Inotropes/Vasoactive Drugs

Goals of todays talk

- Put vasoactive drugs role into overall treatment context
- Discuss individual drugs
- Proof of what is best
- Consider the microcirculation

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Oxygen Delivery

Cardiac output x Hb x % Sat O2

Preload

Effective blood volume
Capacitance
Obstruction
Septal shift
IV fluid
    volume
    C.O.P.

Pump failure

Arrhythmias
Ischaemia
Valvular problems
Septal shift

Afterload

RAA adaptaion
Sepsis
Valvular problems
Pulmonary embolism
Hypertension
Shunts

Heart rate

Anaemia

Fe def
Dilutional
Inflammatory
Vitamin deficiency
Aplastic

Abnormal Hb

Sickle cell
Thalassaemia
met Hb
CO Hb

Hemolysis

free Hb and NO
Pulmonary hypertension
Hypercoagulability

Hyperviscosity

PRV
Acclimatisation

Inspired O2

Altitude
Hyperbaric O2

Hypoventilation

Decreased respiratory drive
    drug induced
CVA
Fatigue (asthma)
Obstruction
    Sleep apnoea syndrome
    Decreased consciousness

Ventilation/perfusion abnormalities

Shunt
    Pneumonia
    Pulmonary oedema
Dead space
    Pulmonary embolism
    Fat embolism
Mixed
    COPD
    Asthma

Cardiac output - what are our goals?

- Adequate “effective” cardiac output
- Adequate blood pressure (>65 mean)
- Adequate macro **and** micro-circulation

Correcting **macro** haemodynamics is a

pre-requisite but not necessarily enough

“Adequate” cardiac output?

- Clinical signs

Normal BP	Normal sensorium
Warm toes	Urine output
< 3 sec capillary refill	Small core-peripheral temperature gradient

- Biochemistry

  ScV02

  Lactate

  Base deficit

- Advanced technology

  “Visualizing” the micro-circulation

Do we have “adequate” blood pressure?

- Arbitrarily defined as a mean BP > 65
- There is no proof that this is correct
- It may need to be tailored to each patient

So How Do We Reach Our Goals ?

.....and in what order?

Surviving Sepsis Campaign

5 Physiological targets - 6 hours :

- ☑ (1) **Central venous pressure** of between 8 and 12 mm Hg

wrong!

- ☑ (2) **Mean arterial pressure** of at least 65 mm Hg
- ☑ (3) **Urine output** =/> 0.5 mL/kg/hr
- ☑ (4) **Central venous oxygen saturation** using a target of at least 70%
- ☑ (5) Normalized **lactate**

CCM 2013;41:580-637

Surviving Sepsis Campaign

How to reach physiological targets :

- ☑ First question: **is patient fluid responsive?**
- ☑ If not, raise the **B.P.** with inotropes/vasopressors
- ☑ Despite **adequate BP - is C.O. adequate** ?

  (ex. ScvO2, lactate clearance etc)

  If not → Dobutamine / RBCs
- ☑ ????(4) Resuscitate the microcirculation

CCM 2009;36(1):296-327

Surviving Sepsis Campaign

Fluid therapy - first 3 hours

- ☑ **Crystalloids** fluid of choice (can use albumin, not HES) at ~ 30 mL/kg
- ☑ **Fluid challenge** can be applied as long as improvement in :

dynamic

  - ☑ ex. pulse pressure variation, stroke volume variation

static

  - ☑ ex. BP, heart rate

Remember - 50% of patients are not fluid responsive!

CCM 2013;41:580-637

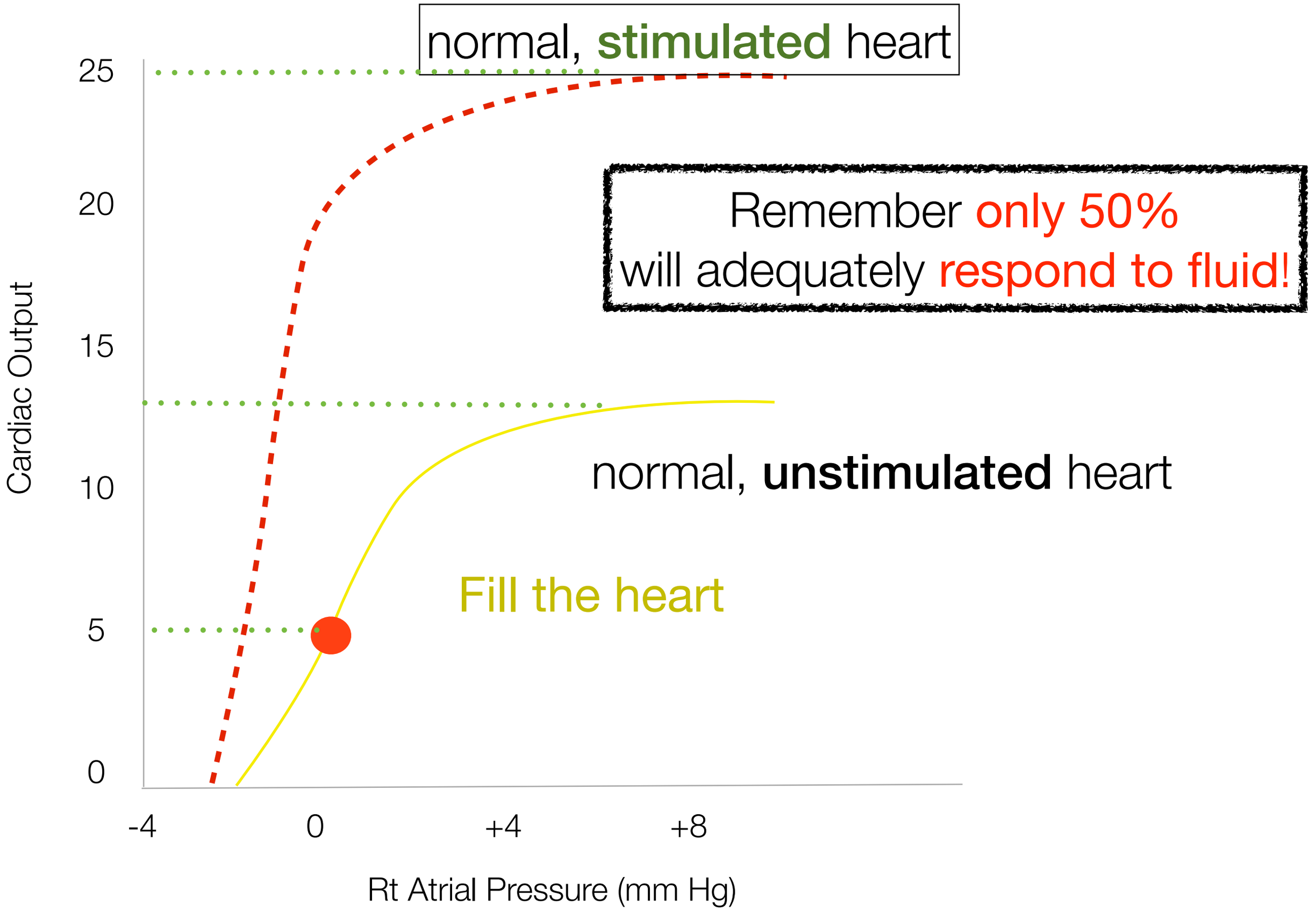
Surviving Sepsis Campaign

Vasopressors

- **Noradrenaline** the first choice
- Adrenaline when an additional agent needed
- **Vasopressin** (0.03 U/min) can be added to noradrenaline if necessary
- Dopamine as an alternative only in highly selected cases (rel bradycardia)
- **Dobutamine** added if:
  - myocardial dysfunction
  - ongoing hypoperfusion **despite** adequate volume and **BP**

CCM 2013;41:580-637

Optimize fluids first, ...then inotropes!



Early Use of Vasopressors After Injury: Caution Before Constriction

Jason L. Sperry, MD, MPH, Joseph P. Minei, MD, Heidi L. Frankel, MD, Micheal A. West, MD, PhD, Brian G. Harbrecht, MD, Ernest E. Moore, MD, Ronald V. Maier, MD, and Ram Nirula, MD, MPH

"These findings provide evidence that the **early** use of vasopressors for hemodynamic support after hemorrhagic shock may be **deleterious**, and should be used **cautiously**.."

J Trauma 2008;64:9-14

Early Vasopressor Use in Trauma Linked to Increased Mortality Risk

"In critically injured patients, **early** treatment with vasopressors was associated with more than an **11**-fold increase in **risk of death**"

Dr. David Plurad.-Annual meeting of the American Association for the Surgery of Trauma- 2010.

But!!!

"**Early** administration of norepinephrine in severely hypotensive septic-shock patients increased cardiac output through an increase in cardiac **preload** and cardiac contractility"

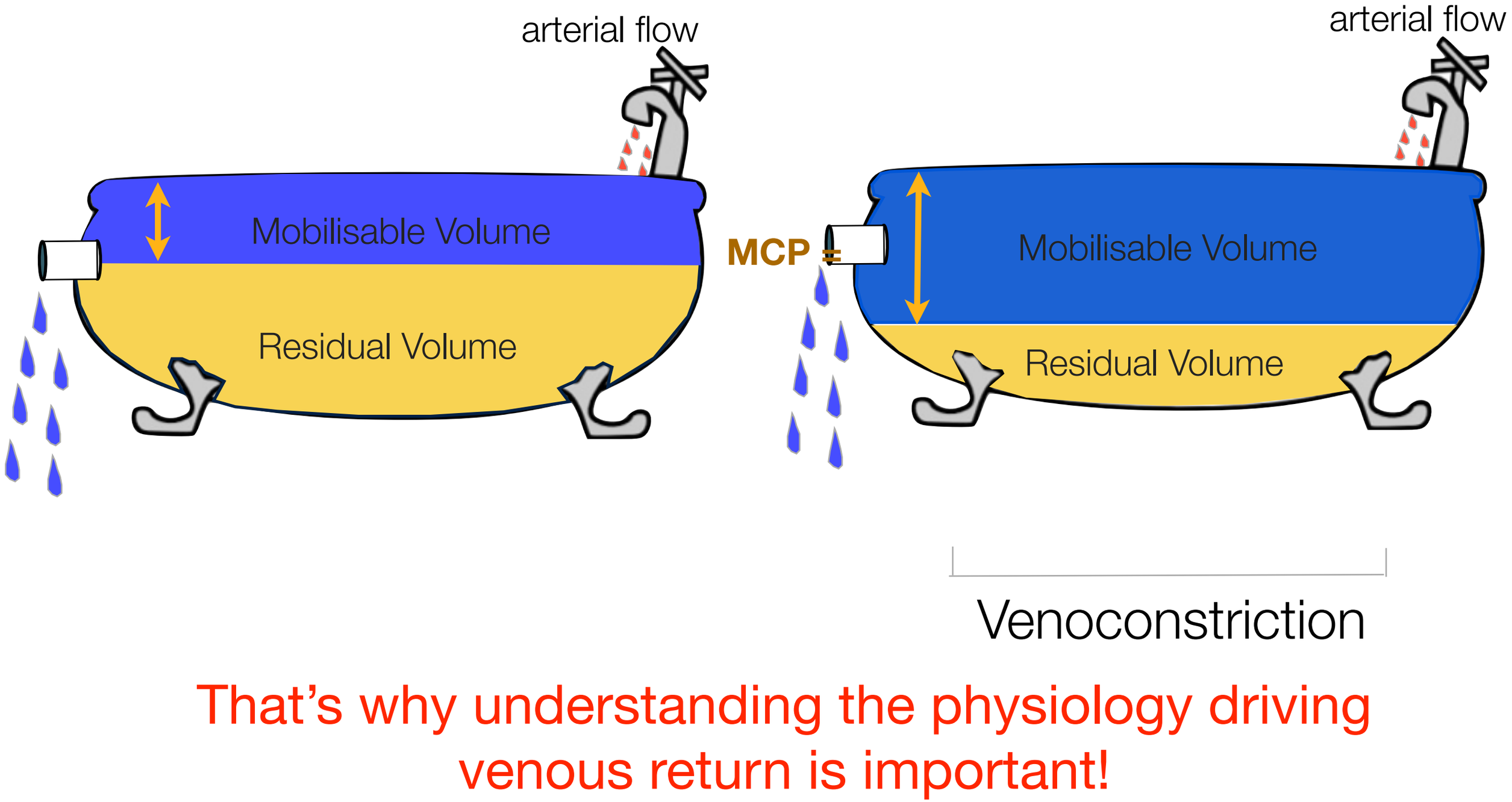
	Before NorAdr	After NorAdr
MAP	54	76
Cardiac Index	3.2	3.6
Cardiac Function Index	4.7	5
Global End Diastolic Index	694	742
Stroke Volume Variation	13	9

Why preload?

Critical Care 2010, 14:R142

Because.....

