Dealing with a “cytokine avalanche”

Clinical case

- 42 yr old female leading cancer researcher (“cytokine specialist”)
- Previously healthy aside from mild asthma
- 2 day history of olecranon bursitis following banal pressure
- Rapid onset of forearm swelling, redness and tenderness
- Soon followed by upper abdominal pain, diarrhoea, nausea and vomiting

Admitted to Ealing A+E

- BP 80/40; HR 115; RR 26; Temp 40°; Sats 97%; GCS 15
- In AMU given :
  - initially fluids, Tazocin, Amikacin,
  - later Clindamycin, Noradrenaline

Transferred to ITU .....

- We find a very sick woman - "cytokine avalanche" despite appearing deceptively "well"

- Care plan organised and executed **emergently**

  ("not a moment to lose")

- inclu. surgical exploration for suspected soft tissue necrosis, CT, PICCO, etc

How sick?

Acid Base	pH 7.19, BD 14, $HCO3^-$ 12 ; lactate 4
CV	Max. Noradrenaline; BP 90/35; CI 5.1 Troponin 3,422; NT Pro BNP 17,464 ECG non specific changes
Lungs	ELWI 7 → 19
Kidney	Creatinine N - ↑181 UO 180/min
Microcirculation	CRT 10 sec
Coagulation	Platelets N → ↓103; PTT N → ↑73
ScVO2	71% → 84%
Liver	Albumin N → ↓19 Alk Phos 2.5 x N; ALT 3xN
Infection markers	WBC 29; CRP 345; PCT 28

CT showed

- ARDS
- "Septic" swollen abdomen with distended gall bladder

  - possible source?
  - Very oedematous arm

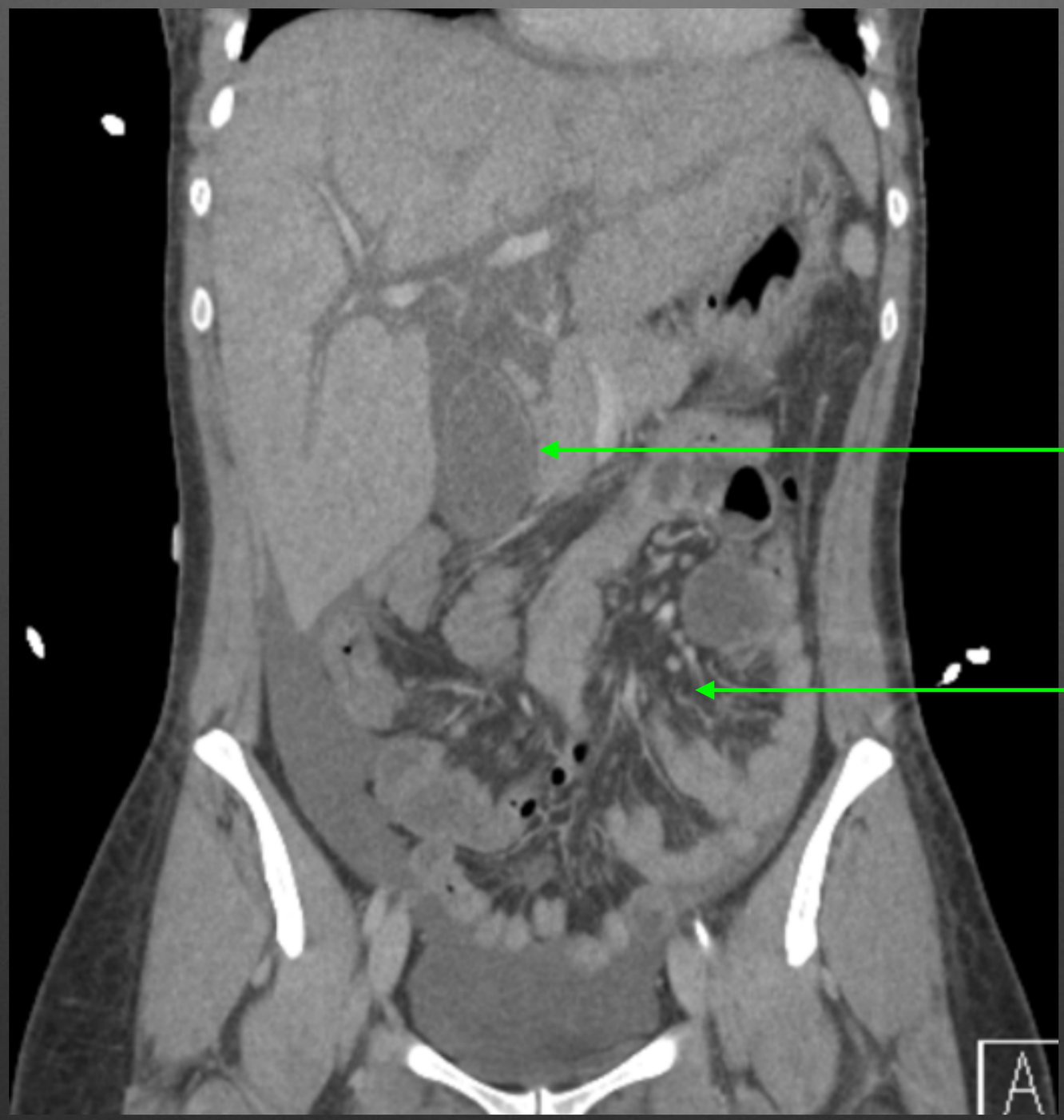
Where is the source?

If source not found and “controlled", she is at extremely high risk of death

Based on suspicion of TSS: linezolid and IVIG added to clindamycin, tazocin

CT showed

"Septic" swollen abdomen

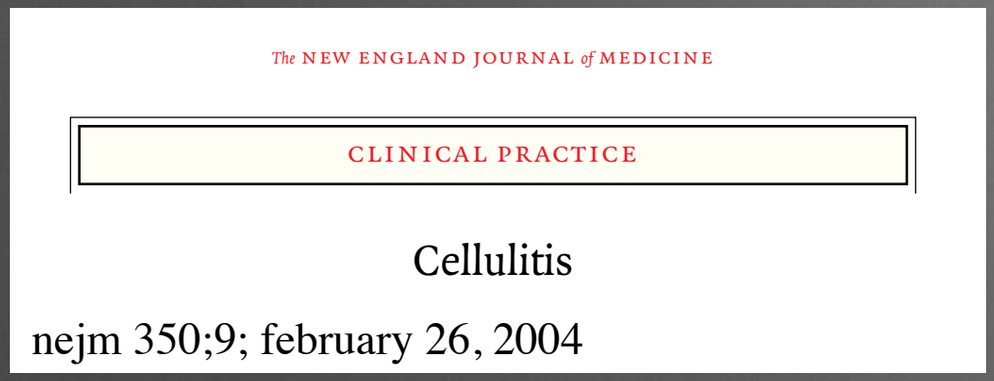


Distended,
thin walled gall bladder

“Third space”
Oedema +++

Source control

Diagnosis and Prognosis



"**... difficult to differentiate cellulitis** from **necrotizing fasciitis**…

surgical exploration ... must **not** be **delayed"**

"… requires **aggressive débridement**… is a **true surgical emergency**"

