

Quel vasopresseur dans le choc septique

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Choc

Hypovolémie

↓ tonus veineux périphérique
↑ perméabilité microvasculaire

Remplissage vasculaire

Hypotension

Vasopresseurs

Défaillance Vasculaire

↓ tonus vasoconstricteur
↓ réponse aux agents vasopresseurs

Inotropes

Défaillance Cardiaque

↓ contractilité myocardique

Thérapeutique hémodynamique du choc

- Trois cibles
 - Hypovolémie : expansion volémique/vasopresseurs
 - Défaillance vasculaire, mécanisme ubiquitaire
 - Vasopresseurs purs : phényléphrine, vasopressine
 - Inopresseurs : dopamine, adrénaline, noradrénaline
 - Défaillance cardiaque
 - Inotropes : dobutamine, levosimendan, IPDE
 - Inopresseurs : adrénaline, noradrénaline

Catécholamine idéale

- Vasopressive
- Sans effet délétère myocardique/effet inotrope si nécessaire
- Pas d'augmentation de la demande en oxygène
- Respect ou "amélioration" des circulations régionales
- Effet adaptable à la situation clinique

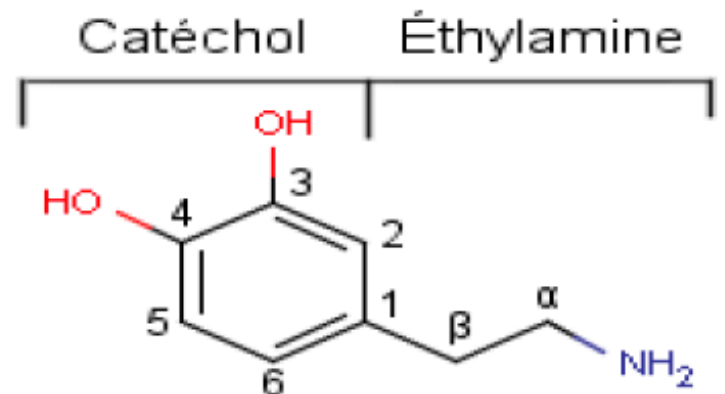
Catécholamines

Catécholamines synthétiques

Dopamine
Noradrénaline
Adrénaline
Isoprénaline
Dobutamine
Dopexamine

Catécholamines naturelles

Dopamine
Noradrénaline
Adrénaline



Catécholamines

	α	$\beta 1$	$\beta 2$
Dopamine	+	++	
Dobutamine	+	+++	+
Adrénaline	+++	++	++
Noradrénaline	+++	+	

Effet alpha : vasoconstriction

Effet bêta 1 : inotropisme

Effet bêta 2 : vasodilatation

La vision classique

	PA	Fréquence cardiaque	Débit cardiaque
adrénaline	↗	↗↗	↗↗
dobutamine	→	↗	↗
dopamine	↗	↗↗	↗
noradrénaline	↗↗	→	↗

Fiabilité de l'effet vasopresseur

Dopamine et choc septique.

- **Agoniste alpha et bêta-1 :**
 - précurseur endogène immédiat de la noradrénaline.
 - demi-vie de 8-38 min.
 - action sur le débit cardiaque et les résistances vasculaires.
 - Classiquement effets variables selon la posologie.
- **Utilisation dans le choc septique à la posologie de 5 à 20 $\mu\text{g}/\text{kg}/\text{min}$.**

Dopamine et choc septique.

- La dopamine est essentiellement un inotrope (+).
- Schreuder et al (20 $\mu\text{g}/\text{kg}/\text{min}$) (Chest 1989)
 - MAP 56 ± 9 à 70 ± 12
 - IC $4 \pm 1,5$ à $4,6 \pm 1,4$
 - RVS 1090 ± 444 à 1161 ± 550



clinical investigations in critical care

Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?*

*Claude Martin, M.D., F.C.C.P.; Laurent Papazian, M.D.;
Gilles Perrin, M.D.; Pierre Saux, M.D.; and François Gouin, M.D.*

Chest 1993, 103:1826-31

32 patients randomized to: either dopamine (until 25 $\mu\text{g}/\text{kg}/\text{min}$) or norepi (until 5 $\mu\text{g}/\text{kg}/\text{min}$)

Objective : to reach and maintain mean BP > 80 mmHg over 6 hours

Dopa (n=16)

Norepi (n=16)

success (n=5)

failure (n=11)

success (n=15)

failure (n=1)

10 to 25 $\mu\text{g}/\text{kg}/\text{min}$

25 $\mu\text{g}/\text{kg}/\text{min}$

1.5 \pm 1.2 $\mu\text{g}/\text{kg}/\text{min}$

5 $\mu\text{g}/\text{kg}/\text{min}$

increase in urine output
decrease in lactate

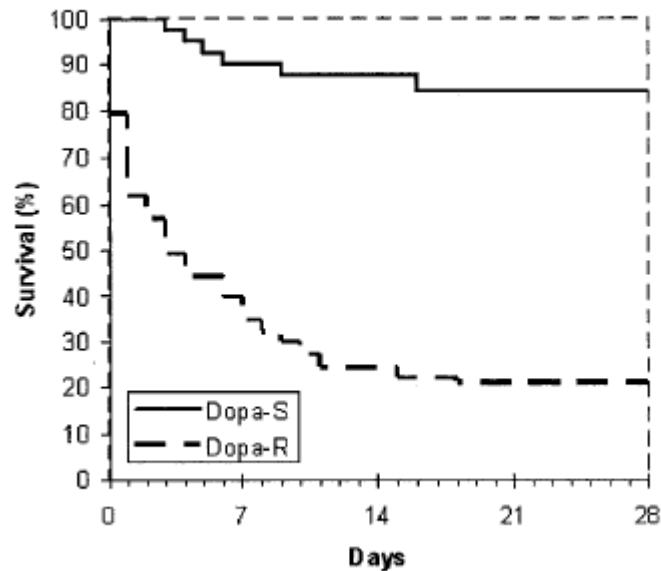
increase in urine output
decrease in lactate

10 successes with Dopa + Norepi (25 $\mu\text{g}/\text{kg}/\text{min}$ + 1.7 \pm 1.8 $\mu\text{g}/\text{kg}/\text{min}$)

increase in urine output
and decrease in lactate

Cardiovascular response to dopamine and early prediction of outcome in septic shock: A prospective multiple-center study*

