CAREFUL WITH THAT COLLOID, EUGENE...

Understanding fluids, urea and electrolyte balance;
a quantitative approach. Part Two.

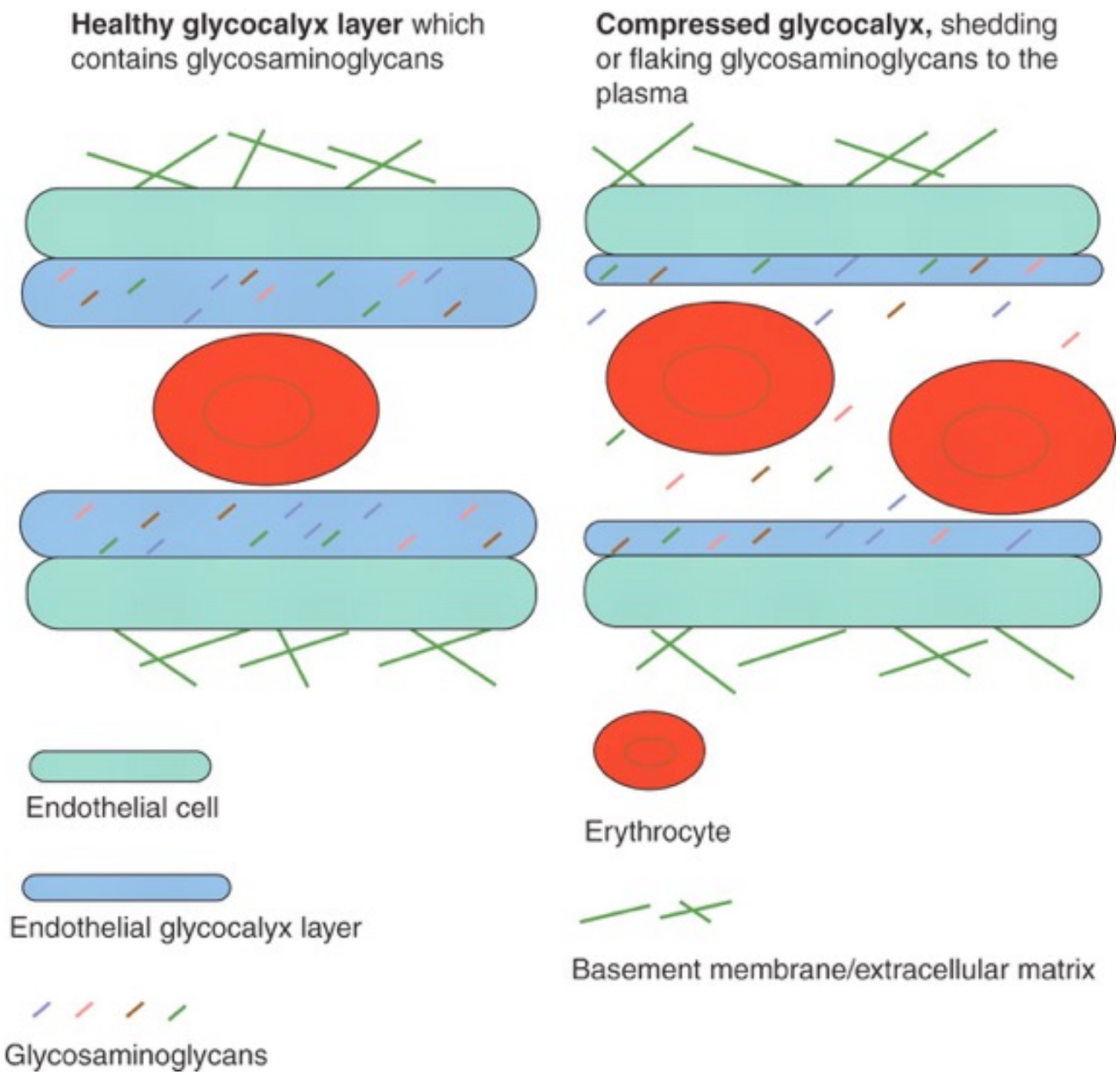
In Part 1 we met Salty Sam and learned about the tonicity of his body water compartments. We found that the ECF bears the brunt of iatrogenic fluid overload and that the plasma part of ECF contains some larger molecules like albumin, and cellular components. We will now consider what implications this has for a rational approach to fluid therapy.