Gram-positive toxic shock syndromes

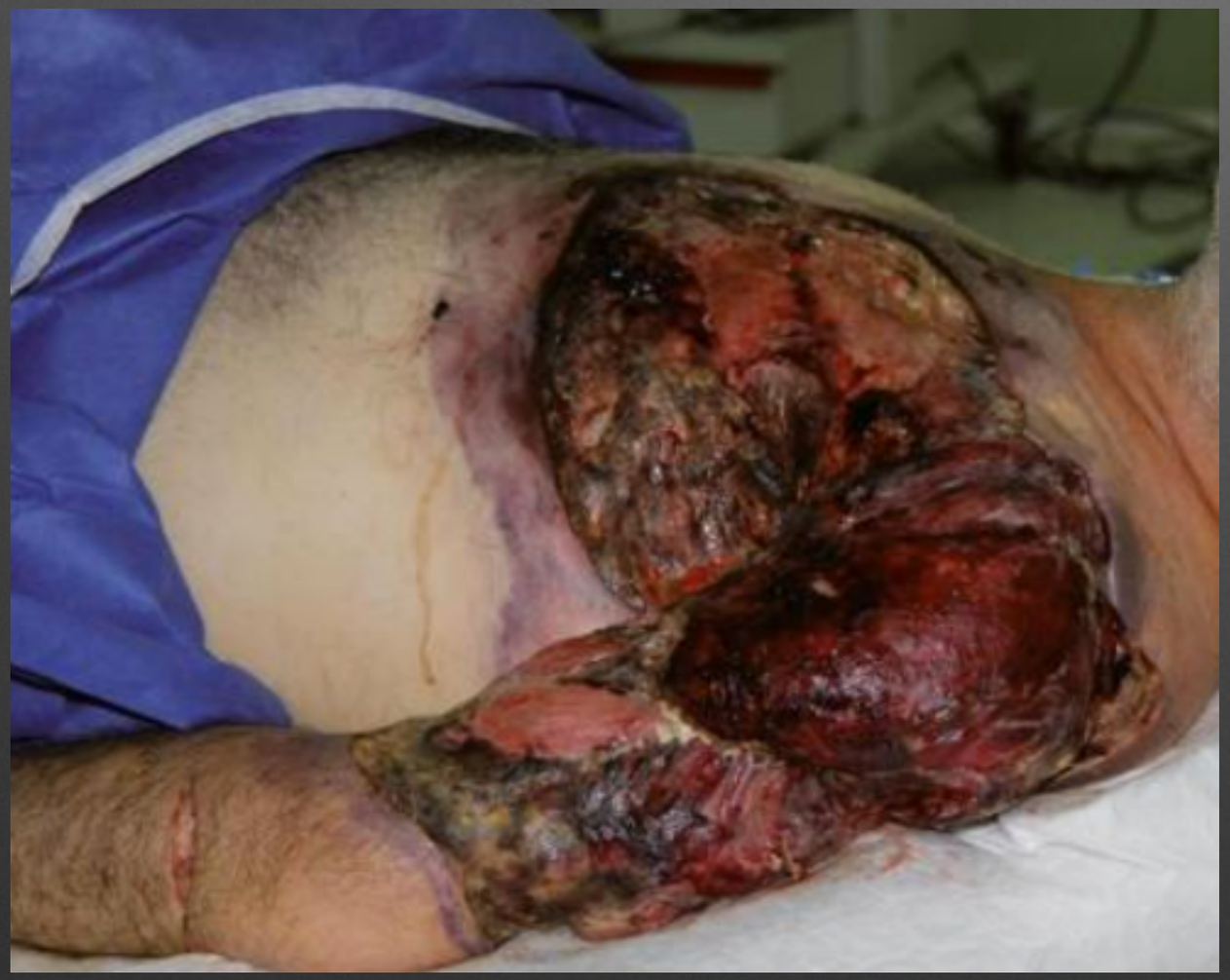
***Lancet Infect Dis* 2009; 9: 281–90**

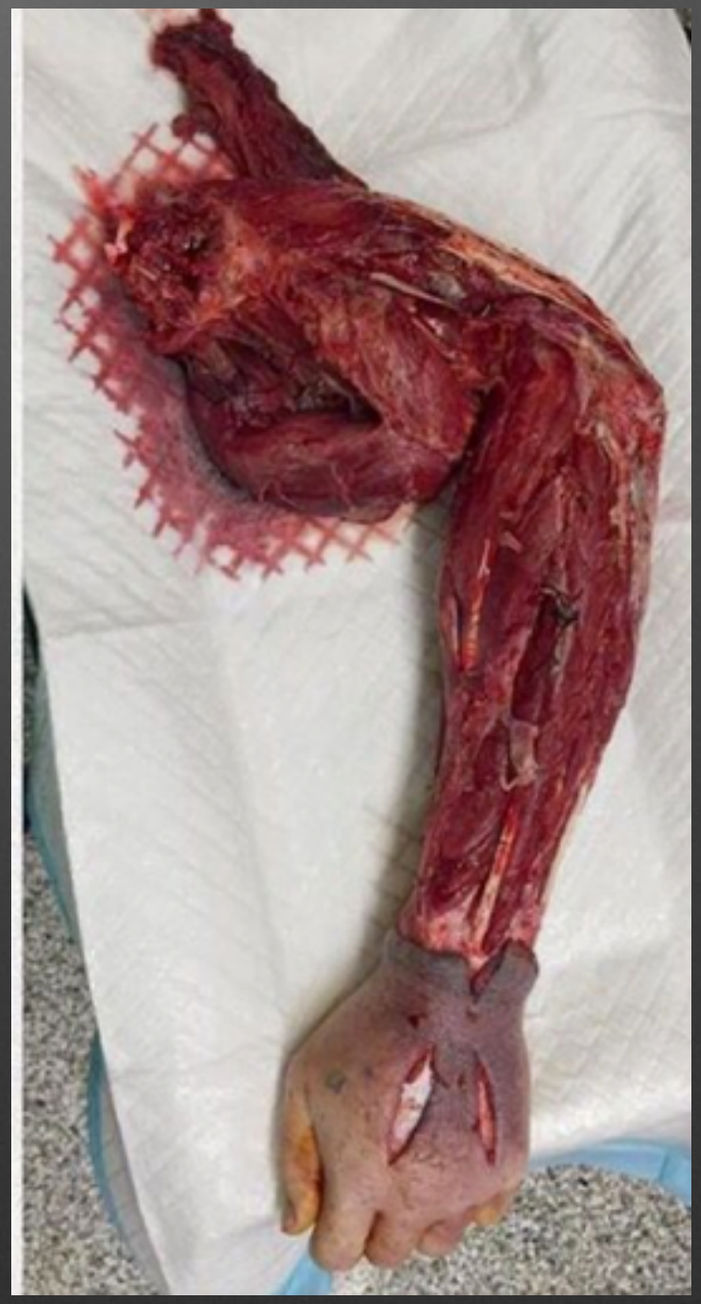
"…progress with a **rapidity** that, once seen, is **never forgotten**."

"**...mortality** rate **higher** than that of **meningo-coccal septicaemia**, TSS has **not** achieved the **same level of awareness** among health-care professionals…"

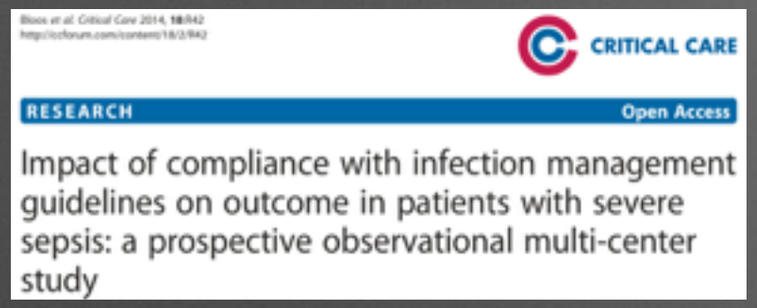
The **mortality** associated with streptococcal TSS has been quoted at from 40% **up to 80%** ..."

WHY I AM NOT A SURGEON





What happens if you delay surgery ?


Bloos et al. Critical Care 2014, 18:R42
http://ccforum.com/content/18/2/R42

CRITICAL CARE

RESEARCH Open Access

Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Time to treatment (hrs)

Survivor

Non survivor

**

“A delay in source control **beyond 6 hours** may have a major impact on patient mortality ”

Outcome from surgery

- Surgical exploration showed very swollen but non-necrotic soft tissues

- Gynaecological exam unremarkable

- Tissue sample " motorcycled" to NWP where microscopy showed G+ cocci

  Presumed diagnosis of cellulitis with a toxin secreting m/o (GAS or Staph).

