Les amines vasopressives dans le choc vasculaire

Focus sur les patients d'Onco-Hematologie

Dr Achille Kouatchet
Département de Médecine Intensive Réanimation et Médecine Hyperbare

Pas de conflit d’interêt

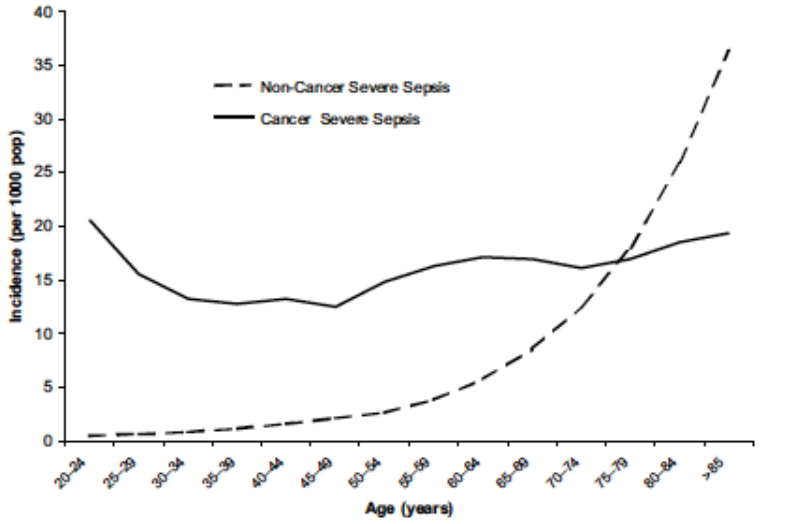
While there is a paucity of the literature on sepsis in the oncological patients, some researchers have tackled this issue. Angus et al showed that one in six patients with severe sepsis have an underlying malignancy. Williams et al constructed a database of patients with cancer admitted to the hospital and compared patients with cancer with severe sepsis to patients with non-severe sepsis.

Abou Dagher G, et al. BMJ Open 2017;7:e013502.

EPIDEMIOLOGIE / DEVENIR (sepsis grave)

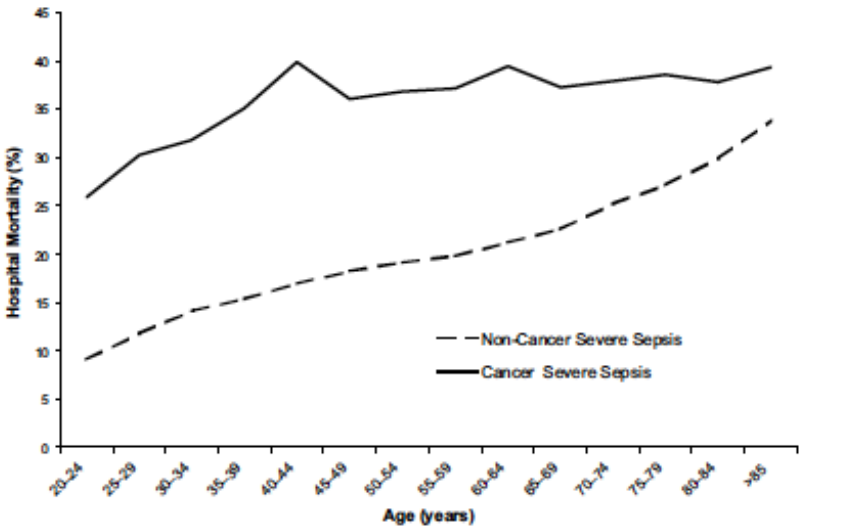
- Incidence chez patient atteint de cancers
  - 16.4 cas pour personnes avec cancer
  - 4 fois plus que les non-cancereux
  - Faible lien avec l'age
- Incidence chez non-cancereux
  - Augmentation exponentielle avec l'age

Figure 1



Age-specific incidence (per 1000 population) of severe sepsis patients with and without cancer.

Figure 2



Age-specific hospital mortality for severe sepsis patients with and without cancer.

EPIDEMIOLOGIE / DEVENIR

Le Cancer est parmi la comorbidité la plus fréquente en cas de sepsis

- 16.8% aux Etats Unis

La maladie cancereuse multiplie le risque de sepsis par 10

Table 1. Characteristics of Patients with Sepsis, According to Subperiod.*

Characteristic	1979–1984 (N=1,332,468)	1985–1989 (N=2,220,659)	1990–1994 (N=2,697,472)	1995–2000 (N=4,068,819)
Demographic characteristics				
Age — yr	57.4±28.9	59.3±22.9	60.8±16.2	60.8±13.7
Male sex — %	49.6	48.9	46.8	48.0
Race — no./100,000 population (% of patients)†				
White	92.1 (81.2)	166.4 (80.3)	167.8 (78.5)	186.3 (76.3)
Black	163.0 (15.2)	301.7 (16.0)	322.8 (17.2)	378.2 (17.7)
Other	187.3 (3.6)	298.0 (3.7)	300.6 (4.3)	370.5 (6.0)
Length of hospital stay — days	17.0±8.5	15.6±6.0	15.3±4.0	11.8±2.6
Coexisting conditions — % of patients				
Chronic obstructive pulmonary disease	5.7	7.3	9.3	12.1
Congestive heart failure	8.6	9.9	13.6	15.2
Cancer	17.1	17.9	18.0	14.5
HIV infection‡	—	1.0	2.1	2.0
Cirrhosis	2.4	2.5	2.2	2.3
Diabetes	12.2	14.5	16.9	18.7
Hypertension	7.0	9.2	13.6	18.6
Pregnancy	0.6	0.5	0.4	0.3
No. of organs with failure — % of patients				
0	83.2	78.1	74.0	66.4
1	13.6	17.9	20.1	24.6
2	2.7	3.5	4.8	7.1
≥3	0.5	0.5	1.1	1.9

Greg S. Martin, N Engl J Med 2003;348:1546-54.

EPIDEMIOLOGIE / DEVENIR

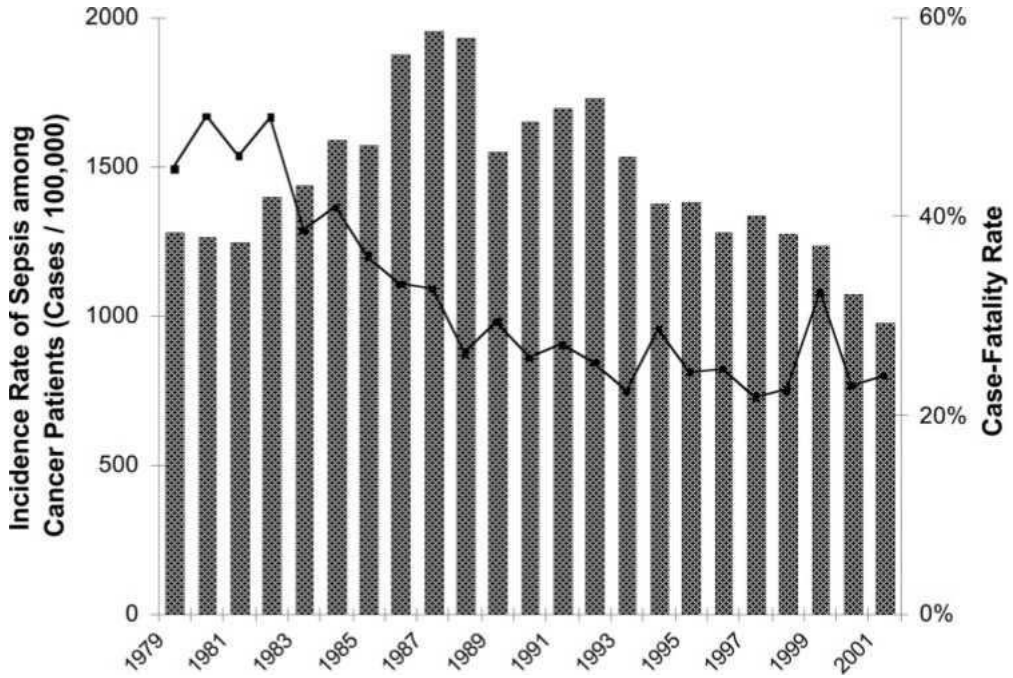
Mortalité hospitalière pour sepsis grave chez patients cancéreux

- Estimé entre 17.9-44.7%[1,2,3,4]

La mortalité des patients atteints de cancer diminue dans le temps

- Comme pour la population générale

- Elle reste supérieure aux patients non cancereux



1 Williams MD
2 Danai A
3 Martin GS
4 Taccone

Timing of vasopressor initiation and mortality in septic shock: a cohort study

Vance Beck[1], Dan Chateau[2], Gregory L Bryson[1], Amarnath Pisipati[3], Sergio Zanotti[4], Joseph E Parrillo[5], Anand Kumar[3,6*] and The Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group

