Journées Francophone de Réanimation

srlf SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE

21 et le 22 Juin 2024 - Hôtel The Russelior, Hammamet

Bétabloquants dans le choc septique

Kamilia CHTARA

Service de Réanimation médicale de SFAX

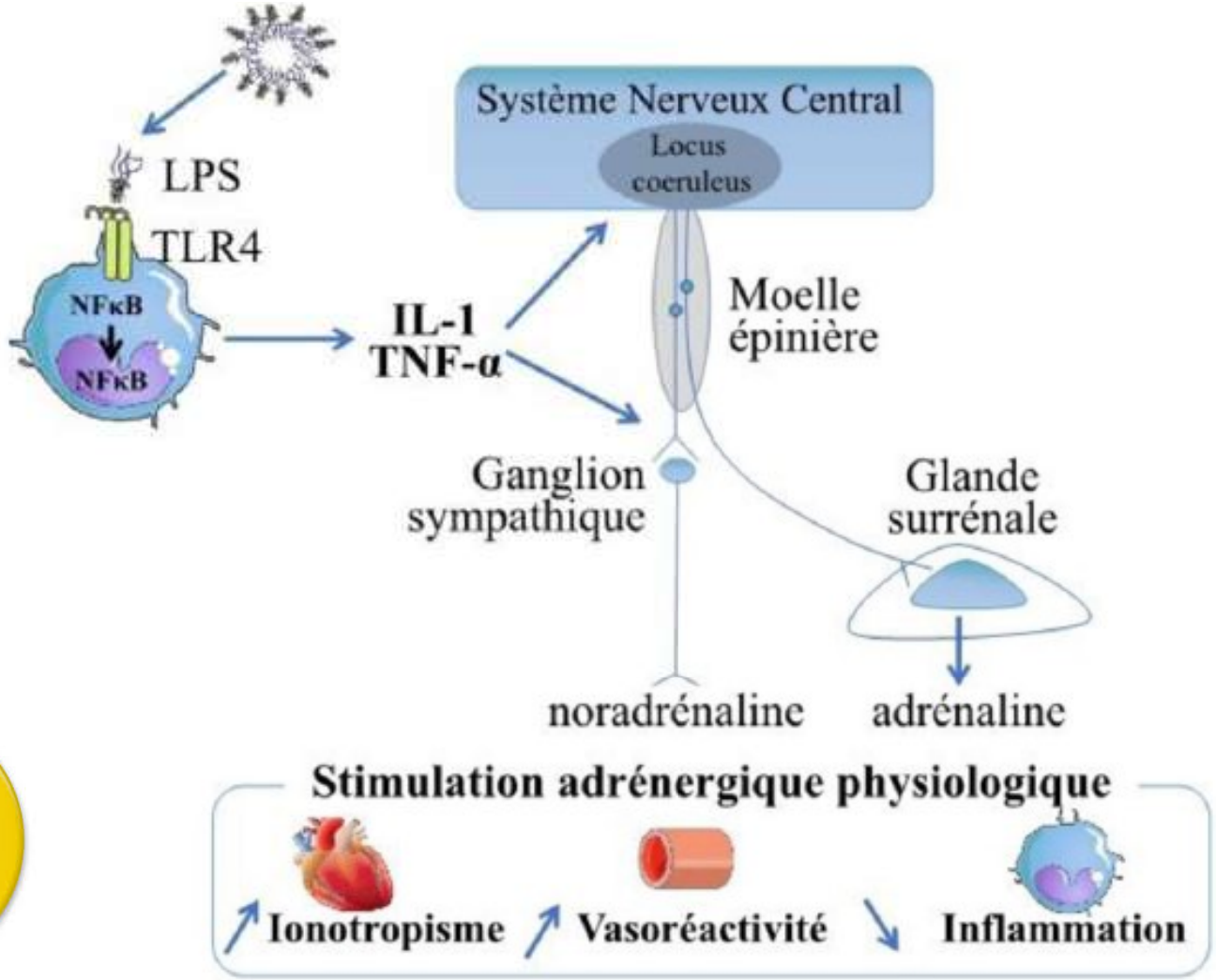
Introduction

- **Urgence** diagnostique et thérapeutique.
- Déséquilibre de l'agent infectieux et les moyens de défense de l'organisme.
- 1ère cause de **mortalité** en réanimation (50_60 %) (SDMV)
- Demeure un **sujet d'actualité**: des recommandations +++ et des consensus

Introduction

- La proposition des β bloquants lors du choc septique depuis les années 70
- Des fondements physiopathologiques **+++**
- Des études expérimentales et cliniques **+++**
- **Mais ! C'est un sujet de controverse**

Choc septique



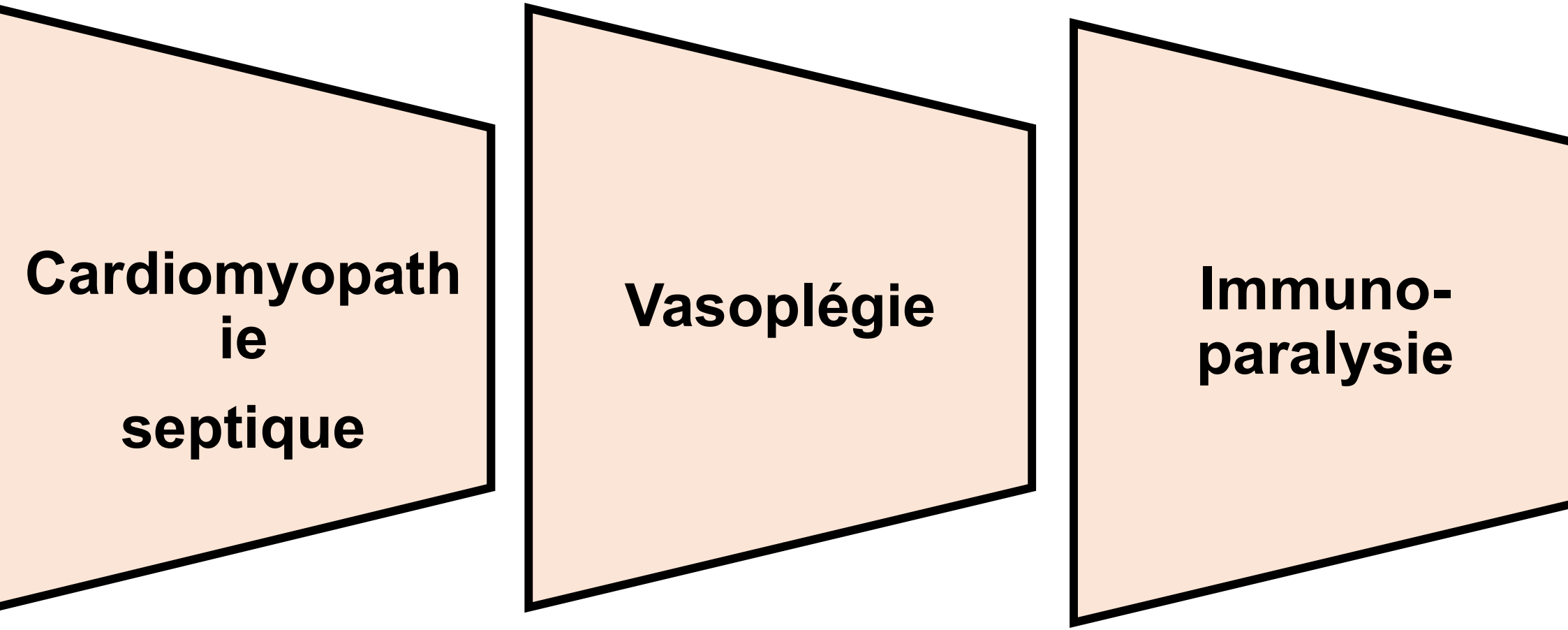
Méd. Intensive Réa (2019) 28:12

Syndrome de Dysautonomie sympathique

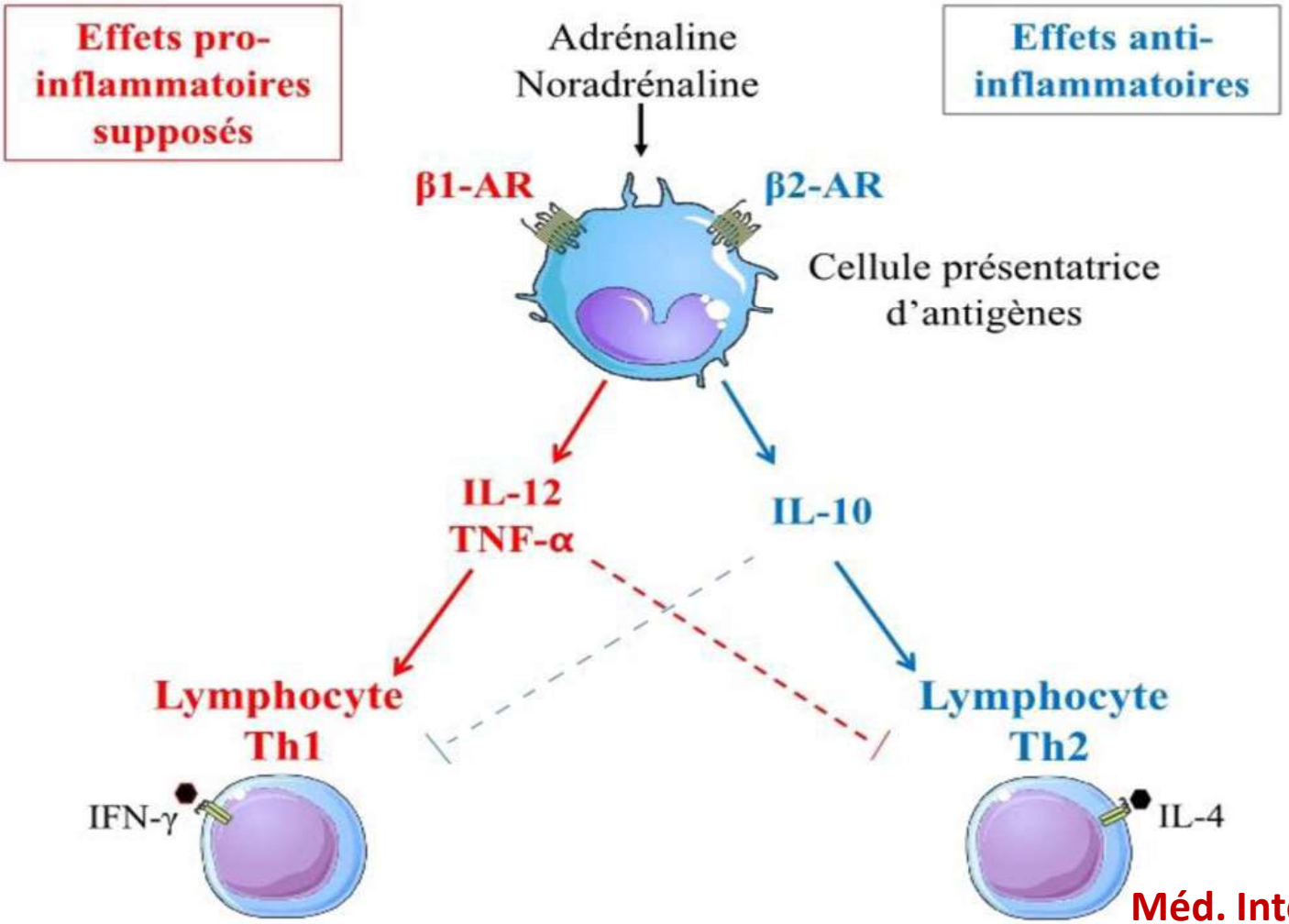
- Stimulation adrénergique **prolongée** et **intense**
- **Reflet d'une suractivation adrénergique**
- **[Adrénaline] et [Noradrénaline] sont 5 à100x plus élevées**
- **Mauvais pronostic**

Syndrome de Dysautonomie sympathique

Participe



Effet des catécholamines sur la balance lymphocytaire Th1/Th2.



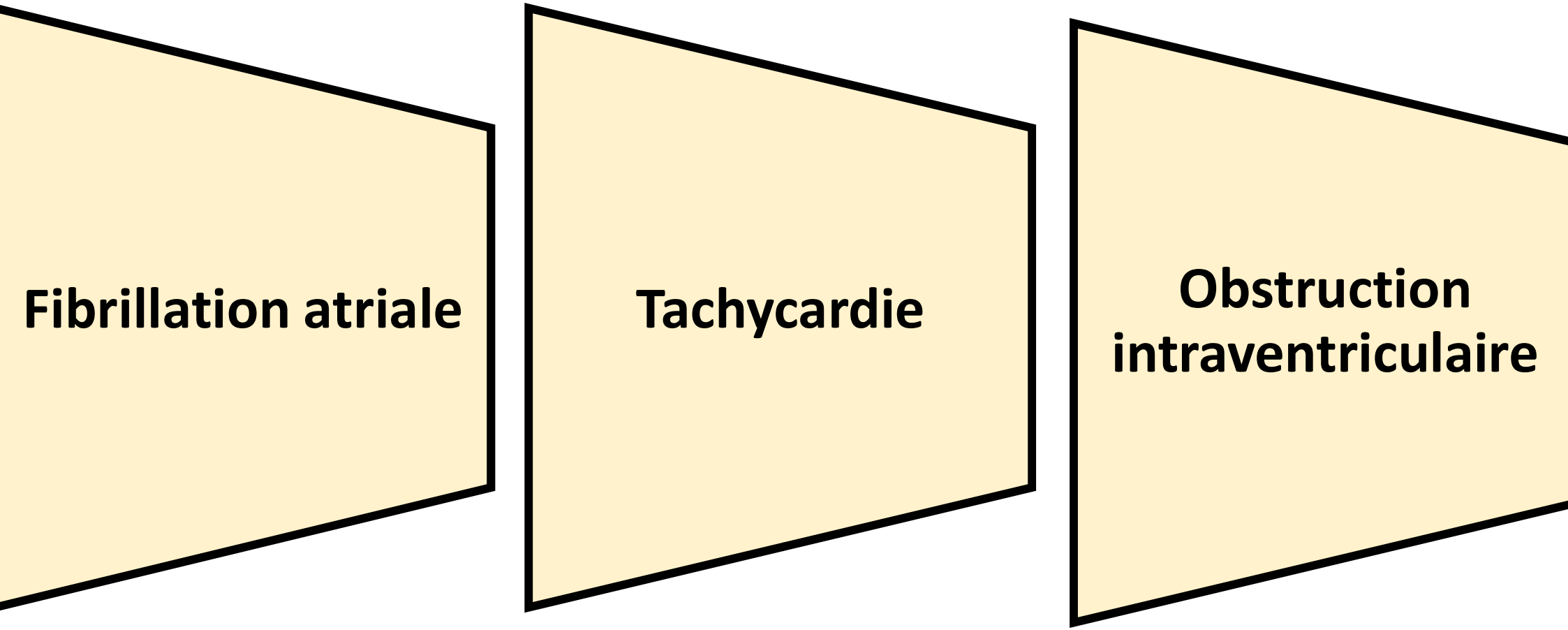
Méd. Intensive Réa (2019) 28:12

Syndrome de Dysautonomie sympathique

Concept décatécholaminisation

Améliorait le Pronostic?

