

**Faut-il traiter la dysfonction
myocardique du sepsis ?**

Prof. Jean-Louis TEBOUL

**Medical ICU
Bicetre hospital
University Paris-South
France**

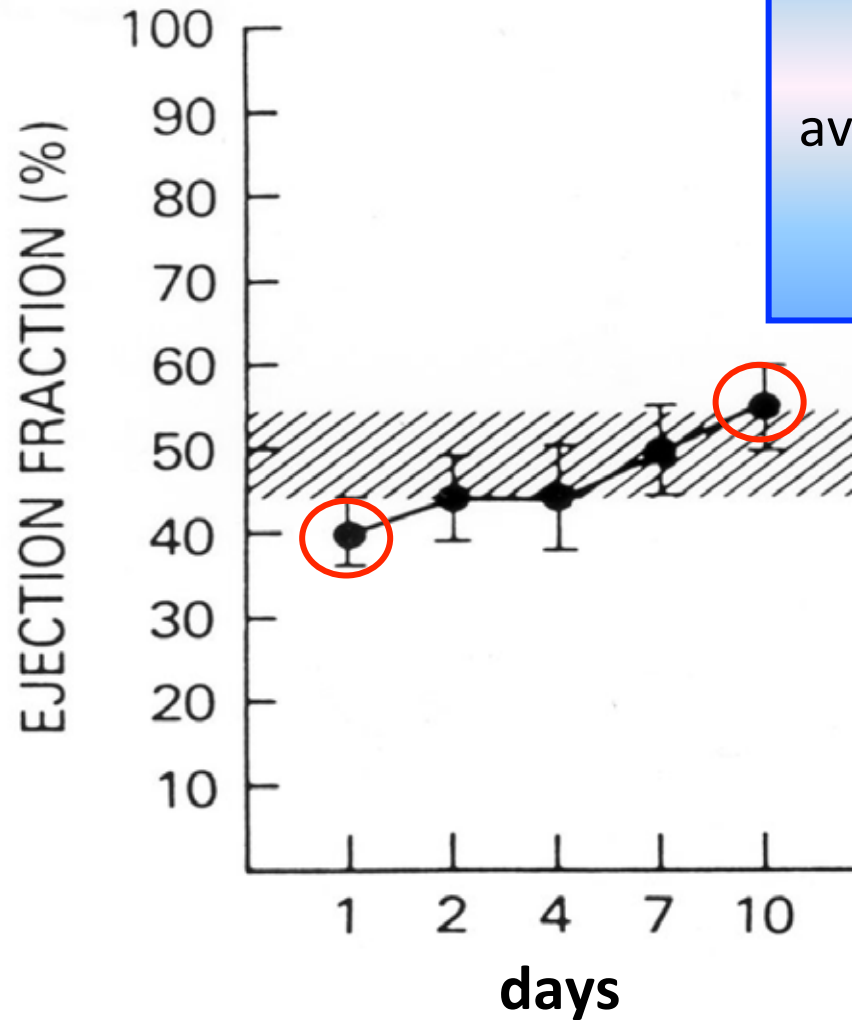
**septic shock
patients**

Diminution précoce de la FEVG,

persistant 4 jours

avec retour à la normale en 7 à 10 jours

chez les survivants



Parker et al Ann Intern Med 1984

Dysfonction myocardique liée au sepsis

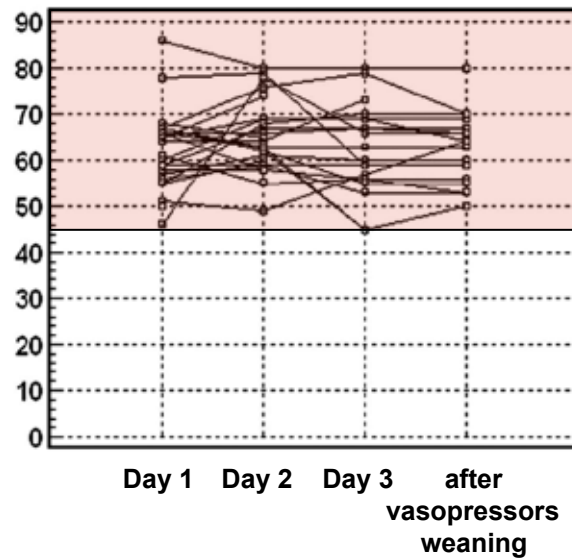
- **Incidence**
- Mécanismes
- Diagnostic
- Traitement

Actual incidence of global left ventricular hypokinesia in adult septic shock

Antoine Vieillard-Baron, MD; Vincent Caille, MD; Cyril Charron, MD; Guillaume Belliard, MD; Bernard Page, MD; François Jardin, MD

Crit Care Med 2008; 36:1701-1706

LV EF %



40% of pts

40% of pts

20% of pts

Dysfonction myocardique liée au sepsis

- Incidence
- **Mécanismes**
- Diagnostic
- Traitement

Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

mécanismes **intracellulaires**

Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

- *débit coronaire ?*

mécanismes **intracellulaires**

Généralement, le **débit coronaire** n'est **pas diminué** au cours du sepsis

... mais chez pts **coronariens**,
éviter les **chutes** trop **profondes** de la **PAD**
(pression motrice de la perfusion coronaire VG)

Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

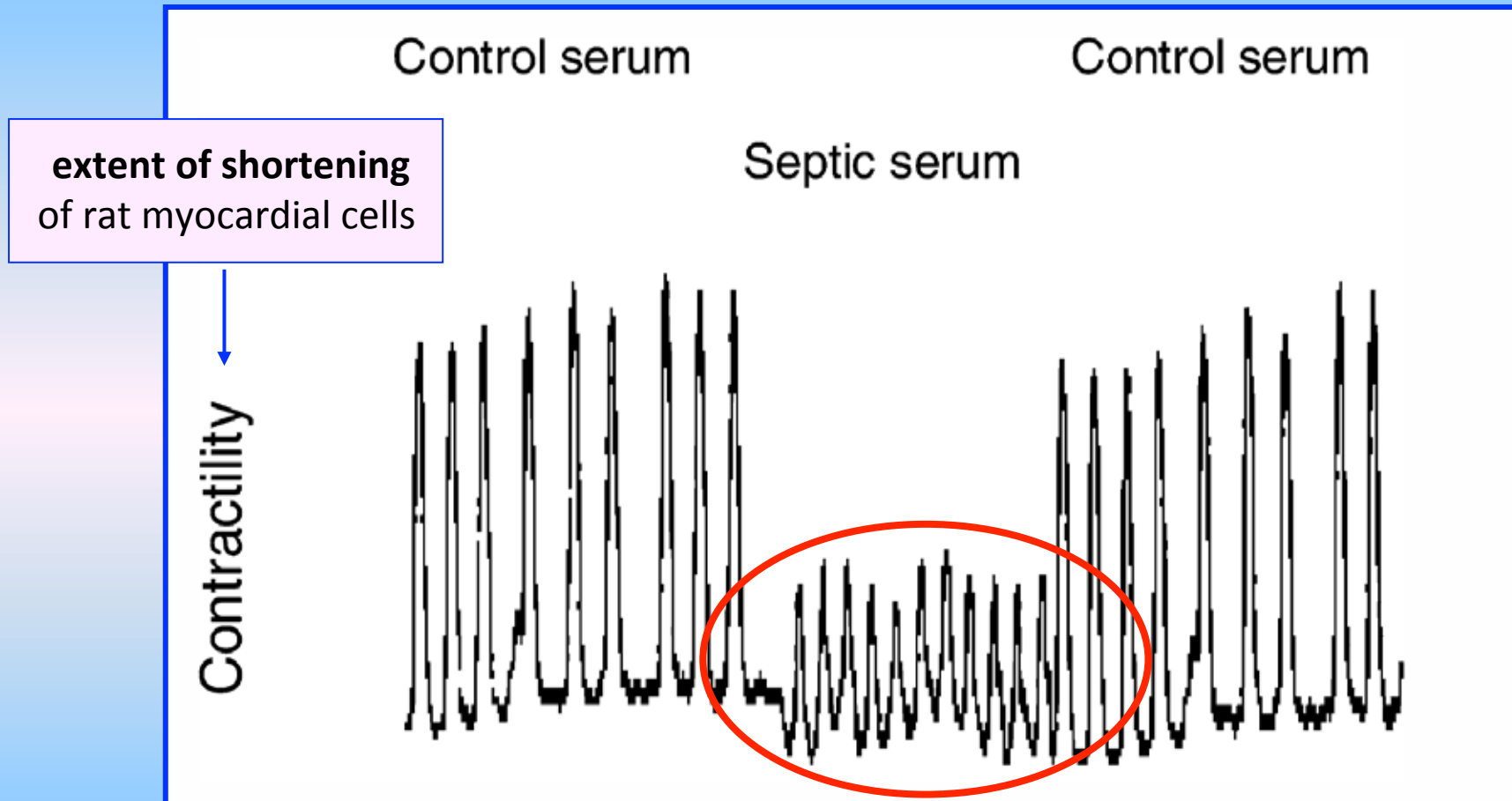
- *débit coronaire ?*
- ***substances circulantes ?***

mécanismes **intracellulaires**

A Circulating Myocardial Depressant Substance in Humans with Septic Shock
Septic Shock Patients with a Reduced Ejection Fraction Have a Circulating Factor That Depresses In Vitro Myocardial Cell Performance

Joseph E. Parrillo, Cynthia Burch, James H. Shelhamer, Margaret M. Parker, Charles Natanson, and William Schuetz

J Clin Invest 1985; 1539-1553

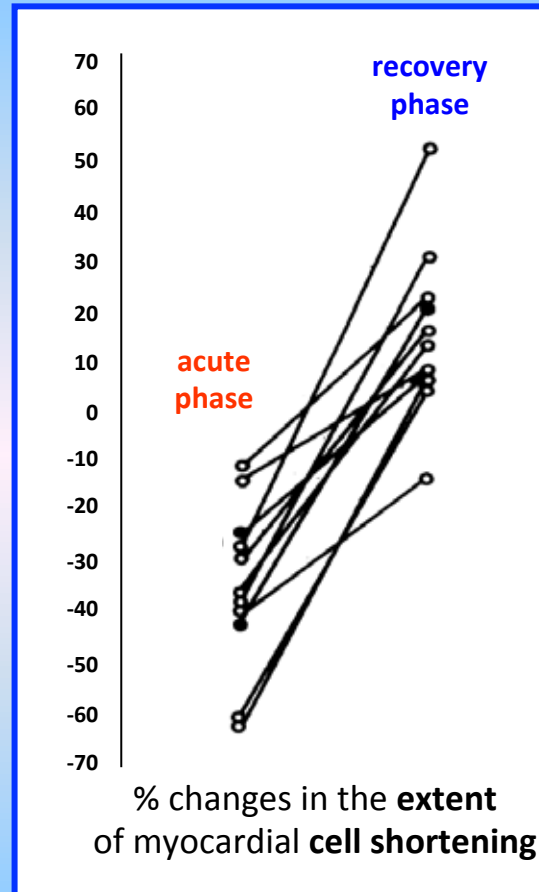


Le sérum de pts en choc septique contenait des substances capables de déprimer la contractilité cardiaque

A Circulating Myocardial Depressant Substance in Humans with Septic Shock
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Le sérum de pts en **choc septique** contenait des **substances** capables de **déprimer** la **contractilité** cardiaque

