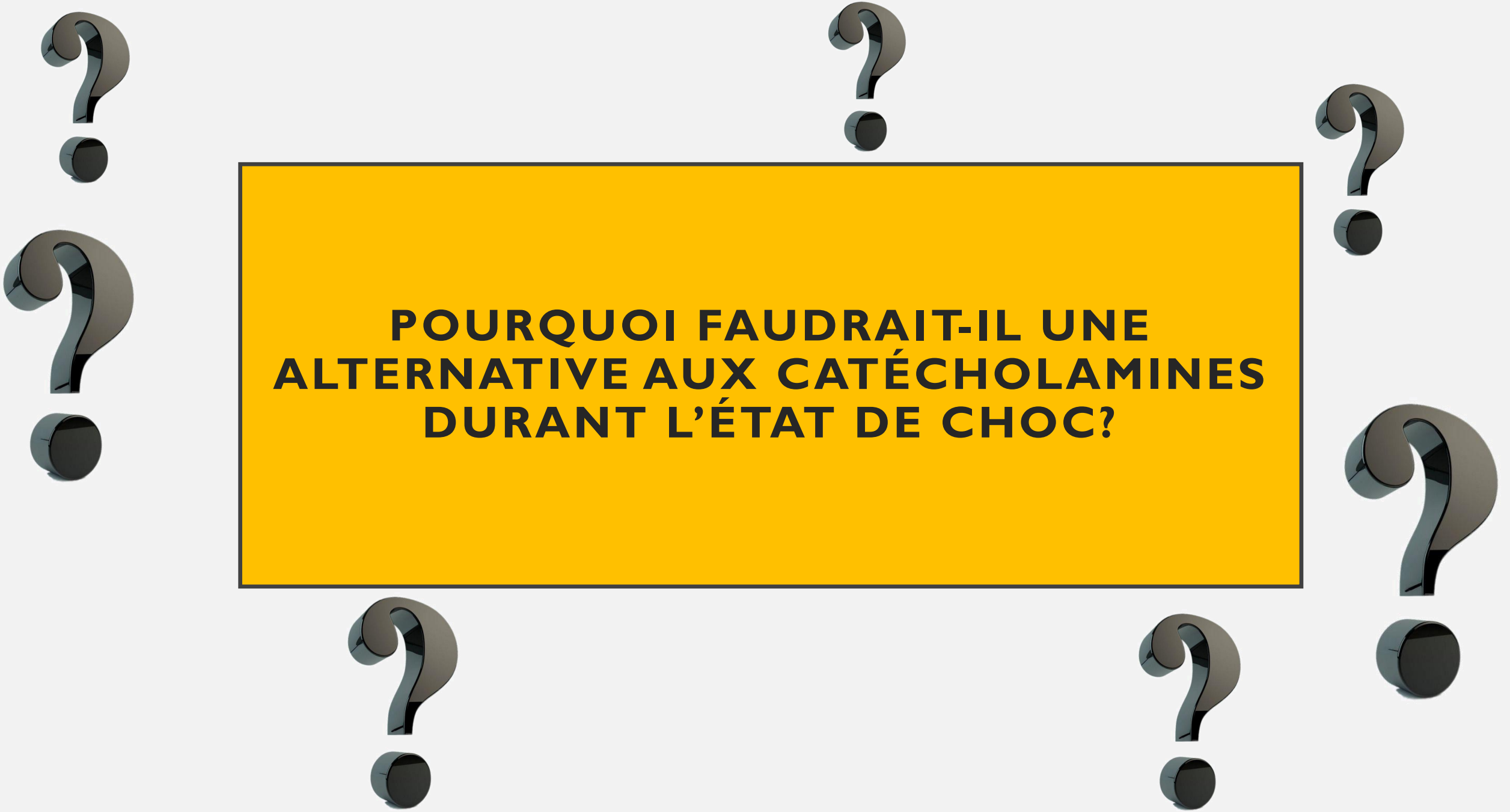
ALTERNATIVES AUX CATÉCHOLAMINES

Antoine Kimmoun

Médecine Intensive et Réanimation Brabois

PAS DE CONFLIT D'INTÉRÊT


POURQUOI FAUDRAIT-IL UNE ALTERNATIVE AUX CATÉCHOLAMINES DURANT L'ÉTAT DE CHOC?

CHOC CARDIOGÉNIQUE

REVIEW Open Access

Experts' recommendations for the management of adult patients with cardiogenic shock

2 Norepinephrine should be used to restore perfusion pressure during cardiogenic shock (strong agreement).

Levy B et al. *Ann. Intensive Care* 2015

CHOC SEPTIQUE

CONFERENCE REPORTS AND EXPERT PANEL

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

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).

Rhodes et al. *Intensive Care Med* 2016

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Les catécholamines peuvent elles avoir des effets indésirables ?

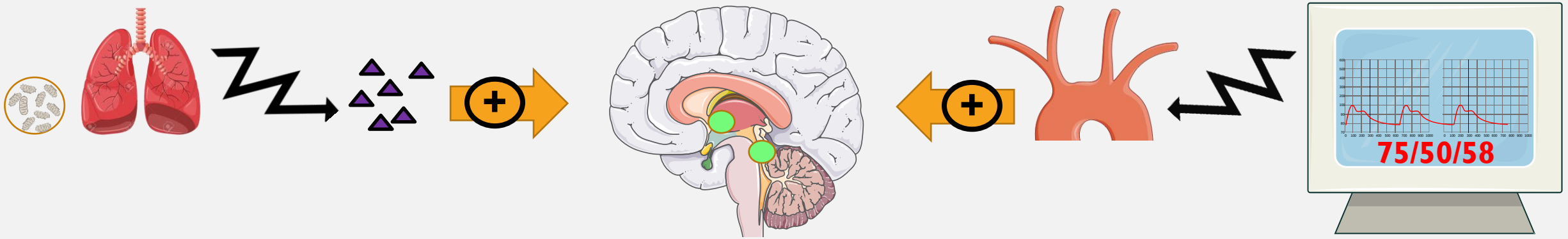
Existe-t-il des alternatives au catécholamines?

PHYSIOLOGIE DU CONTRÔLE DE LA PRESSION ARTÉRIELLE

Physiologie | Physiopathologie | Effets indésirables | Alternative | Futur

Infection — cytokines — baroreflexe — hypotension

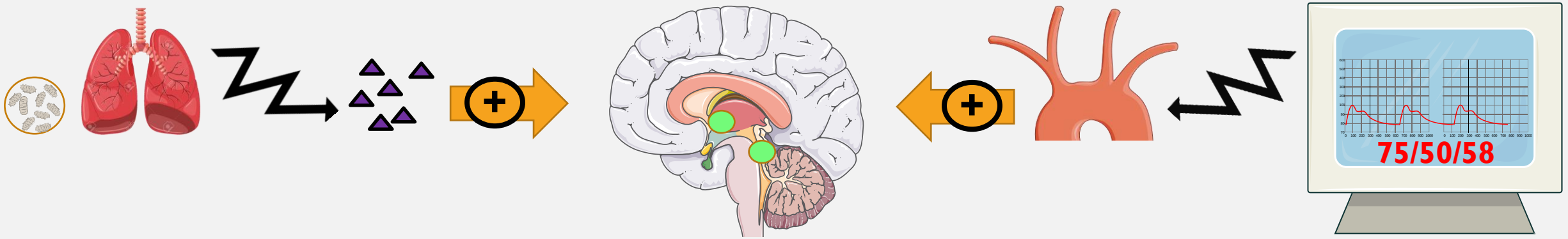
Stimulus



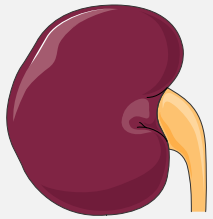
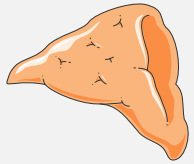
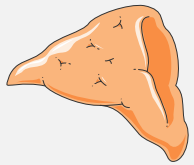
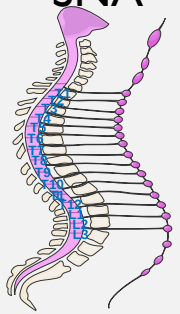
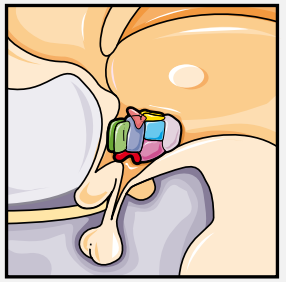
Physiologie	Physiopathologie	Effets indésirables	Alternative	Futur

Stimulus

Infection → cytokines → (+) → baroreflexe → (+) → hypotension



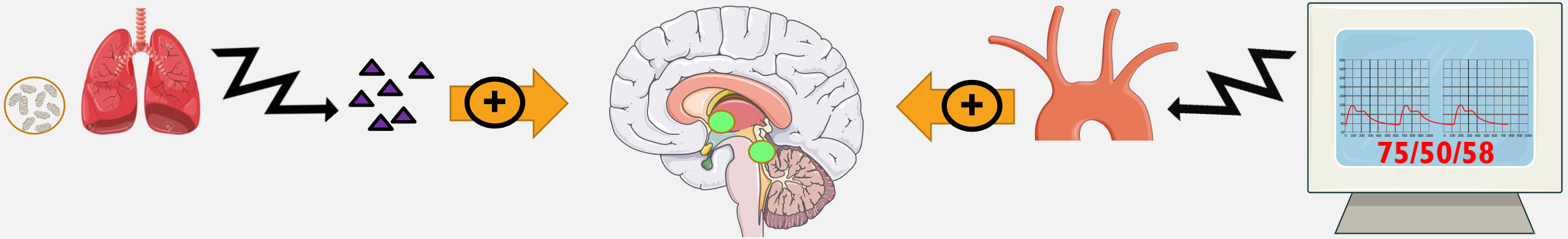
Systèmes activés

SRAA	Axe HHS	SNA	SNA	SHV
				
ANGIOTENSINE	**CORTISOL**	**ADRENALINE**	**NORADRENALINE**	**VASOPRESSINE**

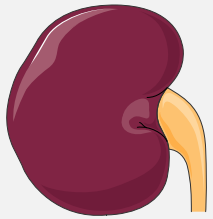
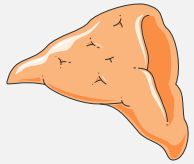
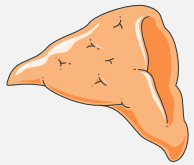
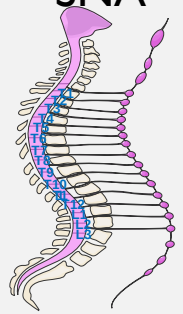
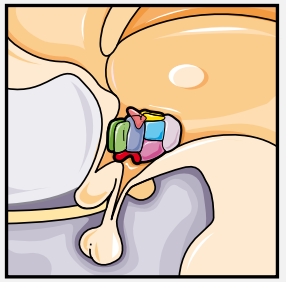
Physiologie	Physiopathologie	Effets indésirables	Alternative	Futur

Stimulus

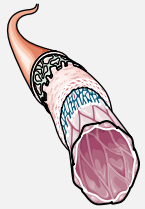
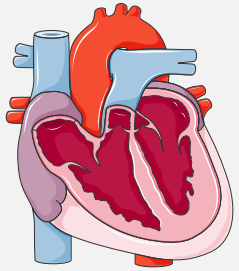
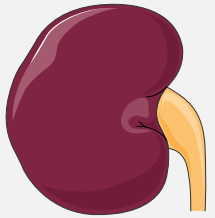
Infection → cytokines → (+) → baroreflexe → (+) → hypotension



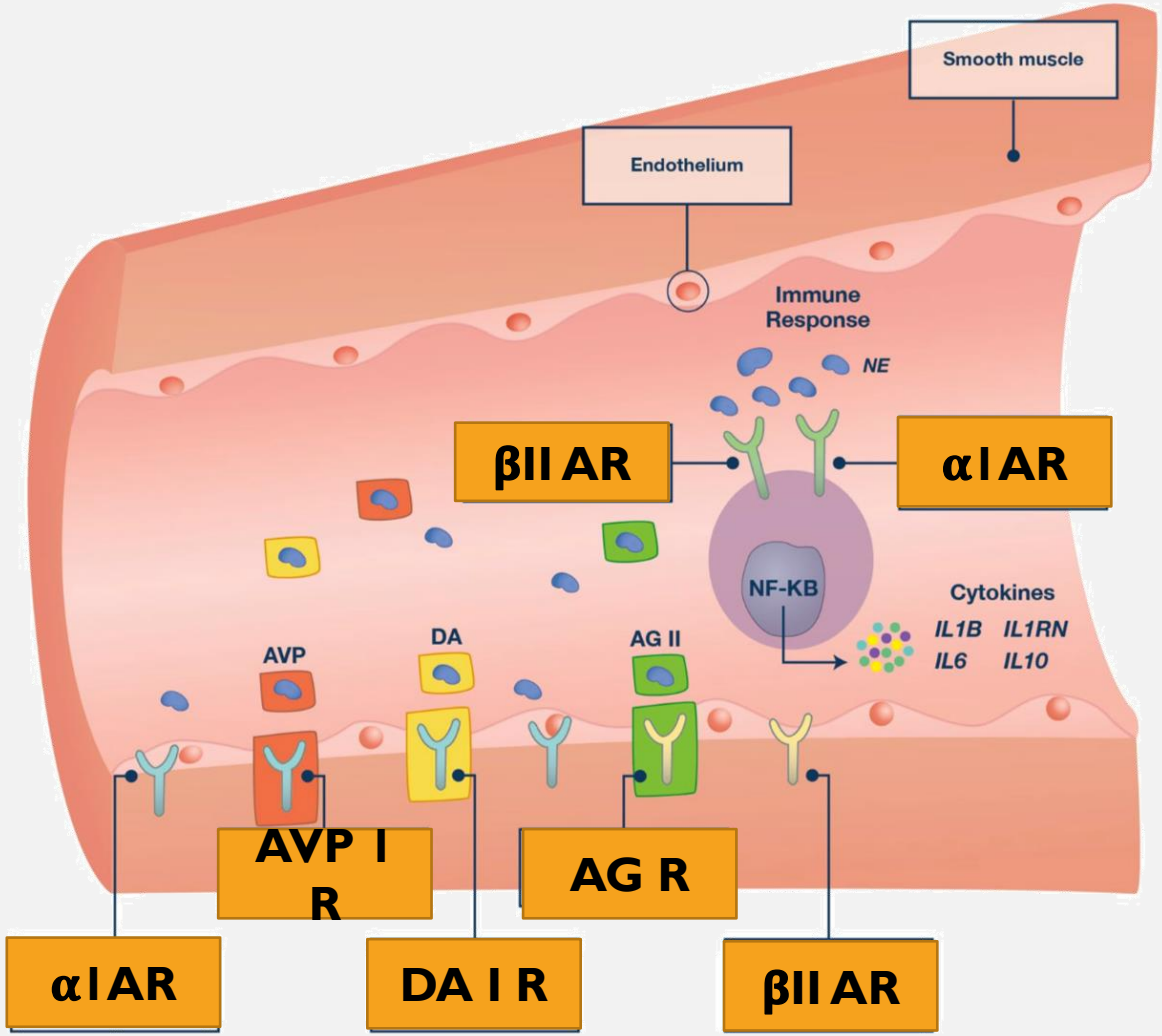
Systèmes activés

Physiologie	Physiopathologie	Effets indésirables	Alternative	Futur
SRAA	Axe HHS	SNA	SNA	SHV
				
