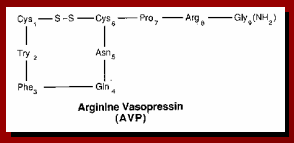
Vasopressine
revue de littérature



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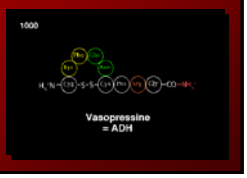
Vasopressine

- Structure et synthèse
- Effet biologique
- Hémodynamie du choc distributif
- Études cliniques
- Applications élargies



Vasopressine: historique

Vincent du Vigneaud *(1901 - 1978)*

- 1895 : on décrit premiers effets vasopresseurs.
- 1905 : description effet anti-diurétique.
- 1913 : traitement des premiers pts avec diabète insipide avec des extraits neurohypophysaires.
- 1955 : Prix Nobel à du Vigneaud pour la synthèse de l'ocytocine et de la vasopressine.

CHEST Vol 120 No.3 Septembre 2001. Pp 989-1002

Vasopressine: structure

- Nanopeptide
- Arginine en position 8.
- Lysine porcine.

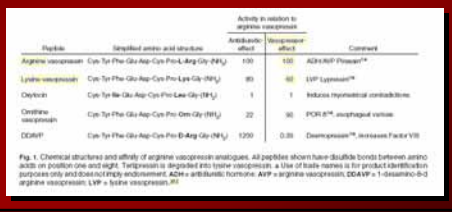
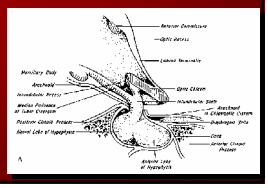


Fig. 1. Chemical structures and affinity of arginine vasopressin analogues. All peptides shown have disulfide bonds between amino acids on position one and eight. Terlipressin is degraded into lysine vasopressin, a Use of trade names is for product identification purposes only and does not imply endorsement. ADH = antidiuretic hormone. AVP = arginine vasopressin, DDAVP = 1-desamino-8-D arginine vasopressin; LVP = lysine vasopressin.[6]

Vasopressine: synthèse

- Production d'une pro-hormone dans noyaux paraventriculaire et supraoptique de l'hypothalamus.
- Migration via la tige hypophysaire.
- Stockage dans l'hypophyse postérieure (neurohypophyse).



Wilson: Williams Textbook of Endocrinology, 9th ed.
1998 W. B. Saunders Company

Vasopressine ou ADH

- Effets multiples :
  - rôle de conservation H_2O sous régulation osmotique.
  - maintient homéostasie cardio-vasculaire via volémie.
  - vasopresseur puissant direct et indirect à fortes doses.
  - stimule production ACTH.
  - relâche facteur VIIIc et vonWillebrand.

Textbook of Medical Physiology. Guyton and Hall. 9th edition

Vasopressine : physiologie

- Demi-vie très courte : 15-20 minutes.
- Rapidement métabolisée dans rein et foie.
- Liaison protéine plasmatique : 10-40%
- Très petites quantités en temps normal :
  - < 4 pg/ml : normovolémique-iso-osmolaire.
  - Ad 10 pg/ml : déprivation eau.
  - Ad 20 pg/ml : effet max a/n osmolarité urinaire.
  - De 100-1000pg/ml : réponse à un choc .

CHEST Vol 120 No.3 Septembre 2001. Pp 989-1002 Drugs Vol 63 No 3 2003 pp 237-56

Vasopressine : physiologie

- 3 types de récepteurs:

Table 4—*Vasopressin Receptors

Receptors	Tissues	Principal Effects	Intracellular Signaling
V1R	Vascular smooth muscle Kidney (bladder, adipocytes, platelets, spleen, testis)	Direct and indirect vasodilation	Phosphoinositide pathway (activate phospholipase C) Increased intracellular Ca^{++}
V2R	Renal collecting duct	Increased permeability to water	Increased cAMP
V3R	Endothelium Pituitary	Vasodilation Neurotransmitter ACTH release	NO mediated Increased cAMP
OTR	Uterus, mammary gland Endothelium	Vasoconstriction Vasodilation	Phospholipase C NO mediated

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Vasopressine : physiologie

- **Régulation osmotique :**
  - Modulation du taux de vasopressine est en étroite relation avec osmolarité sanguine.
    - Récepteurs centraux et périphériques.
- **Régulation non-osmotique :**
  - Maintien de l'homéostasie volémique :
    - Barorécepteurs et volorécepteurs :
      Oreillettes, carotides, arc aortique,…

Vasopressine : physiologie

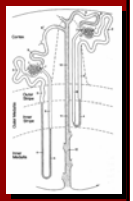
- **Régulation non-osmotique** *(suite):*
  - nécessite de grandes variations : perte d'au moins 10% du volume circulant.
  - mais concentrations plasmatiques beaucoup plus importantes.
- **Autres stimuli non-osmotiques:**
  - nausée, douleur, hypoxie, substances endogènes et exogènes (médicaments).

Vasopressine : physiologie

- **Effet rénal :**
  - via récepteur V2R
  - sans ADH le tubule collecteur est quasi imperméable à l'eau.
  - un manque de production ou d'effet de l'ADH permet une perte d'eau libre rénale très importante. (urine très diluée)
  - ***Diabète insipide*** central ou néphrogénique.

Textbook of Medical Physiology. Guyton and Hall. 9th edition

Vasopressine : physiologie



- **Effet rénal** *(suite) :*
  - La présence d'ADH augmente la perméabilité du tubule à l'eau et donc sa réabsorption.
  - Ce qui en trop grande quantité donne une rétention d'eau libre et une hyponatrémie.
  - **SIADH**...

