Le choc septique: Quels objectifs circulatoires ?

Daniel De Backer
Department of Intensive Care
Erasme University Hospital
Brussels, Belgium

HEMODYNAMIC ALTERATIONS IN SEPTIC SHOCK

Varpula et al
ICM 31:1066;2005

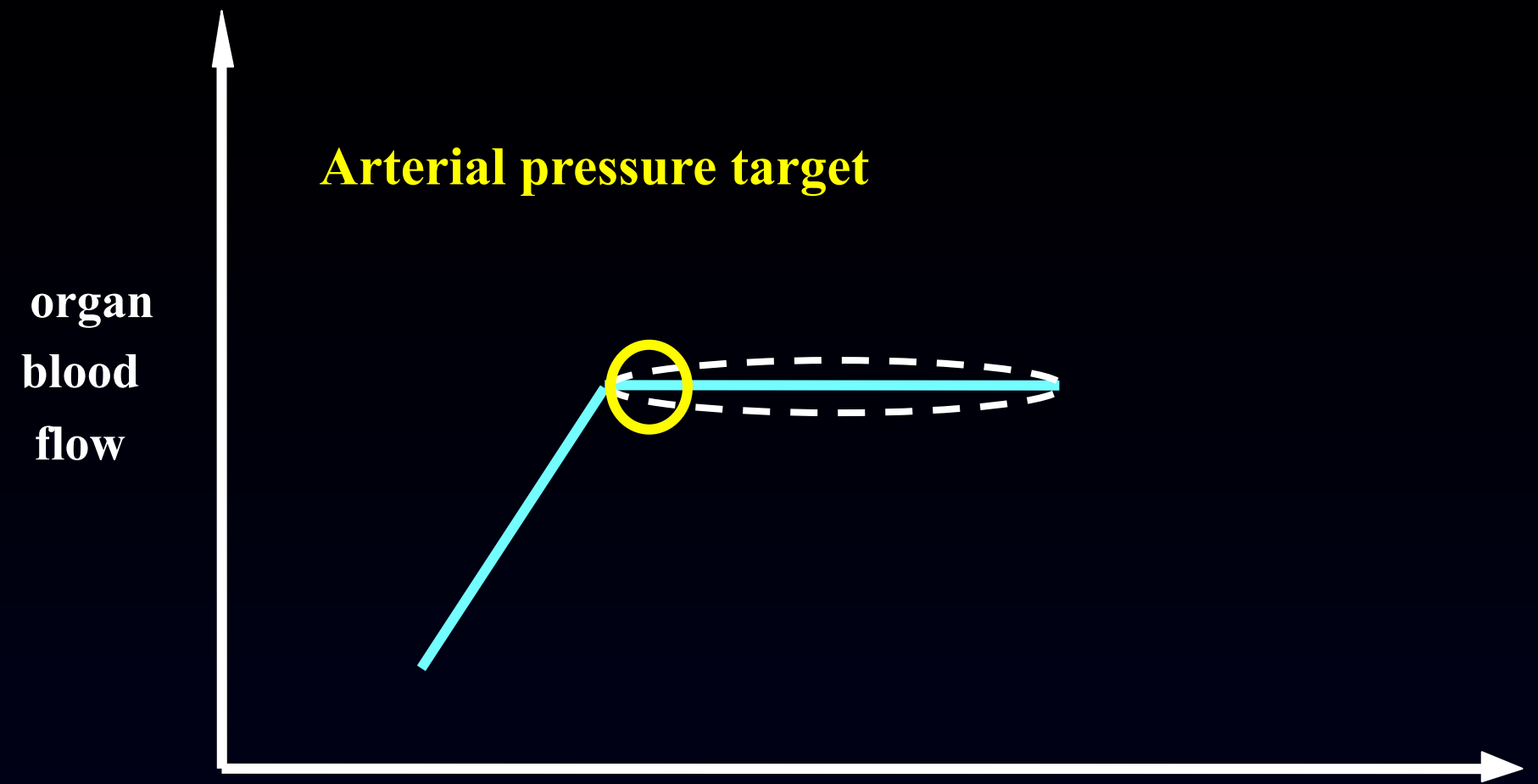
Factors independently associated with poor outcome

	Logistic regression		ROC analysis	
	p	Exp (B)	AUC	95% CI
MAP, mean	0.013	1.156	0.841	0.761–0.921
SvO_2 area under 70%	0.024	0.993	0.737	0.601–0.873
CVP, mean	0.044	0.738	0.712	0.599–0.825

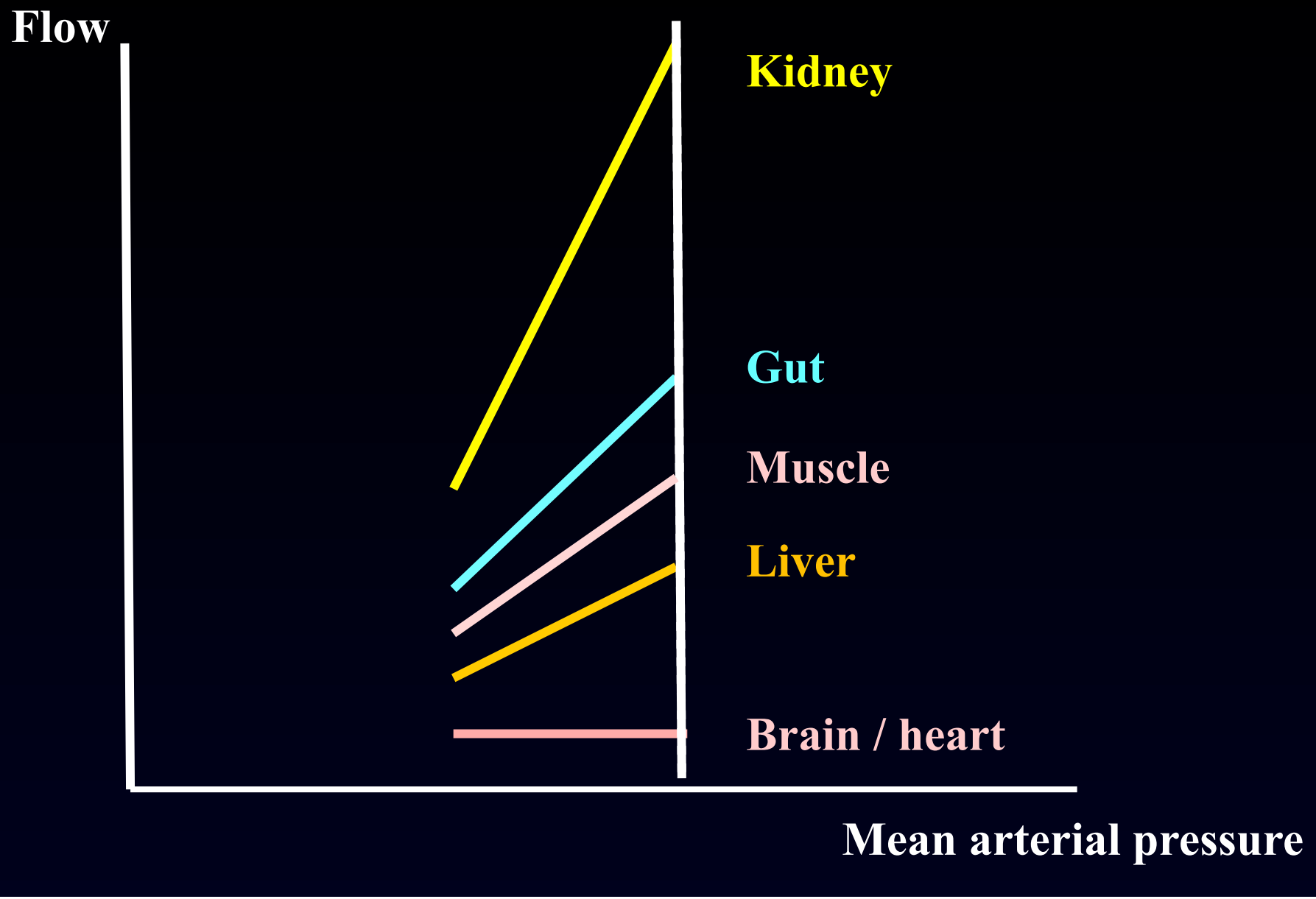
Continuous hemodynamic measurements during the first 48h of shock
(111 consecutive patients)

Arterial pressure: which goal?

Autoregulation of organ blood flow



Different vascular beds have different vascular resistances and different autroregulation thresholds

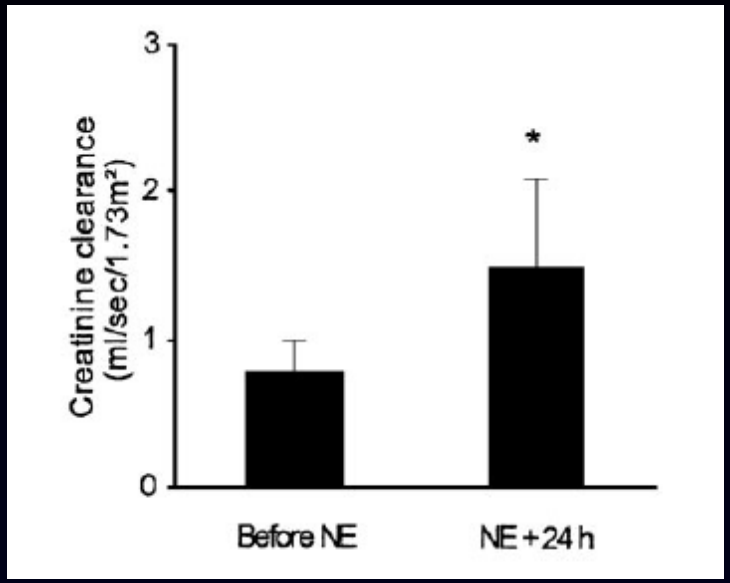


Correction of hypotension improves urine output and renal function in septic patients

Albanese et al
Chest 126:534;2004

Variables	UF		
	Before, mL/h	NE + 2 h, mL/h	NE + 24 h, mL/d
Septic shock (n = 14)	14 ± 13	121 ± 87†	2,450 ± 1,237†

MAP 50 => 78 mmHg



Patients with septic shock (n=14)

DDB USI

PRESSURE GOAL ?

LeDoux et al
CCM 28:2729;2000

Table 4. Indices of regional perfusion as MAP is increased from 65 mm Hg to 85 mm Hg

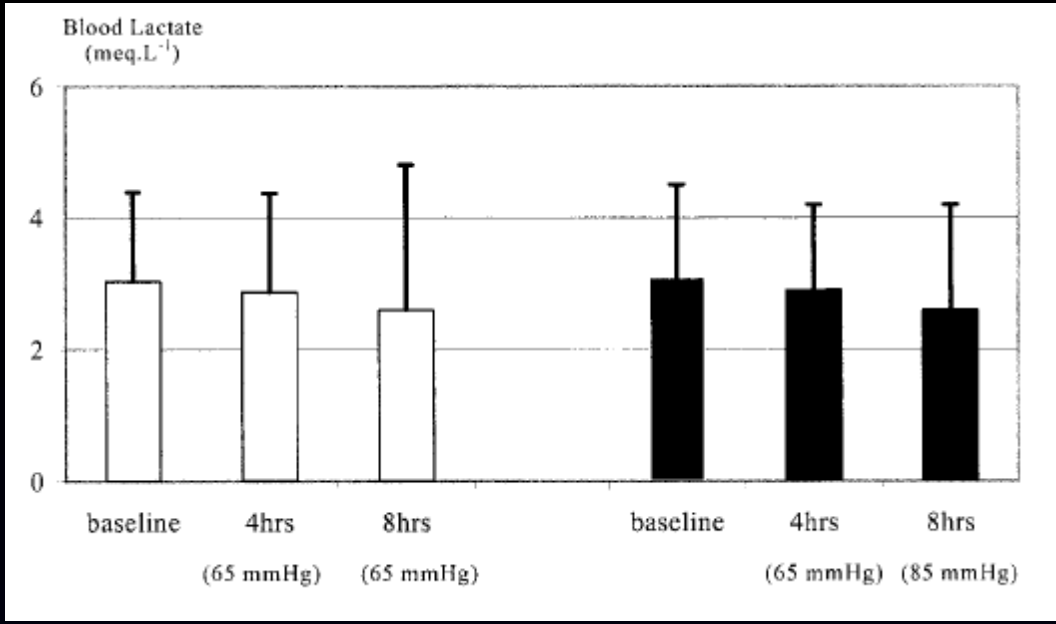
	MAP			
	65 mm Hg	75 mm Hg	85 mm Hg	F/LT
Urinary output (mL)	49 ± 18	56 ± 21	43 ± 13	.60/.71
Capillary blood flow (mL/min/100 g)	6.0 ± 1.6	5.8 ± 1.2	5.3 ± 0.9	.59/.55
Red cell velocity (au)	0.42 ± 0.06	0.44 ± 0.06	0.42 ± 0.06	.74/.97
$Pico_2$ (mm Hg)	41 ± 2	47 ± 2	46 ± 2	.11/.12
Pa-$Pico_2$ (mm Hg)	13 ± 3	17 ± 3	16 ± 3	.27/.40

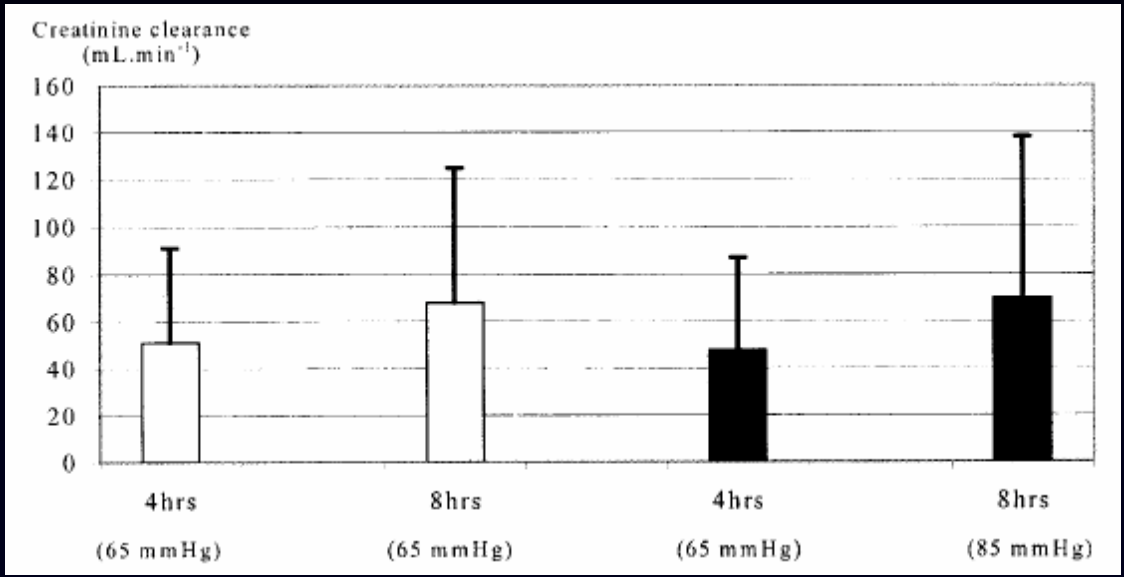
F, *p* value for repeated-measures analysis of variance (ANOVA) as MAP is increased from 65 mm Hg to 85 mm Hg; LT, *p* value for extension of ANOVA for linear trend; au, arbitrary units; $Pico_2$, gastric intramucosal Pco_2; Pa-$Pico_2$, arterial-gastric intramucosal CO_2 gradient.

Data are presented as mean ± SE.

PRESSURE GOAL ?

