

Existe t'il un intérêt aux modulateurs de la fréquence cardiaque dans le choc septique ?

Enseignement du DESC de Réanimation

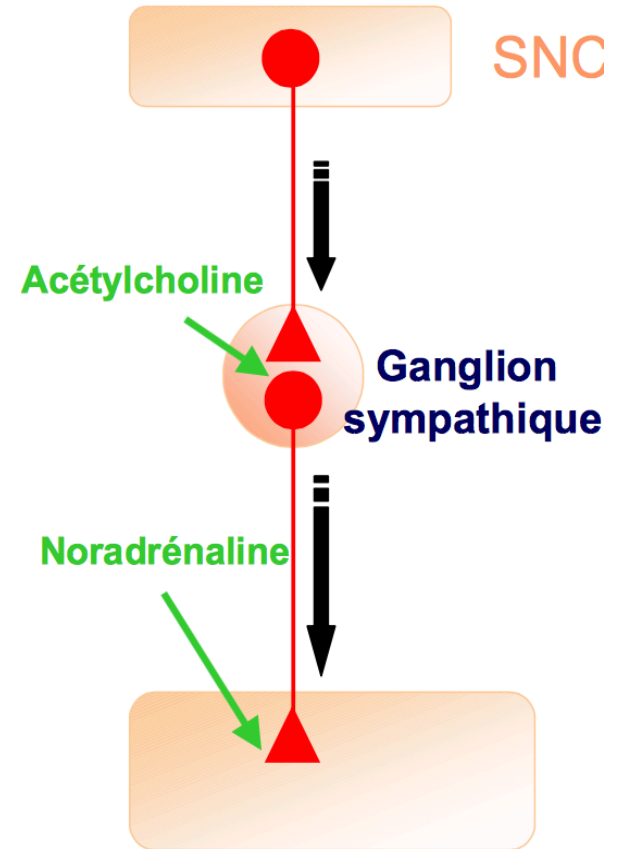
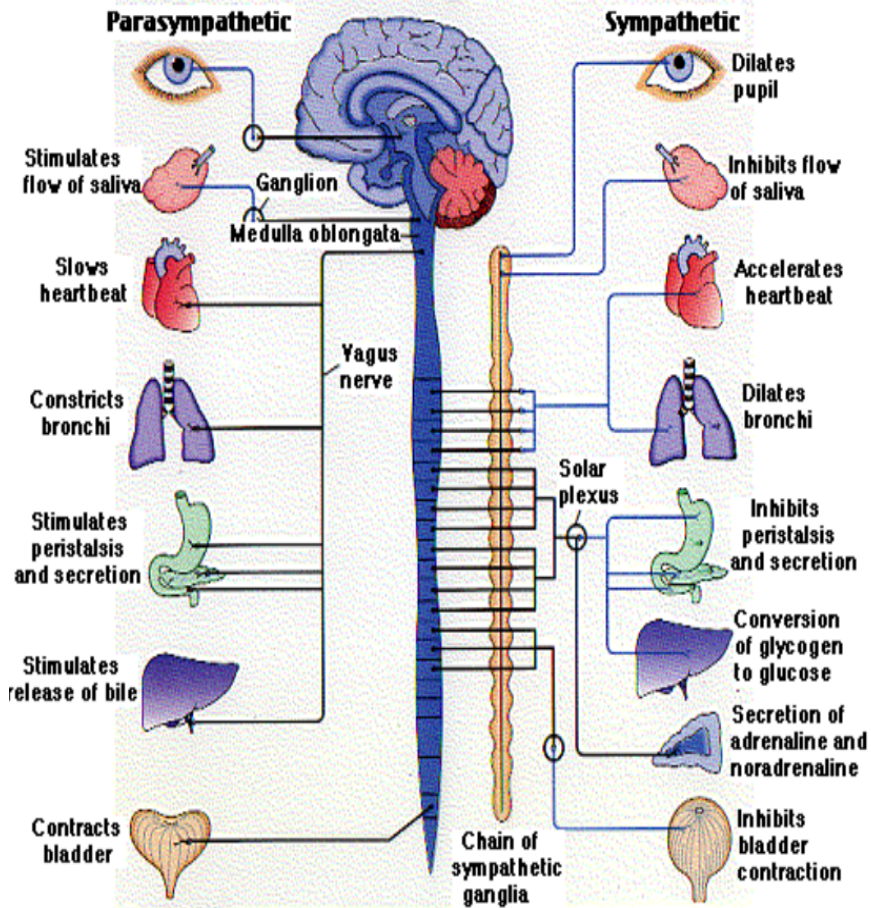
Antoine Kimmoun

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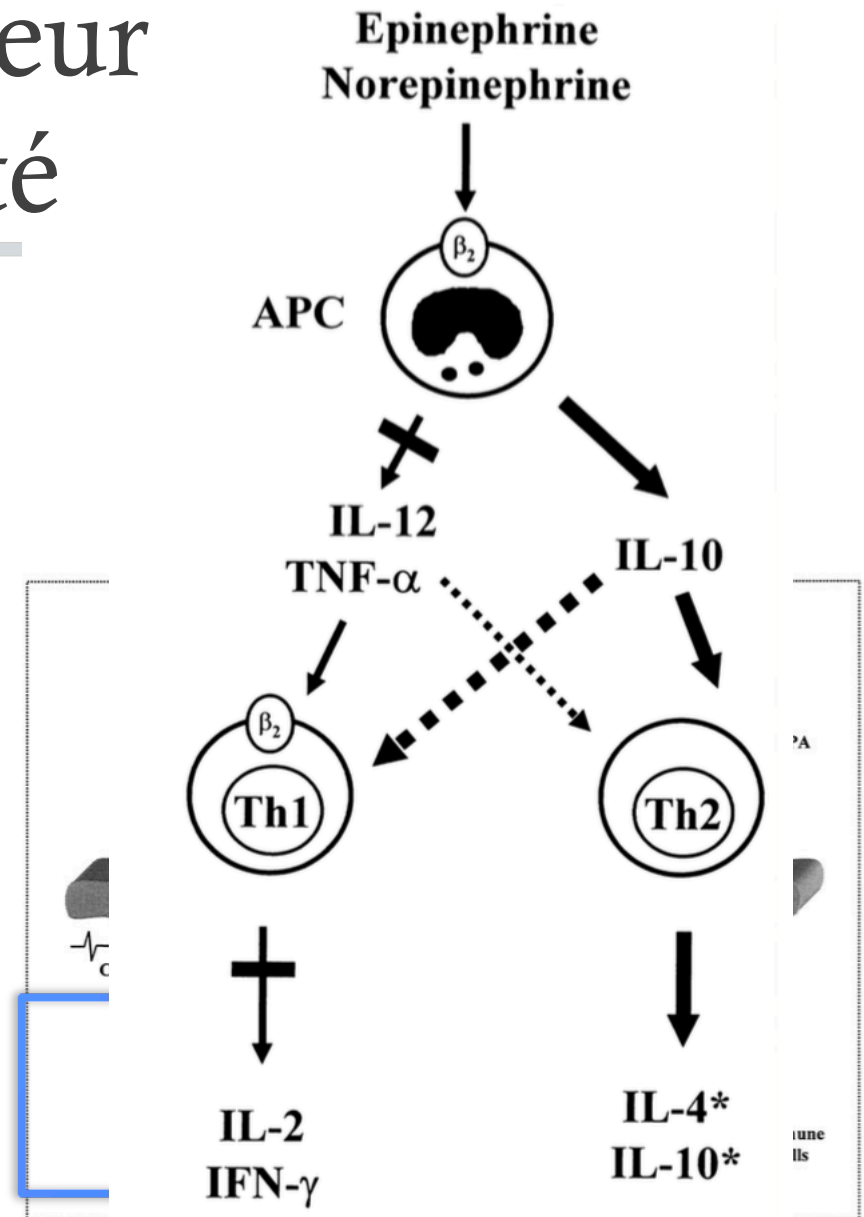
Physiologie du Système Nerveux Autonome



Un impact majeur sur l'immunité

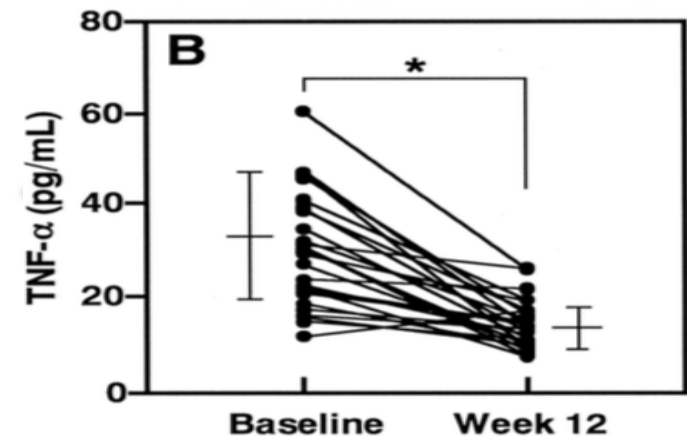
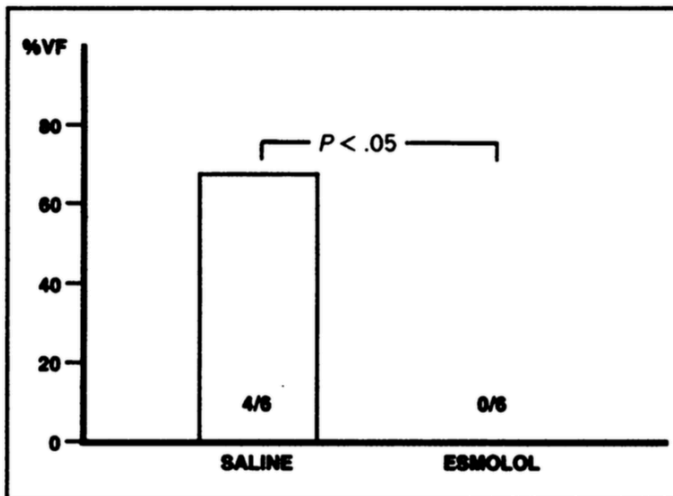
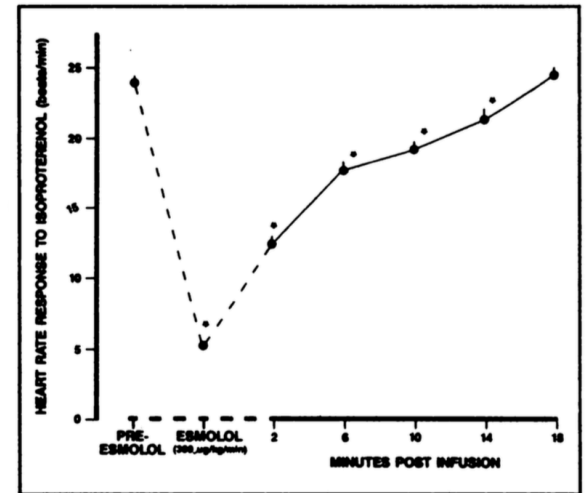
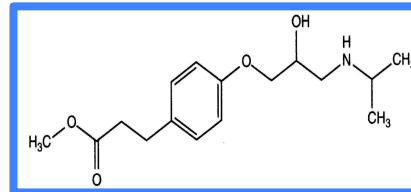
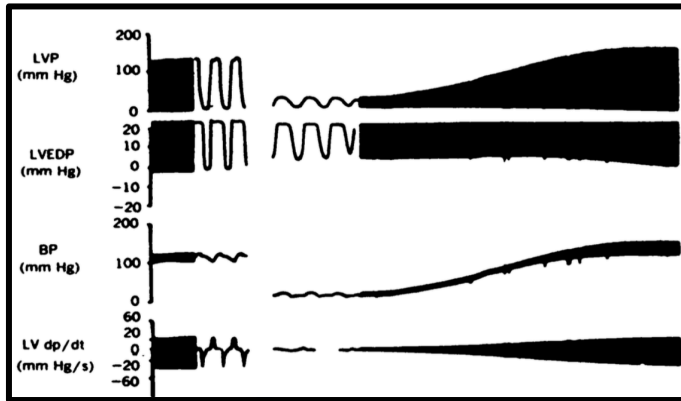
Interaction entre

- le système nerveux central
- Cellules effectrices de l'immunité
 - *Via* adrénorécepteurs β_2 α_1 et α_2
 - Plutôt vers une réponse Th2 humorale ant inflammatoire





B bloquant: modulateur du système nerveux autonome



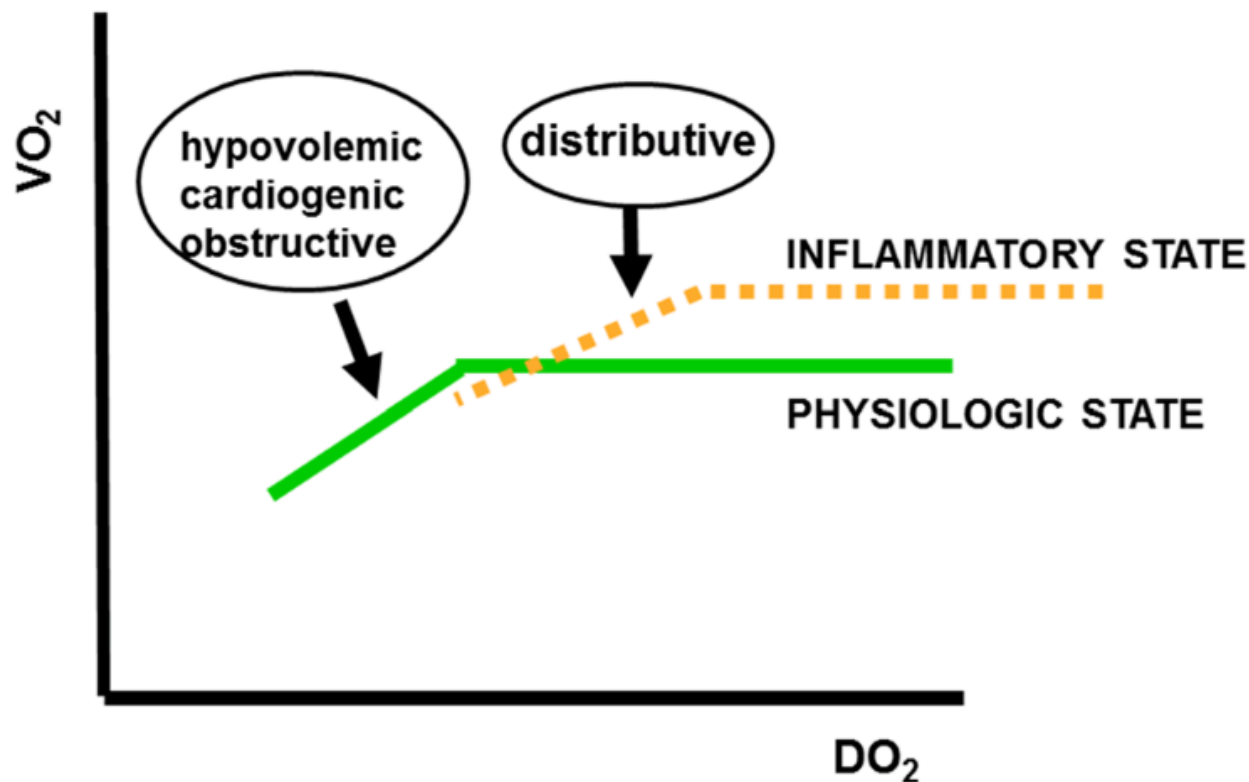
Insane or Inspired?