Vasopressine : physiologie

Rôle vasomoteur :

- Semble peu important dans la physiologie normale et à petite concentration :
  - Des concentrations supra-physiologiques de l'ordre de plus 50 pg/ml sont nécessaires avant avoir un effet sur PAM.
  - De plus pt SIADH n'ont pas tendance HTA.

CHEST Vol 120 No.3 Septembre 2001. Pp 989-1002

Vasopressine : physiologie

- En état de choc toutefois son rôle devient déterminant.
  - Appuyé sur plusieurs données:
    - blocage des V1R donne diminution PA.
    - études animales où les sujets avec diabète insipide tolèrent très mal état de choc.

Vasopressine : physiologie

- Au début d'un état de choc : relâche très importante de vasopressine.
- Cependant à peine 10-20% des stocks de l'hypophyse peuvent être relachés. Ensuite la vasopressine continue d'être sécrétée mais à concentration plasmatique de beaucoup inférieure.

Vasopressine : physiologie

- Explique la réponse biphasique observée dans les modèles de choc septique.
- Dans les études animales de choc on observe des taux de plus de 300 pg/ml en phase initiale de choc, mais qui chutent rapidement en moins d'une heure à moins de 30 pg/ml.

CHEST Vol 120 No.3 Septembre 2001. Pp 989-1002

Vasopressine : physiologie

- Rôle dans le choc est multiple:
  - par effet direct sur V1R.
  - mais aussi effet indirect de potentialisation des récepteurs alpha. Et donc potentialisation de l'effet de la norépinéphrine aussi bien endogène qu'exogène. Semble être plus qu'un effet additif.
  - autres mécanismes... **(perte baroréflexe)**

Vasopressine : physiologie

- En plus effet vasoconstricteur:
  - Effet préservé en acidose et hypoxémie
  - Splanchnique, musculaire,cutané,…
- Effet vasodilatation certains lits vasculaires:
  - Pulmonaire, coronaire, cérébral
  - Semble lié effet via récept. oxytocine

Commercialement disponible

- Arginine vasopressine \ argipressine:
  - Par PPC :Vasopressin
  - Par Ferring : Pressyn AR
- Lysine vasopressine:
  - Par Ferring : Pressyn
- Terlipressine :
  - pro-drogue
  - converti en lysine vasopressine
  - demie-vie : 4-6 heures

Le choc distributif : physiopathologie

- Réponse normale au choc est une vasoconstriction périphérique intense.
- Dans le choc vasoplégique le mécanisme primaire est un échec de vasoconstriction des muscles lisses des vaisseaux et donc une vasodilatation périphérique.

NEJM Volume 345 No 8 August 23,2001 pp. 588-595

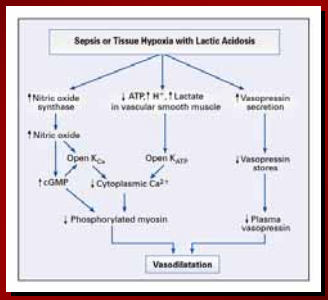
Le choc distributif : physiopathologie

- Étiologies multiples
  - la cause la plus fréquente étant le sepsis.
- À noter que tous les types de choc peuvent évoluer vers un état distributif. Mention de choc dépassé ou irréversible est alors soulevée.

Le choc distributif : physiopathologie

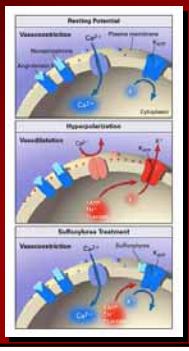
- Mécanisme réponse au choc comprend une augmentation marquée des taux de catécholamines endogènes : norépinéphrine, angiotensine II, endothéline, …
- Donc le mécanisme physiopathologique semble plus un manque de réponse des vaisseaux aux catécholamines qu'un problème de production.

Le choc distributif : Hypothèses



NEJM Volume 345 No 8 August 23,2001 pp. 588-595

Le choc distributif : physiopathologie



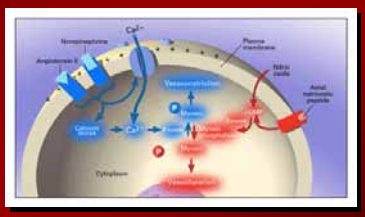
1. Activation canaux K^+ ATP dépendants :

Hyperpolarisation et blocage de l'entrée du Ca^{++} en intracellulaire.

NEJM Volume 345 No 8 August 23,2001 pp. 588-595

Le choc distributif : physiopathologie

2. Induction NO synthétase:



NEJM Volume 345 No 8 August 23,2001 pp. 588-595

Le choc distributif : rôle vasopressine

3. Déficience vasopressine ?

Basé sur…

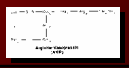
- Dosage relativement bas.
- Baisse stock hypophysaire
- Réaction «hypersensibilité »

Le choc distributif : rôle vasopressine

3. Déficience vasopressine ?

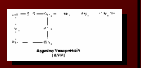
Réplétion vasopressine dans choc distributif :
Pts semblent hypersensibles… pourquoi?

- Taux de vasopressine endogène sont bas les récepteurs sont libres pour une action via vasopressine exogène. (contrairement norépi.)
- Effet potentialisation des catéchol. endogènes.



Le choc distributif : rôle vasopressine

- Vasopressine inactive directement le canal K^+ ATP dépendant rétablissant le potentiel transmembranaire.
- Finalement la vasopressine inhibe l'augmentation GMPc induite par NO et diminue l'effet vasodilatateur de celui-ci en plus de diminuer la synthèse de la forme inductible NO synthétase.