Bourgouin et al
CCM 33:790;2005

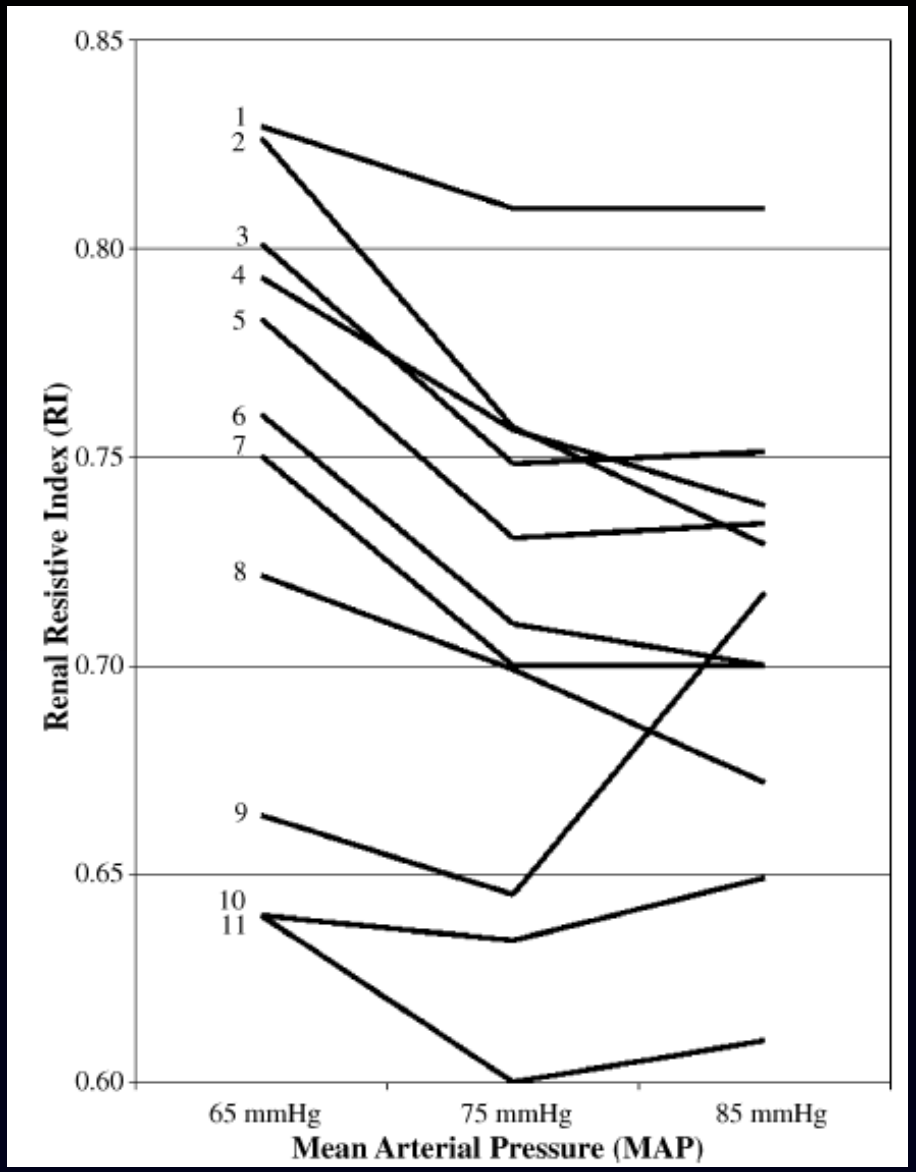




28 pts with septic shock

High variablity in response to increase in MAP

Renal perfusion



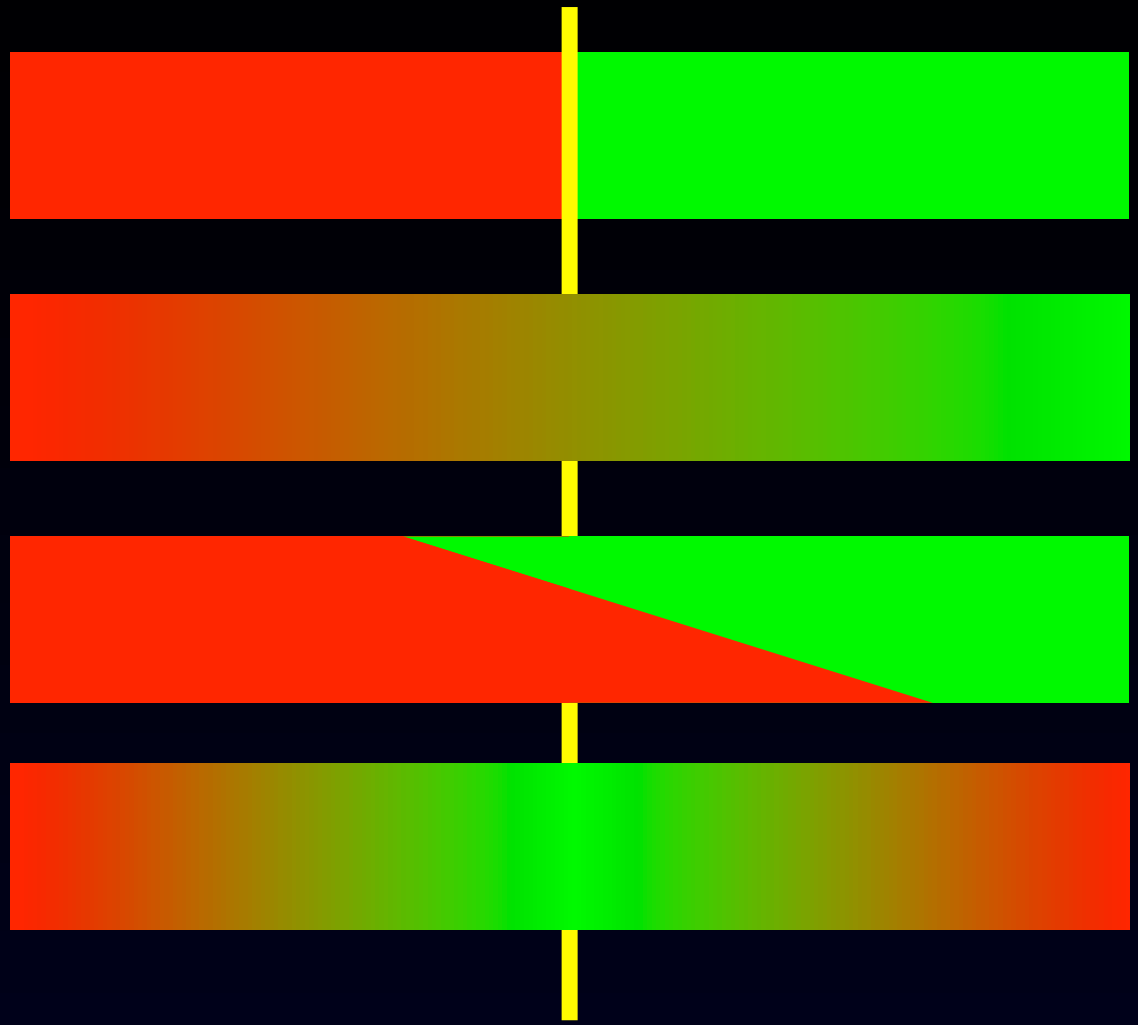
Deruddre et al
ICM 33:1557;2007

11 pts septic shock

Renal Doppler

Central venous pressure

The problem with CVP targets

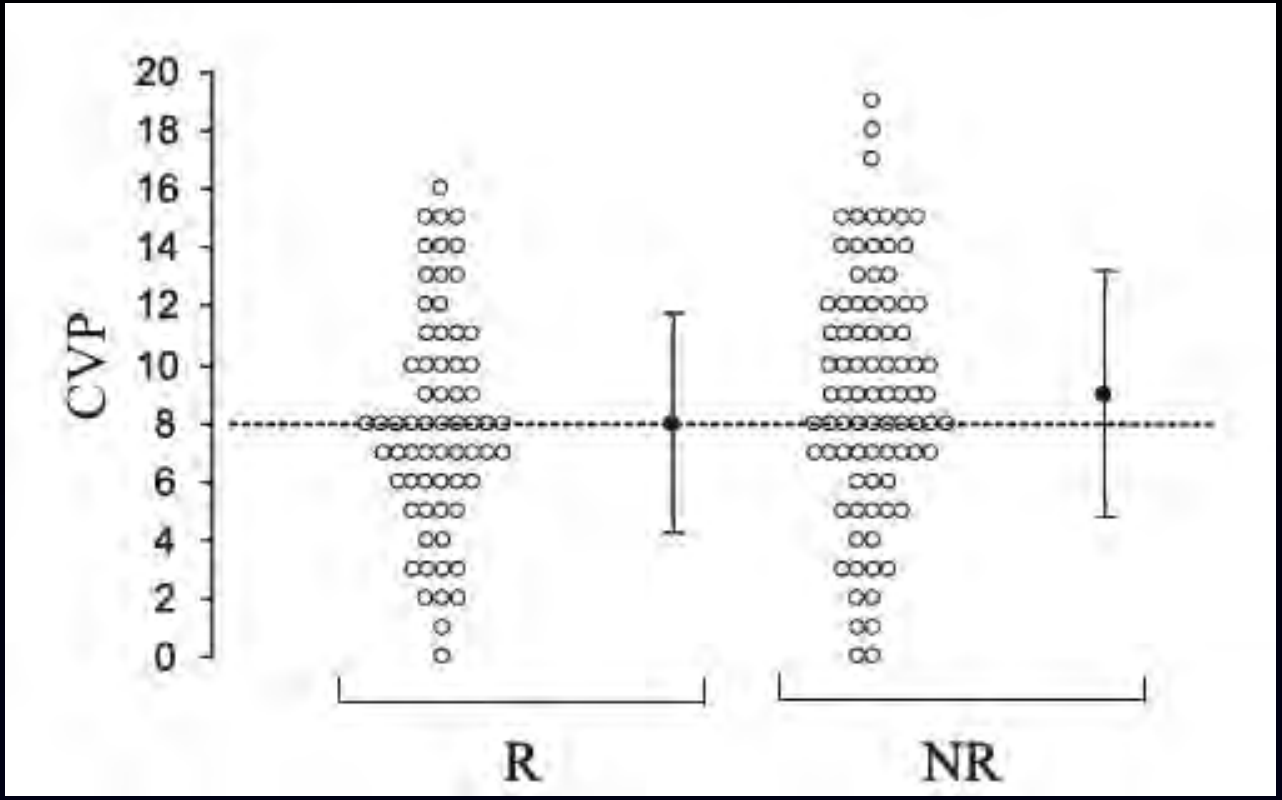


CVP 8 mmHg

DDB USI

Should we guide fluid administration on CVP ?????

Osman et al
ICM 35:64;2007

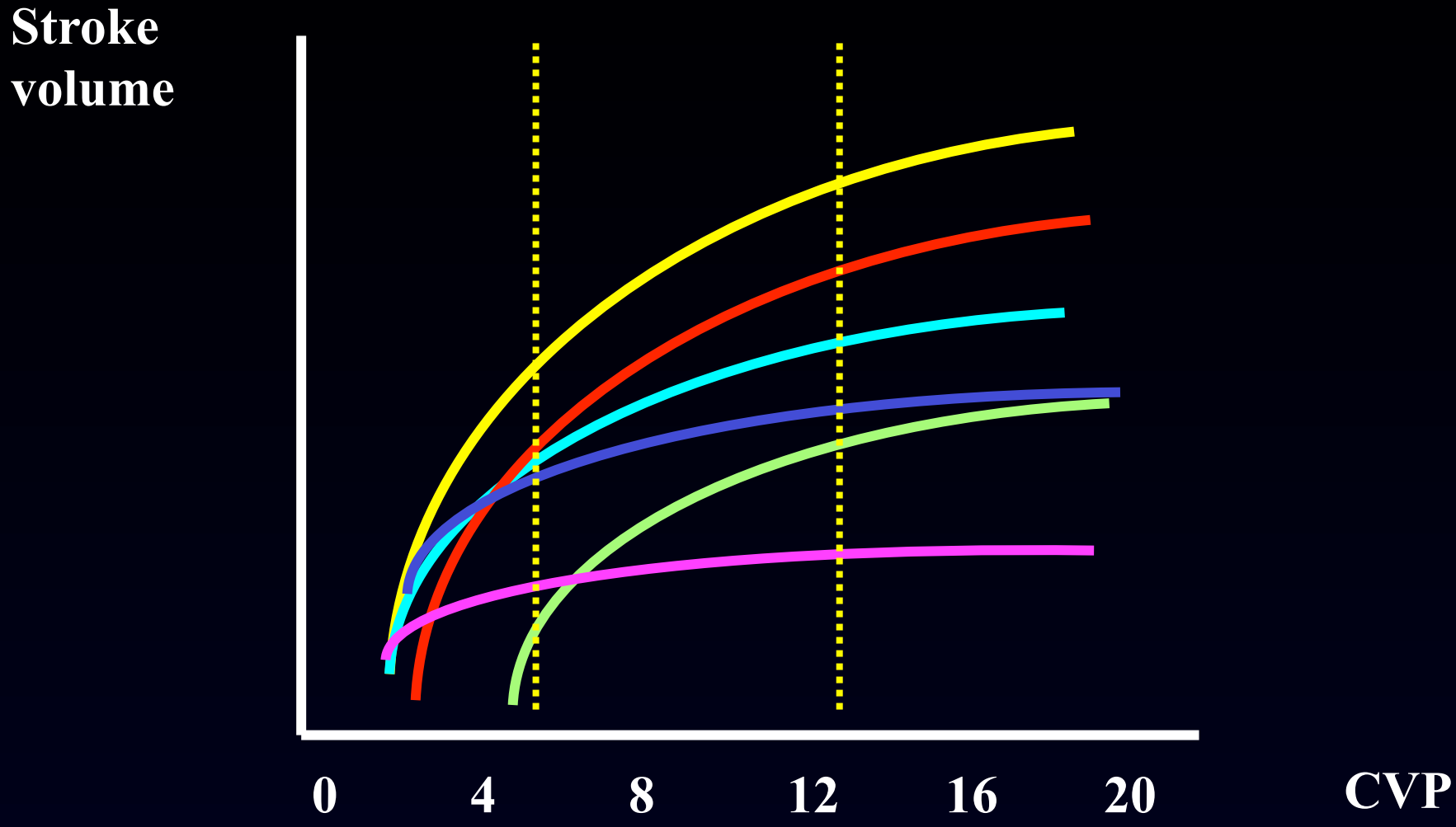


8 mmHg

96 pts with severe sepsis
150 fluid challenges

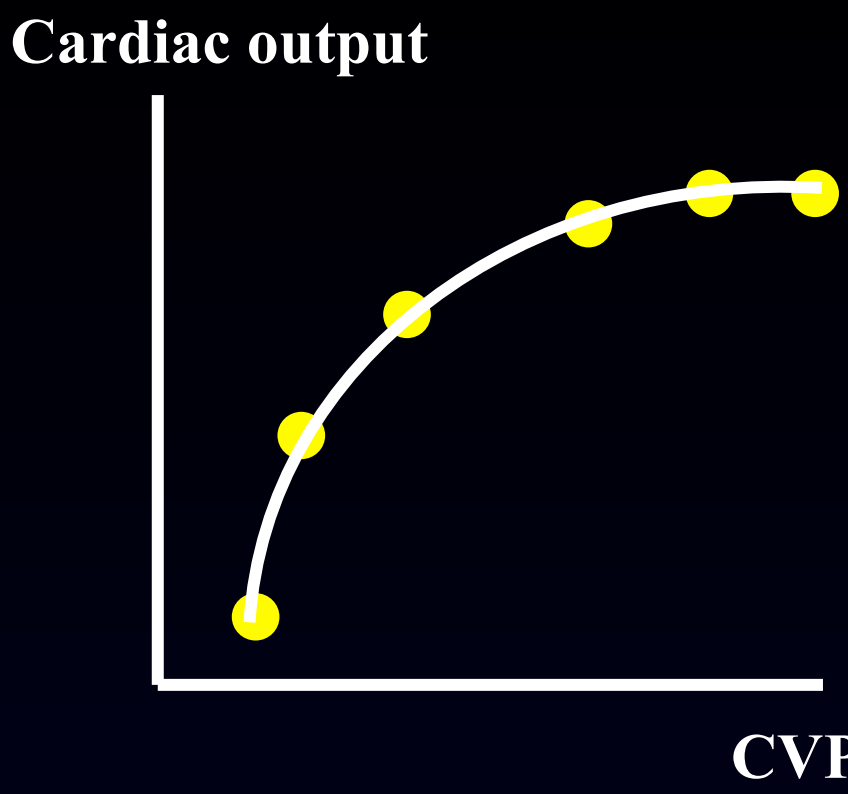
DDB USI

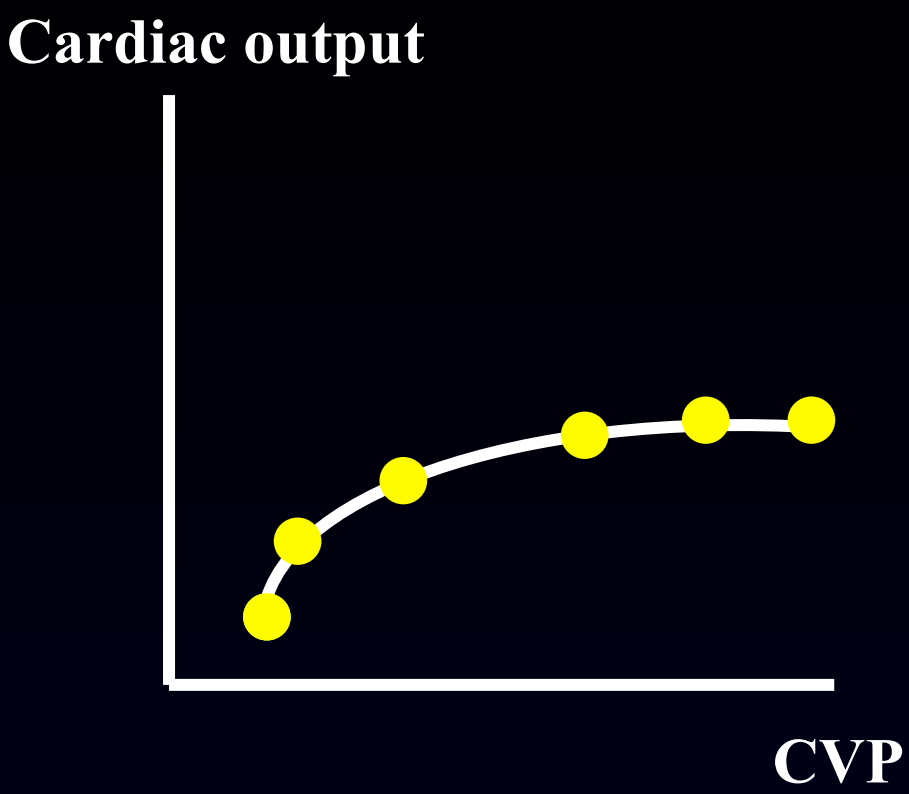
STARLING RELATIONSHIP



DDB USI

The increase in CVP does not imply that cardiac output increased, it only reflects that preload effectively increased





The increase in CVP is the price to pay, not a goal in itself !

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

CCM 2013 **ICM 2013**

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood culture
3) Administer broad sp
4) Administer 30 mL/kg

When you have nothing better, is it wrong to target CVP values ?

TO BE COMPLETED WITHIN 6 HOURS:

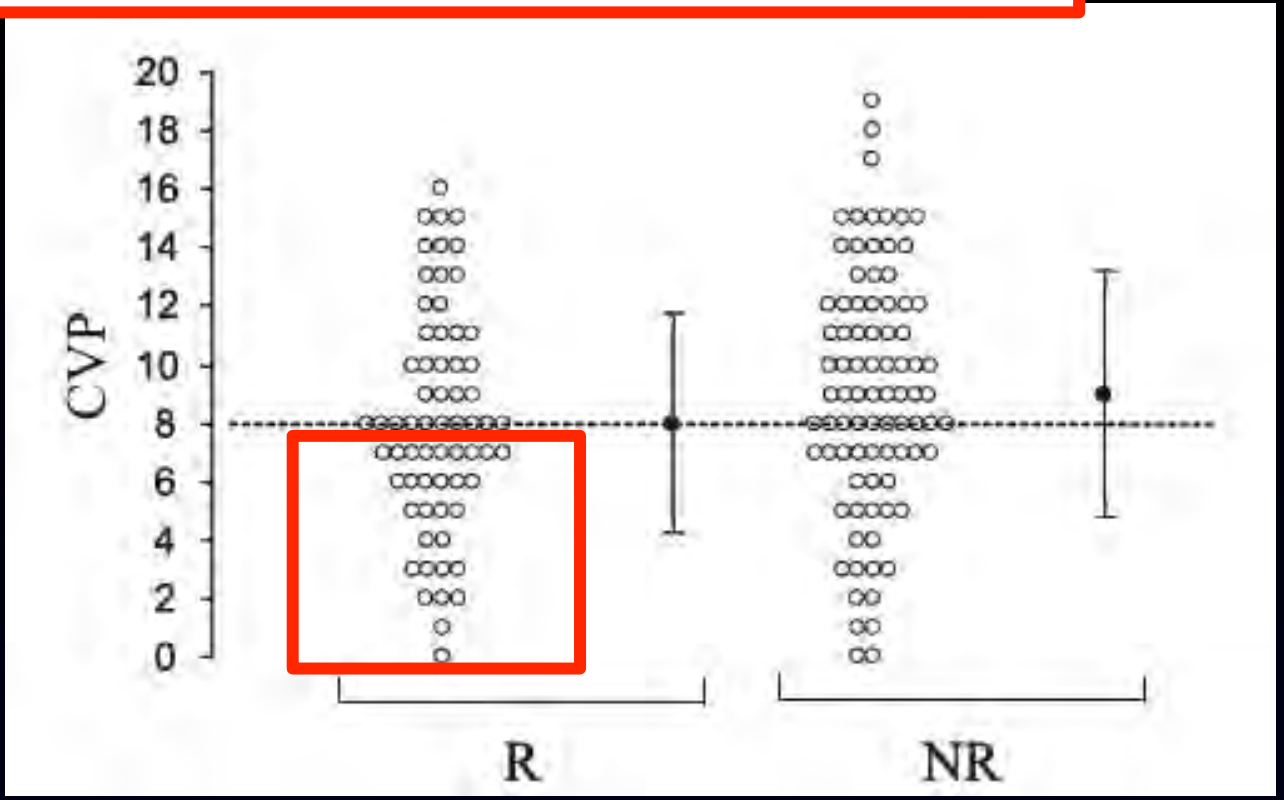
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Should we guide fluid administration on CVP ?????

Most of the patients benefit from fluids when fluid challenge is initiated with a CVP <8mmHg

Osman et al
ICM 35:64;2007



8 mmHg

96 pts with severe sepsis
150 fluid challenges

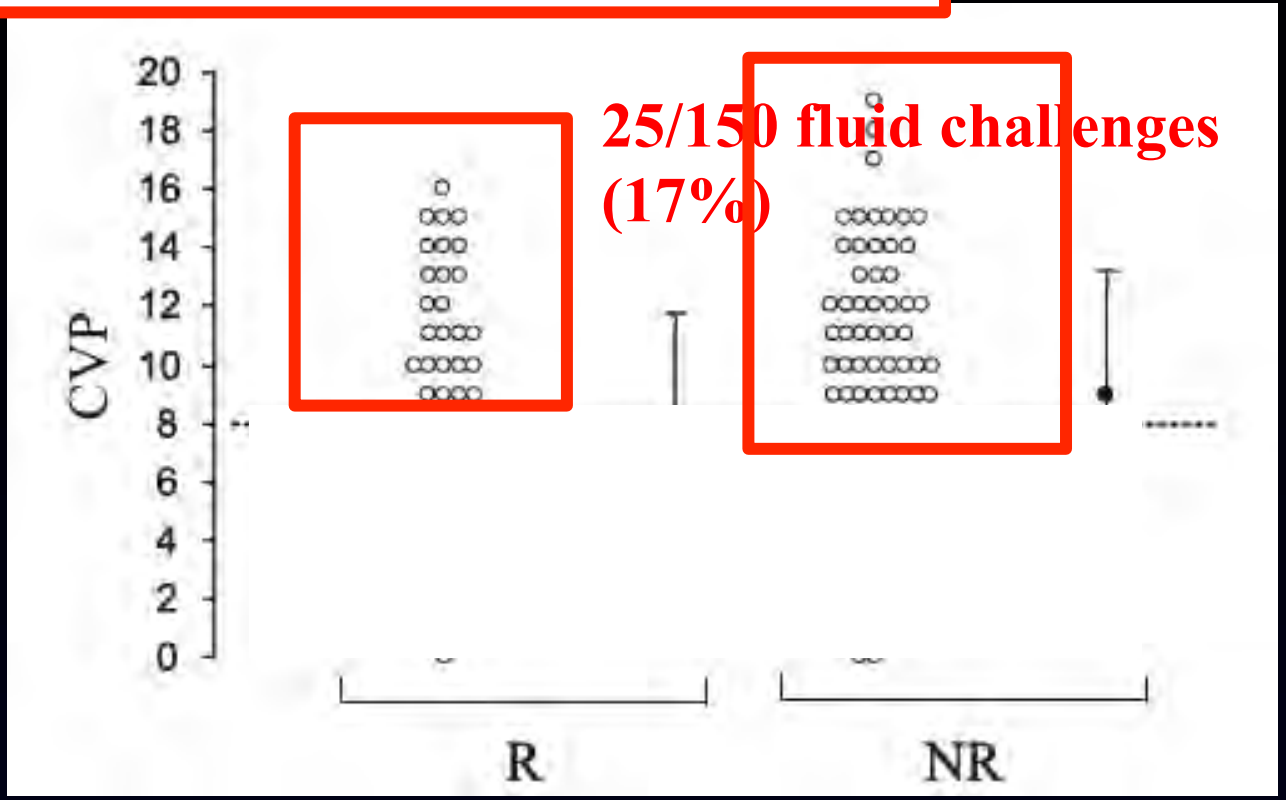
49/77 (64%) fluid challenges initiated when CVP<8 mmHg

DDB USI

Should we guide fluid administration on CVP ?????

Only a minority of the patients may still benefit from fluids at this stage

Osman et al
ICM 35:64;2007



25/150 fluid challenges (17%)

8 mmHg

96 pts with severe sepsis
150 fluid challenges

48/73 (66%) fluid challenges are ineffective if initiated when CVP>8 mmHg

Cardiac output:
Which goals?

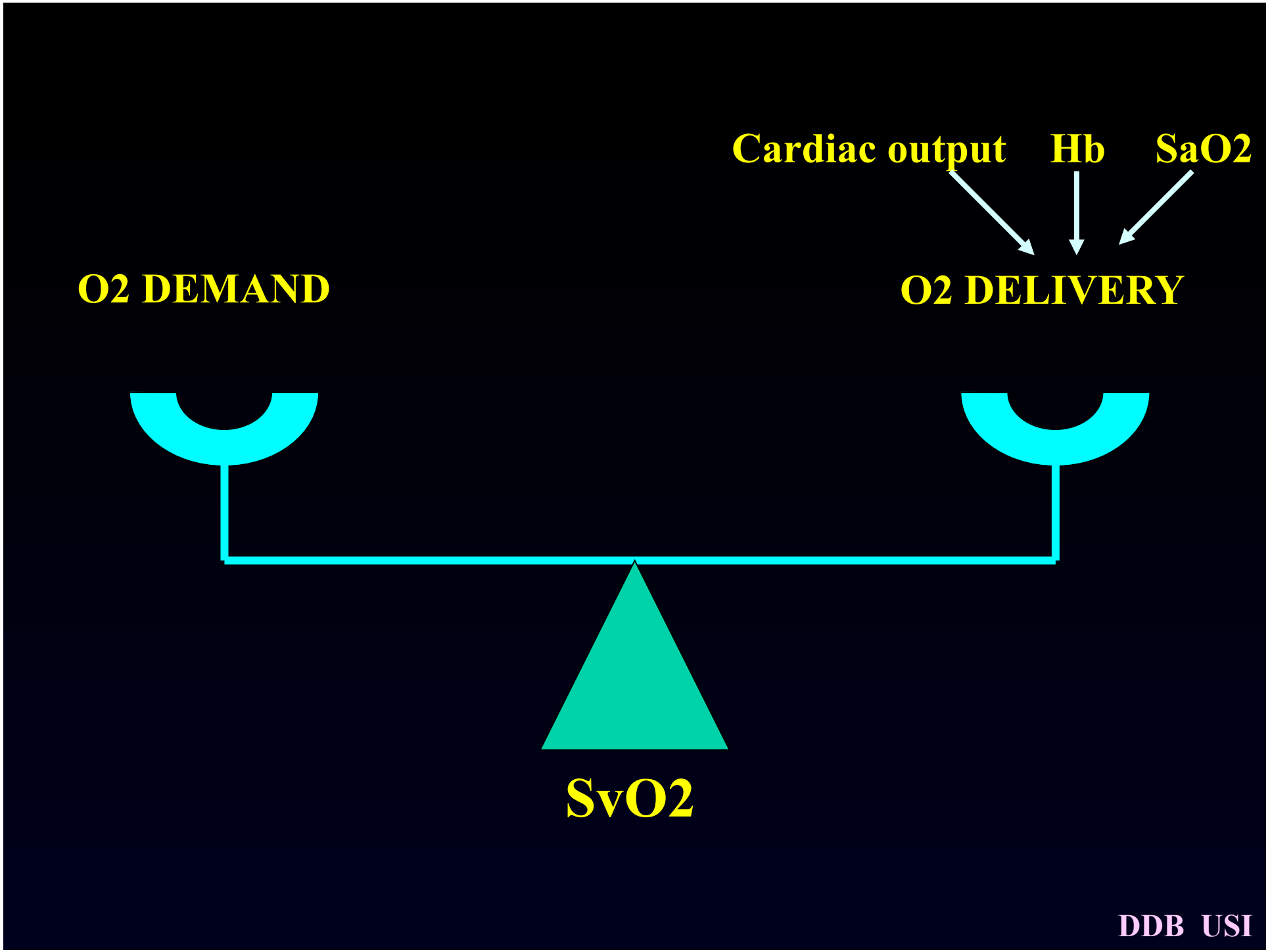
Cardiac output is an adaptive variable.