Table 4 Multivariate correlates of death in septic shock

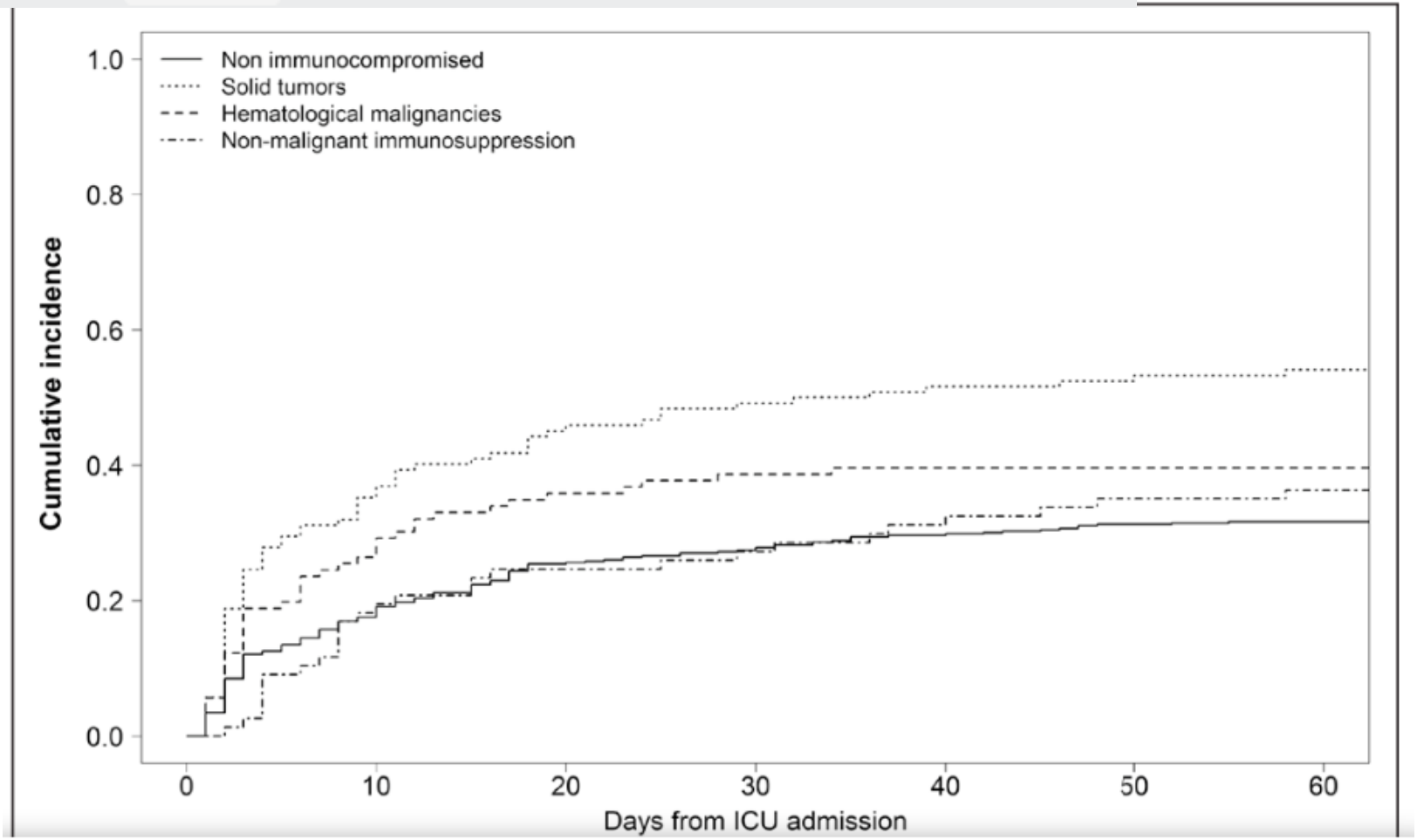
	OR	95% CI	*P* value	Wald χ^2
APACHE II score (per point)	1.11	1.10 to 1.12	<0.0001	544.6
Antimicrobial delay (per hour)	1.07	1.06 to 1.08	<0.0001	335.6
Age (per year)	1.03	1.02 to 1.03	<0.0001	127.1
Liver failure	3.46	2.67 to 4.48	<0.0001	88.3
Hypertension	0.62	0.52 to 0.73	<0.0001	32.2
Hematologic malignancy	1.88	1.46 to 2.41	<0.0001	24.1
Metastatic cancer	1.63	1.32 to 2.01	<0.0001	20.4
Vasopressor delay (per hour)	1.02	1.01 to 1.03	0.0099	20.1
Neutropenia	1.78	1.27 to 2.49	0.0008	11.2
AIDS	1.91	1.29 to 2.81	0.0011	10.7

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; OR, odds ratio.

Beck *et al. Critical Care* 2014, **18**:R97

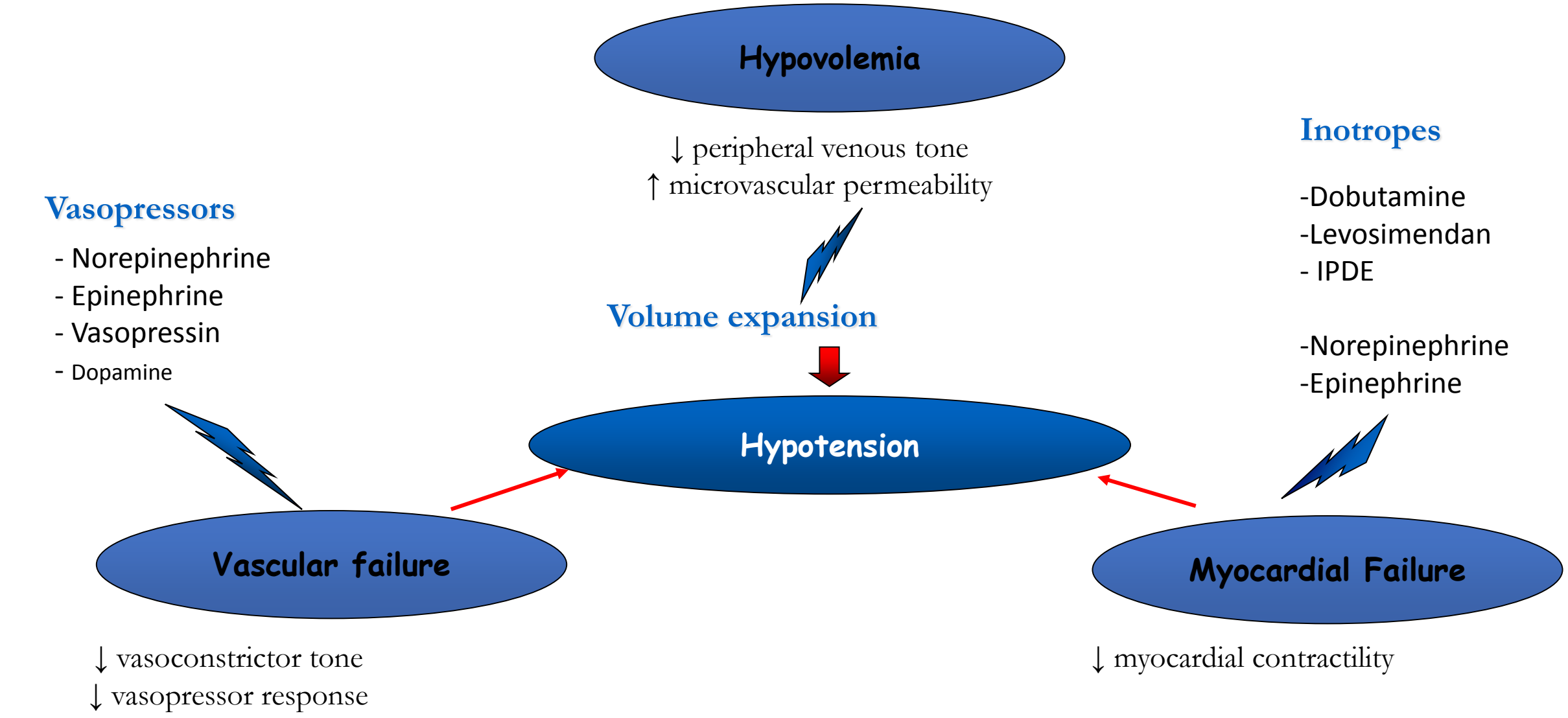
Time Course of Septic Shock in Immunocompromised and Nonimmunocompromised Patients.

Matthieu Jamme, Fabrice Daviaud, +5 authors Frédéric Pène · Published in Critical care medicine 2017 ·



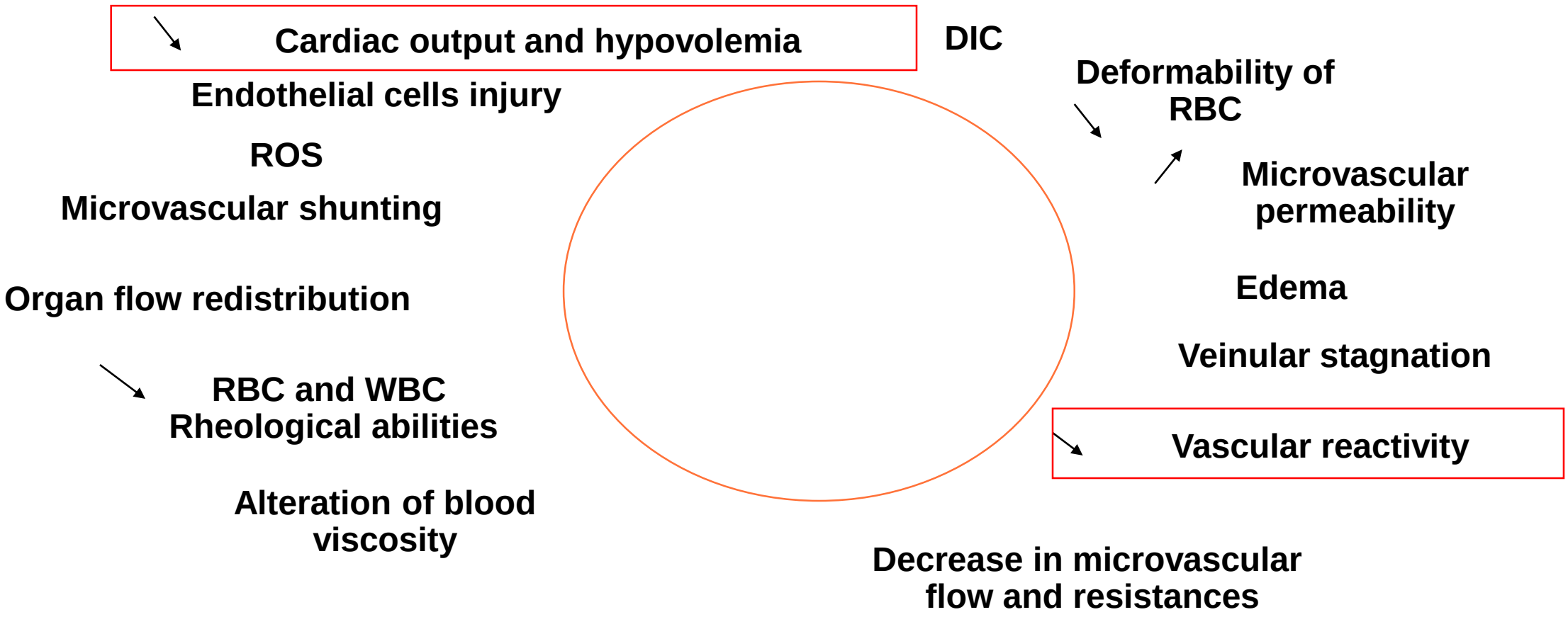
Comment ?