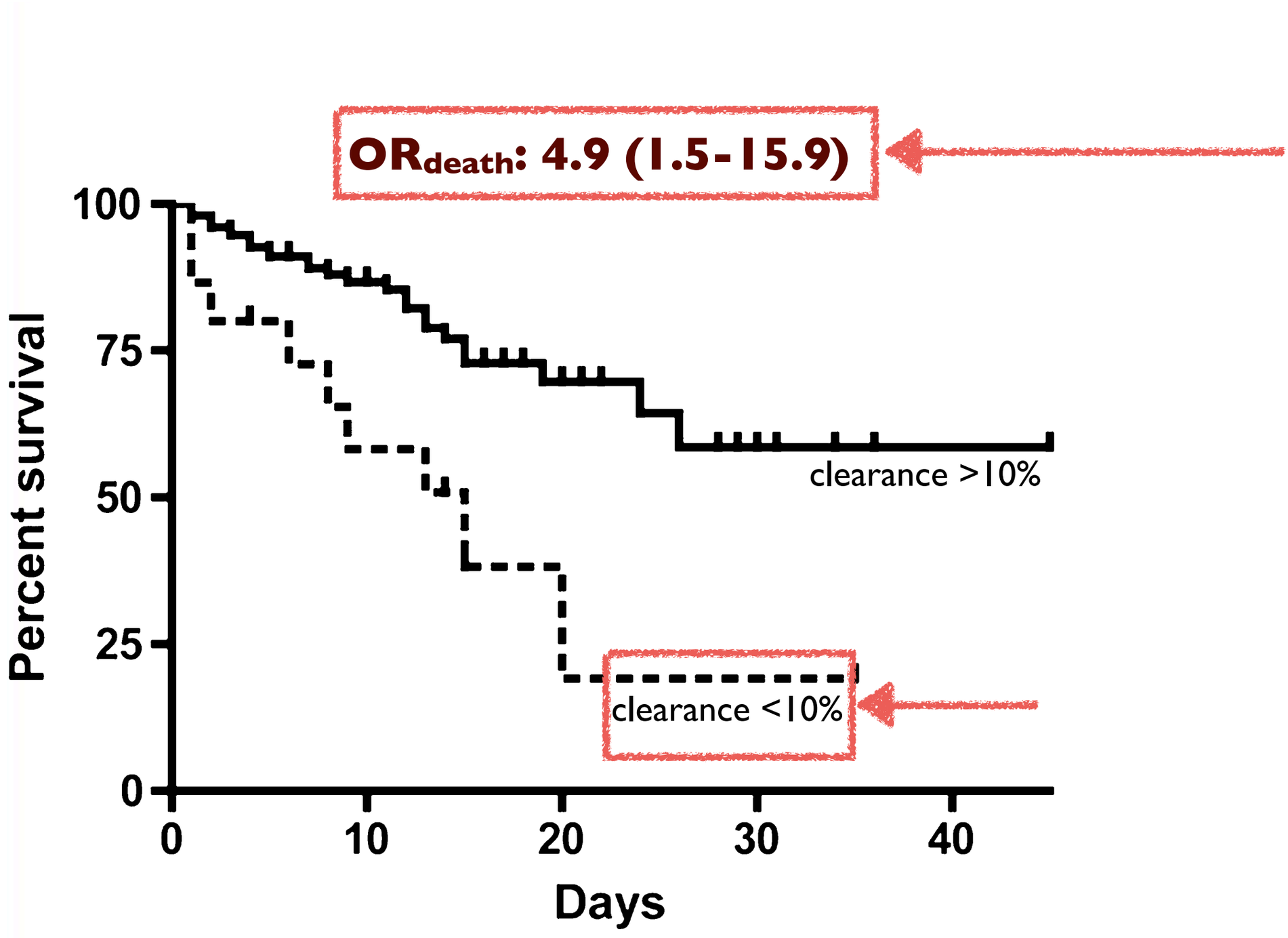
Vasopressors are **5 X more potent** on the **venous** (capacity) side then on the arterial (resistance) side



That’s why understanding the physiology driving venous return is important!

Lactate Clearance As a Sign of Resuscitation

OR_{death}: 4.9 (1.5-15.9)



Shock, Vol 32, No.1, pp 35-39, 2009

Guidelines for Management of Severe Sepsis and Septic Shock

Surviving Sepsis Campaign

"There is not a moment to lose"

- ☑ As many people die of sepsis as of myocardial infarction
- ☑ We should adopt the same "door to needle"sense of **urgency** as with fibrinolysis in STEMI
- ☑ Delay = lives lost!

CCM 2009;36(1):296-327

Goals of todays talk

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Vasoactive agents - general comments

Consider :

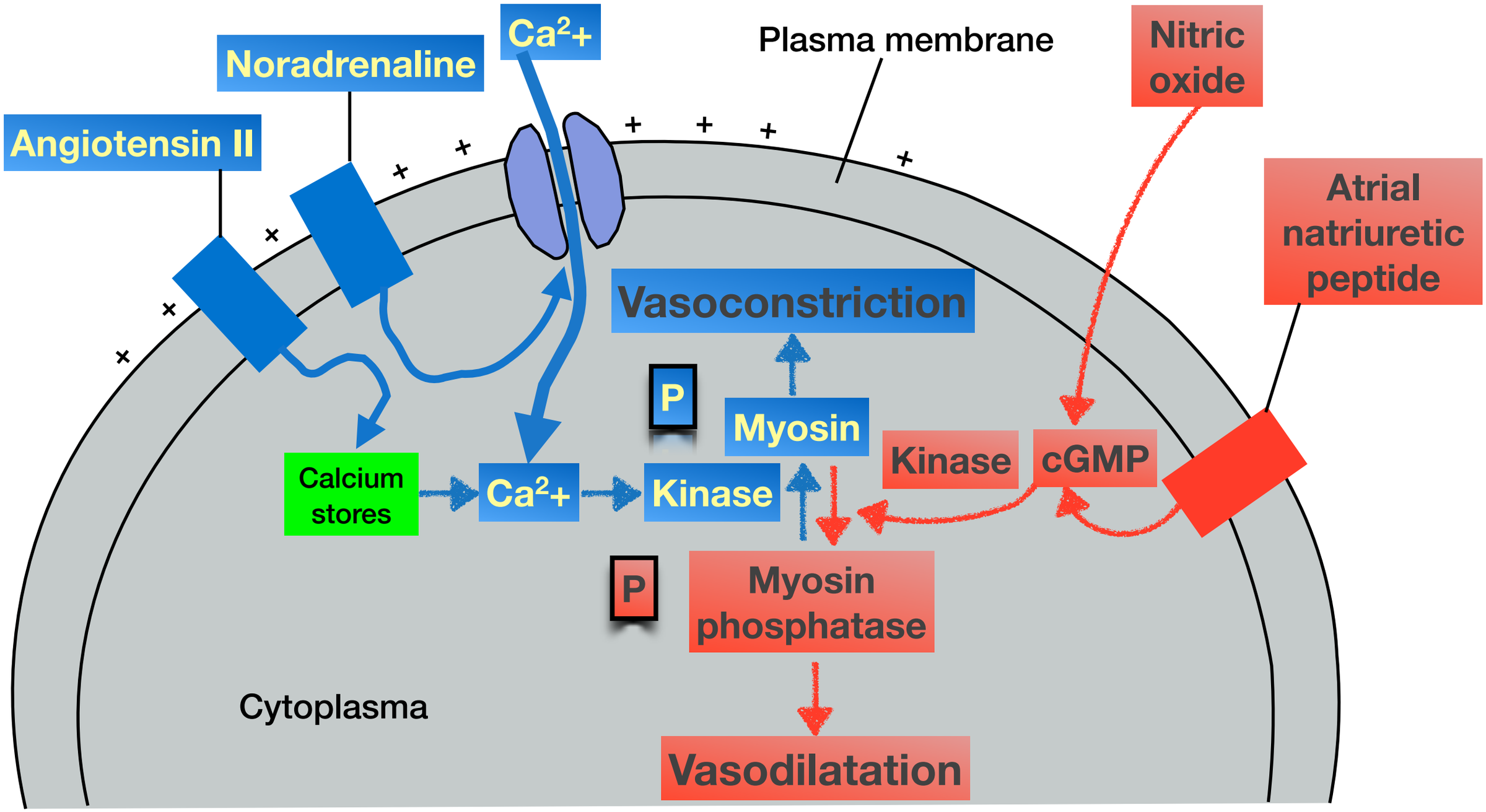
- **Direct** receptor effects
- **Reflex** responses - overall effects are complex

  Ex. Noradrenaline causes tachycardia but vasoconstriction causes a reflex bradycardia

- **Veno** vs **arterial** vasoconstriction

  Low doses mainly increase venous return by **venoconstriction**

Physiology of vasoconstriction/vasodilatation



CV role of adrenergic receptors

α ➔ vasoconstriction ➔ raises SVR / increases venous return

NB. venous side more sensitive to low dose

$\beta 1$ ➔ increases inotropy and heart rate

$\beta 2$ ➔ increased flow to skeletal muscles -> decreased peripheral resistance

Dopamine receptors

- DA 1 ➔ coronary, renal and mesenteric arterial relaxation
- DA2 ➔ inhibit noradrenaline release

Drug effects

Dobutamine

$\beta 1 > \beta 2 > \alpha$

inotropic
Vasodilatory

inotropic
increased BP

Noradrenaline

$\beta 1 > \alpha > \beta 2$

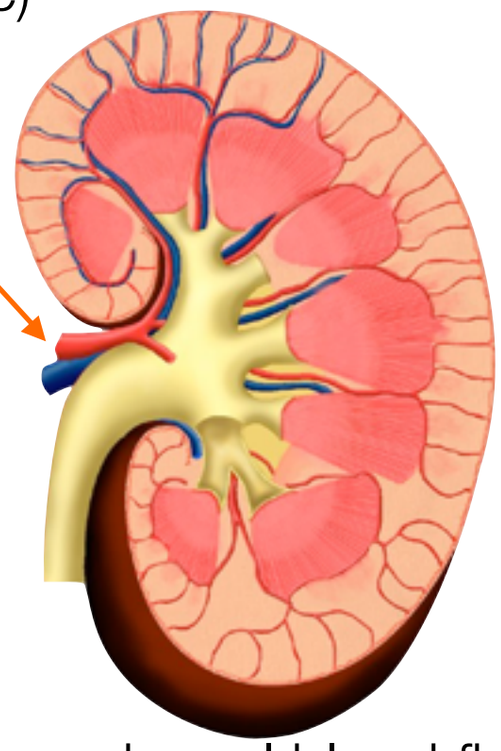
Dopamine

$\beta 1$ ($\beta 2$) → inotropic

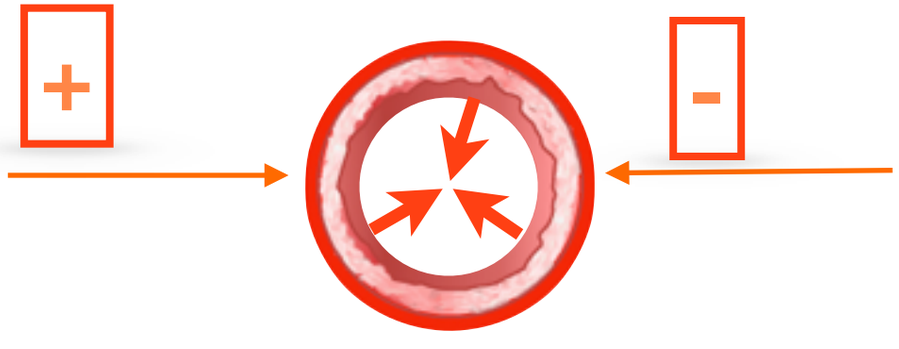
α → high dose α → α 1 - constriction

DA2 → peripheral vasodilation

(low dose) DA1



increased renal blood flow



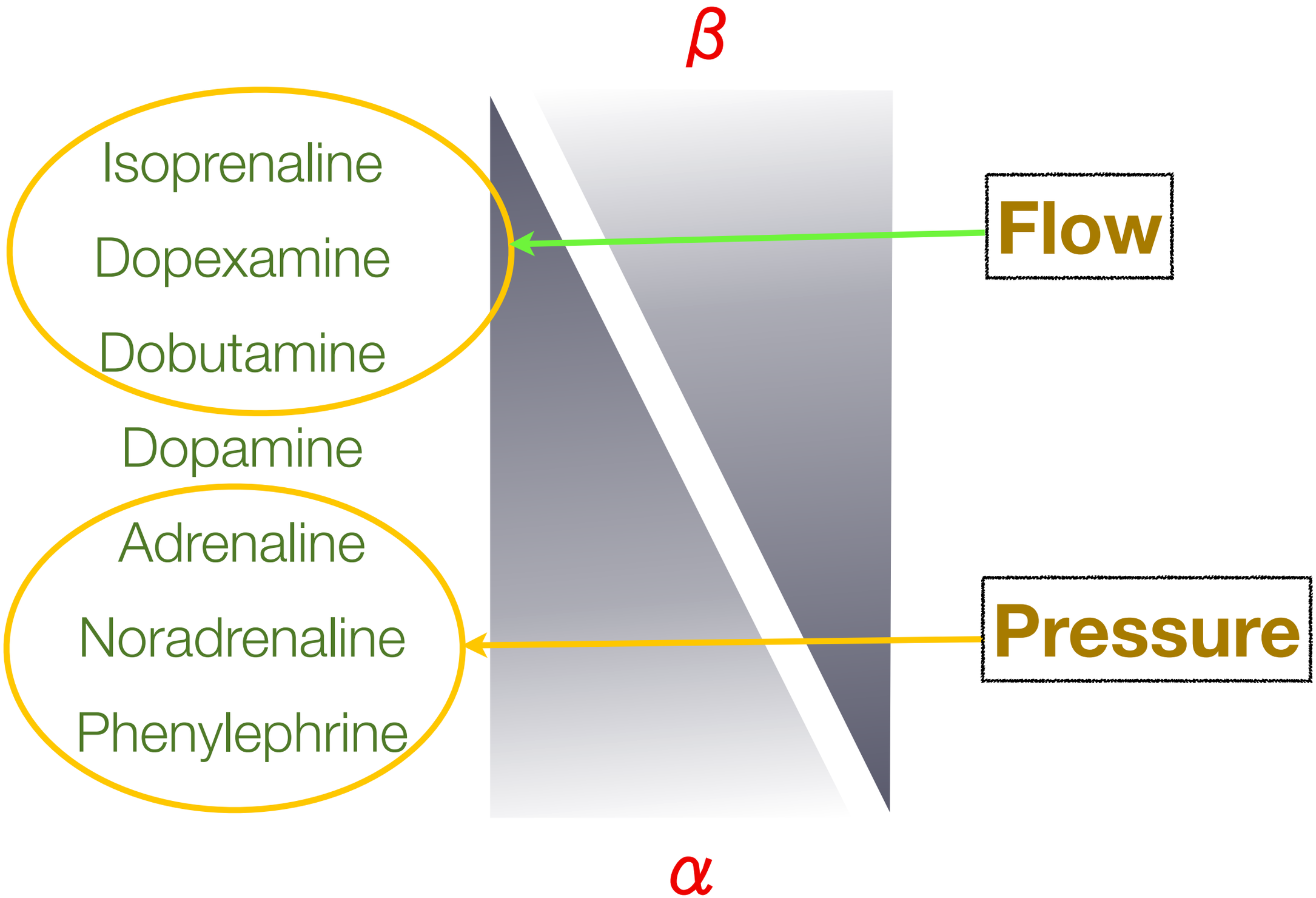
inotropic
Dilator/constrictor

Adrenaline

$\beta 1 = \beta 2 > \alpha$

Opie 1998

Effects of vasoactive catecholamines on **pressure** and **flow**



Individual vasoactive drugs

Drugs commonly used to treat shock

Drug	α	β 1	β 2	Dopamine	Dose
Adrenaline β 1= β 2> α	++++ (high dose)	++++ (low dose)	+++	-	0.01 -1.0 mcg/kg/min
Noradrenaline β 1> α > β 2	+++	+++	little	-	0.01 -1.0 mcg/kg/min
Dopamine β 1(β 2) α (high dose) DA vasodilation	++/+++ (high dose)	++++ (low dose)	++	+++	2-20 mcg/kg/min
Dobutamine β 1> β 2> α	little	++++	++	-	2 - 15 mcg/kg/min
Dopexamine β 2 DA vasodilation	-	little	+++	-	1 - 10 mcg/kg/min
Arginine vasopressin V1/V2/V3	Vasoconstricts all vessels via **non** adrenergic receptor Useful if not responsive to adrenergic agonists				Max. up to 4U/hr