Rationnel physiopathologique



al. Critical Care
6/s13054-014-0688-5

CRITICAL CARE
2014

ARCH Open Access

dence, risk factors and outcomes of new-onset al fibrillation in patients with sepsis: stematic review

uipers[1], Peter MC Klein Klouwenberg[1,2,3] and Olaf L Cremer[1*]

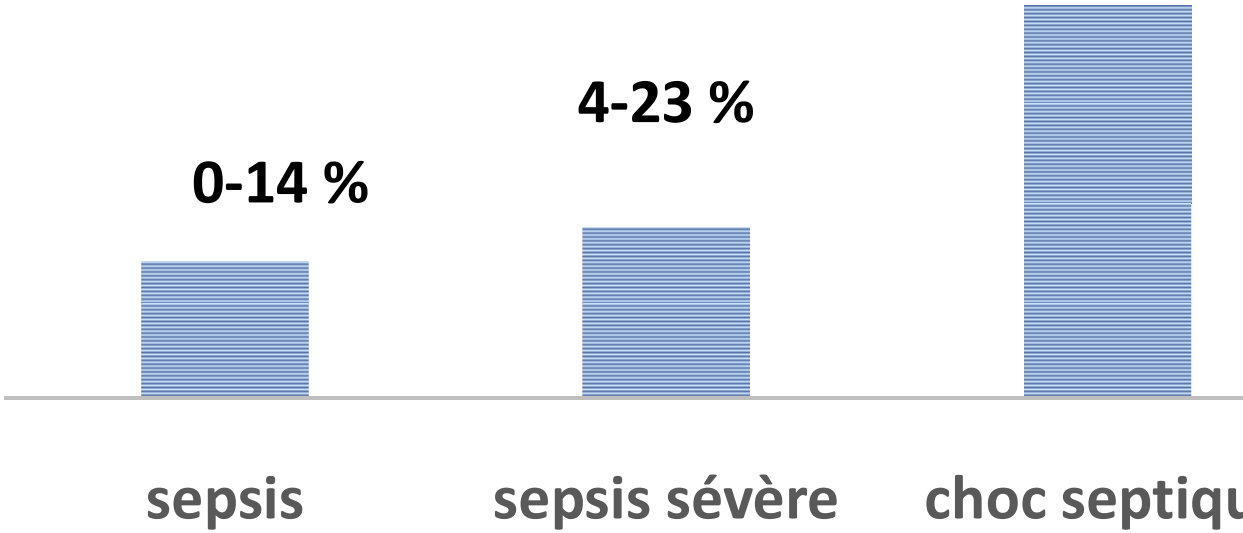
11 études (2004-2013)

INCIDENCE FA

6-46 %

4-23 %

0-14 %



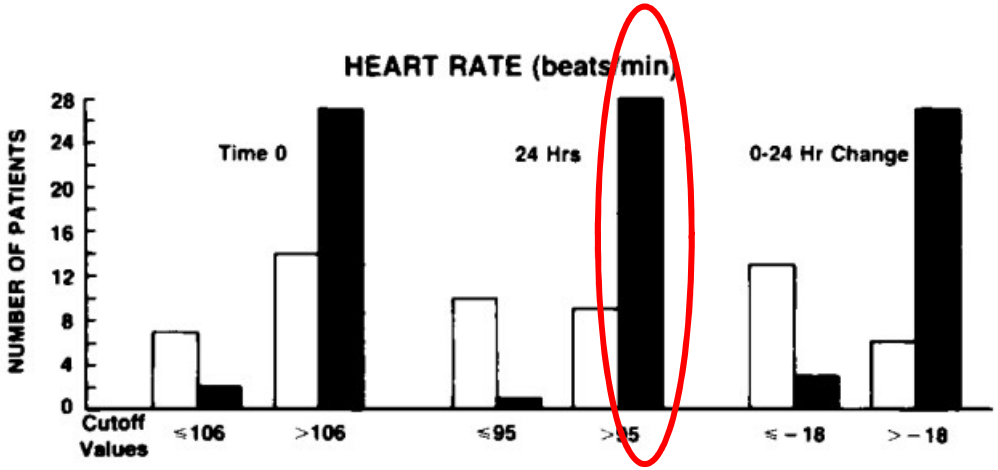
FA facteur independant de ortalité (OR entre 1.96 [1.26 - 03] et 3.32 [1.12 - 9.84]

787/1510-0923$02.00/0
CARE MEDICINE

Vol. 15, No. 10
Printed in U.S.A.

ial cardiovascular variables in survivors and survivors of human septic shock: Heart rate as an ly predictor of prognosis

ARET M. PARKER, MD; JAMES H. SHELHAMER, MD; CHARLES NATANSON, MD;
W. ALLING, MD; JOSEPH E. PARRILLO, MD



- **48 patients en choc septique**
- **Une FC >95 bpm après 24 H est corrélée à la mortalité**

Contents lists available at ScienceDirect

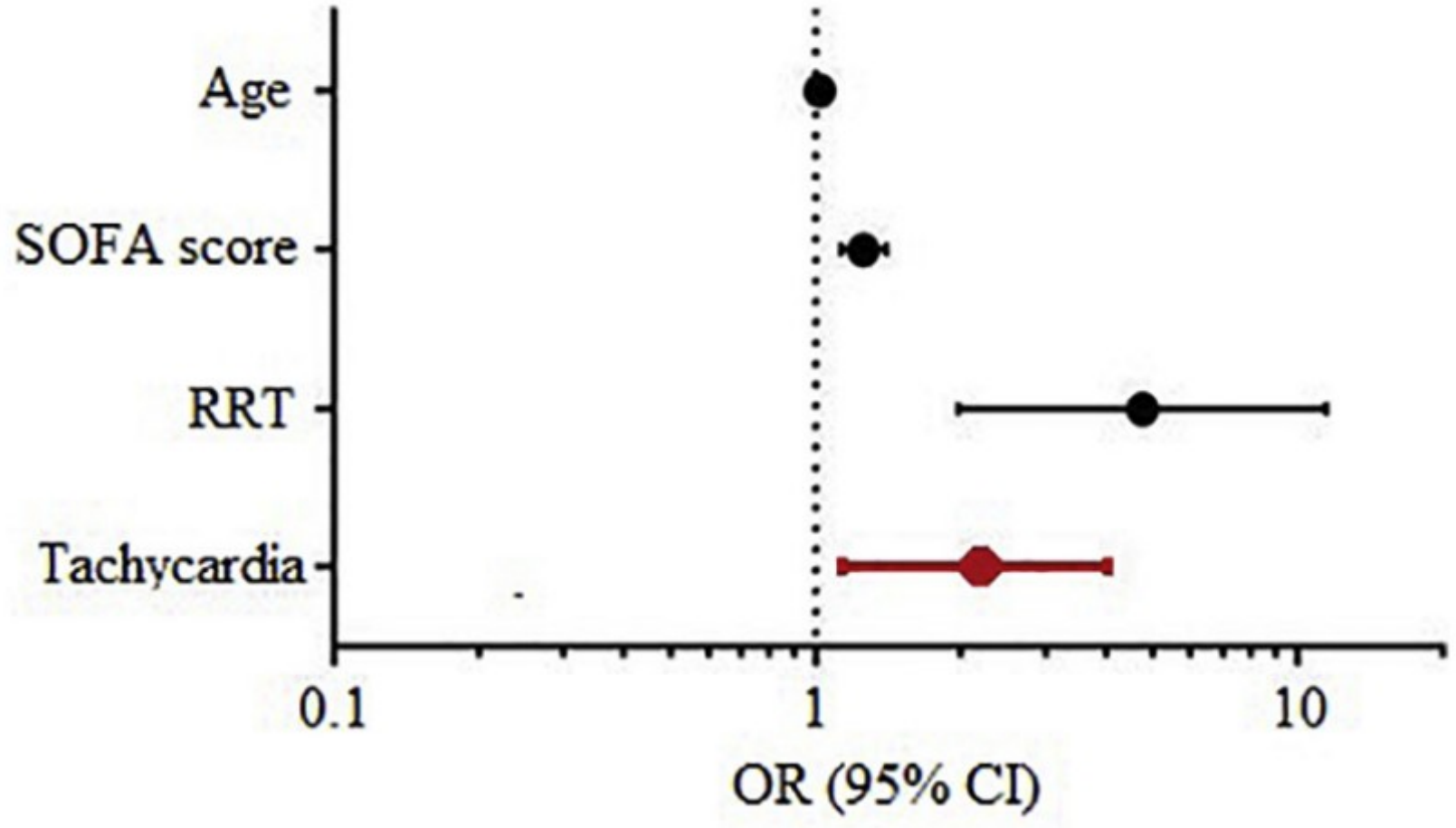
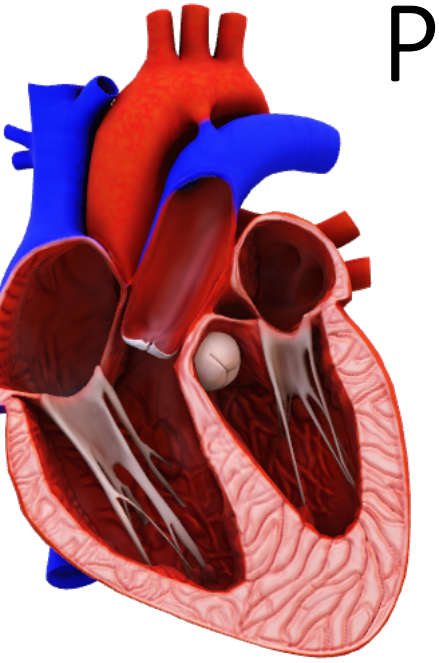
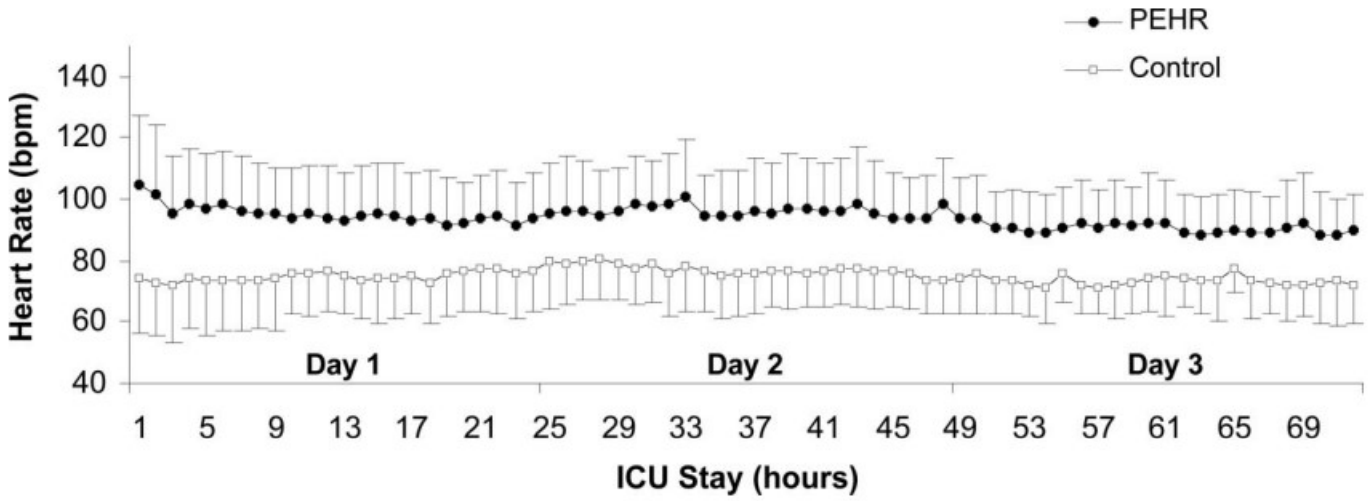
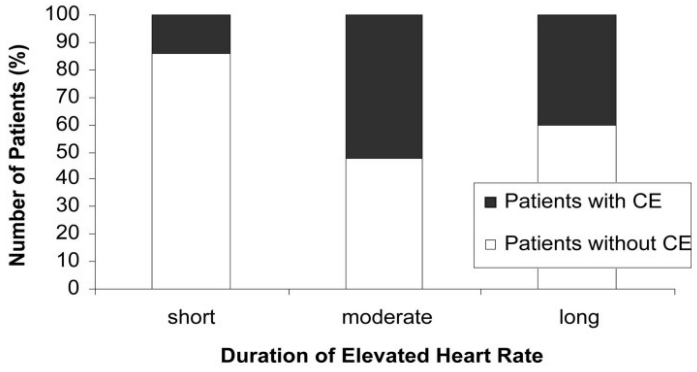


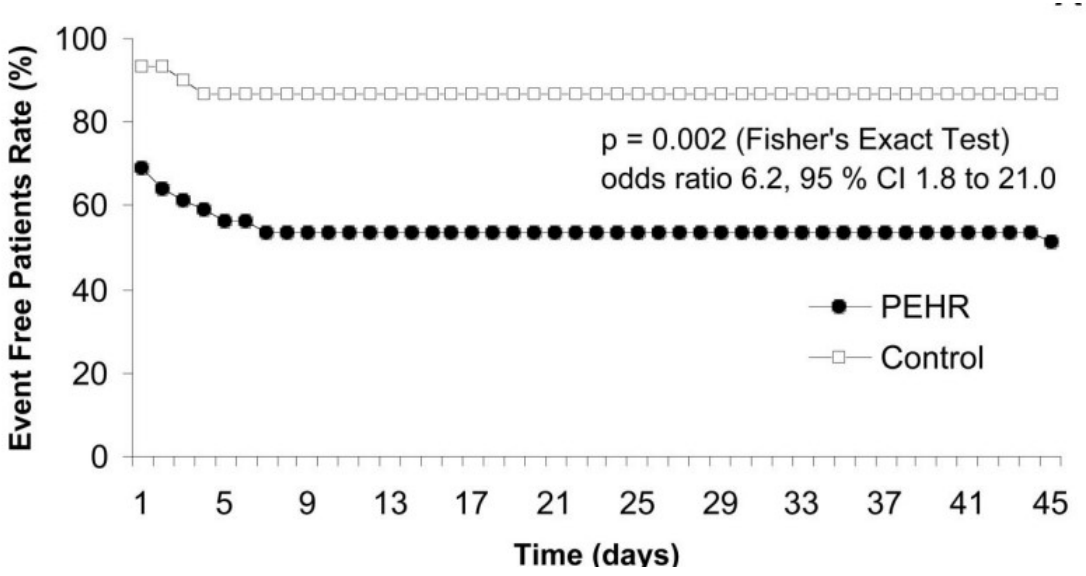
Fig. 3. Odds ratio for mortality for high dose NE group (≥0.3 mcg/kg/min) at the T1 timepoint.