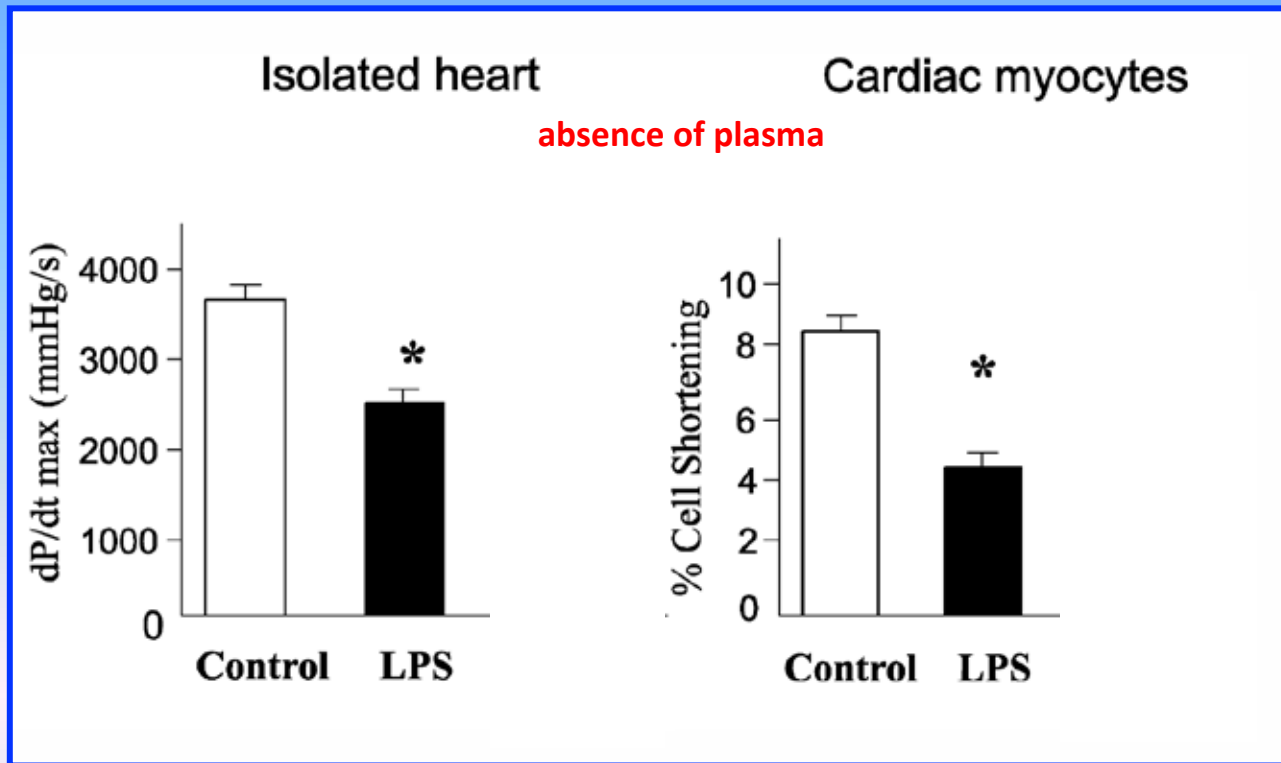
Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

- *débit coronaire ?*
- *substances circulantes ?*

TNF- α , IL₁, autres?

mécanismes **intracellulaires**



La **contractilité** peut **diminuer** en l'absence de plasma

Ceci plaide **contre** un rôle majeur des facteurs circulants dépresseurs myocardiques
mais suggère une **altération intrinsèque du myocarde**
comme **mécanisme prédominant**

Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

- *débit coronaire ?*
- *substances circulantes ?*

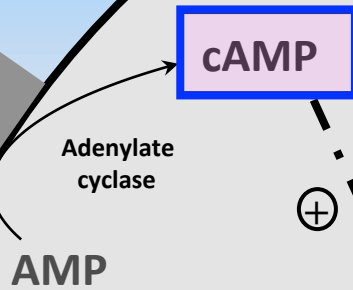
mécanismes **intracellulaires**

- *récepteurs β_1 ?*

membrane du cardiomyocyte

β_1 agoniste

β_1 récepteur



PKa

Ca^{2+}

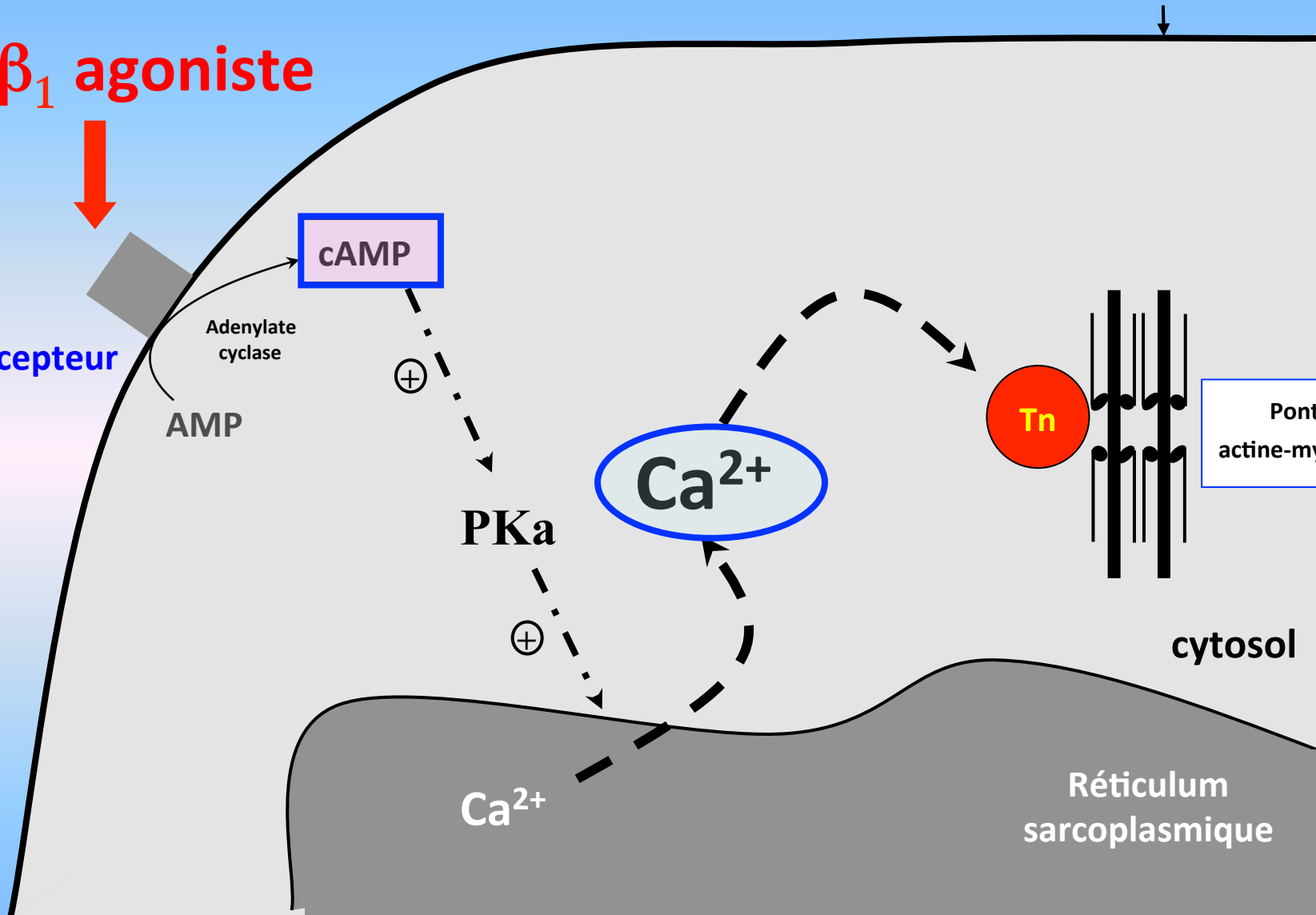
Tn

Ponts actine-myosine

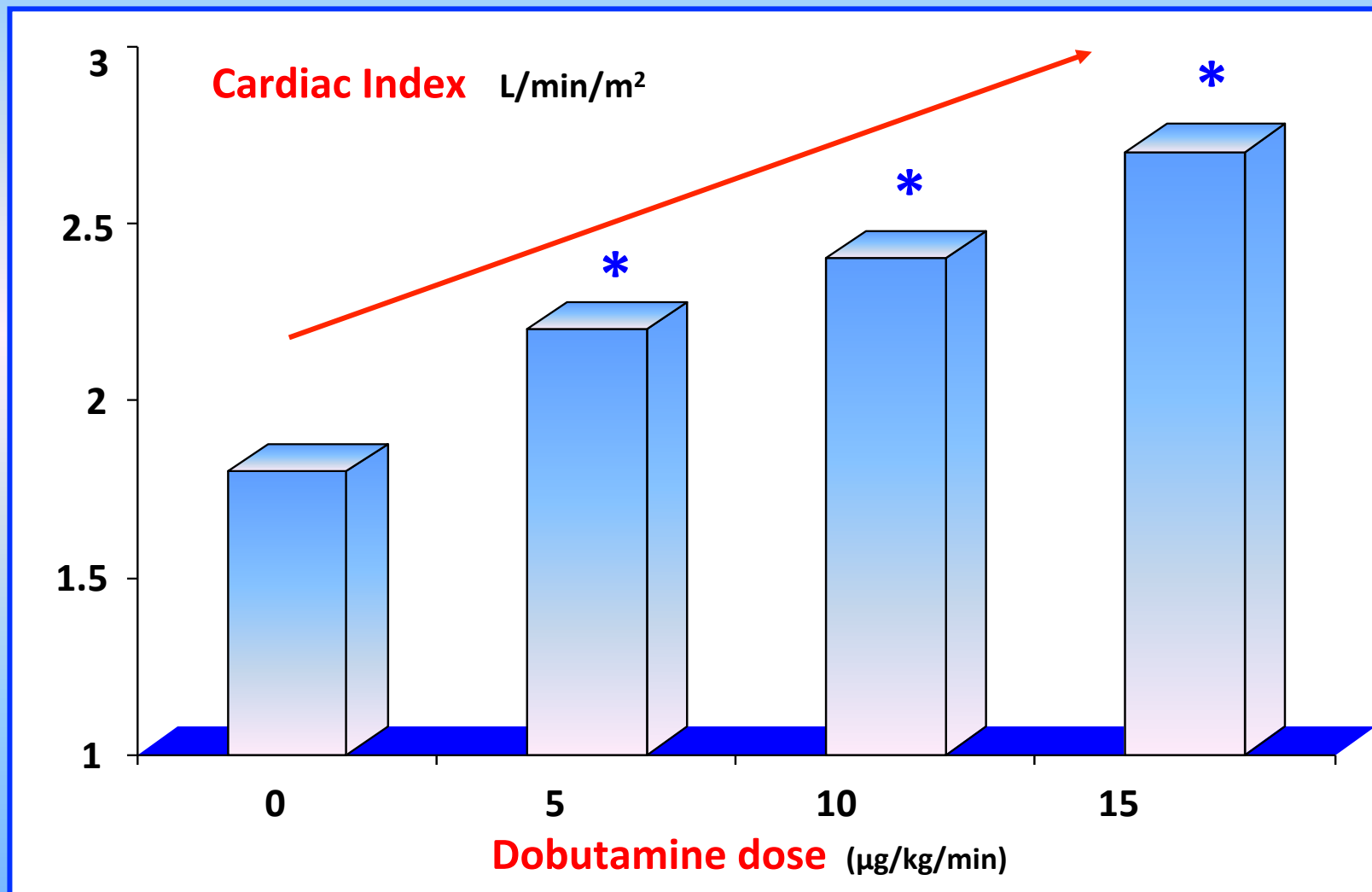
cytosol

Ca^{2+}

Réticulum sarcoplasmique



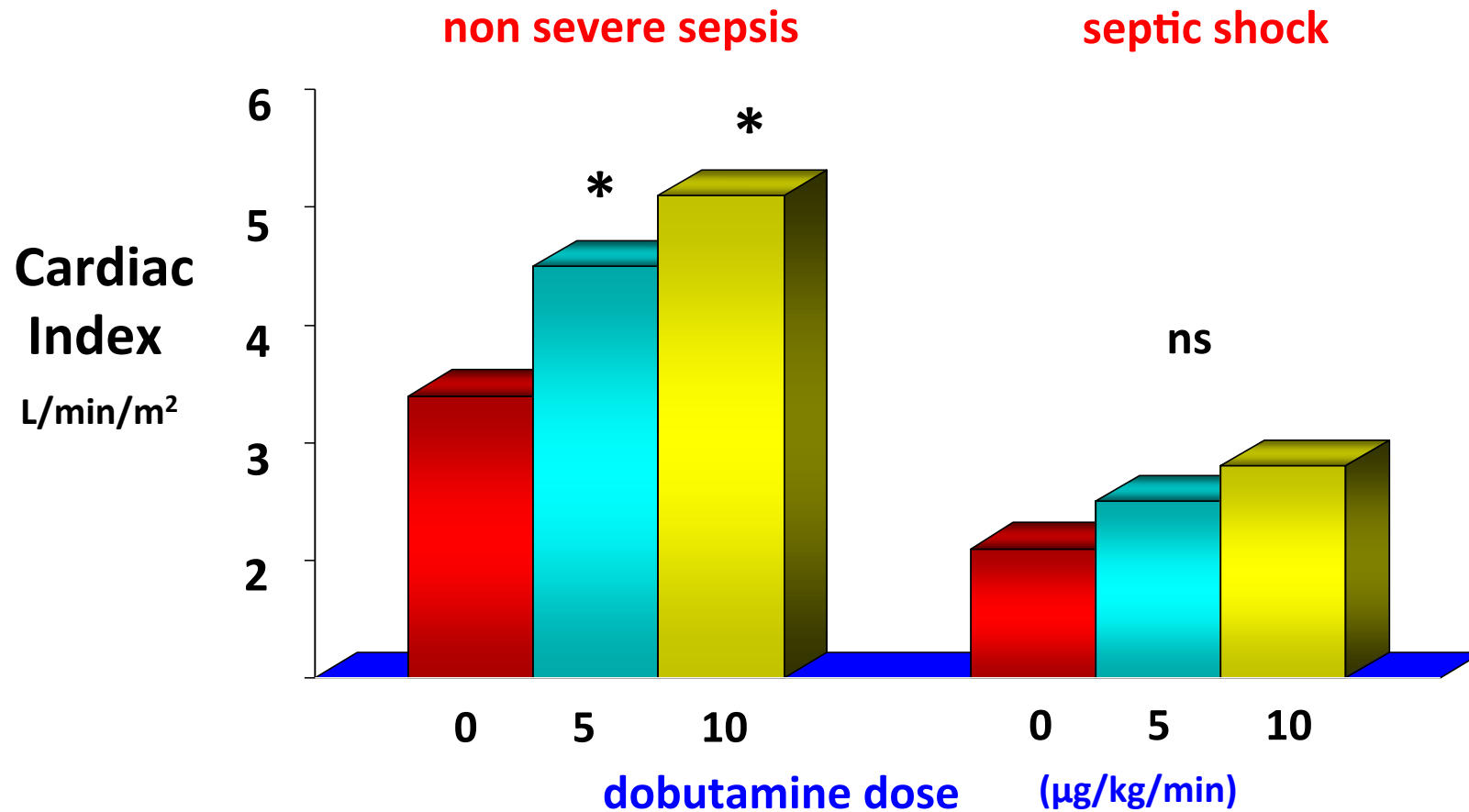
in Patients With Congestive
Heart Failure*



Impaired β -adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines

HENRY J. SILVERMAN, MD; RUBEN PENARANDA, MD; JONATHAN B. ORENS, MD; NORMAN H. LEE, PhD

Crit Care Med 1993; 21:31-39

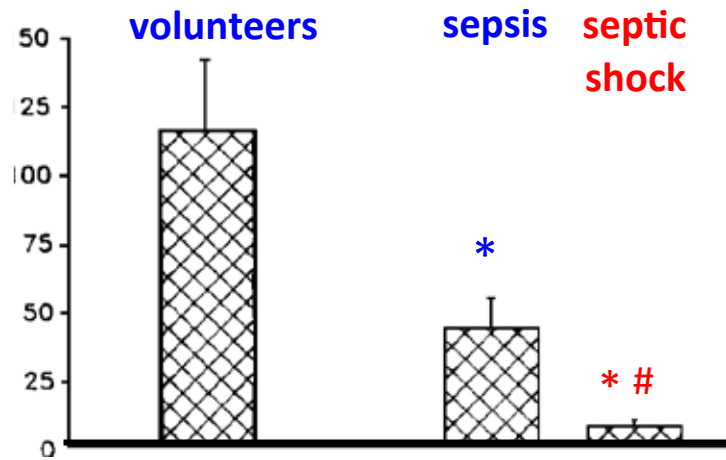


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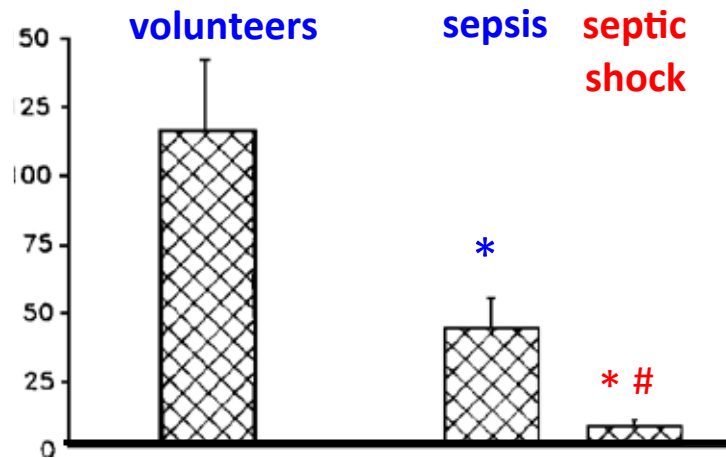
cAMP response to isoproterenol



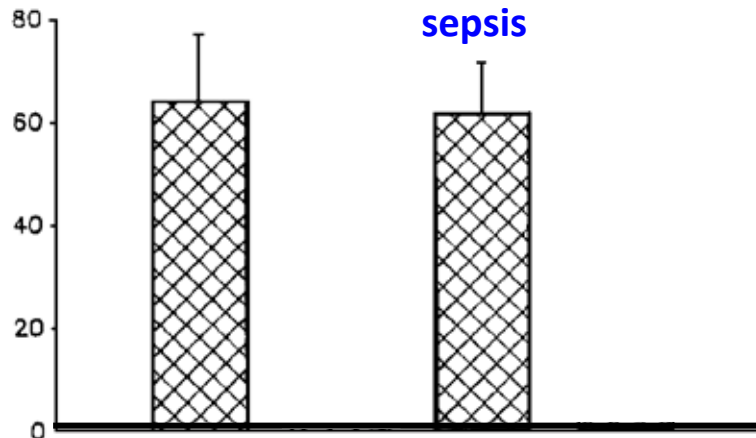
impairment of
 β -adrenergic receptor responsiveness
in sepsis and septic shock

Decreased efficacy of dobutamine in patients with septic shock

cAMP response to isoproterenol



cAMP response to Na-fluoride



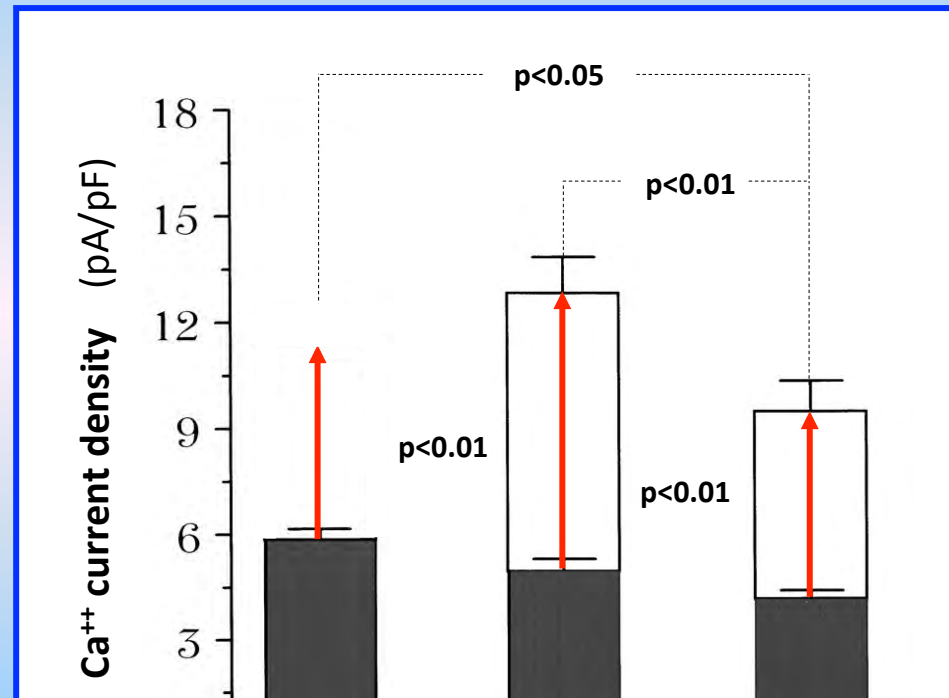
impairment of
 β -adrenergic receptor
responsiveness
in sepsis and septic shock

impairment of
post β -adrenergic receptor
signal transduction
in septic shock

Sequential Changes in Autonomic Regulation of Cardiac Myocytes after *In Vivo* Endotoxin Injection in Rat

NAJAH ABI-GERGES, BENOIT TAVERNIER, ALEXANDRE MEBAZAA, VALÉRIE FAIVRE,
XAVIER PAQUERON, DIDIER PAYEN, RODOLPHE FISCHMEISTER, and PIERRE-FRANÇOIS MÉRY

AM J RESPIR CRIT CARE MED 1999;160:1196-1204



- Phase **précoce**: réponse **accrue**
- Phase plus **tardive**: réponse **réduite**

Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

- *débit coronaire ?*
- *substances circulantes ?*

mécanismes **intracellulaires**

- *récepteurs β_1 ?*
- ***Calcium et myofilaments***

membrane du cardiomyocyte

β_1 agon



β_1 récepteur

AMP

cyclase

Hypothèse: au cours du sepsis,
Réduction de la sensibilité du myofilament au Ca^{++}
par réduction de la capacité du Ca^{++} à se fixer sur Tn