Les études…

Vasopressine : littérature actuelle

Vasopressin pressor hypersensitivity in vasodilatory septic shock.

Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA.

Critic Care Med 1997 Vol.25 No.8 pp1279-1282

Vasopressin pressor hypersensitivity in vasodilatory septic shock.

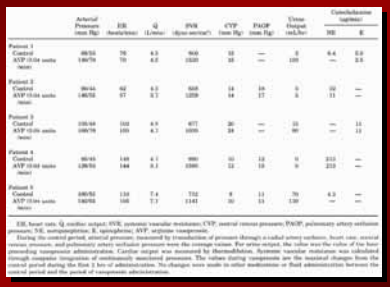
Critic Care Med 1997 Vol.25

- Sur la base d'études animales antérieures.
- Chez 5 pts en choc septique sous vasopresseurs.
- Tentative de petites doses de vasopressine. (i.e. 0,04 unité/min.).
- Amélioration notable de l'hémodynamie et sevrage des autres amines en cours.

Critic Care Med 1997 Vol.25 No.8 pp1279-1282

Vasopressin pressor hypersensitivity in vasodilatory septic shock.

Critic Care Med 1997 Vol.25



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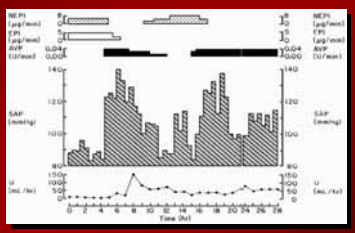
Vasopressin pressor hypersensitivity in vasodilatory septic shock.

Critic Care Med 1997 Vol.25



Critic Care Med 1997 Vol.25 No.8 pp1279-1282

Vasopressin pressor hypersensitivity in vasodilatory septic shock.

Critic Care Med 1997 Vol.25

- Discussion : surprenant que d'aussi petites doses de vaso se traduisent par un effet hémodynamique si marqué.
- D'autant que études antérieures chez volontaires sains montrent peu ou pas d'effet hémodynamique de vaso ad 0,26 u/min.
- Et dose ad 0,4u/min. chez cirrhotiques donne à peine des augmentations de PAM de 10 mmHg.

Critic Care Med 1997 Vol.25 No.8 pp1279-1282

Vasopressine : littérature actuelle

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 vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Circulation 1997

- Définition choc septique :
  - PAS < 90 mmHg
  - RVS < 800 dynes-s/cm^5
  - Température >38.5 ou < 36 °C
  - Pouls > 90/min.
  - Tachypnée >20/min. ou utilisation VM
  - Hémoculture + ou source infection évidente.
  - Leuco > 12000 ou < 4000
- Tous pts nécessitaient support aminergique malgré PCPB > 12mmHg.

Circulation vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Circulation 1997

- Définition choc cardiogénique:
  - Index cardiaque < 2 l/min.
  - PCPB > 15 mmHg
  - PAS < 90 mmHg.
- Tous pts besoin amines.

Circulation vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Circulation 1997

- Dosage vasopressine endogène :

3,1 pg/cc dans groupe sepsis.

22,7 pg/cc dans groupe cardiogénique

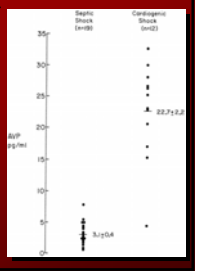


Figure 1. Plasma vasopressin levels (AVP) of patients in septic shock and cardiogenic shock. *P*<.001.

Circulation vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Circulation 1997

- Chez 10 pts infusion vaso à 0,04 U/min.
- Résultats :
  - en moins de 15 minutes.
  - augmentation PAS de 59%.
  - aug. RVS de 79%.
  - légère diminution D.C. de 12%

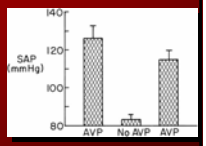


Figure 2. Systolic arterial pressure (SAP) response to vasopressin (AVP) withdrawal and readministration at 0.01 U/min (n=6).

Circulation vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Circulation 1997

- Conclusions :
  - les taux de vasopressine sont anormalement bas en sepsis.
  - la vasopressine exogène à des taux pour seulement remplacer le déficit, résulte en augmentations marquées de la PAS.
  - Donc pts en choc septique semblent hypersensibles à l'effet de la vasopressine.

Circulation vol 95 no.5 march 4, 1997. Pp.1122-25

Vasopressine: littérature actuelle

Low-dose vasopressin in the treatment of vasodilatory septic shock.

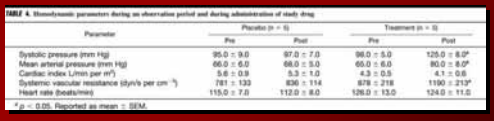
Malay MB, Ashton RC Jr, Landry DW, Townsend RN.

The Journal of Trauma october 1999, Vol.47 No.4 pp 699-705

Low-dose vasopressin in the treatment of vasodilatory septic shock.

The Journal of Trauma 1999

- Étude randomisée contrôlée…
- 10 patients en choc septique:
  - 5 reçoivent placebo.
  - 5 sous vasopressine à 0,04 U/min.



Parameter	Placebo (n = 5)		Treatment (n = 5)	
	Pre	Post	Pre	Post
Systolic pressure (mm Hg)	95.0 ± 9.0	97.0 ± 7.0	96.0 ± 5.0	125.0 ± 8.0*
Mean arterial pressure (mm Hg)	66.0 ± 6.0	68.0 ± 5.0	65.0 ± 6.0	80.0 ± 8.0*
Cardiac index L/min per m^2)	5.6 ± 0.9	5.3 ± 1.0	4.3 ± 0.5	4.1 ± 0.6
Systemic vascular resistance (dyn/s per cm^{-5})	781 ± 133	836 ± 114	878 ± 218	1190 ± 213*
Heart rate (beats/min)	115.0 ± 7.0	112.0 ± 8.0	126.0 ± 13.0	124.0 ± 11.0

*$p < 0.05$. Reported as mean ± SEM.

