = harmful

Conclusion

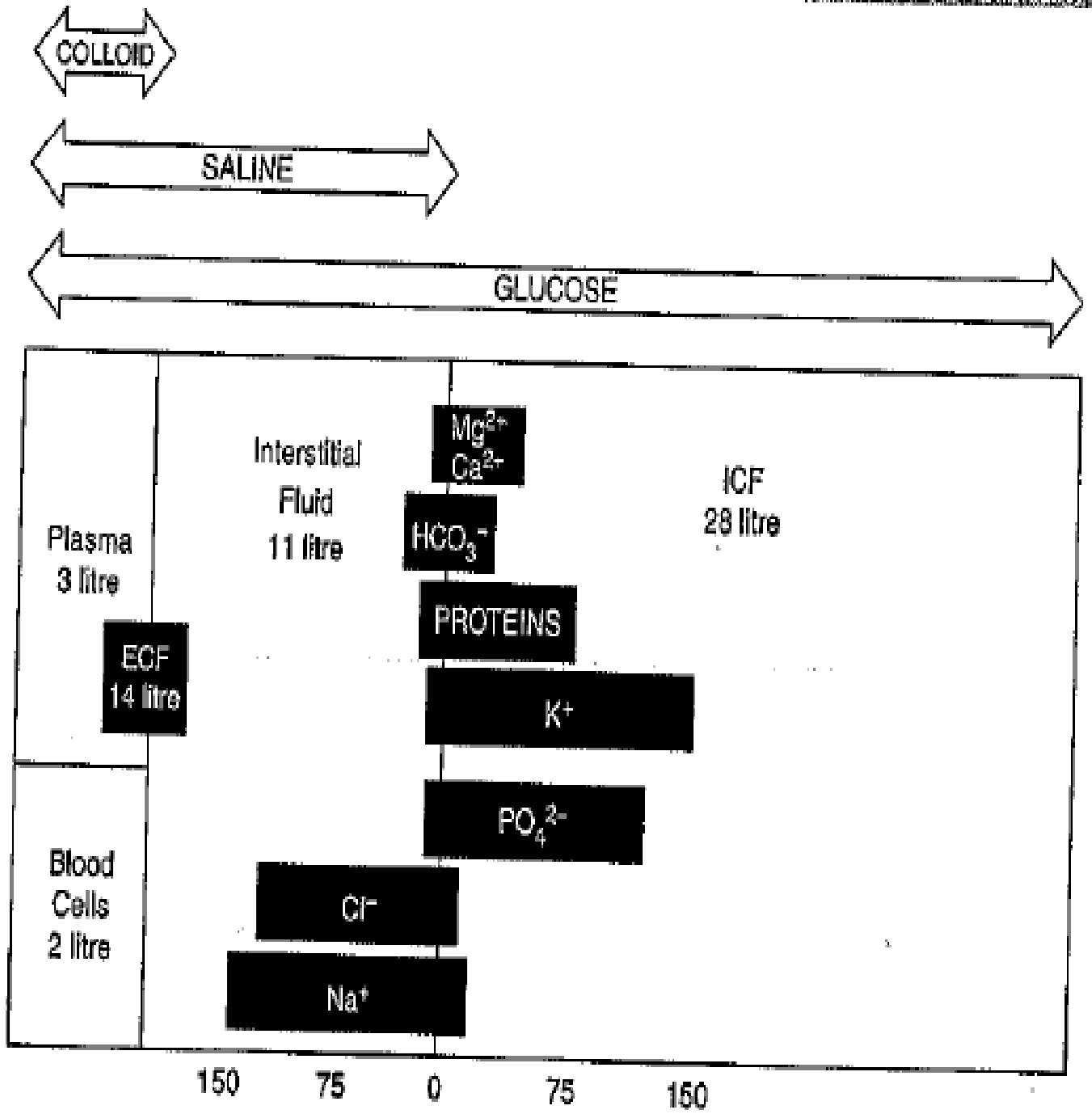
A perfect one-size-fits-all fluid strategy does not exist. In sepsis, clinicians should understand the limitations and potential benefits of each strategy.

- Each fluid should be considered a **drug**, with specific pharmacokinetic, pharmacodynamic, and adverse effect profiles, which can be carefully matched to the patient.
- Whichever fluid is chosen, resuscitation should be titrated to evidence based targets, combining **clinical assessment**, such as signs of tissue perfusion with **dynamic hemodynamic** monitoring.
- **Balanced crystalloids** may be preferred first choice, followed by **albumin**, based on their comparative safety profiles. 0.9% **saline** should only be used after consideration of its potential to cause harm and current evidence would suggest **starches** (HES) **gelatins** should be avoided in sepsis.

