A rational approach to fluid therapy and resuscitation

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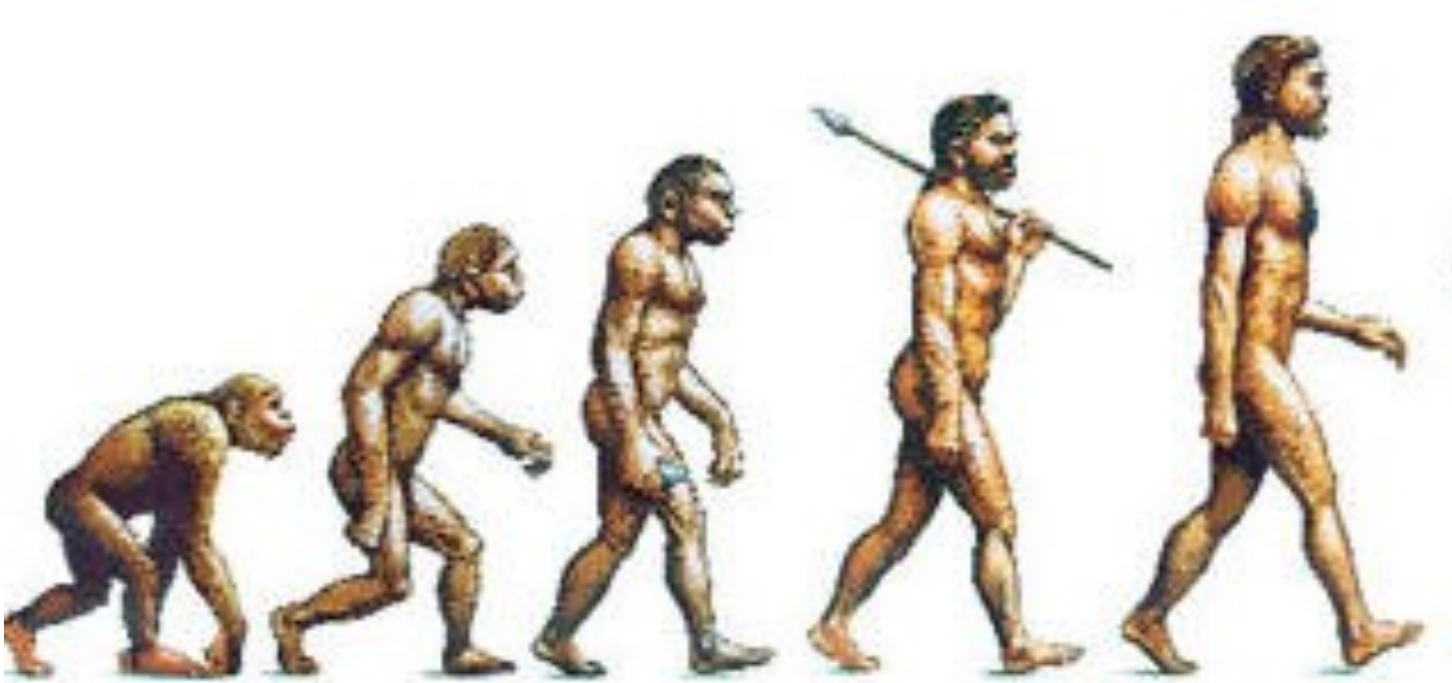
Specialist Trainee identification guide



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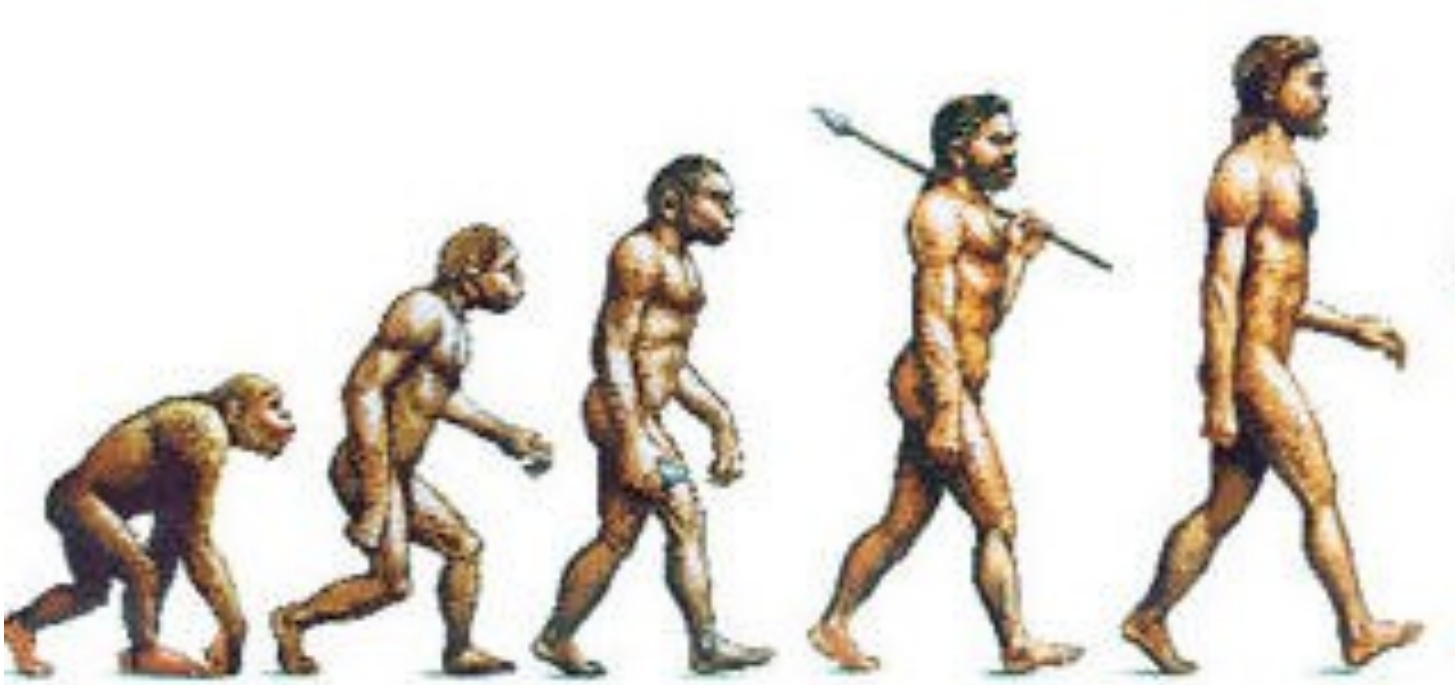

intensivists and anaesthetists

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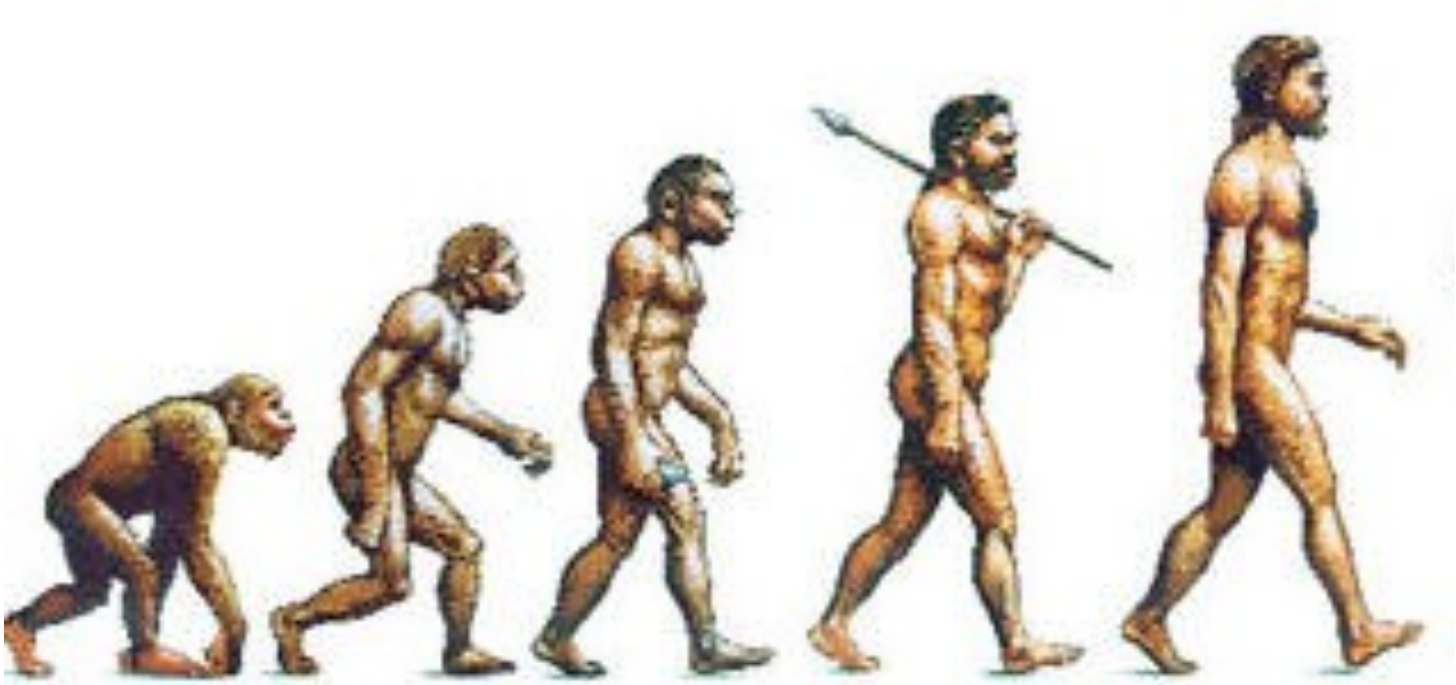
Specialist Trainee identification guide



Everybody else

intensivists and anaesthetists

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Themes

- Why give fluids?
- How much?
- When to stop?
- Which fluids?

Why give fluids?

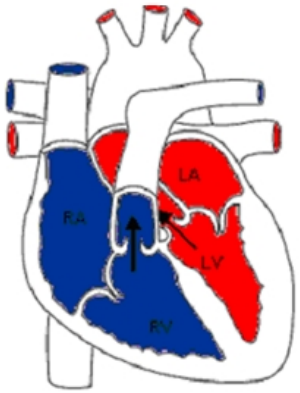
- Primary prevention of threatened AKI
- ?Stabilise and recover from established AKI

Why give fluids?

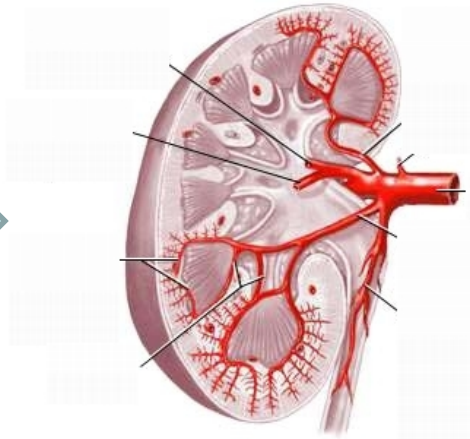
- Primary prevention of threatened AKI
- ?Stabilise and recover from established AKI
- Time- and context-sensitive
- Strategies/endpoints may differ

Why give fluids?

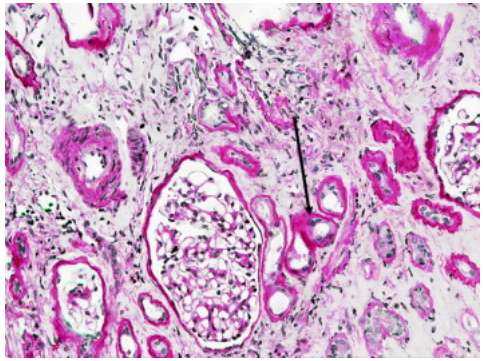
Optimise LV preload



Optimise CO & systemic BP



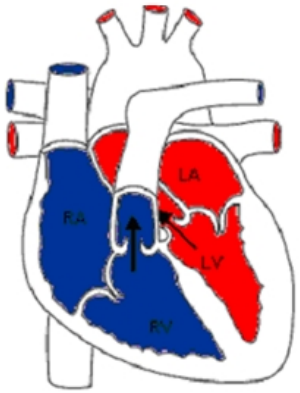
Improve RBF and renal perfusion pressure



Mitigate pre-renal element of AKI

Why give fluids?

Optimise LV preload



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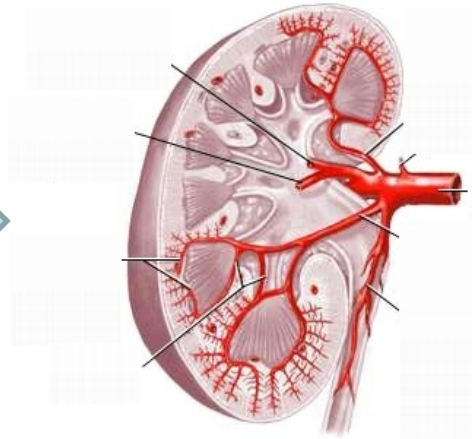

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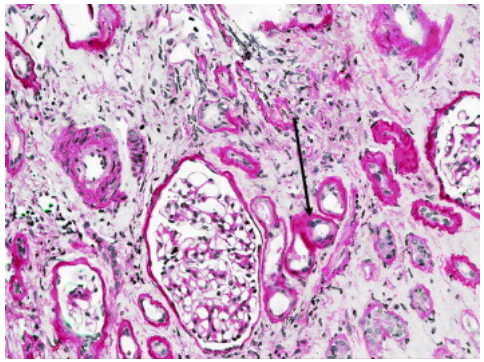

Mitigate pre-renal element of AKI

+ dilution of nephrotoxins, tubular sludge

Why give fluids?

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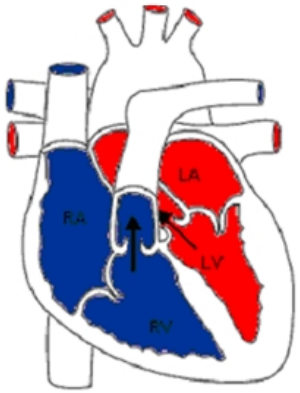

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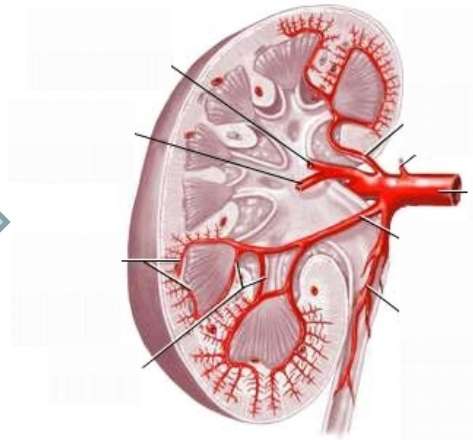

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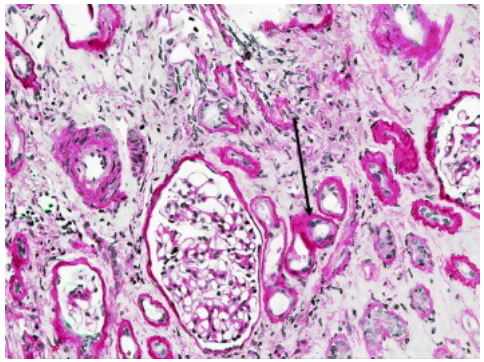

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Do fluids work in AKI?

Johns Hopkins Med J. 1969 Feb;124(2):95-105

Post-traumatic acute renal failure in Vietnam. A comparison with the Korean war experience

Whelton A, Donadiq JV Jr.

- seriously injured casualties in Korean and Vietnam wars
- developments in rapid evacuation and fluid resuscitation
- incidence of AKI improved from 1/200 (Korea) to 1/600 (Vietnam)

Do fluids work in AKI?

J Lab Clin Med. 1980 Aug;96(2):356-62.

Sequential studies on the pathophysiology of glycerol-induced acute renal failure.

Reineck HJ, O'Connor GJ, Lifschitz MD, Stein JH.

- glycerol-injured rodent kidney model. RBF measured by flowmeter.

- Ringer's solution loading completely reversed ~50% drops in RBF occurring sequentially at 3, 6, and 18 hours post glycerol

Do fluids work in AKI?

Crit Care Med 2009, 37:2079-2090

Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study

Brienza N, Giglio MT, Marucci M, Fiore T

- systematic review
- 20 studies, 4220 participants (surgical)
- Postoperative acute renal injury significantly reduced by peri-operative hemodynamic optimization (OR 0.64; CI 0.50-0.83; p = 0.0007 vs control group).

However ...

Are fluids *safe* in AKI?

Crit Care. 2008; 12(3): R74.

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

Payen D, Cornélie de Pont A,Sakr Y *et* al:- Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators

- Observational study
- 3,147 pts in 198 ICUs over 2 weeks. 1,172 (36%) developed AKI.

Are fluids *safe* in AKI?

Hazard ratios: results of multivariate Cox regression analysis for 60-day mortality in critically ill patients with acute renal failure

Characteristic	Hazard ratio	95% CI	*P* value
Age	1.02	1.01–1.03	<0.001
SAPS II (per point)	1.03	1.02–1.04	<0.001
Heart failure	1.38	1.05–1.81	0.02
Medical admission	1.68	1.35–2.08	<0.001
Mean fluid balance, L/24 hours	1.21	1.13–1.28	<0.001
Mechanical ventilation	1.55	1.14–2.11	<0.001
Liver cirrhosis	2.73	1.88–3.95	<0.001

CI, confidence interval; SAPS II, Simplified Acute Physiology Score II.

Payen D *et* al, Crit Care. 2008; 12(3): R74.

Are fluids *safe* in AKI?

Kidney Int. 2009 Aug;76(4):422-7.

Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury

Bouchard J, Soroko SB, Chertow GM, *et al*: Program to Improve Care in Acute Renal Disease (PICARD) Study Group

- 618 pts, multicentre observational study of critically ill pts with AKI
- pts with fluid overload (10% ↑body weight) at dialysis initiation had higher mortality (OR 2.07)
- fluid overload at initiation did not correlate with renal recovery

Are fluids *safe* in AKI?