It should be evaluated in the clinical context.

Cardiac output measurements:

3.0 L/min.M²	Quiet, MV, 36.5°C, Hb 10
3.5 L/min.M²	Quiet, extubated, 36.5°C, Hb 10
4.0 L/min.M²	Quiet, MV, 39.5°C, Hb 10
4.5 L/min.M²	Dyspneic, MV, 38.5°C, Hb 9

Is cardiac output adequate ?



Cardiac output measurements:

3.0 L/min.M²	Quiet, MV, 36.5°C, Hb 10	SvO2 70%
3.5 L/min.M²	Quiet, extubated, 36.5°C, Hb 10	SvO2 70%
4.0 L/min.M²	Quiet, MV, 39.5°C, Hb 10	SvO2 60%
4.5 L/min.M²	Dyspneic, MV, 38.5°C, Hb 9	SvO2 35%

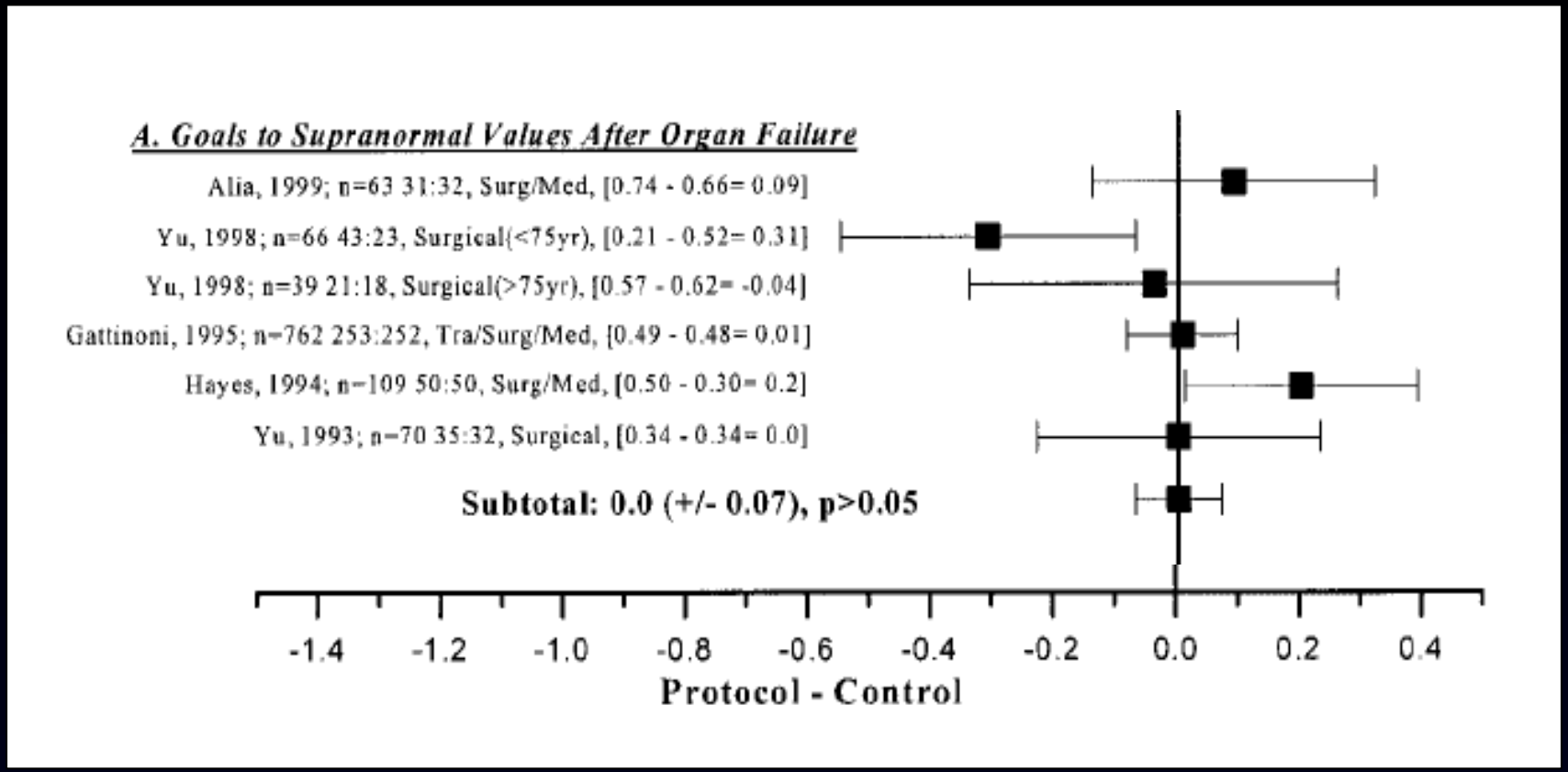
Is cardiac output adequate ?

Cardiac output and SvO2 should be interpreted in the context of signs of tissue perfusion (lactate, organ dysfunction).

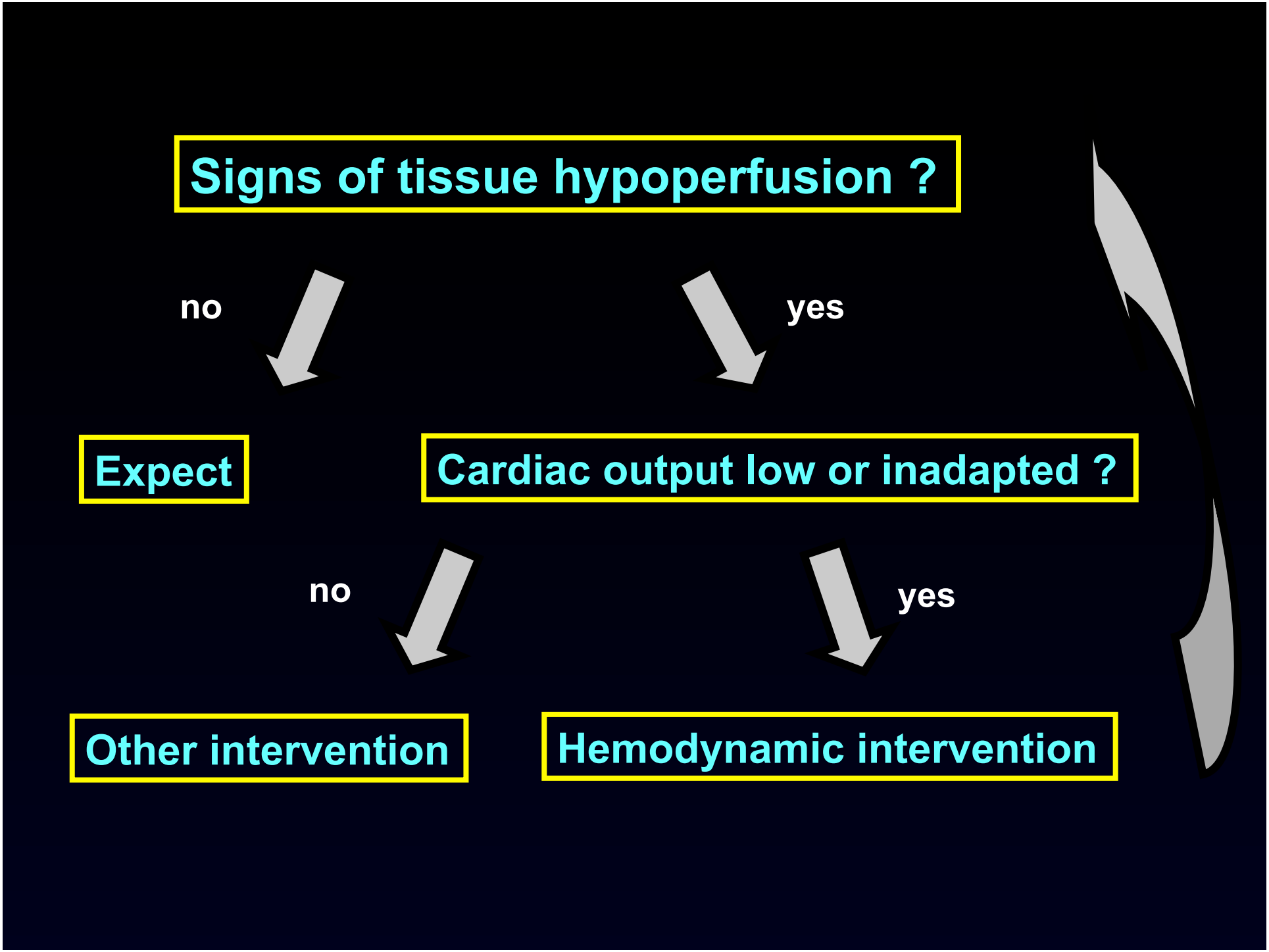
A cardiac or SvO2 value in isolation should not be treated, it should be treated only when associated with signs of tissue hypoperfusion (and organ dysfunction).

Goal directed therapy in septic shock

Kern et al
CCM 30:1686;2002



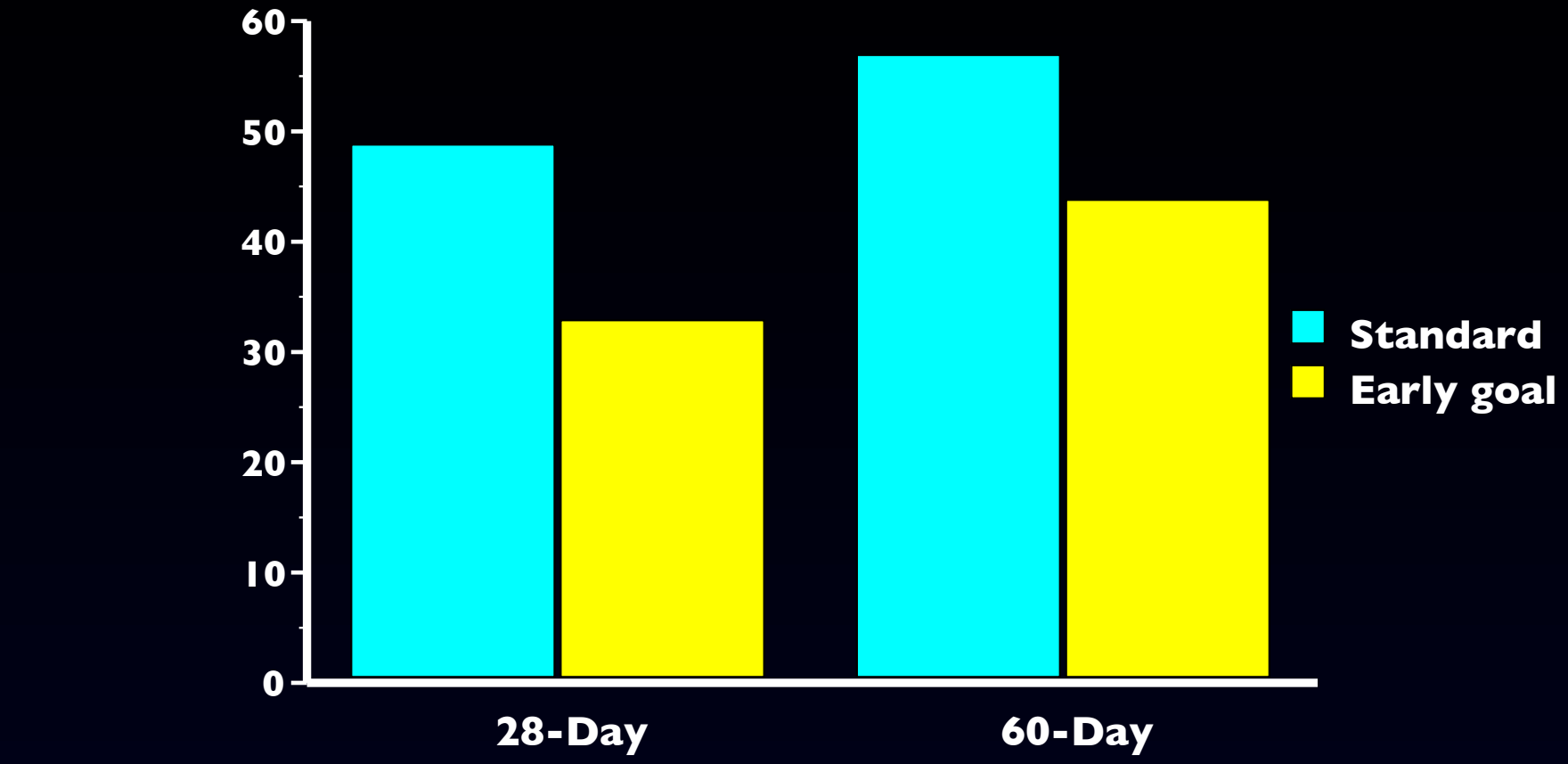
Individualized approach


Signs of tissue hypoperfusion ?
no
yes
Expect
Cardiac output low or inadapted ?
no
yes
Other intervention
Hemodynamic intervention

SvO2 ?

EARLY HEMODYNAMIC OPTIMIZATION

Rivers et al
NEJM 345:1968;2001

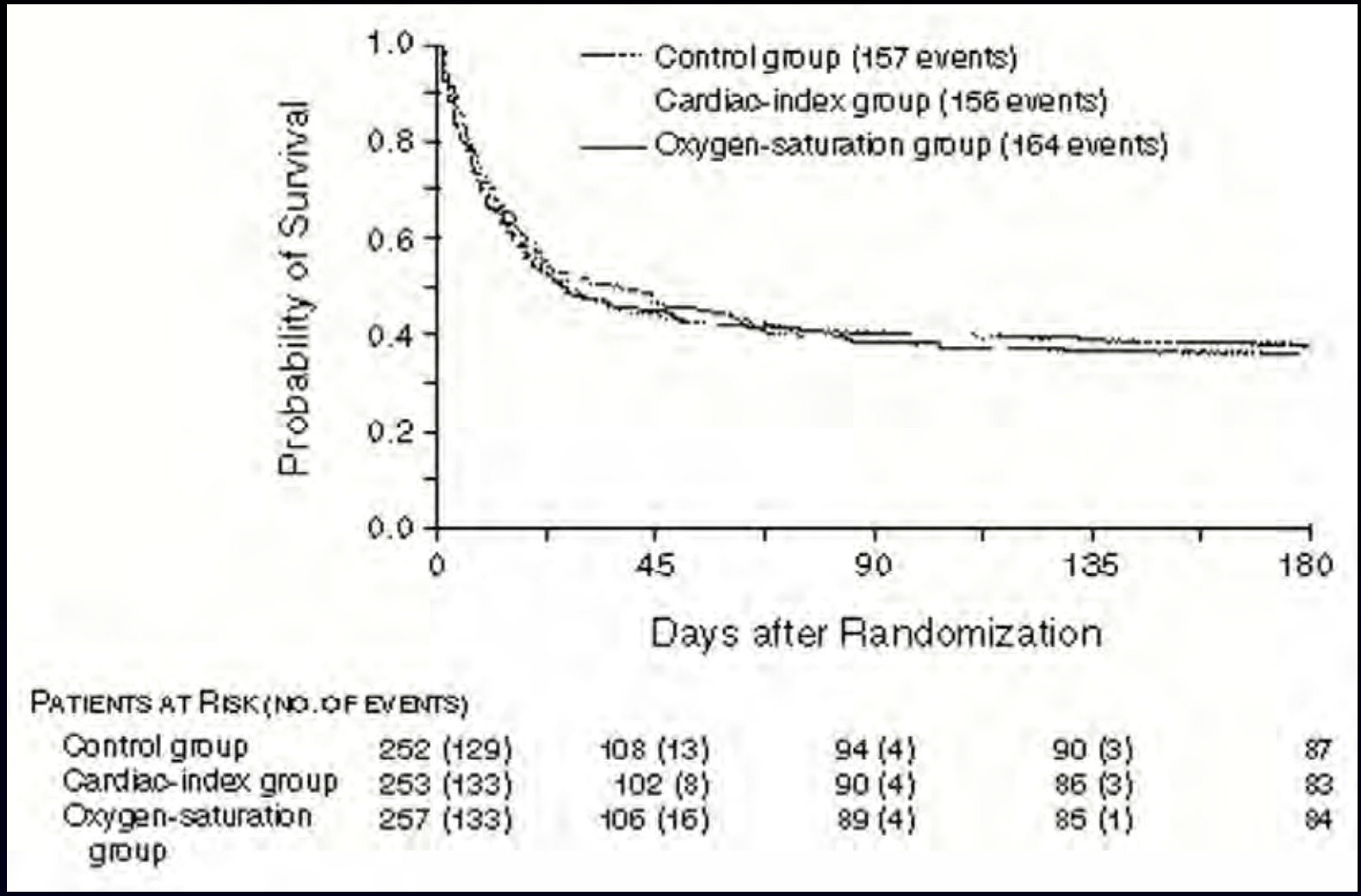


* p<0.05 vs ctrl

DDB USI

SvO2>70%

Gattinoni et al
NEJM 333:1025;1995



PATIENTS AT RISK (NO. OF EVENTS)

Control group	252 (129)	108 (13)	94 (4)	90 (3)	87
Cardiac-index group	253 (133)	102 (8)	90 (4)	86 (3)	83
Oxygen-saturation group	257 (133)	106 (16)	89 (4)	85 (1)	84

762 pts

HEMODYNAMIC MANAGEMENT BASED ON SVO2

Differences between the 2 studies ?