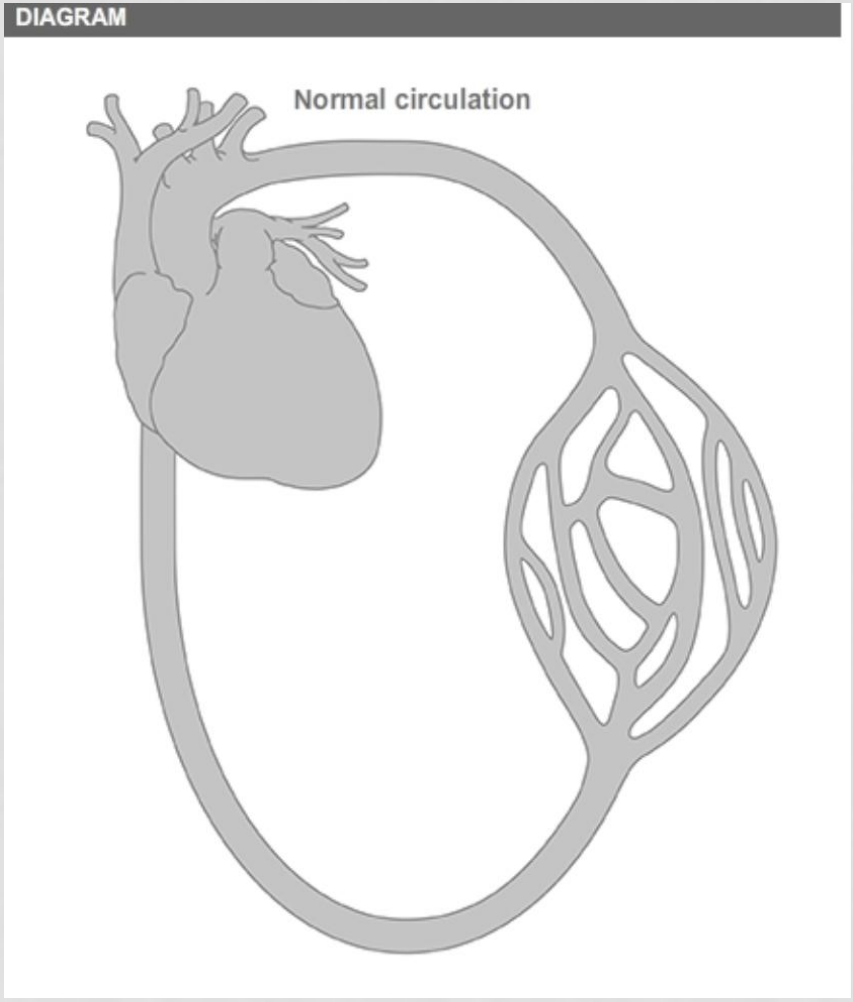
Pathophysiology and fluid therapy



Model for volumes of distribution of isotonic colloids, saline and glucose solutions in a 75 kg patient.


COLLOID
SALINE
GLUCOSE
Plasma
3 litre
ECF
14 litre
Blood
Cells
2 litre
Interstitial
Fluid
11 litre
ICF
28 litre
Mg^{2+}
Ca^{2-}
HCO_3^-
PROTEINS
K^+
PO_4^{2-}
Cl^-
Na^+
150
75
0
75
150

MONITORING



… the **cardiovascular system** during shock resuscitation is like driving with your lights on after dark …

WHY CHANGE ?

Subtle shift in emphasis in the pathogenesis:

1. It seems that the consumption of factors also plays an important role in the progress to haemorrhage
2. Older diagnostic criteria (Bick 1996) mentioned fibrinolytic activation – today suppression of the fibrinolytic system rather, is emphasised. (PAI-1mediated) This does not mean that circulating plasmin does not degrade intravascular fibrin thrombi.

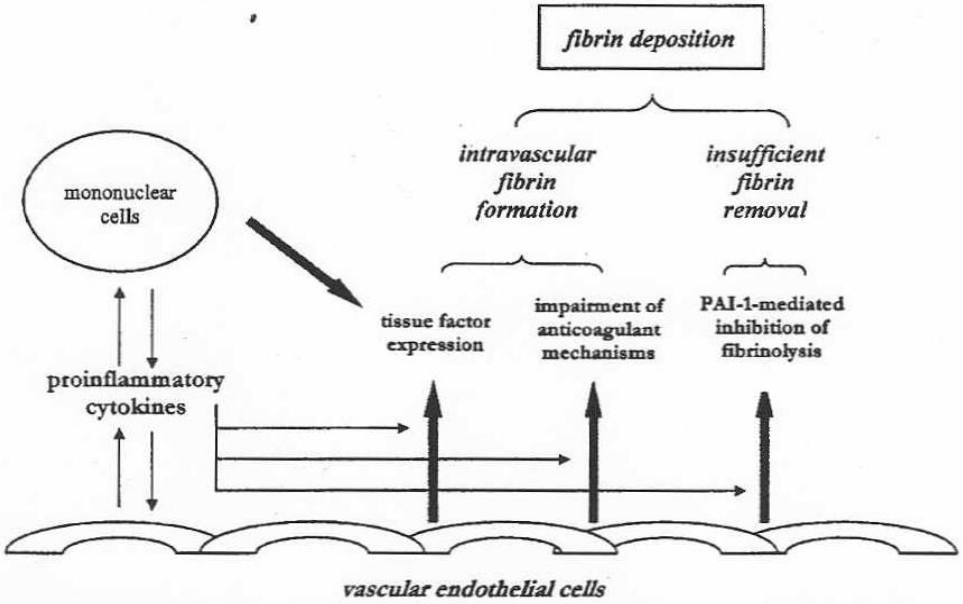


Figure 1 Schematic representation of pathogenetic pathways in DIC. During systemic inflammatory response syndromes, both perturbed endothelial cells and activated mononuclear cells may produce proinflammatory cytokines that mediate coagulation activation. Activation of coagulation is initiated by TF expression on activated mononuclear cells and endothelial cells. In addition, downregulation of physiologic anticoagulant mechanisms and inhibition of fibrinolysis by endothelial cells will further promote intravascular fibrin deposition.

WHY CHANGE ?

Subtle shift in emphasis in the pathogenesis:

3. The emphasis today falls on generation of thrombin in the systemic circulation based on tissue factor-mediated initiation of systemic coagulation activation rather than bleeding
4. Organ failure is much more common than bleeding in DIC / THCD
5. The role of stimulated coagulation – inflammation cross talk on the endothelial level is also emphasised

Pathogenesis of DIC

1. TF initiation of coagulation…..that is…..
2. Insufficiently contained by natural anticoagulant pathways…..
3. And impaired endogenous fibrinolysis