Shock


Hypovolemia
↓ peripheral venous tone
↑ microvascular permeability
Volume expansion
Vasopressors
- Norepinephrine
- Epinephrine
- Vasopressin
- Dopamine
Inotropes
-Dobutamine
-Levosimendan
- IPDE
-Norepinephrine
-Epinephrine
Hypotension
Vascular failure
Myocardial Failure
↓ vasoconstrictor tone
↓ vasopressor response
↓ myocardial contractility

Quand ?

Perturbations hémodynamiques

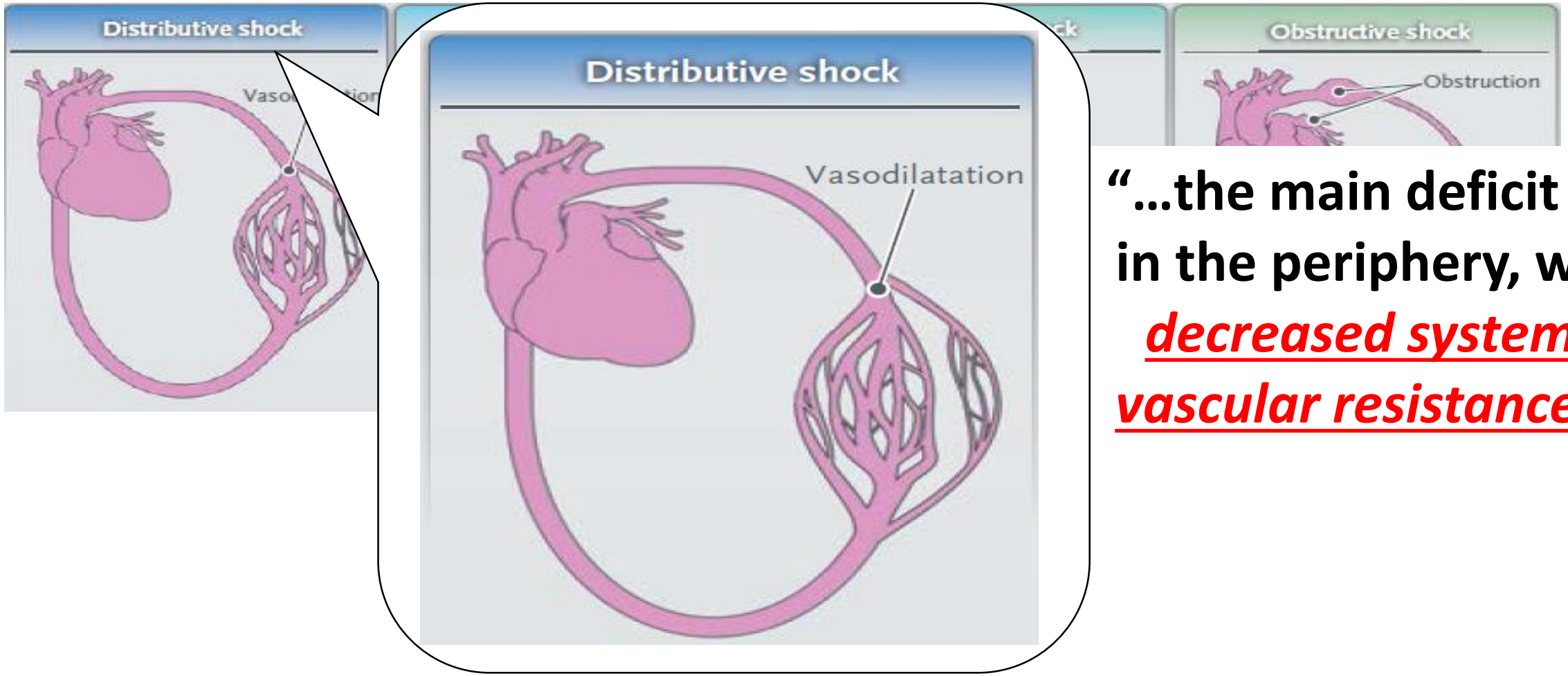


Hinshaw LB CCM 1996;24:1072-78

Circulatory Shock

N Engl J Med 2013;369:1726-34

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.



"…the main deficit lies in the periphery, with *decreased systemic vascular resistance*…"

Réactivité vasculaire

Vasoconstricteurs

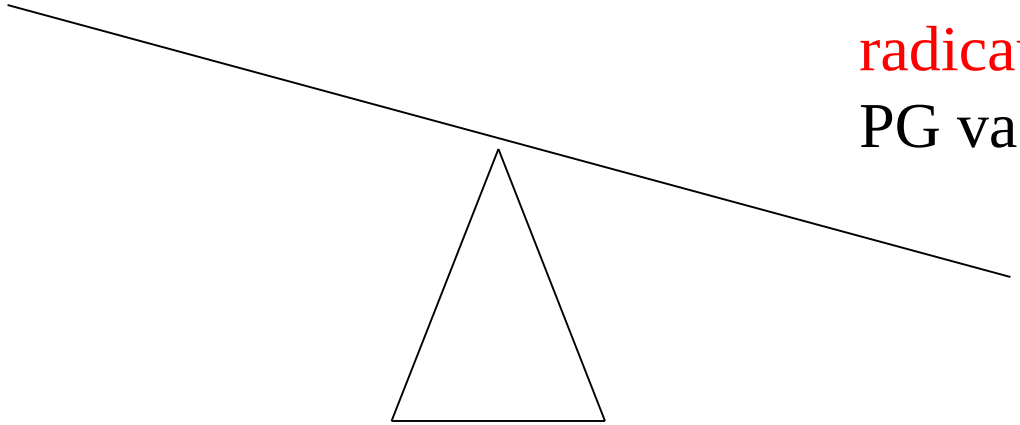
Catécholamines

Rénine Angiotensine

Cortisol

Vasopressine

Endothéline



Vasodilatateurs

Canaux K_{ATP}

Monoxyde d'azote

ADP

PARP

Volémie

Hème oxygénase

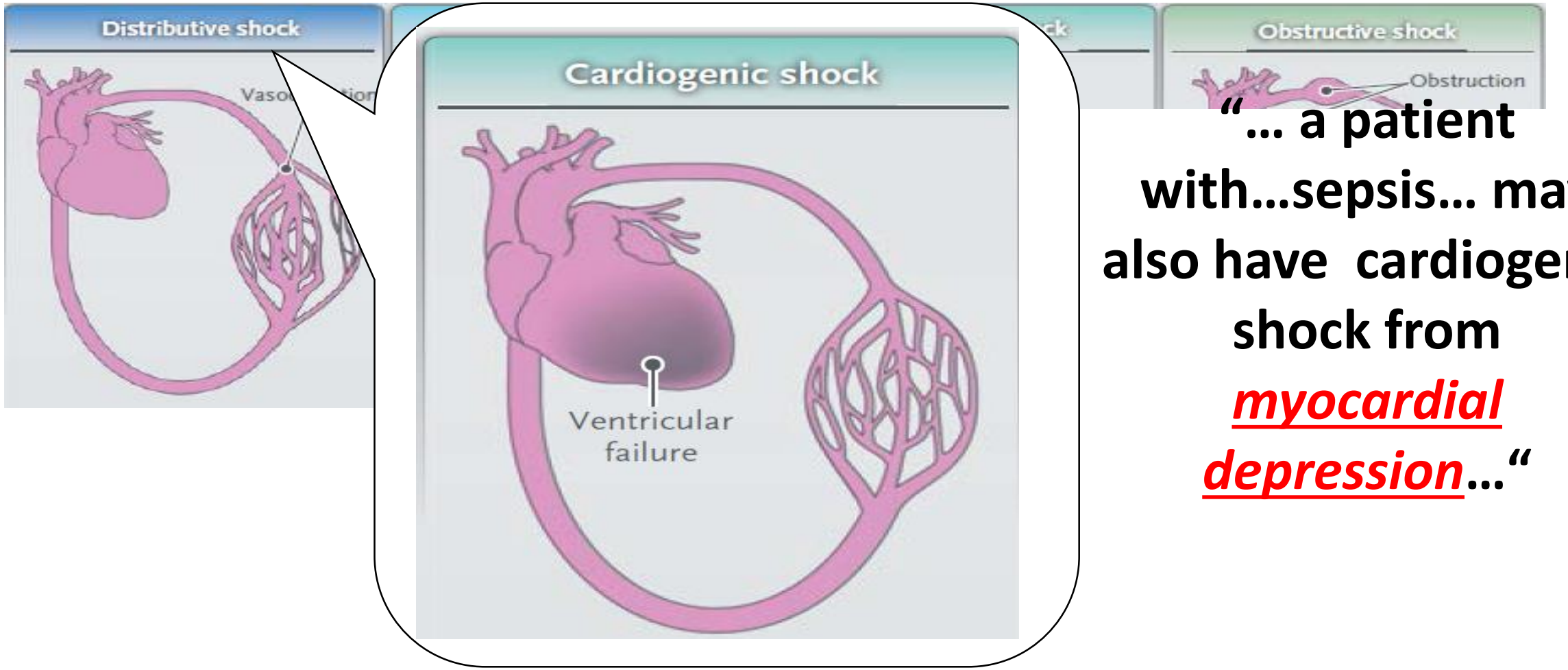
radicaux libres

PG vasodilatatrices

Circulatory Shock

N Engl J Med 2013;369:1726-34

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.



"… a patient with…sepsis… may also have cardiogenic shock from *myocardial depression*…"

Pourquoi ?