ANGIOTENSINE	**CORTISOL**	**ADRENALINE**	**NORADRENALINE**	**VASOPRESSINE**

Organes régulés

Physiologie	Physiopathologie	Effets indésirables	Alternative	Futur
				
VASOCONSTRICTION	**CONTRACTILITÉ**	**INFLAMMATION**	**VOLÉMIE**	

MÉCANISMES CELLULAIRES DE LA RÉPONSE À L'HYPOTENSION

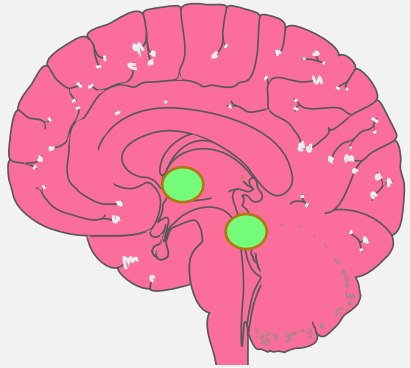


Russel J *Intensive Care Med* 2019

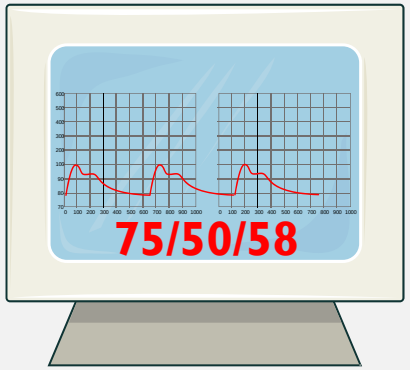
PHYSIOPATHOLOGIE HÉMODYNAMIQUE DE L'ÉTAT DE CHOC

Physiologie	**Physiopathologie**	Effets indésirables	Alternative	Futur

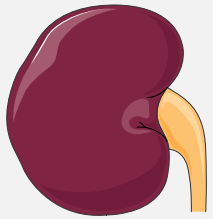
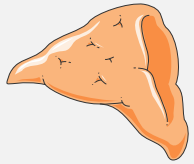
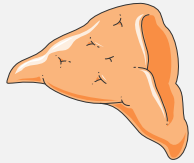
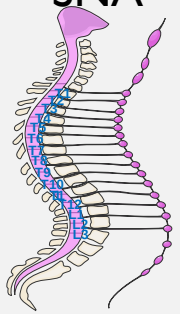
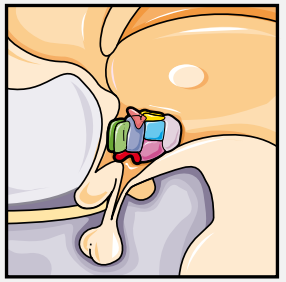
Stimulus

Infection → cytokines → (+) → 

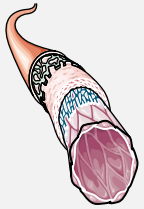
baroreflexe → (+) → 

hypotension → 

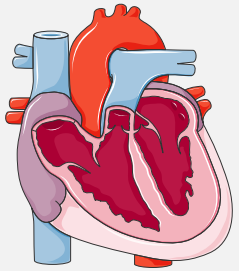
Systèmes activés

SRAA	Axe HHS	SNA	SNA	SHV
				
↗ ANGIOTENSINE	↗ CORTISOL	↗ ADRENALINE	↗ NORADRENALINE	↘ VASOPRESSINE

Dysautonomie



↘ VASOREACTIVITE



↘ CONTRACTILITÉ

↗ INFLAMMATION

EFFETS “INDÉSIRABLES” DES CATÉCHOLAMINES

CARDIOPATHIE DE STRESS: CATÉCHOLAMINE EXOGÈNE

Table 1 Clinical Features on Admission of Patients With Stress Cardiomyopathy

Patient #	Age (yrs)	Sex	Drug	Event	HR (beats/min)	MAP (mm Hg)	Killip Class	Peak Tn-I (ng/ml)	Max QTc (ms)	Hemodynamic Support	Ballooning Pattern	EF (%)
1	46	M	Dobutamine	Dobutamine echo	92	55	1	0.17	475	None	Apical	35
2	51	F	Dobutamine	Dobutamine echo	59	60	2	0.46	652	IABP	Midventricular	35
3	41	F	Dobutamine	Dobutamine echo	63	77	1	4.1	477	None	Midventricular	35
4	30	F	Epinephrine	Suicide attempt	88	55	4	0.47	499	Dopamine	Apical	15
5	24	F	Epinephrine	Liposuction	100	55	3	3.2	540	Dopamine	Apical	15
6	48	F	Epinephrine	Facelift	85	69	3	5.6	568	None	Basal	35
7	44	F	Epinephrine	Keloid repair	136	67	3	12	471	Norepinephrine	Basal	40
8	20	M	Epinephrine	Colonoscopy	100	57	3	7.4	607	None	Basal	40
9	54	F	Epinephrine	Vasovagal syncope	100	121	1	4.4	504	None	Basal	40

Apport exogène de catécholamine

Polymorphisme des Beta-adrénorécepteurs?

Abrham J et al. *J Am Coll Cardiol* 2009

CARDIOPATHIE DE STRESS: CATÉCHOLAMINES ENDOGÈNE

Table 2. Plasma Catecholamine and Neuropeptide Levels.*

Variable	Patients with Stress Cardiomyopathy (N=13)			Patients with Killip Class III Myocardial Infarction (N=7)			Normal Value
	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	
	median (interquartile range)						
Catecholamine precursor (pg/ml)							
Dihydroxyphenylalanine	2859 (2721–2997)†	2495 (2386–2761)†	1656 (1065–2011)	1282 (1124–1656)	1203 (1193–1873)	907 (749–937)	1755‡
Catecholamines (pg/ml)							
Epinephrine	1264 (916–1374)†	1044 (733–1118)†	348 (180–550)	376 (275–476)	330 (220–385)	275 (220–311)	37‡
Norepinephrine	2284 (1709–2910)†	1573 (1235–2589)†	1142 (525–1252)	1100 (914–1320)	829 (727–914)	541 (516–660)	169‡
Dopamine	111 (106–146)†	77 (63–110)	56 (47–77)	61 (46–77)	61 (61–77)	38 (30–61)	15‡
Neuronal metabolites (pg/ml)							
Dihydroxyphenylglycol	2706 (2382–3131)†	2689 (2246–2842)†	2161 (2093–2416)§	1625 (1412–1702)	1583 (1497–1668)	1259 (1191–1446)	800‡
Dihydroxyphenylacetic acid	2758 (2573–3077)	2598 (2354–2892)†	1345 (1194–1682)	1513 (1211–1648)	1228 (1026–1362)	1009 (908–1059)	1497‡
Extraneuronal metabolites (pg/ml)							
Metanephrine	178 (140–187)	509 (385–789)	659 (590–738)§	106 (89–124)	203 (177–213)	205 (189–243)	59‡
Normetanephrine	216 (130–319)	456 (229–569)	661 (551–696)§	160 (145–170)	196 (181–209)	271 (225–288)	55‡
Peptides (pg/ml)							
Neuropeptide Y	186 (162–236)§	185 (158–214)†	136 (90–182)§	77 (60–90)	69 (61–71)	60 (40–65)	51¶
Brain natriuretic peptide	1033 (805–1783)§	450 (205–684)	142 (72–236)	264 (192–483)	268 (249–574)	297 (142–419)	10–93‖
Serotonin and metabolite (pg/ml)							
5-Hydroxytryptamine	2585 (2165–2816)†	2379 (2290–2900)†	1602 (864–1989)	1308 (1074–1721)	1214 (1114–1643)	1065 (1003–1251)	1004**
5-Hydroxyindoleacetic acid	5596 (4531–7380)	7839 (5698–9644)	6471 (3308–7074)	3977 (3604–6074)	4607 (4128–6003)	4282 (3887–4416)	6730**

