Vasopressine et choc cardiogénique

Professeur Yazine MAHJOUB

Pôle d'Anesthésie-Réanimation

CHU Amiens-Picardie

AMIENS-FRANCE

Pas de conflits d’intérêt

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THE PURIFICATION AND THE AMINO ACID CONTENT OF VASOPRESSIN PREPARATIONS*

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Since the discovery (1) of the pressor activity of extracts of the posterior lobe of the pituitary gland, many laboratories have investigated the fractionation of the extracts obtained from this gland. The physiological potency of various preparations, as well as the methods of fractionation employed, have already been reviewed in considerable detail (2–4). In the present paper we report a new method of purification of vasopressin[1] which has yielded preparations of high potency. A study of the amino acid composition of these preparations is also presented.

Earlier investigations have shown the presence of certain amino acids in vasopressin preparations of high potency. In 1933 it was reported that a preparation having a potency of 200 units of pressor activity per mg. contained a relatively large amount of tyrosine and of sulfur (5). Later Irving, Dyer, and du Vigneaud (6), using electrophoretically purified material, found that after preliminary purification the tyrosine and cystine content increased with the pressor potency. They obtained the values 9.9 per cent (tyrosine) and 11.2 per cent (cystine) in their most potent preparation (200 units per mg.). Stehle and Frazer (7) described preparations having a potency of 200 units per mg. which contained 9.5 per cent tyrosine, 7.7 per cent cystine, and 8.9 per cent arginine. They reported that phenylalanine was lacking in their preparations, and that glutamic acid, aspartic acid, and leucine were probably lacking. Later, Stehle and Trister (8) reported the presence of proline and isoleucine in their preparations and the absence of tryptophan, glycine, histidine, and hydroxyproline. More recently Potts and Gallagher (9) reported a prep-

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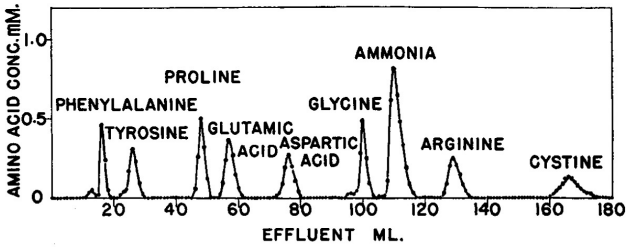
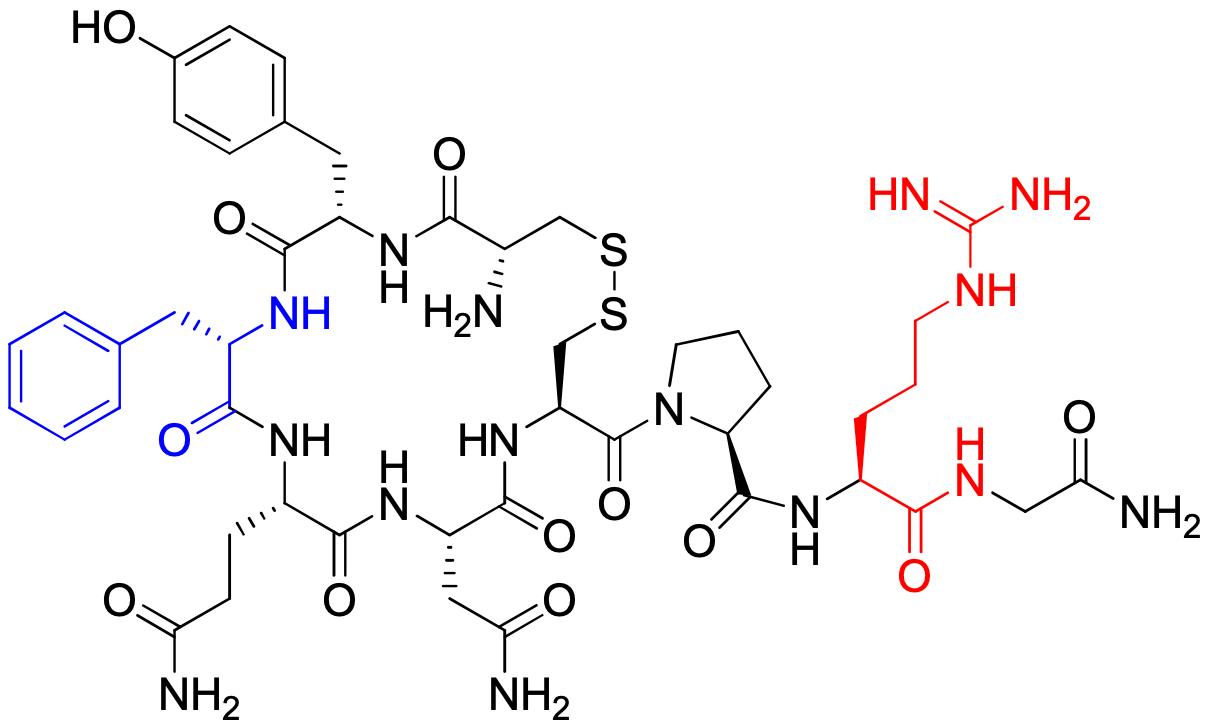
† During part of the time that the investigation was in progress, Dr. Turner was a Fellow in Cancer Research of the American Cancer Society, sponsored by the Committee on Growth of the National Research Council.

[1] The pressor principle of the posterior lobe of the pituitary gland has been variously called pitressin, β-hypophamine, postlobin-V, and vasopressin. The last of these is used in the United States Pharmacopoeia, XIV, 1950, and will be used in the present paper.



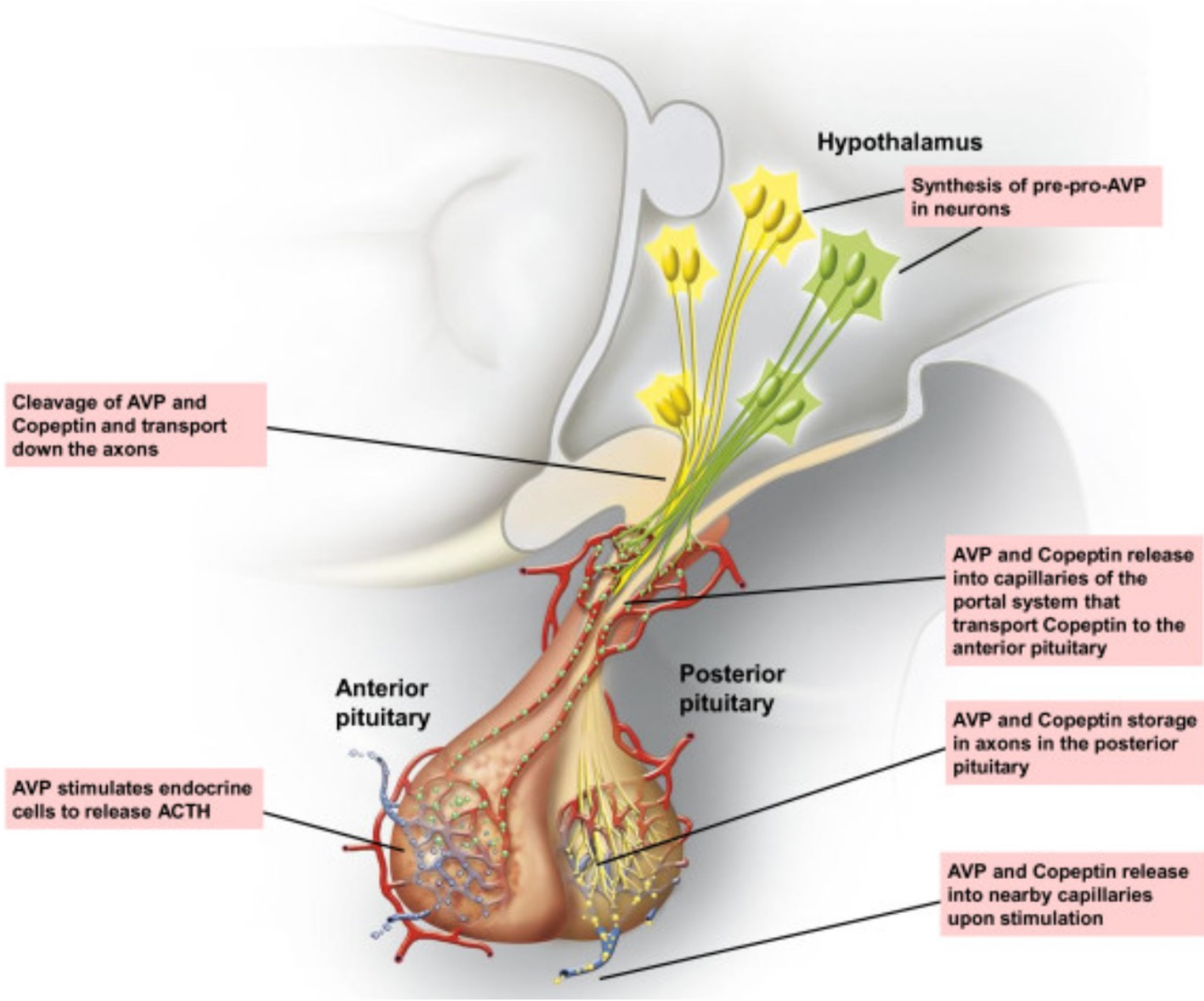
Isolé et synthétisé par Vincent du Vigneaud (Nobel 1955)

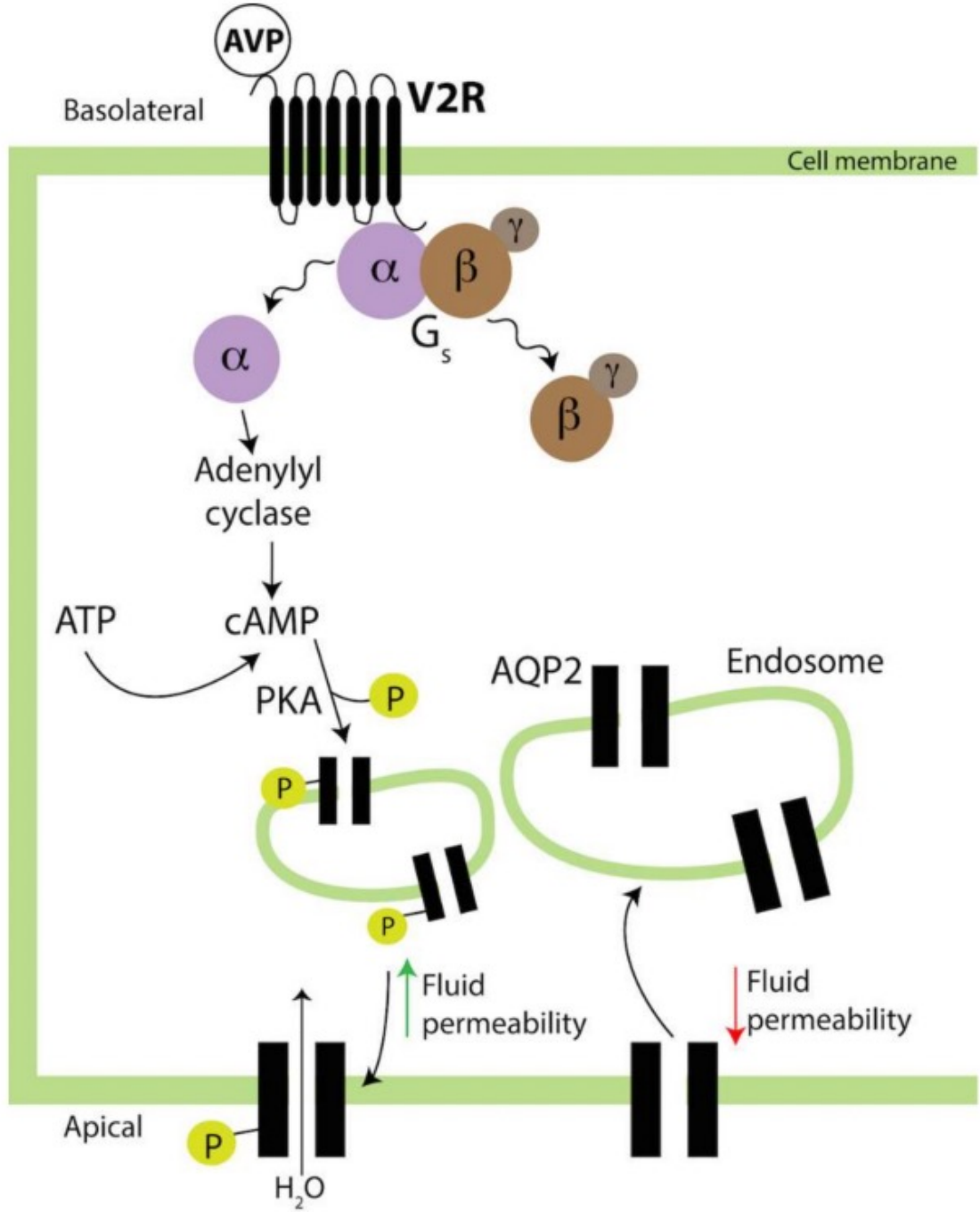


Pont di-S

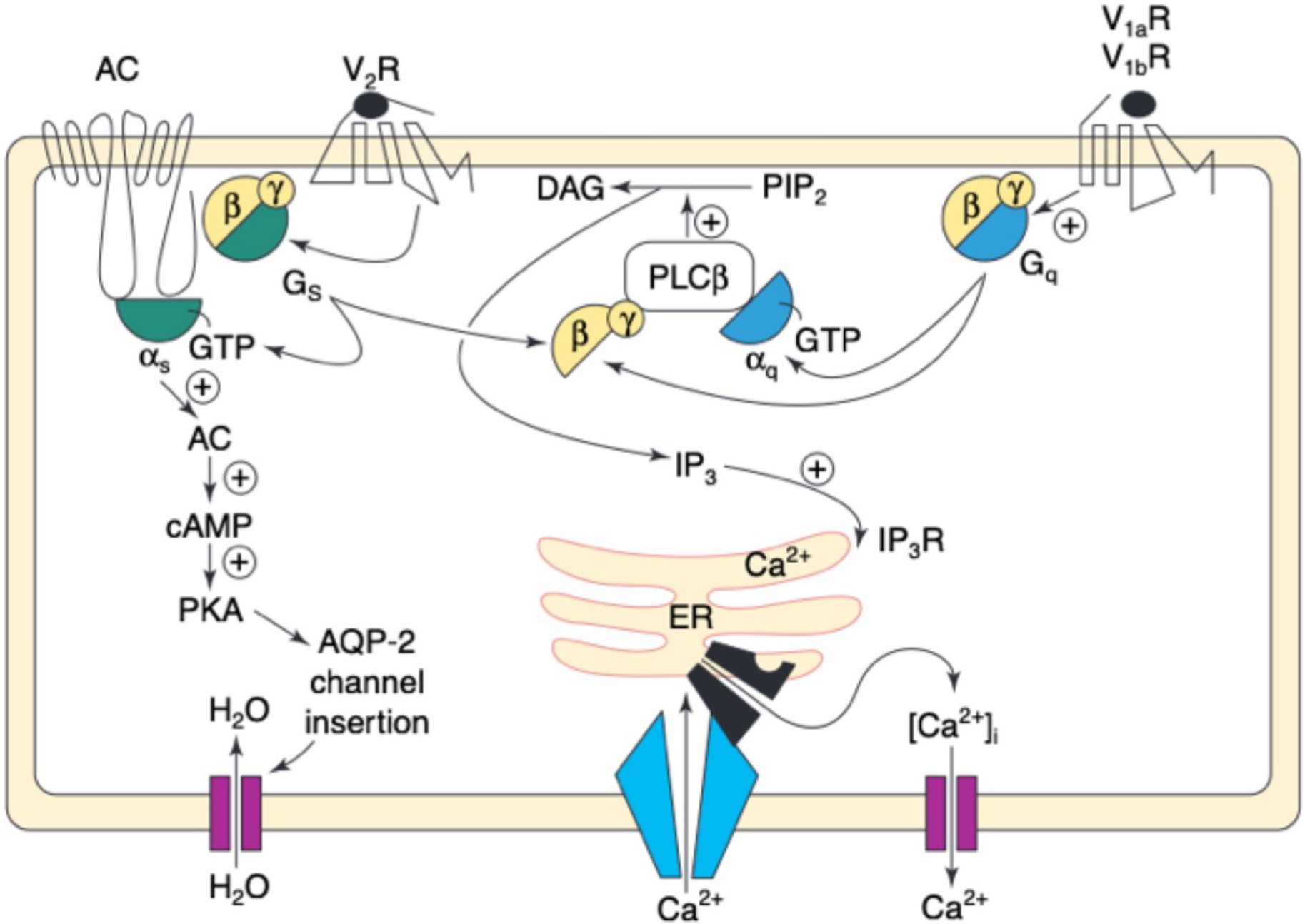
Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH_2

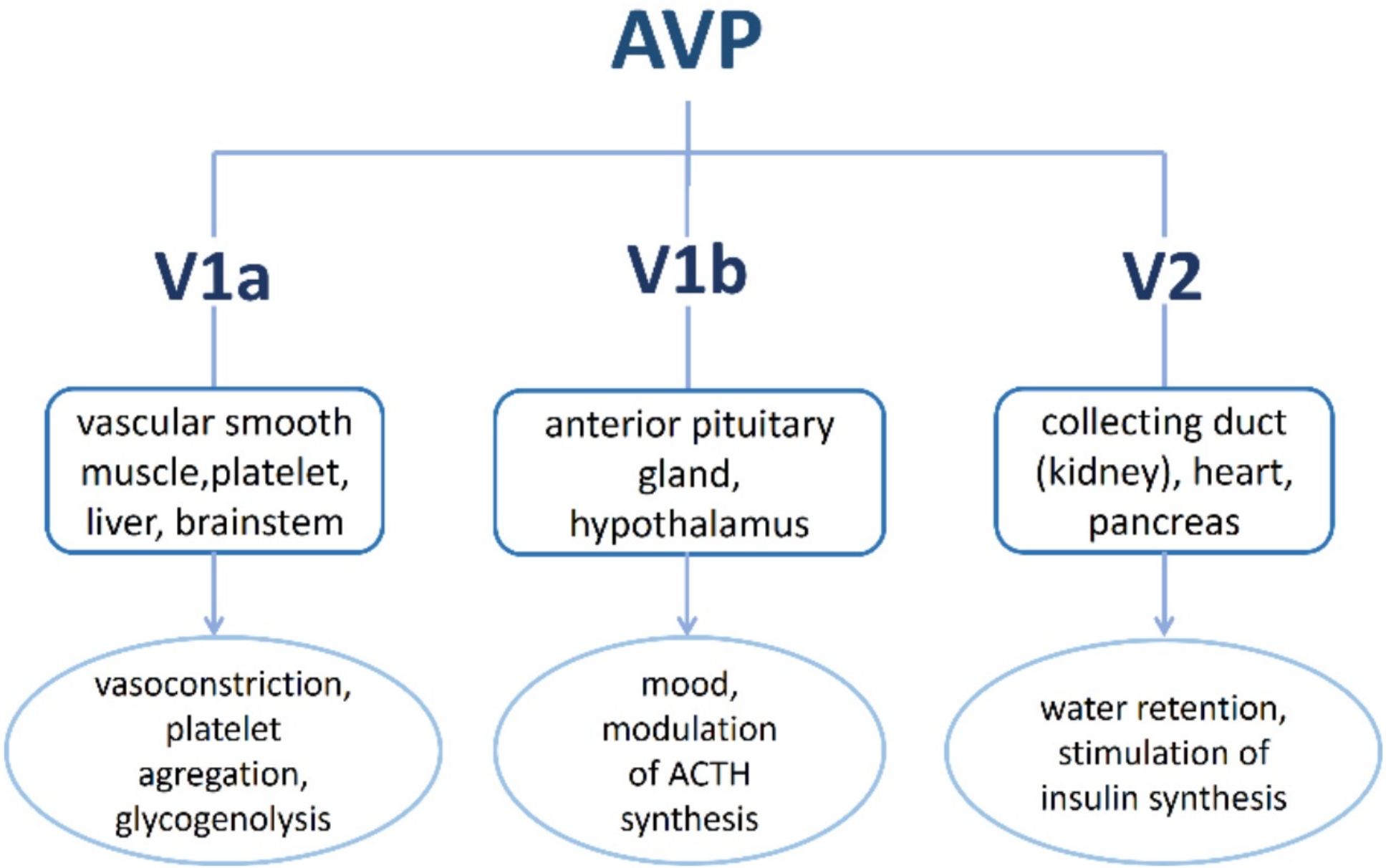
arginine vasopressin (argipressin)


Hypothalamus
Synthesis of pre-pro-AVP in neurons
Cleavage of AVP and Copeptin and transport down the axons
AVP and Copeptin release into capillaries of the portal system that transport Copeptin to the anterior pituitary
Anterior pituitary
Posterior pituitary
AVP and Copeptin storage in axons in the posterior pituitary
AVP stimulates endocrine cells to release ACTH
AVP and Copeptin release into nearby capillaries upon stimulation

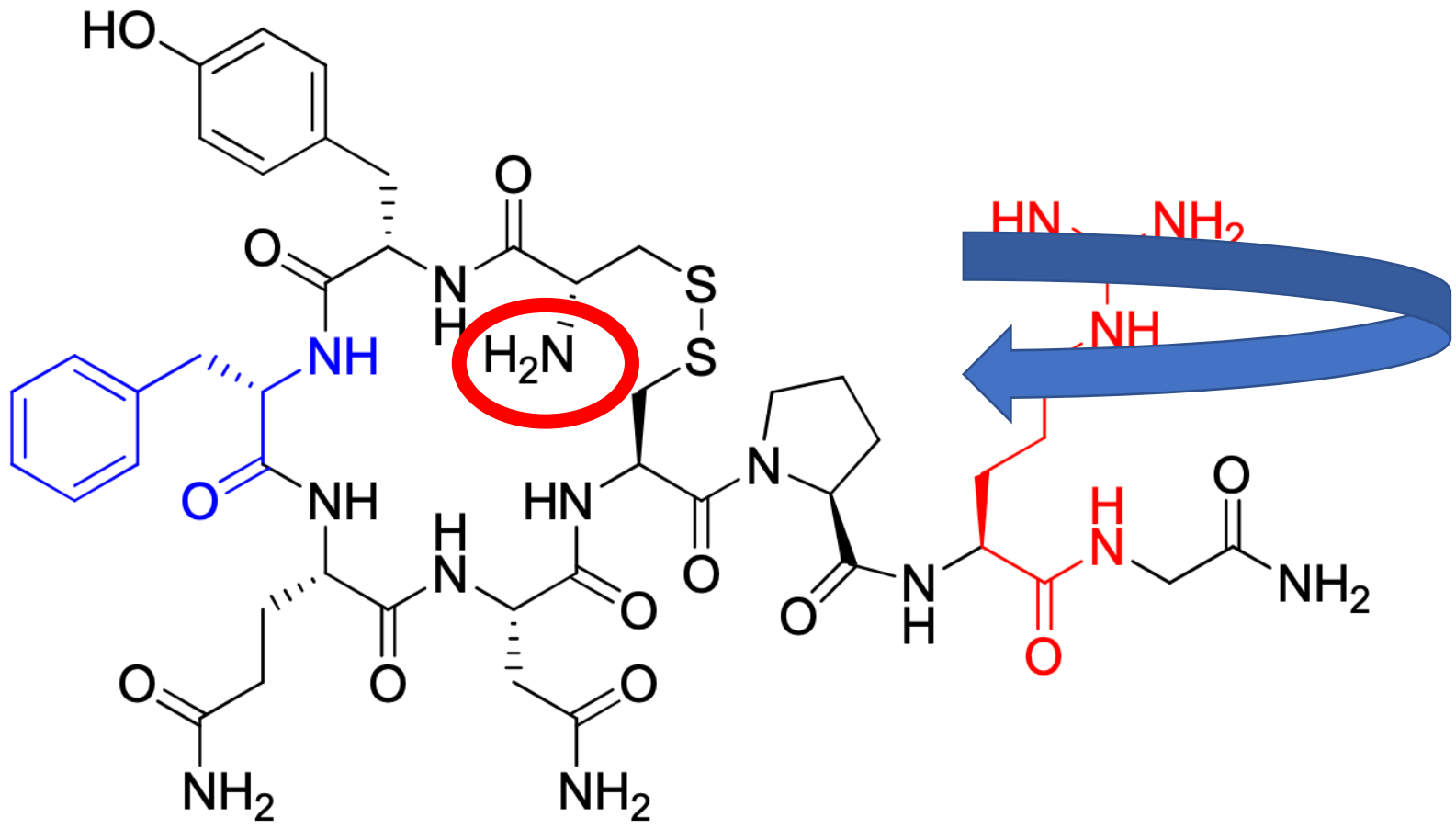


Tubule collecteur


AC
V2R
V1aR
V1bR
DAG
PIP2
PLCβ
β
γ
Gs
Gq
αs
GTP
αq
GTP
AC
cAMP
PKA
AQP-2
channel
insertion
IP3
IP3R
Ca2+
ER
H2O
H2O
[Ca2+]i
Ca2+
Ca2+