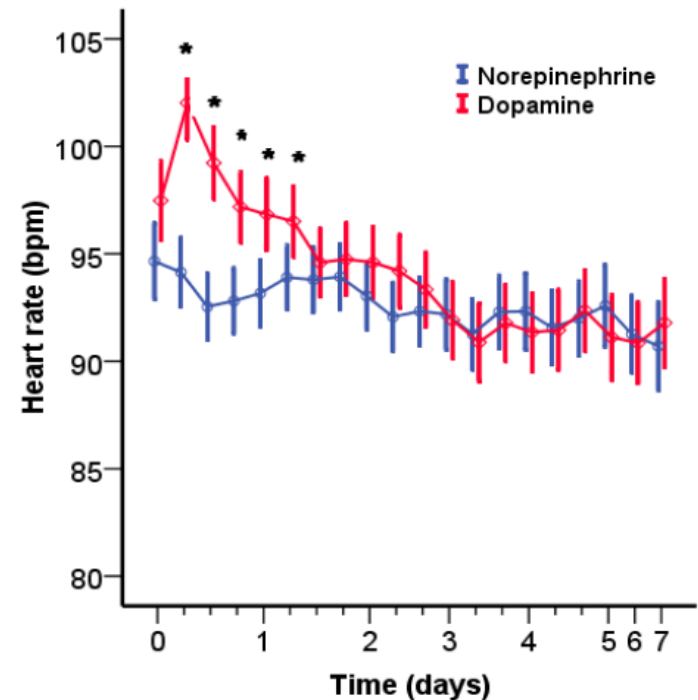
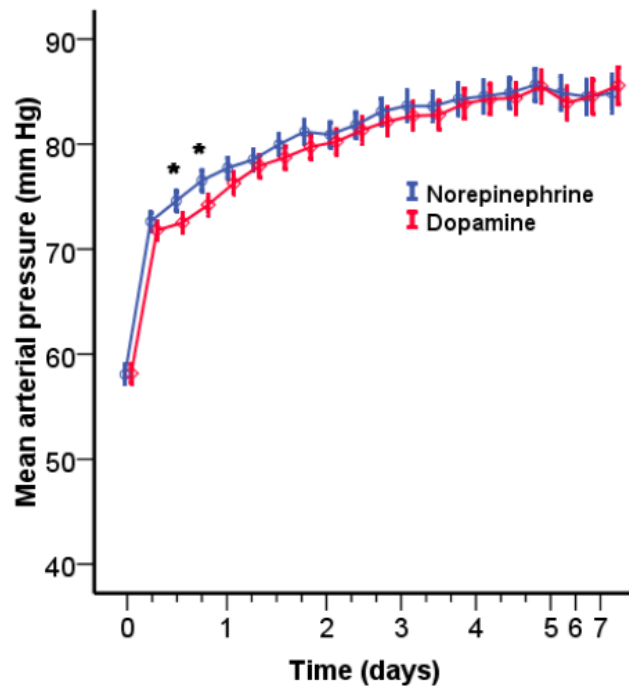
Bruno Levy, MD, PhD; Benjamin Dusang, MD; Djillali Annane, MD, PhD; Sebastien Gibot, MD; Pierre-Edouard Bollaert, MD, PhD; and the College Interregional Des Réanimateurs Du Nord-Est



	Mortalité à J₂₈
Population globale	53,64 %
Groupe Dopamine-sensible (40%)	15,91 %
Groupe Dopamine-résistant (60 %)	78,79 %

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*



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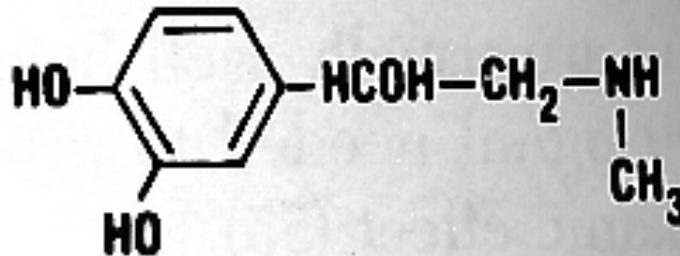
Table 3. Secondary Outcomes and Adverse Events.*

Variable	Dopamine (N = 858)	Norepinephrine (N = 821)	P Value
Adverse events			
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	
Myocardial infarction — no. (%)	19 (2.2)	25 (3.0)	0.29

ADRENALINE VERSUS NORADRENALINE

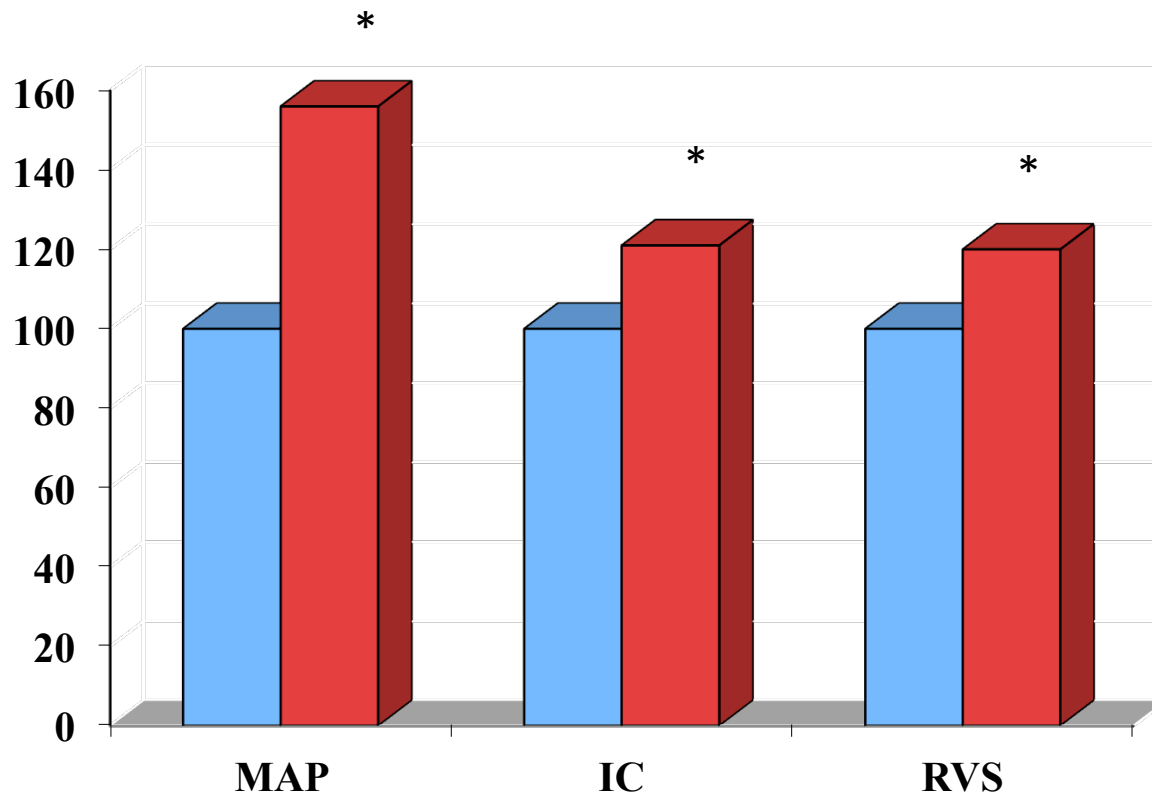
Adrénaline

- Agoniste alpha, bêta 1 et bêta 2.
- Demi-vie plasmatique de 2-3 minutes
- Hormone endogène secrétée par la surrénale
- Effets métaboliques importants