A large multicellular organism like Salty Sam needs a finely-tuned circulation to deliver oxygen and nutrients to its most distant parts. At the arteriolar commencement of a capillary, water is filtered through the glycocalyx and interendothelial junction gaps to the interstitial space (ISF) of the ECF; pressure at the arteriolar part of the capillary (capillary hydrostatic pressure) exceeds interstitial hydrostatic pressure and drives filtration.

In addition to the hydrostatic pressures governing fluid flux across the capillary, we have to consider osmotic pressure gradients. In classic physiology the colloid osmotic pressure of plasma is about 25 mmHg and is mostly (75% in health) attributable to albumin. The interstitial oncotic pressure is lower, about 5 mmHg.

- Studies, however, show that the Starling equation parameters of intravascular and interstitial colloid osmotic pressures do not adequately account for fluid fluxes. We now know that the integrity of the endothelial glycocalyx is the primary determinant of the COP gradient that opposes filtration.

A cartoon illustrating that the intravascular volume contains the non-circulating glycocalyx fluid volume and the circulating plasma volume.



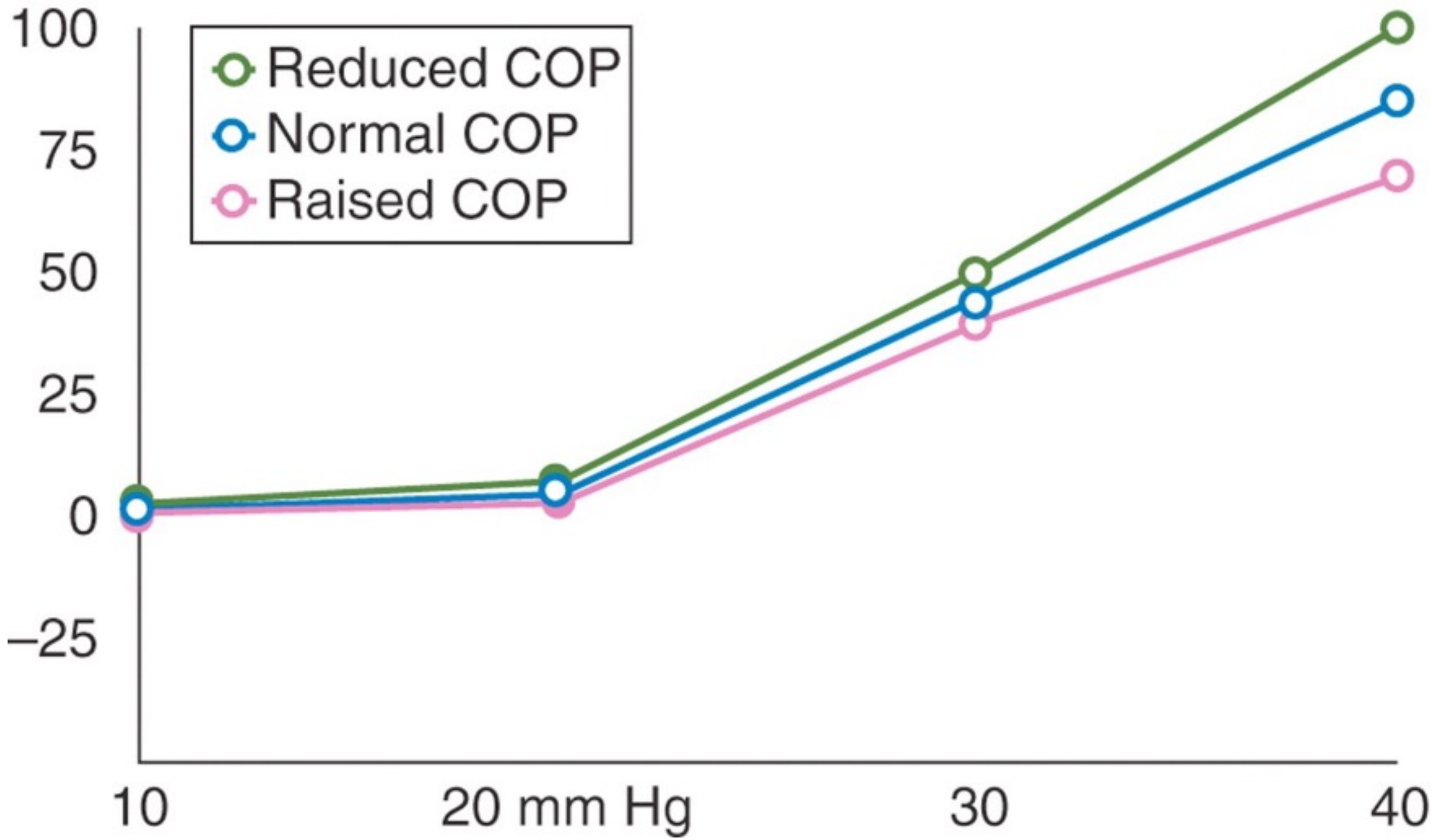
Woodcock T E , Woodcock T M Br. J. Anaesth. 2012;bja.aer515