Meldrum et al. **Crit Care Med** 2005;33:2433

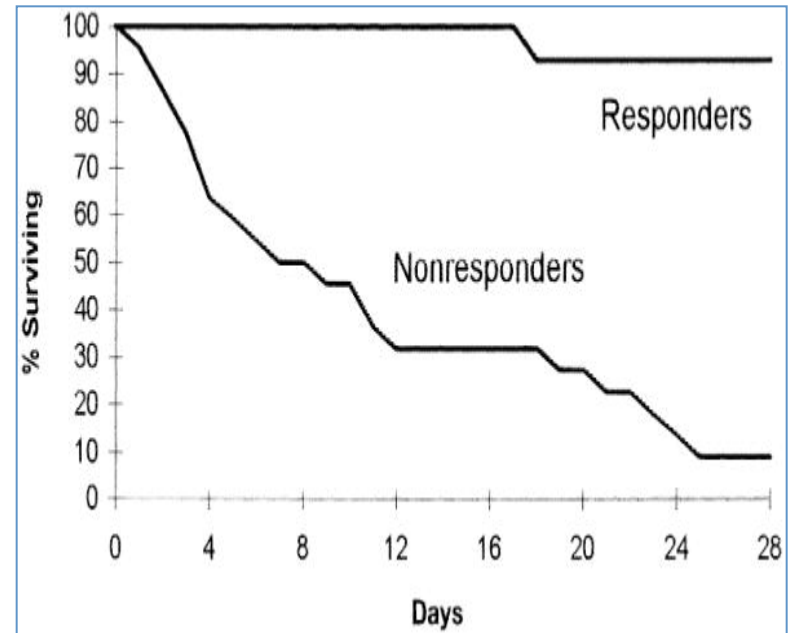
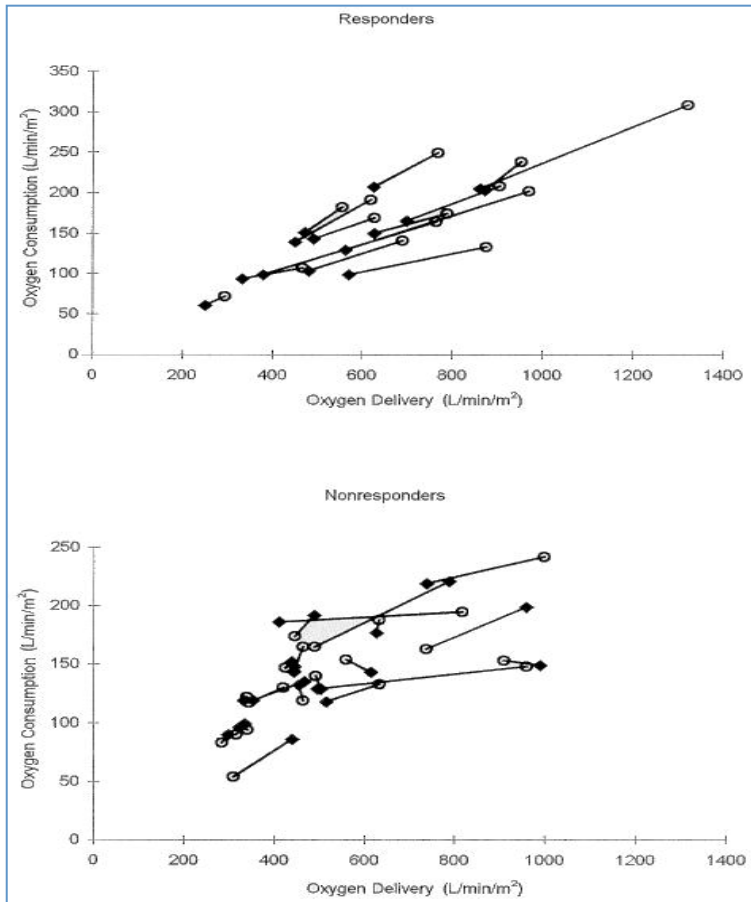
Insane?

Diminuer la fréquence cardiaque...
une fausse bonne idée?

Physiopathologie du choc



Les catécholamines: traitement pronostic du choc



Littérature abondante

Effect of norepinephrine on the outcome of septic shock

Claude Martin, MD, FCCM; Xavier Viviand, MD; Marc Leone, MD; Xavier Thirion, MD, PhD

P.-E. Bollaert
B. Dousset
J.P. Mallie
A. Larcan

Oxygen transport parameters
Influence of treatment on
Hayes, Michelle A. MD, FRCA; Timmins
FRCA; Hinds, Charles J. FRCP

Vasoactive
Steven M. Hollenberg
Robert Wood Johnson Medical School
Camden, New Jersey

Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study)*

Pedro R. Póvoa, MD, PhD; António H. Carneiro, MD; Orquídea S. Ribeiro, BSc; Altamiro C. Pereira, MD, PhD; on behalf of the Portuguese Community-Acquired Sepsis Study Group

Cooper University Hospital,

Amjad Ali², Barry Milcar

mine stress predicts outcome

Open Access

Un fort niveau de preuve

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).

I. Inotropic Therapy

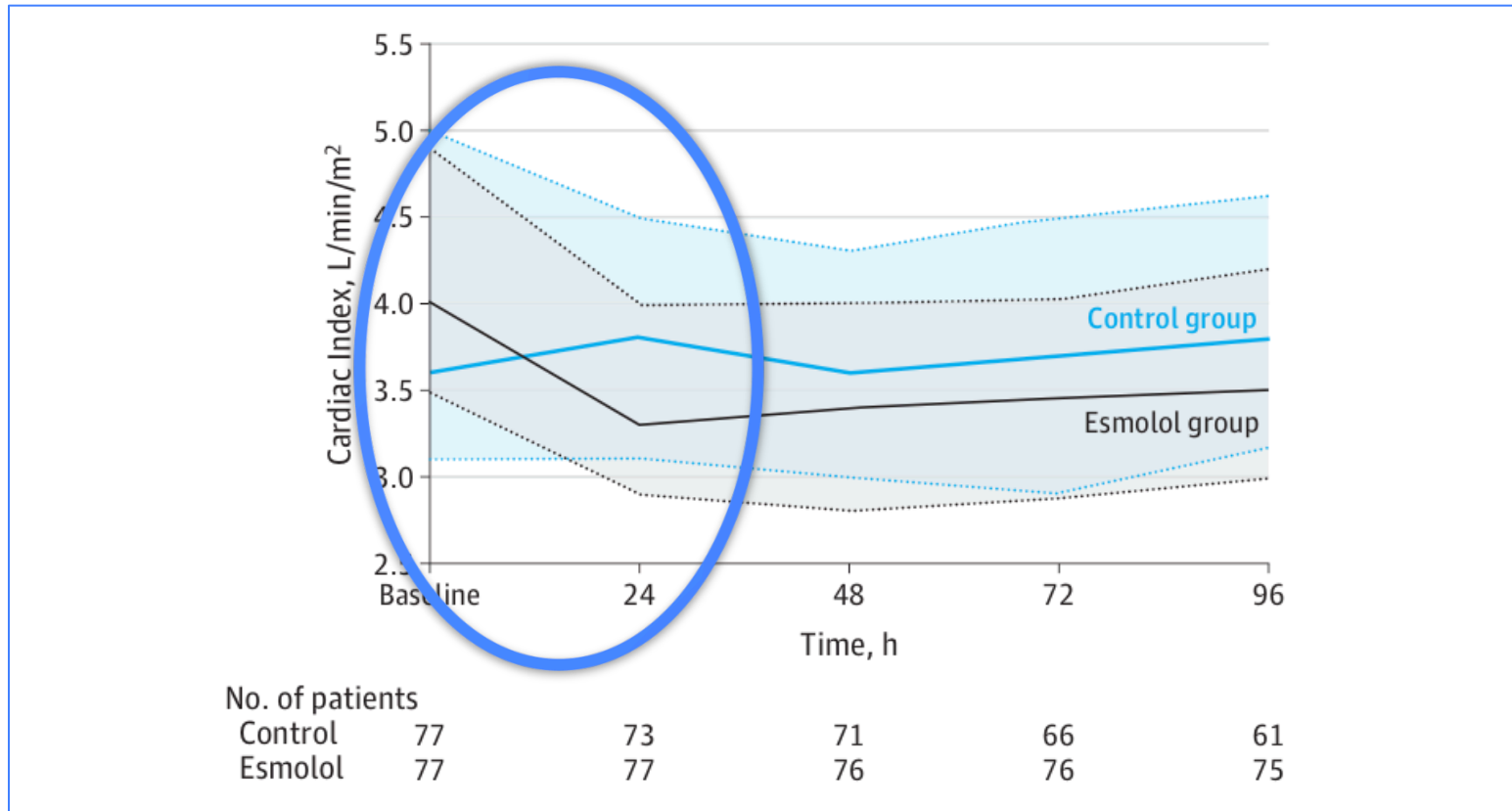
1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).



Rationnel d'un traitement β bloquant dans ce contexte?

Les β bloquants diminuent la fréquence cardiaque et le débit cardiaque...

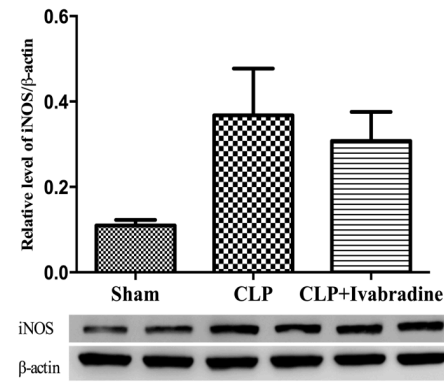
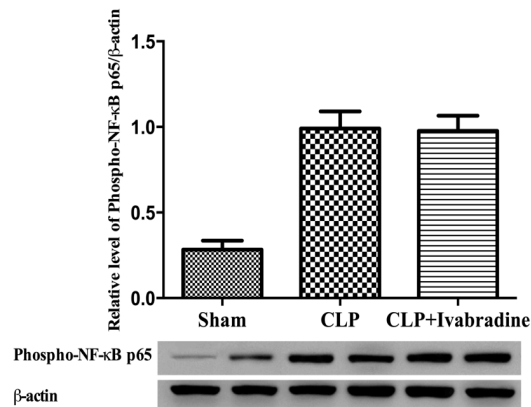
JAMA



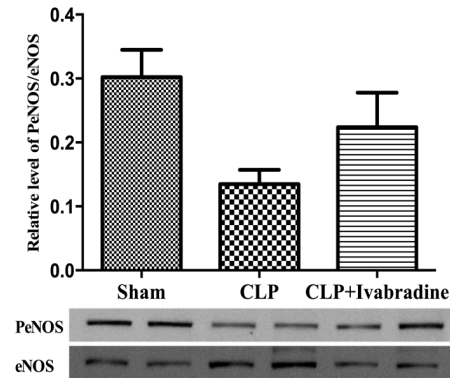
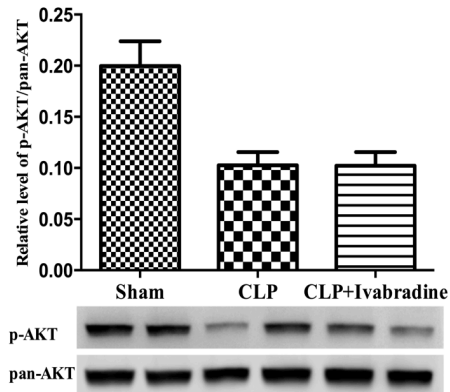
Intérêt de diminuer la fréquence cardiaque dans le choc

Variables	Sham n=8		CLP n=8		CLP+Ivabradine n=8		P
	Median	Minimum- Maximum	Median	Minimum- Maximum	Median	Minimum- Maximum	
Heart rate (min ⁻¹)	376	349-418	431	402-467	329	284-368	
Mean arterial pressure (mmHg)	112	104-120	81	75-96	73	64-86	
Stroke volume (μL)	253	199-302	131	71-186	109	61-195	
Cardiac output (mL/min)	95	75-112	56	30-69	36	16-72	
Ejection fraction (%)	86	84-89	92	87-98	91	83-95	
Lactatemia (mmol/L)	1.2	0.8-1.7	2.5	1.9-3.3	2.6	2-3.7	