Crit Care Med. 2011 Dec;39(12):2665-71

Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes

Liu KD, Thompson BT, Ancukiewicz M, *et al* (for ARDSnet)

• Factorial analysis of Fluid and Catheter Treatment Trial data (fluid restriction in lung injury and ARDS)

• unadjusted, AKI (creat rise) incidence greater in conservative arm (57% vs. 51%, p = .04)

• adjusted for dilutional effect on creat, AKI incidence greater in fluid-liberal arm (66% vs. 58%, p = .007)

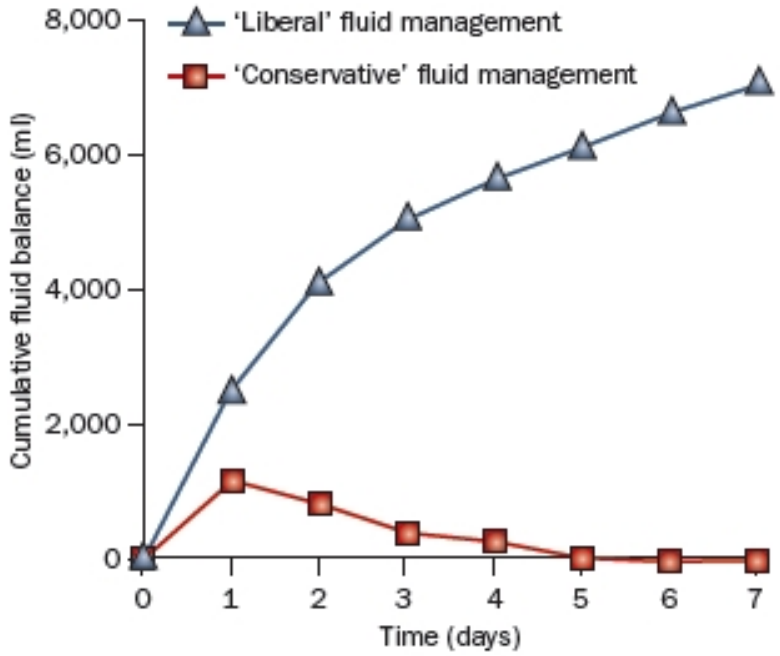


Figure 3 | Cumulative fluid balances achieved in the FACTT trial[88] of liberal (more-conventional) versus conservative (more-restrictive) fluid management strategies in critically ill patients with acute lung injury. No significant differences in renal outcome were found between groups but respiratory parameters were better in patients treated using the conservative approach.

Prowle, J. R. *et al. Nat. Rev. Nephrol. 6, 107–115 (2010)* [from FACTT data]

Are fluids *safe* in AKI?

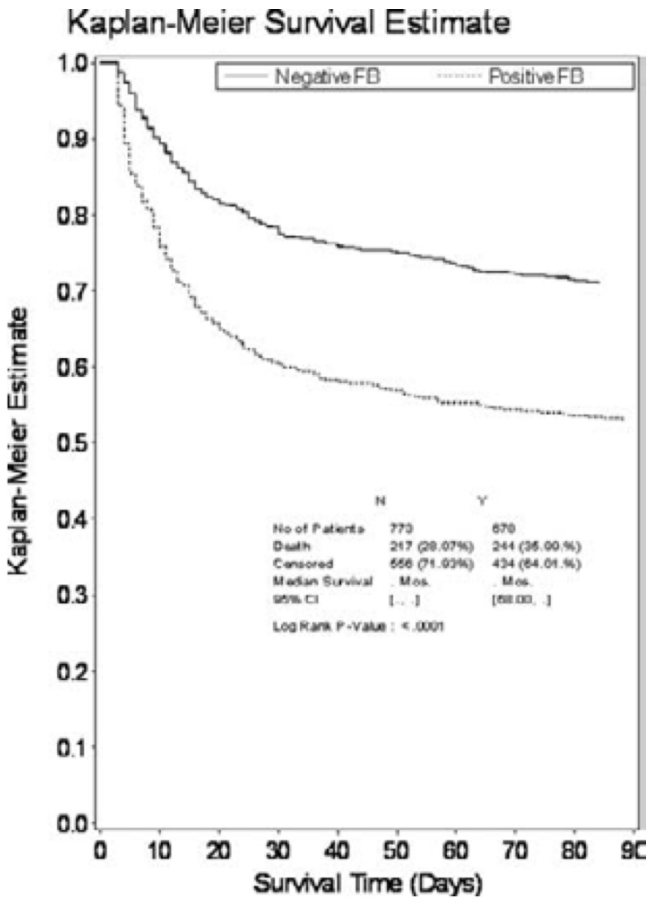
Crit Care Med. 2012 Jun;40(6):1753-60

An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial

RENAL Replacement Therapy Study Investigators, Bellomo R, *et al*

- Analysis of 1453 pts in 35 ICUs from RENAL study (ICU pts on RRT). 44% incidence oedema at randomisation
- daily fluid balance -234 ml/d in survivors, vs. +560ml/d in non- ($p<0.0001$)
- Negative fluid balance during study associated with decreased 90-day mortality (OR 0.318, $P<0.0001$)

Are fluids *safe* in AKI?



Meier graph of survival time from randomization to day 90 stratified by

Bellomo et al Crit Care Med. 2012 Jun;40(6):1753-60

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Are fluids *safe* in AKI?

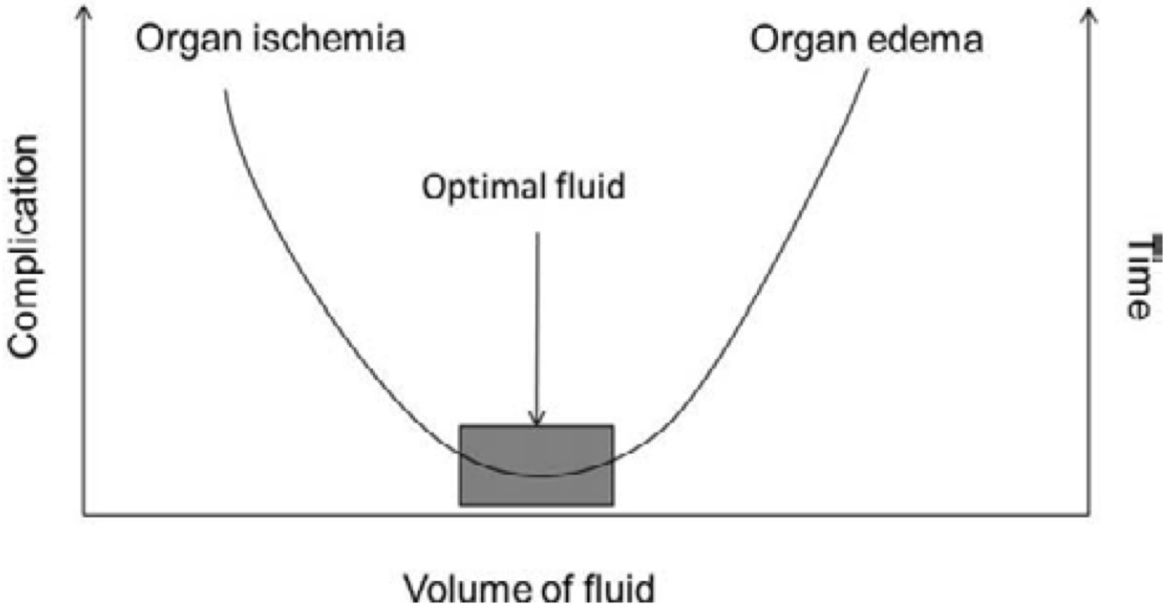


Figure 1. Conceptual model illustrating relationship between time, volume of fluid, and potential complications. The model depicts a curvilinear association between time, volume of fluid, and morbidity. Insufficient volume of fluid early during illness is likely to lead to complications due to organ ischemia. In contrast, late administration of excess fluid after onset of organ dysfunction could potentiate organ edema. Optimal volume of fluid at any given time is likely to preserve organ viability without increasing morbidity.

Crit Care Med 2012 Vol. 40, No. 6

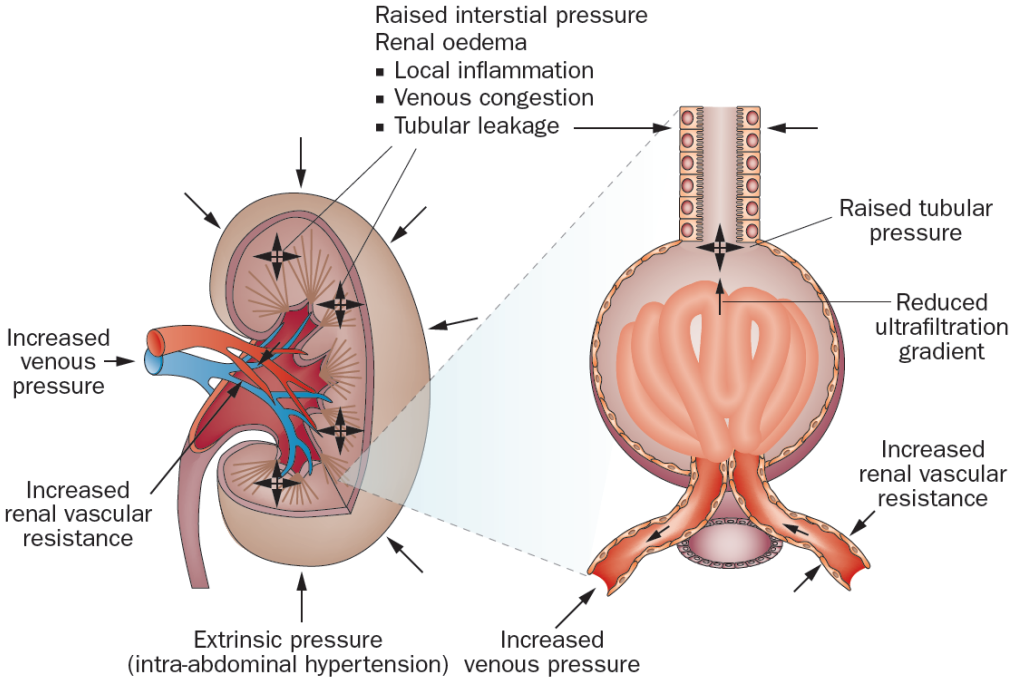


Figure 1 | Fluid overload and interstitial oedema can contribute to the maintenance of AKI. In established AKI, renal dysfunction (reduced GFR) persists despite resuscitation of systemic blood pressure and cardiac output. Increased renal venous pressure reduces the transrenal pressure gradient for RBF. Increased interstitial and tubular pressure might reduce or abolish the net glomerular filtration pressure gradient. Increased preglomerular resistance, in response to tubular injury, further reduces RBF and glomerular capillary hydrostatic pressure, hyperchloraemia might contribute to this effect.[49] Development of intra-abdominal hypertension restricts venous drainage and extrinsically compresses the kidney. Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; RBF, renal blood flow.

Prowle JR, Kirwan C, Bellomo R.
Nature Reviews Nephrology Volume: 10, Pages:37–47

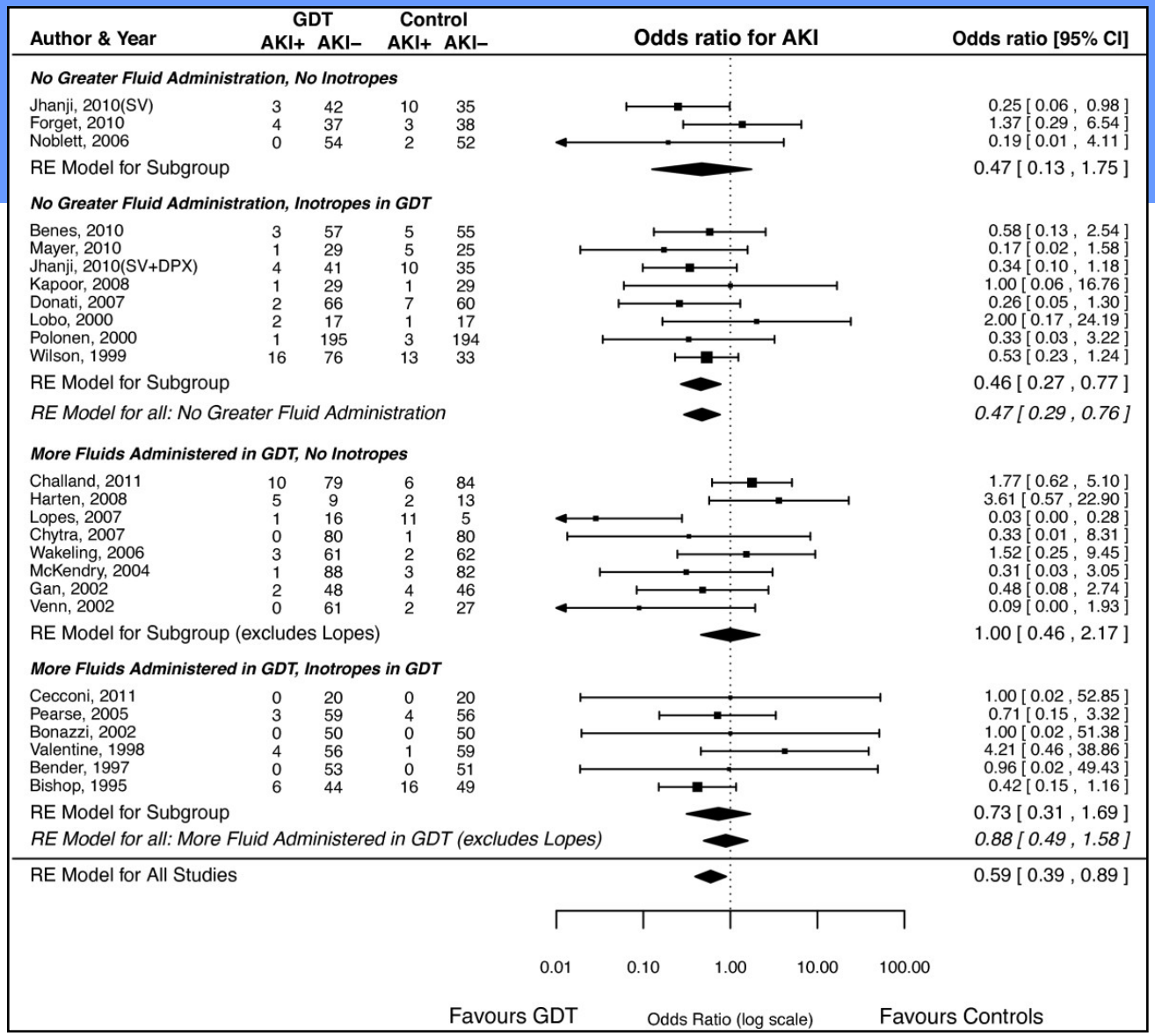
Are fluids *safe* in AKI?

Crit Care. 2012 Aug 7;16(4):230.

Clinical review: Volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review.

Prowle JR, Chua HR, Bagshaw SM, Bellomo R.

- SR of RCTs of goal-directed therapy vs control
- decreased risk of AKI in 24 peri-op studies: OR = 0.59 (0.39 - 0.89)
- mean difference in fluid given = +555ml in treatment group
- greater effect when fluid volume same: OR = 0.47, 0.29 - 0.76)
- greatest effect with inotropes and equal fluid replacement between groups: OR = 0.46, (0.27 - 0.76, P = 0.0036)



Prowle JR *et al*, Crit Care. 2012 Aug 7;16(4):230

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BBC NEWS

UK version | International version | About the versions | Low graphics

Last Updated: Wednesday, 15 March 2006, 09:52 GMT

E-mail this to a friend | Printable version

Six taken ill after drug trials

Six men remain in intensive care after being taken ill during a clinical drugs trial in north-west London.

The six are being treated at Northwick Park hospital

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.

oedema after fluid resuscitation in shocked patient with capillary injury ...
(don't try this at home)

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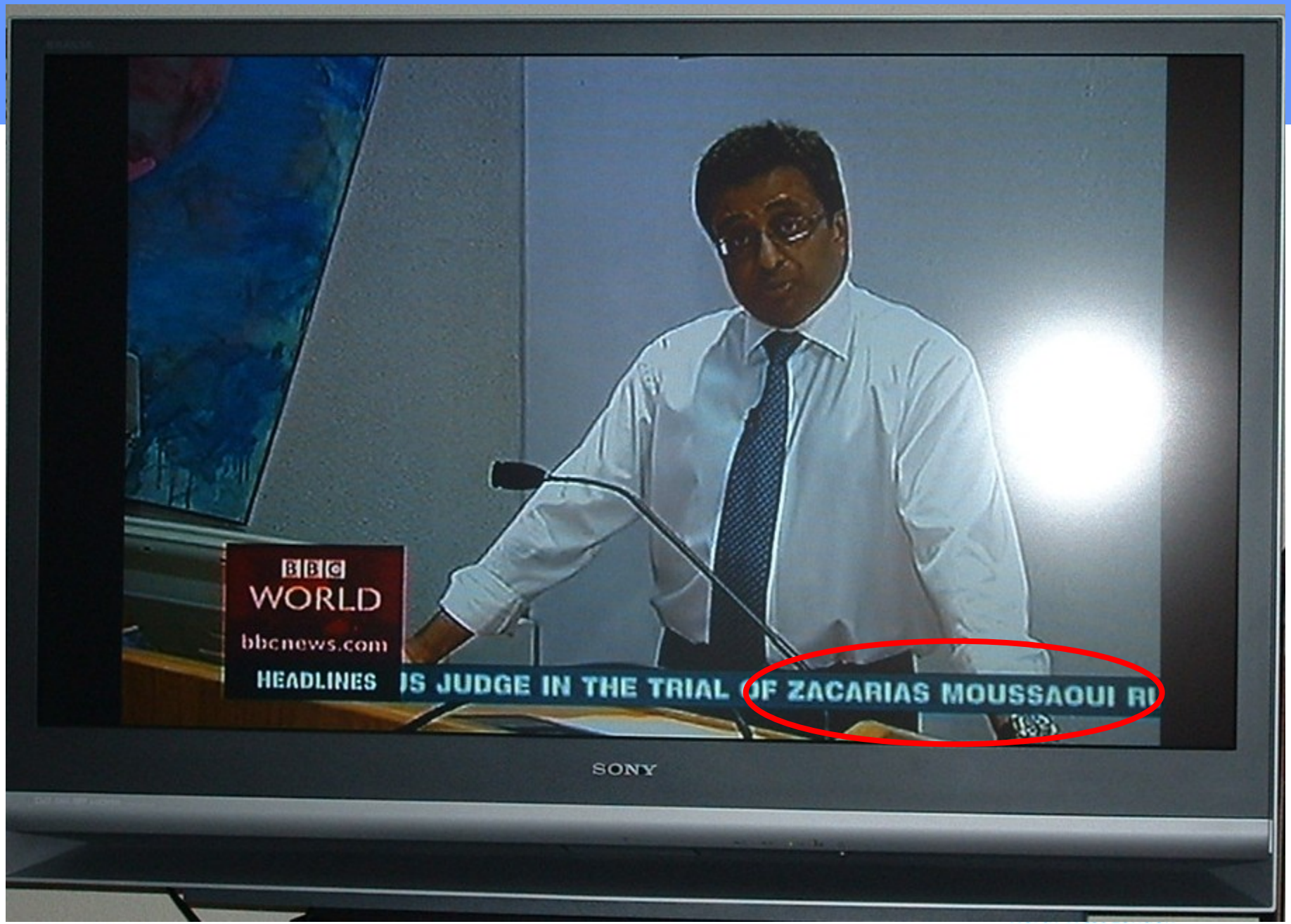
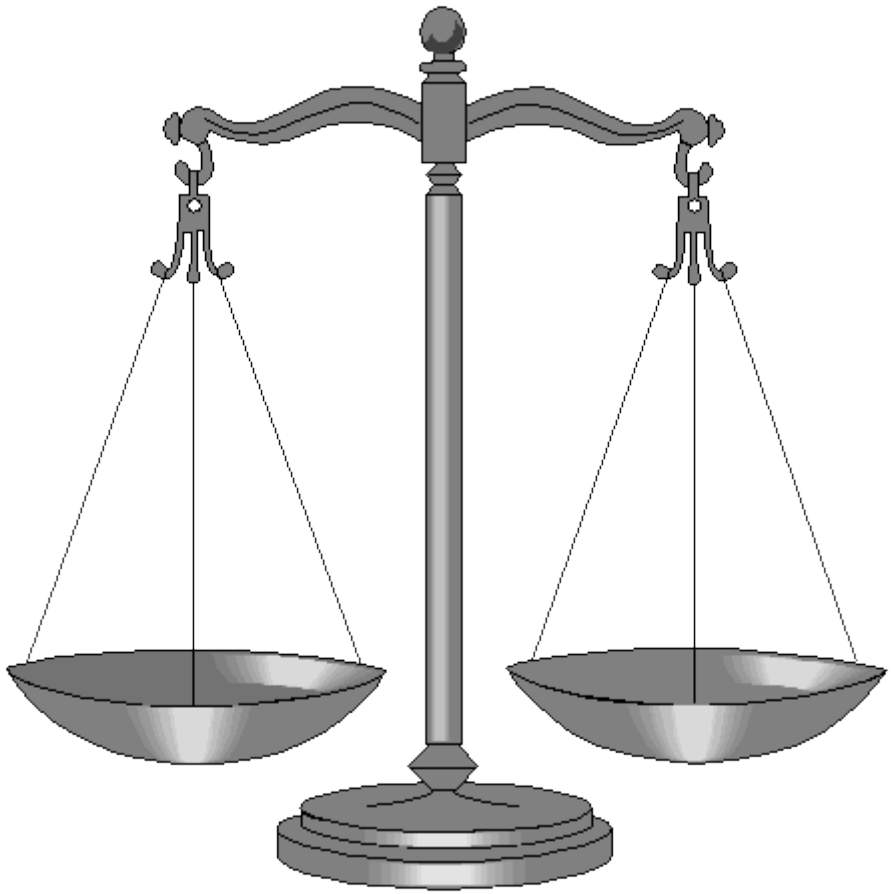