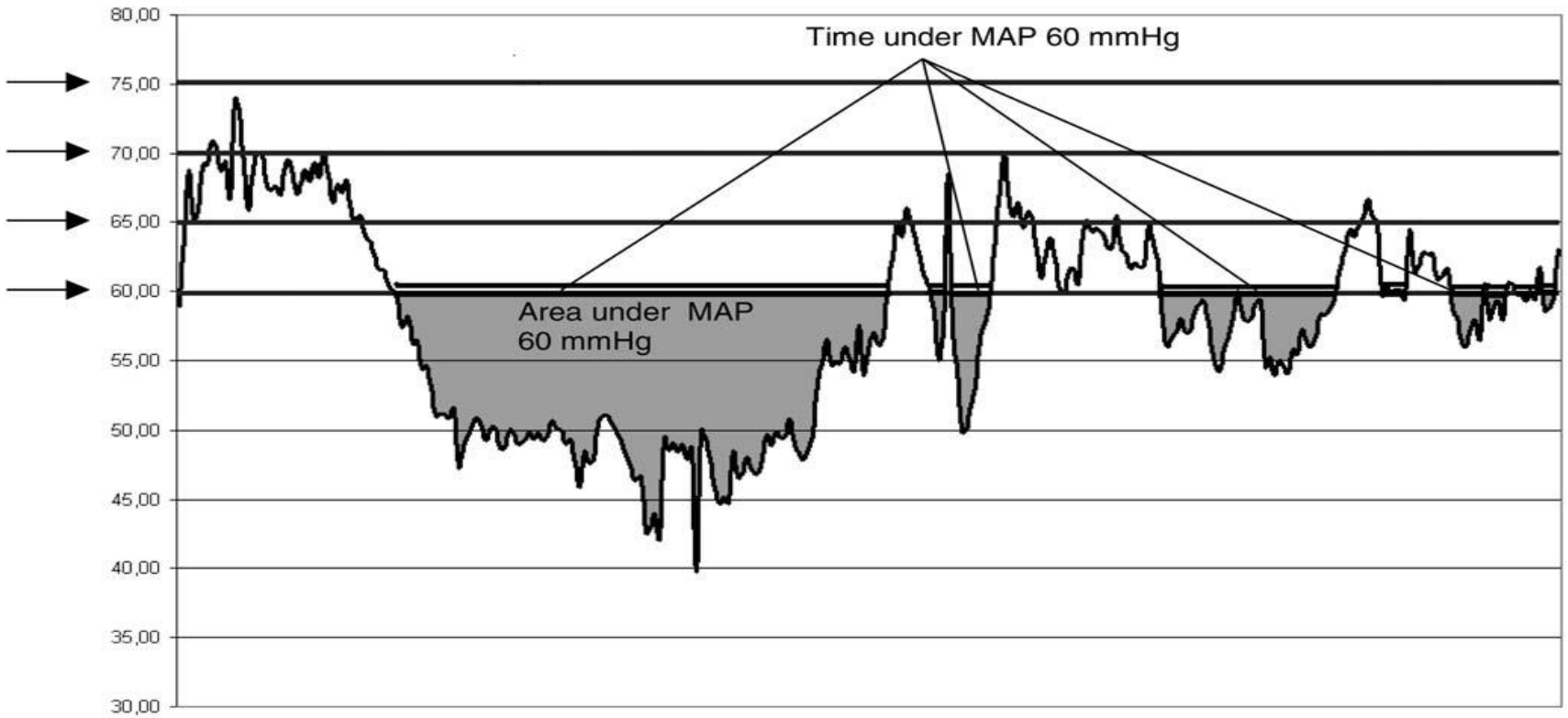
Intensive Care Med (2005) 31:1066–1071
DOI 10.1007/s00134-005-2688-z

ORIGINAL

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

Hemodynamic variables related to outcome in septic shock

111 patients



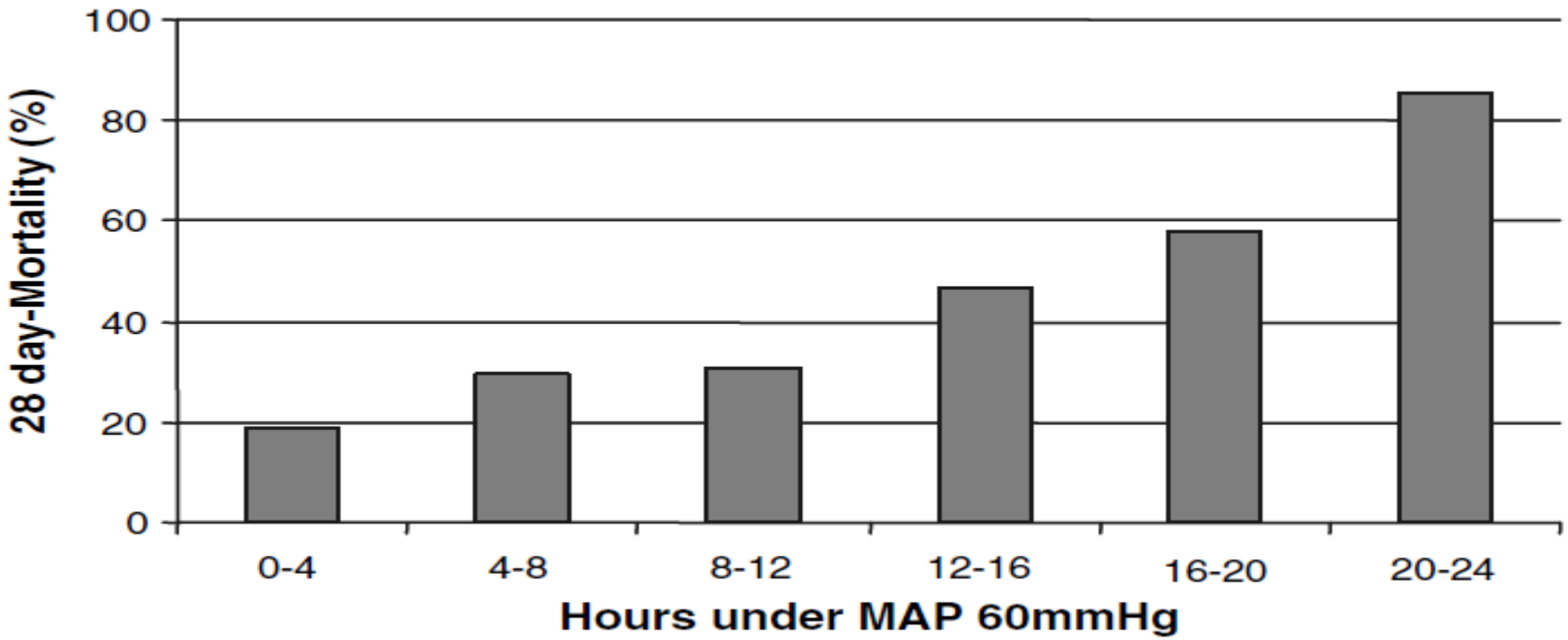
Intensive Care Med (2009) 35:1225–1233
DOI 10.1007/s00134-009-1427-2

ORIGINAL

Martin W. Dünser
Jukka Takala
Hanno Ulmer
Viktoria D. Mayr
Günter Luckner
Stefan Jochberger
Fritz Daudel
Philipp Lepper
Walter R. Hasibeder
Stephan M. Jakob

Arterial blood pressure during early sepsis and outcome

274 patients



Circulatory Shock

N Engl J Med 2013;369:1726-34

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

- Adrenergic agents ($\alpha + \beta$ activity): noradrenaline, adrenaline
- Vasopressin (analogues): AVP, terlipressin, selepressin
- Angiotensin (?)

Circulatory Shock

N Engl J Med 2013;369:1726-34

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

"…we consider noradrenaline… the *vasopressor of first choice*; predominantly α-adrenergic …,… modest β-adrenergic effects… maintain cardiac output…"

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

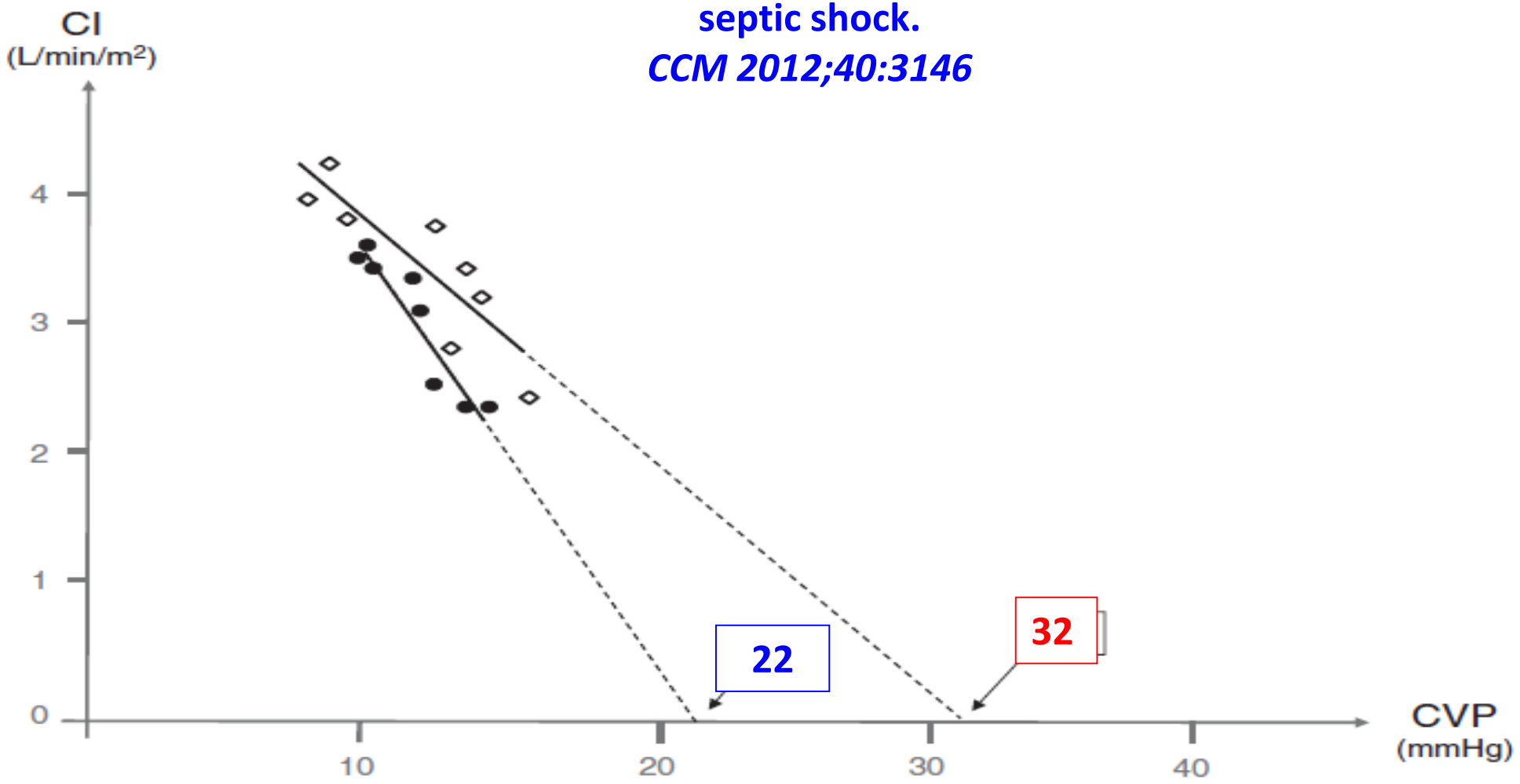
Studies showing **unchanged cardiac output** with NE	Baseline **Cardiac Index** (L/min/m²)	
• Desjars et al Crit Care Med 1987	**5.2**	**5.2**
• Martin et al Chest 1993	**5.3**	
• Martin et al Crit Care Med 1999	**5.7**	
• Albanese et al Chest 2004	**4.7**	
• Albanese et al Crit Care Med 2005	**5.1**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