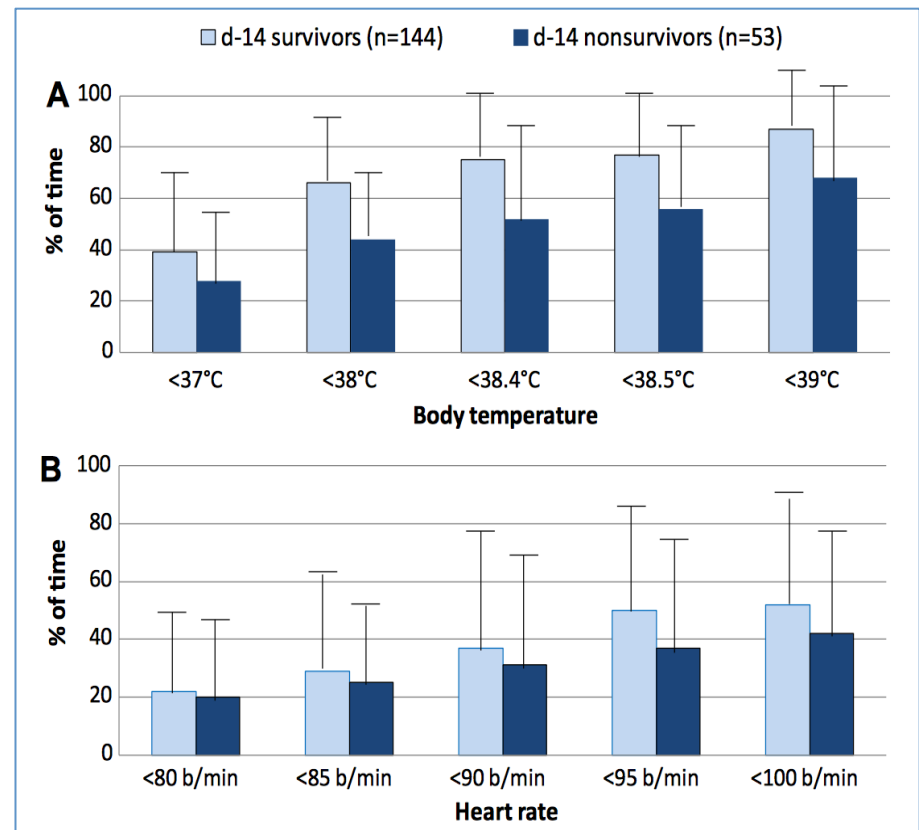
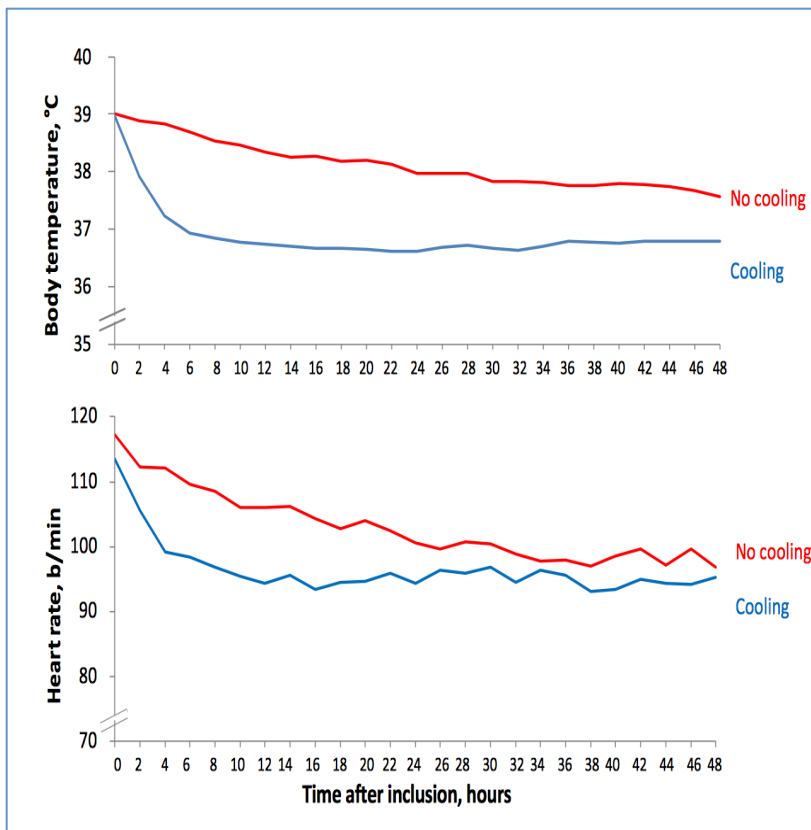
Un intérêt sur l'inflammation?



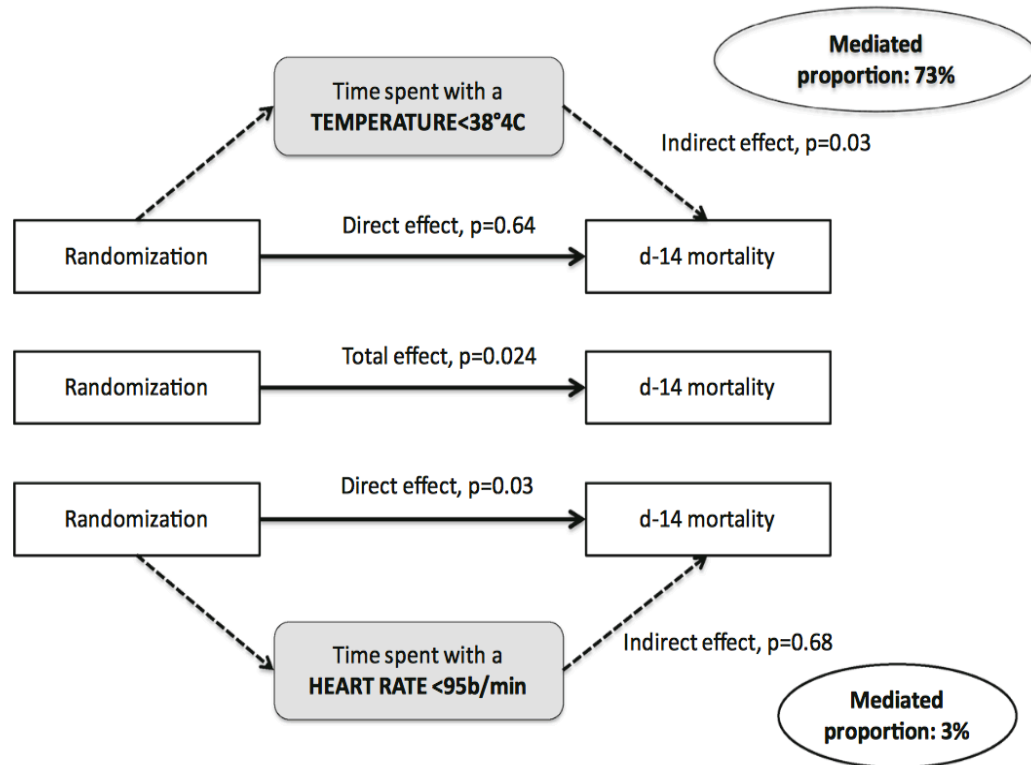
COEUR



Aucun effet bénéfique de la réduction de la fréquence cardiaque chez l'homme?



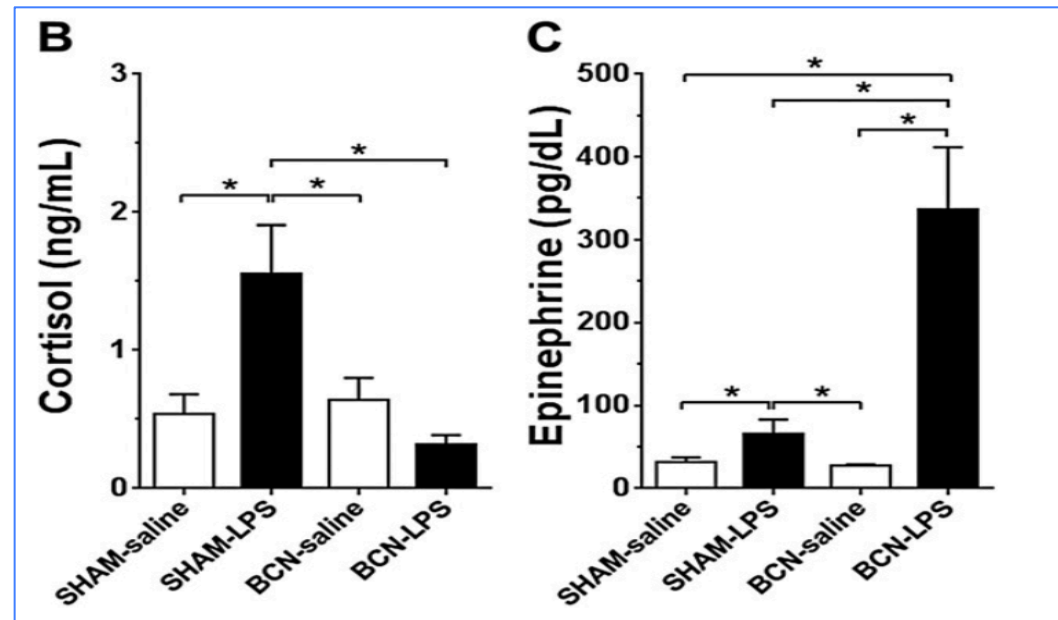
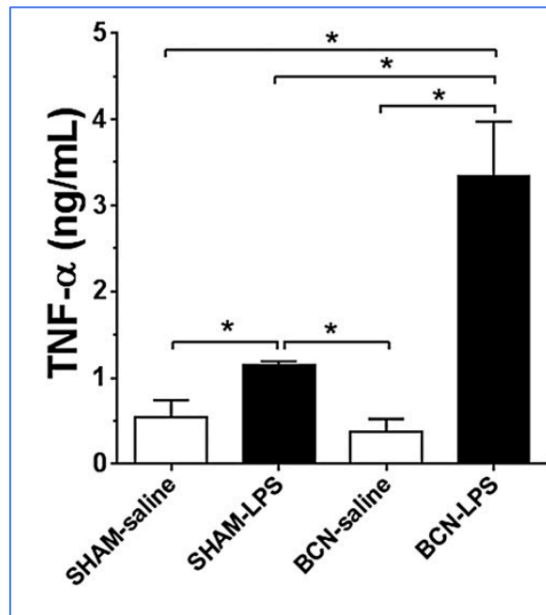
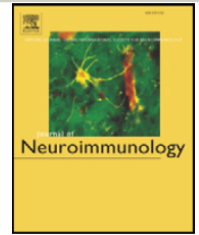
Un impact sur la survie?



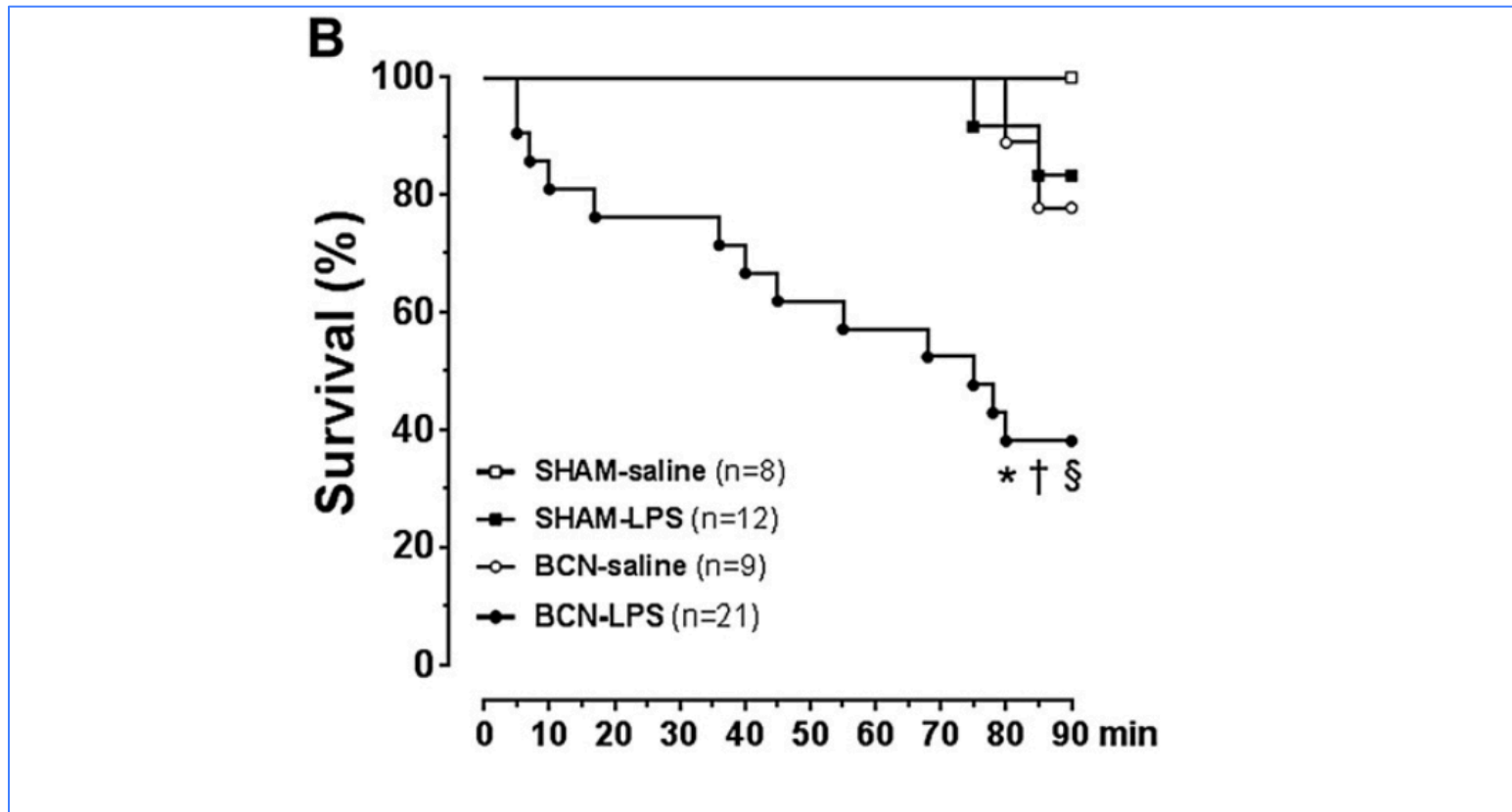
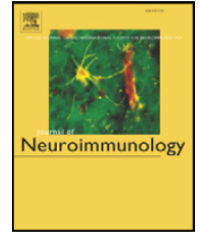
*Moduler le système nerveux autonome pour limiter
l'excès l'inflammation ?*

Faire du mal en voulant faire bien....