BBC
WORLD
bbcnews.com
HEADLINES
S JUDGE IN THE TRIAL OF ZACARIAS MOUSSAOUI RI
SONY

watch this space

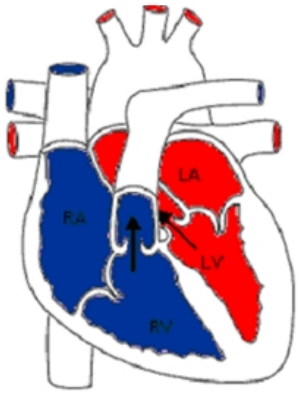
70. Protocolized Care for Early Septic Shock (ProCESS) – NCT00510835 [http://clinicaltrials.gov/ct2/show/NCT00510835]
71. Australasian Resuscitation in Sepsis Evaluation Randomised Controlled Trial (ARISE) – NCT00975793 [http://clinicaltrials.gov/ct2/show/NCT00975793]
72. A multicentre, randomised controlled trial of the clinical and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock (ProMISe) – ISRCTN36307479 [http://www.controlled-trials.com/ISRCTN36307479]
73. Optimisation of peri-operative cardiovascular management to improve surgical outcome (OPTIMISE) – ISRCTN04386758 [http://www.controlled-trials.com/ISRCTN04386758/pearse]

Do fluids work in AKI?



Why give fluids?

Optimise LV preload



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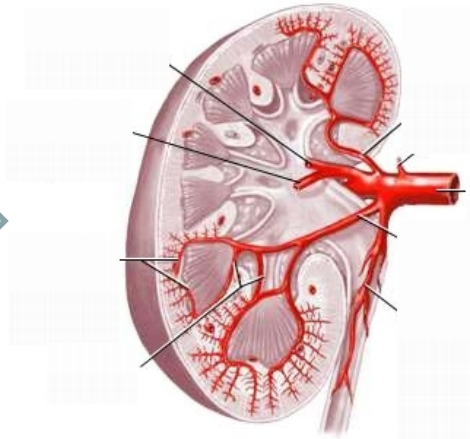
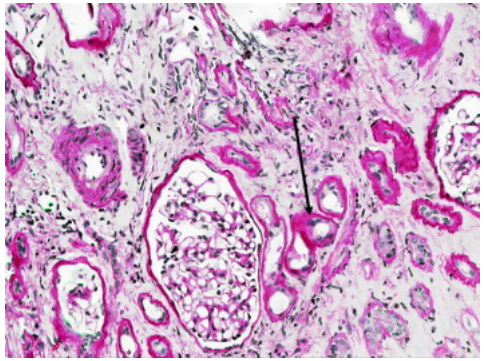


Improve RBF and renal perfusion pressure



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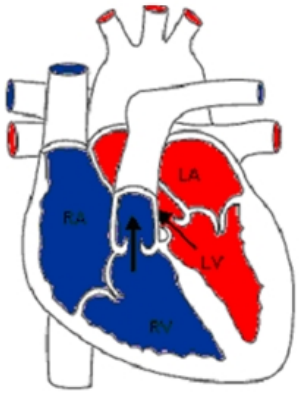

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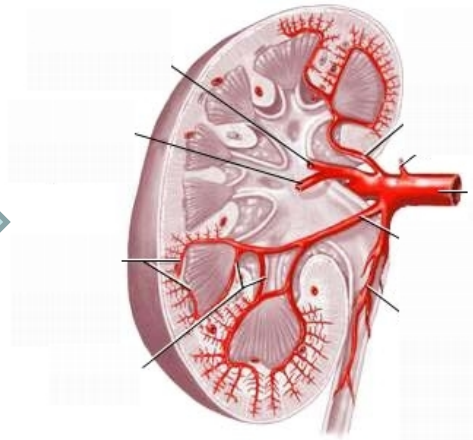

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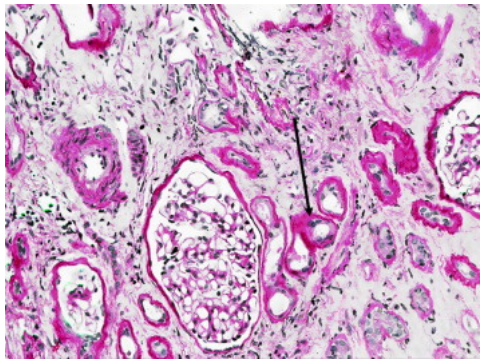


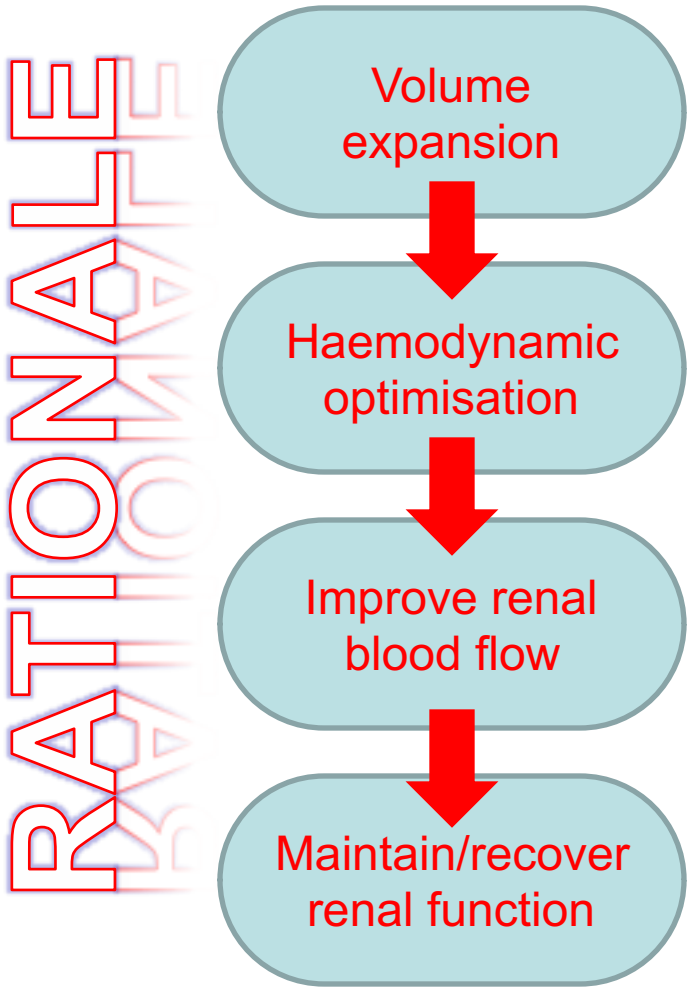
Mitigate pre-renal element of AKI

Clin J Am Soc Nephrol. 2008 July; 3(4): 962–967.

Evaluation and Initial Management of Acute Kidney Injury

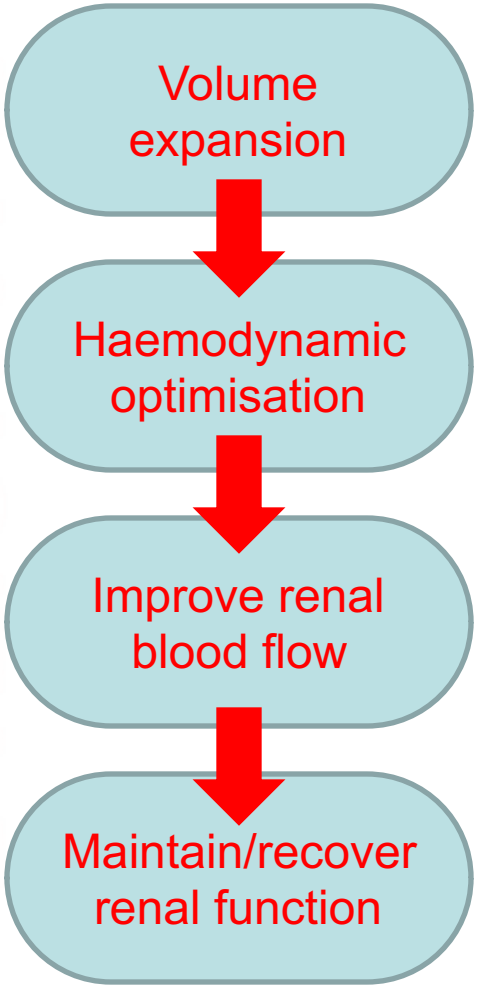
Himmelfarb J, Joannidis M, Molitoris B, *et al*

Does it work?


RATIONALE
Volume expansion
Haemodynamic optimisation
Improve renal blood flow
Maintain/recover renal function
Volume-responsive patient
Volume-responsive kidney

Does it work?

RATIONALE



REALITY

Volume-responsive patient ?
In most cases: yes
But: e.g. CCF, CM

Volume-responsive kidney ?
In most cases: yes (when early)
But: e.g.
- renal artery stenosis
- inflammatory renal disease
- nephrotoxins
- ?sepsis
- "too late": untreated/undertreated VR-AKI

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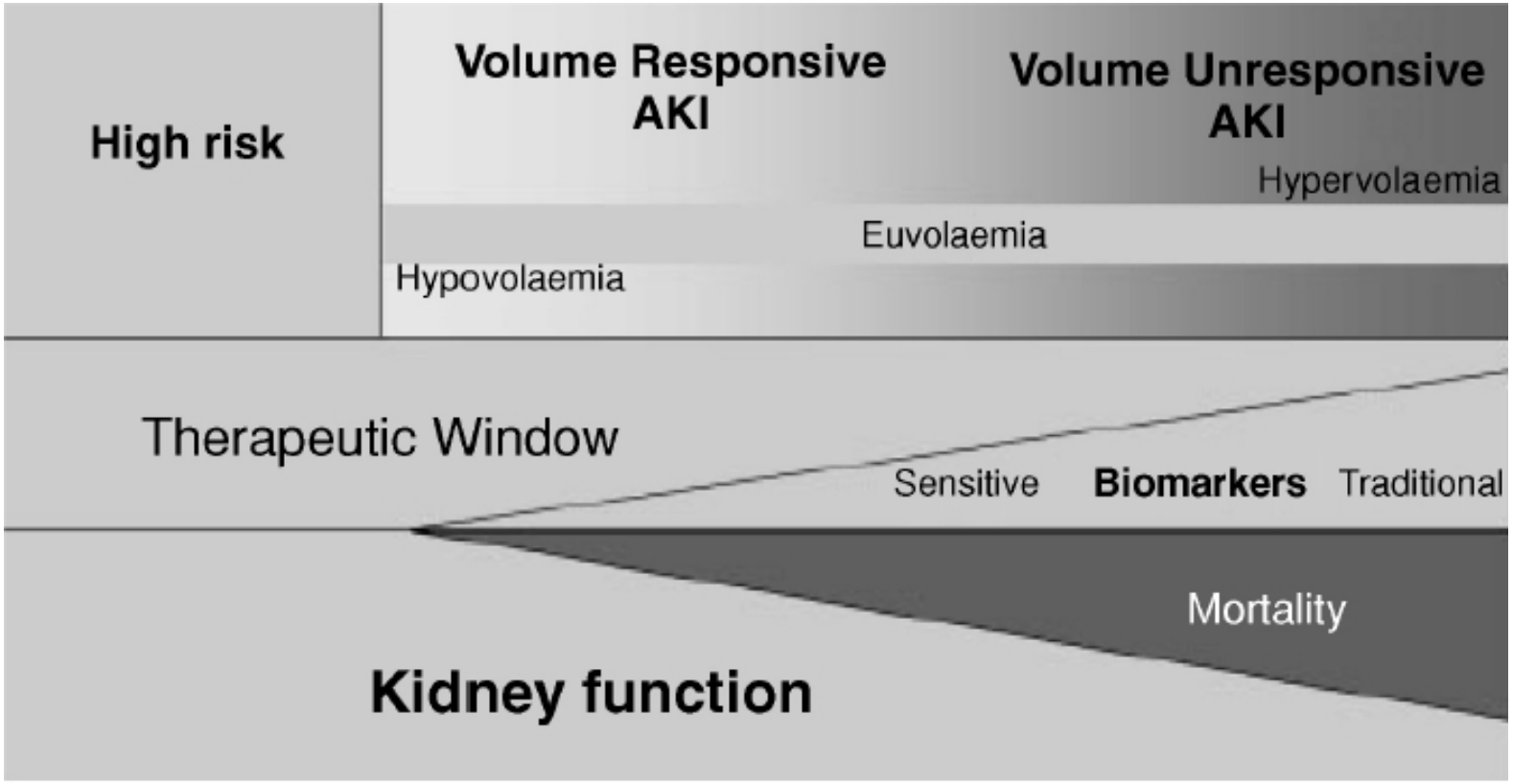
Clinical context: time



Himmelfarb J *et al*. Clin J Am Soc Nephrol. 2008 July; 3(4): 962–967

Clinical context: condition

- Volume-responsive AKI needing primary resuscitation
  - primary shock reversal
  - time-sensitive
- Volume-responsive AKI needing ongoing volume replacement
  - active fluid loss (haemorrhage, GI, burns)
  - third-space loss (sepsis, trauma, major surgery)
- Non-Volume Responsive AKI

Clinical context

in other words:

Clinical context

in other words:

- Some patients did have volume-responsive kidneys... but you missed it

Clinical context

in other words:

- Some patients did have volume-responsive kidneys... but you missed it
- All of these are retrospective diagnoses

Clinical context

in other words:

- Some patients have volume-responsive haemodynamics, and have volume-responsive kidneys

- Some patients did have volume-responsive kidneys... but you missed it
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Clinical context

in other words:

- Some patients have volume-responsive haemodynamics, and have volume-responsive kidneys
- Some patients are not volume responsive (limited CO)

- Some patients did have volume-responsive kidneys... but you missed it
- All of these are retrospective diagnoses

Clinical context

in other words:

- Some patients have volume-responsive haemodynamics, and have volume-responsive kidneys
- Some patients are not volume responsive (limited CO)
- Some patients are volume responsive (haemodynamically), but their kidneys are not
- Some patients did have volume-responsive kidneys... but you missed it
- All of these are retrospective diagnoses

Which aetiologies are volume-responsive?

risk factors for AKI:

- generic
  - age
  - hypovolaemia
  - hypotension
  - sepsis
  - pre-existing disease (DM, renal, hepatic, cardiac)
  - nephrotoxins (NSAID, ACEI, A2RB, contrast medium)
- specific *(e.g.)*
  - rhabdomyolysis
  - tumour lysis
  - bypass (clamp time)

Lameire N *et al*. NDT Plus (2008) 6: 392–402

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Lameire N *et al*. NDT Plus (2008) 6: 392–402

Sepsis and AKI

JAMA. 2005 Aug 17;294(7):813-8.

Acute renal failure in critically ill patients: a multinational, multicenter study.

Uchino S, Kellum JA, Bellomo R, Doig GS *et al* (BEST Kidney Inv.)

- AKI in 1738 critically ill patients (5.7%) of 29269 ICU admissions
- Sepsis as contributing factor in 47.5% of AKI pts; (95% CI, 45.2%-49.5%)

WHEN TO GIVE FLUIDS?

Clinical context: timing

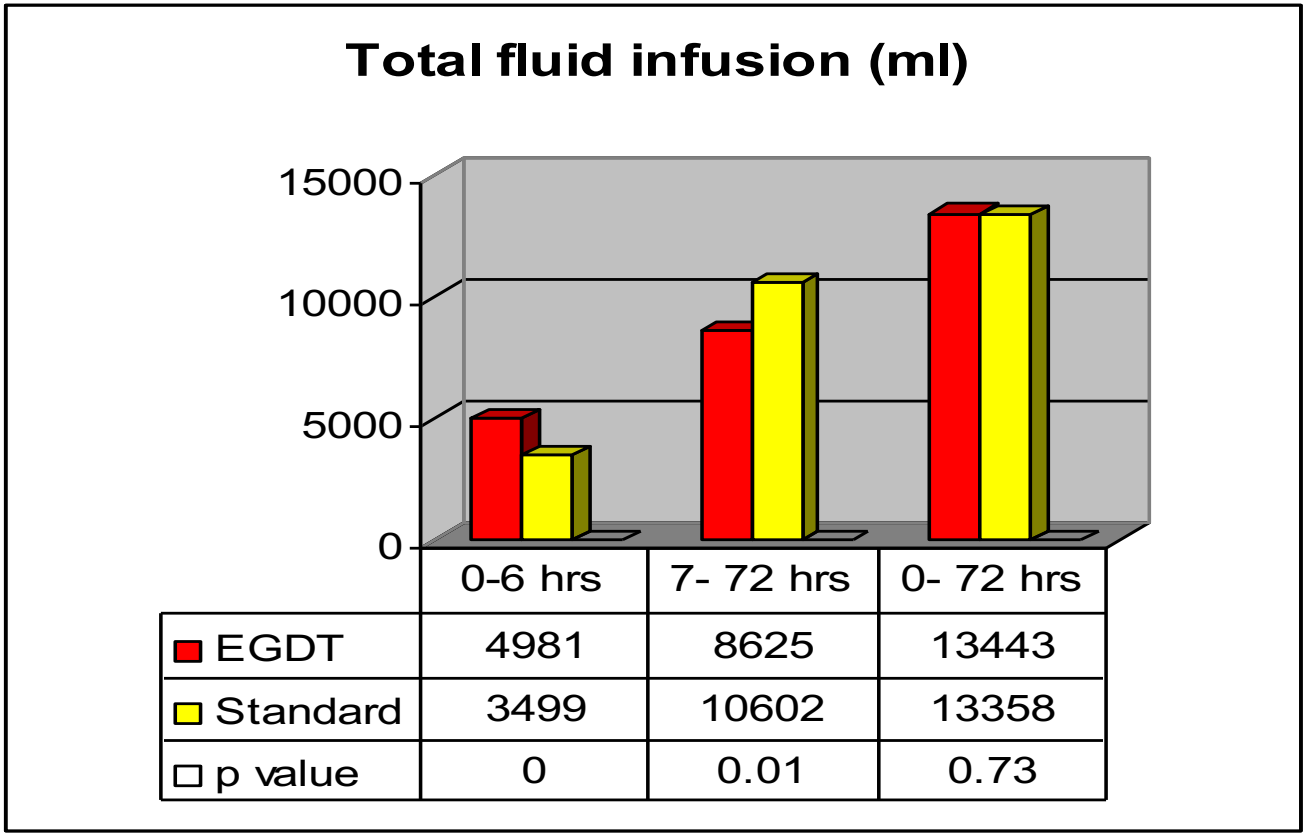
N Engl J Med. 2001 Nov 8;345(19):1368-77

Early goal-directed therapy in the treatment of severe sepsis and septic shock.