AVP
V1a
V1b
V2
vascular smooth muscle,platelet, liver, brainstem
anterior pituitary gland, hypothalamus
collecting duct (kidney), heart, pancreas
vasoconstriction, platelet agregation, glycogenolysis
mood, modulation of ACTH synthesis
water retention, stimulation of insulin synthesis

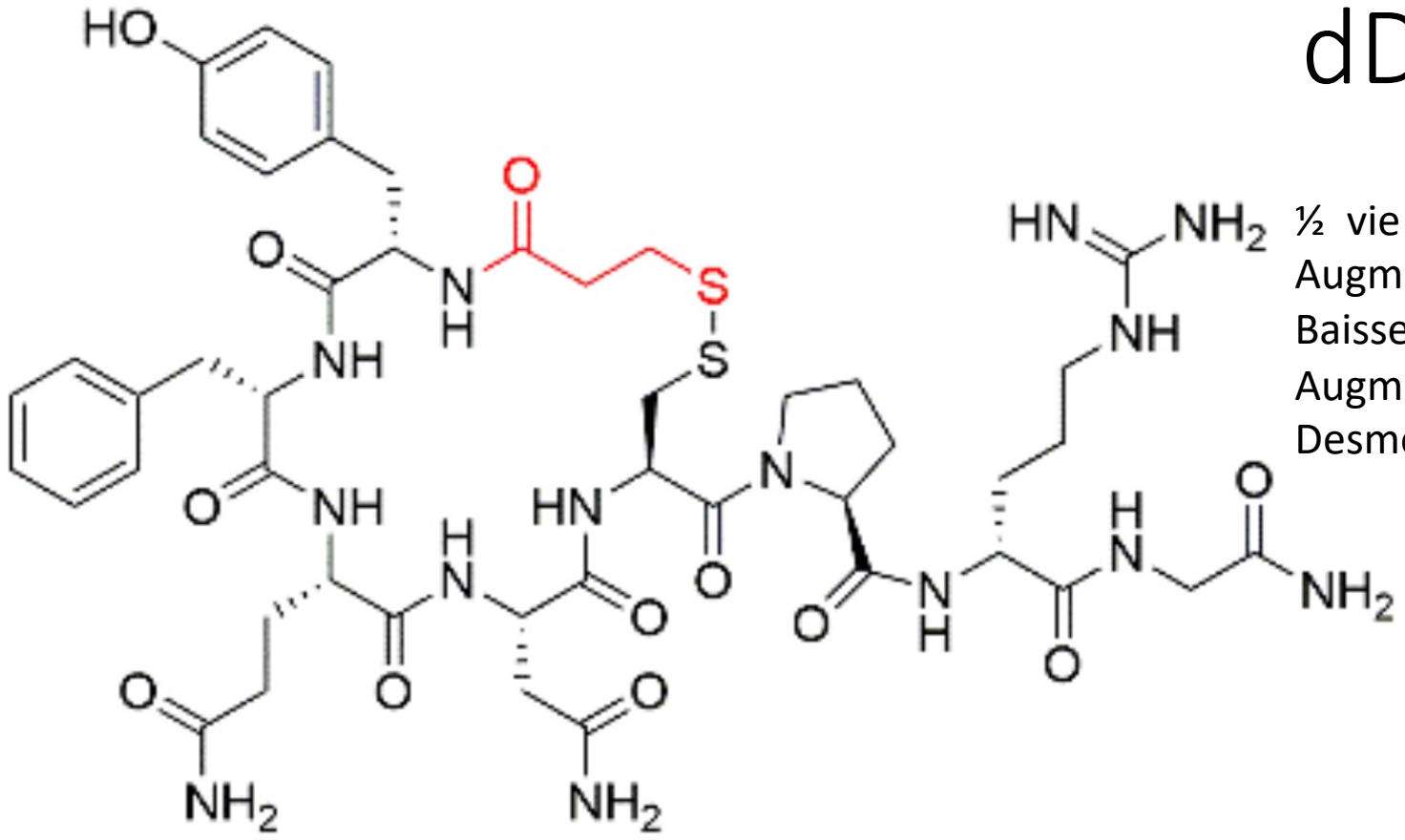
Target Tissue	Receptor	Function
Kidney—Macula densa, intermediate, distal and collector tubules	V2R	Signal transduction, AQP2 shuttling to cell surface and water permeability, *AQP2* mRNA synthesis, intracellular cAMP regulation
Kidney—Mesangial cells, efferent arterioles, renal tubules	V1aR	Vasoconstriction
Kidney	V1bR	Unknown
Vascular Smooth Muscle	V1aR	Vasoconstriction, myocardial hypertrophy, *V1aR* mRNA upregulation, hypertension
	V2R	Vasodilation
Brain—Anterior Pituitary	V1bR	ACTH secretion, stimulation of endocrine response to stress
Brain—diffused expression	V1aR	Regulation of emotional and adaptive behaviors, pain
Brain—HPA axis (adrenal cortex)	V1aR	Cortisol synthesis and secretion
Brain—SCN	V1aR	Circadian rhythm
Brain—Cerebellum (rats)	V2R	Unknown
Pancreas	V1bR	Glucagon release, intracellular Ca^{2+} regulation, cell proliferation
Liver—Hepatocytes	V1aR	Glycogenolysis
Blood—Platelets	V1aR	Platelet aggregation
Blood—Leukocytes	V1aR	Chemotaxis, chemokine and antibody production
Myometrium	V1aR	Uterine contraction
Prostate	V1aR	Unknown, causative upregulation in castration resistant prostate cancer
Skeletal muscle	V1aR	Unknown
Lung	V1aR	Unknown
	V2R	Anti-inflammatory
Bone	V2R	Bone remodeling
Cervical ganglion (rat)	V1aR	Unknown
Spleen (rat)	V1aR	Unknown
Gonads (rat)	V1aR	Unknown



Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH_2

arginine vasopressin (argipressin)

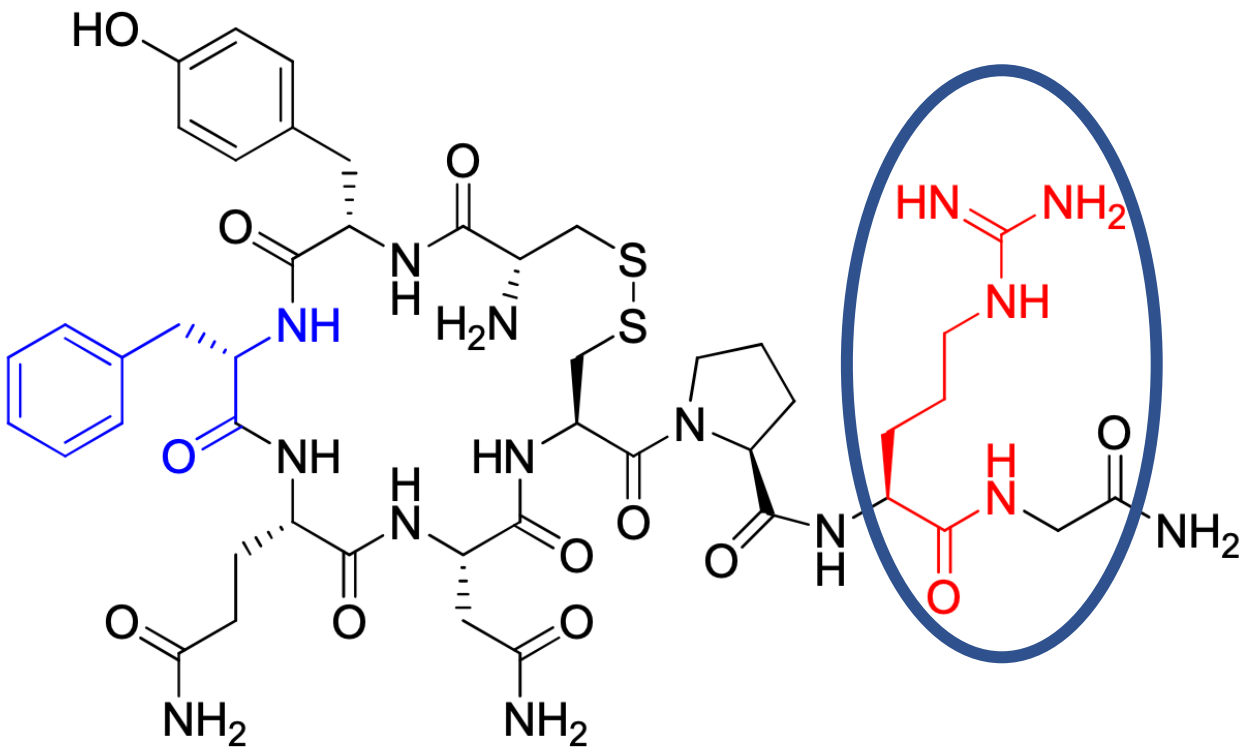
dDAVP



½ vie plus longue: 90-190 minutes
Augmentation de l'affinité V2
Baisse de l'affinité V1
Augmente l'activité F VIII et F vW
Desmopressine =MINIRIN®

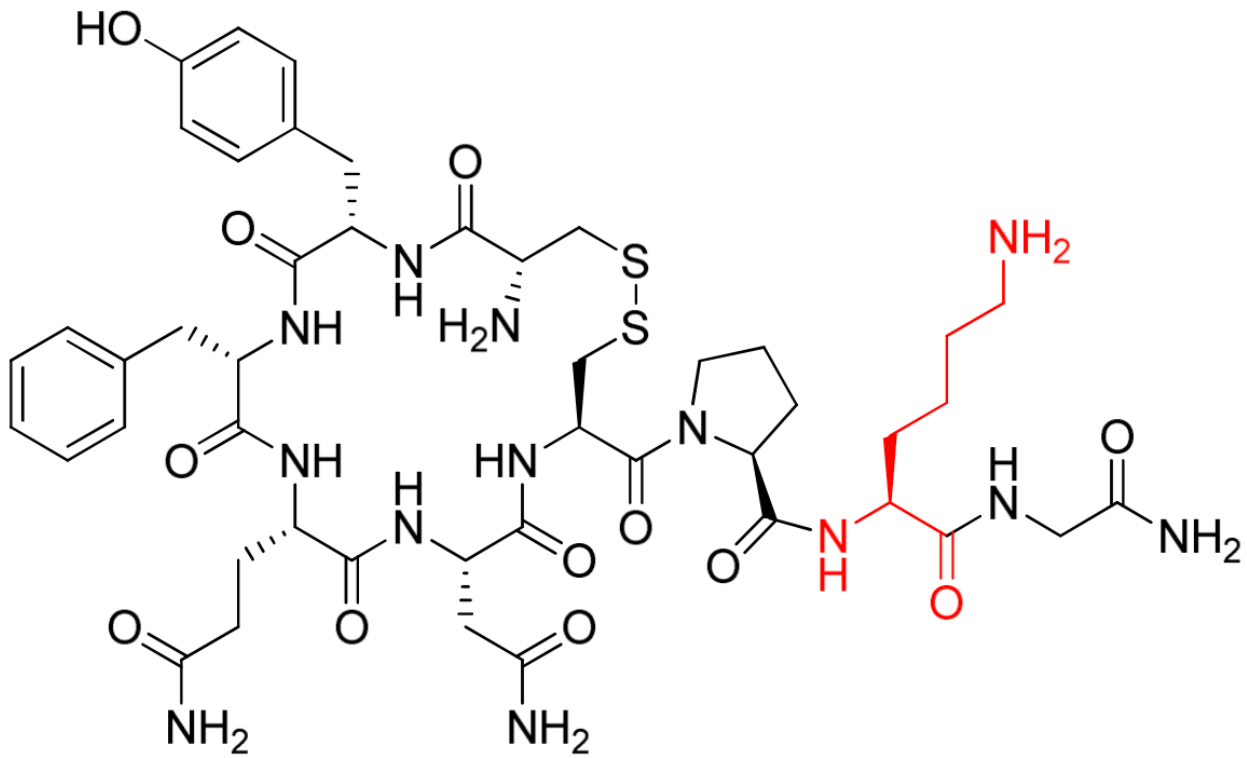
deamino-Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH_2

desmopressin



Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH_2

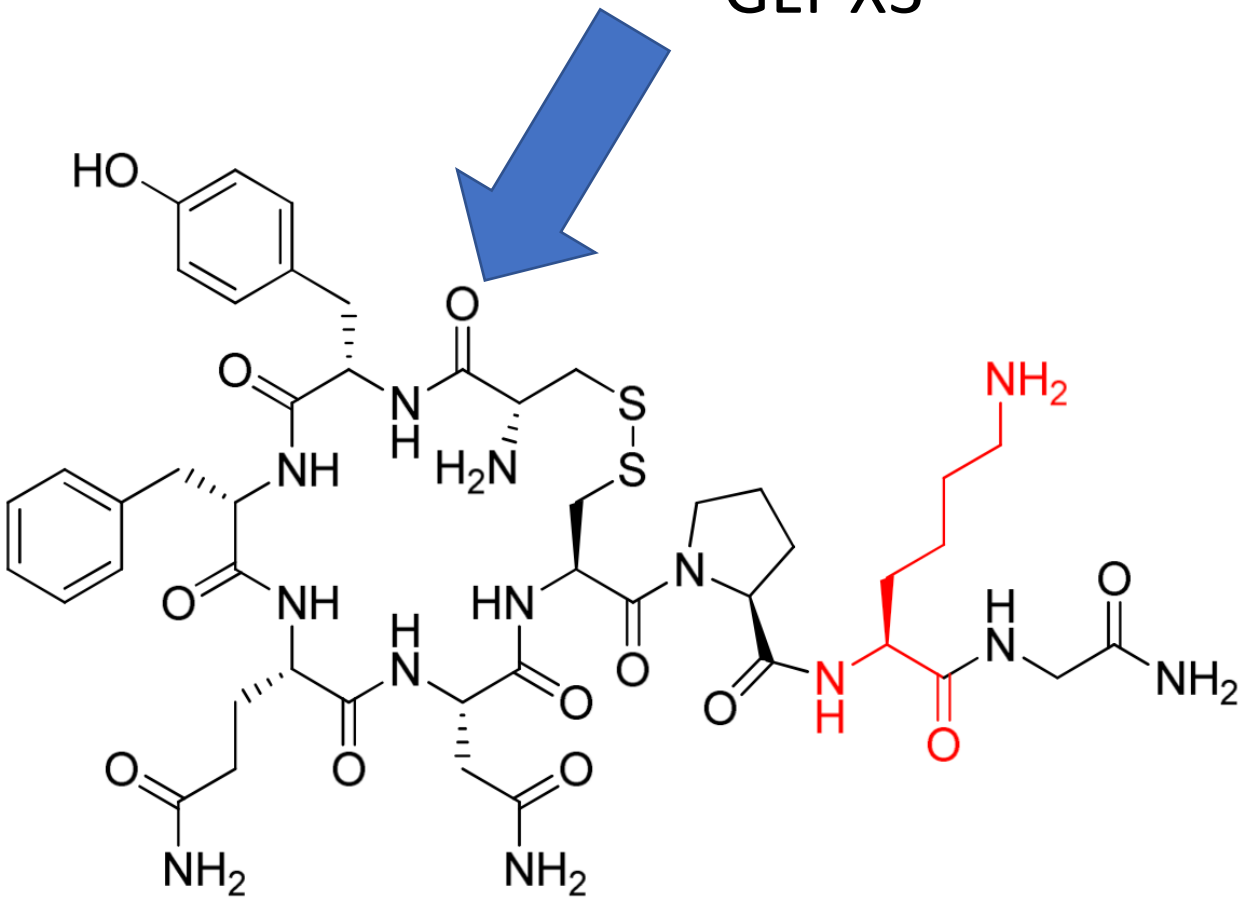
arginine vasopressin (argipressin)



Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Lys - Gly - NH_2

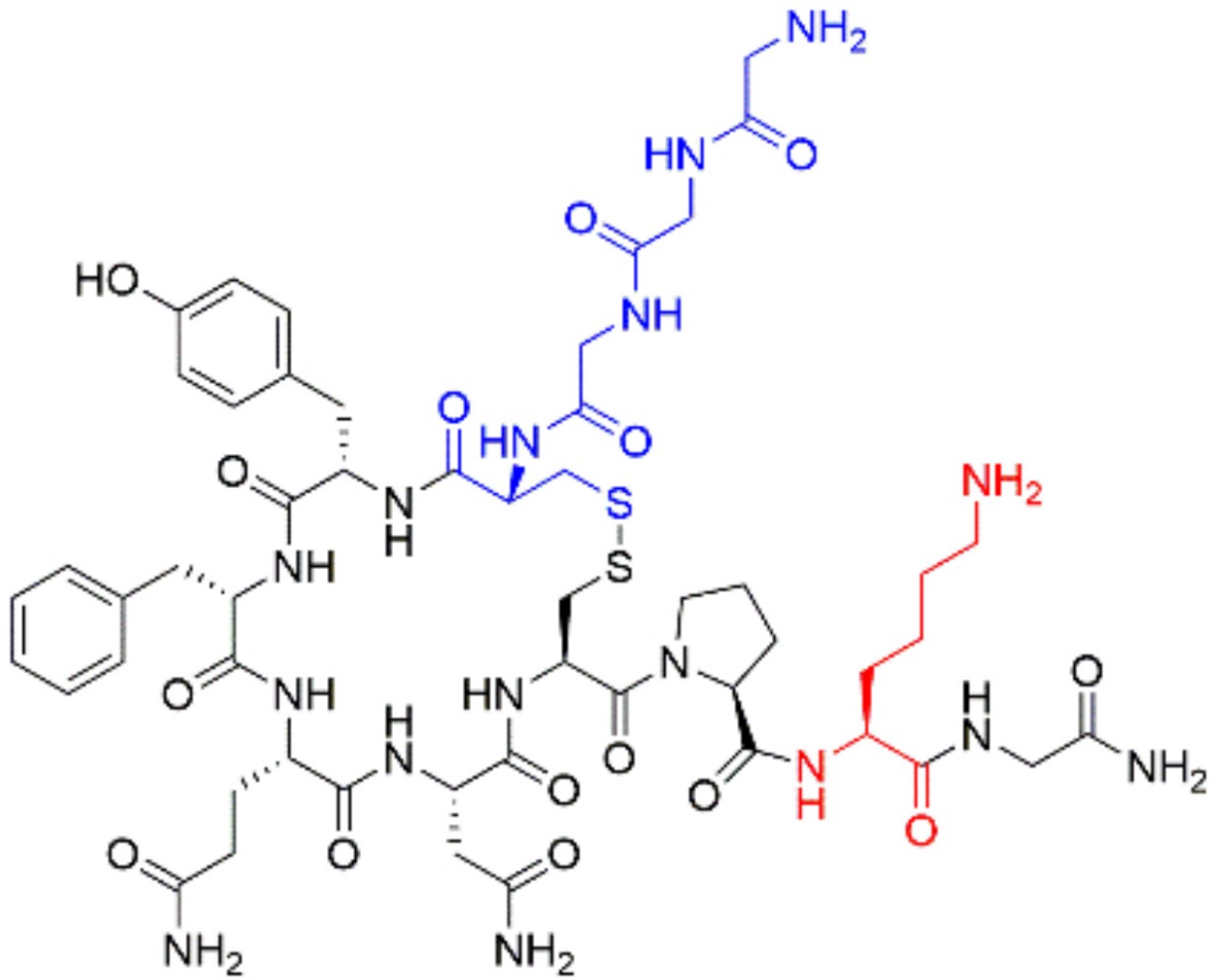
lysine vasopressin (lypressin)

GLY X3



Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Lys - Gly - NH_2

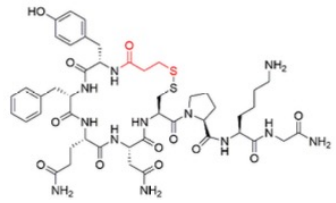
lysine vasopressin (lypressin)



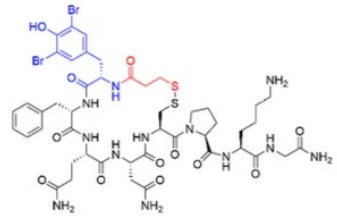
Gly - Gly - Gly - Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Lys - Gly - NH_2

Terlipressine

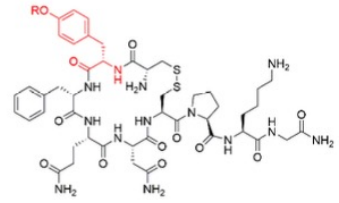
Prodrogue de LVP
Peptidase endothéliale
½ vie plasmatique: 240-360 min
Pic 60-120 min
V1 circulation splanchnique
V/C splanchnique
Augmentation de DS Rénal
Diminution de la pression portale
Diminution de la pression dans les VO
GLYPRESSINE ®
HAEMOPRESSIN ®



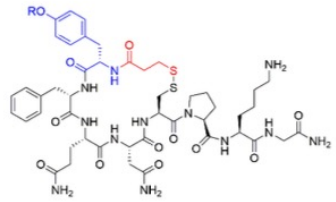
12 dLVP



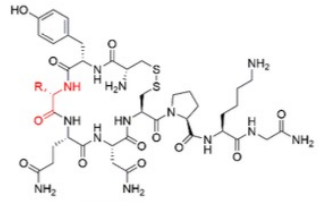
13 [Dbt^2]dLVP



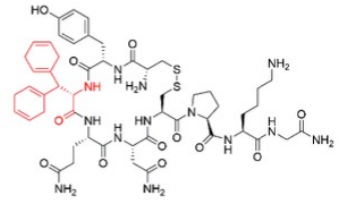
14 R = Me; [Tyr(OMe)^2]LVP, **15** R = Et; [Tyr(OEt)^2]LVP



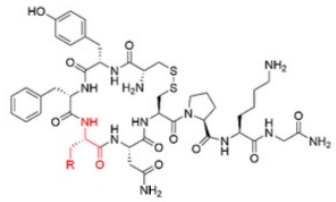
16 R = Et; [Tyr(OEt)^2]dLVP, **17** R = Pr; [Tyr(OPr)^2]dLVP
18 R = Bu; [Tyr(OBu)^2]dLVP, **19** R = Hex; [Tyr(OHex)^2]dLVP



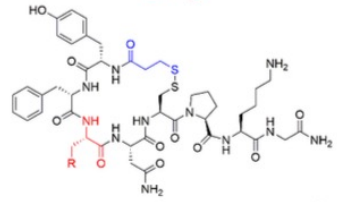
20 R = [Thi^3]LVP
21 R = $CH(CH_2)CH_2CH_3$; [Ile^3]LVP
22 R = CH_2OH; [Ser^3]LVP
23 R = [Tyr^3]LVP