Persistant elevated heart rate









Sander et al,Crit Care Med 2005; 33

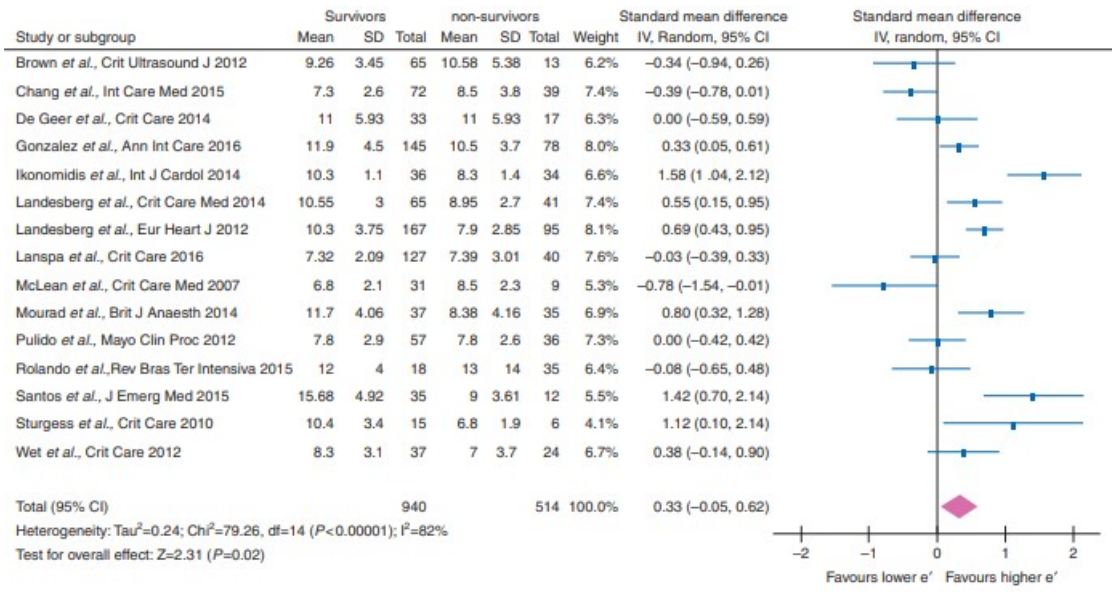
BJA

British Journal of Anaesthesia, 119 (4): 583–94 (2017)

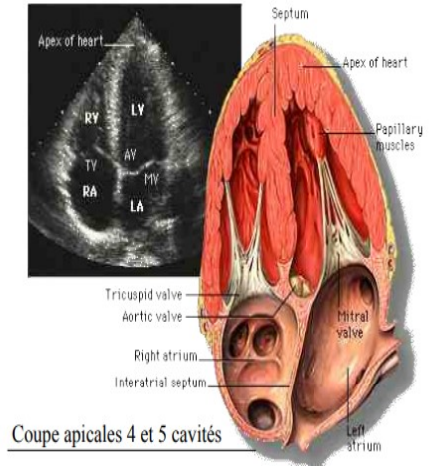
doi: 10.1093/bja/aex254
Review Article

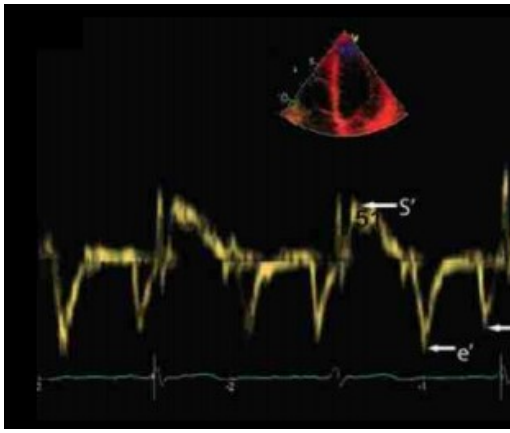
issue Doppler assessment of diastolic function and elationship with mortality in critically ill septic atients: a systematic review and meta-analysis

Sanfilippo[1,*], C. Corredor[2], A. Arcadipane[1], G. Landesberg[3], Vieillard-Baron[4,5], M. Cecconi[6] and N. Fletcher[7]



16 studies with
1507 patients





Baisse de l'onde e' a
doppler tissulaire es
associée à la mortali

et al. Critical Care (2015) 19:262
186/s13054-015-0980-z

CRITICAL CARE

Prospective
218 patients en choc septique
IVO 22%

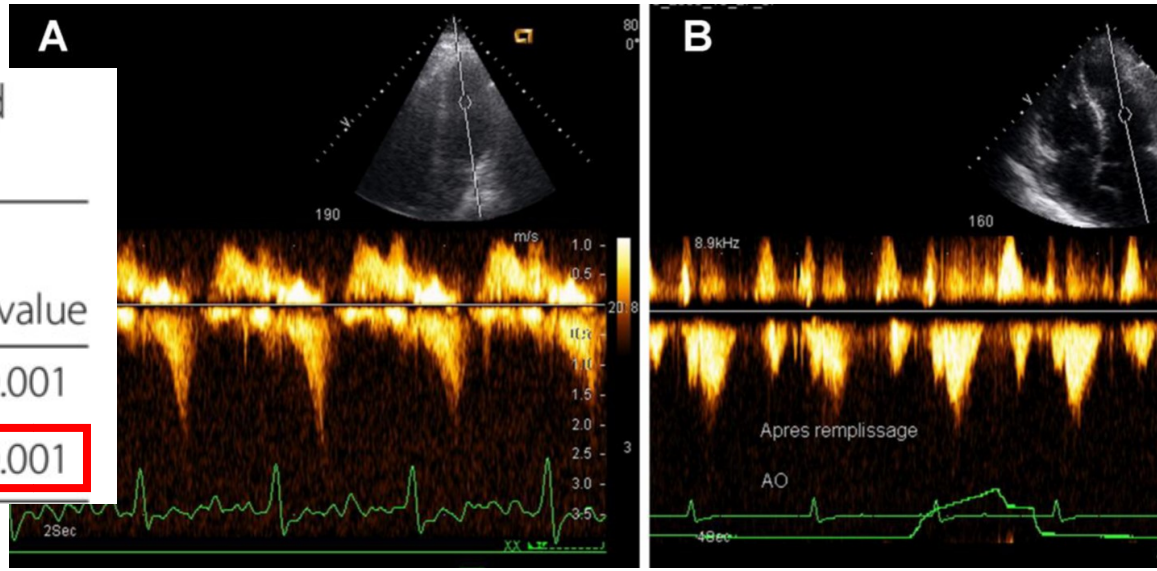
EARCH Open Access

ly dynamic left intraventricular struction is associated with hypovolemia d high mortality in septic shock patients

ouis Chauvet[1], Shari El-Dash[2,3], Olivier Delastre[1], Bernard Bouffandeau[1], Dominique Jusserand[1], aptiste Michot[1], Fabrice Bauer[4], Julien Maizel[2,5] and Michel Slama[2,5*]

e 3 Logistic regression analysis for 28-day mortality and nortality

	28-day mortality			ICU mortality		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
l	1.06	1.04–1.08	0.001	1.06	1.04–1.09	0.001
nce of IVO	2.23	1.08–4.58	0.03	3.77	1.77–8.03	0.001



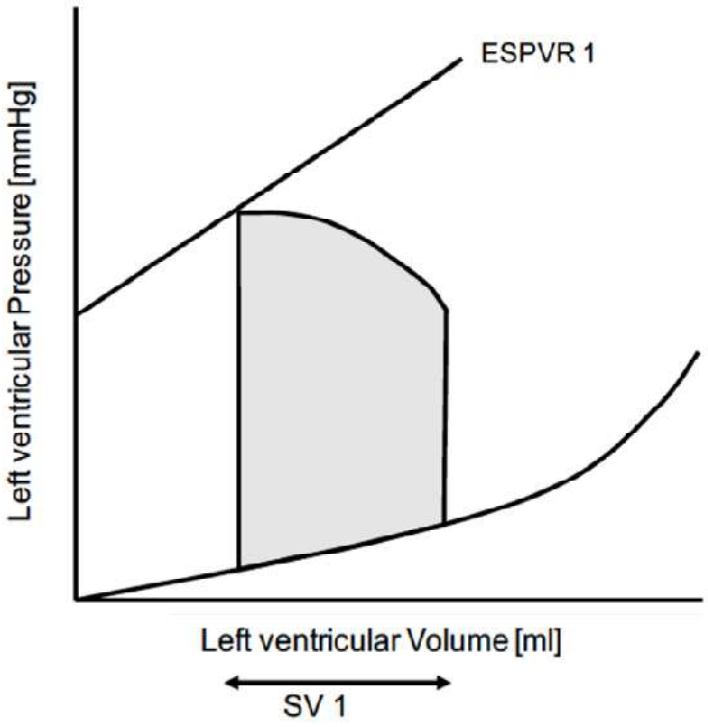
Effets des bétabloquants

FC diminue → **La diastole se prolonge** → **Remplissage de VG +++**

Améliorer obstruction intra VG → **Améliore l'éjection du VG**

Relation pression volume du VG

a



Intensive Care Med (2016) 42:1607–

Quelles molécules?

Esmolol

- β1-bloquant cardiosélectif
- ½ vie de distribution : 2 min
- ½ vie d'élimination: 9 min
- Aucun effet n'est détecté 30 min après son arrêt
- Vois intra veineuse
- Ratio β1/β2 = 35

Landiolol

- β1-bloquant très cardiosélectif (8 x plus que Esmolol Ratio β1/β2=200
- ½ vie d'élimination: très courte 3 à 4 min

Méd. Intensive Réa (2019) 28:12

Principaux résultats des études expérimentales

Preclinical studies on the utility of β-blockers for sepsis treatment published from 2019 to 2021.

Authors	Animal	Sepsis model	Drug	Main conclusion
Kimmoun et al. [10]	Wistar rat	CLP	Esmolol	BB improved cardiac contractility, upregulated vascular α1 AR expression, and exerted an anti-inflammatory effect (as measured by NF-κB level)
Bedet et al. [14]	Mouse	CLP	Atenolol ivabradine	Unlike ivabradine, BB reduced SAP and CO; none of the examined drugs had an effect on 60-h survival
Bangash et al. [20]	Wistar rat	Endotoxemia LPS	Dopexamine* salbutamol	β-Agonists reduced leucocyte–endothelial adhesion in postcapillary veinules as assessed by intravital microscopy
Stolk et al. [21]	C57BL/6 J mouse	Endotoxemia LPS and CLP	Norepinephrine vasopressin	Norepinephrine enhanced immunoparalysis by attenuating production of proinflammatory mediators and stimulating IL-10 production
Van Loon et al. [22]	Sheep	Endotoxemia LPS	Esmolol	BB increased pressure dependency of renal blood flow to renal perfusion pressure by impairing renal autoregulation
Van Loon et al. [23]	Lamb	Endotoxemia LPS	Esmolol	Esmolol improved VACR by decreasing the RV end-systolic pressure in a single-beat PV loop assessment
Carrara et al. [41]	Pig	Intraperitoneal instillation of autologous feces	Esmolol ivabradine	Sepsis-induced cardiac dysautonomia was improved by esmolol and ivabradine, but only esmolol continued to provide benefit under norepinephrine treatment
Carrara et al. [42]	Pig	Intraperitoneal instillation of autologous feces	Esmolol ivabradine	Esmolol improved vascular function via increased peripheral vascular resistance
Guo et al. [43]	SD rat	CLP	Esmolol	Esmolol inhibited inflammation and apoptosis in the intestinal tissue via overexpression NF-κB p65