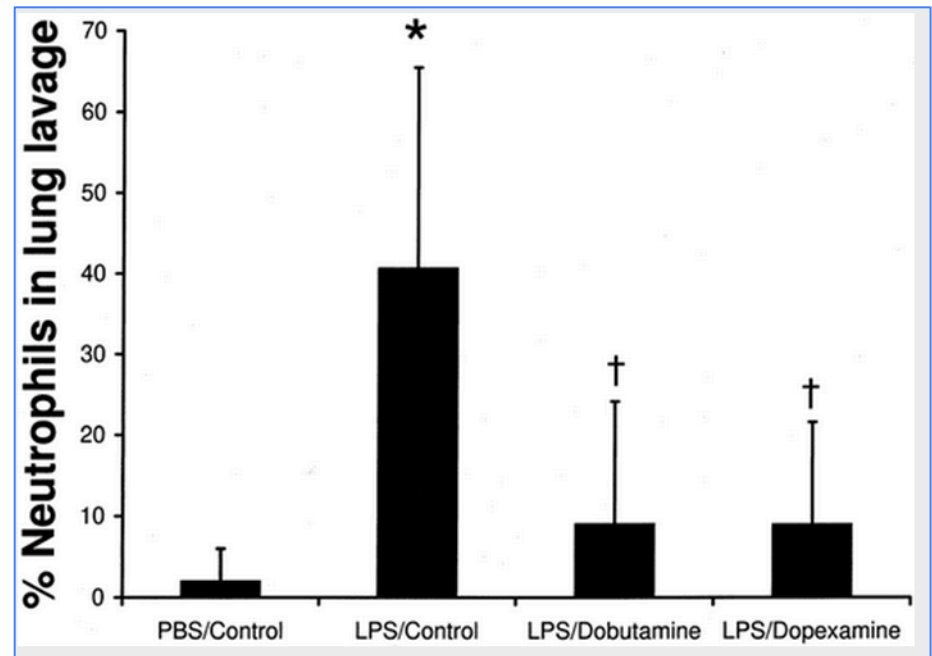
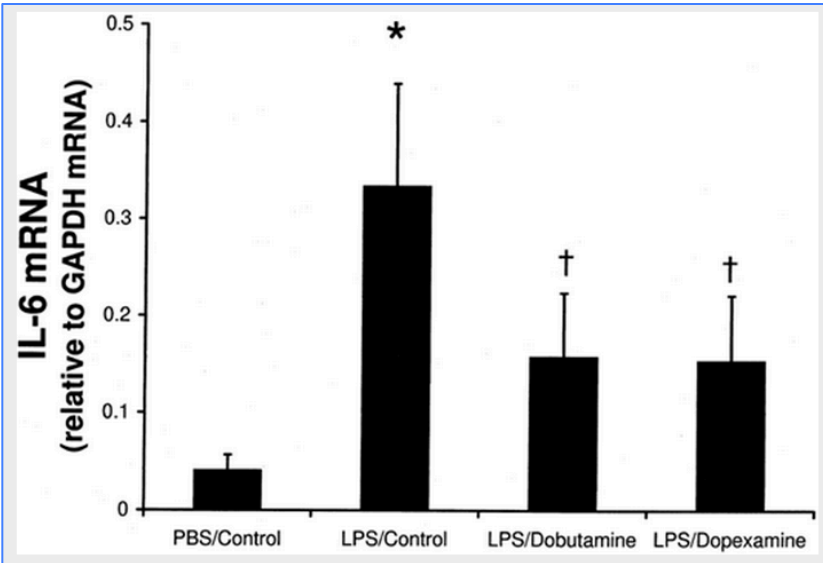
Inhibition du système nerveux autonome



Inhibition « délétère » du système nerveux autonome



Catécholamines pro-inflammatoires?

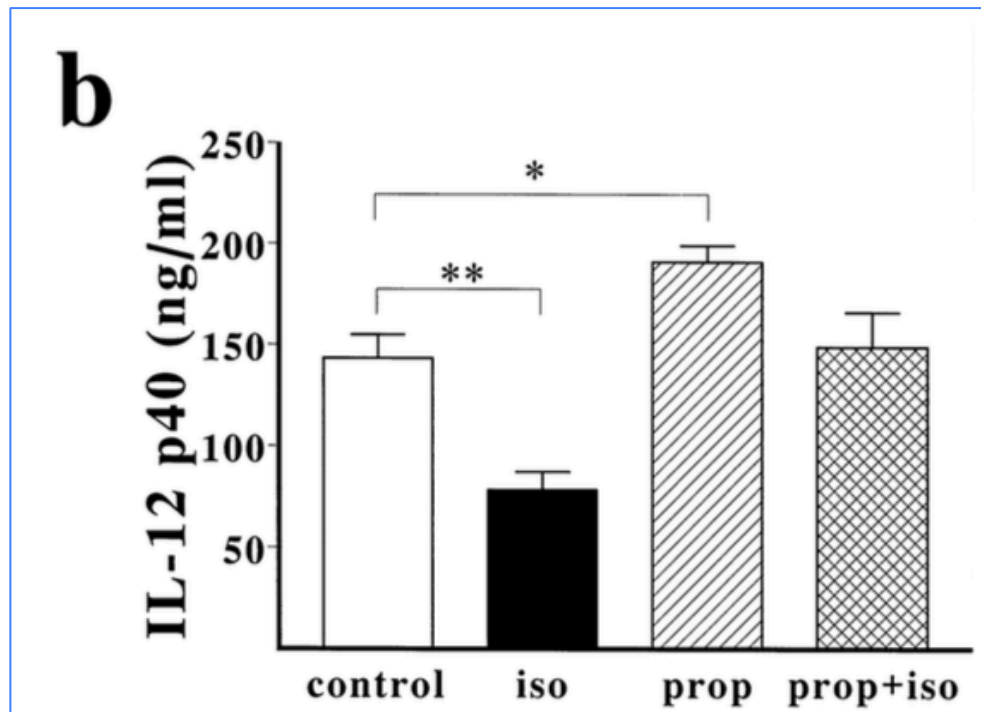
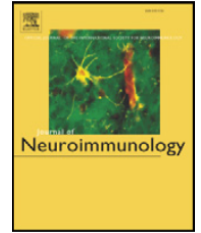


Des effets plutôt anti-inflammatoires

Table 2 Effects of vasoactive drugs on cytokine production or activity. See text for details. TNF = tumor necrosis factor, IL = interleukin

Author	(ref)	Drug	Cytokine	Model	Effect
Zabel	[30]	Pentoxifylline	TNF	Human	Inhibits
Schade	[31]	Pentoxifylline	TNF	Murine	Inhibits
Barton	[32]	Pentoxifylline	TNF, IL-6	Blood	Inhibits
Standiford	[33]	Pentoxifylline	IL-10	Monocytes	Enhances
Giroir	[34]	Amrinone	TNF	Murine	Inhibits
Liao	[35]	Epinephrine	TNF	Rat Liver	Inhibits
			IL-6	Rat Liver	Enhances
Monastra	[36]	Epinephrine	TNF	Murine	Inhibits
Van der Poll	[37]	Epinephrine	TNF	Human	Inhibits/Attenuates
			IL-10	Human	Enhances
Severn	[38]	Epinephrine	TNF	Monocytes	Inhibits/Attenuates
Ritchie	[40]	Dopamine	TNF	Adrenal Cells	Inhibits
Hasko	[41]	Dopamine (D2)	TNF	Murine	Enhances
Severn	[38]	Isoproterenol	TNF	Monocytes	Inhibits
Vander Poll	[39]	Norepinephrine	TNF	Human	Inhibits

β bloquants pro inflammatoires ?



Synthèse contre l'utilisation des β - bloquants

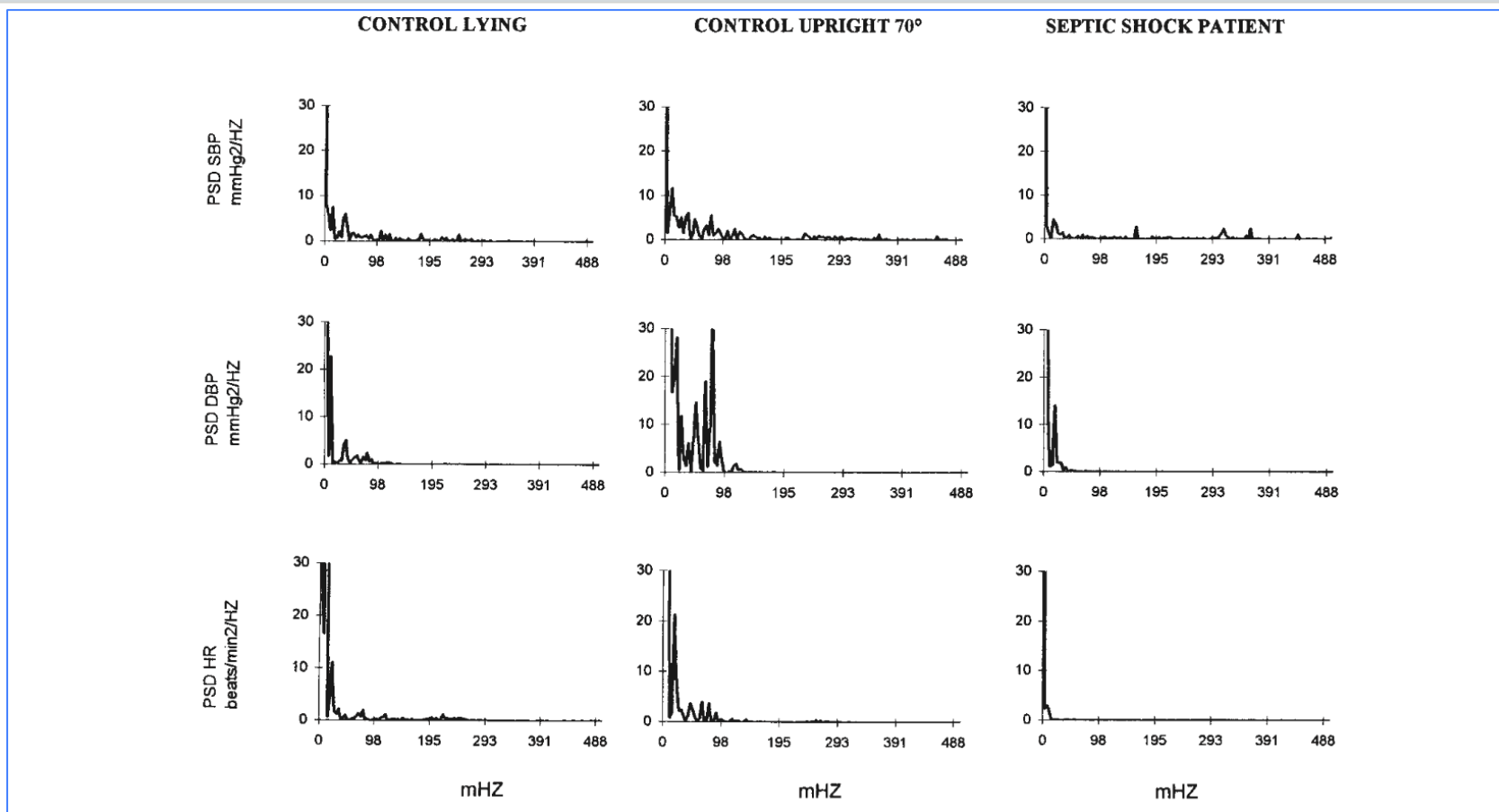
- Contre-intuitif hémodynamiquement dans la prise en charge du choc septique
- L'activation du système nerveux autonome est indispensable à la survie
- Les β bloquants peuvent être pro inflammatoires
- Aucune preuve qu'une réduction du stimulus adrénergique est bénéfique
- La réduction de la fréquence cardiaque ne semble pas bénéfique

Et pourtant...

Inspire ?

Un rationnel mal interprété...

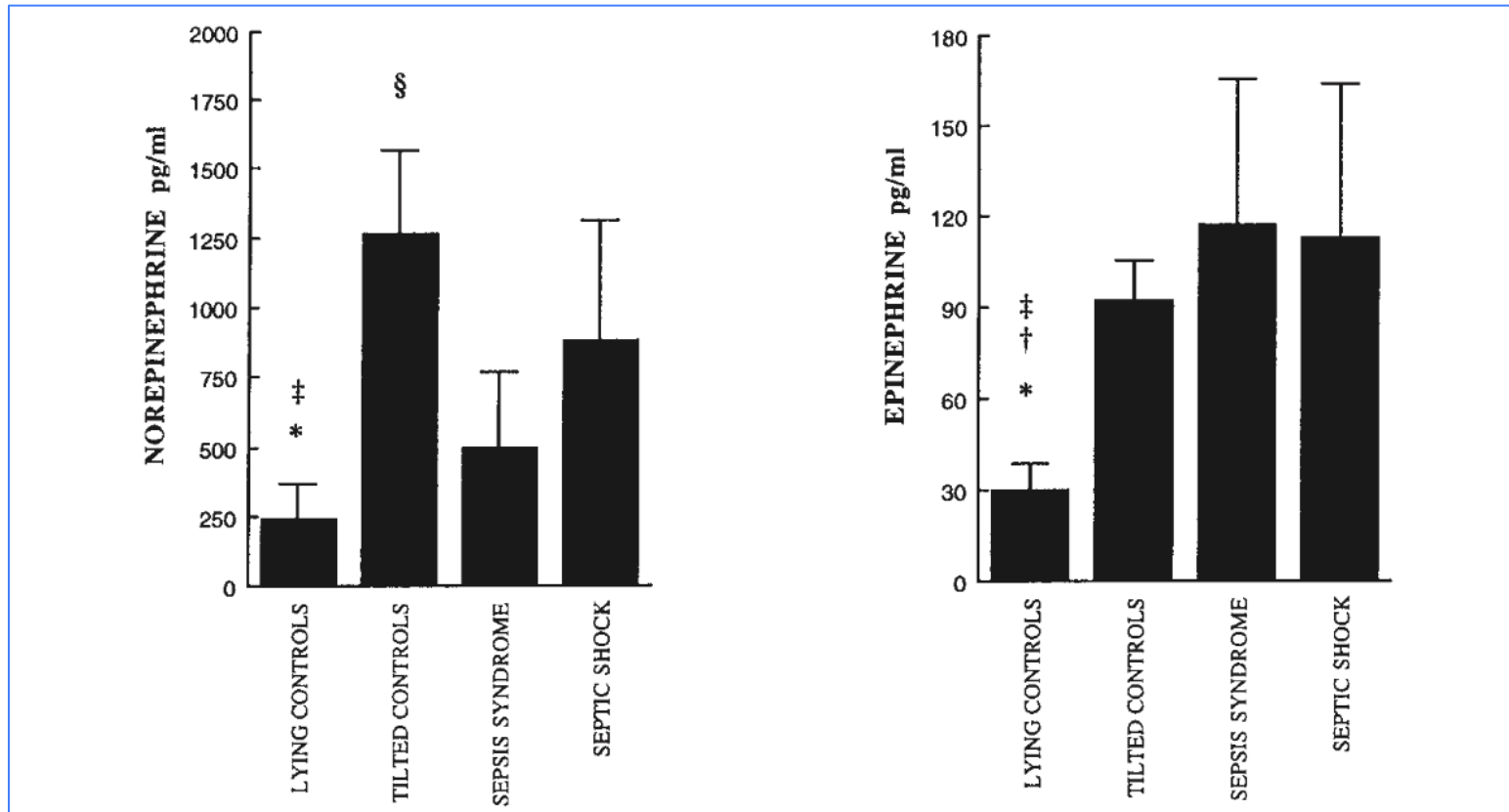
Dysautonomie : facteur de gravité dans le choc septique