Metabolites de la :
Noradrénaline
Dopamine

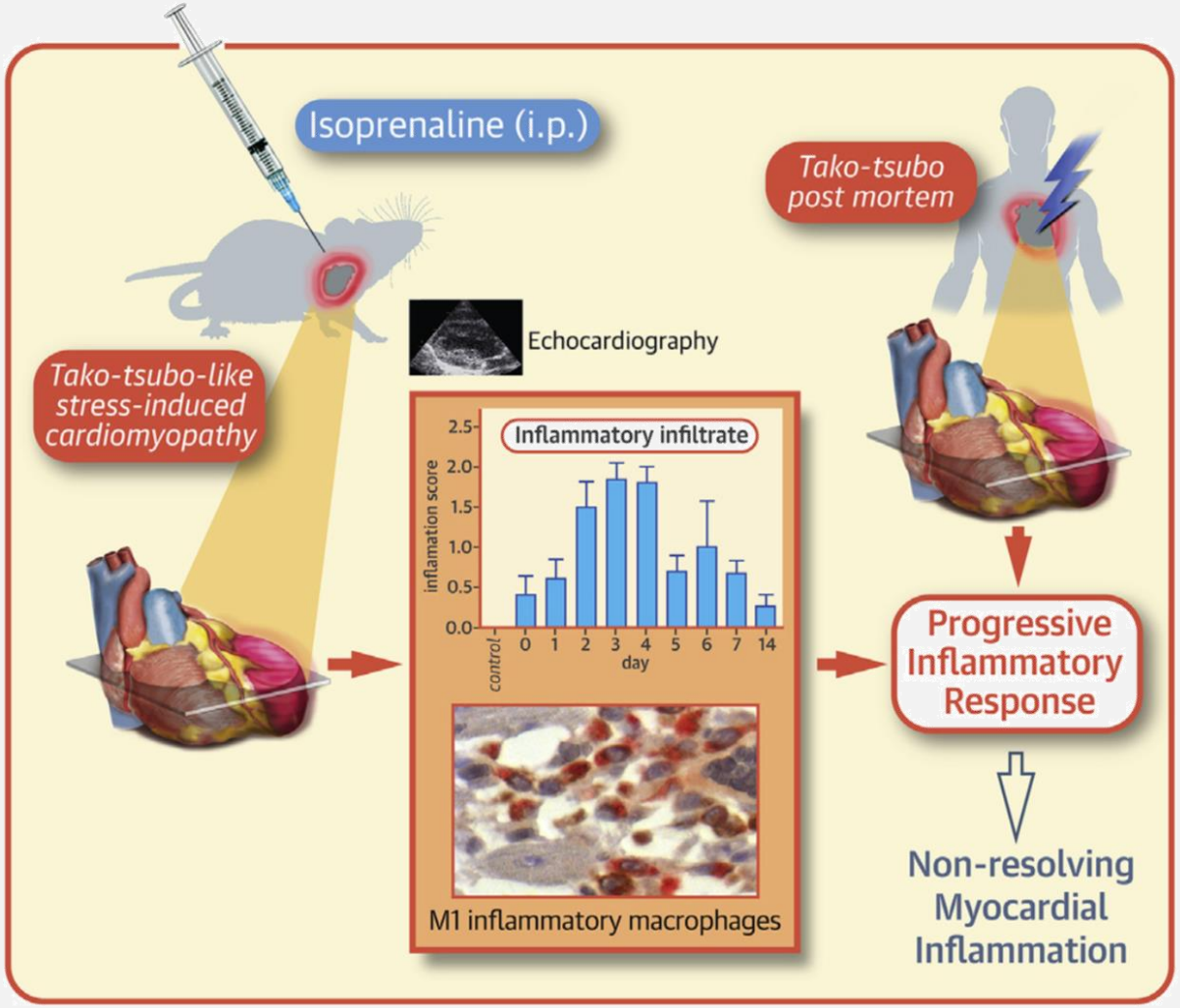
Sexe feminin majoritaire

ATCD neurologique

Origine Autonomique suspectée

Wittstein I.S. J et al. *N Engl J Med* 2005
Templin C et al. *N Engl J Med 2015*

CARDIOPATHIE DE STRESS INDUCTRICE D'INFLAMMATION MYOCARDIQUE



Effets pro-inflammatoire

Wilson H.M et al. *J Am Coll Cardiol Basic Trans Science* 2018

ALTERNATIVES THÉRAPEUTIQUES

Pour diminuer la pression catécholaminergique

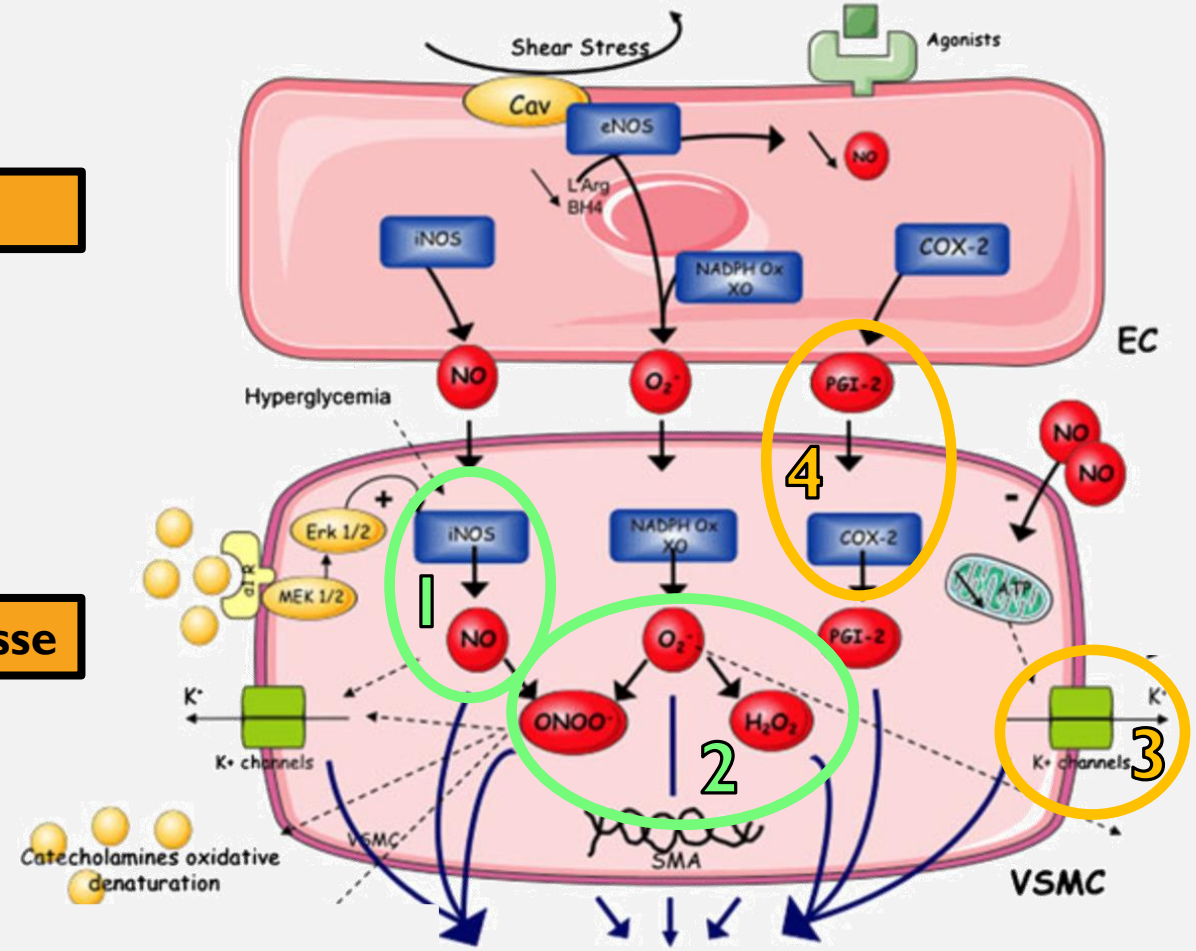
ALTERNATIVES THÉRAPEUTIQUES

Les thérapies qui ne fonctionnent pas

INHIBITEUR DE LA NO SYNTHASE

Cellule endothéliale

Cellule musculaire lisse



Vasodilatateur

1 **Monoxyde d'Azote**

2 **Peroxynitrite**

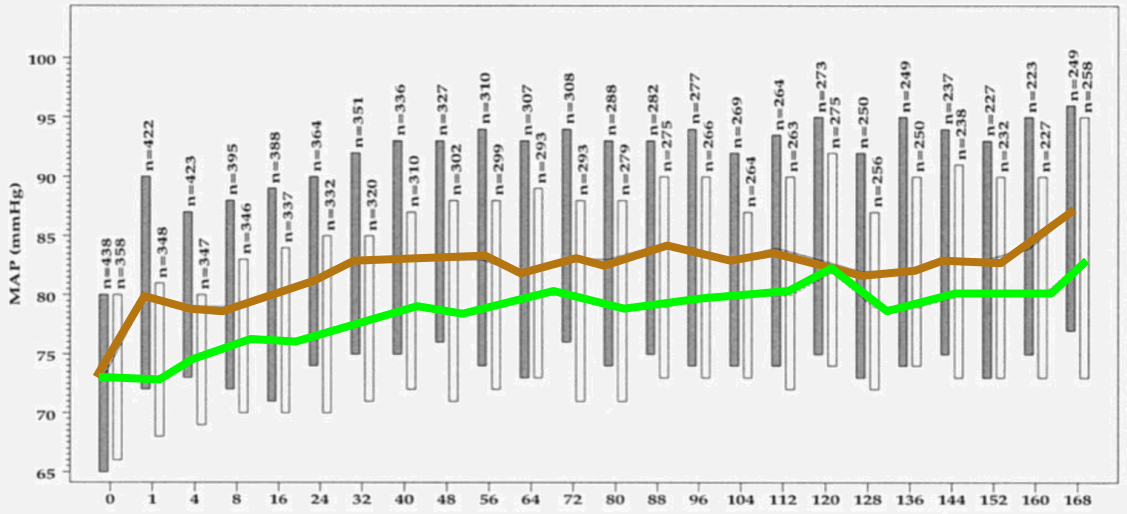
3 **Canaux K+ ATP**

4 **Prostacycline**

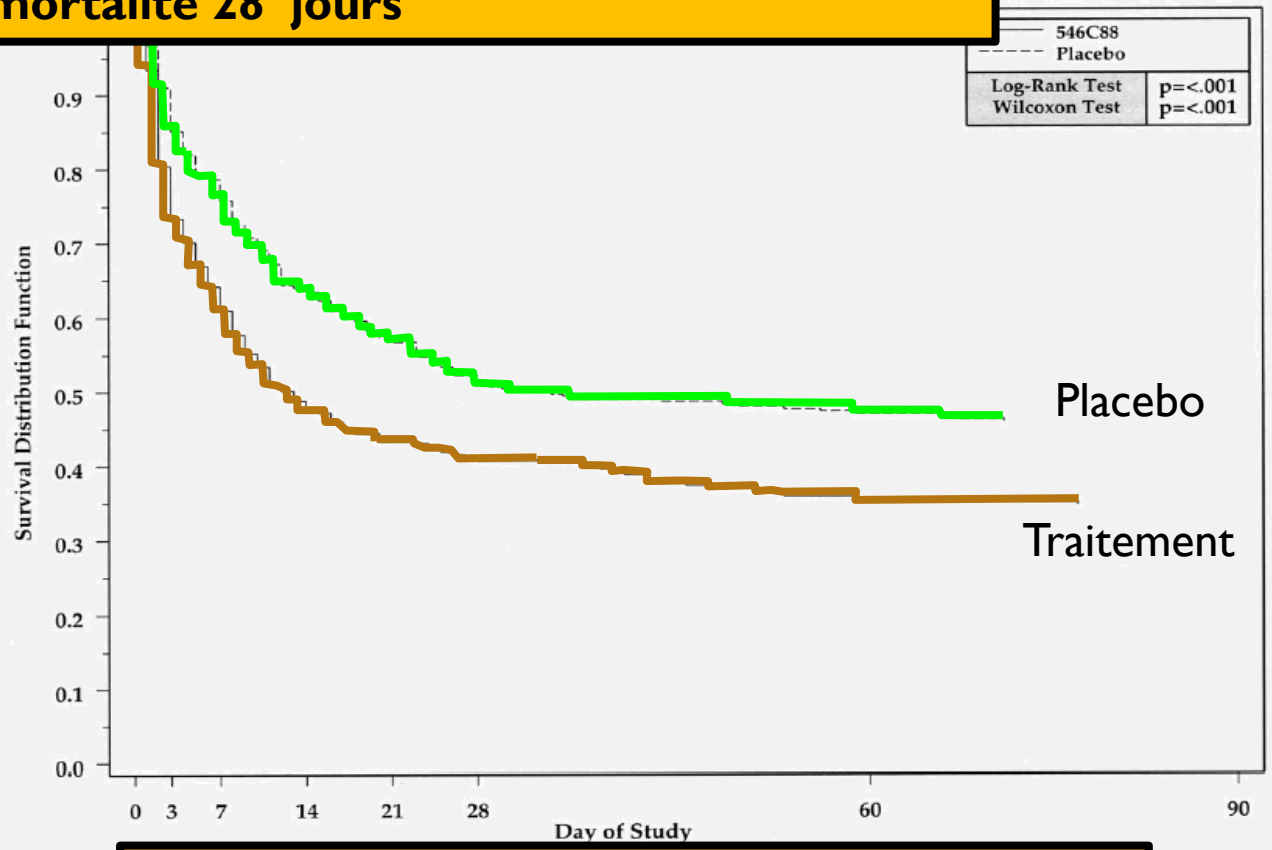
Levy B et al. Intensive Care Med 2010

INHIBITEUR DE LA NO SYNTHASE

Phase III, multicentrique, randomisé, 124 centres, 797/4400 patients, choc septique, objectif laire: mortalité 28 jours



Meilleure PAM….



Plus de complication cardiaque dans le groupe traitement

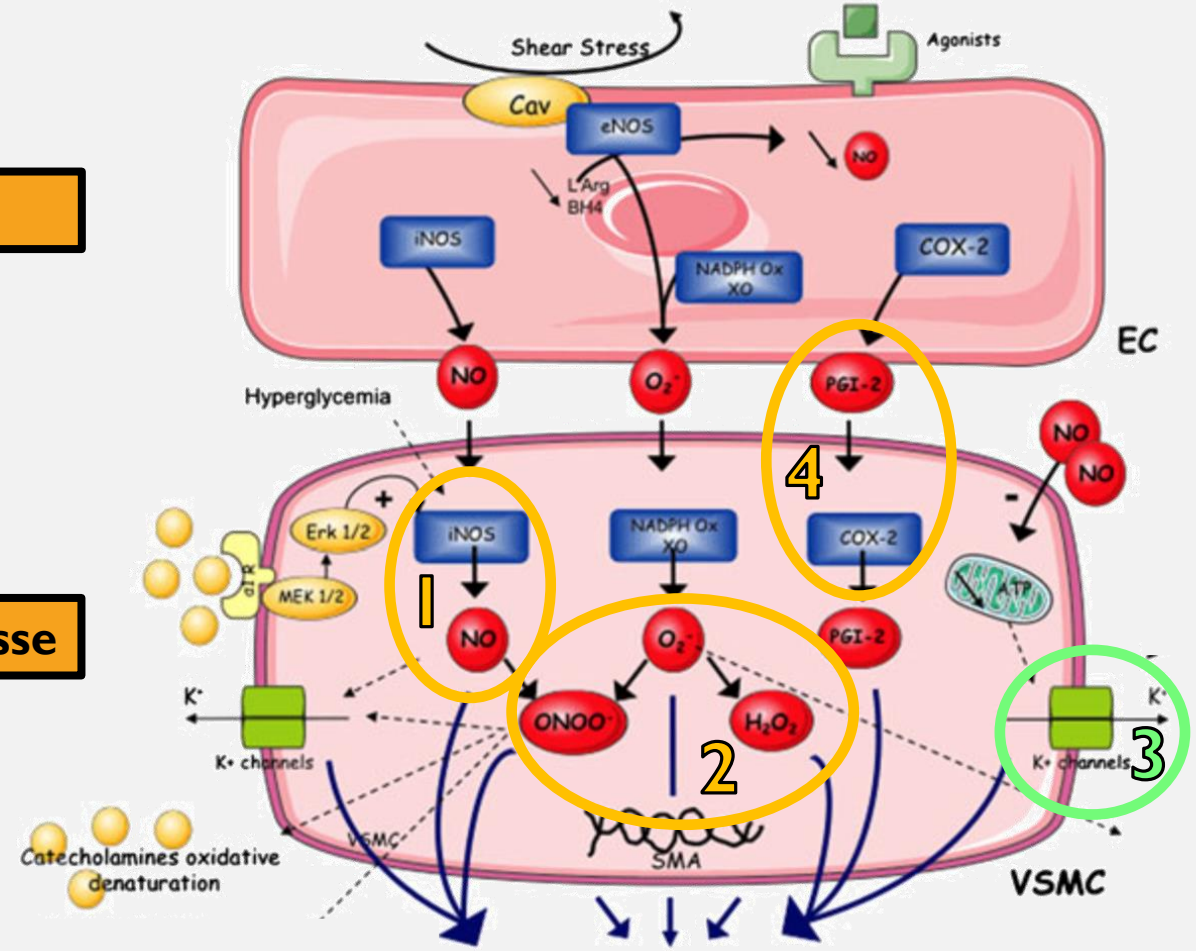
survie plus faible dans le groupe traitement