Gattinoni et al
NEJM 333:1025;1995

Rivers et al
NEJM 345:1968;2001

Rivers et al.:

- Inclusion at Emergency department
- Optimization maintained 6 h
- Baseline ScvO2: 49.2 +/- 13.3 %
- High lactate levels at baseline

Gattinoni et al.:

- Inclusion within 48 h of ICU admission
- Optimization maintained « as long as needed »
- Baseline SvO2: 69.5 +/- 10.5 %

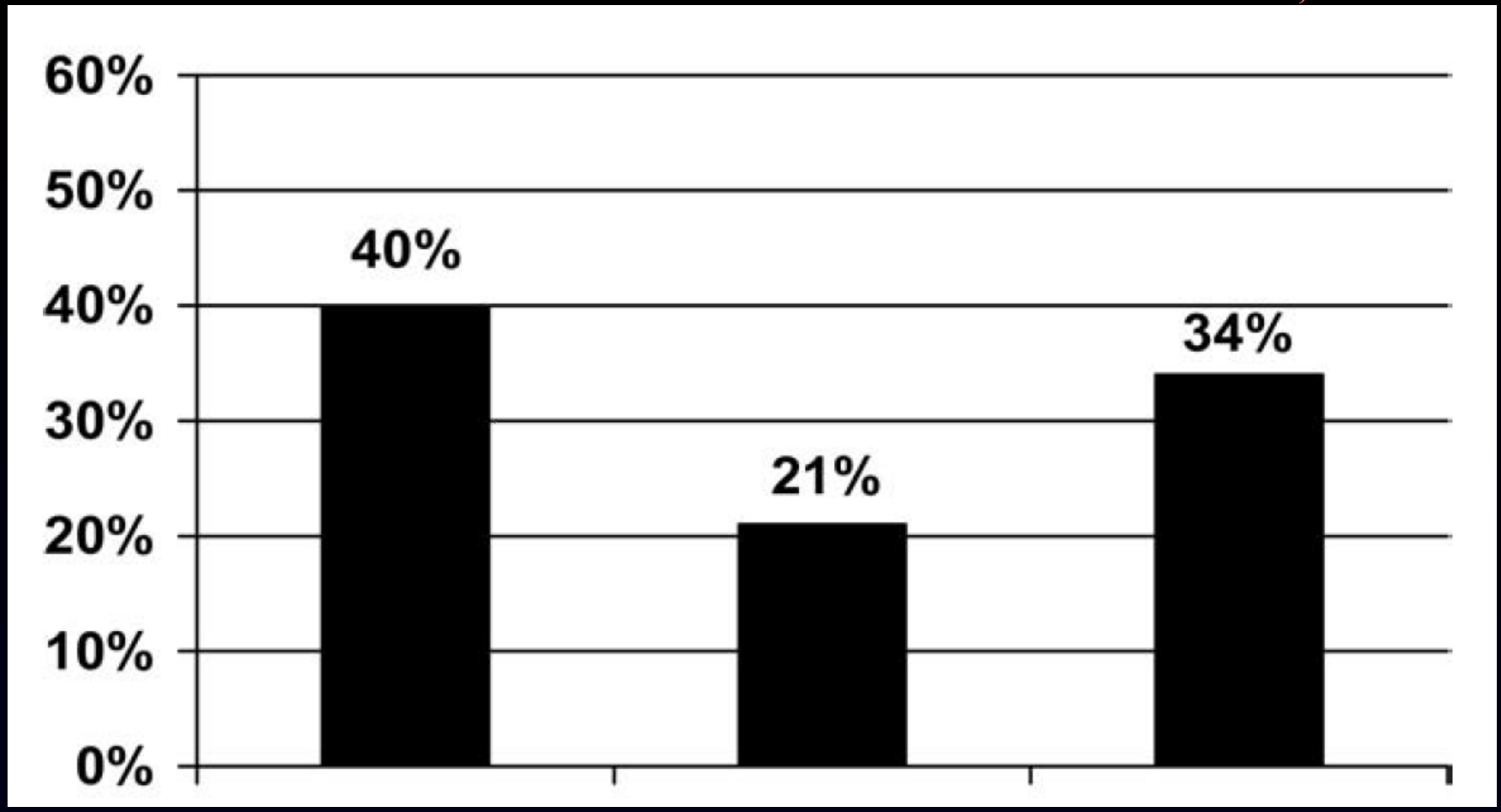
Limits in the interpretation of SvO2

A high SvO2 can be abnormal

(microciculatory alterations and/or mitochondrial dysfunction)

Pope J et al
Ann Emerg Med
15:40;2010

Mortality, %



ScvO2 <70% 70-90% >90%

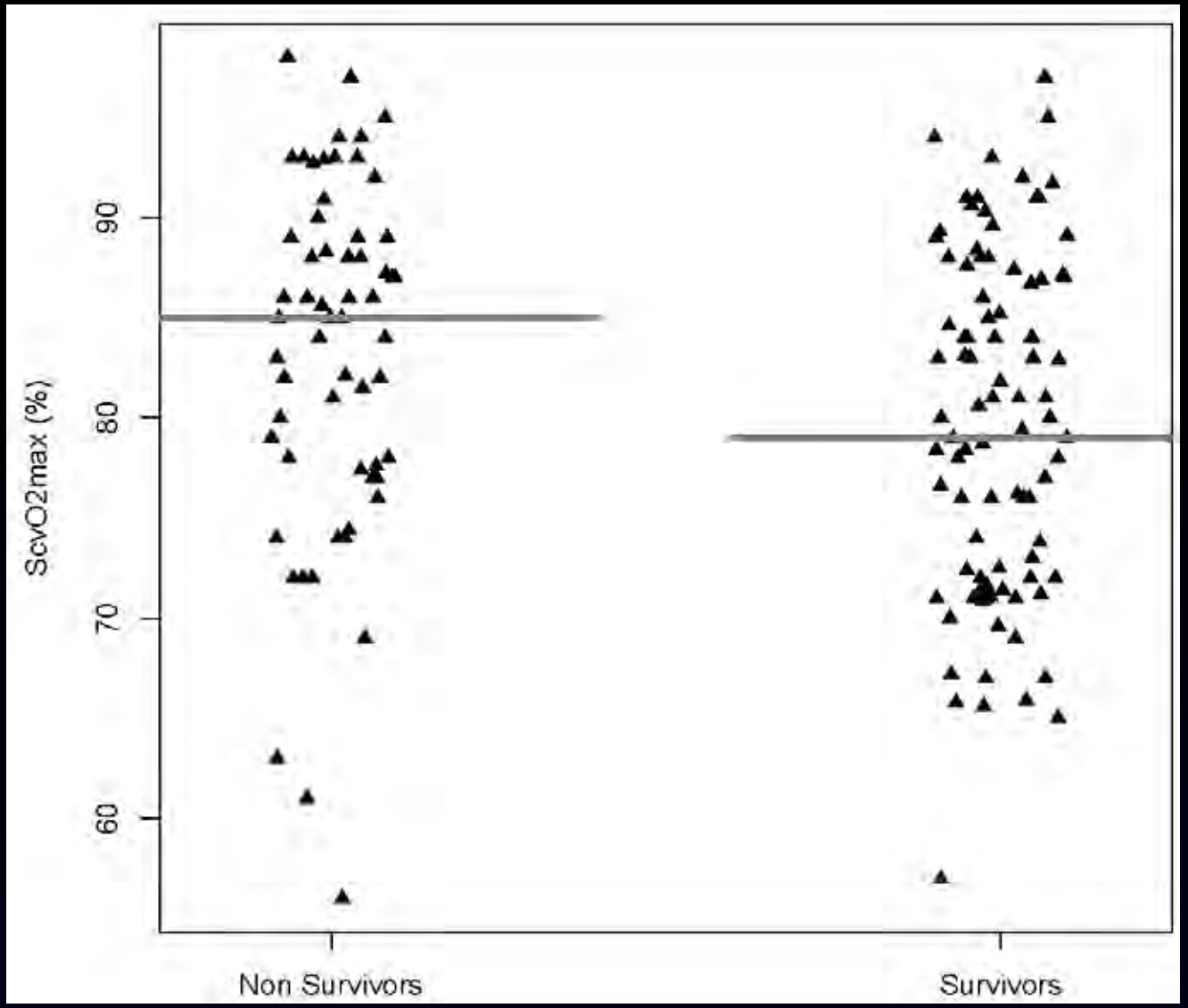
619 pts severe sepsis (ED)

Textoris J et al
Crit Care
15:R176;2011

Table 2 Contingency table of mortality among a $ScvO_{2max}$ cut-off of 80%

		Non survivors	Survivors	Mortality (%)	*P*-value
$ScvO_{2max}$	< 80%	20	46	30	0.04
	≥ 80%	41	45	48	

152 pts septic shock (ICU)



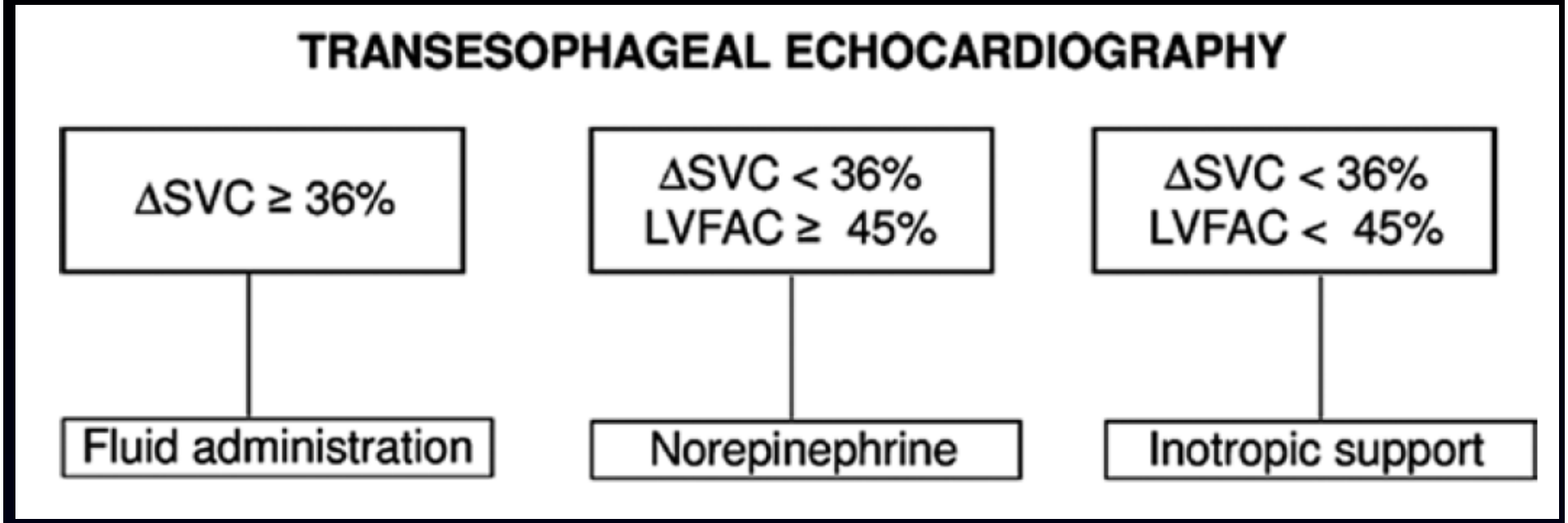
Textoris J et al
Crit Care
15:R176;2011

152 pts septic shock (ICU)

Resuscitation should not be guided on signs of cardiac dysfunction in isolation

A proposal to replace SvO2 by direct evaluation of preload responsiveness and ejection fraction

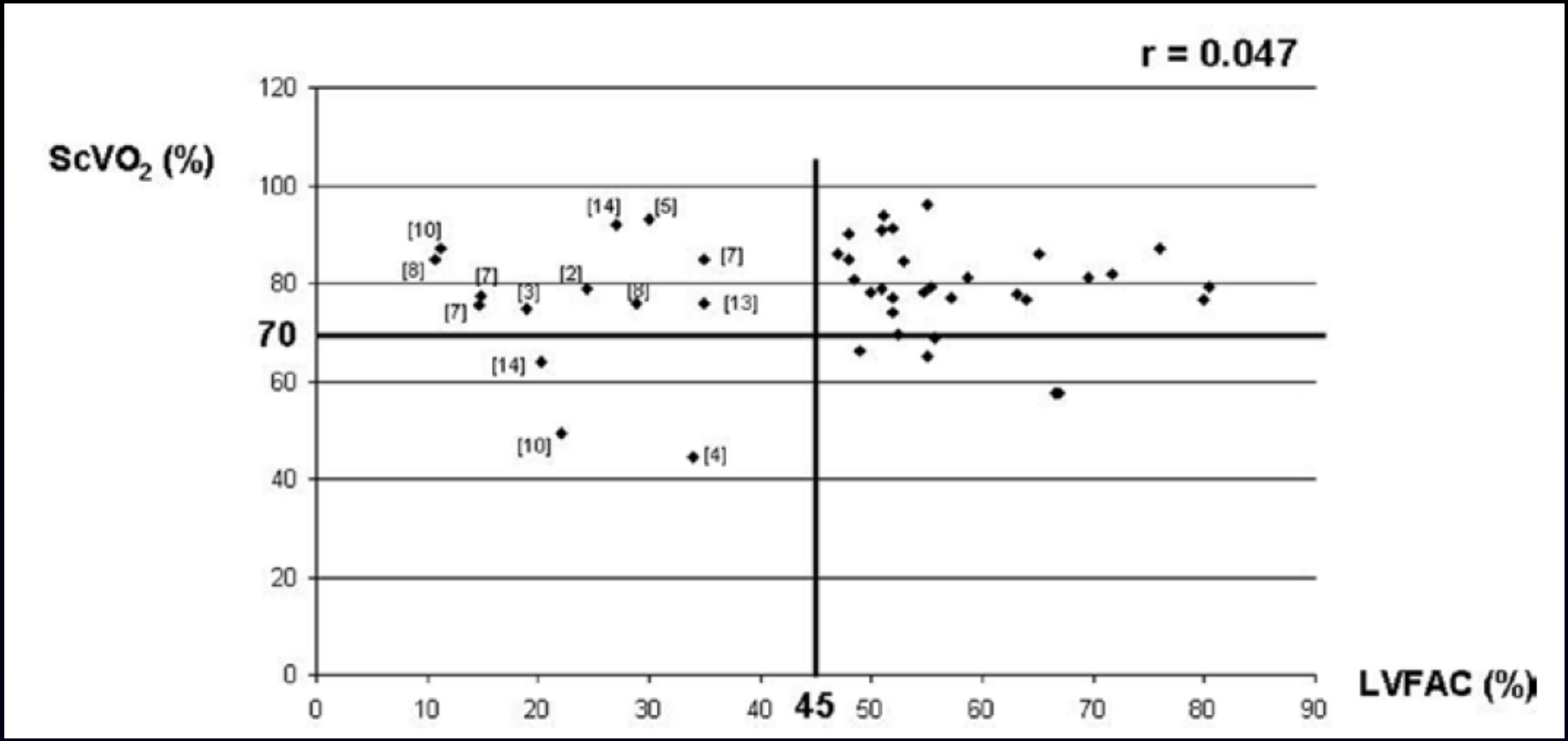
Bouferrache K et al
CCM 40:2821;2012



46 pts septic shock

Divergent information between ScvO2 and EF

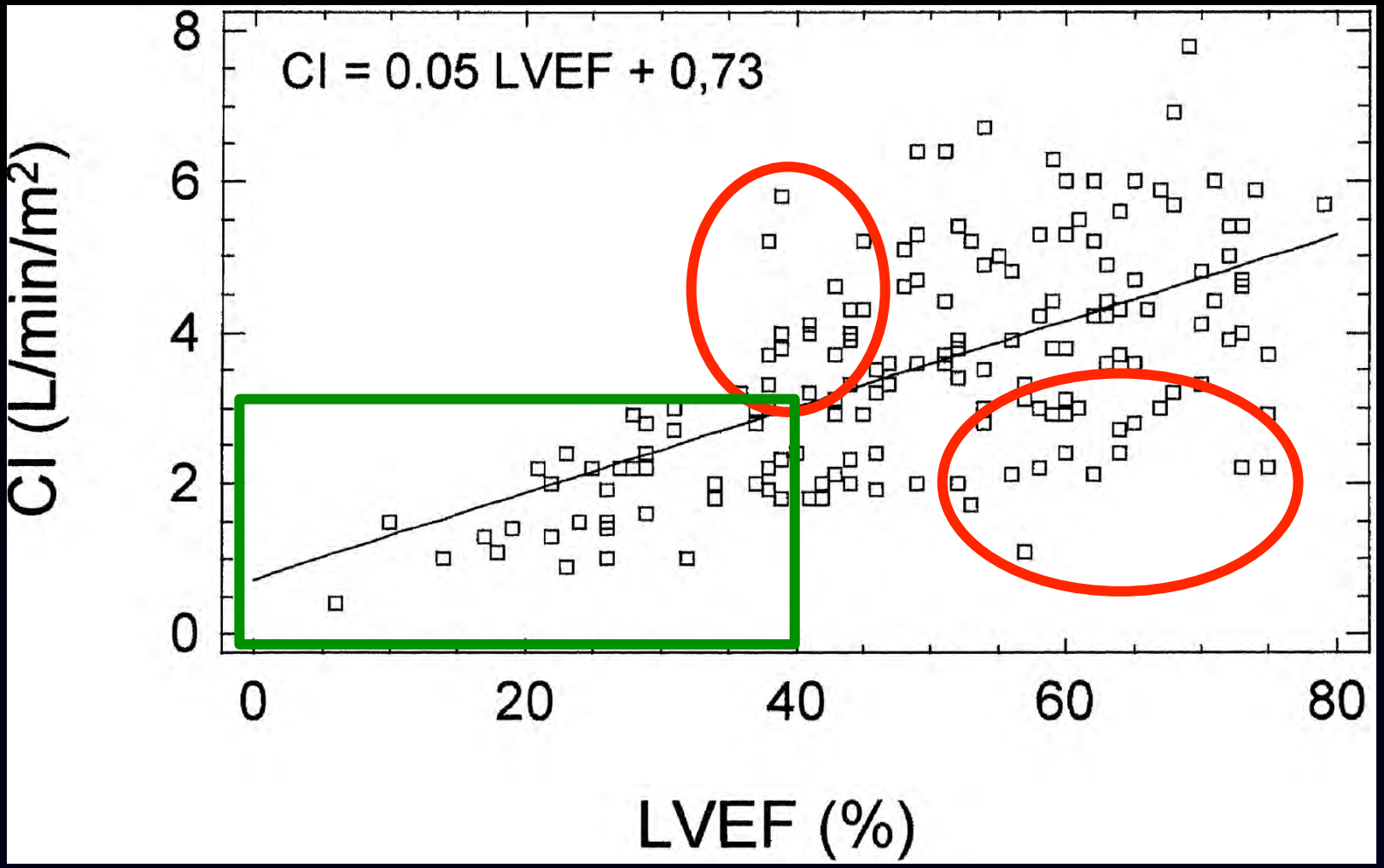
Bouferrache K et al
CCM 40:2821;2012



46 pts septic shock

Echographic evaluation of LVEF in patients with septic shock

Vieillard-Baron et al
AJRCCM 168:1270;2003

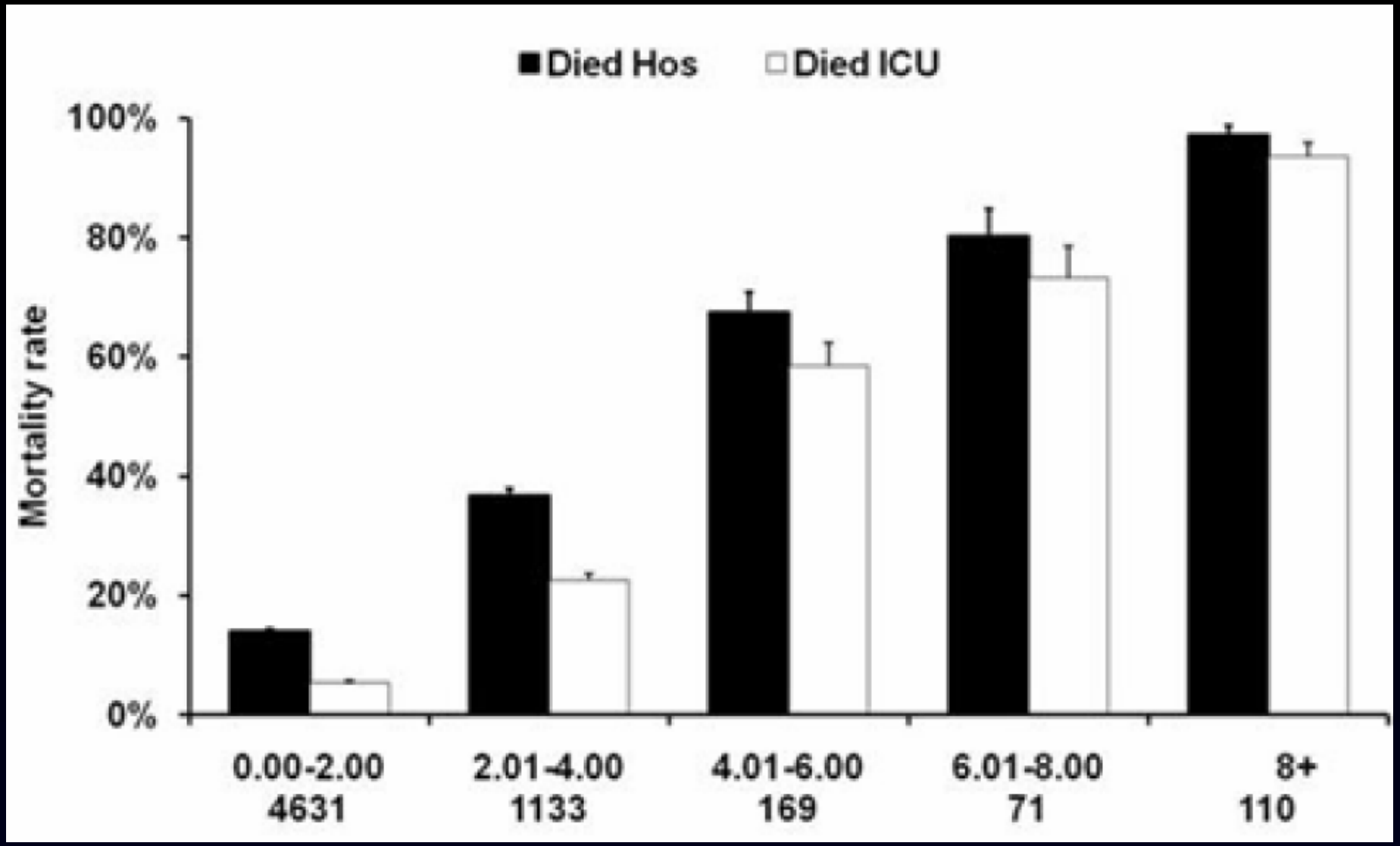


=> Inotropic agents should not be used to correct a low EF

Resuscitation guided on lactate ?