Noradrenaline

- Receptors : potent α agonist, less $\beta 1$, no $\beta 2$

- Vascular effects :

  Dose dependant - **arterial and venous vasoconstriction**

- Cardiac effects :

  Moderate increase in stroke volume (10-15%)

  Heart rate/tachycardia (variable due to reflexes)

- Uses :

  First line agent in septic shock

  Vasodilation and cardiac dysfunction (ex. Sepsis/SIRS)

Noradrenaline

- Dose :

  0.03 - 1.0 mcg/kg/min - potent vasopressor

- In septic patients noradrenaline

  ➔ increased renal blood flow and urine output

- Adverse effects :

  - increased myocardial O2 consumption

  - renal/splanchnic vasoconstriction ➔ renal ischaemia

    esp. if **hypovolaemic** (use with care)

Adrenaline

- Potent α and β 1+2, α = β

  α 1 ➔ venoconstriction -> increased venous return

  β 2 ➔ increased flow to skeletal muscles -> decreased peripheral resistance

- Doses

  Very low dose (0.01 - 0.05 mcg/kg/min) ➔ increased cardiac output

  Higher doses ➔ α receptors outweigh β 2 vasodilation ➔ increase mean BP

- Cardiac effects

  More potent effect on contractility than noradrenaline

  Increased heart rate/tachycardia

- Uses

  When severe cardiac dysfunction is contributing to shock

  Cardiac arrest

  Anaphylactic shock

Adrenaline

- 2nd line agent because :
  - decreased splanchnic/renal flow
  - tachyarrhythmias
  - myocardial ischaemia

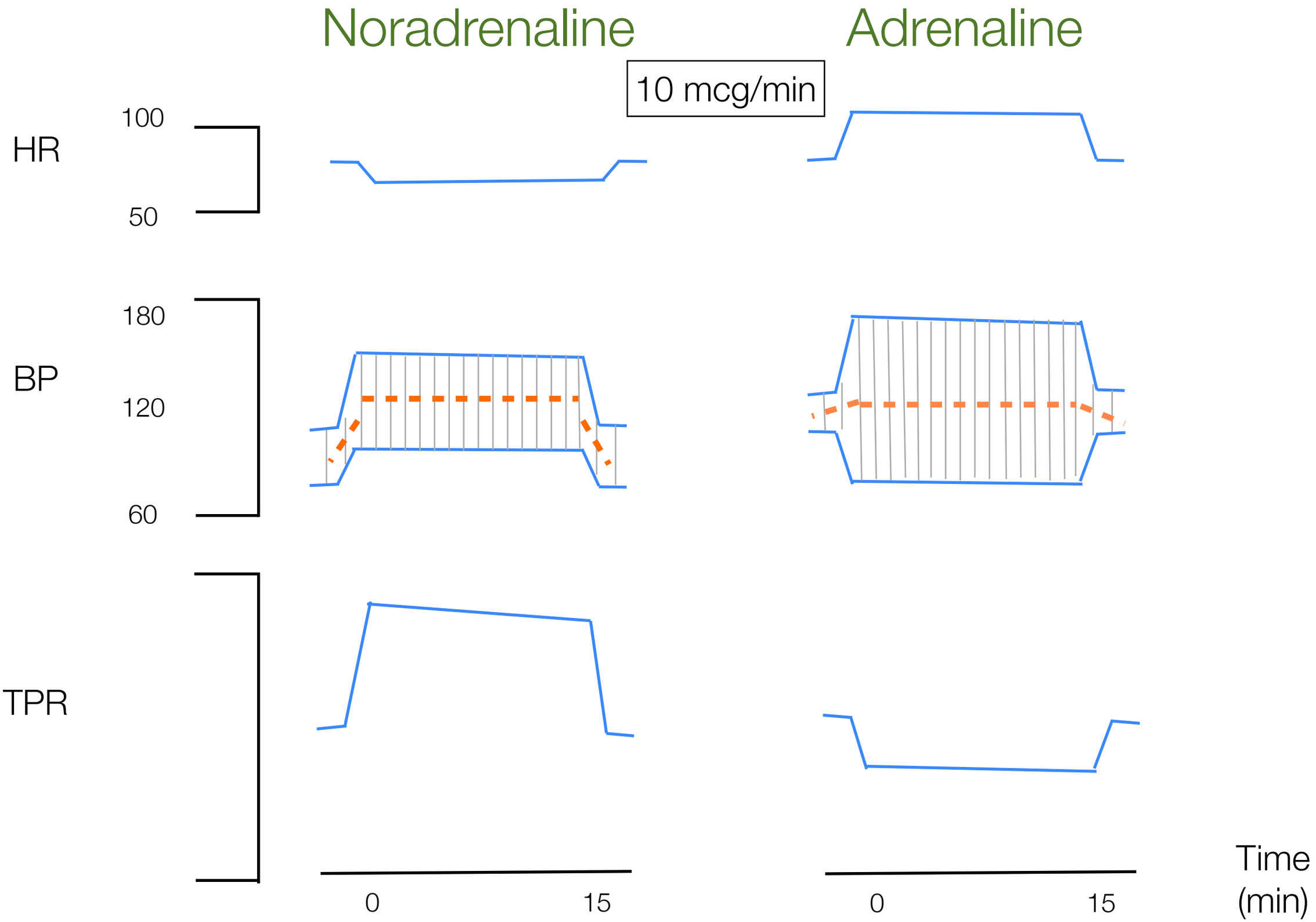
- Potential problems

  Care if on β blockers ➔ unopposed α activity ➔ hypertension

  Reduced splanchnic flow

  Increased myocardial workload ➔ ischaemia

Noradrenaline vs Adrenaline



Arginine Vasopressin

V1 receptors

- Baroreceptor function - Vasoconstricts all blood vessels via <u>non</u> adrenergic receptors
- **Relative deficiency in sepsis** (and other causes of refractory vasodilator shock)
- Minimal pressor effect in normal subjects
- Many who do not respond to catecholamines respond to Vasopressin

Useful for drop in BP during GA if patient on ACEI / Angio II blockers and unresponsive to catecholamines (**3rd system controlling BP**)

Arginine Vasopressin

V2 receptors

- Controls **osmolality** - **primary function**

  Acts on collecting duct to produce concentrated urine

- Vasodilatation
- Increase in **von Willebrands factor and VIIIc**
- Blood levels ~ 1-7 pcg/mL (cf. V1 10-200 pcg/mL)

V3 receptors

- In Anterior pituitary ➔ mediates release of **ACTH**

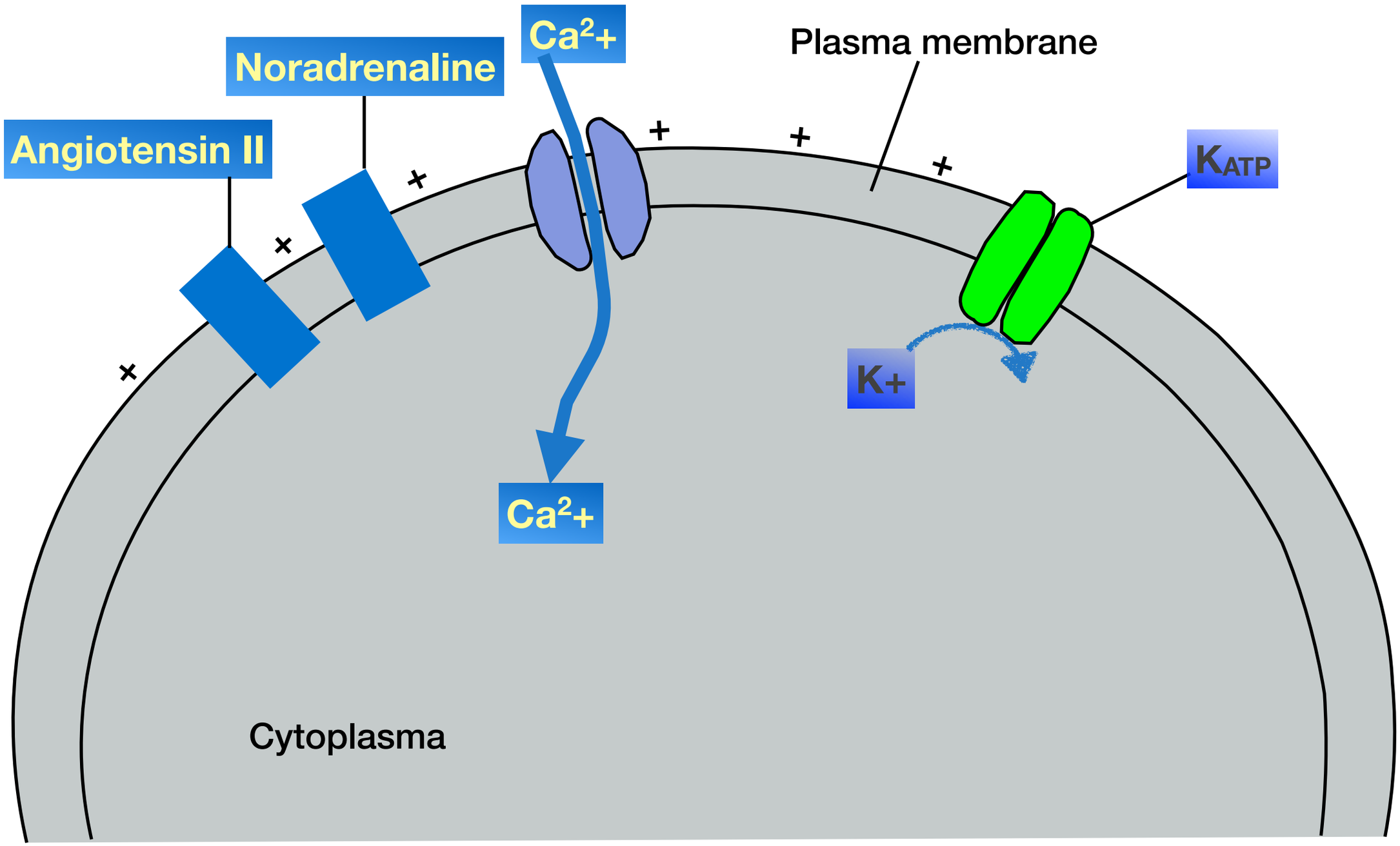
Arginine Vasopressin in Septic Shock

- Vasodilatory shock
  - Mediated by **huge release of NO**

    (also causes myocardial depression)
  - Maybe **resistance** to NorAdrenaline
  - AVP stores eventually **depleted** in post. pituitary
  - AVP acts by :
    - **inhibits iNO**
    - **restores** action of Noradrenaline