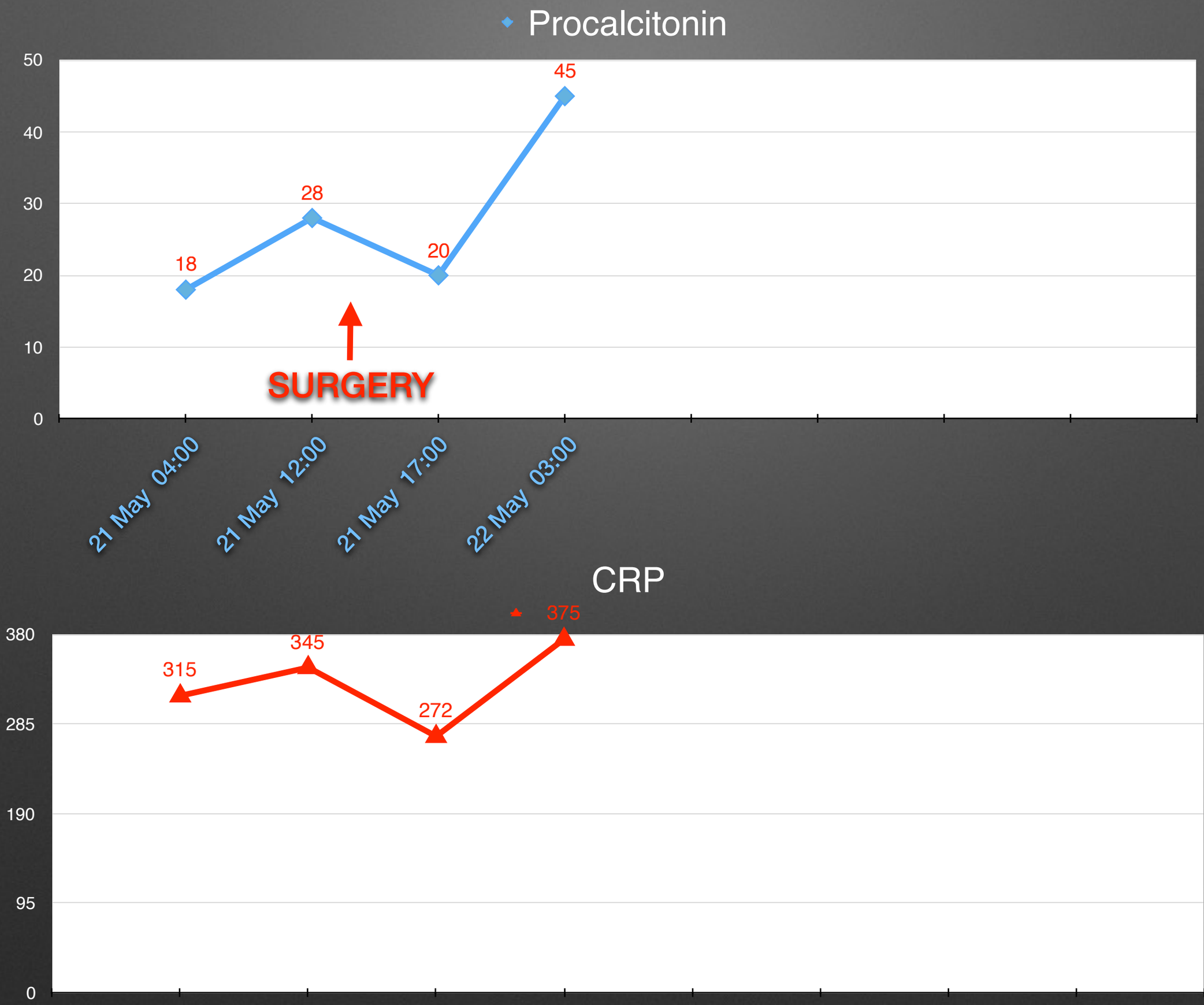
We have a desperately sick patient

“We die of our specialties”

The clinical dilemma

- **All the while, things are getting worse**
  - Early DIC? (rising PTT, falling platelets)
  - The Troponin T increased from 1200 ➔ 3422 !
  - Dr Rosen performed a TOE on Sunday morning - “only at Ealing”
    - Essentially normal (hyper dynamic)
- **Source control ?**
  - **Yes** - so hold tight and "weather the storm"
  - **No** - much higher chance of dying despite our antibiotic cover

PCT and CRP are rising !



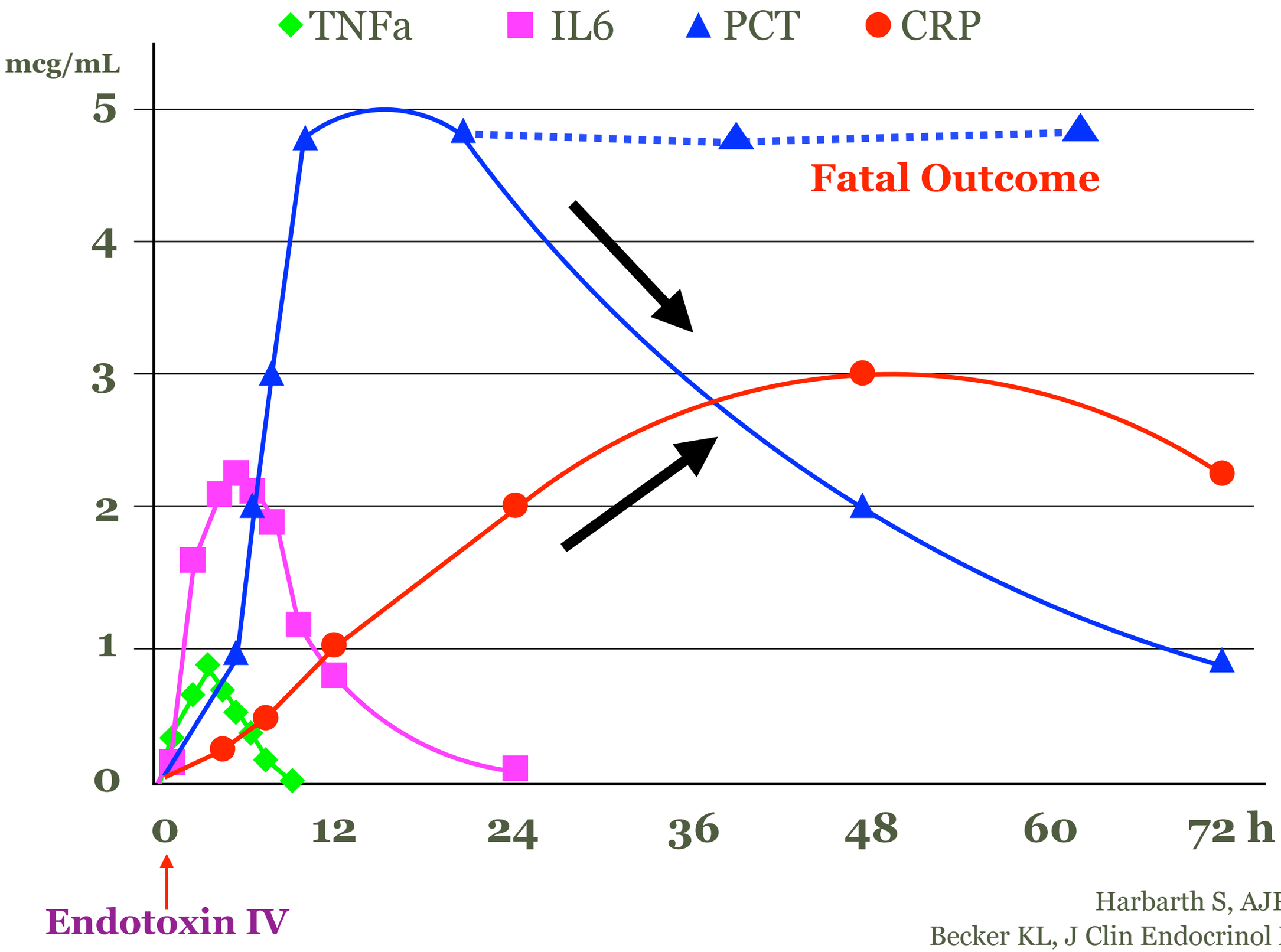
Procalcitonin

- PCT - a “hormokine”
- ⬆ in **systemic bacterial** infections
- Level of **PCT** ∝ **severity** infection
- PCT **attenuated** by viral infections
- ⬆ PCT is **not attenuated** by neither **non-steroidal** nor **steroidal** anti-inflammatory drugs
- PCT plays a **pathophysiological** role

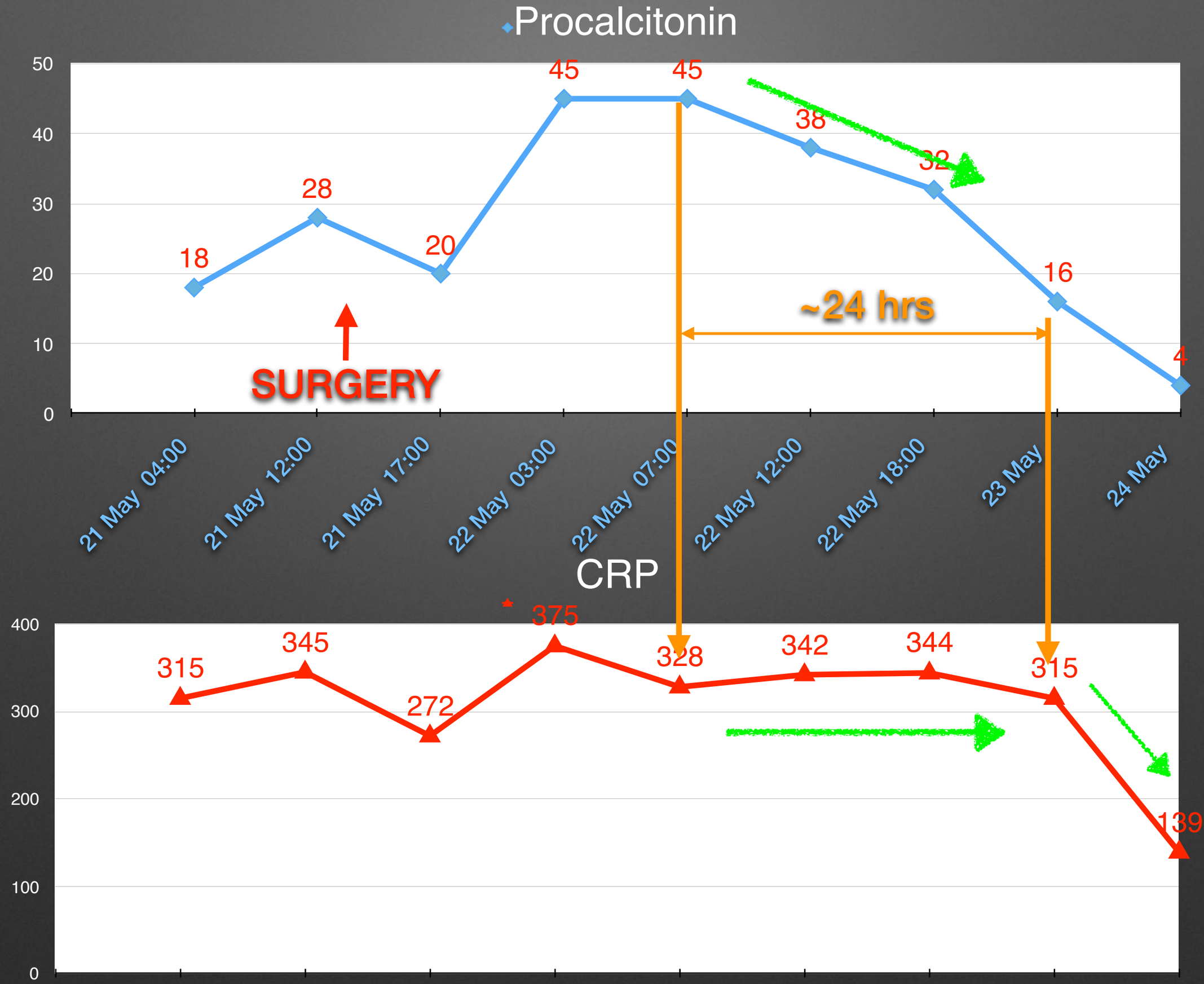
Expert Rev. Anti Infect. Ther. 8(5), 575–587 (2010)