The Journal of Trauma october 1999, Vol.47 No.4 pp 699-705

Low-dose vasopressin in the treatment of vasodilatory septic shock.

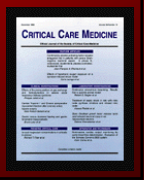
The Journal of Trauma 1999

- Diminution notable des amines dans le groupe sous vasopressine.
- Sevrage complet des autres amines en gardant vaso à 24 hres.
- Tentatives de cessation vaso avec chute PA significative. Avec retour PA initiale à la reprise de vaso.
- 2 décès dans groupe placebo de choc réfractaire.

Vasopressine : littérature actuelle

Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock.

Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA 3rd.



Crit Care Med 2001 Mar;29(3):487-93

Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock

Crit Care Med 2001

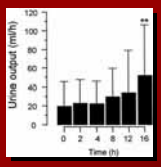
- Étude japonaise cas-contrôle.
- Inclusion :
  - pts en choc < 48 hres
  - PAS < 80 mmHg malgré
    - TVC > 7 ou wedge >10
    - levophed > 0,2 microg/kg/min.
- Traitements : infusion vasopressine à 0,04 U/min. X 16 heures.

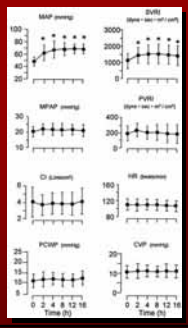
Crit Care Med 2001 Mar;29(3):487-93

Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock

Crit Care Med 2001

- 16 patients.
- Augmentation des PAM de 69 à 96 mmHg.



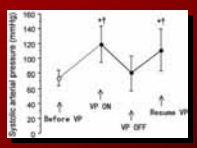


Crit Care Med 2001 Mar;29(3):487-93

Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock

Crit Care Med 2001

- Modification du protocole initial car tel que prévu arrêt de vaso après 16 heures infusion :
  - chute marquée de PA.
  - avec réponse à reprise et sevrage graduel.

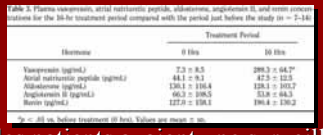


Crit Care Med 2001 Mar;29(3):487-93

Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock

Crit Care Med 2001

- Dosage vasopressine pré et per infusion.



Hormone	Treatment Period	
	0 Hrs	16 Hrs
Vasopressin (pg/mL)	7.3 ± 8.5	289.3 ± 64.7*
Atrial natriuretic peptide (pg/mL)	44.1 ± 9.1	47.3 ± 12.5
Aldosterone (pg/mL)	126.1 ± 116.4	128.1 ± 101.7
Angiotensin II (pg/mL)	66.3 ± 198.5	53.8 ± 64.3
Renin (pg/mL)	127.9 ± 158.1	196.4 ± 136.2

*p < .01 vs. before treatment (0 hrs). Values are mean ± SD.

- Tous les patients avaient une surveillance du segment ST.
- Pas de complication cardiaque notée.

Crit Care Med 2001 Mar;29(3):487-93

Vasopressine : littérature actuelle

***Brief report*: The effects of vasopressin on hemodynamics and renal function in severe septic shock : a case series.**

Cheryl L. Holmes (1), Keith R. Walley (1), Dean R. Chittock (2), Tara Lehman (1), James A. Russell (1)

Intensive Care Medicine Volume 27 Issue 8 (2001) pp 1416-1421

The effects of vasopressin on hemodynamics and renal function in severe septic shock : a case series

Intensive Care Medicine 2001

- Étude rétrospective 50 patients traités avec vasopressine.
- Utilisation surtout dans contexte de choc septique réfractaire.

Intensive Care Medicine Volume 27 Issue 8 (2001) pp 1416-1421

The effects of vasopressin on hemodynamics and renal function in severe septic shock : a case series

Intensive Care Medicine 2001

- Résultats :
  - Augmentation des PAM de 18%
  - Aug. des diurèses de 79%
  - Diminution des autres amines de 33 à 50%
- Complications:
  - 6 arrêts cardiaques
  - Tous avaient vasopressine à plus de 0,05U/min.

Intensive Care Medicine Volume 27 Issue 8 (2001) pp 1416-1421

The effects of vasopressin on hemodynamics and renal function in severe septic shock : a case series

Intensive Care Medicine 2001

- Conclusion:
  - des doses de vasopressine supérieures à 0,04 U/min. ne montrent pas de bénéfice ajouté aux PA observées.
  - et pourraient être reliées aux 6 arrêts cardiaques observés.
  - mais mortalité dans groupe 85%.

Intensive Care Medicine Volume 27 Issue 8 (2001) pp 1416-1421

Vasopressine : littérature actuelle

Beneficial effects of short-term vasopressin infusion during severe septic shock.

Patel BM, Chittock DR, Russell JA, Walley KR.

Department of Critical Care, Mayo Clinic Arizona, Scottsdale, Arizona, USA.

Anesthesiology 2002; 96(3):576-582.

EV2

Beneficial effects of short-term vasopressin infusion during severe septic shock.