Resting potential

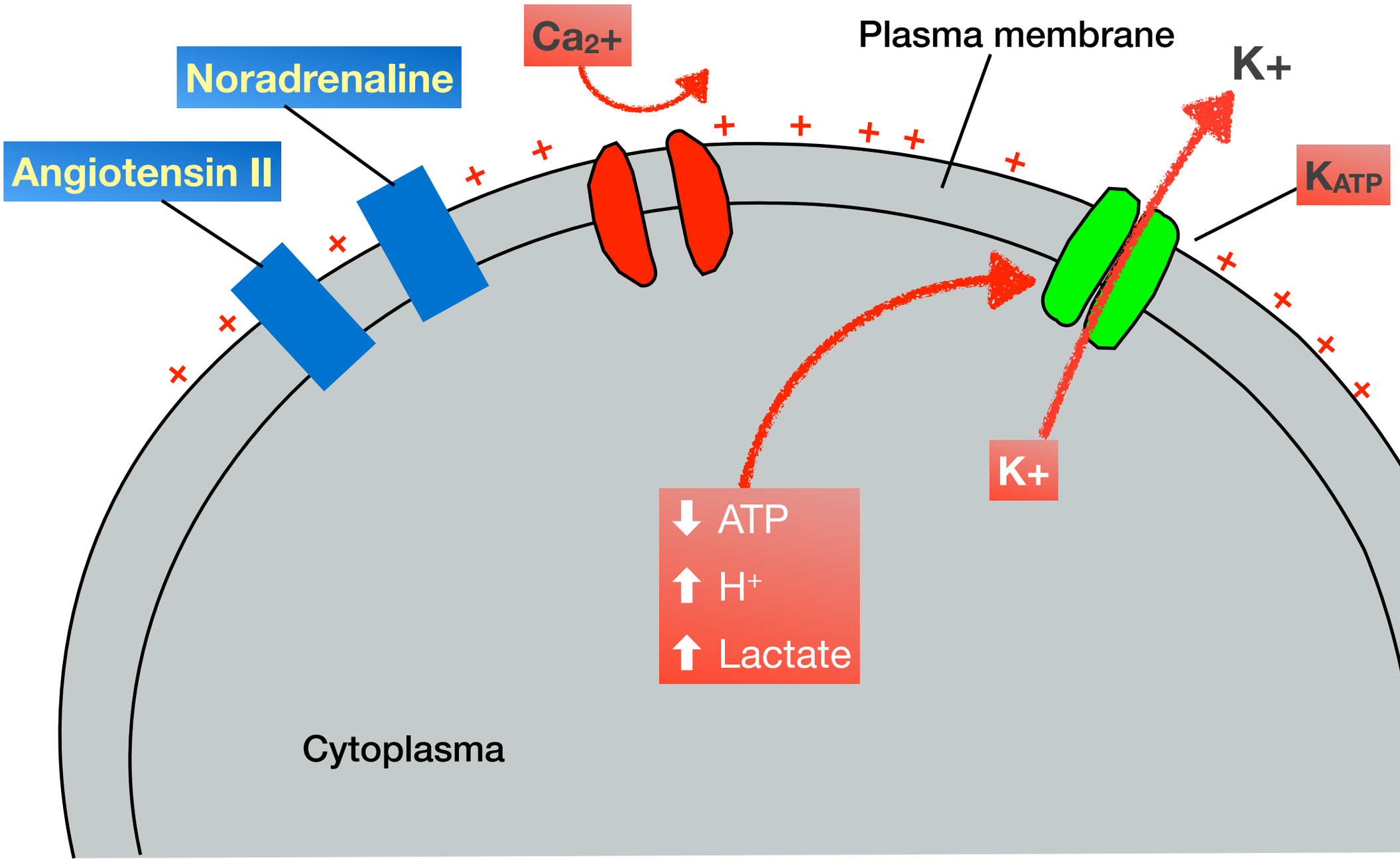
Vasoconstriction



N Engl J Med, Vol. 345, No. 8 · August 23, 2001

Vasodilatation

Hyperpolarization

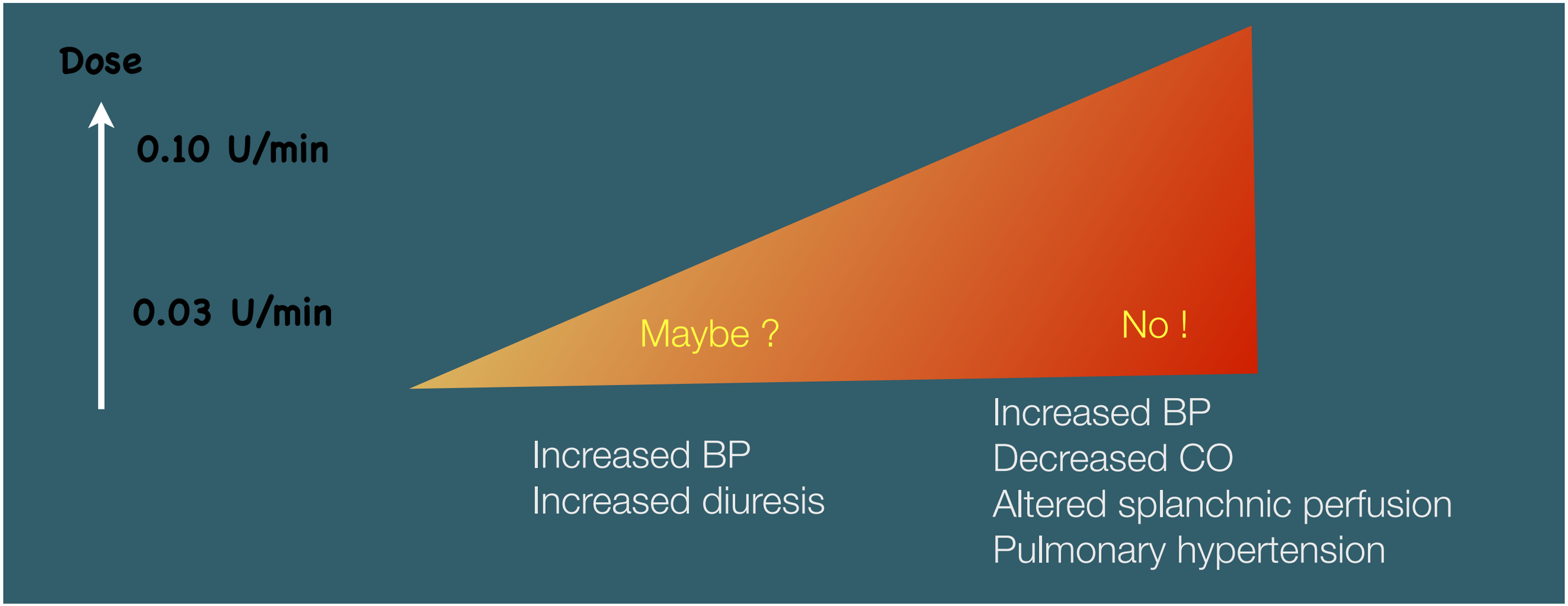


N Engl J Med, Vol. 345, No. 8 · August 23, 2001

Arginine Vasopressin in Septic Shock

- Dose
  - 1 - 4 U/hr - effective since vasodilatory shock patients have blood levels ~ 1/10th expected
  - Decreases Noradrenaline requirements by 70%
  - AVP increases GFR by constricting the **<u>efferent</u>** arteriole in the glomerulus
- Adverse effects
  - Excess vasoconstriction ➔ end organ ischaemia
  - **Never more then 4U/hr ➔** splanchnic/coronary vasoconstriction
  - Decreased cardiac output due to increased afterload

Arginine Vasopressin



Dobutamine

- Receptors : $\beta 1 > \beta 2$
- Vascular effects : vasodilation
- Cardiac effects - lower doses
  - Increased cardiac output - strong inotrope
  - Increased heart rate
  - Effect on BP variable
- Uses
  - Cardiogenic shock
  - Refractory shock from sepsis
- Potential problems
  - Tachydysrhythmias
  - Hypotension from $\beta 2$ effects

Dopamine

- Precursor of Nor and adrenaline
- Receptors : α , $\beta 1 > \beta 2$, dopaminergic
- Effects - dose dependant :

  <5 mcg/kg/min - DA receptor -> vasodilation of renal/mesenteric

  5-10 mcg/kg/min - $\beta 1$ receptor ➔ inotropic/chronotropic

  >10 mcg/kg/min - α receptor ➔ arterial vasoconstriction

- Uses

  Shock from sepsis or SIRS

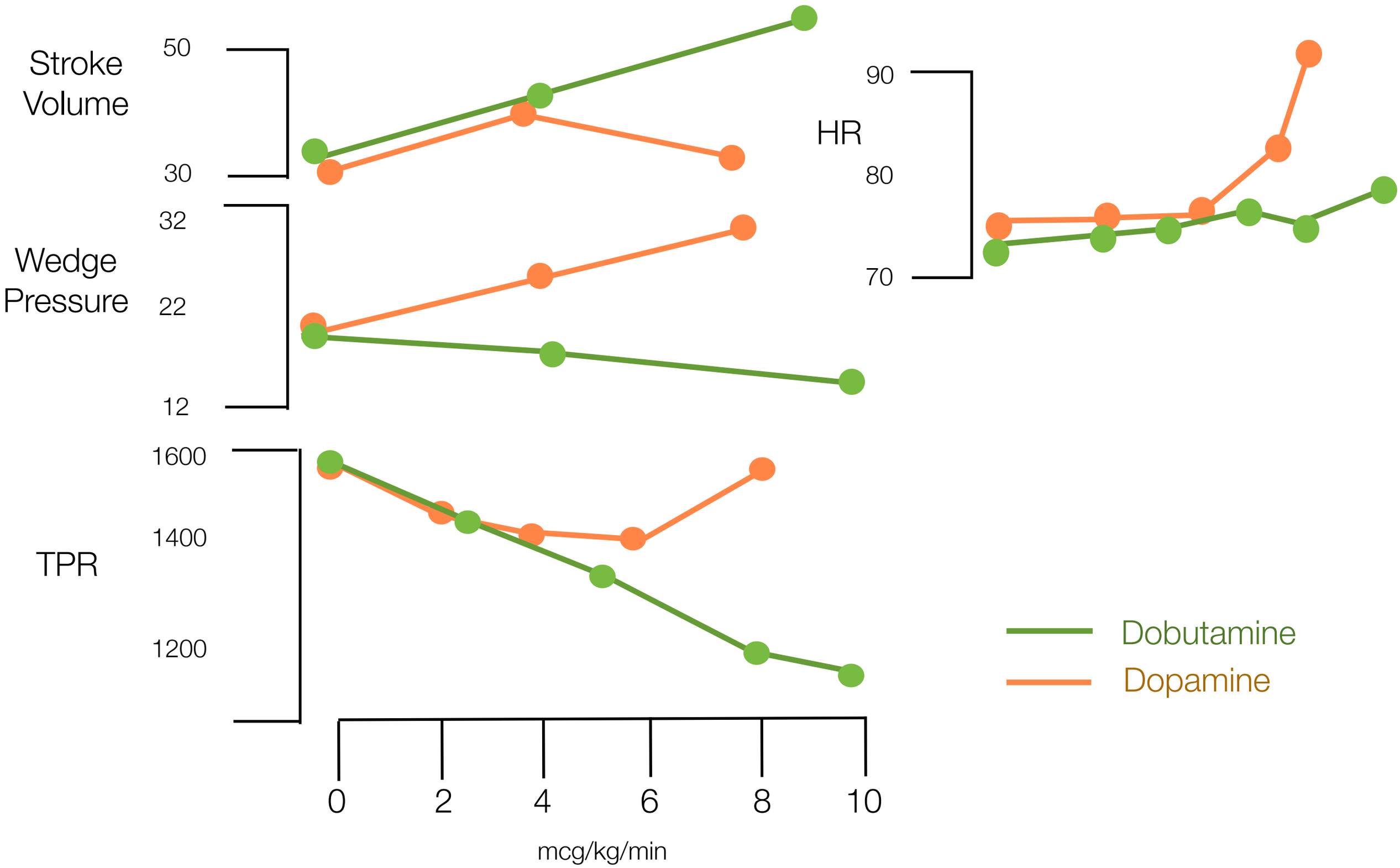
  No longer used in “renal doses”

- Potential problems

  Dysrhythmias

  Raises Pulmonary arterial pressure

Dopamine vs. Dobutamine



Circulation 58:466–475, 1978

If still <u>unresponsive</u> to fluids and vasoactive agents, don't forget

- **Steroids**

  Replacement doses (<200 mg hydrocortisone/ day)

  Restores adrenoceptor sensitivity

- **Methylene blue**

  Inhibits production of excess NO

  2 mg/kg over 20 min

  Causes pulmonary vasoconstriction ...beware!

Lancet;359:April 6, 2002

Goals of todays talk

- Put vasoactive drugs role into overall treatment context
- Discuss individual drugs
- Proof of what is best
- Consider the microcirculation

In Sepsis - does it matter which one we use?

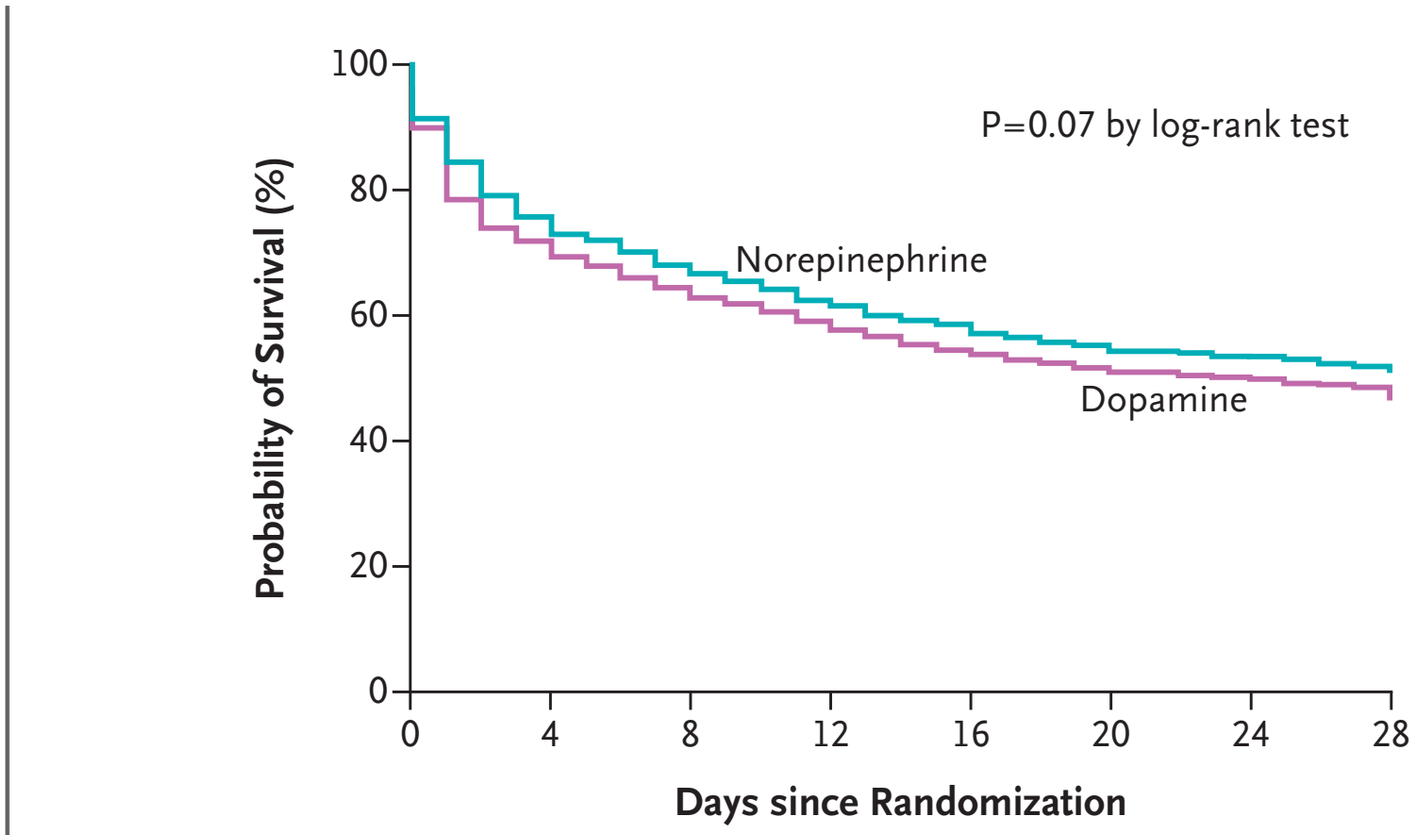
Studies evaluating vasoactive drugs in septic shock

Study	Patients	Methods	Conclusions
"SOAP-II" study	1679	Multi-center Randomized	**No mortality difference** betwen Nor and Dopamine. More adverse effects (arrhythmias) with Dopamine
Povoa- "SACiUCI" study	458	Observational (sub group analysis)	Dopa decreases mortality. Nor and dobut increase mortality
Annane	330	RCT Nor +/- dobut vs. Adrenaline	**No difference** in any important outcome variable
Russell- "VASST" study	778	RCT Nor vs Vasopressin	Better survival with vasopressin in less sick patients. **No overall mortality difference**

“SOAP II”

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

“...**no significant difference** in the rate of death between patients treated with **dopamine** or with **norepinephrine**, ...**dopamine** was associated with a **more adverse** events.”