Knowing the kinetics of PCT, we decide to “hold tight”

Kinetics of Procalcitonin upon Infection



Harbarth S, AJRCCM 2001
Becker KL, J Clin Endocrinol Metal 2004


Procalcitonin
50
40
30
20
10
0
18
28
20
45
45
38
32
16
4
SURGERY
~24 hrs
21 May 04:00
21 May 12:00
21 May 17:00
22 May 03:00
22 May 07:00
22 May 12:00
22 May 18:00
23 May
24 May
CRP
400
300
200
100
0
315
345
272
375
328
342
344
315
139

Resuscitation

Oxygen delivery =

C.O. x Hb x O_2 Sat

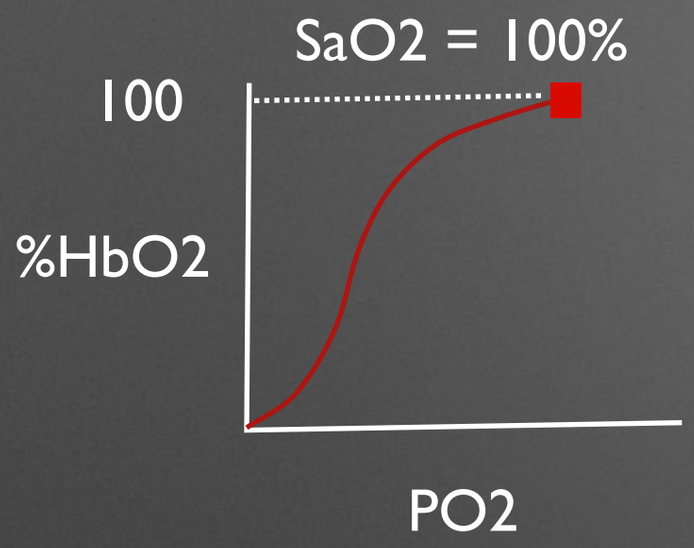
CV parameters

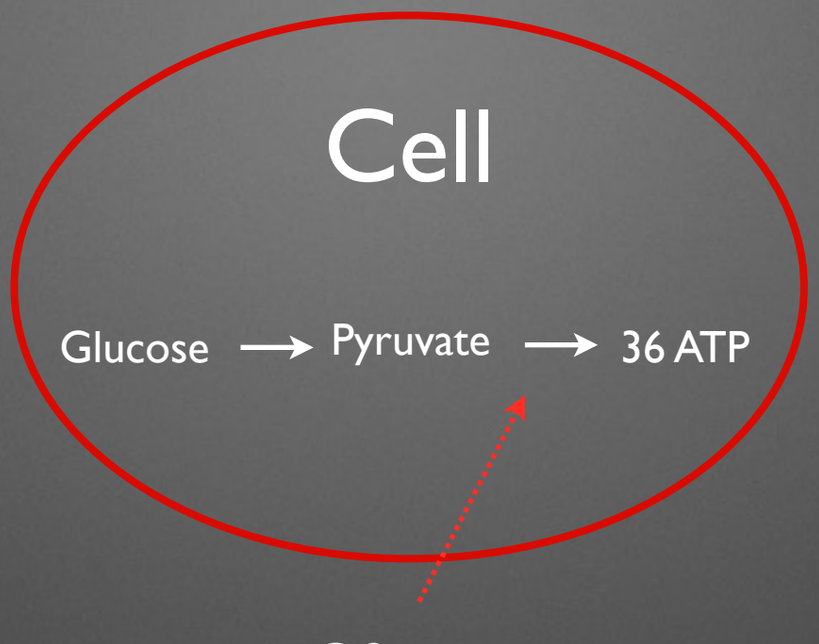
Cardiac Output	8.6 L/min
SVV	9
ELWI	19
Capillary refill time	~10 sec
ScVO2	72% -> 84%

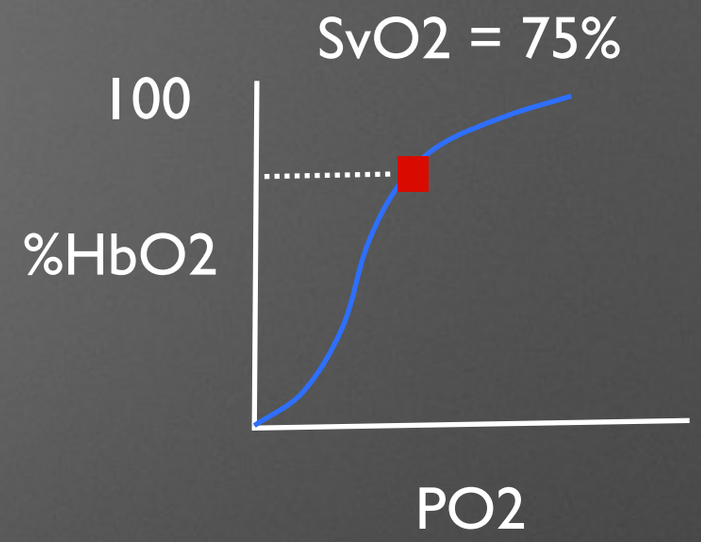
Is cardiac output adequate?

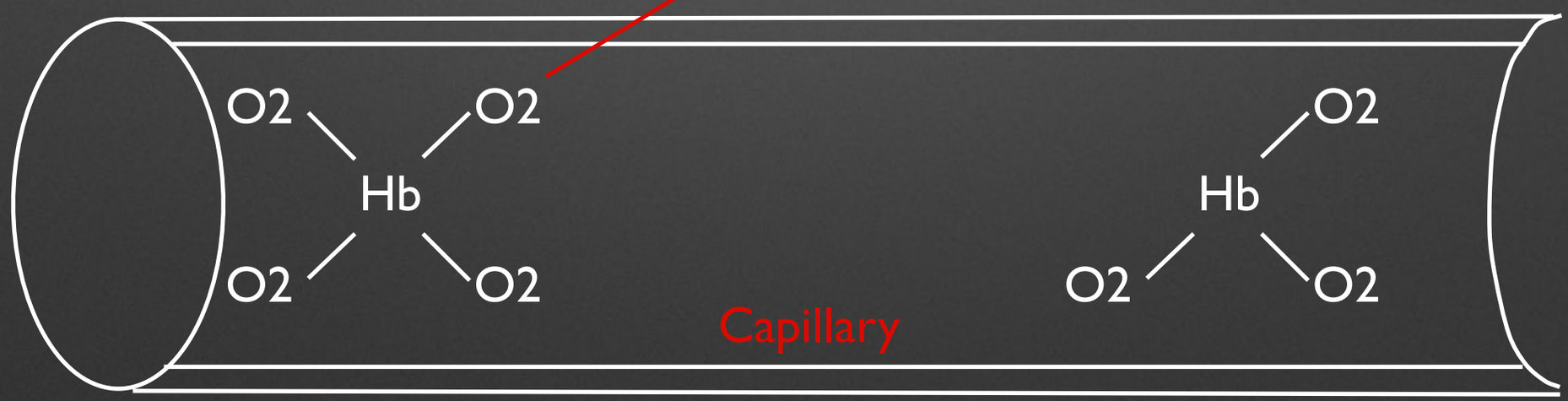
- BP just adequate with high dose noradrenaline
- Metabolic acidosis
- Poor CRT
- ScVO2?