Hyperlactatemia and outome

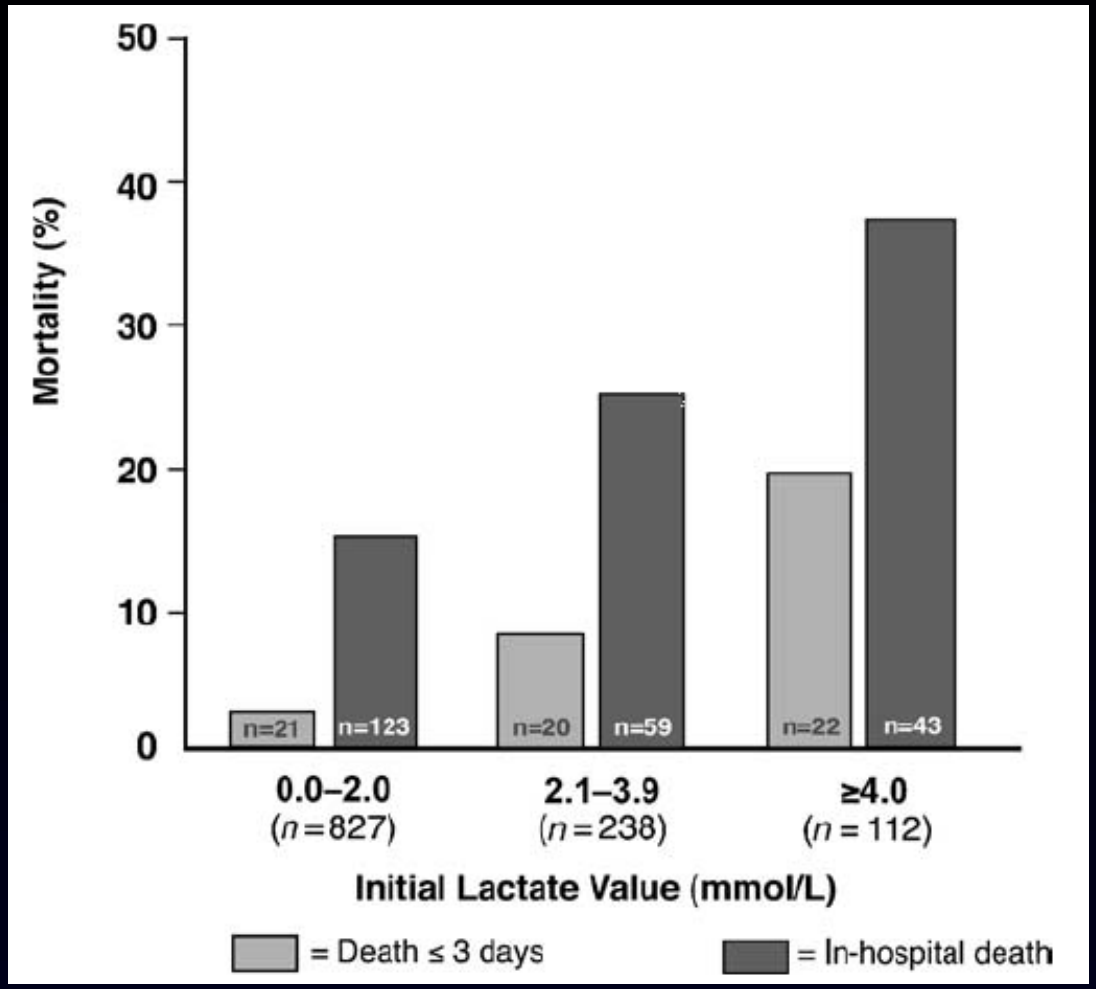
Nichol et al
Crit Care 14:R25;2010



7155 pts (ICU)

DDB USI

Measurement of blood lactate levels in patients with infection may help to identify patients at risk of complications and death

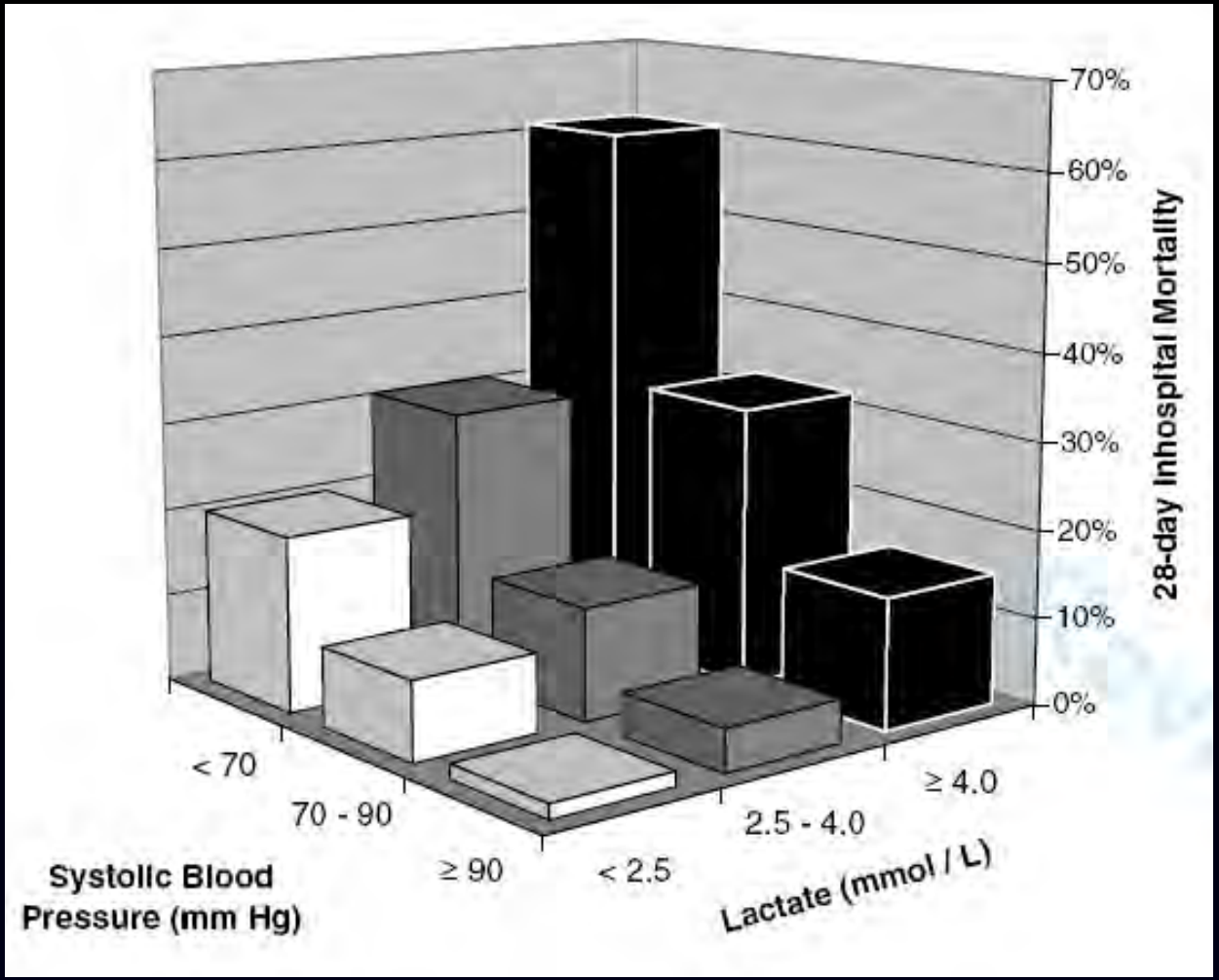


Trzeciak et al
ICM 33:970; 2007

1177 pts admitted for infection to ED

DDB USI

Howell et al
ICM 2007

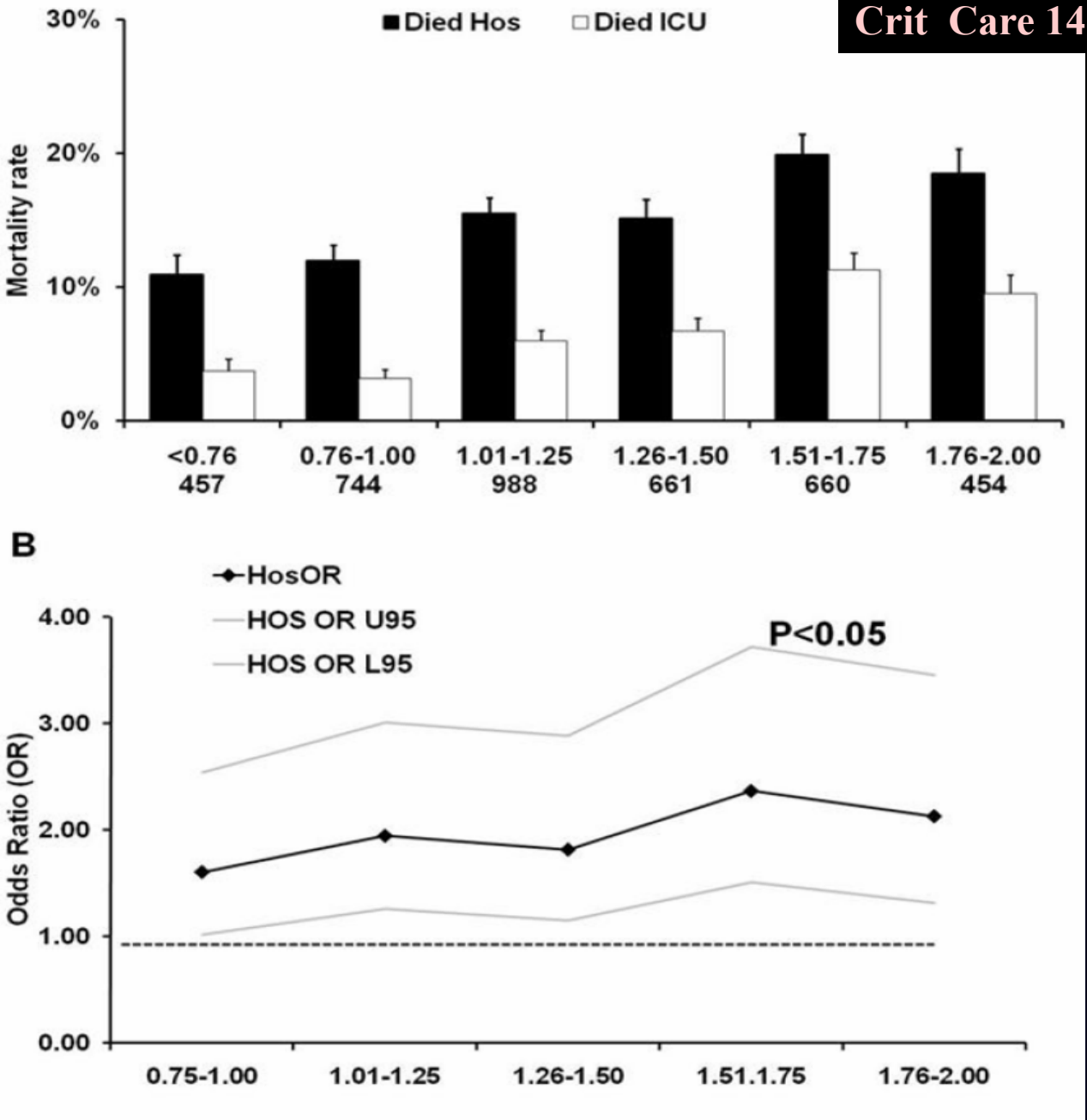


1287 pts admitted for infection to ED

DDB USI

Relative hyperlactatemia

Nichol et al
Crit Care 14:R25;2010

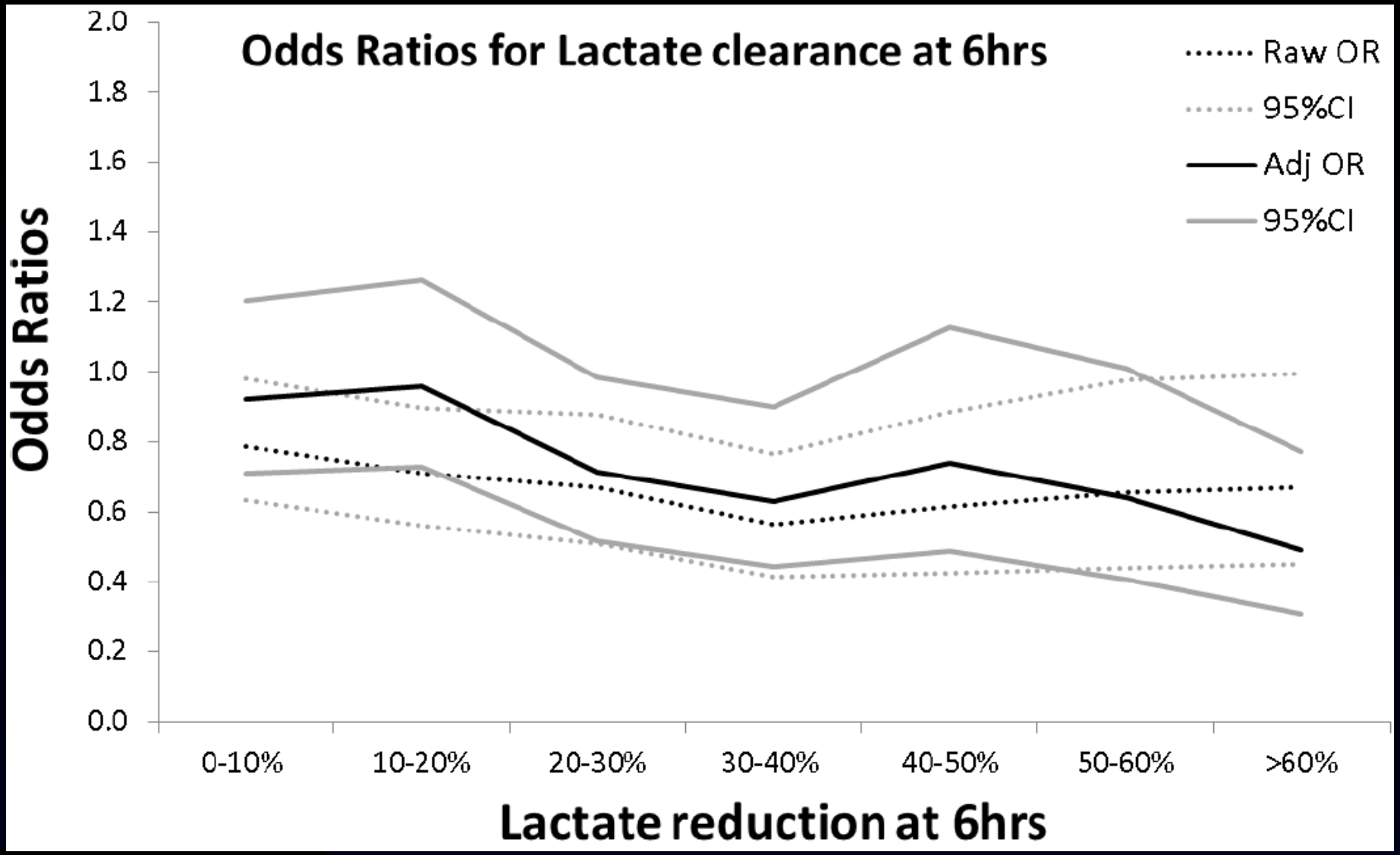


7155 pts
(ICU)

DDB USI

What is the ideal decrease slope ?

Nichol et al
Crit Care 15:R242;2011



5041 pts (ICU)

DDB USI

Lactate guided therapy
What goal ?

Puskarich M et al
Chest 143:1548; 2013

Variable	Unadjusted OR	95% CI	Adjusted OR	95% CI
Lactate normalization	6.3	2.4-17.0	5.2	1.7-15.8
Relative lactate clearance 50%	4.3	1.8-10.2	4.0	1.6-10.0
Relative lactate clearance 10%	1.7	0.8-4.0	1.6	0.6-4.4

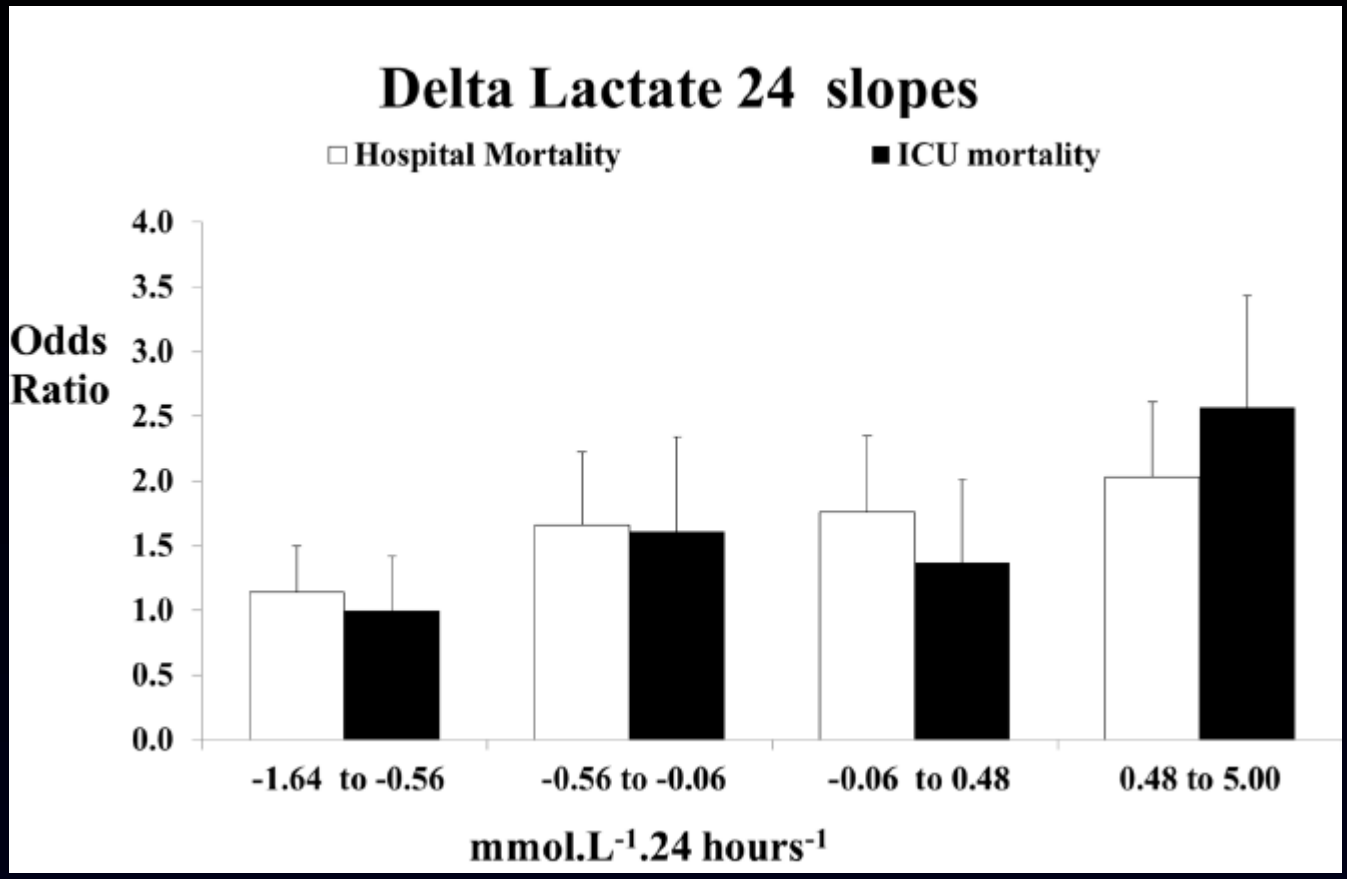
Lactate at 6h

N=185 severe sepsis (ED)

What is the ideal decrease slope ?

Nichol et al
Crit Care 15:R242;2011

Adjusted OR compared to lower quartile



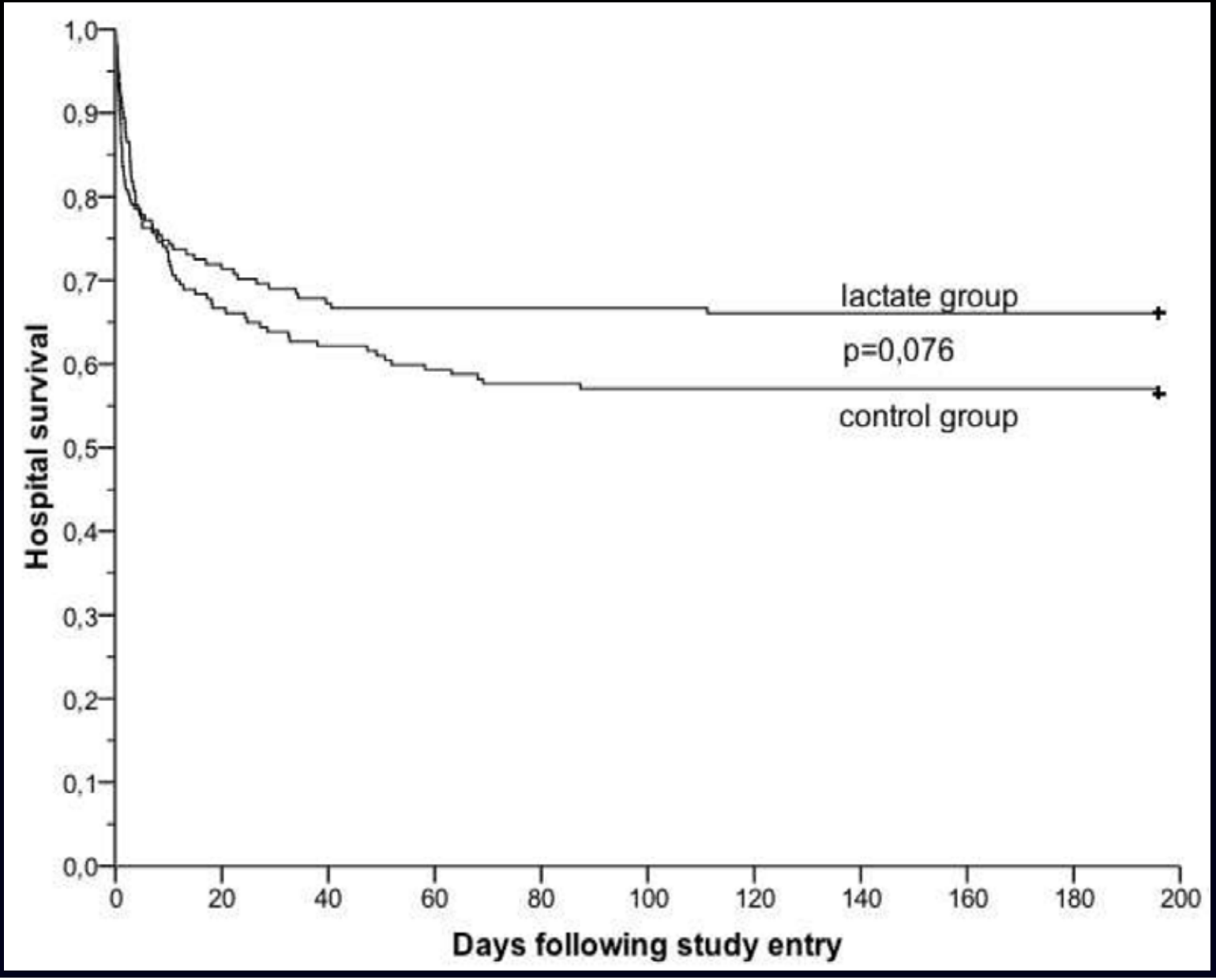
Not just for 6 h…..

5041 pts (ICU)

DDB USI

Lactate guided therapy (-20%/2h for 8h)

Janssens T et al AJRCCM 2010



N=348

MICROCIRCULATION ?