BJA British Journal of Anaesthesia

THE GLYCOCALYX MODEL

The COP of fluid in the interendothelial cell clefts, beneath the glycocalyx, is very low, and the COP gradient opposes filtration from plasma. If the hydrostatic pressure gradient is reduced, filtration falls proportionately. When the COP and hydrostatic gradients are similar, filtration approaches zero. Interstitial fluid proteins can then diffuse back into the interendothelial cell clefts, reducing the COP gradient and preventing fluid absorption into the capillary.

The no absorption rule.



Woodcock T E , Woodcock T M Br. J. Anaesth. 2012;bja.aer515

BJA British Journal of Anaesthesia

Just one more bit of physiology to know; the capillary leak of larger molecules is normally very small, we talk of systemic capillaries having a “reflection coefficient of 0.95” where 1.0 would be totally impermeable to larger molecules, and there is very little albumin in the interstitial fluid of most organs.

- The reflection coefficient of pulmonary capillaries is about 0.85; what are the practical implications?

Did you remember to consider that the pulmonary circulation normally runs at lower hydrostatic pressures than the systemic? You will expect more protein in normal lung interstitial fluid, and expect that the lungs will be particularly vulnerable to oedema with ‘fluid overload’ or capillary leak due to inflammatory mediators.

THE INTERSTICES

The ISF is not just a pool of water through which nutrients pass along a concentration gradient to a cell. The ISF is constantly flowing as a thin film through a proteoglycan brushpile and a web of collagen filaments which evenly distribute the solutes to and away from the cells. The interstitial hydrostatic pressure is normally about 3 mmHg sub-atmospheric.

OEDEMA IS A BAD THING

Fluid overload greatly increases the flux across the capillary to the interstitium, but this is NOT a good thing. The space is very compliant; at a pressure of 3 mmHg above atmospheric its volume could be doubled from 12 to 24 litres, and doubled again to 48 litres at 6 mmHg. The thin-film distribution system breaks down as rivulets of fluid form, and then substantial rivers of ISF aggregate, leaving some cells starved of nutrients in stagnant pools of accumulating waste products.

Let's get back to Salty Sam and Dr Eugene. A few hours after his operation, Sam's blood pressure started to fall and his heart rate started to rise. Dr Eugene diagnosed haemorrhage of more than 15% blood volume as the likeliest cause, and notified the surgeon.

- What volume of which fluid would be a rational response to this situation?

15% of Sam's blood volume would be about 600 ml. You could transfuse red blood cells and plasma, but usually you will choose to use an isotonic salt solution (sodium 130-155), and you should give about 1.5x the deficit (= about 1 l).

The evidence base shows no outcome difference between plasma substitute or crystalloid resuscitation in acute haemorrhage, and as crystalloids are cheap and non-allergenic they are widely recommended! Dr Eugene's i.v. resuscitation and Dr Knife's operation to stop the haemorrhage saved Salty Sam on this occasion.

Middleton-on-Sea Infirmary has a problem with hospital-acquired infections, and a week later we return to find Salty Sam being admitted to the ICU. His systolic arterial pressure is less than 90, and a rapid 500 ml bolus of crystalloid makes no difference to his arterial or venous pressures. A blood culture taken yesterday is growing Gram-negative rods.

CAPILLARY LEAK.

Systemic inflammation reduces capillary reflection coefficients and the trans-capillary escape rate of albumin (which is normally about 5% per hour) may increase to 20% or more. At the same time, myocardial and arteriolar contractility are suppressed (mostly by iNO synthase activity) so that arterial blood pressure falls, while pulmonary artery pressure rises.