From JL Teboul, ISICEM, Brussels 2015

Persichini et al:

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

CCM 2012;40:3146

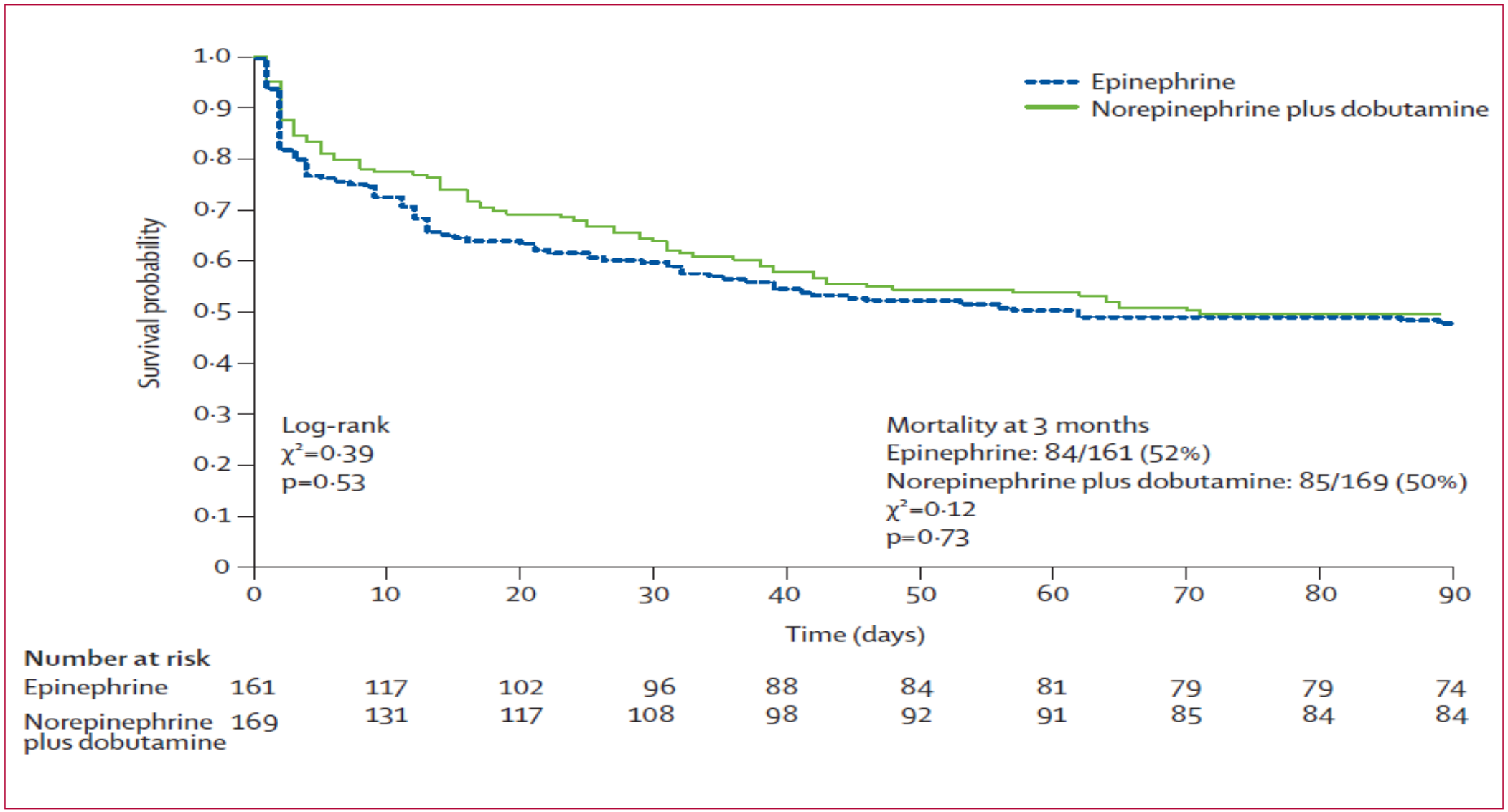


⇒ NoA increases venous return!

Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

*Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group**

Lancet 2007; 370: 676–84


Epinephrine
Norepinephrine plus dobutamine
Survival probability
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
Log-rank
χ²=0·39
p=0·53
Mortality at 3 months
Epinephrine: 84/161 (52%)
Norepinephrine plus dobutamine: 85/169 (50%)
χ²=0·12
p=0·73
0
10
20
30
40
50
60
70
80
90
Time (days)
Number at risk
Epinephrine 161 117 102 96 88 84 81 79 79 74
Norepinephrine plus dobutamine 169 131 117 108 98 92 91 85 84 84

	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)	p
At day 7	40 (25%)	34 (20%)	0·30
At day 14	56 (35%)	44 (26%)	0·08
At day 28	64 (40%)	58 (34%)	0·31
At discharge from intensive care	75 (47%)	75 (44%)	0·69
At discharge from hospital	84 (52%)	82 (49%)	0·51
At day 90	84 (52%)	85 (50%)	0·73

Data are number of deaths (%).

Table 3: **All-cause mortality rates**

Circulatory Shock

N Engl J Med 2013;369:1726-34

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

"…We reserve *adrenaline* as a *second-line agent* for severe cases…"

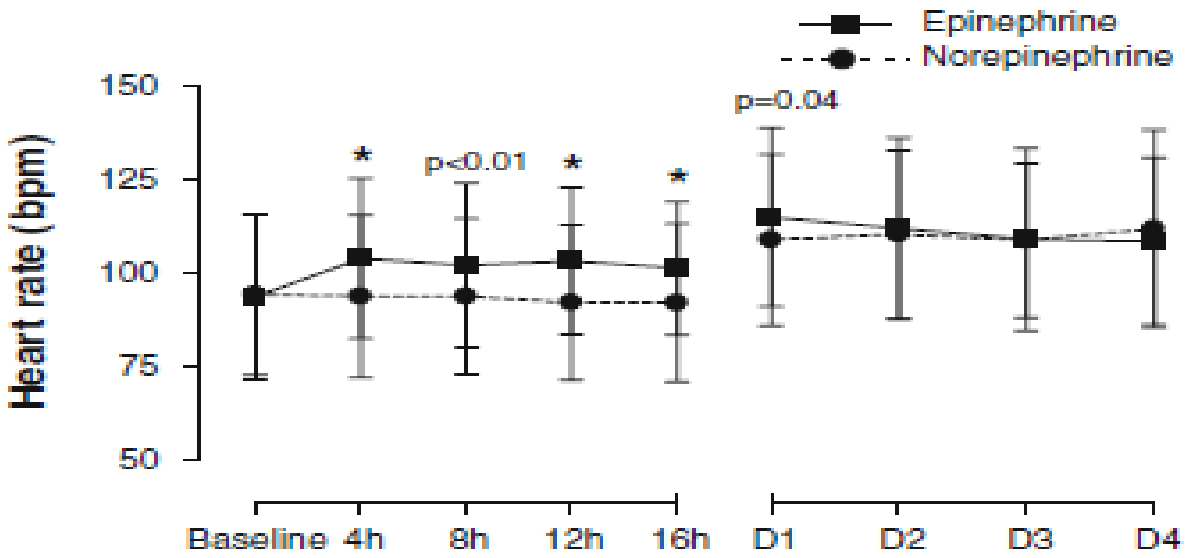
Intensive Care Med (2008) 34:2226–2234
DOI 10.1007/s00134-008-1219-0