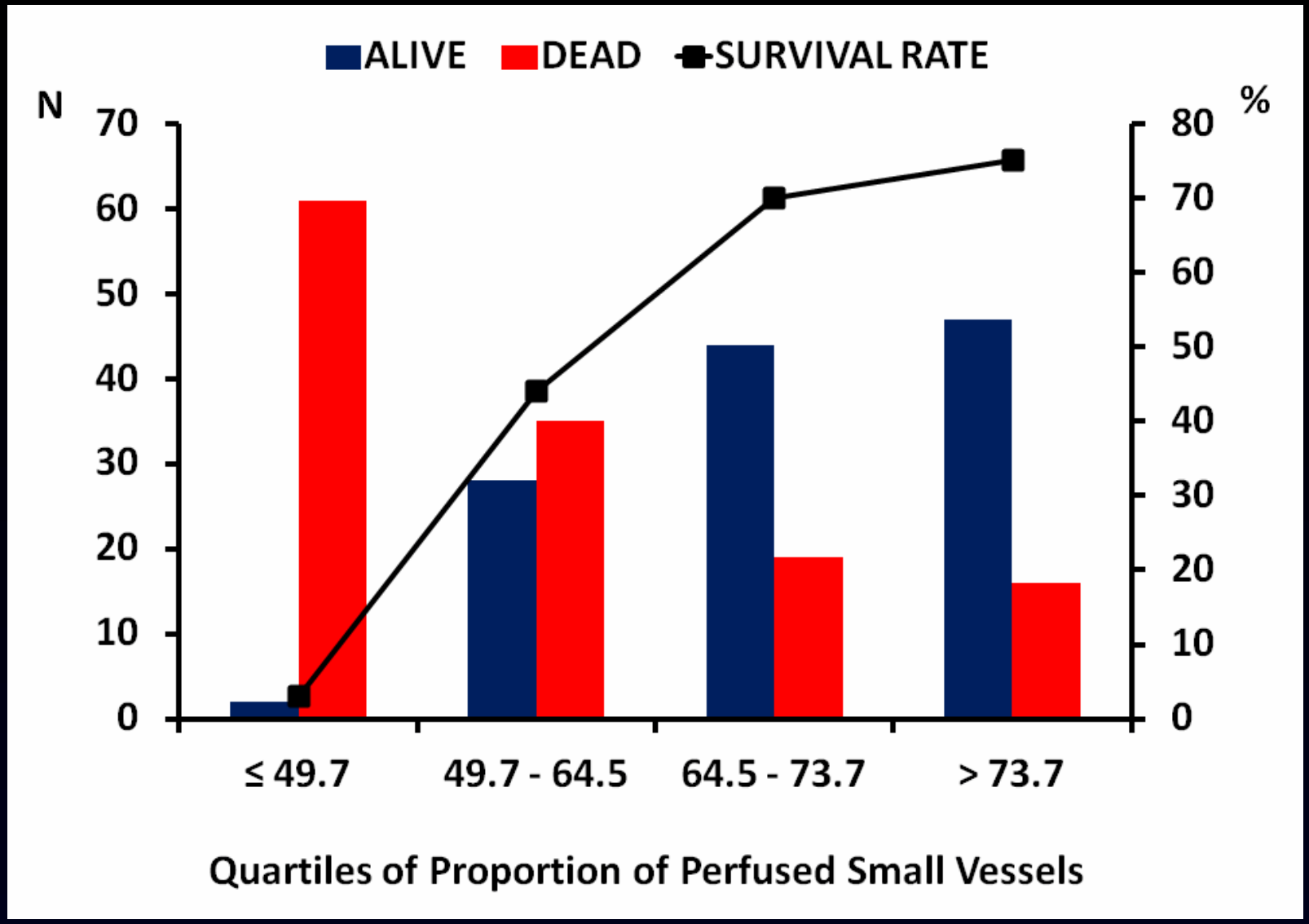
- De Backer et al AJRCCM 2002
- Spronk et al Lancet 2002
- Sakr et al CCM 2004
- De Backer et al CCM 2006
- De Backer et al CCM 2006
- Creteur et al ICM 2006
- Boerma et al CCM 2007
- Trzeciak et al Ann Emerg Med 2007
- Sakr et al CCM 2007
- Trzeciak et al ICM 2008
- Boerma et al ICM 2008
- Dubin et al Crit Care 2009
- Buchele et al CCM 2009
- Boerma et al CCM 2010
- Ospina et al ICM 2010
- Spanos et al Shock 2010
- Pottecher et al ICM 2010
- Morelli et al Crit Care 2010
- Ruiz et al Crit Care 2010
- Dubin et al J Crit Care 2010
- Morelli et al ICM 2011
- Edul et al CCM 2012
- Kanvundis et al ICM 2012
- Hernandez et al CCRP 2012
- Pranskunas et al ICM 2013
- Hernandez et al ICM 2013
- Hernandez et al J Crit Care 2013
- Vellinga et al BMC Anesthesiol 2013

Alterations of sublingual microcirculation in patients with sepsis

- ↓ total vascular density
- ↓ perfusion of capillaries
  (no flow or intermittent flow)
- Preserved venular perfusion
- Heterogeneity between areas
  (close by a few microns)

Association with outcome

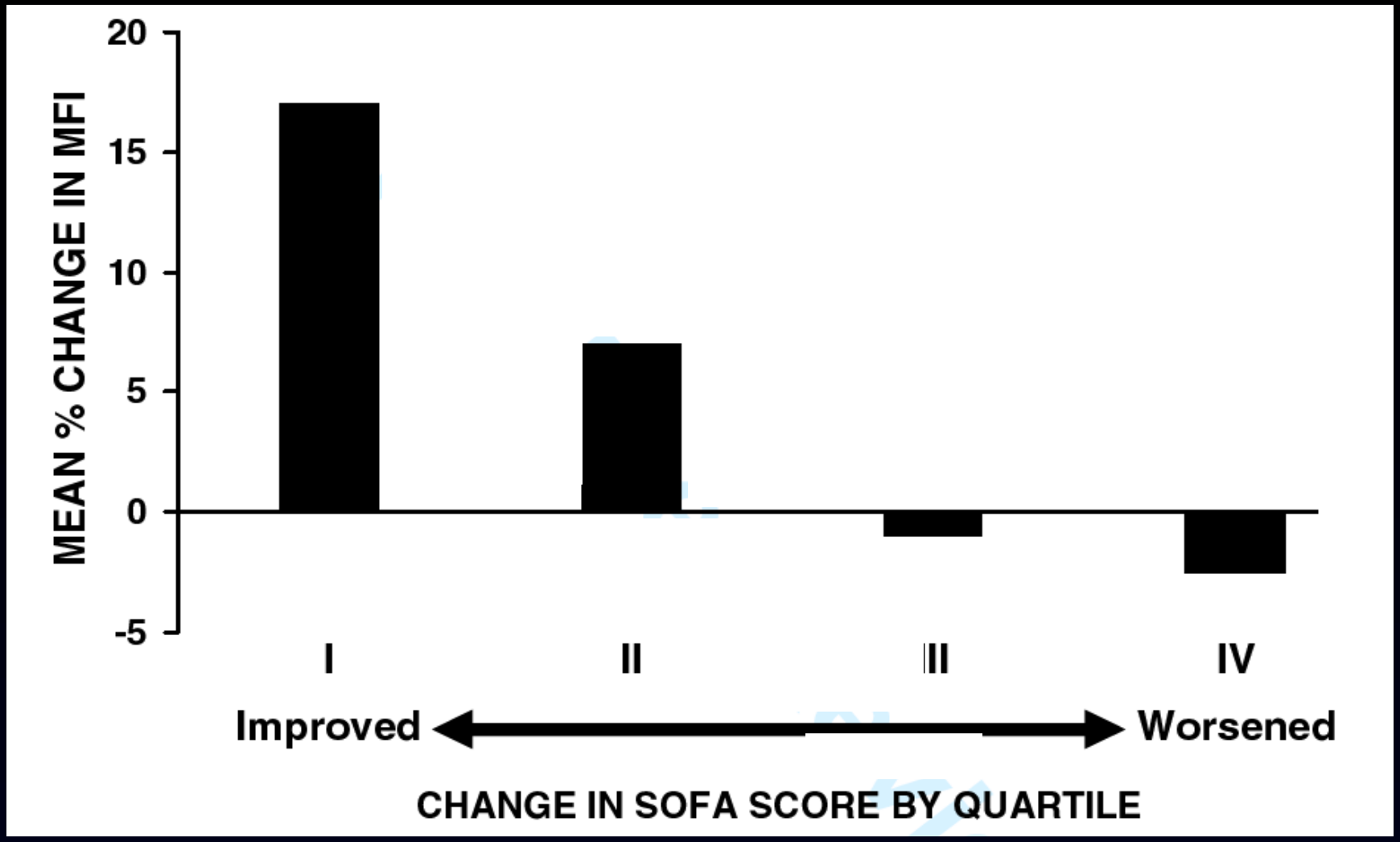
De Backer et al
CCM 41:791;2013



Severe sepsis (n=252)

33 pts with septic shock

Trzeciak et al
ICM 34:2210; 2008



- 1st SDF evaluation within 3 hours after EGDT initiation
- 2nd SDF evaluation 3 to 6 hours after EGDT initiation
- SOFA changes between 0 and 24 h

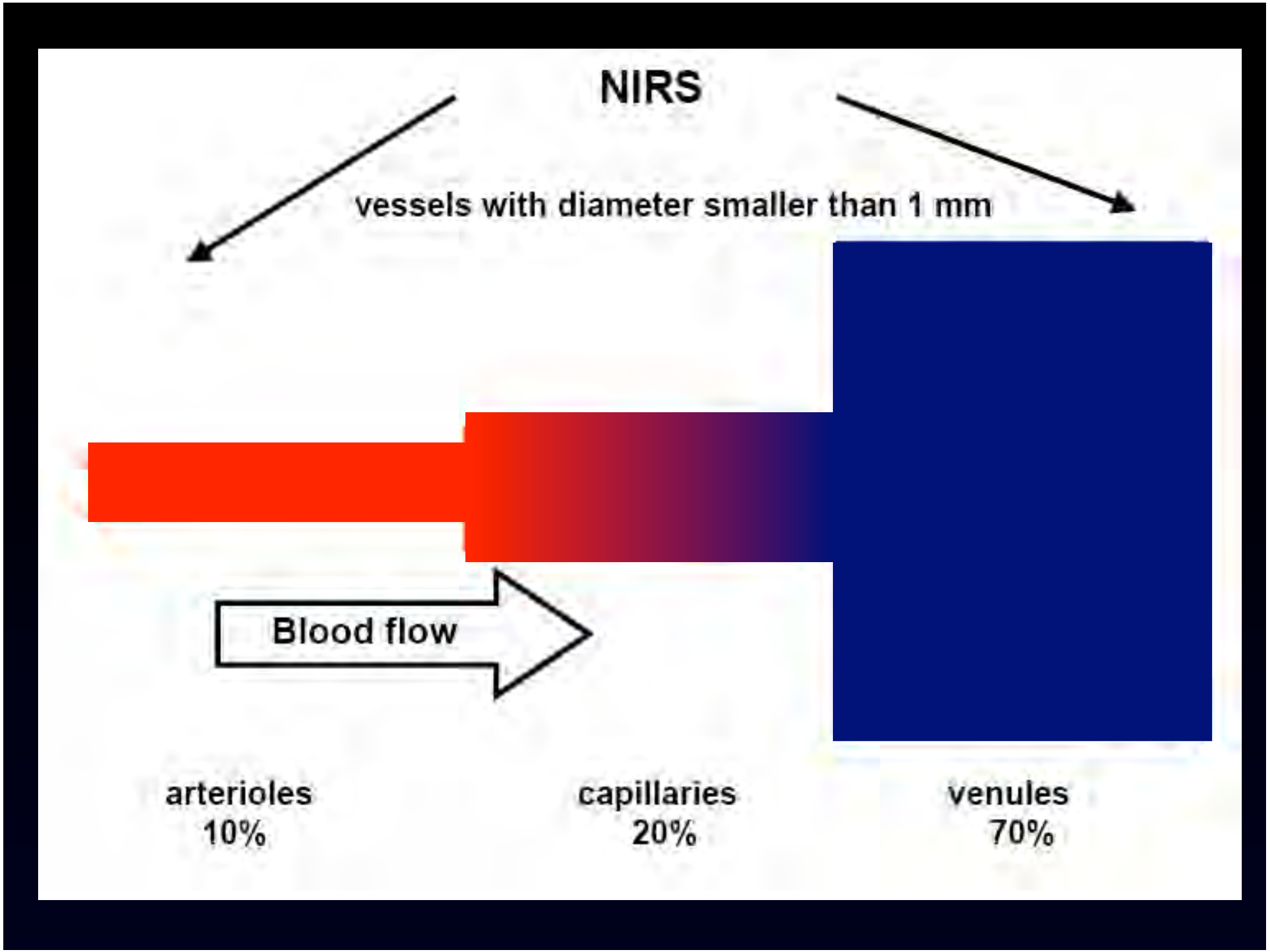
Which targets for the microcirculation ?

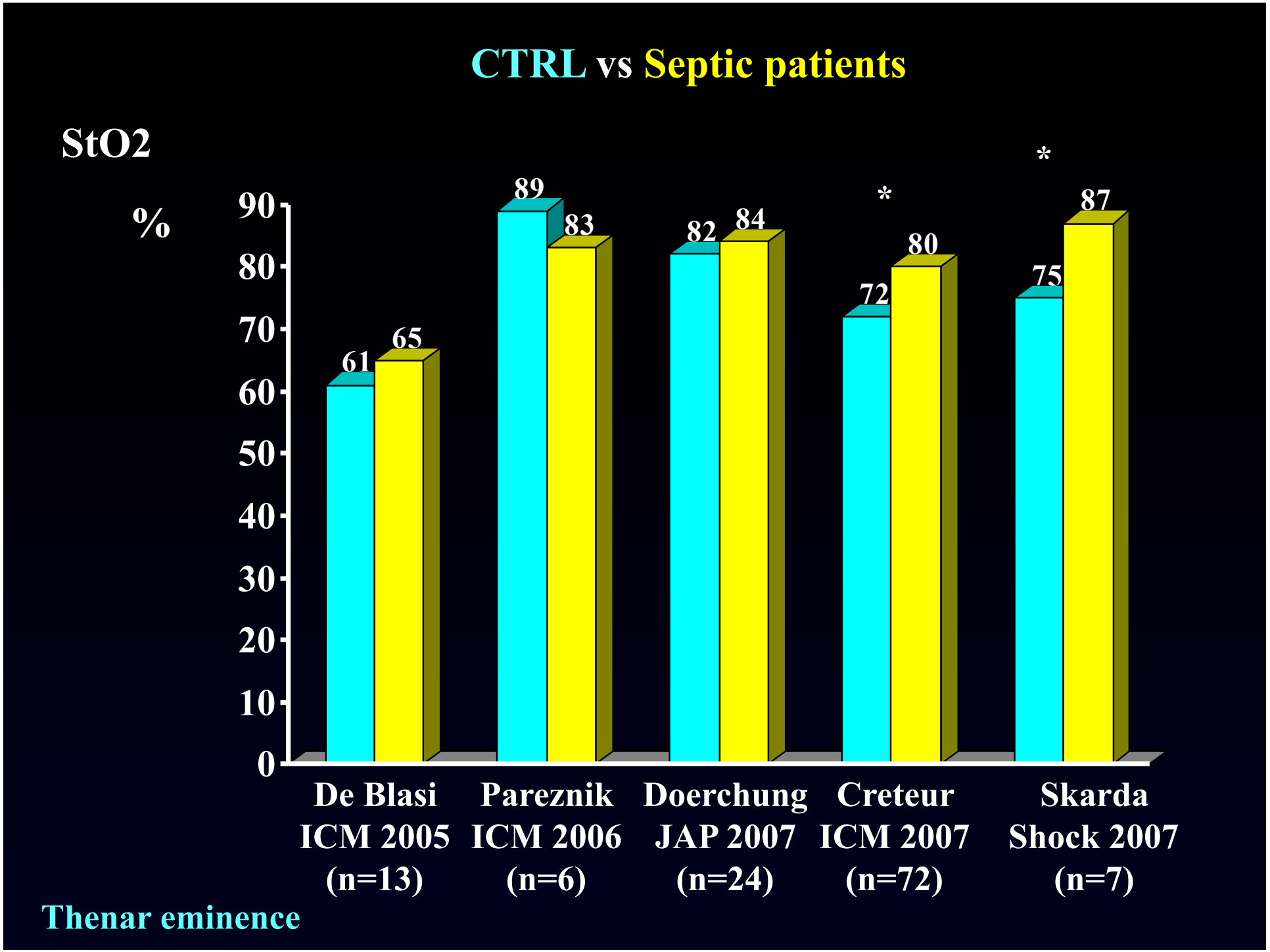
Maybe still premature….

We need to better define:

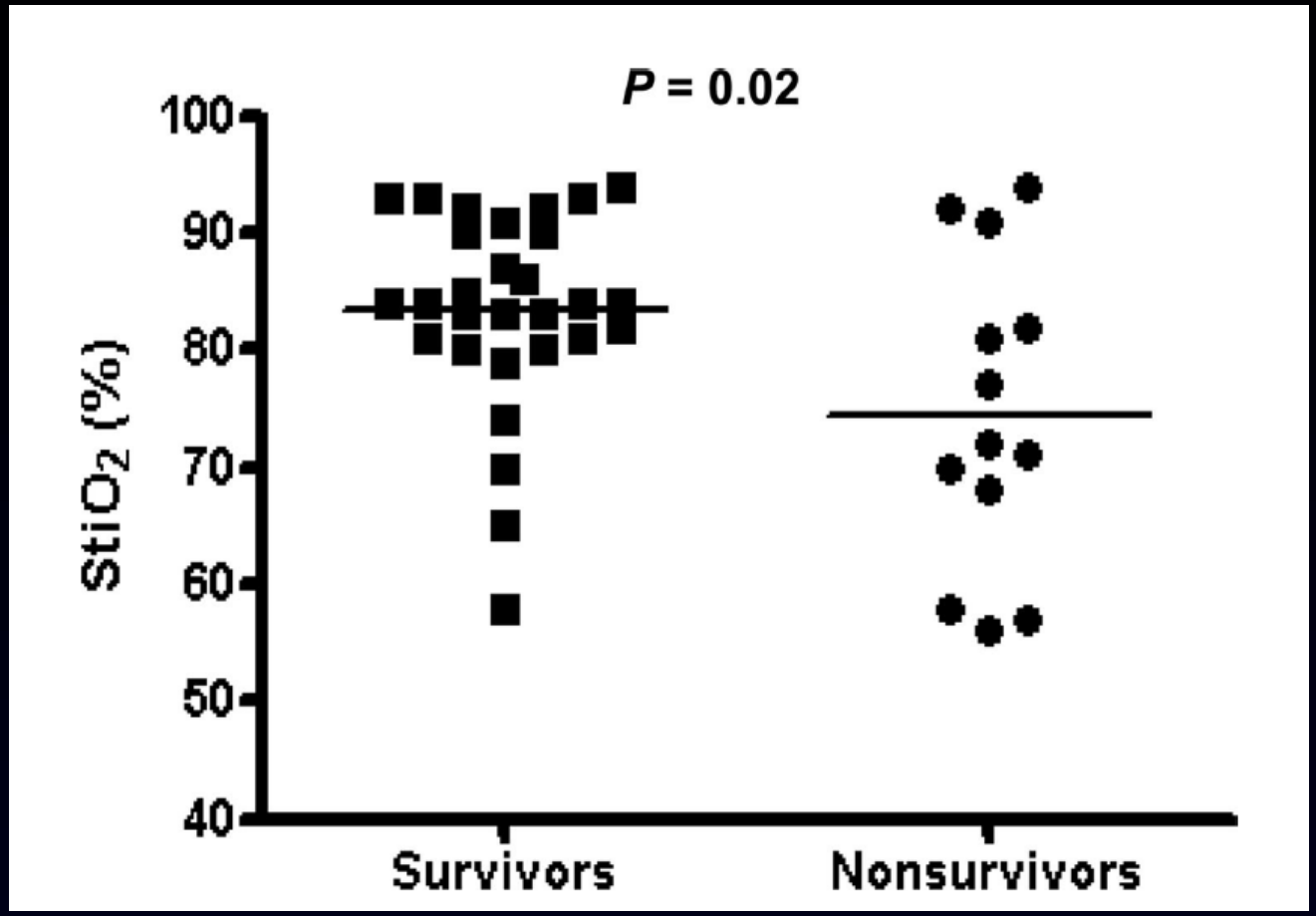
- What are the most important variables
- What target values?
- Which interventions ?