Survie

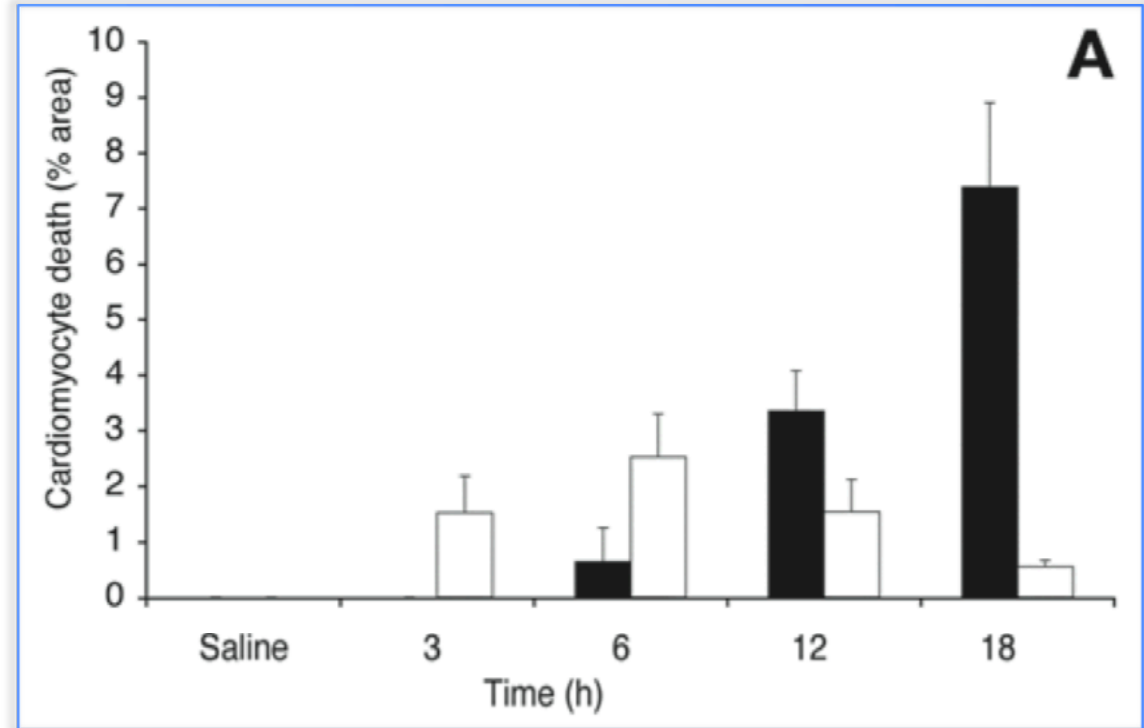
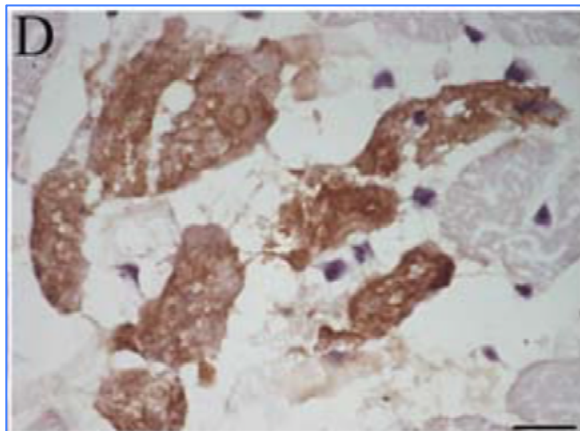
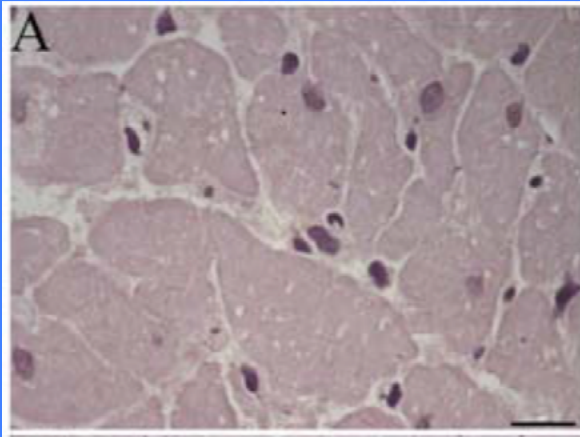
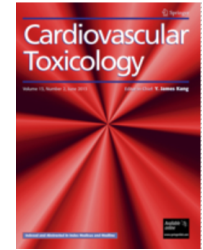
50%

Associée à un hyperadrénergisme

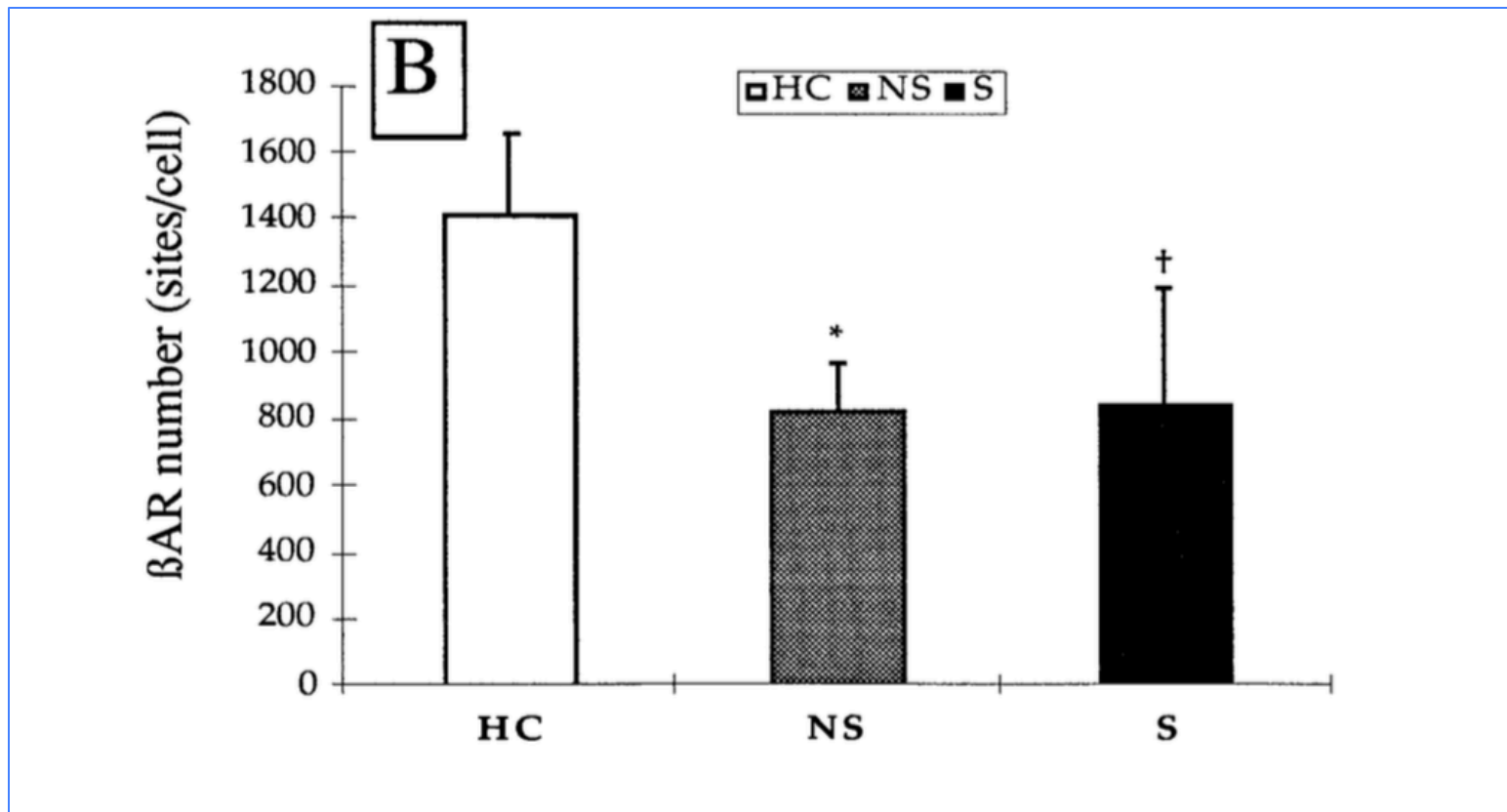


Intérêt de la modulation de cette hyperadrénergisme pour réduire la dysautonomie ?

Toxicité directe des catecholamines



Désensibilisation aux catecholamines



An Inspired Concept!

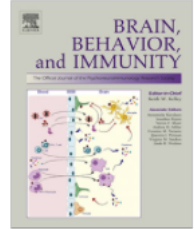
Travaux expérimentaux

Quel β - bloquant utiliser ?

	Receptors	Clearance	Half-time	Route
Propranolol	$\beta_1 - \beta_2$	Hepatic	2-3 hours	Oral/Intravenous
Pindolol	$\beta_1 - \beta_2$	Hepatic-Renal	3-4 hours	Oral/Intravenous
Timolol	$\beta_1 - \beta_2$	Hepatic	3-4 hours	Oral/Intravenous
Nadolol	$\beta_1 - \beta_2$	Renal	20-24 hours	Oral
Atenolol	β_1	Renal	6-7 hours	Oral/Intravenous
Bisoprolol	β_1	Renal	9-12 hours	Oral
Metoprolol	β_1	Hepatic	3-4 hours	Oral/Intravenous
Landilol	β_1	Plasma Hydrolysis	3-4 minutes	Intravenous
Esmolol	β_1	Plasma Hydrolysis	10 minutes	Intravenous

IV / Pharmacocinétique courte / Pharmacodynamie adaptée (VD)

Stimulation des $\beta 2$ adrénorécepteurs



Cell type or tissue	β_2 -AR modulator	NF- κ B stimulus	Overall effect on NF- κ B activity	Reference
<i>Monocytes/Macrophages</i> THP-1	Isoproterenol, Albuterol, Fenoterol, Epinephrine, Norepinephrine	LPS	↓	Farmer and Pugin (2000)
<i>Skeletal muscle cells</i> C2C12 myoblasts C2C12 myotubes	Epinephrine Isoproterenol*	LPS TNF- α	= =	Frost et al. (2004) Kolmus et al. (2014)
<i>Dendritic cells</i> m Dendritic cells	Salmeterol	LPS	↓ ↓	Hu et al. (2012) Herve et al. (2013)



EFFET ANTI-INFLAMMATOIRE
Inhibition des $\beta 2$ adrénorécepteurs ne semble pas opportun

Esmolol: un bon candidat?

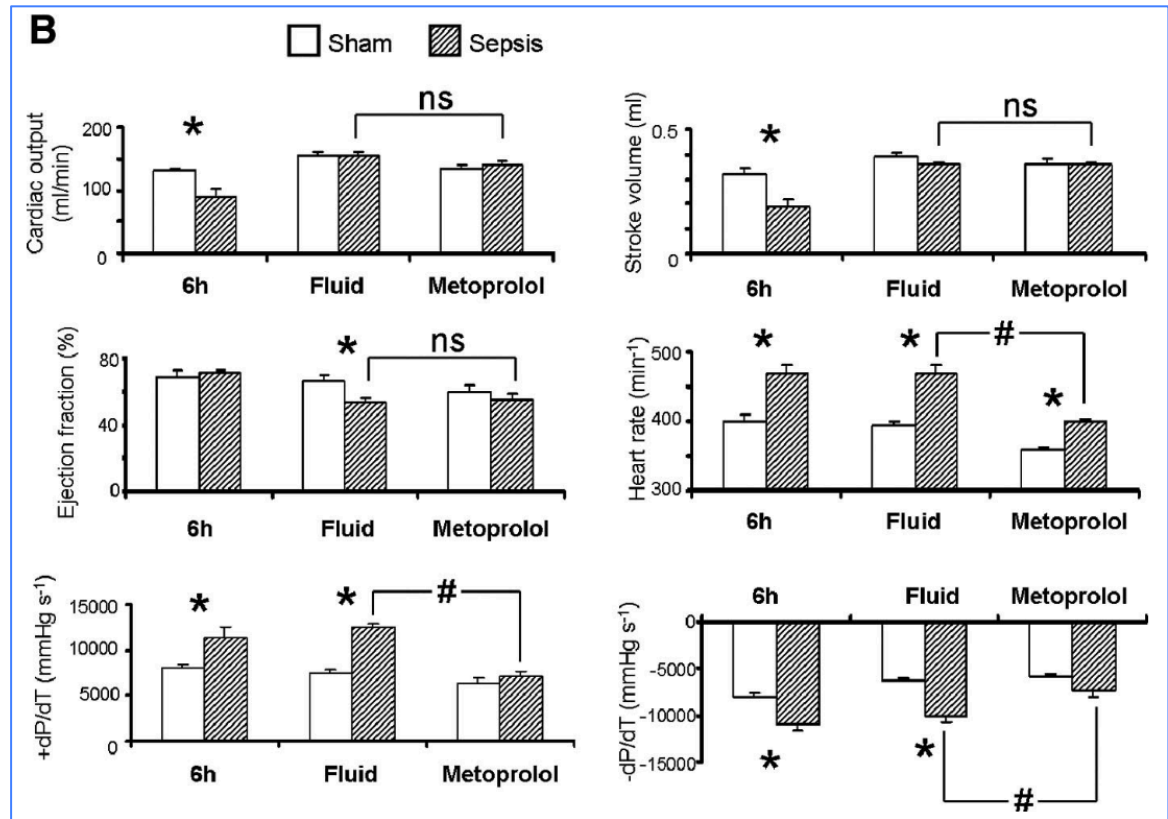
- Administration Intra-Veineuse
- Pharmacocinétique courte
- Pharmacodynamie adaptée
- B 1 ultra-sélectif

Blocage β 1 adrénergique et fonction cardiaque

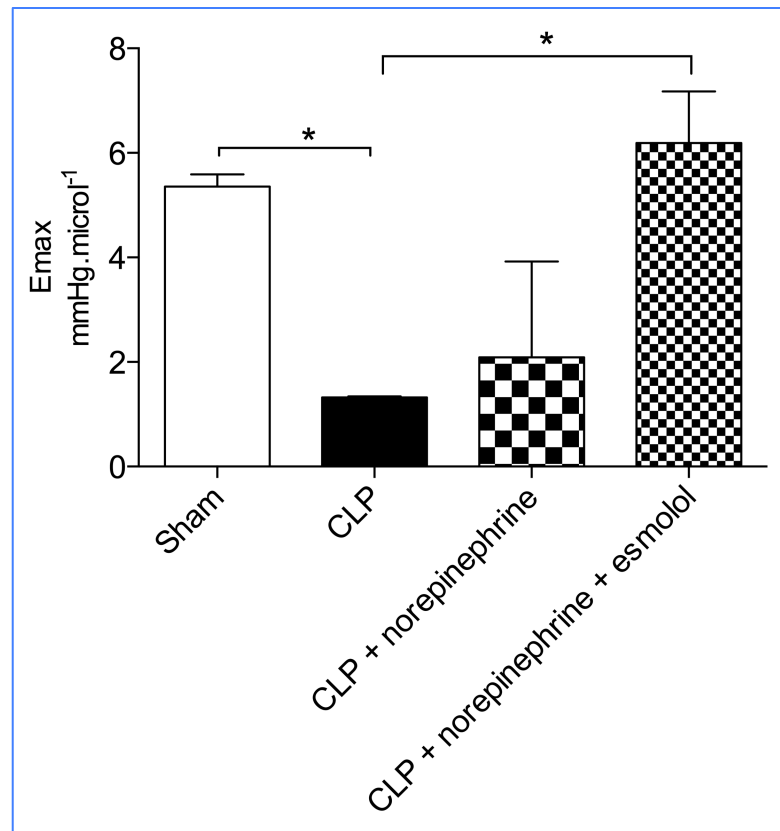
Time	Septic Rats Without Metoprolol
Baseline, 0 hr	116 \pm 4; n=16
6 hrs	134 \pm 4; n=13
24 hrs	117 \pm 11; n=4