Reassuring ScVO2 ?







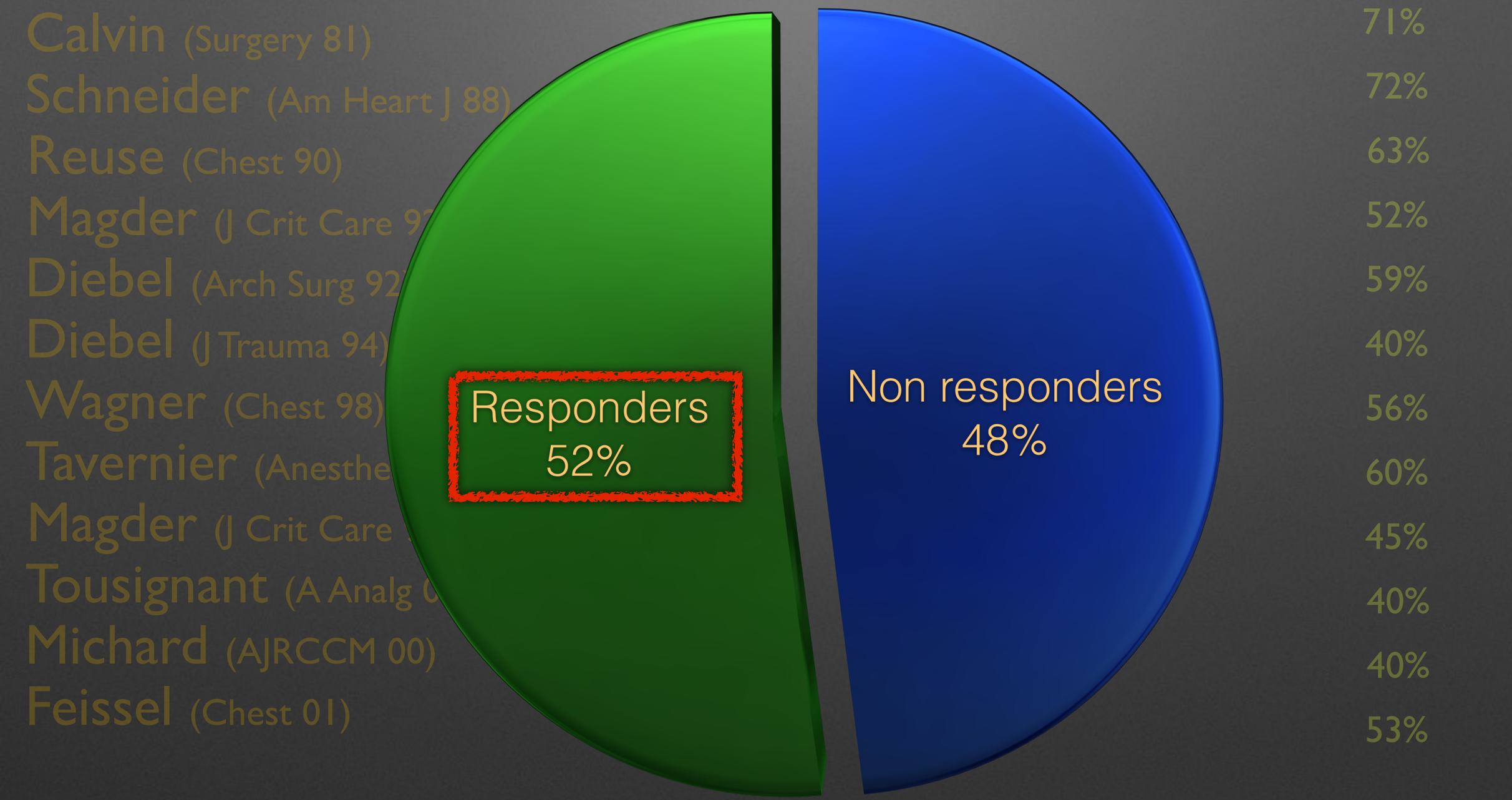


Arterial inflow

Venous outflow

Would you give more fluids?

More fluids? - Half of ITU patients are fluid responders



Michard & Teboul. Chest 121:2000-8, 2002

What to do next?

More fluids?

- CT showed signs of ARDS but massive abdominal “3rd space”

- Already received 8L

- SVV was 9; CI was 5.1L/min/M^2; ELWI went from 7 -> 19!

    - Ventilated using "protective lung ventilation"

Would SVV help decide?

But Limits of Pressure Variation during Positive Pressure Ventilation

	False positive	False negative
L **Low** HR/RR ratio (Extreme bradycardia or high frequency ventilation)		✓
I **Irregular** heart beats	✓	
M **Mechanical** ventilation with low tidal volume	=<8ml/kg IBW	✓
I **Increased** abdominal Pressure (Pneumoperitoneum)	✓	
T **Thorax** open		✓
S **Spontaneous** breathing	✓	✓

Michard et al. Critical Care (2015) 19:144

We added GTN and dobutamine to noradrenaline

What is the logic in giving a vasoconstrictor and vasodilators?

The capillary refill time was **10 seconds**
despite an “adequate” blood pressure helped with high dose noradrenaline

Microvascular dysfunction

	Peripheral perfusion after resuscitation	
	Normal (27)	Abnormal (23)
HR	90	94
MAP	80	81
CVP	14	13
% Normal Lactate	69	31 **
SOFA >0	23	77 **

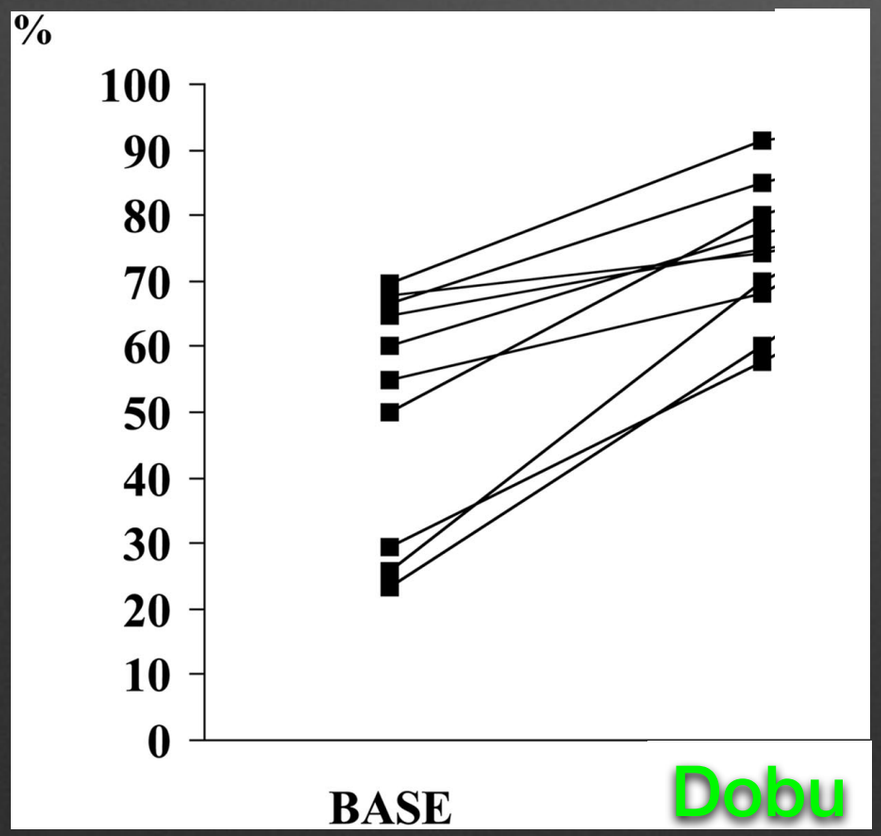
Macro-circulation is a necessary pre-requisite but insufficient. Micro-circulation also essential.

