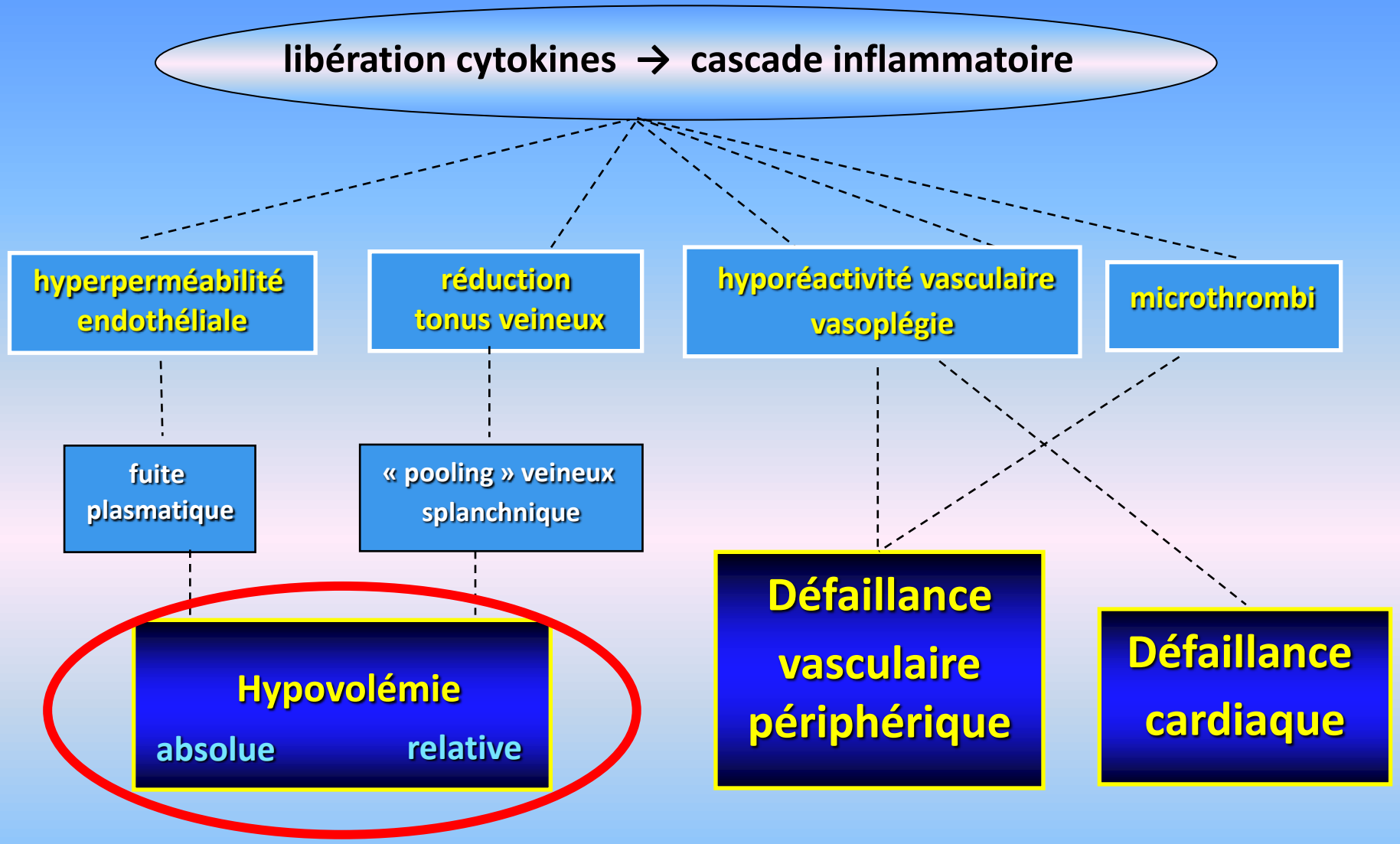

libération cytokines → cascade inflammatoire
hyperperméabilité endothéliale
réduction tonus veineux
hyporéactivité vasculaire vasoplégie
microthrombi
fuite plasmatique
« pooling » veineux splanchnique
Hypovolémie
absolue
relative
Défaillance vasculaire périphérique
Défaillance cardiaque

Hypovolemia and sepsis

Absolute

Increased endothelial cell permeability (« capillary leakage »)

Fluid filtration towards interstitial space

Avila et al. Surg. 1985

Dhillon et al Chest 2005

Relative

Decreased venous tone

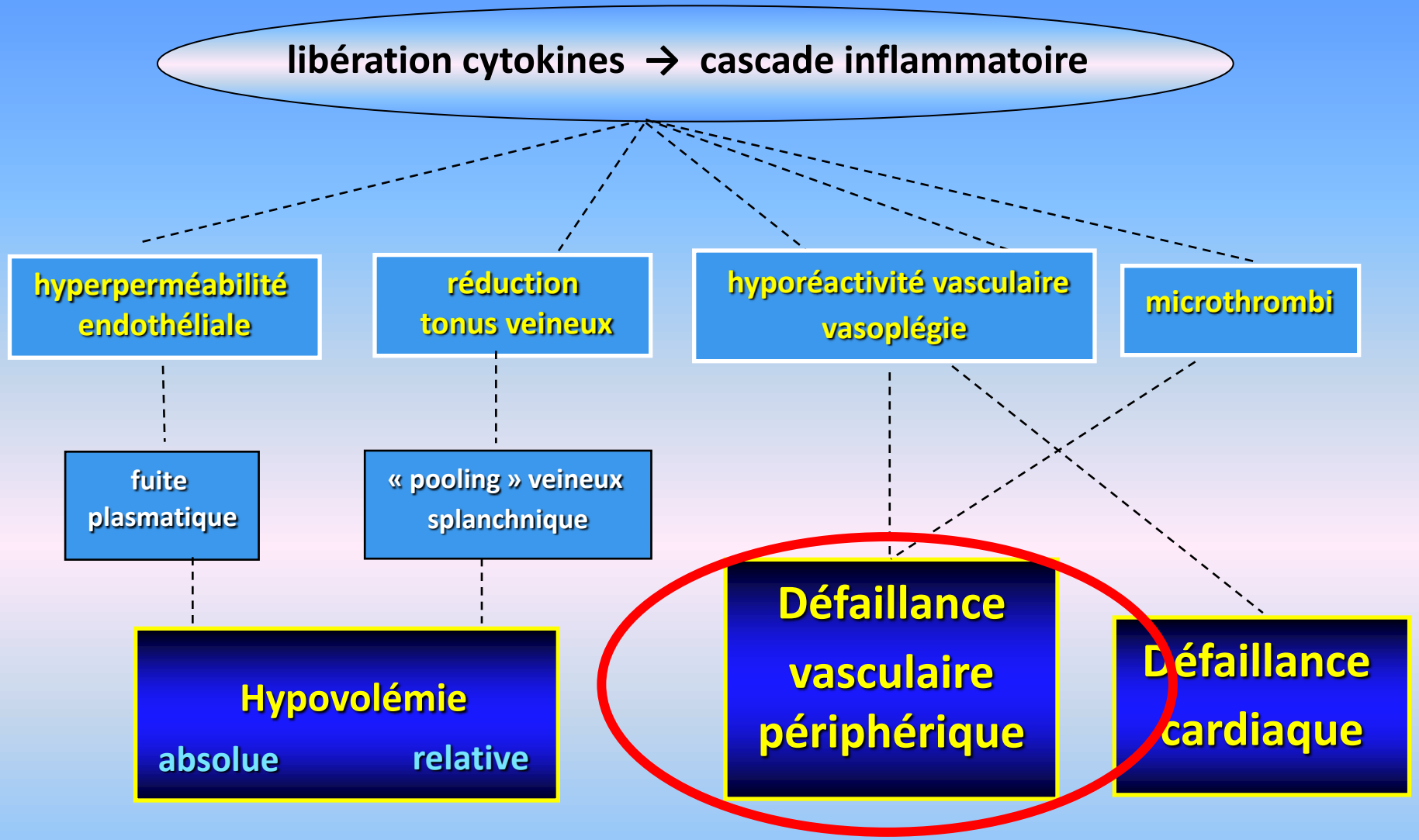
Pinsky et Matuschak J. Crit. Care 1986

Splanchnic venous pooling

Gunteroth Cir. Res. 1977

Ayuse et al. Am. J. Physiol. 1995

Because of frequent profound hypovolemia, the hemodynamic profile, before resuscitation, is hypodynamic rather than hyperdynamic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Défaillance cardiaque

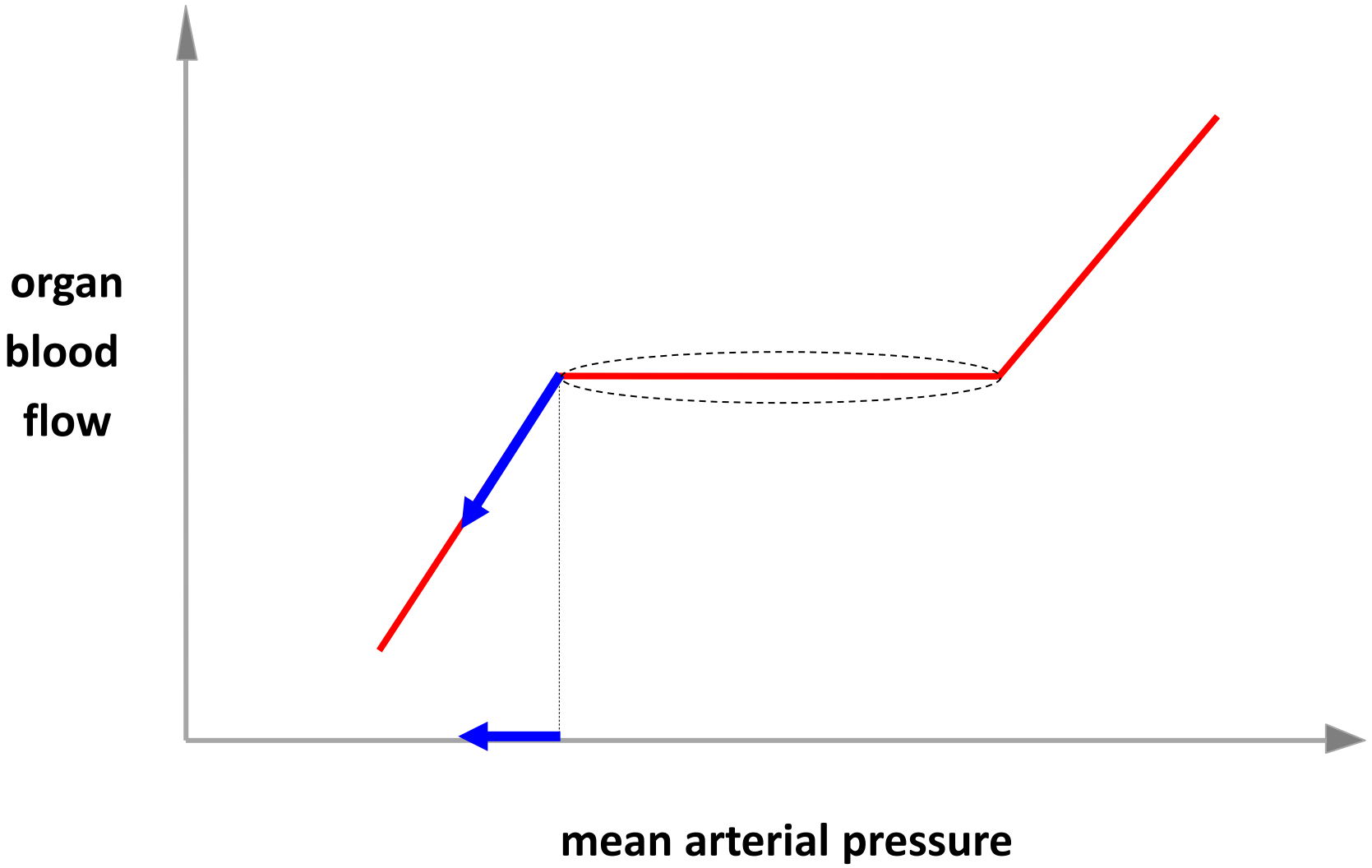
Défaillance vasculaire périphérique

Dépression du tonus vasculaire

Profound hypotension

Tissue hypoxia

Autoregulation of organ blood flow



Défaillance vasculaire périphérique

Dépression du tonus vasculaire

Distribution anormale du débit sanguin inter et intra-organes

Profound hypotension

Tissue hypoperfusion

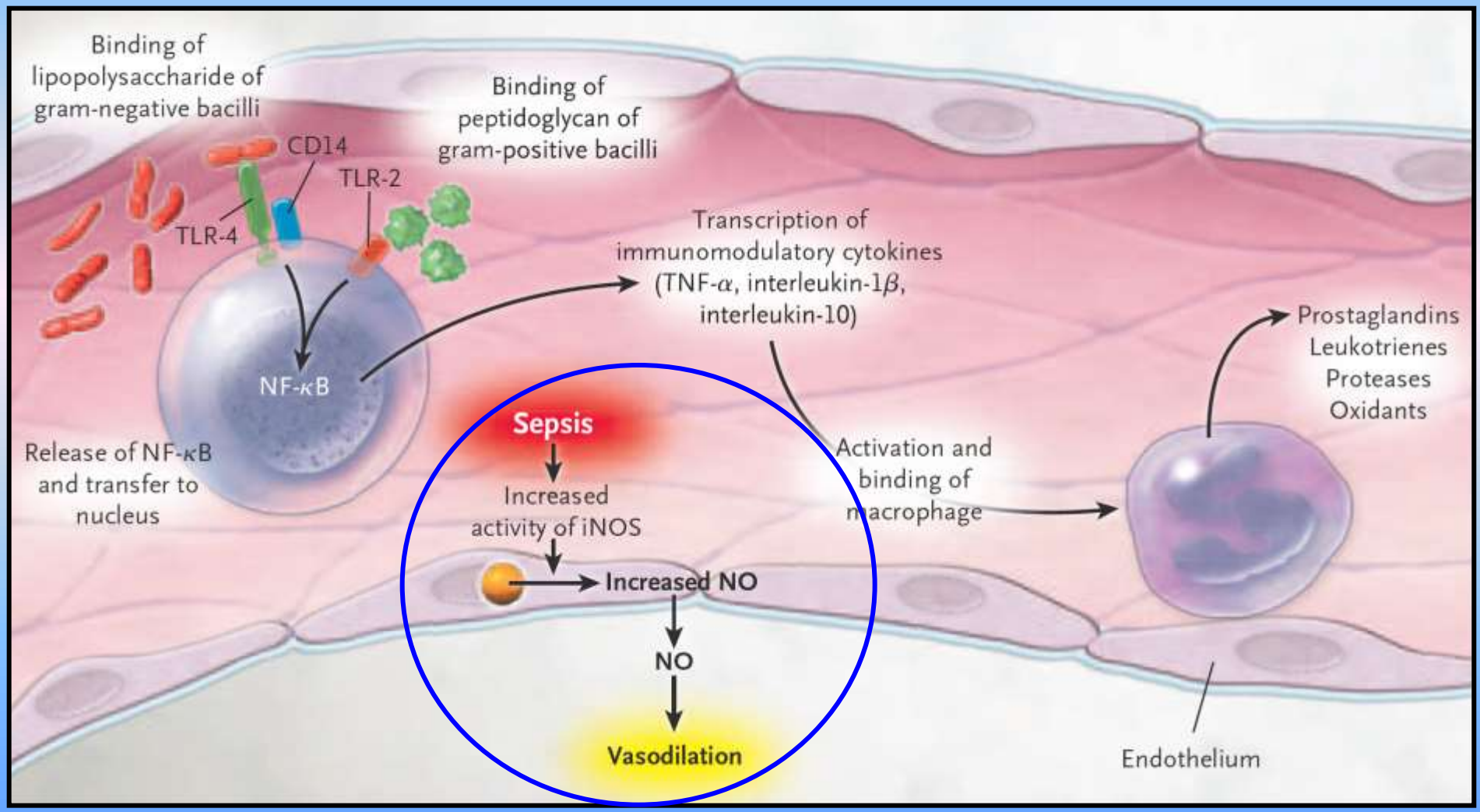
Tissue hypoxia

The NEW ENGLAND JOURNAL of MEDICINE

Management of Sepsis

James A. Russell, M.D.

N Engl J Med 2006;355:1699-71



Microvascular Blood Flow Is Altered in Patients with Sepsis

Daniel De Backer, Jacques Creteur, Jean-Charles Preiser, Marc-Jacques Dubois, and Jean-Louis Vincent

Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium

Am J Respir Crit Care Med 2002; 166: 98-104

After initial resuscitation	Patients with Sepsis
Age, yr	61 (50–72)*
Temperature, ° C	37.0 (36.4–38.0)
Heart rate, bpm	105 (91–110)
Mean arterial pressure, mm Hg	71 (63–79)
Cardiac index, L/min · m^2	3.63 (2.62–4.69)
Sa_{O_2}, %	97 (94–98)
$S\bar{v}_{O_2}$, %	68 (62–73)
Hemoglobin, g/dl	8.3 (7.4–9.9)

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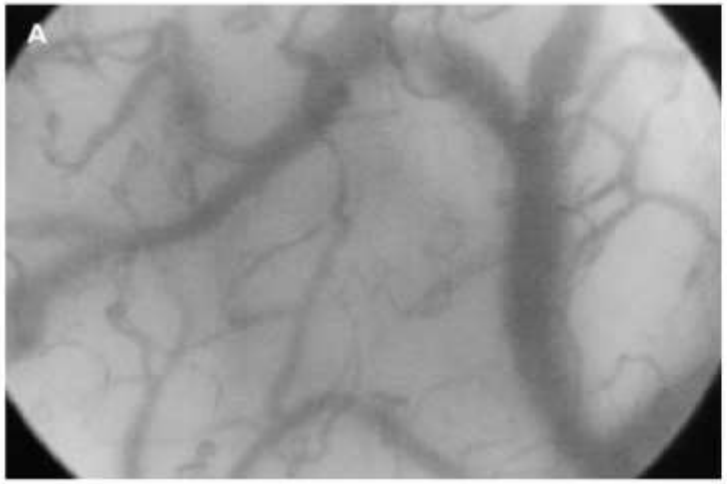
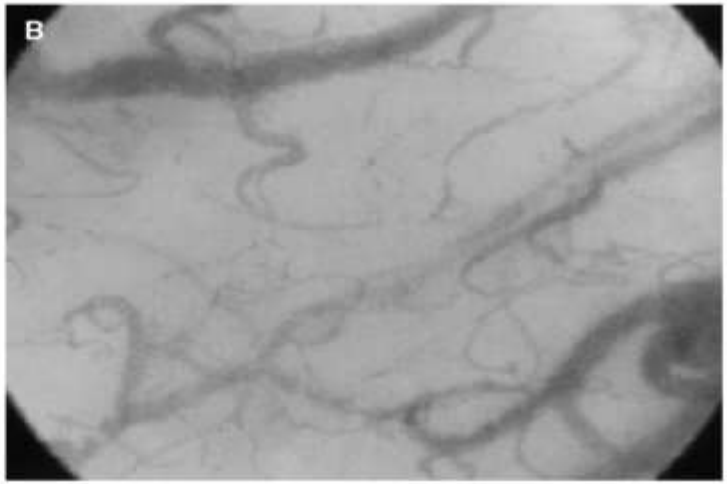


Volunteer



Septic patient

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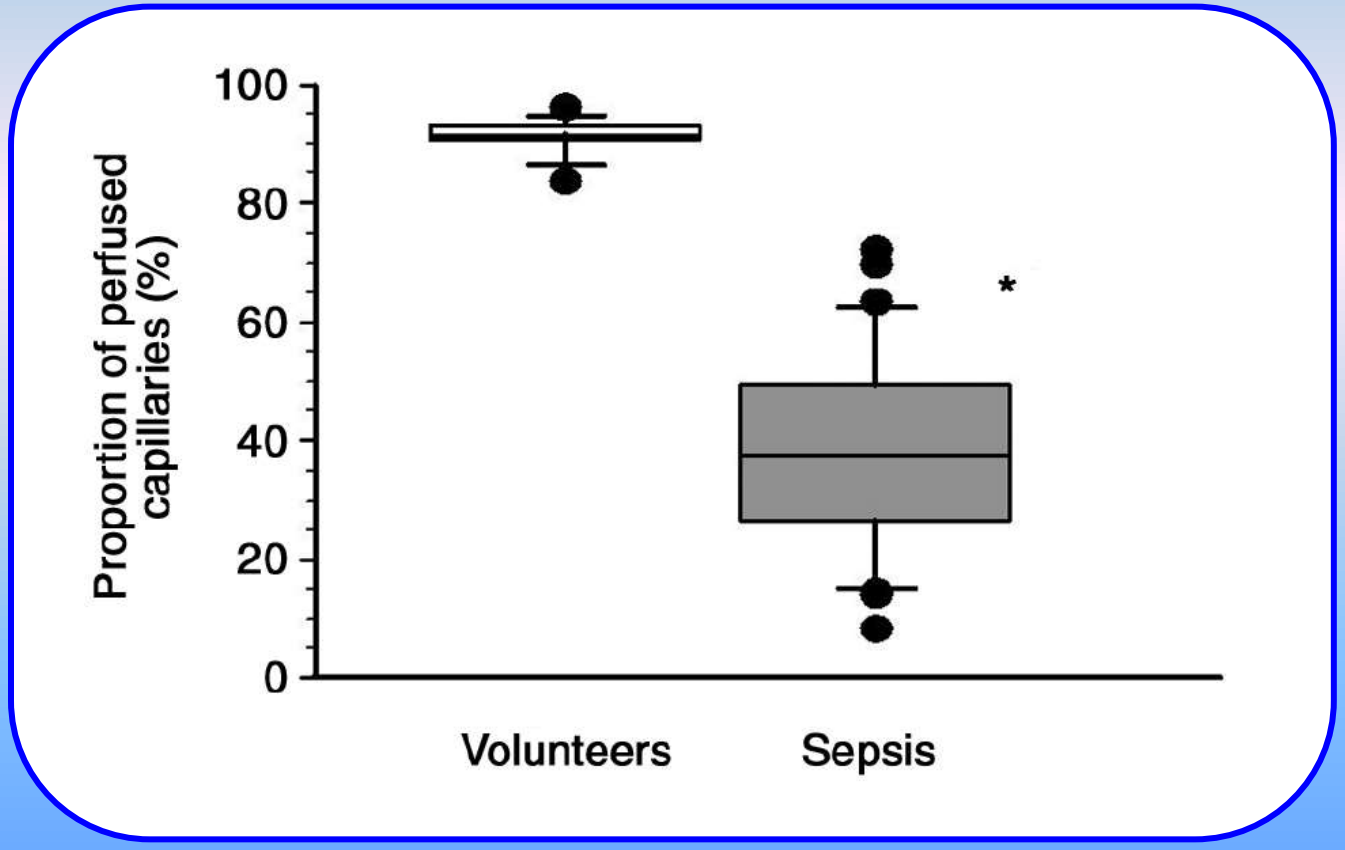

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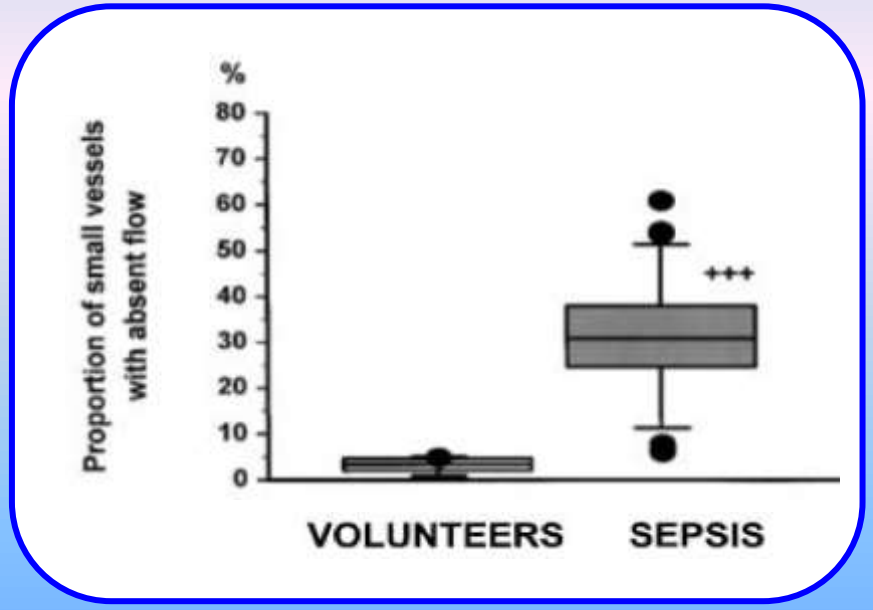

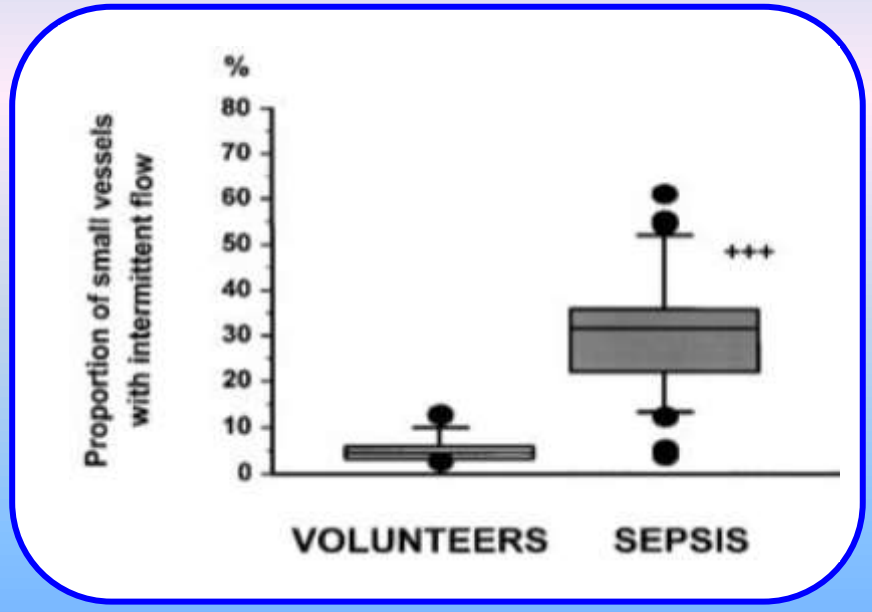

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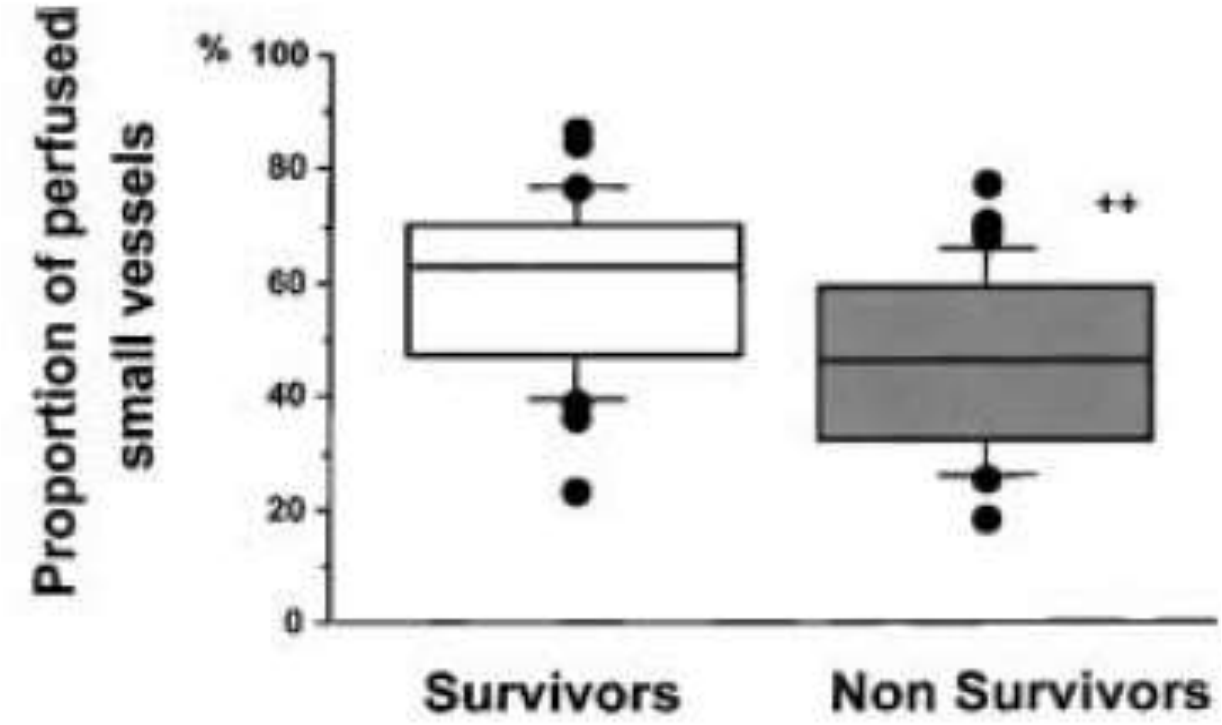
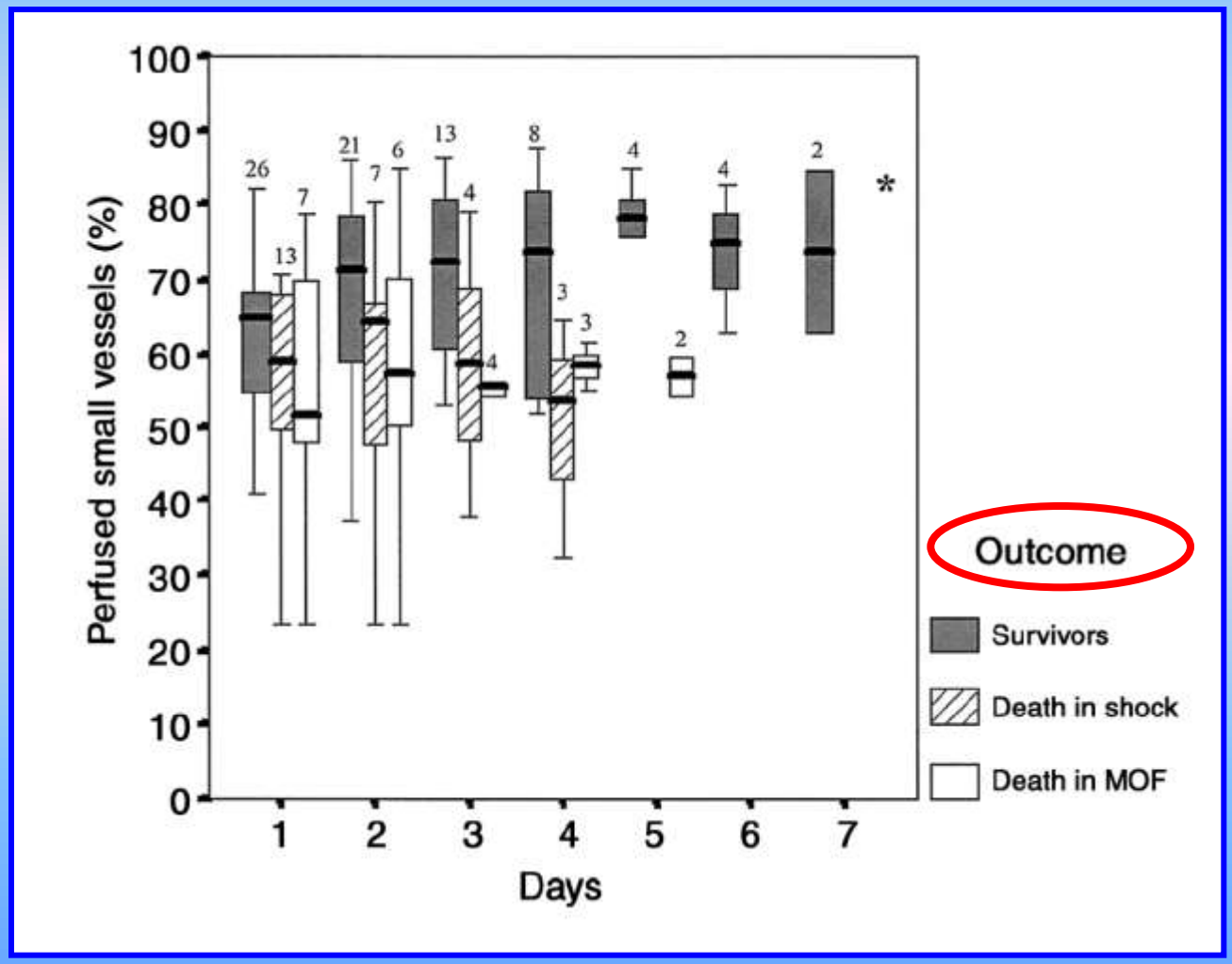
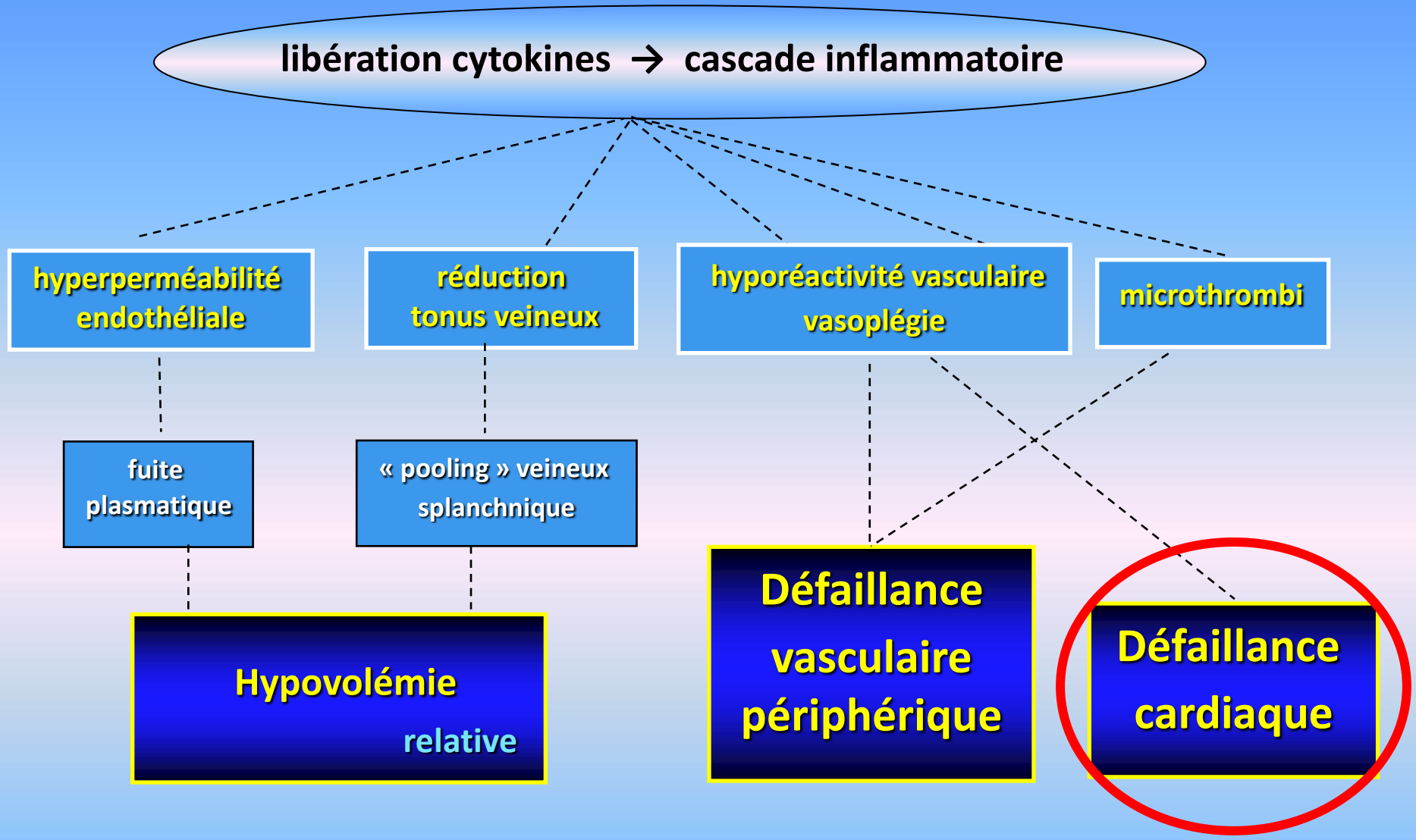


Microvascular dysfunction as a cause of organ dysfunction in severe sepsis

Jean-Louis Vincent and Daniel De Backer

Critical Care 2005, **9(suppl 4):**S9-S12 (DOI 10.1186/cc3748)

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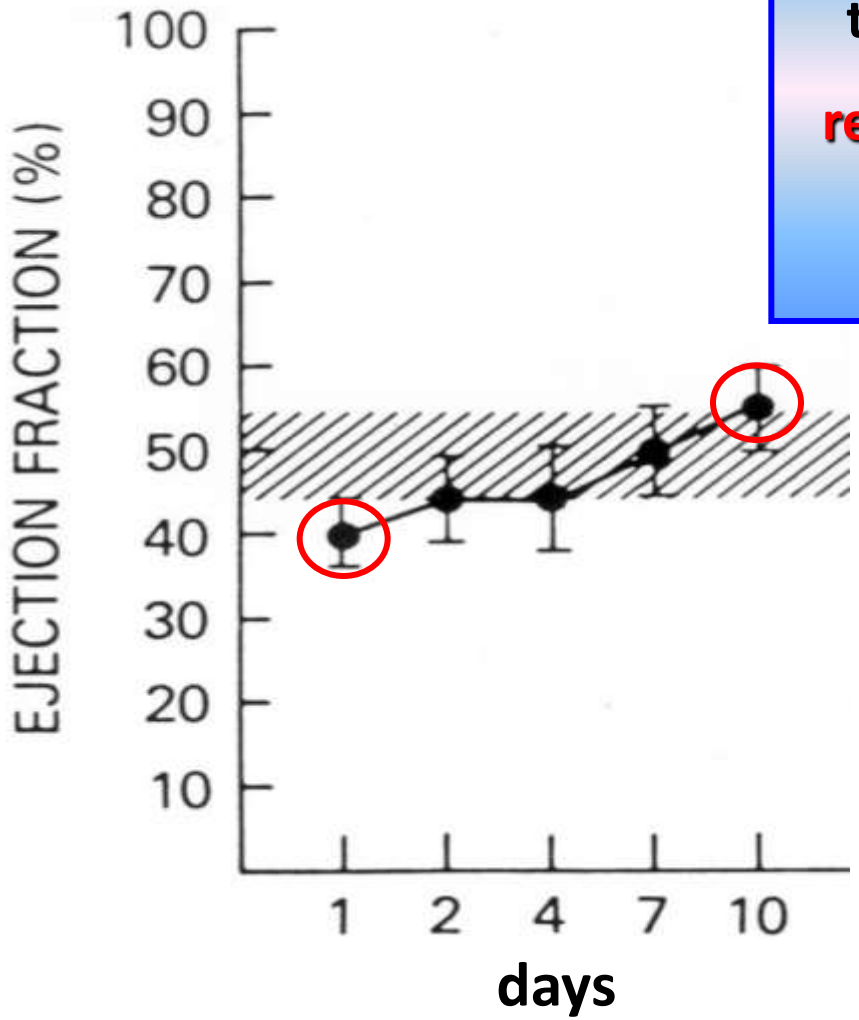
septic shock patients



Early depression of LVEF

that persisted for up to 4 days and

returned to normal within 7-10 days

in survivors

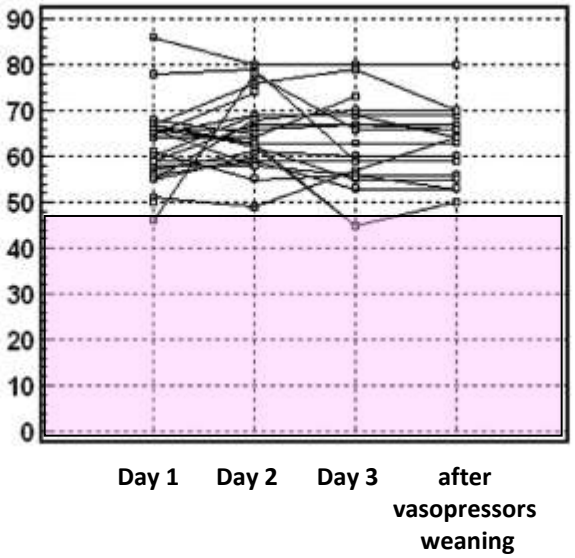
Parker et al Ann Intern Med 1984

Actual incidence of global left ventricular hypokinesia in adult septic shock

Antoine Vieillard-Baron, MD; Vincent Caille, MD; Cyril Charron, MD; Guillaume Belliard, MD; Bernard Page, MD; François Jardin, MD

Crit Care Med 2008; 36:1701–1706

LV EF %



40% of pts

40% of pts

20% of pts

Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

Intrinsic cellular mechanisms

Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

Generally, **coronary blood flow is not decreased** during sepsis

… but in patients with **prior coronary artery disease**,

avoid profound **fall in diastolic blood pressure**

(driving pressure for left coronary blood flow)

Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

- *Coronary blood flow*
- *Circulating factors*

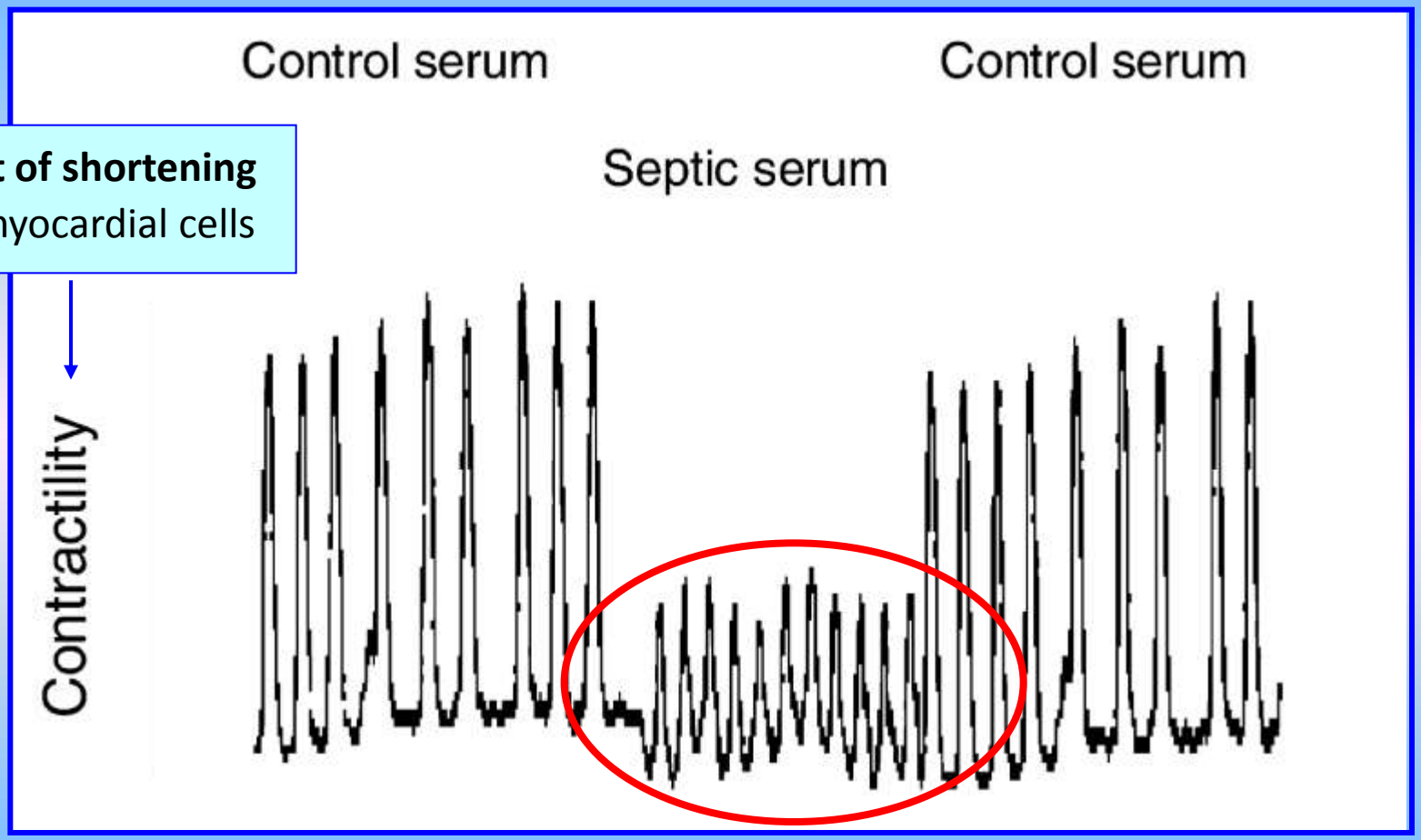
A Circulating Myocardial Depressant Substance in Humans with Septic Shock

Septic Shock Patients with a Reduced Ejection Fraction Have a Circulating Factor That Depresses In Vitro Myocardial Cell Performance

Joseph E. Parrillo, Cynthia Burch, James H. Shelhamer, Margaret M. Parker, Charles Natanson, and William Schuette

J Clin Invest 1985; 1539-1553

extent of shortening of rat myocardial cells



Serum from septic shock patients contained substances that were able to depress cardiac contractility

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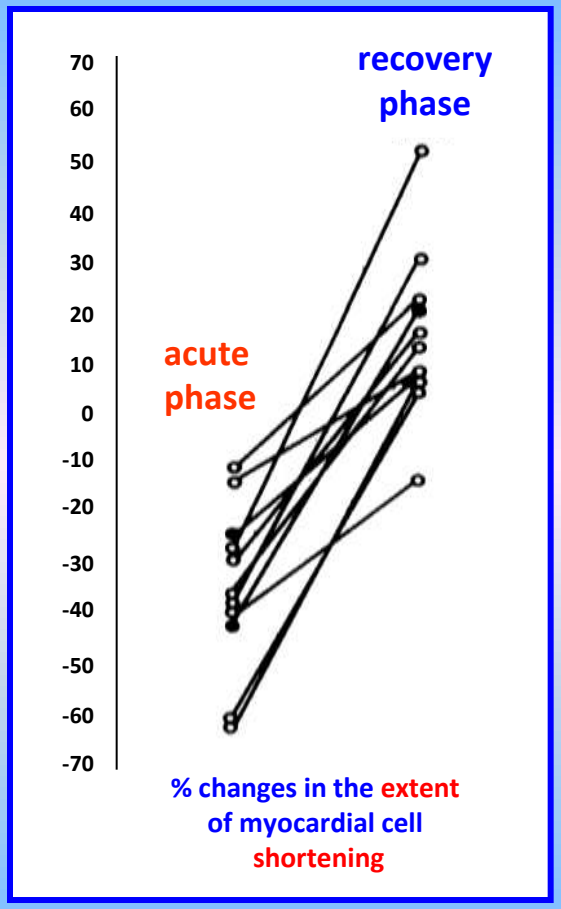


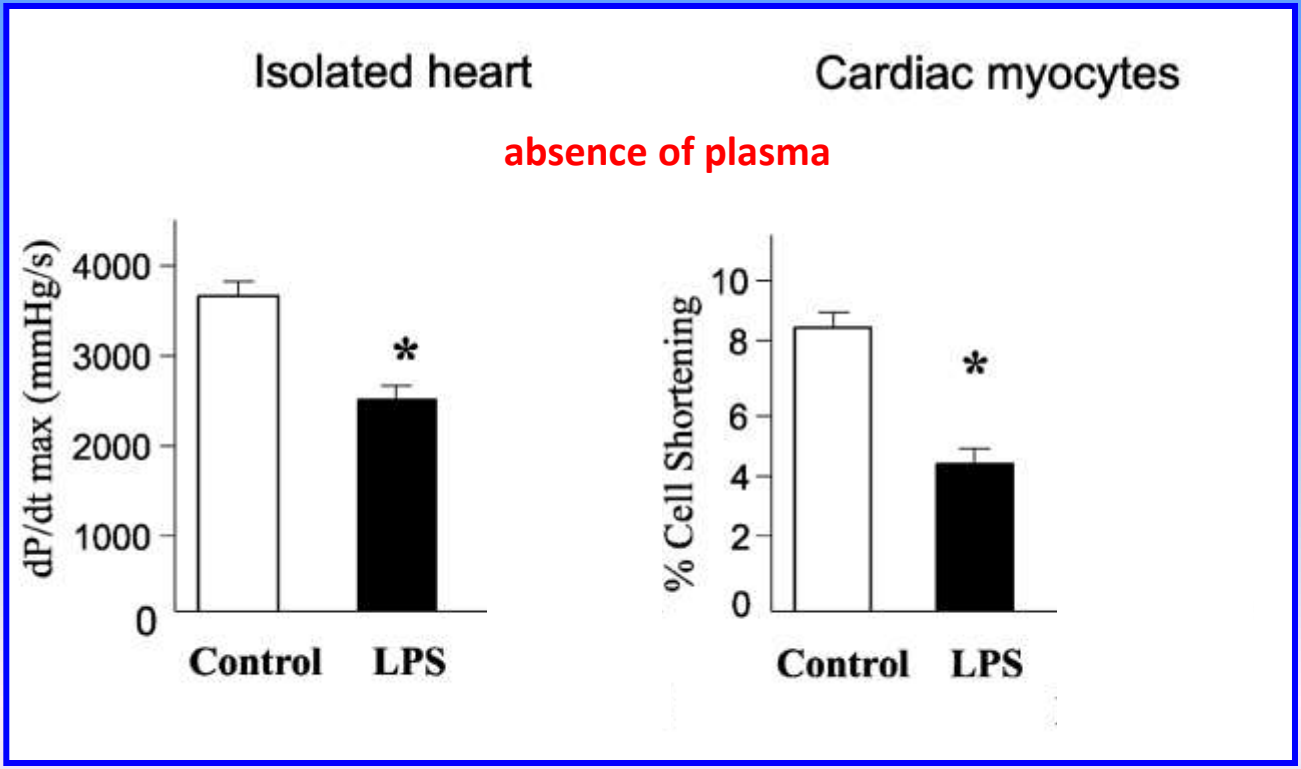
Serum from septic shock patients contained substances that were able to depress cardiac contractility

Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

- *Coronary blood flow*
- ***Circulating factors***

  TNF-α, IL_1, others?