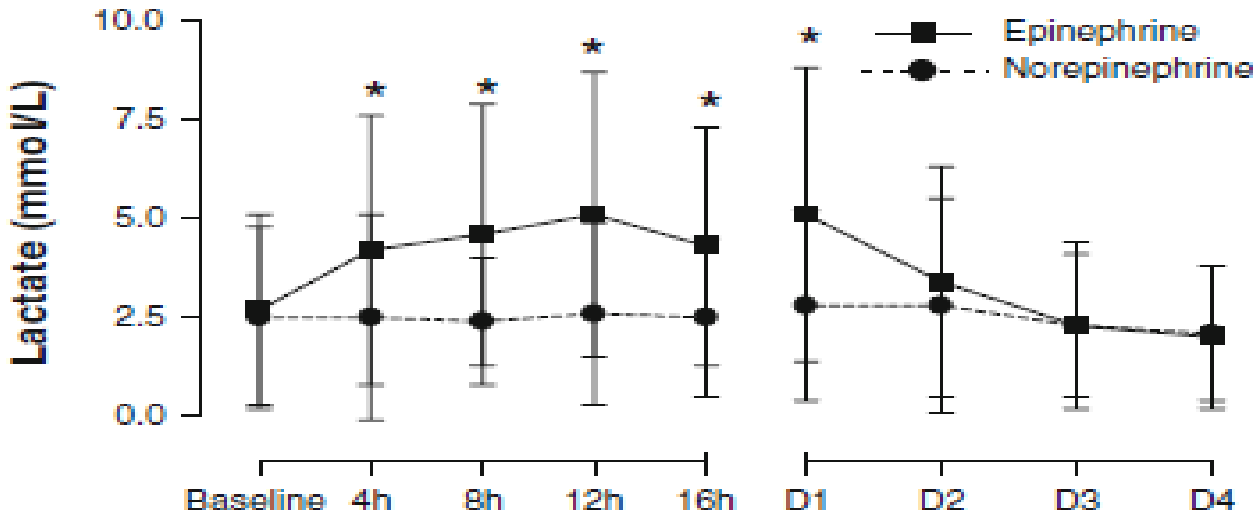
ORIGINAL

280 patients

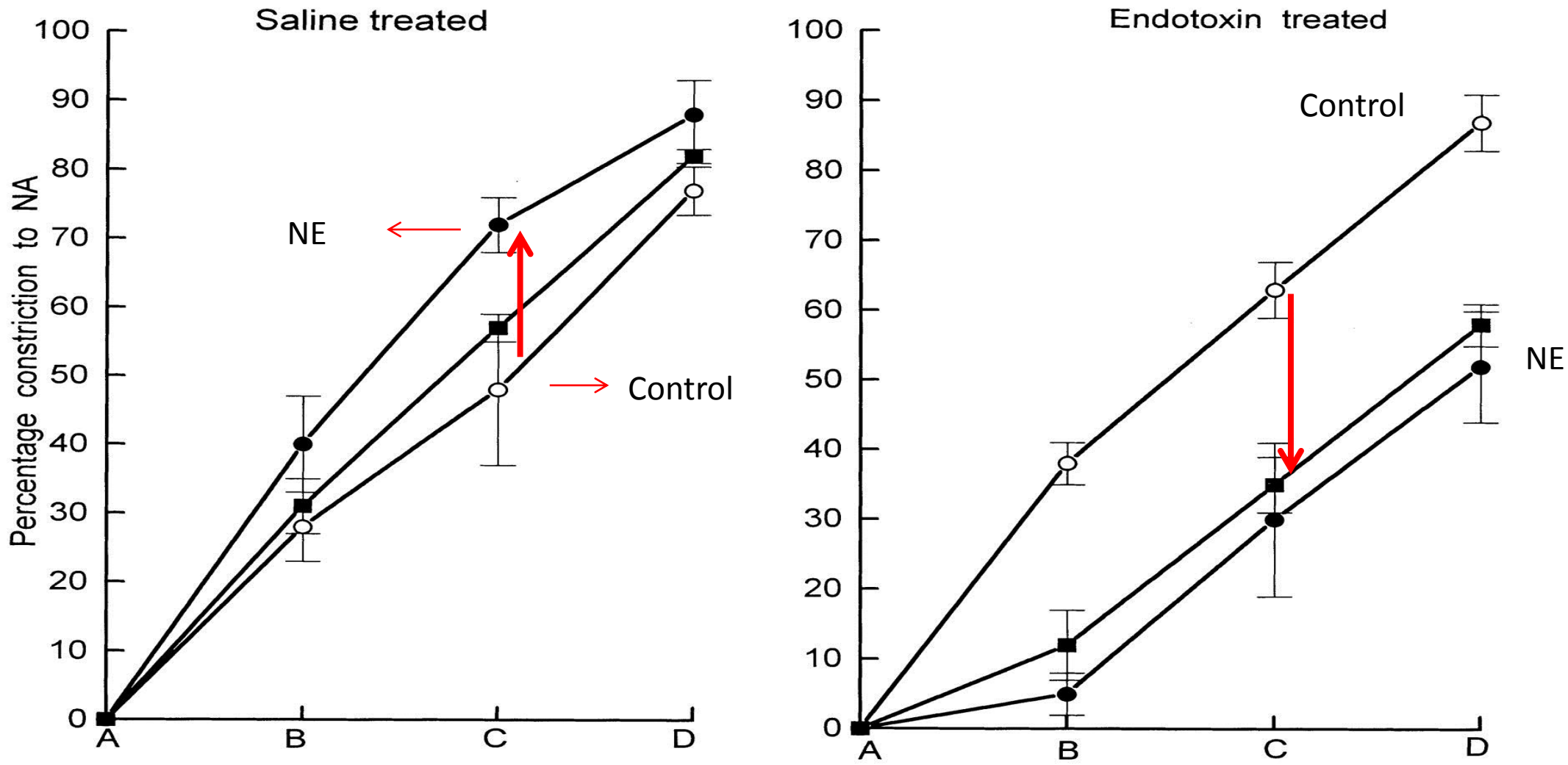
John A. Myburgh
Alisa Higgins
Alina Jovanovska
Jeffrey Lipman
Naresh Ramakrishnan
John Santamaria
the CAT Study investigators

A comparison of epinephrine and norepinephrine in critically ill patients





Local Venous Responses to Endotoxin



American Heart Association

Bhagat K et al. Circulation 1996;94:490-497

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

105 patients
First 6 hours ICU admission
Fluids 1000 (500-1500) mL

60 minutes (30-90)

	Before norepinephrine (introduction/ increase)	After norepinephrine (introduction/ increase)
Heart rate, beats/min	98 ± 21	97 ± 19
MAP, mm Hg	54 ± 8	76 ± 9[a]
DAP, mm Hg	38 ± 6	52 ± 8[a]
CI, L/min/m^2	3.2 ± 1.0	3.6 ± 1.1[a]
SVI, ml/m^2	34 ± 12	39 ± 13[a]
GEDVI, ml/m^2	694 ± 148	742 ± 168[a]
CFI, per minute	4.7 ± 1.5	5.0 ± 1.6[a]
SVRI, dynes/sec/cm^5/m^2	1,471 ± 481	1,822 ± 502[a]

CFI, cardiac function index; CI, cardiac index; DAP, diastolic arterial pressure; GEDVI, global end-diastolic volume index; HR, heart rate; MAP, mean arterial pressure; SVI, stroke volume index; SVRI, index of systemic vascular resistance.

Hamzaoui O *et al* Crit Care 2010

Early?

1) Priority rank?
    a) Vasopressors first?
    b) Fluids and then vasopressors?

2) Time scale?

3) Dose?

Interaction Between Fluids and Vasoactive Agents on Mortality in Septic Shock: A Multicenter, Observational Study

- 3 countries
- 28 hospitals
- 200 849 patients with septic shock (SEPSIS 2 definition)
- Between 1989 and 2007

Waechter *et al* Crit Care Med 2014

TABLE 3. Predicted Cohort Hospital Mortality by Timing and Amount of Total Equivalent Volume of Fluids and Timing of Starting Vasoactive Agents, Sorted by Predicted Hospital Mortality, for the 10 Best and 10 Worst Combinations

TEV0–1[a]	TEV1–6[b]	TEV6–24[c]	Vasoactive Drug Timing[d]	Predicted Hospital Mortality (95% CI)

TEV = total equivalent volume.

[a]Low: 0–0.50 L, medium: 0.51–1.00 L, high: 1.01–9 L.

[b]Low: 0–1.00 L, medium: 1.01–2.40 L, high: 2.41–13.6 L.

[c]Low: 0–1.62 L, medium: 1.63–3.50 L, high: 3.51–16.8 L.

[d]Early: 0–1 hr; intermediate: 1–6 hr; late: 6–24 hr.

1 H

6 H

24 H

NE

TEV0–1[a]	TEV1–6[b]	TEV6–24[c]	Vasoactive Drug Timing[d]	Predicted Hospital Mortality (95% CI)
10 Combinations with the lowest mortality				
High	High	Medium	Intermediate	24.7 (9.6, 39.7)
High	Medium	High	Intermediate	32.2 (13.4, 51.0)
Low	High	Low	Intermediate	33.3 (21.7, 44.9)
High	Medium	Low	Intermediate	33.6 (21.0, 46.1)
Medium	High	Medium	Late	35.6 (17.1, 54.0)
Medium	Low	Medium	Early	37.8 (22.7, 52.9)
Medium	Medium	High	Late	37.9 (28.1, 47.8)
Medium	High	Medium	Intermediate	38.2 (25.3, 51.2)
High	High	High	Late	38.4 (29.3, 47.5)
Medium	High	Medium	Early	39.9 (25.8, 53.9)
10 Combinations with the highest mortality				
Medium	Medium	Low	Early	58.6 (43.1, 74.1)
Medium	Low	Low	Late	59.3 (45.8, 72.7)
High	Medium	Low	Early	62.1 (46.9, 77.3)
High	High	Low	Early	62.3 (48.4, 76.2)
Medium	Low	High	Early	63.2 (42.6, 83.8)
Medium	Medium	Low	Late	63.6 (45.6, 81.7)
High	High	Medium	Late	63.7 (49.2, 78.2)
Medium	High	Low	Late	64.9 (45.6, 84.2)
Low	Low	High	Intermediate	67.6 (56.9, 78.2)
High	Low	Medium	Late	71.1 (52.5, 89.6)