- Consider what consequences these changes have for the circulation and water flux.

On the systemic side, lower hydrostatic pressure at the arterial commencement of the capillary bed reduces water flux to the interstitial space, and damage to the endothelial glycocalyx reduces the oncotic pressure gradient which opposes filtration. In the pulmonary circulation, fluid flux to the interstitium under hydrostatic pressure rises.

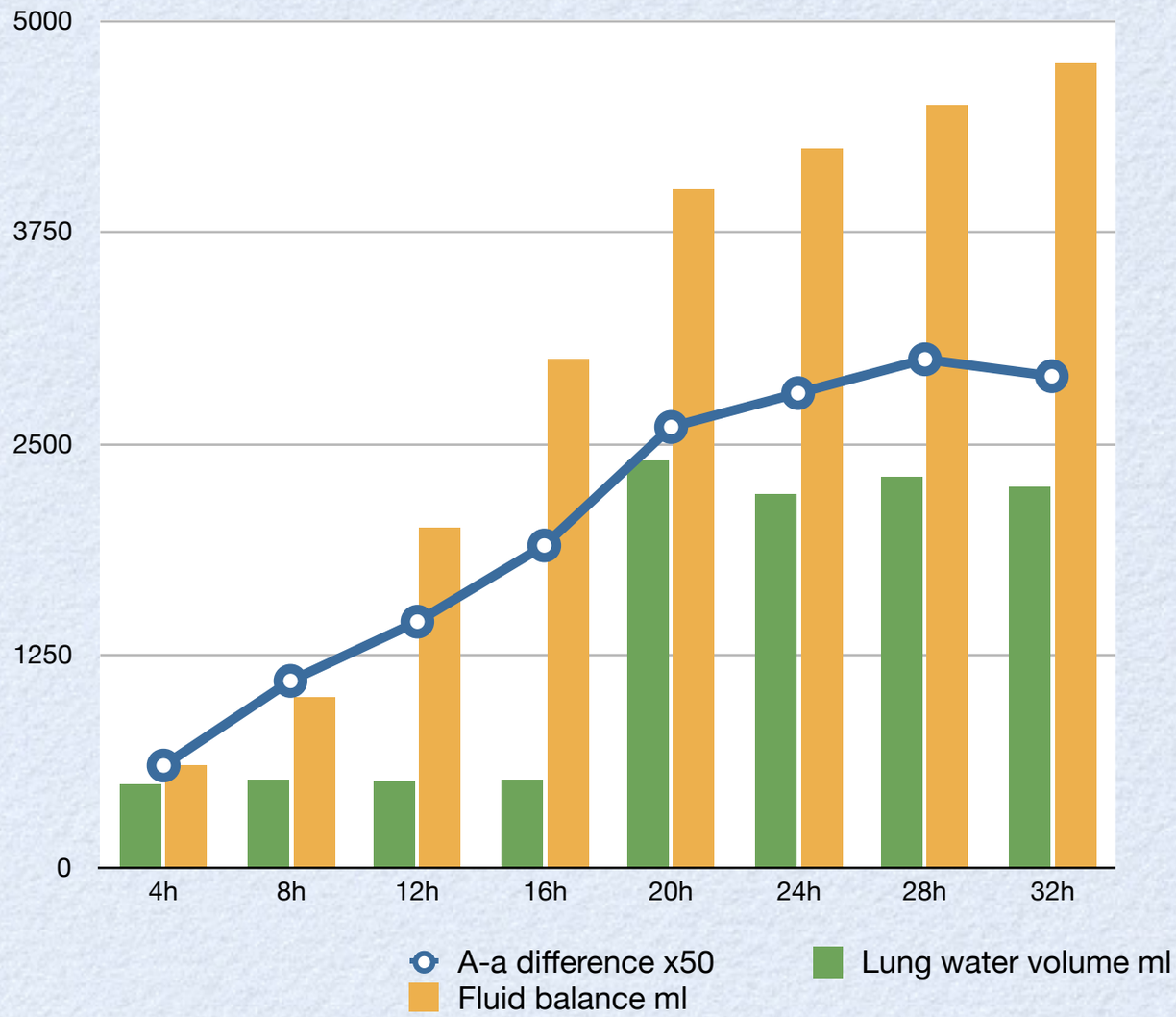
The glycocalyx model is responsible for a "no absorption" rule of transcapillary flux, even when capillary pressure is low.