Anesthesiology 2002

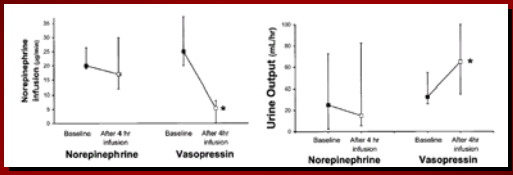
- 24 patients en choc septique
- Randomisés : Vaso vs norépi. double insu
- Dose vaso ad 0,08 u / min.

Diapositive 54

CV2 Prenez garde au secondary outcome comme la pression dans la lecture résultats d'études.
même si TA est idem et on a moins de levo. Et puis... changement de mortalité, bénéfices sur IR,...
Colin Verdant; 2002-03-20

Beneficial effects of short-term vasopressin infusion during severe septic shock.

Anesthesiology 2002



•Amélioration hémodynamique et diurèse
•Pas d'effet néfaste décelé sur ST ni tonométrie gastrique.
•Bref… effet levophed sparing mais sans plus…

High-dose vasopressin is not superior to norepinephrine in septic shock*

Stefan Klinzing, MD; Mark Simon, MD; Konrad Reinhart, MD; Donald L. Bredle, PhD; Andreas Meier-Hellmann, MD
Crit Care Med 2003;31:2646-2650

- 12 patients en choc septique
- NE remplacée par VP pour avoir la même PAM (70 mm Hg)
- Dose nécessaire de VP:

moyenne:0.47 U/min

range: 0.06-1.8 U/min

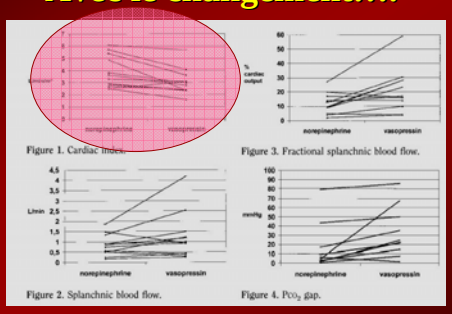
- Mesures: Débit cardiaque, gaz sanguins, PCO2 gap (tonométrie), VO2 par chariot métabolique, flot hépatosplanchnique

Table 1. Patients' characteristics

Patient No.	Gender	Age, Yrs	Diagnosis	APACHE II Score	Norepinephrine Dosage, μg/kg/min	Outcome
1	M	30	Multiple trauma	20	0.36	Died
2	F	75	Peritonitis	24	0.60	Died
3	F	61	Sepsis after cardiogenic shock	32	0.86	Died
4	M	68	Peritonitis	24	0.96	Died
5	M	28	Pneumonia	19	0.18	Died
6	F	71	Peritonitis	28	1.10	Died
7	M	67	Septic necrosis of the femoral head	37	0.94	Died
8	M	67	Catheter infection	27	0.18	Survived
9	F	70	Peritonitis	38	0.40	Survived
10	M	75	Peritonitis	30	0.26	Survived
11	M	64	Pleural empyema	23	0.42	Survived
12	F	74	Urosepsis	33	0.42	Survived

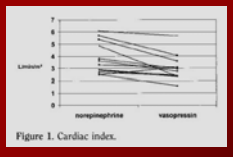
APACHE, Acute Physiology and Chronic Health Evaluation.

Avec le changement….



Avec le changement….

- ↓ FC
- ↓ DC
- ↓ DO2
- ↓VO2



- Résultats inconstants pour le flot hépato-splanchnique

Avec le changement….

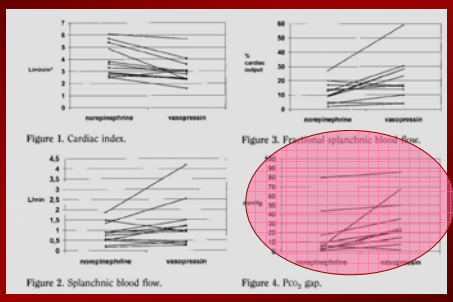


Figure 1. Cardiac index.

Figure 3. Fractional splanchnic blood flow.

Figure 2. Splanchnic blood flow.

Figure 4. Pco_2 gap.

Avec le changement….

- ↑ pCO2 gap

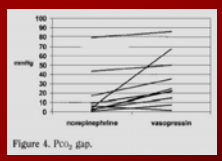


Figure 4. Pco_2 gap.

flow was preserved. An increased gastric Pco_2 gap suggests detrimental effects on mucosal gut blood flow. Based on these limited data, it would not appear beneficial to directly replace norepinephrine with vasopressin in septic shock.

The Effect of Vasopressin on Gastric Perfusion in Catecholamine-Dependent Patients in Septic Shock*

Frank M. P. van Haren, MD; Frans W. Rozendaal, MD; and Johannes G. van der Hoeven, MD, PhD

Objective: **To study the effect of continuous infusion of vasopressin on the splanchnic circulation in patients with severe septic shock.**
Design: **Prospective clinical study.**
Setting: **ICU in a teaching hospital.**
Patients: **Eleven consecutive patients with documented septic shock who remained hypotensive despite norepinephrine infusion at a rate ≥ 0.2 μg/kg/min.**
Interventions: **Insertion of a gastric tonometry catheter, and continuous infusion of vasopressin 0.04 U/min during 4 h.**
Measurements and main results: **Difference between gastric and arterial CO_2 partial pressure ($P[g-a]CO_2$ gap), mean arterial pressure, and cardiac index were recorded at baseline and after 15 min, 30 min, 60 min, 120 min, and 240 min.**
Results: **The median $P(g-a)CO_2$ gap increased from 5 mm Hg at baseline to 19 mm Hg after 4 h ($p = 0.022$). Mean arterial pressure increased from 61 ± 13 mm Hg at baseline to 68 ± 9 mm Hg after 4 h ($p = 0.055$). No significant changes in cardiac index were noted.**
Conclusions: **In norepinephrine-dependent patients in septic shock, continuous infusion of low-dose vasopressin results in a significant increase of the $P(g-a)CO_2$ gap compatible with GI hypoperfusion.** ***(CHEST 2003; 124:2256–2260)***