⊕

PKa

⊕

Ca^{2+}

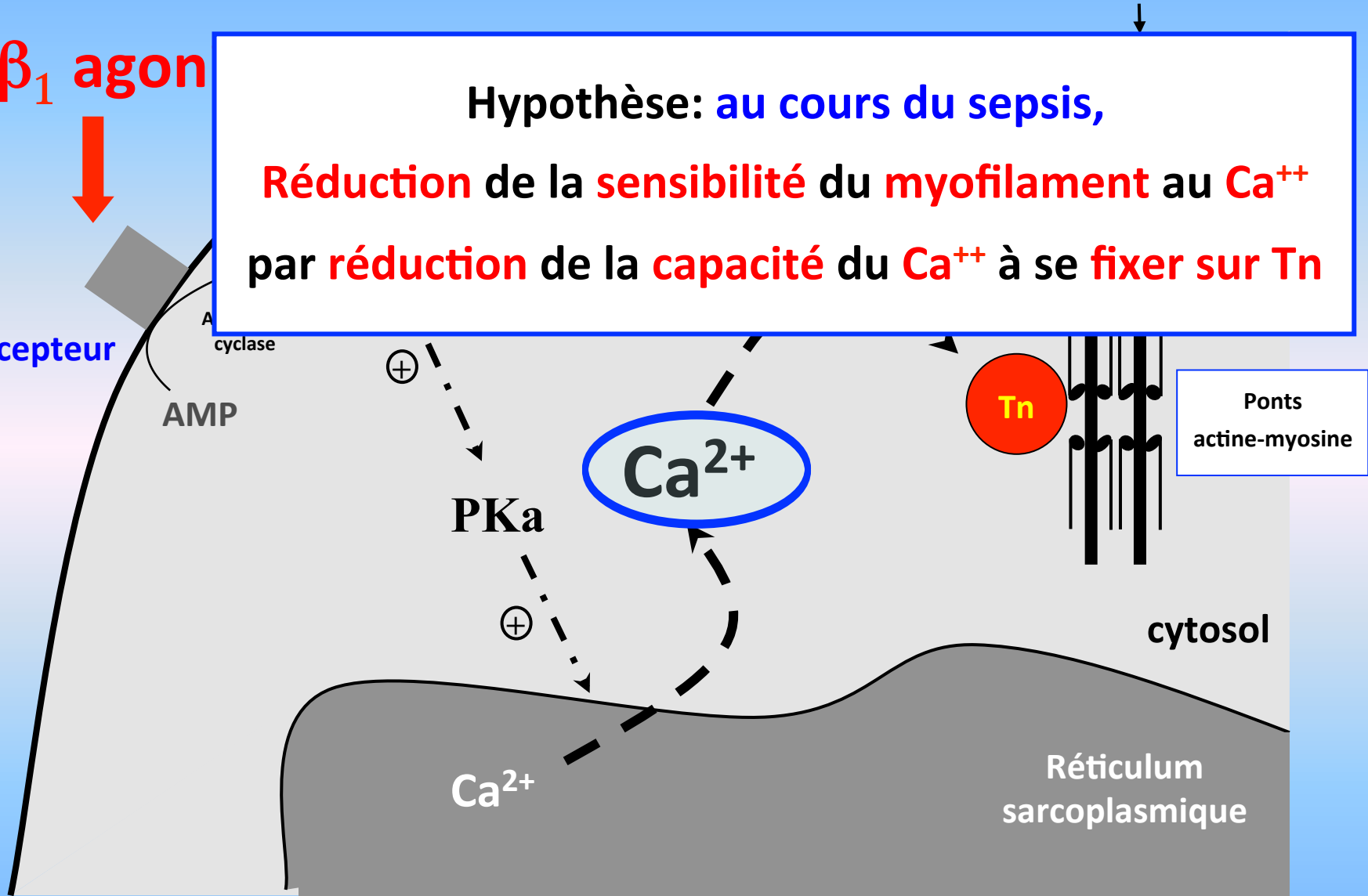
Tn

Ponts
actine-myosine

cytosol

Ca^{2+}

Réticulum
sarcoplasmique

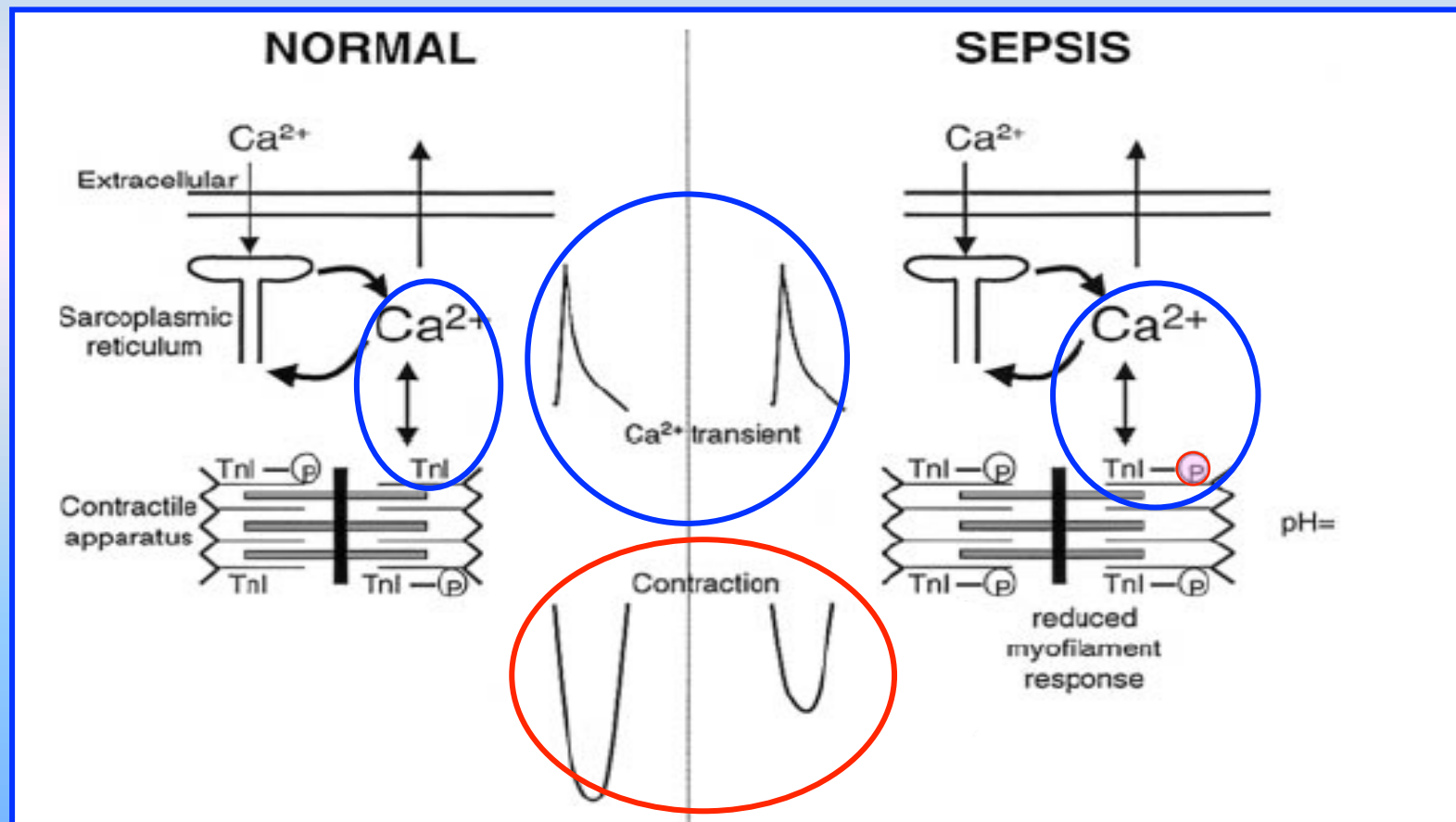


Cardiac contractile impairment associated with increased phosphorylation of troponin I in endotoxicemic rats

BENOIT TAVERNIER,¹ JIAN-MEI LI,^{1,2} MAGDI M. EL-OMAR,^{1,2} SOPHIE LANONE,¹ ZHAO-KANG YANG,² IAN P. TRAYER,¹ ALEXANDRE MEBAZAA,¹ AND AJAY M. SHAH^{1*}

Vol. 15 February 2001

The FASEB Journal



Mécanismes de la dysfonction myocardique septique

mécanismes **supracellulaires**

- *débit coronaire ?*
- *substances circulantes ?*

mécanismes **intracellulaires**

- *récepteurs β_1 ?*
- *Calcium et myofilaments*
- ***NO et peroxynitrite***

Mécanismes de la dysfonction myocardique septique

mécanismes supracellulaires

- *débit coronaire ?*
- *substances circulantes ?*

mécanismes intracellulaires

- *récepteurs β_1 ?*
- *Calcium et myofilaments*
- *NO et peroxy-nitrite*
- **Apoptose**

- A la phase **initiale**, effet **cytokine** serait **prédominant**
- A une phase **ultérieure**, **autres mécanismes** seraient **prédominants**

Dysfonction myocardique liée au sepsis

- Incidence
- Mécanismes
- **Diagnostic**
- Traitement

Diagnosis of sepsis-related cardiac dysfunction

Une FEVG de **50%** suggère dépression myocardique **modérée** si PAS à **130 mmHg**
... mais suggère dépression myocardique **profonde** si PAS à **80 mmHg**



Méthode clef

FEVG

Pour une interprétation correcte, tenir compte de la **PAS** (postcharge)

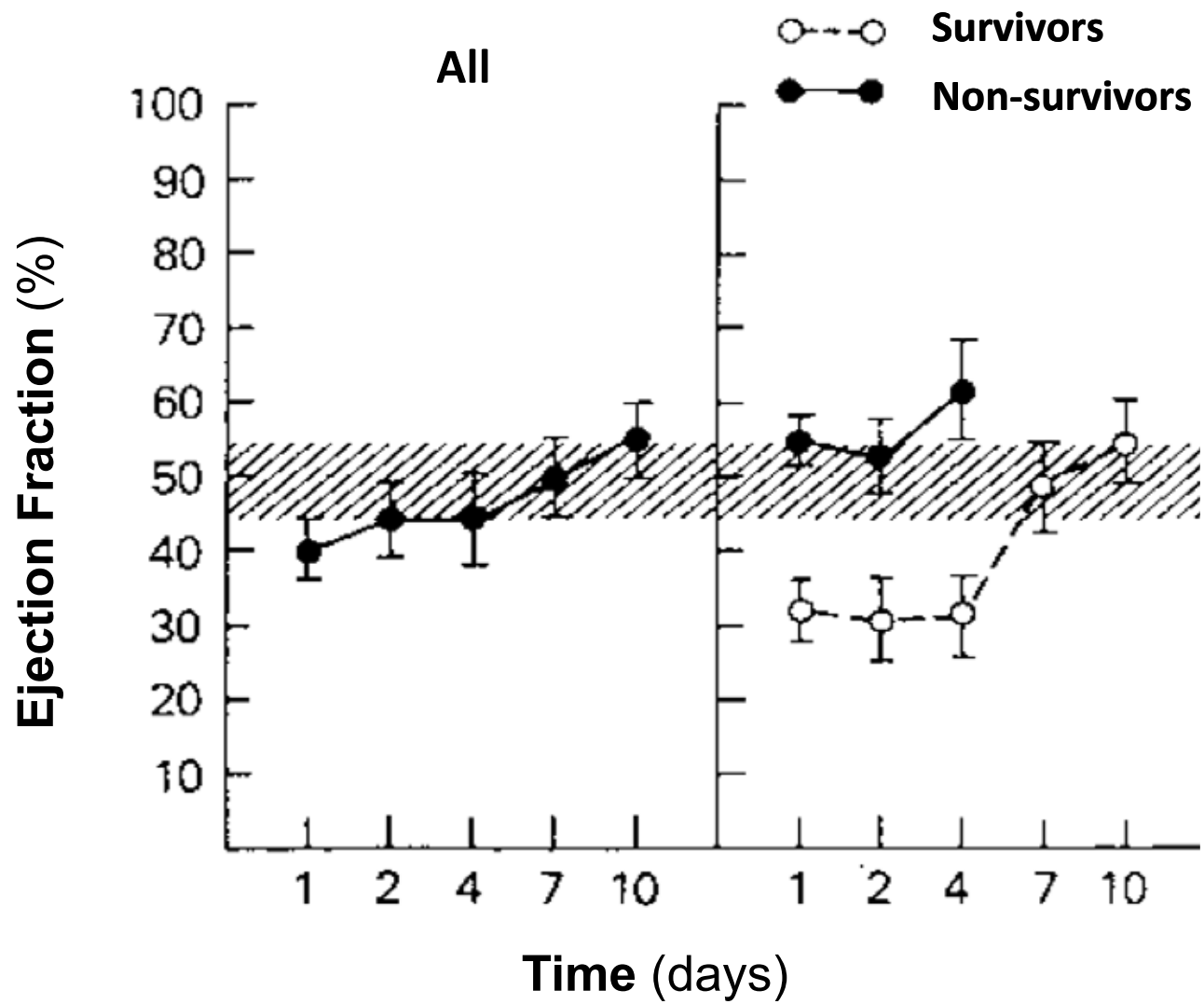
Dysfonction myocardique liée au sepsis

- Incidence
- Mécanismes
- Diagnostic
- **Traitement**

Traitement de la dysfonction myocardique septique

To treat or not to treat?

Basse FEVG et dilatation VG
mécanismes adaptatifs,
devant être respectés



Persistent Preload Defect in Severe Sepsis Despite Fluid Loading*

A Longitudinal Echocardiographic Study in Patients With Septic Shock

François Jardin, MD; Thierry Fourme, MD; Bernard Page, MD; Yann Loubières, MD; Antoine Vieillard-Baron, MD; Alain Beauchet, MD; and Jean-Pierre Bourdarias, MD

CHEST 1999; 116:1354-1359

Variables	Day 1	Day 2	Day n	Recovery
LVEDV, mL/m²				
S	75.3 ± 20.1†	80.3 ± 20.9†/‡	75.4 ± 21.8†	70.5 ± 14.7
NS	64.9 ± 25.0	62.2 ± 15.2	60.2 ± 21.6	
LVESV, mL/m²				
S	42.4 ± 17.9†‡	43.6 ± 15.0†/‡	35.7 ± 14.9‡	27.6 ± 10.2
NS	32.2 ± 17.7	34.8 ± 16.6	30.2 ± 16.4	
LVSV, mL/m²				
S	32.6 ± 13.8‡	36.7 ± 12.1†	39.7 ± 12.0†	42.9 ± 11.3
NS	32.7 ± 17.7	27.4 ± 13.9	30.0 ± 14.5	
LVEF, %				
S	43.9 ± 16.4†/‡	41.6 ± 10.6‡	53.2 ± 11.7‡	60.2 ± 16.4
NS	52.0 ± 14.0	45.7 ± 15.7	51.0 ± 16.8	

REVIEW

Open Access

Septic cardiomyopathy

Antoine Veillard-Baron^{1,2}

	Survivors (n = 99)	Nonsurvivors (n = 101)
Parker et al. [1] <i>20 patients</i>	LVEF (32) ± 4%	(55) ± 3%
Jardin et al. [15] <i>90 patients</i>	LVEF (44) ± 16%	(52) ± 14%
Veillard-Baron et al. [25] <i>67 patients</i>	LVEF (49) ± 18%	(55) ± 15%
Kumar et al. [32] <i>23 patients</i>	LVEF (50) ± 5%	(57) ± 4%

Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis

Stephen J Huang*, Marek Nalci and Anthony S Moxham

Huang *et al. Critical Care* 2013, **17**:R96



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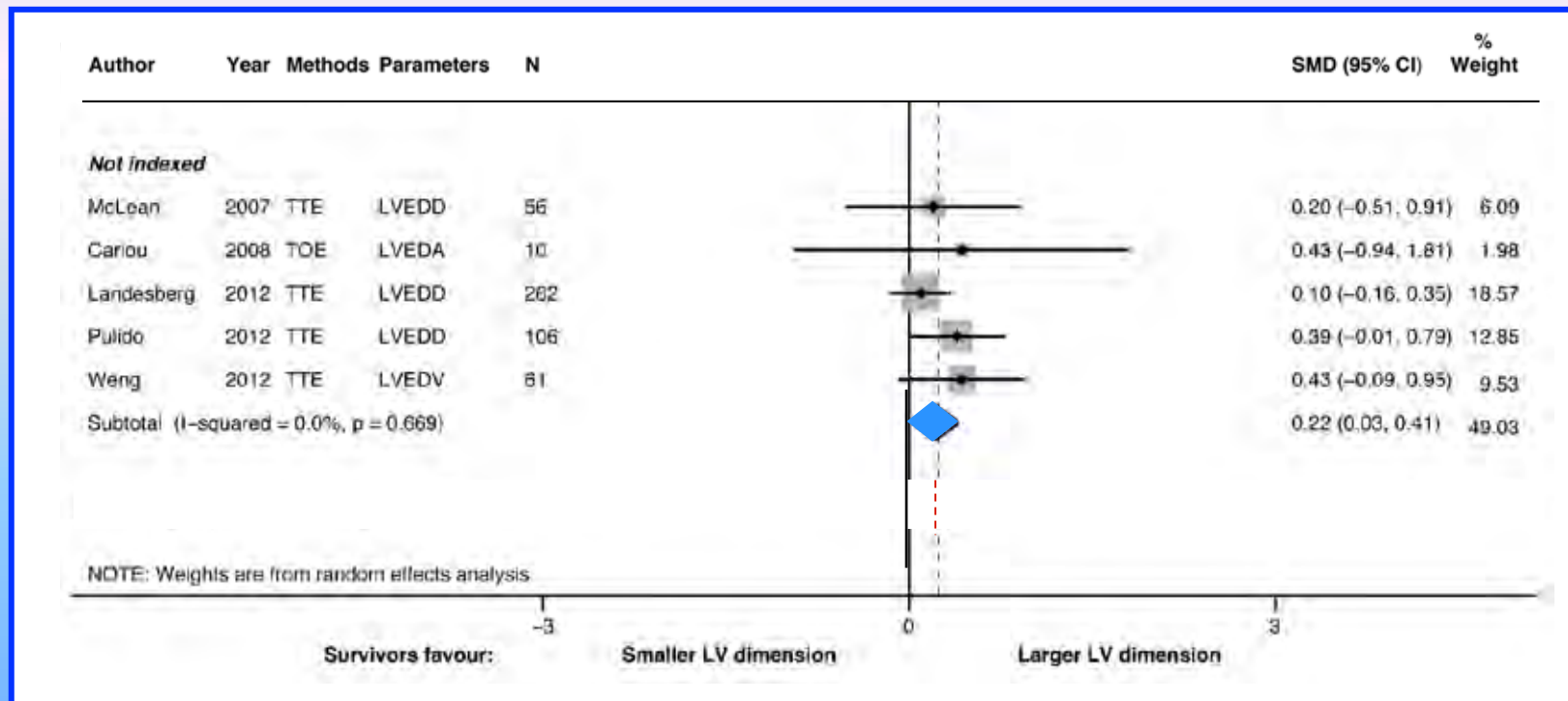
Huang et al. *Critical Care* 2013, **17**:R96

Author	Year	Cardiac assessment method	LV function (mean ± SD)	LV dimension (mean ± SD)	RV function (mean ± SD)	RV dimension (mean ± SD)
Kimchi et al.	1984	Radionuclide	LVEF (46 ± 16%)	-	RVEF (37 ± 2%)	RVEDVI (98 ± 10 mL/m ²)
Dhainaut et al.	1988	PAC-TD	-	-	RVEF (30 ± 12%)	-
Vincent et al.	1989	PAC-TD	-	-	RVEF (25 ± 8%)	-
Vincent et al.	1992	PAC-TD	-	-	RVEF (38 ± 16%)	RVEDVI (90 ± 31 mL/m ²)
Jardin et al.	1999	TEE	LVEF (49 ± 15%)	LVEDVI ^a (69 ± 24 mL/m ²)	-	-
McLean et al.	2007	TTE	LVEF (48 ± 15%)	LVEDD (47 ± 10)	-	-
Carliou et al.	2008	TEE	LVFAC (46 ± 19%)	LVEDA (16 ± 6 cm ²)	-	-
Etchecopar-Chevreuil et al.	2008	TEE	LVEF (47 ± 20%)	LVEDV (97 ± 25 mL)	-	-
Veillard-Baron et al.	2008	TEE	LVEF (51 ± 17%)	LVEDVI ^a (63 ± 23 mL/m ²)	-	-
Sturgess et al.	2010	TTE	LVEF (43 ± 14%)	LVEDVI ^a (67 ± 24 mL/m ²)	-	-
Funari et al.	2012	TTE	LVEF (57 ± 13%)	LVEDD/ht (28 ± 3 mm/m)	-	RVD (TTE) (24 ± 4 mm)
Landesberg et al.	2012	TTE	LVEF (59 ± 11%)	LVEDD (46 ± 10 mm) LVEDVI ^a (56 ± 18 mL/m ²)	RVSV change (7.5 ± 3.7 mL)	RVEDA (21 ± 6 cm ²)
Pulido et al.	2012	TTE	LVEF (57 ± 15%)	LVEDD (46 ± 10 mm)	-	-
Weng et al.	2012	TTE	LVEF (55 ± 16%)	LVEDV (72 ± 24 mL)	-	-

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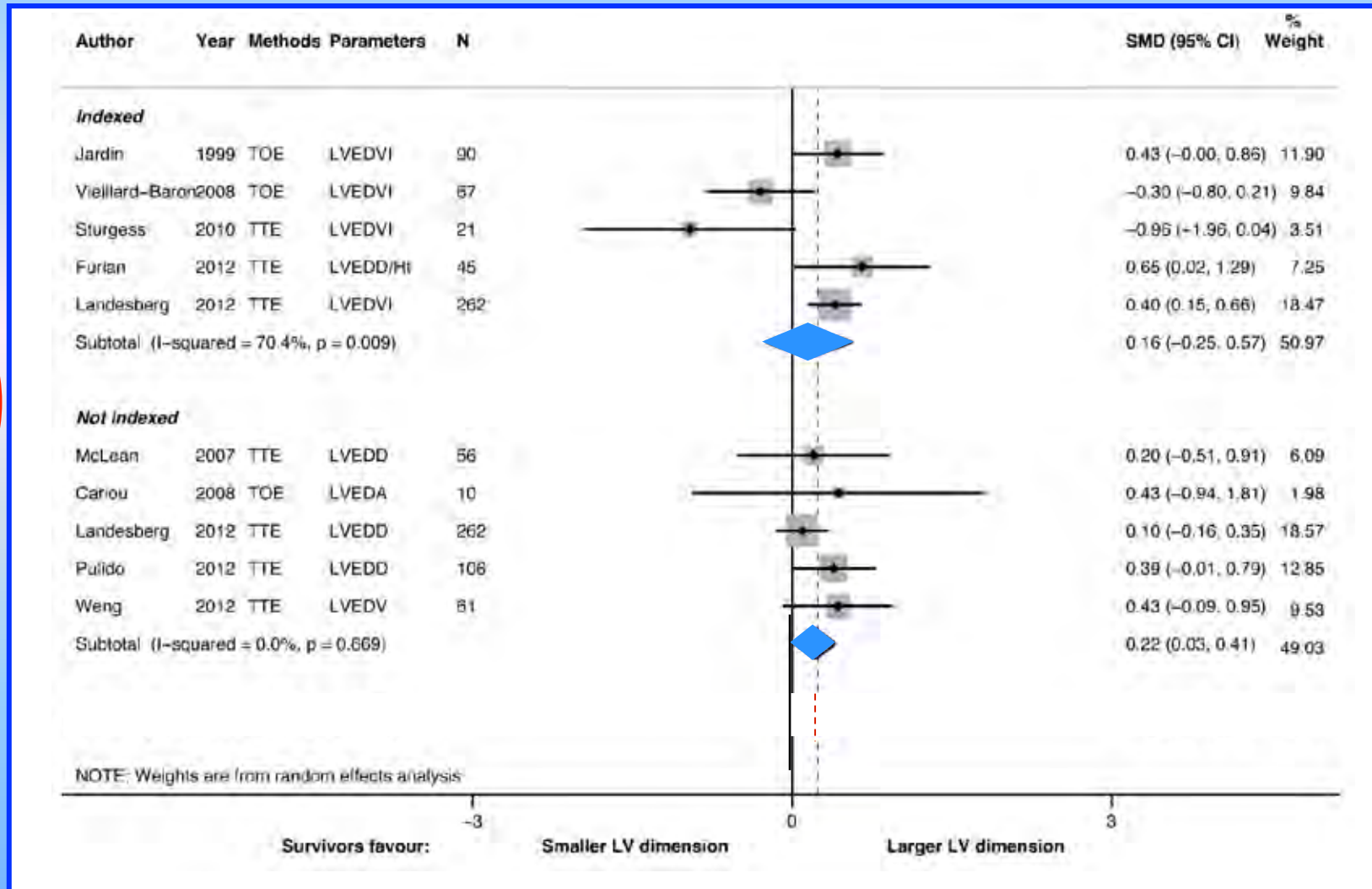