No. at Risk

Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

N Engl J Med 2010;362:779-89.

So, why the confusion?

Beware of secondary endpoints

- A trial does **not** meet its **primary** endpoint
- There is a **secondary** endpoint that is statistically significant (P<0.05)
  - The probability that an identical repeat of the trial will reproduce the same secondary endpoint is **not** 1 in 20 (P<0.05) but **57%** (i.e., almost 1 in 2 !)
- No wonder so many trials showing secondary endpoints are **not reproduced in subsequent studies!!**

Anesthesiology 2009; 110:729-37

Surviving Sepsis Campaign

"There is no high-quality primary evidence to recommend one catecholamine over another"

CCM 2009;36(1):296-327

Untoward Effects of Catecholamines

Overt effects

- Tachyarrhythmias
- Local ischaemia

Especially if inadequately filled

Lancet Vol 370 Aug 25, 2007; 636-637

Untoward Effects of Catecholamines

Covert effects

- Stimulation of **bacterial growth** and virulence
- Increase **biofilm** formation
- Reduce metabolic efficiency

  Enhance **fatty acid** metabolism
- Modify **immune-cell** populations

  Some pro-inflammatory

  Some ant-inflammatory

Lancet Vol 370 Aug 25, 2007; 636-637

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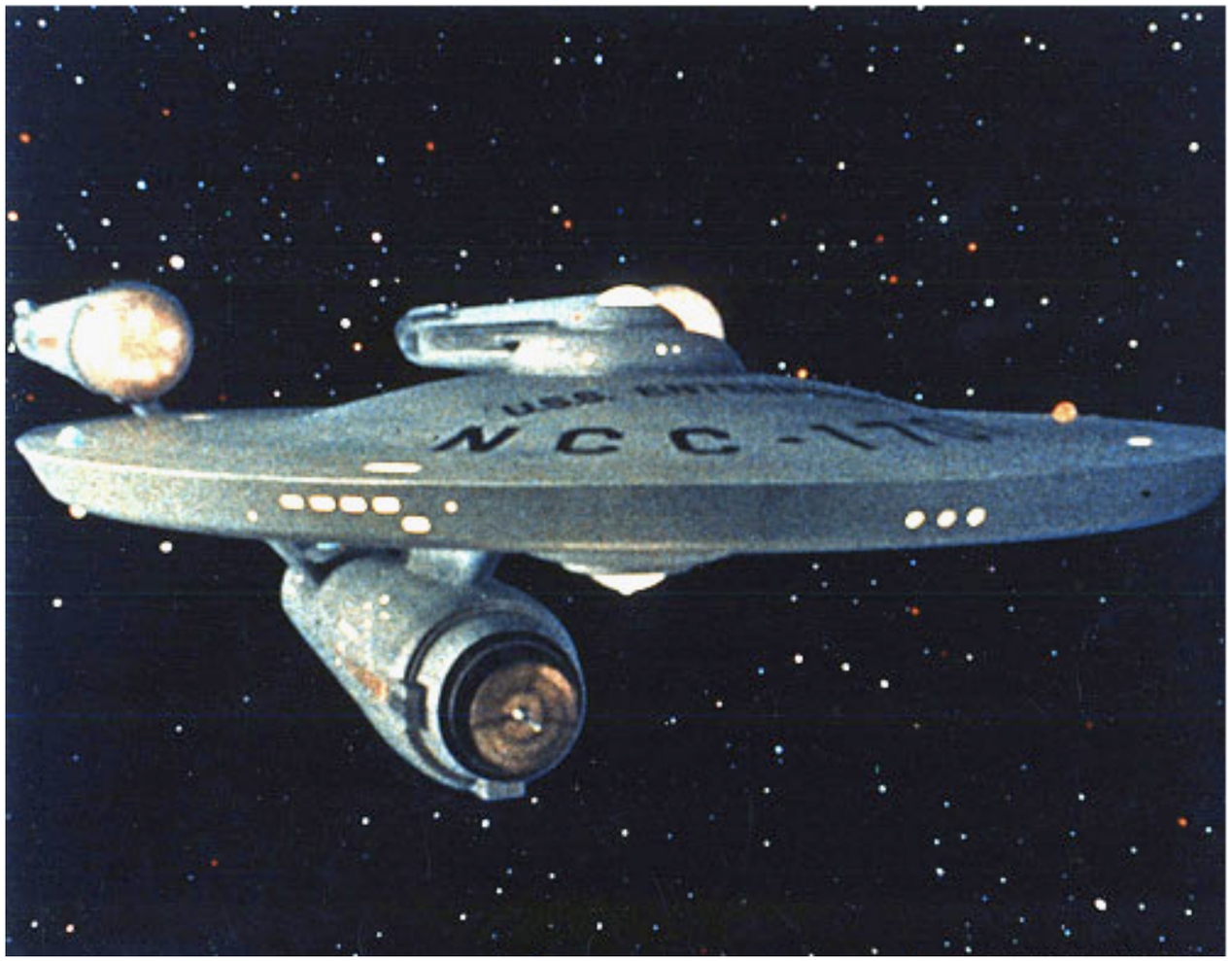
Do we have “adequate” microcirculatory flow?

This seems to be the new “frontier”



Shock and the microcirculation

<u>Shock</u> is defined in terms of a critically low **blood pressure**

- **Physiological definition**
  - inability of the circulation to sustain the cellular respiration needed to maintain normal organ function
- We use **<u>global</u> hemodynamic variables** to diagnose and treat:
  - <u>upstream</u> (blood pressure, U.O.)
  - <u>downstream</u> (SvO2, lactate)

Microvascular perfusion

New insights:

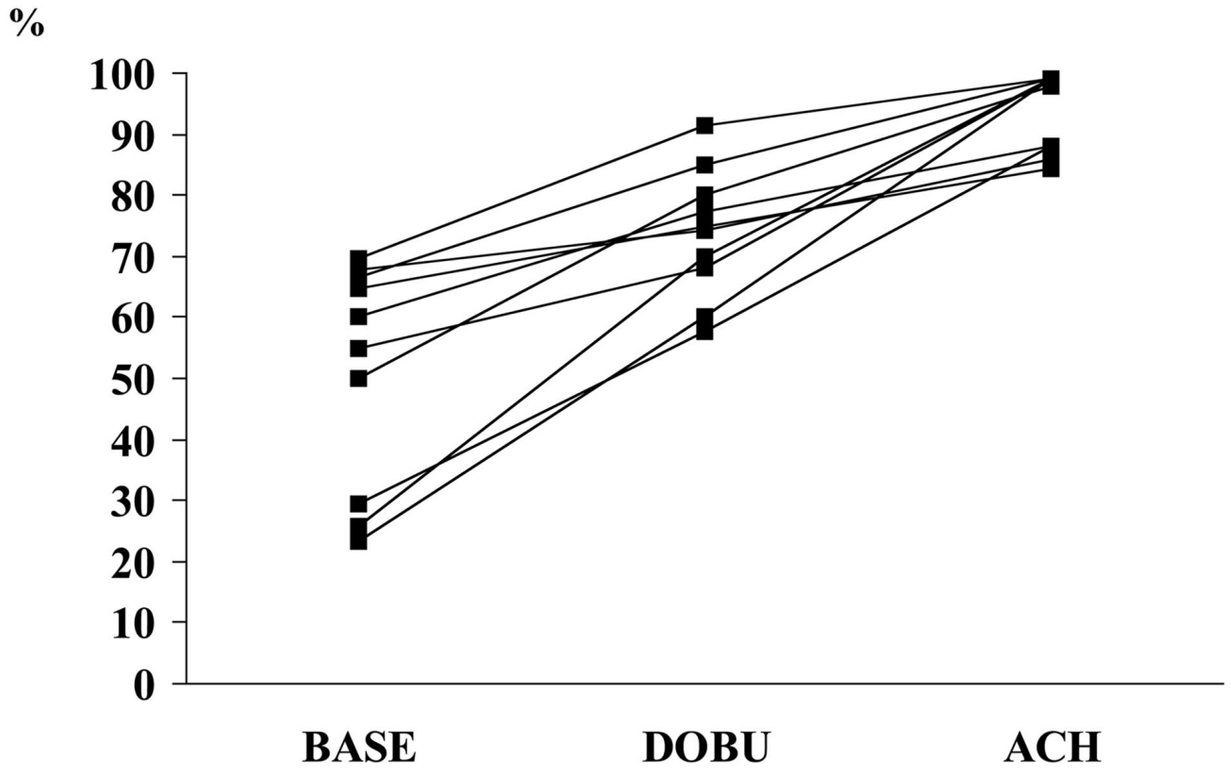
(1) the **independent** perfusion behavior of the **microcirculation** in relation **systemic hemodynamic** variables, (albeit within certain absolute limits of minimal perfusion pressure)

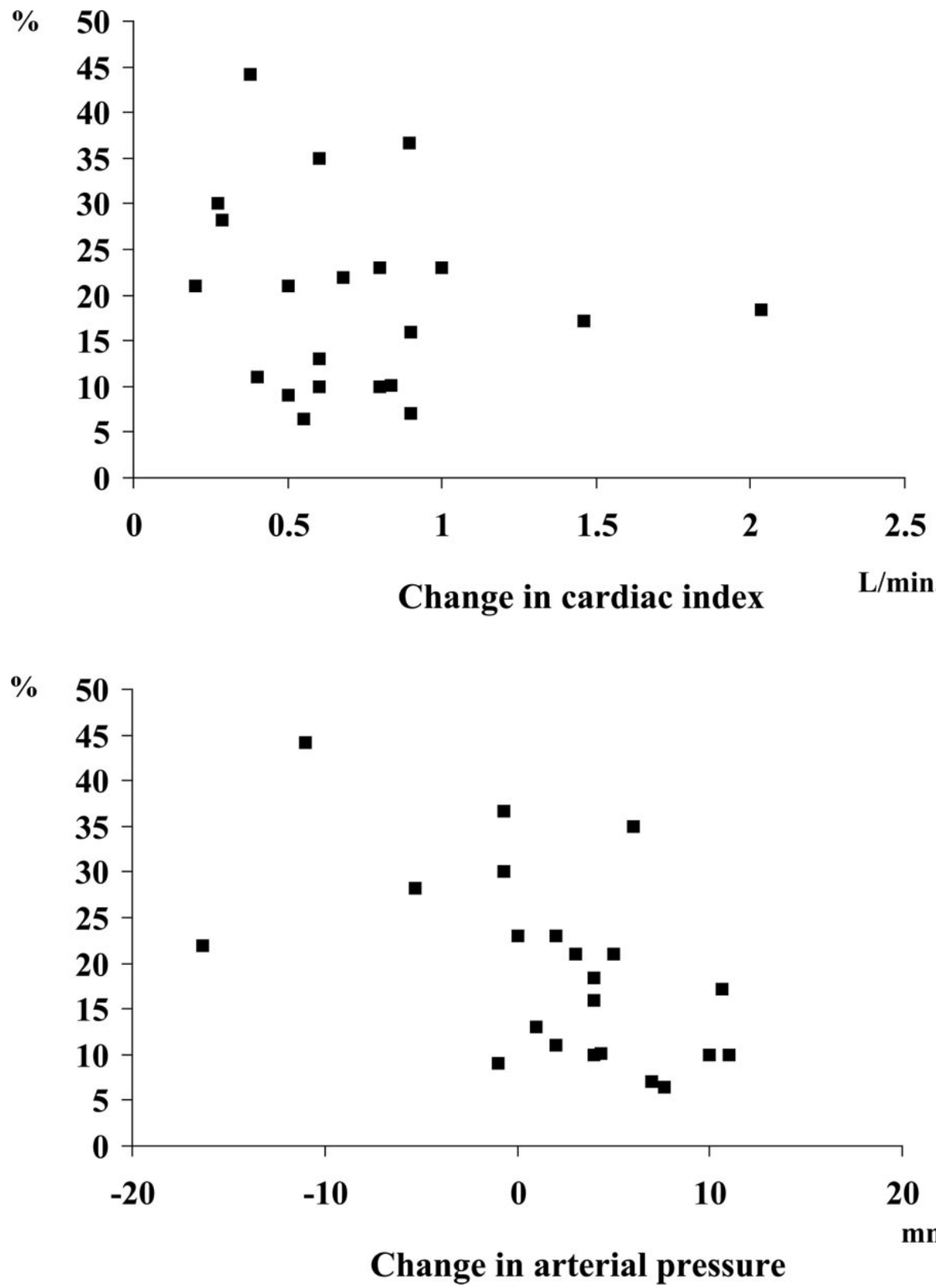
(2) **persistence** of **microcirculatory** alterations are associated with **mortality irrespective** of **correction** of **systemic** hemodynamics