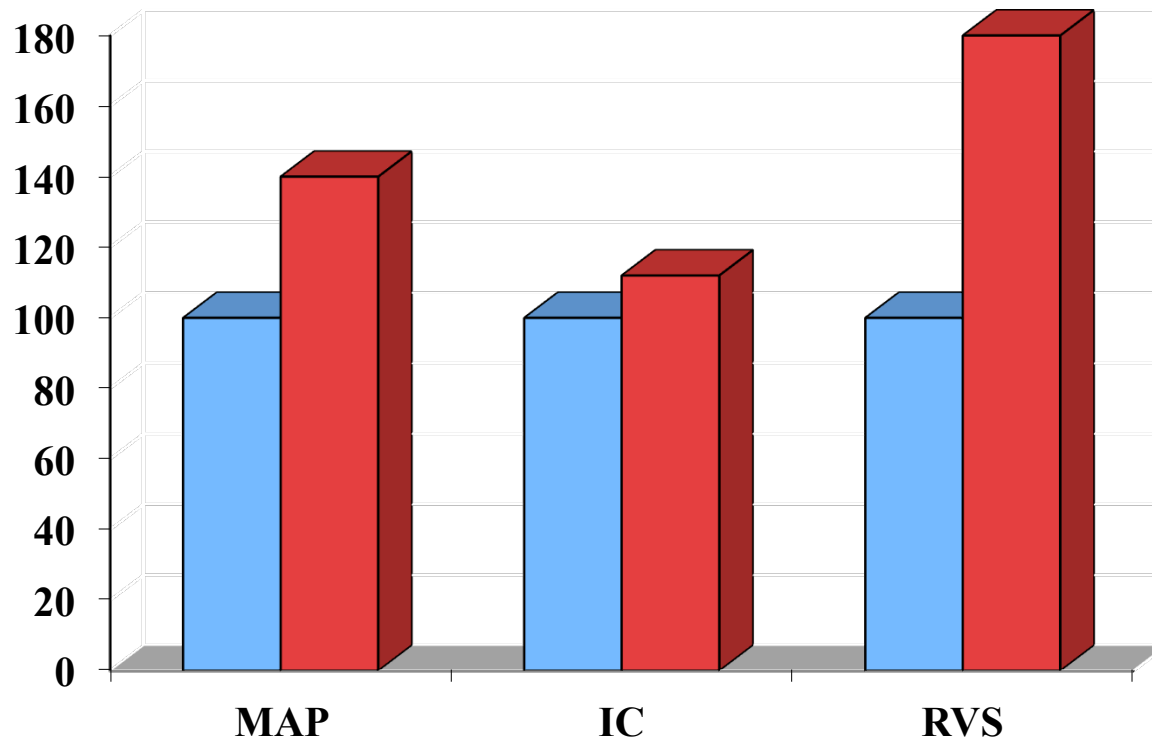
Effets hémodynamiques de l'adrénaline dans le choc septique

Moran JL, Crit Care Med 1993;21:70-77.