Journal of Intensive Medicine 2 (2022) 15

Principaux résultats des études expérimentales

Effets hémodynamiques +++

Contractilité du VG +++

Baisse de VO_2 myocardique

Maintien du DC / baisse de FC

Baisse des lactates

Dysfonction du VD avec congestion ---

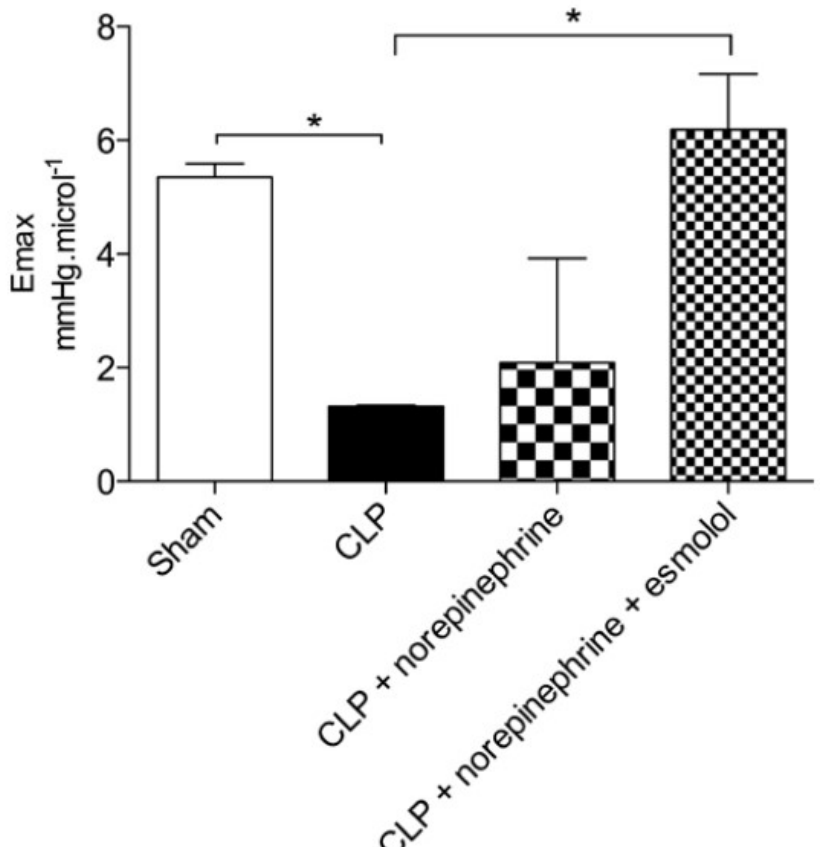
Effets immunomodulateurs +++

Journal of Intensive Medicine 2 (2022) 15

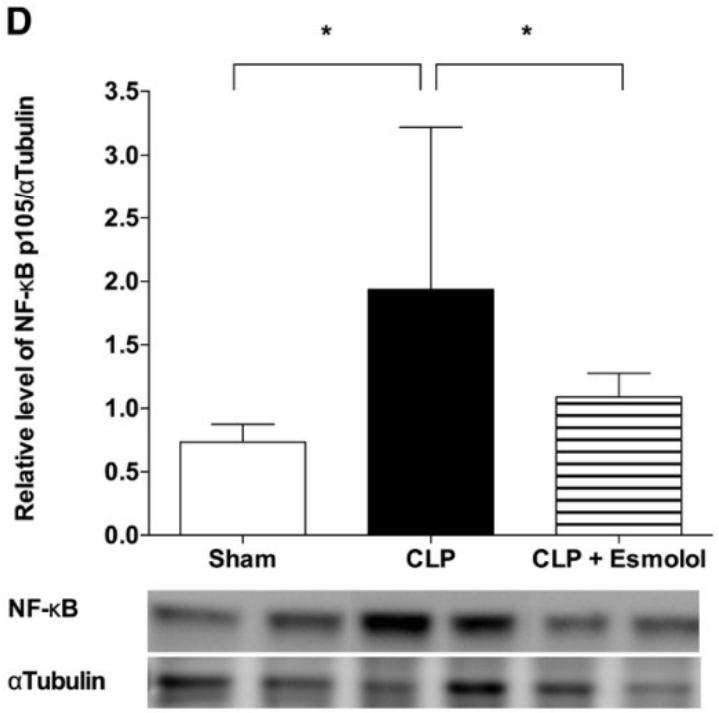
nline Laboratory Investigations

1-Adrenergic Inhibition Improves Cardiac and ascular Function in Experimental Septic Shock*

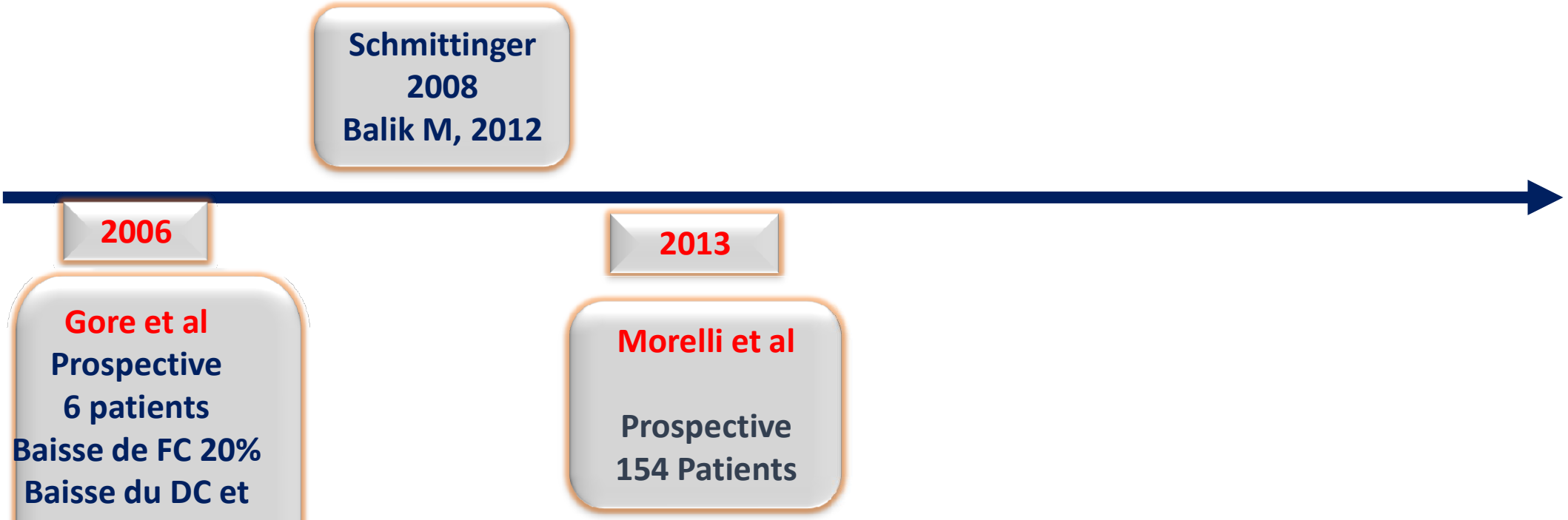
Antoine Kimmoun, MD[1,2,3]; Huguette Louis, PhD[3,4]; Narimane Al Kattani, PhD[2,3]; Julie Delemazure, MD[1,2,3]; Nicolas Dessales, MD[1,2,3]; Chaojie Wei, PhD[2,3]; Pierre Yves Marie, MD, PhD[3,5]; Khodor Issa, PhD[2,3]; Bruno Levy, MD, PhD[1,2,3]



- **Amélioration de la contractilité cardiac**
- **Augmenté l'expression des récepteurs vasculaire**
- **effet anti-inflammatoire. (mesuré par le niveau de NF- κB).**



Les études cliniques



Communication | CARING FOR THE CRITICALLY ILL PATIENT

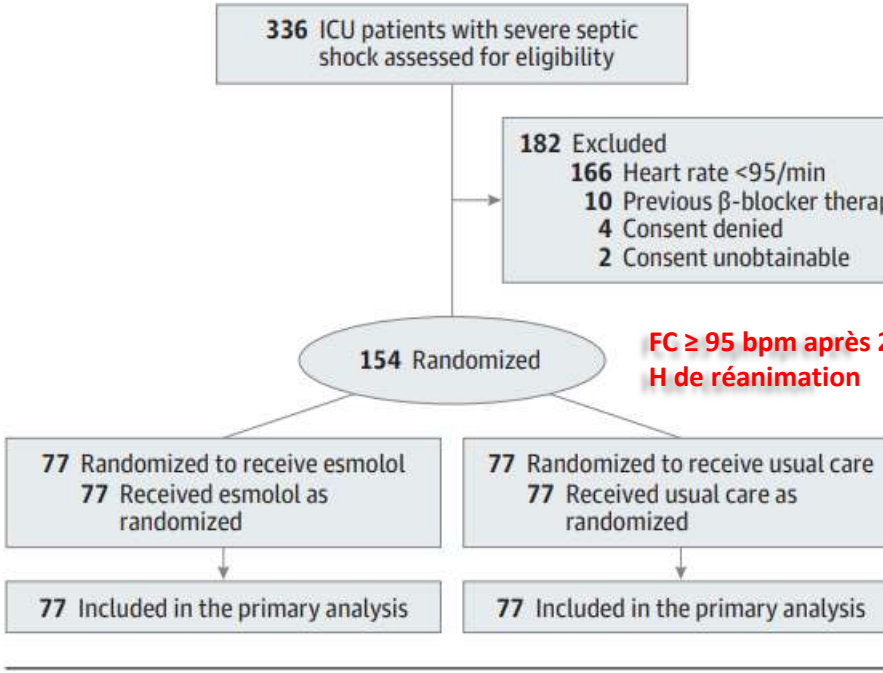
# of Heart Rate Control With Esmolol on Hemodynamic inical Outcomes in Patients With Septic Shock
domized Clinical Trial

, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; cchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; dis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

Maintien de FC entre 80 et 94 bpm sous Esmolol?

Doses de NAD
Indices hémodynamiques et oxygénation
Survie à j28

Figure 1. Flow Chart



FC ≥ 95 bpm après 2
H de réanimation

ch

ry Communication | CARING FOR THE CRITICALLY ILL PATIENT

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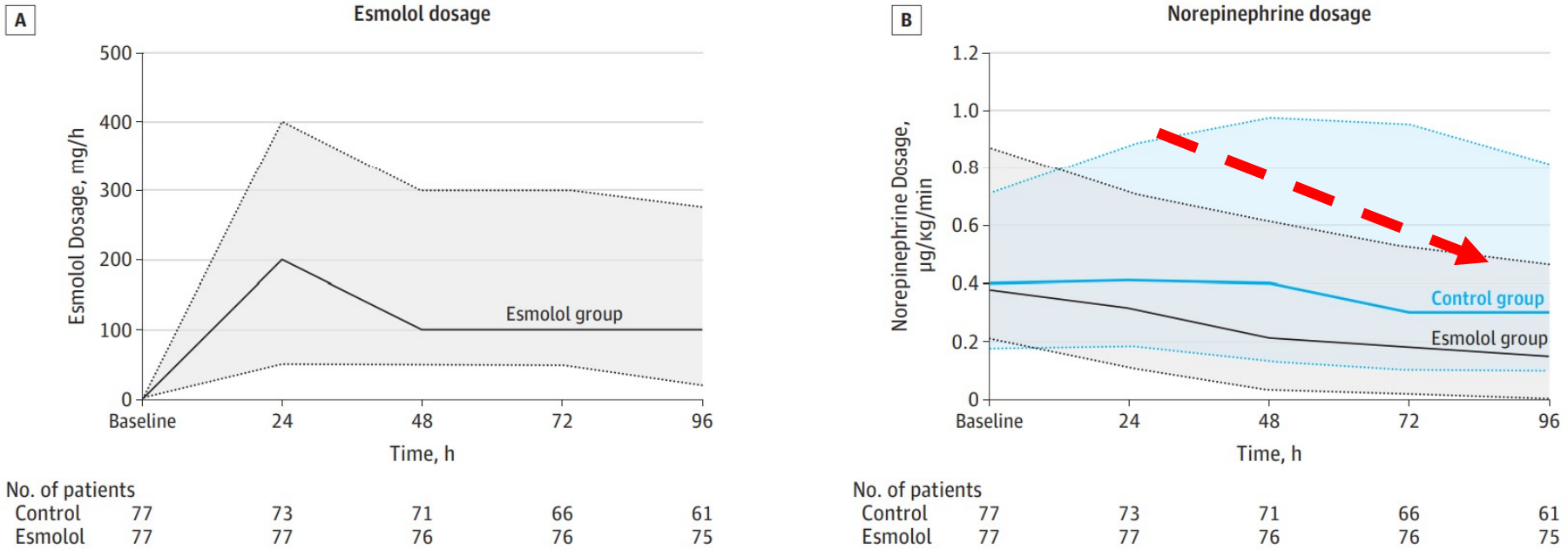

median esmolol dosage was 100mg/h (IQR, 50-300)

ry Communication | CARING FOR THE CRITICALLY ILL PATIENT

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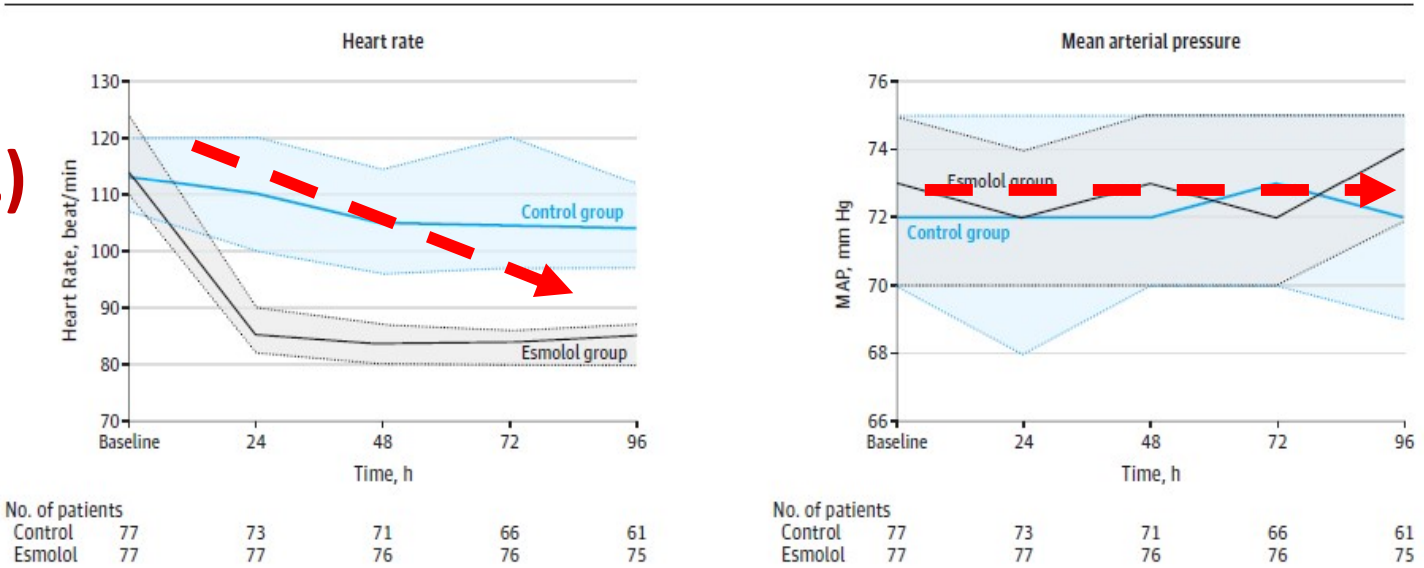
se FC (P < .001)