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**"

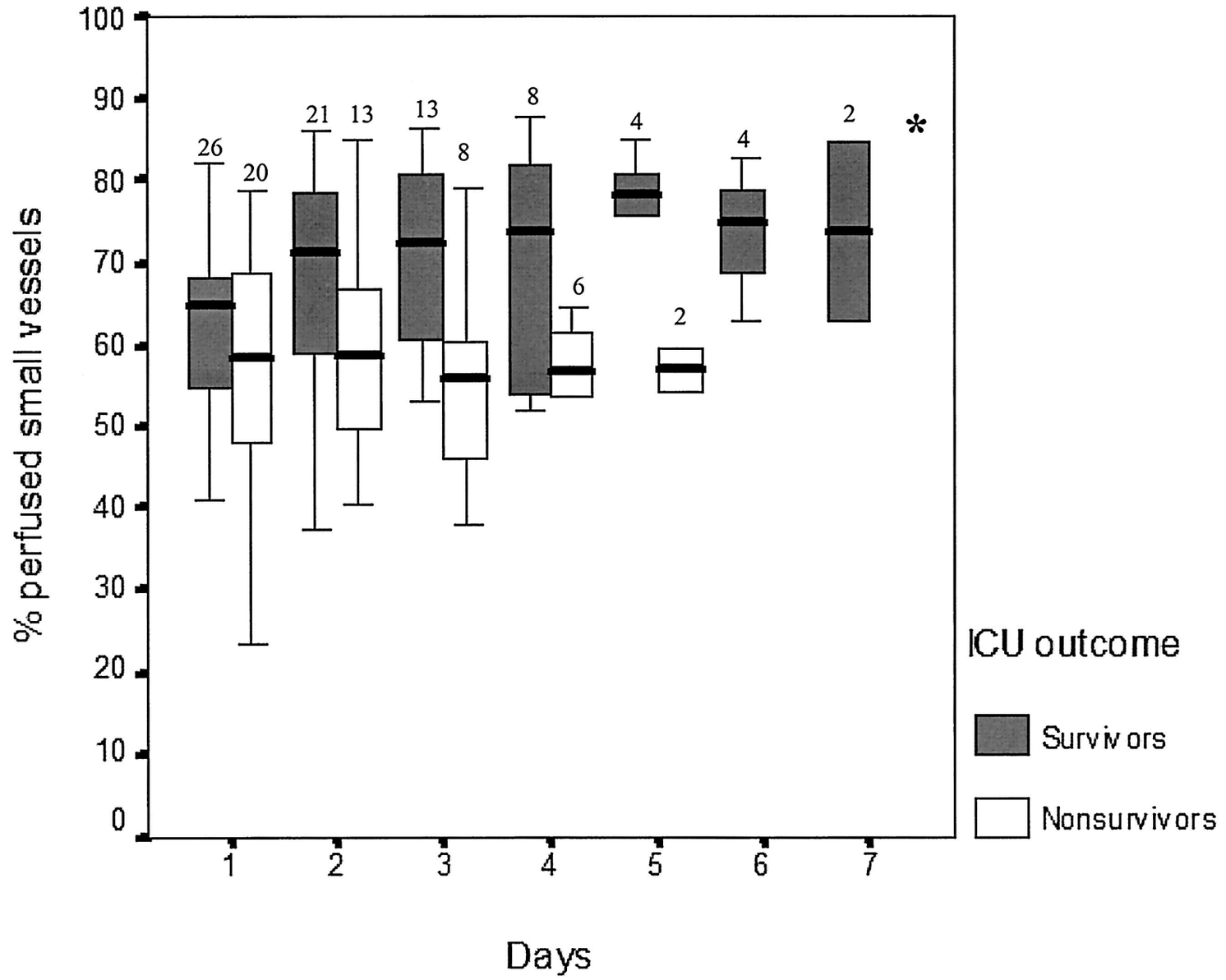
changes capillary perfusion %





Crit Care Med 2006 Vol. 34, No. 2

<u>Persistent</u> microcirculatory alterations are associated with organ failure and death in patients with septic shock

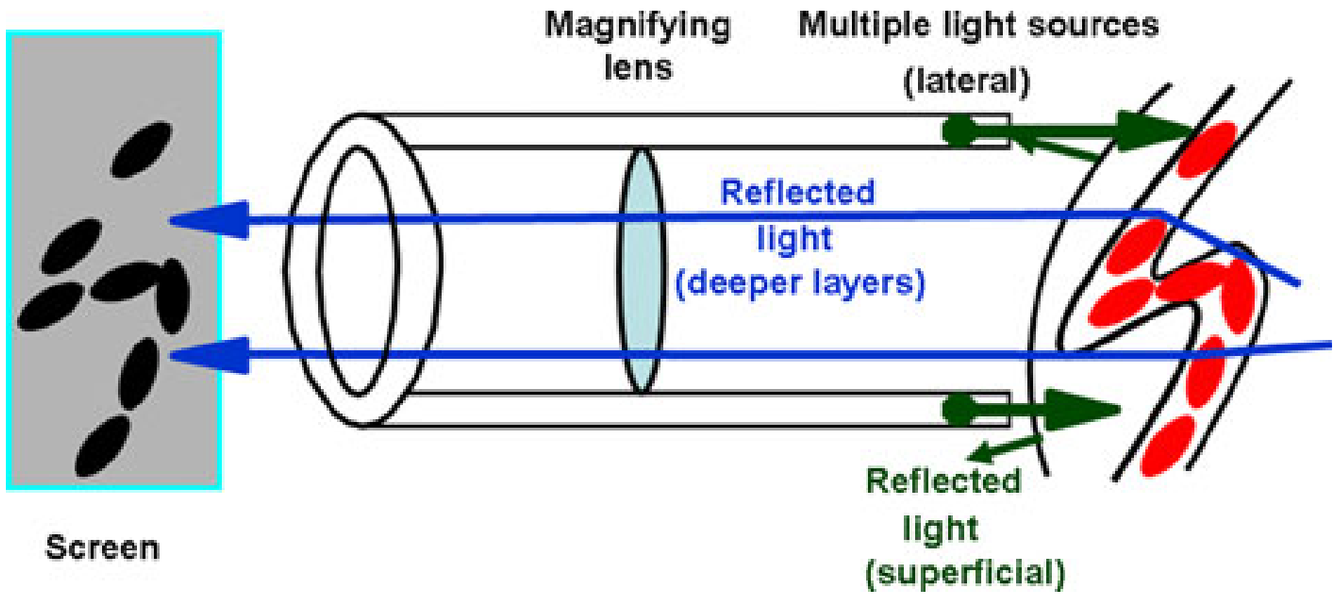


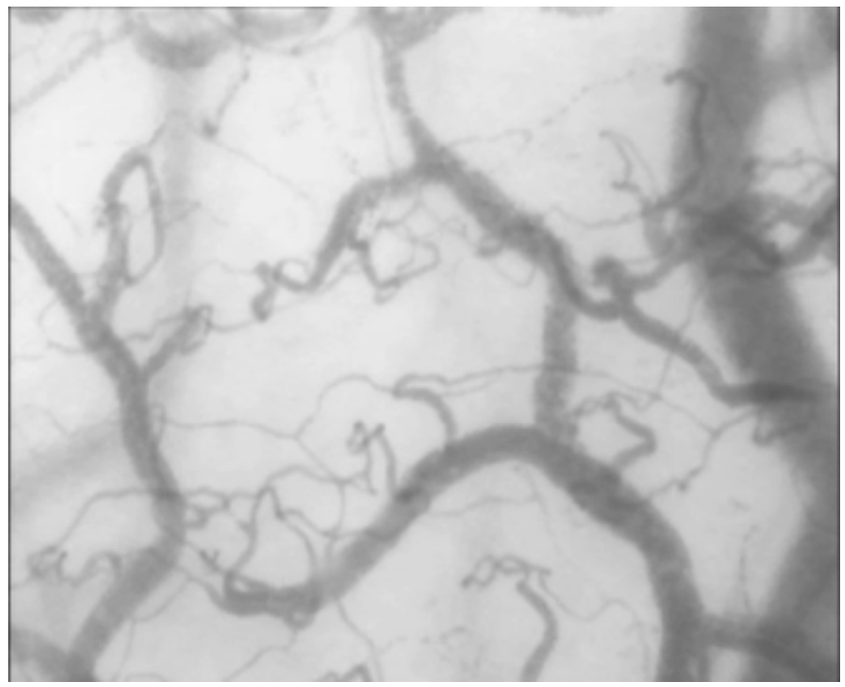
Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients **dying** after the resolution of shock in multiple organ failure had a **lower** percentage of **perfused** small vessels than survivors.

CCM 2004, 32:1825-1831

Do we have “adequate” microcirculatory flow?

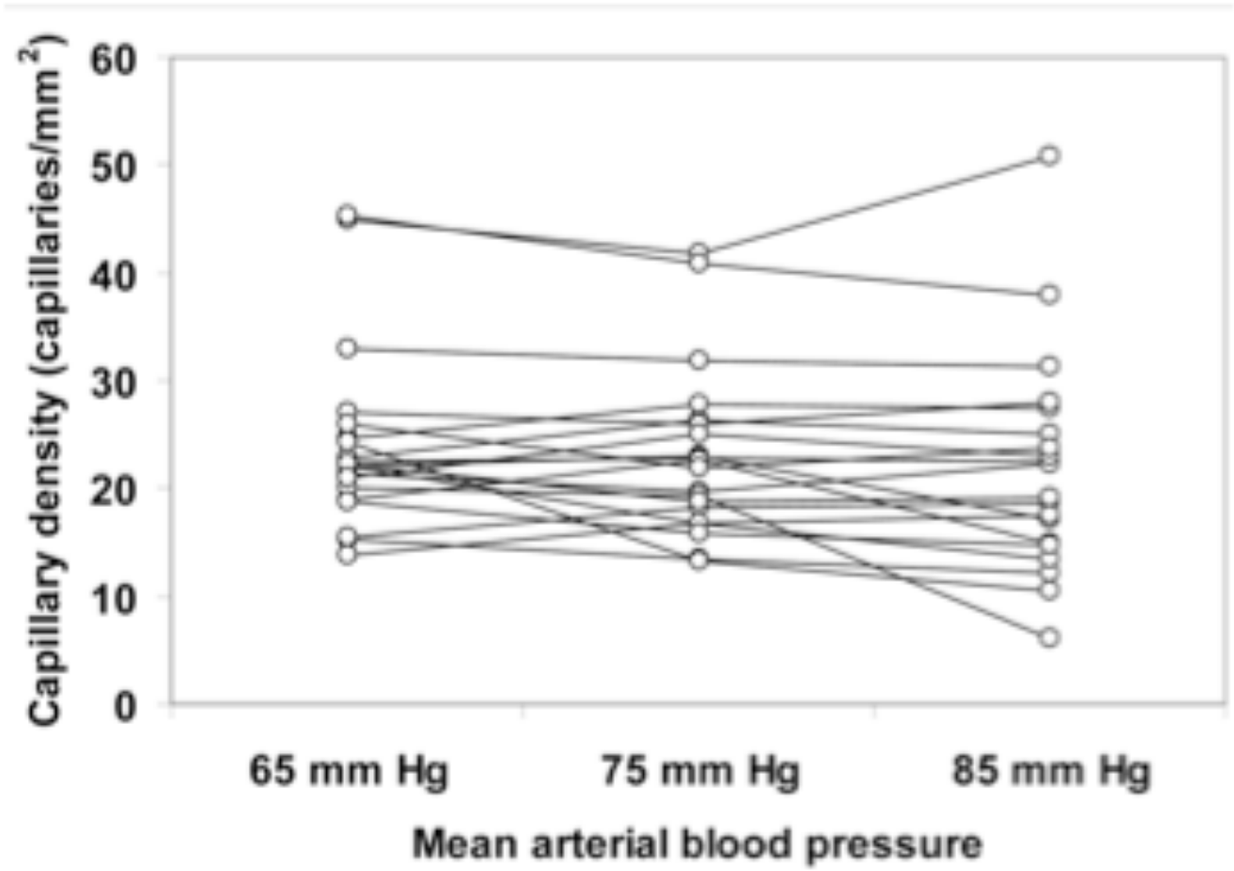
At last we have **new exciting tools** allowing us to “see” the microcirculation





Ex. Side stream Dark Field Spectroscopy

Increasing arterial blood pressure with norepinephrine does <u>not</u> improve microcirculatory blood flow