Cardiac contractility can be decreased during sepsis in the absence of plasma

This argues against a major role of a "circulating myocardial depressant factor" but rather supports an "intrinsic" alteration in the myocardium as the predominant mechanism of septic cardiac dysfunction.

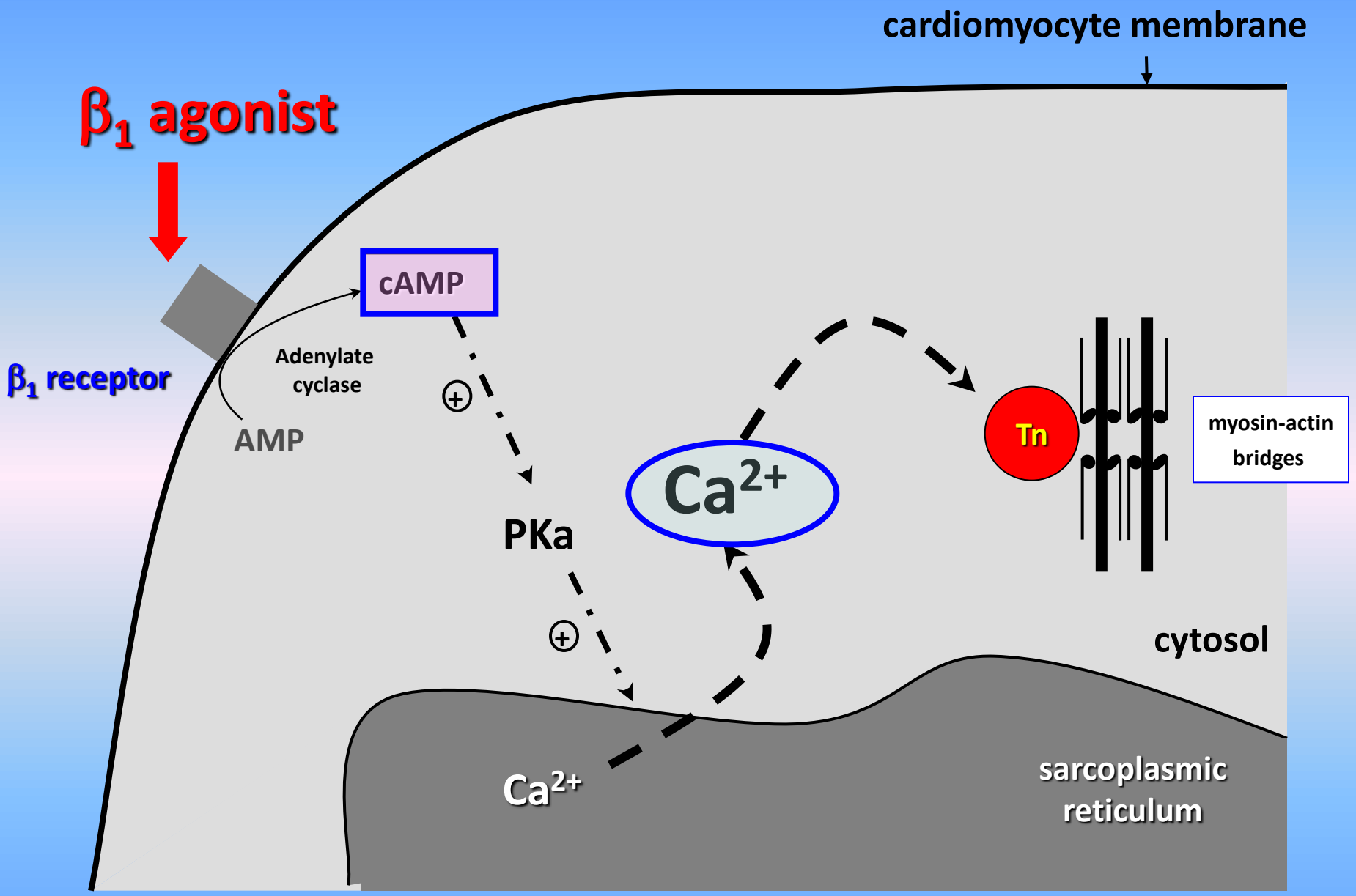
Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

- *Coronary blood flow*
- *Circulating factors*

Intrinsic cellular mechanisms

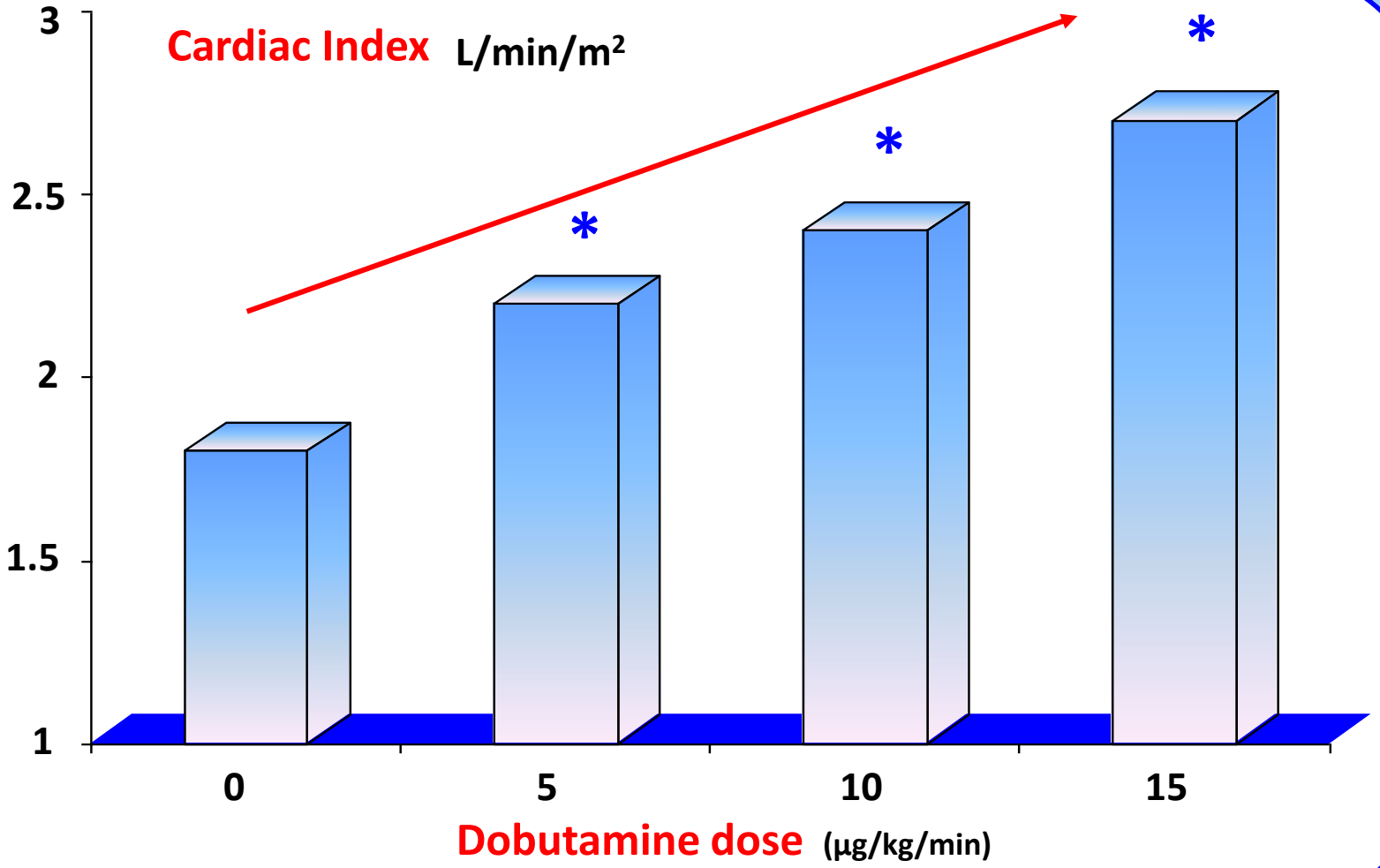
- *β-adrenergic receptors*


cardiomyocyte membrane
β1 agonist
β1 receptor
cAMP
Adenylate cyclase
AMP
PKa
Ca2+
Tn
myosin-actin bridges
cytosol
Ca2+
sarcoplasmic reticulum

Cardiac Index vs Oxygen-Derived Parameters for Rational Use of Dobutamine in Patients With Congestive Heart Failure

Jean-Louis Teboul, M.D.; Laïd Graini, M.D.; Rafik Boujdaria, M.D.; Christine Berton, M.D.; and Christian Richard, M.D.

Chest 1993; 103:81-85

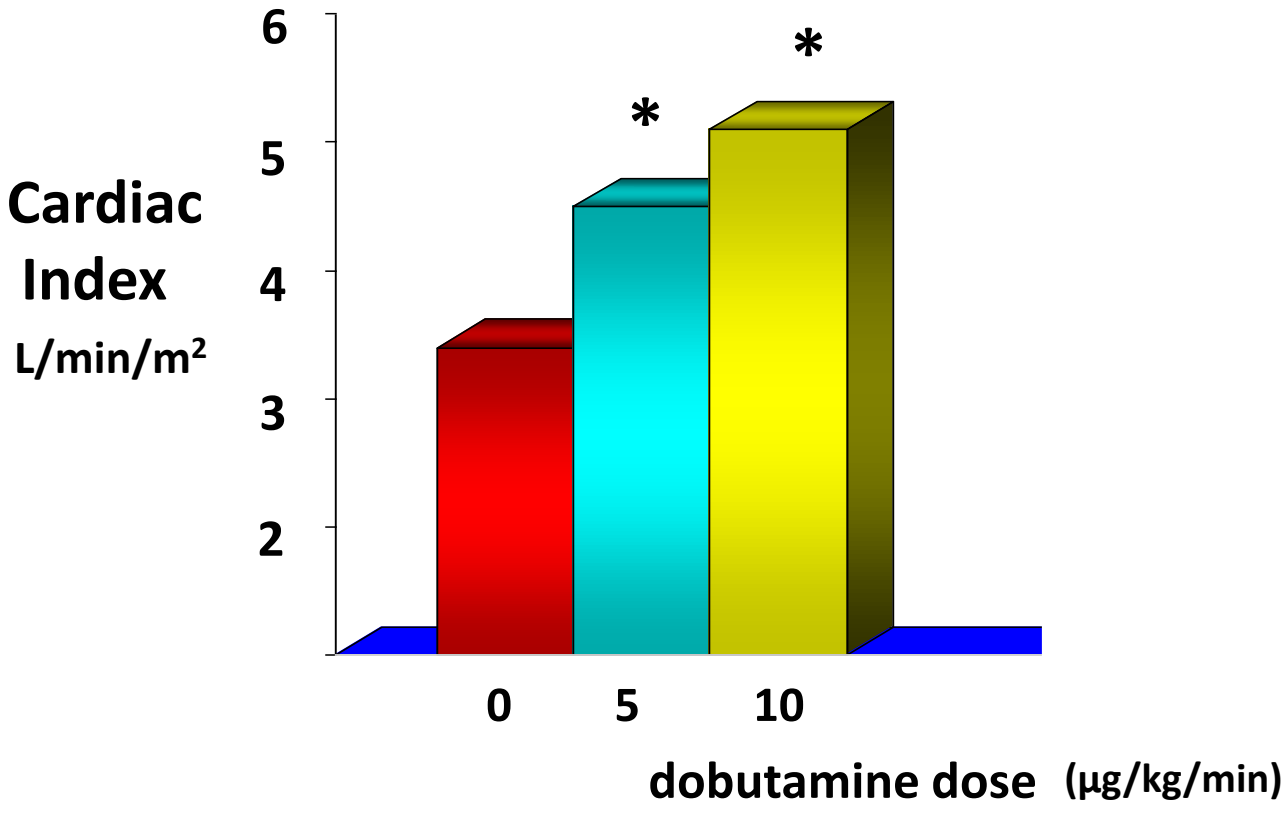


Impaired β-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines

HENRY J. SILVERMAN, MD; RUBEN PENARANDA, MD; JONATHAN B. ORENS, MD; NORMAN H. LEE, PhD

Crit Care Med 1993; 21:31-39

non severe sepsis



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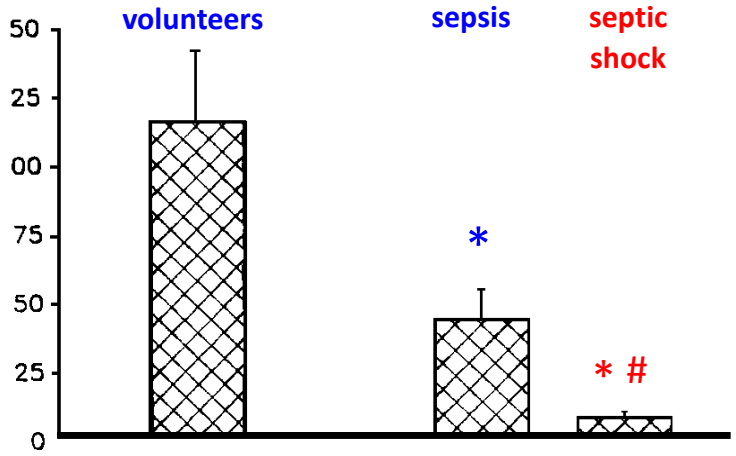
cAMP response to isoproterenol

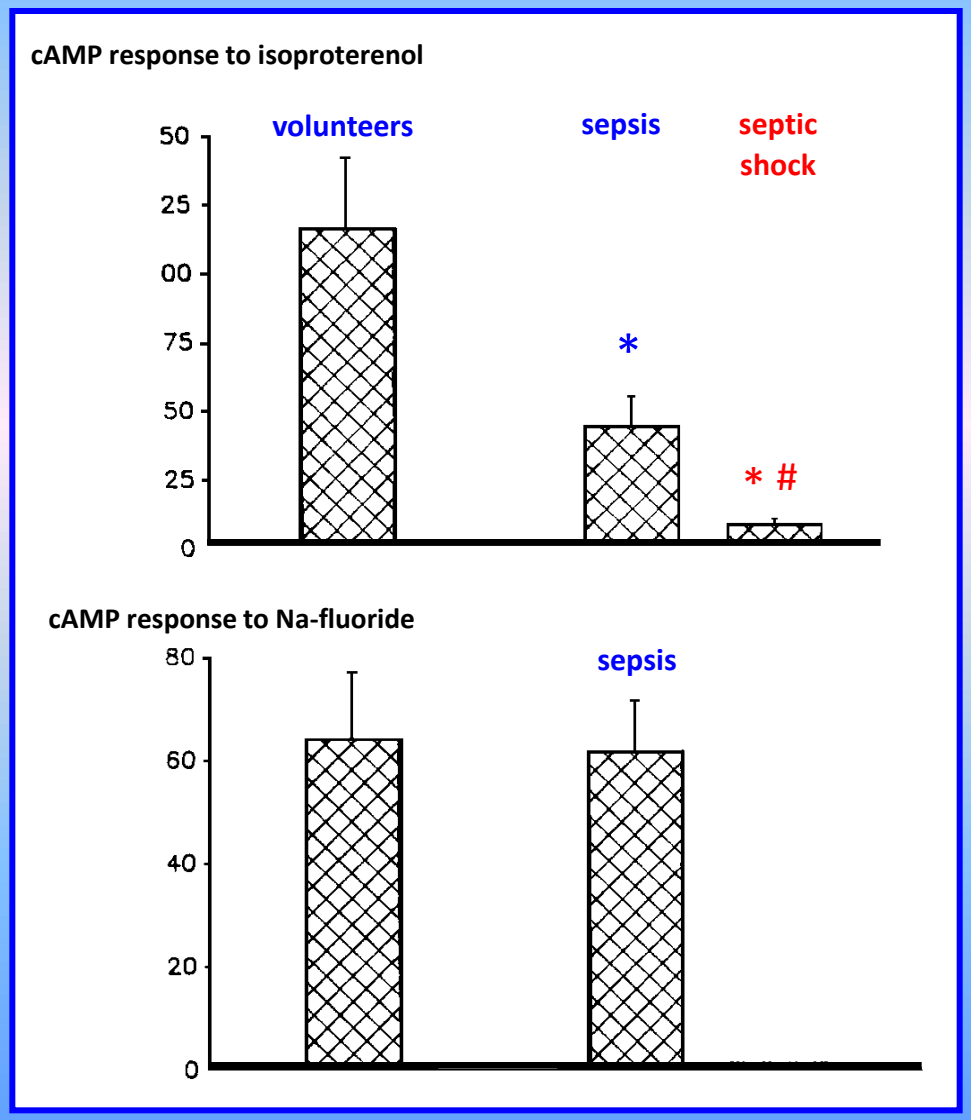


impairment of

β-adrenergic receptor responsiveness

sepsis,
septic shock

Decreased efficacy of dobutamine in patients with septic shock



impairment of

β-adrenergic receptor responsiveness

sepsis,
septic shock

impairment of

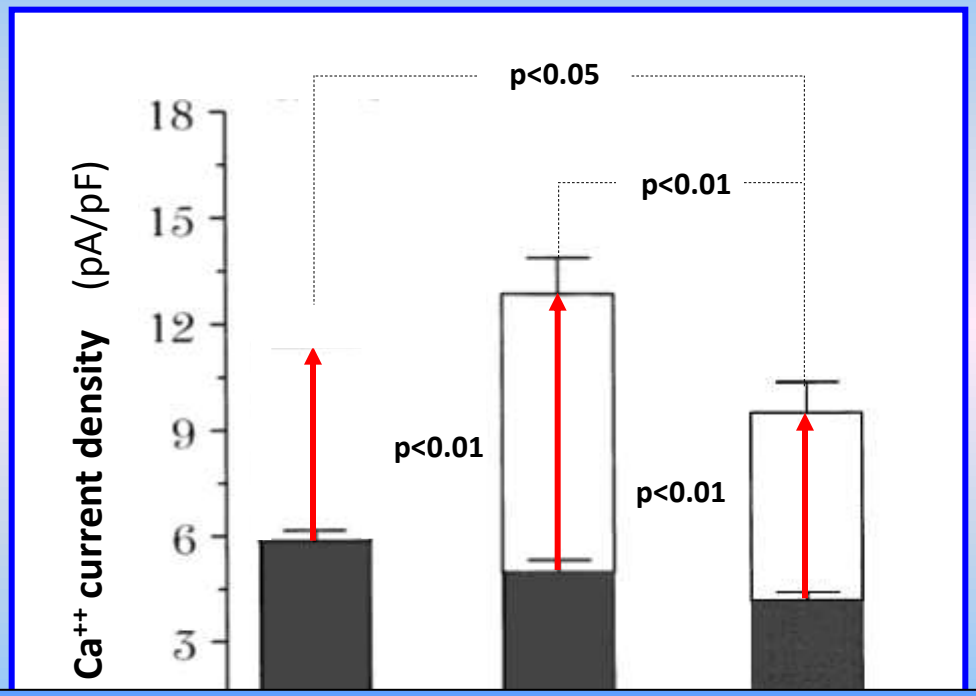
post β-adrenergic receptor signal transduction

septic shock

Sequential Changes in Autonomic Regulation of Cardiac Myocytes after *In Vivo* Endotoxin Injection in Rat

NAJAH ABI-GERGES, BENOIT TAVERNIER, ALEXANDRE MEBAZAA, VALÉRIE FAIVRE, XAVIER PAQUERON, DIDIER PAYEN, RODOLPHE FISCHMEISTER, and PIERRE-FRANÇOIS MÉRY

AM J RESPIR CRIT CARE MED 1999;160:1196–1204



- Initial phase: **enhanced** response to isoproterenol
- later phase: **decreased** response to isoproterenol

Sequential Changes in Autonomic Regulation of Cardiac Myocytes after *In Vivo* Endotoxin Injection in Rat

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INSERM U-446, Laboratoire de Cardiologie Cellulaire et Moléculaire, Université Paris-Sud, Faculté de Pharmacie, Châtenay-Malabry; Département d'Anesthésie-Réanimation Chirurgicale 2, Hôpital Claude Huriez, CHU-Lille, Lille; and Département d'Anesthésie-Réanimation, Hôpital Lariboisière, AP-HP, IFR Circulation-Lariboisière, Paris, France

AM J RESPIR CRIT CARE MED 1999;160:1196–1204.

β-adrenergic stimulation of calcium current **increased 12 h** after endotoxin challenge but **decreased after 36 h**.

This dual response suggests **time-dependent** changes in the **adenylcyclase** pathway

Adenylcyclase activity:

- is **increased** during the **early** phase of sepsis
- but is **decreased** during **later** phase
  - the **number** of β- adrenergic **receptors** is **reduced**
  - adenylcyclase **inhibition** is **increased**

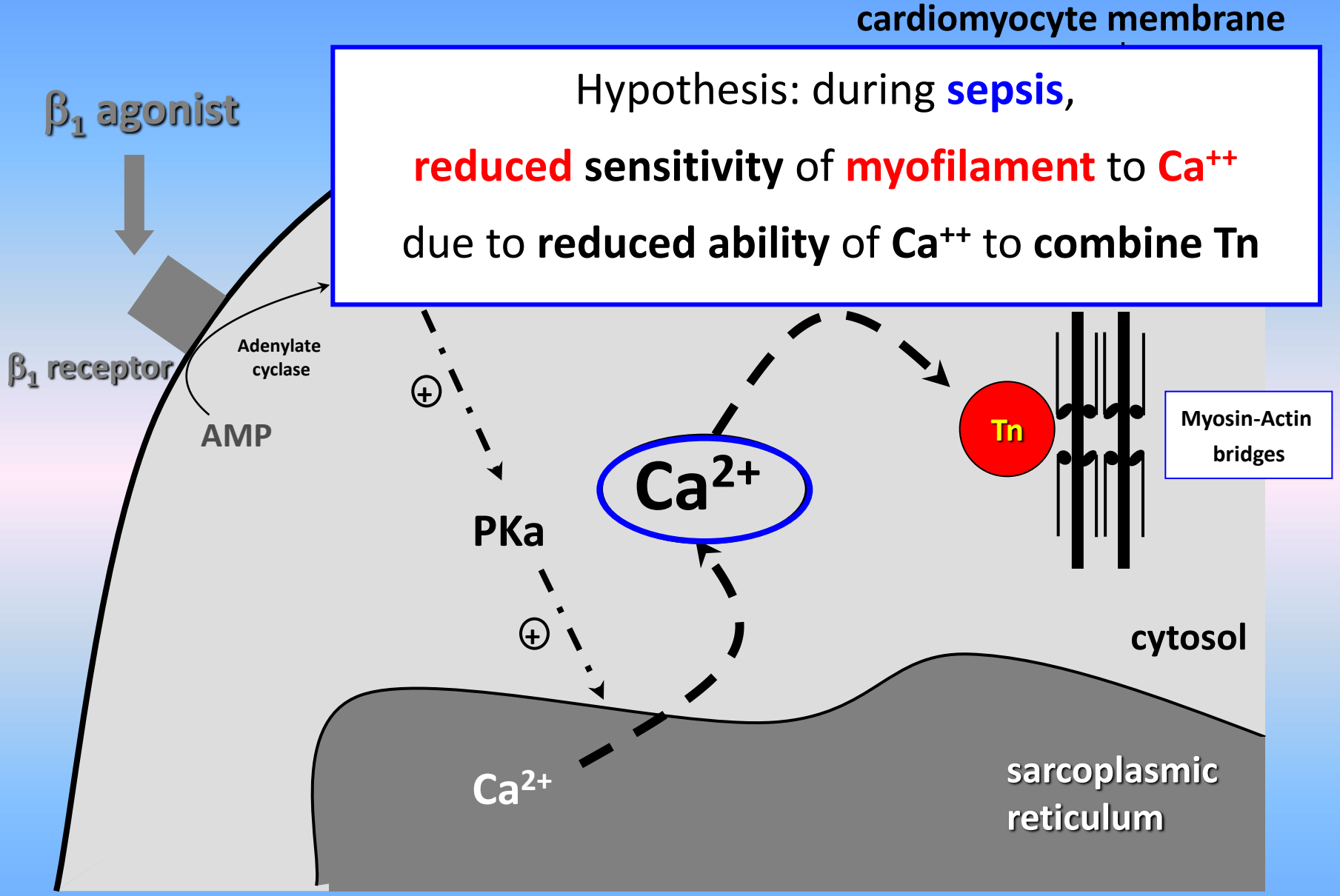
Mechanisms of sepsis-related cardiac dysfunction

Supracellular mechanisms

- *Coronary blood flow*
- *Circulating factors*

Intrinsic cellular mechanisms

- *β-adrenergic receptors*
- ***Calcium and myofilaments***

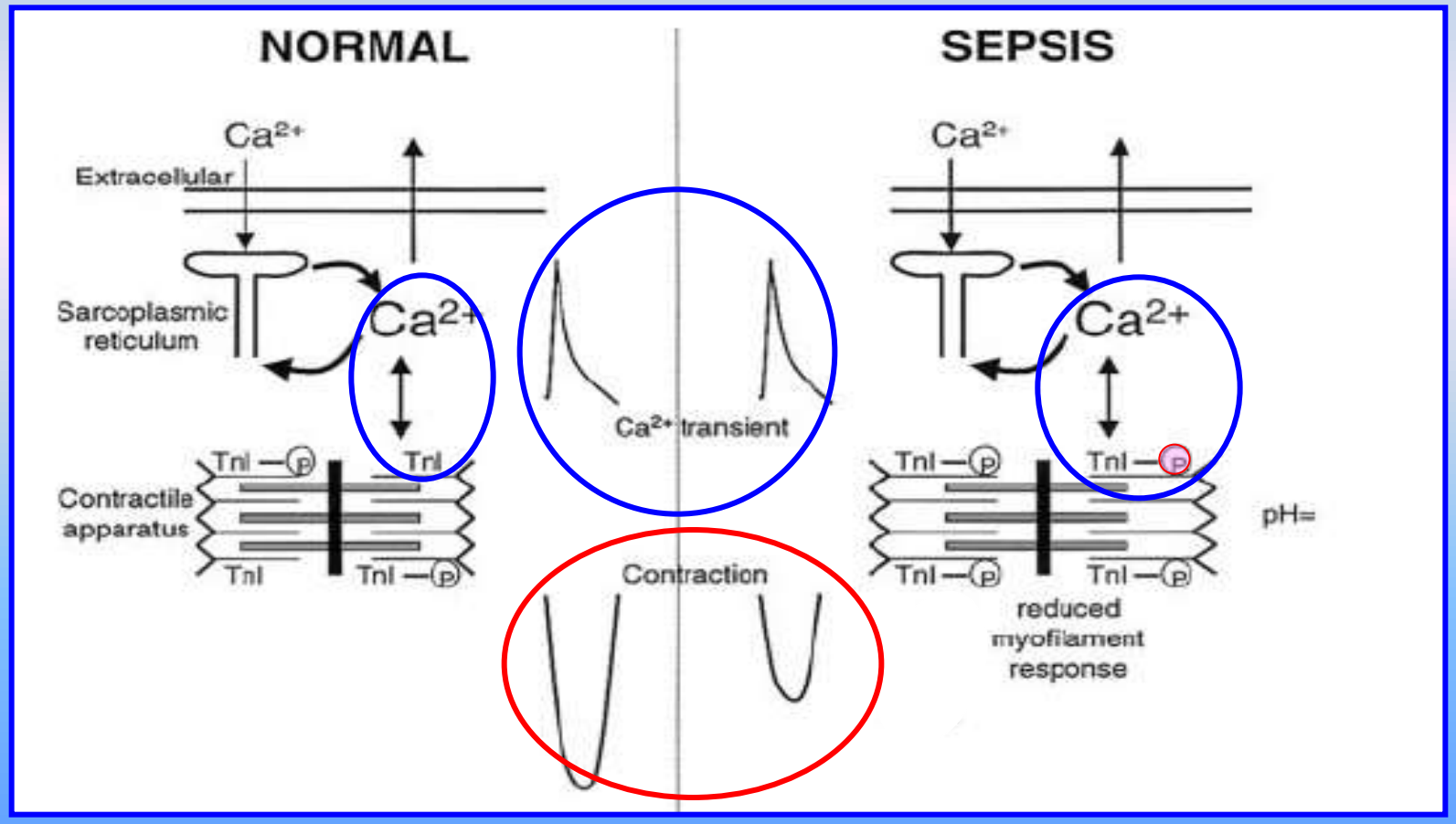

cardiomyocyte membrane
Hypothesis: during sepsis,
reduced sensitivity of myofilament to Ca++
due to reduced ability of Ca++ to combine Tn
β1 agonist
β1 receptor
Adenylate cyclase
AMP
PKa
Ca2+
Tn
Myosin-Actin bridges
cytosol
Ca2+
sarcoplasmic reticulum

Cardiac contractile impairment associated with increased phosphorylation of troponin I in endotoxemic rats

BENOIT TAVERNIER,[*,†] JIAN-MEI LI,[*,‡] MAGDI M. EL-OMAR,[†,‡] SOPHIE LANONE,[*] ZHAO-KANG YANG,[‡] IAN P. TRAYER,[§] ALEXANDRE MEBAZAA,[†] AND AJAY M. SHAH[*]

Vol. 15 February 2001 The FASEB Journal

This suggests an alteration of Ca^{++} myofilament responsiveness



Mechanisms of sepsis-related cardiac dysfunction

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- *Coronary blood flow*
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Intrinsic cellular mechanisms

- *β-adrenergic receptors*
- *Calcium and myofilaments*
- ***Nitric oxide and peroxynitrite pathways***

Mechanisms of sepsis-related cardiac dysfunction

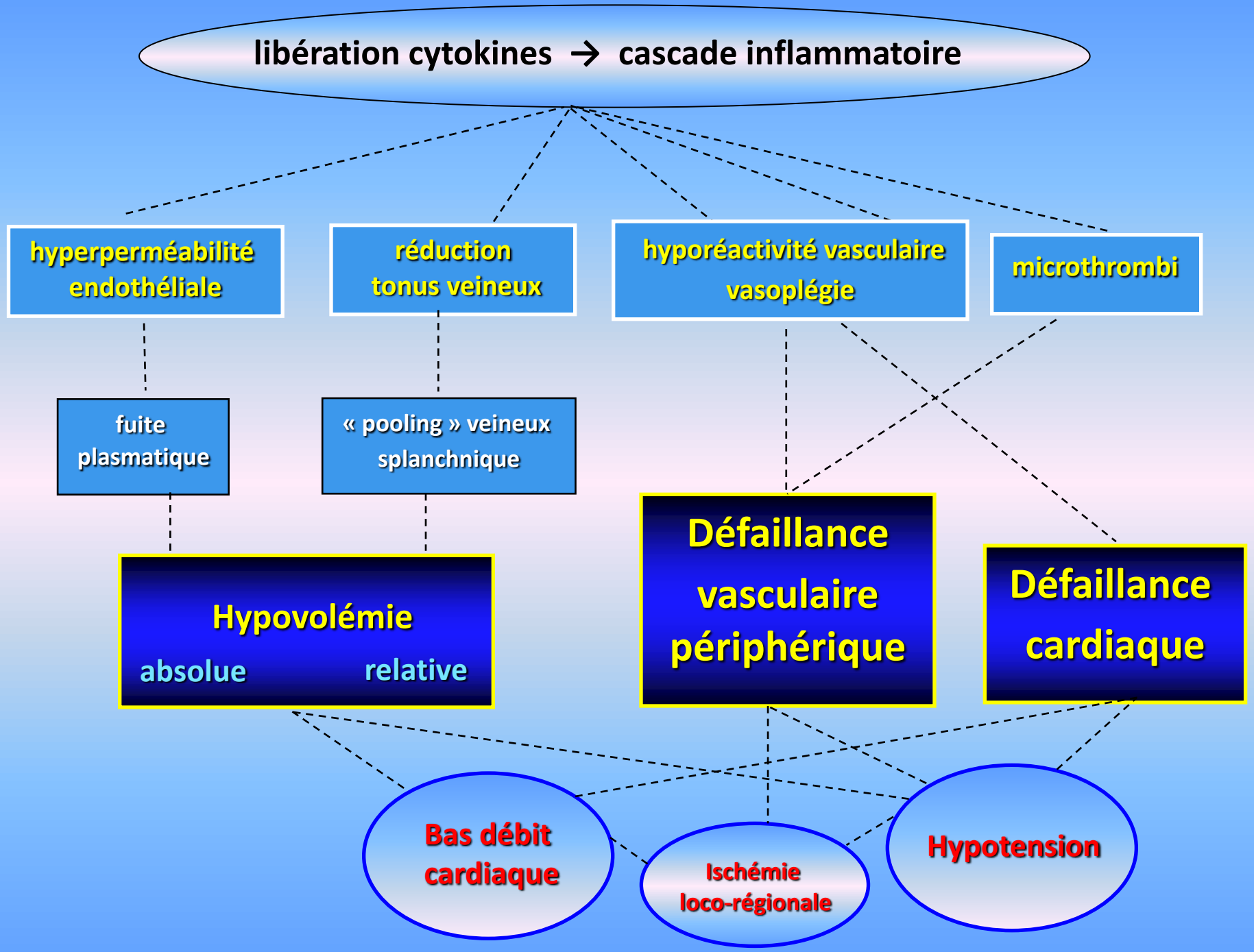
Supracellular mechanisms

- *Coronary blood flow*
- *Circulating factors*

Intrinsic cellular mechanisms

- *β-adrenergic receptors*
- *Calcium and myofilaments*
- *Nitric oxide and peroxynitrite pathways*
- ***Apoptosis***

- Initial phase of sepsis, a **cytokine effect** mainly contributes to **myocardial depression**
- Later phase, **other mechanisms** are likely to be predominant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Hypovolémie
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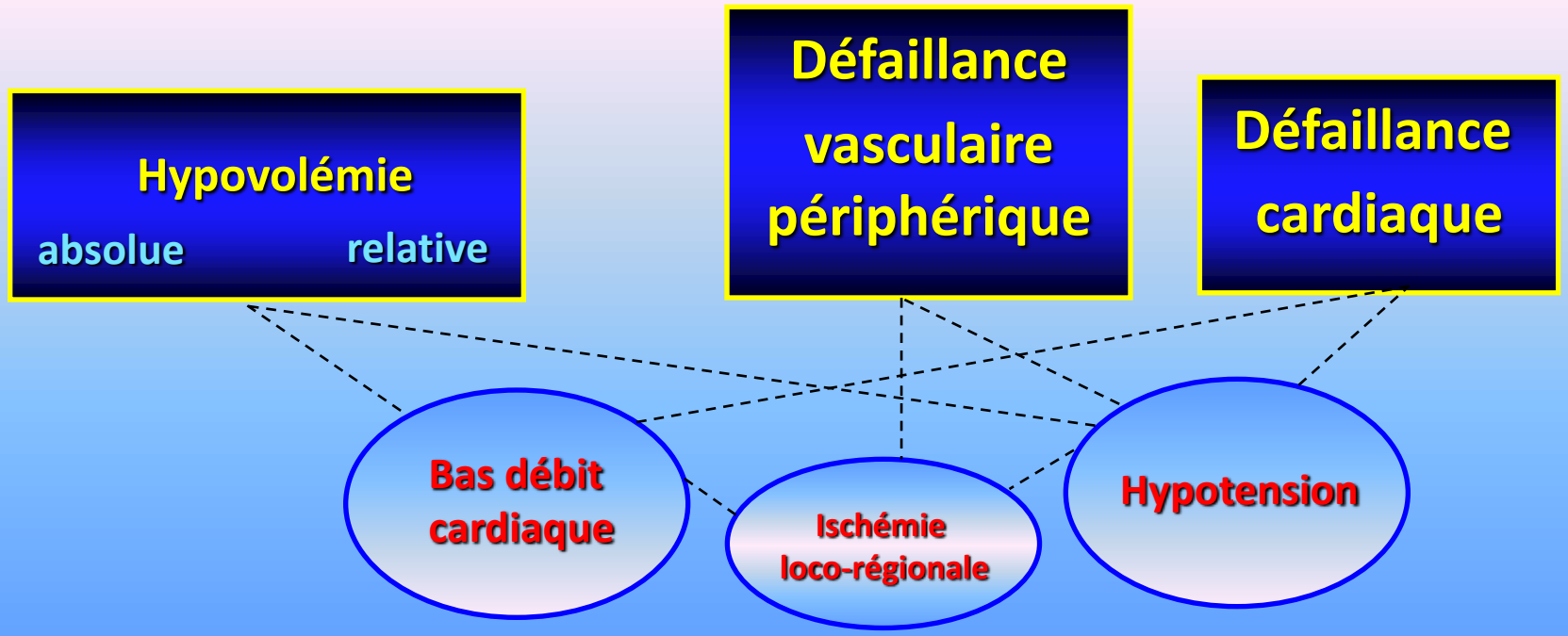
Défaillance cardiaque
Bas débit cardiaque
Ischémie loco-régionale
Hypotension


Hypovolémie
absolue
relative
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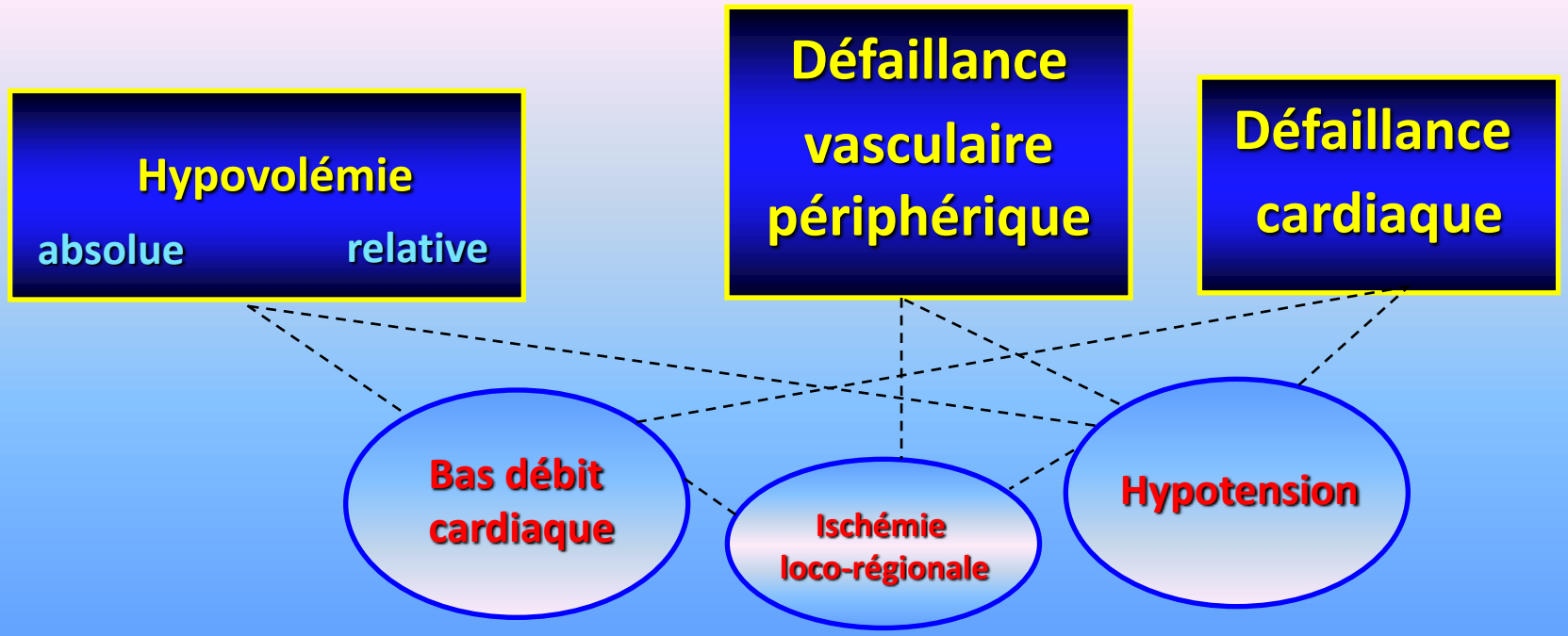
Défaillance cardiaque
Bas débit cardiaque
Ischémie loco-régionale
Hypotension

Fin du 1er épisode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absolue
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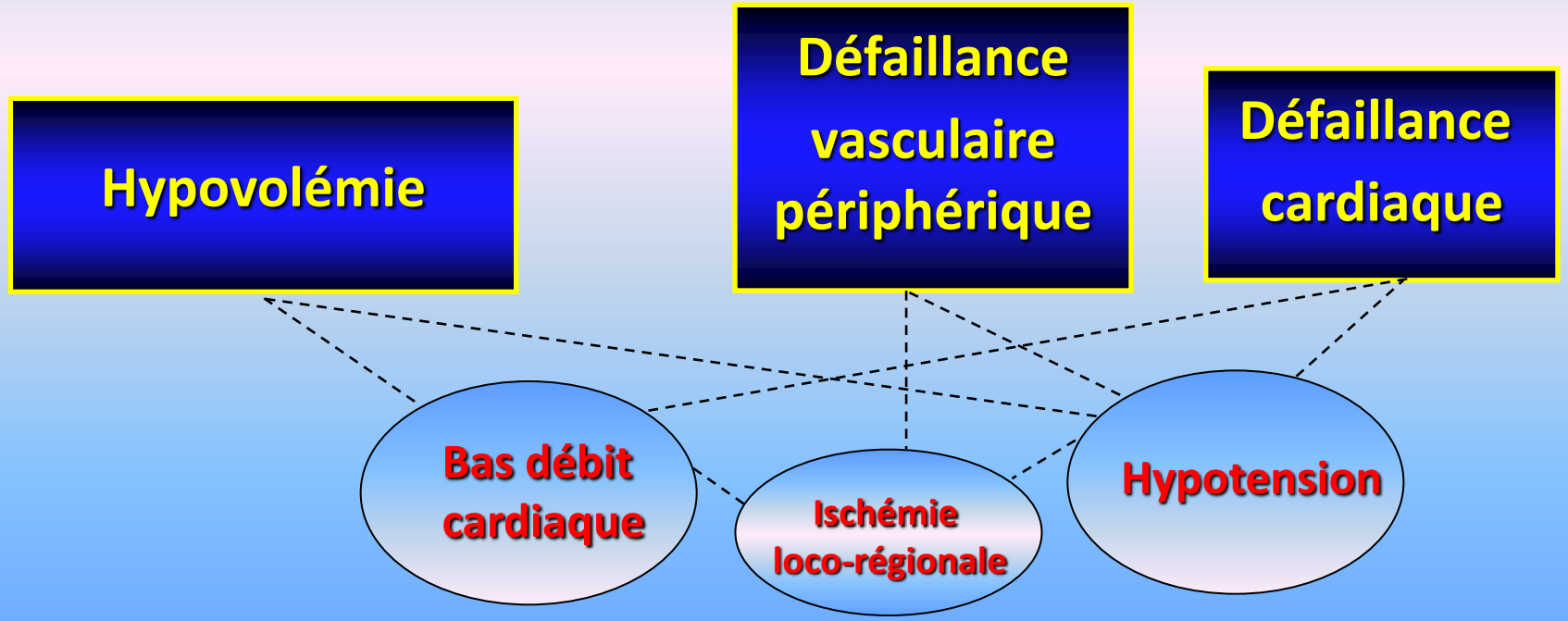
Défaillance cardiaque
Bas débit cardiaque
Ischémie loco-régionale
Hypotension

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant



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

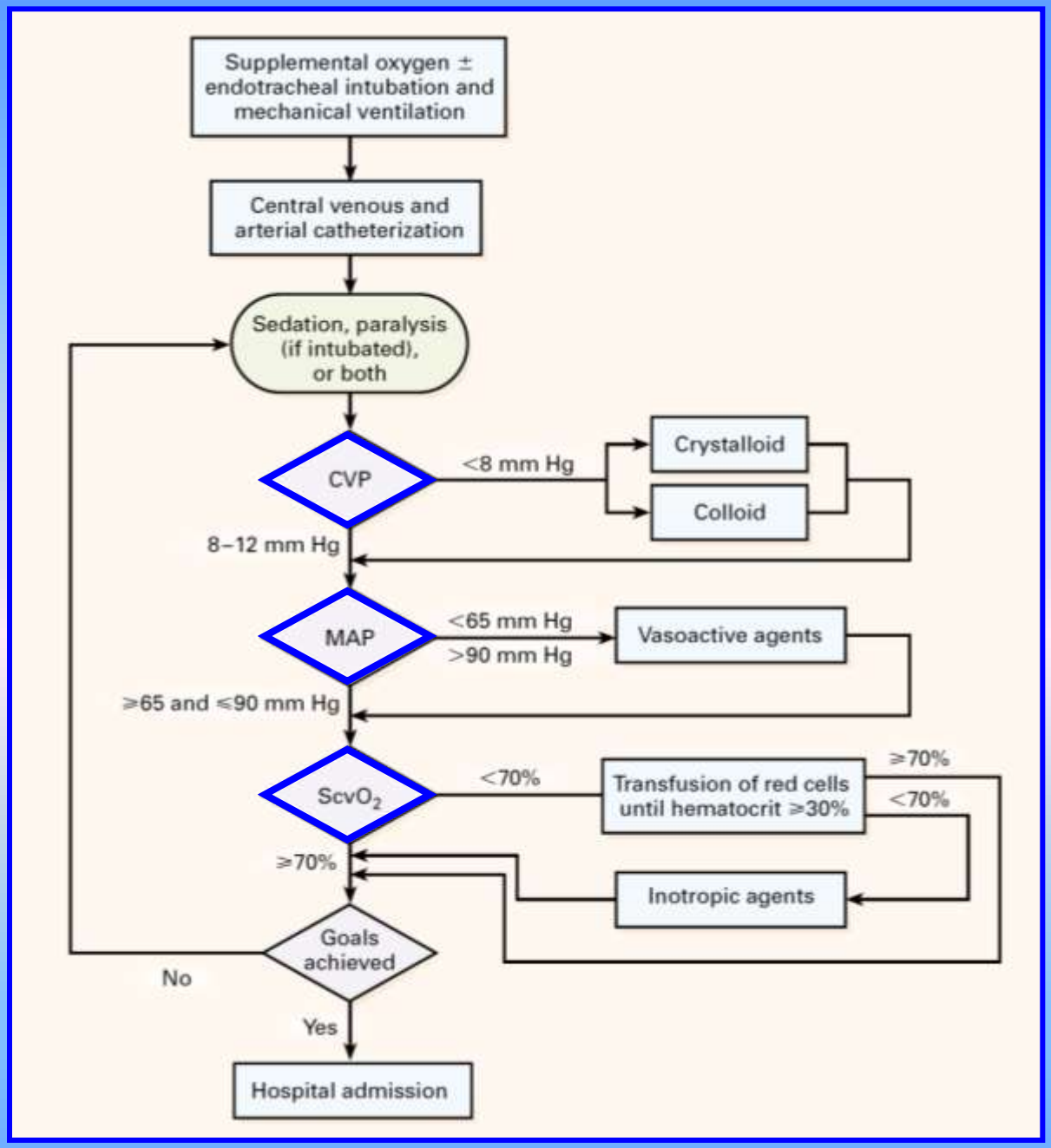
R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Initial resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis-induced hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate $\geq$ 4 mmol/L).