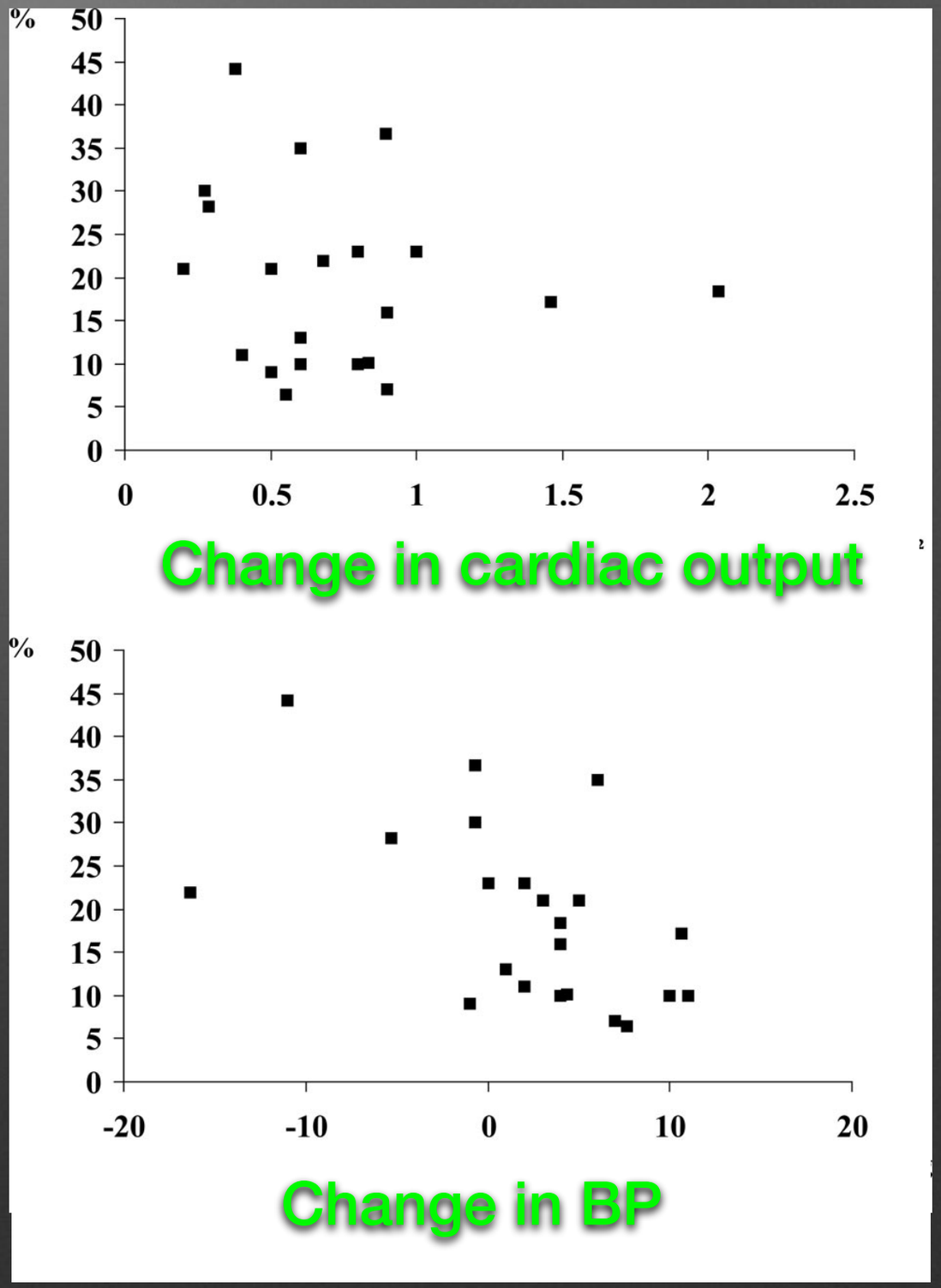
Crit Care Med 2009 Vol. 37, No. 3

Effect of Dobutamine on microcirculation in patients with septic shock are **independent** of its systemic effects

"the **decrease in lactate levels** was proportional to the improvement in capillary perfusion but **not to changes in cardiac index**"

changes capillary perfusion %





Crit Care Med 2006 Vol. 34, No. 2

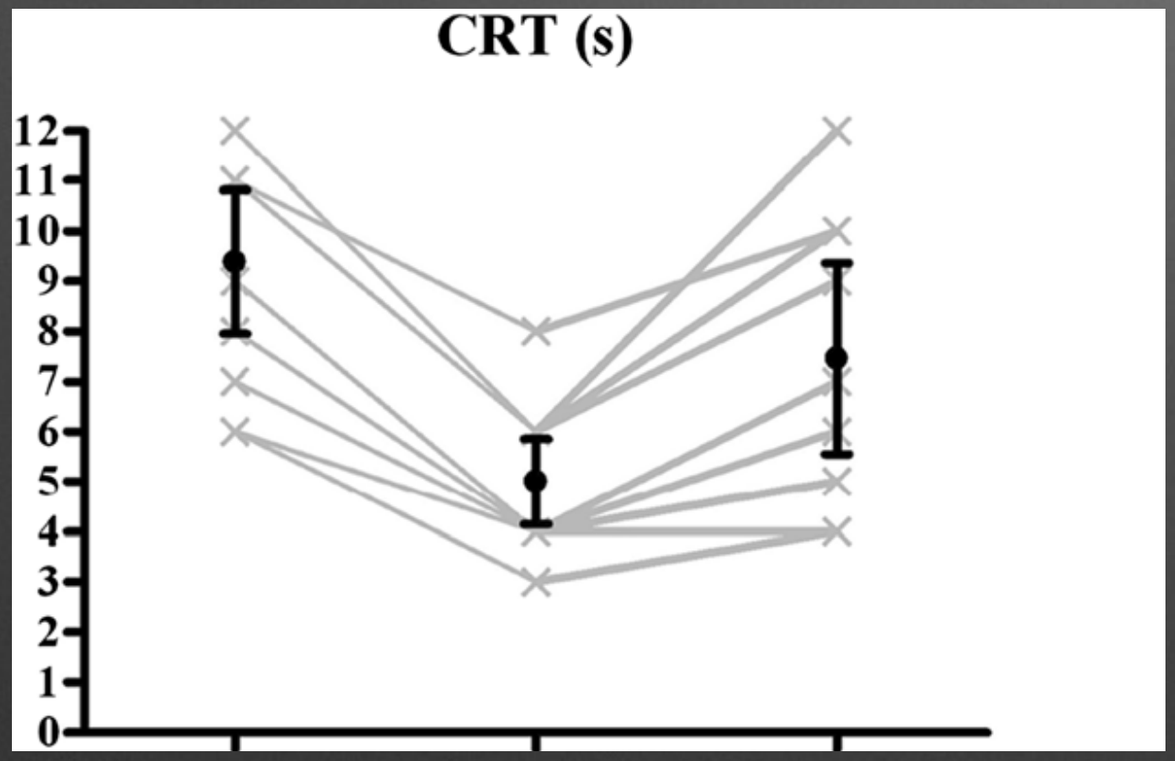
Lima *et al. Critical Care* 2014, **18**:R126
http://ccforum.com/content/18/3/R126