Key words: catecholamines; GI tonometry; intensive care; prospective study; sepsis; septic shock; splanchnic circulation; vasopressin

Abbreviations: APACHE = acute physiology and chronic health evaluation; $P(g-a)CO_2$ gap = difference between gastric and arterial CO_2 partial pressure; SOFA = sequential organ failure assessment

- 11 patients en choc septique hypotendus malgré NE ≥ 0.2 µg/kg/min
- Mesures de tonométrie gastrique pendant infusion de vasopressine à 0.04 U/min pendant 4 heures

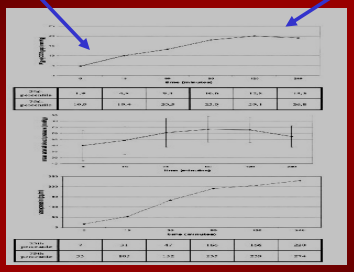
Table 1—*Demographic and Clinical Characteristics

Patient No.	Diagnosis	Gender	Age, yr	APACHE II Score	SOFA Score	Outcome
1	Pneumonia	Female	41	41	15	Died
2	Pneumonia	Male	66	20	9	Died
3	Abdominal sepsis	Female	68	23	9	Died
4	Abdominal sepsis	Male	54	26	13	Died
5	Pneumonia	Male	82	31	11	Died
6	Abdominal sepsis	Female	77	26	11	Died
7	Abdominal sepsis	Male	57	11	10	Survived
8	Pneumonia	Male	51	21	9	Died
9	Abdominal sepsis	Male	70	28	11	Died
10	Pneumonia	Male	81	22	10	Survived
11	Urosepsis, aspiration pneumonia	Male	74	24	11	Died
Mean ± SD			67 ± 14	26.6 ± 8.7	10.8 ± 1.8	

*Data are presented as No. unless otherwise indicated.

5 mm Hg

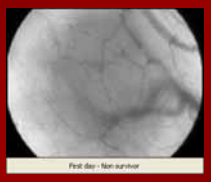
19 mm Hg



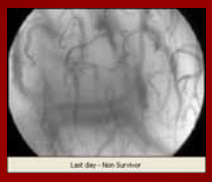
Et la microcirculation?

BRIEF REPORT

Effect of vasopressin on sublingual microcirculation in a patient with distributive shock



First day - Non survivor



Last day - Non Survivor

Effets potentiellement néfastes…

Abnormal thallium 201 scintigraphy during low-dose vasopressin infusions.

Davison R, Kaplan K, Bines A, Spies S, Reed MT, Lesch M.

Thallium 201 (201Tl) myocardial scans were obtained in 16 patients just prior to the discontinuation of a vasopressin infusion (.1 to .2 units/min) administered for the treatment of upper gastrointestinal bleeding. Repeat scintigraphy was performed two to three hours after the vasopressin was stopped. Eleven of the 16 patients (69 percent) demonstrated areas of decreased myocardial 201Tl uptake that resolved after the infusion was stopped. Heart rate-blood pressure product was significantly lower at the time of the second scan. Autopsies were secured in three of 11 scan-positive patients: one had severe coronary artery obstruction, one nonsignificant disease, and another had normal coronary arteries. Vasopressin, even at low doses, can induce abnormalities in myocardial perfusion that are probably mediated by a direct effect on the coronary circulation. They are usually not detectable by routine monitoring techniques and conceivably form the basis for the cardiovascular morbidity associated with the use of this agent.

Chest 1986 Dec;90(6):798-801

Effets potentiellement néfastes…

CARDIOVASCULAR ANESTHESIA
JEFFREY FORTIS
KENNETH J. TOMAS

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS

The Effects of Vasopressin on Systemic Hemodynamics in Catecholamine-Resistant Septic and Postcardiotomy Shock: A Retrospective Analysis

Martin W. Dünser, MD*, Andreas J. Mayr, MD*, Hanno Ulmer, PHD†, Nicole Ritsch, MD*, Hans Knotzer, MD*, Werner Pajk, MD*, Günther Luckner, MD*, Norbert J. Mutz, MD*, and Walter R. Hasibeder, MD*

- **Études autrichienne**
- **Rétrospective des dossiers où vasopressine utilisée**
- **60 pts choc septique et post-cardiotomie**
  - **« catécholamine résistants »**
- **Arginine vasop. 4-6 u/h**

Dunser.Anesth Analgesia 2001. Vol 93 pp 7-13

Effets potentiellement néfastes…

- Résultats :
  - Globalement: amélioration hémodynamie
  - Diminution besoin des autres vasopresseurs

  Toutefois:
  - Augmentation significative transam. et bili
  - Diminution numération plaquettaire

  Effet hypoperfusion gastro-intestinale?

  Thrombose in situ via activation agrégation plaq?