Lopez et al. Crit Care Med 2004

INHIBITEUR DES CANAUX K+ ATP

Cellule endothéliale

Cellule musculaire lisse



1 **Monoxyde d'Azote**

2 **Peroxynitrite**

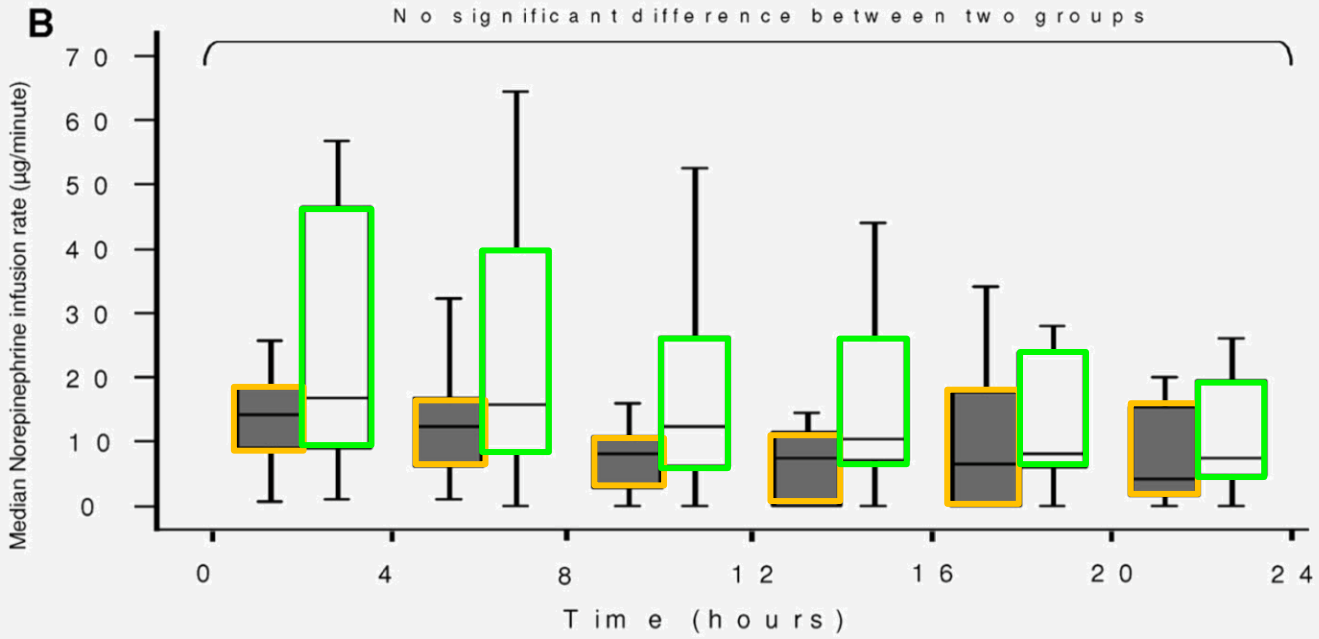
3 **Canaux K+ ATP**

4 **Prostacycline**

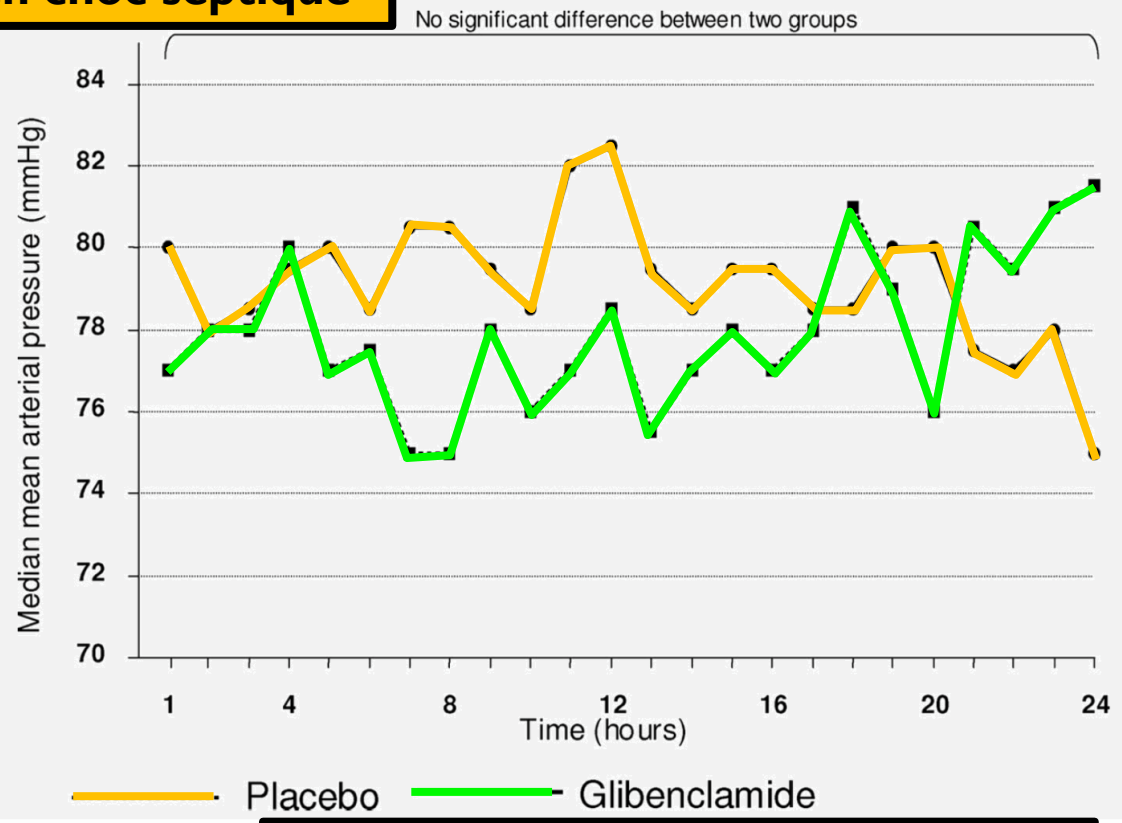
Levy B et al. Intensive Care Med 2010

INHIBITEUR DES CANAUX K ATP

Phase IIb, monocentrique, étude en cross-over, 10 patients en choc septique



Pas de réduction de la dose de Noradrénaline



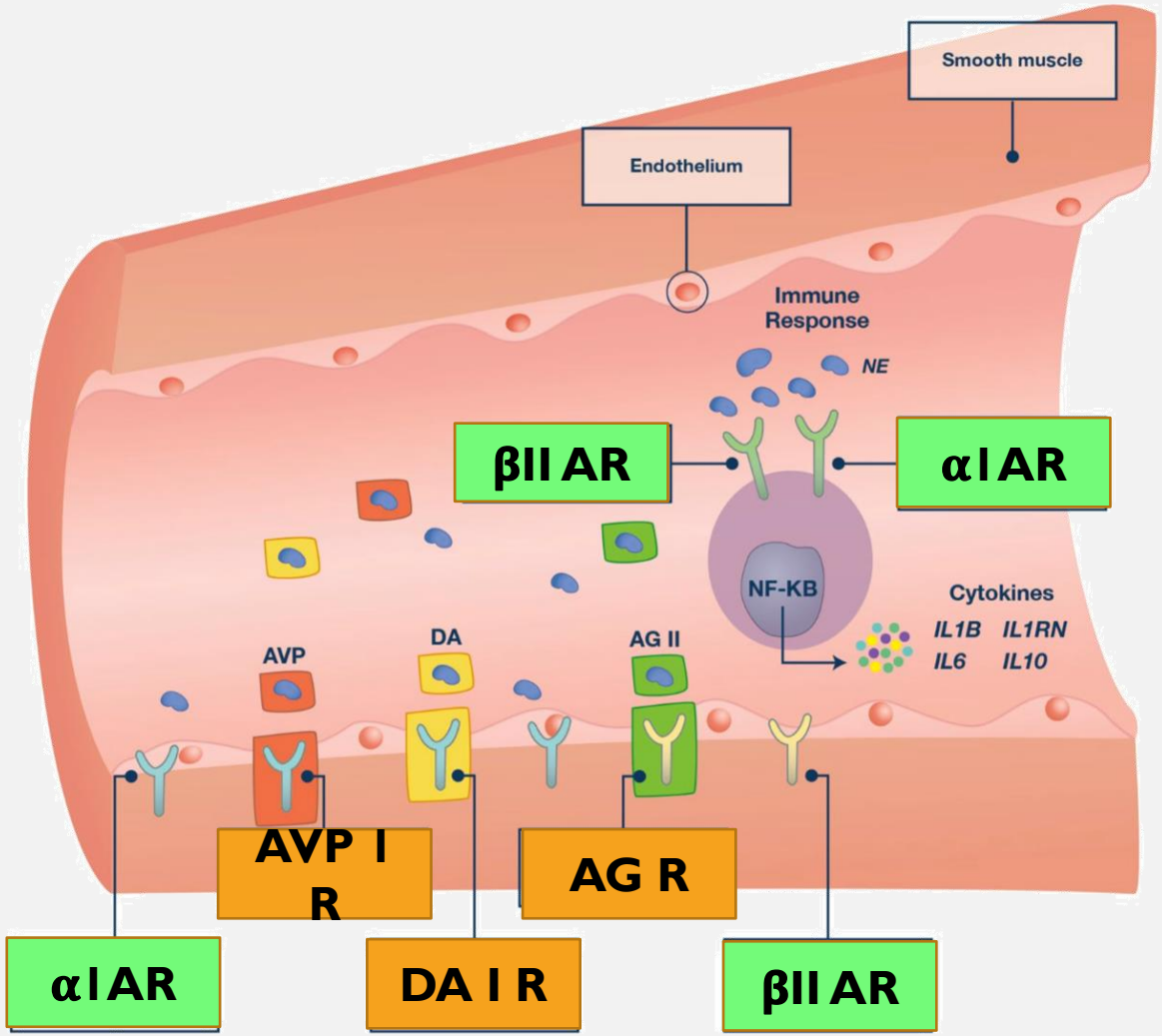
Pas de différence en terme de PAM

Warrillow et al. Crit Care Med 2006

ALTERNATIVES THÉRAPEUTIQUES

Les thérapies qui ont prouvées leurs efficacités

STIMULATION ADRÉNERGIQUE



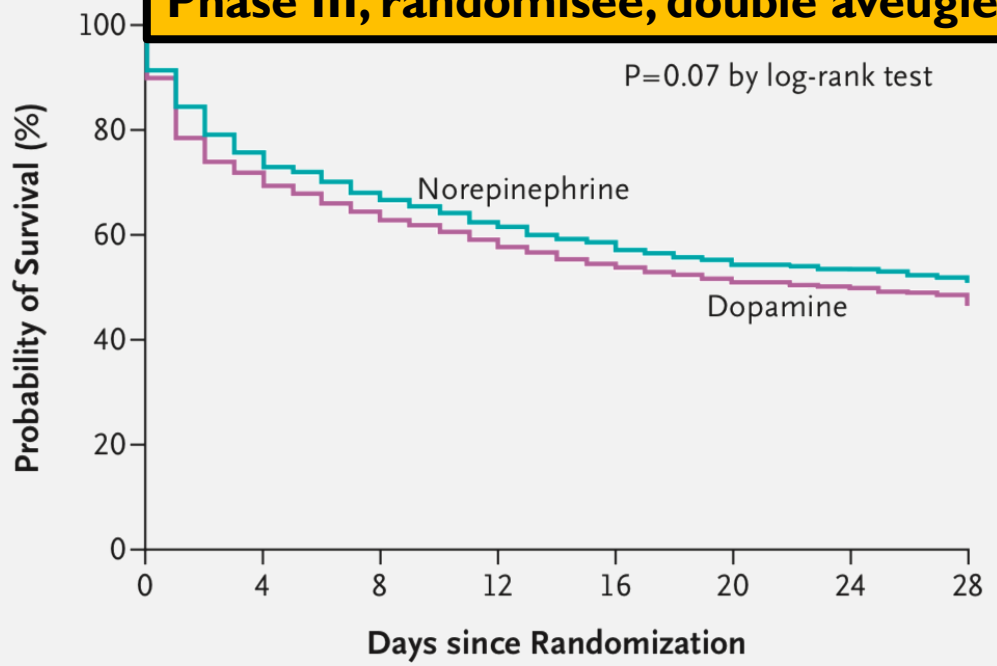
Action inflammatoire

Action vasoconstrictrice

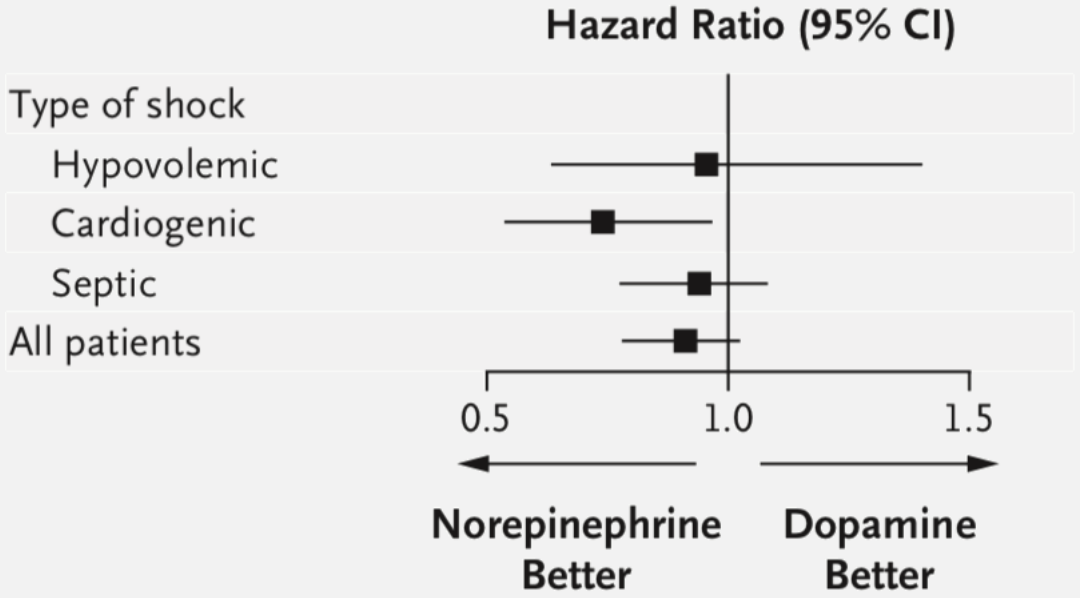
Russel J *Intensive Care Med* 2019

LA NORADRÉNALINE VERSUS LA DOPAMINE DANS L'ÉTAT DE CHOC

Phase III, randomisée, double aveugle, 1679 patients, objectif: mort à 28 jours



No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386



Pas de différence de mortalité

Moins d'effets secondaires

Pas de stimulation Beta 2 adrénergique

De Backer et al. N Engl J Med 2010

PLACE DE LA NORADRÉNALINE POUR LA PRISE EN CHARGE DE LA VASOPLÉGIE SEPTIQUE

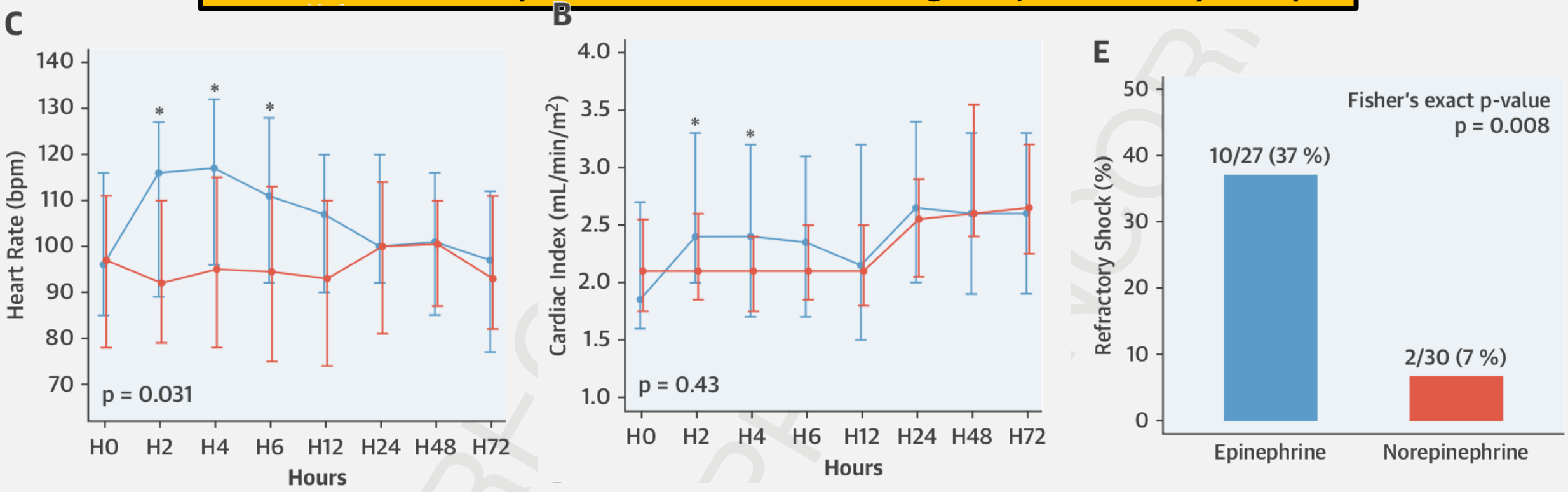
Initiate norepinephrine (NE) and titrate up to 35-90 µg/min to achieve MAP target 65 mm Hg

MAP target achieved

Dellinger et al. Intensive Care Med 2017

LA NORADRÉNALINE +/- DOBUTAMINE VERSUS L'ADRÉNALINE DANS LE CHOC CARDIOGÉNIQUE

Phase III, multicentrique, randomisée, double aveugle, objectif hémodynamique



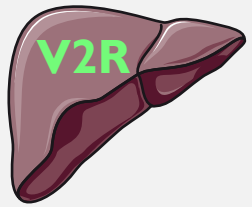
L'Adrénaline a un cout métabolique > Noradrénaline