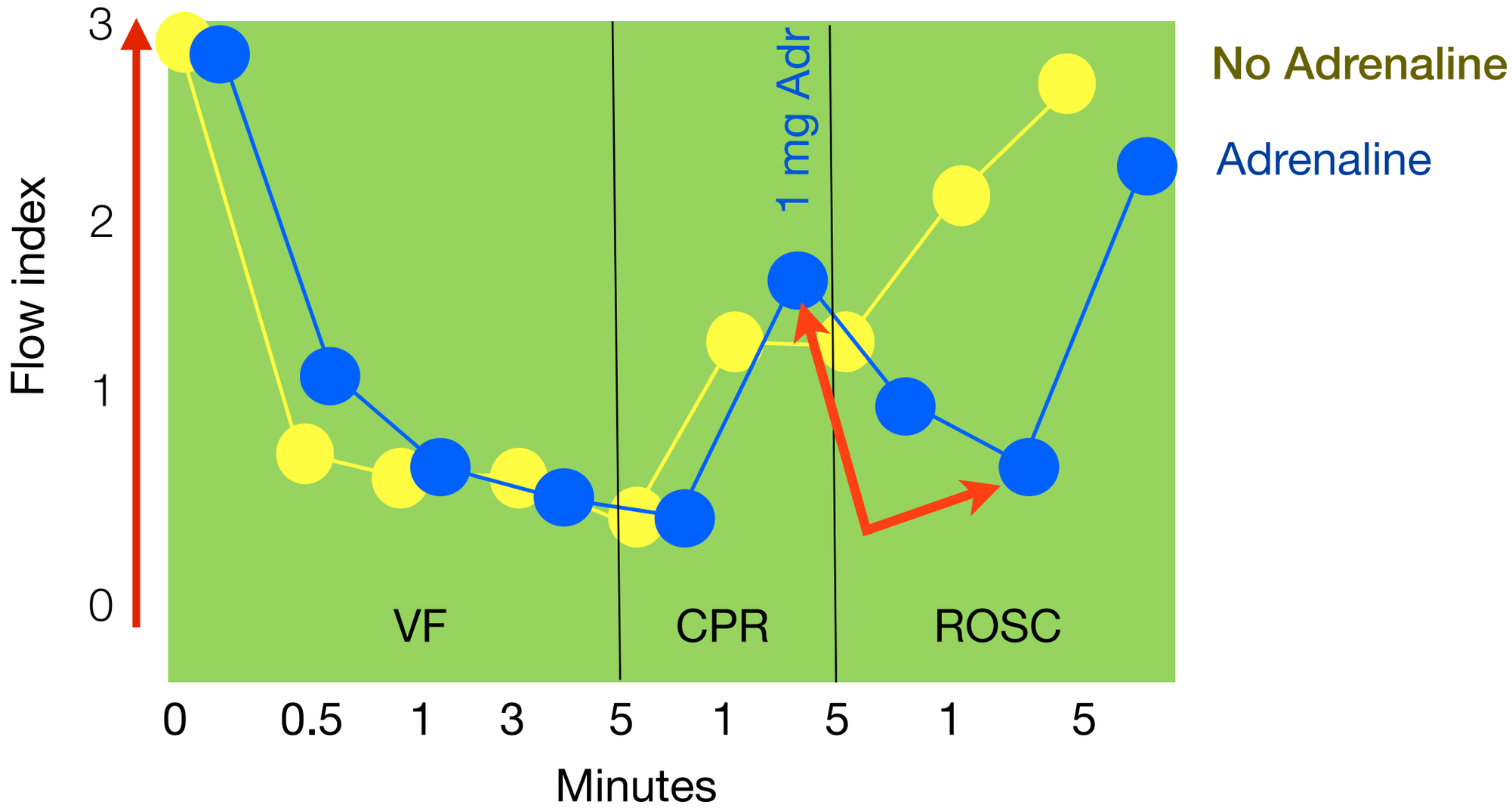


"the increase in MAP (**>75**) with norepinephrine **failed** to **improve** sublingual **microcirculation**, or any other variable related to perfusion"

A minimum, yes, but more is not necessarily better

Critical Care 2009, 13:R92

Effect of adrenaline on microcirculatory blood flow during cardiac arrest in animals



“epinephrine resulted in a massive reduction of microcirculatory blood flow”

Crit Care Med 2006; 34[Suppl.]:S454–S457

Microvascular dysfunction

- 50 ICU patients resuscitated to adequate global haemodynamic endpoints
- After successful resuscitation, peripheral perfusion assessed:
  - Capillary refill, Core-peripheral temperature, Peripheral Flow Index
- Compared lactate levels, on-going organ failure

Crit Care Med 2009 Vol. 37, No. 3

Microvascular dysfunction

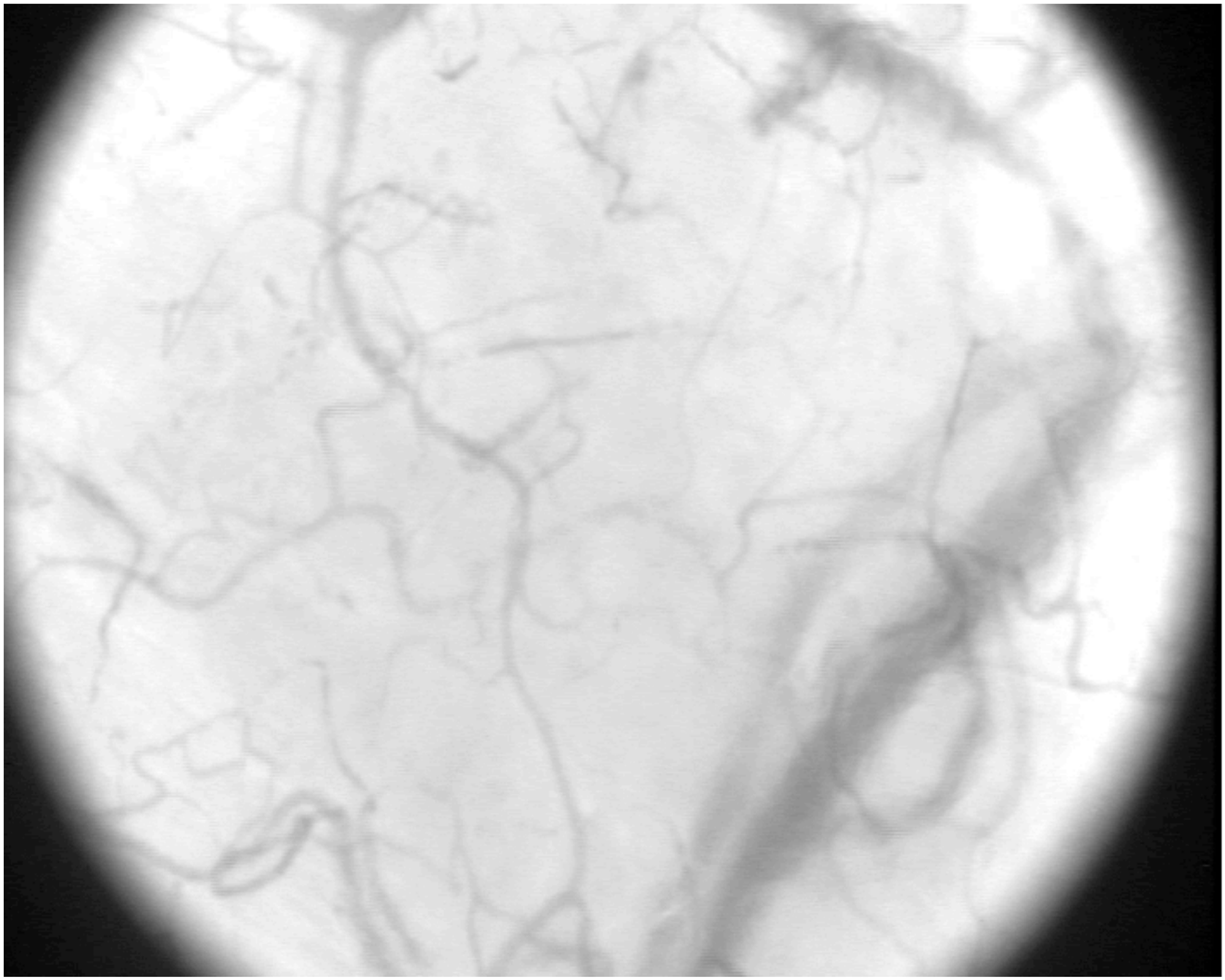
Peripheral perfusion <u>after</u> resuscitation

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

Adequate global values with poor peripheral perfusion probably a sign of compensatory mechanisms still present.