Systemic and splanchnic haemodynamic effect of vasopressin administration in vasodilatory shock Bracco D et al

Intensive Care Med 2001

Vasopressine 50mU/kg bolus puis 50mU/kg/h

- **Augmentation des résist. vacul. périph.**
- **Tous pts développent Delta-PCO_2 au tonom.**
- **Suggestif hypoperfusion muqueuse gastrique**

Intensive Care Med 2001; 27

Effets potentiellement néfastes…

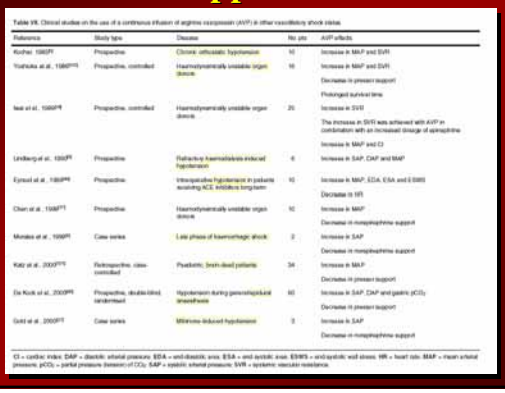
Skin necrosis after extravasation of low-dose vasopressin administered for septic shock

Jeremy M. Kahn, MD; John P. Kress, MD; Jesse B. Hall, MD

Dose usuelle 0,04 unités / minute

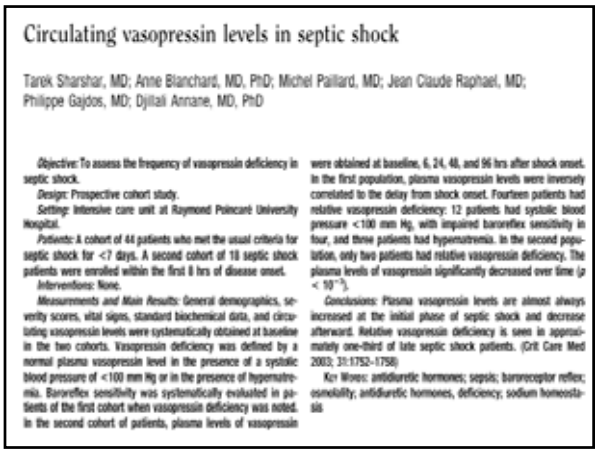
Crit Care Med 2002 Vol. 30, No. 8

Autres applications…



Questions qui restent sans réponses…

- Amélioration outcome primaire… survie… …dysfonction d'organe…
- Sécurité? Contrindications?
- Remplacement Vs titrer à l'effet?
- Si on remplace : quel dosage visé ?
  - Métabolisé par rein et foie (ajuster doses ?)
- Combien temps?



Circulating vasopressin levels in septic shock

Tarek Sharshar, MD; Anne Blanchard, MD, PhD; Michel Paillard, MD; Jean Claude Raphael, MD; Philippe Gajdos, MD; Djillali Annane, MD, PhD

Objective: To assess the frequency of vasopressin deficiency in septic shock.

Design: Prospective cohort study.

Setting: Intensive care unit at Raymond Poincaré University Hospital.

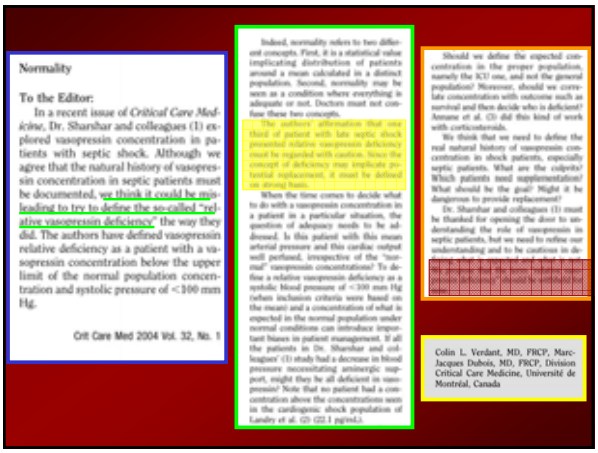
Patients: A cohort of 44 patients who met the usual criteria for septic shock for <7 days. A second cohort of 18 septic shock patients were enrolled within the first 8 hrs of disease onset.

Interventions: None.

Measurements and Main Results: General demographics, severity scores, vital signs, standard biochemical data, and circulating vasopressin levels were systematically obtained at baseline in the two cohorts. Vasopressin deficiency was defined by a normal plasma vasopressin level in the presence of a systolic blood pressure of <100 mm Hg or in the presence of hypernatremia. Baroreflex sensitivity was systematically evaluated in patients of the first cohort when vasopressin deficiency was noted. In the second cohort of patients, plasma levels of vasopressin were obtained at baseline, 6, 24, 48, and 96 hrs after shock onset. In the first population, plasma vasopressin levels were inversely correlated to the delay from shock onset. Fourteen patients had relative vasopressin deficiency: 12 patients had systolic blood pressure <100 mm Hg, with impaired baroreflex sensitivity in four, and three patients had hypernatremia. In the second population, only two patients had relative vasopressin deficiency. The plasma levels of vasopressin significantly decreased over time ($p < 10^{-3}$).

Conclusions: Plasma vasopressin levels are almost always increased at the initial phase of septic shock and decrease afterward. Relative vasopressin deficiency is seen in approximately one-third of late septic shock patients. (Crit Care Med 2003; 31:1752–1758)

Key Words: antidiuretic hormones; sepsis; baroreceptor reflex; osmolality; antidiuretic hormones, deficiency; sodium homeostasis



Normality

To the Editor:

In a recent issue of *Critical Care Medicine*, Dr. Sharshar and colleagues (1) explored vasopressin concentration in patients with septic shock. Although we agree that the natural history of vasopressin concentration in septic patients must be documented, we think it could be misleading to try to define the so-called "relative vasopressin deficiency" the way they did. The authors have defined vasopressin relative deficiency as a patient with a vasopressin concentration below the upper limit of the normal population concentration and systolic pressure of <100 mm Hg.