Goals during the first 6h of resuscitation:

- **(a) Central venous pressure 8-12 mmHg**
- **(b) Mean arterial pressure (MAP) $\geq$ 65 mmHg**
- **(c) Urine output $\geq$ 0.5 mL.kg^{-1} h**
- **(d) Central venous or mixed venous oxygen saturation 70 or 65%, respectively (grade 1C)**



Rivers et al. *New Engl J Med* 2001

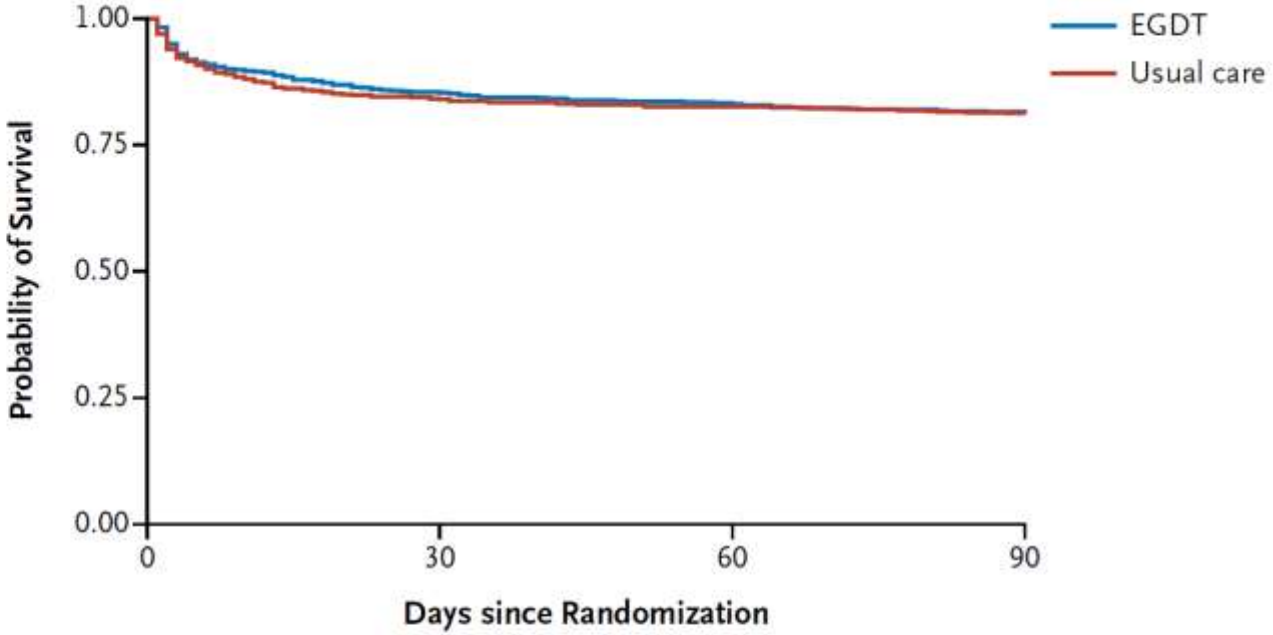
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

N Engl J Med 2014;371:1496-506

Arise

A Survival

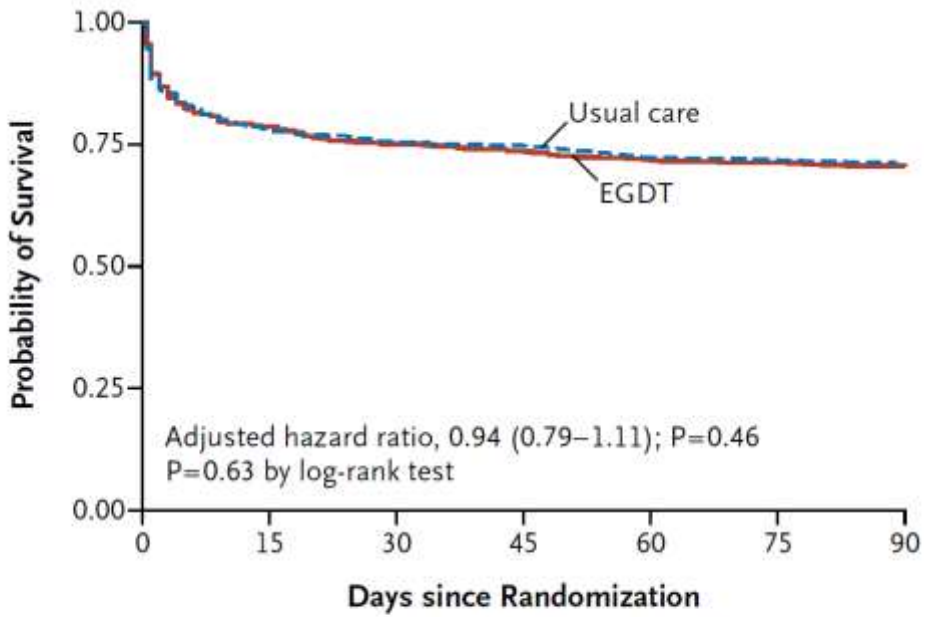


No. at Risk				
EGDT	792	677	660	646
Usual care	796	670	657	646

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

Promise



No. at Risk							
EGDT	625	492	470	461	449	445	440
Usual care	626	487	469	464	448	445	439

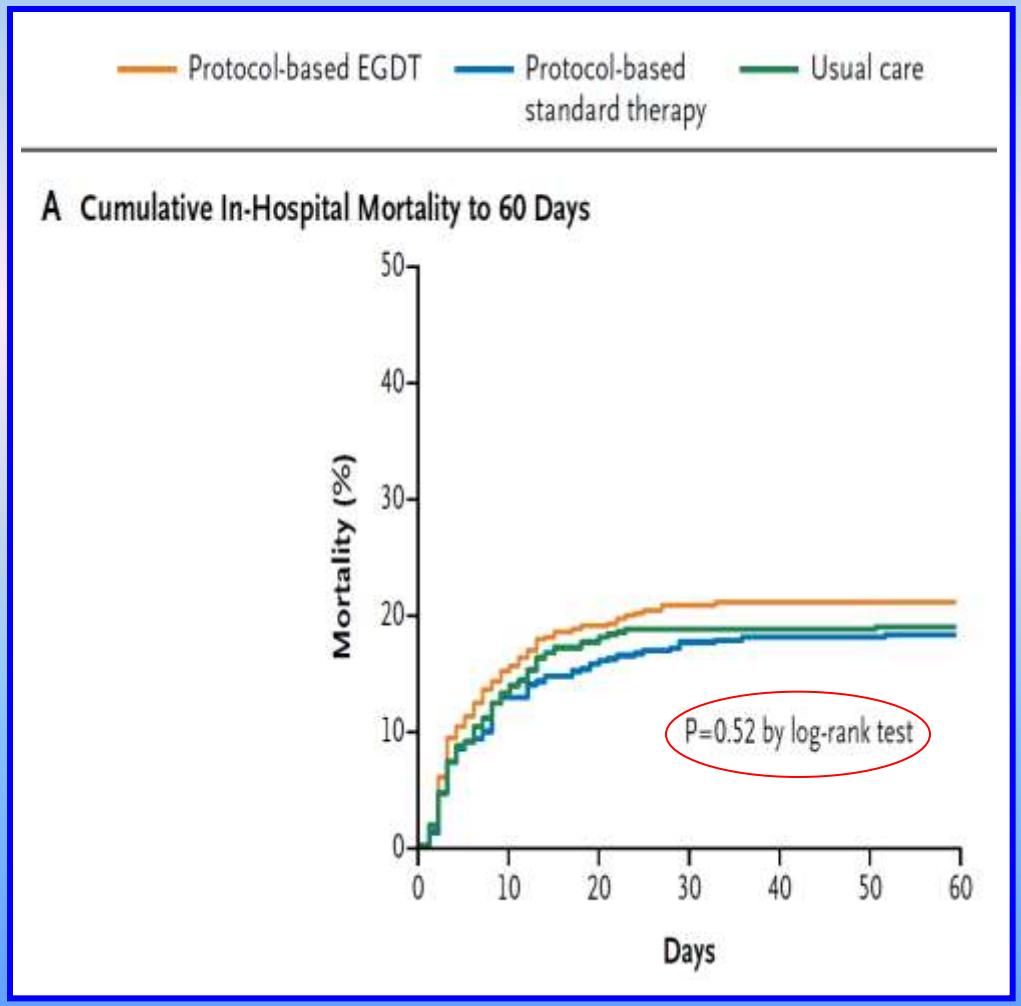
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The ProCESS Investigators*

Process

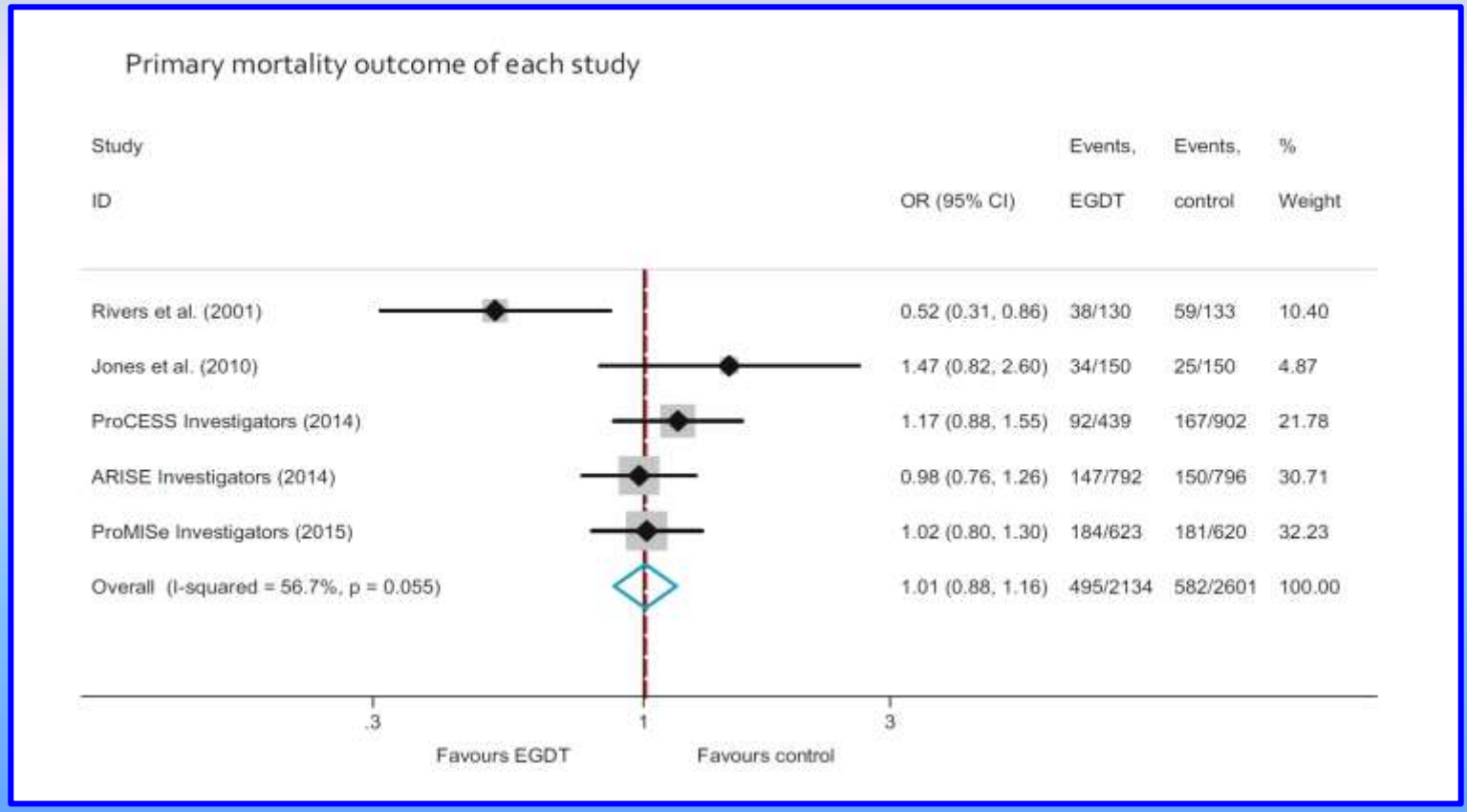


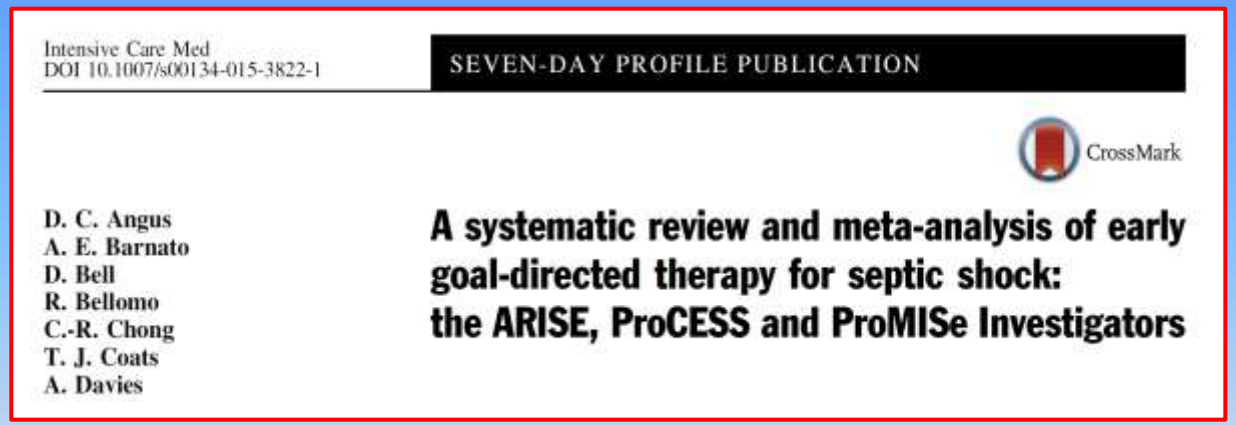
Intensive Care Med
DOI 10.1007/s00134-015-3822-1

SEVEN-DAY PROFILE PUBLICATION

D. C. Angus
A. E. Barnato
D. Bell
R. Bellomo
C.-R. Chong
T. J. Coats
A. Davies

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators





Intensive Care Med
DOI 10.1007/s00134-015-3822-1

SEVEN-DAY PROFILE PUBLICATION

D. C. Angus
A. E. Barnato
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R. Bellomo
C.-R. Chong
T. J. Coats
A. Davies

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

Our **meta-analysis does not** show **improved survival** for patients randomised to receive **EGDT** compared to usual or to less invasive alternative haemodynamic resuscitation protocols

Our findings **do not support** the systematic **use** of **EGDT** in the management of all patients with septic shock or its **inclusion** in the **SSC guidelines**

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

* *"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.*

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant

Hypovolémie

Remplissage vasculaire

Défaillance vasculaire périphérique

- Quel solutés ?
- Quels objectifs

Défaillance cardiaque

Inotropes ?

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant

Hypovolémie

↑

Remplissage vasculaire

- Quel solutés ?
- Quels objectifs

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

G. Fluid Therapy of Severe Sepsis

1. **Crystalloids** as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

N Engl J Med 2012;367:1901-11

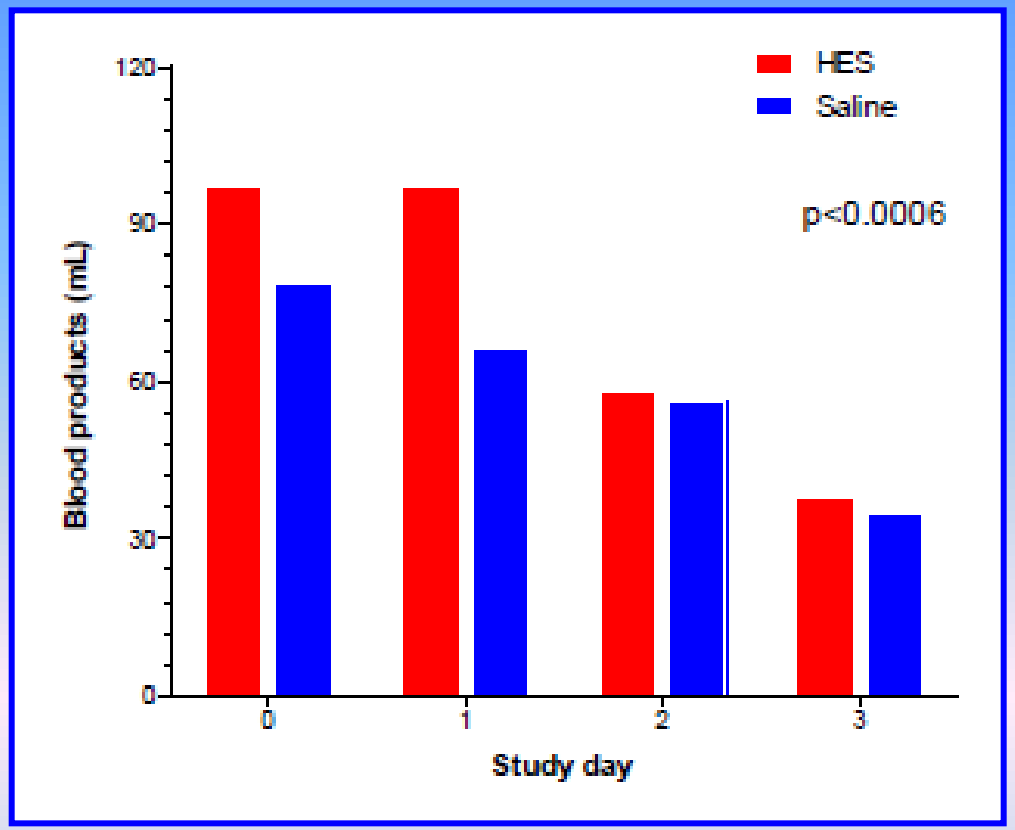
Table 2. Outcomes and Adverse Events.*

Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day [illegible] no./total no. (%)			1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F				0.12
Use of r				0.04

Pas de différence de mortalité

Augmentation du **recours** à **l'épuration extra-rénale** dans le groupe **"amidons"**

Myburgh et al NEJM 2012



Augmentation du **recours** à **la transfusion sanguine** dans le groupe **“amidons”**

Myburgh et al NEJM 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,
Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,
Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D.,
Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D.,
Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D.,
Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D.,
Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D.,
Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D.,
Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D.,
for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

N Engl J Med 2012;367:124-34

Table 3. Primary and Secondary Outcomes.*

Outcome	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)	Relative Risk (95% CI)	P Value
Primary outcome				
Dead or dependent o			17 (1.01–1.36)	0.03
Dead at day 90 — no			17 (1.01–1.36)	0.03
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
Secondary outcome measures				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic				0.32
SOFA score at				0.64
Use of renal-re				0.04

Surmortalité dans le groupe **"amidons"**

Augmentation du **recours** à **l'épuration extra-rénale** dans le groupe **"amidons"**

Perner et al NEJM 2012

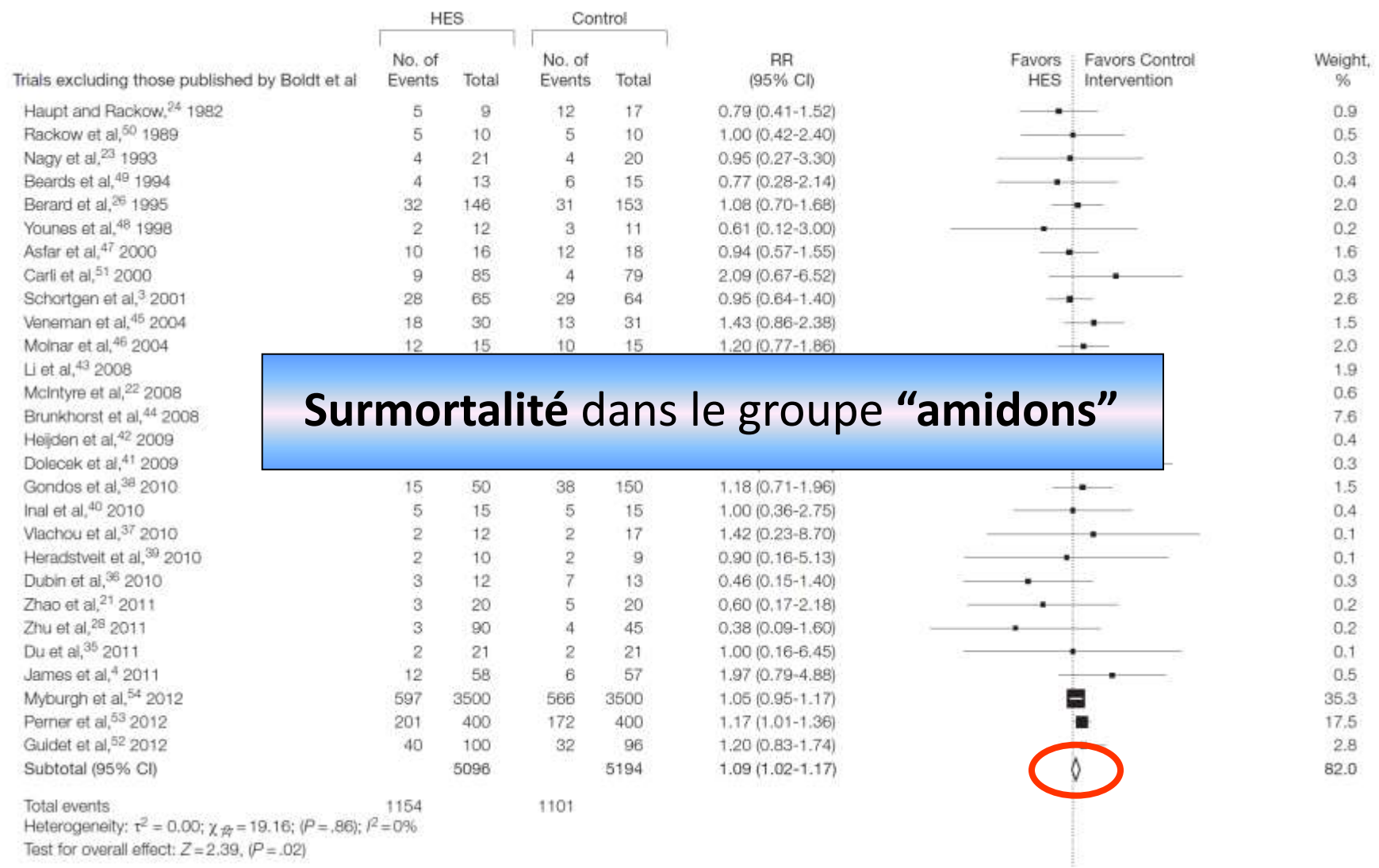
Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

Ryan Zarychanski, MD, MSc
Ahmed M. Abou-Setta, MD, PhD
Alexis F. Turgeon, MD, MSc
Brett L. Houston, BSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Fergusson, PhD, MHA

JAMA. 2013;309(7):678-688

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						1.9
McIntyre et al,[22] 2008						0.6
Brunkhorst et al,[44] 2008						7.6
Heijden et al,[42] 2009						0.4
Dolecek et al,[41] 2009						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: $\tau^2 = 0.00$; $\chi_{\text{df}} = 19.16$; ($P = .86$); $I^2 = 0\%$

Test for overall effect: $Z = 2.39$, ($P = .02$)

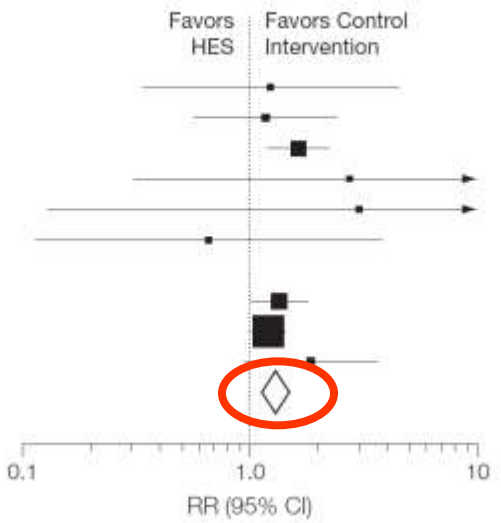
Surmortalité dans le groupe **“amidons”**

Zarychanski et al JAMA 2013

Figure 3. Renal Replacement Therapy and Hydroxyethyl Starch

Source	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)
Berard et al,[26] 1995	5	155	4	152	1.23 (0.34-4.48)
Schortgen et al,[3] 2001	13	65	11	64	1.16 (0.56-2.40)
Brunkhorst et al,[44] 2008	81	297	51	303	1.62 (1.19-2.21)
McIntyre et al,[22] 2008	3	21	1	19	2.71 (0.31-23.93)
Du et al,[35] 2011	1	21	0	21	3.00 (0.13-69.70)
James et al,[4] 2011	2	58	3	57	0.66 (0.11-3.78)
Viachou et al,[37] 2010	0	12	0	17	Not estimable
Perner al,[53] 2012	87	400	65	400	1.34 (1.00-1.79)
Myburgh et al,[54] 2012	235	3500	196	3500	1.20 (1.00-1.44)
Guidet et al,[52] 2012	21	100	11	96	1.83 (0.93-3.59)
Total (95% CI)		4629		4629	1.32 (1.15-1.50)
Total events	448		342		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 5.07$; ($P = .75$); $I^2 = 0\%$
Test for overall effect: $Z = 4.08$, ($P < .001$)



Augmentation du **recours** à **l'épuration extra-rénale**

dans le groupe **"amidons"**

Zarychanski et al JAMA 2013

Table 3. Primary and Secondary Outcomes.*

Outcome	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)	Relative Risk (95% CI)	P Value
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Surmortalité dans le groupe **"amidons"**

Augmentation du **recours** à **l'épuration extra-rénale** dans le groupe **"amidons"**

Perner et al NEJM 2012

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

G. Fluid Therapy of Severe Sepsis

1. **Crystalloids** as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B)

2. **Against** the use of **hydroxyethyl starches** for fluid resuscitation of severe sepsis and septic shock (grade 1B)

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant

Hypovolémie

↑

Remplissage vasculaire

- Quel solutés ?
- **Quels objectifs**

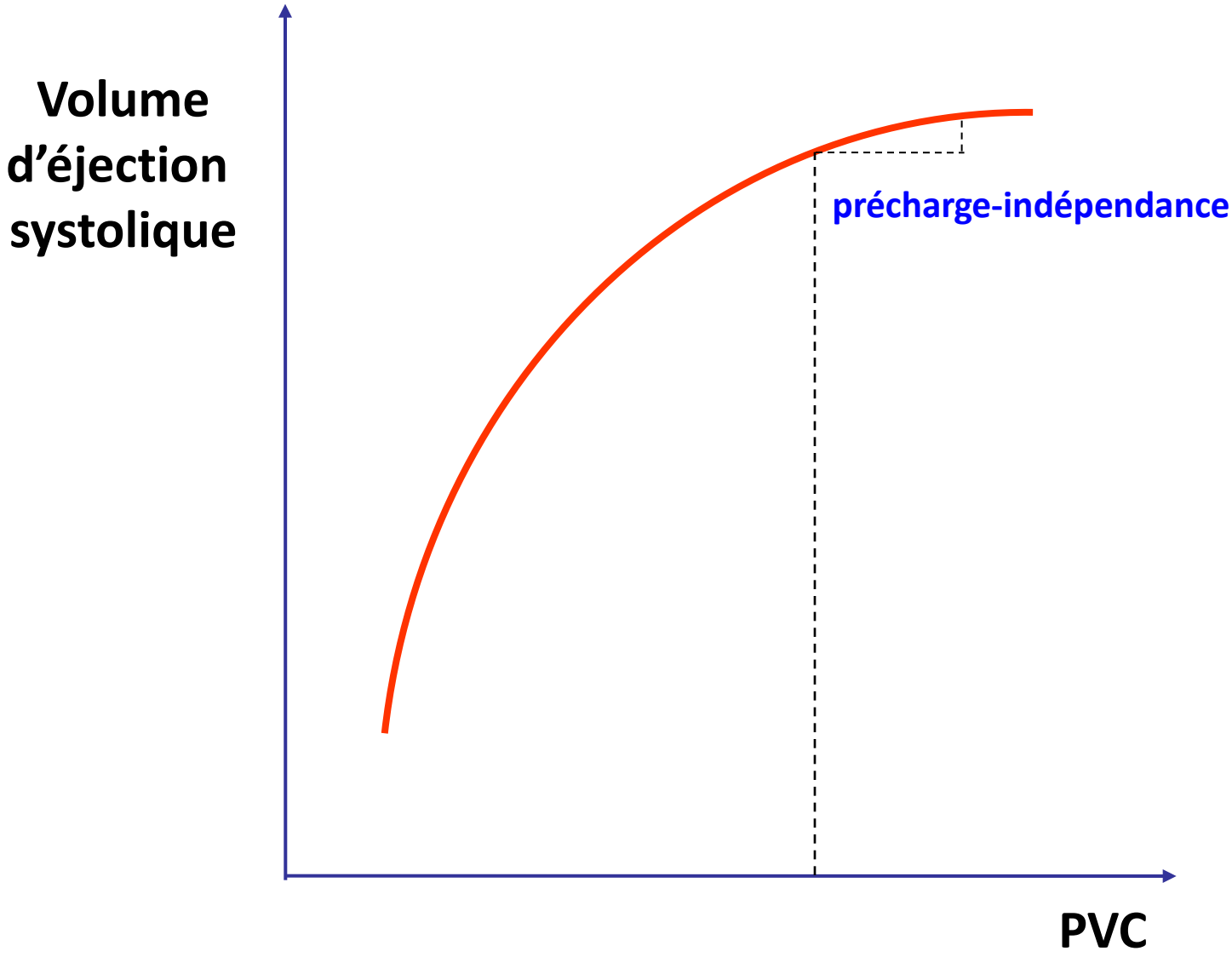
SSC « static » approach

« dynamic » approach

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Stratégie SSC : arrêter le remplissage quand un certain niveau de PVC est atteint



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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Initial resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis-induced hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate ≥ 4 mmol/L).

Goals during the first 6h of resuscitation:

Central venous pressure 8-12 mmHg

(c) Urine output ≥ 0.5 mL.kg^{-1} h

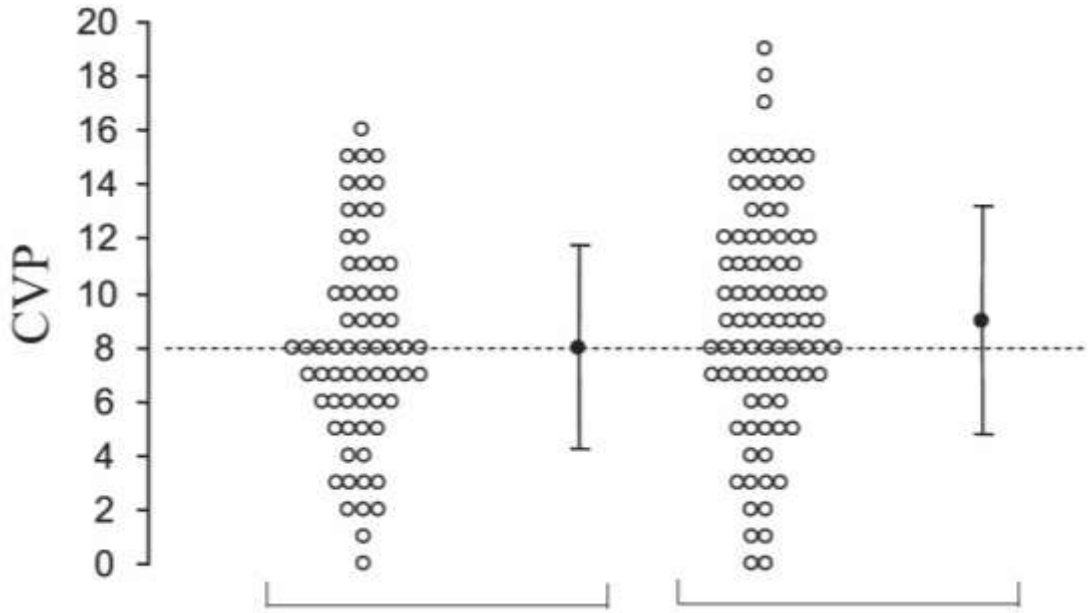
(d) Central venous or mixed venous oxygen saturation 70 or 65%, respectively (grade 1C)

Central venous pressure 12-15 mmHg if MV

Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge*

David Osman, MD; Christophe Ridel, MD; Patrick Ray, MD; Xavier Monnet, MD, PhD; Nadia Anguel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2007; 35:64–68



Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense*

Paul E. Marik, MD, FCCM[1]; Rodrigo Cavallazzi, MD[2]

Crit Care Med 2013; 41:1774-81

1802 pts

43 Citations

- 22 ICU studies
- 20 operating room studies
- 1 human volunteer study

Summary AUC

0.56

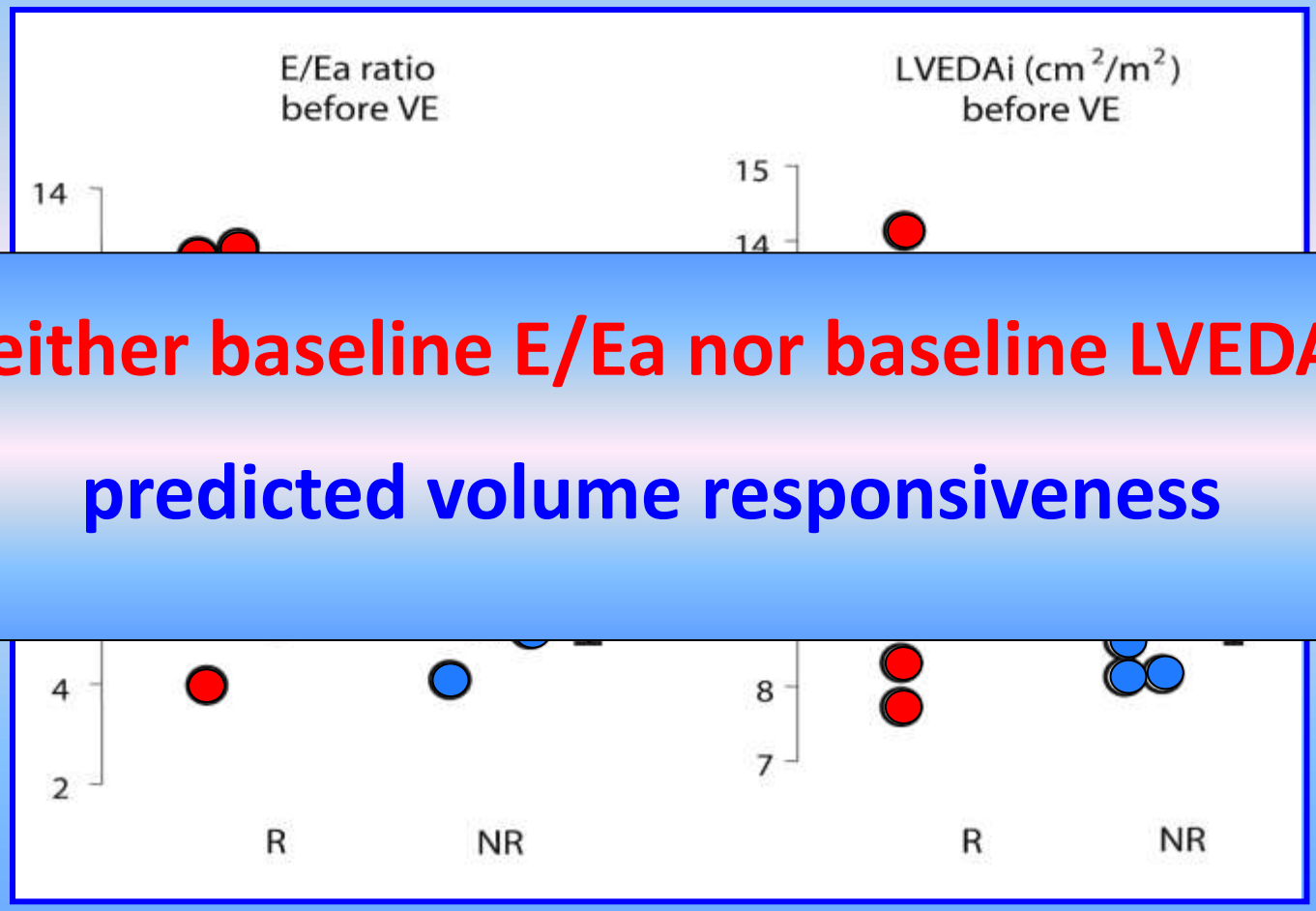
Predicting fluid responsiveness with **CVP** is like

Intensive Care Med (2007) 33:1125–1132

ORIGINAL

Bouchra Lamia
Ana Ochagavia
Xavier Monnet
Denis Chemla
Christian Richard
Jean-Louis Teboul

Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity



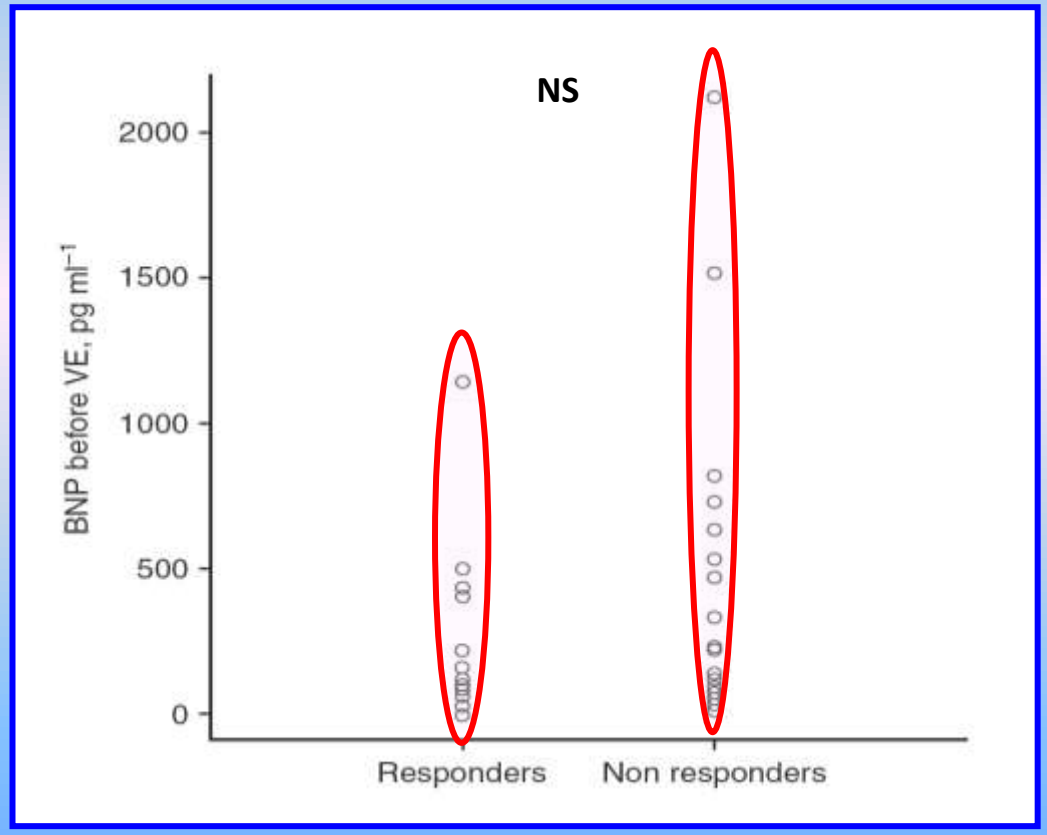
neither baseline E/Ea nor baseline LVEDA

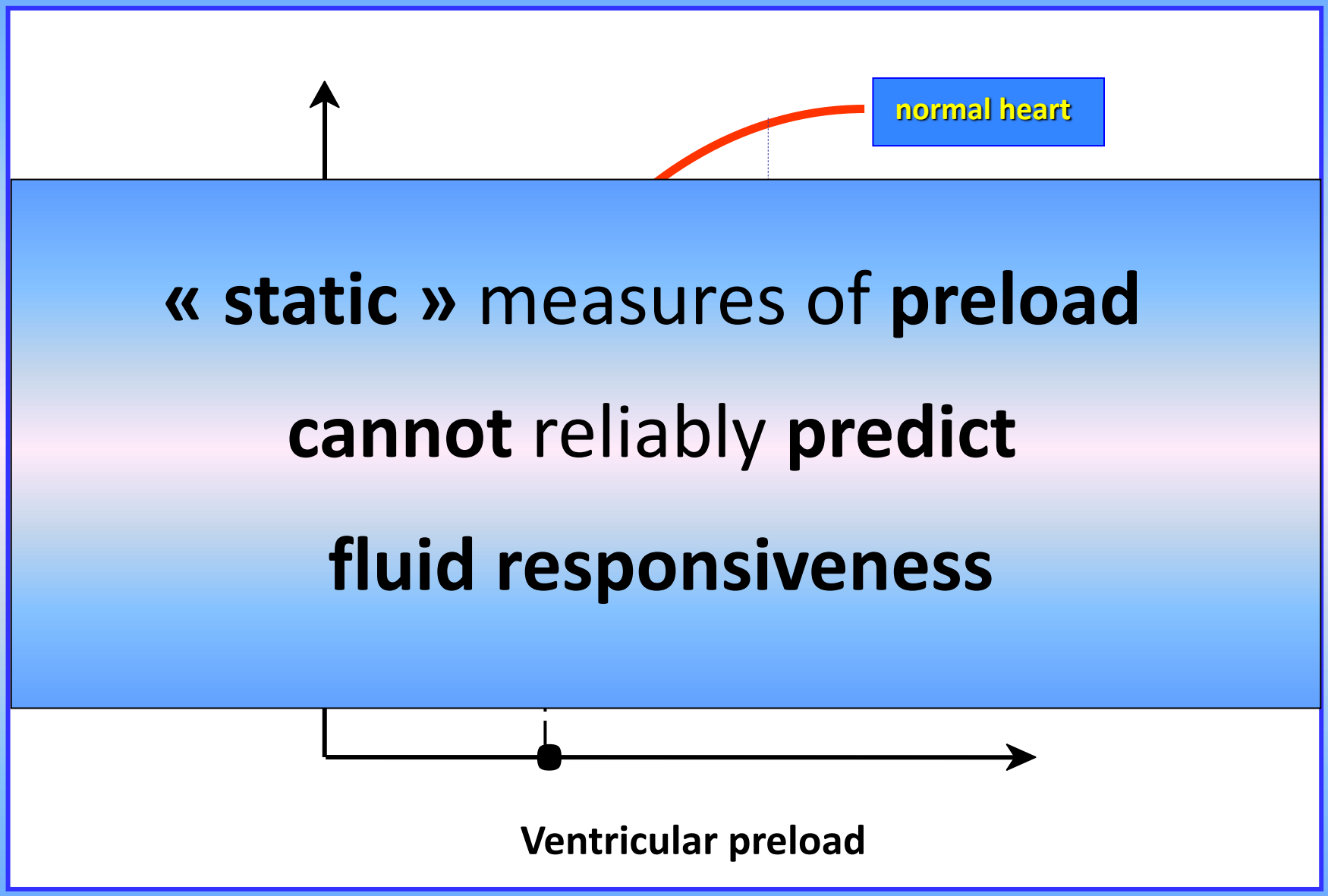
predicted volume responsiveness

B-type natriuretic peptide to assess haemodynamic status after cardiac surgery

A. Mekontso-Dessap[1] *, L. Tual[2], M. Kirsch[2], G. D'Honneur[2], D. Loisance[2], L. Brochard[1] and J.-L. Teboul[3]

Br J Anaesth 2006; 87:777-782




normal heart
« static » measures of preload
cannot reliably predict
fluid responsiveness
Ventricular preload

SSC « static » approach

« dynamic » approach

Intensive Care Med (2014) 40:1795–1815

CONFERENCE REPORTS AND EXPERT PANEL

Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa
Michael R. Pinsky
Jean Louis Teboul
Jean Louis Vincent
Andrew Rhodes

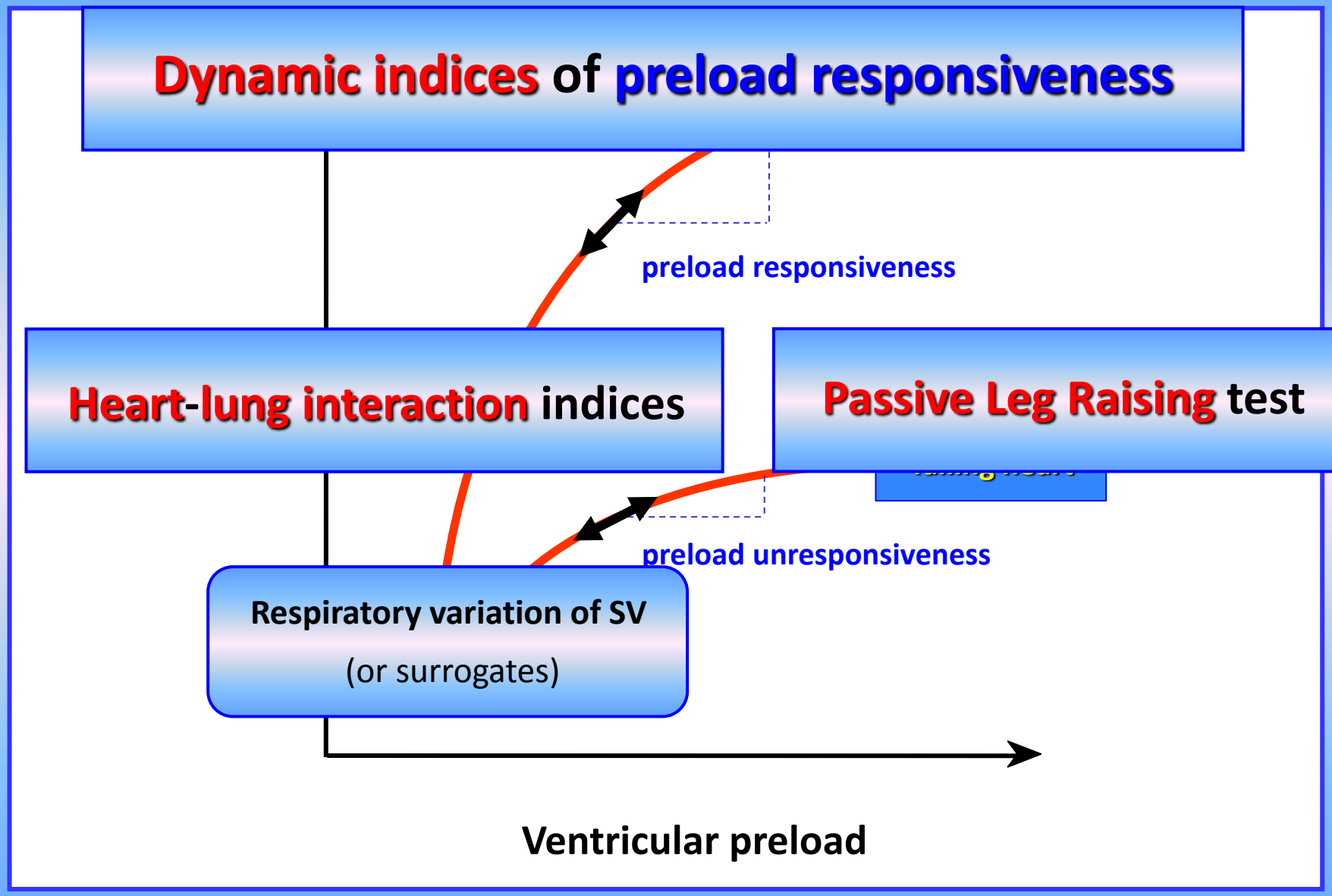
Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

30. We recommend **not to target** any **absolute** value of **ventricular filling pressure** or **volume**

Level 1; QoE moderate (B)

31. We recommend using **dynamic** over static variables to predict **fluid responsiveness**, when applicable

Level 1; QoE moderate (B)


Dynamic indices of preload responsiveness
preload responsiveness
Heart-lung interaction indices
Passive Leg Raising test
preload unresponsiveness
Respiratory variation of SV
(or surrogates)
Ventricular preload

MV induces **cyclic changes** in **SV**
only in pts with
biventricular
preload responsiveness

fluid responsiveness
occurs only in pts with
biventricular
preload responsiveness

correlates with the magnitude
of the
induced by

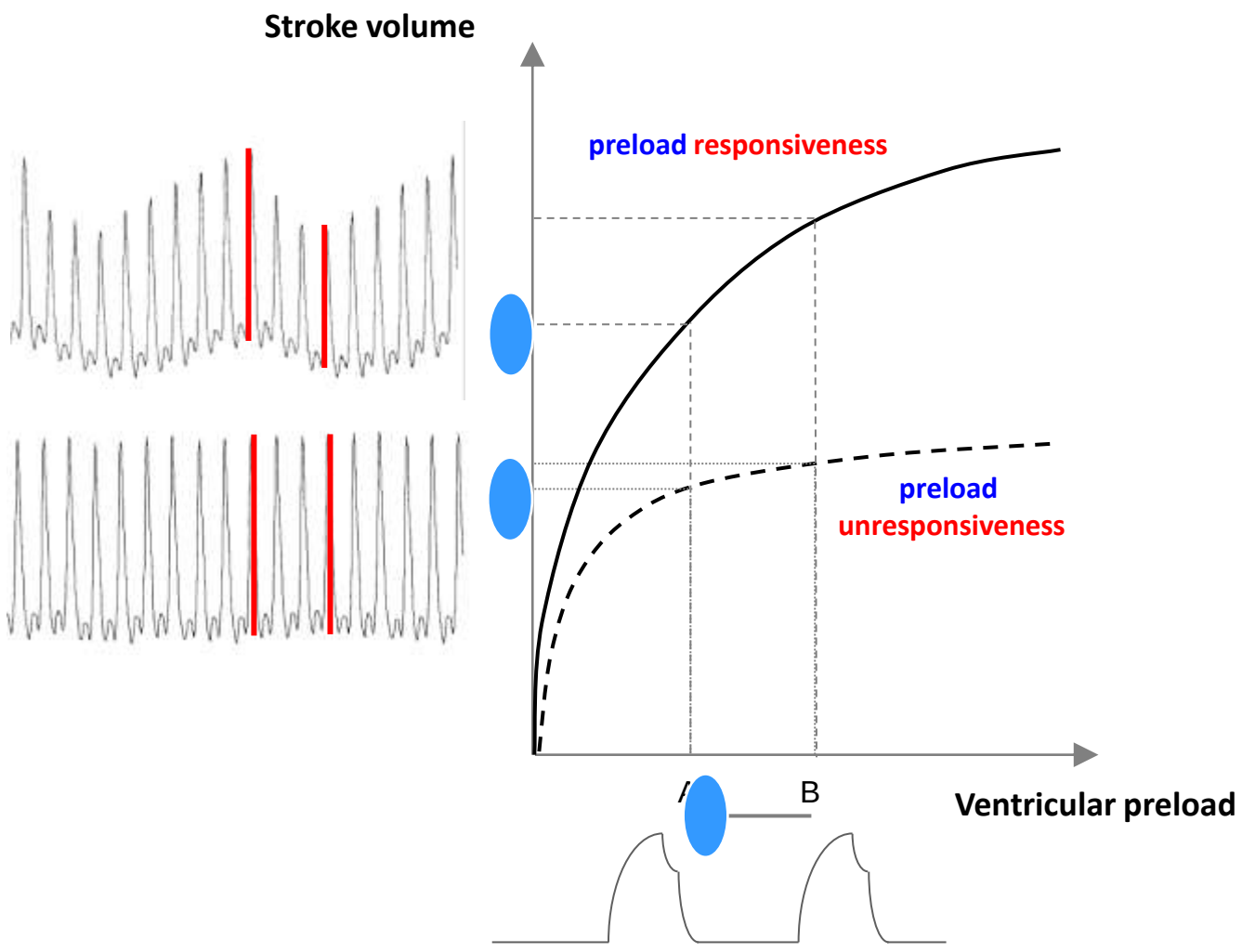
Pulse Pressure Variation

$$\text{Pulse Pressure} = k \cdot \frac{\text{Stroke Volume}}{\text{arterial compliance}}$$

the respiratory changes in **arterial pulse pressure**

should **reflect** the respiratory changes in **LV stroke volume**

Pulse pressure variation should predict fluid responsiveness


Stroke volume
preload responsiveness
preload
unresponsiveness
A
B
Ventricular preload

Clinical Use of Respiratory Changes in Arterial Pulse Pressure to Monitor the Hemodynamic Effects of PEEP