Plus d'évolution vers un choc réfractaire

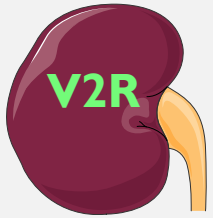
Noradrénaline > Adrénaline

Levy et al. JACC 2018

VASOPRESSINE

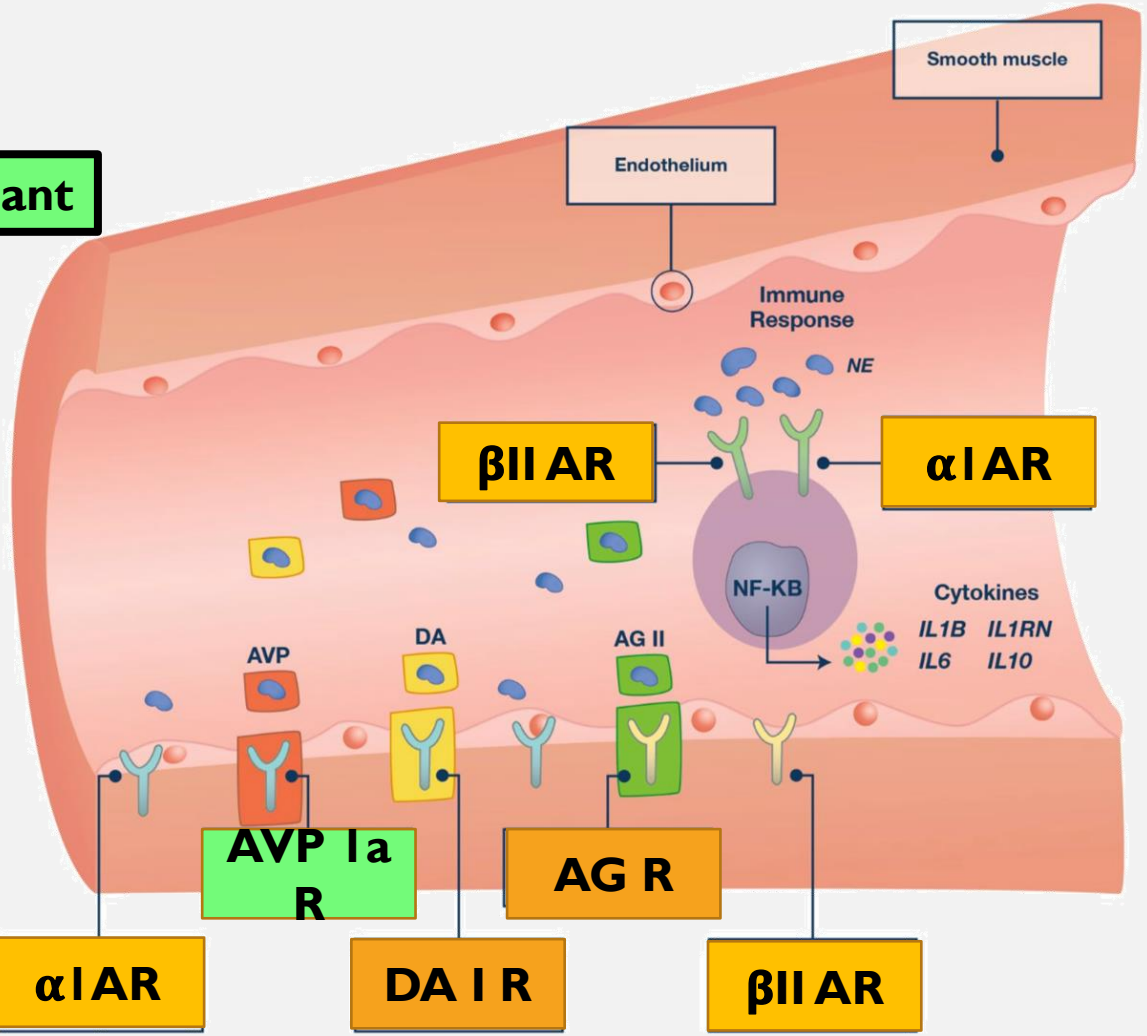


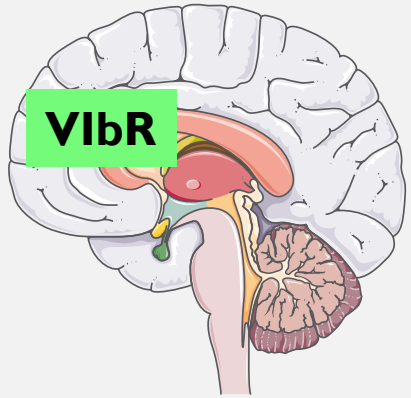
Effets pro-coagulant



Vasodilatateur

Antidiurétique





ACTH

Vasoconstriction

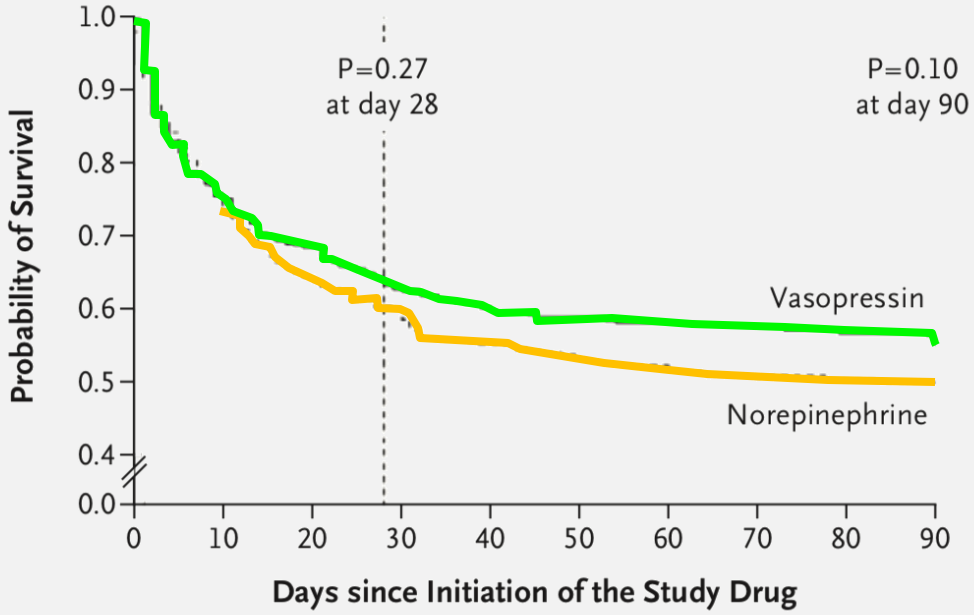
Russel J *Intensive Care Med* 2019

LA VASOPRESSINE DANS LE CHOC SEPTIQUE

Phase III, randomisée, multicentrique, 778 patients, objectif: mortalité à 28 jours

Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.*

Stratum	Norepinephrine Group	Vasopressin Group	P Value†	Absolute Risk Reduction (95% CI)
	no./total no. (%)			%
More severe septic shock				
28-day mortality	85/200 (42.5)	88/200 (44.0)	0.76	−1.5 (−11.2 to 8.2)
90-day mortality	105/199 (52.8)	103/199 (51.8)	0.84	1.0 (−8.8 to 10.8)
Less severe septic shock				
28-day mortality	65/182 (35.7)	52/196 (26.5)	0.05	9.2 (−0.1 to 18.5)
90-day mortality	83/180 (46.1)	69/193 (35.8)	0.04	10.4 (0.4 to 20.3)



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

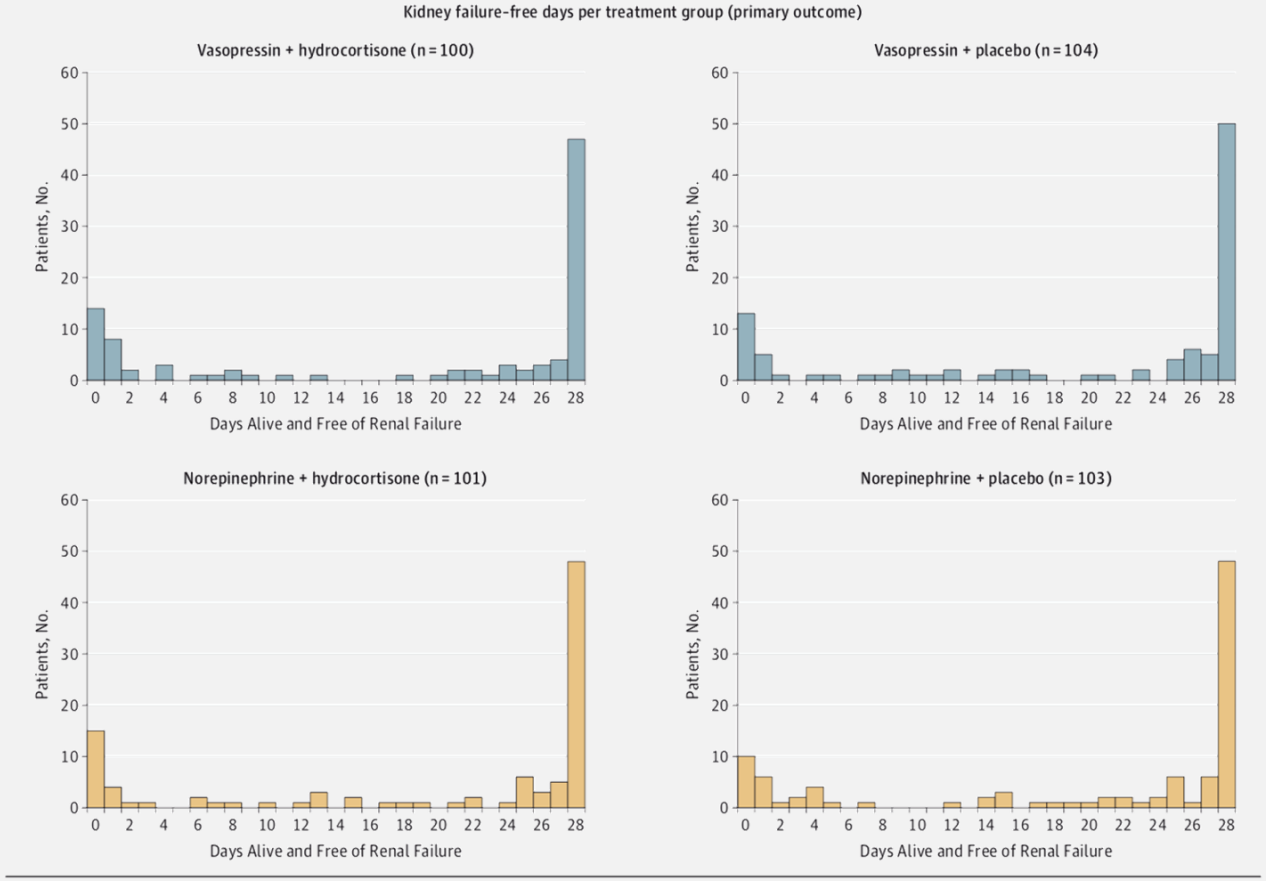
Effet bénéfique sur la mortalité dans les chocs septiques les moins sévères

Effet neutre sur la mortalité àJ28

Russell JA et al. N Engl J Med 2008

VASOPRESSINE + HSHC VS NORADRENALINE DANS LE CHOC SEPTIQUE

Phase III, randomisée, multicentrique, plan factoriel 2X2, 409 patients,
Objectif laire: nombre de jour vivant et sans insuffisance rénale sur les 28 jours post randomisation



Effet neutre

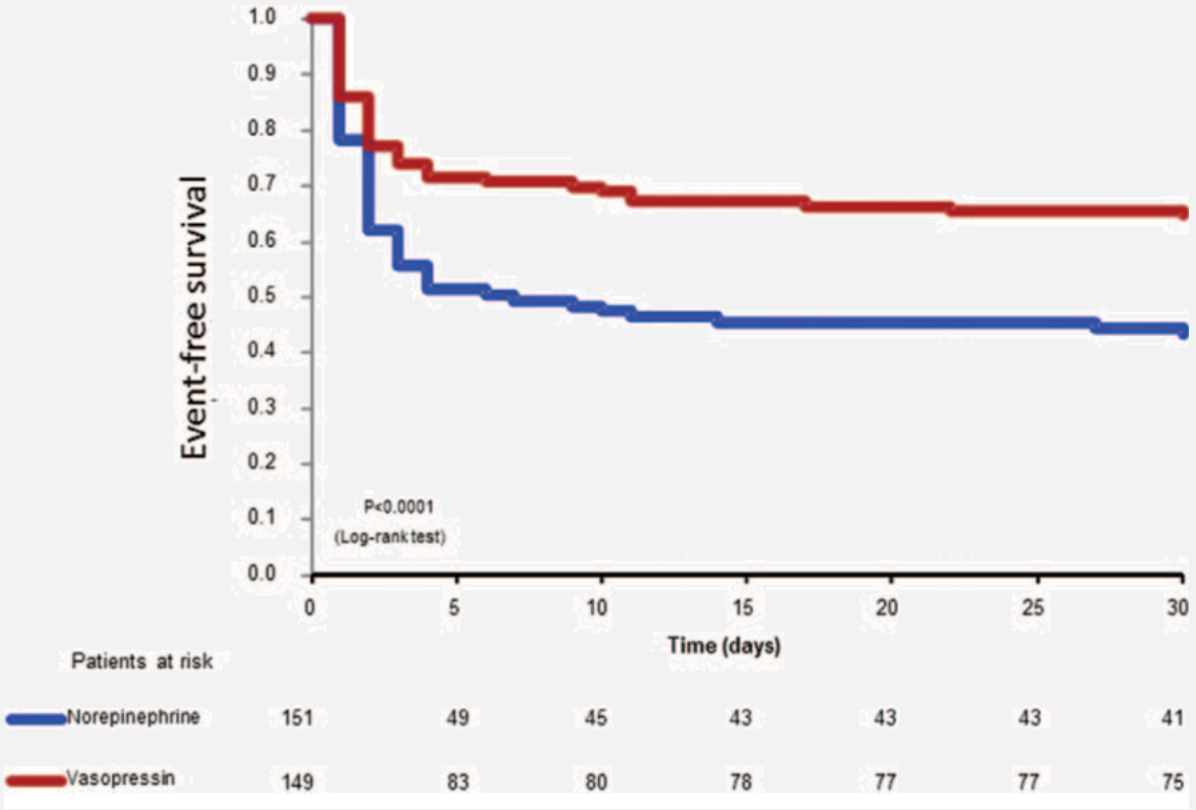
Mais réduction du risque absolu en % de recours à l'EER dans les groupes vasopressine :

−9.9 (−19.3 to −0.6)

Gordon C. et al. *JAMA* 2016

VASOPRESSINE VERSUS NORADRENALINE DANS LE CHOC VASOPLEGIQUE POST CHIRURGIE CARDIAQUE

Phase III, randomisée, monocentrique, 300 patients vasoplégiques avec fonction cardiaque conservée,
Objectif Iaire: nombre de jour vivant sans dysfonction d'organe à 28 jours

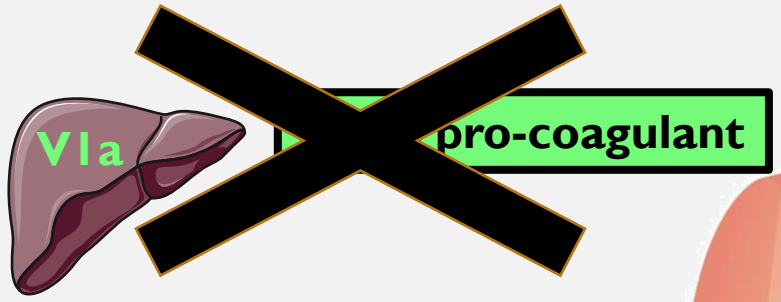


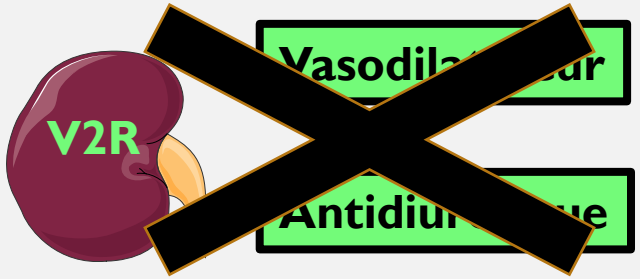
Amélioration de la survie sans événement dans le groupe vasopressine