Best combination

0 – 1 hour : > 1 liter of fluids*

1 – 6 hours : > 2.4 liters of fluids and vasopressor start

6 – 24 hours : 1.6 – 3.5 liters of fluids

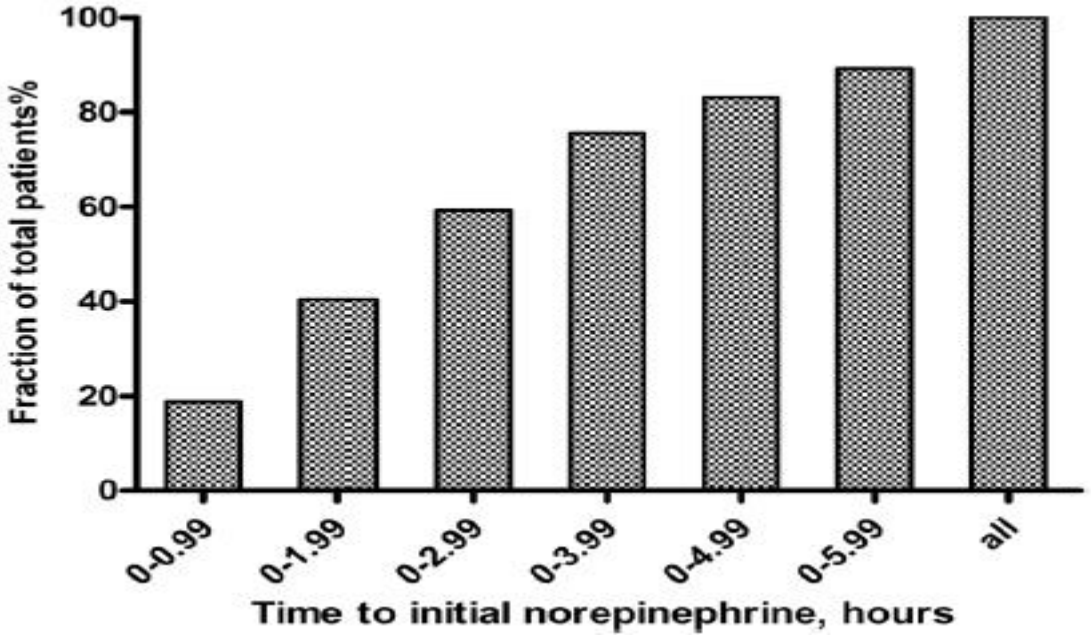
* Fluids expressed as median values.

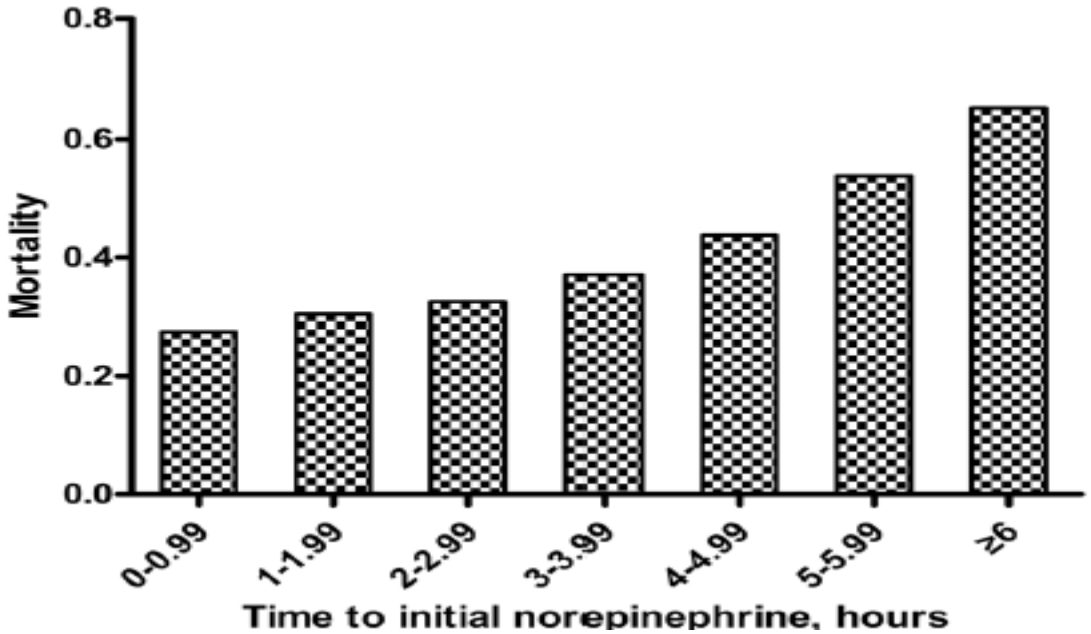
Early versus delayed administration of norepinephrine in patients with septic shock

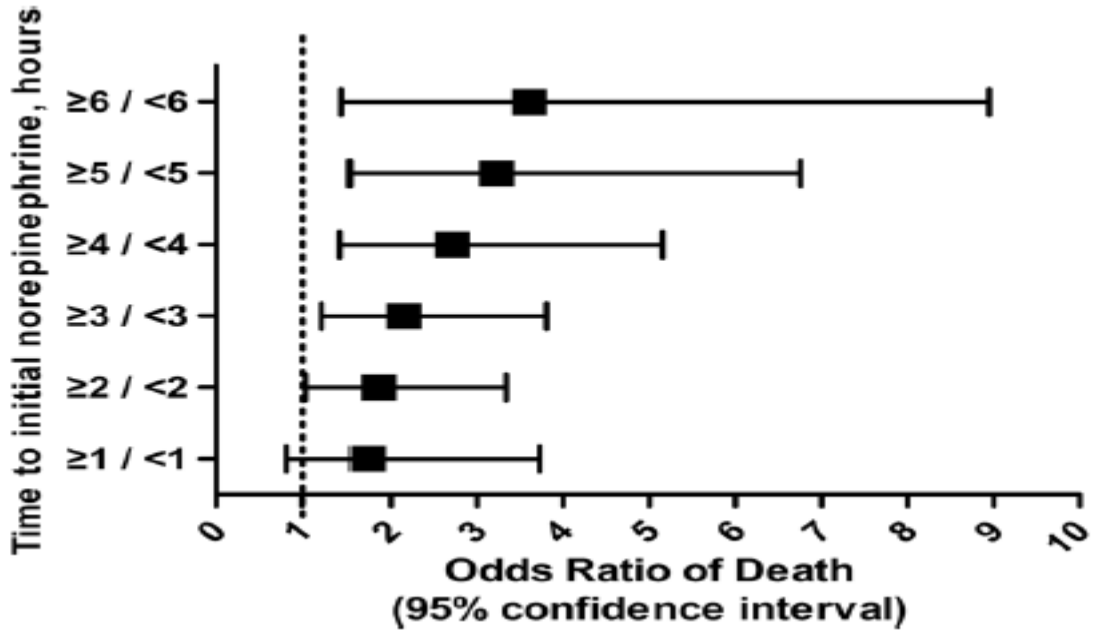
Table 2 Therapeutic intervention and secondary outcomes: Phase I

Characteristic	28-day survivors (n = 133)	28-day non-survivors (n = 80)	*P* value
24-hour norepinephrine administration (mg)	29.4 ± 9.7	34.8 ± 9.6	<0.001
Time to initial norepinephrine administration (h)	2.7 ± 2.1	3.8 ± 2.9	0.002
Time to initial antimicrobial treatment (h)	1.4 ± 1.2	2.2 ± 1.8	0.001
Volume of intravenous fluids within 6 h (L)	3.4 ± 0.9	3.0 ± 0.9	0.003
Volume of intravenous fluids within 24 h (L)	6.5 ± 0.8	6.9 ± 0.5	<0.001
Effective antimicrobial therapy, number (%)	97 (72.9)	45 (56.3)	0.012
Corticosteroid treatment, number (%)	78 (58.6)	50 (62.5)	0.578
Norepinephrine duration (days)	2.4 ± 0.6	3.4 ± 0.9	<0.001
ICU duration (days)	11.2 ± 5.7	10.8 ± 5.4	0.646