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LVEDV
LVEDA

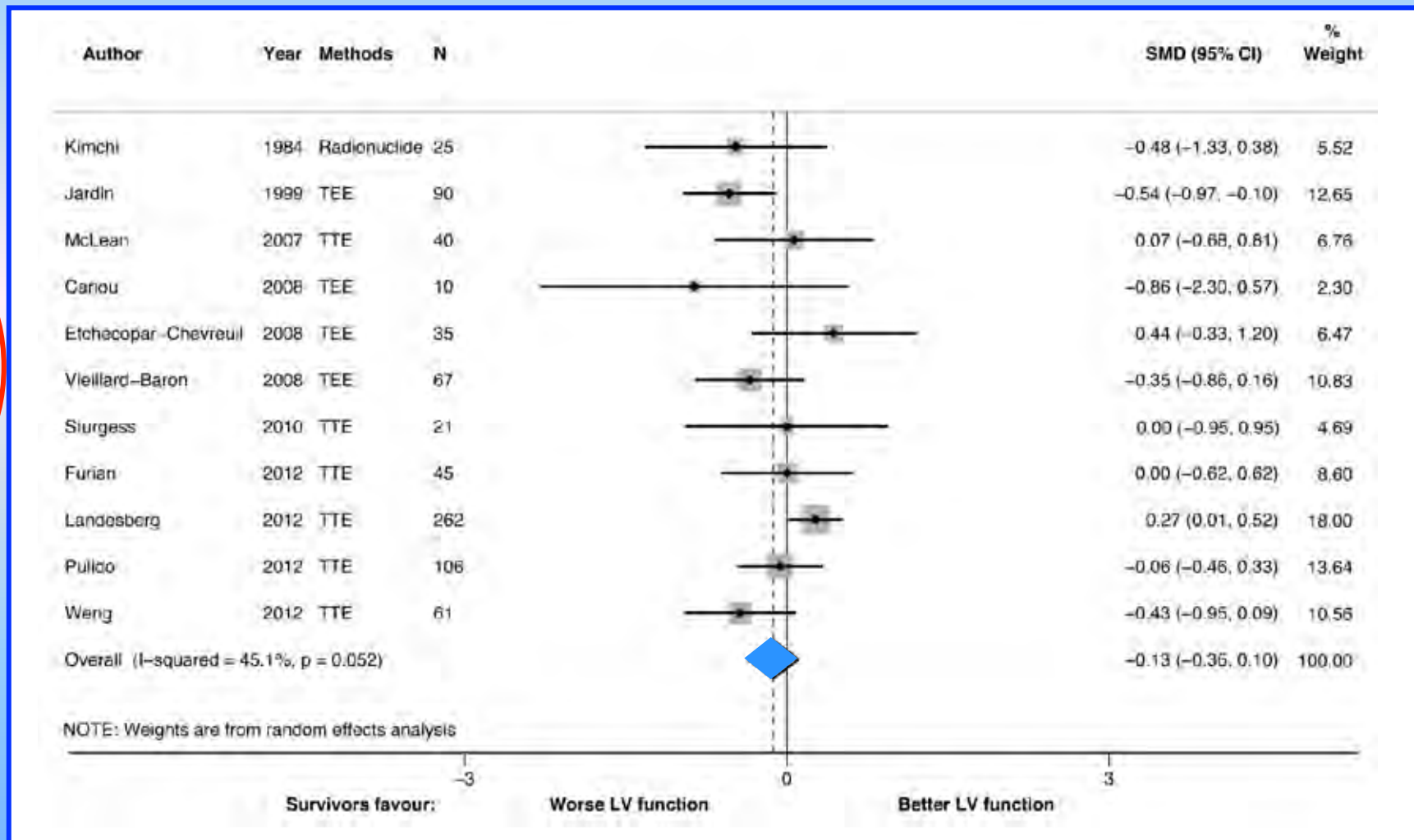


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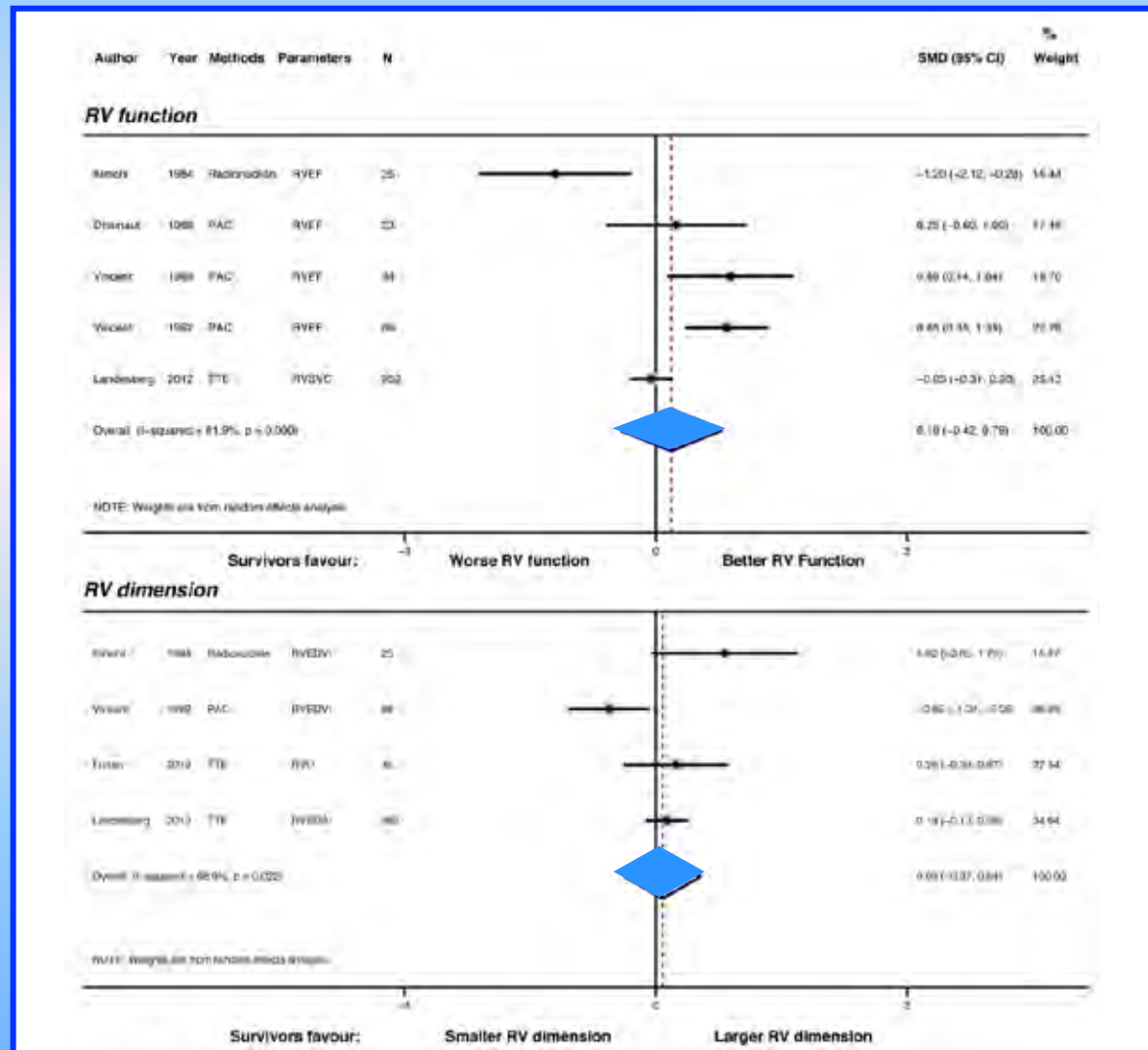
LVEF
LVFAC



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Huang *et al. Critical Care* 2013, **17**:R96

Key messages

- Pooled results do not suggest survivors from severe sepsis or septic shock had lower ejection fractions.
- Overall results seemed to suggest survivors exhibited slightly larger LV dimensions but pooled indexed LV dimensions were similar in survivors and non-survivors.

**Surviving Sepsis Campaign: International
Guidelines for Management of Severe Sepsis
and Septic Shock: 2012**

R. Phillip Dellinger, MD¹; Mitchell M. Levy, MD²; Andrew Rhodes, MB BS³; Djillali Annane, MD⁴;
Herwig Gerlach, MD, PhD⁵; Steven M. Opal, MD⁶; Jonathan E. Sevransky, MD⁷; Charles L. Sprung, MD⁸;
Ivor S. Douglas, MD⁹; Roman Jaeschke, MD¹⁰; Tiffany M. Osborn, MD, MPH¹¹; Mark E. Nunnally, MD¹²;
Sean R. Townsend, MD¹³; Konrad Reinhart, MD¹⁴; Ruth M. Kleinpell, PhD, RN-CS¹⁵;
Derek C. Angus, MD, MPH¹⁶; Clifford S. Deutschman, MD, MS¹⁷; Flavia R. Machado, MD, PhD¹⁸;
Gordon D. Rubenfeld, MD¹⁹; Steven A. Webb, MB BS, PhD²⁰; Richard J. Beale, MB BS²¹;
Jean-Louis Vincent, MD, PhD²²; Rui Moreno, MD, PhD²³; and the Surviving Sepsis Campaign
Guidelines Committee including the Pediatric Subgroup*

Inotropic therapy

1. A trial of **dobutamine** infusion up to 20 µg/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 CO**, or
 - (b) **ongoing** signs of **hypoperfusion**, despite achieving adequate intravascular volume and adequate MAP (grade 1C).

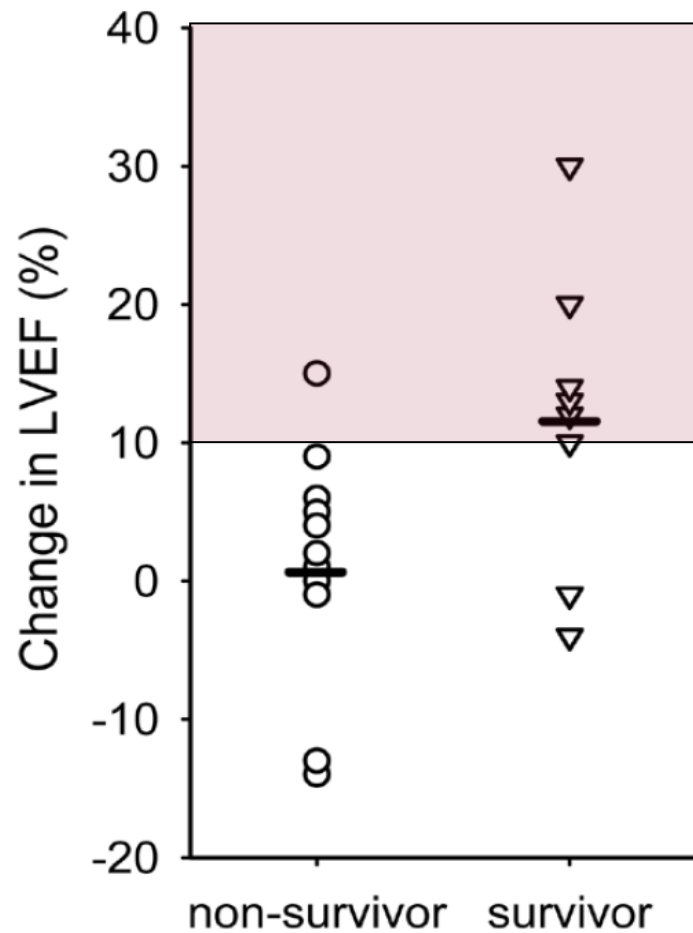
mais

- effets **bénéfiques** de la **dobutamine** difficiles à prédire
(diminution potentielle de l'activité β_1)

Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock

Anand Kumar^{1,2}, Elizabeth Schupp³, Eugene Bunnell³, Amjad Ali⁴, Barry Milcarek² and Joseph E Parrillo²

Critical Care 2008, 12:R35



Dobutamine **augmente** la **FEVG**
de plus de 10%
seulement chez **35%** des pts

Intensive Care Med (2008) 34:917–922
DOI 10.1007/s00134-008-1022-y

BRIEF REPORT

Alain Cariou
Michael R. Pinsky
Mebran Monchi
Ivan Laurent
Christophe Vinsonneau
Jean-Daniel Chiche
Julien Charpentier
Jean-François Dhainaut

Is myocardial adrenergic responsiveness depressed in human septic shock?



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Dobutamine et dysfonction myocardique septique

- effets **bénéfiques** difficiles à prédire
- effets **délétères** potentiels (troubles du rythme, vasodilatation, etc)