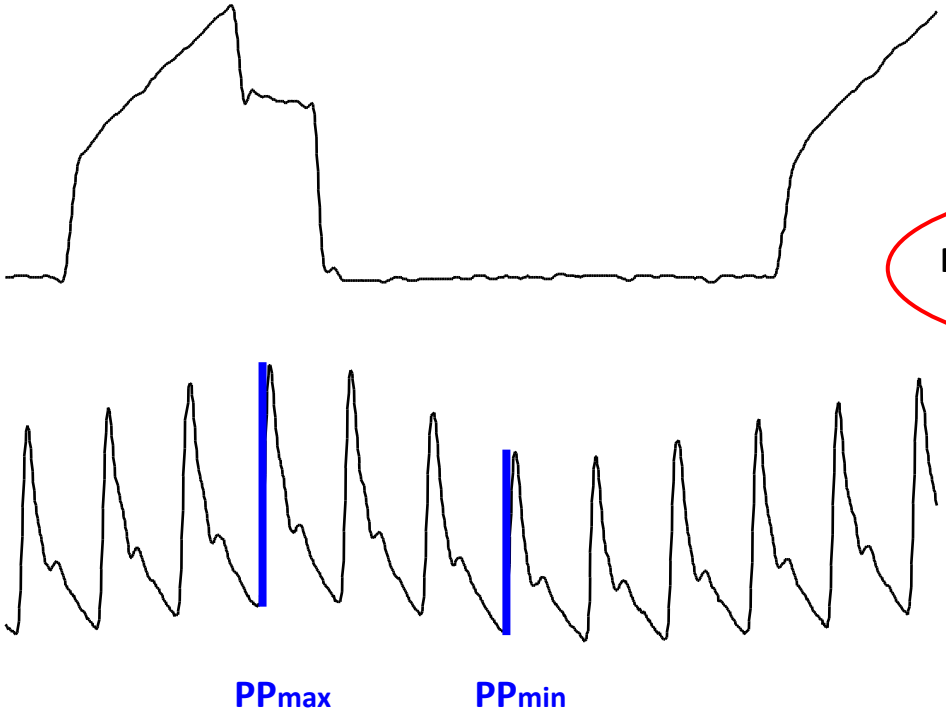
FRÉDÉRIC MICHARD, DENIS CHEMLA, CHRISTIAN RICHARD, MARC WYSOCKI, MICHAEL R. PINSKY, YVES LECARPENTIER, and JEAN-LOUIS TEBOUL

AM J RESPIR CRIT CARE MED 1999;159:935-939

Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

FRÉDÉRIC MICHARD, SANDRINE BOUSSAT, DENIS CHEMLA, NADIA ANGUEL, ALAIN MERCAT, YVES LECARPENTIER, CHRISTIAN RICHARD, MICHAEL R. PINSKY, and JEAN-LOUIS TEBOUL

Am J Respir Crit Care Med 2000; 162:134-8



$$PPV = \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min}) / 2}$$

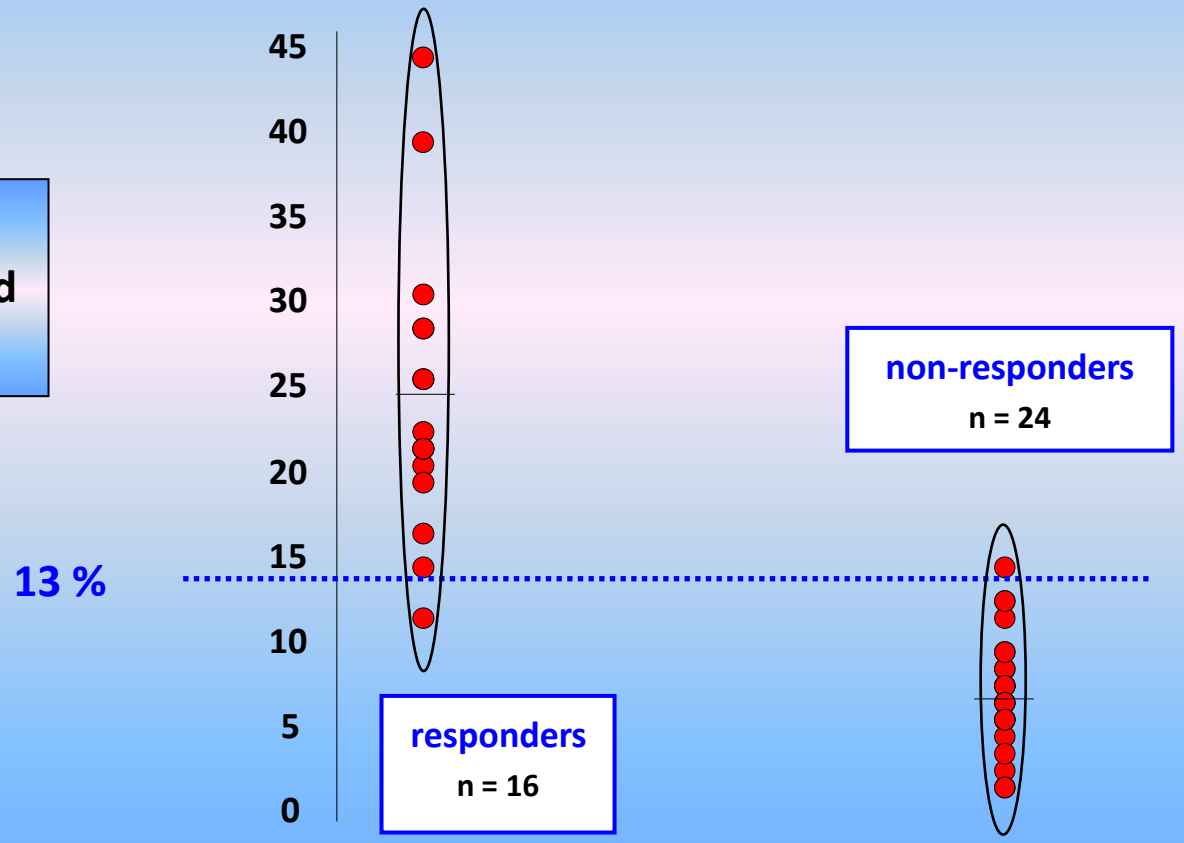
Arterial catheter

Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

FRÉDÉRIC MICHARD, SANDRINE BOUSSAT, DENIS CHEMLA, NADIA ANGUEL, ALAIN MERCAT, YVES LECARPENTIER, CHRISTIAN RICHARD, MICHAEL R. PINSKY, and JEAN-LOUIS TEBOUL

Am J Respir Crit Care Med 2000,162:134–138

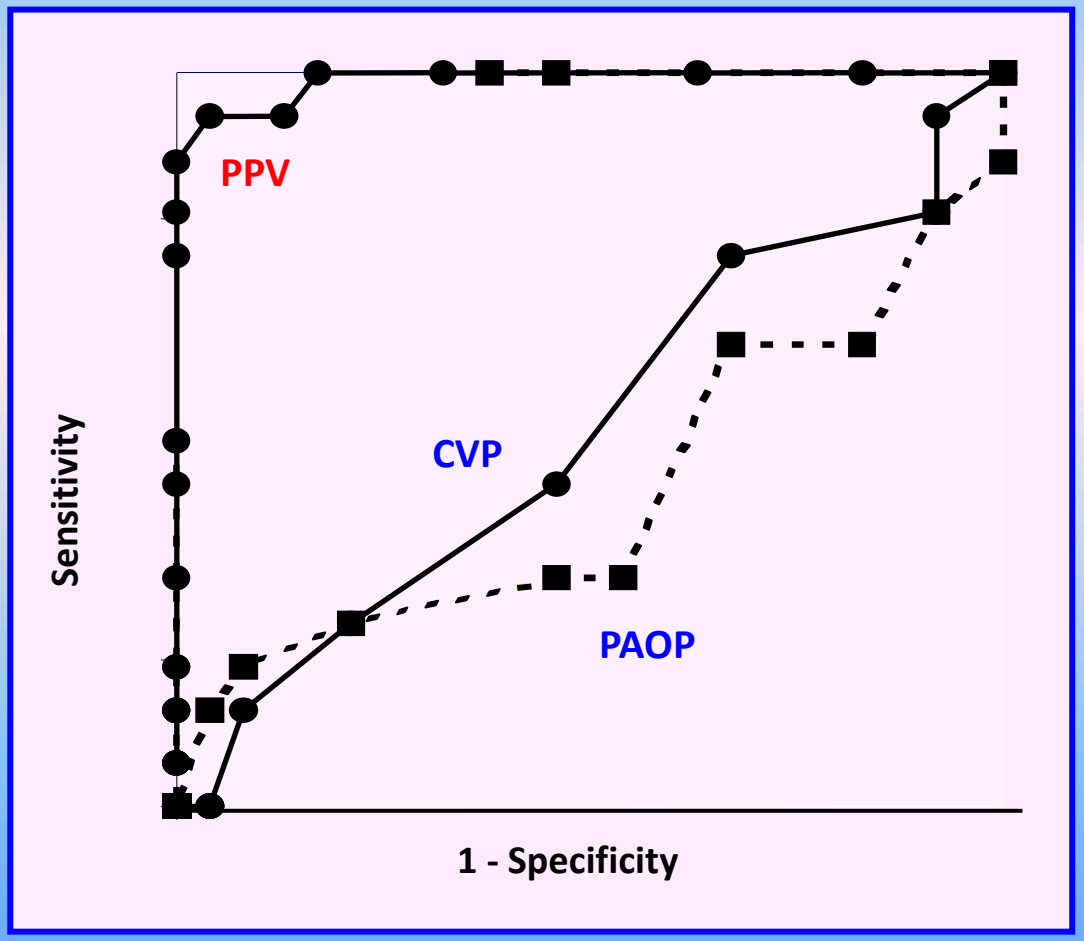
PPV (%)
before fluid Infusion



Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

FRÉDÉRIC MICHARD, SANDRINE BOUSSAT, DENIS CHEMLA, NADIA ANGUEL, ALAIN MERCAT, YVES LECARPENTIER, CHRISTIAN RICHARD, MICHAEL R. PINSKY, and JEAN-LOUIS TEBOUL

Am J Respir Crit Care Med 2000,162:134–138



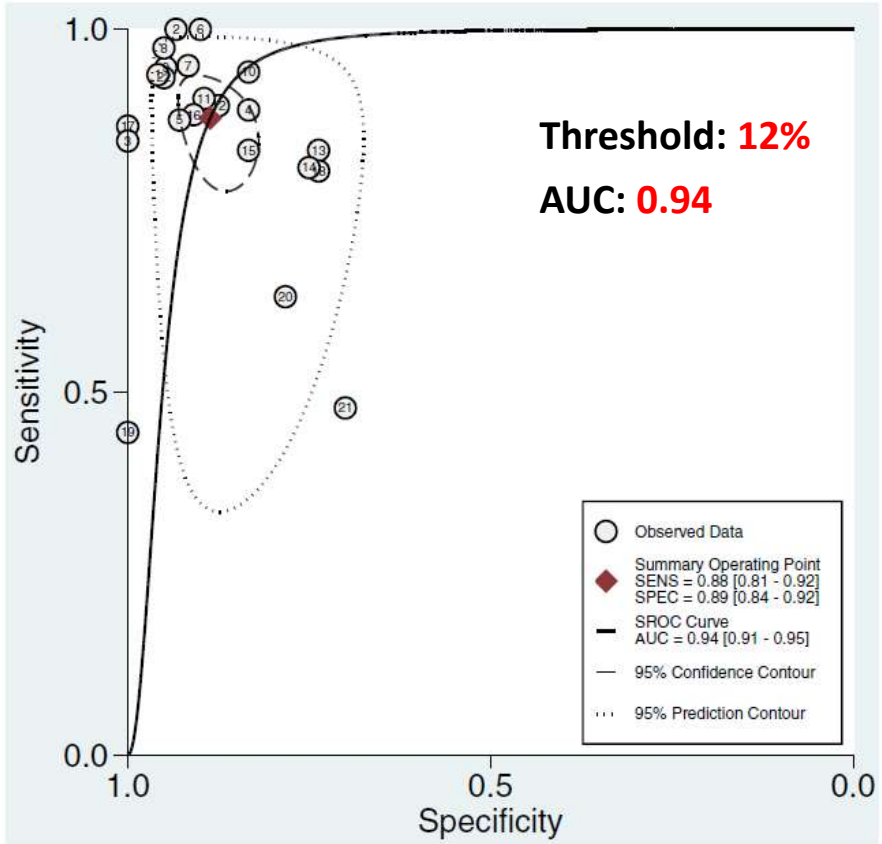
22 studies

Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis

Xiaobo Yang and Bin Du*

Critical Care 2014, **18**:650

807 pts



Pulse Pressure Variation

Calculated automatically and displayed in real-time

by functional hemodynamic monitors

Arterial pressure waveform analysis → **Stroke volume**

Stroke Volume Variation

Calculated automatically and **displayed** in **real-time**

by functional hemodynamic monitors



Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature*

Paul E. Marik, MD, FCCM; Rodrigo Cavallazzi, MD; Taiender Vasu, MD; Amyn Hirani, MD

Crit Care Med 2009; 37:2642–2647

685 pts

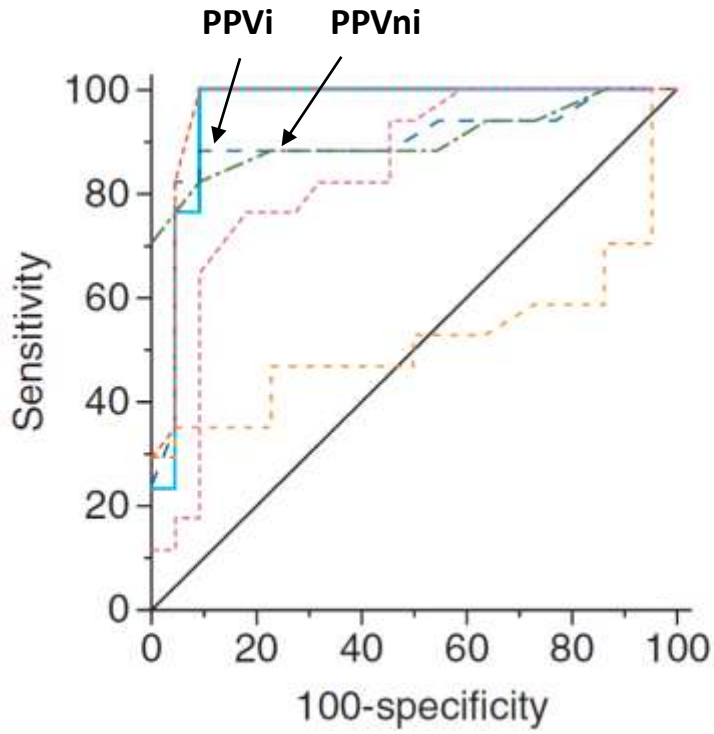
	AUC
PPV	0.94 (0.93–0.95)
SPV	0.86 (0.82–0.90)
SVV	0.84 (0.78–0.88)
LVEDAI	0.64 (0.53–0.74)
GEDVI	0.56 (0.37–0.67)
CVP	0.55 (0.48–0.62)

Prediction of fluid responsiveness by a continuous non-invasive assessment of arterial pressure in critically ill patients: comparison with four other dynamic indices

X. Monnet[1,2]*, M. Dres[1,2], A. Ferré[1,2], G. Le Teuff[4], M. Jozwiak[1,2], A. Bleibtreu[1,2], M.-C. Le Deley[4], D. Chemla[1,3], C. Richard[1,2] and J.-L. Teboul[1,2]

British Journal of Anaesthesia **109** (3): 330–8 (2012)

Non-invasive
finger blood pressure monitoring **device**



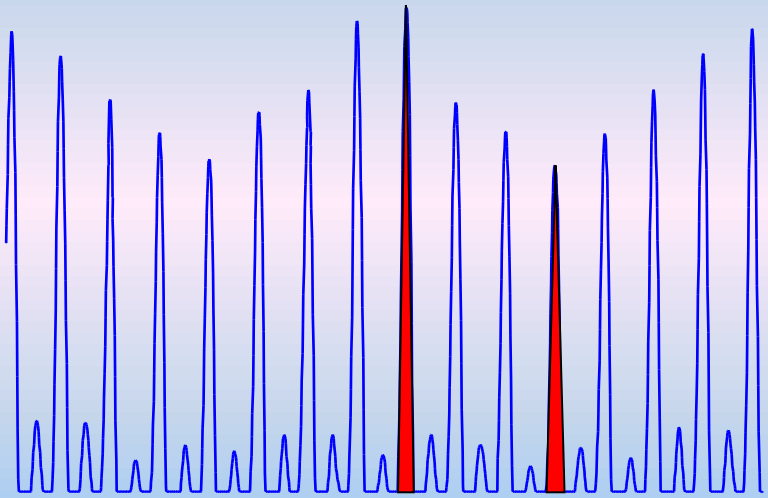
Intensive Care Med (2005) 31:1195–1201

ORIGINAL

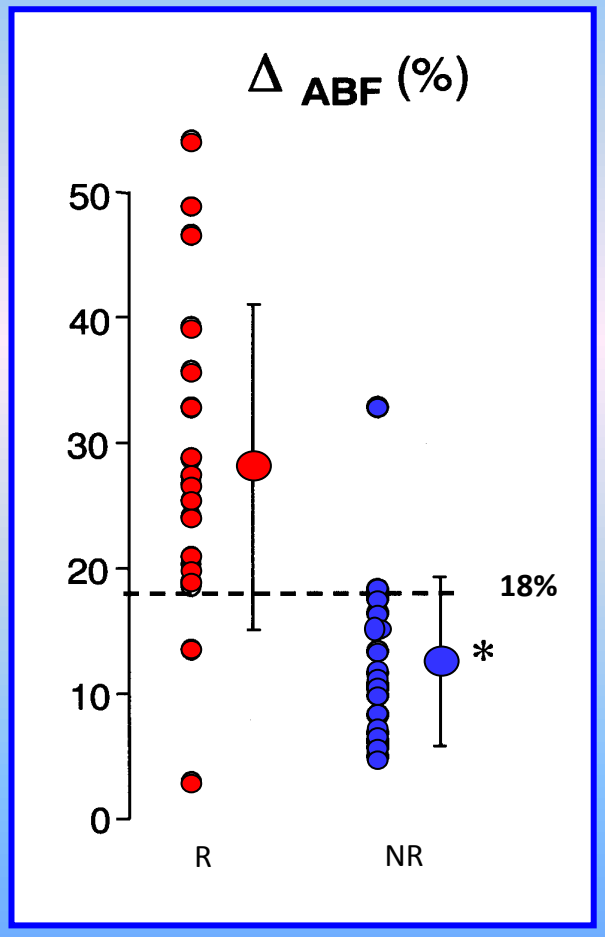
Xavier Monnet
Mario Rienzo
David Osman
Nadia Anguel
Christian Richard
Michael R. Pinsky
Jean-Louis Teboul

Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients

Esophageal Doppler



$$\Delta ABF\ \% = \frac{ABF\ max - ABF\ min}{(ABF\ max + ABF\ min)/2}$$



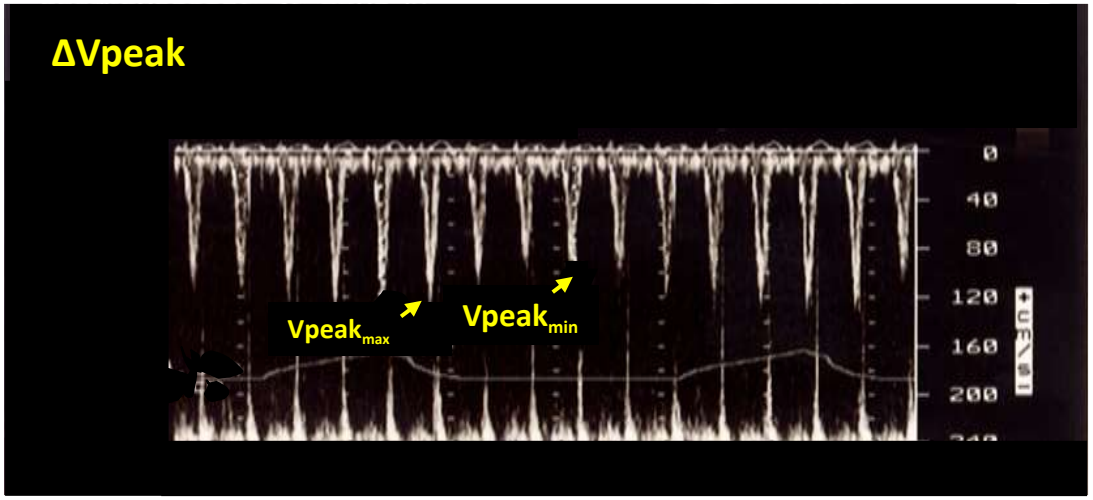
Respiratory Changes in Aortic Blood Velocity as an Indicator of Fluid Responsiveness in Ventilated Patients With Septic Shock*

Marc Feissel, MD; Frédéric Michard, MD; Isabelle Mangin, MD; Olivier Ruyer, MD; Jean-Pierre Faller, MD; and Jean-Louis Teboul, MD, PhD

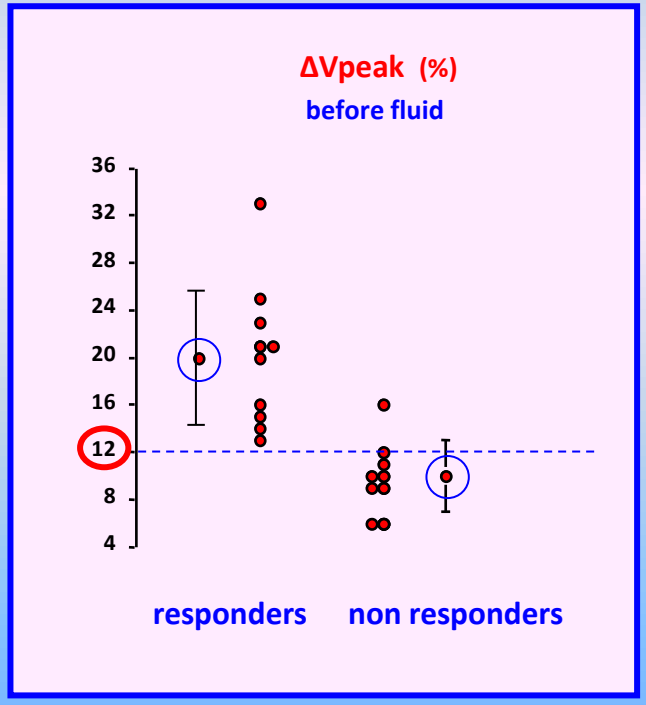
CHEST 2001; 119:867–873

Doppler-echo

ΔVpeak



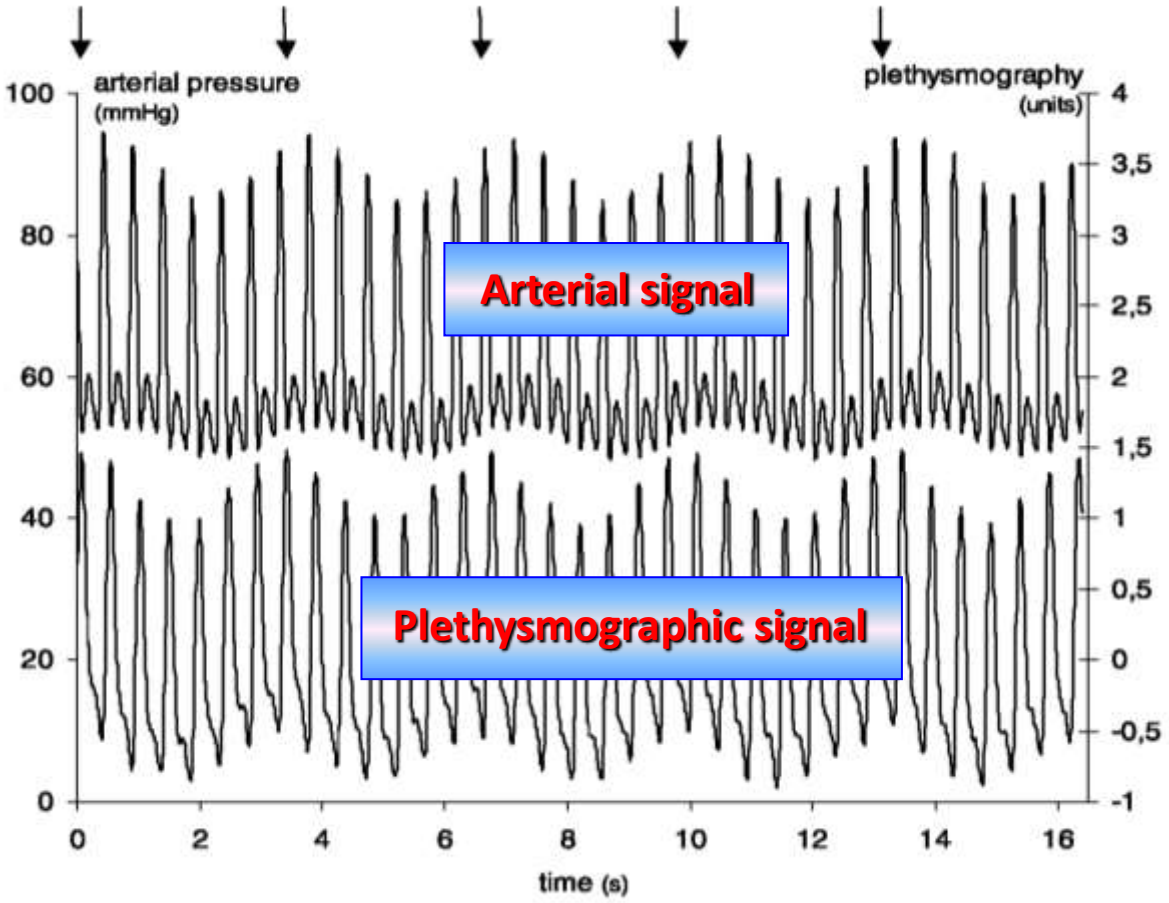
$$\Delta Vpeak = \frac{Vpeak\ max - Vpeak\ min}{(Vpeak\ max + Vpeak\ min) / 2}$$



Arterial Versus Plethysmographic Dynamic Indices to Test Responsiveness for Testing Fluid Administration in Hypotensive Patients: A Clinical Trial

Giuseppe Natalini, Antonio Rosano, Maria Taranto, Barbara Faggian, Elena Vittorielli, Achille Bernardini.

Anesth Analg 2006;103:1478–84



Cut-off values:

ΔPP: 15 %

ΔP_{pleth}: 15 %

Intensive Care Med (2012) 38:1429–1437

REVIEW

Claudio Sandroni
Fabio Cavallaro
Cristina Marano
Chiara Falcone
Paolo De Santis
Massimo Antonelli

Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: a systematic review and meta-analysis

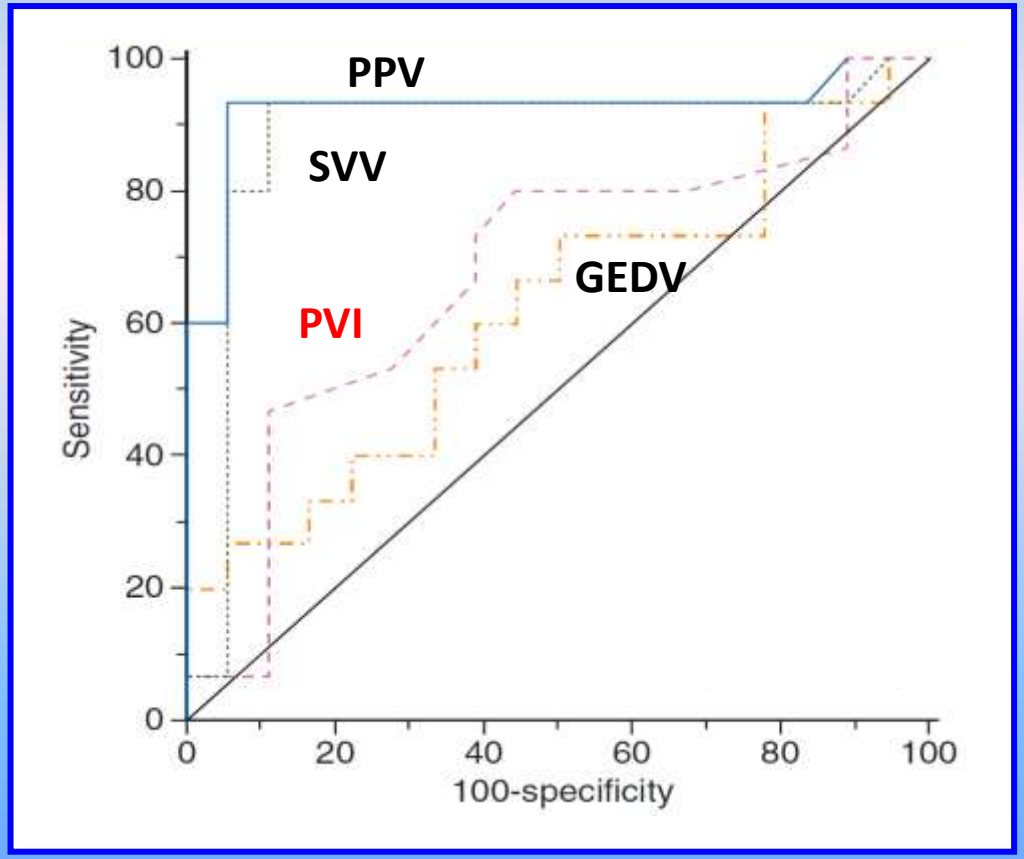
References (first author)	Index	Number of patients/boluses	% Responders	Best threshold	AUC (SE)	Sensitivity	Specificity
Natalini	ΔPOP	22/31	61.0	15.0	0.70 (0.094)	0.63	0.83
Solus-Biguenet	ΔPOP	8/54	42.0	9.5	0.68 (0.071)	0.64	0.68
Cannesson	ΔPOP	25/25	60.0	13.0	0.85 (0.081)	0.93	0.90
Feissel	ΔPOP	23/28	64.0	14.0	0.94 (0.050)	0.94	0.80
Wyffels	ΔPOP	32/32	62.5	11.8	0.89 (0.061)	0.90	0.83
Hoiseth	ΔPOP	25/34	64.7	11.4	0.72 (0.082)	0.86	0.67
Cannesson	ΔPOP[b]	25/25	64.0	12.0	0.94 (0.043)	0.87	0.89
	PVI	25/25	64.0	14.0	0.93 (0.051)	0.81	1.00
Zimmermann	PVI	20/20	75.0	9.5	0.97 (0.033)	0.93	1.00
Desgranges	PVI	28/28	68.0	12.0	0.84 (0.077)	0.74	0.67
Hood (large bolus)	PVI	25/25	88.0	10.0	0.96 (0.031)	0.86	1.00
Hood (small bolus)	PVI	25/63	36.5	10.0	0.71 (0.071)	0.65	0.67
Overall[a]		233/365	62.3 ± 14.0	9.5–15.0	0.85 [0.79–0.92]	0.80 [0.74–0.85]	0.76 [0.68–0.82]

British Journal of Anaesthesia 110 (2): 207–13 (2013)

BJA

Pleth variability index is a weak predictor of fluid responsiveness in patients receiving norepinephrine

X. Monnet[1,2*], L. Guérin[1,2], M. Jozwiak[1,2], A. Bataille[1,2], F. Julien[1,2], C. Richard[1,2] and J.-L. Teboul[1,2]

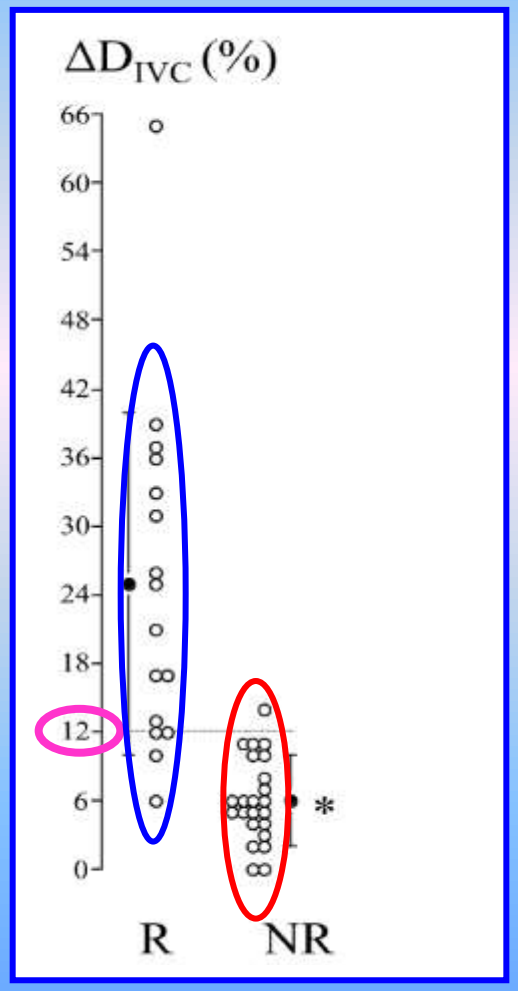


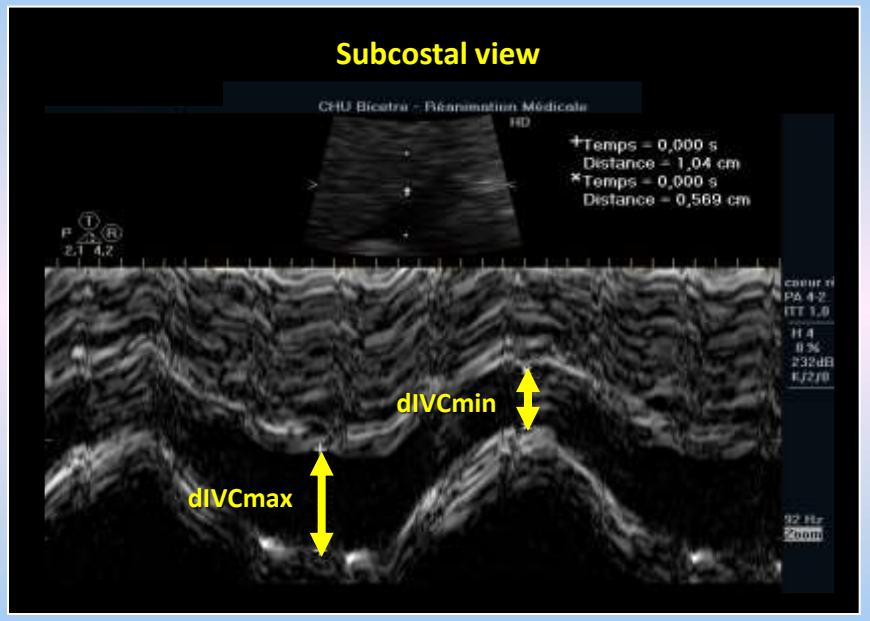
Intensive Care Med (2004) 30:1834–1837

BRIEF REPORT

Marc Feissel
Frédéric Michard
Jean-Pierre Faller
Jean-Louis Teboul

The respiratory variation in inferior vena cava diameter as a guide to fluid therapy



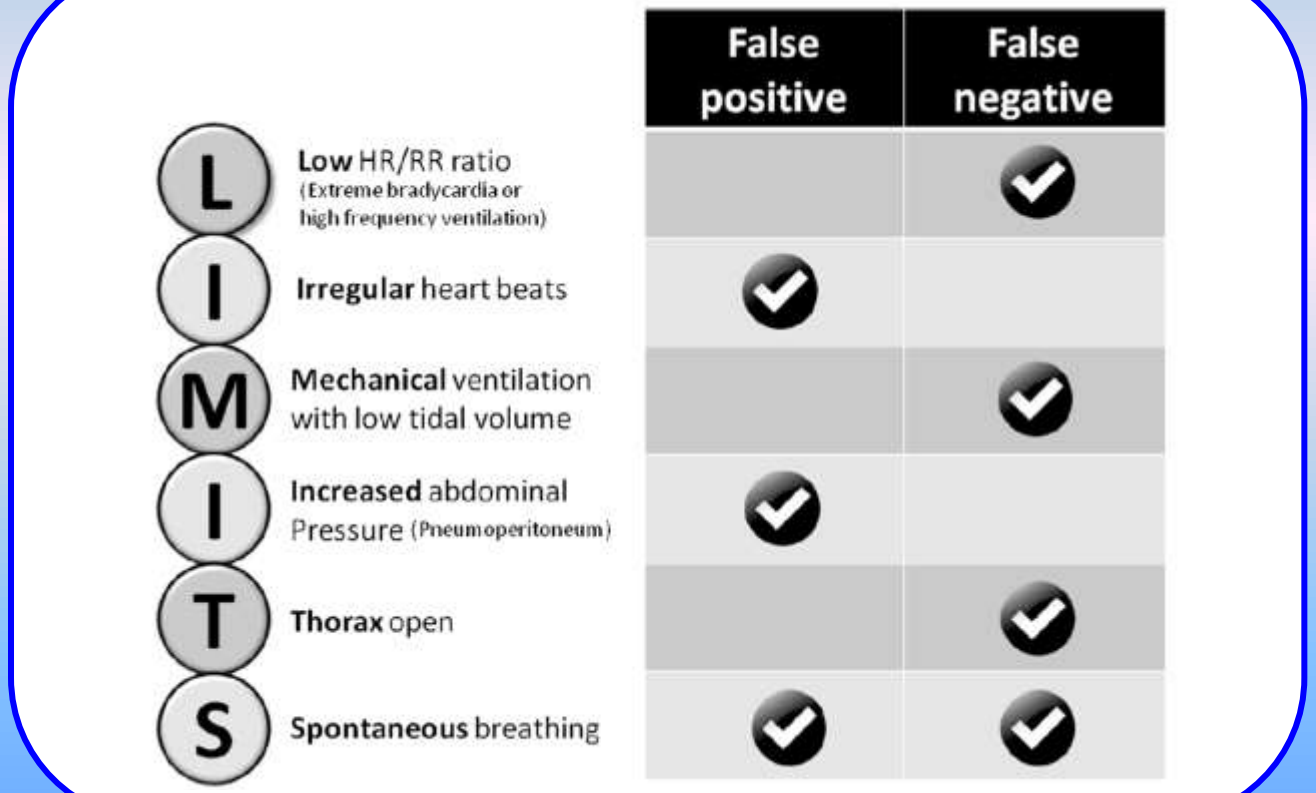


$$\Delta\ dIVC\ \% = \frac{dIVCmax - dIVCmin}{(dIVCmax + dIVCmin)/2}$$

Applicability of pulse pressure variation: how many shades of grey?

Frederic Michard[1*], Denis Chemla[2] and Jean-Louis Teboul[3]

Critical Care (2015) 19:144



Limitations of respiratory variability indices

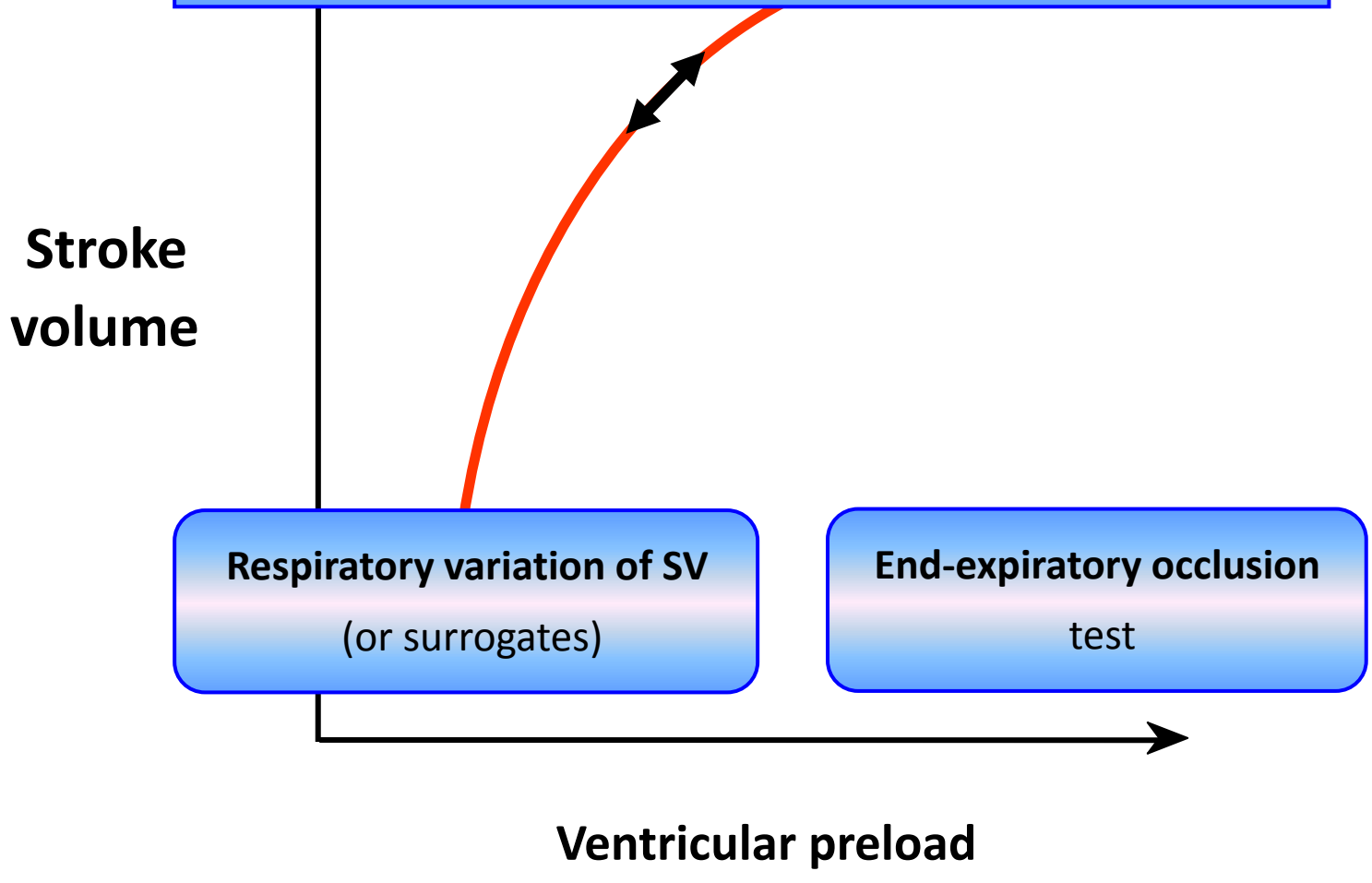
- impossible to interpret in pts with **spontaneous breathing activity**
- impossible to interpret in patients with **arrhythmias**
- difficult to interpret if **tidal volume** is **too low**
- difficult to interpret if **lung compliance** is **too low**

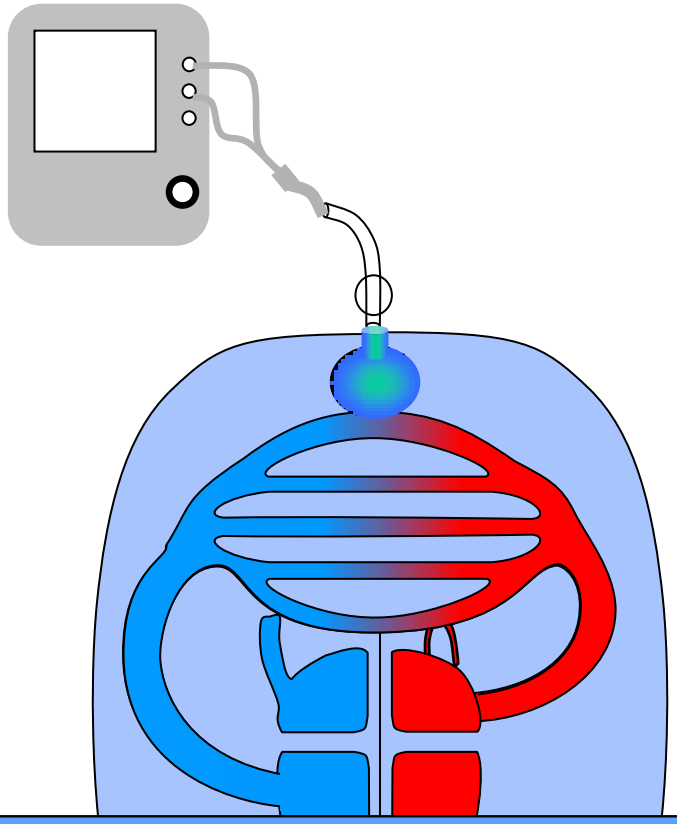
In all these situations and in case of any doubt about interpretation

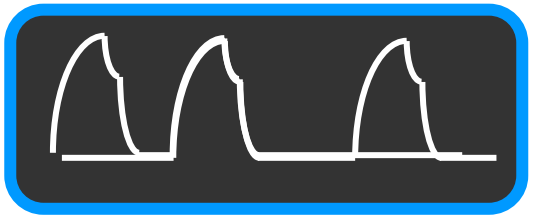
other reliable dynamic tests are required

… and are now available

Heart-lung interaction indices







End-expiratory occlusion

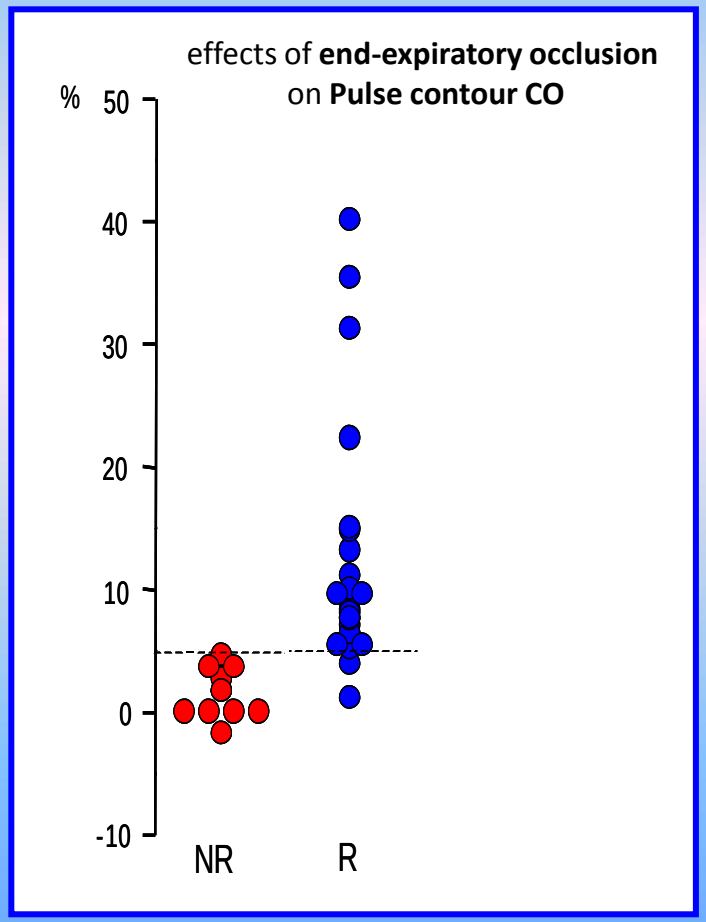
Fluid responders should be identified

by an **increase** in their **CO** during the **end-expiration occlusion** test

Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients

Xavier Monnet, MD, PhD; David Osman, MD; Christophe Ridel, MD; Bouchra Lamia, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2009; 37:951–956



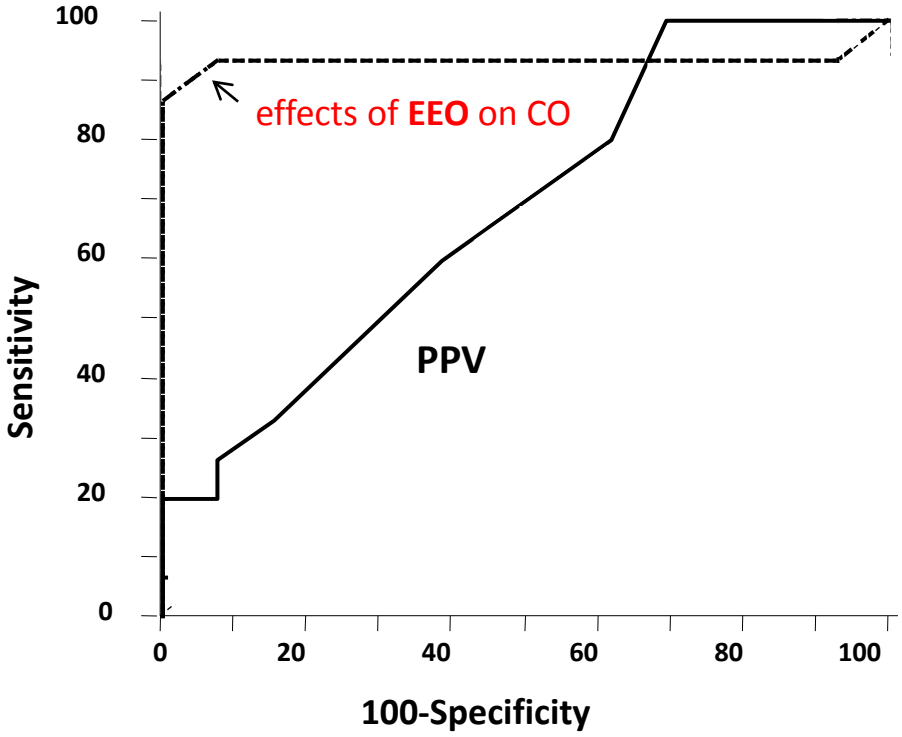
Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance

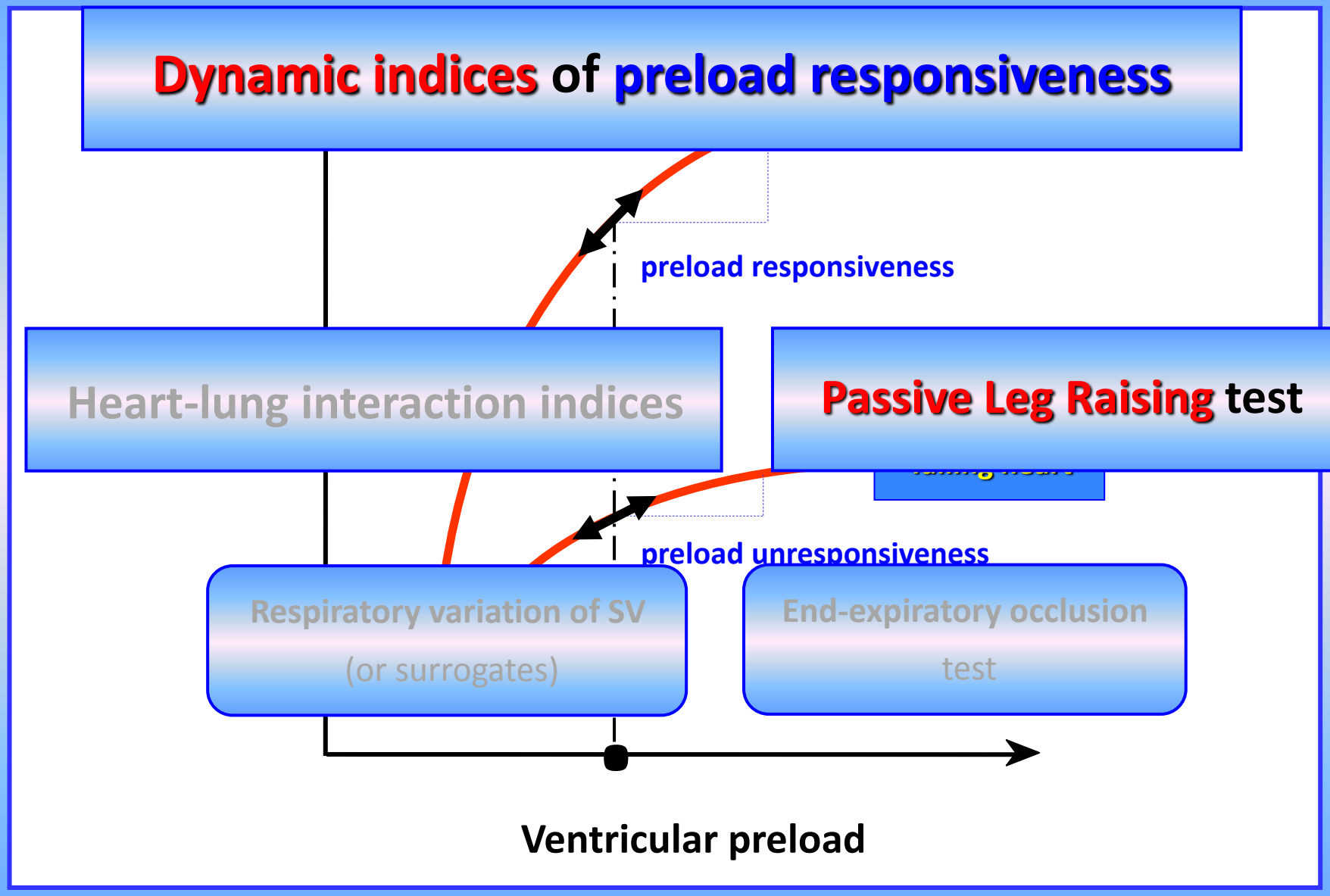
Xavier Monnet, MD, PhD; Alexandre Bleibtreu, MD; Alexis Ferre, MD; Martin Dres, MD; Rim Gharbi, MD; Christian Richard. MD: Jean-Louis Teboul. MD. PhD

Crit Care Med 2012; 40:152–157

Lung compliance

< 30 mL/cmH_2O




Dynamic indices of preload responsiveness
preload responsiveness
Heart-lung interaction indices
Passive Leg Raising test
preload unresponsiveness
Respiratory variation of SV
(or surrogates)
End-expiratory occlusion
test
Ventricular preload

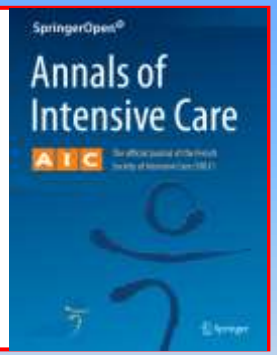
Annals of Intensive Care 2011, **1**:1

Annals of Intensive Care
a SpringerOpen Journal

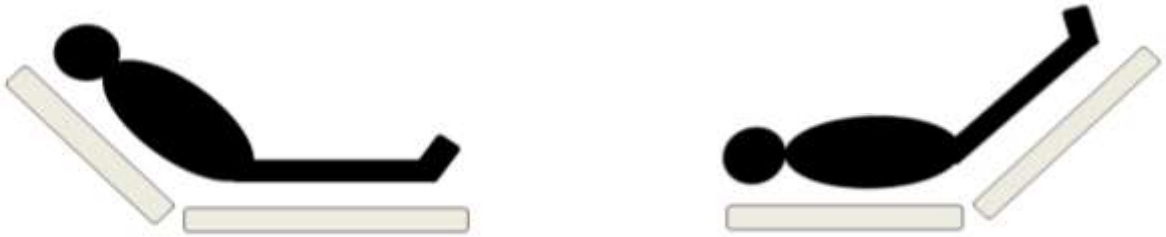
REVIEW Open Access

Hemodynamic parameters to guide fluid therapy

Paul E Marik[1*], Xavier Monnet[2], Jean-Louis Teboul[2]



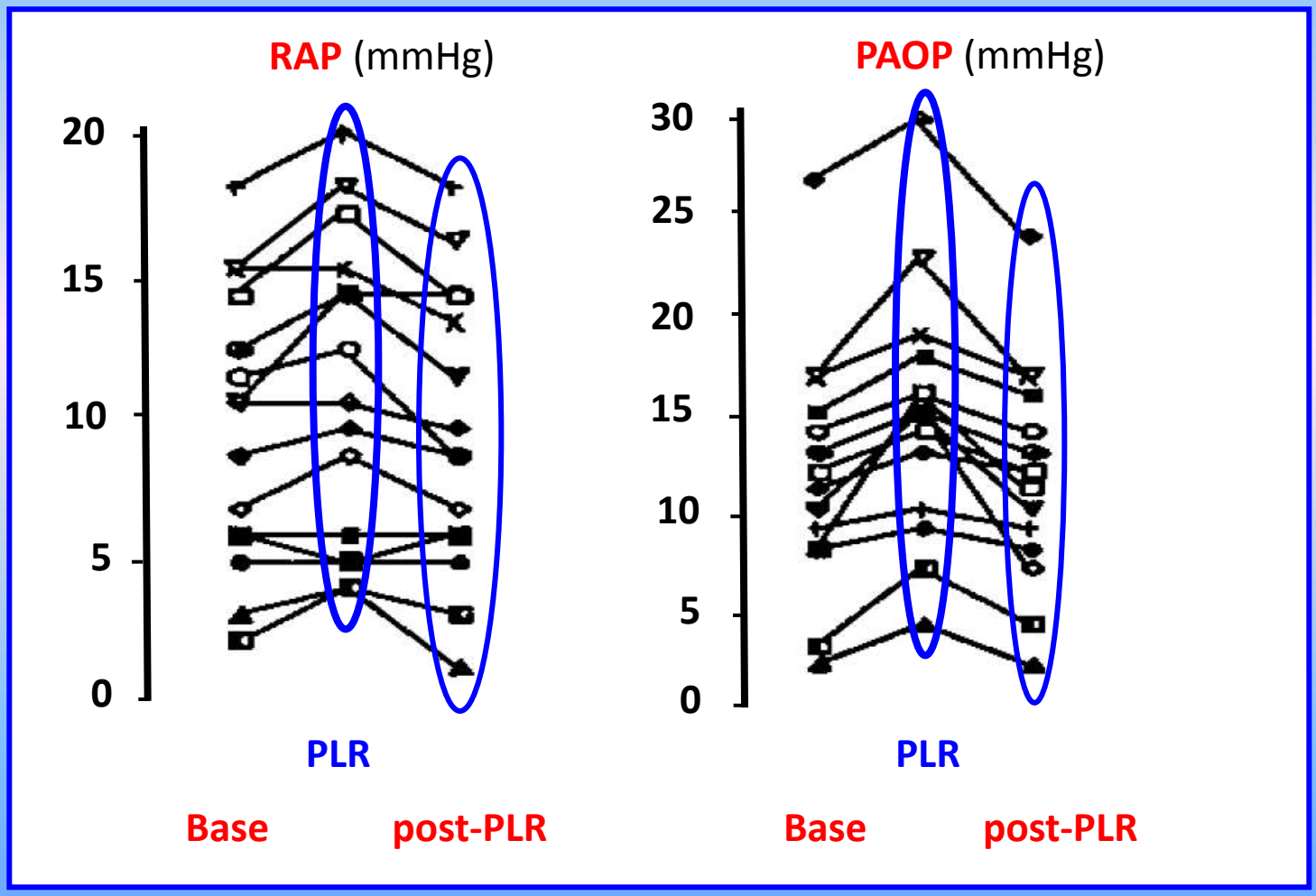
transfer of blood
from the legs and abdominal
compartments



Changes in BP Induced by Passive Leg Raising Predict Response to Fluid Loading in Critically Ill Patients*

Thierry Boulain, MD; Jean-Michel Achard, MD; Jean-Louis Teboul, MD; Christian Richard, MD; Dominique Perrotin, MD; and Guy Ginies, MD

CHEST 2002; 121:1245–1252

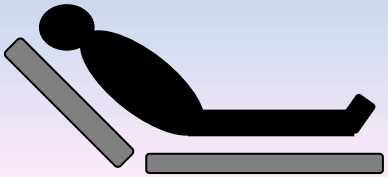


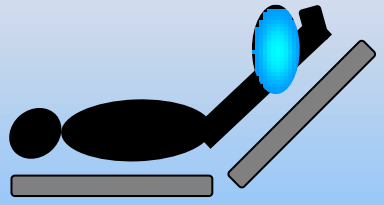
Intensive Care Med (2008) 34:659–663

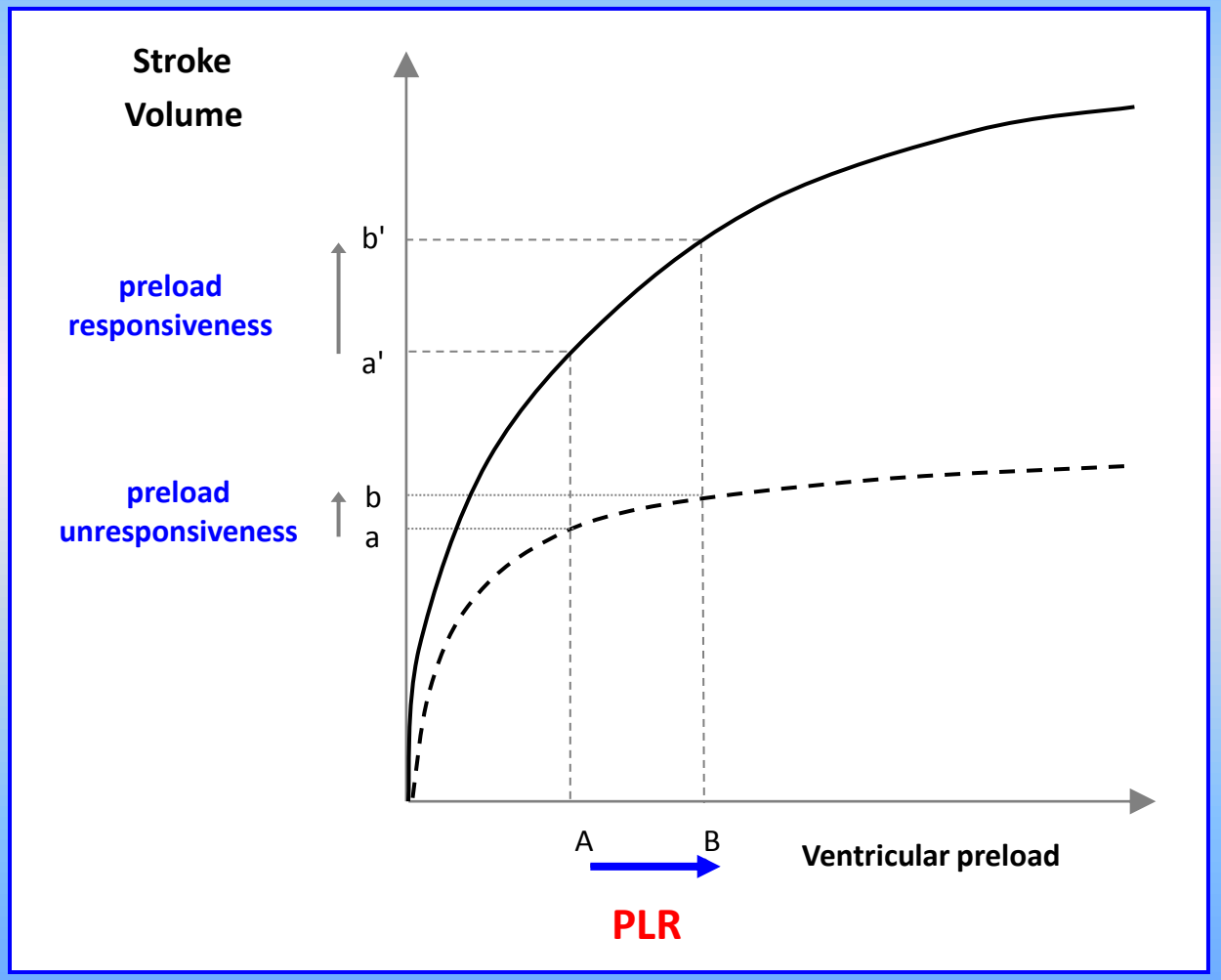
CLINICAL COMMENTARY

Xavier Monnet
Jean-Louis Teboul

Passive leg raising





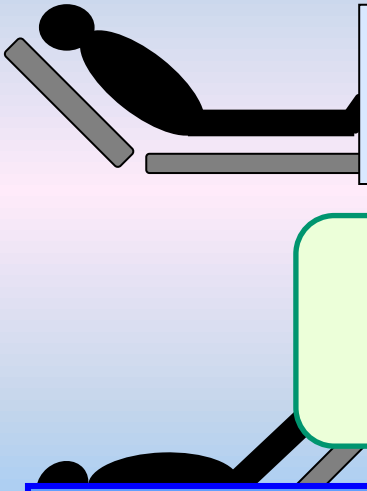


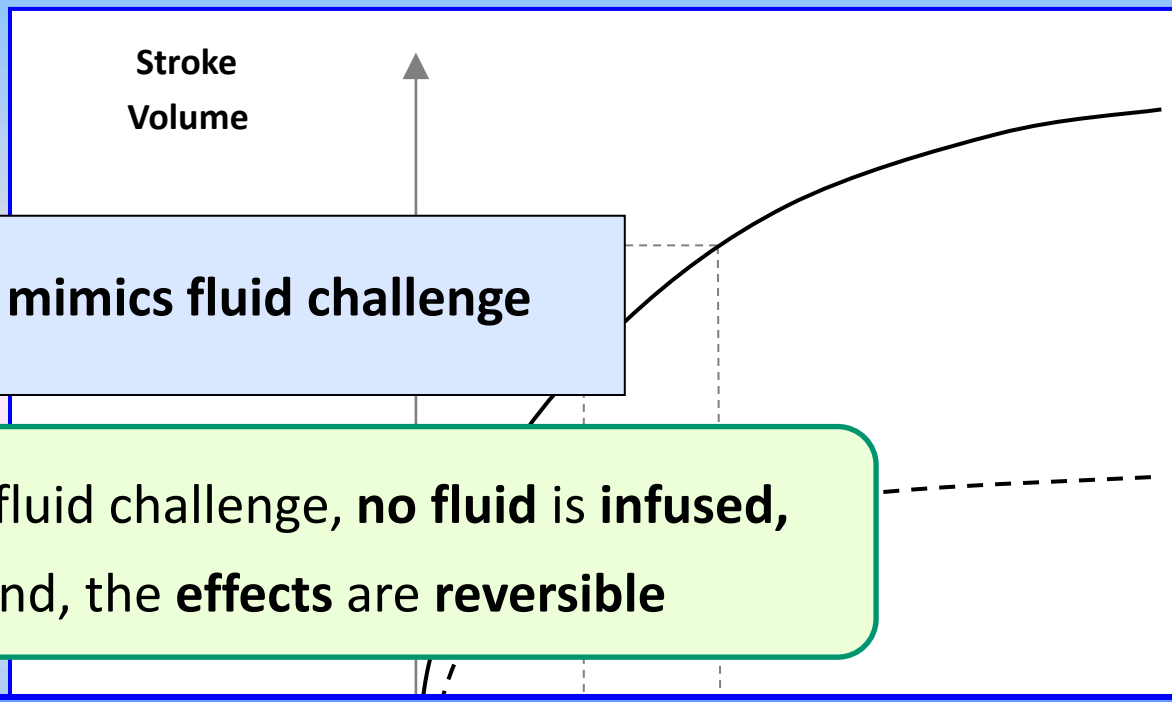
Intensive Care Med (2008) 34:659–663

CLINICAL COMMENTARY

Xavier Monnet
Jean-Louis Teboul

Passive leg raising





PLR mimics fluid challenge

Unlike fluid challenge, **no fluid** is **infused,**

and, the **effects** are **reversible**

The hemodynamic response to PLR

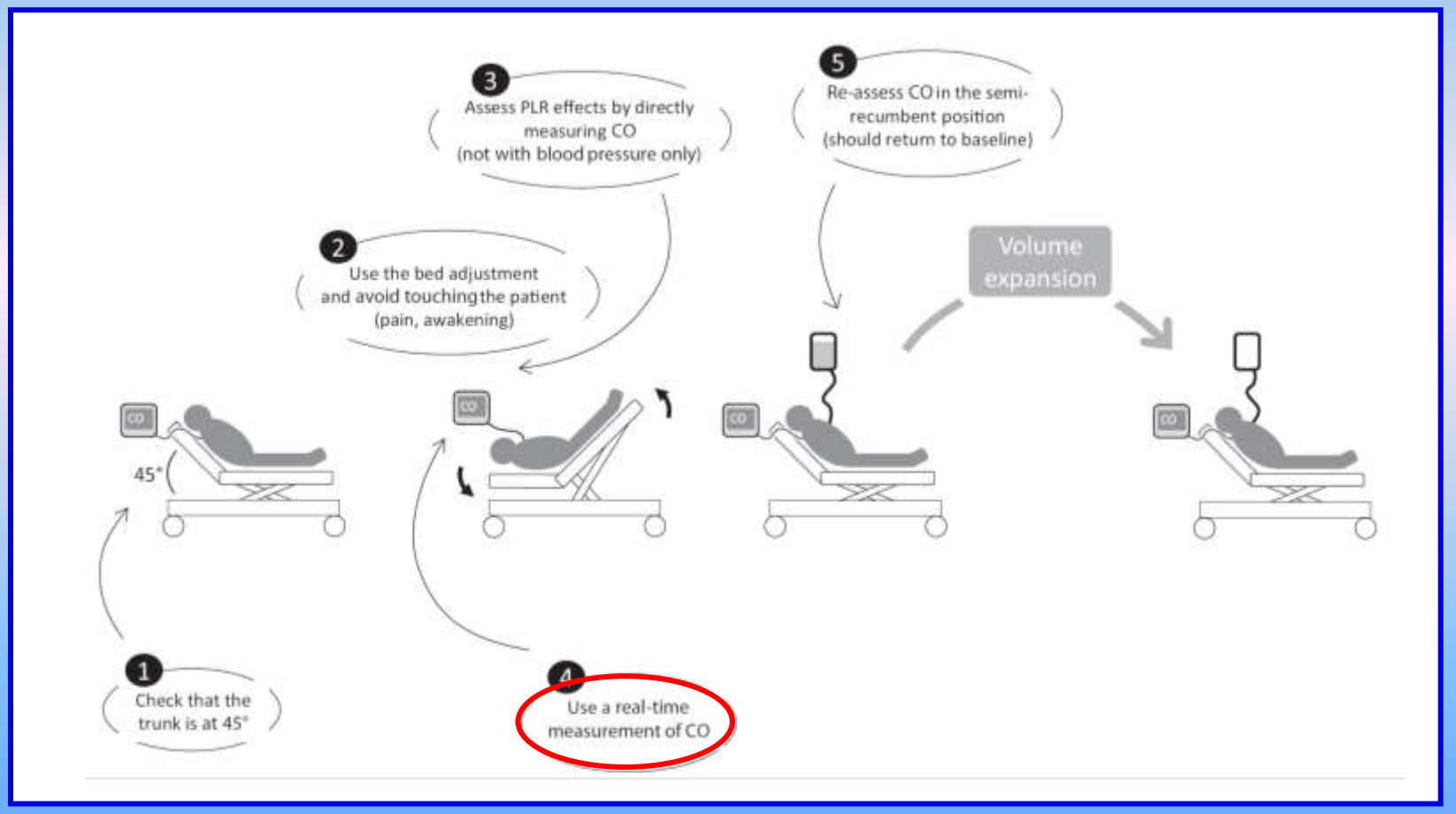
can predict the hemodynamic response to volume infusion

EDITORIAL

Passive leg raising: five rules, not a drop of fluid!

Xavier Monnet[1,2*] and Jean-Louis Teboul[1,2]

Crit Care 2015, 19:18



Passive Leg Raising: the advantages

- **PLR** provides a good **prediction** of **fluid responsiveness**

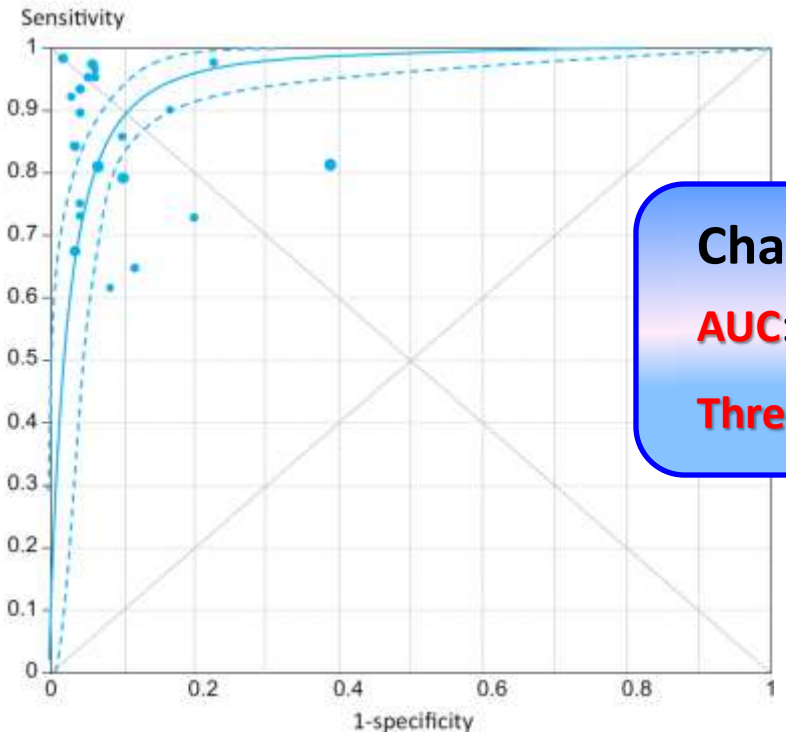
Intensive Care Med 2016

ORIGINAL

Xavier Monnet
Paul Marik
Jean-Louis Teboul

Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis

21 *clinical studies*



Changes in CO

AUC: 0.95 ± 0.01

Threshold: 10%

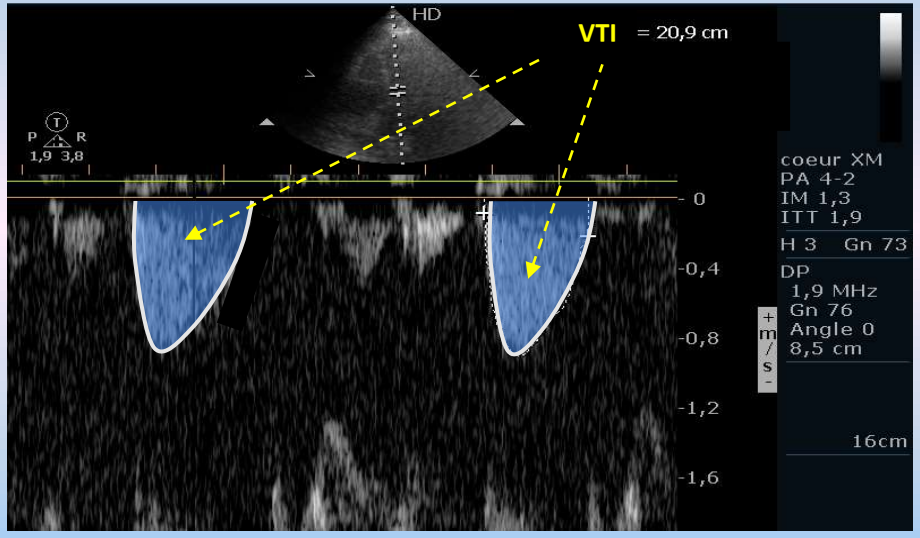
995 pts

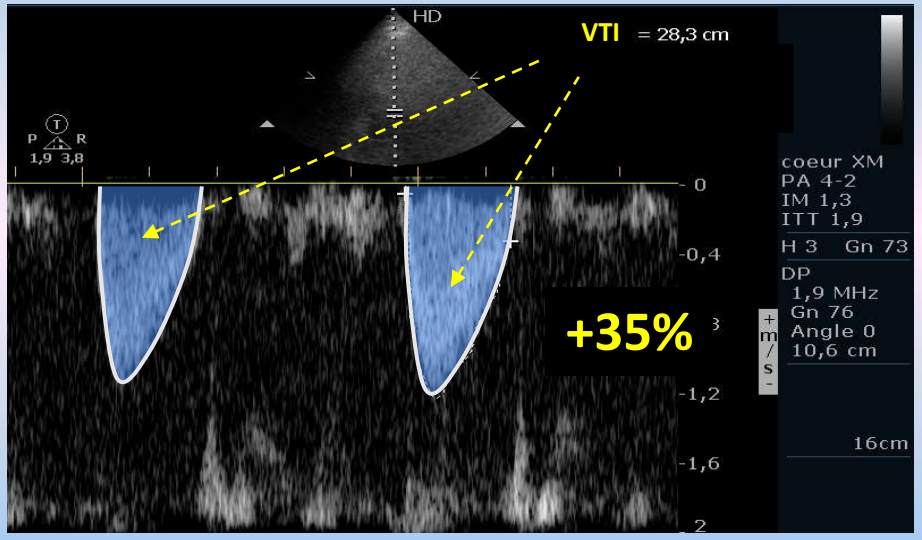
Intensive Care Med (2007) 33:1125–1132
DOI 10.1007/s00134-007-0646-7

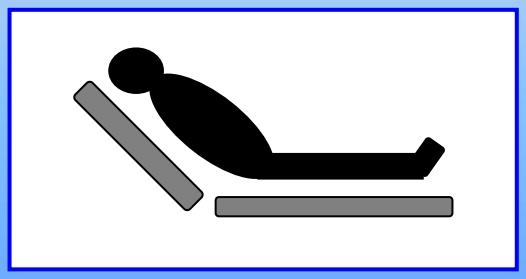
ORIGINAL

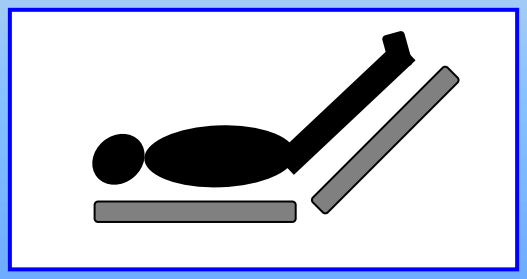
Bouchra Lamia
Ana Ochagavia
Xavier Monnet
Denis Chemla
Christian Richard
Jean-Louis Teboul

Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity









Intensive Care Med (2007) 33:1125–1132
DOI 10.1007/s00134-007-0646-7

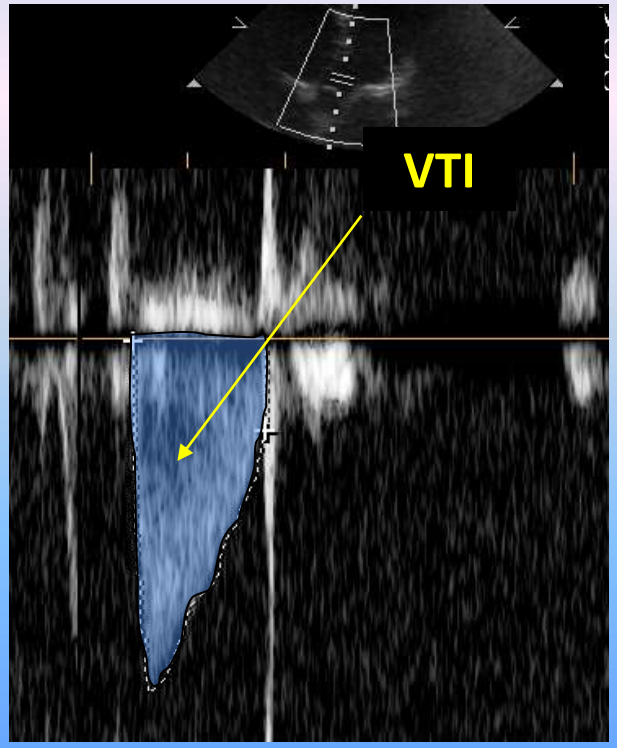
ORIGINAL

Bouchra Lamia
Ana Ochagavia
Xavier Monnet
Denis Chemla
Christian Richard
Jean-Louis Teboul

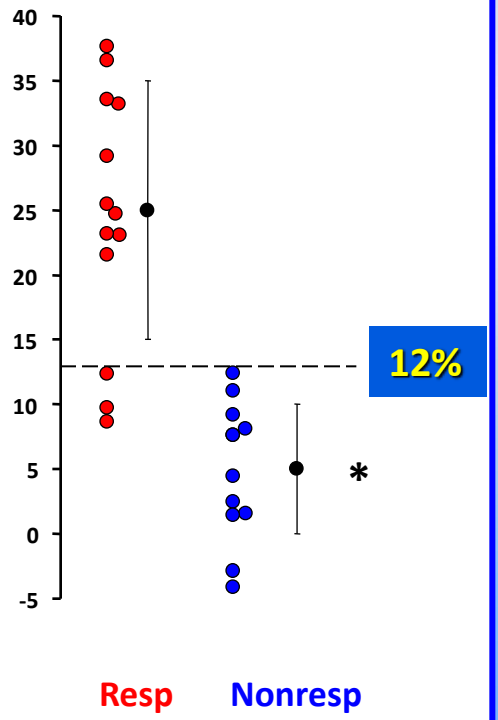
Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity

24 pts with circulatory failure and **SB**

TTE before and after 500 mL saline



PLR-induced **changes** in **VTIAo** (%)



Passive Leg Raising: the advantages

- **PLR** provides a good **prediction** of **fluid responsiveness**
- **Unlike** fluid challenge, effects of **PLR** are rapidly **reversible**

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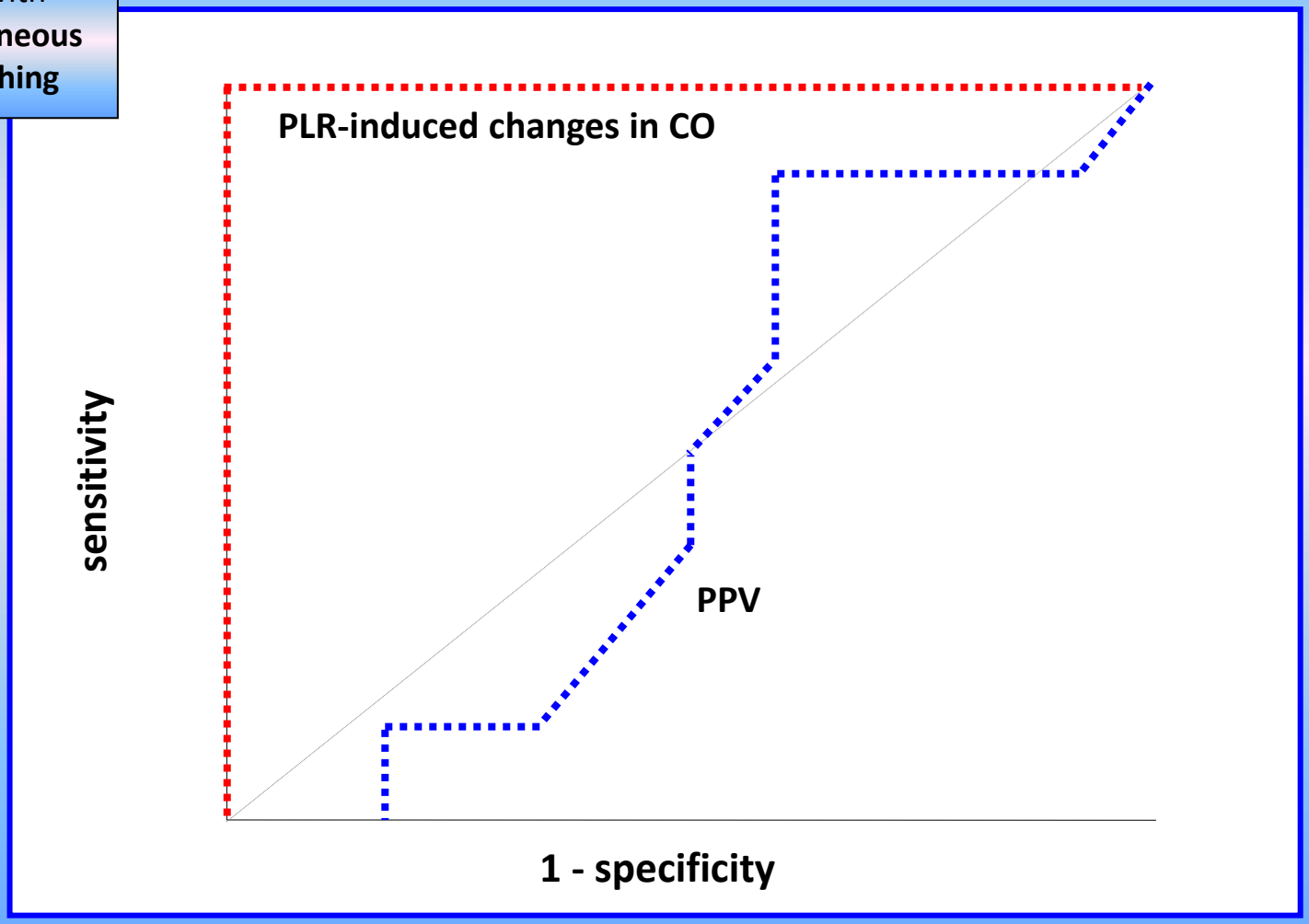
- **PLR** may **well assess** fluid responsiveness
  … in situations where **PPV fails** to do it
    - **Spontaneous Breathing** activity

Passive leg raising predicts fluid responsiveness in the critically ill*

Xavier Monnet, MD, PhD; Mario Rienzo, MD; David Osman, MD; Nadia Anguel, MD; Christian Richard, MD; Michael R. Pinsky, MD, Dr hc; Jean-Louis Teboul, MD, PhD

Crit Care Med 2006; 34:1402–1407

Pts with **spontaneous breathing**



Passive Leg Raising: the advantages

- **PLR** provides a good **prediction** of **fluid responsiveness**
- **Unlike** fluid challenge, effects of **PLR** are rapidly **reversible**
- **PLR** may **well assess** fluid responsiveness
  … in situations where **PPV fails** to do it
  - **Spontaneous Breathing** activity
  - **Low** lung **compliance**

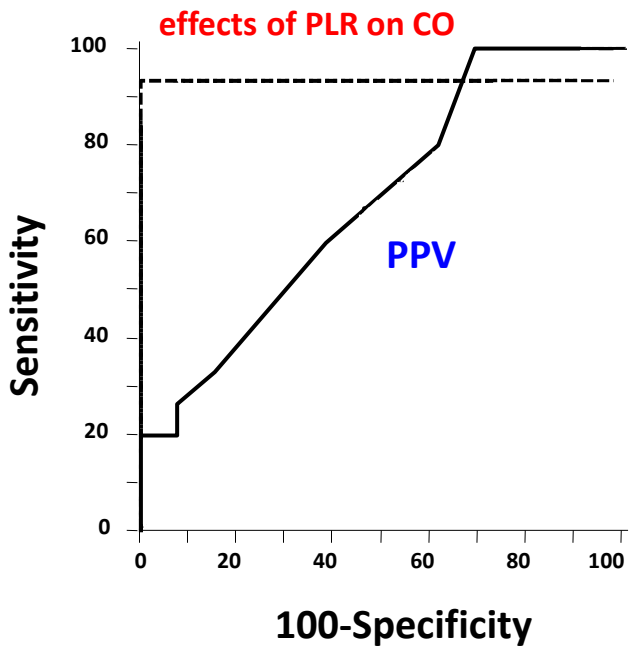
Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance

Xavier Monnet, MD, PhD; Alexandre Bleibtreu, MD; Alexis Ferre, MD; Martin Dres, MD; Rim Gharbi, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2012; 40:152–157

Lung compliance

< 30 mL/cmH_2O



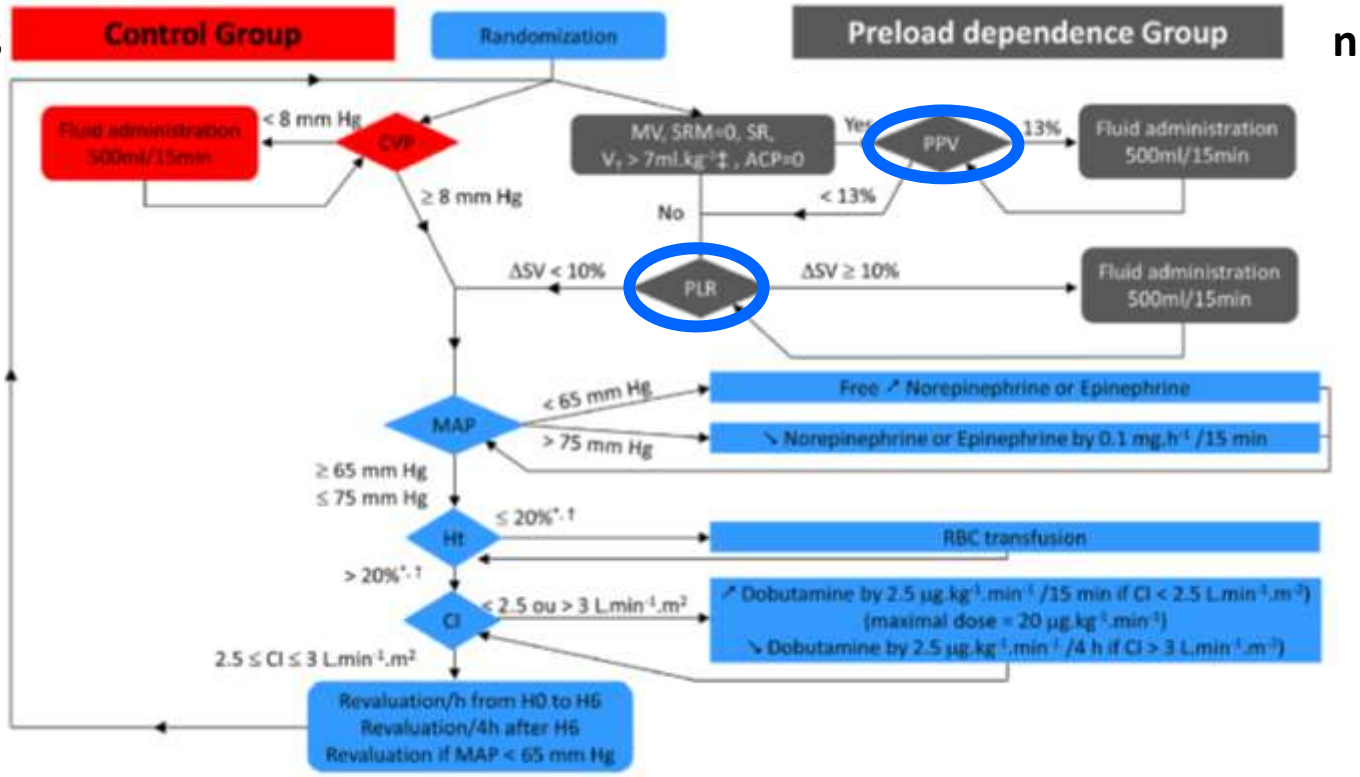
Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial

Jean-Christophe Richard[1,2,3*], Frédérique Bayle[1], Gael Bourdin[1], Véronique Leray[1], Sophie Debord[1], Bertrand Delannoy[1], Alina Cividjian Stoian[1,2], Florent Wallet[1], Hodane Yonis[1,2] and Claude Guerin[1,2,3]

Critical Care (2015) 19:5

Septic shock pts

n = 30 pts



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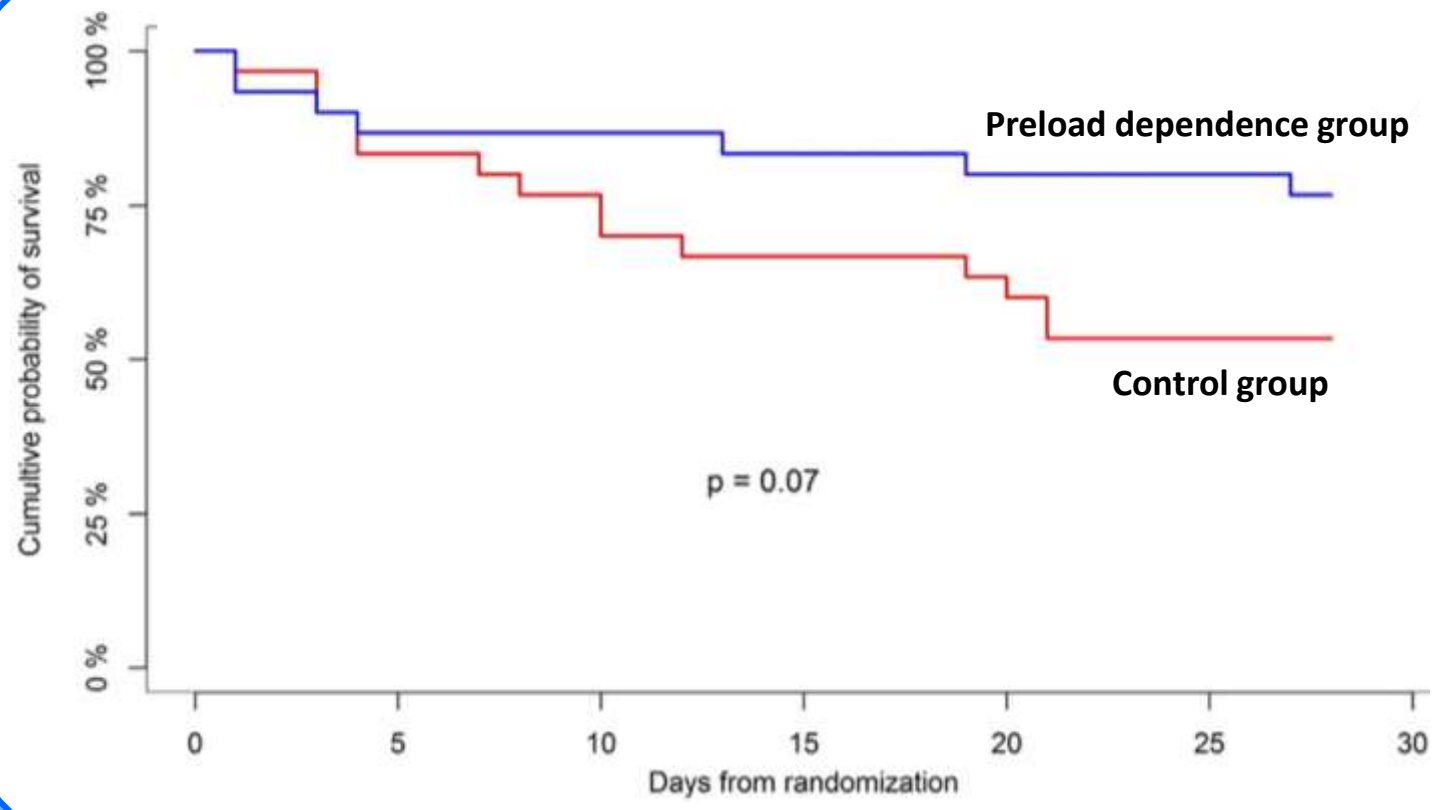
Critical Care (2015) 19:5



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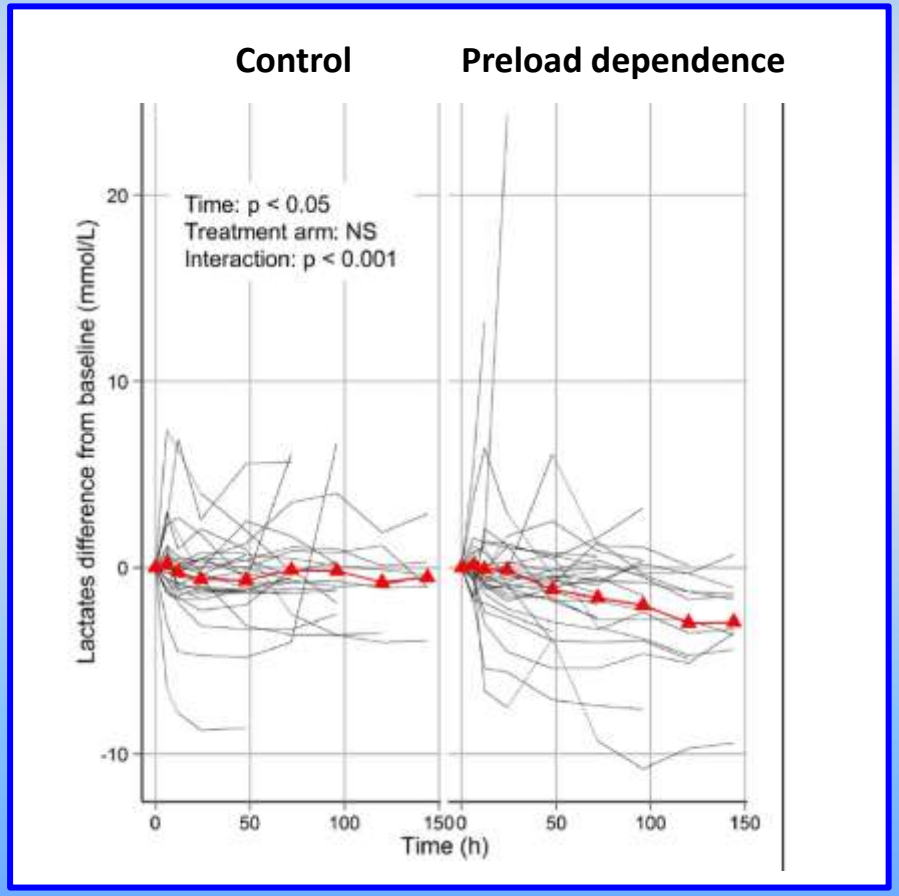
Critical Care (2015) 19:5



Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial

Jean-Christophe Richard[1,2,3*], Frédérique Bayle[1], Gael Bourdin[1], Véronique Leray[1], Sophie Debord[1], Bertrand Delannoy[1], Alina Cividjian Stoian[1,2], Florent Wallet[1], Hodane Yonis[1,2] and Claude Guerin[1,2,3]

Critical Care (2015) 19:5

	Control (n = 30)	Preload dependence (n = 30)
Intravascular volume expansion ITT (mL.day^{-1})	986 [654-1,624]	446 [295-1,105] *
Intravascular volume expansion PP (mL.day^{-1})	917 [639-1,511]	383 [211-604] *
RBC transfusion (mL.day^{-1})	178 [82-304]	103 (0-183] *

Intensive Care Med (2014) 40:1795–1815

CONFERENCE REPORTS AND EXPERT PANEL

Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa
Michael R. Pinsky
Jean Louis Teboul
Jean Louis Vincent
Andrew Rhodes

Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

31. We recommend using **dynamic** over static variables to predict **fluid responsiveness**, when applicable

Level 1; QoE moderate (B)

Patient se présentant pour choc septique “extra-hospitalier”

L’**hypovolémie** étant **constante** il est logique d’effectuer un **remplissage précocément sans** se soucier de la **prédiction** de la **réponse** au remplissage

- Be **smart** ….. but **not** too much
- **Don’t waste** too much **time**

Patient se présentant pour choc septique “extra-hospitalier”

L’**hypovolémie** étant **constante** il est logique d’effectuer un **remplissage précocément sans** se soucier de la **prédiction** de la **réponse** au remplissage

→ rythme de **1000** mL sur la **1ère heure** semble raisonable pour débuter

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

N Engl J Med 2014;371:1496-506

Median **time** from presentation to the ED **until randomization**:

- **2h 48 min** in the EDGT group — Fluid **volume** infused during this period: **35** mL/kg
- **2h 42 min** in the usual-care group — Fluid **volume** infused during this period: **35** mL/kg

→ rythme de **1000** mL sur la **1ère heure** semble raisonable pour débuter

Patient se présentant pour choc septique “extra-hospitalier”

L’**hypovolémie** … précocément

sans se sou…

→ rythme…

➢**plus** …

…tanée

➢**mo**… (↘ SpO_2)

One size *does not* fit all!!