- What other mechanism for returning water to the venous circulation does the lung possess?

- Well done if you remembered the lymphatic drainage.

  In experimentally-prepared sheep, thoracic duct lymph flow increases dramatically in inflammatory conditions. But when the interstitial fluid volume reaches a critical level, the small lymph channels get pinched off, thoracic duct flow falls, and pulmonary oedema ensues; a mechanism of acute ARDS.

Dr Eugene started fluid resuscitation with Hartmann's Solution, and plotted Sam's progress in fluid balance, extravascular lung water volume and alveolar-arterial oxygen tension difference.



- What are the criteria for Acute Respiratory Distress Syndrome? Look back at Sam's chart on the last slide, at how many hours did he fulfill the criteria for ARDS?
- Do you know how Dr Eugene measured lung water at the bedside??

ARDS is a Syndrome, not a disease. Criteria include acute pulmonary oedema not due to heart failure or fluid overload ("non-cardiogenic pulmonary oedema"), hypoxaemia, and reduced pulmonary compliance. At 20 h Sam had both pulmonary oedema and hypoxaemia.

By injecting ice-cold indocyanine green into a central vein, and recording and analysing the thermal and green curves at an artery.

- What were the consequences of resuscitation with Hartmann's Solution?

ECF volume, including plasma volume, will be increased, but the colloid osmotic pressure of the plasma will be reduced. There is a risk of oedema if therapy continues beyond the amount needed to restore plasma volume to an adequate level.

- If Dr Eugene had used colloids as well as crystalloids, what difference would you expect in haemodynamics and water flux?

Colloidal molecules with substantial molecular weight (150 or more) would increase the COP of plasma, opposing filtration and so the volume transfused to resuscitate the plasma volume should (in theory) be a little smaller. The onset of pulmonary oedema might might in theory have been delayed or even prevented, but clinical measurements do not show any advantage of colloid resuscitation for prevention or treatment of oedema.

- The effect of synthetic colloids on the colloid osmotic pressure within the endothelial glycocalyx is complex and poorly understood. If a molecule protects the eGLX, it will preserve the gradient. If it damages the eGLX, it will predispose to tissue oedema. It is not possible to recommend synthetic colloids for their effect on the COP.

Sam remained oliguric in spite of crystalloid resuscitation, his pH was 7.15, potassium 6.7 mmol l^{-1} and urea 40 mmol l^{-1}. Dr Eugene started haemofiltration. The filtrate is plasma water with ions and small molecules like urea, while the filtrate-replacement solution is urea-free.

- At what rate is Sam making urea? How much urea has been removed from Sam after Nurse has poured the first ten litres of filtrate down the sluice?

Remember that in health, Sam makes more than 500 mmol urea a day, but in a catabolic critical illness he will make maybe 600 mmol urea every 24 hours (about 25 mmol per hour). The filtrate contains 40 mmol l^{-1} urea, so the first ten litres of filtration removes 400 mmol.

- With plasma urea 40 mmol l^{-1} and urea production at 600 mmol per day, what daily volume of filtration would be needed just to stop the plasma urea rising?
- When the plasma urea is eventually reduced to 20 mmol l^{-1}, what daily filtration volume is now needed to stop the plasma urea rising?

15 litres per day of filtrate at 40 mmol l^{-1} balances production of 600 mmol per day. More than 15 litres per day will cause the plasma urea to fall.

When the plasma urea is down to 20, 30 litres of filtrate will be needed to prevent urea rising.

... and at plasma urea 10, it would take 60 litres per day! Best to stop filtration and give Sam a deserved break from the injurious effects of extracorporeal circulation.

We tend to haemofilter at about 2 litres per hour, so on a good day of no interruptions we get 48 litres urea clearance. If production is 600 mmol per day, the plasma urea after several days will bottom out at about 15 mmol l^{-1}.

FURTHER REFLECTIONS...

- when capillary pressure is low and filtration close to zero, the COP of a colloid resuscitation fluid will confer no advantage over isotonic salt solutions .
- indiscriminate use of colloids can be harmful.
- haemofiltration gives you complete control over ECF volume and composition, and additional crystalloid therapy is both irrational and unnecessary. Just add nutrition

If you are still with me so far, well done.

In Part 3 of Salty Sam and Dr Eugene's story we will look at acid base balance.