PAM consta

emodynamic Variables of Study Patients

	Median (Interquartile Range)						*P* Value, Wilcoxon-Mann-Whitney
	Baseline	24 Hours	48 Hours	72 Hours	96 Hours	Area Under the Curve	
mm Hg							
lol	12 (10 to 15)	14 (11 to 16)	14 (11 to 15)	13 (10 to 15)	13 (11 to 15)	1 (−1 to 3)	.17
ol	13 (9 to 15)	12 (10 to 15)	12 (10 to 15)	13 (9 to 15)	12 (9 to 15)	0 (−2 to 2)	
lol	17 (14 to 20)	17 (15 to 20)	17 (15 to 19)	17 (14 to 19)	16 (14 to 18)	0 (−2 to 2)	.48
ol	17 (14 to 20)	17 (14 to 20)	17 (15 to 19)	17 (14 to 19)	17 (14 to 19)	0 (−2 to 1)	
lol	31 (28 to 34)	30 (27 to 33)	29 (27 to 32)	30 (26 to 32)	29 (25 to 32)	−1 (−1 to 0)	.34
ol	31 (27 to 34)	29 (27 to 34)	30 (27 to 32)	30 (25 to 33)	28 (25 to 33)	−1 (−2 to 1)	
e pressure, dyn.s/cm^5/m^2							
lol	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
ol	1271 (967 to 1548)	1265 (1031 to 1608)	1326 (1086 to 1614)	1359 (1026 to 1678)	1276 (985 to 1586)	90 (−74 to 231)	
lol	253 (188 to 309)	293 (206 to 393)	270 (195 to 415)	281 (198 to 385)	286 (197 to 360)	38 (−12; 84)	.02
ol	282 (214 to 347)	289 (197 to 389)	286 (231 to 348)	286 (216 to 384)	261 (221 to 326)	8 (−24 to 40)	
rk index, mL/m^2							
tricle							
lol	27 (23 to 33)	31 (24 to 34)	32 (26 to 37)	32 (25 to 39)	34 (28 to 41)	3 (−1 to 8)	.03
ol	24 (19 to 31)	26 (19 to 31)	28 (21 to 34)	27 (21 to 32)	31 (23 to 36)	1 (−3 to 5)	
ntricle							
lol	9 (6 to 12)	9 (7 to 12)	9 (7 to 11)	9 (7 to 12)	9 (7 to 12)	0 (−2 to 2)	.69
ol	8 (6 to 10)	9 (7 to 10)	8 (7 to 12)	8 (6 to 11)	8 (7 to 11)	0 (−1 to 1)	
ion, mL/24 h							
		5000 (4300 to 5400)	4600 (4300 to 5000)	4300 (4000 to 4600)	4000 (3600 to 4300)	3975 (3663 to 4200)	<.001
		5200 (4700 to 5800)	5400 (4900 to 5700)	5200 (4800 to 5600)	5400 (4725 to 6000)	4425 (4038 to 4775)	

POD

PCP

PAPm

Ø de différznce significative

$RVSI_{Esmolol}$ > >>$RVSI_{control}$

$RVPI_{Esmolol}$ >>> $RVPI_{control}$

Stroke Work Index $_{Esmolol}$ > >> Stroke Index $_{control}$

Communication | CARING FOR THE CRITICALLY ILL PATIENT

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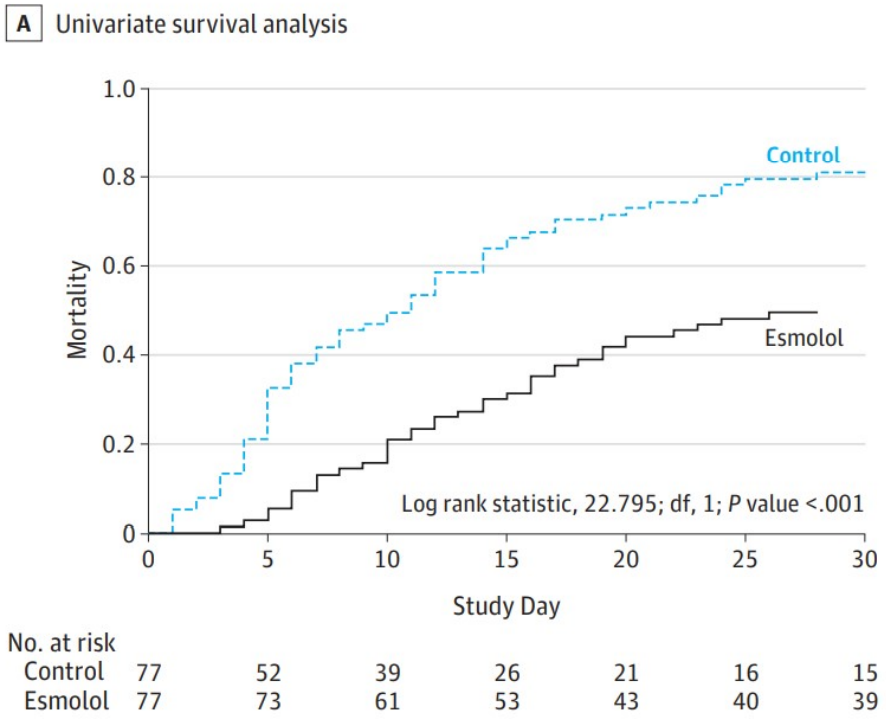
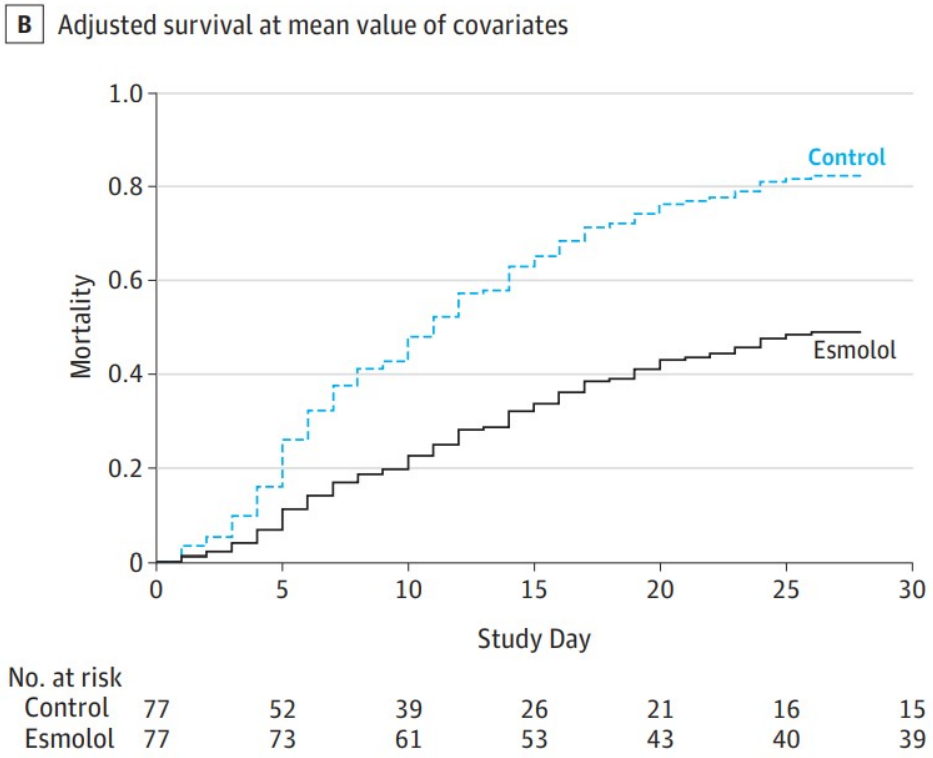
La mortalité diminue :**49.4% vs 80.5% in the control group (*P* .001)**





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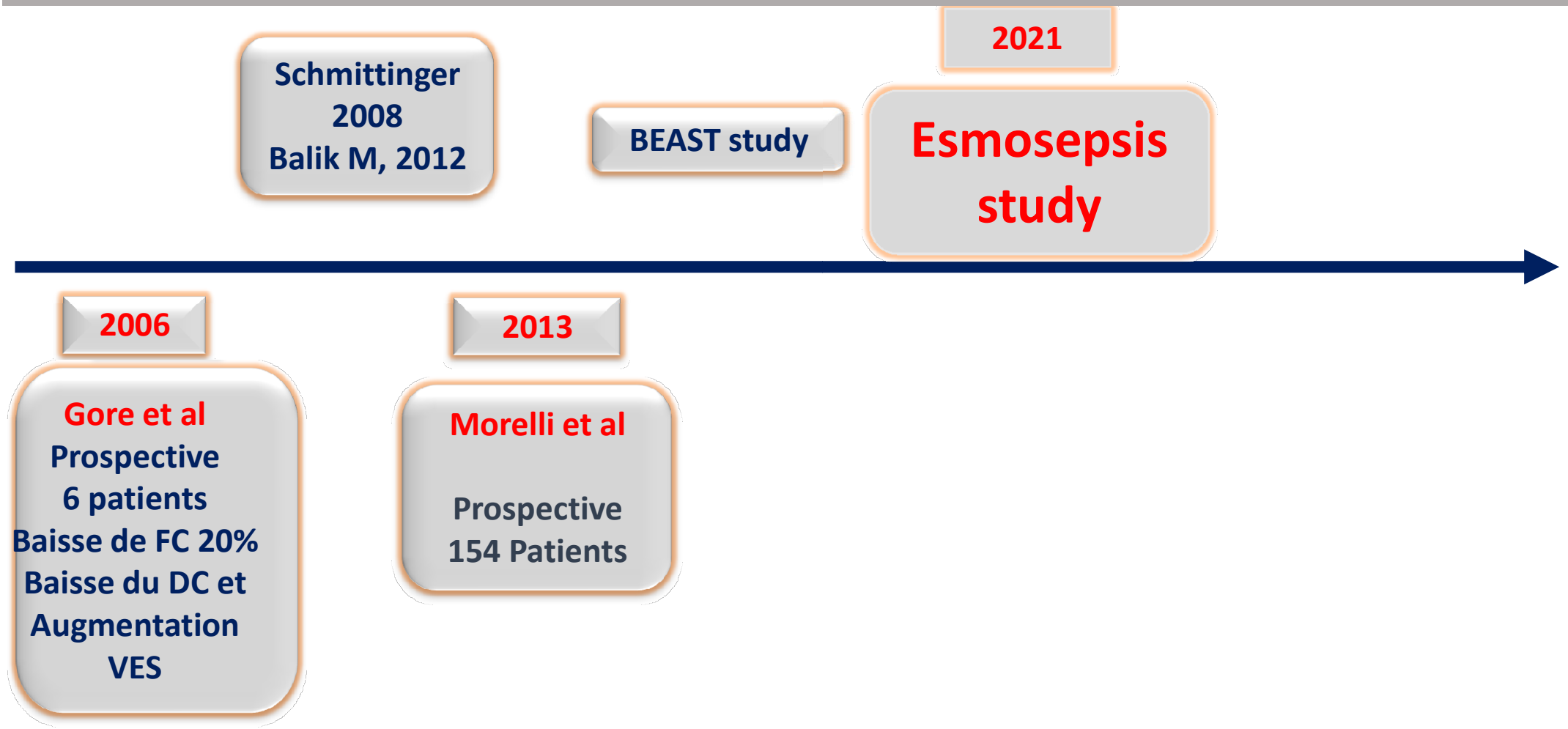
- Mortalité dans le groupe placebo élevée
- l'utilisation du Levosimendan dans la moitié des patients en choc septique
- L'absence d'explication de la baisse des doses de NAD

Les études cliniques



y et al. Crit Care (2021) 25:21
ps://doi.org/10.1186/s13054-020-03445-w

Critical Care

RESEARCH Open Access

Hemodynamic and anti-inflammatory effects of early esmolol use in hyperkinetic septic shock: a pilot study

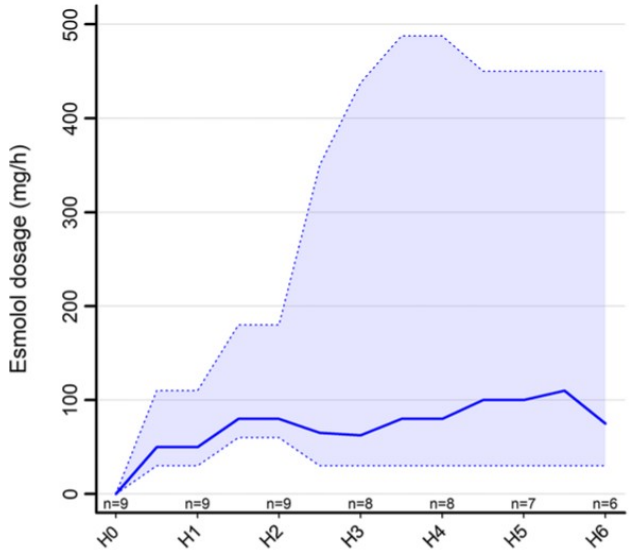
uno Levy[1,2,3,7*], Caroline Fritz[1,2,3], Caroline Piona[1,2,3], Kevin Duarte[4], Andrea Morelli[4,5], Philippe Guerci[6], toine Kimmoun[1,2,3] and Nicolas Girerd[4]

Esmosepsis study

Esmolol pendant 6 H
Début: 7,5 ug/kg/min sans dépasser 200 ug/kg/min
Obj baisse de 20 % FC

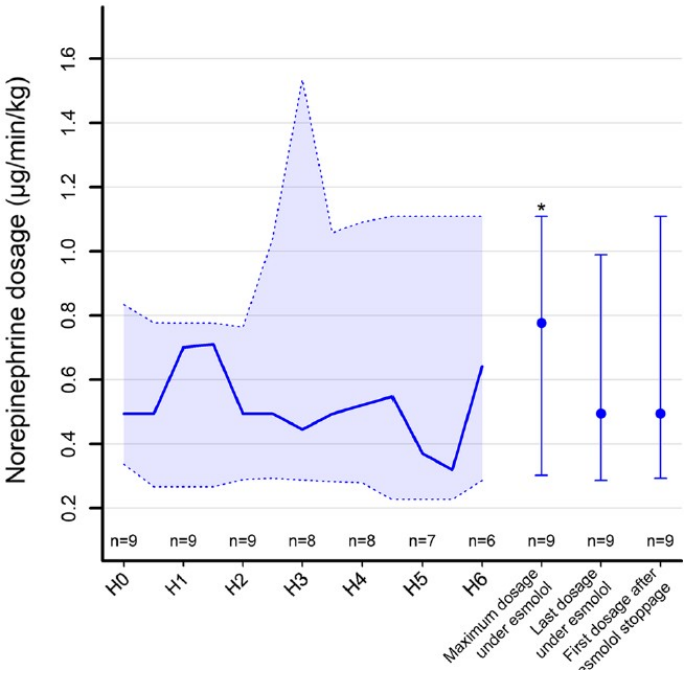
9 patients en choc septique:
(1)Avant la 6ème H de NAD et Optimisation de la volémie;
(2)IC > 3 l/min/m2
(3)FC > 100 bpm