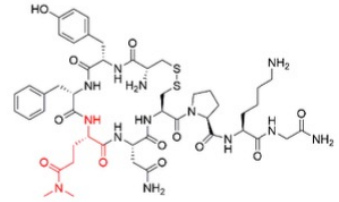
24 [diHPhe^3]LVP



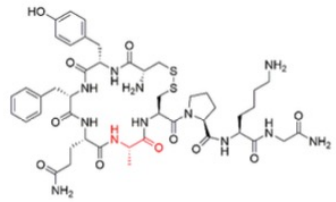
25 R = $CH(CH_3)_2$; [Leu^4]LVP; **26** R = CH_3; [Abu^4]LVP
27 R = H; [Ala^4]LVP



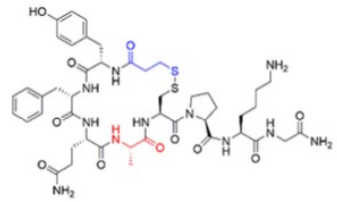
28 R = $CH(CH_3)_2$; [Leu^4]dLVP, **29** R = CH_3; [Abu^4]dLVP
30 R = H; [Ala^4]dLVP
31 R = [Cha^4]dLVP
32 R = $CH_2CH_2NH_2$; [Orn^4]dLVP
33 R = $CH_2CH_2NHCH(NH_2)$=NH; [Arg^4]dLVP



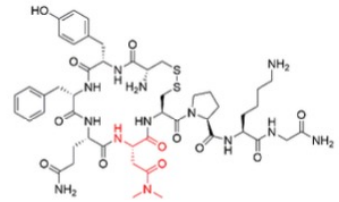
34 [diMeGln^4]LVP



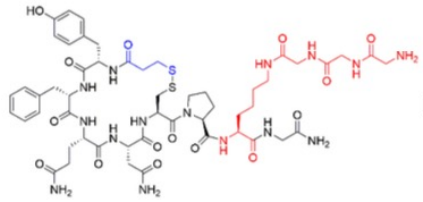
35 [Ala^5]LVP



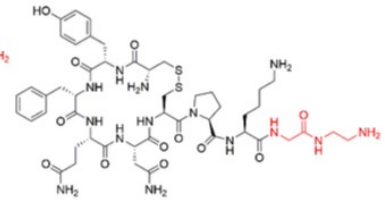
36 [Ala^5]dLVP



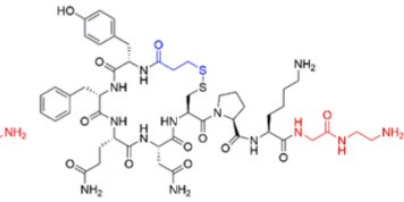
37 [diMeAsn^5]LVP



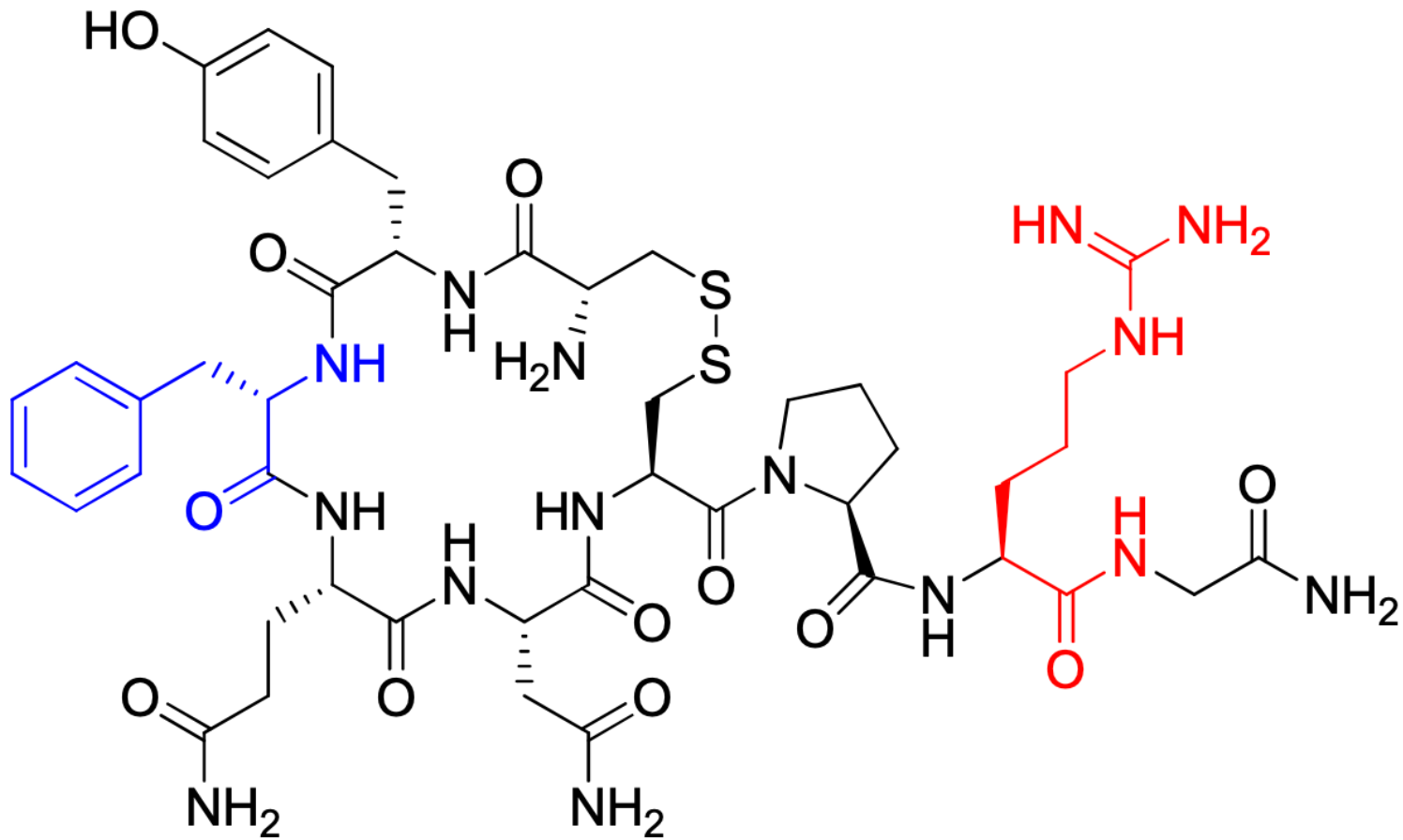
38 [Lys(*N*-Gly)$_3$^{8}]dLVP



39 [Eda^9]LVP



40 [Eda^9]dLVP

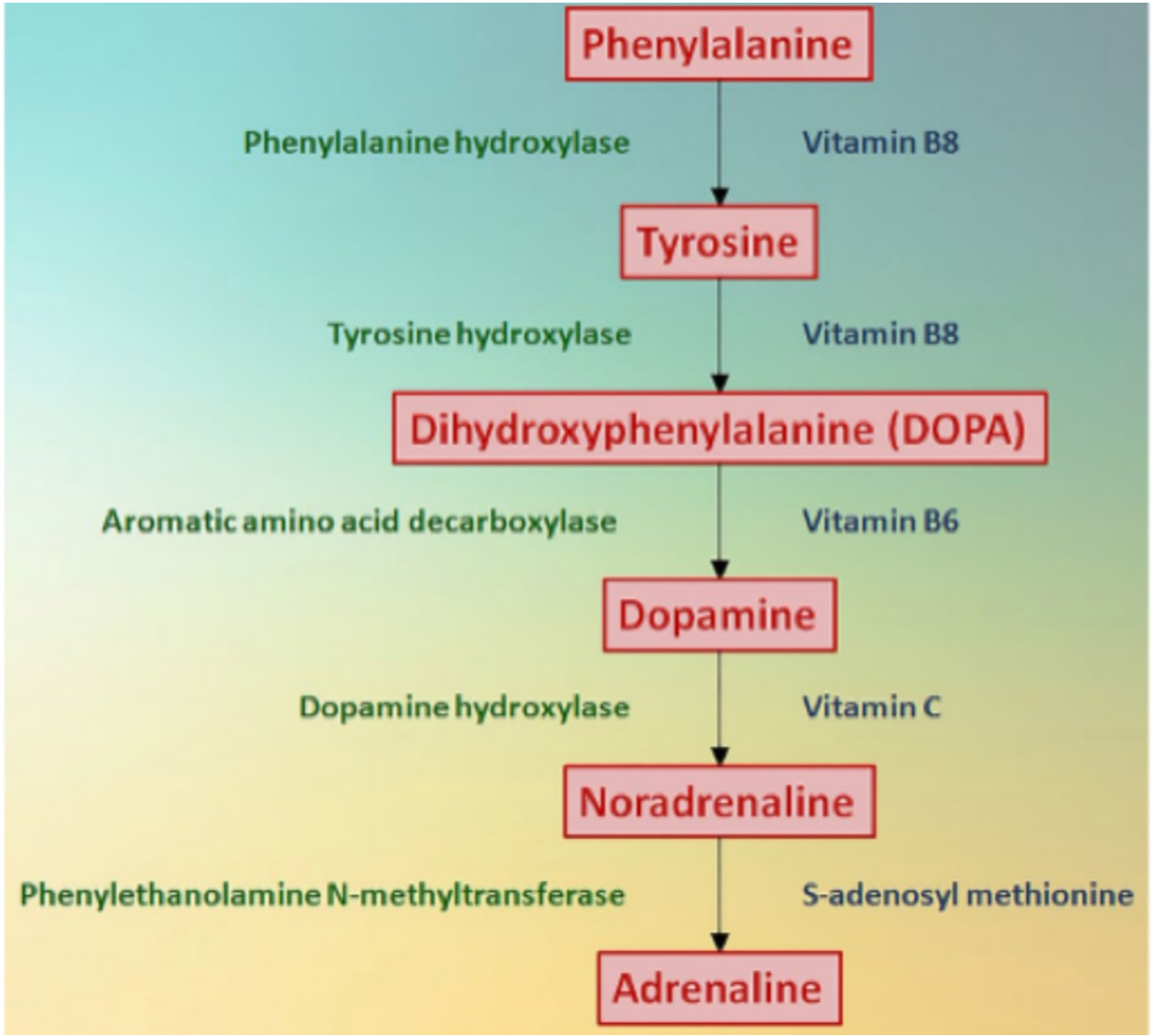


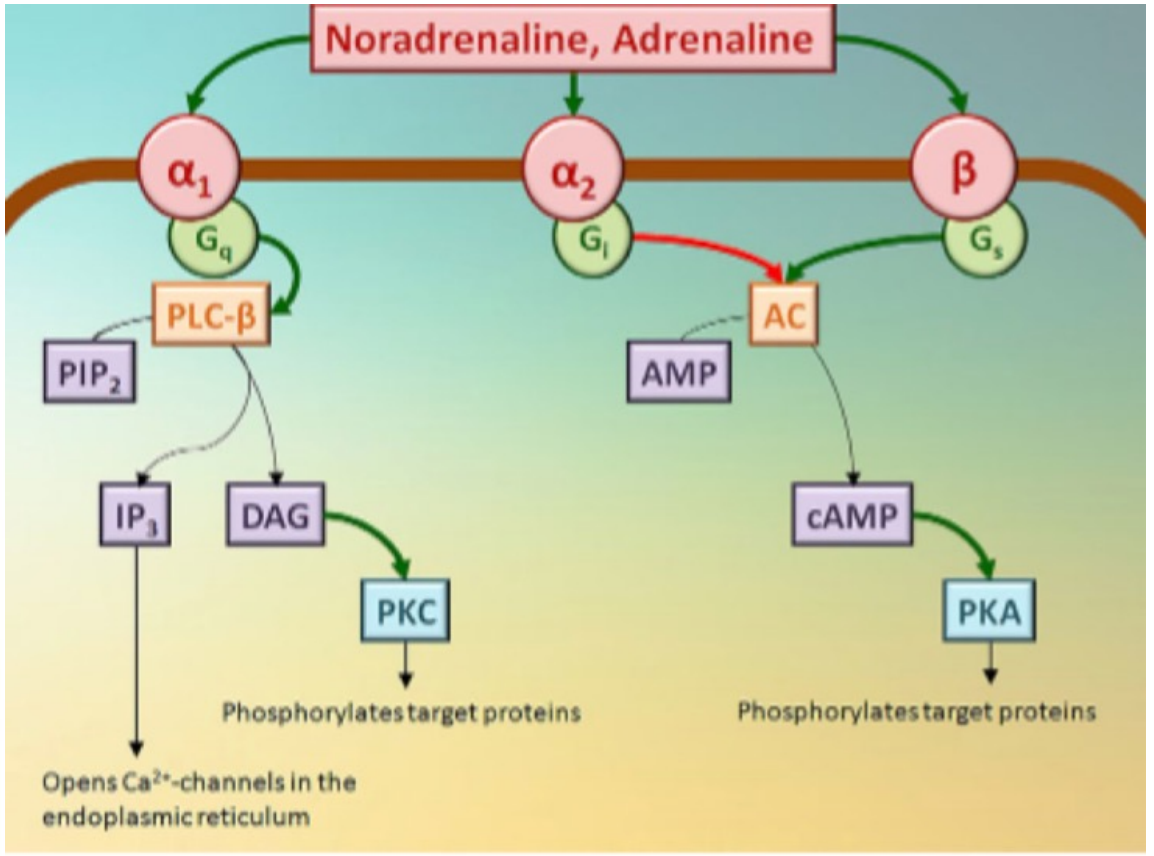
Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH_2

arginine vasopressin (argipressin)

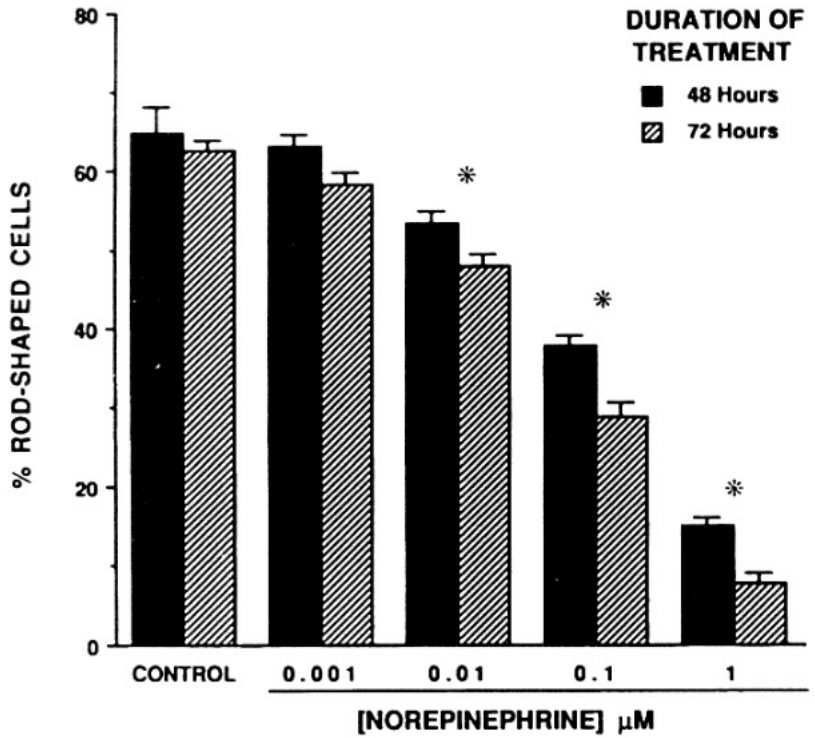
Alternative aux catécholamines

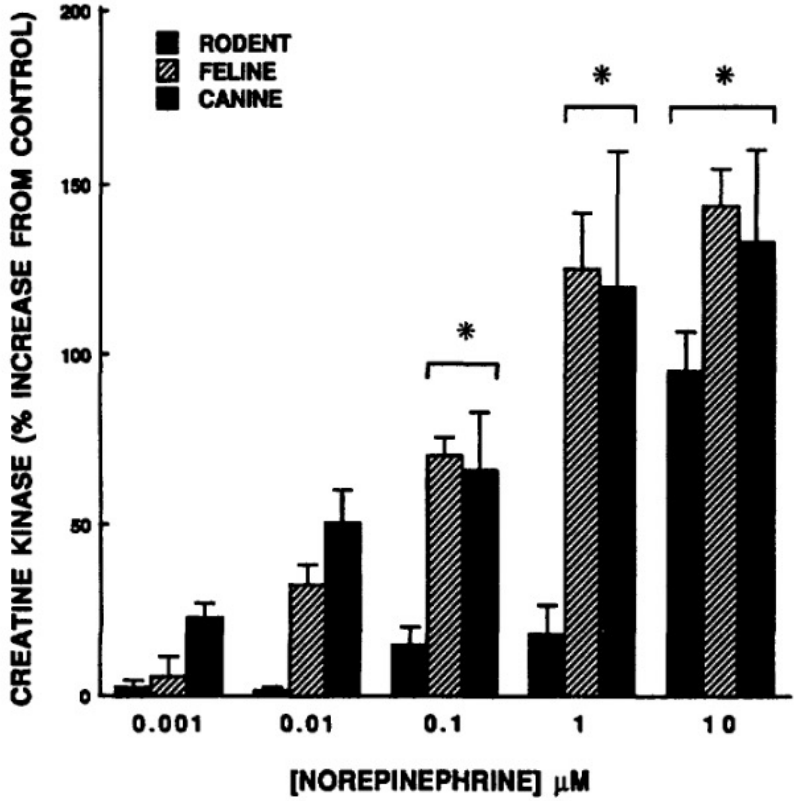
- Effets délétères des catécholamines

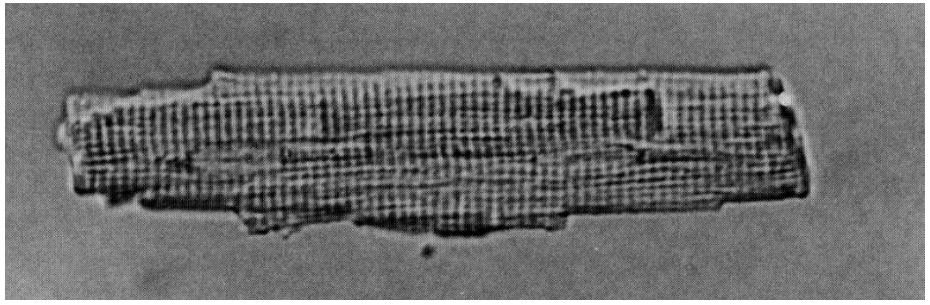

Phenylalanine
Phenylalanine hydroxylase
Vitamin B8
Tyrosine
Tyrosine hydroxylase
Vitamin B8
Dihydroxyphenylalanine (DOPA)
Aromatic amino acid decarboxylase
Vitamin B6
Dopamine
Dopamine hydroxylase
Vitamin C
Noradrenaline
Phenylethanolamine N-methyltransferase
S-adenosyl methionine
Adrenaline

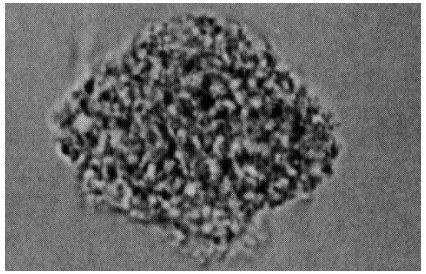

Noradrenaline, Adrenaline
α1
α2
β
Gq
Gi
Gs
PLC-β
AC
PIP2
AMP
IP3
DAG
PKC
cAMP
PKA
Phosphorylates target proteins
Phosphorylates target proteins
Opens Ca2+-channels in the endoplasmic reticulum

Effet sur les cellules myocardiques



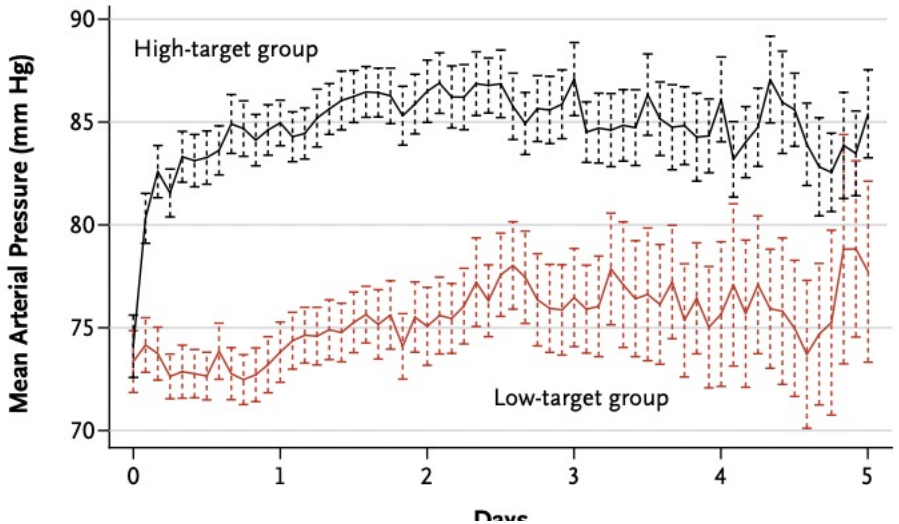


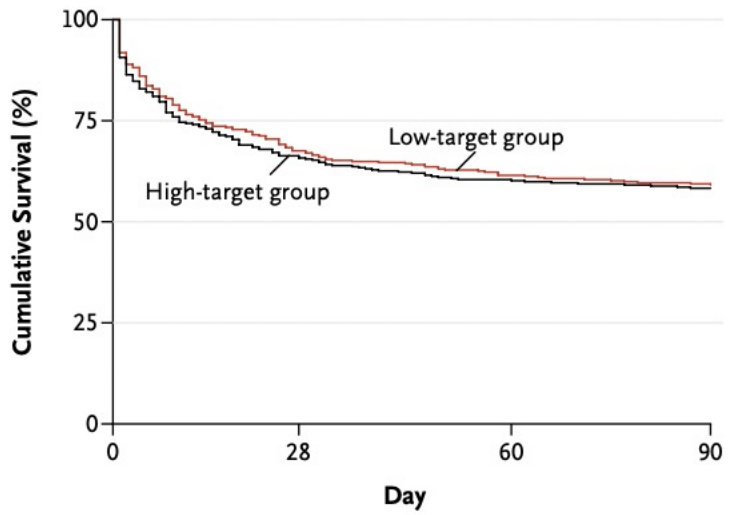




Mann DL, circulation 1992

80-85 vs 65-70 mmHg





No. at Risk

Low target	379	256	233	225
High target	375	249	227	219

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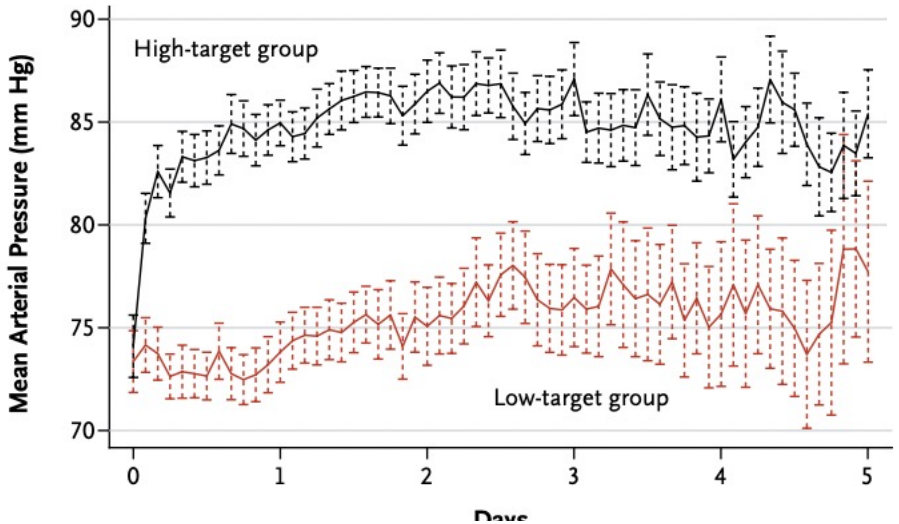
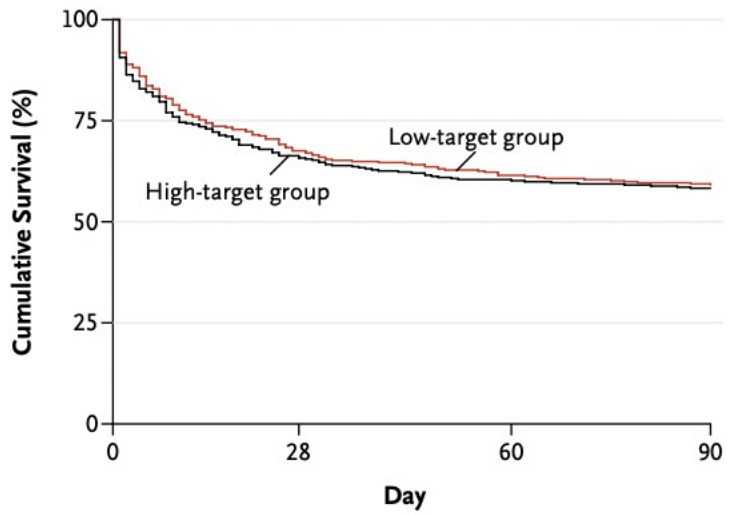
High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D.,