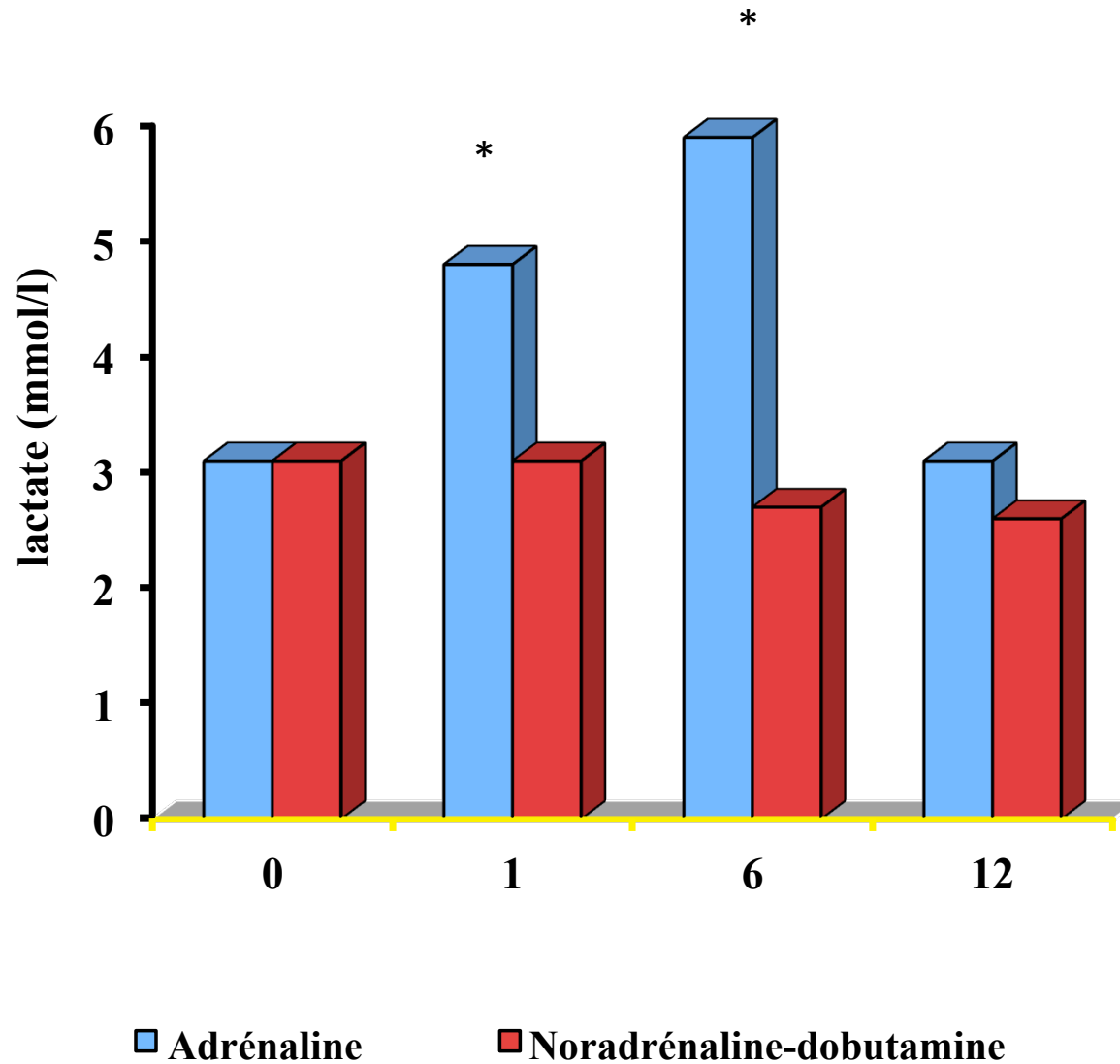


Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension

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



Hyperlactatémie et adrénaline

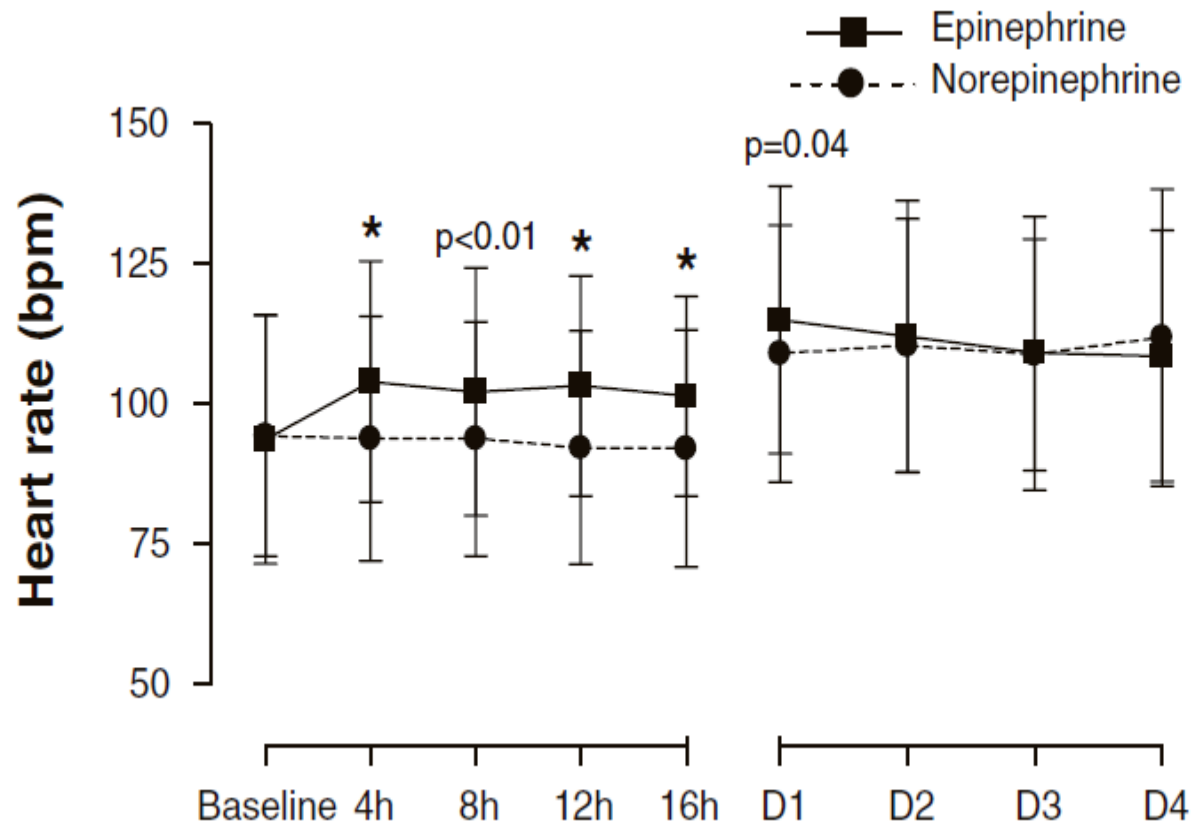


Effets métaboliques de l'adrénaline

- Augmentation de la VO_2
- Tachycardie
- Hyperglycémie
- Hyperlactatémie
- Hypokaliémie
- Acidose métabolique
- Effets sur la circulation hépato-splanchnique

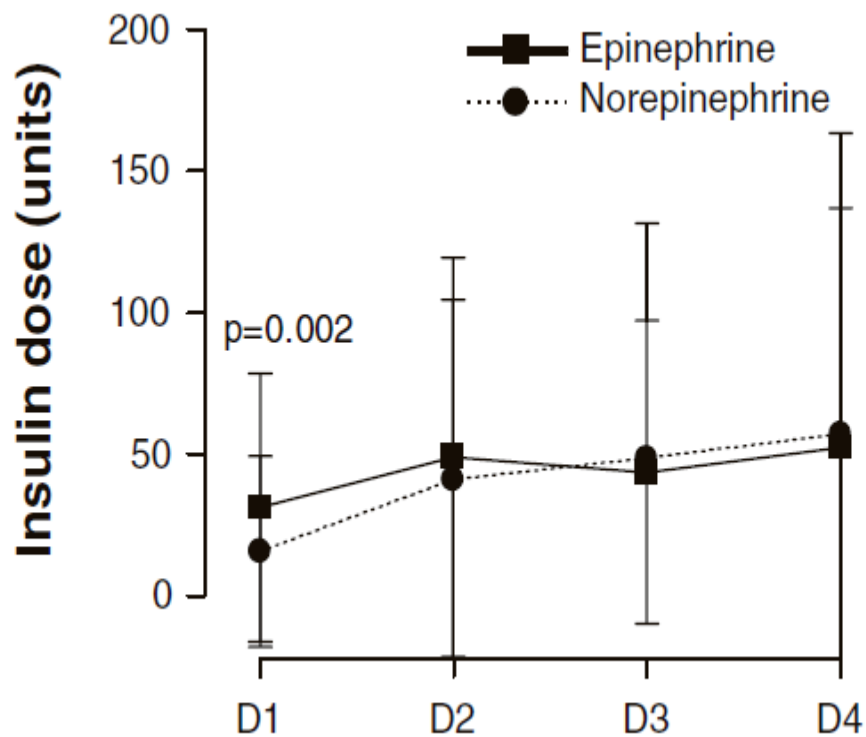
John A. Myburgh
Alisa Higgins
Alina Jovanovska
Jeffrey Lipman
Naresh Ramakrishnan
John Santamaria
the CAT Study investigators