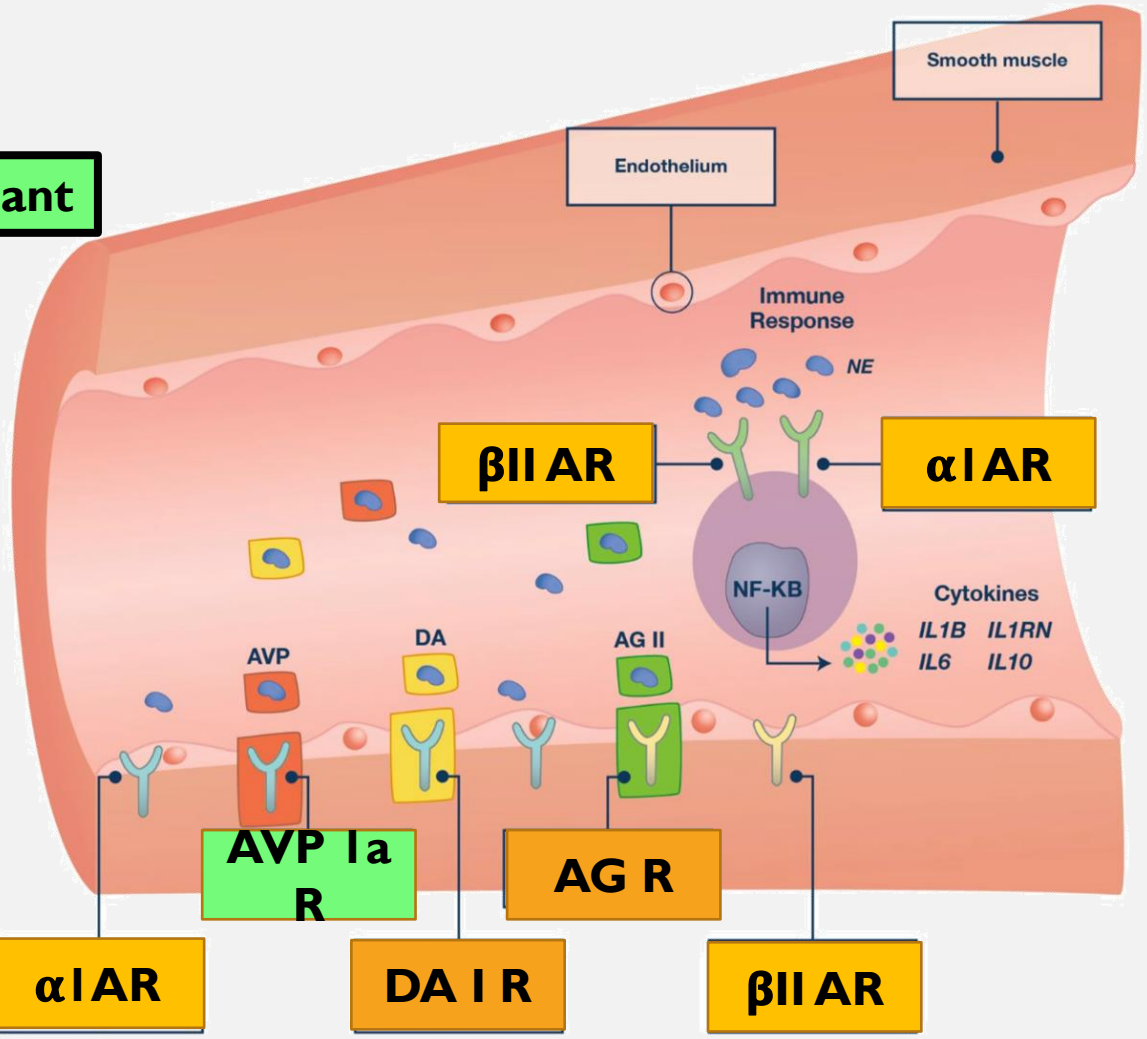
Diminution du nombre d'évènement arythmique dans le groupe vasopressine

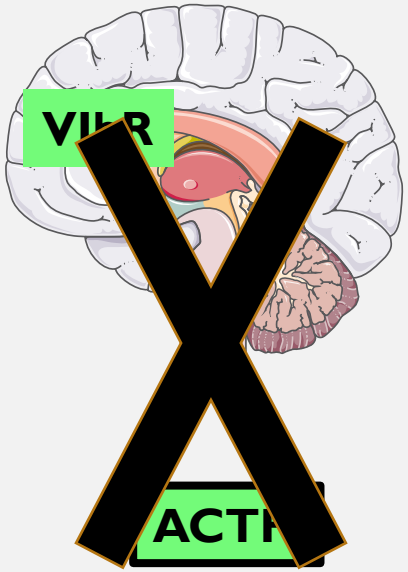
Hajjar C. et al. *Anesthesiology* 2016

SÉLÉPRESSINE







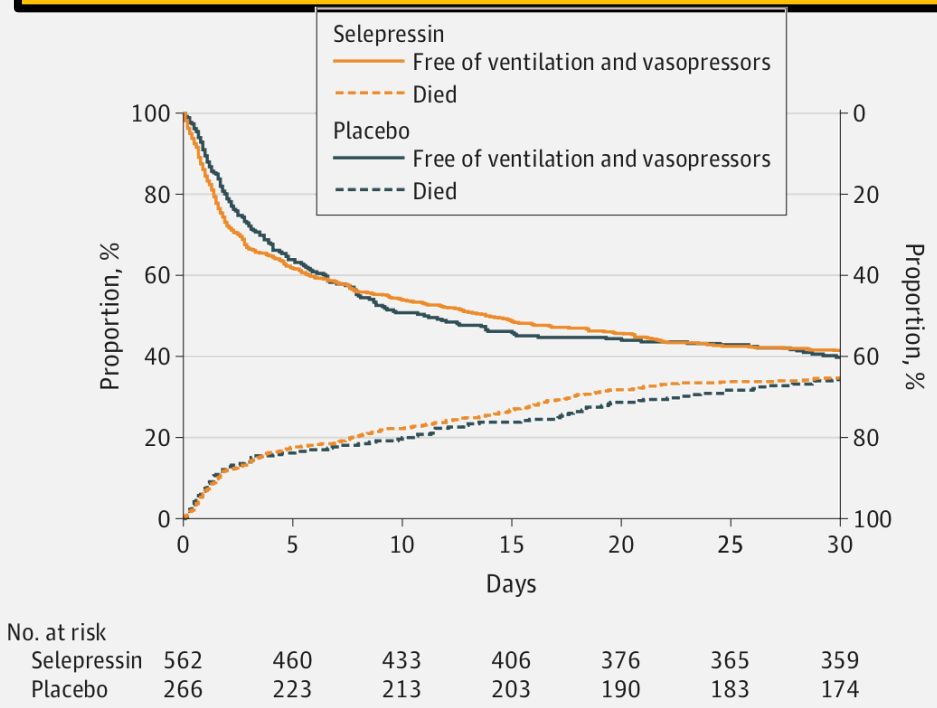


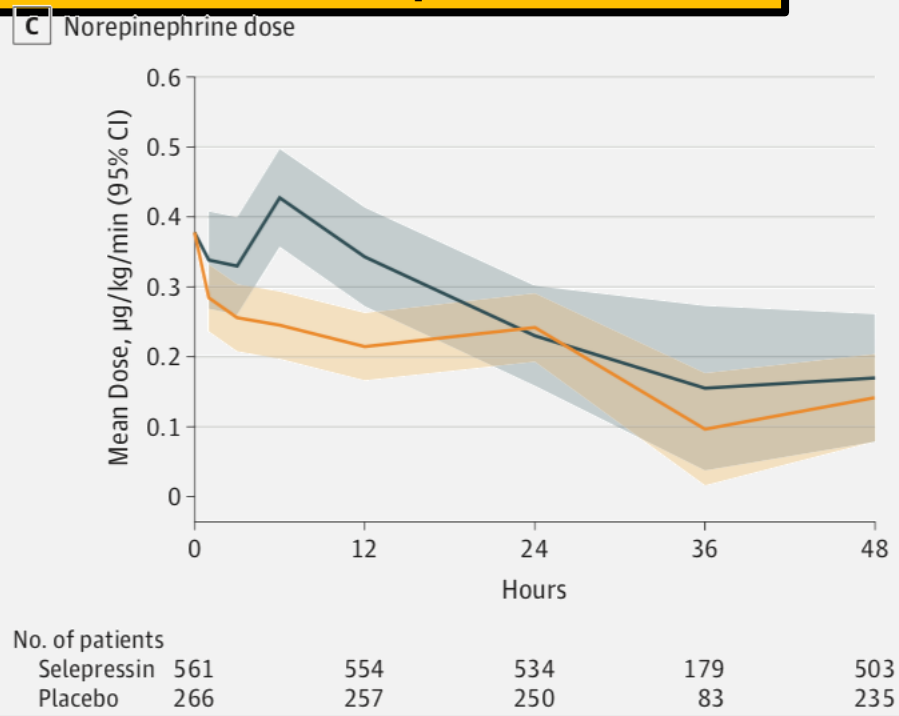
Agoniste ultra-selectif

Russel J *Intensive Care Med* 2019

SÉLÉPRESSINE

Phase IIb III, 828 patients randomisés, contrôlé versus placébo, patients en chocs septiques,
Objectif laire: nombre de jour sans vasopresseur et sans ventilation mécanique





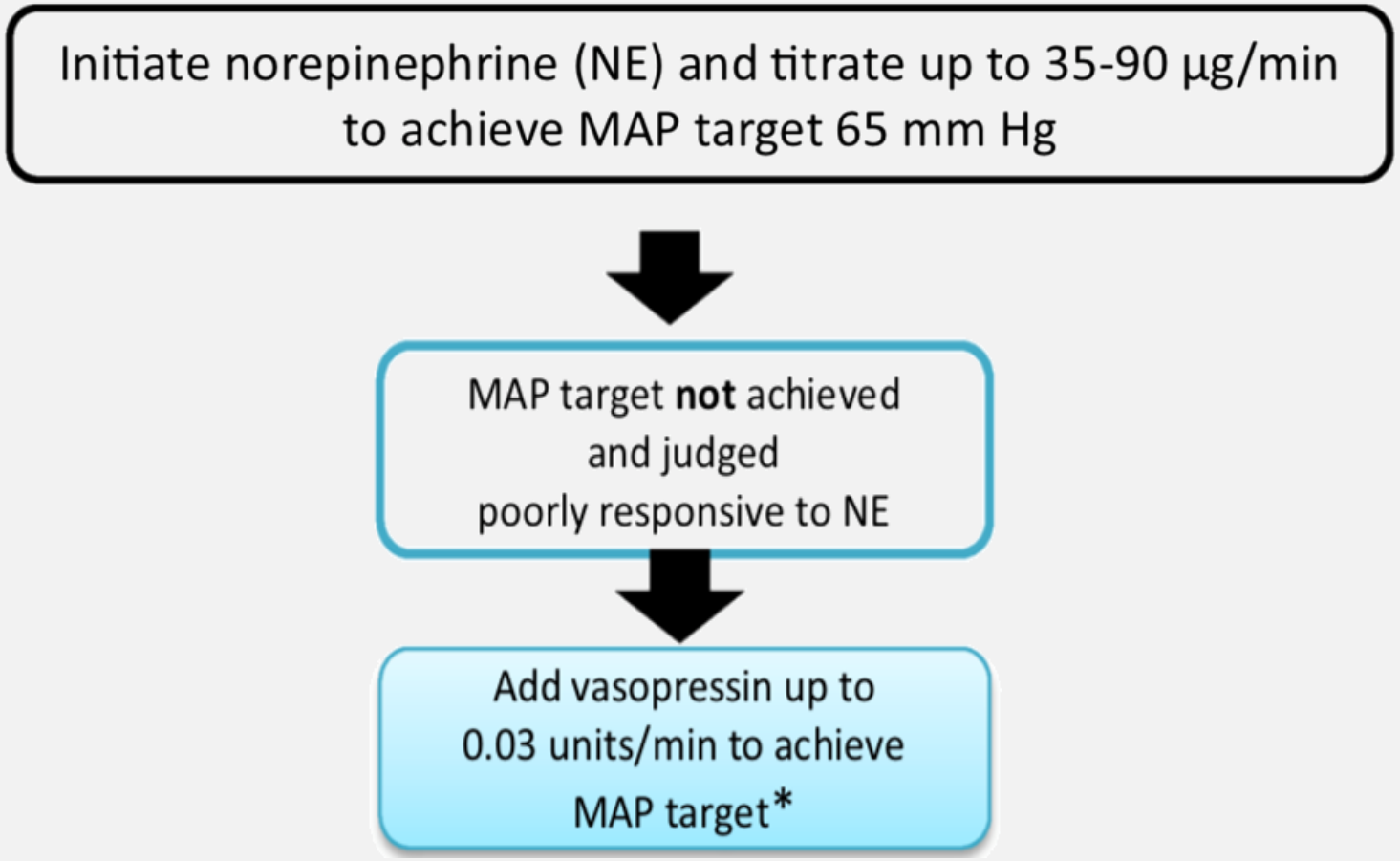
Effet neutre sur le nombre de jour sans VM et Vasopresseur

Pas de réduction de la dose de noradrénaline

Effet neutre sur la mortalité

Laterre P.F et al. JAMA 2019

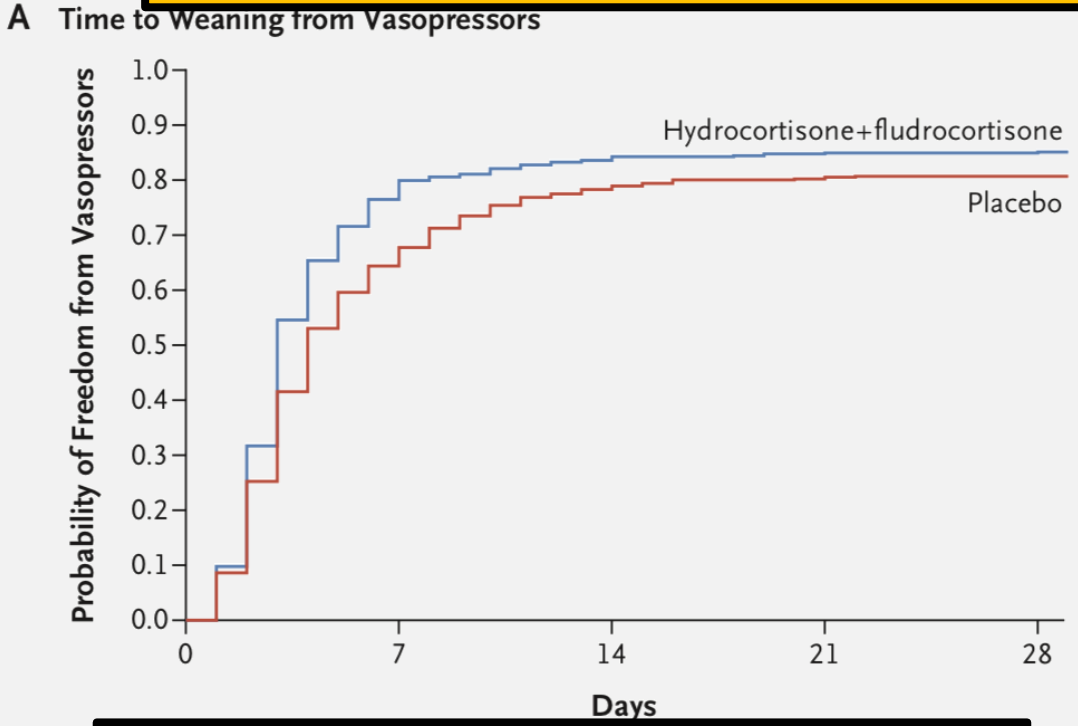
PLACE DE LA VASOPRESSINE DANS LA PRISE EN CHARGE DE LA VASOPLÉGIE SEPTIQUE



Dellinger et al. Intensive Care Med 2017

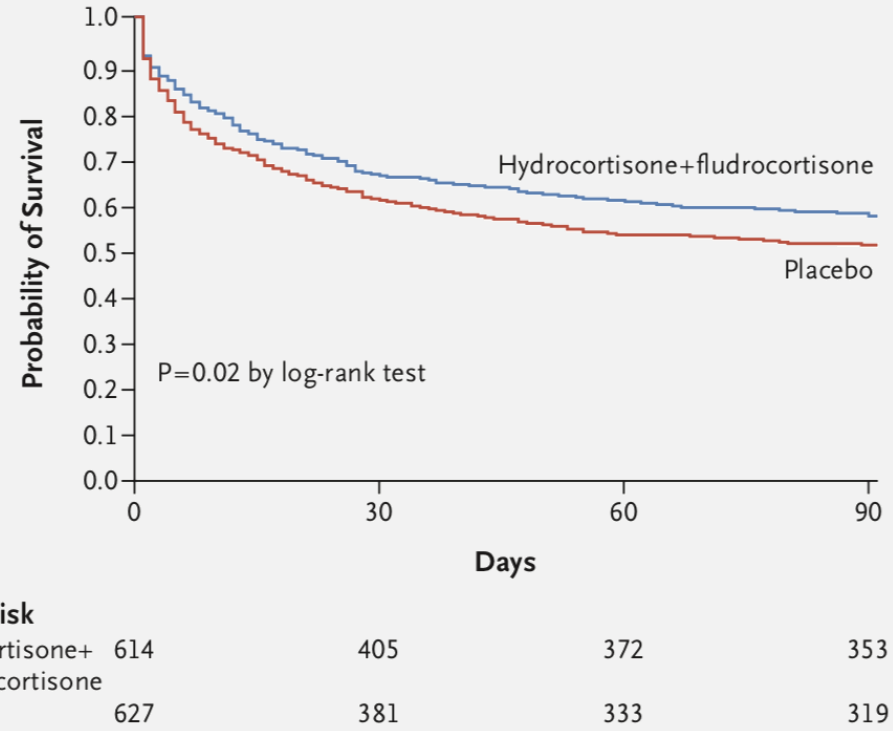
LES GLUCOCORTICOÏDES

Phase III, multicentrique, double aveugle, versus placebo objectif I^aire^: mortalité à 90 jours



Sevrage plus précoce des vasopresseurs

Impact de la Fludrocortisone ?