Median dose of norepinephrine (IQR) — μg/kg/min			
Day 1	0.45 (0.17–1.21)	0.58 (0.26–1.80)	<0.001
Day 2	0.16 (0.03–0.48)	0.38 (0.14–0.90)	<0.001
Day 3	0.02 (0.00–0.16)	0.14 (0.01–0.50)	<0.001
Day 4	0.00 (0.00–0.05)	0.03 (0.00–0.22)	<0.001
Day 5	0.00 (0.00–0.03)	0.01 (0.00–0.15)	<0.001
Duration of catecholamine infusion — days	3.7±3.2	4.7±3.7	<0.001
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02

80-85 vs 65-70 mmHg





No. at Risk

Low target	379	256	233	225
High target	375	249	227	219

The NEW ENGLAND JOURNAL of MEDICINE

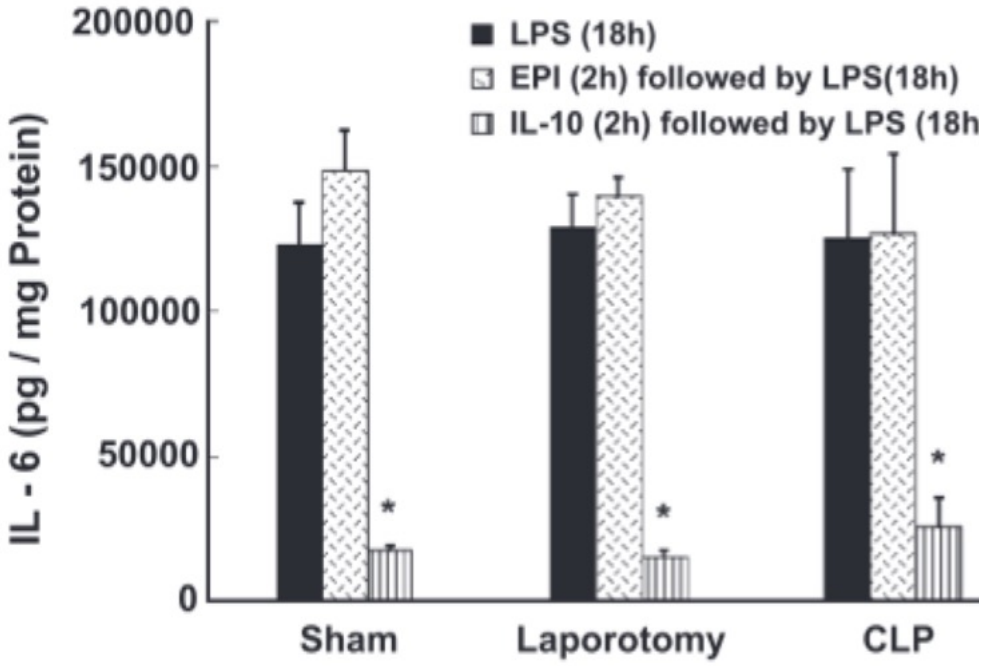
ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

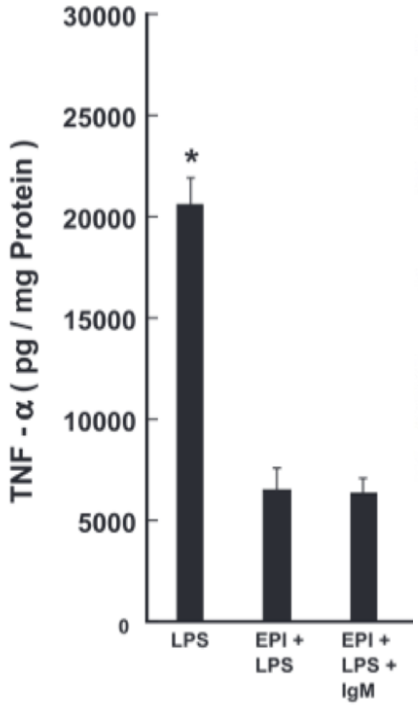
High versus Low Blood-Pressure Target in Patients with Septic Shock

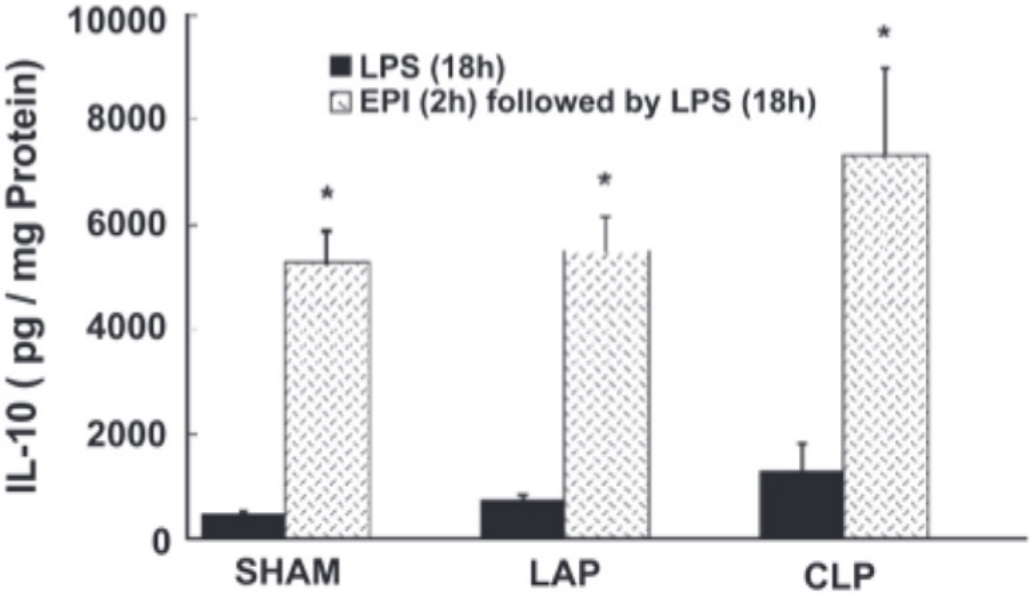
Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D.,

Median dose of norepinephrine (IQR) — μg/kg/min			
Day 1	0.45 (0.17–1.21)	0.58 (0.26–1.80)	<0.001
Day 2	0.16 (0.03–0.48)	0.38 (0.14–0.90)	<0.001
Day 3	0.02 (0.00–0.16)	0.14 (0.01–0.50)	<0.001
Day 4	0.00 (0.00–0.05)	0.03 (0.00–0.22)	<0.001
Day 5	0.00 (0.00–0.03)	0.01 (0.00–0.15)	<0.001
Duration of catecholamine infusion — days	3.7±3.2	4.7±3.7	<0.001
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02

Modulation de la synthèse des IL par les macrophages



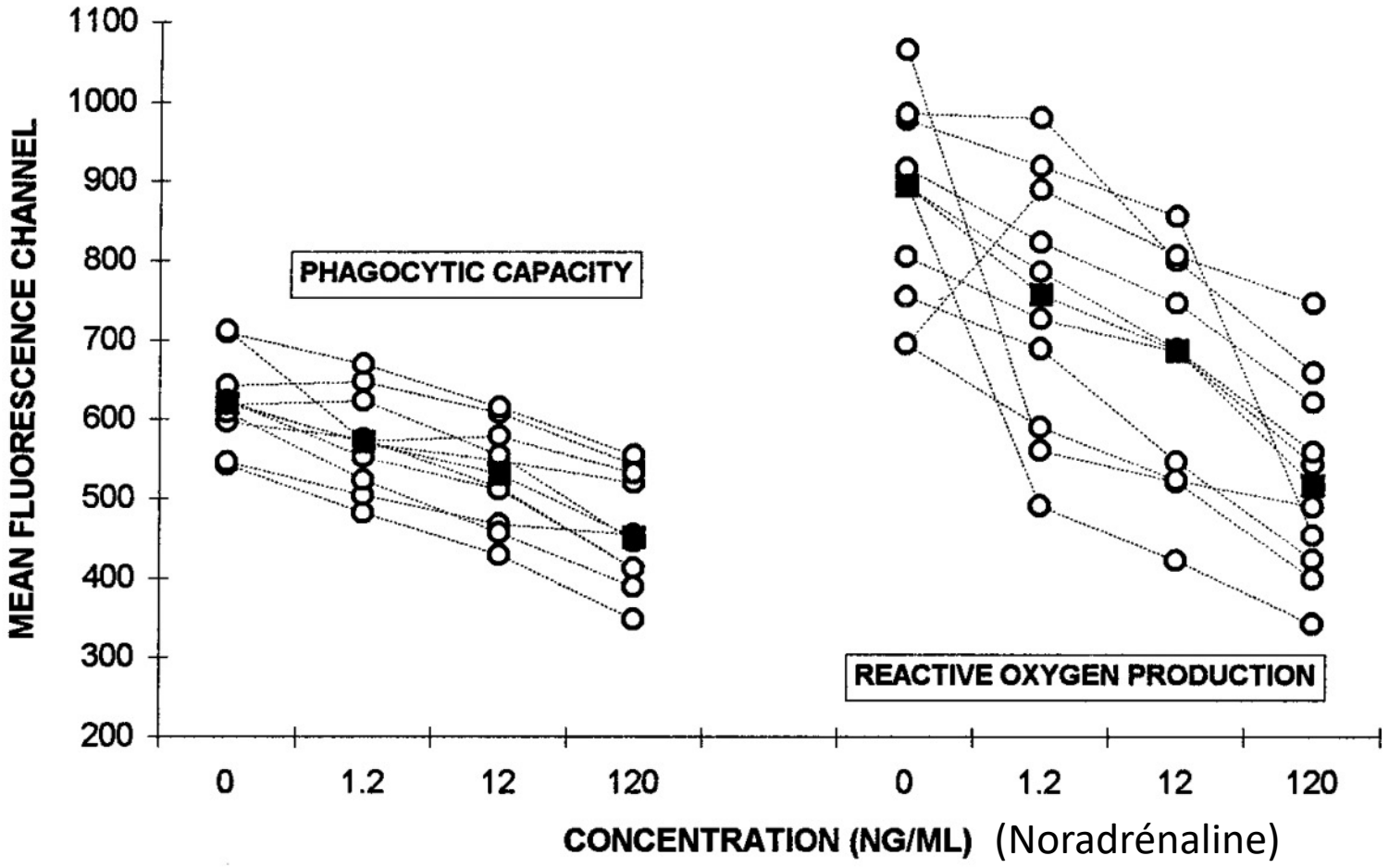




Modèles animaux péritonites

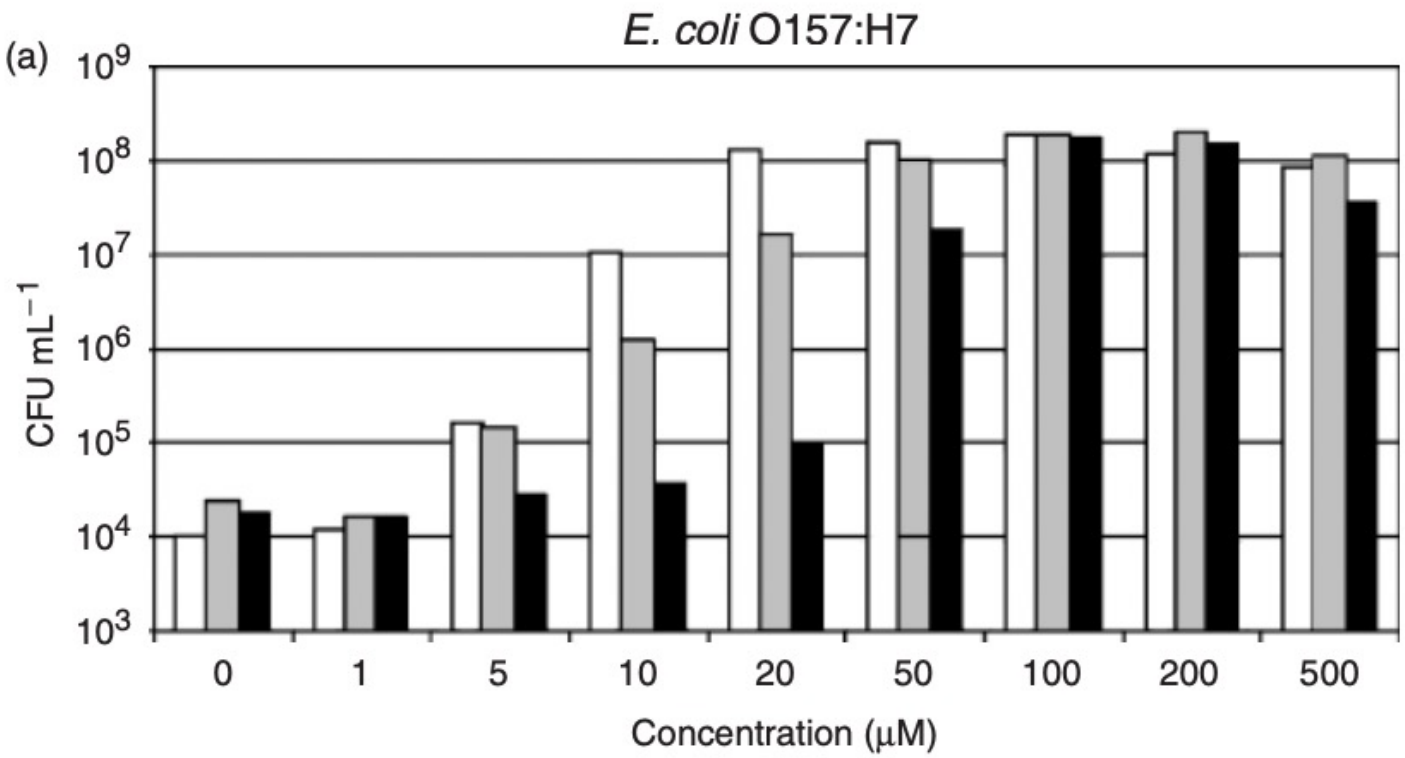
Muthu K, J Neuroimmunol 2005

Capacité de phagocytose des PNN

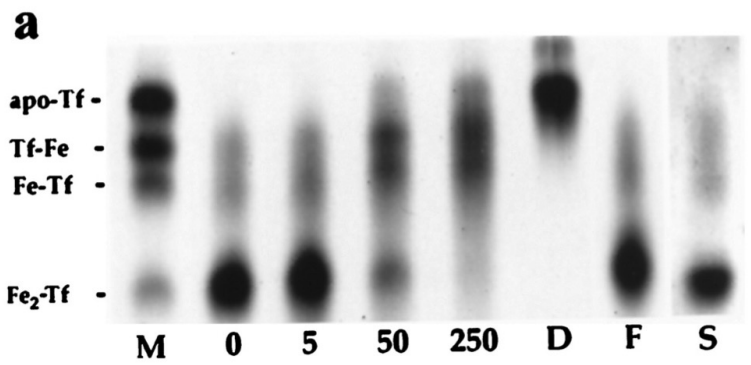


Wenisch C, Clin Diag lab immunol 1996

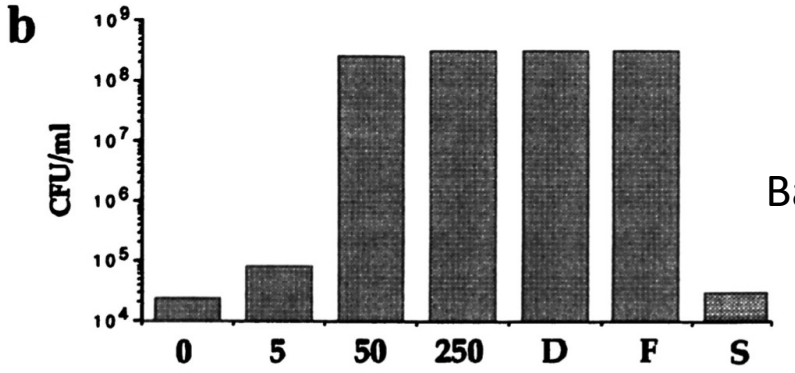
Prolifération bactérienne



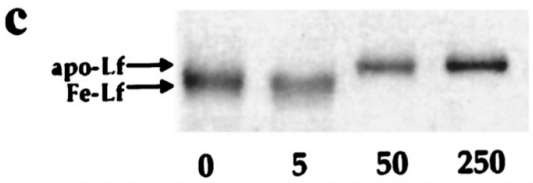
Freestone PPE, *FEMS microbiol 2007*



transferrine



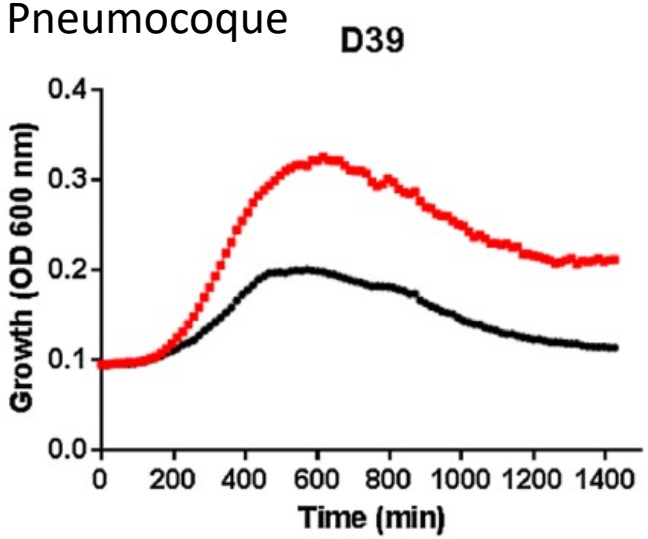
Bactéries

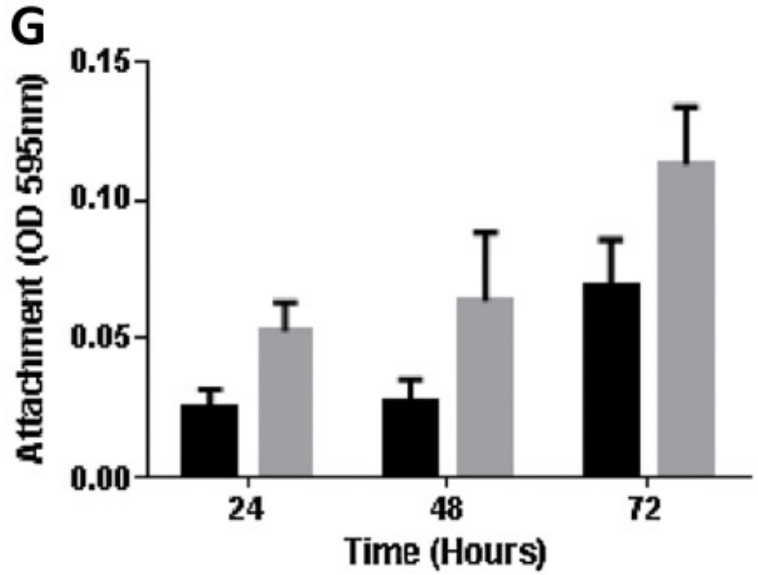


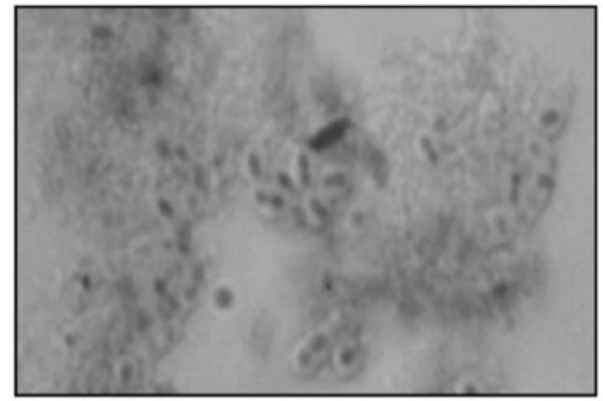
lactoferrine

Freestone PPE, *J Bacteriol 2000*

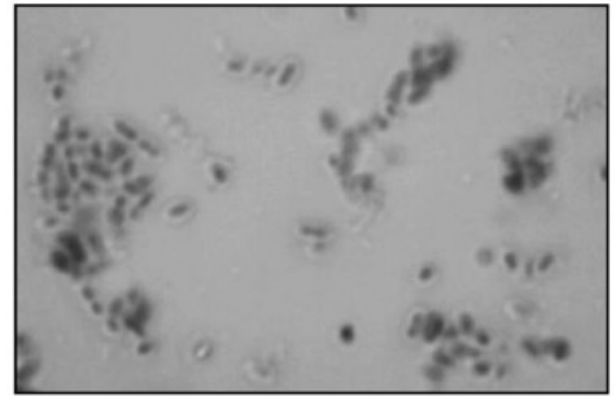
Pneumocoque







Control



NE

Biofilm

Transcriptional regulators	Function	Fold change in expression		
		D39	*pspA*⁻	*pspC*⁻
***comX* (SPD_0014)**	Transcriptional regulator ComX1	5.33 (0.15)	0.85 (0.03)	0.92 (0.09)
***rgg* (SPD_0144)**	Transcriptional regulator	1.72 (0.12)	0.40 (0.06)	1.13 (0.15)
***ritR* (SPD_0344)**	DNA-binding response regulator	0.77 (0.04)	0.73 (0.02)	0.97 (0.04)
***rgg/mutR* (SPD_0939)**	Transcriptional regulator	28.4 (2.2)	0.79 (0.06)	1.09 (0.13)
Sugar hydrolases				
***strH* (SPD_0063)**	N-acetyl hexosaminidase	6.56 (0.30)	0.6 (0.02)	0.97 (0.04)
***bga3* (SPD_0065)**	β-galactosidase	21.4 (2.0)	0.78 (0.04)	1.1 (0.05)
***nanB* (SPD_1499)**	Neuraminidase B	22.39 (1.10)	1.23 (0.12)	0.78 (0.08)
***nanA* (SPD_1504)**	Neuraminidase A	10.77 (0.89)	1.44 (0.07)	0.98 (0.04)
Cation metabolism				
***piuA* (SPD_1652)**	Iron-compound ABC transporter	6.08 (0.20)	0.27 (0.03)	1.02 (0.03)
***psaA* (SPD_1463)**	ABC transporter substrate-binding protein	1.22 (0.04)	0.48 (0.03)	1.04 (0.03)
Sugar metabolism				
***pflB* (SPD_0420)**	Pyruvate formate lyase	0.59 (0.03)	0.89 (0.02)	1.03 (0.06)
***spxB* (SPD_0722)**	Pyruvate oxidase	0.16 (0.07)	0.69 (0.03)	0.84 (0.12)
***galK* (SPD_1634)**	Galactokinase	25.36 (2.39)	0.78 (0.04)	0.92 (0.07)
Oxidative stress response				
***tpxD* (SPD_1464)**	Thiolperoxidase	0.66 (0.07)	0.74 (0.06)	0.81 (0.1)

The relative gene expression levels of wildtype D39 and the *pspA* and *pspC* mutants was calculated from 3 independent experiments and standard deviation is indicated in parenthesis. The expression of target genes was normalised to the housekeeping gene *gyrB*.