Rivers E, Nguyen B, Havstad S, *et al*

- Prospective RCT 263 pts in septic shock in ED
- Early goal-directed management to ScVO2 (indirect measure of tissue perfusion) , vs. conventional treatment,
- 72 hours standard ICU care for both groups

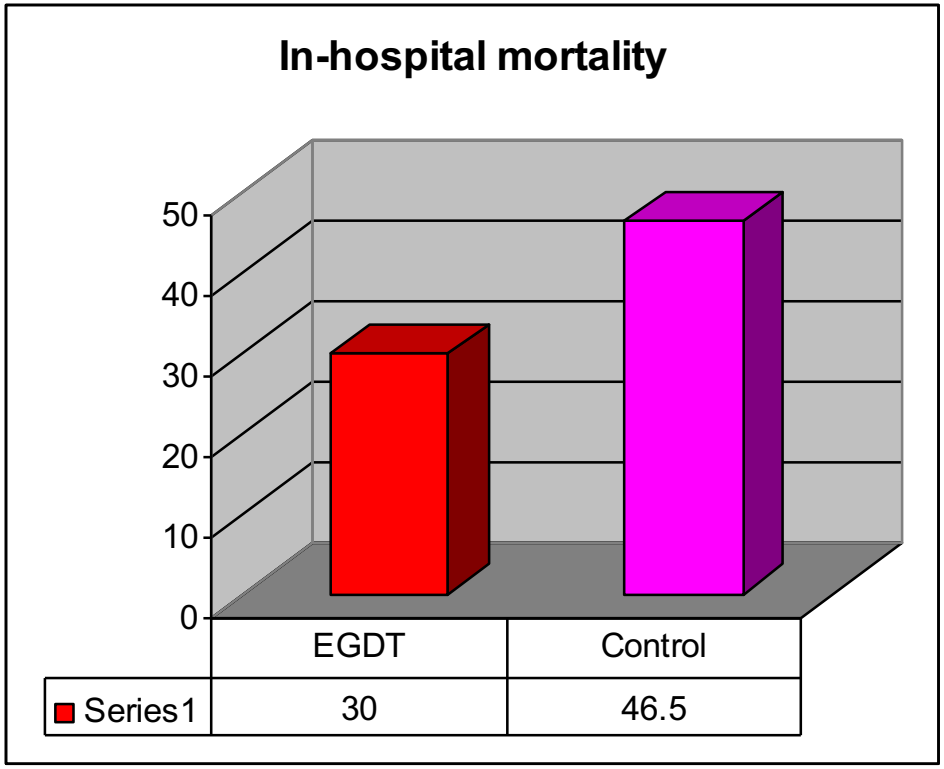
Clinical context: timing



	0-6 hrs	7- 72 hrs	0- 72 hrs
EGDT	4981	8625	13443
Standard	3499	10602	13358
p value	0	0.01	0.73

(data from): Rivers E *et al* N Engl J Med. 2001 Nov 8;345(19):1368-77

Clinical context: timing



(data from): Rivers E *et al* N Engl J Med. 2001 Nov 8;345(19):1368-77

Clinical context: timing

Shock. 2006 Dec;26(6):551-7.

A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial.

Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP

- Prospective RCT of 465 pts in septic shock
- Treatment group: protocolised rapid shock reversal using CVP, MAP, U/O as goals, vs. conventional clinical management
- Mortality (53.7% vs. 71.6%, P = 0.006) with reduced incidence of AKI

Clinical context: timing

N Engl J Med 2014; 370:1683-1693

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators

- Prospective RCT of 1341 pts in septic shock
- Treatment groups: EGDT vs. protocolised standard Rx, vs. usual care
- No difference 60-day mortality (21.0% EGDT vs. 18.2% protocolised standard Rx vs. 18.9% usual care, P = 0.31-0.83) or duration of RRT (7.1 vs 8.5 vs. 8.8 days, p=0.92)

Clinical context: timing

N Engl J Med 2014; 371:1496-1506

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group

- 1600 septic pts in 51 centres (mainly Aus/NZ)
- Treatment group: EGDT using Detroit protocol including ScvO2, vs. conventional clinical management
- EGDT group had higher fluids in first 6 hours (1964ml vs. 1713ml, $p<0.001$)
- No difference in 90-day mortality (18.6% vs. 18.8%, $p=0.90$); or RRT (13.4% vs. 13.5%, $p= 0.94$).

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North West London

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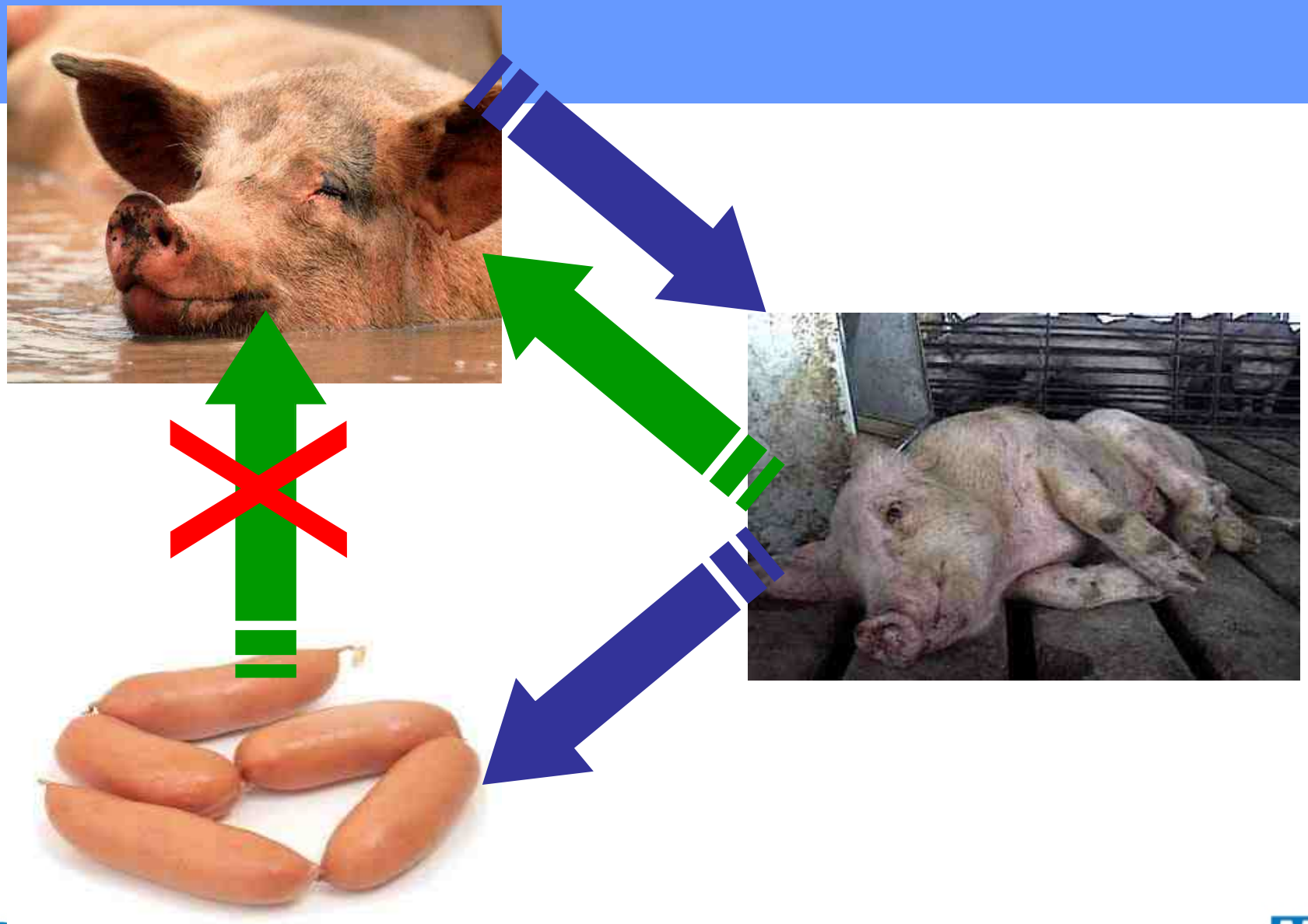

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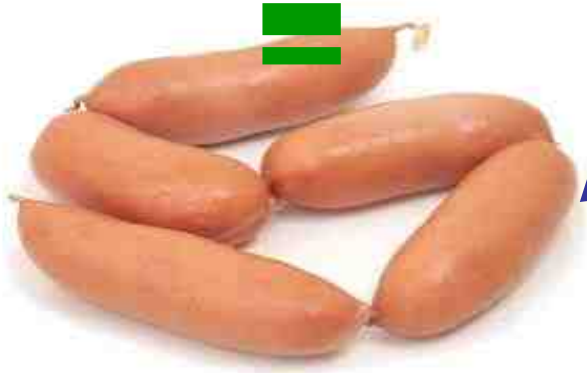

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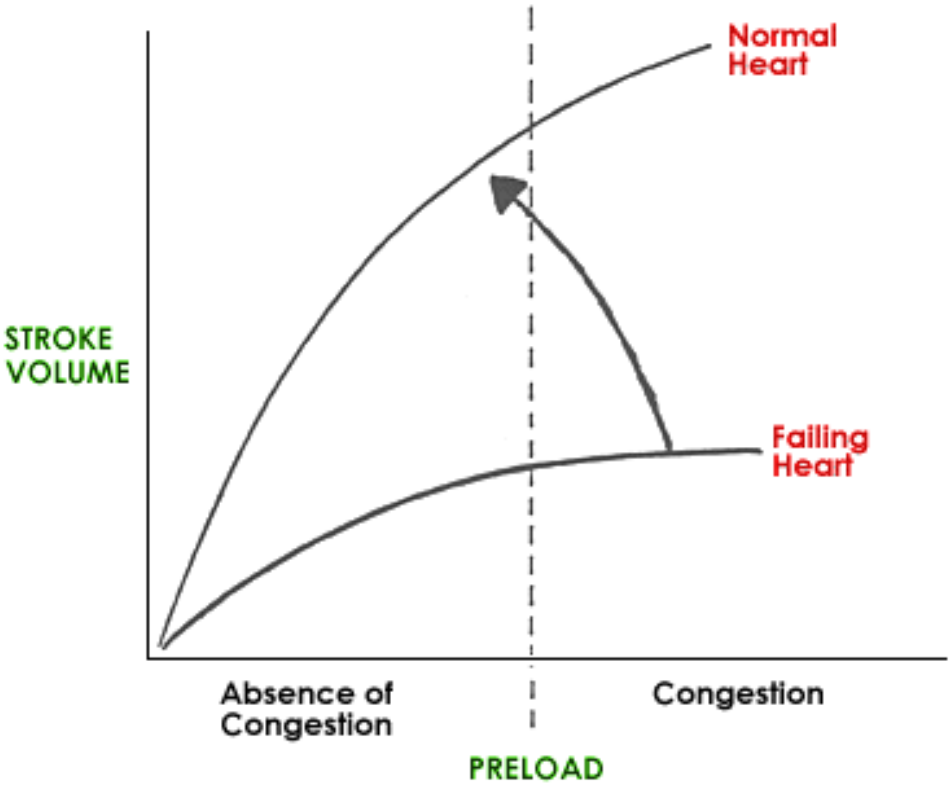
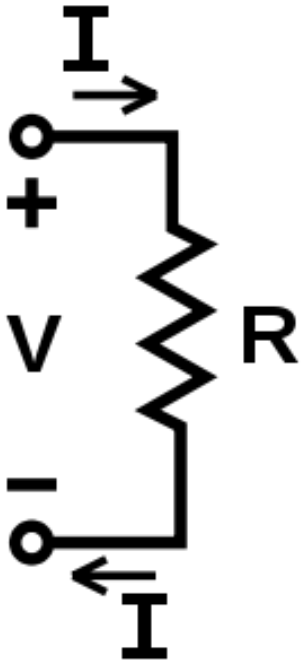
HOW MUCH FLUID TO GIVE?