Patient se présentant pour choc septique “extra-hospitalier”

L’**hypovolémie** étant **constante** il est logique d’effectuer un **remplissage précocément sans** se soucier de la **prédiction** de la **réponse** au remplissage

→ rythme de **1000** mL sur la **1ère heure** semble raisonable pour débuter

➢**plus** si :

- **PA pincée** suggérant un VES bas
- **marbrures**, **moiteur** de la peau, ↗ **temps** de **recoloration cutanée**
- **fièvre élevée**
- origine **abdominale** du sepsis

➢**moins** si apparition d’une **mauvaise tolérance respiratoire** (dyspnée, ↘ SpO_2)

Après la 1ère heure, si le choc **persiste** : évaluer la **précharge-dépendance**

critical care review

Predicting Fluid Responsiveness in ICU Patients*

A Critical Analysis of the Evidence

Frédéric Michard, MD, PhD; and Jean-Louis Teboul, MD, PhD

CHEST 2002, 121:2000-8

Source	Patients	EC	Fluid	Volume	Speed of	Definition of	Rate of Response, %
Calvin et al[2]							71
Schneider et al[3]							72
Reuse et al[4]							63
Magder et al[5]							52
Diebel et al[6]							59
Diebel et al[7]							40
Wagner and Leatherman[8]							56
Tavernier et al[9]							60
Magder and Lag							45
Tousignant et al[11]							40
Michard et al[12]						15%	40
Feissel et al[13]	19	19	HES	8 mL/kg	30	ΔCO > 15%	53
Total	334	406					52

Only **52%** of patients **responded**

to **fluid** administration

in terms of **CO increase**

Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006; 34:344–353

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	*p* Value
SAPS II score[a] (per point increase)	1.0 (1.0–1.1)	<.001
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial SOFA score (per point increase)	1.1 (1.0–1.1)	.002
Blood stream infection	1.7 (1.2–2.4)	.004
Cirrhosis	2.4 (1.3–4.5)	.008
Pseudomonas infection	1.6 (1.1–2.4)	.017
Medical admission	1.4 (1.0–1.8)	.049
Female gender	1.4 (1.0–1.8)	.044

Patient se présentant pour choc septique "extra-hospitalier"

L'**hypovolémie** étant **constante** il est logique d'effectuer un **remplissage précocément sans** se soucier de la **prédiction** de la **réponse** au remplissage

→ rythme de **1000** mL sur la **1ère heure** semble raisonable pour débuter

➢**plus** si :

- **PA pincée** suggérant un VES bas
- **marbrures**, **moiteur** de la peau, ↗ **temps** de **recoloration cutanée**
- **fièvre élevée**
- origine **abdominale** du sepsis

➢**moins** si apparition d'une **mauvaise tolérance respiratoire** (dyspnée, ↘ SpO_2)

Après la 1ère heure, si le choc **persiste** : évaluer la **précharge-dépendance**

➢soit **lever de jambes passif** (**écho** ou moniteur de DC en temps réel)
➢soit delta **PP** (si interprétable et si **KTA** ou moniteur de DC "**pulse contour**")
➢soit variabilité du diamètre VCI si interprétable (**écho**)

Si **précharge-dépendance** : évaluer l'**eau pulmonaire extravasculaire** et l'**index de perméabilité vasculaire pulmonaire** (thermodilution transpulmonaire), ou la PAPO (Swan-Ganz)

Si **précharge-indépendance, ne plus remplir** sauf si forts risques d'OAP

Patient se présentant pour choc septique “intra-hospitalier”

L’**hypovolémie** étant **inconstante**, il raisonable d’effectuer un **remplissage** plus **prudent** toujours **sans** se soucier de la **prédiction** de la **réponse** au remplissage

→ rythme de **500** mL sur les **30 premières minutes** pour débuter

- **plus** si :
  - **PA pincée** suggérant un VES bas
  - **marbrures**, **moiteur** de la peau, ↗ **temps** de **recoloration cutanée**
  - **fièvre élevée**
  - origine **abdominale** du sepsis, **pertes** liquidiennes évidentes
- **moins** si apparition d’une **mauvaise tolérance respiratoire** (dyspnée, ↘ SpO_2)

Après la 1ère demi-heure, si le choc **persiste** : évaluer la **précharge-dépendance**

- soit **lever de jambes passif** (**écho** ou moniteur de DC en temps réel)
- soit delta **PP** (si interprétable et si **KTA** ou moniteur de DC “**pulse contour**”)
- soit variabilité du diamètre VCI si interprétable (**écho**)

Si ARDS associé, évaluer l’**eau pulmonaire extravasculaire** et l’**index de perméabilité vasculaire pulmonaire** (thermodilution transpulmonaire), ou la PAPO (Swan-Ganz)

Si **précharge-dépendance**, **ne plus remplir** sauf si forts risques d’OAP

Fin du 2ème épisode

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant

Hypovolémie → Remplissage vasculaire

Défaillance vasculaire périphérique → **Vasopresseurs**

Défaillance cardiaque

Vasopresseurs et choc septique

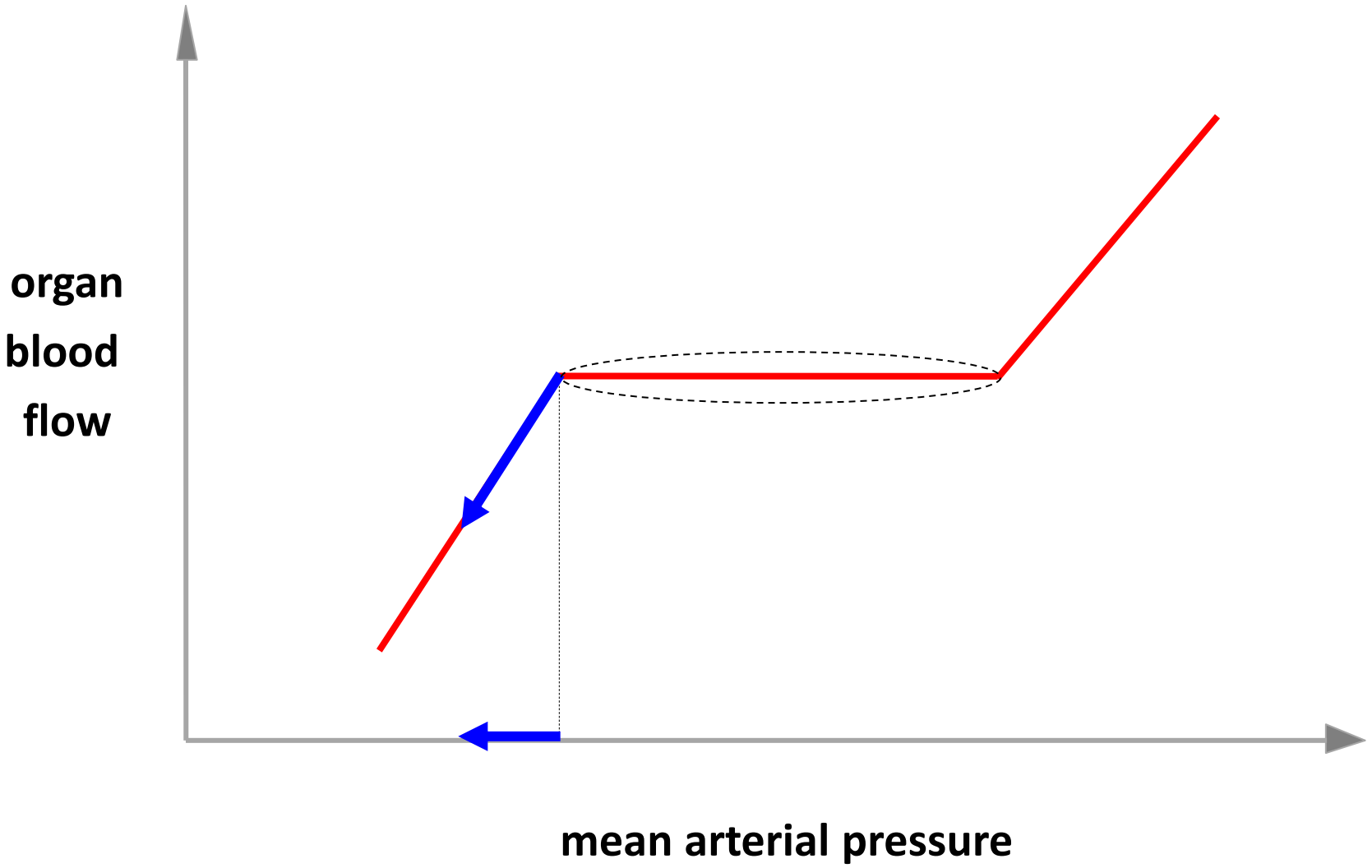
1- Pourquoi ?

2- Quel agent ?

3- Quand le débuter ?

4- Quelle cible?

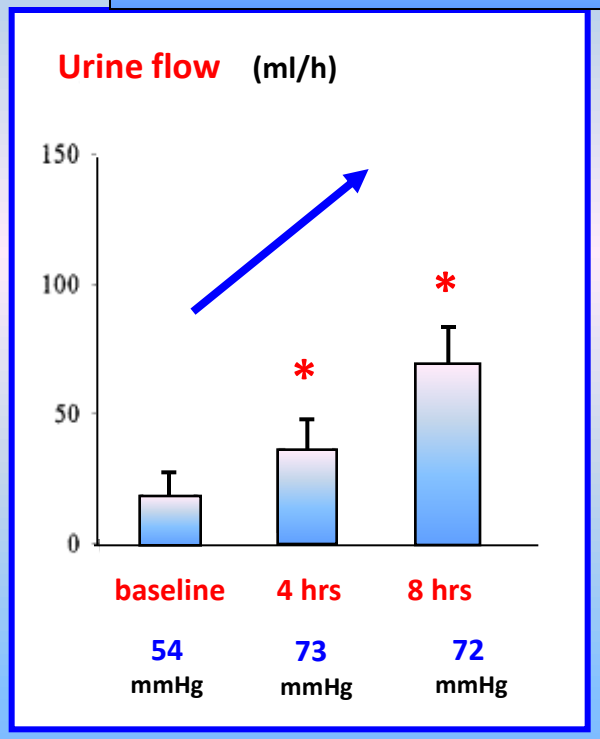
Autoregulation of organ blood flow

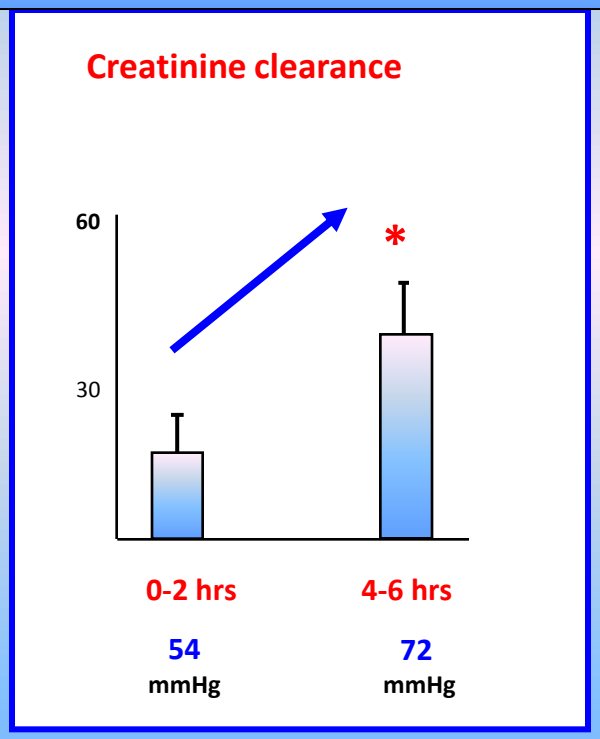


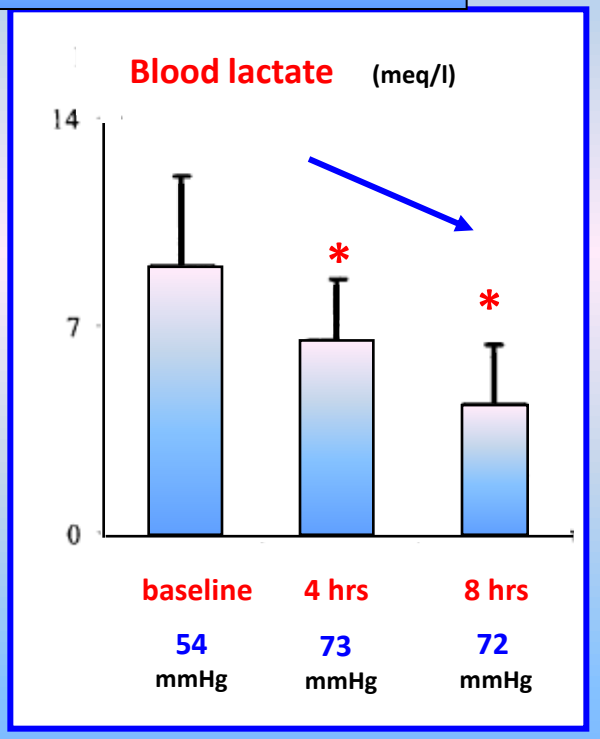
Terlipressin or norepinephrine in hyperdynamic septic shock: A prospective, randomized study*

Jacques Albanèse, MD; Marc Leone, MD; Anne Delmas, MD; Claude Martin, MD, FCCM

Probable "**arterial pressure**" effect

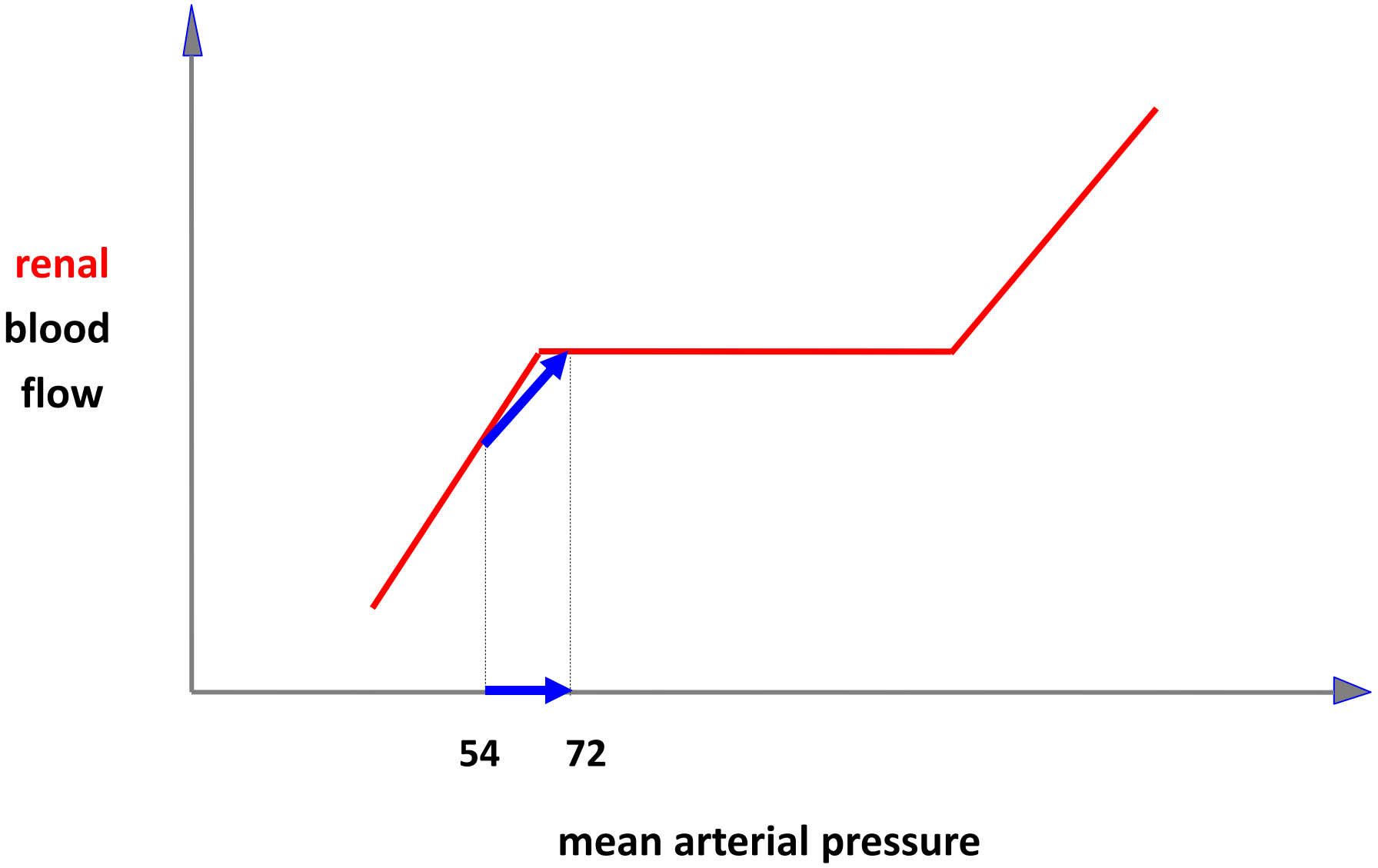






while cardiac output did not change

Autoregulation of renal blood flow



Vasopresseurs et choc septique

1- Pourquoi ?

2- Quel agent ?

3- Quand le débuter ?

4- Quelle cible?

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

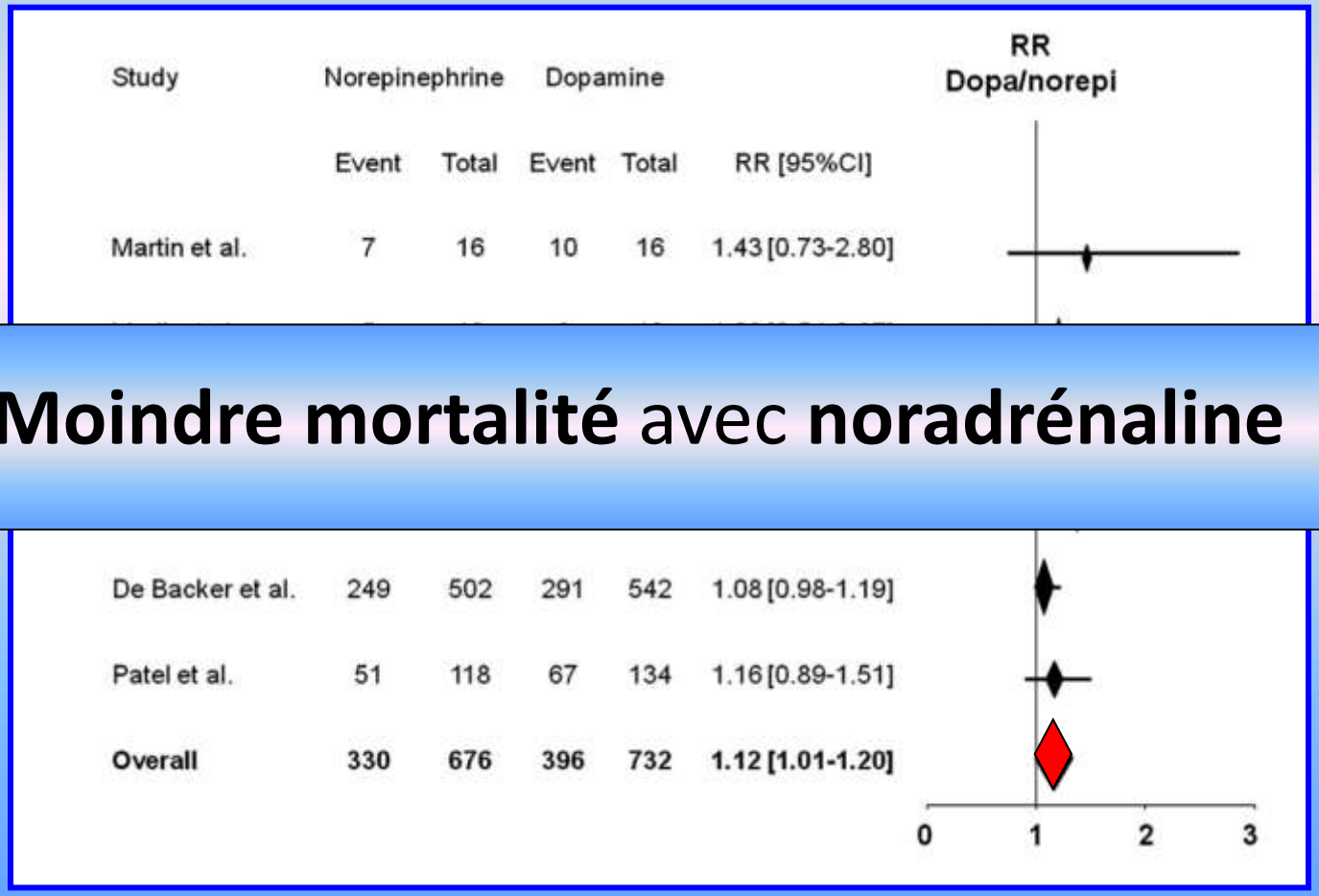
R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

- **Norepinephrine** as the **first choice** vasopressor (1B)

Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Crit Care Med 2012; 40:725–730



Moindre mortalité avec **noradrénaline**

Vasopresseurs et choc septique

1- Pourquoi ?

2- Quel agent ?

3- Quand le débuter ?

4- Quelle cible?

Five arguments to initiate norepinephrine early

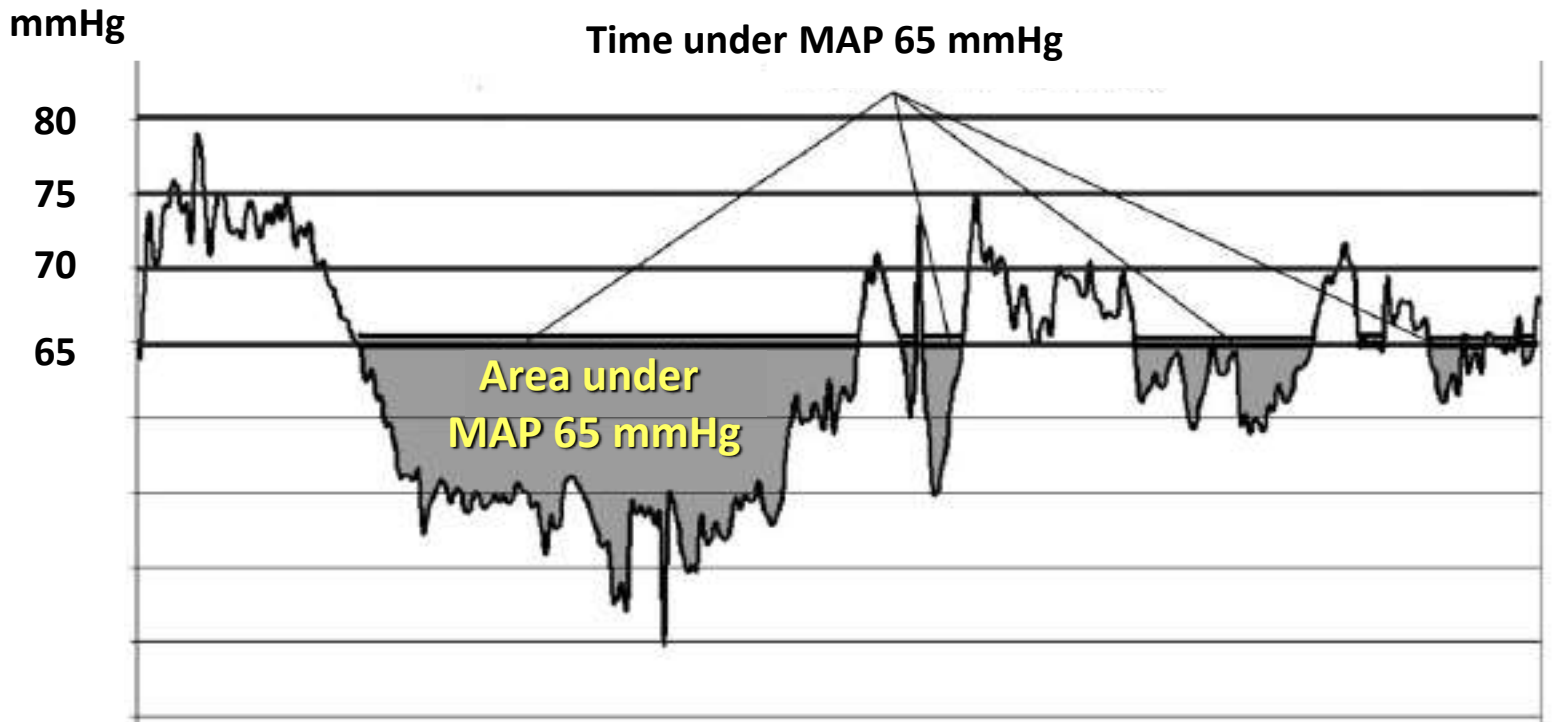
1- Duration and **degree** of hypotension associated with **increased mortality**

Intensive Care Med (2005) 31:1066–1071
DOI 10.1007/s00134-005-2688-z

ORIGINAL

Marjut Varpula
Minna Tallgren
Katri Saukkonen
Liisa-Maria Voipio-Pulkki
Ville Pettilä

Hemodynamic variables related to outcome in septic shock



Area under MAP 65 mmHg **Best predictor of 30-day mortality**

Five arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- NE increases cardiac output, when initiated **early**

Effects of NE on Cardiac Output in patients with septic shock

Studies showing **unchanged cardiac output** with NE	Baseline **Cardiac Index** (L/min/m²)
• Desjars et al Crit Care Med 1987	**5.2**
• Martin et al Chest 1993	**5.3**
• Martin et al Crit Care Med 1999	**5.7**
• Albanese et al Chest 2004	**4.7**
• Albanese et al Crit Care Med 2005	**5.1**

5.2

Effects of NE on Cardiac Output in patients with septic shock

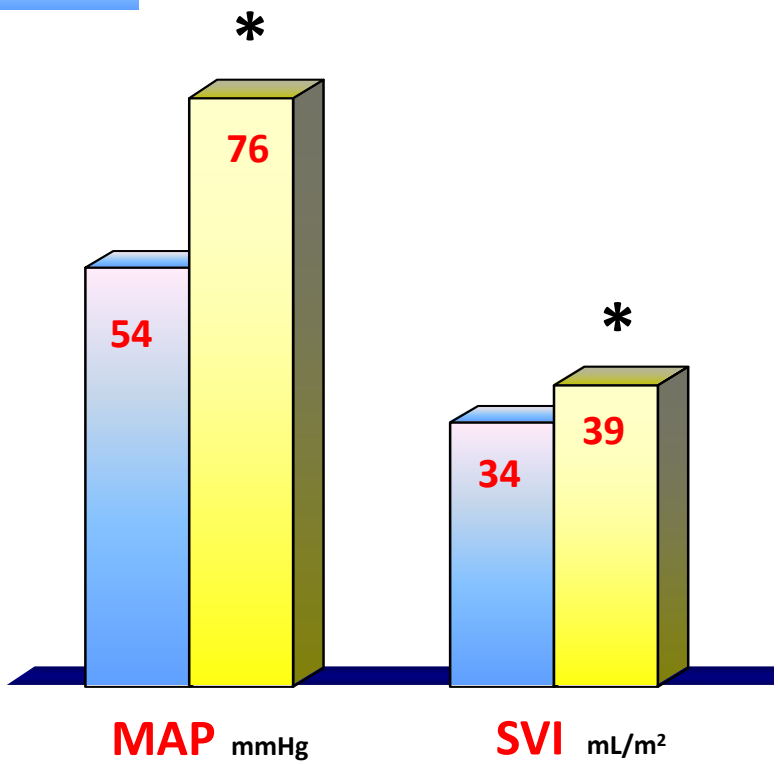
Studies showing **unchanged cardiac output** with NE	Baseline **Cardiac Index** (L/min/m²)	
• Desjars et al Crit Care Med 1987	**5.2**	**5.2**
• Martin et al Chest 1993	**5.3**	
• Martin et al Crit Care Med 1999	**5.7**	
• Albanese et al Chest 2004	**4.7**	
• Albanese et al Crit Care Med 2005	**5.1**	
Studies showing **increased cardiac output** with NE		
• Martin et al Crit Care Med 1999	**4.3**	**3.5**
• Ledoux et al Crit Care Med 2000	**4.7**	
• Jhanji et al Crit Care Med 2009	**3.9**	
• Deruddre et al Intensive Care Med 2007	**3.4**	
• Dubin et al Crit Care 2009	**2.9**	
• Georger et al Intensive Care Med 2010	**3.1**	
• Hamzaoui et al Crit Care 2010	**3.2**	
• Monnet et al Crit Care Med 2011	**2.7**	
• Thooft et al Crit Care 2011	**3.5**	

Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension

Olfa Hamzaoui, Jean-François Georger, Xavier Monnet, Hatem Ksouri, Julien Maizel, Christian Richard, Jean-Louis Teboul*

Critical Care 2010, **14**:R142

105 pts



Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

Xavier Monnet, MD, PhD; Julien Jabot, MD; Julien Maizel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2011; 39:689–694

25 patients with

- **Septic shock**
- NE infusion already in place
- **Diastolic arterial pressure ≤ 40 mmHg,** that justified **to increase NE**
- **Positive PLR test**, defined by an increase in CO ≥ 10% during PLR

Monitoring by

- **PiCCO2**
- **Transesophageal echocardiography**

Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

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Crit Care Med 2011; 39:689–694

0.24 [0.12-0.48] µg/kg/min

↗ NE

0.48 [0.36-0.71] µg/kg/min

B1 **PLR1** **B2** **PLR2**

B1	PLR1	B2	PLR2
Heart rate Arterial pressure CVP LV EDA E wave	Heart rate Arterial pressure CVP LV EDA E wave	Heart rate Arterial pressure CVP LV EDA E wave	Heart rate Arterial pressure CVP LV EDA E wave
CO thermo GEDVi	Pulse contour CO	CO thermo GEDVI	Pulse contour CO

Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

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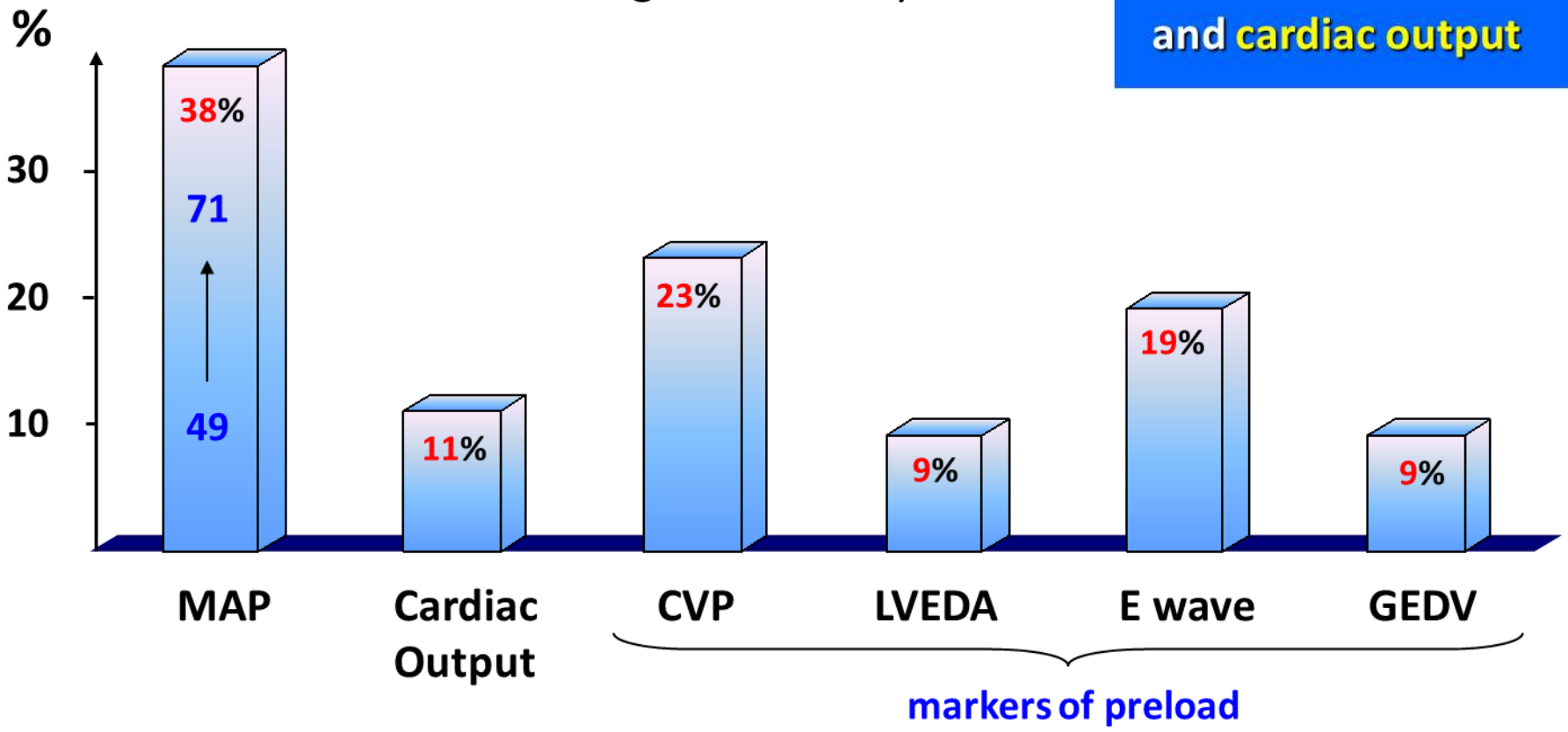
Crit Care Med 2011; 39:689–694

Changes induced by **NE**

NE ↗ cardiac preload and cardiac output



Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension

Olfa Hamzaoui, Jean-François Georger, Xavier Monnet, Hatem Ksouri, Julien Maizel, Christian Richard, Jean-Louis Teboul*

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Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

Xavier Monnet, MD, PhD; Julien Jabot, MD; Julien Maizel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2011; 39:689–694

Messages of these two studies

- NE increases **cardiac preload** … as **fluid** infusion does
- NE **increases CO** in **preload-dependent** patients
- **NE reduces** the degree of **preload-dependency**

How does **NE impact** the **venous circulation**?

by blood **redistribution**
from **unstressed** to **stressed** volume?

Intensive Care Med (2013) 39:1487–1488

EDITORIAL

Jean-Louis Teboul

Mean systemic pressure: we can now estimate it, but for what?

Mean systemic pressure
is the **driving** pressure for **venous return**

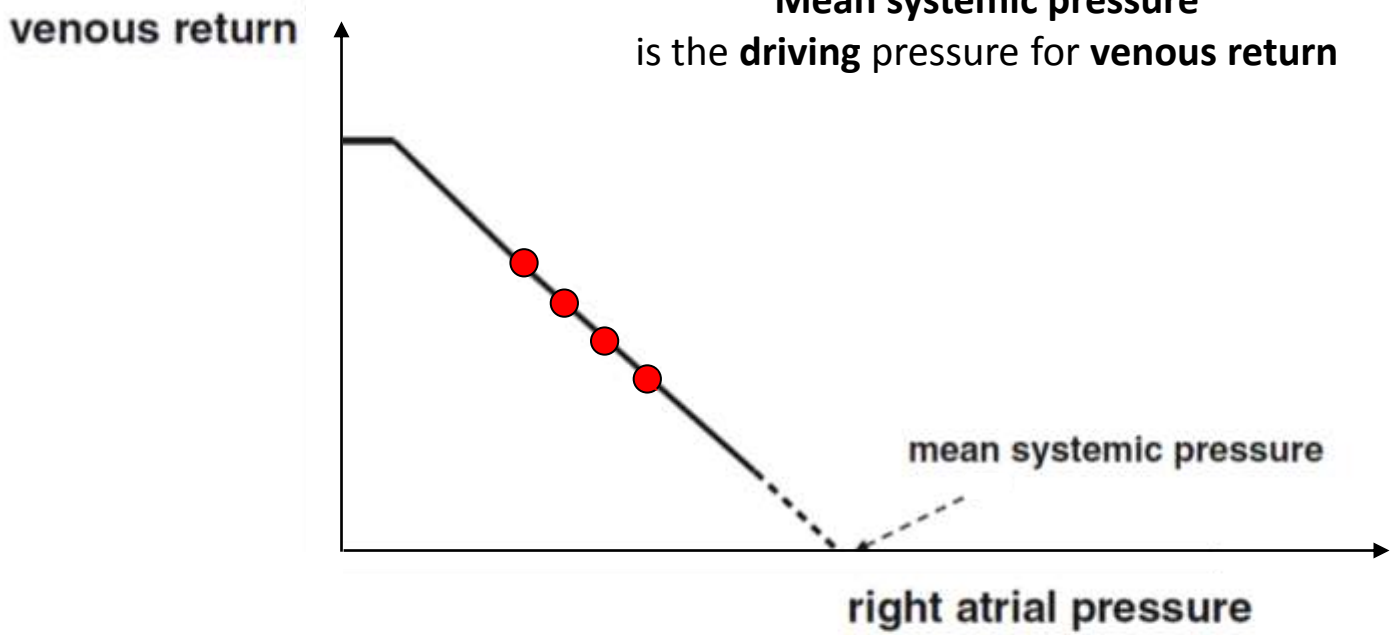
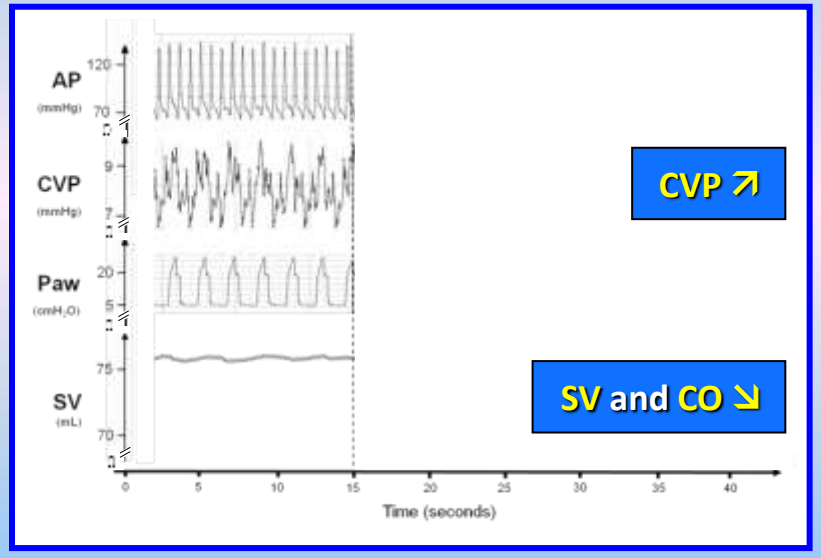


Fig. 1 Relationship between right atrial pressure and venous return according to Guyton's model.

Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*

Romain Persichini, MD; Serena Silva, MD; Jean-Louis Teboul, MD, PhD; Mathieu Jozwiak, MD; Denis Chemla, MD, PhD; Christian Richard, MD; Xavier Monnet, MD, PhD

Crit Care Med 2012; 40:3146–3153



CVP and CO
during an inspiratory occlusion

Repeated **twice** at two levels of **PEEP before** and **after changing** the **NE dose**

Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*

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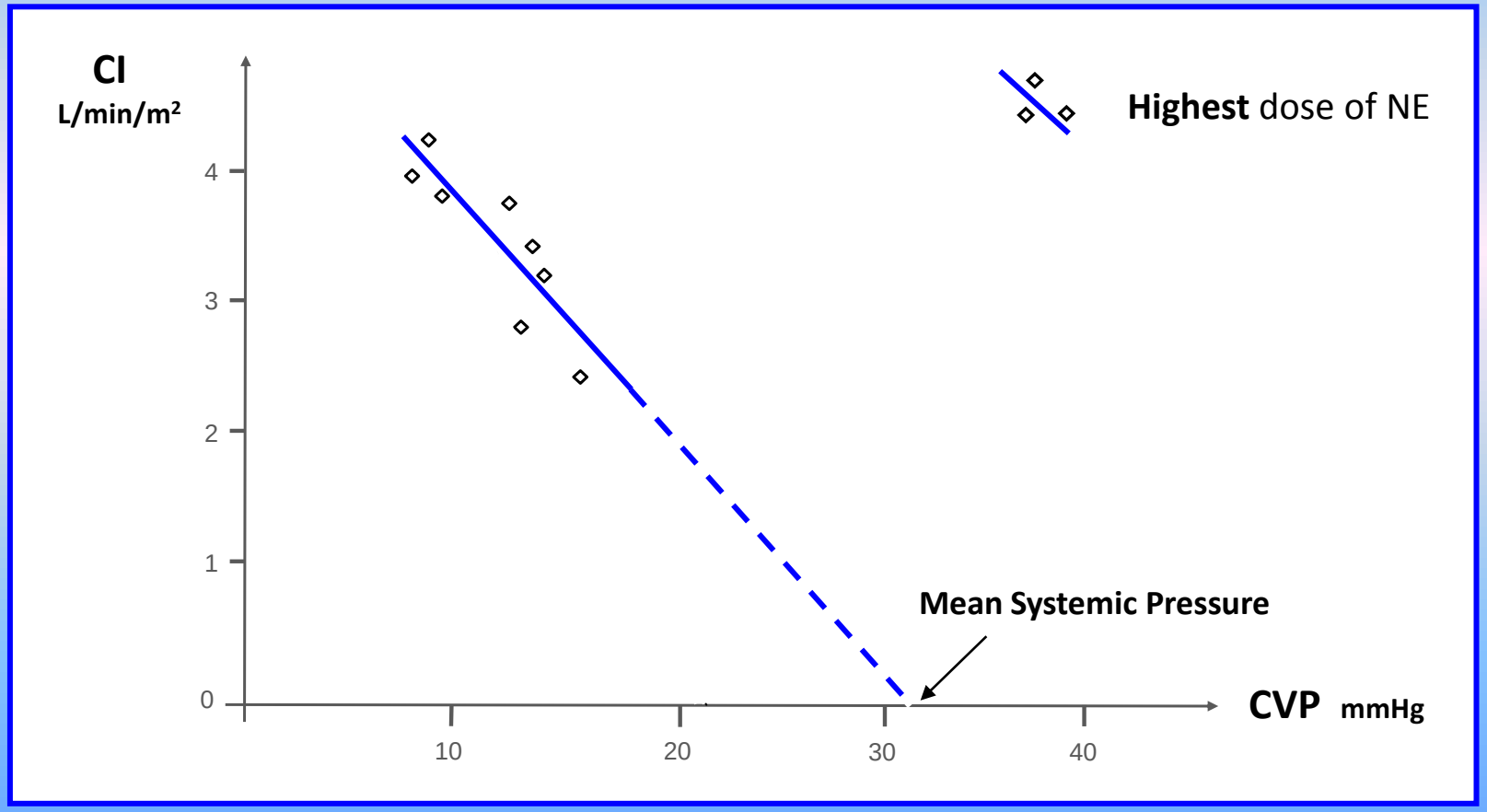
Crit Care Med 2012; 40:3146–3153



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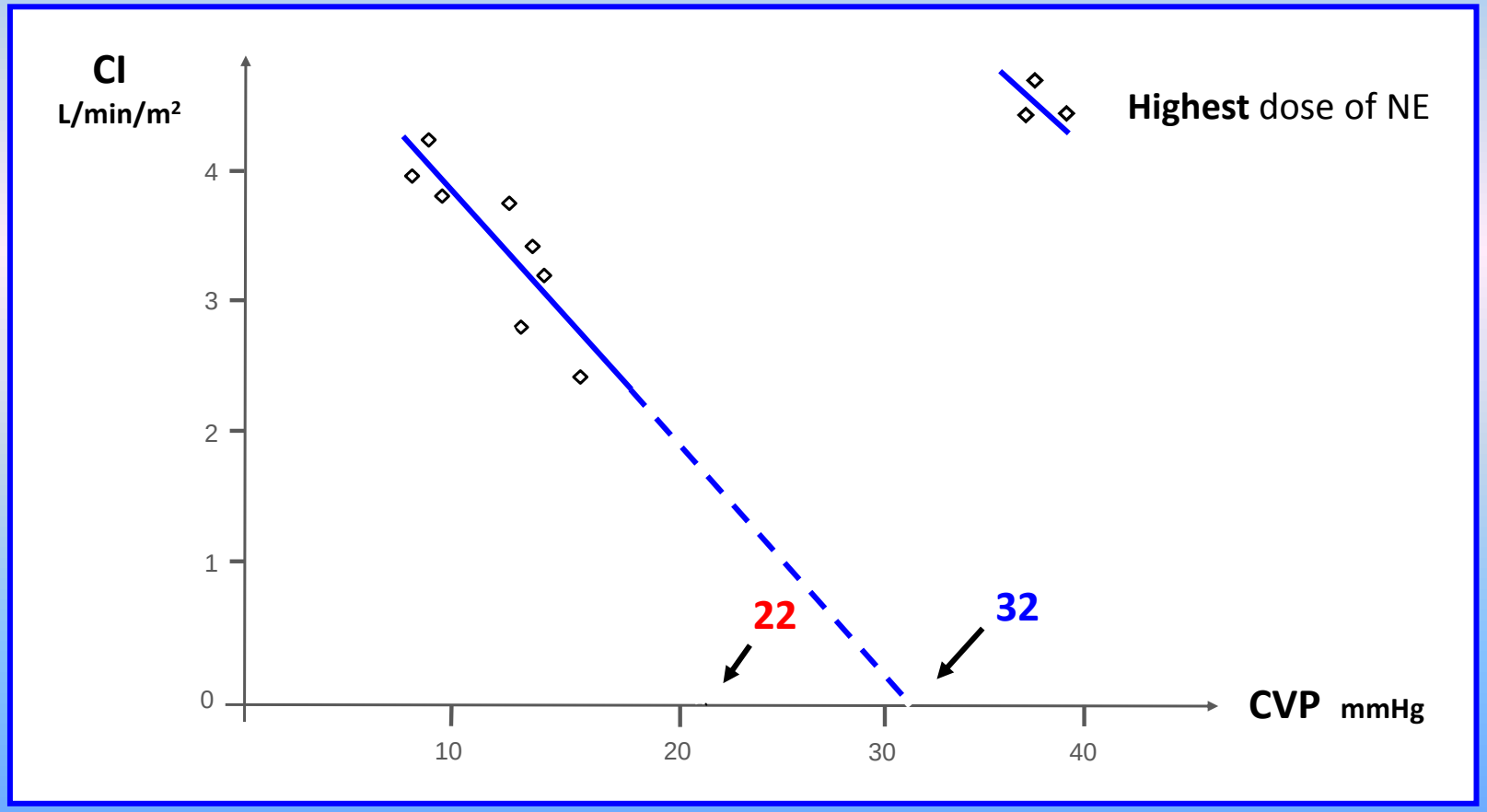

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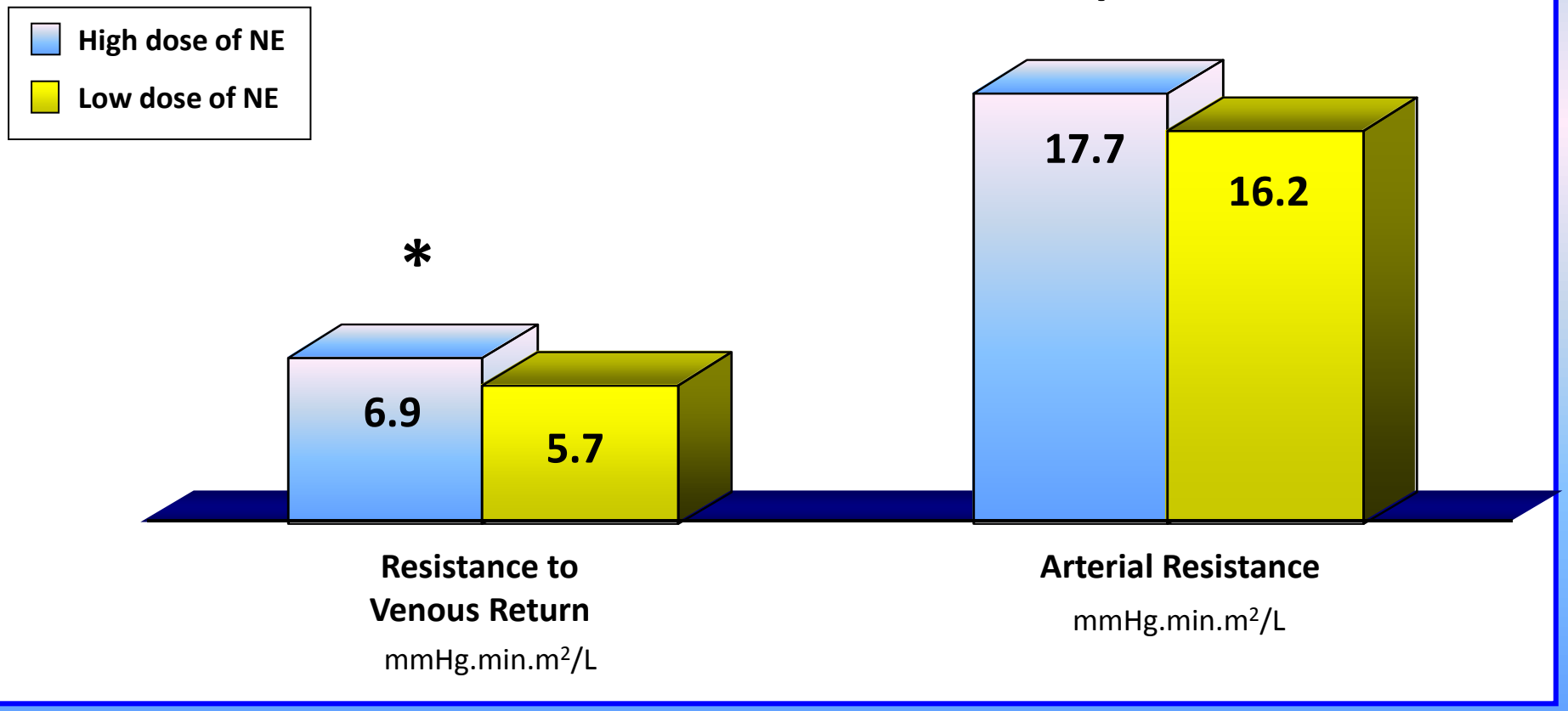
Crit Care Med 2012; 40:3146–3153

Resistance to venous return (Mean Systemic Pressure – CVP) / CI

Arterial resistance (MAP- Mean Systemic Pressure) / CI



Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*

Romain Persichini, MD; Serena Silva, MD; Jean-Louis Teboul, MD, PhD; Mathieu Jozwiak, MD; Denis Chemla, MD, PhD; Christian Richard, MD; Xavier Monnet, MD, PhD