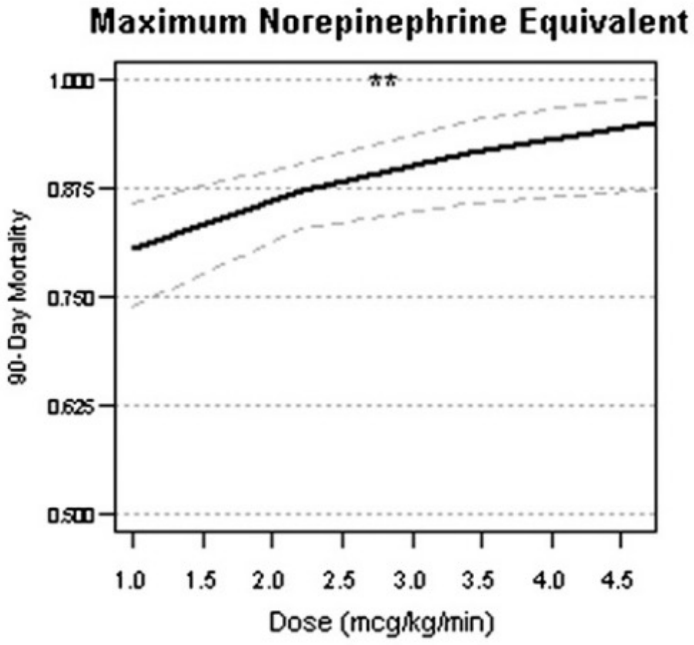
Gènes de virulence

Sandrini *et al. BMC Microbiology* 2014, **14**:180

CHEST Original Research
CRITICAL CARE

Survival After Shock Requiring High-Dose Vasopressor Therapy

Samuel M. Brown, MD; Michael J. Lanspa, MD; Jason P. Jones, PhD;



Characteristic	Survivors	Nonsurvivors	*P* Value
Maximum NE equivalent, μg/kg/min	1.4	1.8	< .01

Etude restrospective

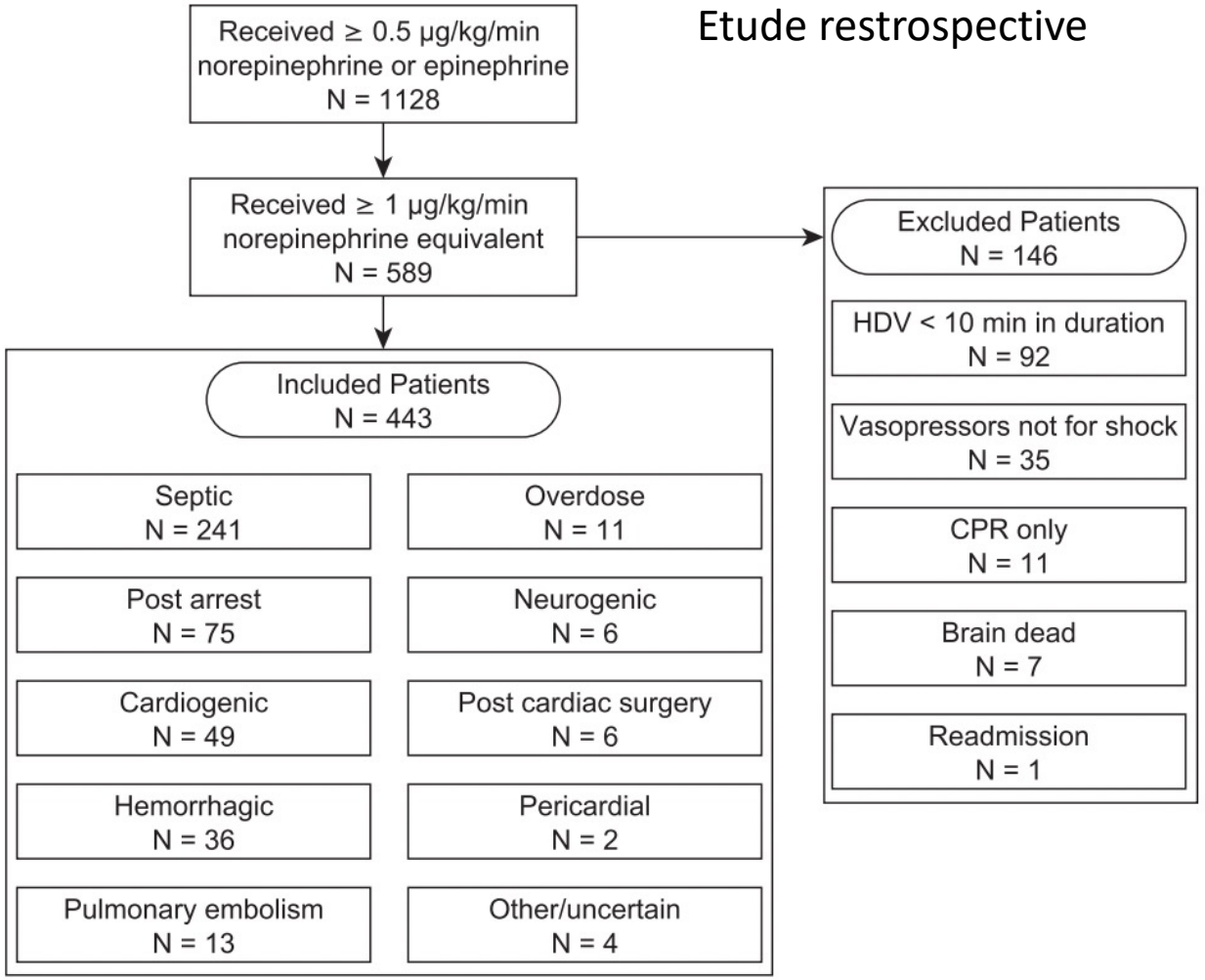
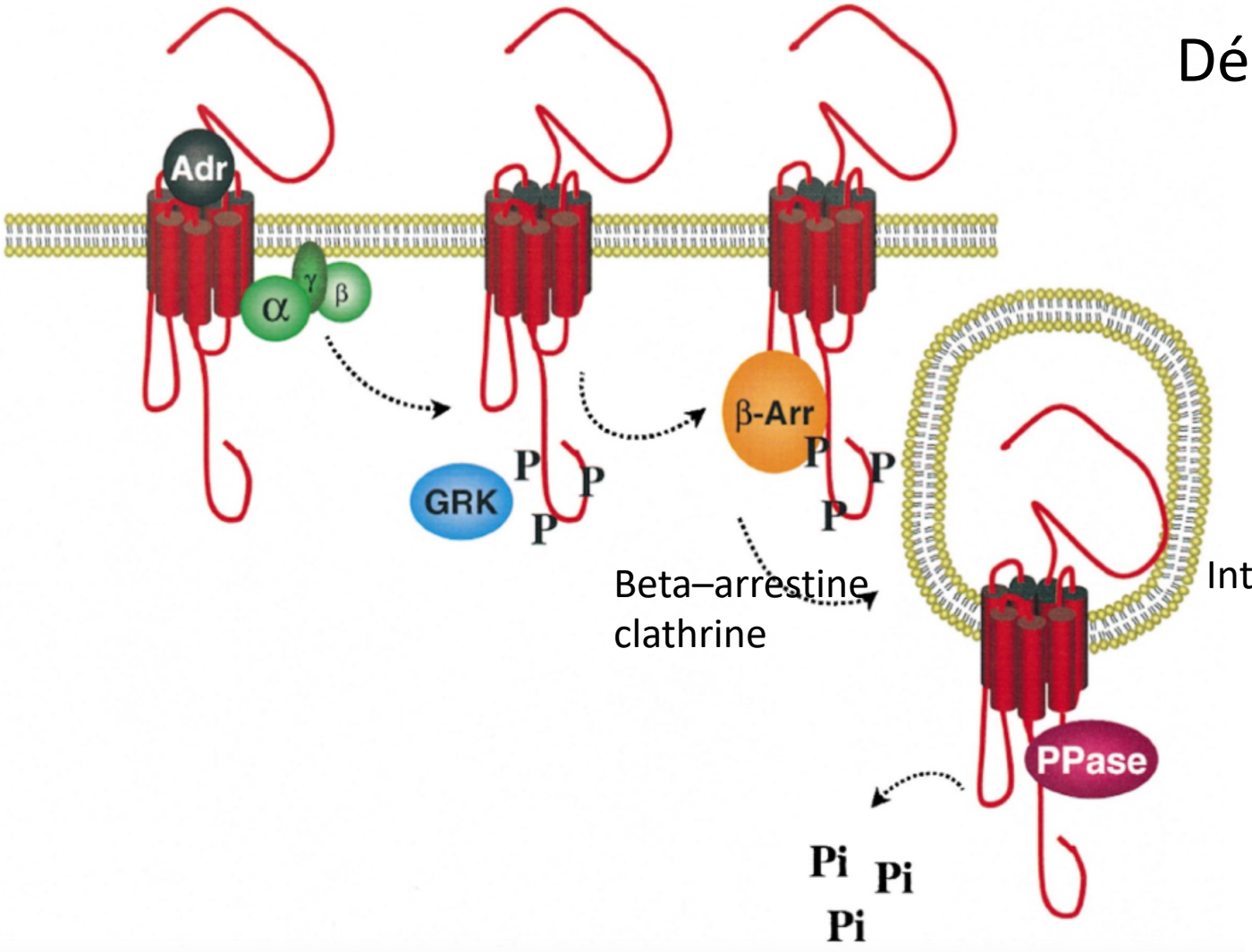


FIGURE 1. Flow chart representing patient selection process and diagnostic categories. HDV = high-dose vasopressor therapy.

Alternative aux catécholamines

- Choc réfractaire

Choc réfractaire: désensibilisation des récepteurs



Désensibilisation homologue

Circulation (*Circulation*. 2003;107:2313-2319.)

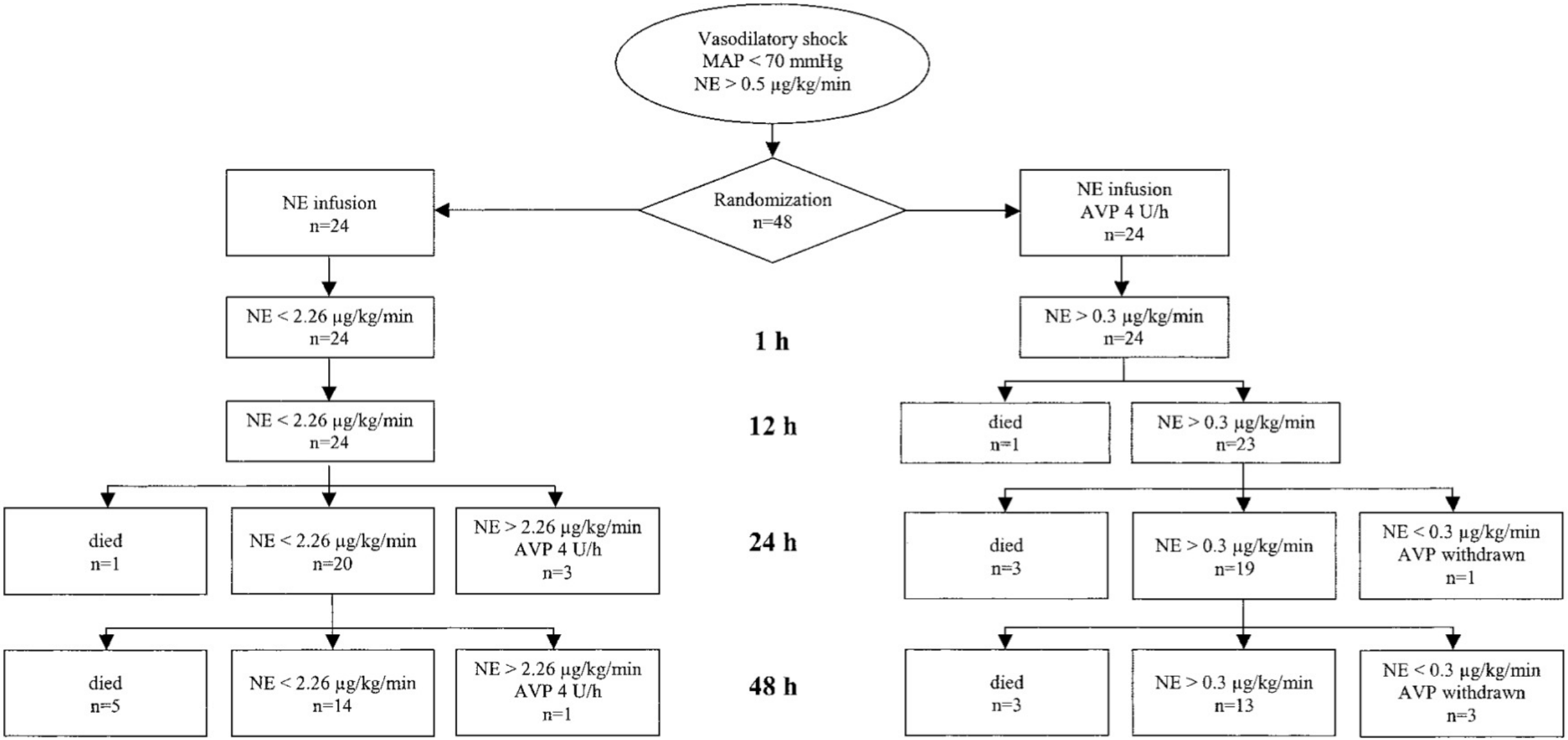
Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

Martin W. Dünser, MD; Andreas J. Mayr, MD; Hanno Ulmer, PhD; Hans Knotzer, MD; Günther Sumann, MD; Werner Pajk, MD; Barbara Friesenecker, MD; Walter R. Hasibeder, MD

Post cardiotomie (40%)
SIRS (30%)
Choc septique (30%)
NA>0,5 ug/kg/min
Swann-Ganz

Choc vasoplégique résistant aux catécholamines



Overview of patient enrollment and study design.

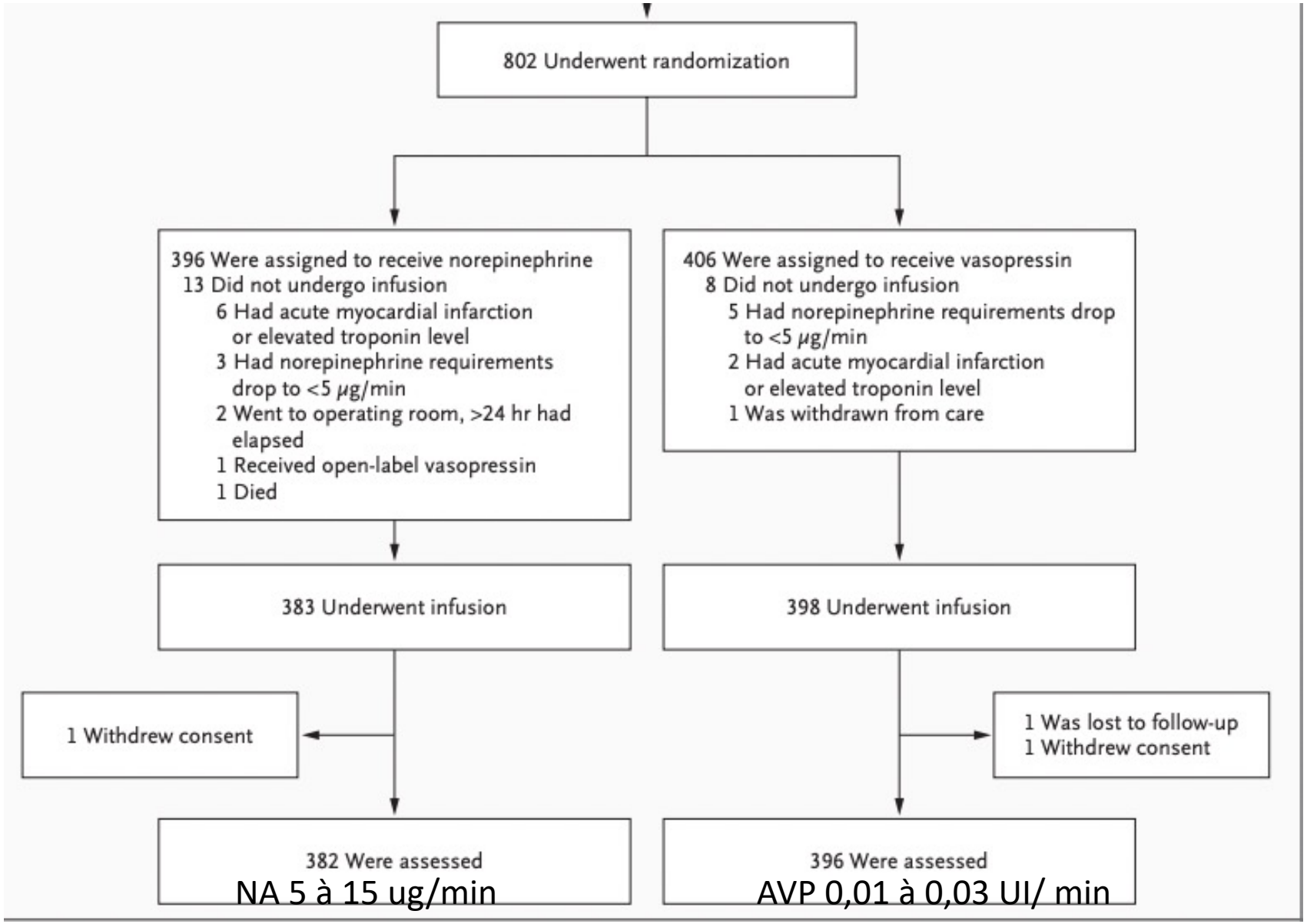
	0 Hours (n=48)	1 Hour (n=48)	12 Hours (n=47)	24 Hours (n=39)	48 Hours (n=27)	*P*
HR, bpm						
AVP group†§	115±17	103±16‡	99±16‡	99±15‡	93±15‡	0.003*
NE group	103±20	102±15	103±15	108±20	98±19	
MAP, mm Hg						
AVP group†	63±7	82±10‡	78±9‡	76±9‡	81±8‡	<0.001*
NE group	67±8	71±12	67±9	66±11	75±12	
CI, $L \cdot min^{-1} \cdot m^{-2}$						
AVP group	4.1±1.4	3.7±1.2	4.3±1.7	4.1±1.1	4.1±1	0.001*
NE group	3.5±1	3.5±1.2	3.4±1.1	3.3±1	3.6±1.2	
SVI, $mL \cdot beat^{-1} \cdot m^{-2}$						
AVP group	36±12	35±11	42±14	41±14	44±15	0.005*
NE group	36±12	34±11	34±10	32±12	36±10	
LVSWI, $gxm \cdot m^{-2} \cdot beat^{-1}$						
AVP group†	23±10	31±13‡	35±14‡	34±14‡	39±16‡	<0.001*
NE group	24±10	26±11	24±11	24±10	30±12	
$Prco_2$, mm Hg						
AVP group	53±18	55±15	60±21	63±25		0.03*
NE group†	54±17	64±23‡	71±20‡	67±24‡		
$Pr\text{-}aco_2$, mm Hg						
AVP group	9±15	11±12	17±17	20±24		0.014*
NE group	12±17	21±25	26±21	21±24		

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2008 VOL. 358 NO. 9

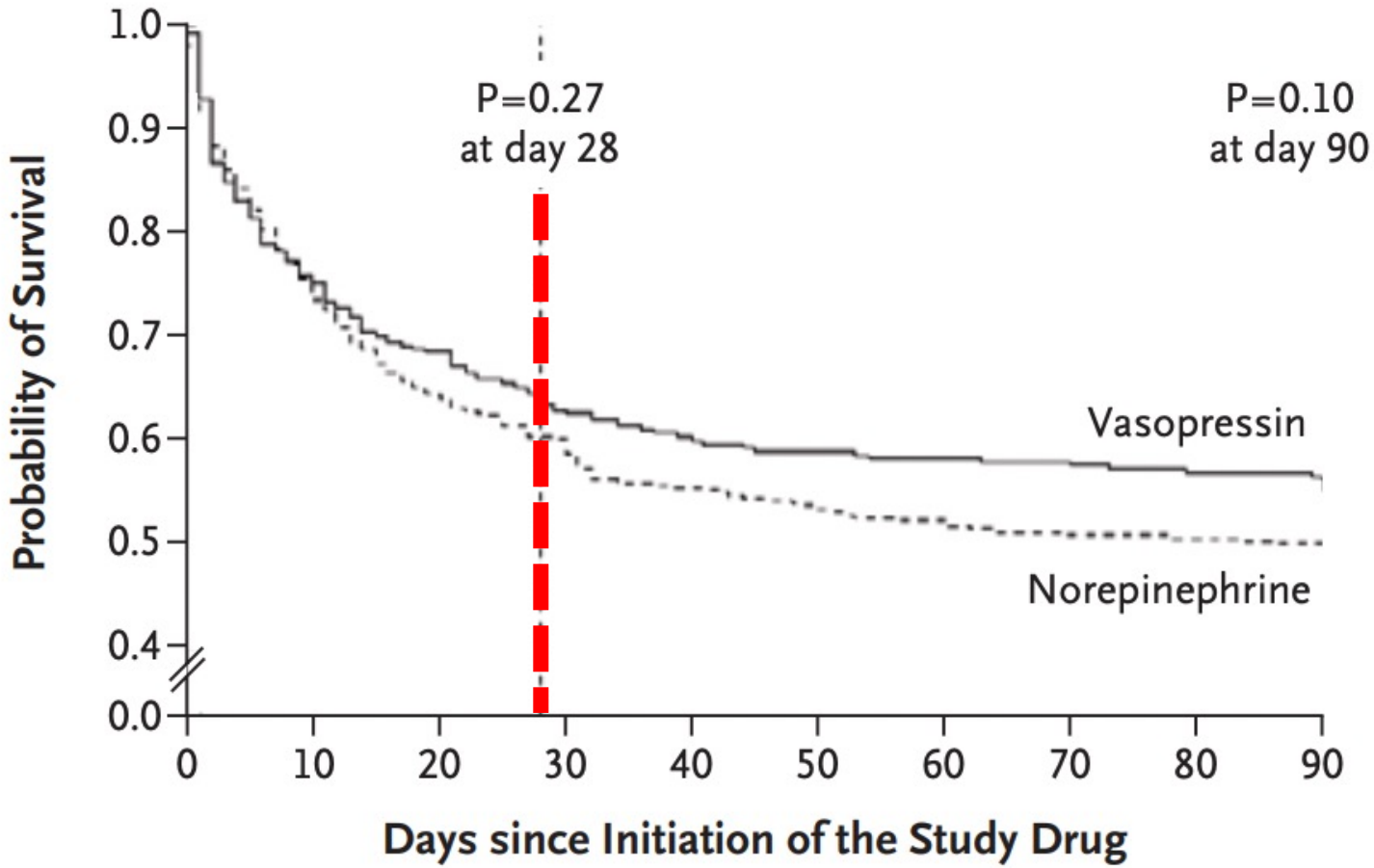
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

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*



27 centres
Canada
Australie
US

Choc septique sous NA



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

- Petites doses (max 0,03UI/min)
- Début tardif

Time from meeting inclusion criteria to study-drug infusion — hr	11.5±9.4	11.9±8.9	0.57