Optimising cardiac output

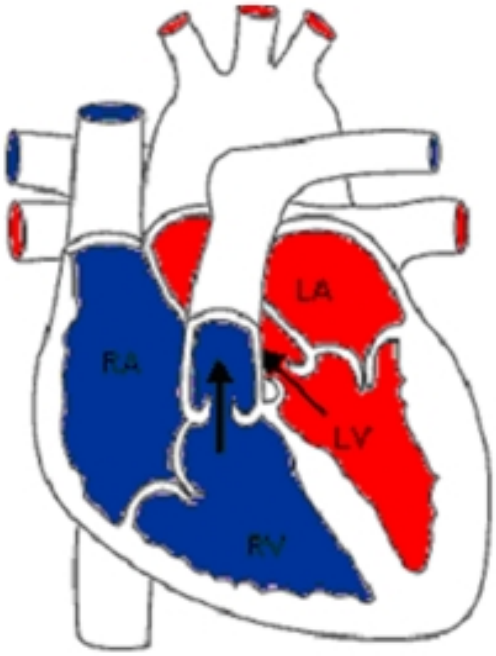


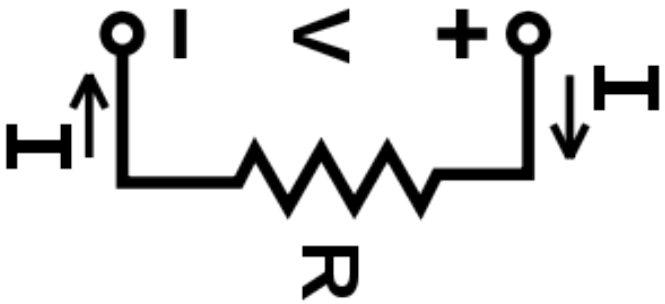
Optimising end-organ perfusion

$$V = I R$$

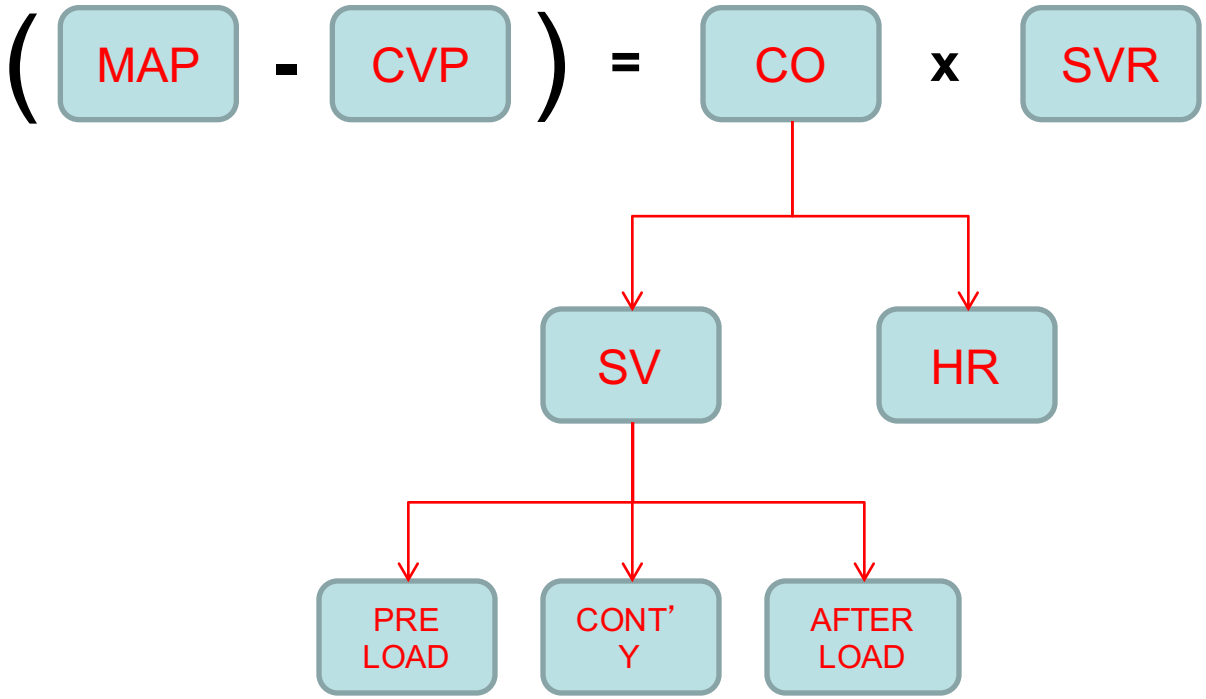


Optimising end-organ perfusion

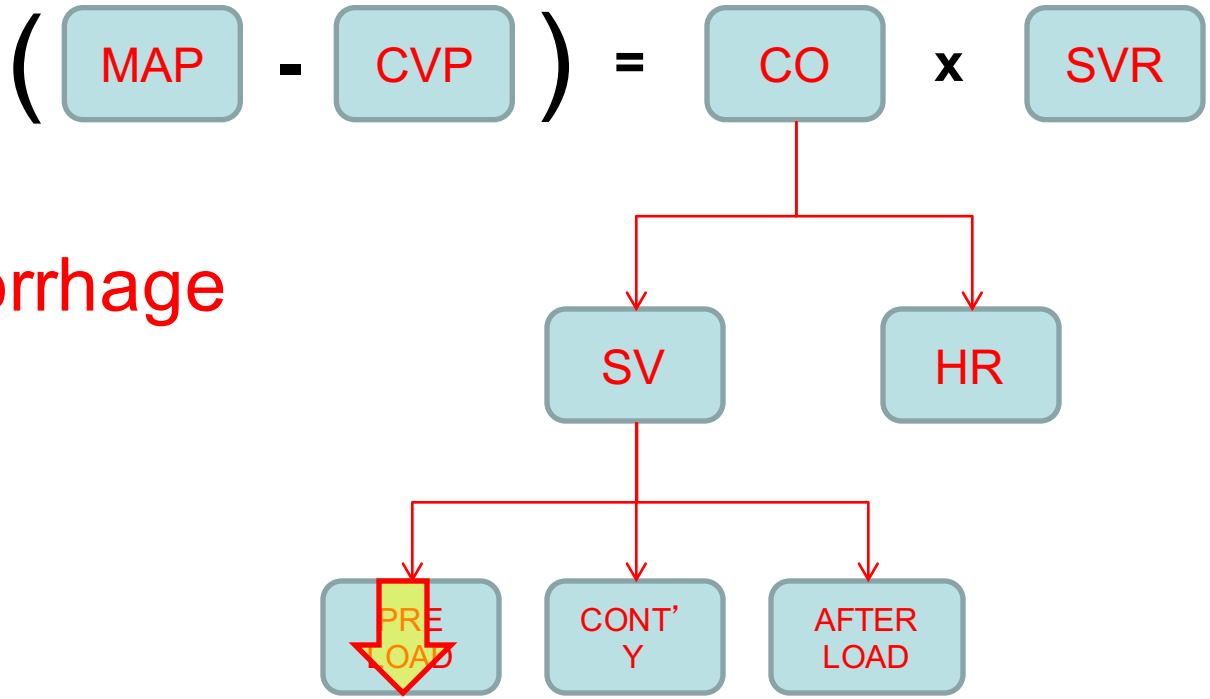




Optimising end-organ perfusion

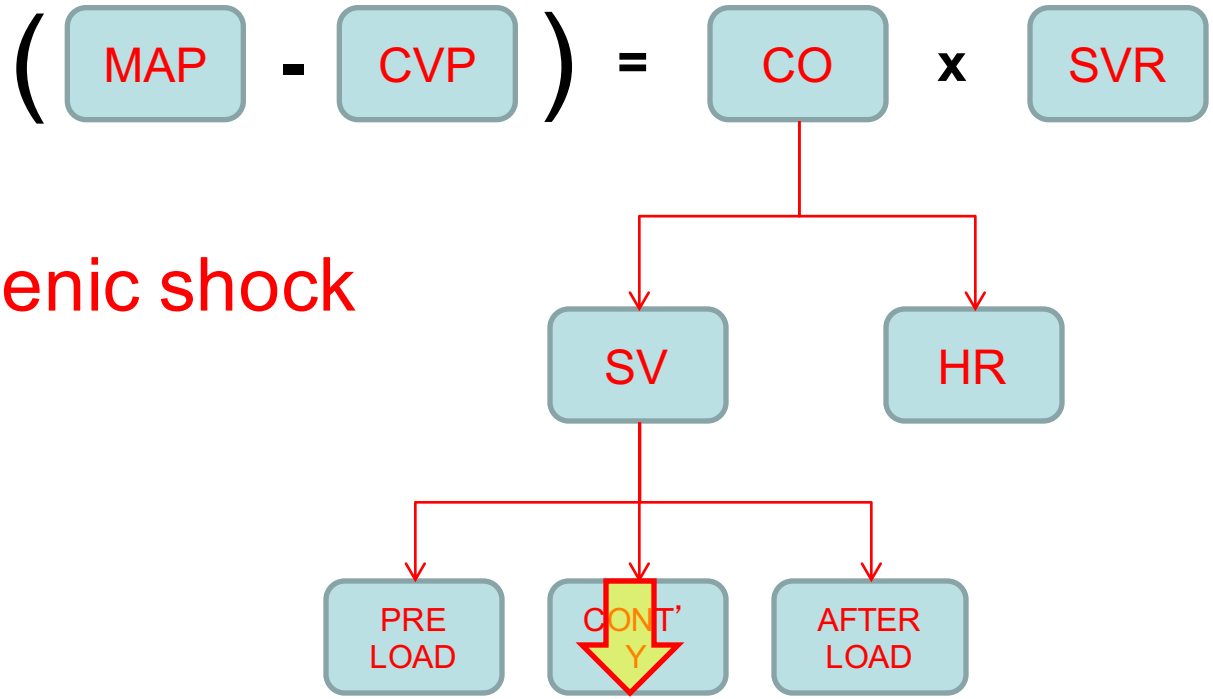


Optimising end-organ perfusion



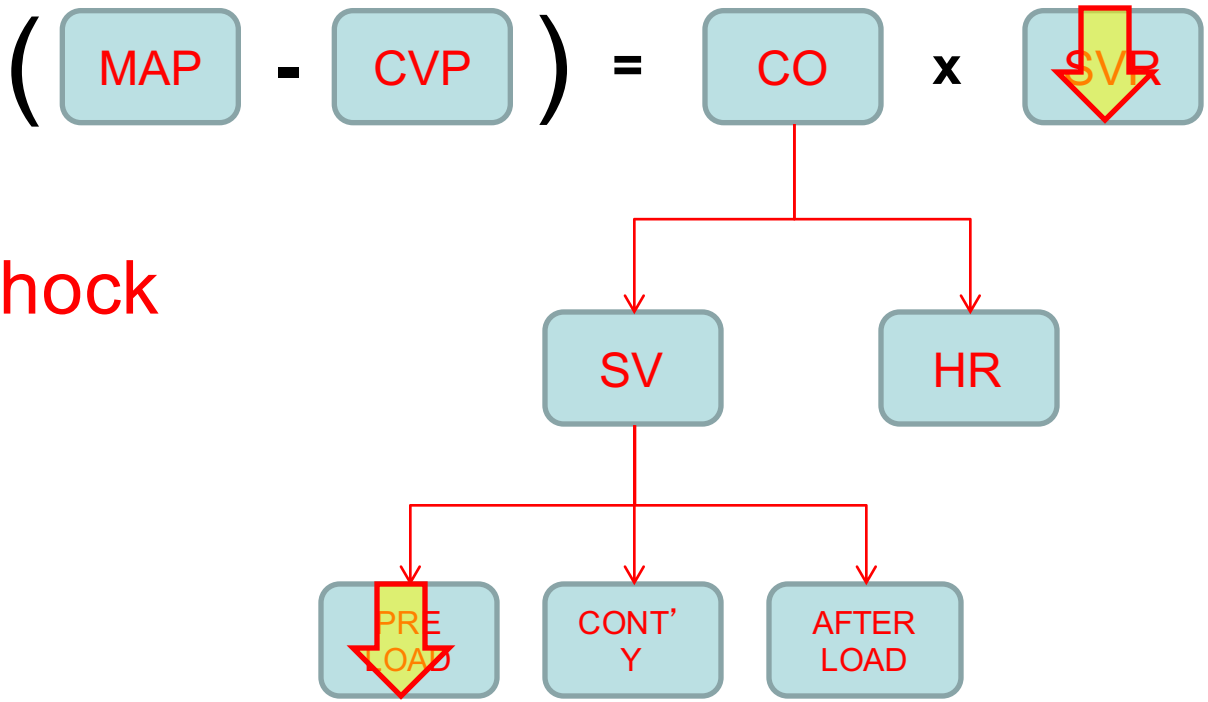
Haemorrhage

Optimising end-organ perfusion



Cardiogenic shock

Optimising end-organ perfusion



How to assess volume response

preload measures?

- Clinical:
  - JVP
- Non-invasive
  - Echo
- Invasive
  - CVP
  - PAWP

CO measures

- Clinical:
  - pulse
  - BP
  - response to leg raise
    - (in vent'd pts)
- Flow measures
  - Δ pulse pressure
  - Δ stroke volume
- Direct cardiac output
  - PA cath
  - peripheral dilution
  - ODM

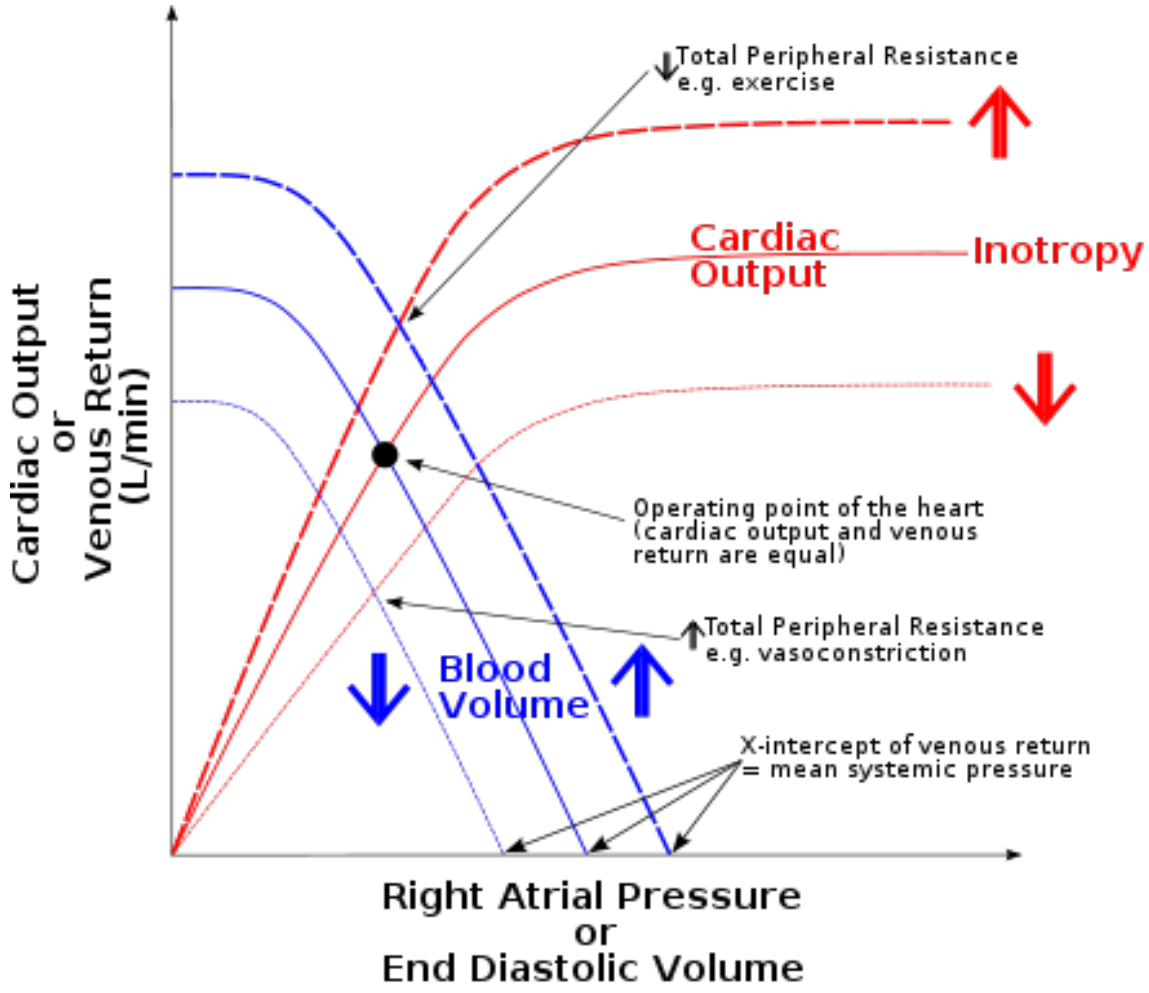
organ perfusion

- Clinical:
  - peripheries
  - urine output
- Generic measures
  - lactate
  - lactate *reversal*
  - ScVO2
- Renal

How to assess volume response

- 3 rules
  - flow measures (CO/SV) are better than preload
  - dynamic is better than static
  - in a shocked patient, generic, *available* perfusion markers (e.g. lactate reversal) can be a useful proxy for renal biomarkers

volume challenge: a rational approach



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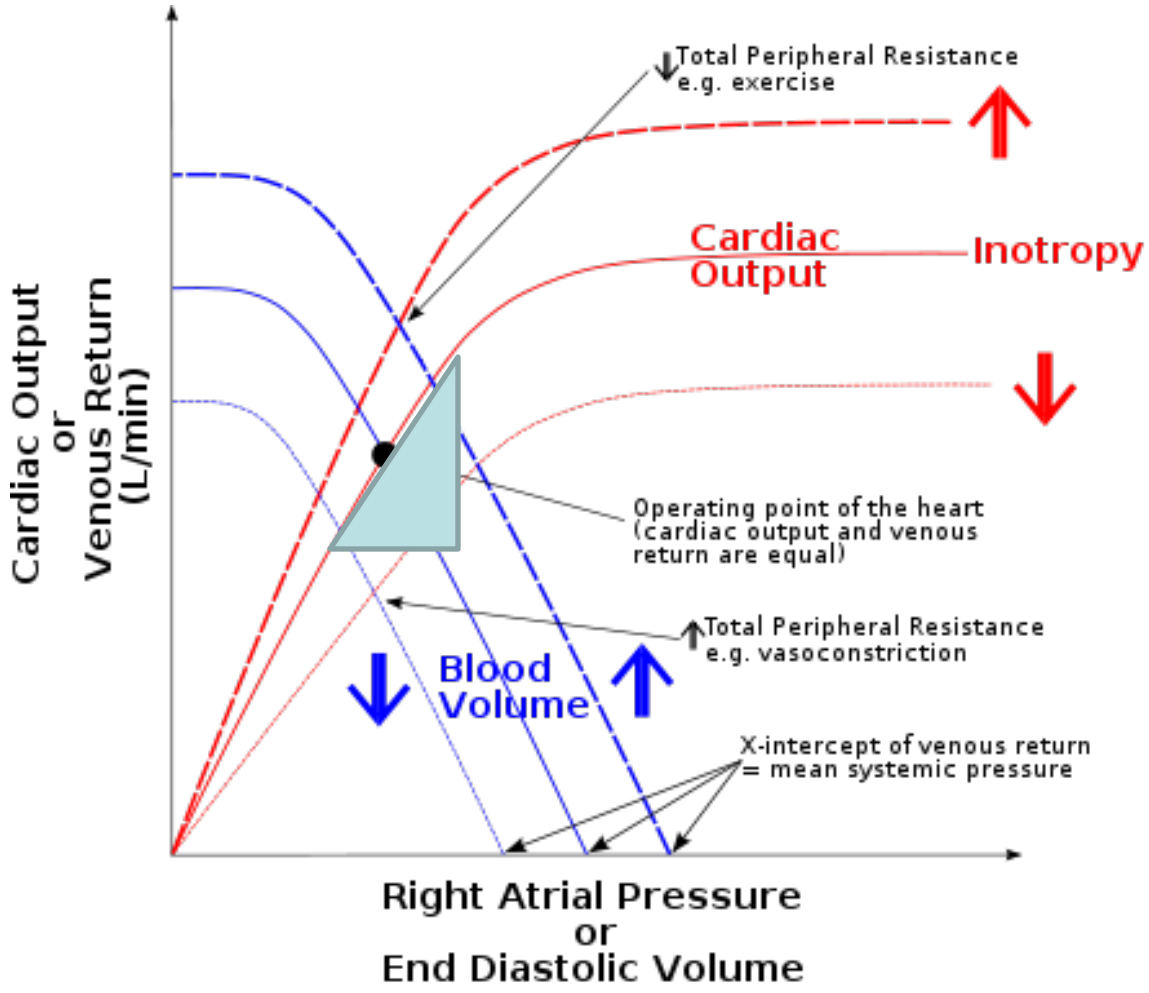
volume challenge: a rational approach



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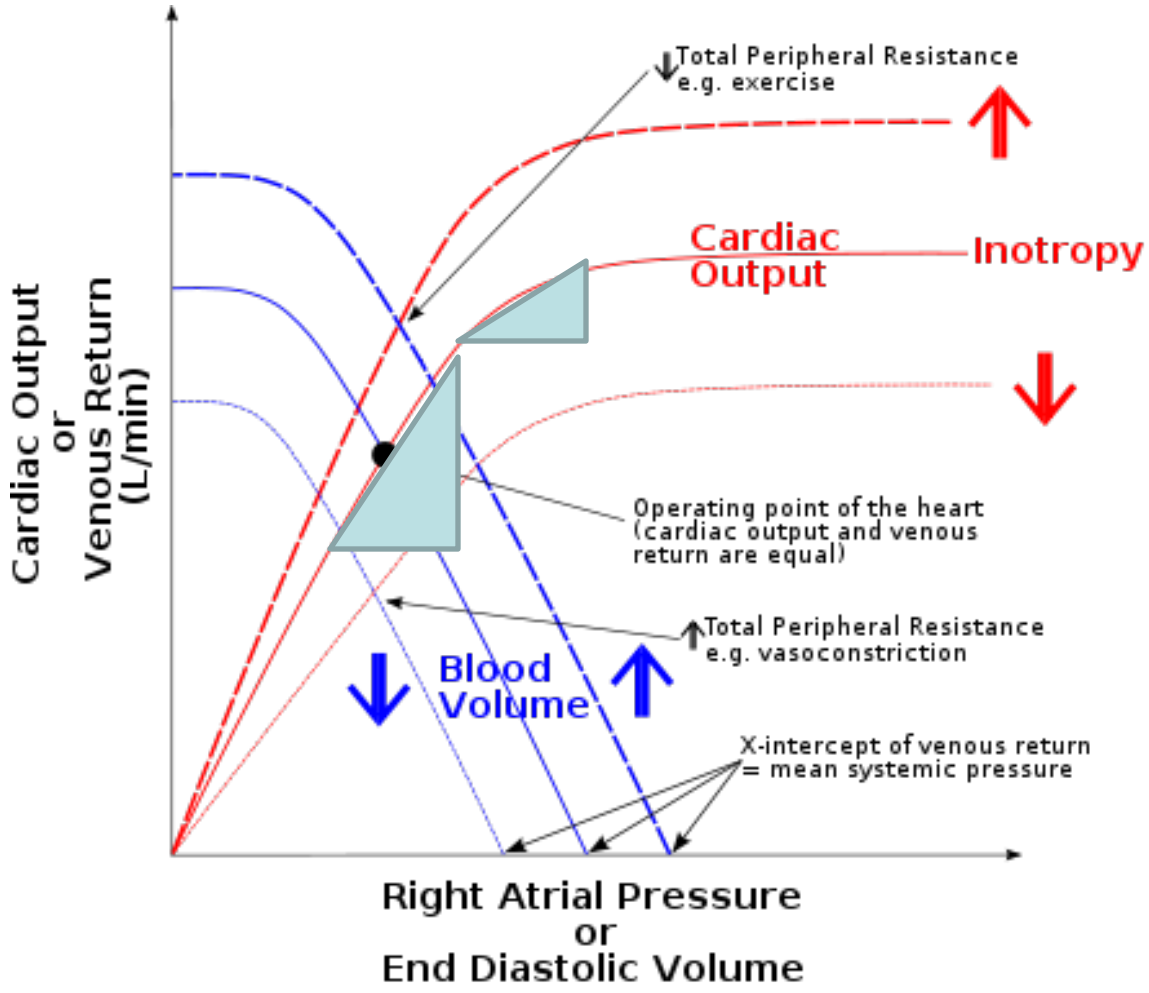
volume challenge: a rational approach