A comparison of epinephrine and norepinephrine in critically ill patients



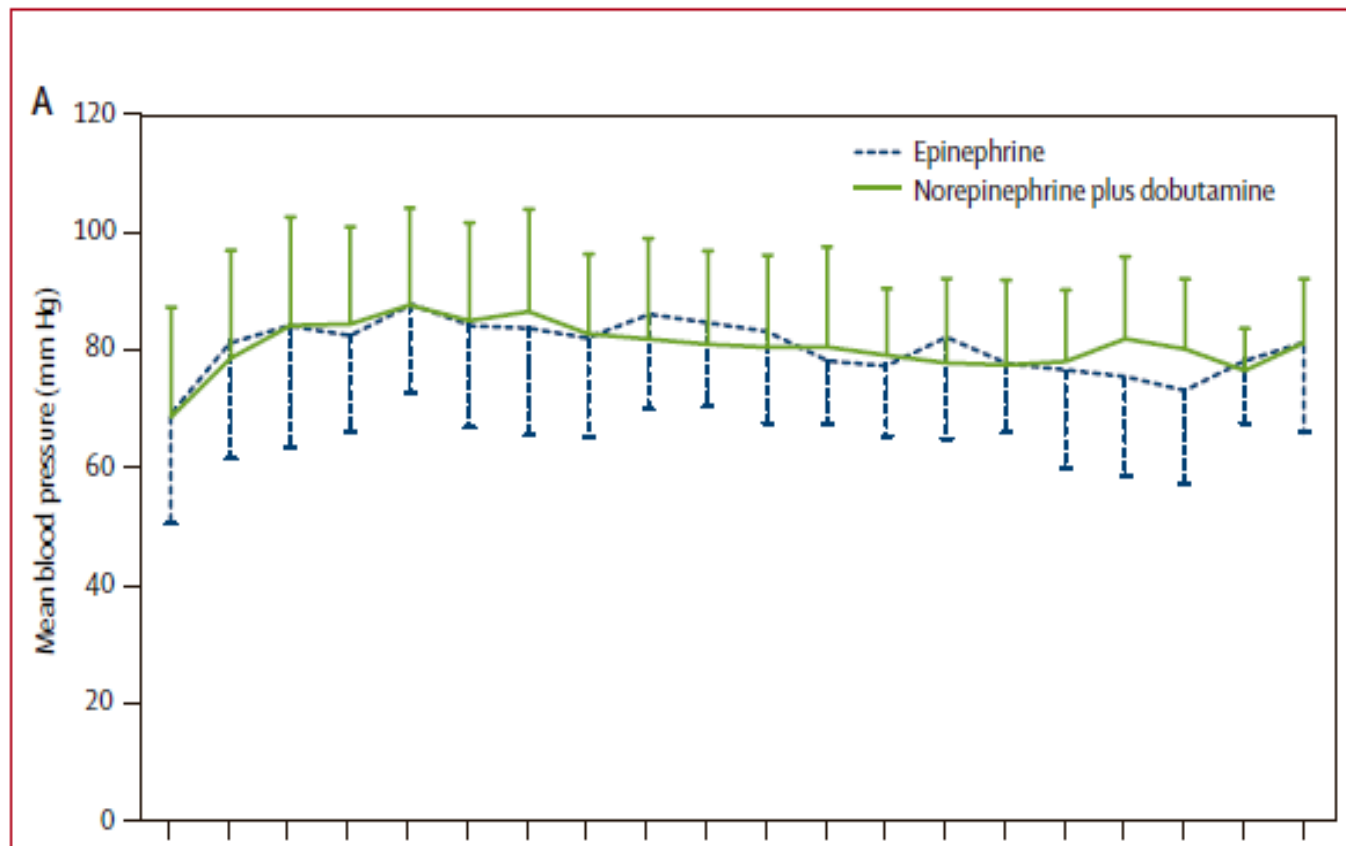
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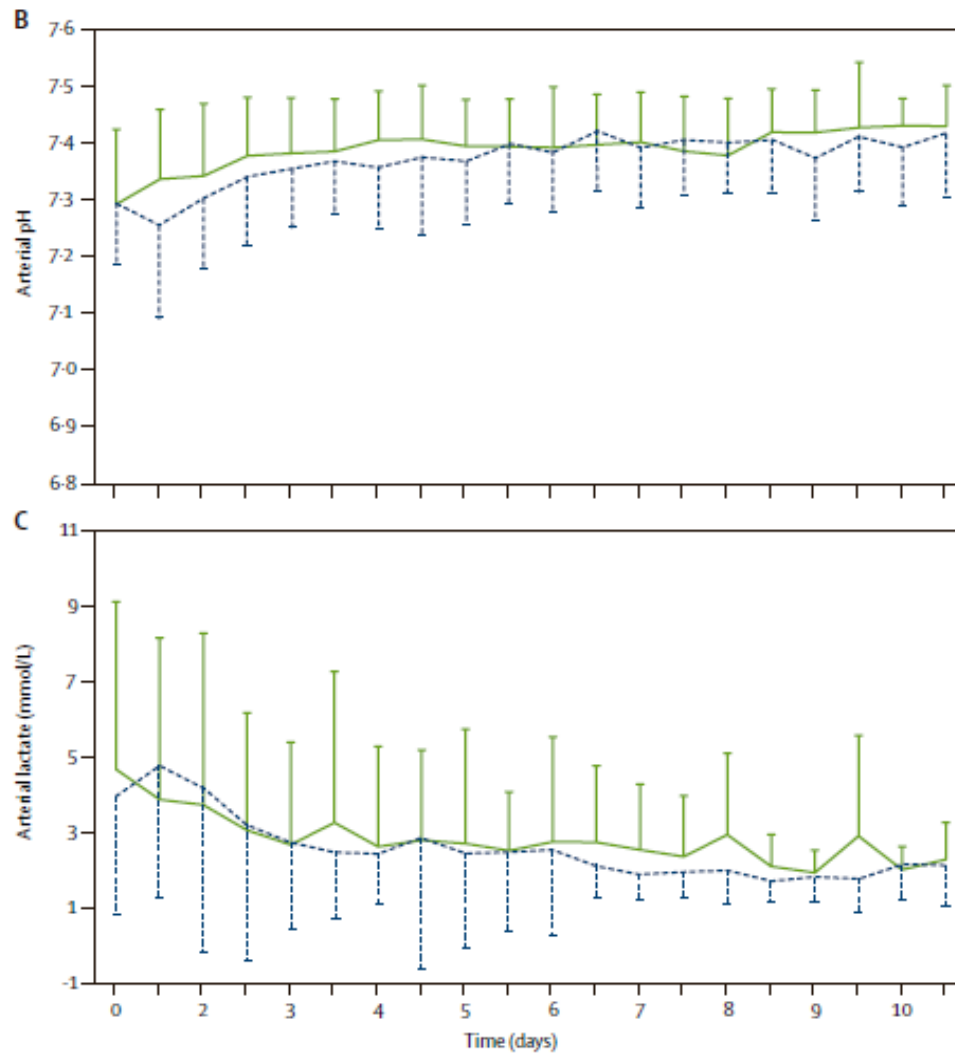


Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

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

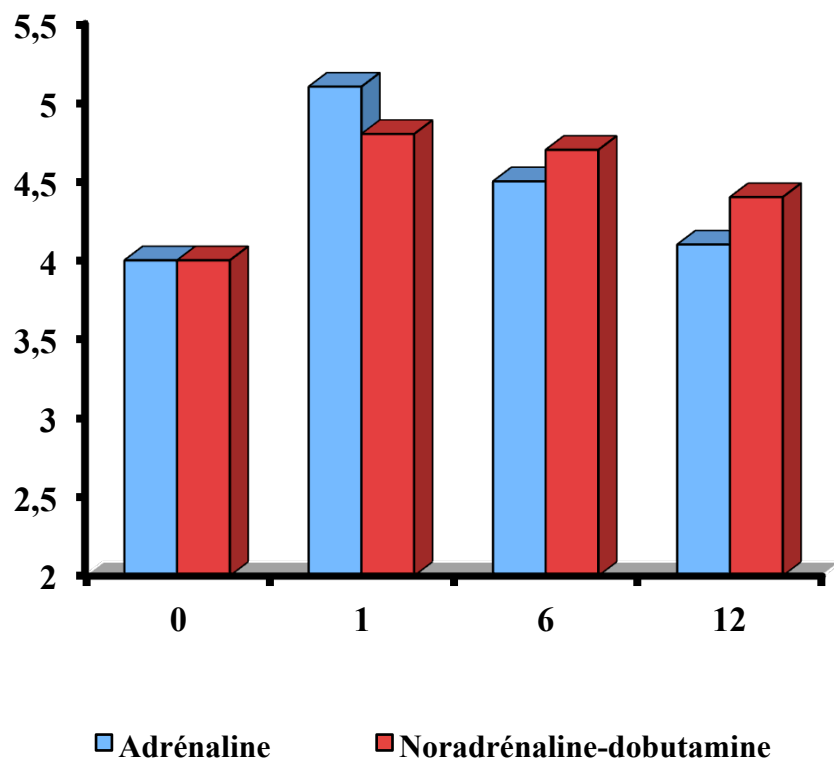


Acidose métabolique et hyperlactatémie



Effets hémodynamiques de l'association noradrénaline-dobutamine dans le choc septique.

Levy B, Intensive Care Med 1997, 23; 282-287.



- Effet mixte vasopresseur et inotrope identique à celui de l'adrénaline.
- Effets hémodynamiques systémiques reproductibles et prévisibles.

Question 3 :

Quelle est la place des médicaments inotropes positifs et vasoactifs ?

Traitement vasoconstricteur

Les médicaments vasoconstricteurs doivent être utilisés si le remplissage vasculaire ne permet pas d'obtenir une PAM > 65 mmHg (grade B). L'utilisation précoce de ces agents est recommandée car elle permet de limiter la survenue des défaillances viscérales (grade E).

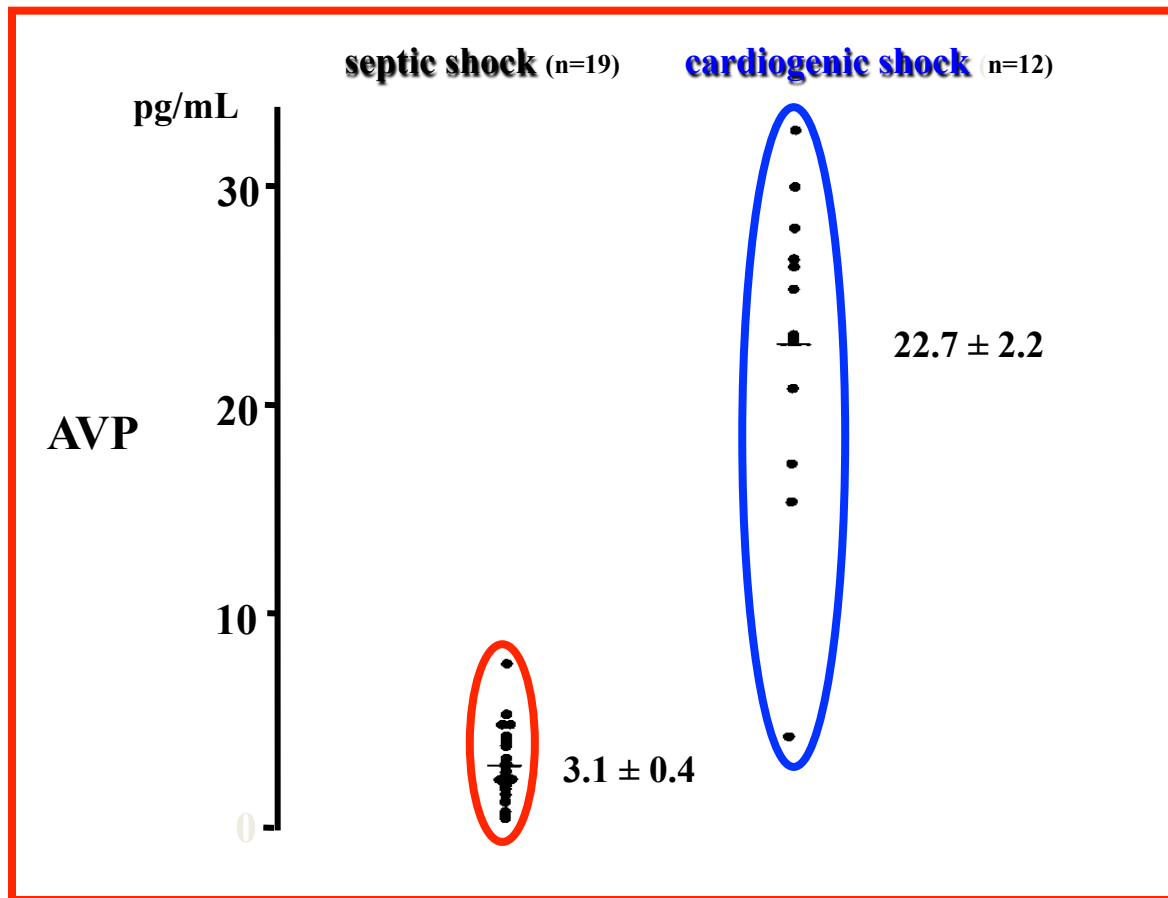
La noradrénaline étant la plus puissante des amines vasoconstrictrices, elle doit être utilisée en première intention (grade E).

La vasopressine (0,01 à 0,04 U/min) ou la terlipressine (bolus de 1 à 2 mg) peut être utilisée dans les chocs réfractaires (grade E).

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Donald W. Landry, MD, PhD; Howard R. Levin, MD; Ellen M. Gallant, MD;
Robert C. Ashton, Jr, MD; Susan Seo, BA; David D'Alessandro, BA;
Mehmet C. Oz, MD; Juan A. Oliver, MD