Bai X *et al* Crit Care 2014



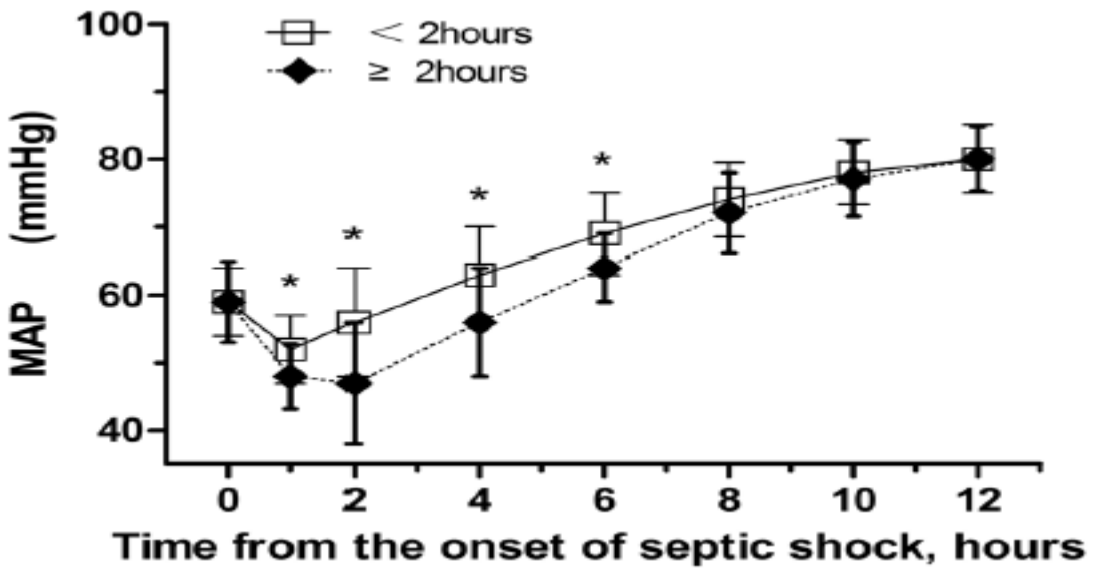


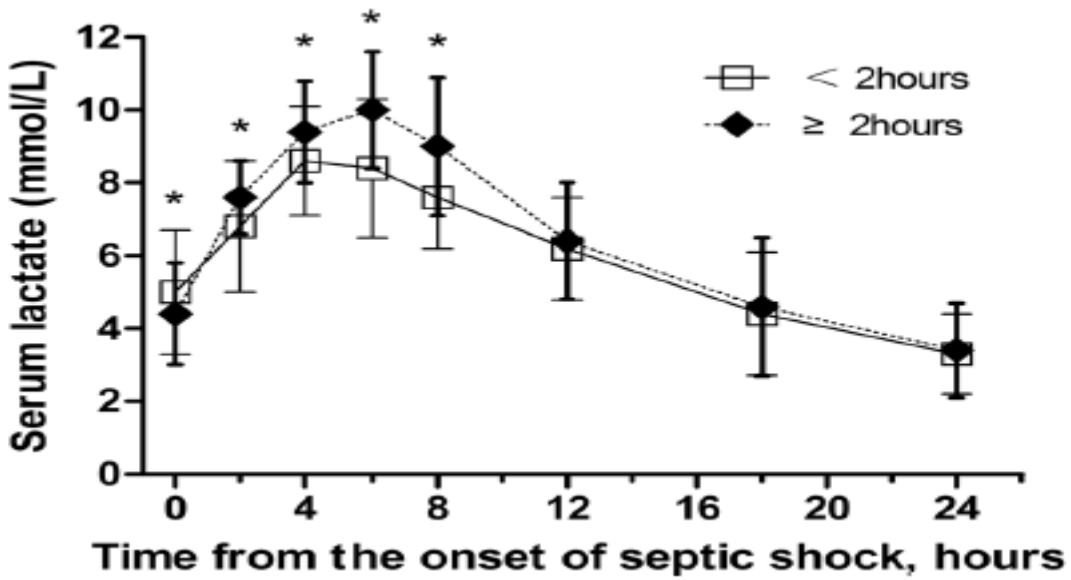


Bai X *et al* Crit Care 2014

Early versus delayed administration of norepinephrine in patients with septic shock

Characteristic	<2 hours (number = 86)	≥2 hours (number = 127)	*P* value
24-hour norepinephrine administration (mg)	29.4 ± 9.7	32.8 ± 10.0	0.013
Time to initial antimicrobial treatment (h)	1.6 ± 1.4	1.7 ± 1.5	0.126
Volume of intravenous fluids within 6 h (L)	3.1 ± 0.9	3.3 ± 0.8	0.092
Volume of intravenous fluids within 24 h (L)	6.2 ± 0.6	6.9 ± 0.7	<0.001
Effective antimicrobial therapy, number (%)	55 (64.0)	87 (68.5)	0.489
Corticosteroid treatment, number (%)	54 (62.8)	74 (58.3)	0.508
Norepinephrine duration (days)	2.6 ± 0.6	2.9 ± 1.0	0.001
Hypotension duration (h)	4.6 ± 1.2	6.1 ± 1.0	<0.001
ICU duration (days)	10.7 ± 6.0	11.2 ± 5.2	0.520





Bai X *et al* Crit Care 2014

Timing of vasopressor initiation and mortality in septic shock: a cohort study

8670 patients

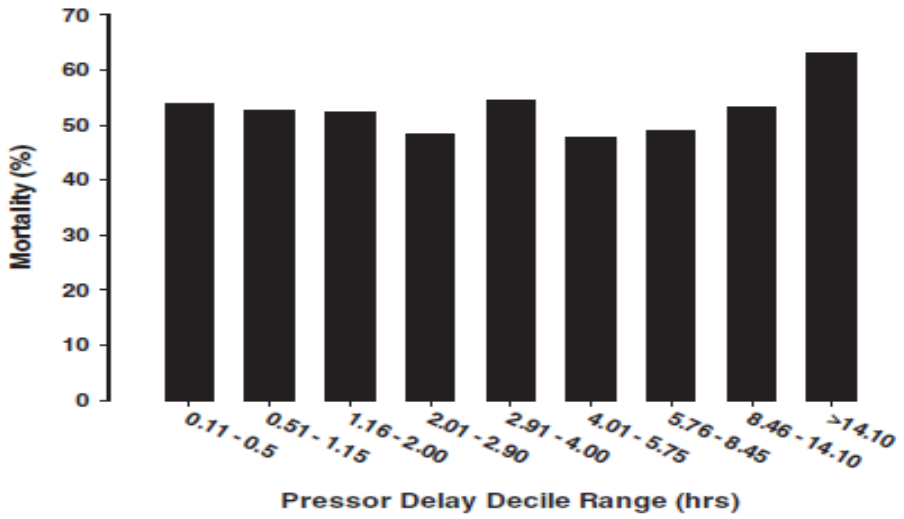


Figure 1 Unadjusted mortality in each pressor delay decile.

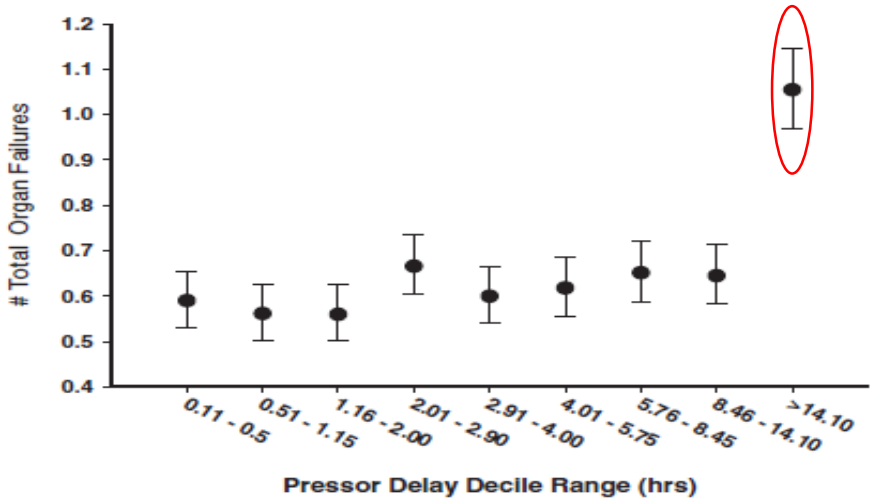


Figure 3 Mean (±95% confidence interval) incremental organ failures (day 2 to day 10 after presentation) with increasing pressor delays.

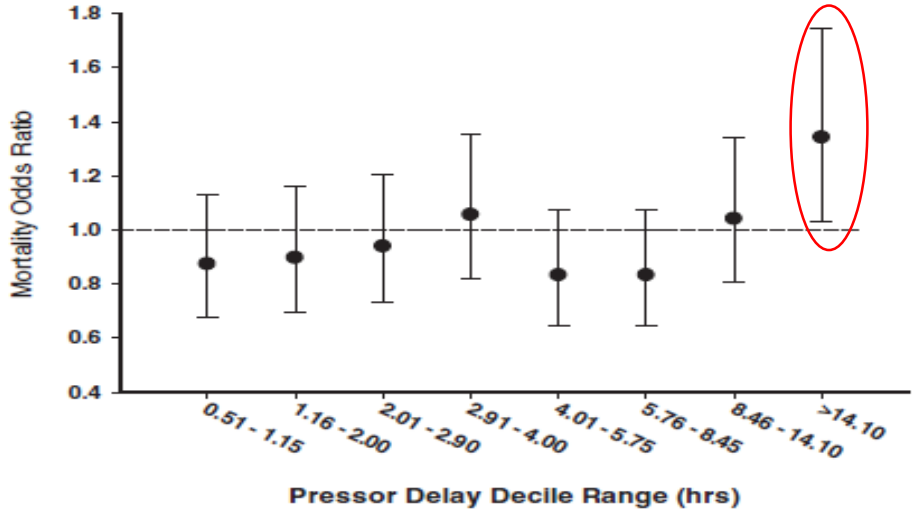


Figure 2 Odds ratio (±95% confidence interval) of mortality for each pressor delay decile (reference decile, 0.11 to 0.5 hours).

Beck V *et al* Crit Care 2014

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Crit Care Med 2016

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

shock if the clinical examination does not lead to a clear diagnosis (BPS).

5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).
6. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

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Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa

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

No.	Statement/recommendation	GRADE level of recommendation; quality of evidence	Type of statement
13.	We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis	Ungraded	Best practice
14.	We suggest that, when further hemodynamic assessment is needed, echocardiography is the preferred modality to initially evaluate the type of shock as opposed to more invasive technologies	Level 2; QoE moderate (B)	Recommendation
15.	In complex patients, we suggest to additionally use pulmonary artery catheterization or transpulmonary thermodilution to determine the type of shock	Level 2; QoE low (C)	Recommendation
16.	We recommend early treatment, including hemodynamic stabilization (with fluids and vasopressors if needed) and treatment of the shock etiology, with frequent reassessment of response	Ungraded	Best practice
17.	We recommend arterial and central venous catheter insertion in shock not responsive to initial therapy and/or requiring vasopressor infusion	Ungraded	Best practice
18.	In patients with a central venous catheter, we suggest measurements of $ScvO_2$) and V-$ApCO_2$ to help assess the underlying pattern and the adequacy of cardiac output as well as to guide therapy	Level 2; QoE moderate (B)	Recommendation
19.	We recommend serial measurements of blood lactate to guide, monitor, and assess	Level 1; QoE low (C)	Recommendation
20.	We suggest the techniques to assess regional circulation or microcirculation for research purposes only	Level 2; QoE low (C)	Recommendation

Conclusion

- Cruel manque de données sur la population atteinte de neoplasie
- Il n’existe pas de données type Evidence Based Medicine sur une stratégie d’utilisation des catécholamines en ces de sepsis grave chez le patient atteint de cancer
- Les nouveaux vasoconstricteurs devront être evalués dans cette population