PAM

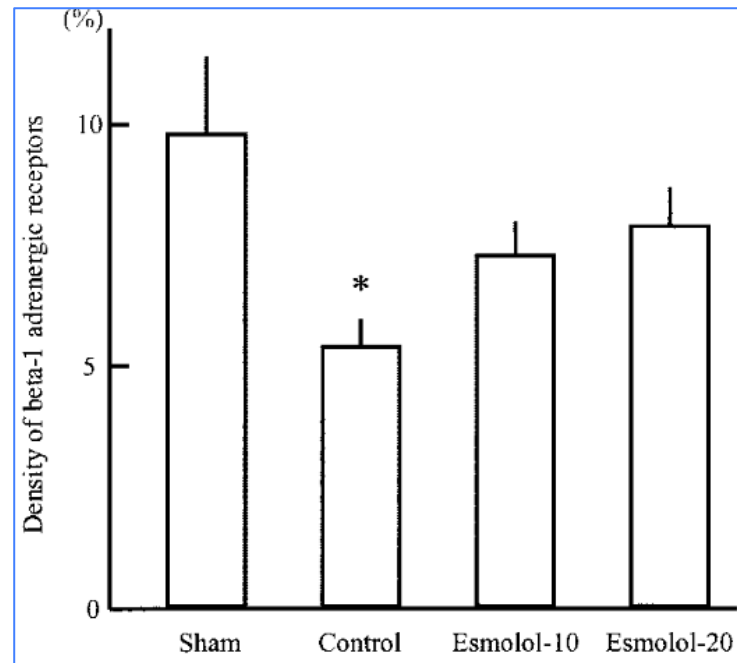
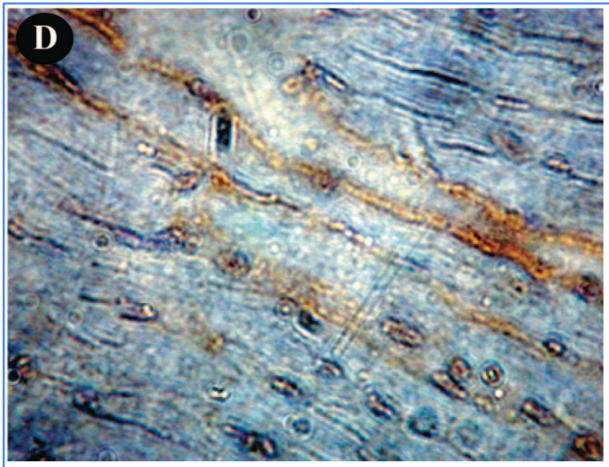
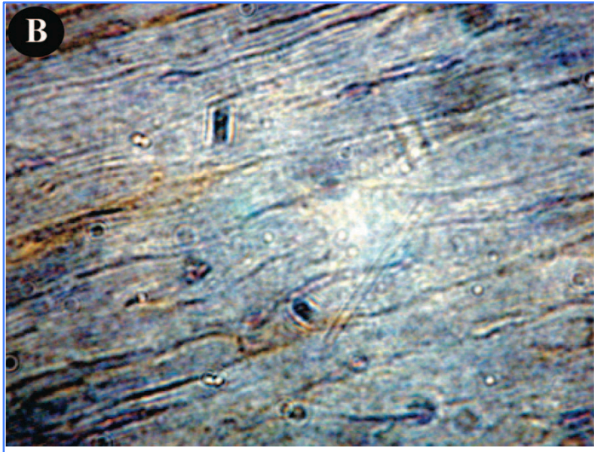
Time	Septic Animals With Metoprolol
Baseline, 0 hr	110 \pm 3; n=13
6 hrs	131 \pm 4; n=13
24 hrs	90 \pm 16; n=4



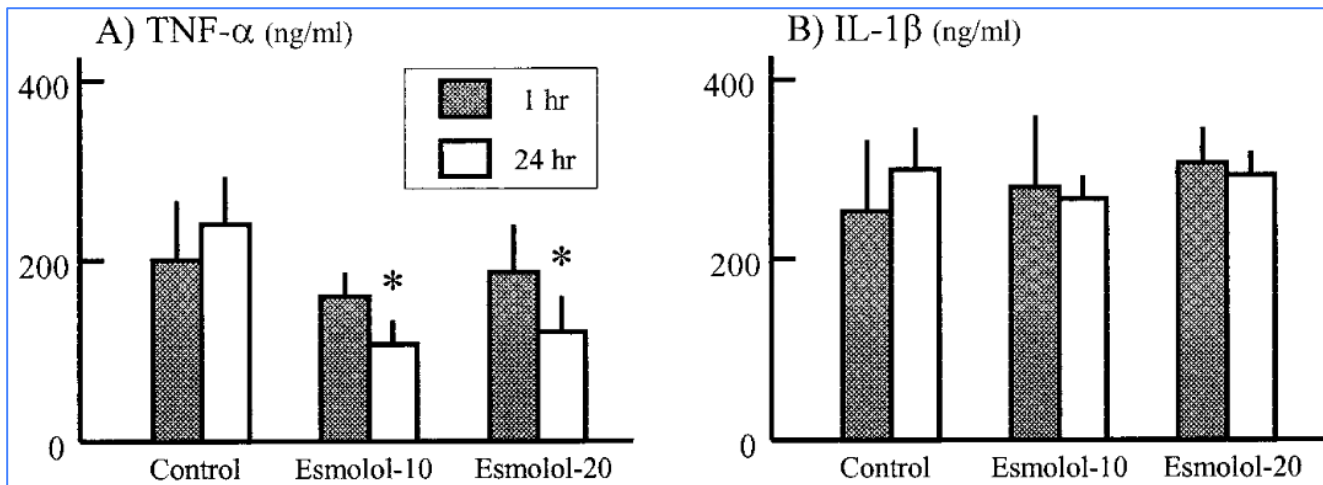
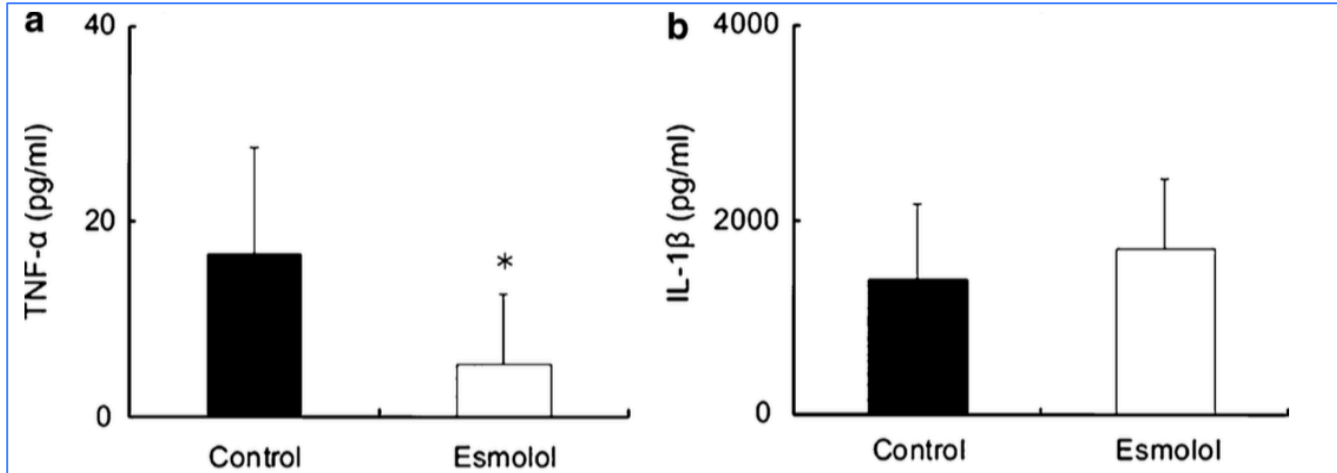
Blocage β 1 adrénergique et fonction cardiaque



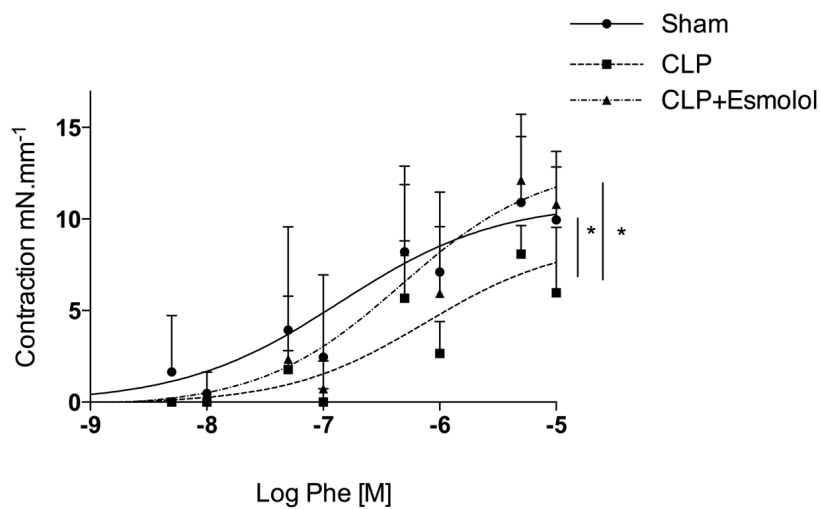
Blocage β 1 adrénergique et fonction cardiaque



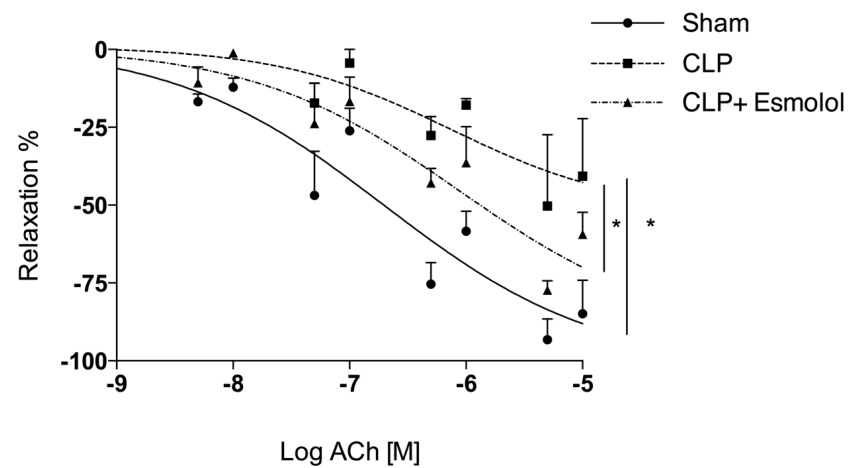
Blocage β 1 adrénergique et inflammation