Circulation 1997; 95:1122-1125



Beneficial Effects of Short-term Vasopressin Infusion during Severe Septic Shock

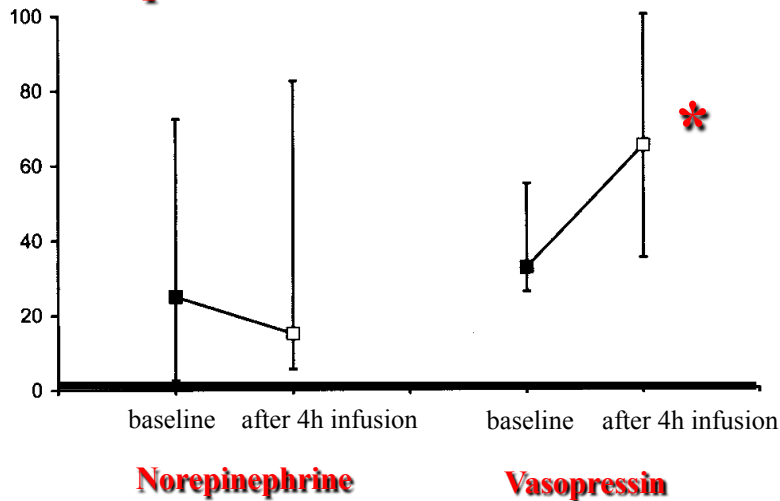
Bhavesh M. Patel, M.D., F.R.C.P.(C.), Dean R. Chittock, M.D., F.R.C.P.(C.),† James A. Russell, M.D., F.R.C.P.(C.),‡ Keith R. Walley, M.D., F.R.C.P.(C.)‡*

**24 pts receiving high-dose norepinephrine
randomized to a double blinded 4-h infusion of
either norepinephrine or vasopressin
while the prestudy norepinephrine titrated down to maintain mean BP**

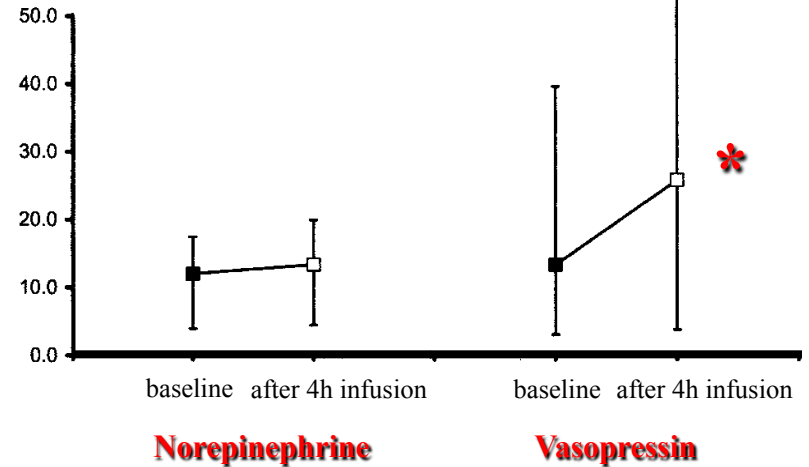
Beneficial Effects of Short-term Vasopressin Infusion during Severe Septic Shock

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Keith R. Walley, M.D., F.R.C.P.(C.)‡

Urine output



Creatinine clearance



alors que DC et PA inchangés après 4 h de perfusion dans chaque bras

Vasopressin—Not only good news!*

Hans G. Bone, Martin Westphal, Hugo C. Van Aken

Crit Care Med 2002; 30:2604-2605

Réduction de la contractilité cardiaque et vasoconstriction artérielle pulmonaire

Scharte et al. *Crit Care Med* 2001

Leather et al. *Crit Care Med* 2002

Réduction de la perfusion muqueuse digestive

Westphal et al. *Crit Care Med* 2002

Démasquage d'une ischémie myocardique

Medel et al. *Anaesth Analg* 2001

Problème de doses ?

Besoin encore d'évaluation

The NEW ENGLAND
JOURNAL *of* MEDICINE

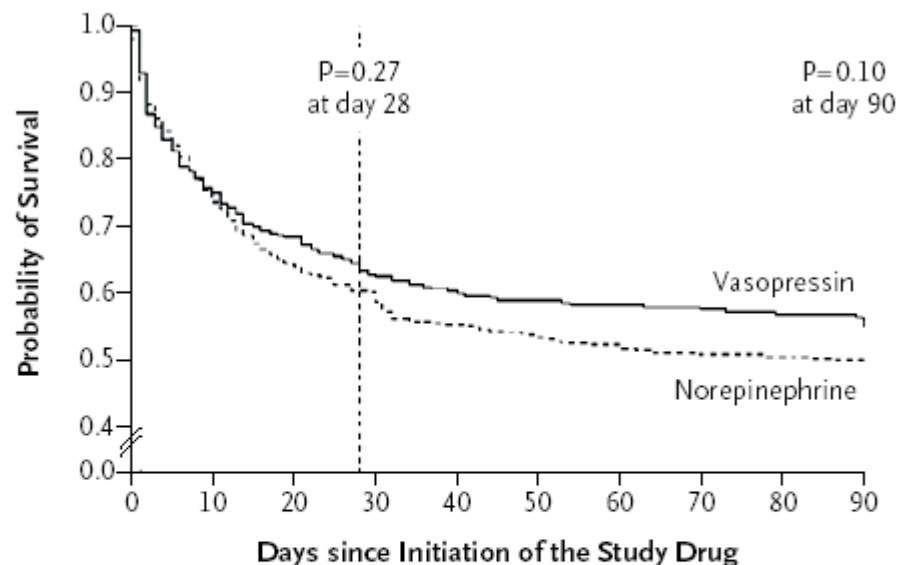
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Vasopressin versus Norepinephrine Infusion
in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D.,
Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D.,
John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D.,
and Dieter Ayers, M.Sc., for the VASST Investigators*



No. at Risk

Vasopressin	397	301	272	249	240	234	232	230	226	220
Norepinephrine	382	289	247	230	212	205	200	194	193	191

Figure 2. Kaplan–Meier Survival Curves for Patients Who Underwent Randomization and Infusion.

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

Table 3. Serious Adverse Events in Patients Who Had Septic Shock.

Variable	Norepinephrine Group (N = 382)	Vasopressin Group (N = 396)	P Value ^a
	no. (%)		
At least one serious adverse event	40 (10.5)	41 (10.3)	1.00
Acute myocardial infarction or ischemia	7 (1.8)	8 (2.0)	1.00
Cardiac arrest	8 (2.1)	3 (0.8)	0.14
Life-threatening arrhythmia	6 (1.6)	8 (2.0)	0.79
Acute mesenteric ischemia	13 (3.4)	9 (2.3)	0.39
Hyponatremia†	1 (0.3)	1 (0.3)	1.00
Digital ischemia	2 (0.5)	8 (2.0)	0.11
Cerebrovascular accident	1 (0.3)	1 (0.3)	1.00
Other‡	2 (0.5)	5 (1.3)	0.45



Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.*					
Stratum	Norepinephrine Group <i>no./total no. (%)</i>	Vasopressin Group <i>no./total no. (%)</i>	P Value†	Absolute Risk Reduction (95% CI) %	Relative Risk (95% CI)
More severe septic shock					
28-day mortality	85/200 (42.5)	88/200 (44.0)	0.76	-1.5 (-11.2 to 8.2)	1.04 (0.83 to 1.3)
90-day mortality	105/199 (52.8)	103/199 (51.8)	0.84	1.0 (-8.8 to 10.8)	0.98 (0.81 to 1.18)
Less severe septic shock					
28-day mortality	65/182 (35.7)	52/196 (26.5)	0.05	9.2 (-0.1 to 18.5)	0.74 (0.55 to 1.01)
90-day mortality	83/180 (46.1)	69/193 (35.8)	0.04	10.4 (0.4 to 20.3)	0.78 (0.61 to 0.99)

* Patients with more severe septic shock were defined as those who required at least 15 μg of norepinephrine per minute or the equivalent at the time of randomization. Those with less severe septic shock were defined as those who required 5 to 14 μg of norepinephrine per minute or the equivalent at the time of randomization.