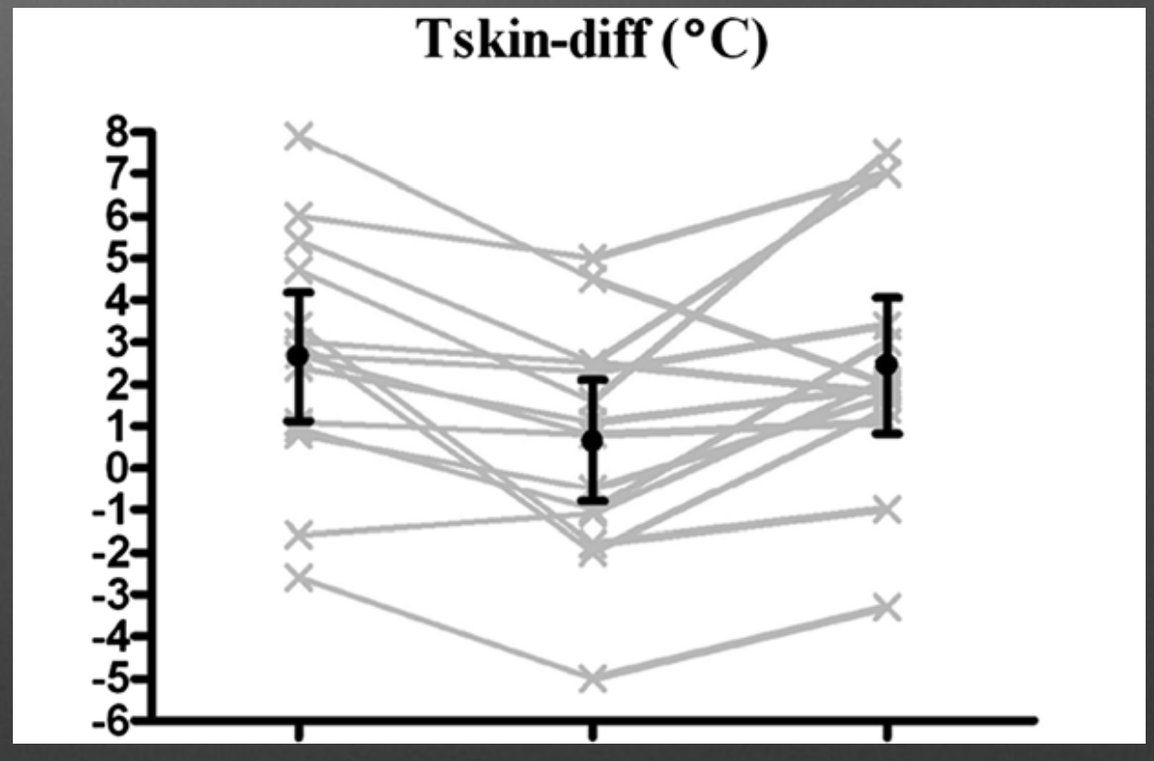
CRITICAL CARE

RESEARCH Open Access

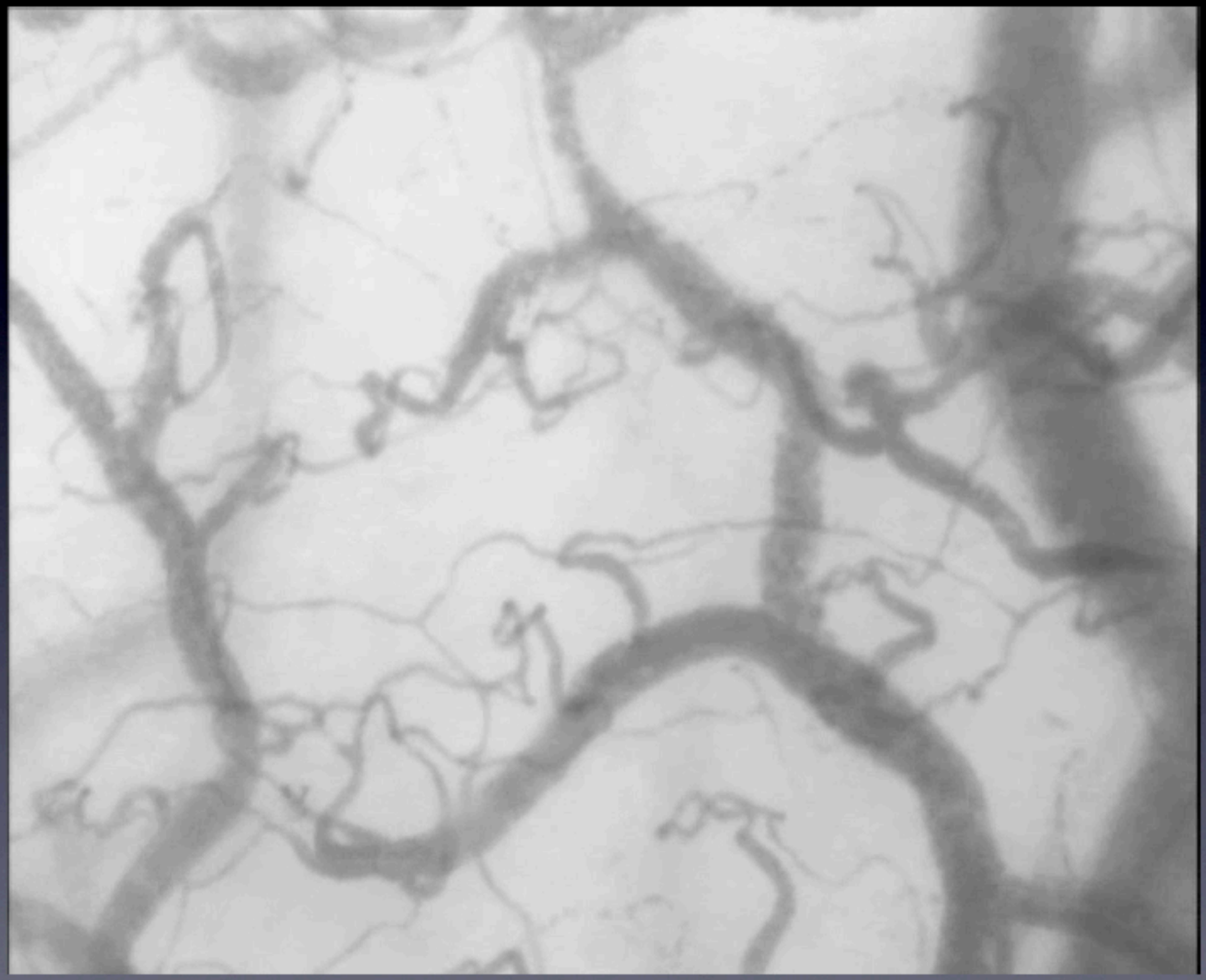
Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock

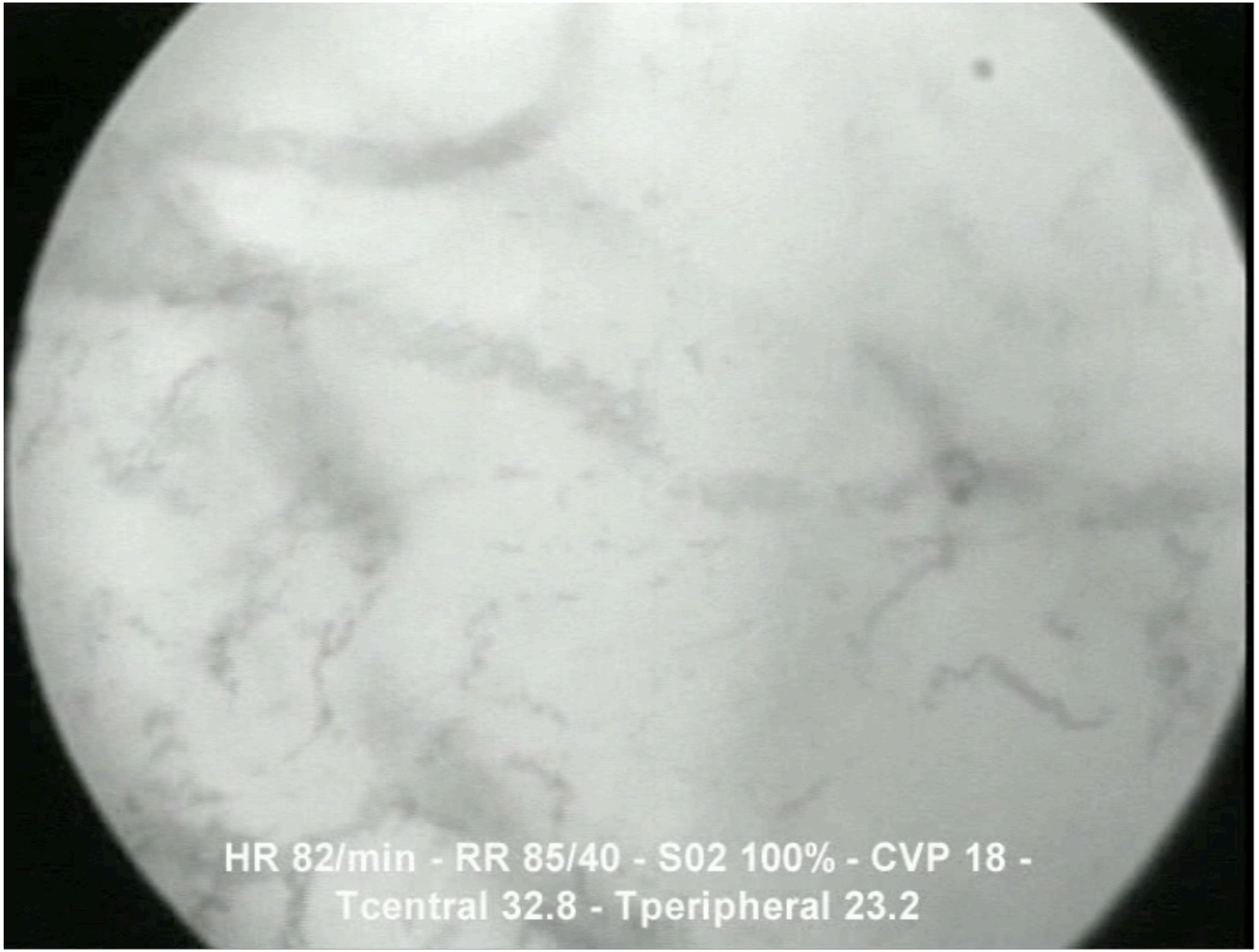
Alexandre Lima*, Michel E van Genderen, Jasper van Bommel, Eva Klijn, Tim Jansem and Jan Bakker





Normal microcirculation




HR 82/min - RR 85/40 - S02 100% - CVP 18 -
Tcentral 32.8 - Tperipheral 23.2

Septic cardiomyopathy

- Troponin >3422 / NT Pro BNP 17444
- TTE -WNL but suspicion of turbulence at aortic valve
- TOE on Sunday morning (!) -WNL
- NB. Troponin returned to normal by day 10