Blocage β 1 adrénergique et fonction vasculaire

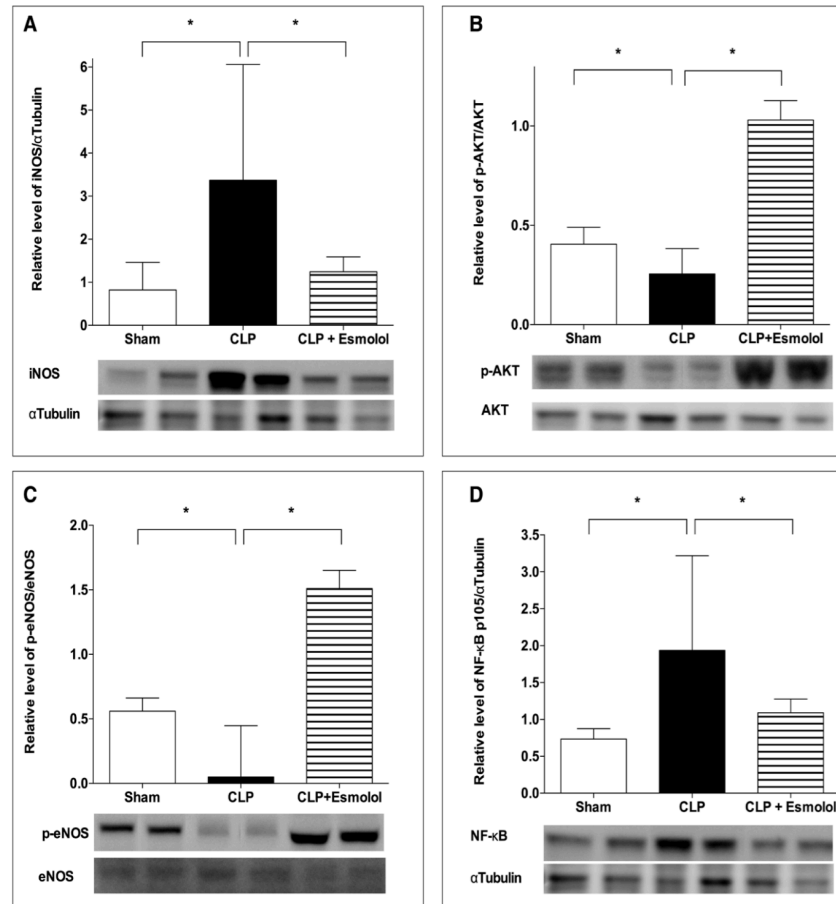


A

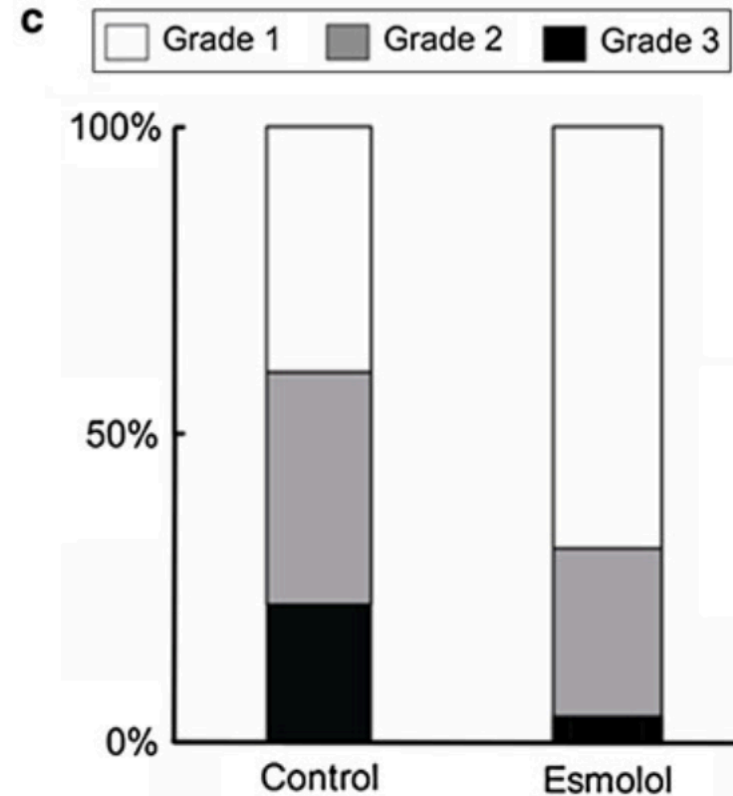
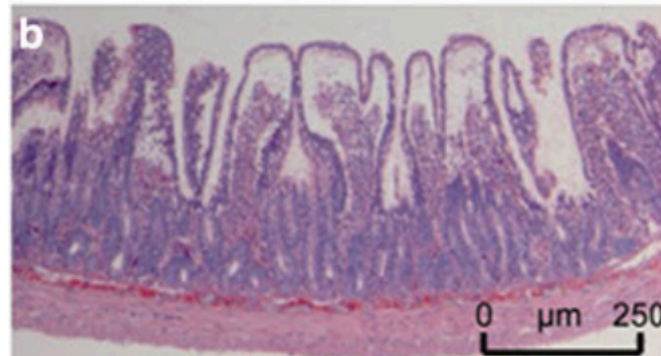
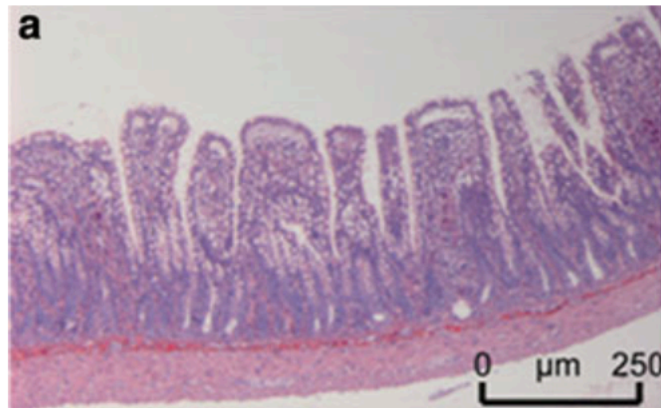


B

Amélioration de la vasoréactivité par modulation inflammatoire

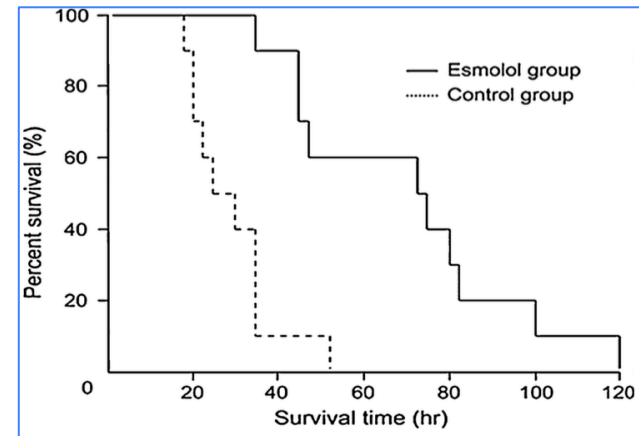
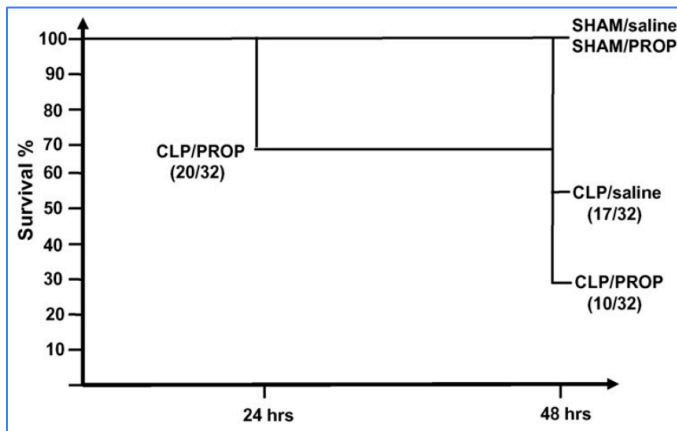
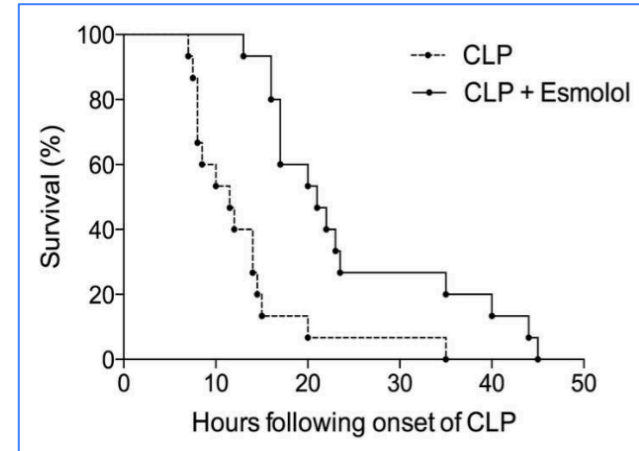
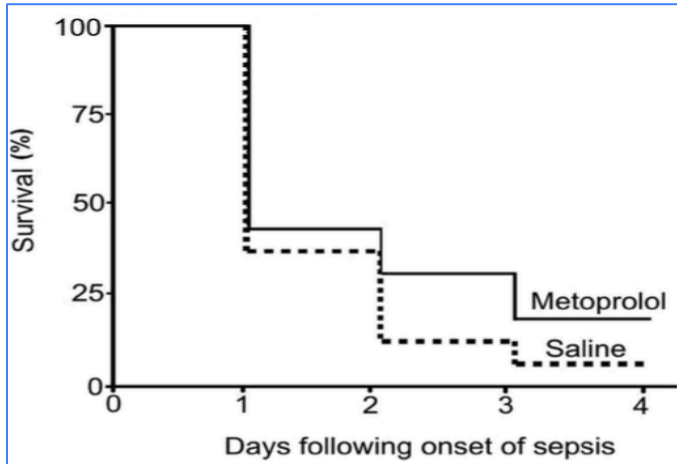


Blocage β 1 adrénergique et tractus digestif





Blocage β 1 adrénergique et survie



Ackland GL et al. **Crit Care Med** 2010;38:388–394
Suzuki T et al. **Crit Care Med** 2005; 33:2294 –2301

Kimmon A et al. **Crit Care Med** 2015; in press
Mori K et al. **Intensive Care Med** 2011;37:1849–1856

A still unproven Concept!

Travaux cliniques



Travaux préliminaires

Table II. Hemodynamics

	<i>Basal</i>	<i>Esmolol</i>
Cardiac index (L/minute × m ²)		
Normal range (2.5-4.0)	4.89 ± 1.00	3.88 ± 0.88*
Heart rate (beats/minute)		
Normal range (60-100)	114 ± 15	91 ± 12*
Blood pressure (mm Hg)		
Normal range (90-140)	108 ± 14	100 ± 12
Normal range (50-90)	62 ± 6	64 ± 7
Pulmonary artery wedge pressure (mm Hg)		
Normal range (4-12)	14 ± 4	13 ± 6
Systemic vascular resistance index (dyne/sec/cm ⁻⁵ /m ²)		
Normal range (1,300-2,800)	1,366 ± 539	1,360 ± 521
Pulmonary vascular resistance index (dyne/sec/cm ⁻⁵ /m ²)		
Normal range (100-240)	179 ± 94	208 ± 160
Stroke volume index (ml/bt × m ²)		
Normal range (33-47)	43 ± 6	43 ± 11
Leg blood flow (ml/min × 100 ml leg volume)	4.84 ± 1.91	5.07 ± 1.28
Hepatic clearance (ml/min × kg)	2.73 ± 1.32	3.13 ± 1.35

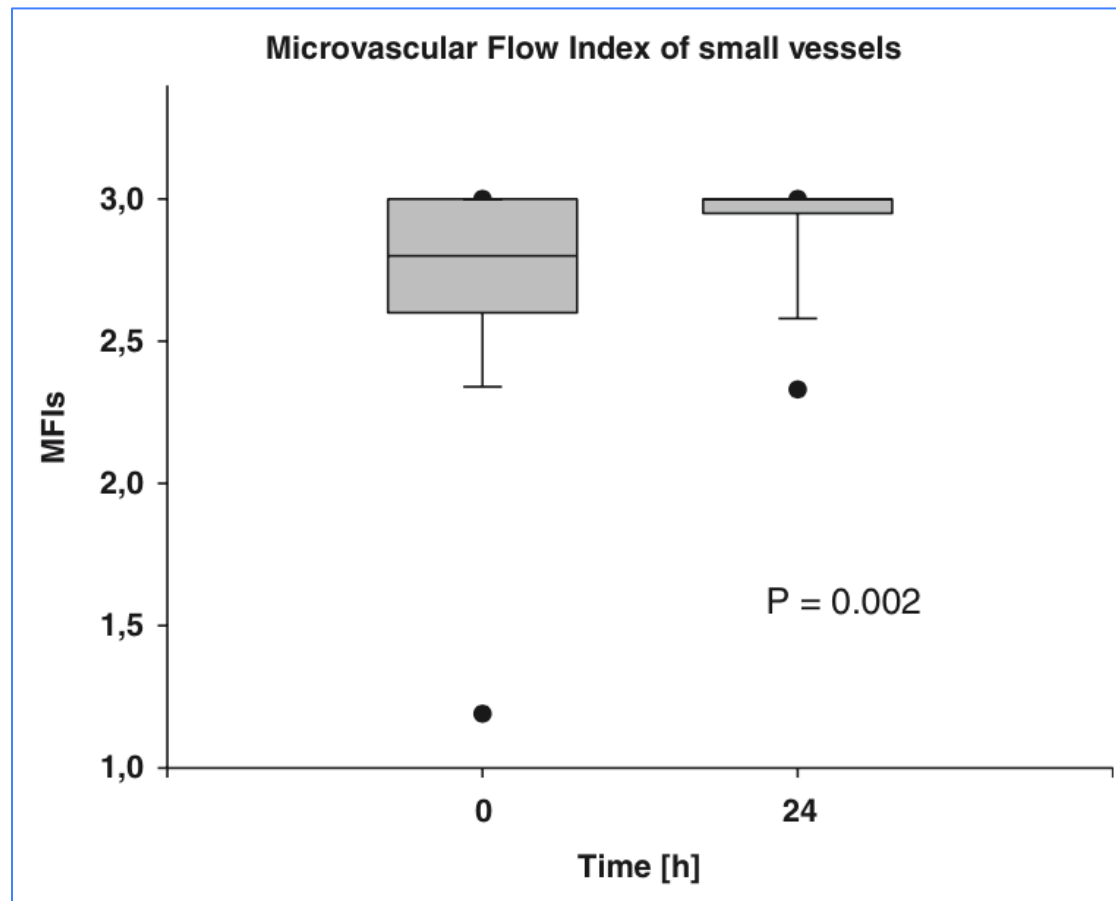
PAS DE CHOC

Travaux en choc septique par la suite

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Time point	T0	T2	T6	T12	T24	T30	p value
<i>Infusion</i>							
Esmolol (mg/h)	0	213±64	245±82	255±117	273±90	0	NS
Nor (µg/kg/min)	0.13±0.16	0.14±0.17	0.15±0.14	0.15±0.15	0.17±0.19	0.12±0.12	NS
<i>Hemodynamics, arterial lactate and calculated parameters</i>							
HR (beats/min)	142±11	127±12	120±11	113±7	112±9	116±11	<0.001
MAP (mmHg)	91±11	89±9	87±11	86±8	84±9	89±8	NS
PAMP (mmHg)	29±4	30±5	29±3	28±3	30±4	28±4	NS
PAWP (mmHg)	16±3	15±2	15±2	15±3	15±2	14±2	NS
CO (l/min)	9.2±1.9	8.8±2.0	8.8±2.1	8.2±1.6	8.2±1.7	8.7±1.6	NS
CI (l/min/m ²)	4.9±0.8	4.7±0.9	4.7±1.0	4.3±0.7	4.4±0.7	4.7±0.7	NS
SV (ml)	67±16	69±14	73±14	72±12	73±15	77±13	NS
SVR (dyn/s/cm ⁵)	721±212	751±171	733±209	763±203	764±213	749±200	NS
Lactate (mmol/l)	1.7±0.5	1.7±0.4	2.0±0.6	2.1±0.4	1.7±0.3	1.8±0.5	NS
DO ₂ (ml/min)	1309±207	1311±206	1314±204	1316±199	1311±185	1308±198	NS
SvO ₂ (%)	70±8	67±5	65±5	63±5	60.2±4	64±5	NS
VO ₂ (ml/min)	326±130	345±108	367±101	376±101	394±70	385±103	NS
OER (%)	25±8	26±6	28±7	29±7	31±6	30±8	NS
<i>Echocardiography</i>							