Index cardiaque
Dose de NAD (PAM>70 mmHg
La microcirculation et circulation régionale
La fonction cardiaque
Le profil des cytokines



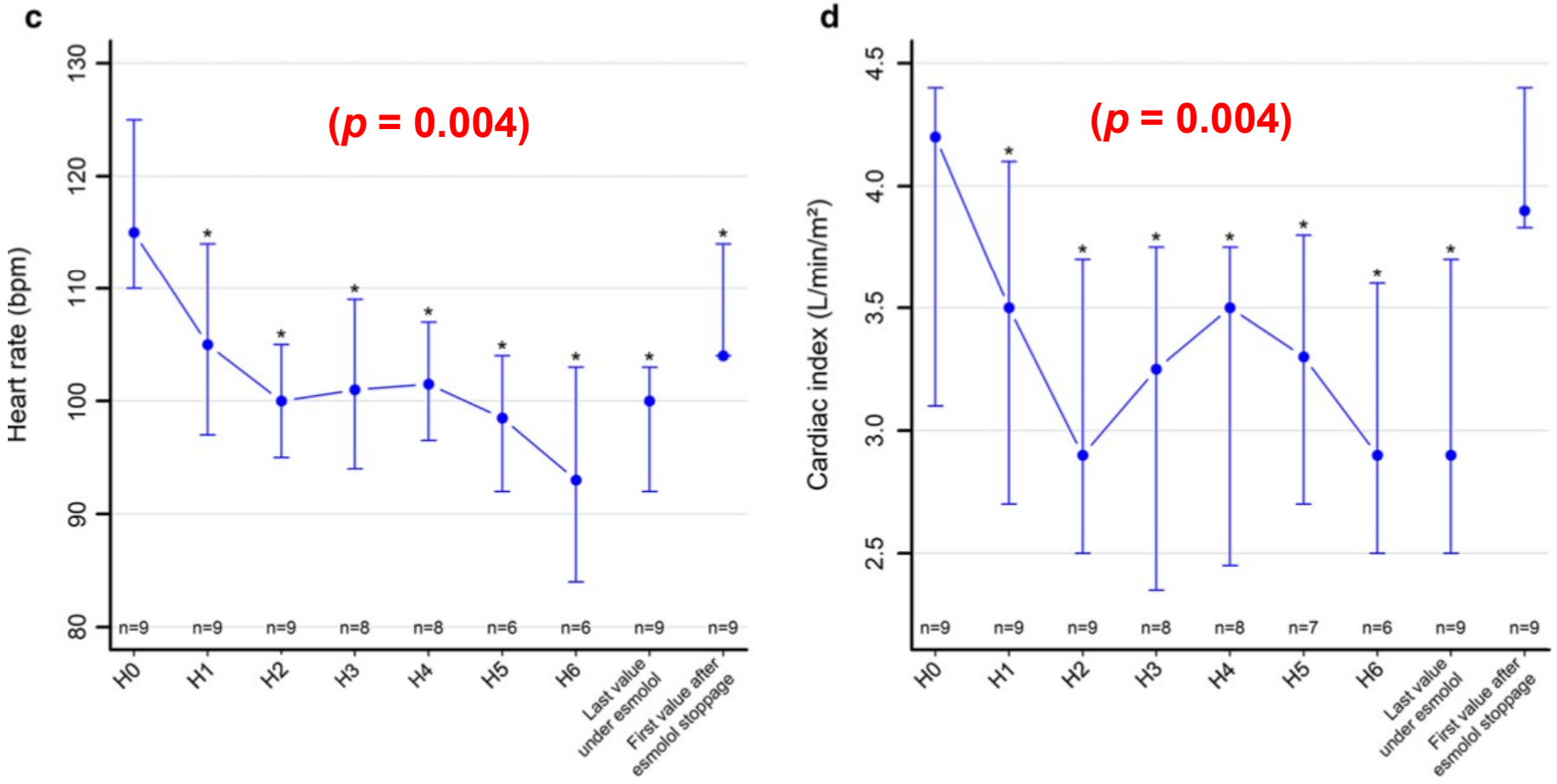
Délai d'introduction de l'Esmolol : 9 H (6.4–11.6)

b



Augmentation significative de NAD (µg/kg) 29.7 (20.2–50) vs 38.1 (18.1–66.5) p=0.027

Baisse significative de la FC et IC sous Esmolol



Effet délétère de l'Esmolol sur la fonction cardiaque

Table 3 Echocardiographic parameters. Comparison H0–H6

	HO	H6	Δ H0–H6 (H6–H0)	*p* value
LVEF (%)	53 (50; 55)	45 (30; 57)	−8 (−18; 2)	0.074
LVEDV	89 (56; 114)	100 (44; 119)	9 (−21; 43)	0.38
VTI (cm)	17 (15; 17)	14 (12; 16)	−2 (−3; −1)	0.008
TDSa (cm/s)	11.0 (8.0; 13.0)	9.0 (7.0; 12.0)	−1.0 (−2.1; 0.0)	0.031
Peak E wave velocity (m/s)	0.90 (0.70; 1.00)	0.84 (0.80; 1.00)	0.00 (−0.10; 0.12)	0.95
Peak E' wave velocity (m/s)	0.11 (0.09; 0.12)	0.09 (0.08; 0.10)	−0.01 (−0.03; −0.01)	0.023
Peak A wave velocity (m/s)	0.77 (0.68; 1.03)	0.57 (0.47; 0.75)	−0.21 (−0.27; −0.06)	0.016
E/A	0.91 (0.80; 1.33)	1.52 (0.97; 1.88)	0.47 (0.20; 0.62)	0.031
E/E'	7.6 (6.5; 9.0)	9.5 (8.4; 12.3)	2.6 (1.0; 3.3)	0.023
DTI S' (cm/s)	9.0 (7.2; 14.0)	9.0 (8.0; 11.0)	−1.0 (−3.0; 0.0)	0.16
TAPSE (mm)	17.5 (16.0; 21.5)	15.5 (14.0; 16.5)	−1.0 (−4.0; −0.5)	0.031

Paramètres Hémodynamiques

	H0	H6	Δ H0–H6 (H6–H0)	p
L/min/m^2)	4.2 (3.1; 4.4)	2.9 (2.5; 3.7)	– 0.6 (– 1.2; – 0.5)	0.00
(mL/m^2)	29.8 (27.3; 37.8)	28.2 (27.2; 36.5)	– 0.2 (– 5.2; – 0.0)	0.25
(W/m^2	0.61 (0.54; 0.70)	0.48 (0.40; 0.58)	– 0.10 (– 0.17; – 0.06)	0.00
Ri (dyn s m^2 cm^{-5})	1164 (1143; 1412)	1379 (1333; 1876)	190 (139; 427)	0.00
(1/min)	6.1 (4.8; 7.4)	3.7 (3.5; 4.8)	– 1.9 (– 2.6; – 1.0)	0.00
LW(mL/kg)	8 (7; 12)	9 (8; 11)	0 (– 1; 1)	0.91
P (mmHg)	8 (5; 8)	8 (6; 12)	1 (0; 2)	0.58
F (%)	20 (17; 21)	17 (15; 19)	– 3 (– 3; – 2)	0.00
uresis (mL/h)	100 (50; 150)	50 (10; 70)	– 60 (– 90; – 50)	0.01
SO_2 (%)	73.6 (70.0; 87.0)	75.3 (71.0; 77.0)	– 3.5 (– 7.0; 3.5)	0.47
O_2i (ml/min/m^{-2})	444 (333; 615)	366 (319; 437)	– 68 (– 98; – 64)	0.03
$_2$i (ml/min/m^{-2})	79 (61; 119)	93 (72; 96)	– 6 (– 13; 16)	0.84
repinephrine (µg/kg)	29.7 (20.2–50)	38.1 (18.1–66.5)	10.4 (5.7–25.5)	0.02

Paramètres gazométriques-Lactates

ble 4 Arterial-venous gas parameters and lactate. Comparison H0–H6

	H0	H6	Δ H0–H6 (H6–H0)	*p* va
	7.34 (7.30; 7.39)	7.36 (7.31; 7.40)	0.01 (– 0.09; 0.02)	1.00
CO_2 (mmHg)	34.4 (32.0; 36.0)	32.4 (26.2; 36.0)	– 3.3 (– 6.0; 6.4)	0.84
CO_2 (mmHg)	37.4 (26.4; 42.0)	39.0 (36.5; 41.0)	– 0.9 (– 1.0; 2.9)	1.00
lta PCO_2 (mmHg)	6.0 (4.0;7.3)	6.0 (5.3;10.0)	4.0 (– 2.0; 6.3)	0.31
O_2 (%)	95.9 (94.3; 98.0)	96.9 (94.2; 98.0)	0.5 (– 0.7; 1.0)	0.62
ctate (mmol/L)	2.2 (1.5; 4.8)	2.4 (1.5; 4.5)	– 0.1 (– 0.3; 0.2)	0.69

Microcirculation et circulation régionale

Table 5 SDF, ICG clearance and NIRS parameters. Comparison H0–H6

	H0	H6	Δ H0–H6 (H6–H0)	*p* value
SDF				
Total vessel density	17.90 (14.88; 18.53)	16.98 (14.48; 19.56)	−0.29 (−0.82; 1.41)	1.00
Perfused vessel density	13.66 (11.34; 14.49)	14.51 (12.31; 15.91)	1.00 (−1.26; 2.28)	0.69
Proportion of perfused vessel	67.41 (58.98; 75.55)	73.37 (66.26; 81.58)	3.96 (−1.92; 13.83)	0.31
Microvascular flow index	1.96 (1.50; 2.44)	1.66 (1.33; 2.44)	−0.08 (−0.54; 0.00)	0.38
Plasma disappearance rate of indocyanine green				
Clearance rate (%/min)	10.8 (4.5; 17.0)	11.0 (4.7; 15.0)	0.2 (0.2; 0.5)	0.62
Retention rate at 15 min (%)	19.8 (6.9; 50.0)	19.0 (17.0; 49.4)	−0.6 (−0.8; 6.1)	0.81
Near-infrared spectroscopy				
StO_2	74 (70; 85)	74 (72; 84)	1 (−6; 2)	0.82
StO_2 overshoot (%)	82 (76; 94)	84 (80; 90)	−2 (−3; 2)	0.84
StO_2 desaturation slope (%/min)	−6.6 (−7.2; −4.5)	−6.9 (−8.7; −6.4)	−0.2 (−4.2; 0.1)	0.44
StO_2 resaturation slope (%/s)	1.1 (0.8; 2.2)	1.2 (1.1; 1.7)	−0.0 (−0.2; 0.3)	1.00

SDF Sidestream dark field, *StO_2* tissue oxygen saturation

Effet de l'Esmolol sur la fonction immunitaire: Diminution des cytokines pro-inflammatoires

	H0	H6	H6-H0	p
IL 8	10,42 [8,97-13,71]	8,78 [8,28-12-87	-068 [-0,83-0,53	0,004
IL 6	13,26 [12,38-13,82]	12,05 [9,99-13,81]	-0,54 [-1,96,0,37]	0,012
IL 10	7,30 [7,06-8,13]	6,96 [5,34-7,44]	-1,02 [-1,89—0,85)	0,008
TNF	5,98 [4,54-6,88]	5,52[4,60-6,42]	-0,46 [-0,54—0,006]	0,020

	H0	H6	H6-H0	p
IL 10	7,30 [7,06-8,13]	6,96 [5,34-7,44]	-1,02 [-1,89—0,85)	0,008

et al. Crit Care (2021) 25:21
//doi.org/10.1186/s13054-020-03445-w

Critical Care

ESEARCH Open Access

emodynamic and anti-inflammatory effects f early esmolol use in hyperkinetic septic hock: a pilot study

o Levy[1,2,3,7*], Caroline Fritz[1,2,3], Caroline Piona[1,2,3], Kevin Duarte[4], Andrea Morelli[4,5], Philippe Guerci[6], oine Kimmoun[1,2,3] and Nicolas Girerd[4]

L'introduction précoce de l'Esmolol

1/3 des cas

- Hypotension sévère
- Baisse significative de L'IC

2/3 des cas

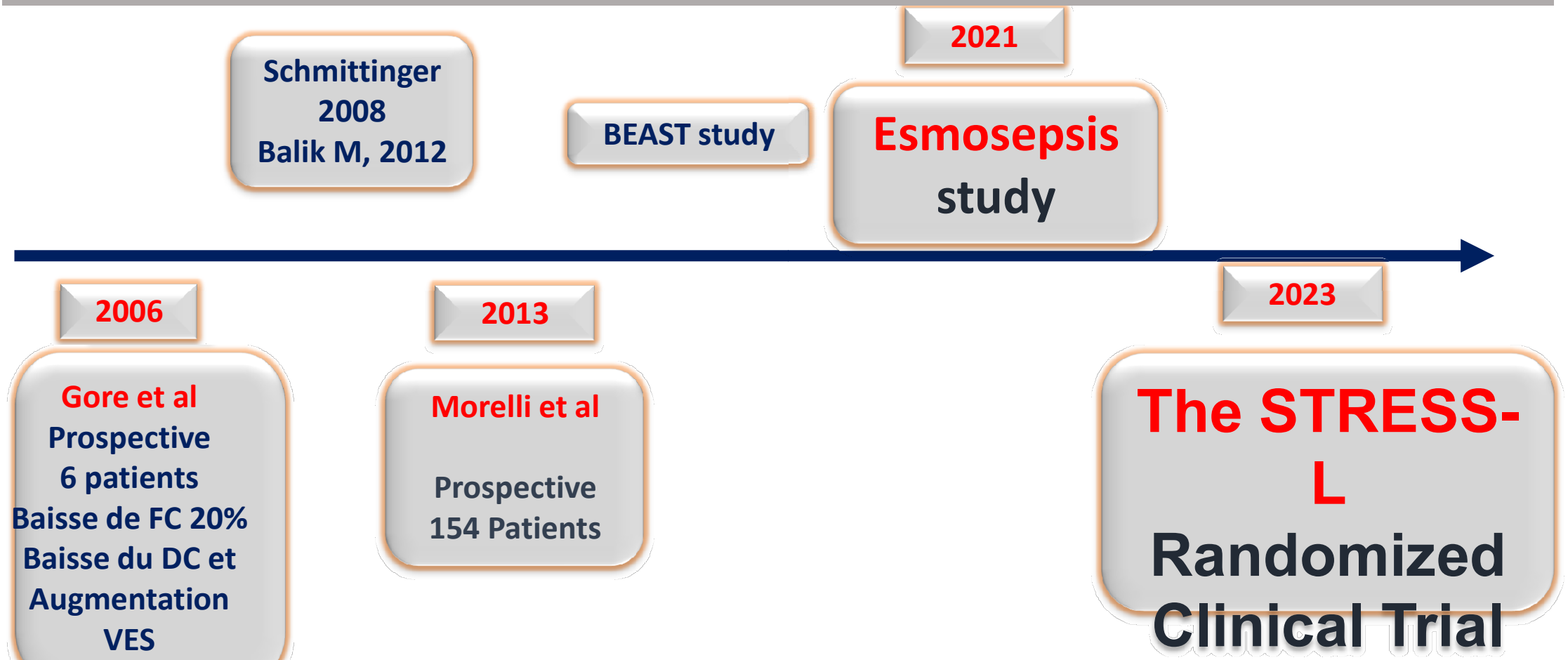
- Hypotension modérée
- Augmentation de NAD
- Dysfonction cardiaque
- Pas d'effets microcirculation lactate et ScVO2.