Intensive Care Med (2010) 36:83–91
DOI 10.1007/s00134-009-1687-x

ORIGINAL

Anthony C. Gordon
James A. Russell
Keith R. Walley
Joel Singer

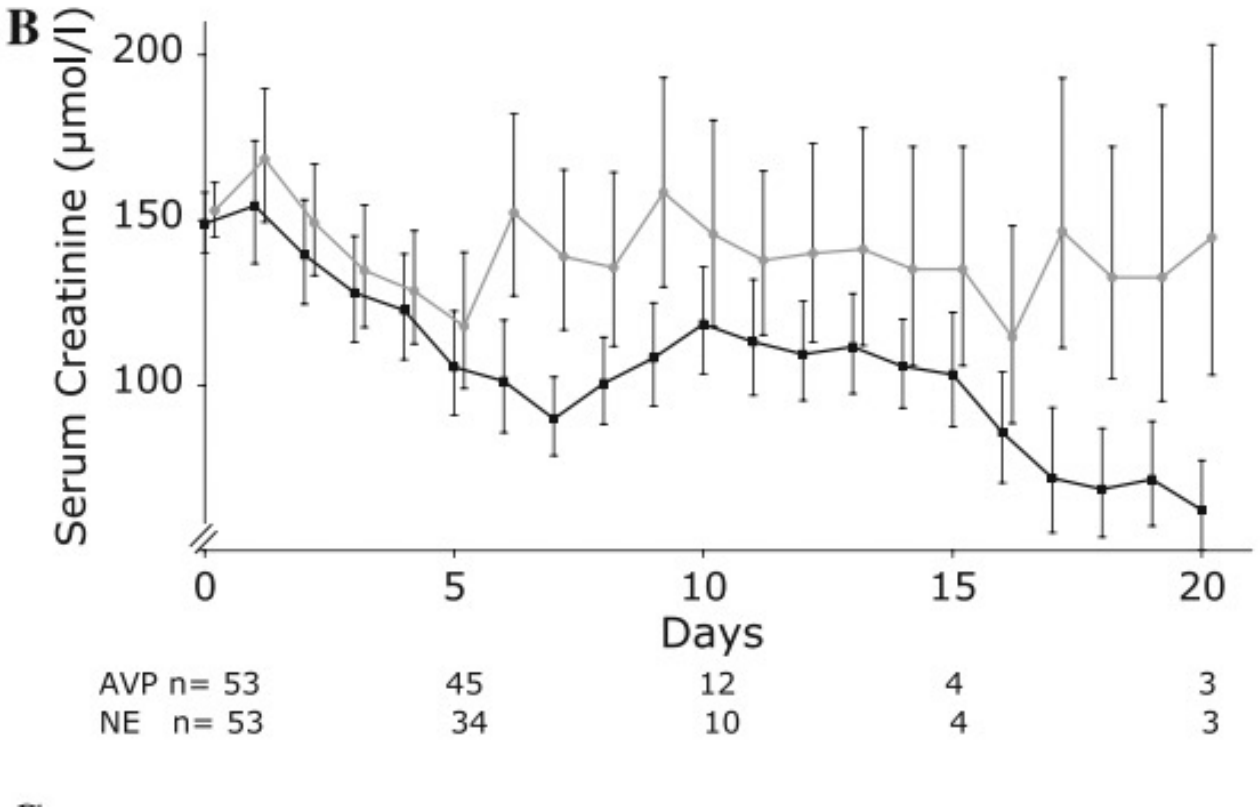
The effects of vasopressin on acute kidney injury in septic shock

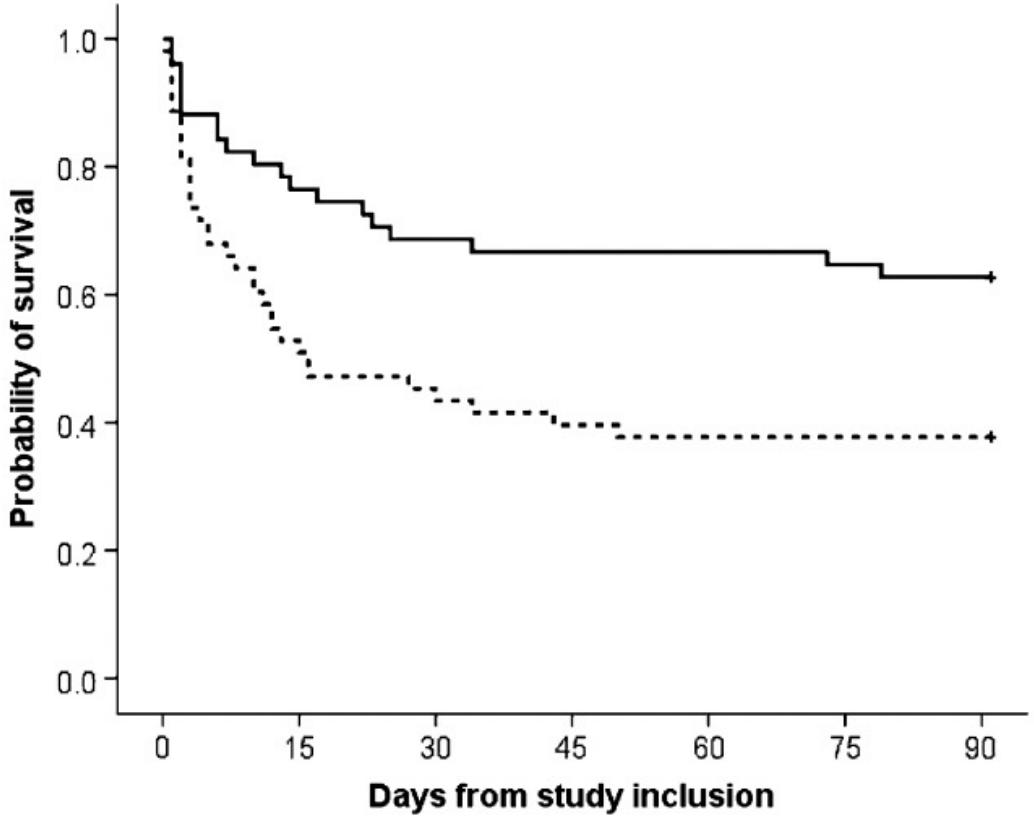
Etude post hoc VASST

Table 1 RIFLE criteria definitions used in this study

	Serum creatinine change criteria
Risk	Increased serum creatinine ×1.5
Injury	Increased serum creatinine ×2
Failure	Increased serum creatinine ×3 or Increased serum creatinine ≥44 μmol/l if baseline ≥350 μmol/l
Loss	Persistent acute renal failure = complete loss of renal function for >4 weeks
End stage	End-stage kidney disease (>3 months)

Catégorie « RISK »





Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock*

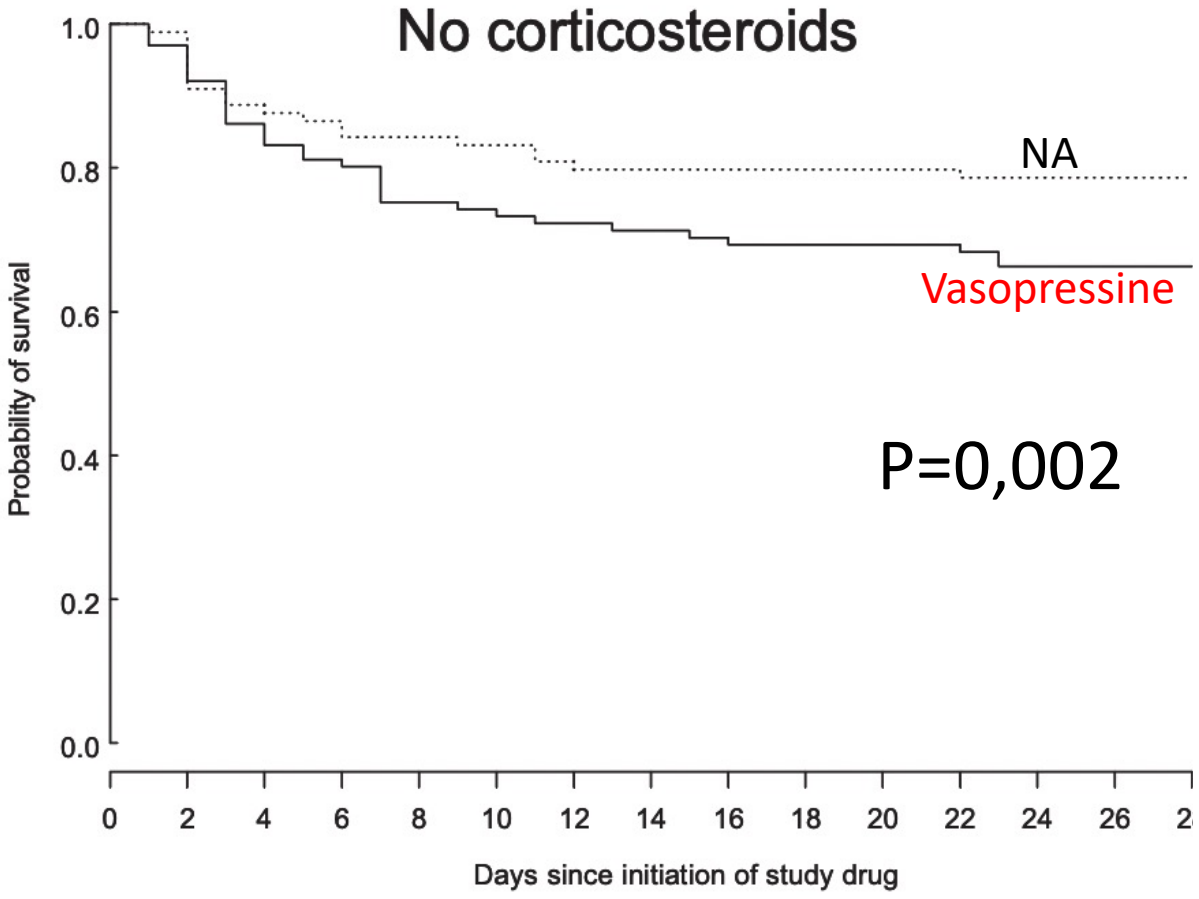
Crit Care Med 2009 Vol. 37, No. 3

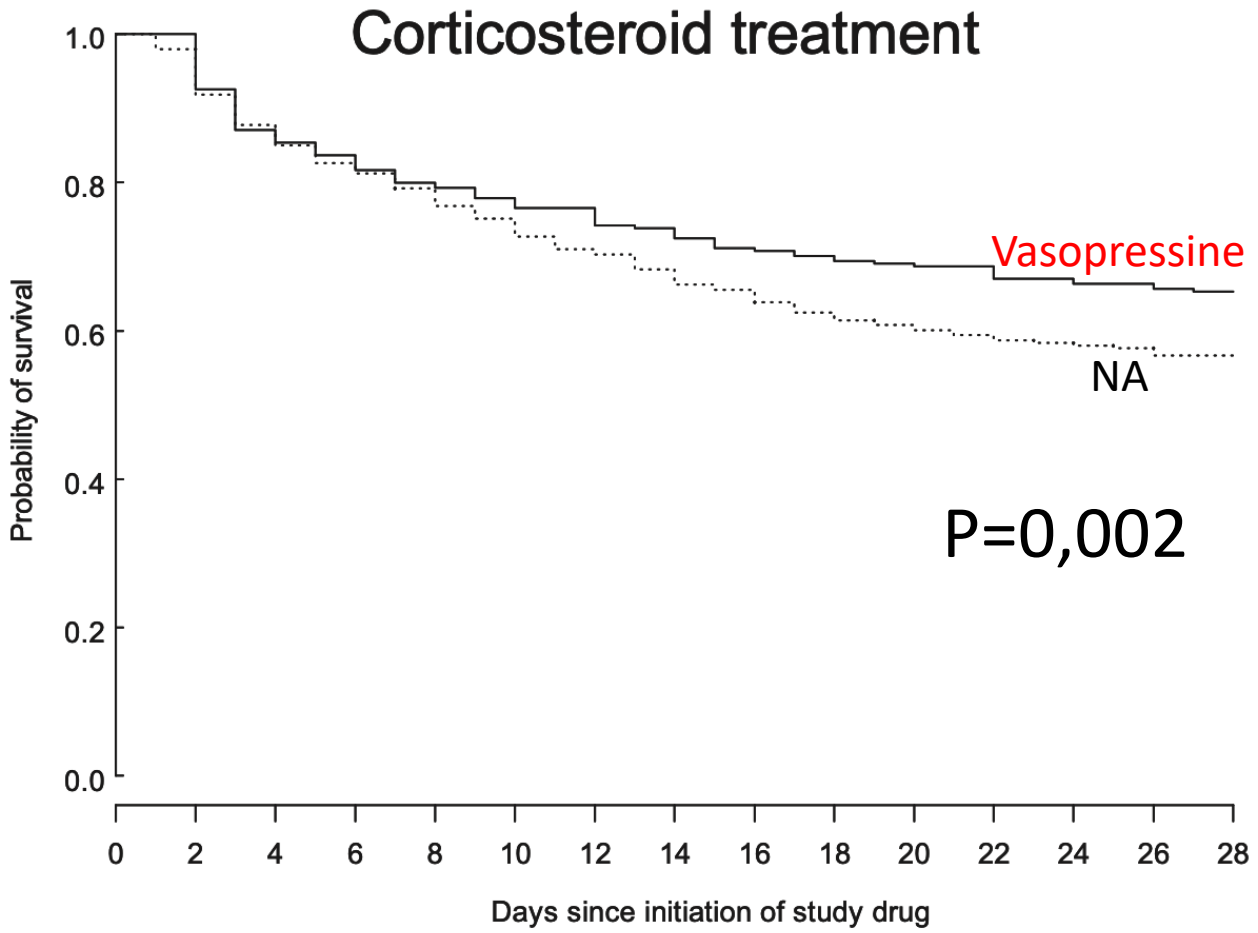
James A. Russell, MD; Keith R. Walley, MD; Anthony C. Gordon, MB, BS, MD; D. James Cooper, BM, BS, MD; Paul C. Hébert, MD; Joel Singer, PhD, MD; Cheryl L. Holmes, MD; Sangeeta Mehta, MD; John T. Granton, MD; Michelle M. Storms, BScN; Deborah J. Cook, MD; Jeffrey J. Presneill, MB BS, PhD; Dieter Ayers for the Vasopressin and Septic Shock Trial (VASST) Investigators

Post hoc VASST

	Steroids			No Steroids		
n	Norepinephrine 293	Arginine Vasopressin 296	*p* Value[a]	Norepinephrine 89	Arginine Vasopressin 101	*p* Value[b]
Age (yrs.) (x ± SD)	61.4 ± 15.7	59.0 ± 16.2	0.06	63.1 ± 16.6	60.4 ± 17.2	0.28
Sex (n, % male)	176 (60.1)	183 (61.8)	0.66	53 (59.6)	63 (62.4)	0.69
Acute Physiology and Chronic Health Evaluation II (x ± SD)	27.9 ± 6.7	27.4 ± 7.2	0.41	24.7 ± 6.9	26.0 ± 8.9	0.28
Renal (n, %)	203 (69.5)	205 (69.3)	0.95	55 (62.5)	59 (58.4)	0.57
Respiratory (n, %)	264 (90.1)	261 (88.2)	0.45	77 (87.5)	81 (80.2)	0.18
Hematologic (n, %)	70 (24.0)	91 (30.7)	0.07	14 (15.9)	27 (26.7)	0.07
Neurologic (n, %)	67 (22.9)	78 (26.4)	0.33	22 (25)	23 (22.8)	0.72
Surgical (n, %)	94 (34.4)	105 (37.1)	0.51	38 (47.5)	46 (49.5)	0.78
Less severe shock (n, %)	126 (43.0)	131 (44.3)	0.76	56 (62.9)	65 (64.4)	0.84
More severe shock (n, %)	167 (57.0)	165 (55.7)		33 (37.1)	36 (35.6)	
Activated protein C (n, %)	53 (18.1)	52 (17.6)	0.87	3 (3.4)	9 (8.9)	0.12

[a]Statistical test (χ^2 or *t* test) comparing steroids plus norepinephrine vs. steroids plus vasopressin (Arginine vasopressin); [b]Statistical test (χ^2or *t* test) comparing no steroids plus norepinephrine vs. no steroids plus vasopressin (Arginine vasopressin).


No corticosteroids
1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
NA
Vasopressine
P=0,002
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Days since initiation of study drug


Corticosteroid treatment
1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
Vasopressine
NA
P=0,002
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Days since initiation of study drug

JAMA | Original Investigation *JAMA*. 2016;316(5):509-518.

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock
The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

18 Hôpitaux UK

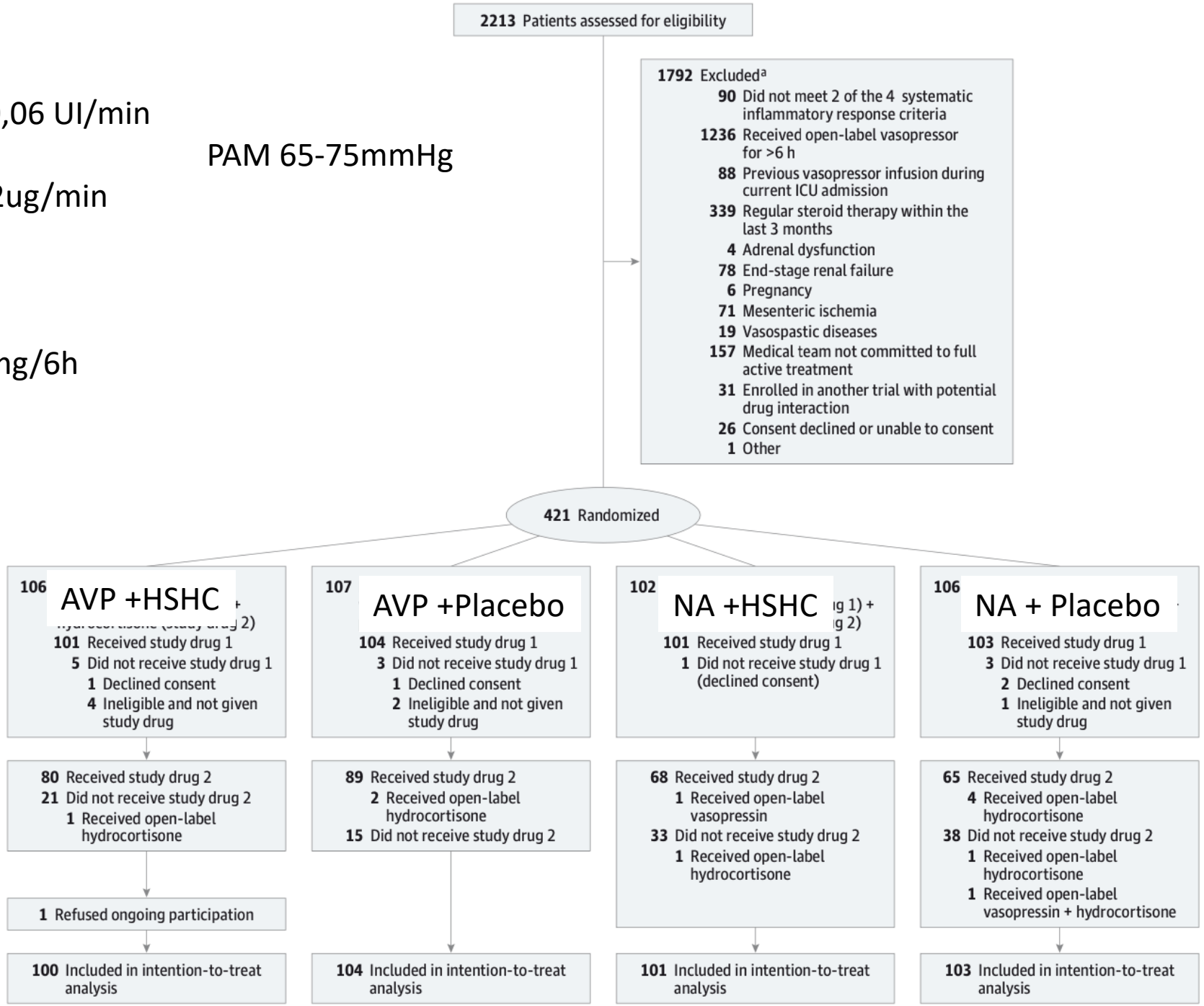
AVP max 0,06 UI/min
ou
NA max 12ug/min

PAM 65-75mmHg

Choc septique

puis

HSHC 50 mg/6h
Ou
Placebo



	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute Difference (95% CI)[b]
	Hydrocortisone[a]	Placebo	Total[a]	Hydrocortisone	Placebo	Total	
28-d Survivors who never developed kidney failure, No./total (%)[c]	46/81 (56.8)	48/84 (57.1)	94/165 (57.0)	46/77 (59.7)	47/80 (58.8)	93/157 (59.2)	−2.3 (−13.0 to 8.5)[d]
Kidney failure-free days in other patients, median (IQR), d[e]	5 (0-23)	12 (1-25)	9 (1-24)	13 (0-25)	14 (1-24)	13 (1-25)	−4 (−11 to 5)[d]
28-d Mortality, No./total (%)	33/100 (33.0)	30/104 (28.8)	63/204 (30.9)	29/101 (28.7)	27/103 (26.2)	56/204 (27.5)	3.4 (−5.4 to 12.3)
ICU mortality, No./total (%)	32/100 (32.0)	26/104 (25.0)	58/204 (28.4)	24/101 (23.8)	27/103 (26.2)	51/204 (25.0)	3.4 (−5.2 to 12.0)
Hospital mortality, No./total (%)	35/100 (35.0)	33/104 (31.7)	68/204 (33.3)	31/101 (30.7)	29/103 (28.2)	60/204 (29.4)	3.9 (−5.1 to 12.9)
Kidney failure, No./total (%)	41/101 (40.6)	46/104 (44.2)	87/205 (42.4)	46/101 (45.5)	51/103 (49.5)	97/204 (47.5)	−5.1 (−15.2 to 5.0)
Survivors	21/67 (31.3)	26/74 (35.1)	47/141 (33.3)	26/72 (36.1)	29/76 (38.2)	55/148 (37.2)	−3.8 (−15.5 to 7.9)
Nonsurvivors	20/33 (60.6)	20/30 (66.7)	40/63 (63.5)	20/29 (69)	22/27 (81.5)	42/56 (75)	−11.5 (−29.6 to 6.6)

Choc septique

- Pas d’intérêt clairement démontré de remplacer la NA par l’AVP ou de rajouter de l’AVP à la NA
- sur le pronostic du choc septique

HAS
HAUTE AUTORITÉ DE SANTÉ

REANIMATION
Nouveau médicament
Février 2019

AMM 31 mai 2018

SYNTHESE D'AVIS DE LA COMMISSION DE LA TRANSPARENCE

REVERPLEG (argipressine), analogue de la vasopressine

Hypotension réfractaire consécutive à un choc septique

Intérêt clinique insuffisant pour justifier son remboursement dans le traitement de l'hypotension réfractaire aux catécholamines consécutive à un choc septique

40 IU /2ml dans 48 ml
0,8 UI/ml

L'essentiel

- REVERPLEG a l'AMM dans le traitement de l'hypotension réfractaire aux catécholamines consécutive à un choc septique chez les patients âgés de plus de 18 ans.
- Son efficacité hémodynamique a été démontrée sur le maintien la pression artérielle moyenne (PAM) cible, avec une réduction des doses de noradrénaline, chez des patients ayant un choc septique déjà stabilisé (hors-AMM). Il n'existe pas de donnée de bon niveau de preuve démontrant une efficacité en termes de réduction de la morbi-mortalité chez des patients atteints d'hypotension artérielle du choc septique réfractaire aux catécholamines.
- Son impact sur la morbi-mortalité n'est pas démontré.
- L'intérêt clinique de diminuer les doses de noradrénaline en ajoutant un autre vasopresseur, sans avantage supplémentaire démontré en termes d'efficacité et/ou de tolérance n'est pas établi.
- Il persiste des incertitudes sur les posologies de REVERPLEG qui seront utilisées en conditions réelles d'utilisation dans le choc septique et sur le risque de toxicité associé.