No. at Risk				
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

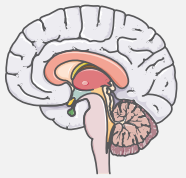
Diminue la mortalité

Population très sévère

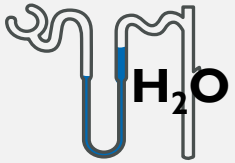
Annane N et al. Engl J Med 2018

LES THÉRAPIES QUI PROUVERONT PEUT ÊTRE LEURS EFFICACITÉS

ANGIOTENSINE II

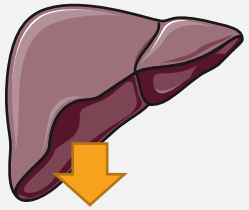


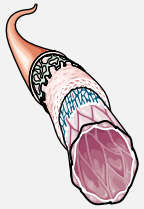
SNA



Volémie

Enzyme conversion angiotensine





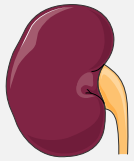
Vaisseaux — **Vasoconstriction**

angiotensinogène → Angiotensine I → Angiotensine II

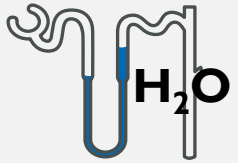
hypotension (+) (+)

Rénine

retroncontrole



Aldostérone

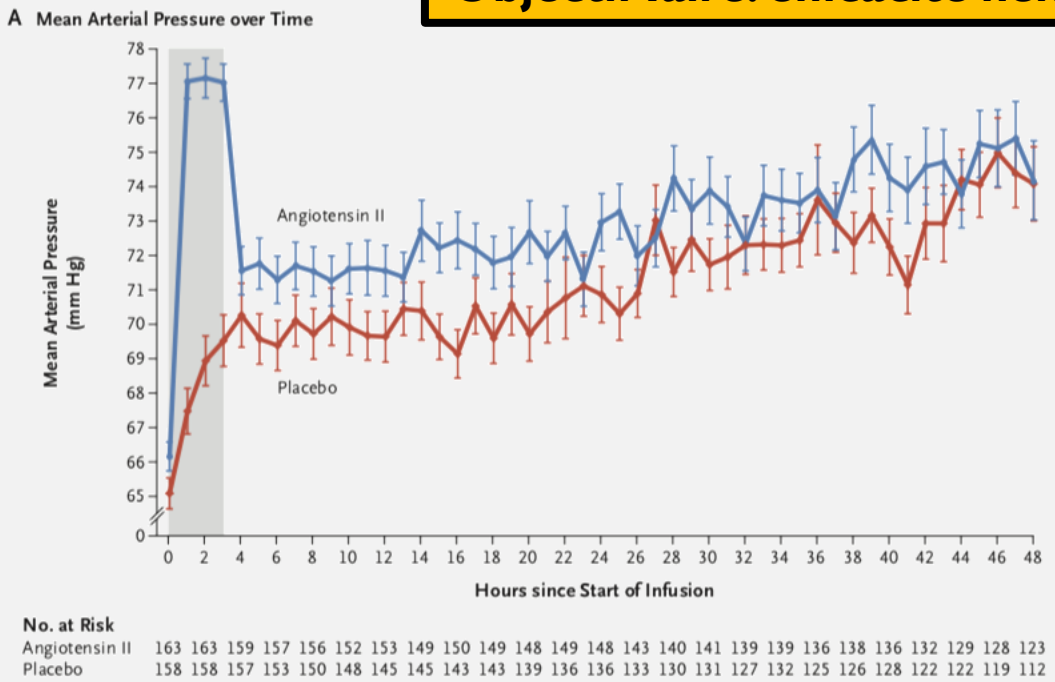


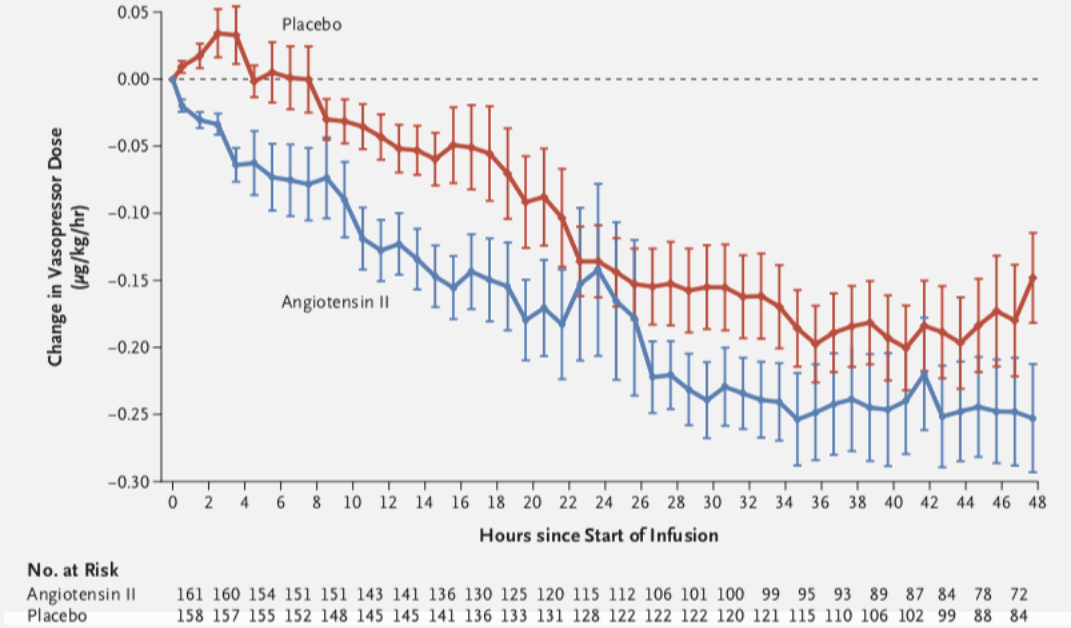
Volémie

Vasopressine

ANGIOTENSINE II

Phase III, multicentrique, randomisée, double aveugle, 344 patients,
Objectif laire: efficacité hémodynamique sur la PAM à 3H >75mmHg





Meilleure pression artérielle moyenne

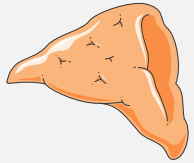
Moins de catécholamines

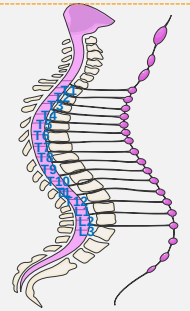
Khanna et al. N Engl J Med 2017

LE FUTUR ÉVENTUEL

BÉTA-BLOQUANTS

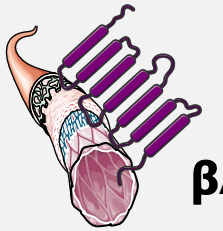
Systèmes activés



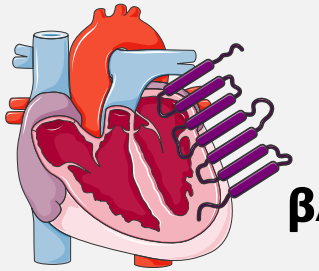


ADRENALINE | **NORADRENALINE**

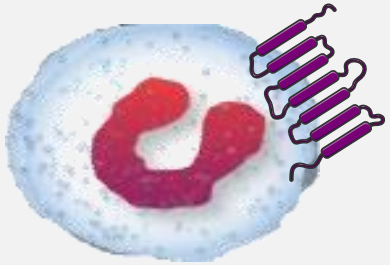
Dysautonomie



βAR



βAR

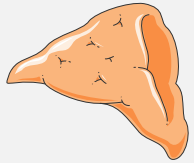


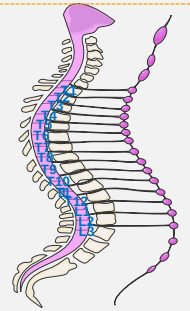
βAR

VASOREACTIVITE | **CONTRACTILITÉ** | **INFLAMMATION**

BÉTA-BLOQUANTS

Systèmes activés

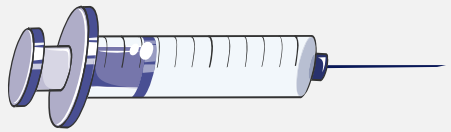


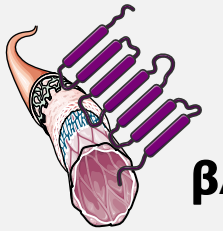


↗ADRENALINE **↗NORADRENALINE**

Dysautonomie

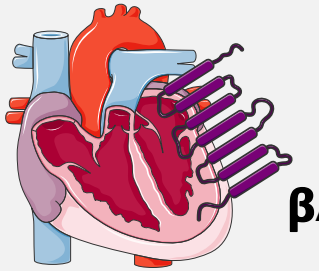
BETA BLOQUANT





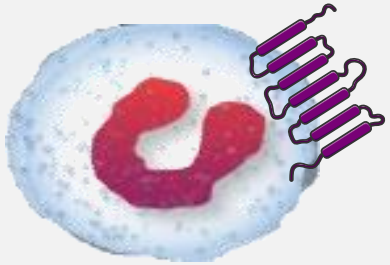
βAR

↘VASOREACTIVITE



βAR

↘CONTRACTILITÉ

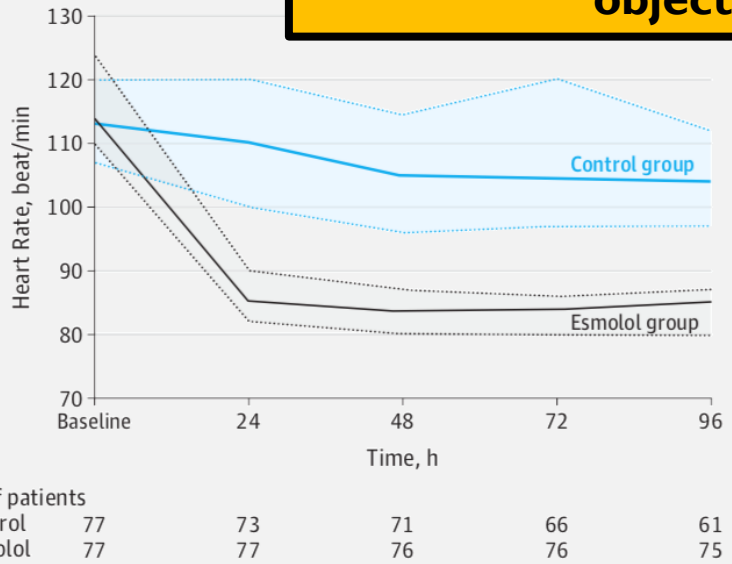


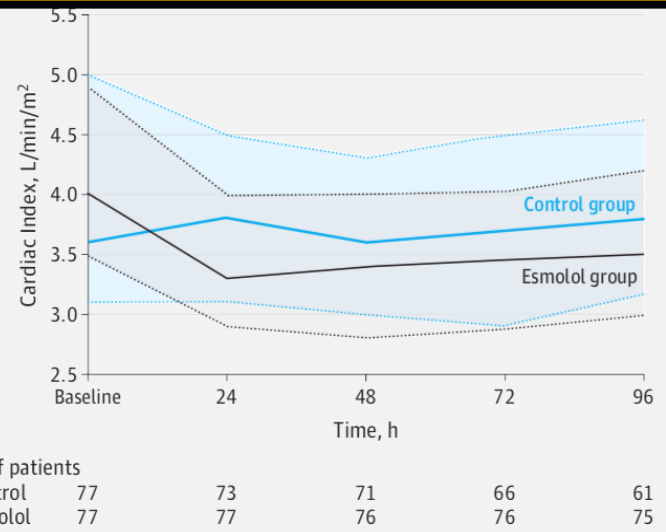
βAR

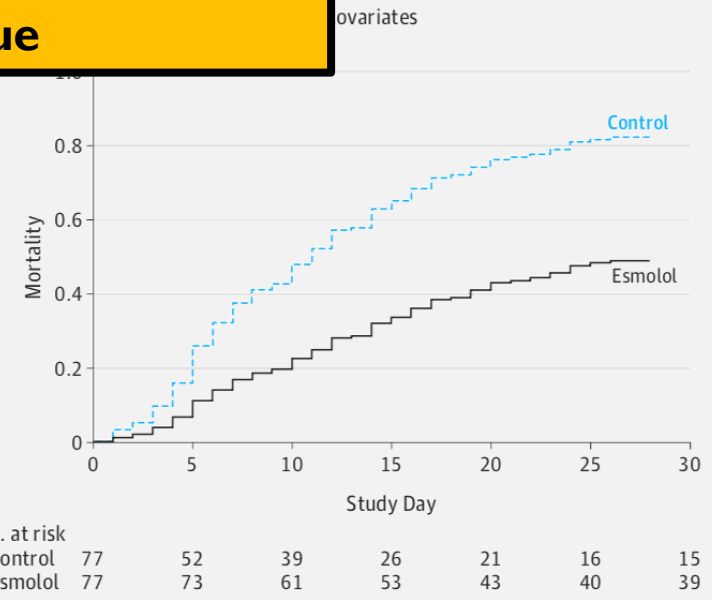
↘INFLAMMATION

BÉTA-BLOQUANTS

Phase IIb, monocentrique, randomisée, sans aveugle, 144 patients stabilisés
objectif laire : réduction de la fréquence cardiaque