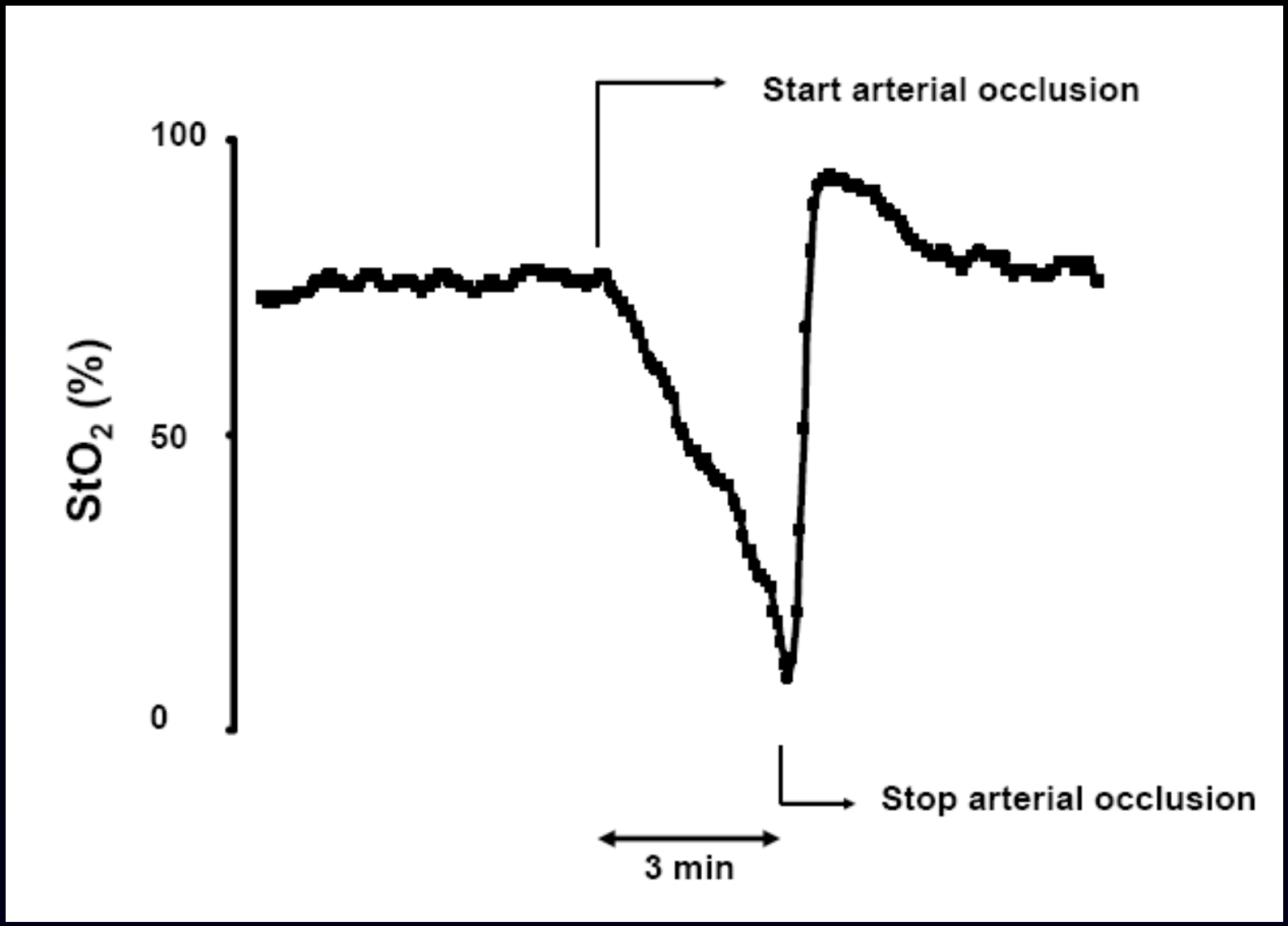
Tissue PO2/SO2
Near Infrared Spectroscopy


NIRS
vessels with diameter smaller than 1 mm
Blood flow
arterioles
10%
capillaries
20%
venules
70%


CTRL vs Septic patients
StO2
%
90
80
70
60
50
40
30
20
10
0
61
65
89
83
82
84
72
80
75
87
*
*
De Blasi
ICM 2005
(n=13)
Pareznik
ICM 2006
(n=6)
Doerchung
JAP 2007
(n=24)
Creteur
ICM 2007
(n=72)
Skarda
Shock 2007
(n=7)
Thenar eminence

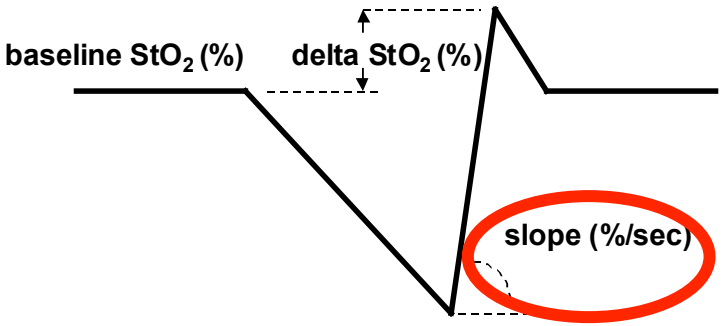
Leone M et al
Anesthesiology
111:366; 2009

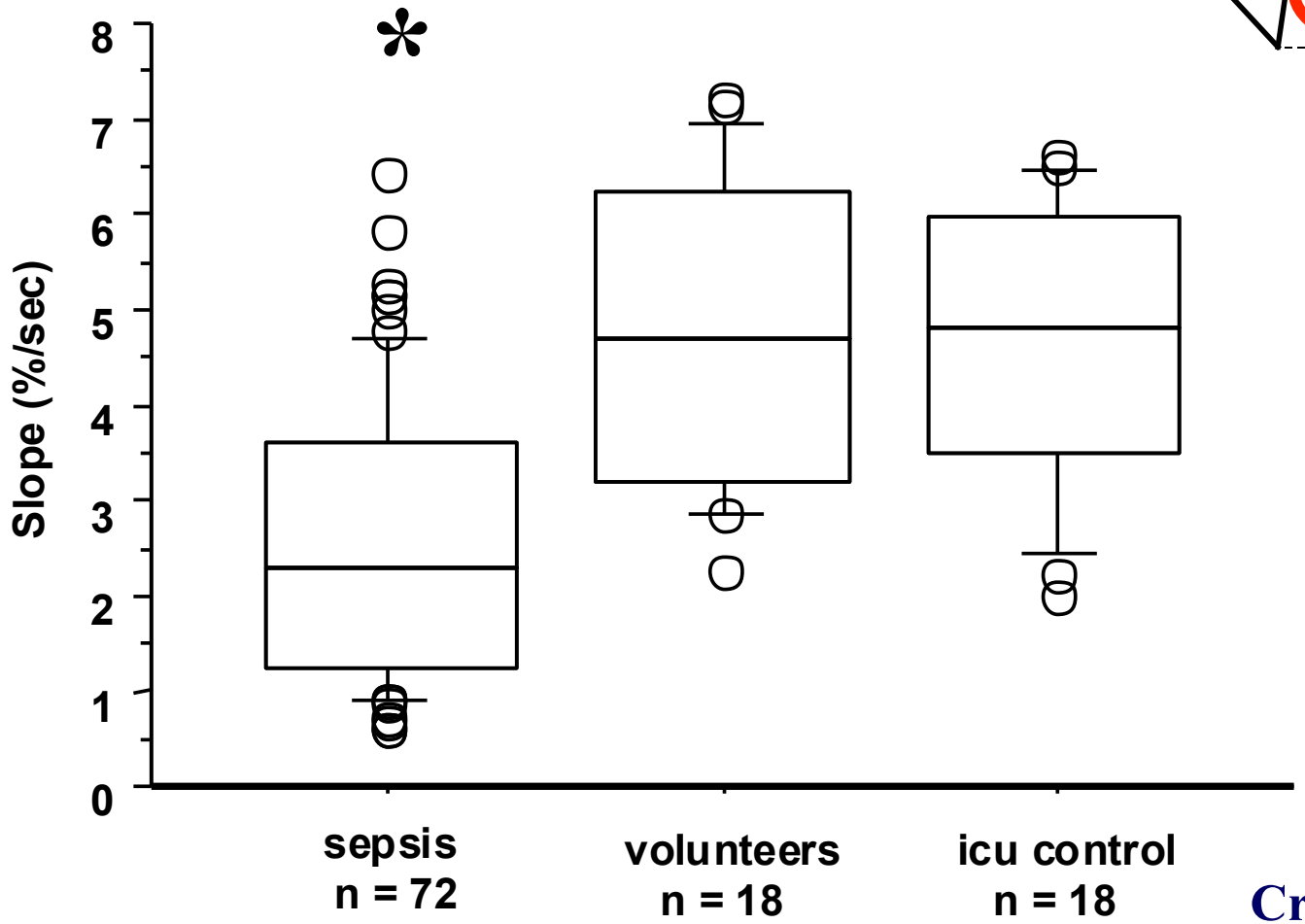



Start arterial occlusion
100
50
0
StO2 (%)
Stop arterial occlusion
3 min

Endothelial reacitivity is impaired in sepsis

* p < 0.001 vs volunteers and ICU control

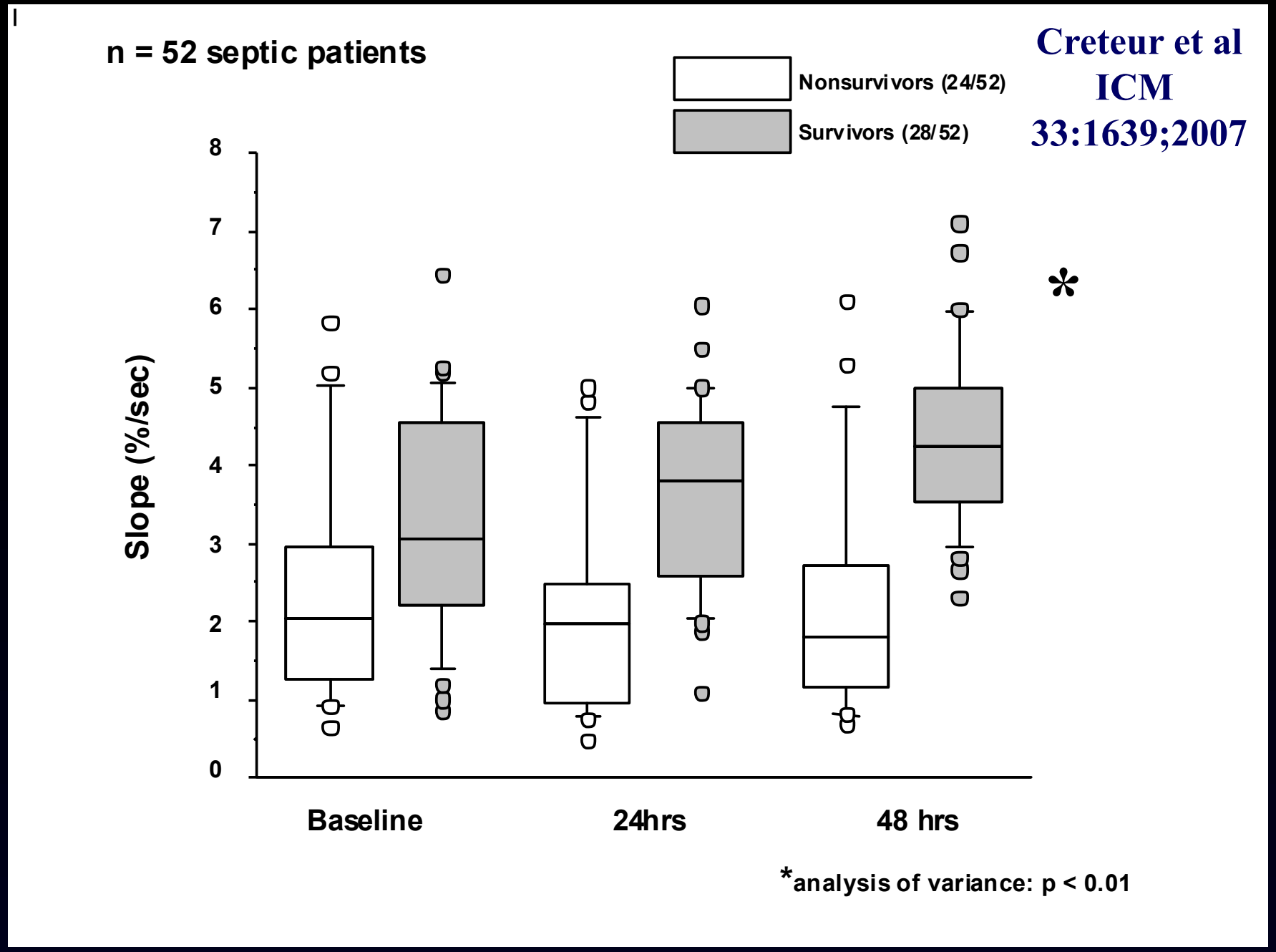


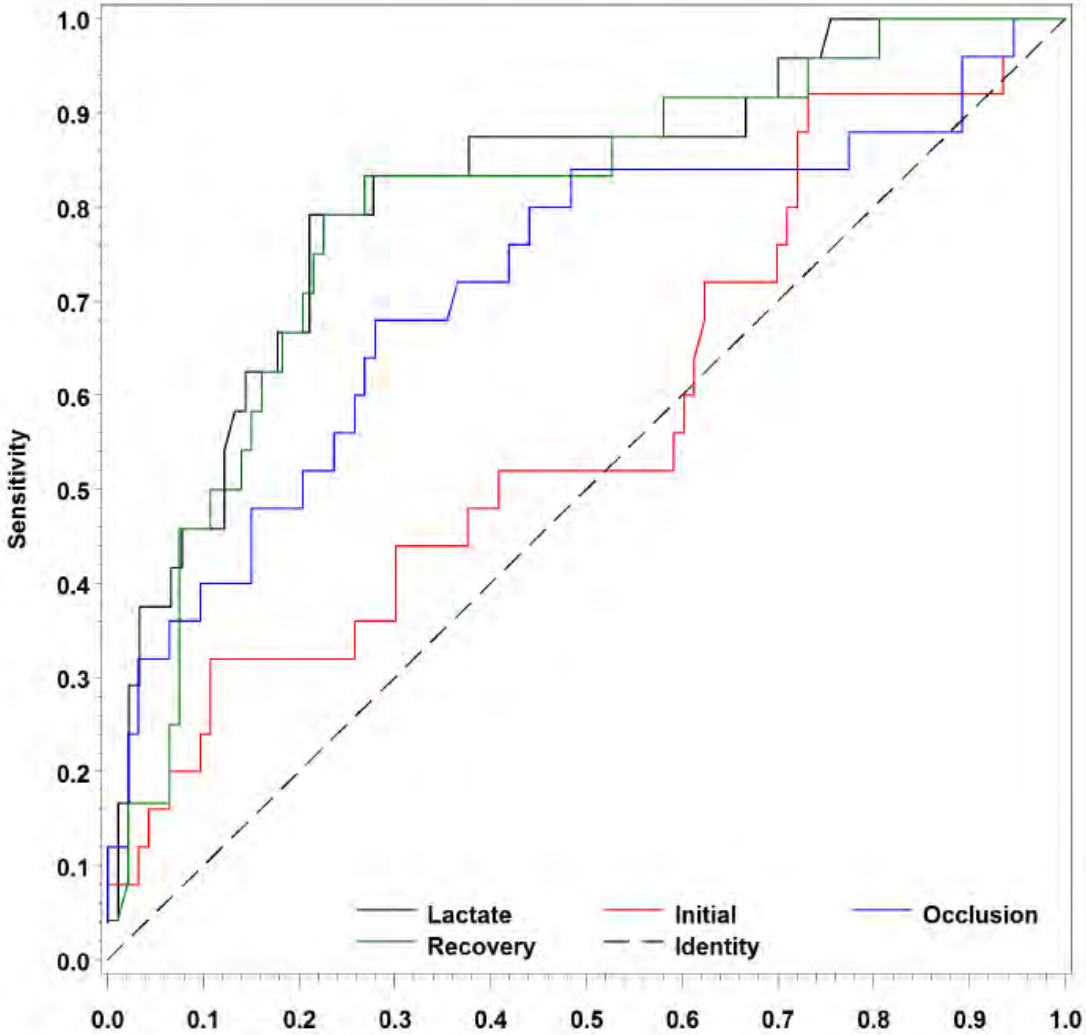


Creteur et al
ICM 2007

Alterations of NIRS vasoreactivity test in patients with sepsis

- Girardis et al ICM 2003
- De Blasi et al ICM 2005
- Pareznik et al ICM 2006
- Podbregar et al Crit Care 2007
- Doerschung et al JAP 2007
- Creteur et al ICM 2007
- Skarda et al Shock 2007
- Nanas et al Aenesth Intens Care 2009
- Payen et al Crit Care 2009
- Donati et al Crit Care 2009
- Mesquida et al ICM 2009
- Mozina et al Crit Catre 2010
- Georger et al ICM 2010
- Shapiro et al Crit Care 2011
- Soga T et al Emerg Med J 2013


n = 52 septic patients
Nonsurvivors (24/52)
Survivors (28/52)
Creteur et al
ICM
33:1639;2007
Slope (%/sec)
0
1
2
3
4
5
6
7
8
*
Baseline
24hrs
48 hrs
*analysis of variance: p < 0.01

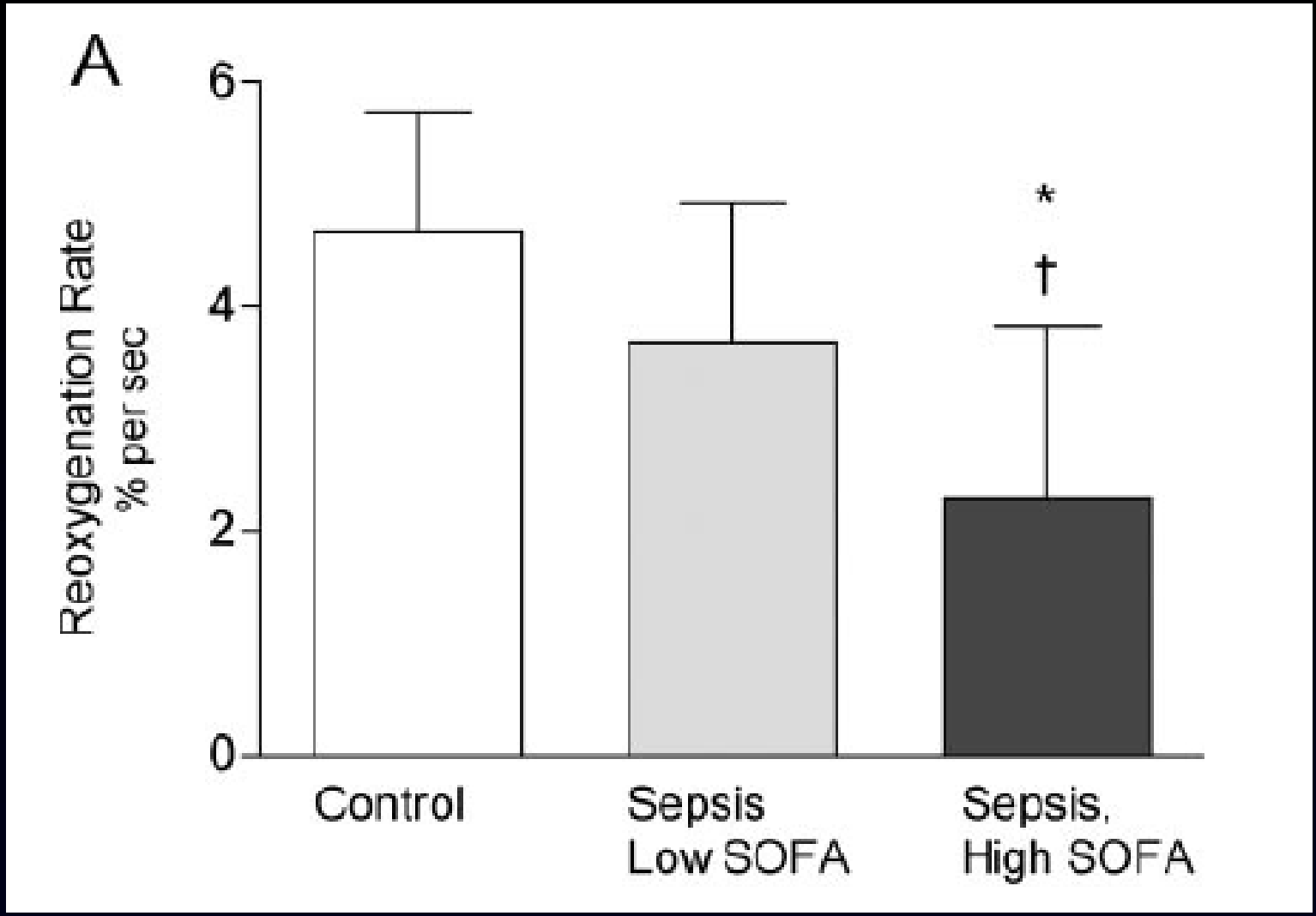


Shapiro et al
Crit Care 15 R223; 2011

168 pts at emergency dpt

Parameter	Died (*n* = 25)	Survived (*n* = 143)	*P* value*	AUC (95% CI)
Serum lactate, mmol/L	4.7 ± 2.7 (4.2) (*n* − 24)	1.9 ± 1.4 (1.5) (*n* − 128)	< 0.001	0.85 (0.76 to 0.93)
Systolic blood pressure, mmHg	105 ± 30 (102)	122 ± 30 (123)	0.004	0.68 (0.56 to 0.80)
Mean age, years	69 ± 14 (72)	62 ± 18 (67)	0.100	0.60 (0.49 to 0.72)
StO_2				
Initial (%)	76 ± 11 (79)	79 ± 7 (80)	0.341	0.56 (0.43 to 0.69)
Occlusion (%/minute)	8.8 ± 5.1 (8.2)	12.0 ± 4.7 (11.9)	0.002	0.70 (0.57 to 0.83)
Recovery (%/second)	1.7 ± 1.5 (1.3)	3.7 ± 1.7 (3.8)	< 0.001	0.81 (0.71 to 0.91)