† Two-sided P values are based on Pearson's chi-square test.

R. P. Dellinger
Mitchell M. Levy
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Charles L. Sprung

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

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

Very high dose : futile or not
futile

NOREPINEPHRINE: NOT TOO MUCH, TOO LONG

Claude Martin, Sophie Medam, François Antonini, Julie Alingrin, Malik Haddam, Emmanuelle Hammad, Bertrand Meyssignac, Coralie Vigne, Laurent Zieleskiewicz, and Marc Leone

Service d'Anesthésie et de Réanimation, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, and Aix Marseille Université, Marseille, France

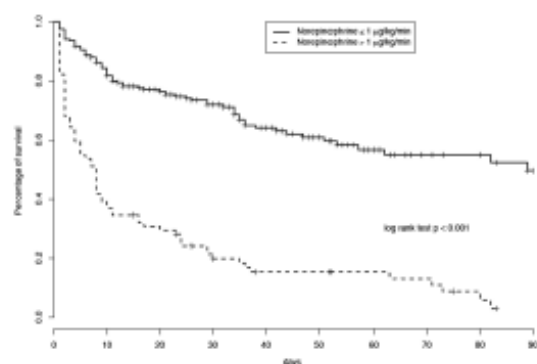


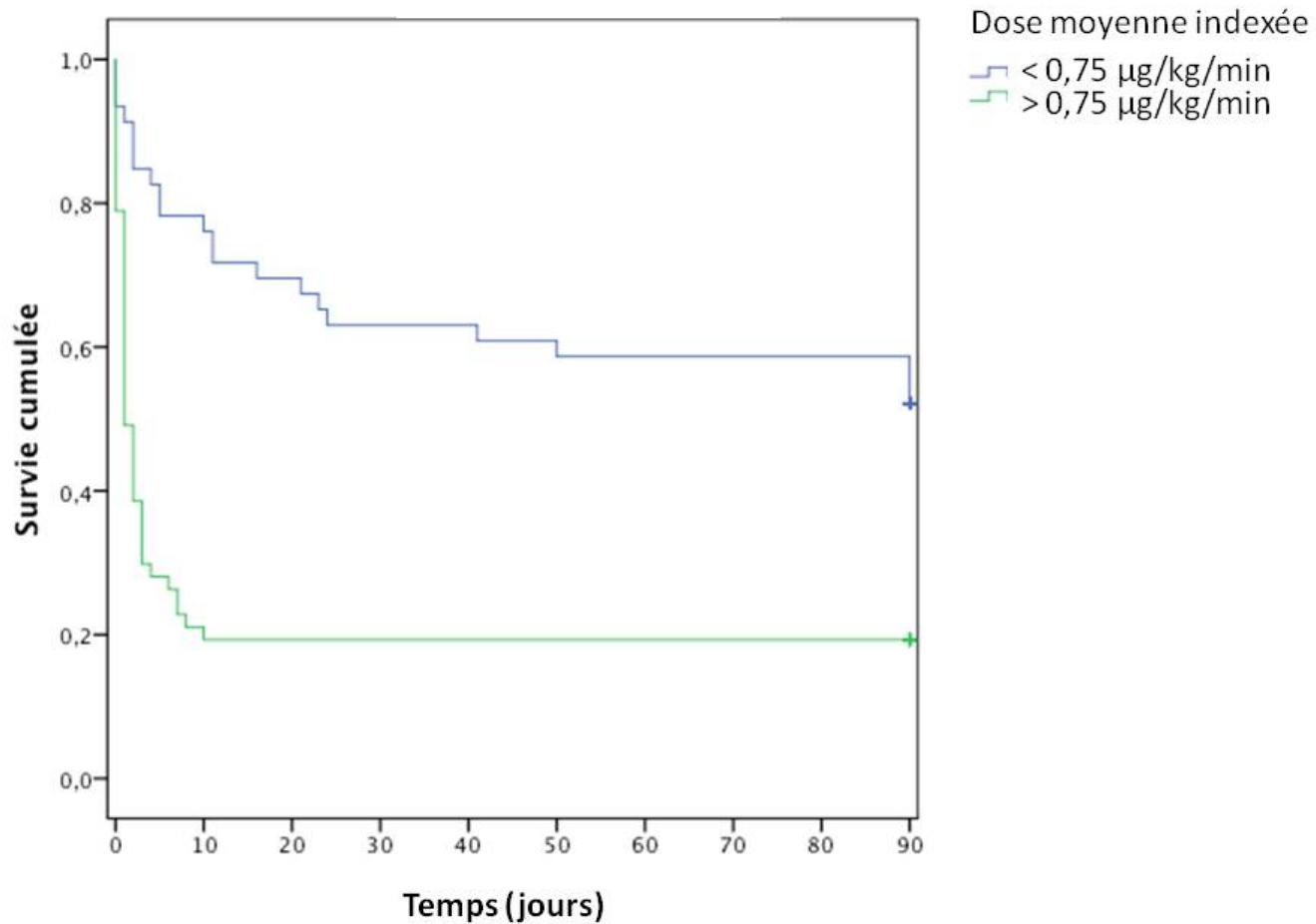
FIG. 3. Survival analysis at day 90 according to norepinephrine (NE) dosage with a cutoff at $1 \mu\text{g}/\text{kg}$ per minute.

TABLE 4. Multivariate analysis: independent predictors of mortality

Variables	OR (95% CI)	P
Age	1.02 (1.00–1.04)	0.019
Thrombocytopenia <100 G/L	3.8 (1.8–8.5)	0.002
Dose of norepinephrine $\geq 1 \mu\text{g}/\text{kg}$ per minute	9.7 (4.5–23)	<0.00
Urine output <500 mL/24 h	8.7 (3.6–25)	<0.00

Personal study

- 100 patients with septic shock treated with more than $1 \mu\text{g}/\text{kg}/\text{min}$ of norepinephrine for at least one hour
- Mortality : 60 %
- Prediction of mortality analysed with logistic regression
 - Mean dose $> 0.75 \mu\text{g}/\text{kg}/\text{min}$ associated with a SOFA D0 > 10 .



Mortality	D28	D90
< 0,75	35,4	47,8
> 0,75	80,4	80,7

} P < 0,001

Conclusions

- Recommandations officielles
 - Jamais de dopamine
 - Noradrénaline en première intention
 - Vasopressine en cas d'échec
- Monitoring important
- Sevrage dès que possible