Diminue la fréquence cardiaque

Sans diminution du débit cardiaque

Amélioration de la survie

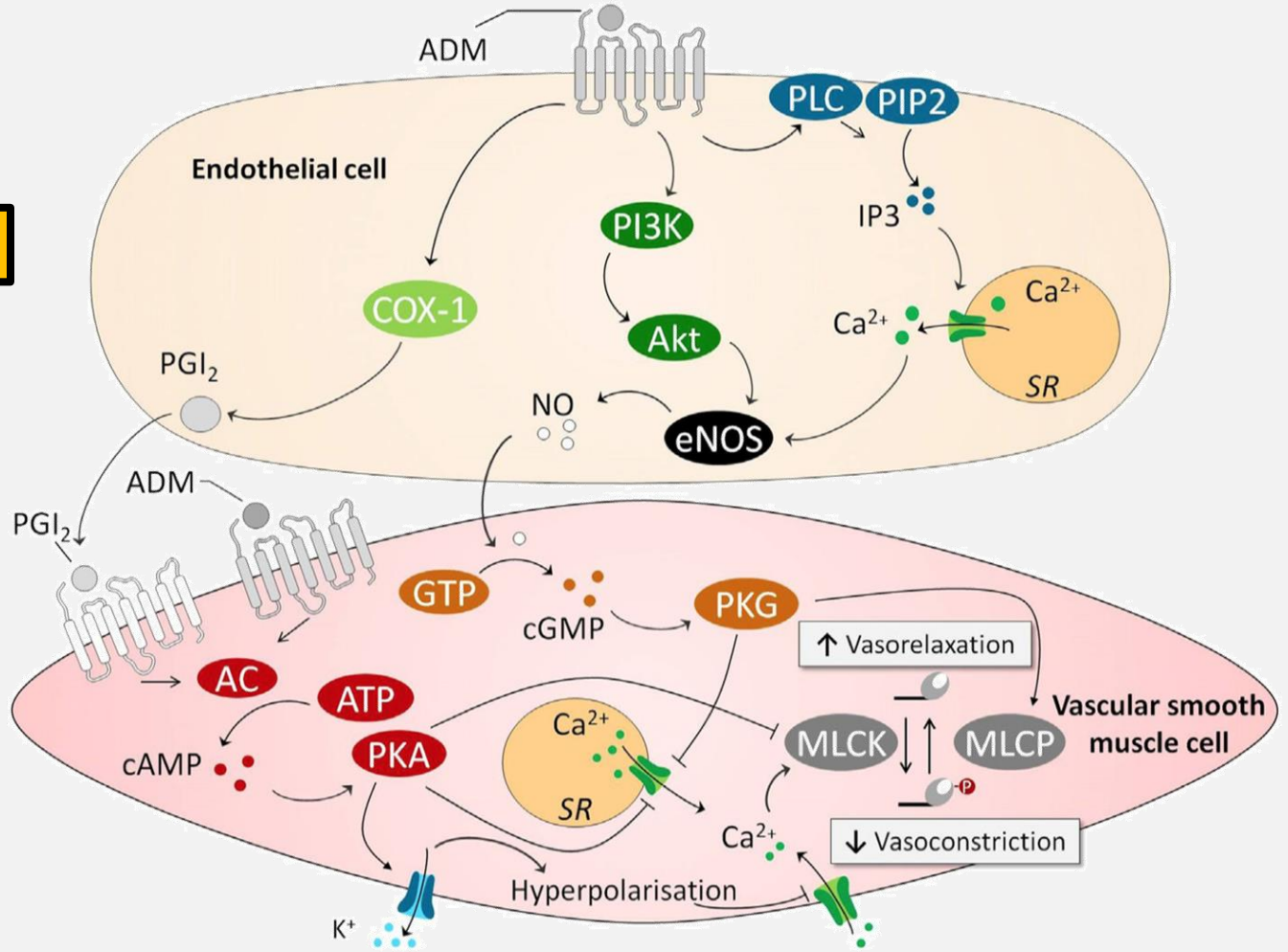
Monocentrique, effectifs faibles… contre-intuitif => à reproduire

Morelli et al. JAMA 2014

ADRÉNOMODULINE

Cellule endothéliale

Cellule musculaire lisse

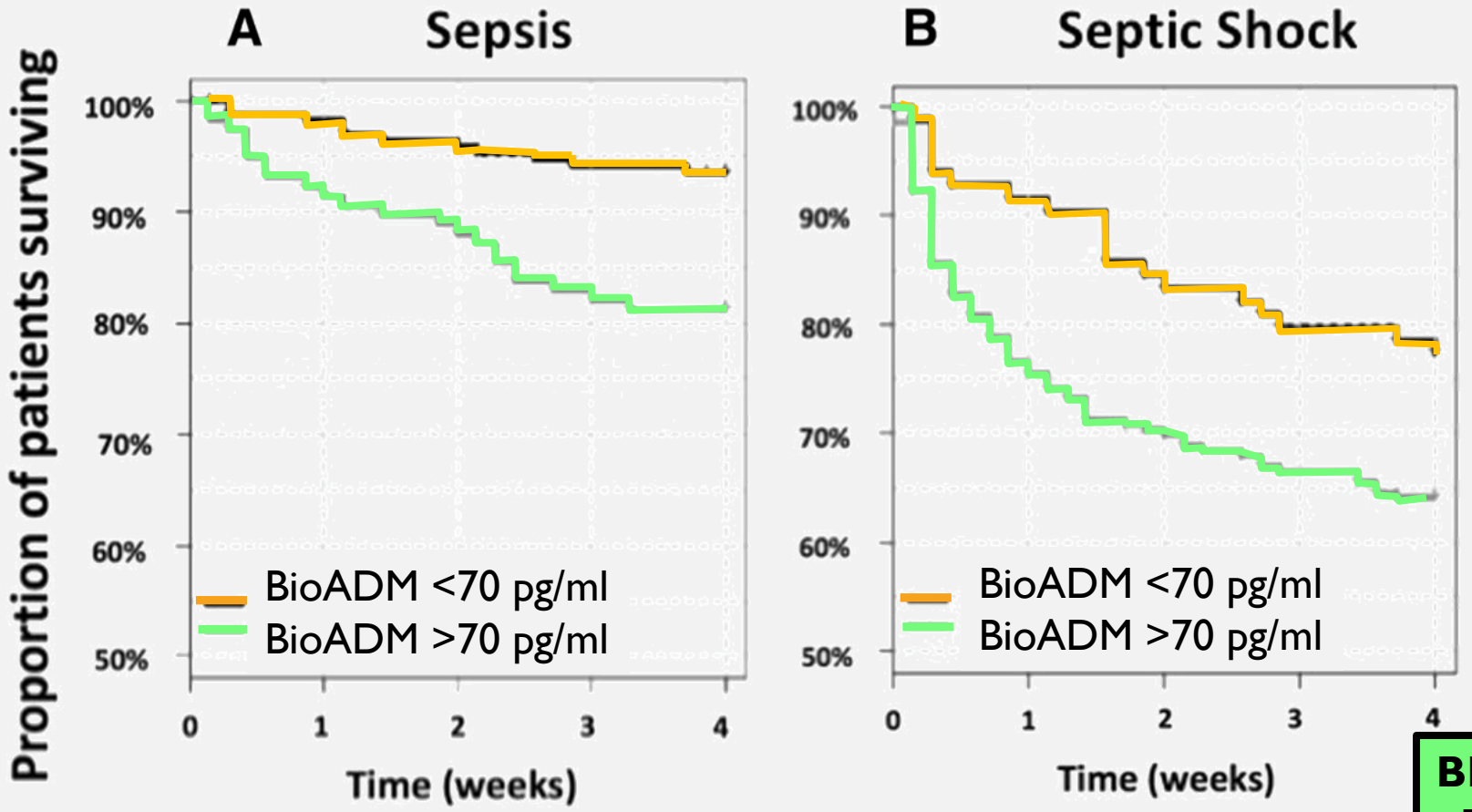


Vasodilatation

Maintien de la barriere endotheliale

Geven C et al. *Front Immunol* 2018

ADRÉNOMODULINE



BIOADM> 70 pg/ml= Population à cibler

Mebazaa A et al. *Crit Care* 2018

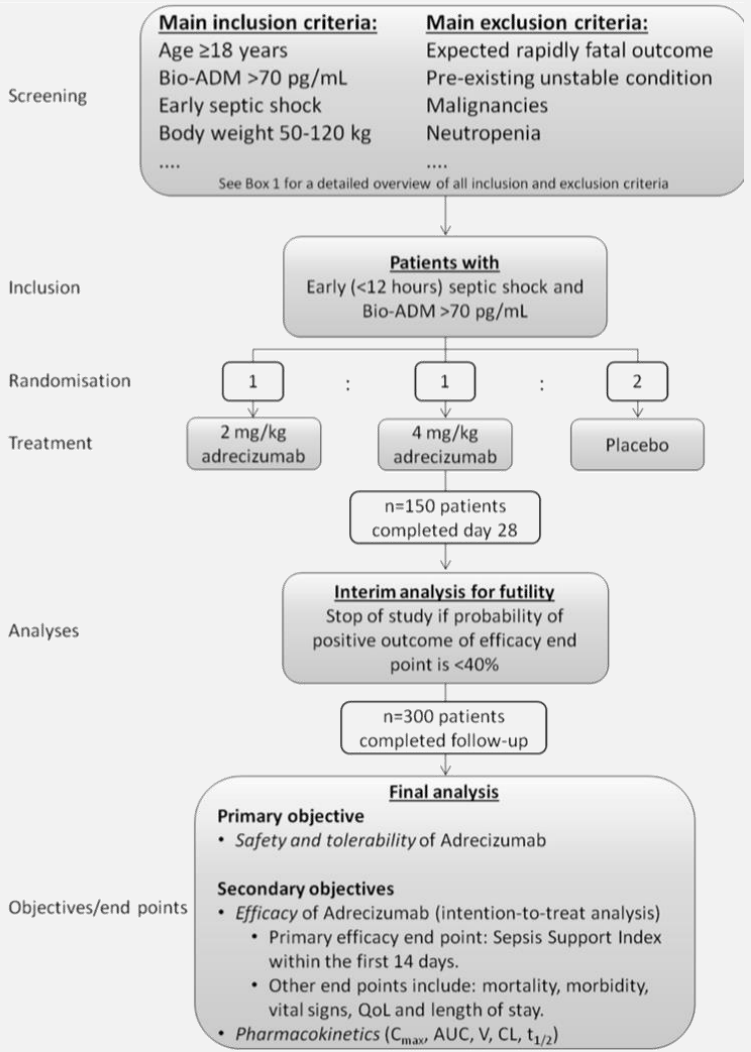
ADRECIZUMAB : ADRENOS II

Choc septique

BIO-ADM>70 pg/ml

Doses différentes

Tolérabilité et critère composite



Sélection sur critère biologique

Geven C et al. *BMJ Open* 2018

CONCLUSION

Vasoplégie

→ **Traitement étiologique**

- sepsis
- post CEC
- cardiaque

Expansion volémique

Premiere ligne

Noradrénaline

→ *Répondeur*

Non répondeur

Deuxième ligne

Fonction cardiaque conservée

→ **Noradrénaline + Vasopressine +/- HSHC+ Fludrocortisone**

← *Répondeur*

Fonction cardiaque altérée

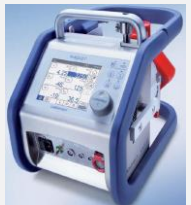
→ **Dobutamine + Noradrénaline +/- HSHC+ Fludrocortisone**

→ *Répondeur*

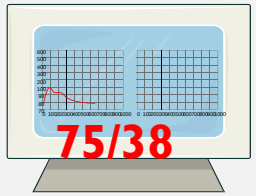
Rescue

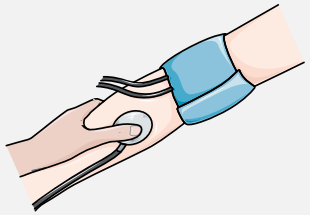
Non répondeur + Noradrénaline

→ **Noradrénaline**

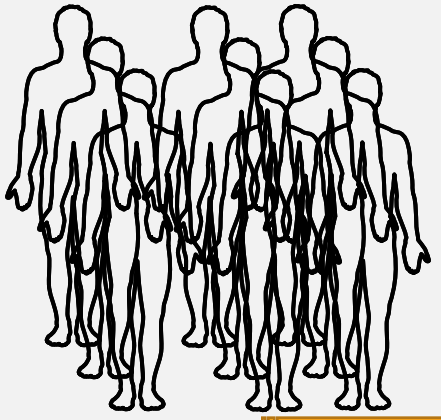


Aujourd'hui

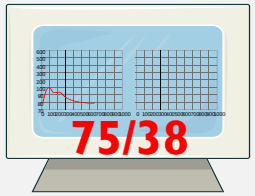


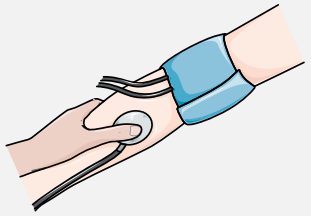


NORADRENALINE



Demain





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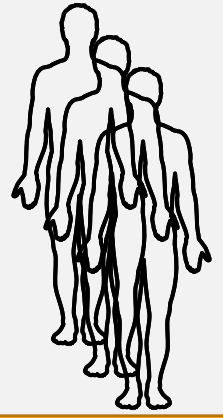


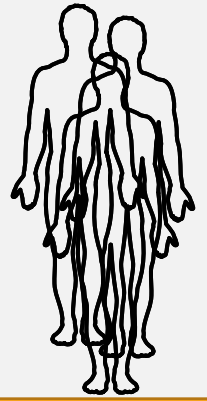
NORADRENALINE

+/-

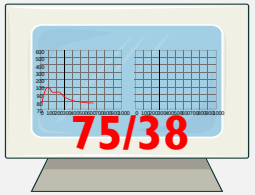
VASOPRESSINE

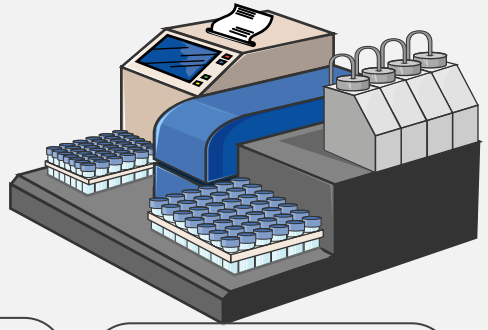
+/-

ANGIOTENSINE



Après-demain





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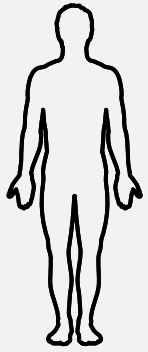


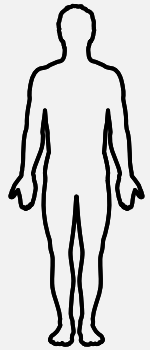
NORADRENALINE

+/-

VASOPRESSINE

+/-

ANGIOTENSINE



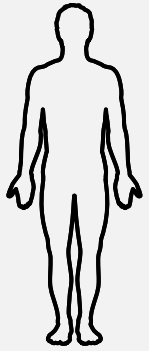
NORADRENALINE

+

ANGIOTENSINE

+

HEMODYMIMAB



Personalisation de la médecine réanimatoire