Suite à la diminution de la FC, la performance myocardique est variable d'un patient à un autre

Elle dépend de la relation étroite entre la précharge, la post et la contractilité

Titration lente et prudente pour atteindre en toute sécurité la stabilité hémodynamique

Les études cliniques



Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

iolol and Organ Failure in Patients With Septic Shock
TRESS-L Randomized Clinical Trial

ehouse, MD; Anower Hossain, PhD; Gavin D. Perkins, MD; Anthony C. Gordon, MD; Julian Bion, MD;
ung, MD; Danny McAuley, MD; Mervyn Singer, MD; Janet Lord, PhD; Simon Gates, PhD;
nith, MD; Niall S. MacCallum, PhD; Joyce Yeung, MD; Richard Innes, MD; Ingeborg Welters, MD;
ta, MSc; Emma Skilton, BSc; Belinder Ghuman, BSc; Maddy Hill, MPH; Scott E. Regan, BA;
try, PhD; Ranjit Lall, PhD; for the STRESS-L Collaborators

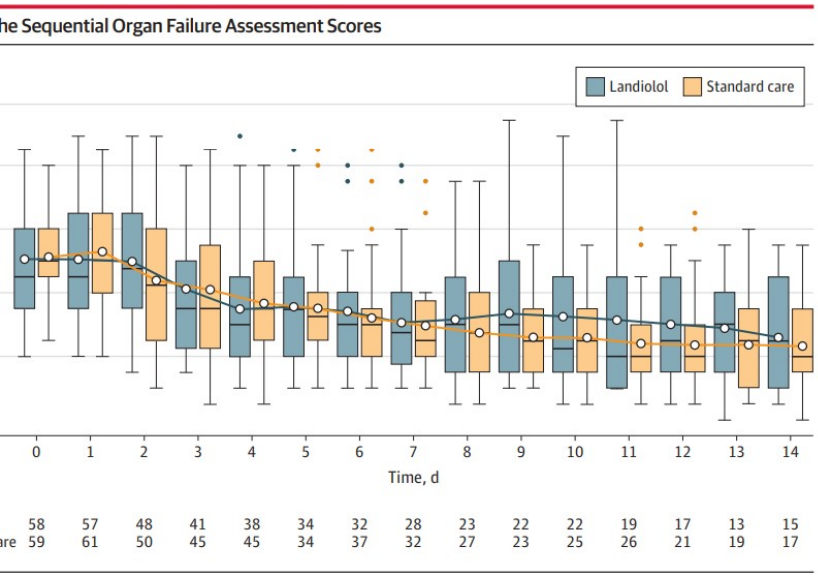
SOFA score pendant 14 j

Mortalité à j28 et à 90 j

- Étude randomisée multicentrique
- 126 adultes – FC >95/min - choc septique sous Nad plus que 24 h (0.1 µg/kg/min) 2018 - 2021
- (1) 63 pts Landiolol +
- (2) 63 pts Landiolol -

The STRESS-L Randomized Clinical Trial

Étude arrêtée précocement



	Landiolol	Placebo	P
SOFA	8,8 ± 3,8	8,1 ±3,2	0,24
Mortalité J28 (%)	37,1	25,3	0,16
PAM (mmHg)	73,2 ±7,6	76 ± 6,5	**0,03**
FC (bpm)	92,4 ±10,4	98,6 ± 12,2	**0,02**

[Critical Care Original Research]

CHEST

Effect of Ultrashort-Acting β-Blockers on Mortality in Patients With Sepsis With Persistent Tachycardia Despite Initial Resuscitation

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Daisuke Hasegawa, MD; Ryota Sato, MD; Narut Prasitlumkum, MD; Kazuki Nishida, MD; Kunihiko Takahashi, PhD; Tomoaki Yatabe, MD, PhD; and Osamu Nishida, MD, PhD

7 RCTs : 613 patients

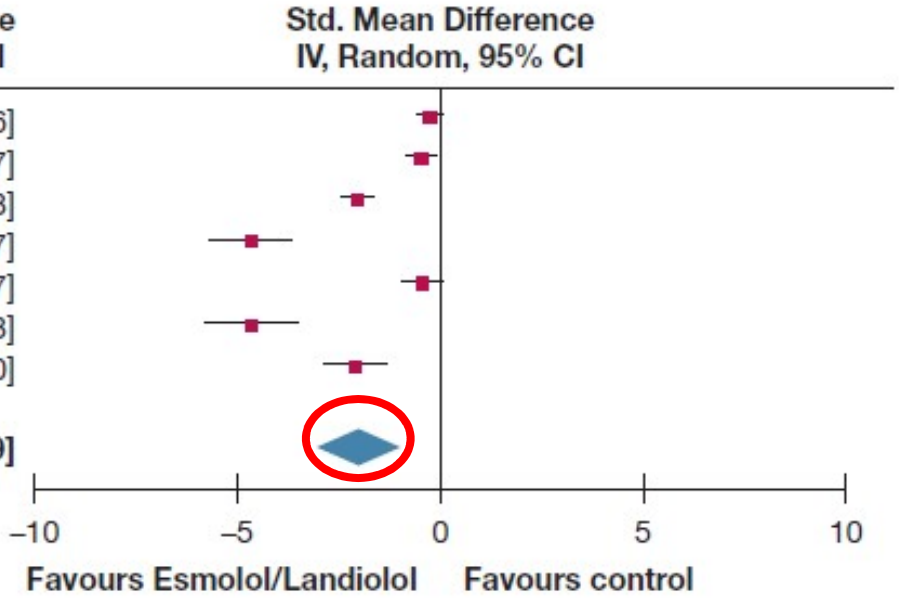
TABLE 2] Characteristics of the Included Patients

Study		Age, y	Men, %	APACHE II Score	Norepinephrine Dose at Baseline, μg/kg/min	28-d Mortality[a]
Kakihana et al[23]	Landiolol	67.8 ± 13.8	68.4	23.1 ± 8.9	0.2 ± 0.2	9/75 (12)
	Control	66.4 ± 15.2	50.7	22.2 ± 8.6	0.2 ± 0.2	15/75 (20)
Liu et al[21]	Esmolol	58.0 ± 15.0	58.0	18.8 ± 6.5	1.06 ± 1.43	31/50 (62.0)
	Control	57.0 ± 18.0	56.0	19.1 ± 7.5	0.76 ± 0.79	34/50 (68.0)
Wang et al[20]	Esmolol	67.2 ± 12.5	70.0	18.4 ± 6.3	Not reported	9/30 (30/0)
	Control	62.5 ± 14.5	60.0	15.7 ± 6.3	Not reported	11/30 (36.7)
Xinqiang et al[18]	Esmolol	61.4 ± 6.9	58.3	20.8 ± 3.1	0.38 ± 0.04	6/24 (25.0)
	Control	61.2 ± 6.4	54.2	21.2 ± 2.7	0.39 ± 0.04	15/24 (62.5)
Wang et al[19]	Esmolol	34 (21-60)[b]	63.3	21.2 ± 5.7	0.25 ± 0.16	12/30 (40.0)
	Control	38 (20-57)[b]	63.3	20.8 ± 5.6	0.28 ± 0.21	20/30 (66.7)
Yang et al[24]	Esmolol	51.0 ± 22.6	Not reported	20.1 ± 9.2	Not reported	Not reported
	Control	55.0 ± 25.4	Not reported	21.3 ± 8.3	Not reported	Not reported
Morelli et al[22]	Esmolol	66 (52-75)[c]	70.1	Not reported	0.38 (0.21-0.87)[d]	38/77 (49.4)
	Control	69 (58-78)[c]	68.8	Not reported	0.40 (0.18-0.71)[d]	62/77 (80.5)

C diminue

dy or Subgroup	Esmolol/Landiolol Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
ihana 2020	94.7	18.2	75	99.5	19	75	15.1%	–0.26 [–0.58, 0.06]
2019	106	17	50	114	17	50	15.0%	–0.47 [–0.86, –0.07]
elli 2013	84.9	6.4	77	108.6	15.2	77	15.0%	–2.02 [–2.41, –1.63]
ng 2015	84.4	3.5	30	111.2	7.2	30	13.3%	–4.67 [–5.67, –3.67]
ng 2017	90.9	14.8	30	97.7	15.3	30	14.7%	–0.45 [–0.96, 0.07]
qiang 2015	84.4	3.5	24	111.2	7.2	24	12.8%	–4.66 [–5.78, –3.53]
g 2014	89	8	21	113	14	20	14.0%	–2.08 [–2.85, –1.30]
al (95% CI)			307			306	100.0%	–1.99 [–2.99, –0.99]

erogeneity: Tau² = 1.69; Chi² = 157.23, df = 6 (*P* < .00001); I² = 96%
t for overall effect: Z = 3.90 (*P* < .0001)

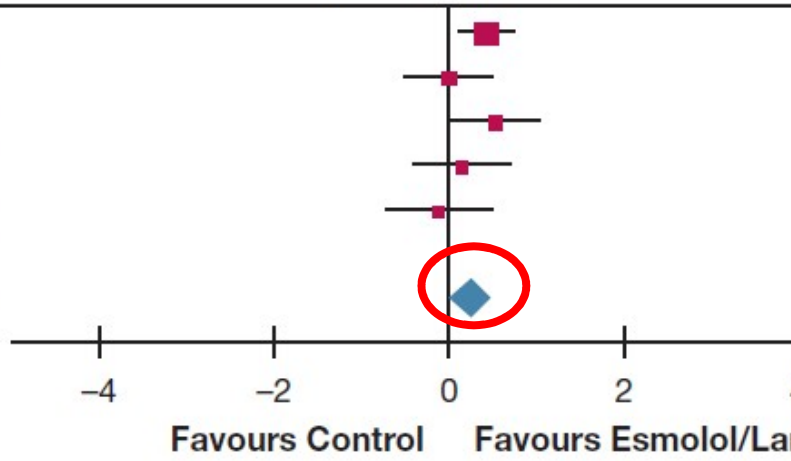


Heart Rate, beats per minute

EI augmente

y or Subgroup	Esmolol/Landiolol Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
li 2013	28.3	7.56	77	24.7	9.07	77	37.1%	0.43 [0.11, 0.75]
2015	36	10	30	36	9	30	18.0%	0.00 [–0.51, 0.51]
2017	38.2	10.1	30	31.9	13.2	30	17.4%	0.53 [0.01, 1.04]
ng 2015	36.8	1.9	24	36.5	2.1	24	14.7%	0.15 [–0.42, 0.71]
2014	37	7.8	21	38	9	20	12.8%	–0.12 [–0.73, 0.50]
(95% CI)			182			181	100.0%	0.26 [0.03, 0.49]

ogeneity: Tau² = 0.01; Chi² = 4.72, df = 4 (*P* = .32); I² = 15%
or overall effect: Z = 2.18 (*P* = .03)



Stroke Volume Index, mL/m²

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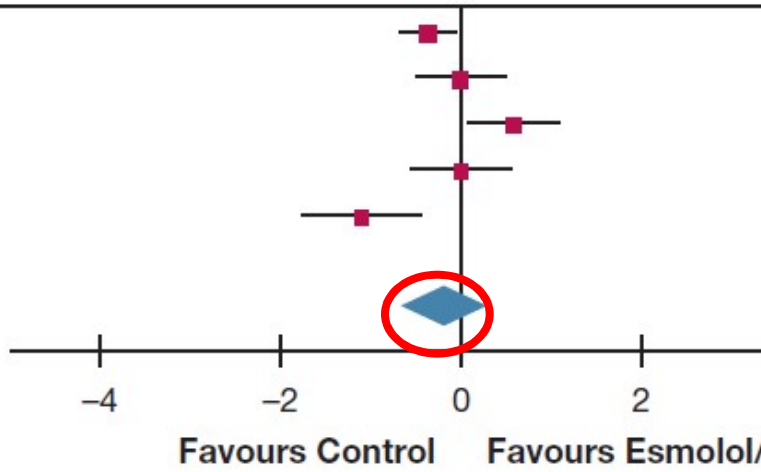
IC inchangé

or Subgroup	Esmolol/Landiolol Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
li 2013	3.49	0.84	77	3.9	1.31	77	23.5%	−0.37 [−0.69, −0.05]
2015	3.2	0.6	30	3.2	0.5	30	20.2%	0.00 [−0.51, 0.51]
2017	3.46	0.94	30	2.92	0.88	30	20.0%	0.59 [0.07, 1.10]
ang 2015	3.7	0.19	24	3.7	0.17	24	19.1%	0.00 [−0.57, 0.57]
2014	3.3	0.7	21	4.4	1.2	20	17.3%	−1.11 [−1.77, −0.44]
(95% CI)			**182**			**181**	**100.0%**	**−0.16 [−0.63, 0.31]**

ogeneity: Tau² = 0.22; Chi² = 18.15, df = 4 (*P* = .001); I² = 78%

or overall effect: Z = 0.67 (*P* = .50)