Oxygen delivery =

C.O. x Hb x O_2 Sat

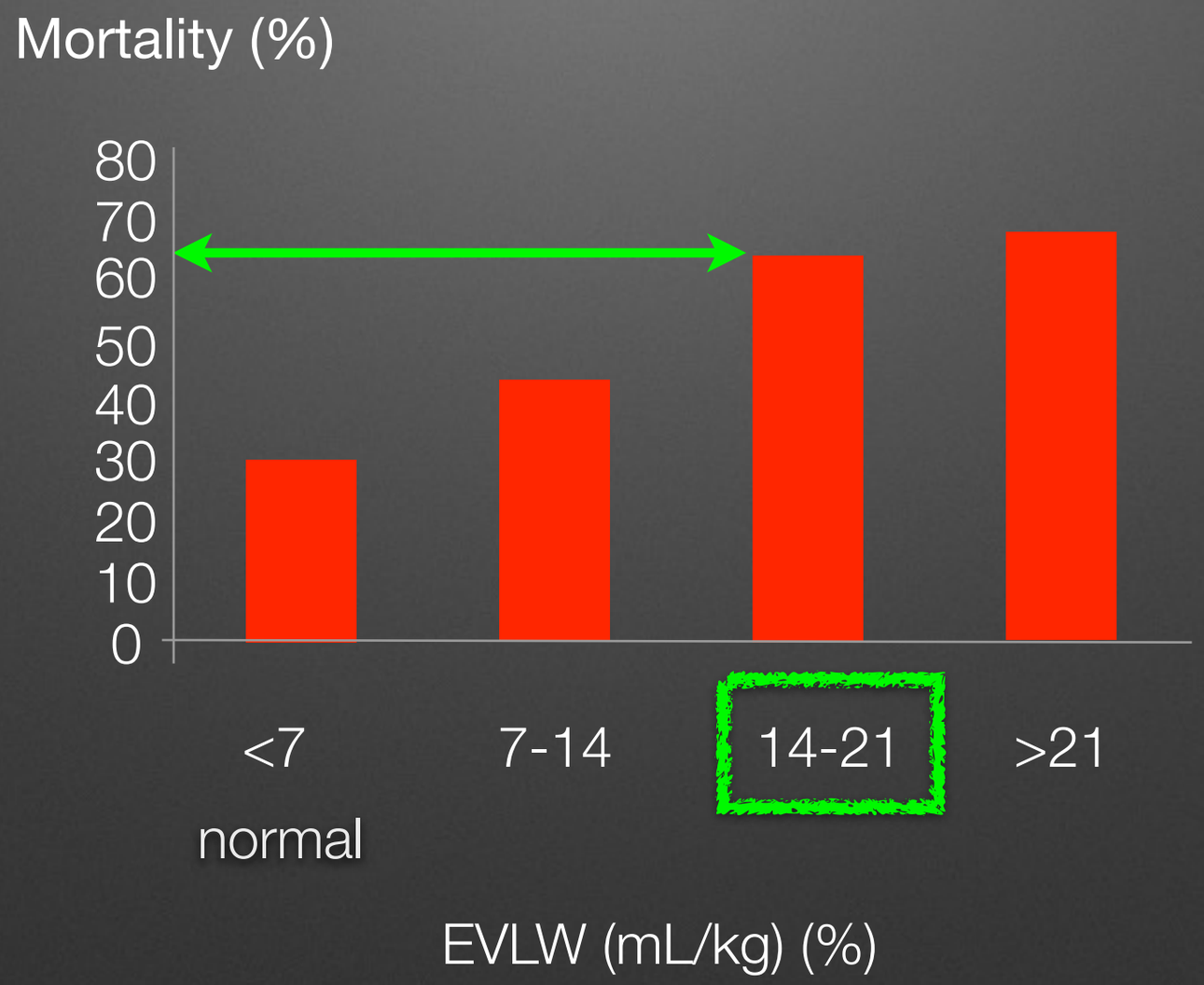
What about the lungs?

ELWI 7 → 19

P/F ~28

CT showed marked ARDS

EVLW as a predictor of mortality



CHEST / 122 / 6 / DECEMBER, 2002

Worried about risk of ARDS?

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

"Patients with severe ARDS were younger, had fewer comorbidities but a significantly worse outcome (>40% mortality)."

"…there is a latent period of 18-24 h between the insult and the development of the full-blown clinical syndrome"

JAMA 2016;315(8):788-800

What will you do about her acidosis?

Clinical Case

Septic shock post GAS cellulitis

pH	**7.19**	pCO2	**5.49**
$HCO3^-$	**15**	Base deficit	**14**
Na^+	**142**	Cl^-	**118**
Albumin (g/L)	**19**	lactate	**4**

(1) standard base deficit = 11

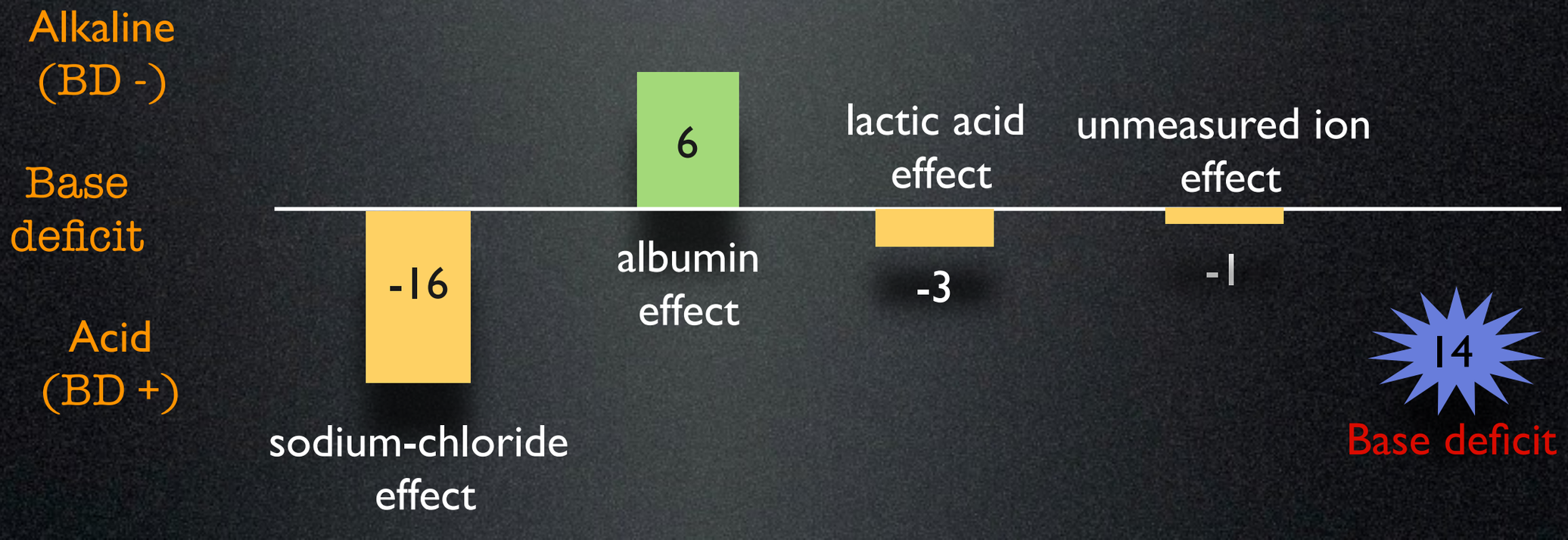
(2) sodium-chloride effect = ([Na^+] - [Cl^-]) - 40 = (142 - 118) - 40 = -16

(3) albumin effect = 0.25 X [42- albumin] = 0.25 X [42 - 19] = 6

(4) lactic acid effect = 4-1= 3

(5) unmeasured ion effect

= base deficit + (sodium-chloride effect) + albumin effect - lactate effect = 11 + (-16) + 6 -2 = 1



How do we treat the acidosis?

- Give NaBicarb?
- But will increase CO_2 and we want to continue protective lung ventilation
- Massive Na^+ load (8.4% = 84 gm/L cf. 0.9% = 9 gm/L)

  (**1L** 8.4% = **9.3 L** normal saline)
- Gave Frusemide to decrease the Cl-

Final Outcome

- Micro called to confirm a Group A Strep so changed to Penicillin V and Clindamycin

- Procalcitonin was a vital component in the **life and death decision** as to whether to continue search for another "source"

- Patient extubated and discharged to ward 3 days later

- Home 10 days after that

Recap

- Soft tissue necrosis is **deadly**
- Diagnosis - **high index of suspicion**
- Treatment
    - Source control
        - **emergent** and **aggressive**
    - Antibiotics
        - Including **toxin suppression** and IVIG
    - Resuscitation
        - Macro and **Micro**
- Procalcitonin ?

Recap

‘Prof Mark Baker, from NICE, told the BBC: “

The problem with those patients who died unnecessarily of sepsis is that **staff did not think about it.....** It requires a **depth of thought and experience....**

.... we have got used to **implementing guidelines without thinking**.”

Remember, there is not a moment to lose

Why we do what we do

To All Staff in ICU

thank you so much for your care, diligence, refusal to leave any stone unturned and, above all, saving Ana's life.

Sizzling Regards,
Malcolm, Fiona & James

I feel very lucky and peivileged to have had such a super team looking after me. Words will never express how grateful I feel.

You are awesome!

Best wishes, Ana

???