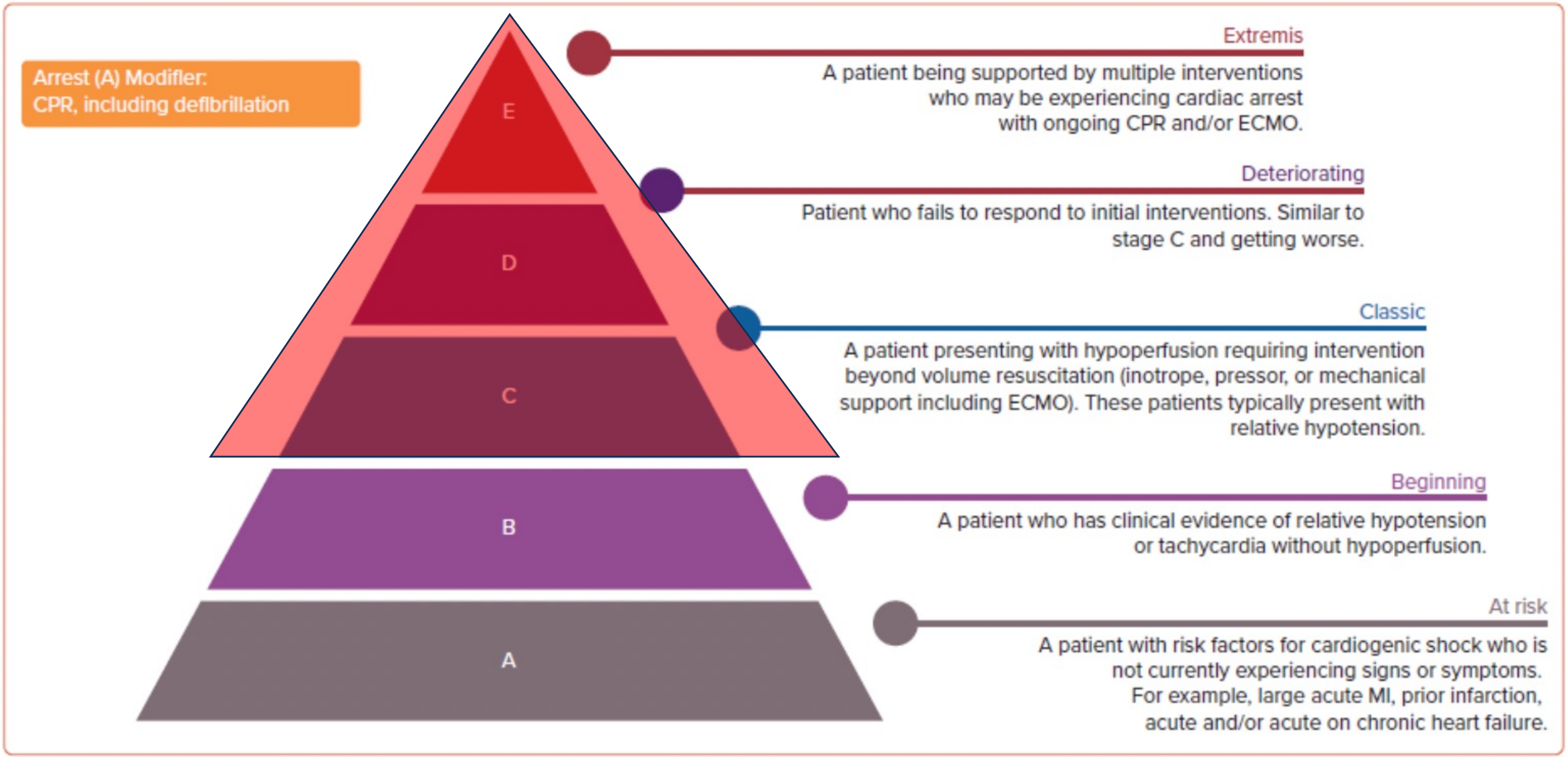
0,01 UI/min (0,6 UI/h)
à 0,03 UI /min (1,8 UI/h)

Conseil d'État, 1ère - 4ème chambres réunies, 17/03/2021, 435139,

DECIDE :

Article 1er : La requête de la société Amomed Pharma et de la société Centre spécialités pharmaceutique est rejetée.

Figure 1: The SCAI Shock Pyramid and the Stages of Shock 2021



CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; SCAI = Society for Cardiovascular Angiography and Interventions. Source: Baran et al.[19] Reproduced with permission from the Society for Cardiovascular Angiography and Interventions.

ANESTHESIOLOGY
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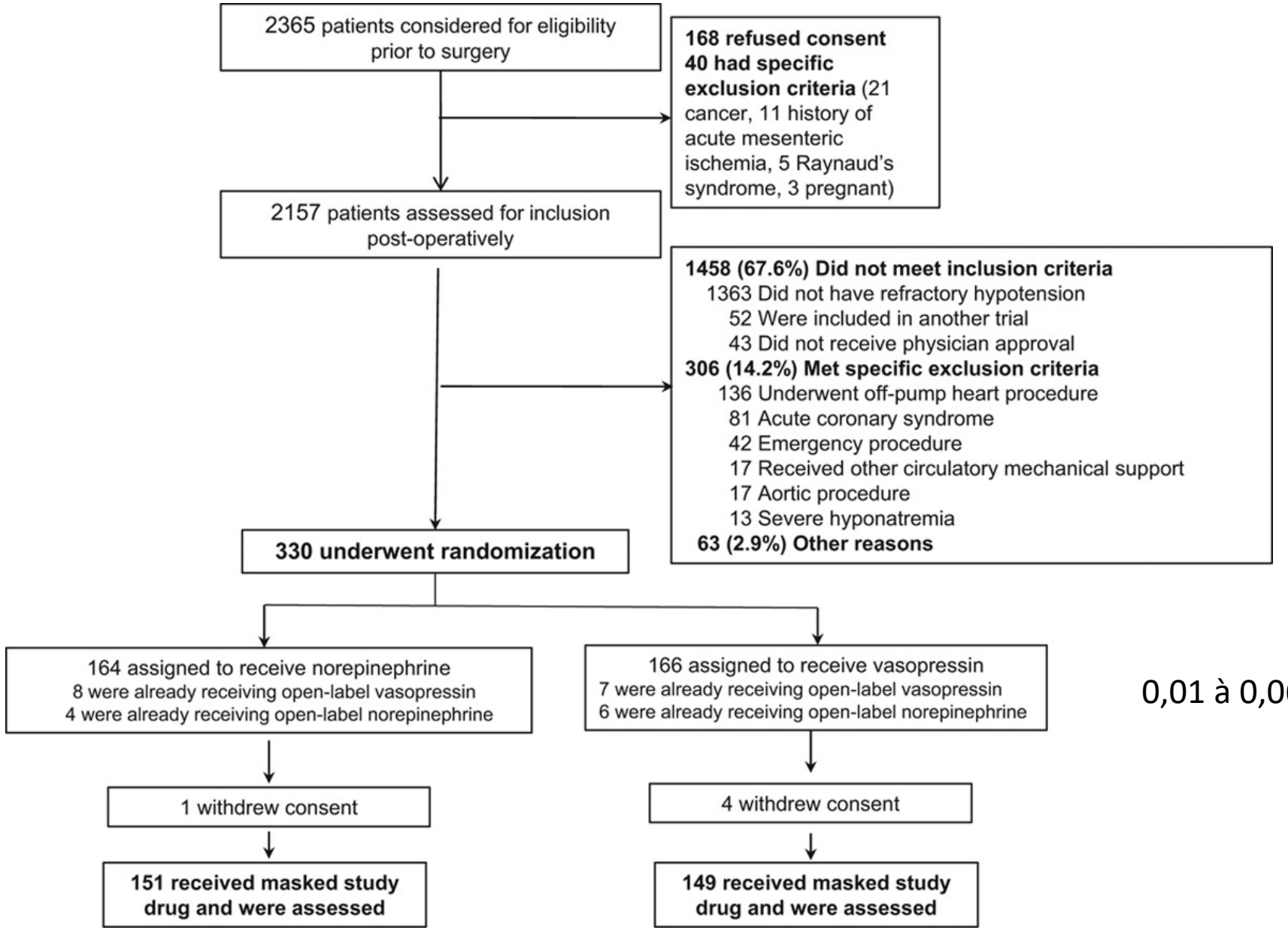
Critical Care Medicine | January 2017

Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial

Ludhmila Abrahao Hajjar, M.D., Ph.D. ; Jean Louis Vincent, M.D., Ph.D.; Filomena Regina Barbosa Gomes Galas, M.D., Ph.D.; Andrew Rhodes, M.D., Ph.D.; Giovanni Landoni, M.D.; Eduardo Atsushi Osawa, M.D., Ph.D.; Renato Rosa Melo, M.D.; Marcia Rodrigues Sundin, M.D.; Solimar Miranda Grande, M.D.; Fabio A. Gaiotto, M.D., Ph.D.; ... Show more

Choc vasoplégique post cardiotomie (CABG ou valve)
PAM<65 mmHg malgré remplissage
CI>2,2 l/min/m2

End-point composite:
Mortalité à 30 jours + complications majeurs



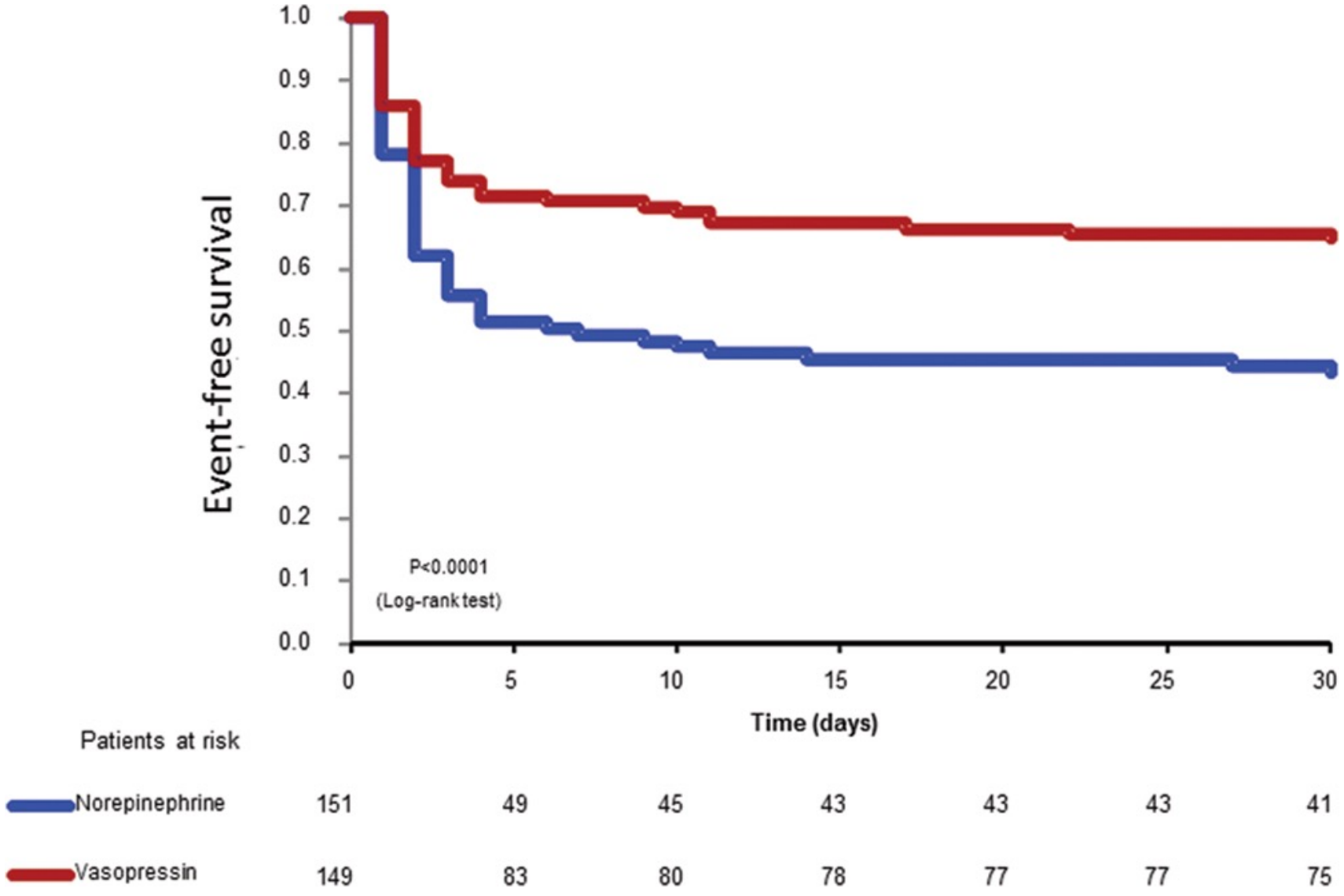
10 à 60 ug/min

0,01 à 0,06 UI/min

Variable	Norepinephrine (n=151)	Vasopressin (n=149)	*P* value†	
Adrénaline	44 (29.1%)	39 (26.2%)	peropératoire	
Dobutamine	55 (36.4%)	51 (34.2%)		
Length of dobutamine infusion (h). median (IQR)	54 (33 - 89)	40 (26 - 68)	0.01	*
MAP, median (IQR)				
Before drug infusion	55 (50 - 60)	58 (49 - 60)	0.90	*
15 min	63 (60 - 67)	65 (62 - 70)	0.028	*
30 min	68 (65 - 70)	69 (66 - 73)	0.25	*
60 min	70 (68 - 75)	72 (69 - 75)	0.06	*
12 h	73 (70 - 77)	74 (70 - 77)	0.08	*
Cardiac index, median (IQR)				
Before drug infusion	2·8 (2.6 - 3.0)	2.9 (2·6 - 3)	0.71	*
15 min	2·8 (2.6 - 3.0)	2.8 (2·6 - 3)	0.98	*
30 min	2·8 (2.5 - 3.0)	2.8 (2·6 - 3)	0.71	*
60 min	2·7 (2.6 - 3.0)	2.7 (2·6 - 2·9)	0.91	*
12 h	2·7 (2.5 - 2.9)	2.7 (2·5 - 2·8)	0.99	*
24 h	2·7 (2.5 - 2.9)	2.7 (2·5 - 2·9)	0.94	*

- **60 % des patients avec I+**
- **Durée médiane >24h**

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)	Unadjusted Odds Ratio or Hazard Ratio or Between-group Difference (95% CI)	*P* Value	Adjusted* Odds Ratio or Hazard Ratio or Between-group Difference (95%CI)	*P* Value
Primary outcome, n (%)	74 (49.0)	48 (32.2)	0.55 (0.38 to 0.80)	0.0014	0.52 (0.36 to 0.75)	0.0005
30-d mortality	24 (15.9)	23 (15.4)	0.99 (0.56 to 1.76)	0.98	1.11 (0.62 to 1.96)	0.73
MV > 48 h	13 (8.6)	8 (5.4)	0.62 (0.26 to 1.49)	0.28	0.62 (0.26 to 1.51)	0.30
Sternal wound infection	15 (9.9)	7 (4.7)	0.46 (0.19 to 1.13)	0.09	0.48 (0.19 to 1.18)	0.11
Reoperation	10 (6.6)	10 (6.7)	0.8 (0.52 to 1.23)	0.31	0.79 (0.51 to 1.22)	0.28
Stroke	4 (2.6)	4 (2.7)	1.03 (0.26 to 4.11)	0.97	1.08 (0.27 to 4.39)	0.91
Acute renal failure	54 (35.8)	15 (10.3)	0.26 (0.15 to 0.46)	< 0.0001	0.26 (0.15 to 0.46)	< 0.0001
Secondary outcomes, n (%)						
Infection	23 (15.2)	16 (10.7)	0.67 (0.34 to 1.33)	0.25	0.71 (0.35 to 1.42)	0.33
Septic shock	13 (8.6)	9 (6.0)	0.68 (0.28 to 1.65)	0.40	0.73 (0.3 to 1.81)	0.50
Atrial fibrillation	124 (82.1)	95 (63.8)	0.38 (0.22 to 0.65)	0.0004	0.37 (0.22 to 0.64)	0.0004
Ventricular arrhythmias	32 (21.2)	27 (18.1)	0.82 (0.46 to 1.46)	0.50	0.8 (0.45 to 1.43)	0.45
Length of ICU stay (d), median (IQR)	6 (4 to 9)	5 (4 to 7)	−2.42 (−4.11 to −0.73)	0.0050	−2.28 (−3.94 to −0.62)	0.0071
Length of hospital stay (d), median (IQR)	13 (10 to 20)	10 (8 to 12)	−3.76 (−6.1 to −1.42)	0.0016	−3.66 (−6.01 to −1.32)	0.0022


Event-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P<0.0001
(Log-rank test)
0
5
10
15
20
25
30
Time (days)
Patients at risk
Norepinephrine 151 49 45 43 43 43 41
Vasopressin 149 83 80 78 77 77 75

Nguyen *et al. Critical Care* (2023) 27:291
https://doi.org/10.1186/s13054-023-04574-8

Critical Care

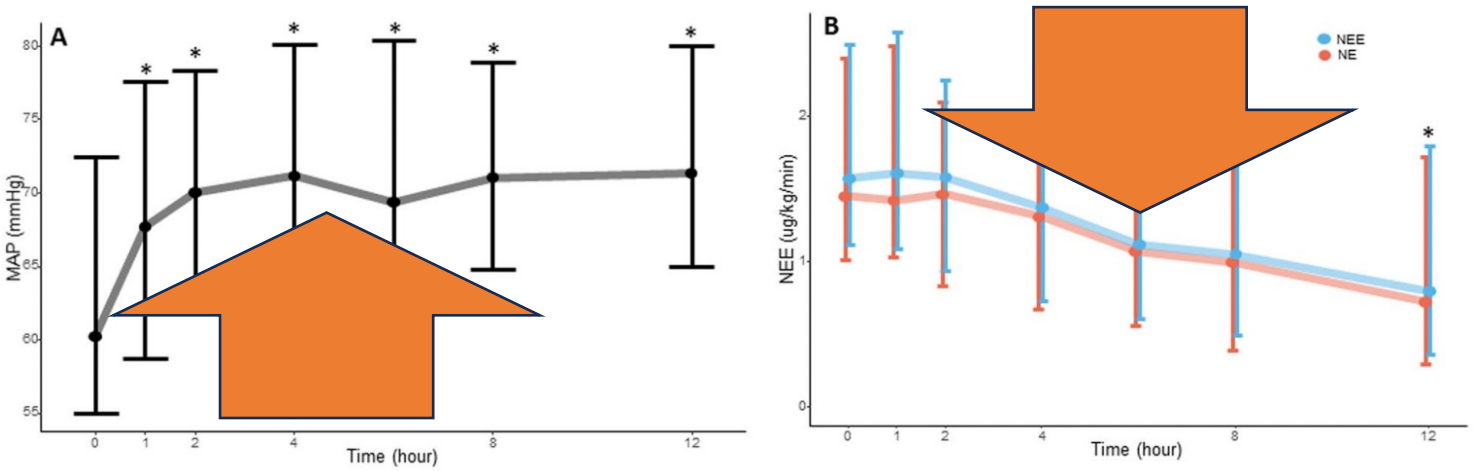
CORRESPONDENCE Open Access

Real life use of vasopressin in patients with cardiogenic shock: a retrospective cohort analysis

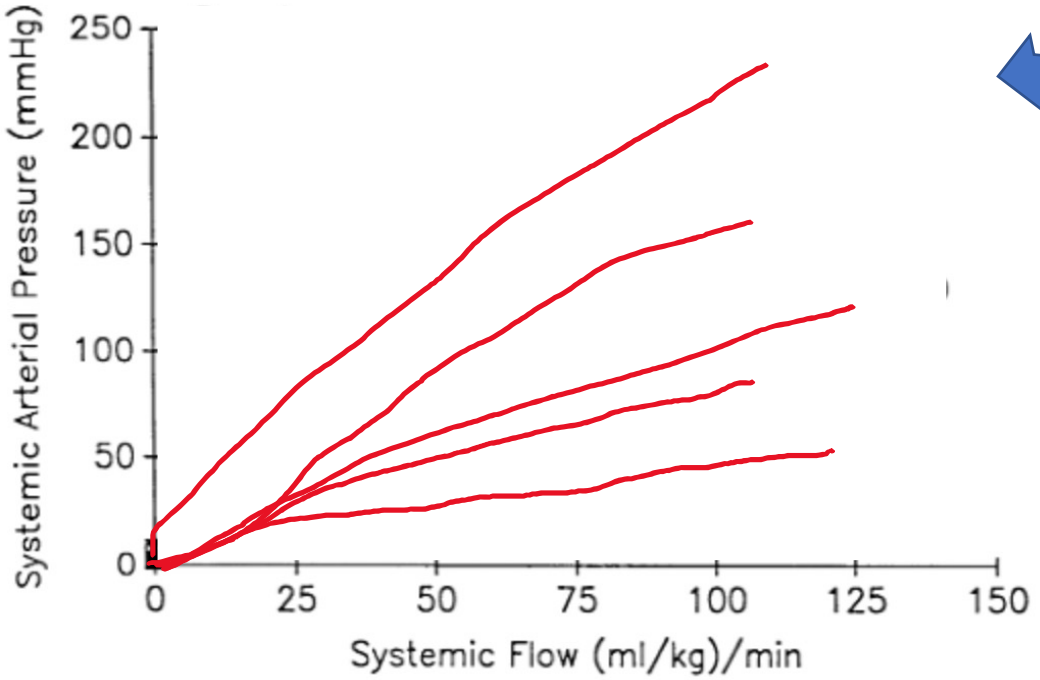
Maxime Nguyen[1,2,3,4*], Vivien Berthoud[1], Alexis Rizk[1], Bélaïd Bouhemad[1,2,3,4] and Pierre-Grégoire Guinot[1,2,3,4]

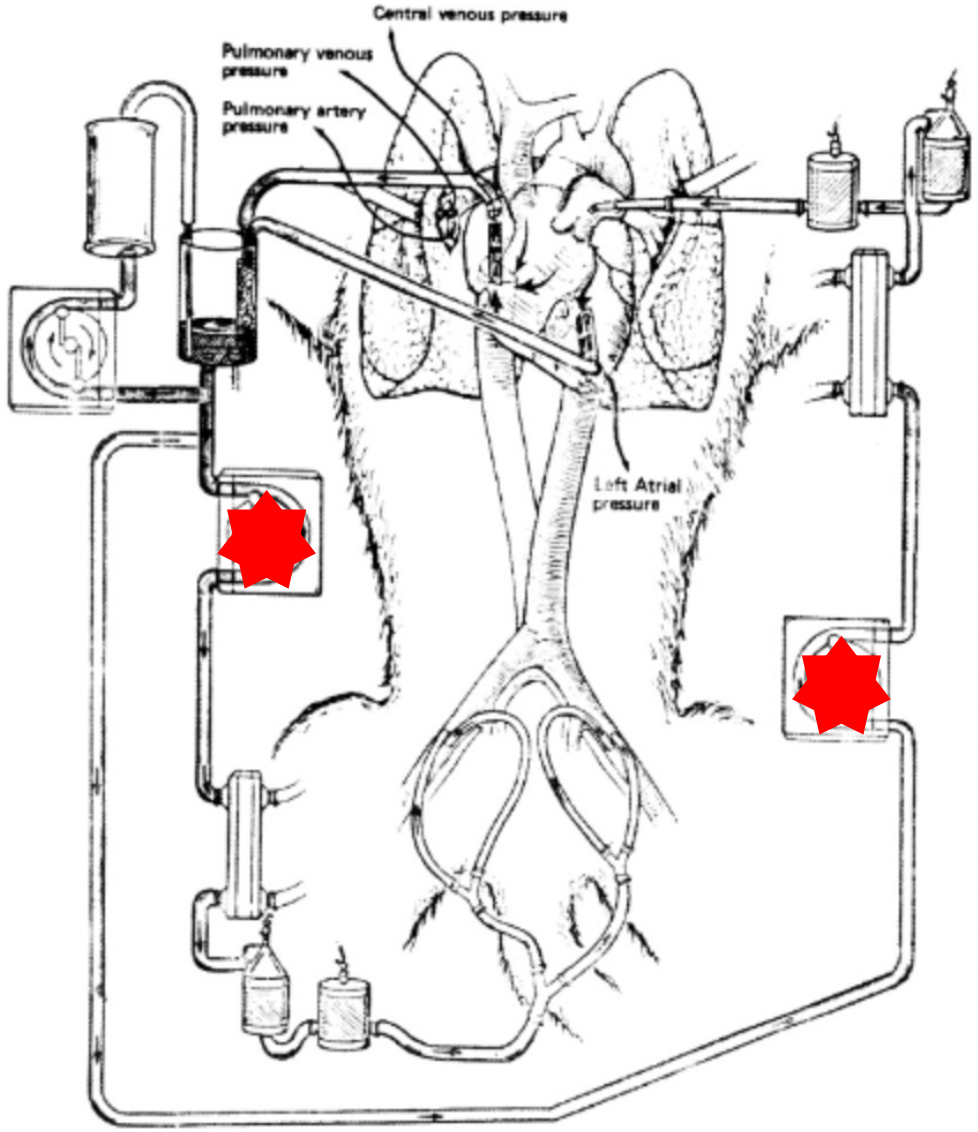
Choc cardiogénique avec vasoplégie réfractaire