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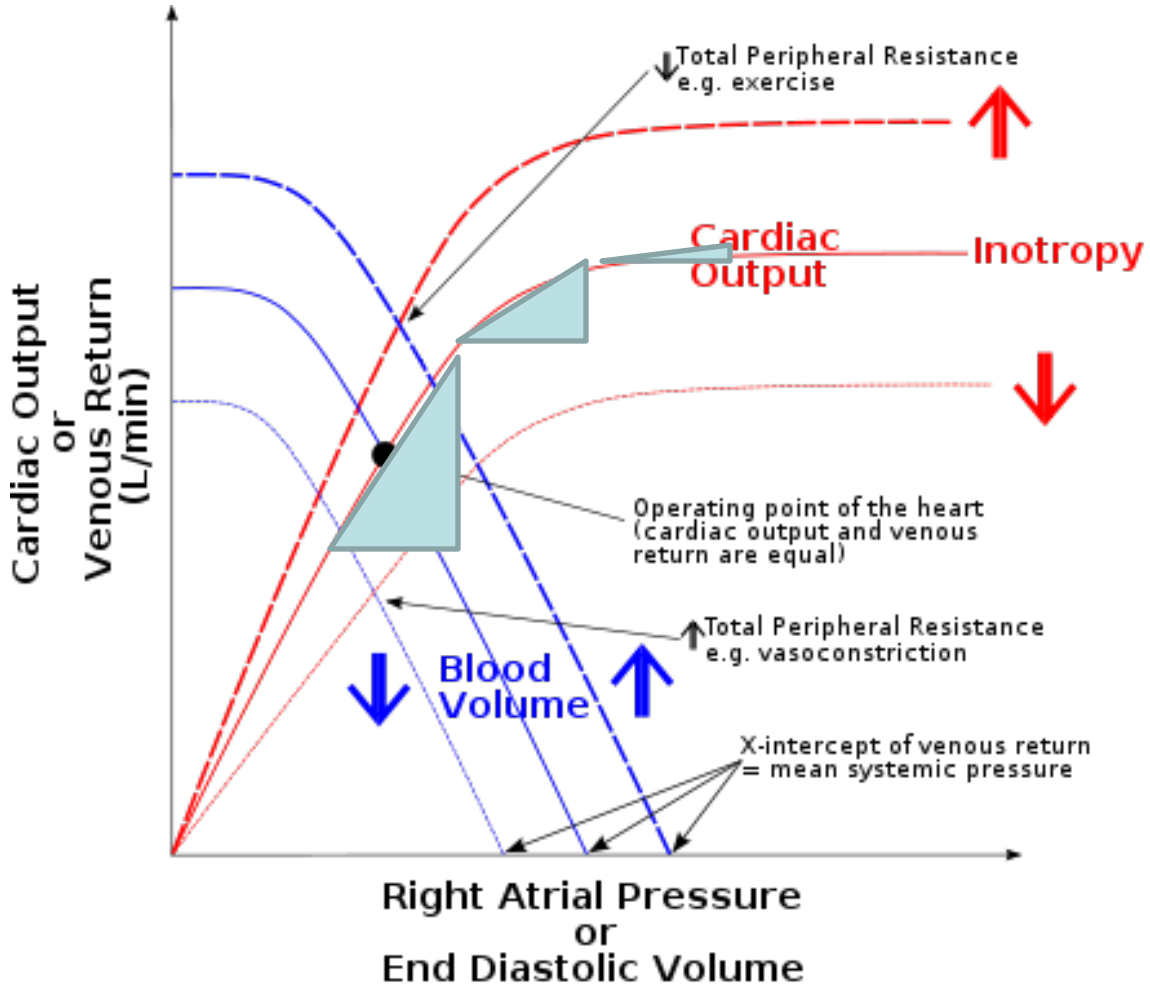
volume challenge: a rational approach



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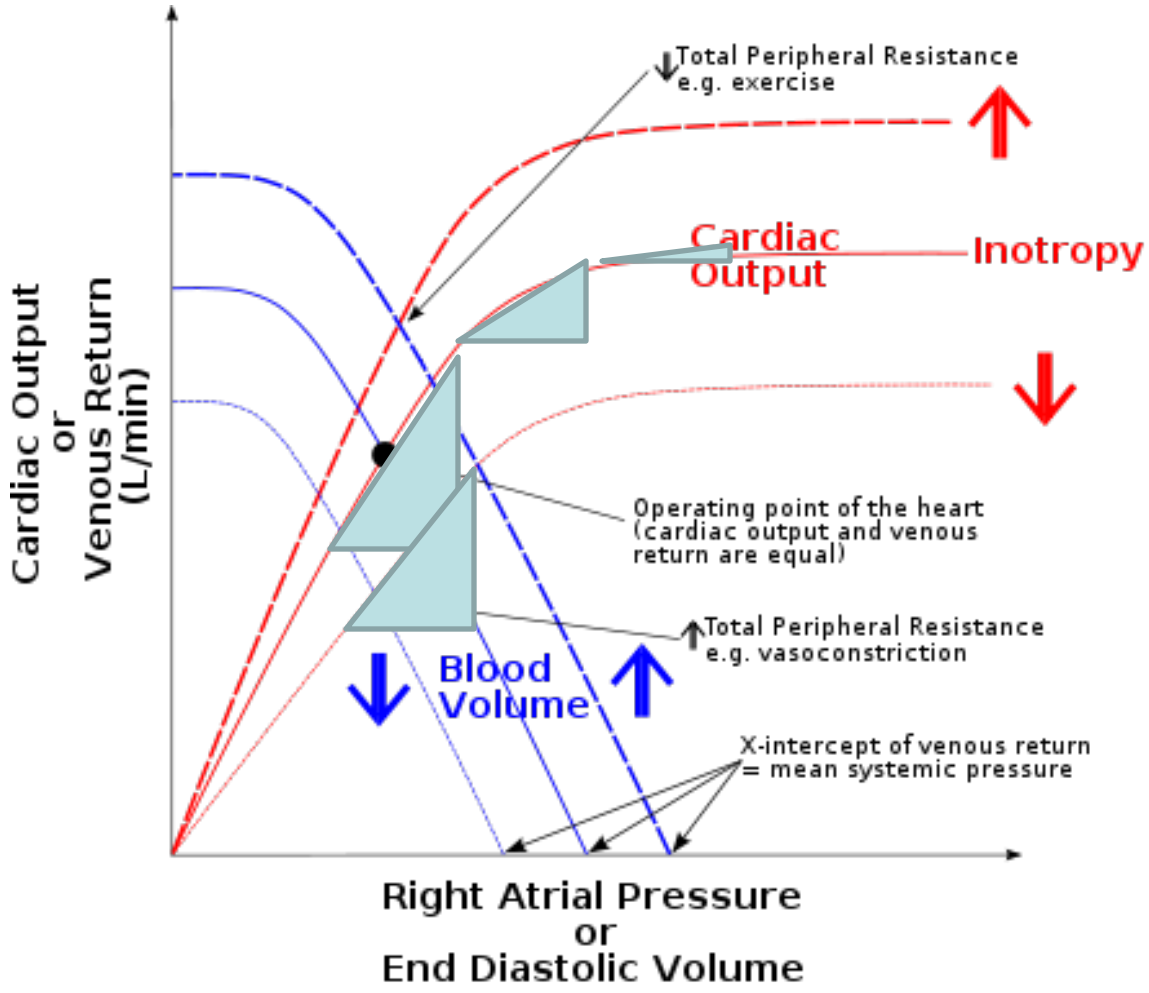

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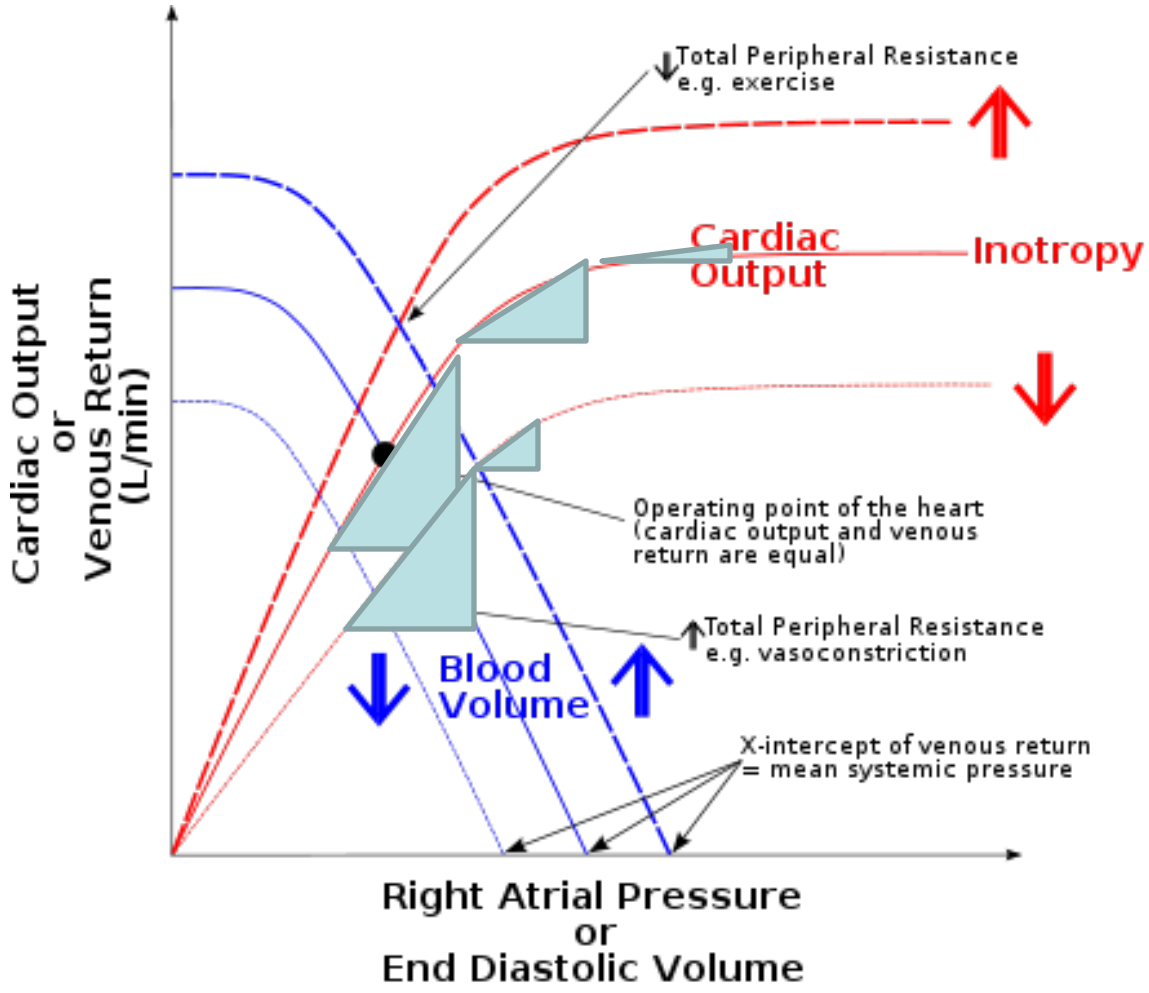

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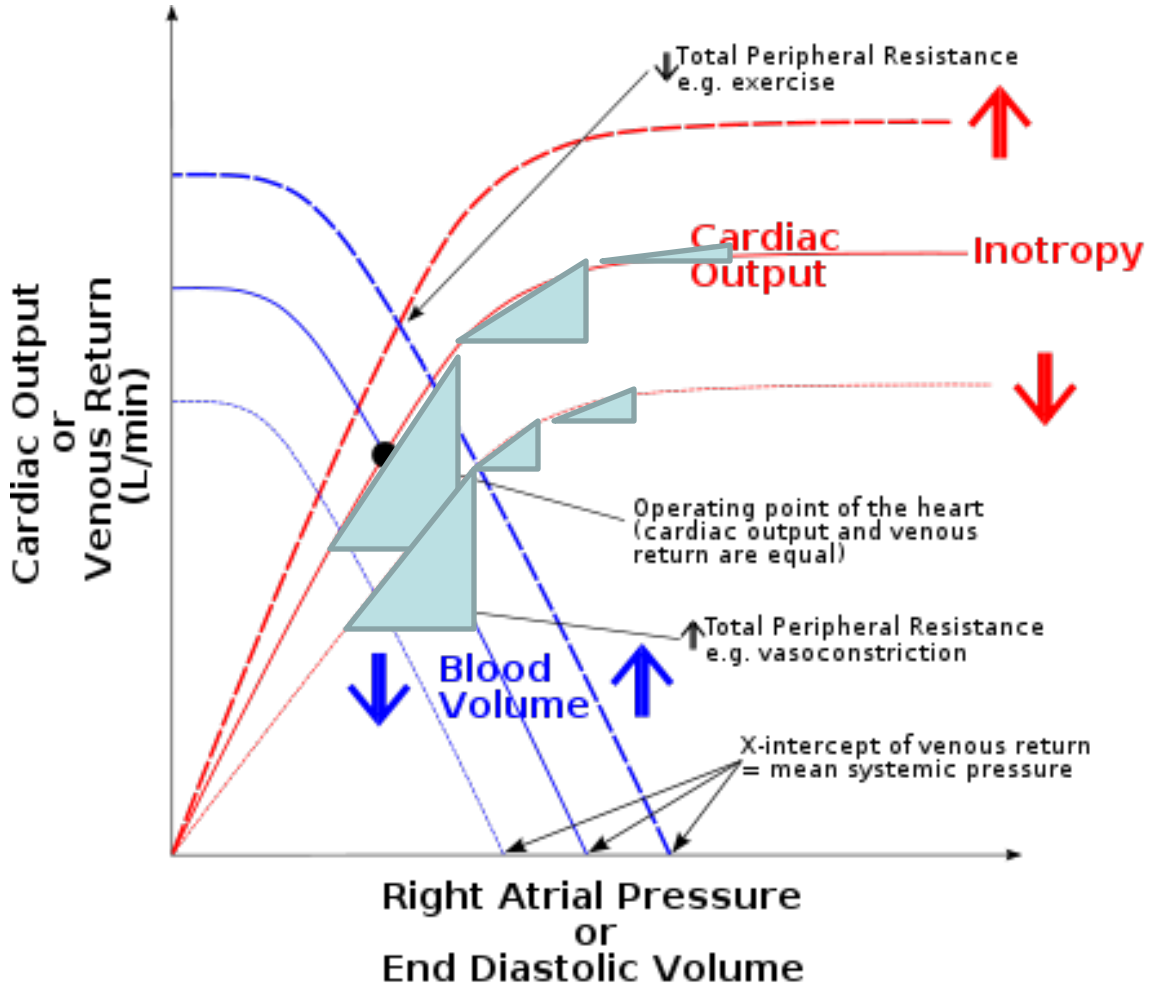
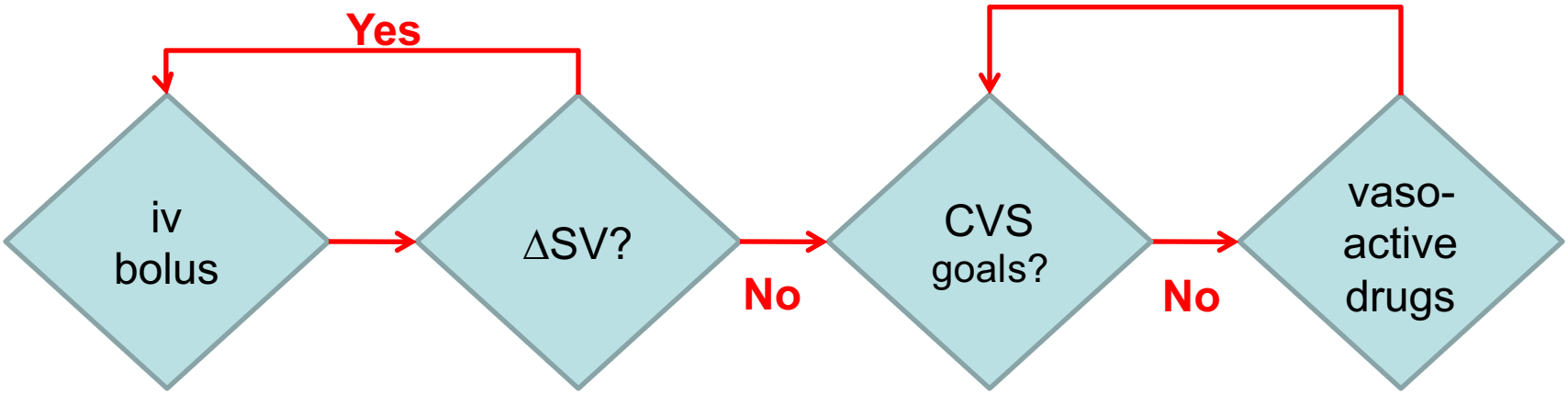
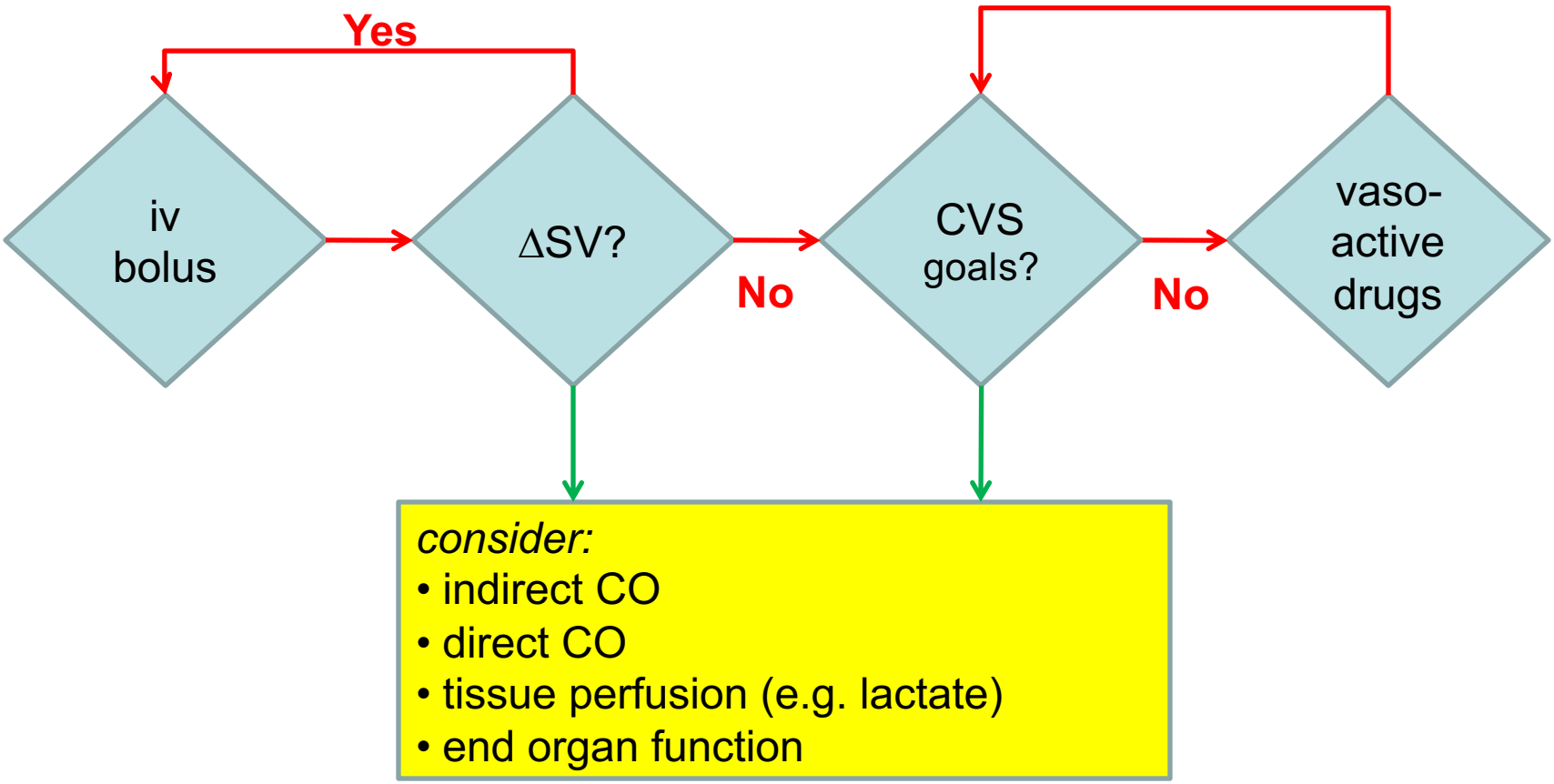


What is the correct approach?