l'administration de **dobutamine** devrait être réservée aux pts

→ **tester la réponse** à la **dobutamine**
avant toute administration prolongée

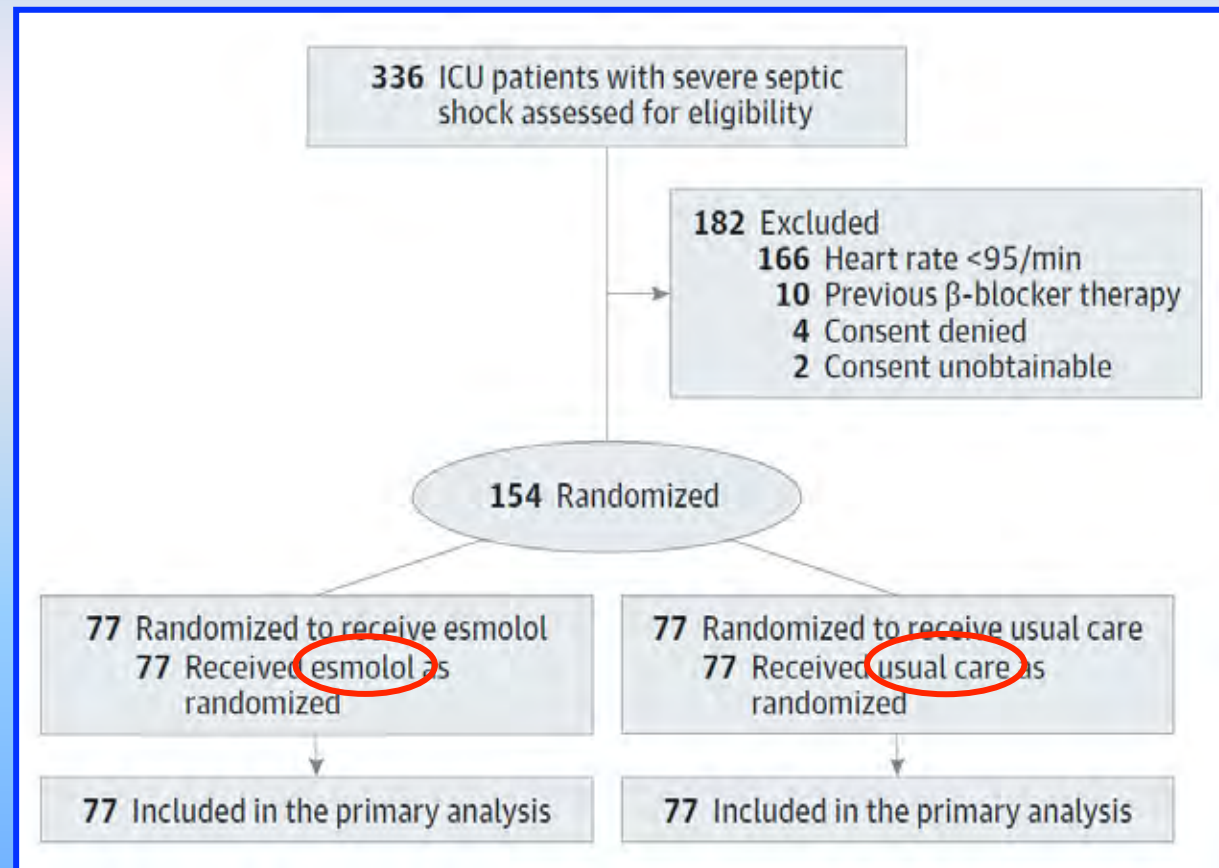
malgré remplissage et vasopresseurs

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

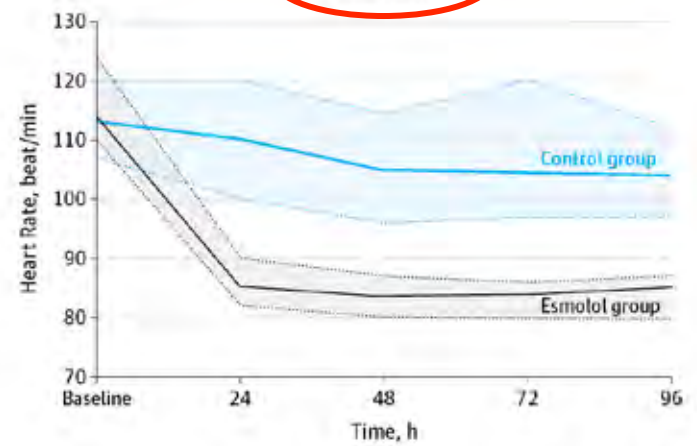
A Randomized Clinical Trial

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

JAMA 2013; 310:1683-1691

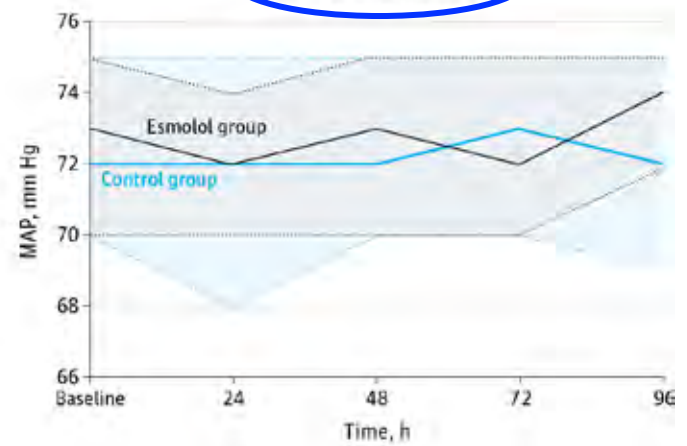


Heart rate



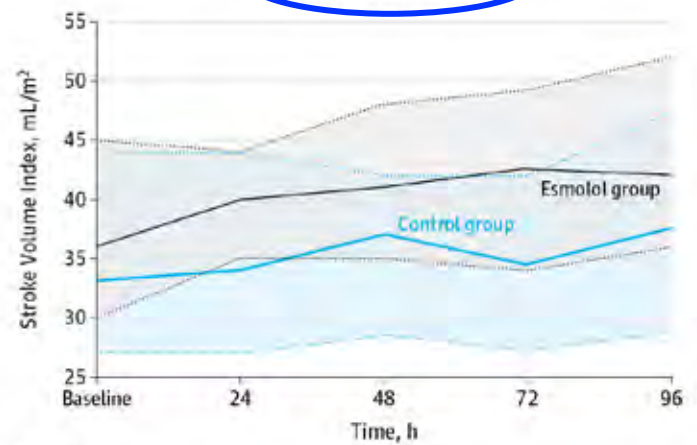
No. of patients	Baseline	24	48	72	96
Control	77	73	71	66	61
Esmolol	77	77	76	76	75

Mean arterial pressure



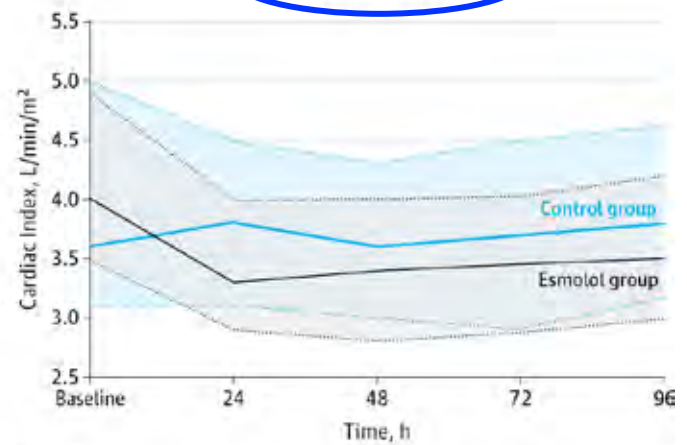
No. of patients	Baseline	24	48	72	96
Control	77	73	71	66	61
Esmolol	77	77	76	76	75

Stroke volume index



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

Cardiac index



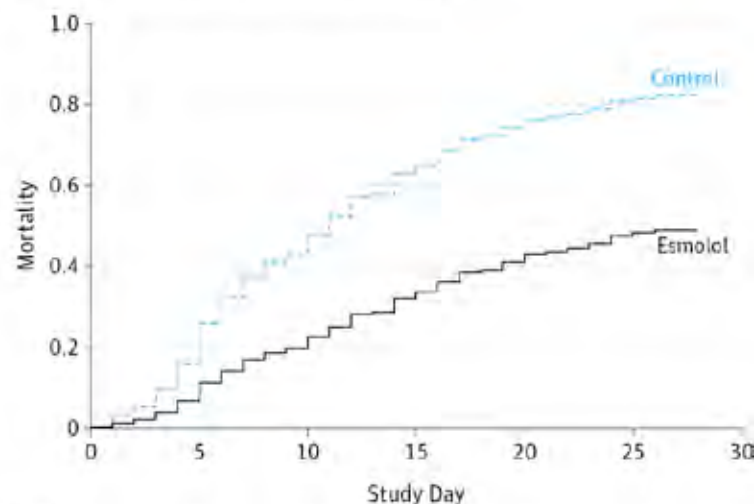
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Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock A Randomized Clinical Trial

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JAMA 2013; 310:1683-1691

B Adjusted survival at mean value of covariates



No. at risk	0	5	10	15	20	25	30
Control	77	52	39	26	21	16	15
Esmolol	77	73	61	53	43	40	39

Outcome	No. (%)		P Value
	Esmolol (n = 77)	Control (n = 77)	
Mortality			
28 d	38 (49.4)	62 (80.5)	<.001
ICU	44 (57.1)	68 (88.3)	<.001
Hospital	52 (67.5)	70 (90.9)	<.001
Length of ICU stay, d			
Median (IQR)	19 (11-27)	14 (7-25)	.03
Survivors', median (IQR)	17 (9-28)	21 (11-34)	.70
Cause of death, No./total, (%)			
Multiple organ failure	15/52 (28.8)	26/70 (37.1)	
Refractory hypotension	32/52 (61.6)	44/70 (62.9)	.71
Unknown cause	5/52 (9.6%)		

Traitement de la dysfonction myocardique septique

To treat or not to treat?

Alternatives à la dobutamine ?