Cardiac index, L/min/m²

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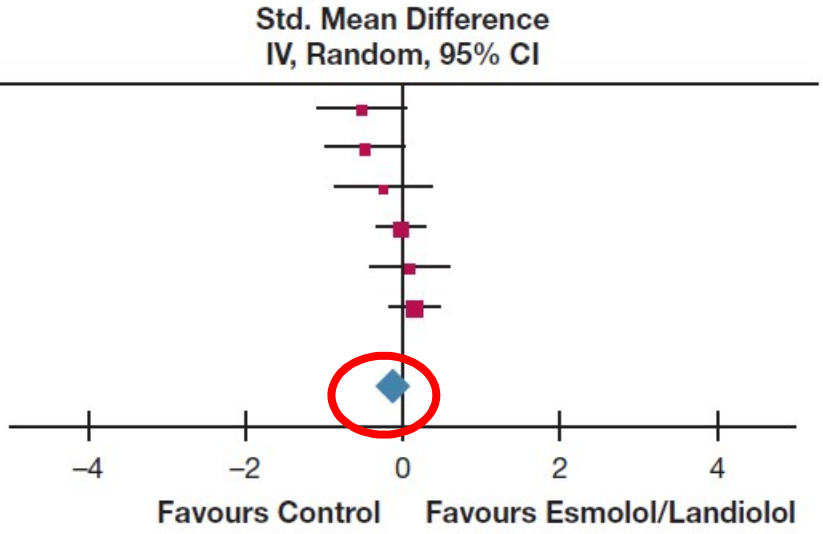
PAM inchangée

Study or Subgroup	Esmolol/Landiolol Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Xinqiang 2015	70.7	1.8	24	71.6	1.6	24	11.5%	−0.52 [−1 .10, 0.06]
Wang 2017	78.3	8.5	30	82.7	9.6	30	13.7%	−0.48 [−0.99, 0.03]
Yang 2014	77	8.5	21	79	7.3	20	10.4%	−0.25 [−0.86, 0.37]
Morelli 2013	71.8	4.3	77	71.9	4.9	77	25.3%	−0.02 [−0.34, 0.29]
Wang 2015	71	22	30	69	21	30	14.0%	0.09 [−0.41, 0.60]
Kakihana 2020	84.1	14.4	75	81.8	15.4	75	24.9%	0.15 [−0.17, 0.47]
Total (95% CI)			**257**			**256**	**100.0%**	**−0.11[−0.33, 0.12]**

Heterogeneity: Tau² = 0.02; Chi² = 7.44, df = 5 (*P* = .19); I² = 33%
Test for overall effect: Z = 0.93 (*P* = .35)

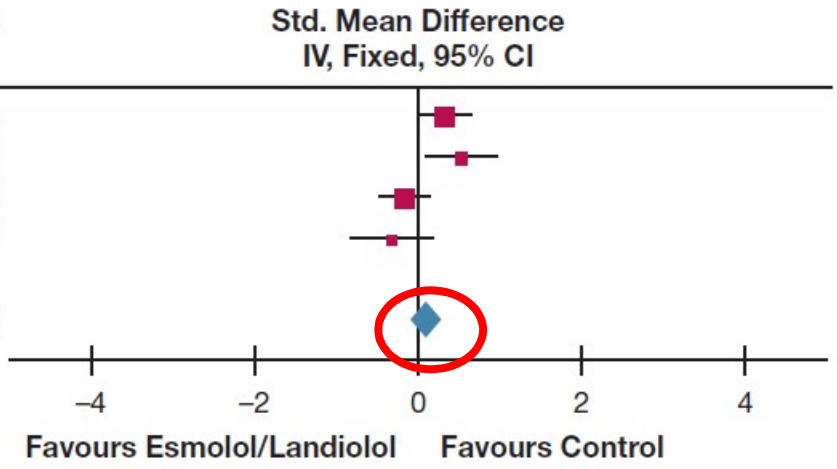


Mean Arterial Pressure, mmHg

Doses de NAD inchangée

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Kakihana 2020	0.21	0.23	75	0.15	0.12	75	33.7%	0.33 [0.00, 0.65]
Liu 2019	1.24	1.92	44	0.46	0.59	38	17.9%	0.53 [0.09, 0.97]
Morelli 2013	0.57	0.7	77	0.69	0.79	77	34.9%	−0.16 [−0.48, 0.16]
Wang 2015	0.21	0.18	30	0.28	0.24	30	13.5%	−0.33 [−0.84, 0.18]
Total (95% CI)			**226**			**220**	**100.0%**	**0.10 [−0.08, 0.29]**

Heterogeneity: Chi² = 10.75, df = 3 (*P* = .01); I² = 72%
Test for overall effect: Z = 1.09 (*P* = .27)



Norepinephrine dose, µg/kg/min

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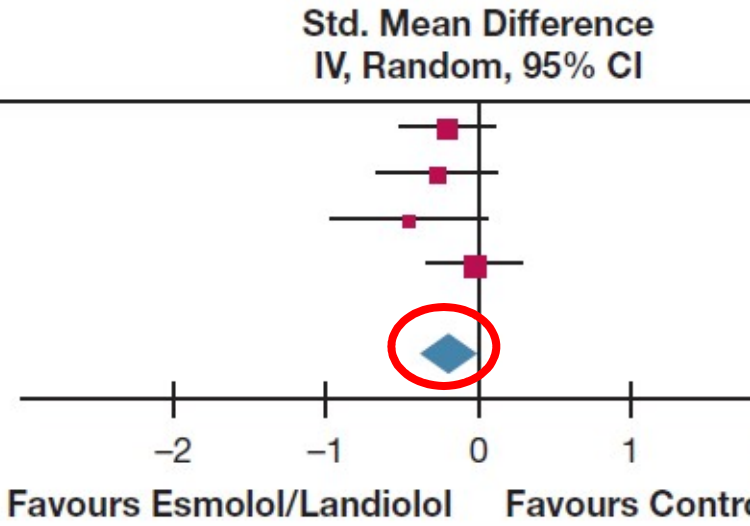
aisse des GB

Subgroup	Esmolol/Landiolol Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2020	13,800	8,900	75	15,700	9,700	75	32.4%	−0.20 [−0.52, 0.12]
	14,600	9,000	50	17,400	11,400	50	21.5%	−0.27 [−0.66. 0.12]
13	10,300	3,700	30	12,200	4,500	30	12.7%	−0.46 [−0.97, 0.06]
7	14,200	6,300	77	14,400	10,200	77	33.4%	−0.02 [−0.34. 0.29]
% CI)			232			232	100.0%	**−0.19 [−0.37, −0.01]**

neity: Tau² = 0.00; Chi² = 2.26, df = 3 (*P* = .52); I² = 0%

verall effect: Z = 2.03 (*P* = .04)



White Blood Cell Count, cells/µL

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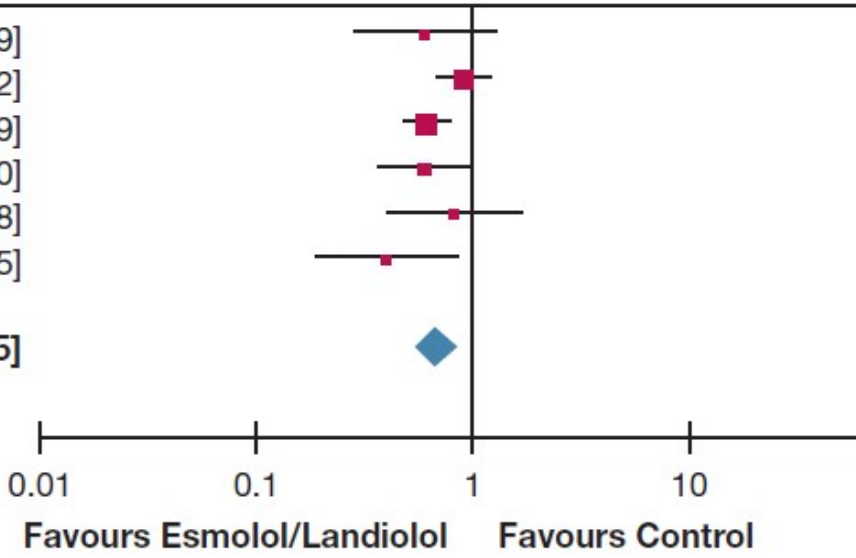
En terme de mortalité

udy or Subgroup	Esmolol/Landiolol Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
kihana 2020	9	75	15	75	7.4%	0.60 [0.28, 1.29]
u 2019	31	50	34	50	29.3%	0.91 [0.68, 1.22]
orelli 2013	38	77	62	77	33.2%	0.61 [0.48, 0.79]
ang 2015	12	30	20	30	14.5%	0.60 [0.36, 1.00]
ang 2017	9	30	11	30	8.2%	0.82 [0.40, 1.68]
nqiang 2015	6	24	15	24	7.5%	0.40 [0.19, 0.85]
tal (95% CI)		**286**		**286**	**100.0%**	**0.68 [0.54, 0.85]**
tal events	105		157			

eterogeneity: Tau² = 0.02; Chi² = 7.21, df = 5 (*P* = .21); I² = 31%
st for overall effect: Z = 3.40 (*P* = .0007)



This systematic review and meta-analysis suggested that esmolol or landiolol use in patients with persistent tachycardia despite initial resuscitation was associated with significantly lower 28-day mortality.

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sis of β-adrenergic blockade therapy on septic shock and sepsis: A atic review and meta-analysis of randomized controlled studies

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6 RCTs : 363 patien

(2013-2017)

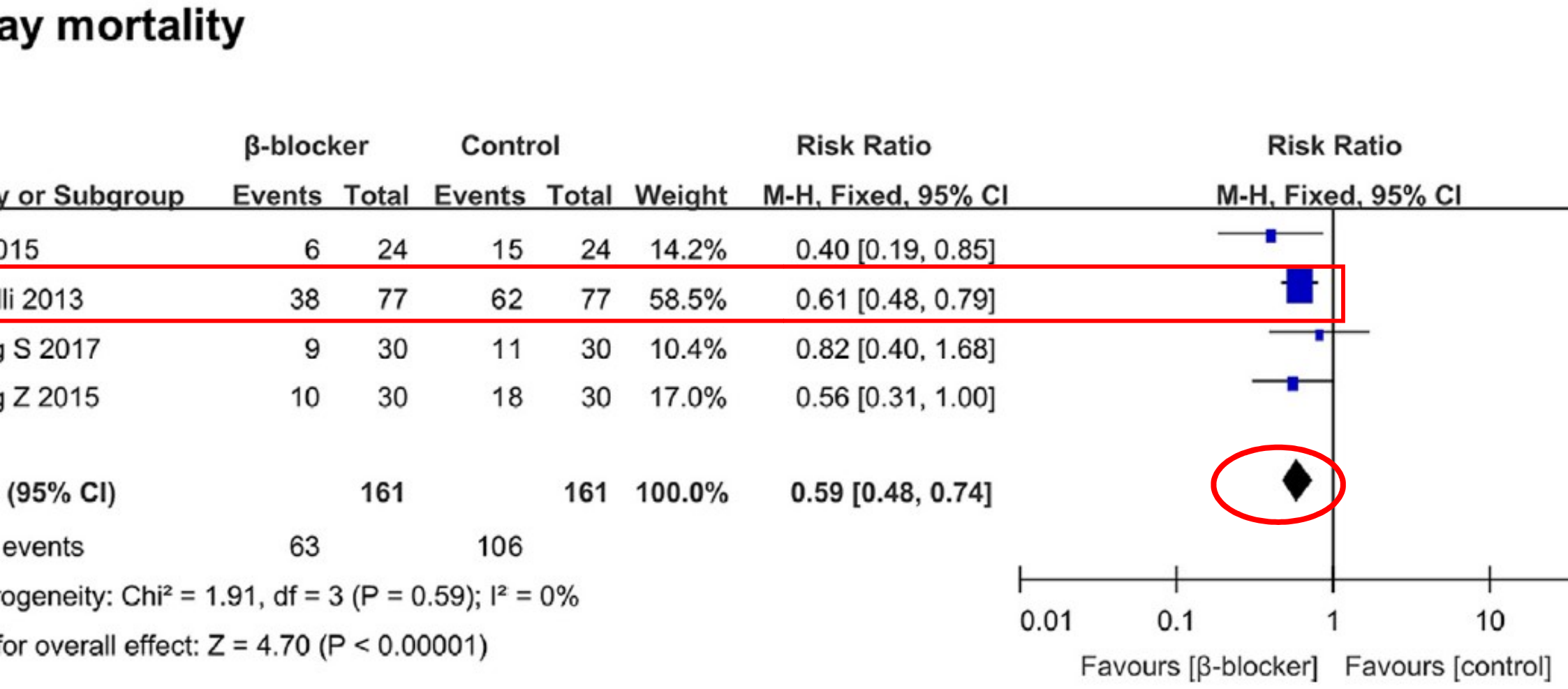

Fig. 2. Forest plots depicting the pooled outcomes of 28-day mortality of β-blocker versus control group.

Divergence des résultats

- Critères d'inclusion : Définition du sepsis +++
- Protocoles d'utilisation des β Bloquants (molécules – délai et durée)
- Hétérogénéité des patients (Gravité – fonction cardiaque – Volémie)

Distinguer 3 types des TC lors du choc septique

Adaptative

Compensatrice

Non compensatrice

Messages clés:
Bétabloquants lors du choc septique

Pourrait être envisagés pour réduire la FC et améliorer l'état HD Mais !

- **Pas** à la phase **précoce** du CHOC: (optimiser la volémie et privilège la réponse adaptative initiale)
- **Après** évaluation de la **fonction cardiaque**
- **Titration lente et prudente**
- **Chez les patients pas trop grave**

Non Recommandés
Besoin de preuves solides