Crit Care Med 2004 Vol. 32, No. 1

Indeed, normality refers to two different concepts. First, it is a statistical value implicating distribution of patients around a mean calculated in a distinct population. Second, normality may be seen as a condition where everything is adequate or not. Doctors must not confuse these two concepts.

The authors' affirmation that one third of patient with late septic shock presented relative vasopressin deficiency must be regarded with caution. Since the concept of deficiency may implicate potential replacement, it must be defined on strong basis.

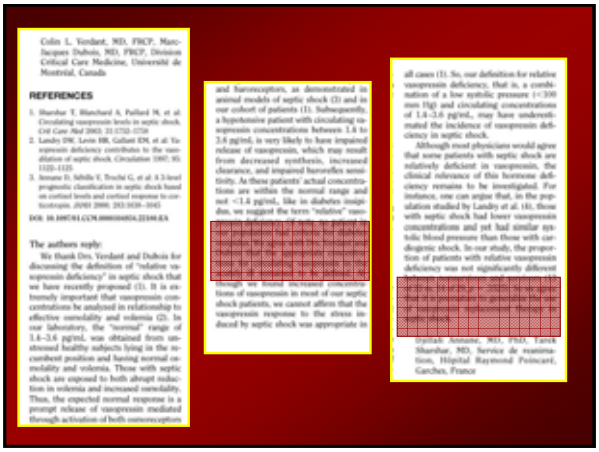
When the time comes to decide what to do with a vasopressin concentration in a patient in a particular situation, the question of adequacy needs to be addressed. Is this patient with this mean arterial pressure and this cardiac output well perfused, irrespective of the "normal" vasopressin concentrations? To define a relative vasopressin deficiency as a systolic blood pressure of <100 mm Hg (when inclusion criteria were based on the mean) and a concentration of what is expected in the normal population under normal conditions can introduce important biases in patient management. If all the patients in Dr. Sharshar and colleagues' (1) study had a decrease in blood pressure necessitating aminergic support, might they be all deficient in vasopressin? Note that no patient had a concentration above the concentrations seen in the cardiogenic shock population of Landry et al. (2) (22.1 pg/mL).

Should we define the expected concentration in the proper population, namely the ICU one, and not the generic population? Moreover, should we correlate concentration with outcome such as survival and then decide who is deficient? Annane et al. (3) did this kind of work with corticosteroids.

We think that we need to define the real natural history of vasopressin concentration in shock patients, especially septic patients. What are the culprits? Which patients need supplementation? What should be the goal? Might it be dangerous to provide replacement?

Dr. Sharshar and colleagues (1) must be thanked for opening the door to understanding the role of vasopressin in septic patients, but we need to refine our understanding and to be cautious in de-

Colin L. Verdant, MD, FRCP, Marc-Jacques Dubois, MD, FRCP, Division Critical Care Medicine, Université de Montréal, Canada



Colin L. Verdant, MD, FRCP, Marc-Jacques Dubois, MD, FRCP, Division Critical Care Medicine, Université de Montréal, Canada

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2. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95: 1122–1125
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DOI: 10.1097/01.CCM.0000108854.22108.EA

The authors reply:

We thank Drs. Verdant and Dubois for discussing the definition of "relative vasopressin deficiency" in septic shock that we have recently proposed (1). It is extremely important that vasopressin concentrations be analyzed in relationship to effective osmolality and volemia (2). In our laboratory, the "normal" range of 1.4–3.6 pg/mL was obtained from unstressed healthy subjects lying in the recumbent position and having normal osmolality and volemia. Those with septic shock are exposed to both abrupt reduction in volemia and increased osmolality. Thus, the expected normal response is a prompt release of vasopressin mediated through activation of both osmoreceptors and baroreceptors, as demonstrated in animal models of septic shock (3) and in our cohort of patients (1). Subsequently, a hypotensive patient with circulating vasopressin concentrations between 1.4 to 3.6 pg/mL is very likely to have impaired release of vasopressin, which may result from decreased synthesis, increased clearance, and impaired baroreflex sensitivity. As these patients' actual concentrations are within the normal range and not <1.4 pg/mL, like in diabetes insipidus, we suggest the term "relative" vasopressin deficiency.

Although we found increased concentrations of vasopressin in most of our septic shock patients, we cannot affirm that the vasopressin response to the stress induced by septic shock was appropriate in all cases (1). So, our definition for relative vasopressin deficiency, that is, a combination of a low systolic pressure (<100 mm Hg) and circulating concentrations of 1.4–3.6 pg/mL, may have underestimated the incidence of vasopressin deficiency in septic shock.

Although most physicians would agree that some patients with septic shock are relatively deficient in vasopressin, the clinical relevance of this hormone deficiency remains to be investigated. For instance, one can argue that, in the population studied by Landry et al. (4), those with septic shock had lower vasopressin concentrations and yet had similar systolic blood pressure than those with cardiogenic shock. In our study, the proportion of patients with relative vasopressin deficiency was not significantly different

Djillali Annane, MD, PhD, Tarek Sharshar, MD, Service de reanimation, Hôpital Raymond Poincaré, Garches, France

La vasopressine dans le traitement du choc….

La vasopressine….

5. Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first line agent. If used in adults, it should be administered at infusion rates of 0.01–0.04 U/min. It may decrease stroke volume.

Grade E.

Donc la vasopressine….

- Une avenue potentiellement intéressante….plutôt une thérapie substitutive qu'une thérapie vasopressive
- Attendons étude VASST….ne pas oublier les études sur les inhibiteurs de la NOS.. (excellent vasopresseur mais en augmentant la mortalité…)
- Si utilisé: en deuxième intention et ne pas dépasser 0.04 U/min