Crit Care Med 2012; 40:3146–3153

In spite of an increase in venous resistance,

venous return increases with **NE**

through an **increase** in **Mean Systemic Pressure**

related to blood **redistribution**

from unstressed to stressed volume

This is **fine**

since **unstressed volume** is **abnormally increased**

during sepsis and further **overfilled** by fluid loading

Hamzaoui O, Jozwiak M, Sztrymf B, Prat D, Jacobs F, Monnet X, Richard C, Teboul JL

Norepinephrine exerts an inotropic effect at the early phase of human septic shock

ESICM 2015

n = 38 pts

	before NE	with NE
MAP mmHg	56 ± 7	78 ± 9
LVEF %	49 ± 13	56 ± 13

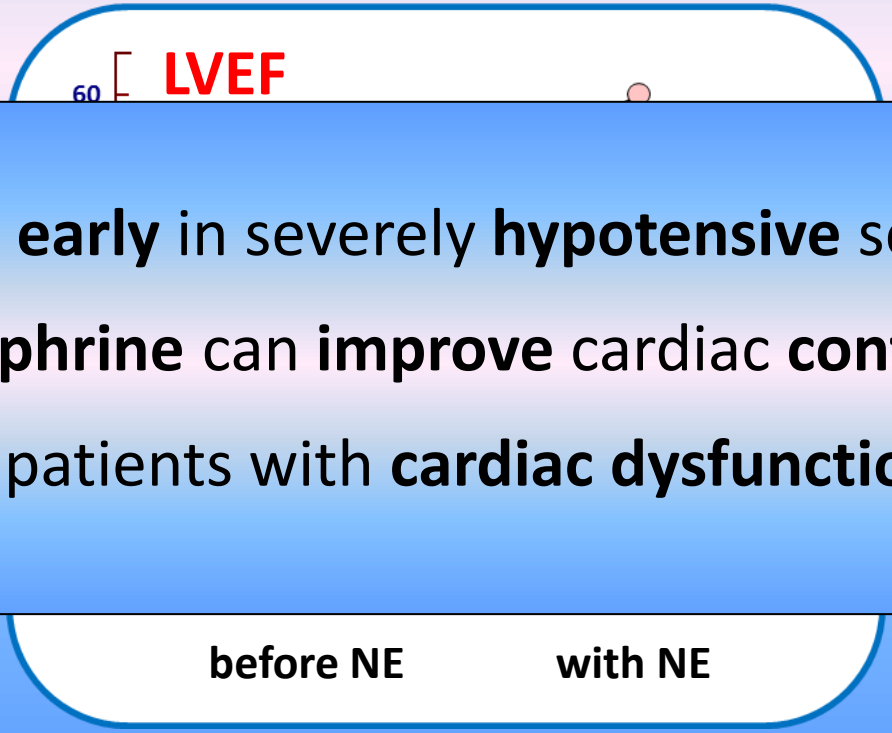
Hamzaoui O, Jozwiak M, Sztrymf B, Prat D, Jacobs F, Monnet X, Richard C, Teboul JL

Norepinephrine exerts an inotropic effect at the early phase of human septic shock

ESICM 2015

pts with **LVEF < 45%**

MAP	**56 ± 7**	**78 ± 9**



When initiated **early** in severely **hypotensive** septic patients,

norepinephrine can **improve** cardiac **contractility**

in patients with **cardiac dysfunction**

Five arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- NE improves microcirculation, when initiated **early**

Intensive Care Med (2010) 36:1882–1889

ORIGINAL

Jean-François Georger
Olfa Hamzaoui
Anis Chaari
Julien Maizel
Christian Richard
Jean-Louis Teboul

Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients

	Before norepinephrine (introduction/increase)	After norepinephrine (introduction/increase)
SAP (mmHg)	86 ± 19	126 ± 18*
DAP (mmHg)	38 ± 7	52 ± 8*
MAP (mmHg)	54 ± 8	77 ± 9*
Heart rate (min^{-1})	98 ± 25	101 ± 28
Temperature (°C)	37.5 ± 1.4	37.5 ± 1.3
CI ($L/min/m^2$)	3.1 ± 1.0	3.6 ± 1.3*
GEDVI (mL/m^2)	687 ± 117	730 ± 156*
$ScvO_2$ (%)	68 ± 9	72 ± 7*

Intensive Care Med (2010) 36:1882–1889

ORIGINAL

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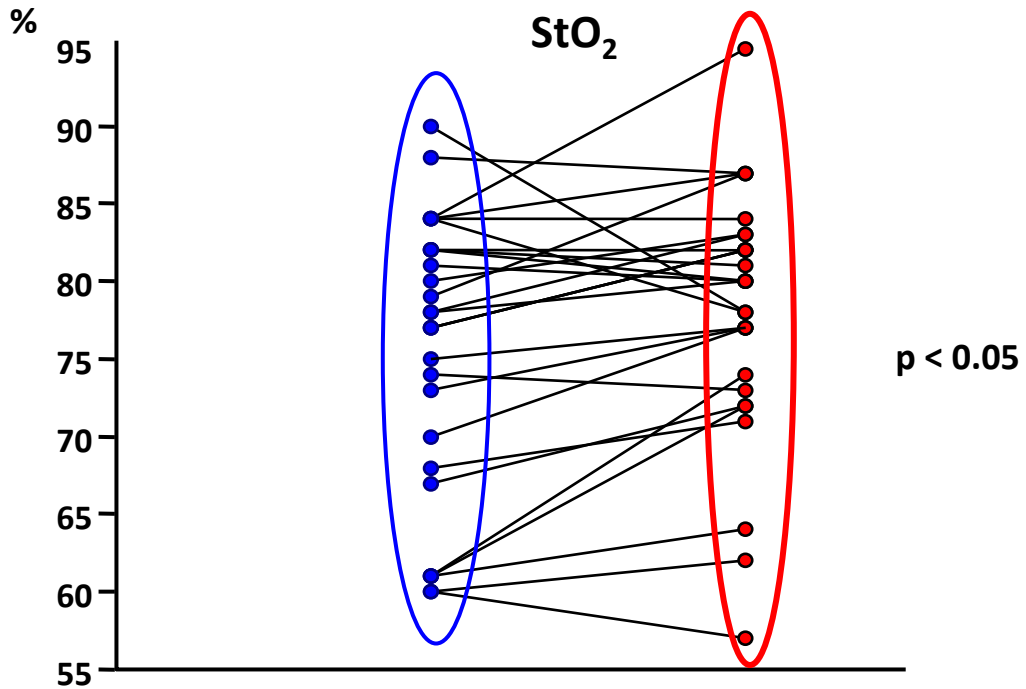
Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients

MAP mmHg **54 ± 8** **77 ± 9**

StO_2

healthy volunteers
82 ± 4%

Septic shock
75 ± 9% *



Intensive Care Med (2010) 36:1882–1889

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Christian Richard
Jean-Louis Teboul

Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients

MAP	**mmHg**	**54 ± 8**	**77 ± 9**

StO_2 recovery slope

(%/s)

0.5

0.0

before NE

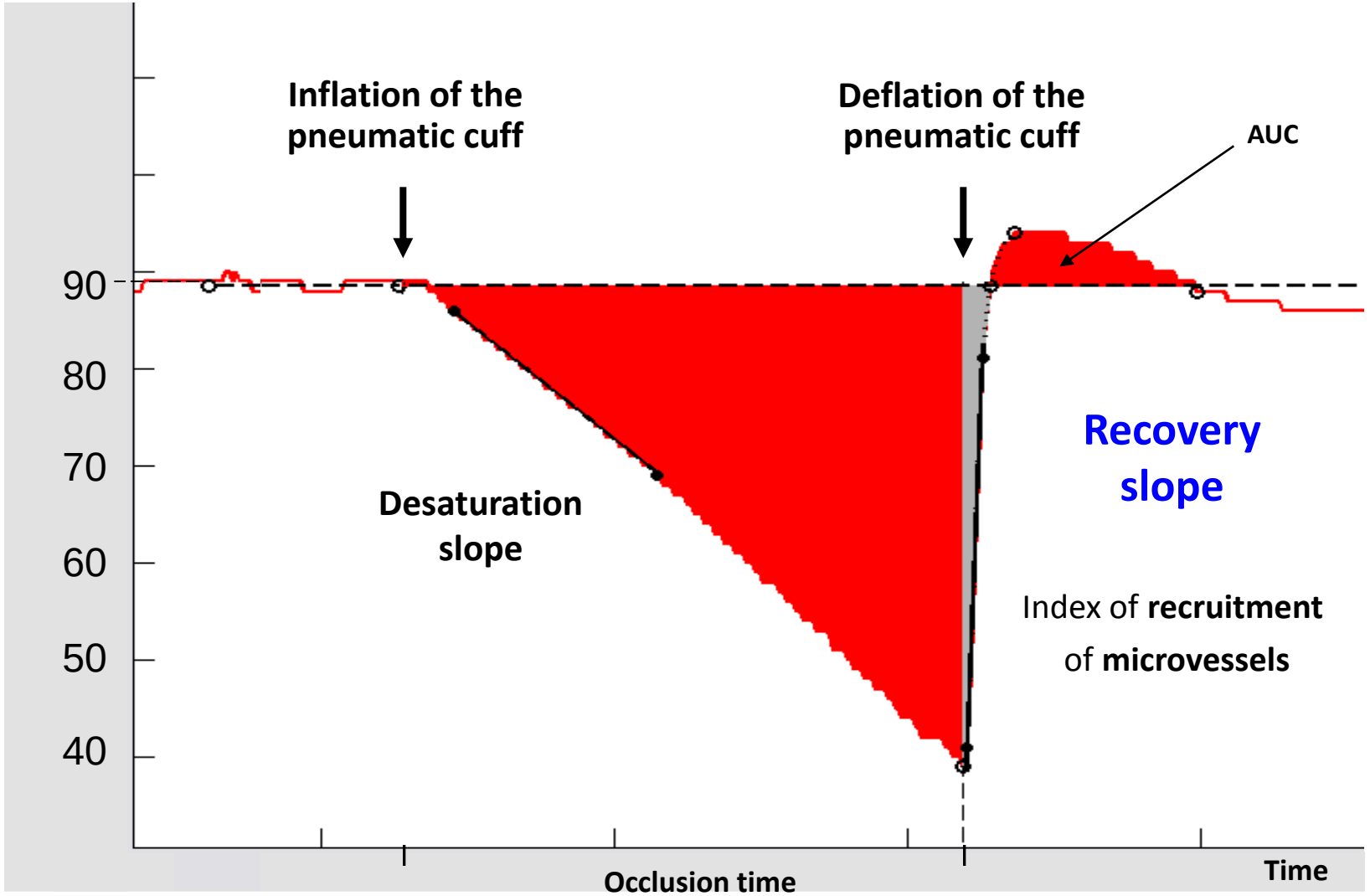
with NE

Early correction of hypotension

resulted in improved muscle tissue oxygenation

and microcirculatory reserve capacities

Vascular Occlusion Test



Five arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- **NE improves microcirculation**, when initiated **early**

4- Early initiation of **vasopressors prevents** harmful fluid **overload**

Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006; 34:344–353

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	*p* Value
SAPS II score[a] (per point increase)	1.0 (1.0–1.1)	<.001
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial SOFA score (per point increase)	1.1 (1.0–1.1)	.002
Blood stream infection	1.7 (1.2–2.4)	.004
Cirrhosis	2.4 (1.3–4.5)	.008
Pseudomonas infection	1.6 (1.1–2.4)	.017
Medical admission	1.4 (1.0–1.8)	.049
Female gender	1.4 (1.0–1.8)	.044

Five arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- **NE improves microcirculation**, when initiated **early**

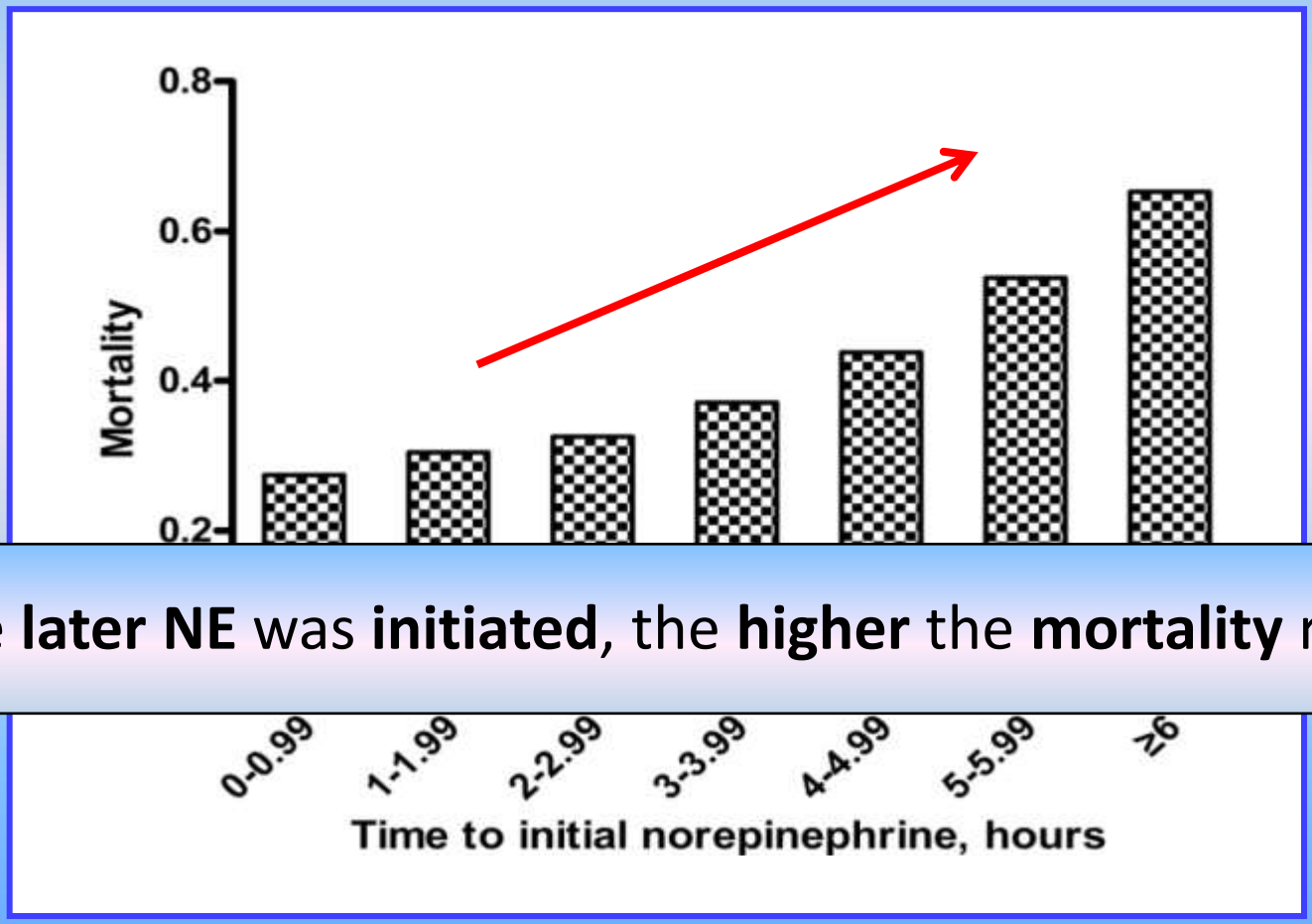
4- **Early** initiation of **vasopressors prevents** harmful fluid **overload**

5- Delayed initiation of **vasopressors** associated with **increased mortality**

Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu*, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li*

Critical Care 2014, **18**:532



The **later NE** was **initiated**, the **higher** the **mortality** rate

Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu*, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li*

Critical Care 2014, **18**:532

Table 5 Multivariate logistic regression analysis of independent risk factors for 28-day mortality

Variable	Adjusted Odds Ratio of Death	95% Confidence interval	*P* value
Risk factors			
Time to initial norepinephrine administration (h)	1.392	1.138–1.702	0.003
Time to initial antimicrobial treatment (h)	1.330	1.067–1.659	0.011
Serum lactate at septic shock onset (mmol/L)	1.710	1.174–2.537	0.005
APACHE II score	1.243	1.096–1.409	<0.001
Protective factors			
Effective antimicrobial therapy	0.477	0.231–0.982	0.040
Volume of intravenous fluids within 6 h (L)	0.676	0.468–0.977	0.033

Time to **initial NE** administration: **independent** predictor of **mortality**

…. the **later**, the **worse**

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Rationale. Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved.

Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used; however, using vasopressors early as an emergency measure in patients with severe shock is frequently necessary, as when diastolic blood pressure is too low.

Vasopresseurs et choc septique

1- Pourquoi ?

2- Quel agent ?

3- Quand le débuter ?

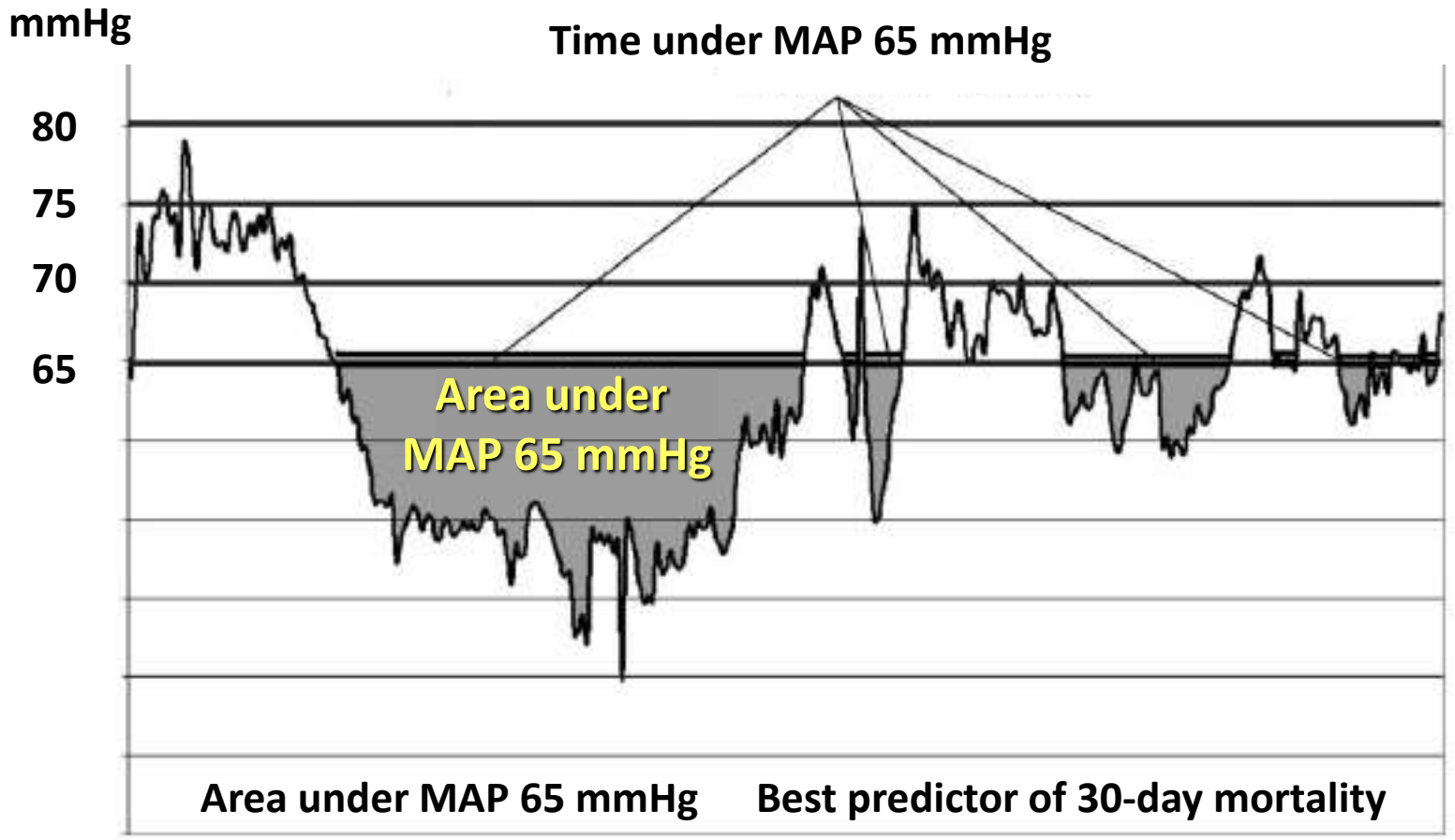
4- Quelle cible?

Intensive Care Med (2005) 31:1066–1071
DOI 10.1007/s00134-005-2688-z

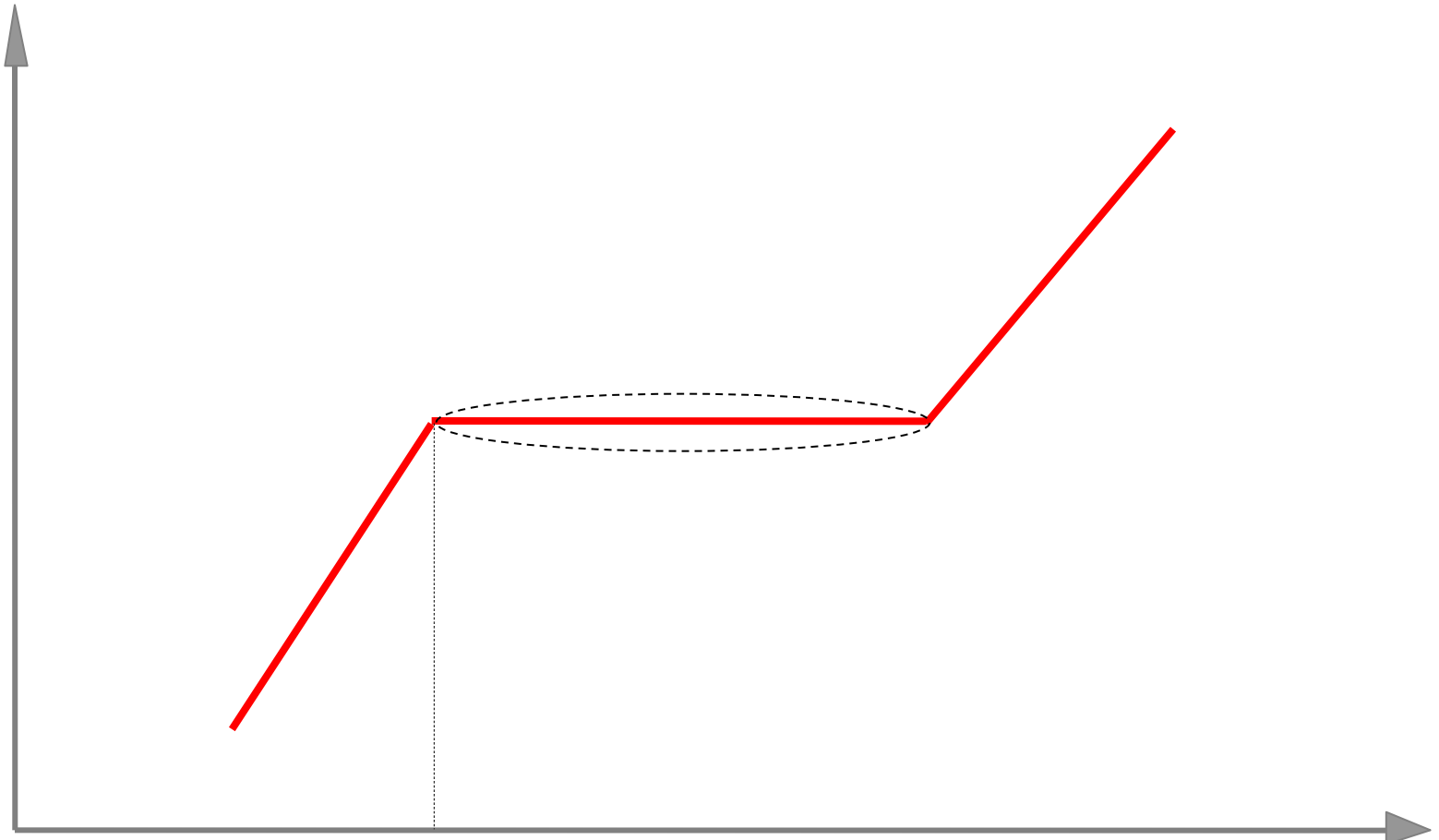
ORIGINAL

Marjut Varpula
Minna Tallgren
Katri Saukkonen
Liisa-Maria Voipio-Pulkki
Ville Pettilä

Hemodynamic variables related to outcome in septic shock



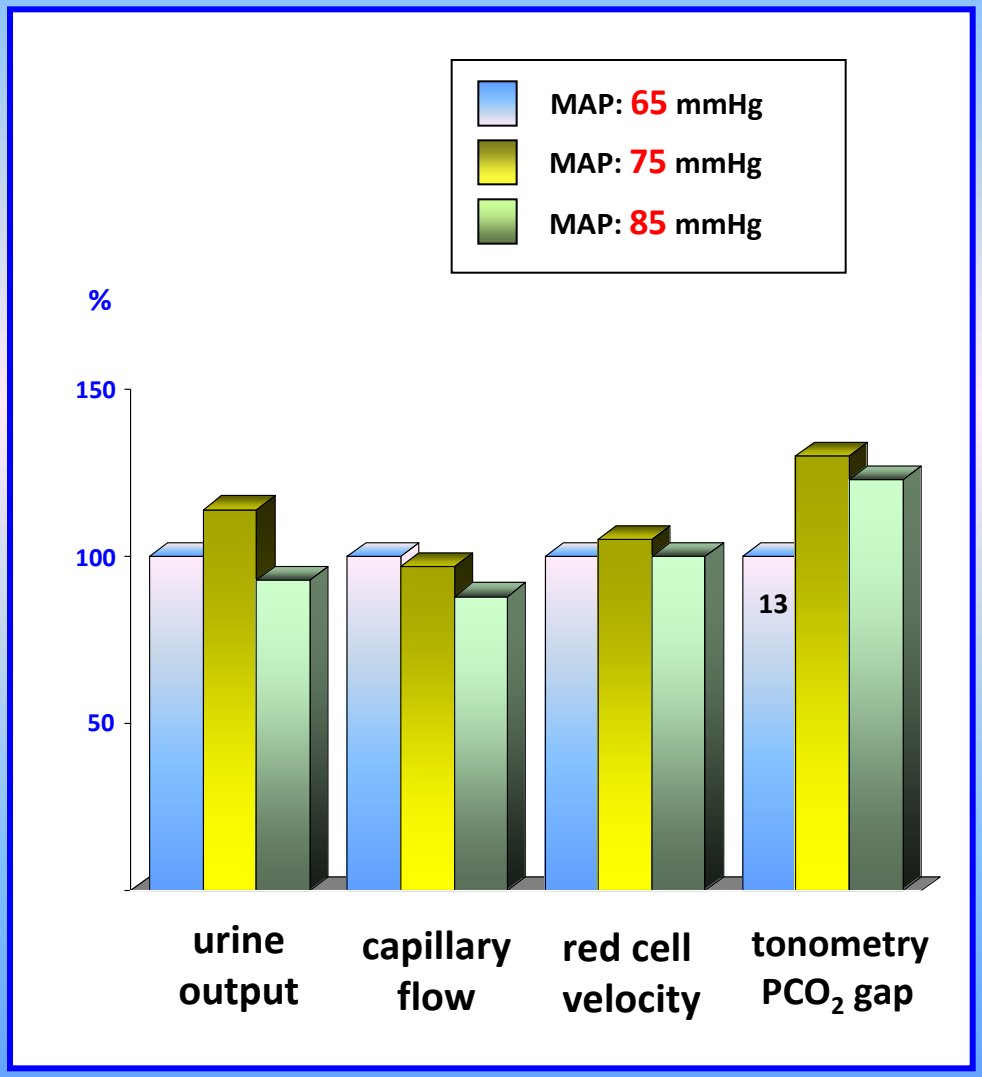
Autoregulation of organ blood flow



Effects of perfusion pressure on tissue perfusion in septic shock

David LeDoux, MD; Mark E. Astiz, MD, FCCM; Charles M. Carpati, MD; Eric C. Rackow, MD, FCCM

Crit Care Med 2000; 28:2729–2732



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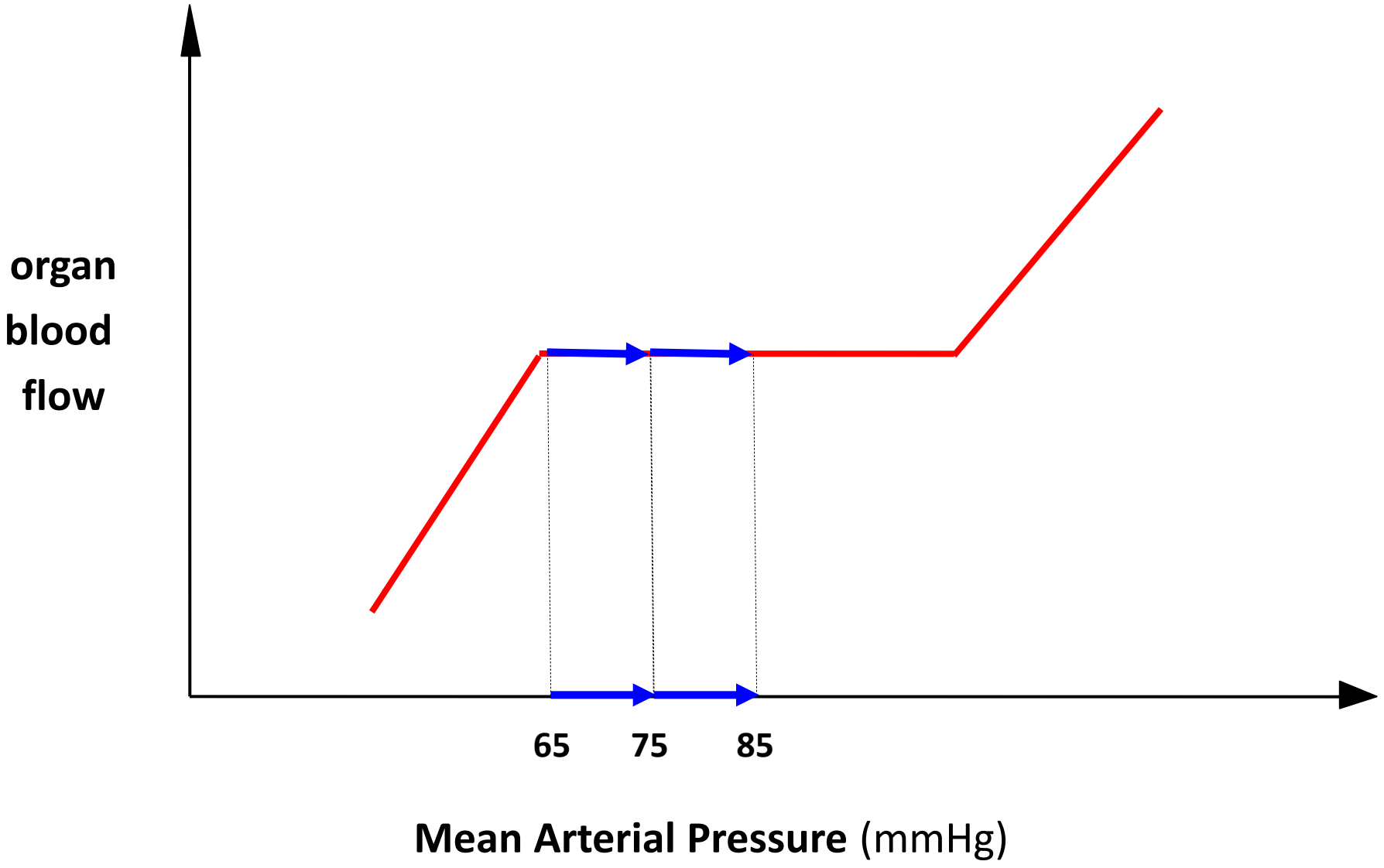

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Crit Care Med 2000; 28:2729–2732

Increasing mean arterial pressure in patients with septic shock: Effects on oxygen variables and renal function*

Aurélie Bourgoin, MD; Marc Leone, MD; Anne Delmas, MD; Franck Garnier, MD; Jacques Albanèse, MD; Claude Martin, MD, FCCM

Crit Care Med 2005; 33:780 –786

increasing **MAP above 65 mmHg**

results in **little benefit**

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Vasopressors

- Vasopressor therapy initially to target a **MAP** of **65** mmHg (grade 1C)

Is it **dangerous** to **target a MAP** value

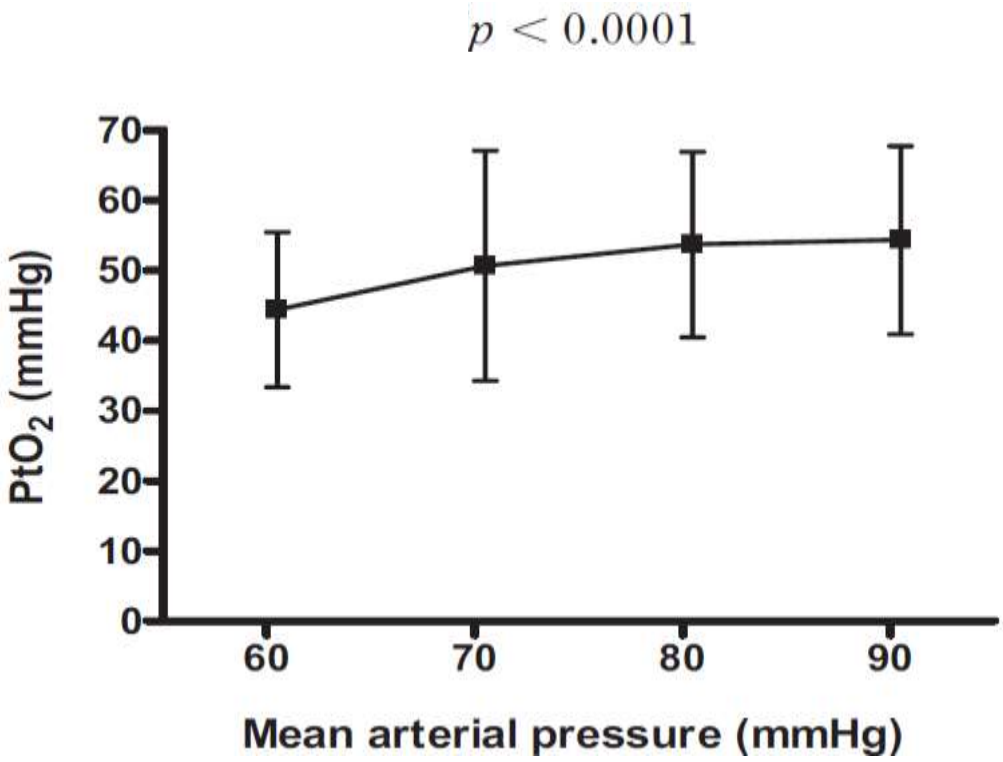
up to **“normal values”** (around 85 mmHg)

in **septic** shock?

The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock*

Shaman Jhanji, MRCP, FRCA; Sarah Stirling, MRCP, FRCA; Nakul Patel, MBBS;
Charles J. Hinds, FRCP, FRCA; Rupert M. Pearse, FRCA, MD

Crit Care Med 2009: 37:1961–1966

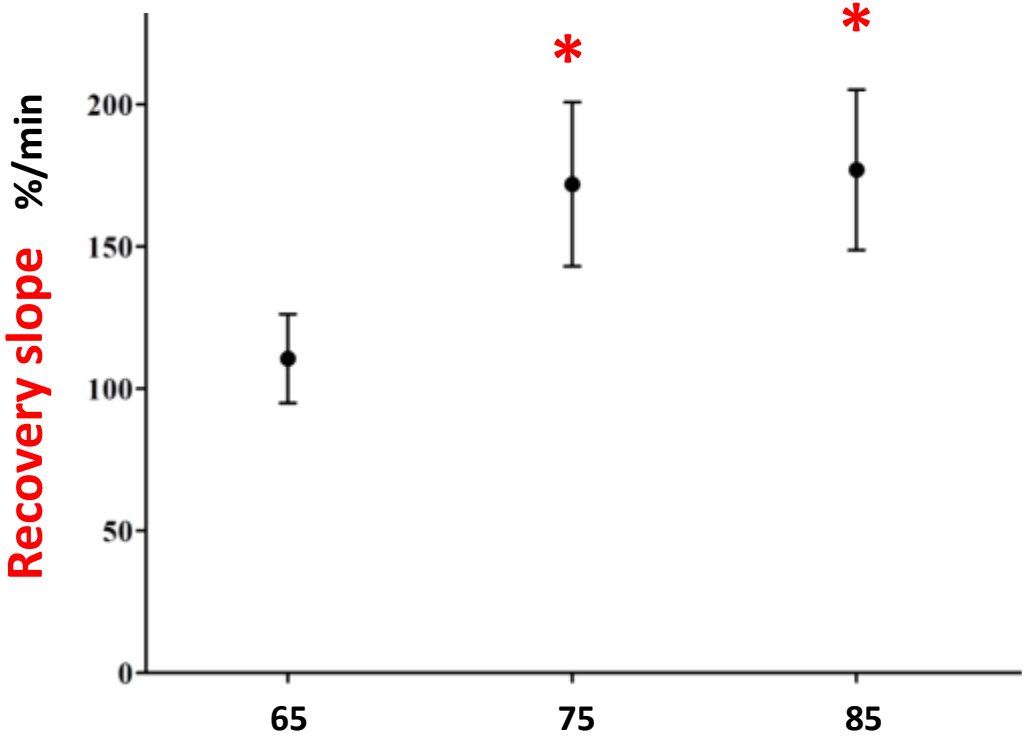


Effects of changes in arterial pressure on organ perfusion during septic shock

Aurélie Thooft, Raphaël Favory, Diamantino Ribeiro Salgado, Fabio S Taccone, Katia Donadello, Daniel De Backer, Jacques Creteur and Jean-Louis Vincent*

Critical Care 2011, **15**:R222

13 pts with septic shock



Effects of changes in arterial pressure on organ perfusion during septic shock

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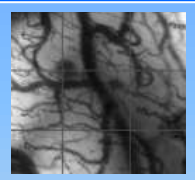
Critical Care 2011, **15**:R222

6 pts with septic shock



Perfused Vessel Density

	65 mmHg	75 mmHg	85 mmHg	65 mmHg
To				
Sm				
PV				
Sm				
Al				
La				
Small PPV (%)	83.6 (76.1-91.0)	87.9 (81.8-94.0)	91.1 (87.9-94.3)	86.4 (76.3-96.5)
MFI	2.4 (2.2-2.7)	2.7 (2.4-2.9)	2.9 (2.8-2.9)*	2.5 (2.2-2.9)

No worsening but **improvement** in **microcirculation**

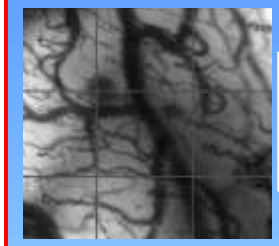
for **MAP target** up to **85 mmHg** with **NE**

Microvascular Flow Index

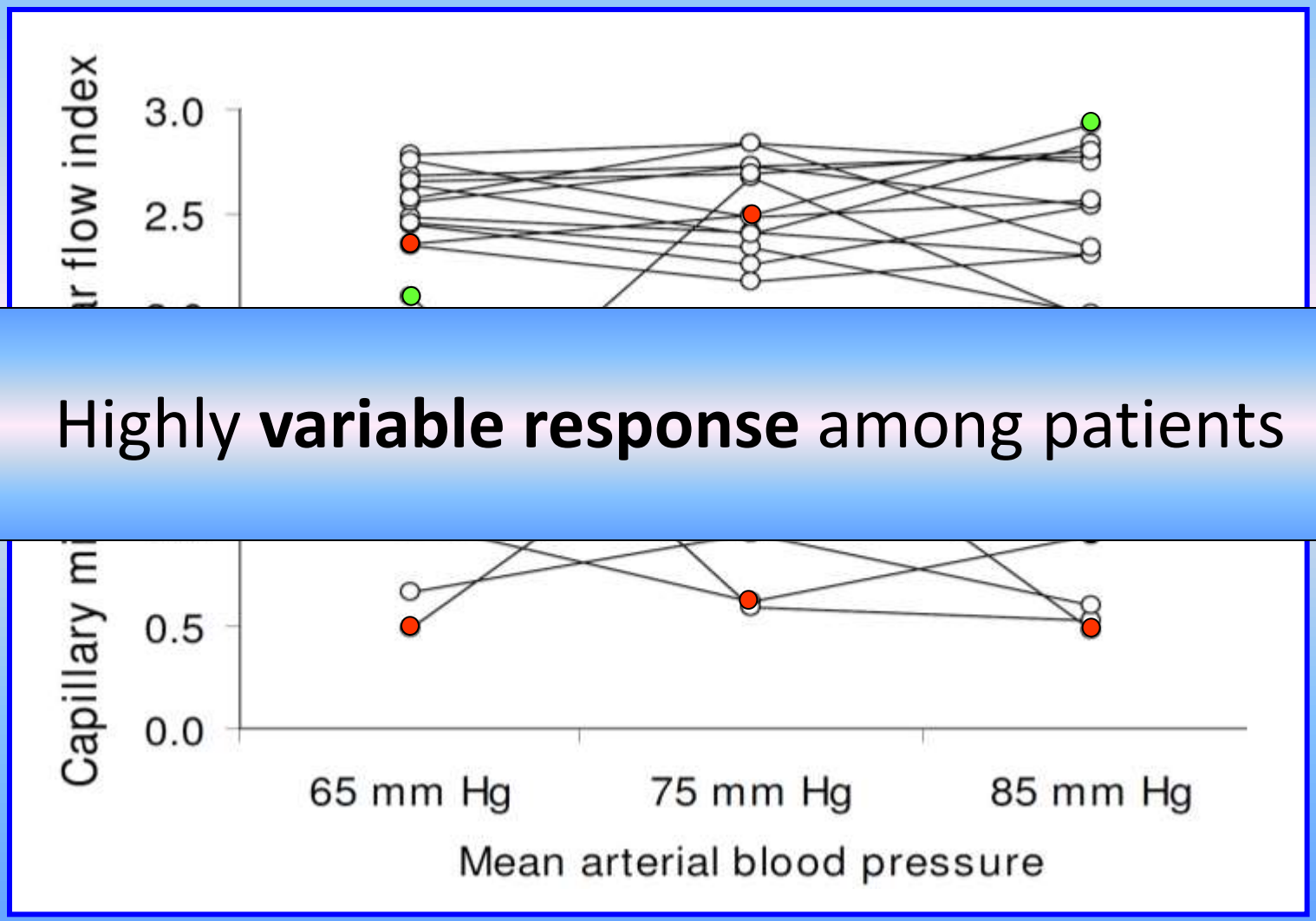
Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study

Arnaldo Dubin[1,2], Mario O Pozo[3], Christian A Casabella[1], Fernando Pálizas Jr[3], Gastón Murias[3], Miriam C Moseinco[1], Vanina S Kanoore Edul[1,2], Fernando Pálizas[3], Elisa Estenssoro[4] and Can Ince[5]

Critical Care 2009, **13**:R92



20 pts with septic shock



Highly **variable response** among patients

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Vasopressors

- Vasopressor therapy initially to target a **MAP** of **65** mmHg (grade 1C)

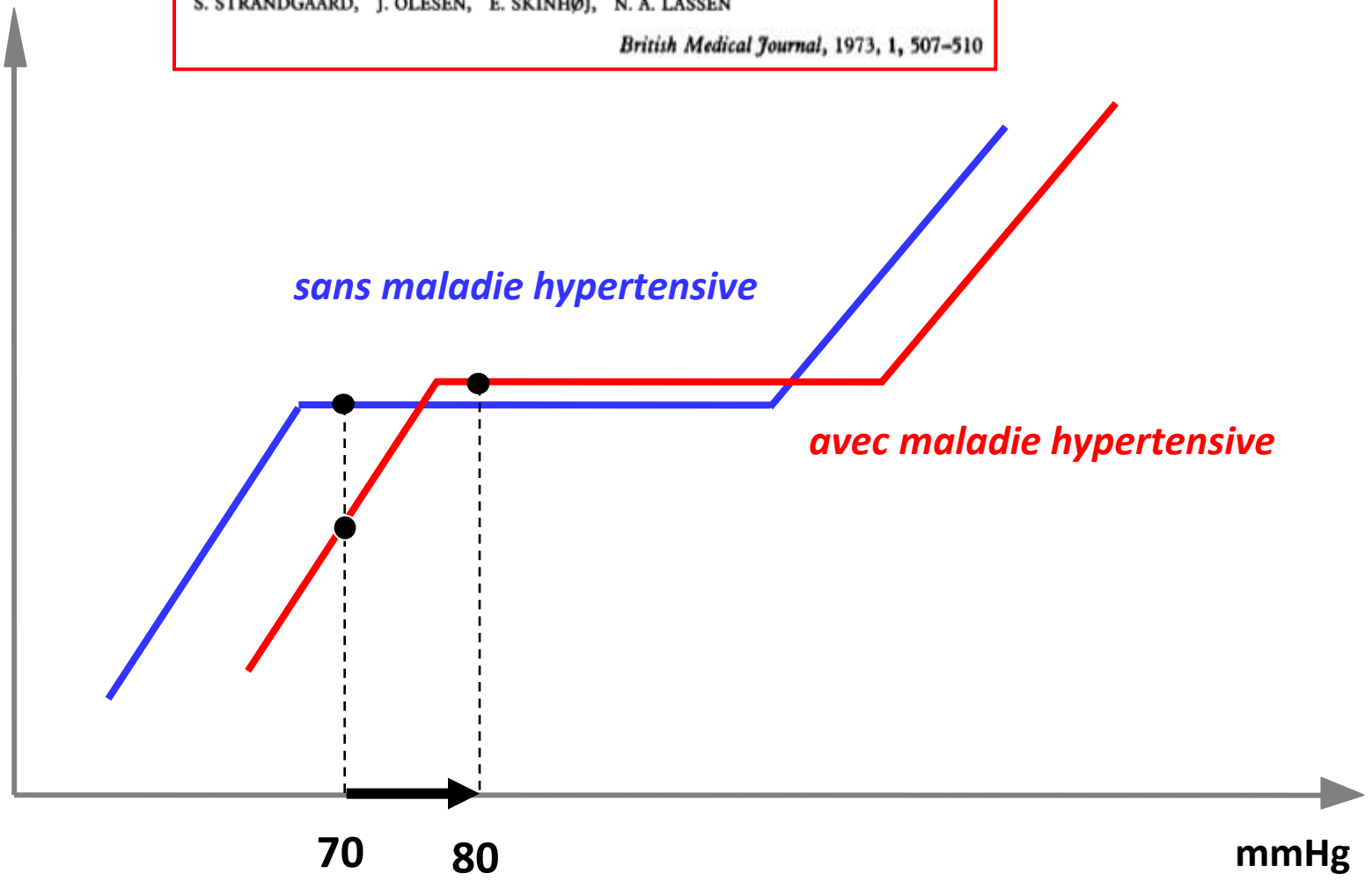
Probablement **plus** si :

- **Antécédents** d'**HTA**

Autoregulation of Brain Circulation in Severe Arterial Hypertension

S. STRANDGAARD, J. OLESEN, E. SKINHØJ, N. A. LASSEN

British Medical Journal, 1973, 1, 507–510



The NEW ENGLAND JOURNAL of MEDICINE

BLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO

80-85 mmHg

65-70 mmHg

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D.,

388 pts

388 pts

Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.

Variable	Low-Target Group (N = 388)	High-Target Group (N = 388)	P Value
Primary outcome: death at day 28 — no. (%)*	132 (34.0)	142 (36.6)	0.57
Secondary outcomes — no./total no. (%)			
Death at day 90†	164 (42.3)	170 (43.8)	0.74
Survival at day 28 without organ support‡	241 (62.1)	235 (60.6)	0.66
Doubling of plasma creatinine	161 (41.5)	150 (38.7)	0.42
No chronic hypertension	71/215 (33.0)	85/221 (38.5)	0.32
Chronic hypertension	90/173 (52.0)	65/167 (38.9)	0.02
Renal-replacement therapy from day 1 to day 7	139 (35.8)	130 (33.5)	0.50
No chronic hypertension	66/215 (30.7)	77/221 (34.8)	0.36
Chronic hypertension	73/173 (42.2)	53/167 (31.7)	0.046
Serious adverse events — no. (%)			
Any	69 (17.8)	74 (19.1)	0.64
Acute myocardial infarction§	2 (0.5)	7 (1.8)	0.18
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02

Bénéfices en termes de **fonction rénale** avec une **PAM** cible **plus élevée** en cas d'antécédents d'HTA

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Vasopressors

- Vasopressor therapy initially to target a **MAP** of **65** mmHg (grade 1C)

Probablement **plus** si :

- Antécédents d'HTA
- **PVC élevée**

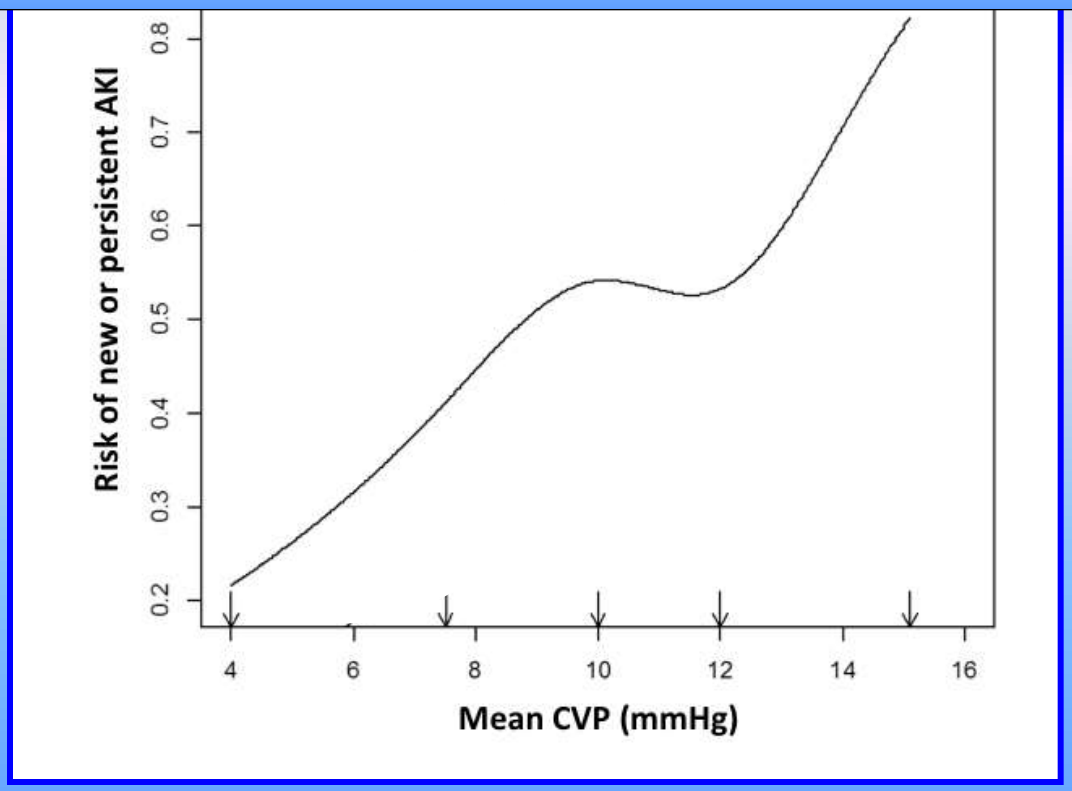
Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study

Matthieu Legrand[1,2*], Claire Dupuis[1], Christelle Simon[1], Etienne Gayat[1,3], Joaquim Mateo[1], Anne-Claire Lukaszewicz[1,2,4] and Didier Payen[1,2,4]

Critical Care 2013, **17**:R278

Association between **elevated CVP** and **AKI**

suggests a role of **venous congestion** in the development of AKI



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

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Vasopressors

- Vasopressor therapy initially to target a **MAP** of **65** mmHg (grade 1C)

Probablement **plus** si :

- Antécédents d'HTA
- PVC élevée
- **Pression abdominale élevée**

Intensive Care Med (2014) 40:1795–1815

CONFERENCE REPORTS AND EXPERT PANEL

Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa
Michael R. Pinsky
Jean Louis Teboul
Jean Louis Vincent
Andrew Rhodes

Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

Target blood pressure in circulatory shock

- We recommend **individualizing** the target blood pressure during shock resuscitation.