membrane du cardiomyocyte

β_1 agoniste

Ca^{2+} sensitizers

β_1 récepteur

cAMP

Adenylate cyclase

AMP

⊕

PKa

⊕

Ca^{2+}

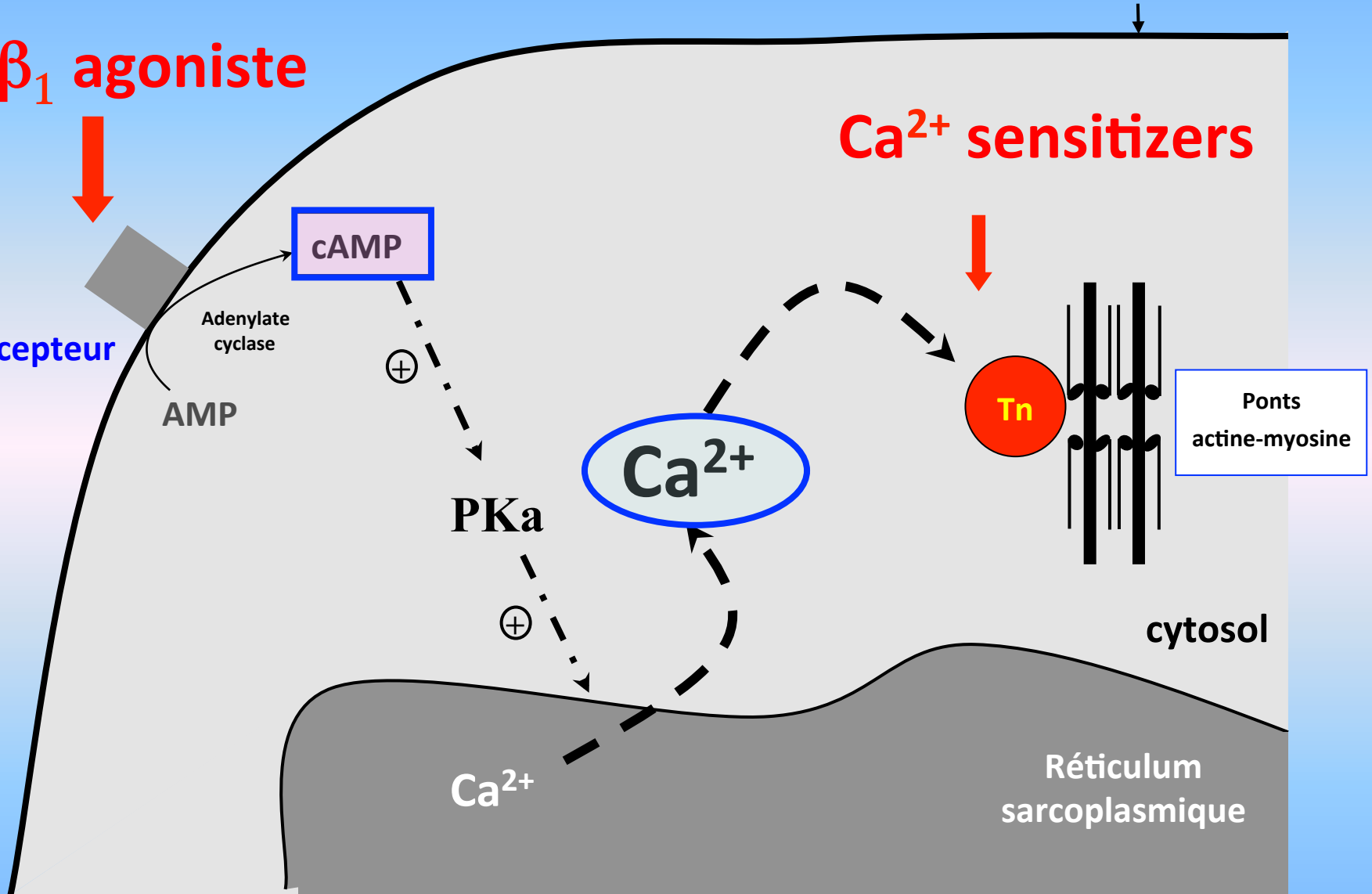
Tn

Ponts actine-myosine

cytosol

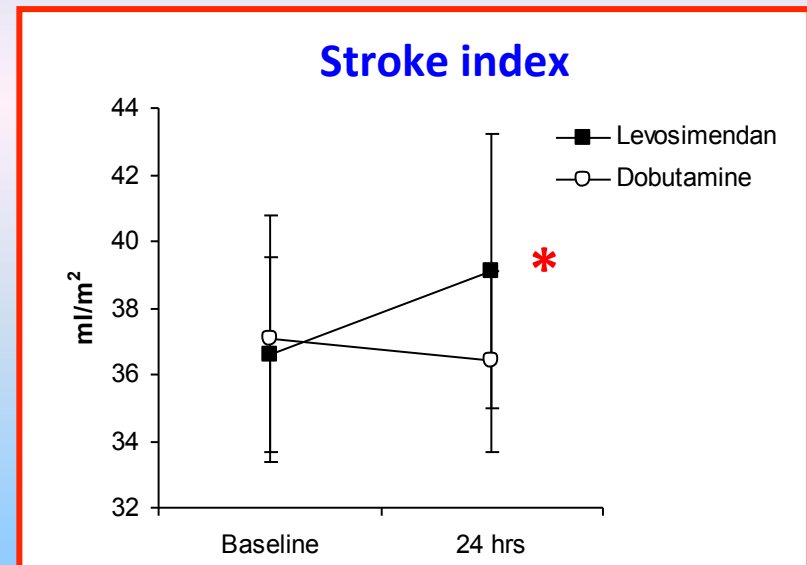
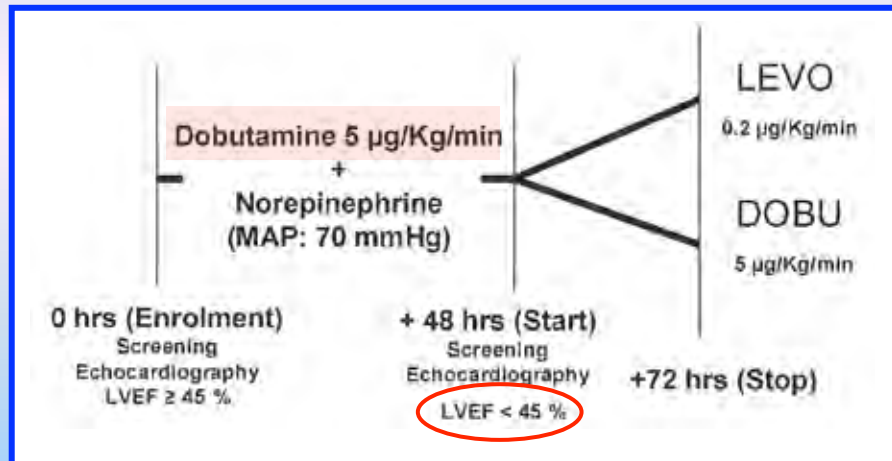
Ca^{2+}

Réticulum sarcoplasmique



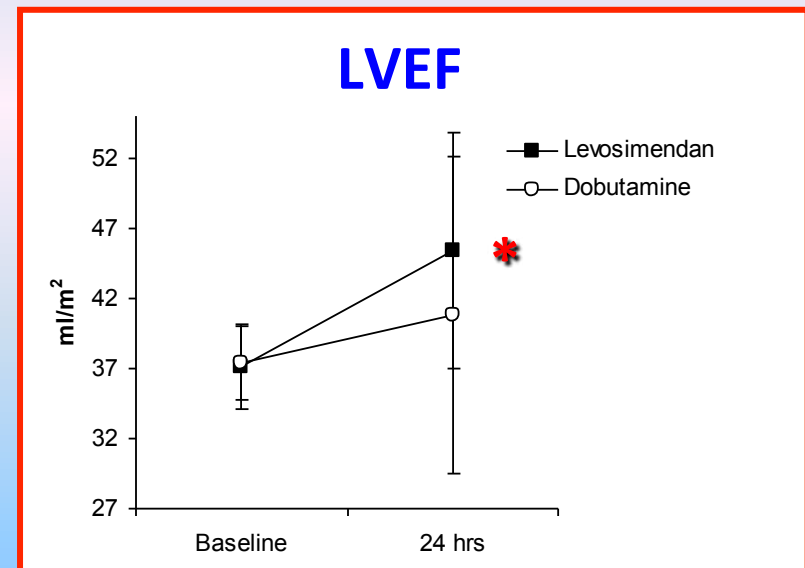
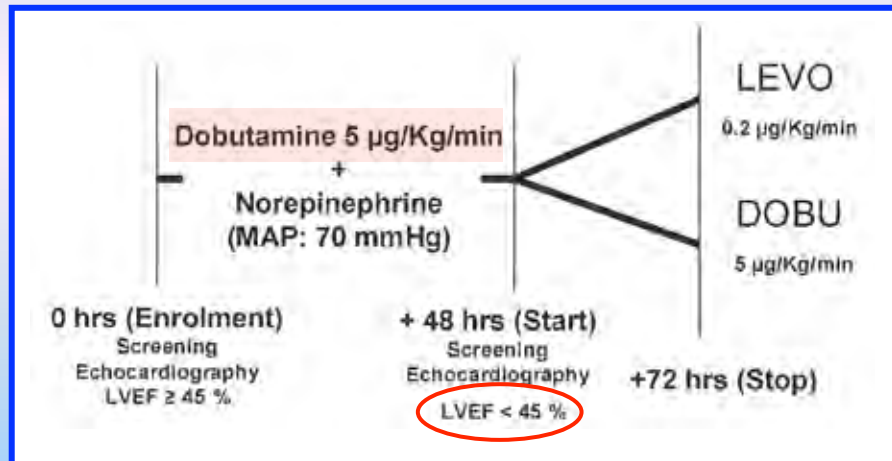
Andrea Morelli
Stefano De Castro
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Monica Rocco
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Leonardo De Luca
Emanuele Di Angelantonio
Alessandra Orecchioni
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Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression



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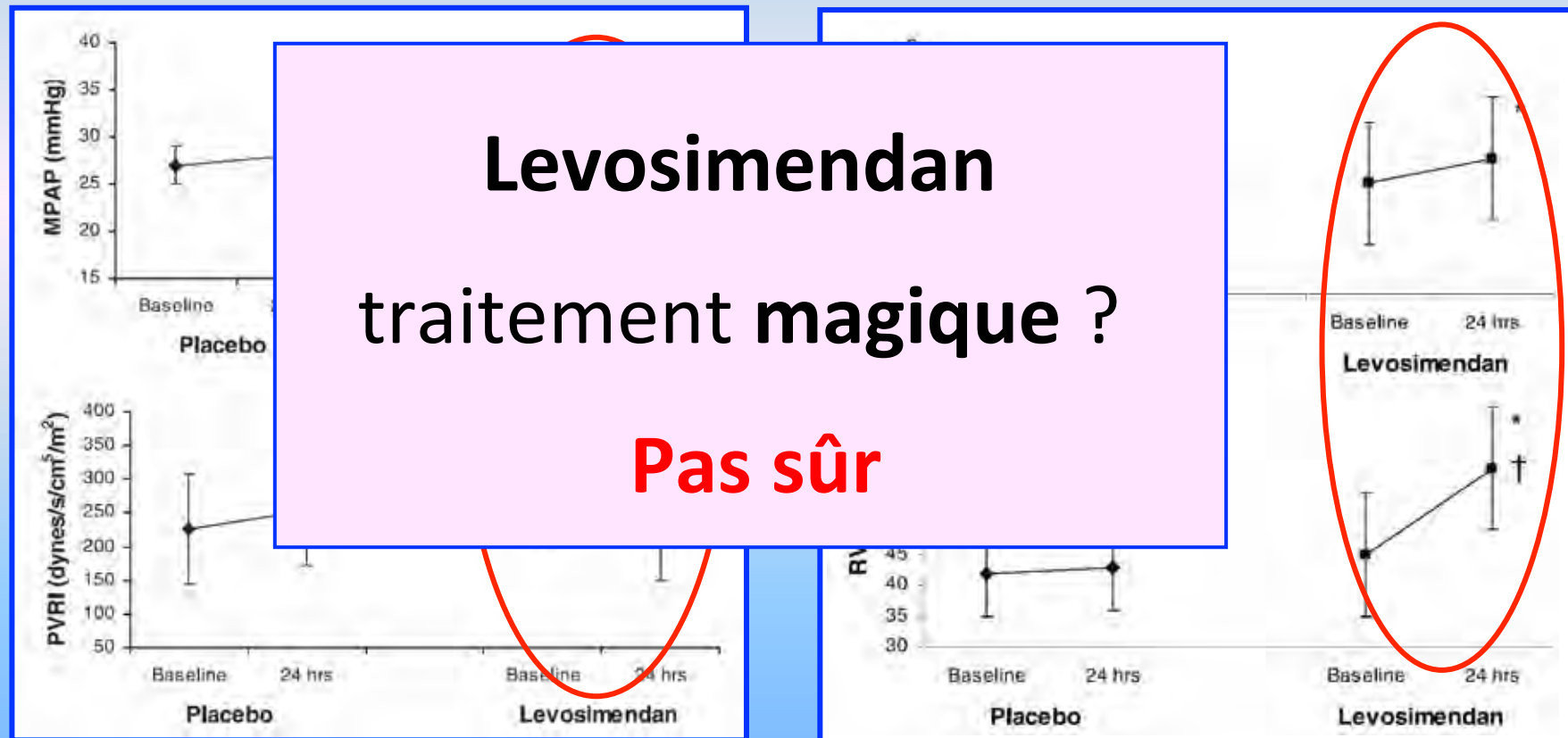
Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression



Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study*

Andrea Morelli, MD; Jean-Louis Teboul, MD, PhD; Salvatore Maurizio Maggiore, MD, PhD; Antoine Vieillard-Baron, MD; Monica Rocco, MD; Giorgio Conti, MD; Andrea De Gaetano, MD, PhD; Umberto Picchini, Dr in statistics; Alessandra Drecchioni, MD; Jacopo Carbone, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Martin Westphal, MD

Crit Care Med 2006; 34:2287-2293



Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

Alexandre Mebazaa, MD, PhD

Markku S. Nieminen, MD, PhD

Milton Packer, MD

Alain Cohen-Solal, MD, PhD

Franz X. Kleber, MD

Stuart J. Pocock, PhD

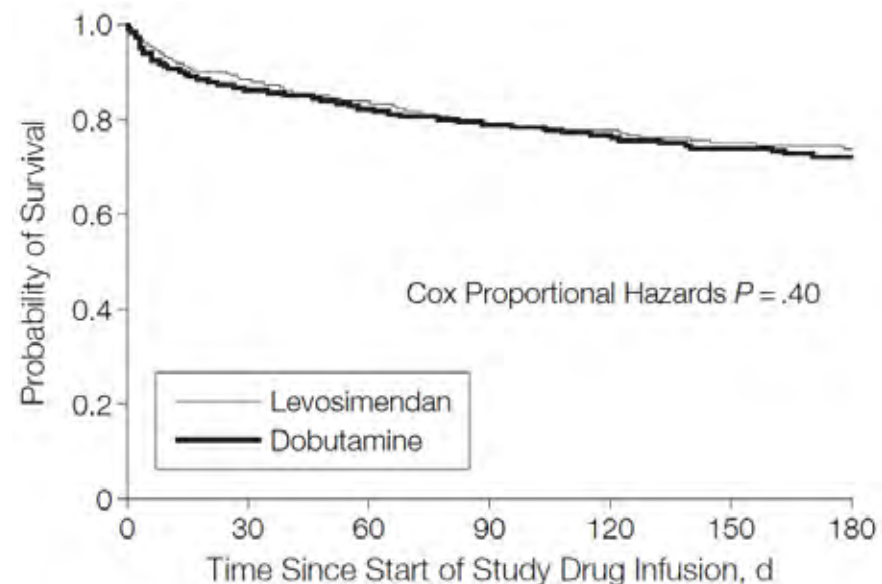
Roopal Thakkar, MD

Robert J. Padley, MD

Pentti Pöder, MD, PhD

Matti Kivikko, MD, PhD

for the SURVIVE Investigators



Traitement de la dysfonction myocardique septique

To treat or not to treat?

- **S'assurer** que le patient n'est **pas hypovolémique**
 - **évaluer la réponse au remplissage**
 - indices **statiques** de **précharge** (ex: PVC) peu appropriés
 - indices **dynamiques** de **précharge-dépendance** +++
- **S'assurer** que l'**hypotension** est bien **corrigée**

Conclusions

- Les mécanismes contribuant à la **dysfonction myocardique septique** sont **complexes** et **intriqués**
- **Traiter** ou **non** la dysfonction cardiaque est encore un sujet de débat (place de l'écho et de la **ScvO₂**)
- Dans tous les cas, **corriger** d'abord **hypovolémie** et **hypotension**
- Quand la décision de traiter est prise, la **dobutamine** est encore recommandée,
... mais elle peut être **inefficace** ou délétère chez pts les plus **graves**
- La place des **Ca⁺⁺ sensitizers** nécessite davantage d'évaluation

Merci