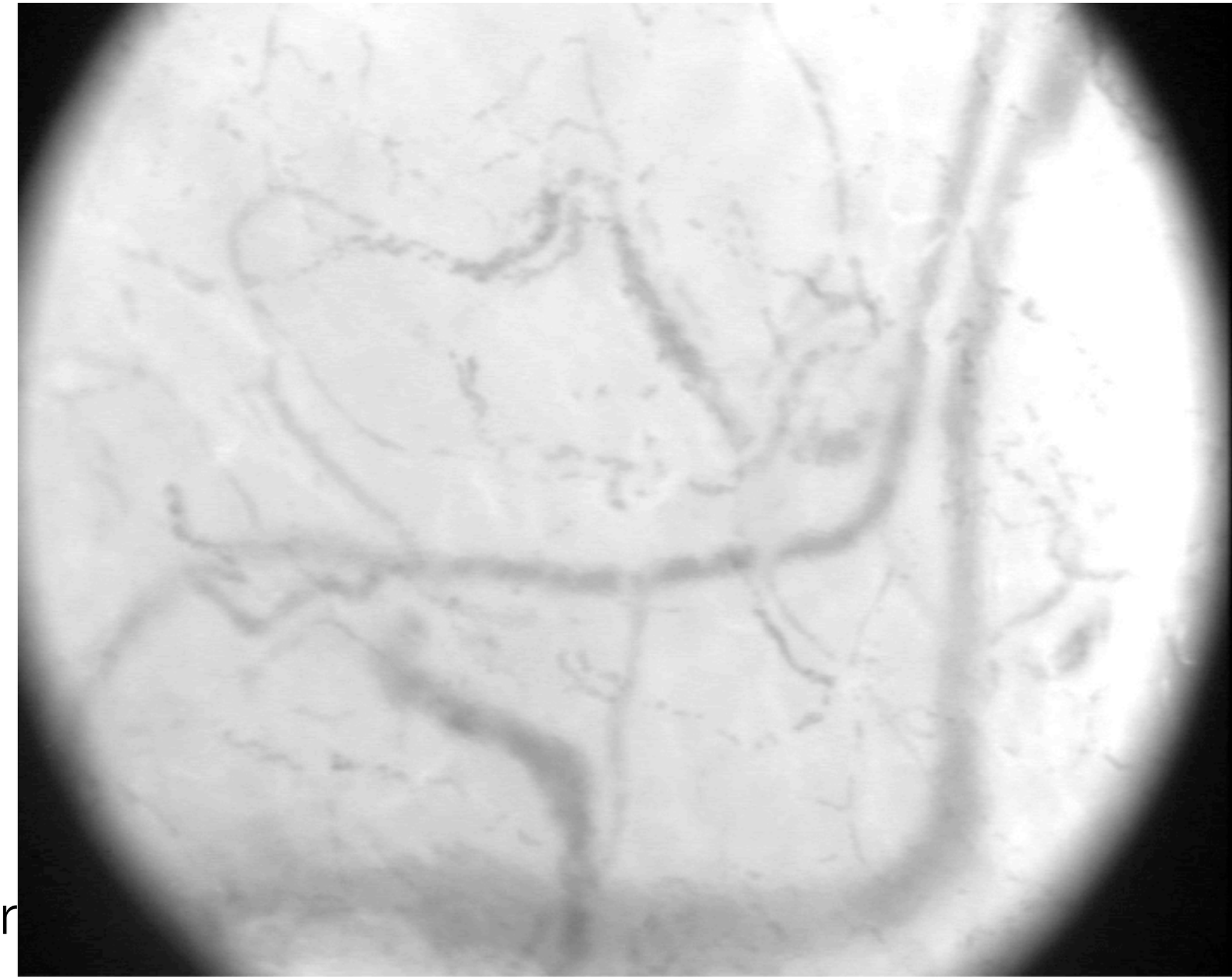
Crit Care Med 2009 Vol. 37, No. 3

Before Terlipressin



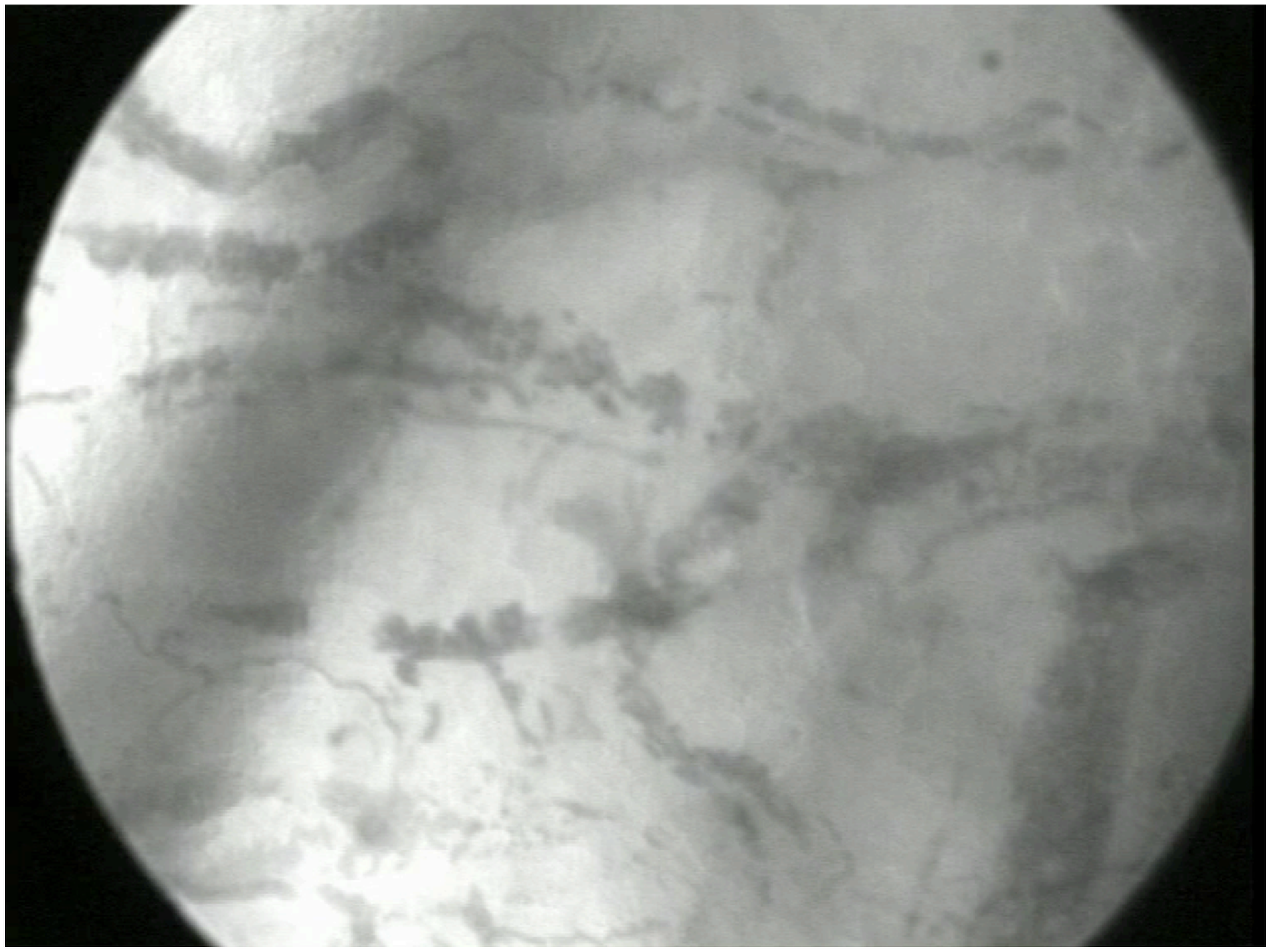
MAP 58
HR 98
CVP 13
UO 20 ml/hr

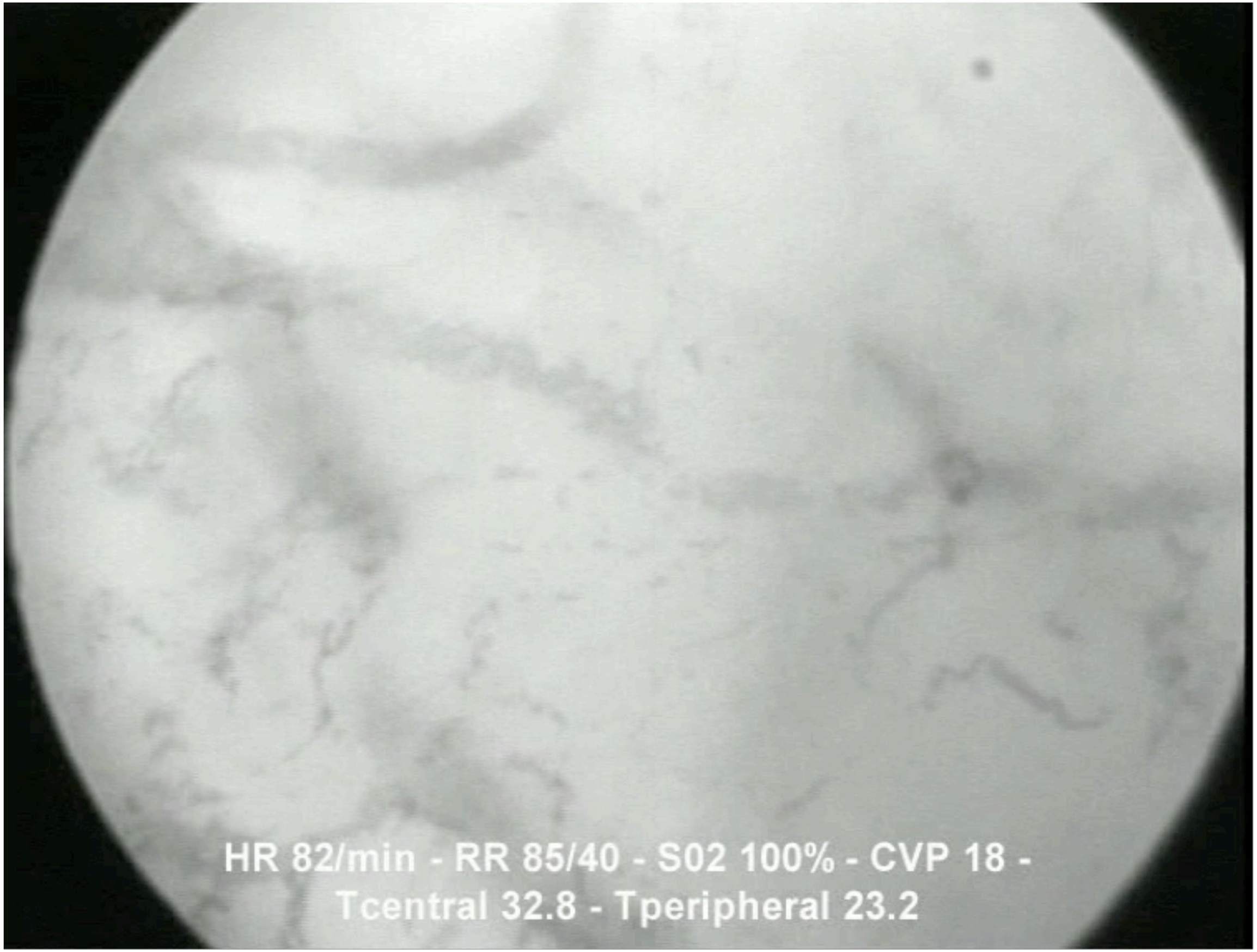
After Terlipressin



MAP 80
HR 98
CVP 12
UO 110 ml/hr

Microcirculation in cardiogenic shock




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

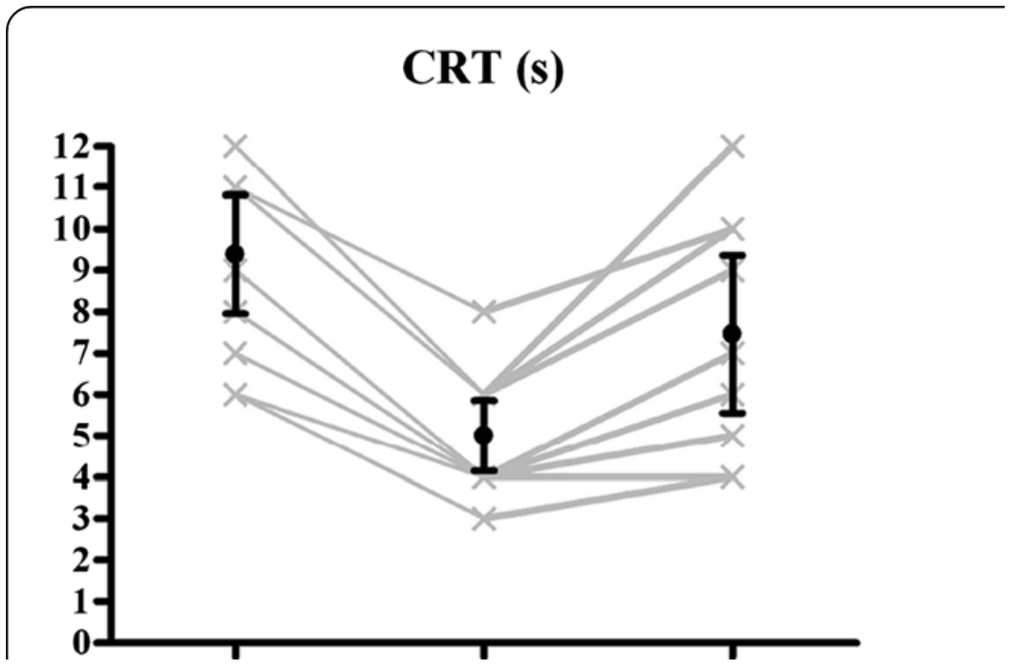
Lima *et al. Critical Care* 2014, **18**:R126
http://ccforum.com/content/18/3/R126

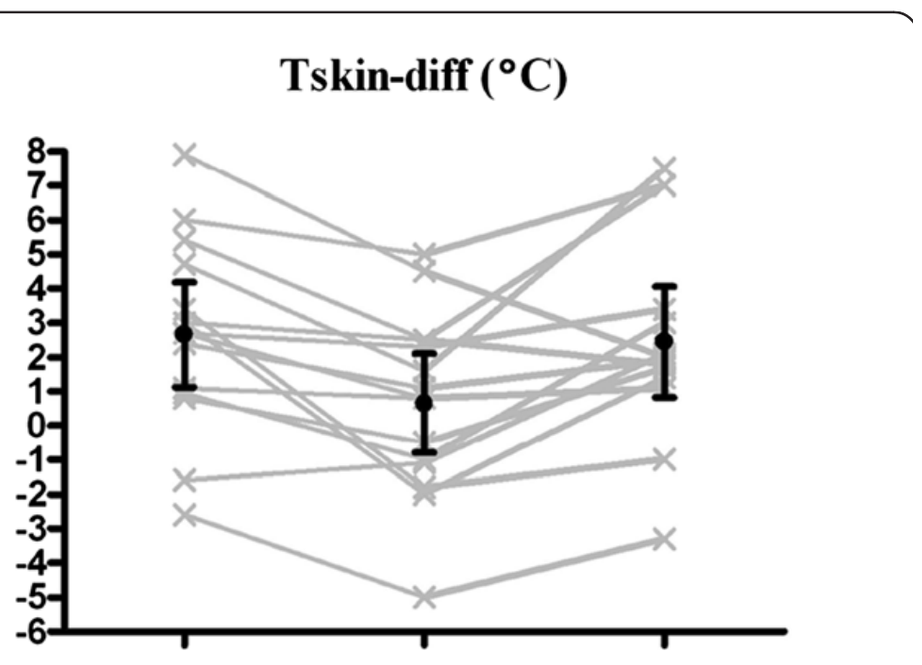
CRITICAL CARE

RESEARCH Open Access

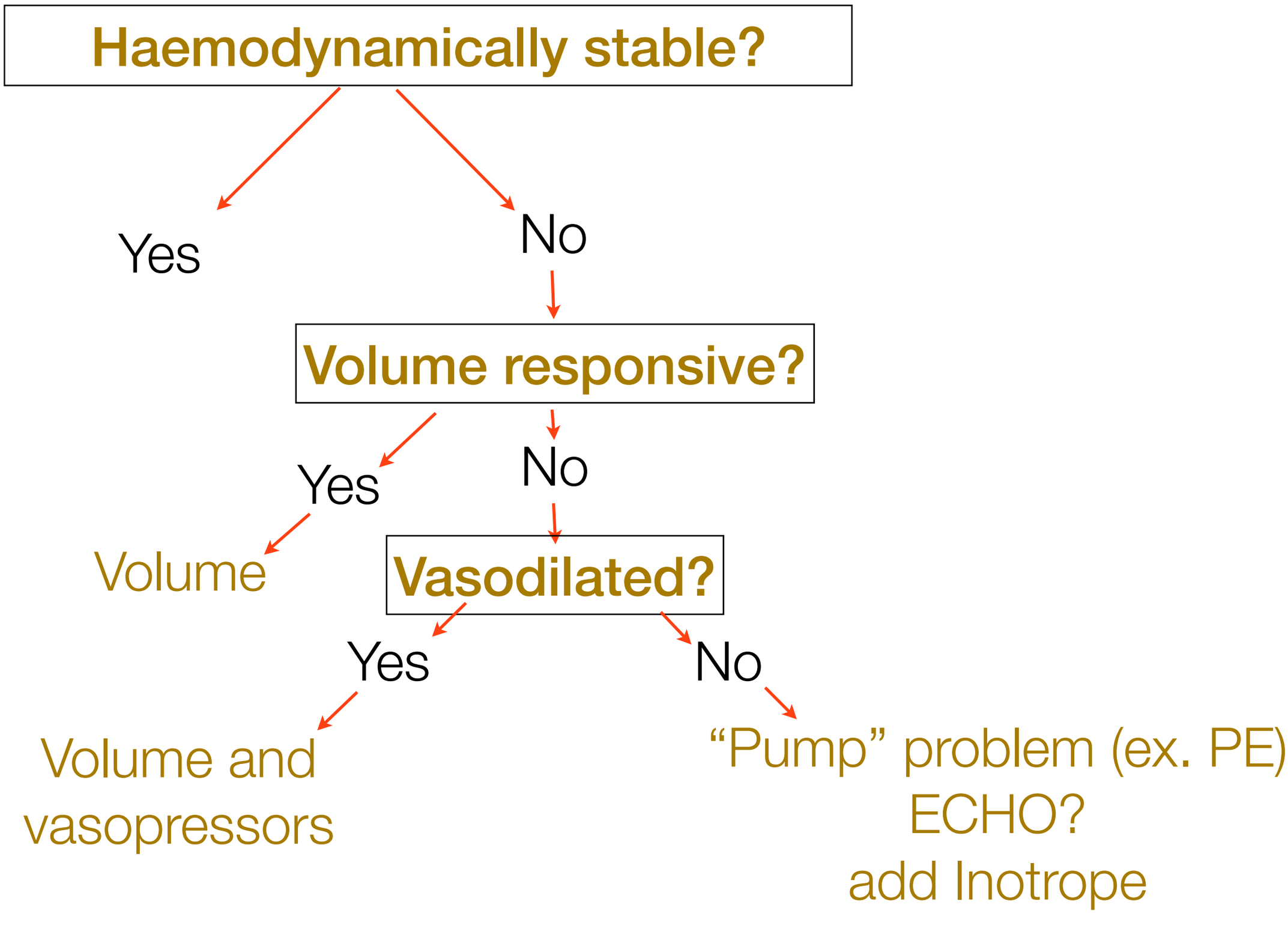
Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock

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





Recap - one approach



RECAP

- Aim is an adequate **<u>effective</u> cardiac output**
- **Time** is of the essence
- Get the **sequence** right

  Fluid - get **fluid responsiveness** right

  Pressors - get **BP** up

  Dobutamine/RBCs - get **effective CO** right

  Microcirculation - stay tuned!

Goals of todays talk

- Put vasoactive drugs role into overall treatment context
- Discuss individual drugs
- Proof of what is best
- Consider the microcirculation

???

Download :

http://www.jvsmedicscorner.com

(Mallory / Everest2013)