- Be guided, but not restricted, by initial diagnosis
- Treat all as potentially volume-responsive – *especially* (but not only) if hypotensive/shocked
- Give titrated volume challenges, with a clear idea of intended goals
- Do it early and do it intensively, and know when to stop (& add vasconstrictors)

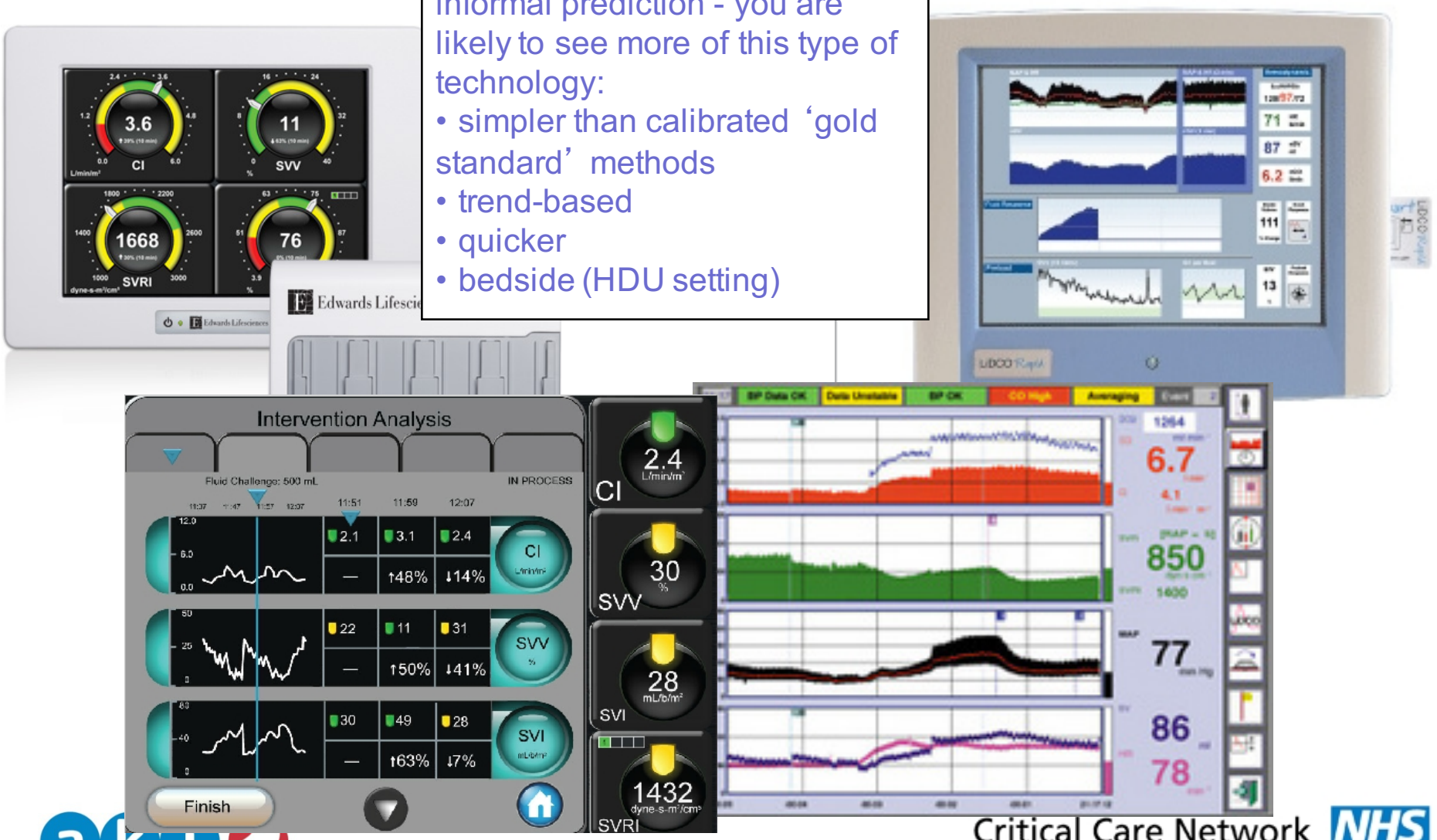

Yes
iv bolus
ΔSV?
No
CVS goals?
No
vaso-active drugs


Yes
iv bolus
ΔSV?
No
CVS goals?
No
vaso-active drugs
consider:
• indirect CO
• direct CO
• tissue perfusion (e.g. lactate)
• end organ function

How to assess volume response

informal prediction - you are likely to see more of this type of technology:

- simpler than calibrated ‘gold standard’ methods
- trend-based
- quicker
- bedside (HDU setting)



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How to assess volume response

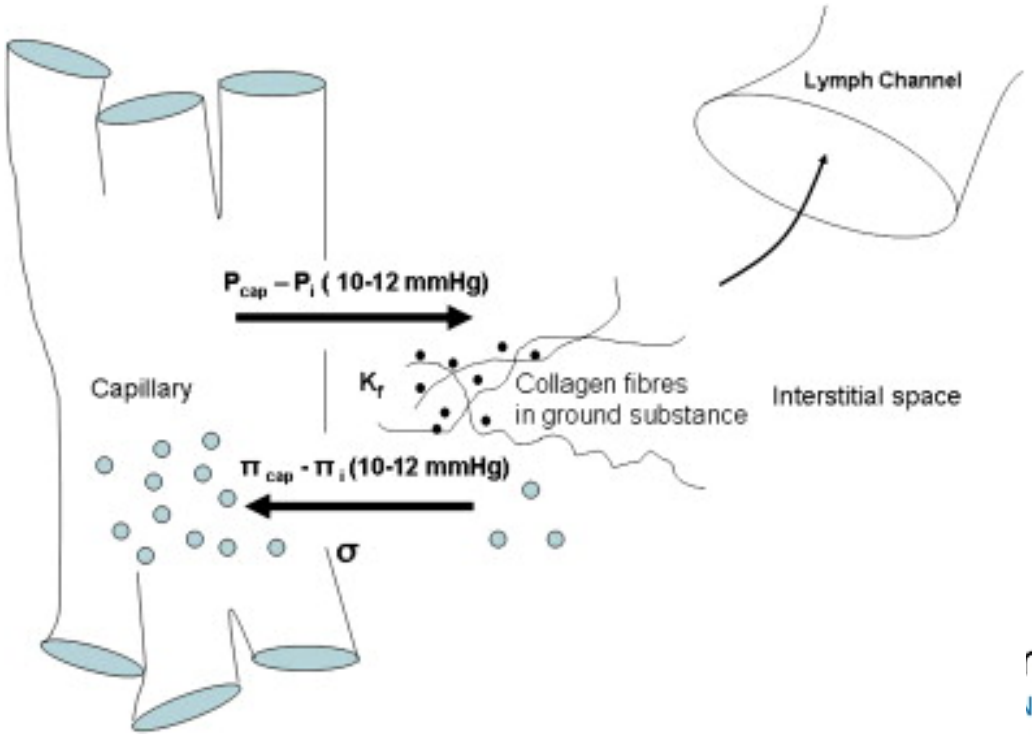
? an era of ubiquitous, routine, flow-guided volume-response management outside ICU?

WHICH FLUIDS?


Faultless
Professional Formula
Regular
Starch
Crisp Finish
Spring Breeze Scent

Colloids: rationale

- higher oncotic pressure
- less total resuscitation volume required
- more rapid attainment of circulatory goals
- more persistent in circulation



Which fluids?

Cochrane Database Syst Rev. 2000;(2):CD000567

Colloids versus crystalloids for fluid resuscitation in critically ill patients.

Alderson P, Schierhout G, Roberts I, Bunn F.

- Albumin vs crystalloid 18 trials
- HES vs crystalloid 7 trials
- modified gelatin vs. crystalloid 4 trials
- dextran vs crystalloid 8 trials
- dextran in hypertonic saline vs. crystalloid 8 trials

- Pooled relative risk: 0.88 (0.74 to 1.05)

- Reviewers' conclusion: no benefit from colloids

Which fluids?

N Engl J Med. 2008 Jan 10;358(2):125-39

Intensive insulin therapy and pentastarch resuscitation in severe sepsis

Brunkhorst FM, Engel C, Bloos F, *et al*

- VISEP study: 537 patients with severe sepsis
- 2x2 factorial design, intensive insulin therapy vs. control *and* low-MW synthetic colloid (Pentastarch, HES 200/0.5) vs. Hartman's . Stopped early due to hypos and SAEs
- HES group had higher rate of AKI: 34.9% vs. 22.8%, P=0.002
- HES group had greater % of days on RRT: 18.3% vs. 9.2%
- ratio of Hartman's to HES given: 1.32

Which fluids?

N Engl J Med. 2012 Jul 12;367(2):124-34. Epub 2012 Jun 27.

Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.

Perner A, Haase N, Guttormsen AB, *et al* (for 6S Study Group)

- 798 septic ICU patients; 130/0.42 HES vs. Ringer's lactate ,up to 33ml/kg
- At 90 days HES group had higher mortality (51% vs. 43%, P=0.03)
- HES group had higher RRT rate (22% vs. 16%, P=0.04)
- HES group had more severe bleeding (10% vs. 6%, P=0.09)

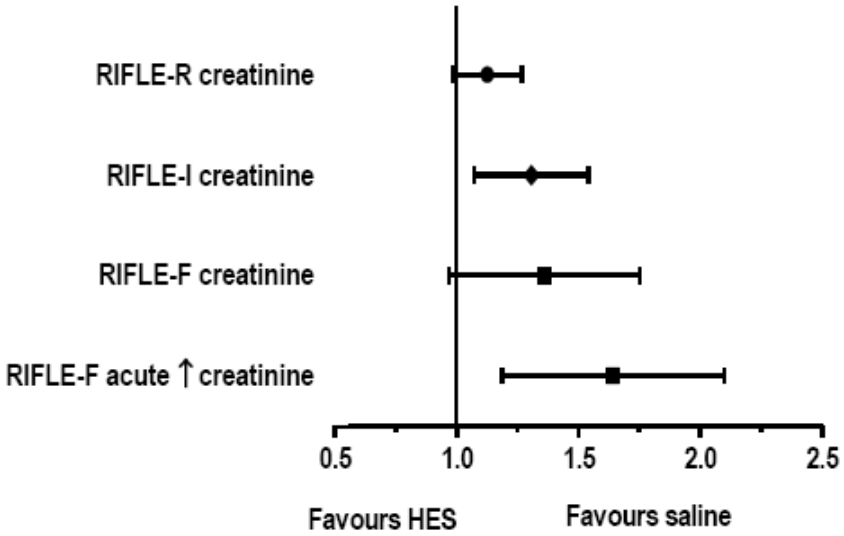
Which fluids?

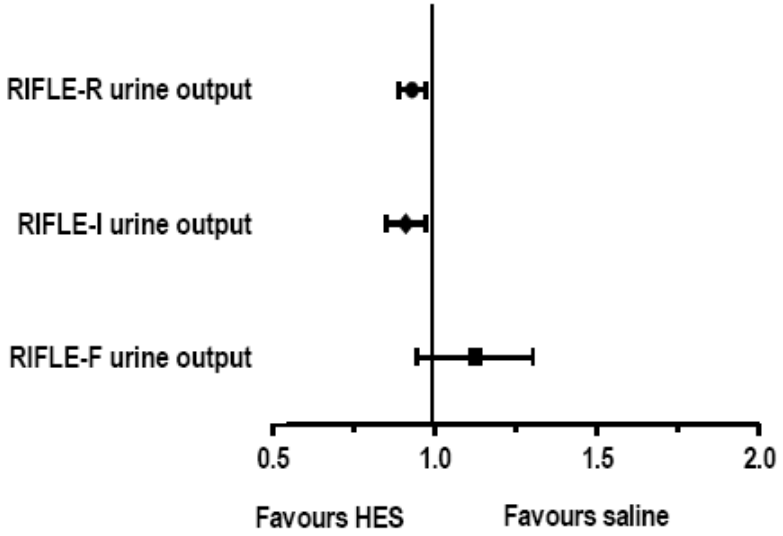
N Engl J Med. 2012 Nov 15;367(20):1901-11

Hydroxyethyl starch or saline for fluid resuscitation in intensive care.

Myburgh JA, Finfer S, Bellomo R et al (for CHEST investigators)

- 7000 ICU pts needing volume expansion, assigned to HES 130/0.4 vs. N Saline
- No mortality difference (P=0.26)
- RRT used in more HES than saline pts (7.0% vs. 5.8%, P=0.04)
- In 1st 7 days ↓urine output (P=0.003), ↑creatinine (P=0.004) in HES vs. saline
- More adverse events in HES pts (5.3% vs. 2.8%, P<0.001) – pruritis, rash





Myburgh JA *et al* N Engl J Med. 2012;367(20):1901-11

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Millions of surgery patients at risk in drug research fraud scandal

Millions of NHS patients have been treated with controversial drugs on the basis of "fraudulent research" by one of the world's leading anaesthetists, The Daily Telegraph can disclose.

Guidelines for British anaesthetists regarding colloids are being revised after it emerged that four of the key studies on which they were based are to be formally retracted Photo: ALAMY

By Heidi Blake, Holly Watt and Robert Winnett
10:31PM GMT 03 Mar 2011

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Which fluids?

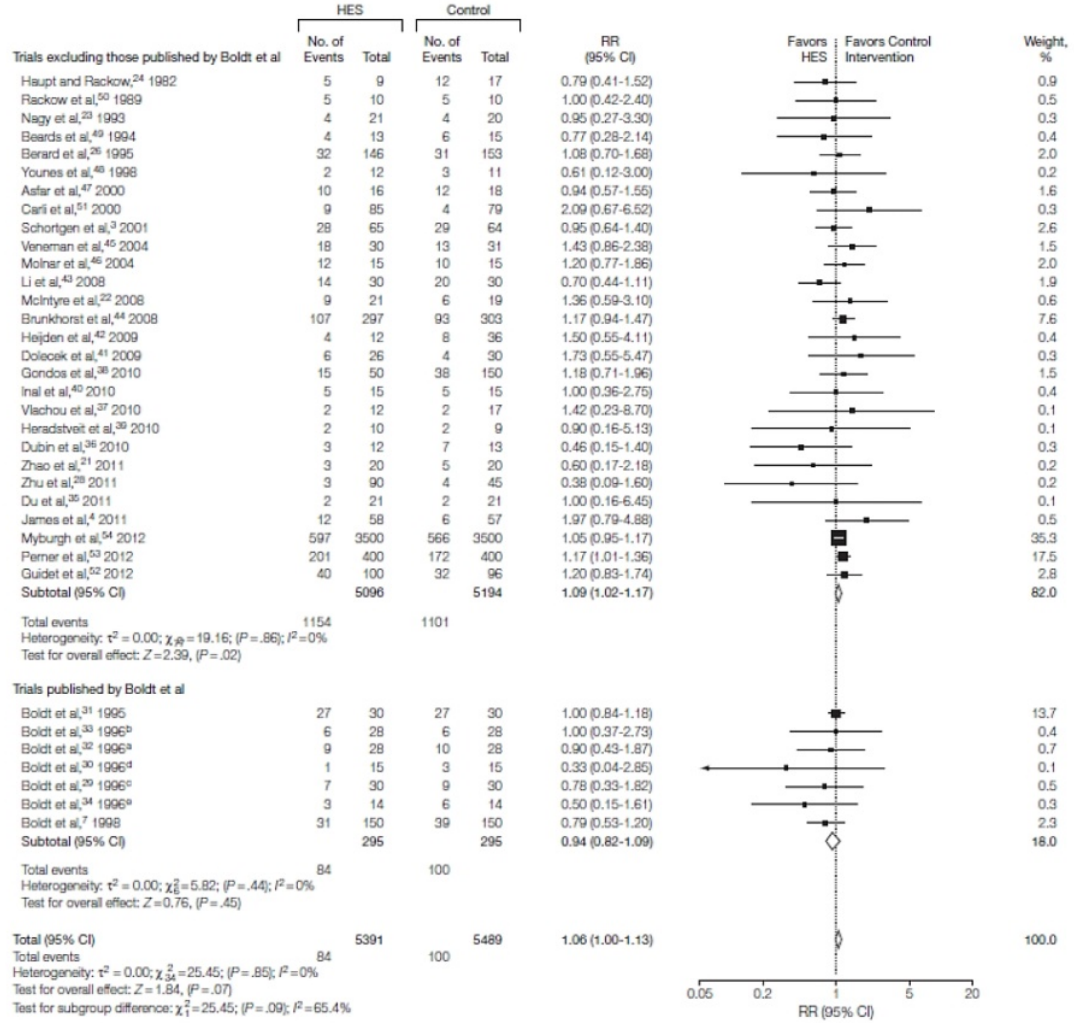
JAMA. 2013 Feb 20;309(7):678-88.