Microcirculation préservée

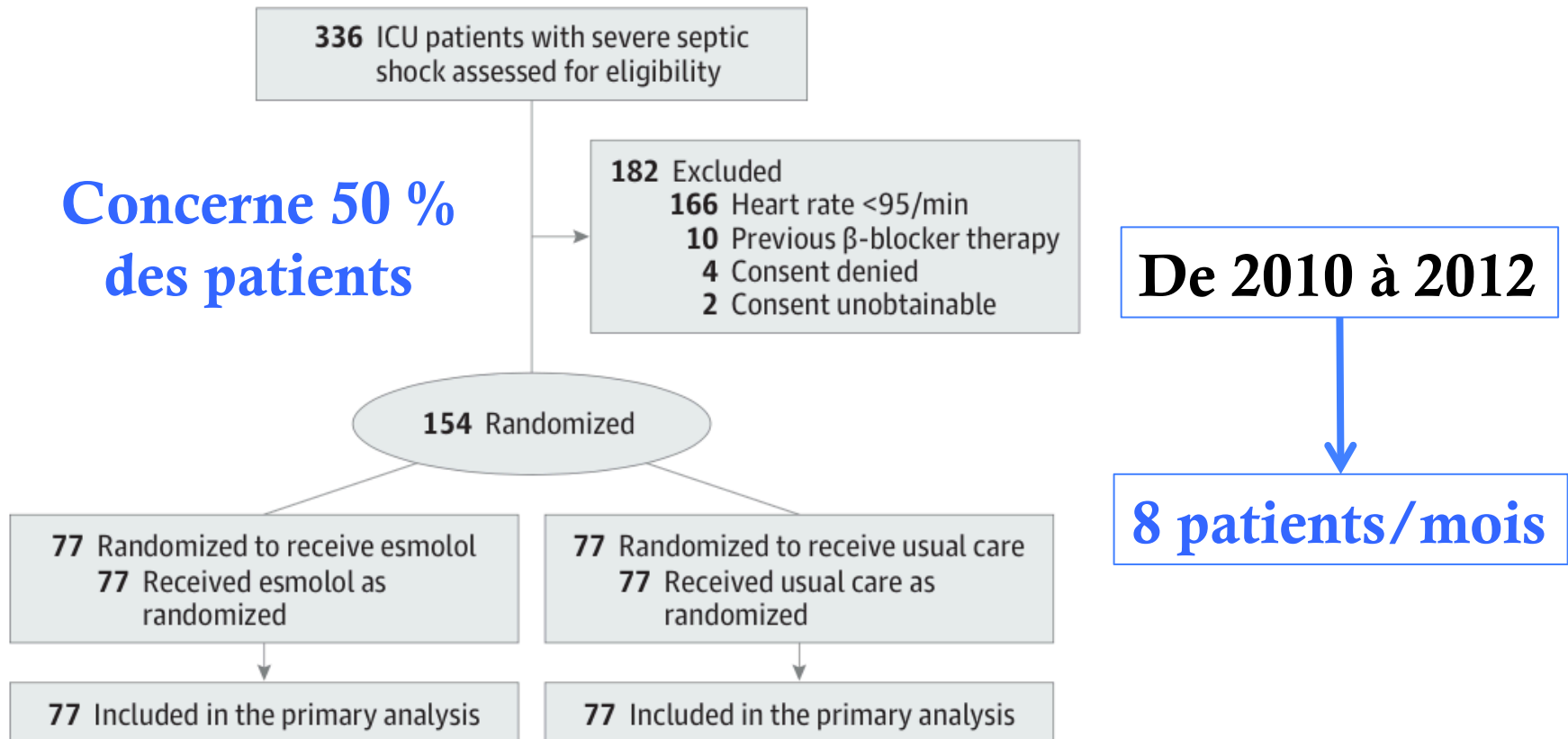


L'adjonction d'Esmolol permet:

- Une réduction effective de la fréquence cardiaque
- Une réduction proportionnelle du débit cardiaque
- Sans altération de la pression artérielle
- Avec des résistances vasculaires identiques
- Sans majoration des posologies de catécholamines

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock A Randomized Clinical Trial

JAMA

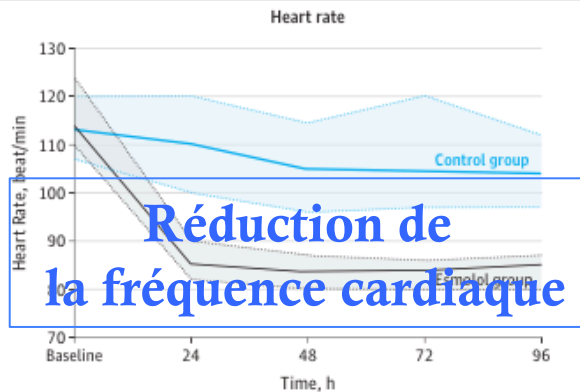


**Concerne 50 %
des patients**

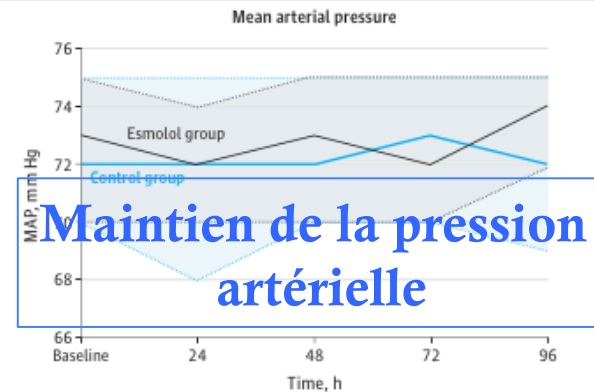
Objectif de 80 à 94 batt/min

Effets hémodynamiques

JAMA

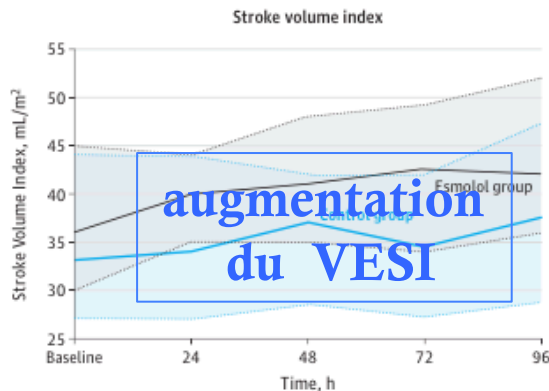


No. of patients	Control	Esmolol
Baseline	77	77
24	73	77
48	71	76
72	66	76
96	61	75

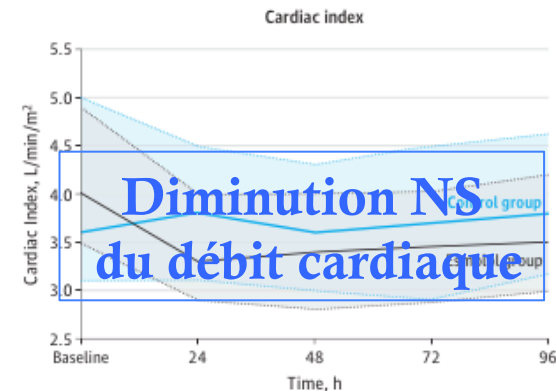


No. of patients	Control	Esmolol
Baseline	77	77
24	73	77
48	71	76
72	66	76
96	61	75

Mais levosimendan dans 50% des cas



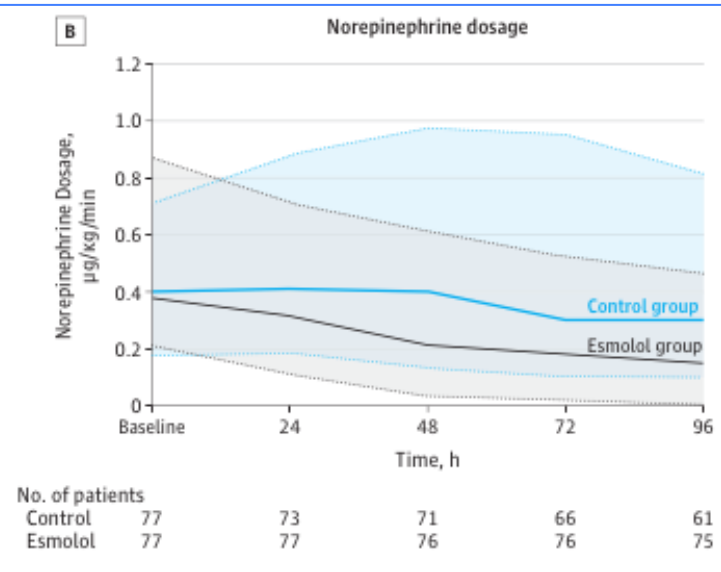
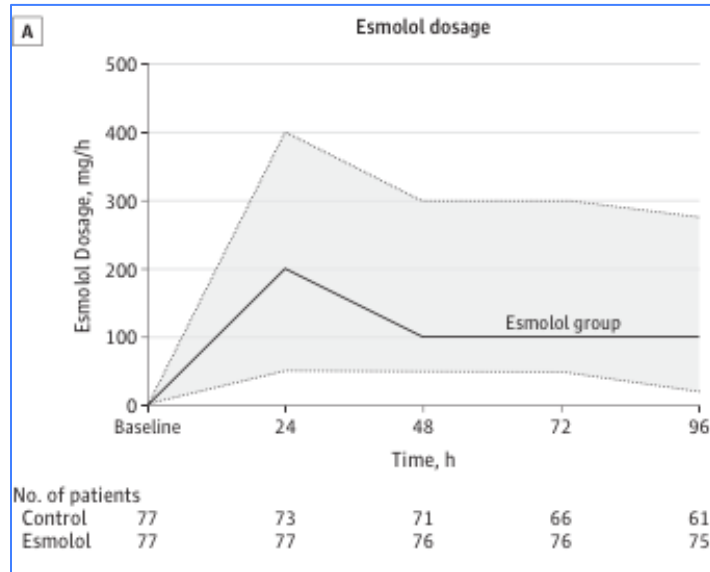
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No. of patients	Control	Esmolol
Baseline	77	77
24	73	77
48	71	76
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Réactivité vasculaire

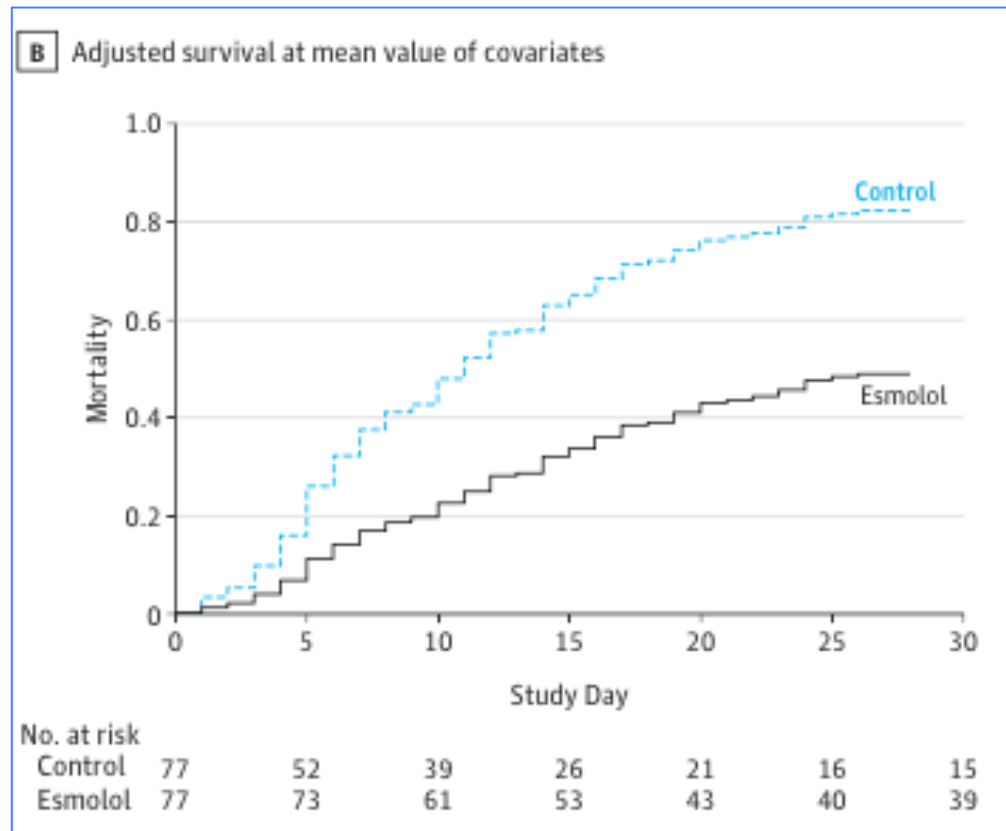
JAMA



Group	Median (Interquartile Range)					Area Under the Curve	P Value, Wilcoxon-Mann-Whitney
	Baseline	24 Hours	48 Hours	72 Hours	96 Hours		
SVRI							
Esmolol	1148 (970 to 1362)	1382 (1171 to 1653)	1370 (1149 to 1668)	1403 (1141 to 1708)	1411 (1137 to 1616)	264 (33 to 439)	<.001
Control	1271 (967 to 1548)	1265 (1031 to 1608)	1326 (1086 to 1614)	1359 (1026 to 1678)	1276 (985 to 1586)	90 (-74 to 231)	

Survive

JAMA



Beaucoup de commentaires...

- Des 1
contr

	Esmolol (n = 77)	Control (n = 77)
Age, median (IQR), y	66 (52-75)	69 (58-78)
Men, No. (%)	54 (70)	53 (69)
Body mass index, median (IQR) ^a	29 (26-33)	28 (25-32)
SAPS II score, median (IQR) ^b	52 (47-60)	57 (49-62)
Norepinephrine dosage, median (IQR), µg/kg/min	0.38 (0.21-0.87)	0.40 (0.18-0.71)
Arterial lactate, median (IQR), mmol/L	1.5 (1.1-2.7)	1.9 (1.1-3.1)
Platelet count, median (IQR), × 10 ³ /µL	178 (126-272)	129 (73-206)

oupe

- Une
com

it
jours

- Analyse statistique basée sur les aires sous la courbe questionnable
- Un titre et une conclusion qui ne reflète pas l'objectif primaire

Synthèse

- We hypothesized that intravenous β -blockade titrated to achieve heart rate control in septic shock represents an effective approach to enhance myocardial function

The answer is YES on heart rate control and nothing more

**Existe t'il un intérêt aux
 β - bloquants dans le choc
septique?**

**Existe t'il un intérêt aux
 β - bloquants dans le choc
septique?**

A l'heure actuelle: non!

EN TOUS LES CAS PAS EN DEHORS DE PROTOCOLES DE
RECHERCHES....

**Faut il continuer à étudier
cette classe thérapeutique
dans le choc septique?**

**Faut il continuer à étudier
cette classe thérapeutique
dans le choc septique?**

Oui!

AVEC QUELLE MODALITE?

Hypothèses futures de travail à valider

- L'utilisation de la fréquence cardiaque comme objectif est-elle licite?
- Des doses inférieures ne seraient pas aussi efficaces?

Ibrahim-zada I et al. **J Trauma Acute Care Surg** 2014;76:320Y328

- Quelles sont les effets hémodynamiques de l'administration **précoce** d'esmolol? (moment de l'injection)
- En dernier, quel est l'impact sur la survie des patients en choc septique de l'adjonction d'un traitement par esmolol?

ESMOSEPSIS

- Patient en choc septique
- Sous Esmolol dans les 12 premières heures du choc
 - Fréquence cardiaque $>100/\text{min}$
 - Index Cardiaque $> 3 \text{ l}/\text{min}/\text{m}^2$
 - FeVG $> 50\%$
- Evaluation hémodynamique multimodale
- 7/25 inclus
- *Concerne pour le moment : $<15\%$ des patients en choc septique*