  Recommendation Level 1: QoE moderate (B)

- We recommend to **initially target a MAP of ≥ 65 mmHg.**

  Recommendation: Level 1; QoE low (C)

- We suggest a **higher MAP** in septic patients with a **history of hypertension.**

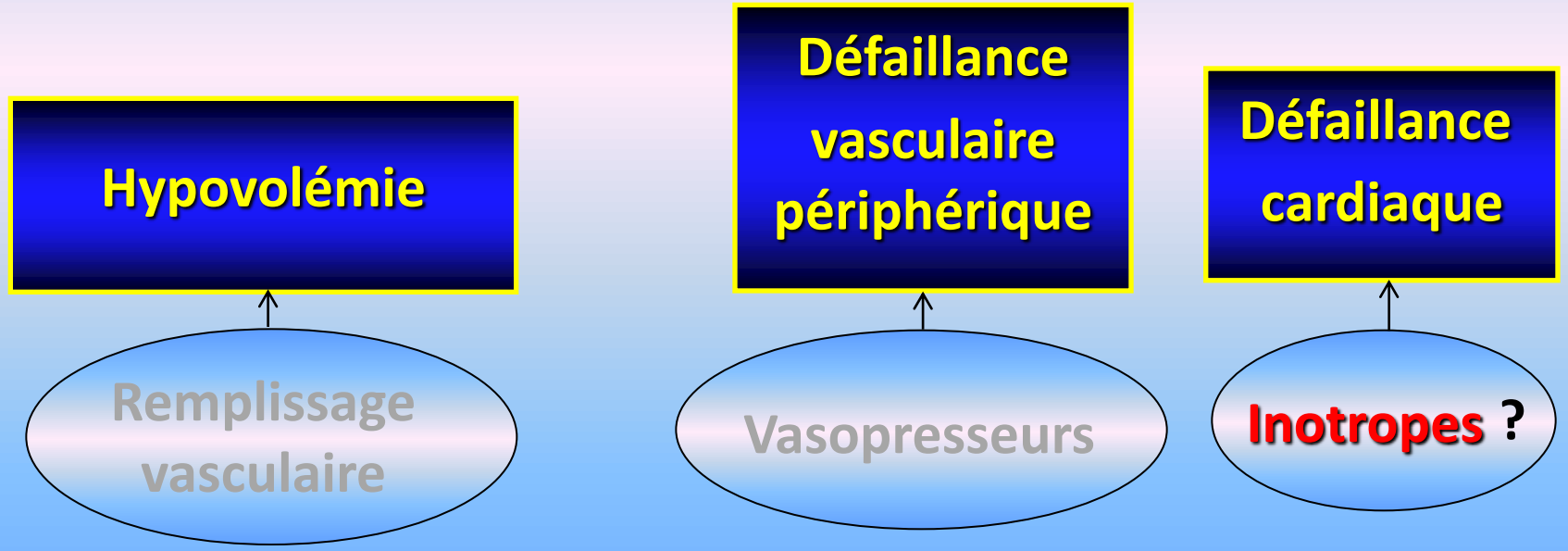
  Recommendation: Level 2; QoE low (B)

Fin du 3ème épisode

Objectif thérapeutique hémodynamique

Restaurer le plus vite possible une perfusion tissulaire efficace

1) Restaurer une **PAM** suffisante
2) Restaurer un **débit cardiaque** suffisant

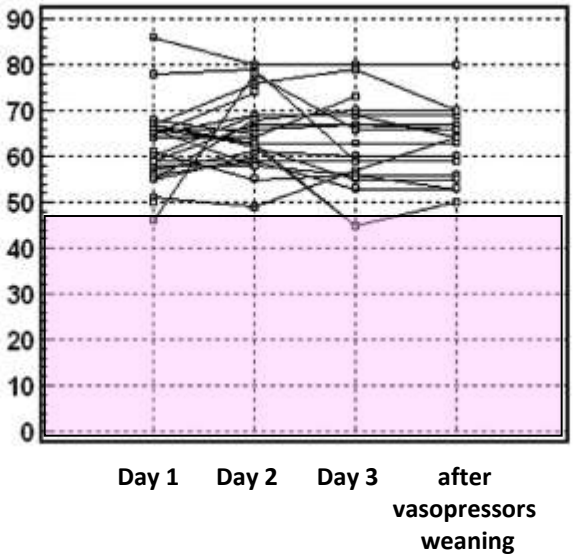


Actual incidence of global left ventricular hypokinesia in adult septic shock

Antoine Vieillard-Baron, MD; Vincent Caille, MD; Cyril Charron, MD; Guillaume Belliard, MD; Bernard Page, MD; François Jardin, MD

Crit Care Med 2008; 36:1701–1706

LV EF %



40% of pts

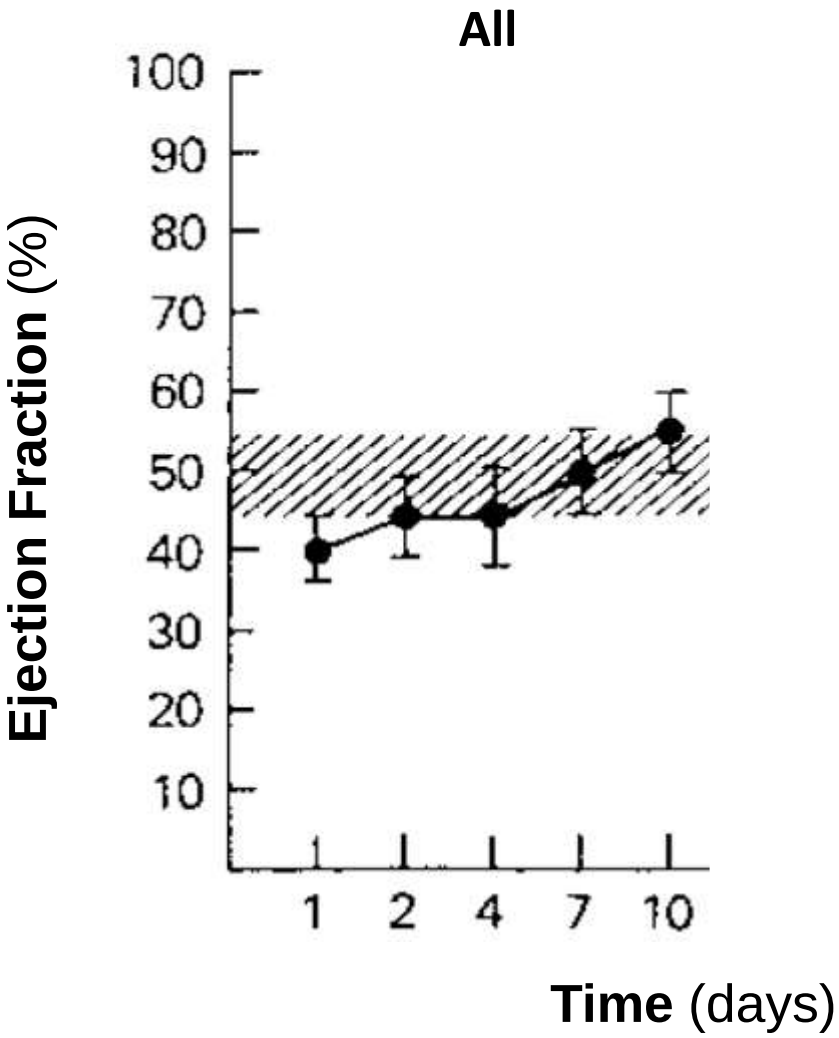
40% of pts

20% of pts

Treatment of sepsis-related cardiac dysfunction

To treat or **not to treat?**

If **low LVEF** and **LV dilatation** are adaptive mechanisms, then, they might be respected **?**



Parker et al Ann Intern Med 1984

Vieillard-Baron *Annals of Intensive Care* 2011, **1**:6
http://www.annalsofintensivecare.com/content/1/1/6

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Septic cardiomyopathy

Antoine Vieillard-Baron[1,2]

	Survivors (n = 99)	Nonsurvivors (n = 101)
Parker et al. [1] *20 patients*	*LVEF* 32 ± 4%	55 ± 3%
Jardin et al. [15] *90 patients*	*LVEF* 44 ± 16%	52 ± 14%
Vieillard-Baron et al. [25] *67 patients*	*LVEF* 49 ± 18%	55 ± 15%
Kumar et al. [32] *23 patients*	*LVEF* 50 ± 5%	57 ± 4%

Persistent Preload Defect in Severe Sepsis Despite Fluid Loading*

A Longitudinal Echocardiographic Study in Patients With Septic Shock

François Jardin, MD; Thierry Fourme, MD; Bernard Page, MD; Yann Loubières, MD; Antoine Vieillard-Baron, MD; Alain Beauchet, MD; and Jean-Pierre Bourdarias, MD

CHEST 1999; 116:1354–1359

Variables	Day 1	Day 2	Day *n*	Recovery
LVEDV, mL/m^2				
S	75.3 ± 20.1†	80.3 ± 20.9†/‡	75.4 ± 21.8†	70.5 ± 14.7
NS	64.9 ± 25.0	62.2 ± 15.2	60.2 ± 21.6	
LVESV, mL/m^2				
S	42.4 ± 17.9†‡	43.6 ± 15.0†/‡	35.7 ± 14.9‡	27.6 ± 10.2
NS	32.2 ± 17.7	34.8 ± 16.6	30.2 ± 16.4	
LVSV, mL/m^2				
S	32.6 ± 13.8‡	36.7 ± 12.1†	39.7 ± 12.0†	42.9 ± 11.3
NS	32.7 ± 17.7	27.4 ± 13.9	30.0 ± 14.5	
LVEF, %				
S	43.9 ± 16.4†/‡	41.6 ± 10.6‡	53.2 ± 11.7‡	60.2 ± 16.4
NS	52.0 ± 14.0	45.7 ± 15.7	51.0 ± 16.8	

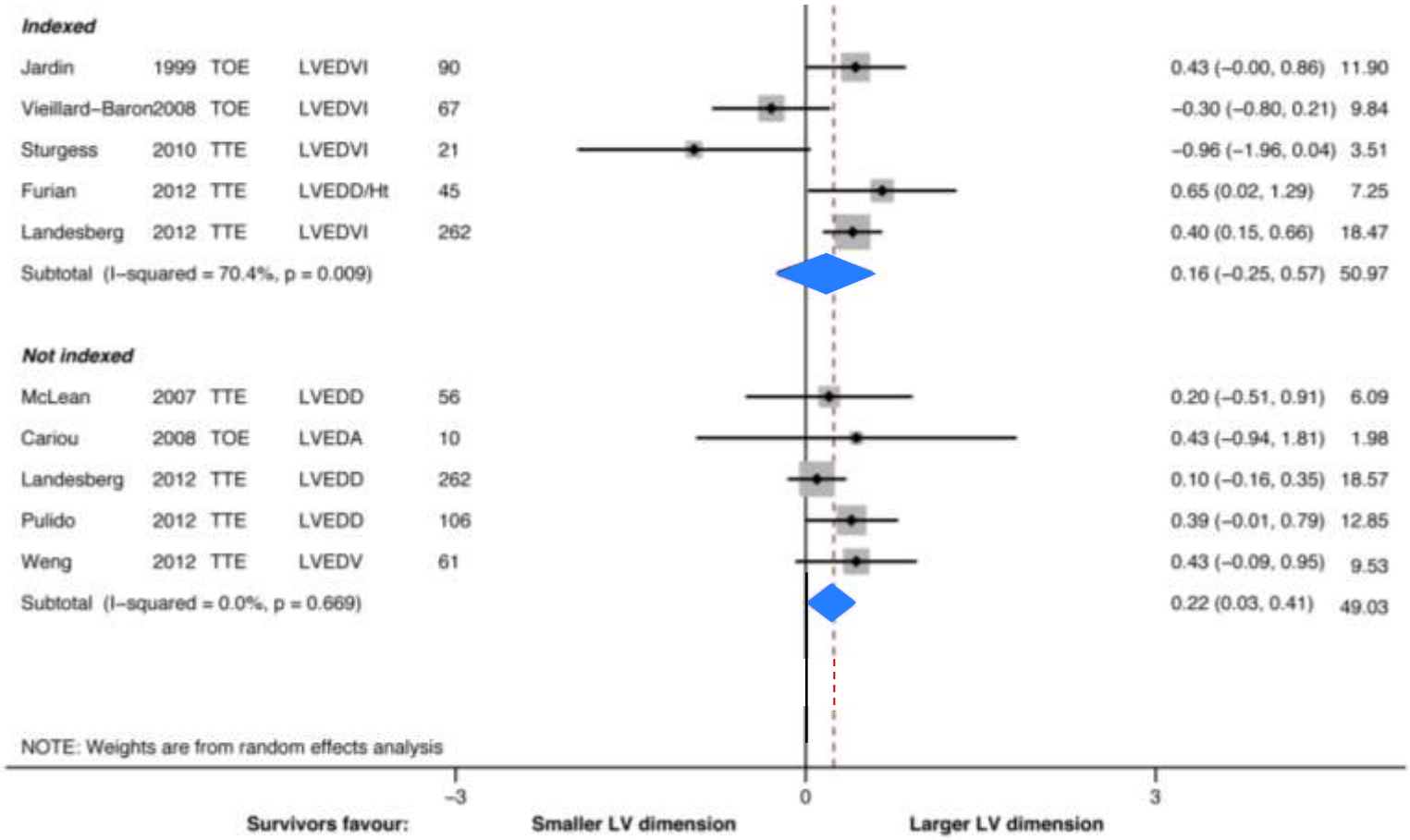
Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis

Stephen J Huang*, Marek Nalos and Anthony S McLean

Huang *et al. Critical Care* 2013, **17**:R96

LVEDV

LVEDA



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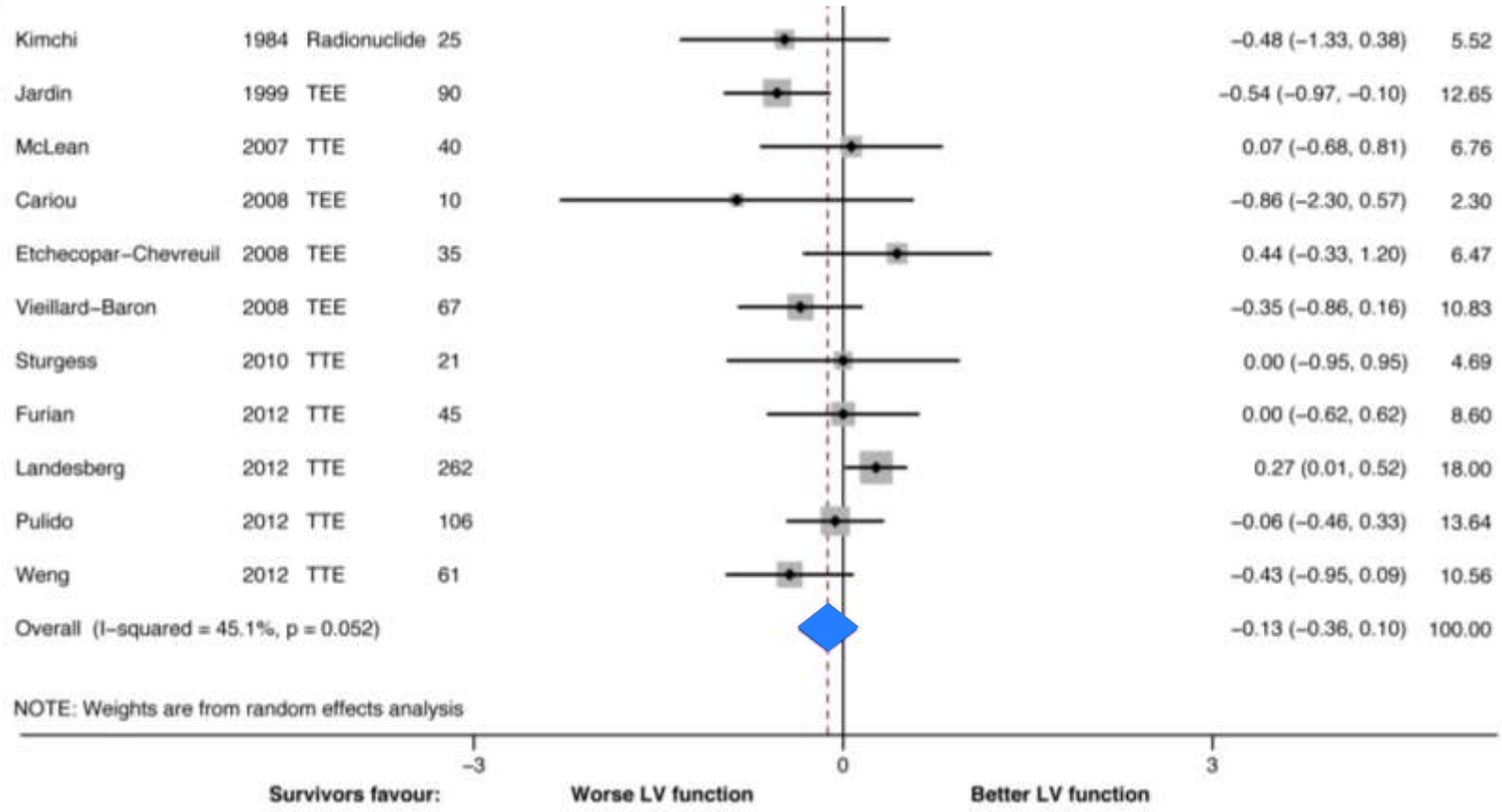
LVEF

LVFAC



Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis

Stephen J Huang*, Marek Nalos and Anthony S McLean

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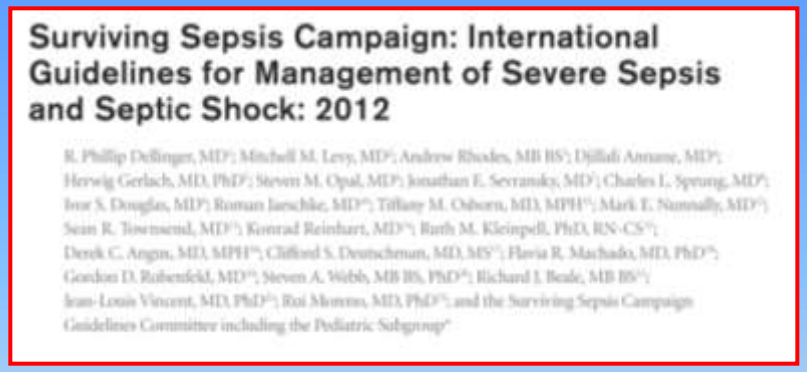
Key messages

- Pooled results do not suggest survivors from severe sepsis or septic shock had lower ejection fractions.
- Overall results seemed to suggest survivors exhibited slightly larger LV dimensions but pooled indexed LV dimensions were similar in survivors and non-survivors.



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Inotropic therapy

1. A trial of **dobutamine** infusion up to 20 µg/kg/min be administered or added to vasopressor (if in use) in the presence of:

(a) myocardial dysfunction as suggested by **elevated cardiac filling presures** and **low CO**, or

(b) ongoing signs of **hypoperfusion**, despite acheiving adequate intravascular volume and adequate MAP (grade 1C).

but

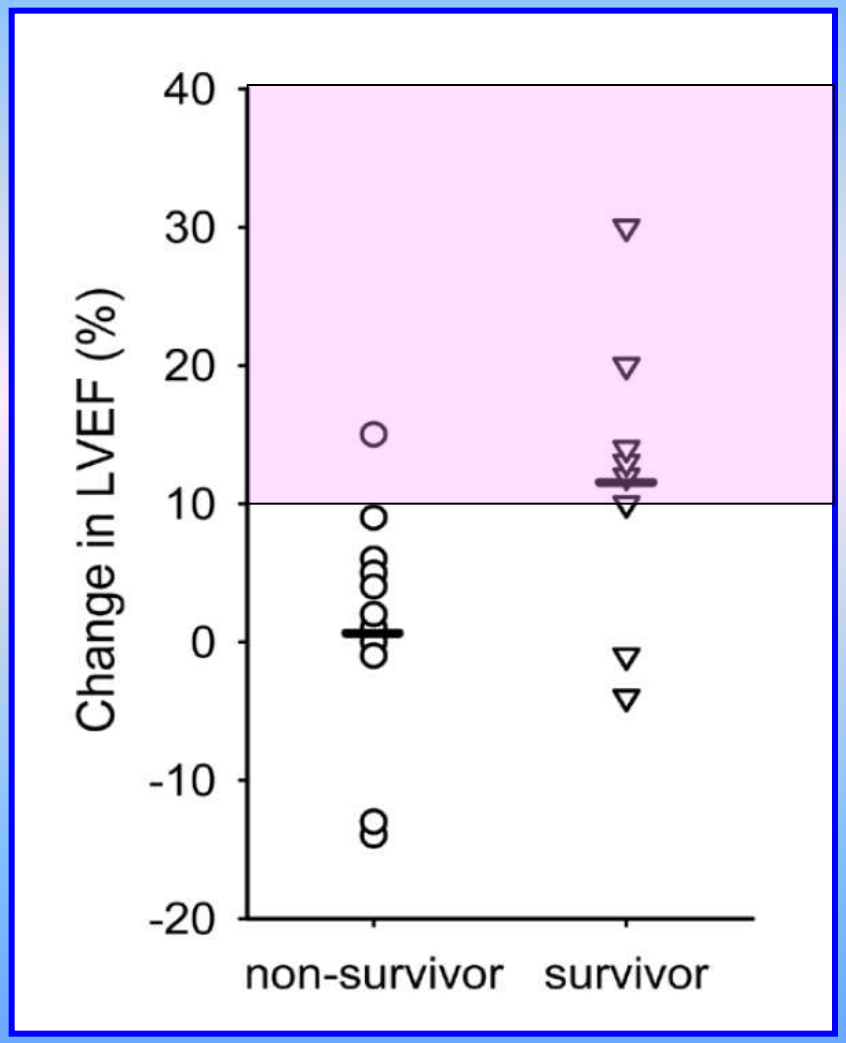
- **beneficial effects of dobutamine are unpredictable**

(potential decreased efficacy)

Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock

Anand Kumar[1,2], Elizabeth Schupp[3], Eugene Bunnell[3], Amjad Ali[4], Barry Milcarek[2] and Joseph E Parrillo[2]

Critical Care 2008, **12**:R35



Dobutamine increased LVEF

by more than 10%

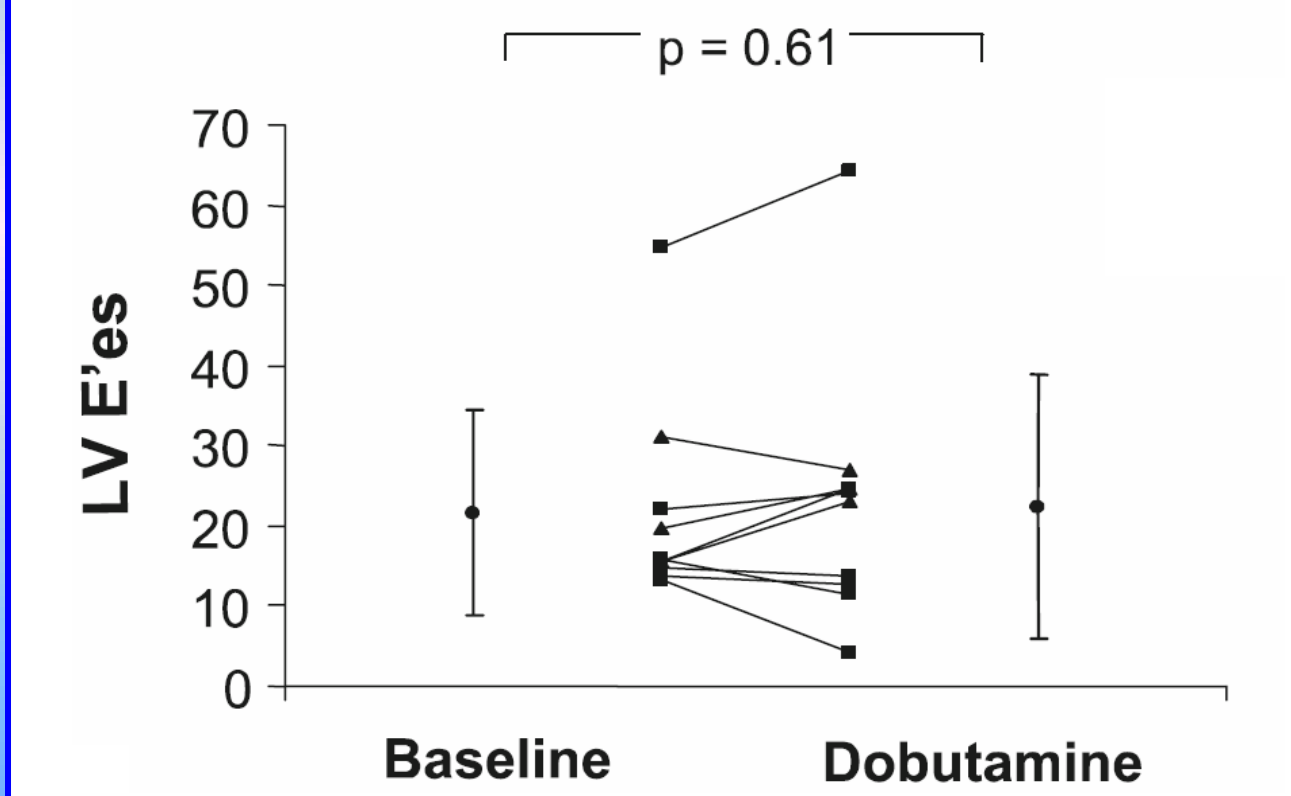
only in 35% of pts

Intensive Care Med (2008) 34:917–922
DOI 10.1007/s00134-008-1022-y

BRIEF REPORT

Alain Cariou
Michael R. Pinsky
Mehran Monchi
Ivan Laurent
Christophe Vinsonneau
Jean-Daniel Chiche
Julien Charpentier
Jean-François Dhainaut

Is myocardial adrenergic responsiveness depressed in human septic shock?



Dobutamine and septic myocardial dysfunction

- **beneficial** effects are **unpredictable** (potential decreased efficacy)
- **detrimental** effects may occur (arrhythmias, vasodilation, etc)

administration of dobutamine should be restricted to patients:

- with persisting shock
-
-

→ test the response to dobutamine

before any prolonged administration

despite fluid resuscitation and vasopressors

Treatment of sepsis-related cardiac dysfunction

To treat or not to treat?

Alternatives to dobutamine?

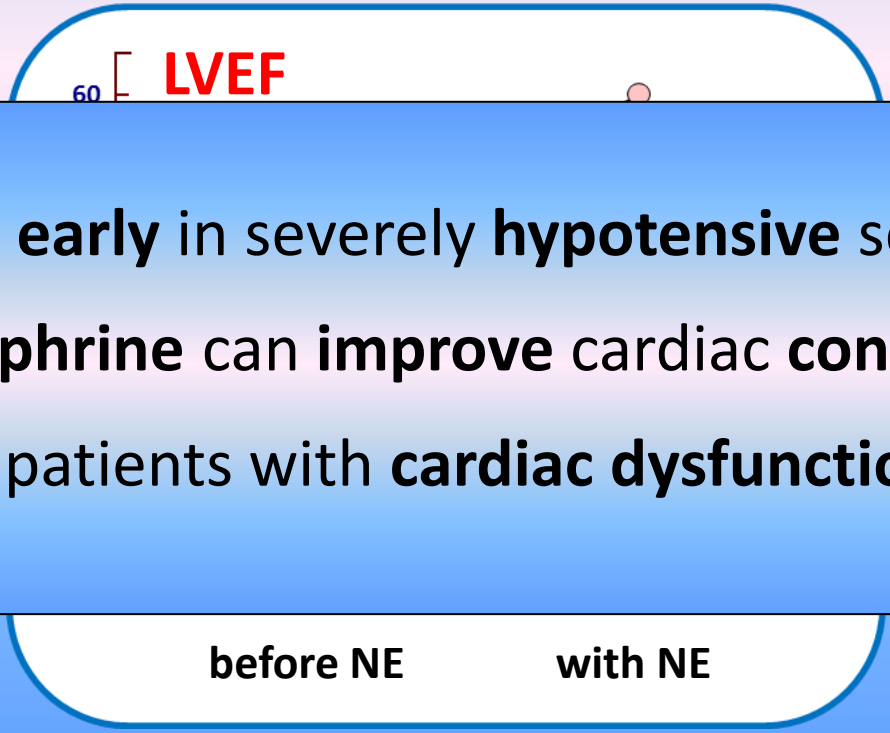
Hamzaoui O, Jozwiak M, Sztrymf B, Prat D, Jacobs F, Monnet X, Richard C, Teboul JL

Norepinephrine exerts an inotropic effect at the early phase of human septic shock

ESICM 2015

pts with **LVEF < 45%**

MAP	**56 ± 7**	**78 ± 9**



When initiated **early** in severely **hypotensive** septic patients,

norepinephrine can **improve** cardiac **contractility**

in patients with **cardiac dysfunction**

Hamzaoui O, Jozwiak M, Sztrymf B, Prat D, Jacobs F, Monnet X, Richard C, Teboul JL

ESICM 2015

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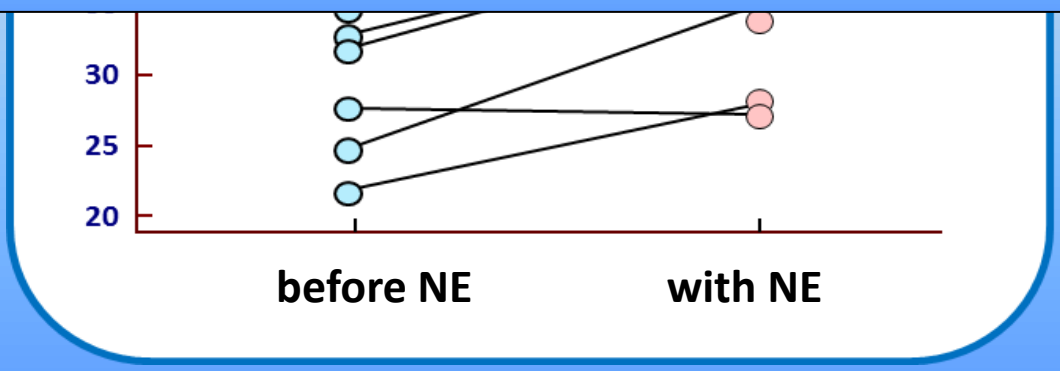
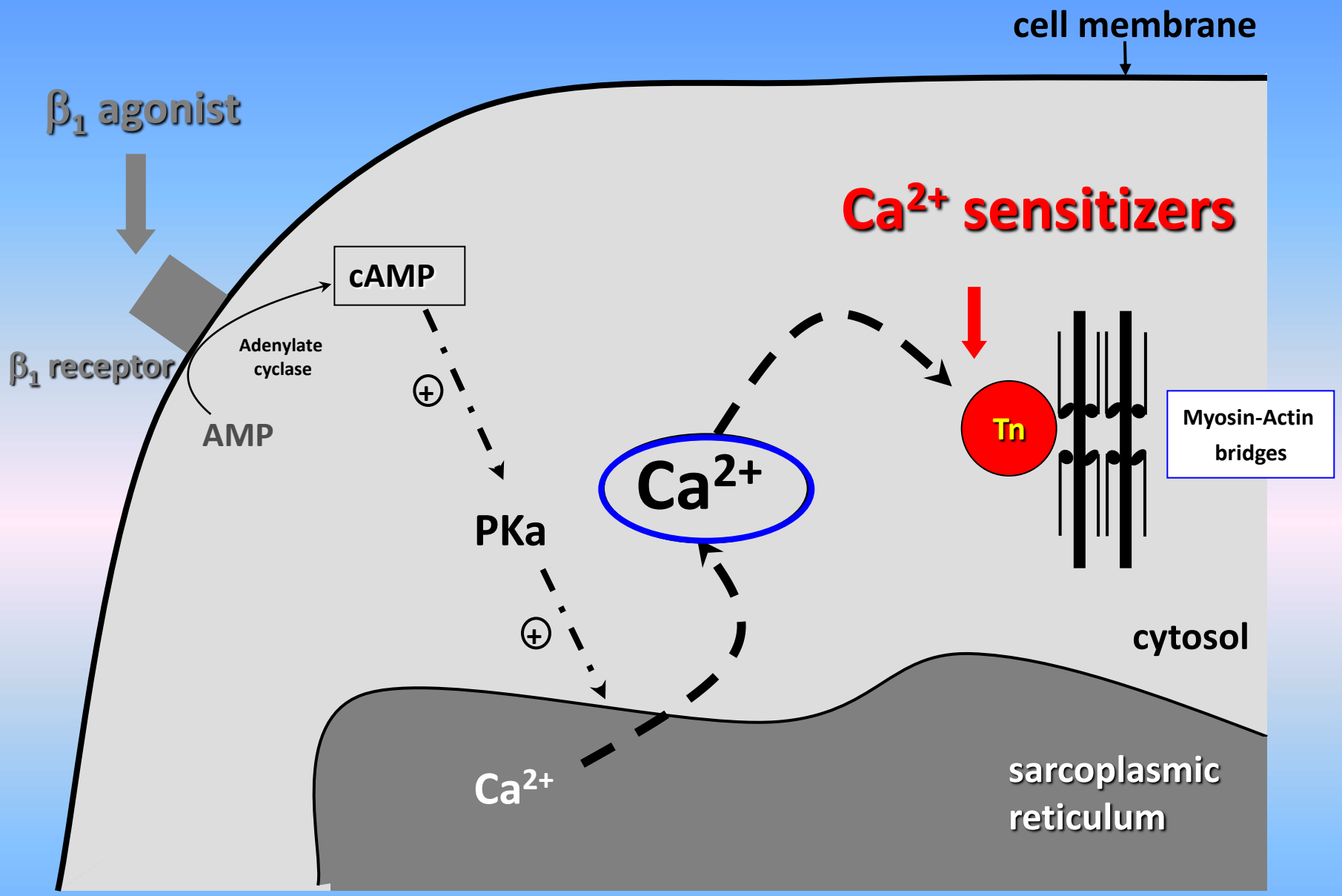
When initiated **early** in severely **hypotensive** septic patients, **norepinephrine** can **improve** cardiac **contractility** in patients with **cardiac dysfunction**



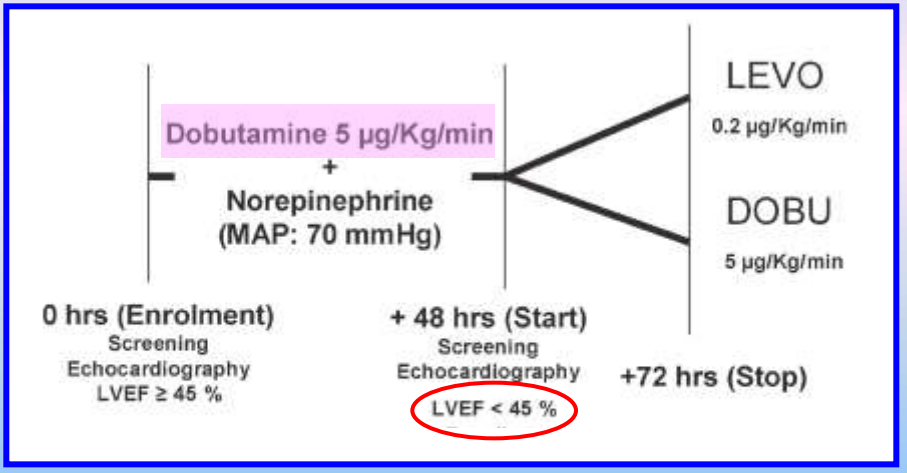

cell membrane
β1 agonist
Ca2+ sensitizers
cAMP
β1 receptor
Adenylate cyclase
AMP
Tn
Myosin-Actin bridges
Ca2+
PKa
cytosol
Ca2+
sarcoplasmic reticulum

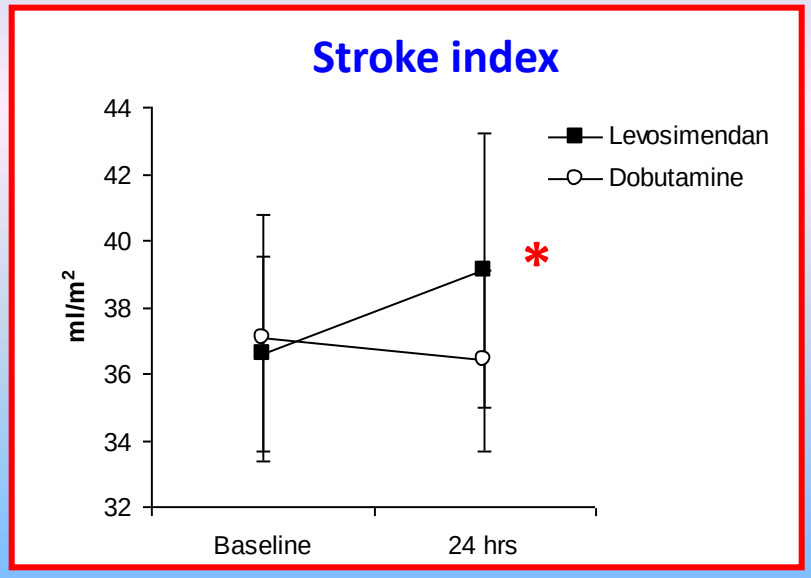
Intensive Care Med (2005) 31:638–644

ORIGINAL

Andrea Morelli
Stefano De Castro
Jean-Louis Teboul
Mervyn Singer
Monica Rocco
Giorgio Conti
Leonardo De Luca
Emanuele Di Angelantonio
Alessandra Orecchioni
Natesa G. Pandian
Paolo Pietropaoli

Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression





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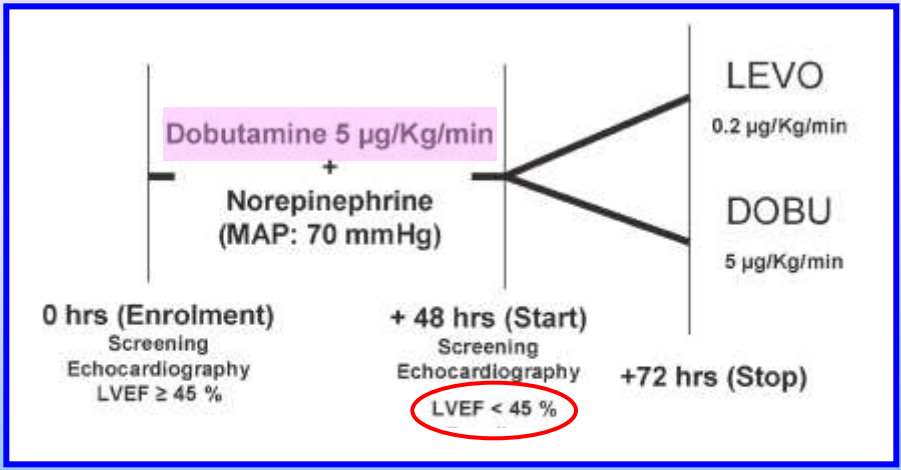
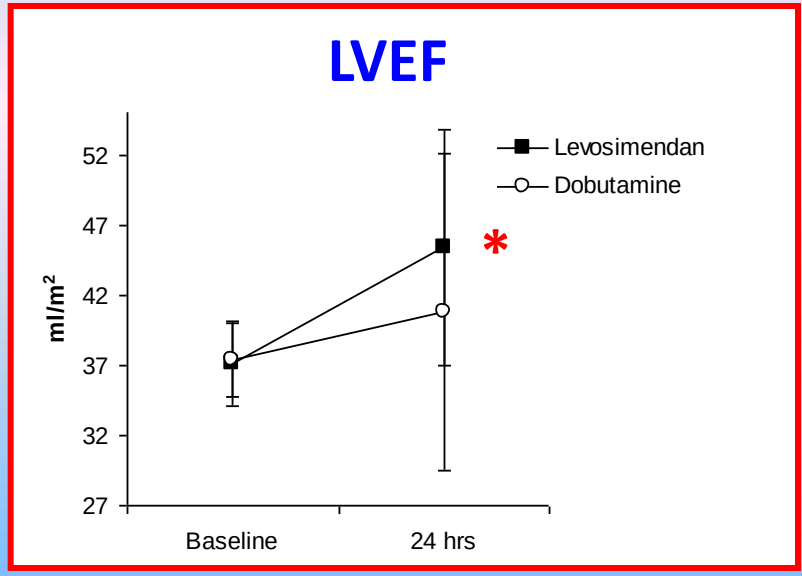
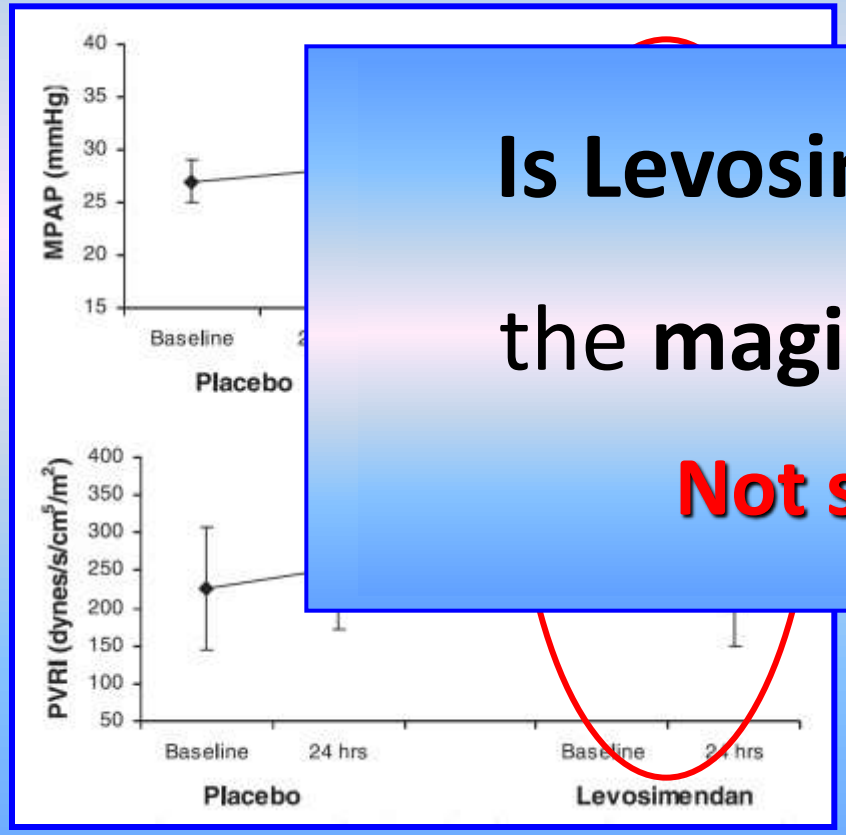




Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study*

Andrea Morelli, MD; Jean-Louis Teboul, MD, PhD; Salvatore Maurizio Maggiore, MD, PhD; Antoine Vieillard-Baron, MD; Monica Rocco, MD; Giorgio Conti, MD; Andrea De Gaetano, MD, PhD; Umberto Picchini, Dr in statistics; Alessandra Orecchioni, MD; Iacopo Carbone, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Martin Westphal, MD

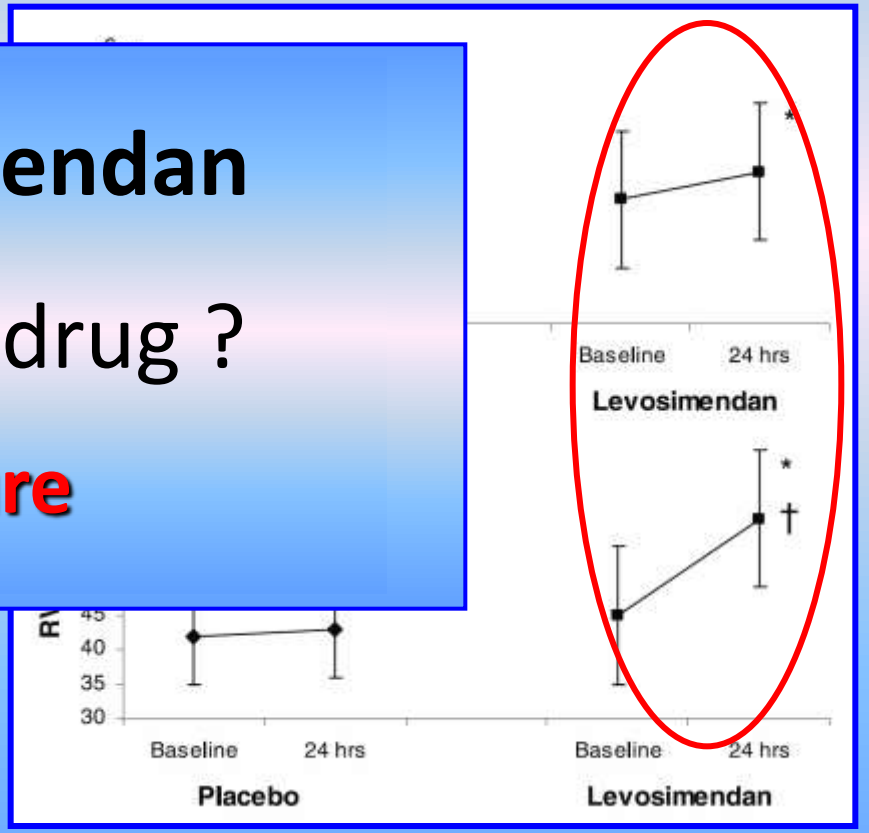
Crit Care Med 2006; 34:2287–2293



Is Levosimendan

the **magic** drug ?

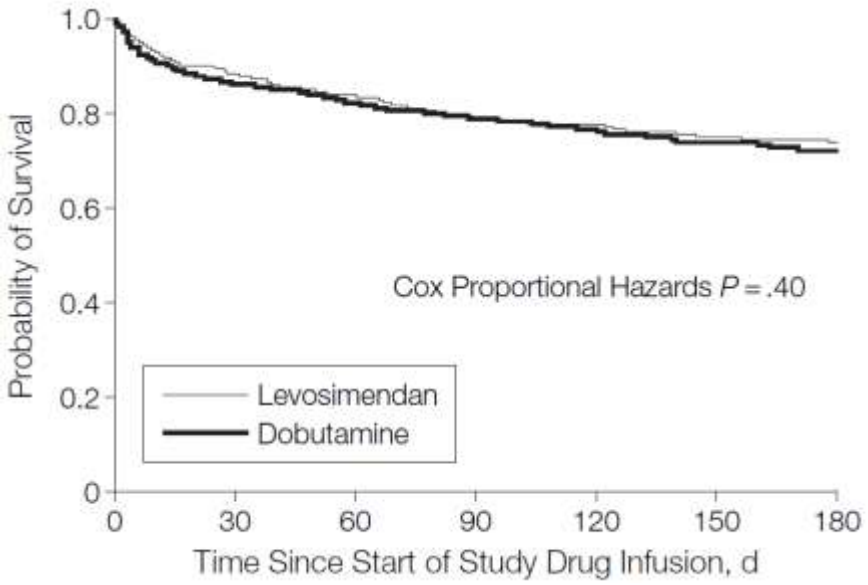
Not sure



Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

Alexandre Mebazaa, MD, PhD
Markku S. Nieminen, MD, PhD
Milton Packer, MD
Alain Cohen-Solal, MD, PhD
Franz X. Kleber, MD
Stuart J. Pocock, PhD
Roopal Thakkar, MD
Robert J. Padley, MD
Pentti Põder, MD, PhD
Matti Kivikko, MD, PhD
for the SURVIVE Investigators



Treatment of sepsis-related cardiac dysfunction

To treat or not to treat?

- Make sure that the patient **is not** still **hypovolemic**
  → assess **fluid responsiveness**
    - **static** measures of **preload** (i.e. CVP) are **not appropriate**
    - **dynamic** indices of **preload responsiveness** are **reliable**
- Make sure that **hypotension** is **corrected**

Fin du 4ème épisode