Adjonction systémique d'AVP à la NA

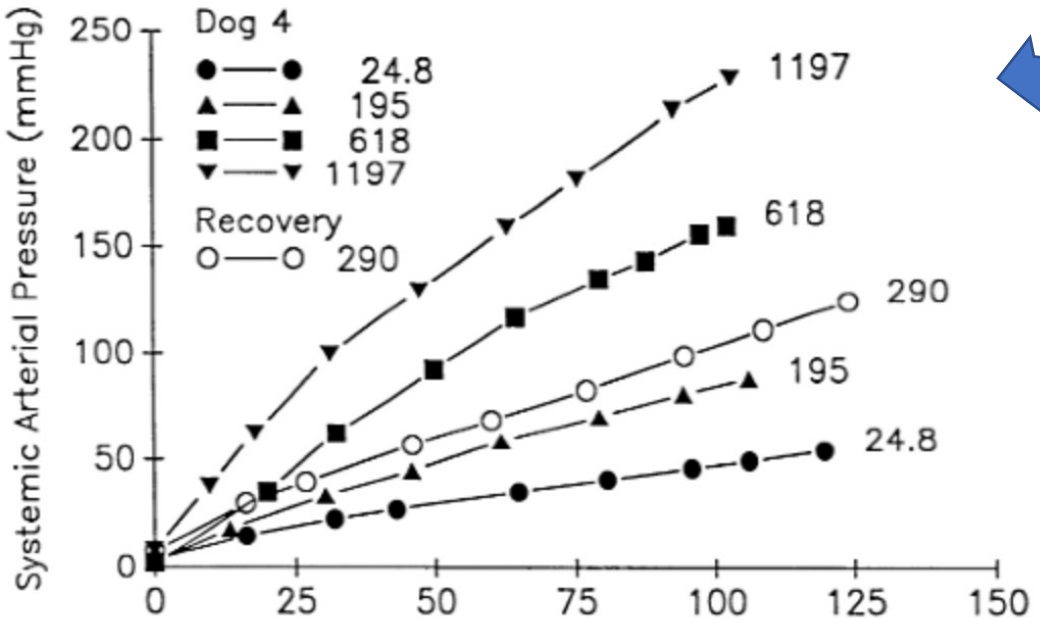


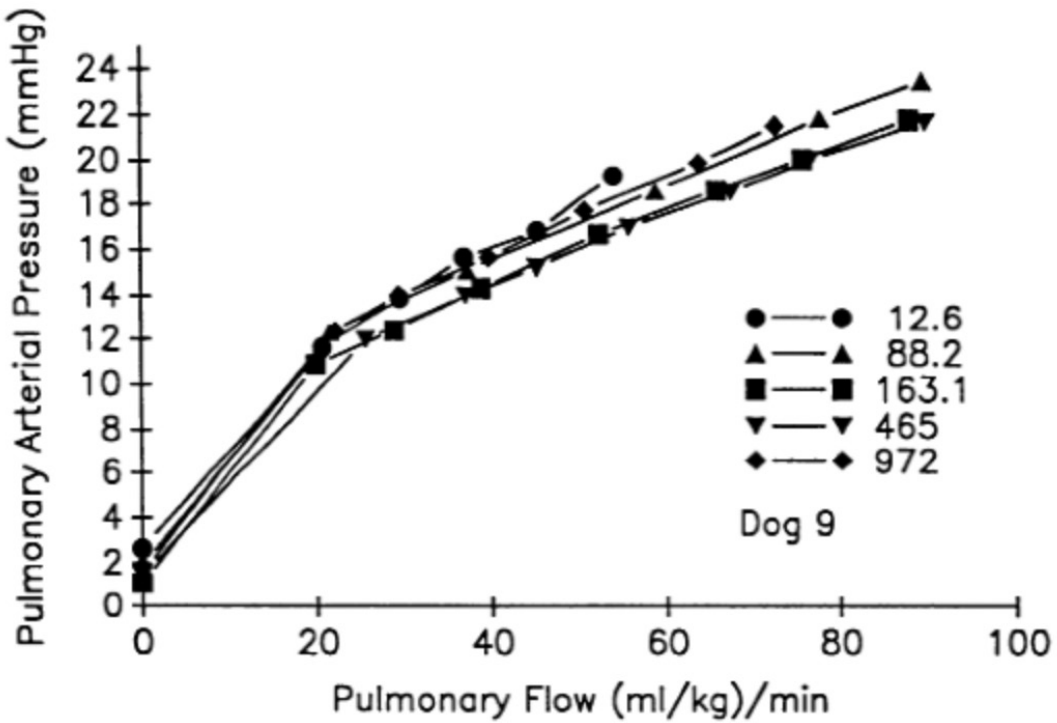
Autre intérêt hémodynamique?

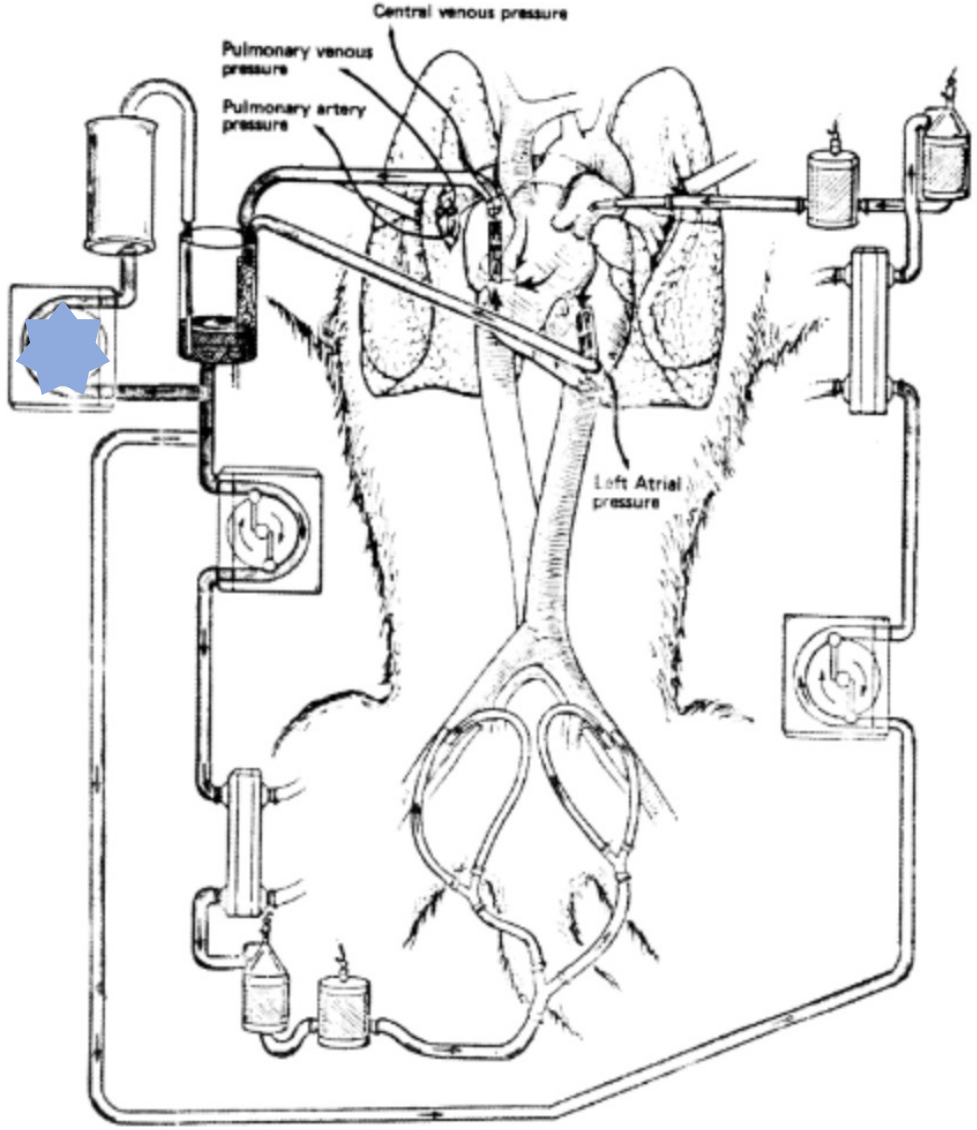




Wallace AW, Am J Physiol 1989

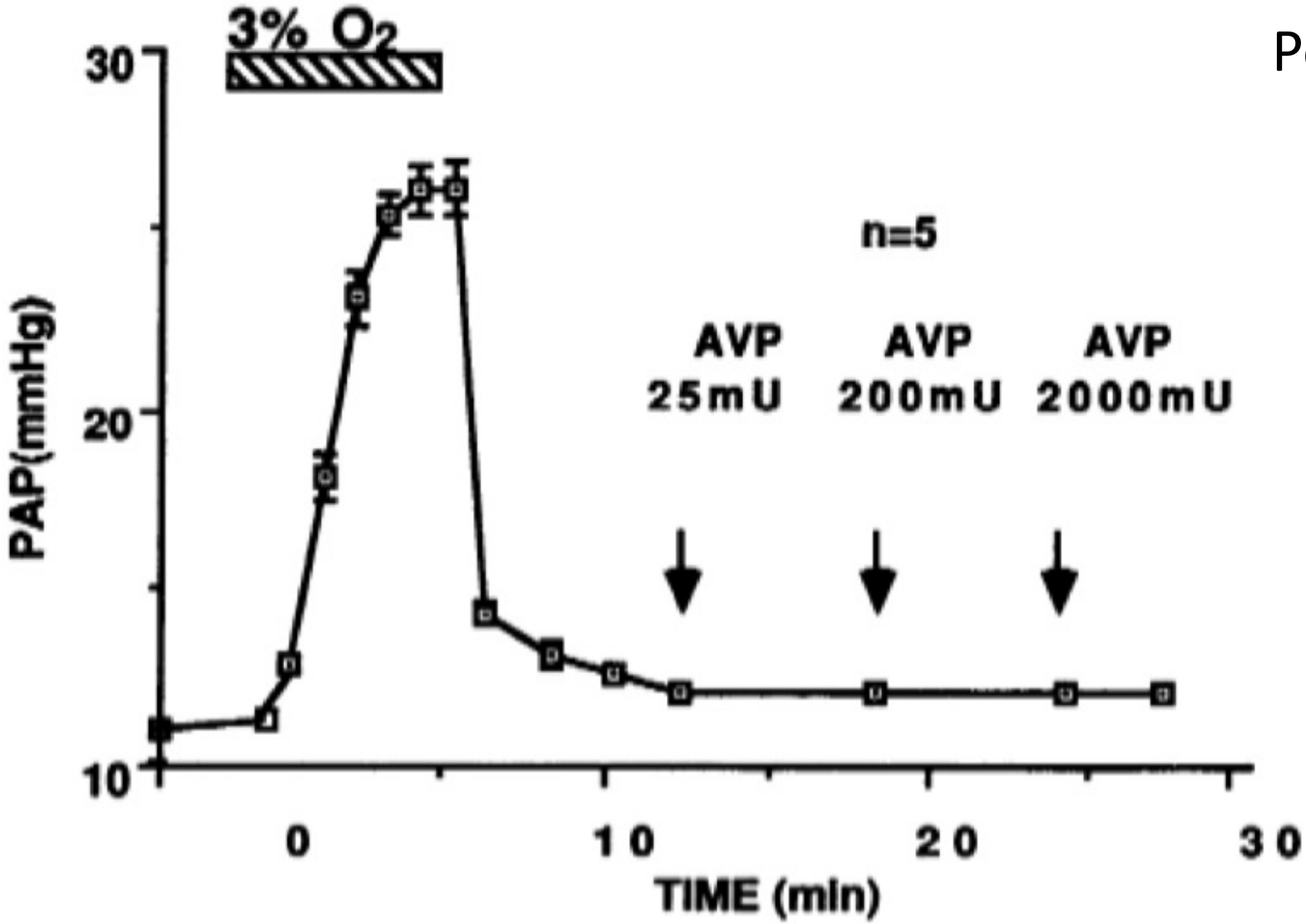




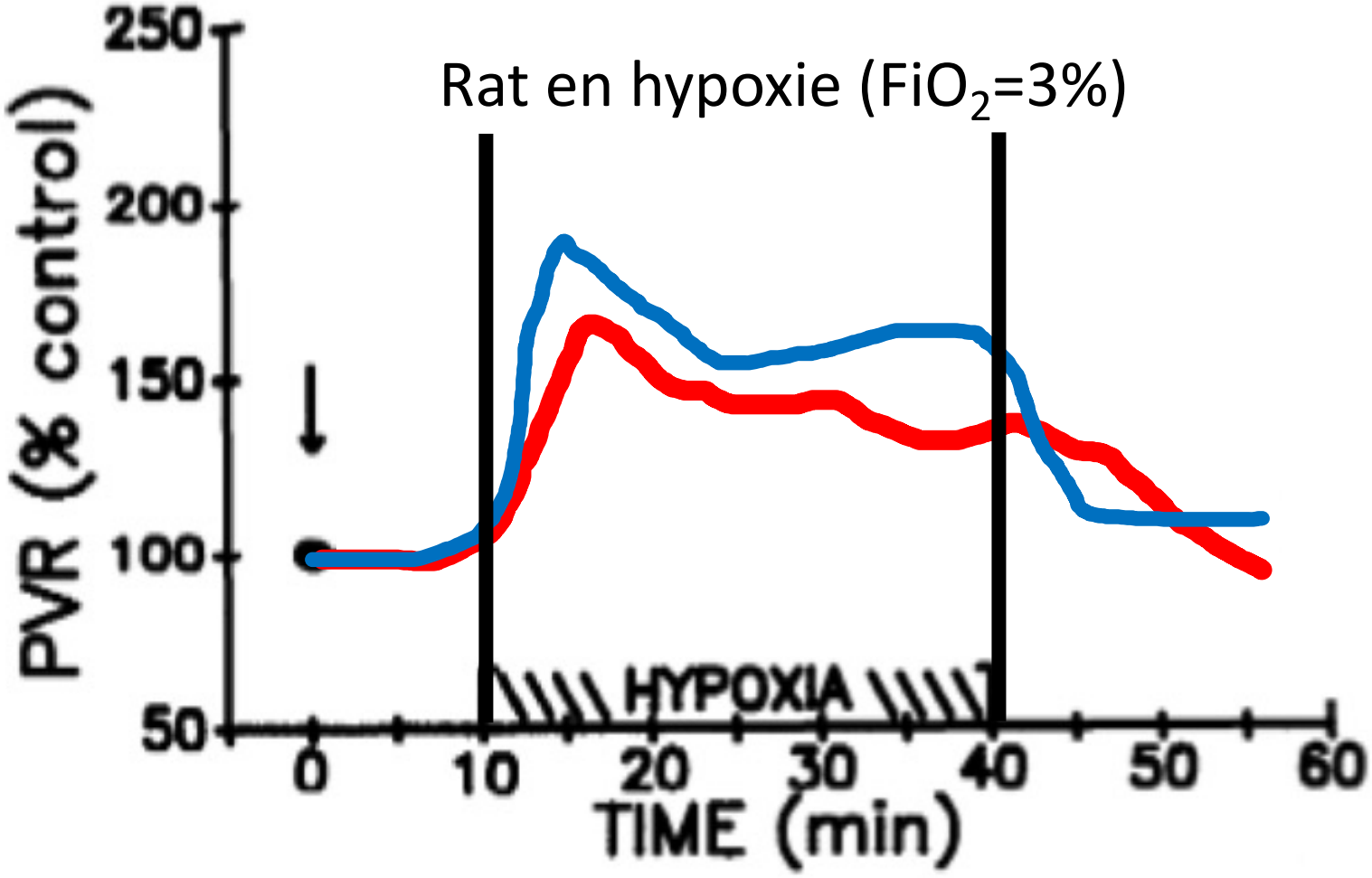


Wallace AW, Am J Physiol 1989

Poumon isolé

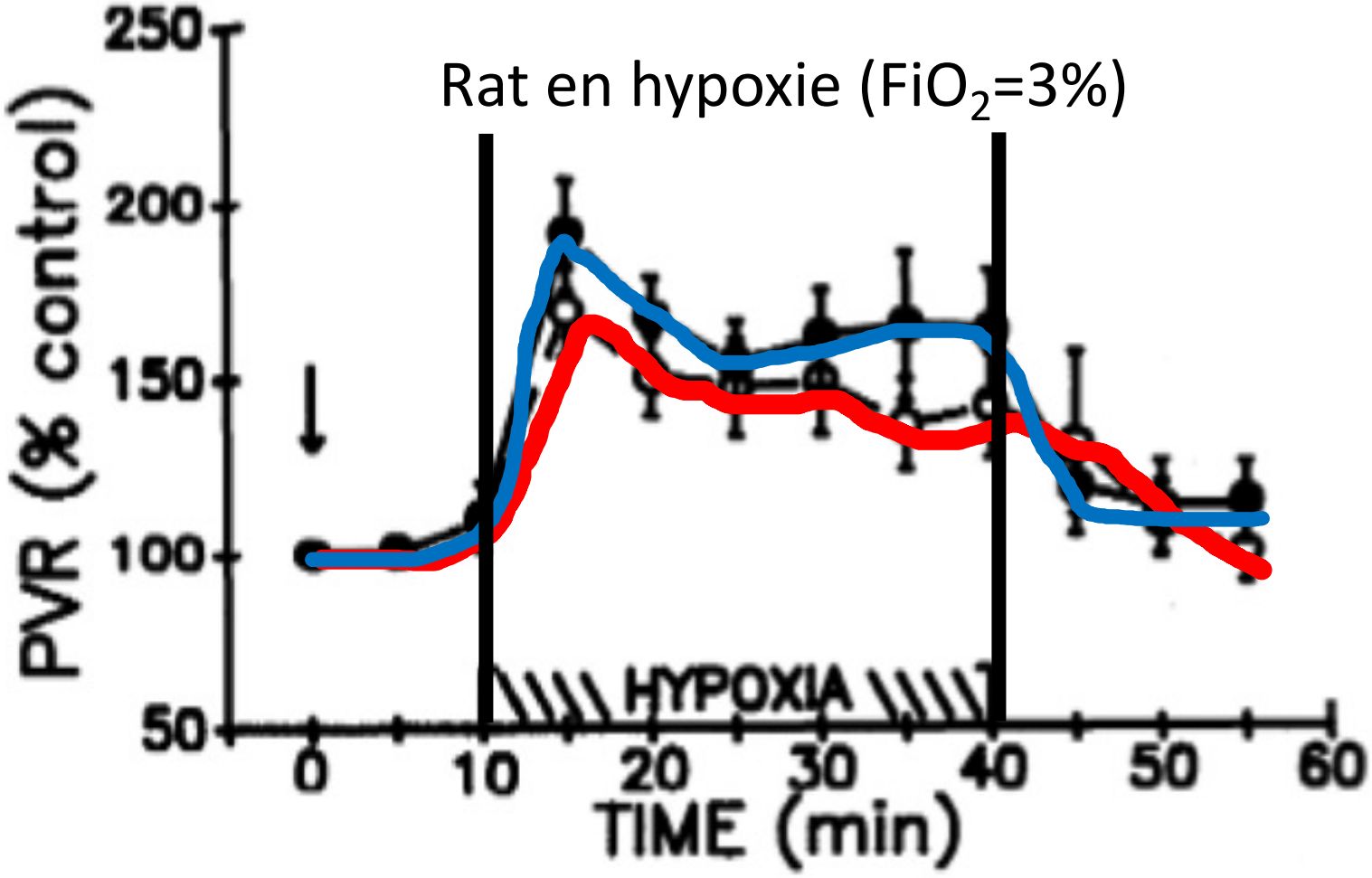


Walker BR, Am J Physiol 1989



Walker BR, Am J Physiol 1989

Rat en hypoxie (FiO_2=3%)



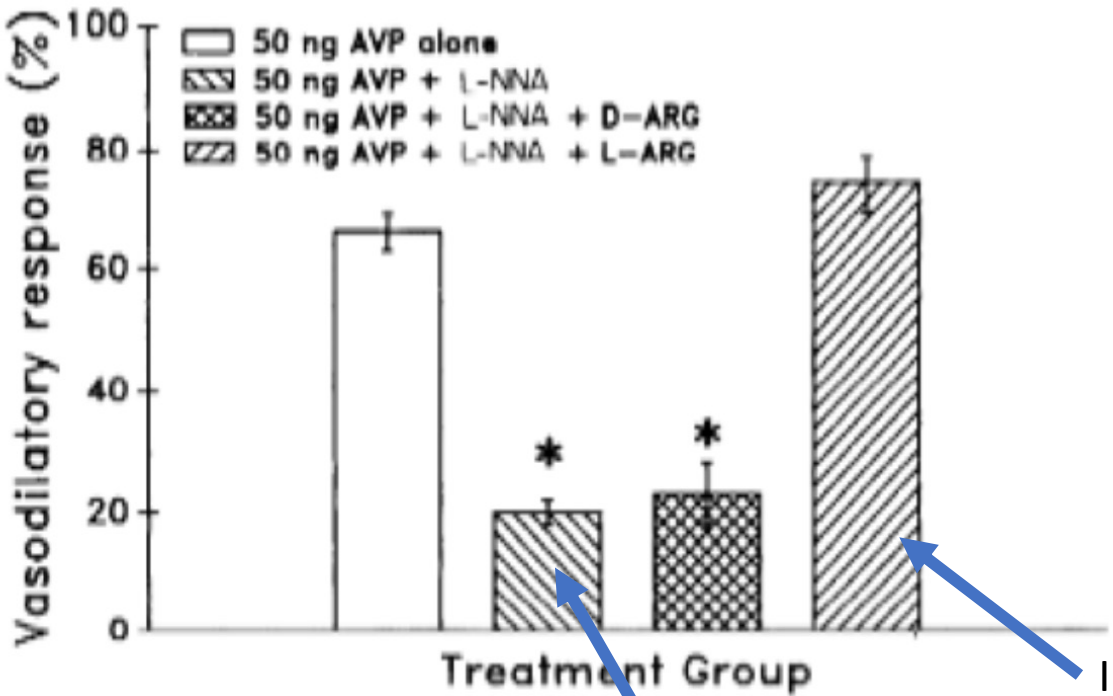
AVP

Contrôle

Walker BR, Am J Physiol 1989

Role of nitric oxide in vasopressinergic pulmonary vasodilatation

ROY D. RUSS AND BENJIMEN R. WALKER



Inhibiteur NOS + excès de substrat

Inhibiteur NOS

Am J Physiol. 262 (*Heart Circ. Physiol.* 31): H743–H747, 1992.

Conclusion

- Pas de preuve de l'intérêt sur le pronostic du choc septique

- Choc cardiogénique?
  - Prévention IRA et AC/FA/ choc post cardiotomie?
  - Choc avec Dysfonction VD aigüe + HTAP?

Merci pour votre attention