Doerschug et al
AJP 293:1065;2007

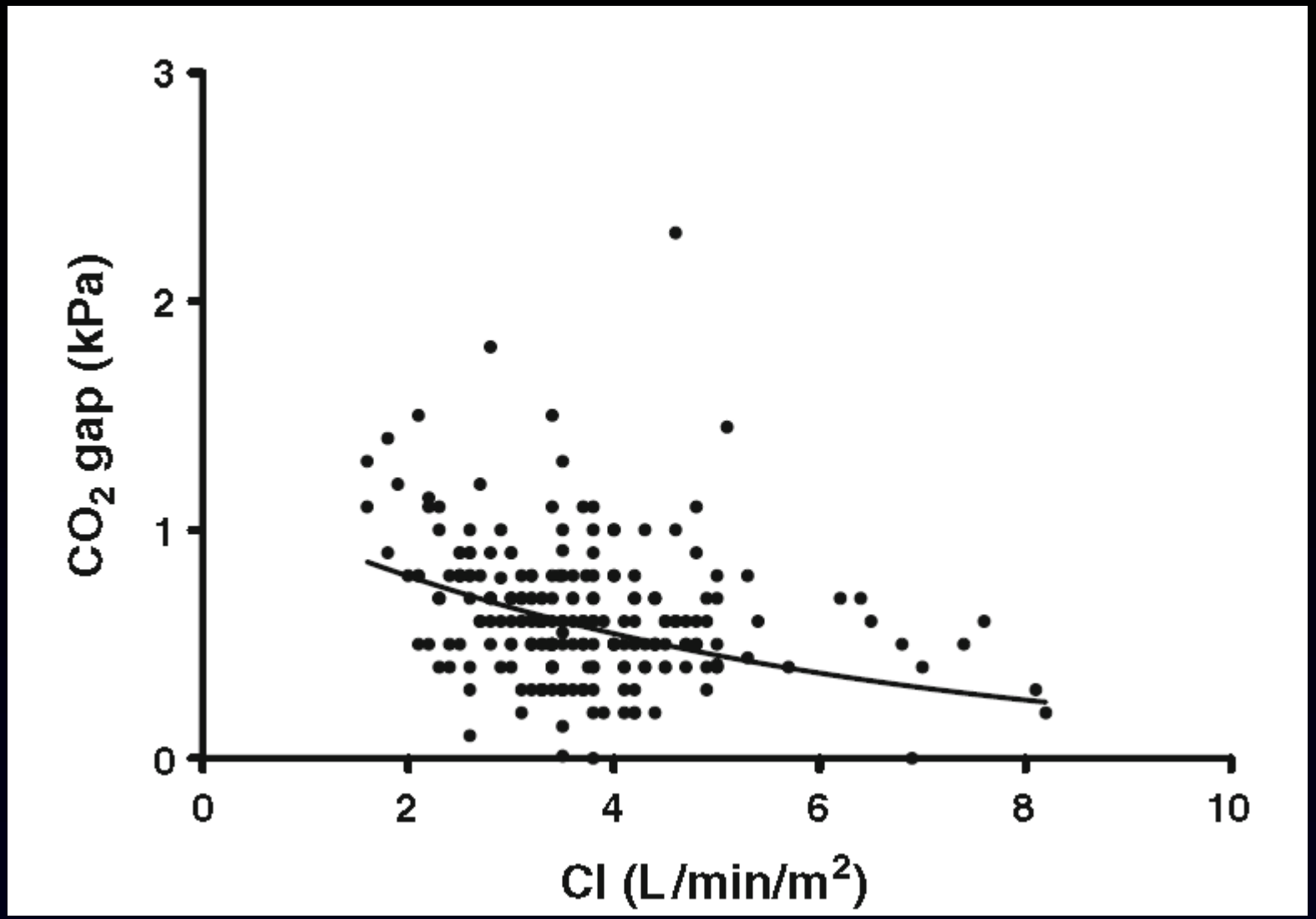


Severe sepsis 24 / volunteers 15

Tissue PCO_2
Veno-arterial difference in PCO_2

Veno-arterial PCO2 gradient

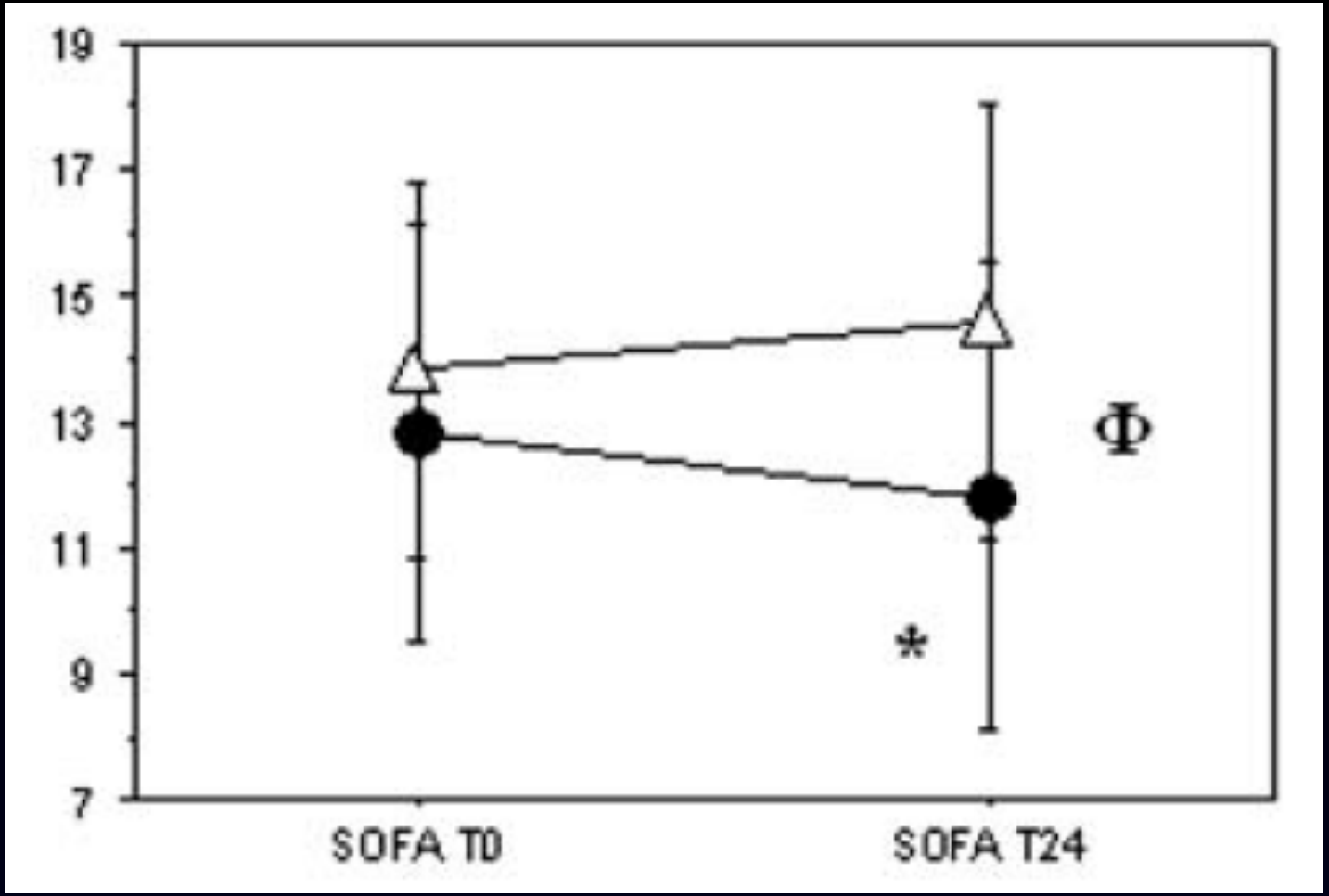
Van Beest et al
ICM 2013



Septic shock
(n=53)

Veno-arterial PCO2 gradient

Vallee F et al
ICM 34:2218;2008



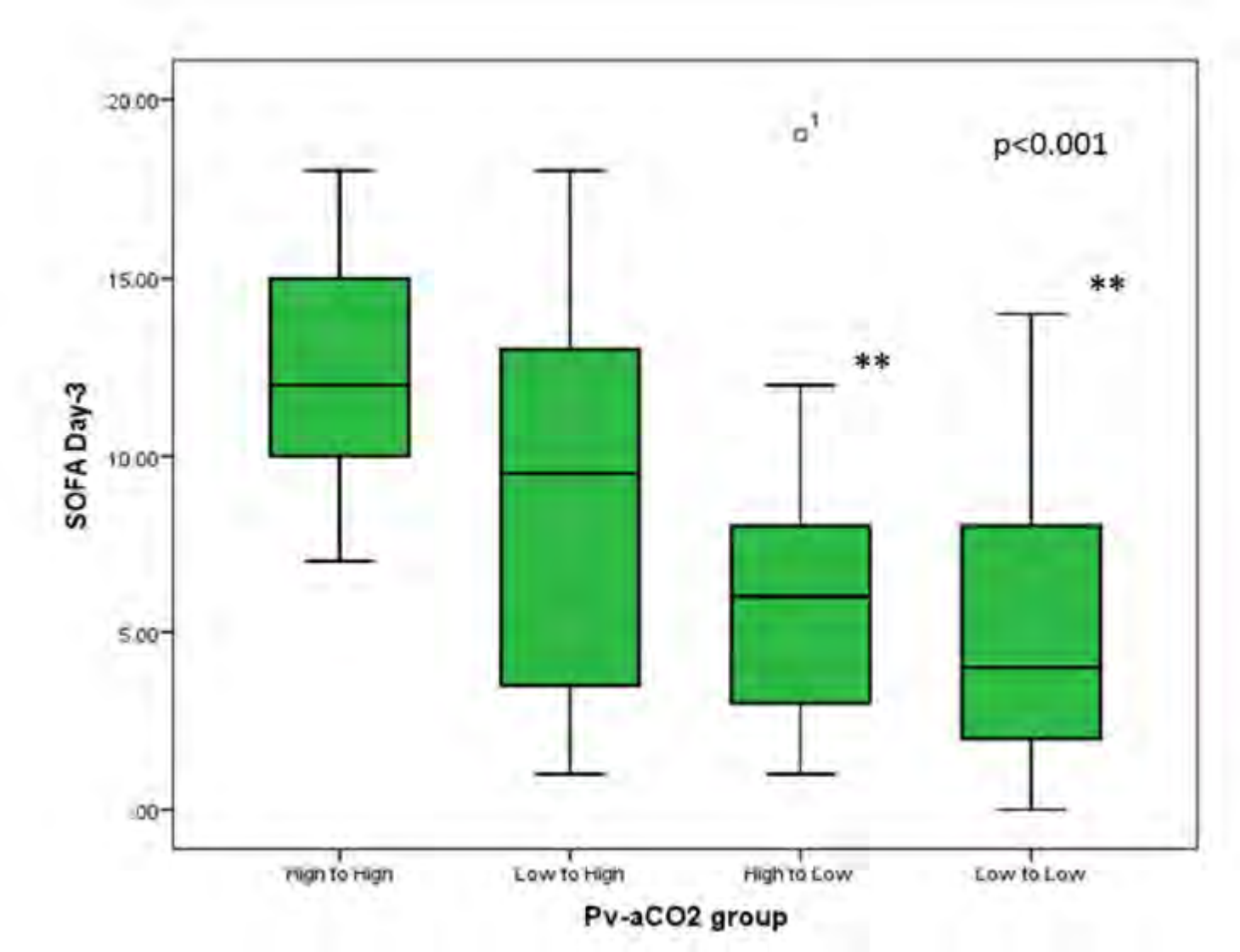
Non Survivors
Survivors

PvaCO2 <6 mmHg
PvaCO2 >6mmHg

Septic shock (n=46)

Evolution of veno-arterial PCO2 gradient

Ospina-Tascon G et al
Crit Care 2013

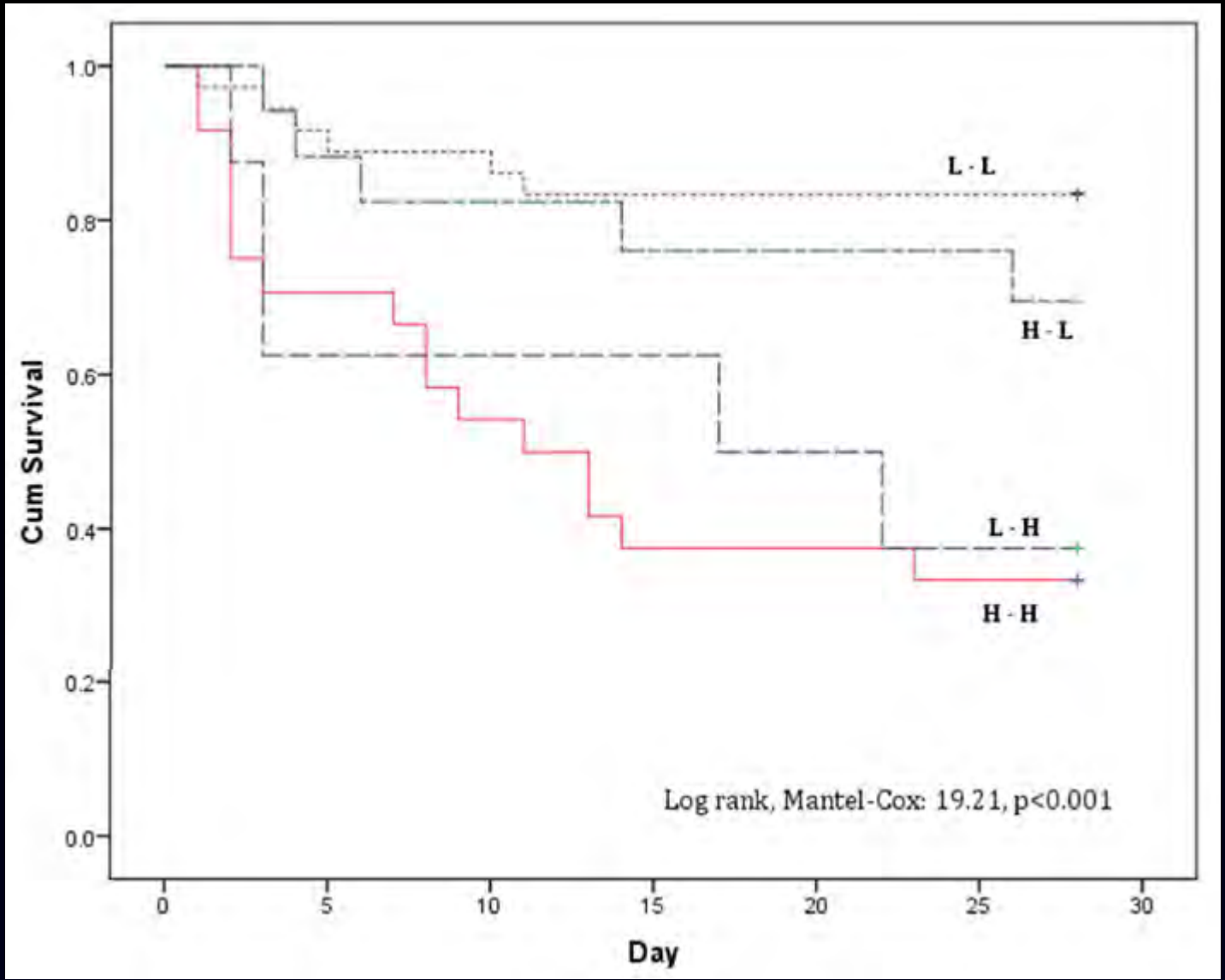


PvaCO2 <6 mmHg
PvaCO2 >6mmHg

Septic shock
(n=85)

Evolution of veno-arterial PCO2 gradient

Ospina-Tascon G et al
Crit Care 2013

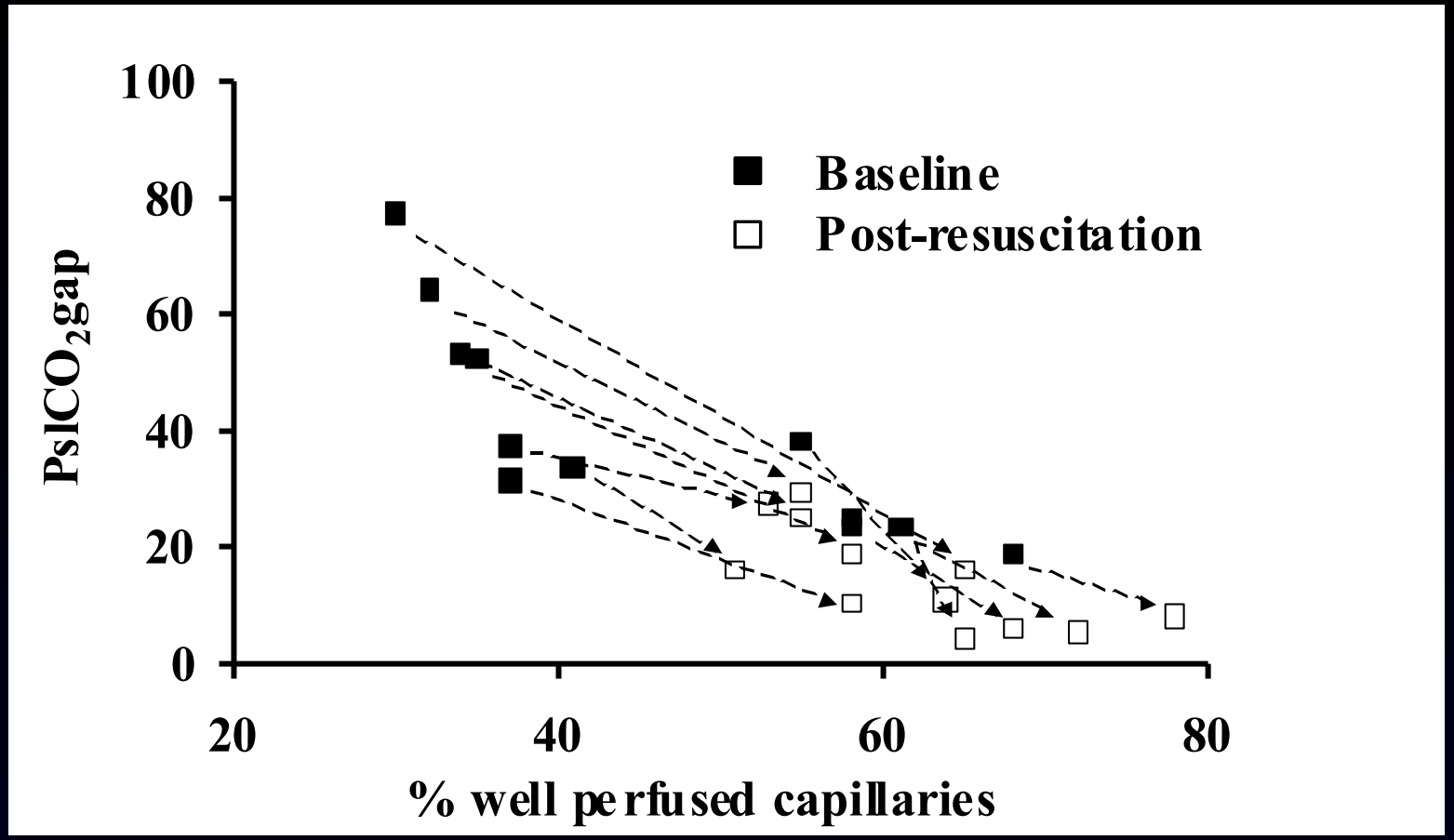


PvaCO2 <6 mmHg
PvaCO2 >6mmHg

Septic shock
(n=85)

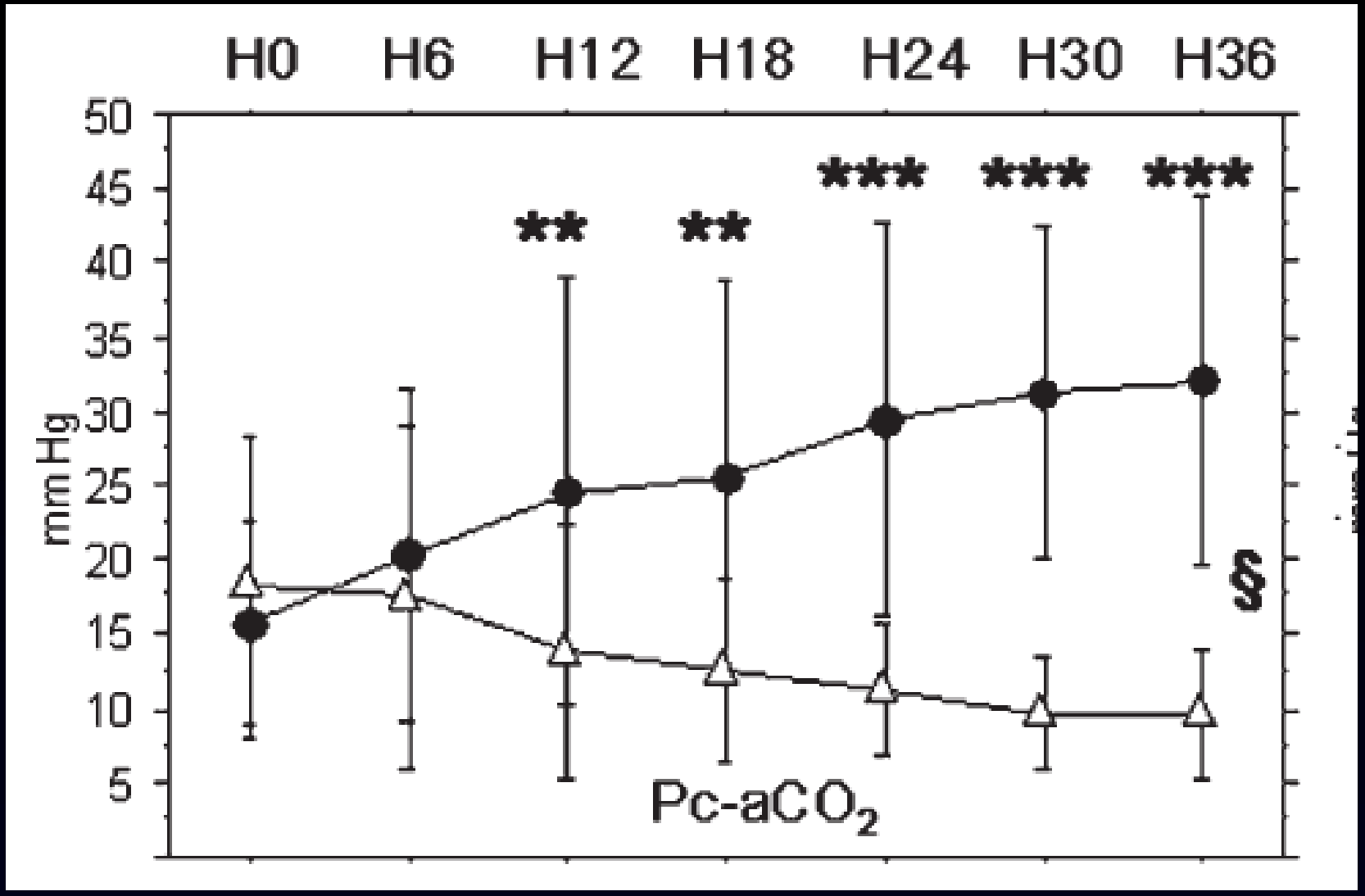
Sublingual microcirculation and sublingual PCO2

Creteur et al
ICM 32:516;2006



Ear Lobe PCO2

Vallee F et al
Chest 138:1062;2012



Septic shock
(n=46)

Quels objectifs circulatoires dans le choc septique?