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

Zarychanski R1, Abou-Setta AM, Turgeon AF *et al*

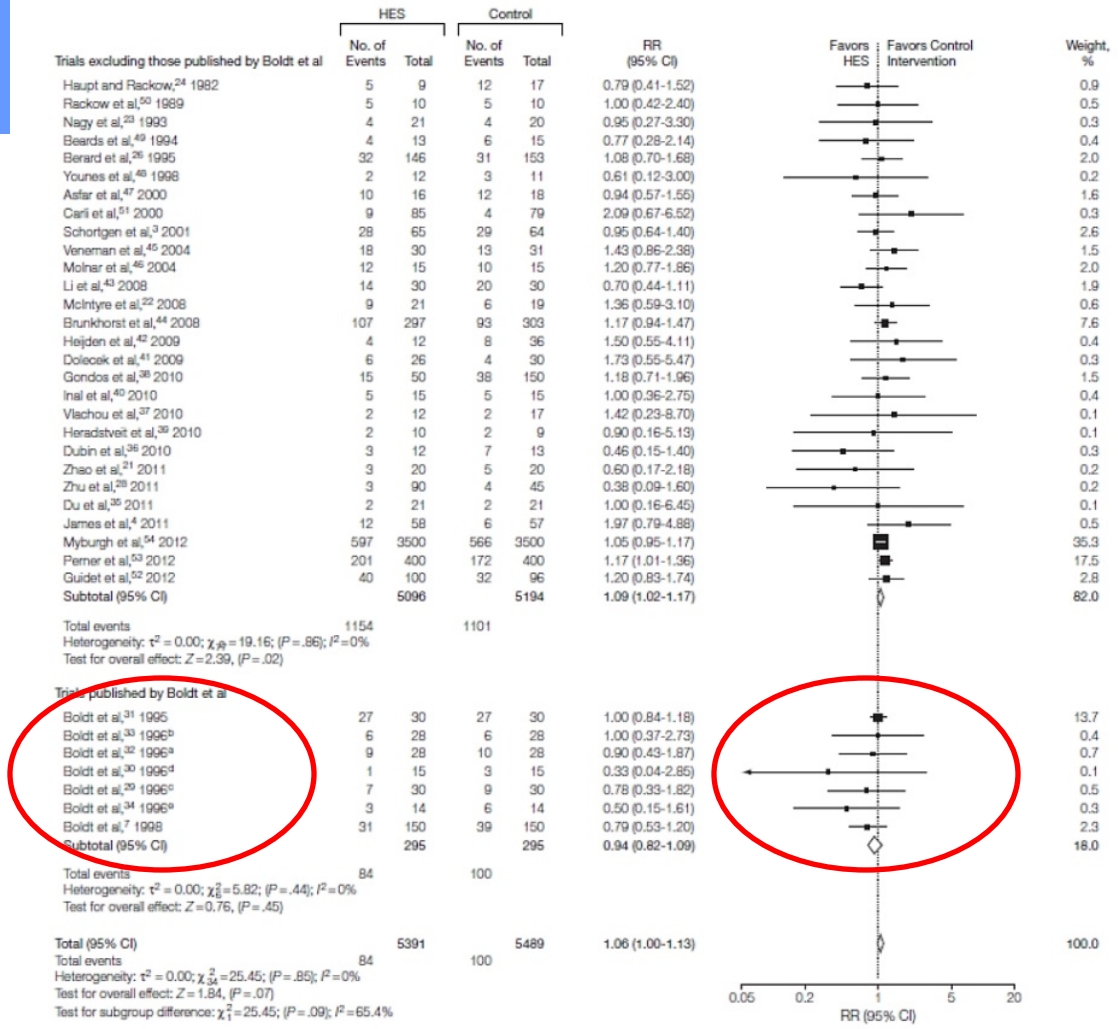
- 10,880 pts in 38 eligible trials comparing HES to crystalloids
- Relative risk ratio for mortality HES vs. crystalloids 1.07 (1.00 -1.14)

Figure 2. Mortality and Hydroxyethyl Starch



The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

Figure 2. Mortality and Hydroxyethyl Starch



Trials excluding those published by Boldt et al	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)	Weight, %
Haupt and Rackow,[24] 1982	5	9	12	17	0.79 (0.41-1.52)	0.9
Rackow et al,[50] 1989	5	10	5	10	1.00 (0.42-2.40)	0.5
Nagy et al,[23] 1993	4	21	4	20	0.95 (0.27-3.30)	0.3
Beards et al,[49] 1994	4	13	6	15	0.77 (0.28-2.14)	0.4
Berard et al,[26] 1995	32	146	31	153	1.08 (0.70-1.68)	2.0
Younes et al,[48] 1998	2	12	3	11	0.61 (0.12-3.00)	0.2
Asfar et al,[47] 2000	10	16	12	18	0.94 (0.57-1.55)	1.6
Carli et al,[51] 2000	9	85	4	79	2.09 (0.67-6.52)	0.3
Schortgen et al,[3] 2001	28	65	29	64	0.95 (0.64-1.40)	2.6
Veneman et al,[45] 2004	18	30	13	31	1.43 (0.86-2.38)	1.5
Molnar et al,[46] 2004	12	15	10	15	1.20 (0.77-1.86)	2.0
Li et al,[43] 2008	14	30	20	30	0.70 (0.44-1.11)	1.9
McIntyre et al,[22] 2008	9	21	6	19	1.36 (0.59-3.10)	0.6
Brunkhorst et al,[44] 2008	107	297	93	303	1.17 (0.94-1.47)	7.6
Heijden et al,[42] 2009	4	12	8	36	1.50 (0.55-4.11)	0.4
Dolecek et al,[41] 2009	6	26	4	30	1.73 (0.55-5.47)	0.3
Gondos et al,[38] 2010	15	50	38	150	1.18 (0.71-1.96)	1.5
Inal et al,[40] 2010	5	15	5	15	1.00 (0.36-2.75)	0.4
Vlachou et al,[37] 2010	2	12	2	17	1.42 (0.23-8.70)	0.1
Heradstveit et al,[39] 2010	2	10	2	9	0.90 (0.16-5.13)	0.1
Dubin et al,[36] 2010	3	12	7	13	0.46 (0.15-1.40)	0.3
Zhao et al,[21] 2011	3	20	5	20	0.60 (0.17-2.18)	0.2
Zhu et al,[28] 2011	3	90	4	45	0.38 (0.09-1.60)	0.2
Du et al,[35] 2011	2	21	2	21	1.00 (0.16-6.45)	0.1
James et al,[4] 2011	12	58	6	57	1.97 (0.79-4.88)	0.5
Myburgh et al,[54] 2012	597	3500	566	3500	1.05 (0.95-1.17)	35.3
Perner et al,[53] 2012	201	400	172	400	1.17 (1.01-1.36)	17.5
Guidet et al,[52] 2012	40	100	32	96	1.20 (0.83-1.74)	2.8
Subtotal (95% CI)		**5096**		**5194**	**1.09 (1.02-1.17)**	**82.0**
Total events	1154		1101			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{26} = 19.16$; ($P = .86$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.39$, ($P = .02$)						
Trials published by Boldt et al						
Boldt et al,[31] 1995	27	30	27	30	1.00 (0.84-1.18)	13.7
Boldt et al,[33] 1996[b]	6	28	6	28	1.00 (0.37-2.73)	0.4
Boldt et al,[32] 1996[a]	9	28	10	28	0.90 (0.43-1.87)	0.7
Boldt et al,[30] 1996[d]	1	15	3	15	0.33 (0.04-2.85)	0.1
Boldt et al,[29] 1996[c]	7	30	9	30	0.78 (0.33-1.82)	0.5
Boldt et al,[34] 1996[e]	3	14	6	14	0.50 (0.15-1.61)	0.3
Boldt et al,[7] 1998	31	150	39	150	0.79 (0.53-1.20)	2.3
Subtotal (95% CI)		**295**		**295**	**0.94 (0.82-1.09)**	**18.0**
Total events	84		100			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 5.82$; ($P = .44$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.76$, ($P = .45$)						
Total (95% CI)		**5391**		**5489**	**1.06 (1.00-1.13)**	**100.0**
Total events	84		100			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{34} = 25.45$; ($P = .85$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.84$, ($P = .07$)						
Test for subgroup difference: $\chi^2_1 = 25.45$; ($P = .09$); $I^2 = 65.4\%$						

The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

Which fluids?

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- 10,880 pts in 38 eligible trials comparing HES to crystalloids
- Relative risk ratio for mortality HES vs. crystalloids 1.07 (1.00 -1.14)
- When 590 pts in 7 trials excluded,
  - 10,290 pts remained with RR 1.09 (1.02 - 1.17)
  - 8725 pts with renal failure, higher with HES, RR 1.27 (1.09-1.47)
  - 9258 pts with RRT, higher with HES, RR 1.32 (1.15 – 1.50)


Cl-

- Hyperchloraemia
  - ↓RBF
  - ↓ sodium excretion
  - acidosis

Which fluids?

Clin Sci (Lond). 2003 Jan;104(1):17-24..

(Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study

Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP

- 9 healthy male volunteers
- Crossover study of 2L in 2 hrs of 09.% saline vs. Hartmann's
- body wt, haematocrit serium biochemistry over 6 hr
- all developed sustained hyperchloraemia (> 105mmol/l) and lower serum bicarbonate after NaCl
- 56% of NaCl retained at 6h vs. 30% of Hartmann's

Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery

0.9% Saline Compared to Plasma-Lyte

Andrew D. Shaw, MB, FRCA, FCCM, Sean M. Bagshaw, MD,† Stuart L. Goldstein, MD,‡ Lynette A. Scherer, MD,§ Michael Duan, MS,‖ Carol R. Schermer, MD,¶ and John A. Kellum, MD#*

Annals of Surgery • Volume 255, Number 5, May 2012

- analysis of US hospital claims database (20% of all US discharges)
- >30,000 N Saline recipients vs. 1000 balanced crystalloid
- unequal groups; extreme samples (purely saline or purely balanced)

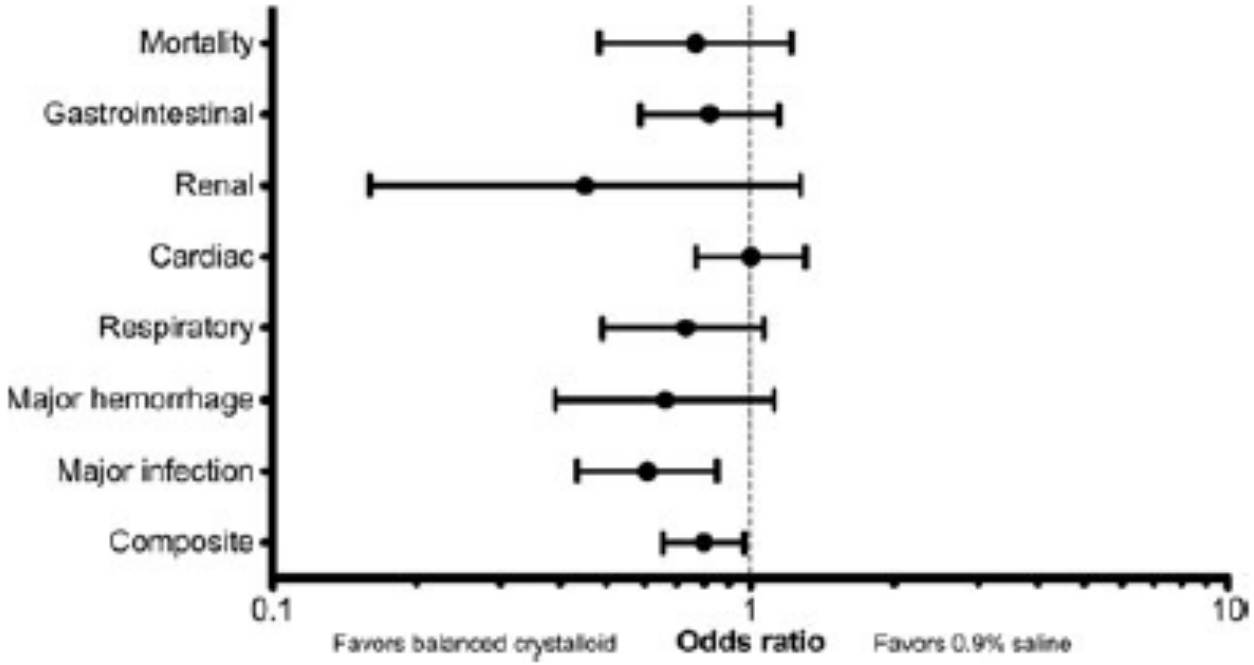


FIGURE 2. Odds ratios and 95% confidence intervals for pre-specified clinical outcomes.

Annals of Surgery • Volume 255, Number 5, May 2012

Which fluids?

JAMA. 2012 Oct 17;308(15):1566-72. doi: 10.1001/jama.2012.13356.

Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults.

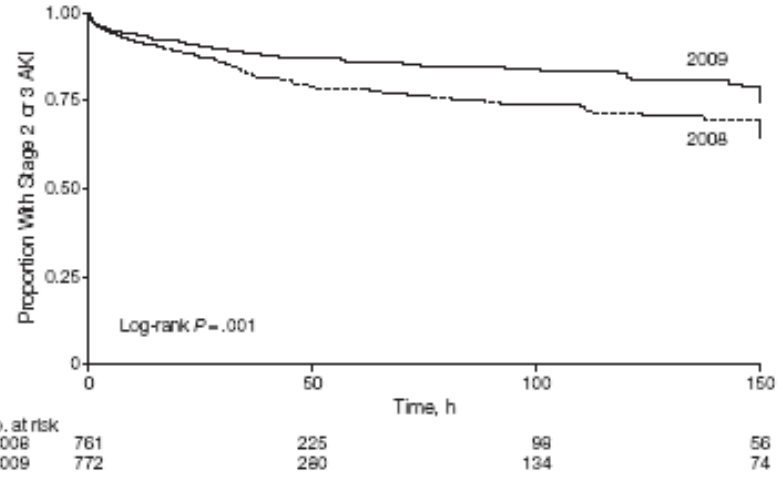
Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M.

- open label sequential time period pilot study in single unit
- 760 pts liberal use of chloride-rich fluids (0.9% saline, 4% succinylated gelatin, or 4% albumin])
- 773 pts balanced crystalloid (Hartmann's, Plasma-Lyte, 20% albumin)

- lower incidence of AKI in chloride-restricted group (OR 0.52, p<0.001)

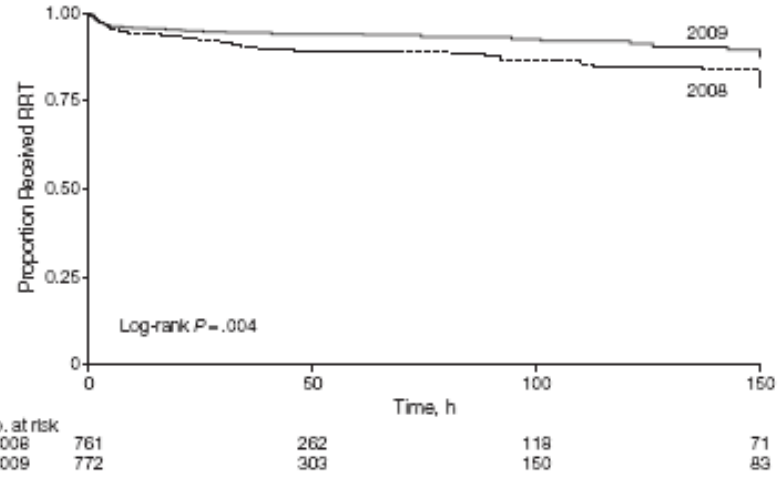
- lower use of RRT in chloride-restricted group (OR 0.52, p=0.04)

Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)



Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline.

Figure 2. Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)



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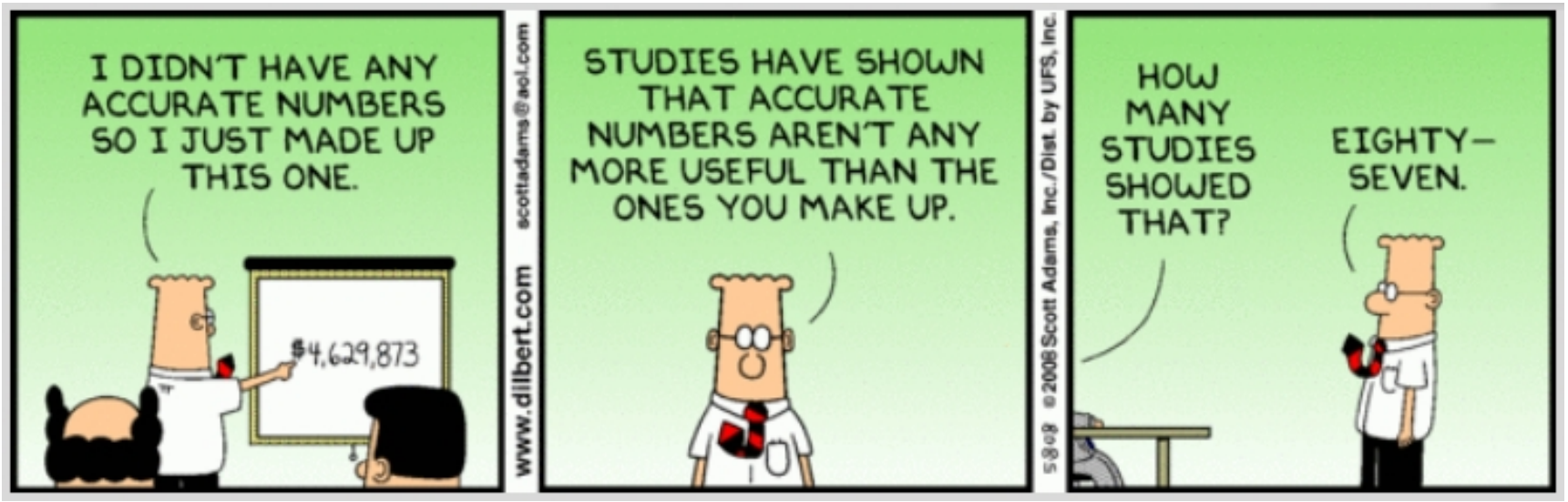
A rational approach?

- In acute illness
  - Intervene early
  - give incremental guided volume challenges to achieve adequate stroke volume.
  - Use balanced crystalloid. Avoid starch, caution with Cl-
  - Low threshold for vasoconstrictors and/or RRT.
- Early transition to conservative strategy:
  - Neutral or negative daily fluid balance
  - avoid oedema, weight gain

Thank you



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Critical Care Network NHS
North West London

Further reading

Prowle JR, Kirwan C, Bellomo R.
Nature Reviews Nephrology Volume: 10, Pages:37–47

Further reading

Edwards and Mythen *Extreme Physiology & Medicine* 2014, 3:16
http://www.extremephysiolmed.com/content/3/1/16

Extreme Physiology & Medicine

REVIEW Open Access

Fluid therapy in critical illness

Mark R Edwards[1,2*] and Michael G Mythen[3,4,5]

Edwards MR, Mythen MG. *Extrem Physiol Med.* 2014 Sep 29;3:16

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